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Dysphagia: daily concerns and formulative approaches for drug therapy

Doctoral Thesis

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Summary

This doctoral thesis aimed to argue about the specific subject of dysphagia and its relative concerns. Dysphagia is defined as the sensation of delayed passage of the bolus from the mouth to the stomach and issues regarding swallowing of drug therapy are going to be discussed and faced in this work. In fact, focus was mainly pointed on the difficulty of solid oral dosage forms deglutition and, on problems related to compounding and administration of drug therapy. Two model drugs were examined: pravastatin sodium and potassium canrenoate. Their diffuse prescription makes them two interesting molecules in order to optimize alternative dosage forms with respect to the solid one.

The pharmaceutical market offers a wide availability of dosage forms but solid ones are by far the most common due to some advantages that they have in terms of production, stability of the molecule, and costs. Sometimes, not all active molecules are formulated in the preferable form suitable to dysphagic people as well. Population with swallowing inability requires some specific arrangements to assume the prescribed drug therapy.

Compounding commercial dosage forms is not always possible, for example in case of gastro-enteric or controlled-release formulations. Nevertheless, the lack of awareness and proper background make errors happen in the several care settings (hospital, nursing homes, long-term care facilities) where dysphagic patients are admitted. Other problems may occur during manipulation process such as, for example, invaluable drug losses, active molecule instability, palatability decrease, cross-contamination among the drug powders crushed in the same device.

To overcome some issues related to drug intake in dysphagic people, the purpose of the work was to optimize compounding process in order to produce suitable dosage forms for this specific target population.

The work was organized in the following parts. After a general introduction of dysphagia issue, biopharmaceutics considerations concerning drug compounding were argued in the first part of the thesis.

In the second chapter, current clinical practice was dealt with. Whatever was daily performed in the hospital setting, for instance, tablet splitting to facilitate drug intake reducing tablet size, or inappropriate prescriptions of solid oral dosage forms when other

therapeutic forms would be available, or occupation risks related to hospital workers during bedside compounding were discussed.

The third chapter of the work addressed the optimization of some dosage forms. Liquid dispersions of pravastatin sodium and potassium canrenoate were set up and enteral delivery via feeding tubes was analyzed for both of them. Pravastatin sodium was further studied to prepare a gelified form to replace tablet. Rheological and kinetic release profile studies were evaluated. The same statin was used to refine an orodispersible film able to disintegrate in the mouth after contact with saliva.

All these dosage forms, studied and tuned in the laboratory, might be able to replace commercial tablets. They might guarantee drug therapy to those who, due to their inability to swallow solid forms, would not have therapeutic alternative with the exception of extemporaneously and bedside produced preparations.

1. Introduction

1.1. Dysphagia: definition and general aspects

The term of dysphagia, which comes from the Greek words *dys* (difficulty) and *phagia* (to eat), defines any disorder in swallowing process that may affect ability in feeding, respiratory activity and communicative functions. It is also described as an issue to move down food from the oral cavity to the stomach. The physiology of deglutition process is generally referred to swallowing of solid food in adult. Nevertheless, deglutition of liquids and deglutition in newborns or children require a proper attention. In this thesis, adults and elderly people are the major subjects to whom the work is intended. People may assume and swallow substances from outside such as food, beverages, drugs, foreign bodies (i.e., teeth), and others; or substances from upper deglutory route such as saliva, mucus, cells from nasal, oral, pharyngeal cavities or airways; or substances from lower deglutory route such as gastric or enteral contents.

Swallowing is a complex phenomenon involving several anatomical structures (Figure 1): oral cavity, pharynx, larynx, trachea, esophagus, stomach, duodenum, and nervous central system. It starts as a voluntary process and it becomes a reflex movement due to the trigger zone stimulation in the swallowing center.

Deglutition (or normal deglutition) in healthy adult people comprises four main phases:

1) Oral preparatory phase: is a voluntary step and under cortical control. Food is chewed, reduced in small pieces, mixed with saliva to form a bolus.
2) Oral phase: bolus will be brought back to soft palate and pharynx by tongue, ready to be swallowed. A discriminant aspect is tongue mobility to facilitate mastication.
3) Pharyngeal phase: defined also as reflexive phase of swallowing where bolus goes down towards pharynx. The swallowing reflex is controlled by some sensory and motor activities managing cranial nerves in the 'swallowing center' of the medulla oblongata. Respiration is temporarily stopped to permit bolus passage while epiglottis is closed.
4) Esophageal phase: bolus scrolls down thanks to peristaltic movements and through the lower esophageal sphincter enters the stomach.[1,3]

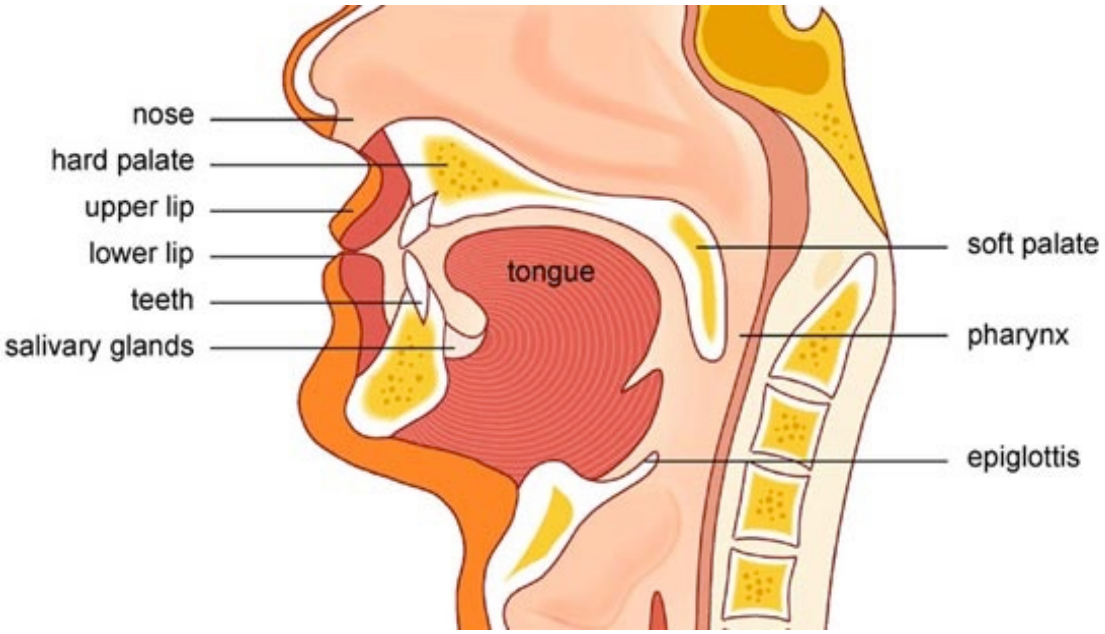

Figure 1: Anatomical structures involved in swallowing process.

Deglutition problems may be due to a single phase of swallowing or to more than one step simultaneously determining the severity of the inability. Just to give an idea about the timing of a physiological deglutition action, the duration of a single act in 40 years old healthy volunteers was estimated to last ≤740 ms, fast laryngeal closure (≤160 ms), strong bolus propulsion (≥0.33 mJ), and tongue propulsion forces of 22 mN. On the contrary, patients with brain damage or neurodegenerative pathologies presented: prolonged swallow response (≥806 ms), delayed laryngeal closure (≥245 ms), weak bolus propulsion forces (≤0.20 mJ) and impaired tongue propulsion of 9 mN.[4,5] During the deglutition sequence, the bolus complete transit should be assured and staying of bolus portions should be avoided to prevent any food entrance into the airways.

1.1.1. Age-related disorder

The ability to swallow is also related to physiological aging process[6]; aged healthy people refer a normal reduction of the muscular force of the oral cavity muscles and coordination of buccal movements involved in deglutition.[7] In addition, several primary

pathologies, their severe progression and drug therapy as well, may compete on the onset of dysphagia. In this regard, swallowing issues may emerge as an acute event that appears suddenly and has a brief length, or as a chronic event that develops gradually.

Sometimes, deglutition impairments are underestimated or unknown because elderly people are reluctant to talk and refer about this further difficulty to their relatives, or their personal medical doctor, or their caregivers. The underestimations of several symptoms referred to dysphagia in elderly and fragile persons may hide some other consequences such as, for instance, malnutrition, dehydration, pneumonia and, unbalance in electrolytes intake. Moreover, physicians might be immediately unable to diagnoses dysphagia at early stage of the condition because elderly people generally show co-morbidity and assume a number of several drugs. Furthermore, exact diagnosis of dysphagia may be complex because swallowing dysfunctions may remain asymptomatic and do not cause any relevant clinical concerns until they become dominant or associated with other pathologies.

1.1.2. Etiology

Several causes determine the onset of dysphagia. The already mentioned factor linked to age-related functionality is for sure a crucial feature. Elderly population shows a reduction in muscle strength of oral cavity, thus the tongue force and pressure are less durable and effective during the movements. Decline in receptor activity affects their responsiveness and consequently, a general decrease in swallowing action.[3] Moreover, a reduction in saliva production and xerostomia influence bolus formation firstly and then, deglutition itself. Sarcopenia, defined as a loss of muscle tissue and strength and quite frequent in old people, may be a further factor involved in dysphagia scenario.

Additionally, some other relevant chronic illnesses are concomitant to dysphagia issue and get complex the clinical state of patient. It is well-known that dysphagia may be associated with diseases of central nervous system such as stroke, Alzheimer's and Parkinson's diseases, dementia syndrome, cognitive disability, motor neuron disease, multiple sclerosis, amyotrophic lateral sclerosis, depression and others.

Deglutition disability arises after metabolic disorders like diabetes, hyper- or hypothyroidism or after oncological injuries for example brain, neck, and oropharyngeal area tumors.

Some active molecules may be involved in swallowing dysfunctions either through a direct pharmacological effect causing adverse drug reactions, or through an indirect effect related to activity (inflammation due to antibiotics, immunosuppressive or antineoplastic agents), or through injuries directly induced to the oropharyngeal or esophageal mucosae.[3,8] Some examples are following reported: xerostomia is generally also correlated to the assumption of some drugs that, with their anticholinergic effects, may affect saliva production.[9] They may get complicated, aggravate and accelerate swallowing problems about the existing situation at oral cavity level. Drugs may cause esophageal lesions after a direct contact of the active molecule with the mucosa or, indirectly, by changing the pH of the district. Furthermore, some antipsychotic drugs show extrapyramidal side effects leading to dysphagia as further difficulty. To give a non-exhaustive idea, a partial list of drugs involved in swallowing dysfunction is shown. Drugs may be grouped according to:

- drugs inducing dysphagia: antipsychotic (i.e., haloperidol, risperidone, clozapine), anticholinergics, antidepressant (i.e., nitrazepam, clonazepam), analgesics, antiepileptics, cytotoxics;
- drugs inducing xerostomia (i.e., anticholinergics, antispasmotics, antidepressants, anticonvulsants);
- drugs causing esophageal injuries: antibiotics (i.e., tetracycline, lincomycin, penicillins and all their derivatives, non-steroidal anti-inflammatory drugs, potassium, calcium, iron salts, bisphosphonates, ascorbic acid).[3]

Other noteworthy aspects regard radiotherapy and surgery as causes of dysphagia. Radiotherapy, alone or in combination with chemotherapy, results usual treatment for cancers. Such cares in oropharyngeal area determine the onset of dysphagia and the severity depends on the dose, on the frequency of the treatment and on the treated area.[10,11] Obviously, radiotherapy coupled with chemotherapy increases the occurrence of dysphagia. Sometimes, such treatments are combined with surgery in neck, head, throat, and thoracic areas. The possibility to hit and damage nerves involved in the above

areas is directly associated with the possibility to develop dysphagia also connected to decrease of tongue motion and oral cavity sensitivity.

1.1.3. Prevalence

The increased prevalence of dysphagia or swallowing issues may be revealed with advancing age, intensity of required care and number of co-morbidity diagnosed to patient. Around the word, prevalence of dysphagia is similar according to data reported in literature: in a cohort of Japanese 65 or more aged-people (65-74 years old), 8.8% showed signs of dysphagia which increased to 19.0% in the 75-84 years old and to 28.2% in over 85 years old people.[12] Data collected in a German hospital and specifically in a geriatric ward were in agreement with the previous Japanese frequency; in fact, people with mean age of 83 years old were diagnosed with swallowing dysfunction.[13] In Spain, values ranged between 16.6% of the 70-79 years old patients up to 33.0% in case of patients beyond 80 years of age.[14] In Unites States of America prevalence of dysphagia in senior citizens of 65 or more years old achieved 35%.[15] Data collected from an Italian care setting, a large teaching hospital, showed that percentages varied according to different wards: general medicine (26.1%), neurosurgery (17.1%), neurology (16.7%), intensive care unit (14%), geriatrics (9%), and head and neck surgery (8.5%). Mean age ranged between 61-80 years old.[16]

Obviously, the prevalence increases with the level of care that needs to be provided to the patients.[17] For instance, swallowing impairments in long-term care facilities may reflect a long-term therapy with drugs causing dysphagia (i.e., antipsychotics).[18] Pathologies involving central nervous system may have a preponderant impact on dysphagia due to behavioral, neurological and motoric implications. Authors report that Parkinson's disease affects onset of dysphagia from 52% up to 82%, amyotrophic lateral sclerosis up to 60%, myasthenia gravis 40%, multiple sclerosis 44%, and Alzheimer' disease up to 84%.[19] After stroke, the occurrence of dysphagia depends on size and location of damaged brain area, but anyway, dysphagia is generally diagnosed in 50.5% of the population.[20] Patients suffer from schizophrenia or bipolar affective disorders are diagnosed with dysphagia in about one third of the recruited population.[18]

1.1.4. Diagnosis

Background information about patient history may help to understand first suspects of dysphagia or swallowing impairments. Evaluations on patients about unbalanced nutritional status, weight loss, frequent infections, and pulmonary aspiration may underline possible deglutition difficulties. Moreover, speech or cognitive disorders may be concomitant with problems related to deglutition. To observe patient while eating and drinking may facilitate understanding of the dysphagia severity.[3]

Therefore, a multidisciplinary team of specialists that varies from medical doctors as neurologist, otorhinolaryngologist, geriatrician, gastroenterologist, radiologist, dietitian, to speech and language therapists and pharmacists, is able to provide a clinical assessment of the patient.[3]

Early assessments about cognitive status of patient are fundamental to decide any further diagnostic investigation. If patient results collaborative, a prompt diagnosis of dysphagia may be beneficial for patient to implement a proper practical strategy while mealtime and swallowing (specific training to perform and follow some practices, for example how to tilt the head). Then, nurses and caregivers may perform some bedside screening through several methods: the volume-viscosity swallow test (V-VST) using different aliquots of water (from 5 ml to 20 ml) to evaluate the patient capability to assume liquids or, the duration of the act or, if coughing occurs. Furthermore, nurses and caregivers may test ability using materials with different viscosities to appreciate deglutition in case of liquids, semi-solids, or solids supplies.[21] Oxygen desaturation measurement is an additional parameter to evaluate aspiration and penetration of the bolus in the airways: desaturation of more 2% may be considered statistically significant and thus, it may be considered as a first signal of impaired deglutition.[22] Endpoints of these evaluations are generally coughing, choking or wet voice and are different clinical signs to estimate the severity of dysphagia and impaired deglutition. At this point, speech and language therapists may provide a formal assessment of swallowing by a clinical validation through previously performed data collection.

In addition, some other evaluations such as video fluoroscopic swallowing examination (VFSE) and flexible endoscopic evaluation of swallowing (FEES) are appropriate technique useful in diagnosis. VFSE may be considered the gold standard relative to oral and pharyngeal phase of deglutition: it provides dynamic images of the bolus progression through the oro-gastric-enteric tract giving information on safety and efficacy of deglutition. Radiation exposure limits the repetition of the test and patient has to be cooperative to collaborate during the evaluation. FEES, instead, is non-invasive technique, presents a higher sensitivity than VFSE in the detection of pulmonary aspiration of bolus. It has been validated for oropharyngeal dysphagia diagnosis.[23] After that, heterogeneous team of specialists gives a specific evaluation of the patient status to decide an effective treatment. Once performed each available evaluation and according to the dysphagia severity, medical doctors may decide to prescribe food and beverages at modified consistency or to switch to enteral nutrition and enteral administration of drug therapy.

1.1.5. Intervention strategies

Dedicated training and education intended for patients, caregivers, relatives and health care providers are fundamental in management of dysphagia after diagnosis. Some different adjustments and medication reviews are necessary whenever it is possible to reduce drugs just to essential ones. Afterwards, additional interventions and exercise program should be performed and taken in place such as proper head movements during swallowing, or reduction of volume and, modified viscosity of bolus to make easier and safer deglutition. Just as an example, a simple anterior neck flexion decreases the velocity of the bolus pushed into the esophagus when airway protection is delayed while occurs the bolus passage between oral and pharyngeal phase of deglutition.[24]

Dietary modifications may be a further useful approach to reduce risks of aspiration and penetration of bolus into airways. Thin liquid or too smooth substances should be generally avoided and replaced with thickened or viscous liquid, simpler to be swallowed. Other strategies might regard reductions in bolus volume, or modifications in viscosity properties to improve texture, or food temperature and taste adjustments.[6,25]

If all previous methods are not efficacious, enteral or parenteral nutrition should be taken into account even though these practices are not risk-free. Clinical evaluations of geriatricians are fundamental to judge patient status and decide which procedure is necessary to follow.[23]

As known, the most preferred route for drug administration is the oral route and the solid oral dosage forms (SODFs) are the most common forms of medicinal products on the pharmaceutical market. Solid forms, mainly tablets or capsules, present several dimensions and shape. They generally appear round, oval, oblong, with smooth or wrinkled surfaces. The deglutition of SODFs, in case of swallowing impairments, results unsafe and difficult even though the difficulty depends on patient-related factors that affect the ability to swallow medicinal product or on therapy-related factors. For example, patient-related factors include patient position (i.e., bedridden or up-right), ability to assume different amount of water to drive drug intake, compliance to assume or not SODFs. In addition, several therapy factors may be listed: number of medicinal products to assume, frequency of repeated doses every day, physical characteristics of the solid forms (i.e., size, shape, surface, texture).[3]

Data collected from a literature review and evidence in routine clinical practice in the hospital report that altering the prescribed dosage forms to overcome administration issues with SODFs is a frequent practice. Crushing tablet or opening capsule are the most recurrent operations done by health care providers. The obtained powders or contents are mixed with food or beverages for making easy the administration.

Drug manipulation may determine high risks for potential drug instability, alterations in drug performance, onset of perilous side effects, reduction of palatability, loss of the drug. Consequently, a non-authorized use of the drug is done after any alteration and manufacturer company is not more responsible for any side effects linked to compounding of original form. Daily, health care providers in general, or more specifically nurses have to face the huge problem to convert solid form in a suitable one, and additionally, they have to considerer the eventual enteral delivery of the drug via feeding tube. Sometimes, no guidelines, appropriate support and information are available to sustain nurse work.[26,27]

SODFs manipulations remain a predominant source for medication errors[28] as well as dangerous impact on population and legal implications for nurses and prescribers. Since any manipulation or compounding process is out of approved authorization and labeled product specifications, this practice may be judged as illegal according to civil law.[29]

Improvements in pharmaceutical technology offer some more sophisticated options (i.e., orodispersible, transdermal, liquid forms) to overcome drug administration problems in patients presenting swallowing alterations either for pediatric or for elderly people. Actually, it may not always be possible to provide pharmaceutical forms suitable for this specific target of population.

Therefore, this doctoral thesis focused on all discussed concerns and aimed to propose several pharmaceutical approaches intended to partially cover needs of people suffering from swallowing inability. The combined work of researchers and pharmacists should provide suitable dosage forms whereas they do not exist yet. They also should face with pharmaceutical company to enlarge possible medicinal products to be placed on the market.

The project was developed together with an Italian geriatric hospital, Italian National Research Centers on Aging (INRCA) settled in the municipality of Ancona. The work was elaborated according to the specific requests and needs of this hospital.

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1.2. Biopharmaceutical considerations

ORAL DRUG THERAPY IN ELDERLY WITH DYSPHAGIA: BETWEEN A ROCK AND A HARD PLACE!

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Abstract: Demographic indicators forecast that by 2050, the elderly will account for about one-third of the global population. Geriatric patients require a large number of medicines, and in most cases, these products are administered as solid oral dosage forms, as they are by far the most common formulations on the market. However, this population tends to suffer difficulties with swallowing. Caregivers in hospital geriatric units routinely compound solid oral dosage forms for dysphagic patients by crushing the tablets or opening the capsules to facilitate administration. The manipulation of a tablet or a capsule, if not clearly indicated in the product labeling, is an off-label use of the medicine, and must be supported by documented scientific evidence and requires the patient's informed consent. Compounding of marketed products has been recognized as being responsible for an increased number of adverse events and medical errors. Since extemporaneous compounding is the rule and not the exception in geriatrics departments, the seriousness and scope of issues caused by this daily practice are probably underestimated. In this article, the potential problems associated with the manipulation of authorized solid oral dosage forms are discussed.

Keywords: geriatric medicine, dysphagia, compounding, modified-release formulations, gastrointestinal tract toxicity

Introduction

Biodemography scientists have registered a significant lengthening of lifespan in the last 50 years. This is essentially due to the progress made in medicine and public health. Counterintuitively, the morbidity among elderly is continuously growing and the need for medical care increases with geriatric patient age.[1] Also, considering the limits due to unpredictable happenings and the absence of reliable old records, the demographic trend draws a scary picture. It is estimated that, by 2050, people aged 65 or more will account for about 25% of the total population of developed countries and 15% of the people living in developing countries.[2] This change in society composition will have strong repercussions in many societal policies, and a huge impact is expected in medical and health care system.

Medicine faces the great responsibility to deal with a continuously growing elderly population, and geriatric medicine is (and will be) the main actor of this revolution. A geriatric patient has many peculiar features that challenge the everyday work of clinicians, pharmacists, nurses, and health care providers (HCPs). Due to the aging process, the elderly show different pharmacokinetics and pharmacodynamics with respect to young adults,[3] and the presence of different pathologic conditions (also known as comorbidity) obliges geriatric physicians to prescribe a large number of medicines, putting the patient in polypharmacotherapy. This situation further complicates the scenario.[4,5]

Difficulty in swallowing and dysphagia may be seen as a marginal problem, considering the acute and chronic diseases that these patients have to deal with.[6] Unfortunately, this is not the case. Dysphagia is most common among the elderly population because the aging process can negatively affect the oral, pharyngeal, and esophageal phases of the swallowing process. It can become worse by reduced saliva production.[7,8] Difficulty in swallowing may be responsible for malnutrition, weight loss, and dehydration. At the same time, food and/or liquid entering the airways can provoke respiratory infections.[9]

In patients over 65 years of age, the prevalence of dysphagia ranges from 7% to 13%,[10–12] a percentage that increases with age and if patients are affected by stroke, postoperative cognitive dysfunction, or neurodegenerative diseases such as Parkinson's and dementia.[9,13–17] Worthy of note is the fact that swallowing difficulties have been reported in about 50% of patients in nursing homes.[18]

Since the elderly patients are intrinsically predisposed to dysphagia and the number of elderly is increasing, the number of dysphagic patients will increase in the near future. This global demographic trend, fueled by falling birth rates and the continuous increase in life expectancy, is now certain, and brings with it significant social distress and a variety of chronic disabilities that will challenge health care systems and increase the need for pharmacologic and surgical treatments.[19,20]

Elderly patients with dysphagia are between a rock and a hard place, because they require a large number of prescriptions like other geriatric patients,[4,5,21] but difficulties with swallowing or dysphagia limit or preclude the administration of solid oral dosage forms, which are by far the most common formulations on the market.[22] The problem could easily be bypassed if all the active pharmaceutical ingredients (APIs) contained in marketed products were available in formulations other than solid oral dosage forms. Unfortunately, this is not the case, and in clinics, compounding is a daily practice as caregivers dispense crushed tablets or opened capsules to facilitate the administration of solid oral dosage forms to dysphagic patients.[23,24]

The US Food and Drug Administration defines compounding as

> '*A practice in which a licensed pharmacist, a licensed physician, or, in the case of an outsourcing facility, a person under the supervision of a licensed pharmacist, combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient'.*[25]

Tablet and capsule manipulation can include tablet splitting, tablet crushing, and capsule opening, followed by the dispersion/dissolution of the tablet material or capsule content (eg, powder or granules) in water, beverages, gels, or food to allow better deglutition.[26] When deglutition is completely impaired, the solution, suspension, or low-viscosity gel is delivered directly into the stomach by an enteral tube. The manipulation of a tablet or a capsule can seem trivial and insignificant.[27] On the contrary, this is absolutely untrue: compounding of marketed products has been recognized as responsible for adverse events and medical errors.[28–32]

Representative is the title of a paper recently published by Verrue et al[33] on tablet splitting 'Tablet-splitting: a common yet not so innocent practice'. This sentence resumes quite well what happens in the everyday nursing practice. In fact, tablet splitting is, most

of the time, an off-label use of the medicinal product and, even if it can be considered *a priori* safer than tablet crushing, it can have a negative impact on therapy outcome.

Before reaching the market, a medicinal product is carefully evaluated for its safety and efficacy through clinical trials, and all the technical data are reviewed and evaluated by the appropriate regulatory agency. Obviously, safety and efficacy are guaranteed if the product is used on-label, that is, by following the information reported in its labeling that includes product information leaflet and summary of the product characteristics. From the legislative point of view, the manipulation of a marketed formulation is defined as an off-label use of the drug. In fact, when a medicinal product is approved by the regulatory authorities, it can be administered to treat the diseases listed in the product labeling at the specified dose regimens and route of administration. This applies to the dosage form as well. Any manipulation of an approved medicinal product, such as by tablet splitting or crushing, or change in the administration route from oral to intragastric is, if not specified in the product information leaflet and summary of the product characteristics, an off-label use of the medicine. In these circumstances, the prescriber, the pharmacist, and the nurse may become legally responsible for any adverse effect resulting from taking the medicine.[34]

Compounding can affect the biopharmaceutical features of the product and its therapeutic outcome, resulting in an increased probability of adverse reactions for the patient.[35] Patient risk is particularly important for APIs with a narrow therapeutic window, for drugs that are irritant to the gastrointestinal tract (GIT) mucosa, for drugs formulated in modified-release solid oral dosage forms, and for any product that is hormonal or steroid-based, cytotoxic, and teratogenic.[36,37] For this reason, the act of manipulating a solid dosage form should be undertaken only if is impossible to give the medicine by an alternative route, or in a different licensed formulation.[38]

Given the threats associated with the practice of compounding marketed medicinal products and its wide use for dysphagic patients in hospital geriatric units and home care, we believe that the risks for the patients and the ethical and legal issues connected to these procedures are underestimated and worthy of discussion.

This review focuses on concerns related to the manipulation of medicinal products and concentrates its attention on biopharmaceutical/pharmacokinetics issues and GIT toxicity that may derive from this practice.

Biopharmaceutical considerations

Biopharmaceutics has a fundamental role in rationalizing and improving medicinal product performances and should be taken into consideration when compounding is contemplated.

Once a solid dosage form is administered orally to patients, the API has to be released and/or dissolved from the dosage form to the body fluids in order to be absorbed and distributed in the various organs and tissues. Virtually, no API possesses adequate characteristics to be administered on its own to patients, and its formulation in an adequate dosage form is needed. During the formulation step, an API is combined with different excipients and, with the aid of *ad hoc* technologic procedures, is shaped into the final medicinal product that has the required features for administration through the chosen route. The API can be formulated in a variety of dosage forms to obtain medicinal products with the desired consistency: solid (tablets, capsules, granules), semisolid (creams, ointments), or liquid. Solid dosage forms are the leading formulations on the market, and of these, >60% of APIs intended for oral administration are formulated as tablets and capsules.[2,22]

The oral route is highly preferable because patients can take the medicine themselves and, accordingly, it is associated with superior patient compliance and adherence. Solid dosage forms are also preferred by pharmaceutical companies because not only does the API stability tend to be higher in the solid state but also they cost much less to manufacture than the parenteral forms. Thus, solid dosage forms are the first choice for oral administration.[22]

The predominance of solid oral dosage forms, especially tablets and capsules, is the leading cause of potential issues in dysphagic patients. In fact, when administration through a different route is not possible and/or a different formulation is not available, the physician and the pharmacist face an important decision: should they prepare an *ad hoc* formulation in the hospital pharmacy or in an accredited laboratory, or should they manipulate the commercial formulation? Obviously, the best choice is to set up an *ad hoc* formulation, but this is not always possible since some APIs, especially those most recently approved, are not available in bulk. At the moment, the compounding of marketed medicinal products is the most common method for administering medication to dysphagic patients in hospitals and clinics, but the safety risks it poses have been

largely underestimated.[23,39,40]

Crushing a solid dosage form in a mortar cannot be considered satisfactory from the point of view of reproducibility and quality control. API particle size should be measured to guarantee at least the reproducibility of the manipulation procedure, but the presence of excipients makes the measurement challenging.[41] API particle size has a direct relation to the dissolution rate and apparent solubility, and this correlation is particularly significant for low water-soluble compounds.[42] Because of this, different particle sizes or particle size distributions generate diverse plasmatic curves and pharmacologic effects.[43]

Today, the presence of many modified-release formulations in the market makes the decision 'whether to crush a tablet or not' more difficult and much more dangerous. So, compounding should only be recommended by HCPs with sufficient knowledge of biopharmaceutics and the proprietary information about the technology used to prepare the tablet or capsule. In fact, the first step for assessing the actual risks for the patient is to distinguish between a conventional-release (also called immediate-release) and a modified-release dosage form.

Conventional-release dosage form compounding may generate faster absorption and higher bioavailability (Figure 1).[44,45] These issues become more significant and extremely dangerous for the geriatric dysphagic patient in the case of drugs with a narrow therapeutic index, such as warfarin, carbamazepine, digoxin, lithium, and theophylline, for which small changes in systemic concentration can lead to significant changes in pharmacodynamics.[46] Additional problems may come from the imprecision of the dose, the reduced stability in solution, and the mixing with food, beverages, or viscous gels to facilitate swallowing.

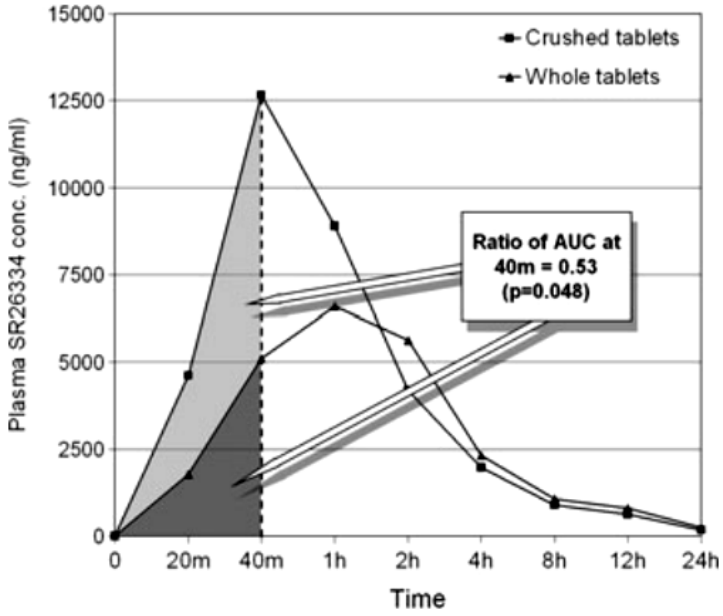

Figure 1: Median plasma concentrations of clopidogrel metabolite SR26334 following administration of whole or crushed 300 mg clopidogrel tablet.
Notes: The crushed tablet has been administered through a nose-gastric tube. Reproduced from Zafar MU, Farkouh ME, Fuster V, Chesebro JH. Crushed clopidogrel administered via nasogastric tube has faster and greater absorption than oral whole tablets. *J Interv Cardiol*. 2009;22(4):385–389, with permission from John Wiley and Sons. Copyright 2009.44
Abbreviations: AUC, area under the curve; conc, concentration.

While the manipulation of conventional-release medications presents dangers, even greater risk is posed by compounding of modified-release dosage forms, which considerably affect the product biopharmaceutics with harmful consequences for the patient. In general, the compounding of modified-release dosage forms is not recommended and should be highly discouraged.[47,48] In these dosage forms, compounding can strongly alter not only the amount of API released over time but also its release site, affecting its efficacy and toxicity potential. Useful resources in this regard are 'Oral Dosage Forms That Should Not Be Crushed 2015'[48] and the 'Don't Rush to Crush' handbook.[49]

In the case of prolonged-release oral solid medications, which are designed to release the API over an extended period of time, administration of a crushed form results in rapid absorption of the entire dose with adverse outcomes for the patient.[36,50] Enteric-coated formulations of acid-labile APIs are designed to pass through the stomach intact and deliver the drug in the intestines. Crushing the medications subverts the intention of the

formulators because the drug is then inactivated by gastric acid.[51,52]

With the availability of many modified-release solid oral dosage forms on the market, the 'to crush or not to crush' dilemma is extremely critical. In fact, albeit a recent European Medical Agency guideline states,

> '*If applicable, specific recommendations should be provided to ensure optimum conditions of use (eg, instructions not to chew or crush tablets, etc)*',

most of the marketed modified-release formulations do not have the 'not to chew or crush' recommendation.[53]

Issues connected to the compounding of a solid oral dosage form are manifold, but 'dose dumping' is certainly the most serious consequence, since it presents the highest risk of morbidity and mortality for the patient. Dose dumping can be defined as

> *'an unintended, rapid drug release of the entire amount or a significant fraction of the active substance contained in a modified release dosage form'*.[54]

As an example, we can briefly mention the story of an 83-year-old female who died after 3 weeks of chewing rather than swallowing the intact prolonged-release diltiazem capsule, because she found it difficult to swallow.[55] In another case study, Schier et al[50] reported the death of a woman after repeated daily administration of crushed prolonged-release nifedipine tablet through a nasogastric tube. Her death was ascribed to severe hypotension caused by high plasma concentration of nifedipine generated by the immediate release of the entire 90 mg dose (ie, dose dumping), which instead was formulated for release over an extended period of time.

However, some modified-release dosage forms have been designed to allow compounding. In a recent study, healthy subjects were administered intact or crushed capsules containing microencapsulated oxycodone or immediate-release oxycodone tablets.[56] Once the capsule is opened and the microparticles are crushed, the medicine remains bioequivalent with the capsule swallowed intact (Figure 2): this makes the formulation suitable for compounding for dysphagic patients. On the contrary, crushed modified-release tablets become bioequivalent to the powder of the immediate-release oxycodone (Figure 2).

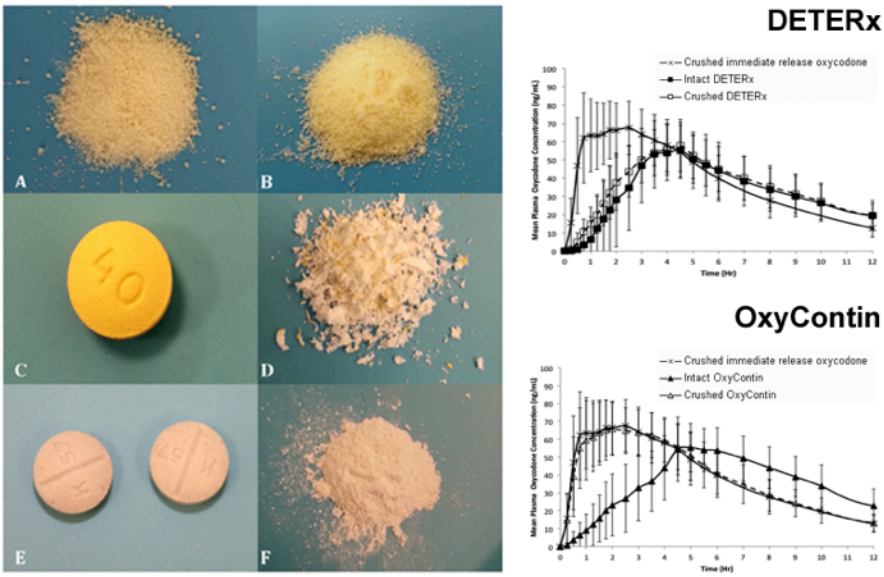

Figure 2: Left side: (A) intact microspheres (40 mg) obtained by empting one capsule of Deterx®; (B) crushed microspheres (40 mg) from one capsule of Deterx; (C) OxyContin® tablet intact (40 mg); (D) Oxycontin tablet crushed (40 mg); (E) two 20 mg intact immediate-release oxycodone tablets; (F) powder from two crushed immediate-release oxycodone tablets. Right side: mean plasma concentration–time curve profiles generated by the administration of intact and crushed Deterx compared with crushed immediate-release oxycodone (upper figure); mean plasma concentration–time curve profiles generated by the administration of intact and crushed Oxycontin compared with crushed immediate-release oxycodone (lower figure). Reproduced from Gudin J, Levy-Cooperman N, Kopecky EA, Fleming AB. Comparing the effect of tampering on the oral pharmacokinetic profiles of two extended-release oxycodone formulations with abuse-deterrent properties. *Pain Med*. 2015;16(11):2142–2151, by permission of Oxford University Press.[56]

As is evident, not all solid dosage forms are suitable for splitting or crushing. But even when compounding is permissible, human error by HCPs may dissipate the product and alter the dose administered, which can have serious clinical consequences, especially for APIs with a narrow therapeutic index.[33,57] Even though the problem of oral drug therapy in geriatric dysphagic patients is not new, most scientists in academia and industry do not seem very sensitive to this issue. In a recent literature search, Messina et al[58] evidenced the complete absence of scientific publications addressing the age appropriateness of medicinal products for the elderly. Regulatory agencies in North America and Europe are slowly moving the first step toward the elaboration of *ad hoc* strategies for the development of geriatric medicines. Unfortunately, no guidelines on the adequacy of dosage forms to geriatric patients are available at the moment.[59]

Damage to patient GIT

Drug toxicity in the GIT is a common and important medical problem linked to extemporaneous compounding that can affect part or all of the GIT, with consequences ranging from minor pathologies such as drug-induced diarrhoea to perforation or fatal hemorrhage.[60] The morbidity and associated medical costs due to drug-induced GIT toxicity, as well as the mortality that may ensue, are probably underestimated.

A number of APIs, including ferrous sulfate,[61] bisphosphonates,[62] potassium chloride,[63] nonsteroidal anti-inflammatory agents (NSAIDs),[64] and tetracycline,[65] have been identified as being responsible for GIT mucosal injuries. Sample endoscopic and microscopic views of GIT mucosae damaged by NSAIDs are shown in Figure 3.

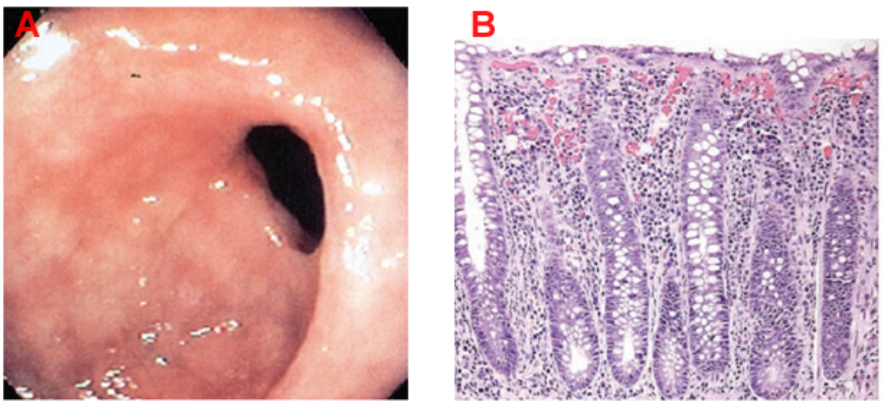

Figure 3: Sample endoscopic and microscopic views of gastrointestinal tract mucosae damaged by NSAIDs.
Notes: (A) Endoscopic view of a stricture in the cecum of the colon in a patient after long-term NSAID use. The stricture has resulted in significant narrowing of colonic lumen. Such diaphragms have also been reported to occur in the small intestine. (B) Histologic section from a colonic biopsy showing a moderate inflammatory infiltrate in the lamina propria, mild lymphocytic infiltration of the glandular epithelium, and scattered eosinophils. Adapted by permission from Macmillan Publisher Ltd: *Nat Clin Pract Gastroenterol Hepatol,* Pusztaszeri MP, Genta RM, Cryer BL, Drug-induced injury in the gastrointestinal tract: clinical and pathologic considerations, 2007;4(8):442–453, copyright 2007.[74]
Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

To provide protection from these APIs, formulators use gastro-resistant enteric coatings made of polymers that remain intact in the stomach but dissolve and release the API in the more alkaline pH of the small intestine. Enteric coatings not only serve to prevent stomach irritation but also make it possible to delay the release of APIs that are inactivated by the stomach contents, or to delay the onset of action at a specific site

within the GIT.

Gastrointestinal symptoms resulting from either prescribed medications or over-the-counter drugs are frequently encountered in geriatric practice. The manipulation of solid oral dosage forms to allow easy administration in dysphagic patients may increase the incidence and severity of adverse reactions involving the upper and lower GIT.

We subsequently discuss the APIs used in elderly patients that are responsible for GIT mucosal injuries, especially when the formulations are manipulated to allow swallowing.

Ferrous sulfate

Liabeuf et al[61] reported a series of cases of ulceration of the oral mucosa linked to direct contact with ferrous sulfate in elderly patients, particularly when swallowing disorders were present, and advised that appropriate pharmaceutical formulations (eg, syrups) should be administered to at-risk patients. The mucosal damage caused by high local iron concentrations may be related to the formation of reactive oxygen species.[66] Indeed, these species and free radicals have been implicated in mucosal alterations in gastric or intestinal injuries. The mucosal toxicity of ferrous sulfate has also been reported for the hypopharynx,[67] the esophageal lumen,[68] and the tracheobronchial tree.[69] Mouth ulcerations and necrosis have been found after administering crushed tablets containing ferrous sulfate.[61]

Bisphosphonates

Bisphosphonates are a class of drugs developed over the past 20 years, primarily as antiresorptive agents for treating diseases related to bone remodeling. Soon after the release of alendronate, esophagitis and esophageal strictures were reported, and consequently, the drug labeling had to be changed. Subsequent endoscopic studies in healthy subjects showed that alendronate also caused gastric erosions and ulcers. Persistent mouth ulcerations have been reported by patients who sucked bisphosphonate tablets or let them dissolve in their mouth.[70] Alendronate has the potential to cause ulcers within the esophagus and stomach, as well as occasional esophageal strictures. Although controlled trials have failed to demonstrate an increased incidence of these adverse events, several case studies and reports have described exudative and ulcerative

esophagitis in patients who strictly adhered to recommended use directions, which resolved upon cessation of the therapy.[62]

Risedronate, a third-generation bisphosphonate, seems to be considerably less ulcerogenic and fibrogenic than alendronate and may be a safer alternative for those unable to tolerate alendronate.[62] In summary, given all the side effects described earlier for this class of drugs, it is recommended that tablets be swallowed whole, and are never split, chewed, or crushed, even in the case of dysphagic patients.

Potassium chloride

Drug-induced esophagitis caused by potassium chloride is usually present at the junction of the middle and distal thirds of the esophagus above the level of an enlarged heart compressing the distal esophagus. This compound can also lead to the development of strictures, most frequently at or above the level of an enlarged left atrium.[63]

Potassium chloride causes small bowel ulceration as a result of local vascular injury and thrombosis.[71] Zografos et al[72] analyzed 650 cases of drug-induced esophagitis from 1970 to 2009 and reported that five deaths were related to potassium-induced esophageal injury. In particular, these patients developed fistulas from the esophagus into the aorta or left atrium, perforation into the mediastinum, bleeding ulcer, or inanition related to the esophageal stricture. The appearance of dysphagia or swallowing difficulties should be taken seriously for review of oral potassium therapy. It is recommended that oral potassium chloride supplements in liquid form should be administered to patients with cardiomegaly and disorders of esophageal motility.[71]

Quite interestingly, Sinar et al[73] performed a controlled multicenter investigation of the effects of oral potassium chloride supplements on the gastrointestinal mucosa. One hundred and twenty healthy men with no endoscopically apparent gastrointestinal lesions were confined to a research ward for 18 days. After the treatment was completed, endoscopic examinations of the esophagus, stomach, and duodenum were performed and evaluated by specialists blinded to the particular treatment given. Mild to moderate gastrointestinal irritation, characterized by erythema and edema, was found with similar frequency in all four treated groups.

Nonsteroidal anti-inflammatory drugs

Much attention has been focused on NSAIDs, the most commonly prescribed therapeutic class associated with GIT toxicity. In fact, NSAIDs can damage every level of the GIT from the esophagus to the large intestine.[64,74]

Among geriatric patients, the risk of NSAID-induced gastrointestinal complications due to long-term use may be as high as 15%.[75] Although NSAIDs cause damage throughout the GIT, the predominant gastrointestinal site of injury is the stomach. NSAIDs produce two types of mucosal injury in the stomach.[76] The first type of damage occurs shortly after the ingestion of the agent and seems to result primarily from local effects on the gastric mucosa (hyperemia, erosions, and/or subepithelial hemorrhages). The second type of lesion induced by NSAIDs is gastric ulceration, and it is due to their systemic effect on prostaglandin synthesis through inhibition of cyclooxygenase. The clinical consequences of utmost concern among NSAID users are symptomatic gastrointestinal ulcers and ulcer complications such as severe gastrointestinal bleeding and perforation.

In contrast to what happens in the stomach, direct contact of NSAIDs with the intestinal mucosa has a major role in the pathogenesis of NSAID toxicity in the small intestine. Aspirin and nabumetone are rapidly absorbed in the stomach and duodenum and do not undergo enterohepatic recirculation. By contrast, compounds such as indomethacin that are metabolized through enterohepatic cycling are associated with greater intestinal toxicity, even when administered parenterally.[77]

NSAIDs can cause diffuse intestinal inflammation and increased intestinal mucosal permeability, a pathologic condition known as NSAID enteropathy, clinically characterized by occult blood loss, iron deficiency, anemia, malabsorption, and protein loss.[78]

NSAID-induced lesions can develop in the healthy colon or at sites of preexisting colonic disease, such as diverticular disease or chronic inflammatory bowel disease. In some cases, NSAID therapy can reveal previously undiagnosed bowel disease. The most common pattern of NSAID-associated colonic damage is a nonspecific colitis.[79]

To prevent recurrent damage to GIT mucosae, particularly at the esophageal level, a joint effort of patients, physicians, nurses, and pharmacists is required. All patients should be advised to take the medicine only when sitting or standing, take water, and remain upright for at least an hour after administration.[80] These warnings are of particular importance in elderly patients with dysphagia, or impaired mobility, such as bedridden

patients. Several formulations based on NSAIDs are enteric-coated to reduce stomach irritation and minimize drug degradation. Also, in this case, crushing an enteric-coated medication exposes the GIT to the risk of irritation.

Tetracyclines

Antibacterials such as tetracycline and clindamycin are the offending agents in over 50% of the reported cases of drug-induced esophageal disorders.[81] Drug-induced esophagitis caused by tetracycline or derivates is often manifested in double-contrast studies by the development of small, discrete ulcers, typically in the mid-esophagus near the level of the aortic arch or left main bronchus.[82] Crowson et al[65] treated three patients with esophageal ulceration associated with the ingestion of tetracycline or its derivative doxycycline, and found a strong temporal relationship between taking the capsules and the onset of the esophageal ulceration. They recommended an alternative to this class, when possible, for patients with any esophageal obstructive element, and advised patients not to take them within 1 hour of going to bed.

Gencosmanoglu et al[83] described two different clinical patterns of esophageal injury induced by tetracycline or doxycycline, comparing these patterns with respect to demographic, endoscopic, and clinical characteristics of the patients. They analyzed 48 patients diagnosed with doxycycline- or tetracycline-induced esophageal injury who were divided into two groups according to the type and location of their esophageal lesions. They found that mid-esophageal ulceration was induced predominantly by doxycycline, whereas distal esophagitis was induced by tetracycline. This work highlighted that the type of tetracyclines taken by patients may provide physicians with some clues about the pattern of esophageal injury, because mid-esophageal ulceration seems to be more frequently associated with doxycycline, and distal esophagitis candidiasis with other tetracyclines.

In another study, five cases of doxycycline-induced esophagitis with endoscopic images were reported.[84] The authors demonstrated a strong correlation between esophagitis and how the medicines were taken. Swallowing the medicine with a small amount of water and recumbent posture after ingestion were the main predisposing factors, especially in the case of potentially harmful medications such as tetracyclines.[84]

Legal and ethical considerations

In hospital geriatric units, compounding is very common, but recently, serious concerns have been raised about the safety of this practice, with legal and ethical ramifications. Like any medical activity, the administration of solid oral dosage forms to dysphagic patients is burdened by the possible materialization of unwanted events for the patient. Since any manipulation of a medicinal product that is not clearly described in the product instructions is an off-label use of the product, the prescriber becomes legally responsible for any adverse effect that may ensue.[34,85] The off-label use of medicines must be supported by documented scientific evidence and requires the patient's informed consent.[86]

The prescriber has an ethical responsibility to provide patients with the information they need to make free and conscious decisions about their health care. In the case of elderly patients, who generally tend to passively accept physicians' proposals, such communication is an especially important part of the doctor–patient relationship. Doctors must explain in understandable terms the limits of the medical intervention and the possible consequences, describe the advantages and risks that could arise from the therapy, make it clear that manipulation of the dosage form of the medicine is an off-label use, and obtain the patient's informed consent.

Obtaining informed consent may be complicated in geriatric patients, and even more so in dysphagic ones because of the clinical conditions linked to or responsible for the swallowing disorder. Additional issues may come from the coexistence of neurologic disorders or postoperative cognitive dysfunction.[17]

These are the aspects of great ethical and professional interest in working with a segment of the population that is socially, physically, and mentally vulnerable.[87] The legal ramifications of off-label use, the ethical requirements to explain in understandable terms to patients and to obtain informed consent from those who may have limited cognitive abilities pose a considerable challenge to prescribers.

Concluding remarks

The concomitant presence of different acute and chronic diseases in geriatric patients obliges physicians to prescribe a large number of medicines, most of which are sold as

solid oral dosage forms; there is an almost complete absence of age-appropriate formulations that would allow personalization of therapy, especially in patients with dysphagia. Thus, HCPs in geriatric units or home cares quite often manipulate solid formulations to facilitate their administration, a practice that in most cases is an off-label use of the medicine prescribed. Since the path to have geriatric tailored medicinal products on the market is neither simple nor short, physicians, in the absence of reliable alternatives, are obliged to prescribe solid oral dosage forms and advise their compounding in the hospital pharmacy.

However, before taking this hazardous route, alternative solutions and possible adverse events must be carefully evaluated. The prescriber should consider the possibility of substituting the solid with a liquid dosage form or of using alternative routes of administration in a case-by-case manner. If this is not feasible, the physician, in close collaboration with the pharmacist, should evaluate the risk-to-benefit ratio of administering a compounded marketed formulation. Pharmacists should have a pivotal role in this decision, since they have a solid background in biopharmaceutics, pharmaceutical technology, and drug delivery. In this evaluation, important factors to be taken into consideration are the formulation technology, especially whether the formulation is a modified-release form (which in most cases would exclude its manipulation), and whether the APIs have a narrow therapeutic window or are irritants for the GIT mucosa. If it is decided that the manipulation of a prolonged-release dosage form is truly necessary, the dose should be evaluated carefully to avoid dose dumping. If the compounding of a gastro-resistant tablet or capsule has to be performed, particular attention should be paid to the reason/s for the presence of an enteric coating. Gastric mucosa irritation, drug inactivation in gastric fluids, and inconstant or limited absorption in the stomach are the possible motivations.

If the final decision is to compound a marketed formulation, the prescriber should discuss this decision with the patient, describing the documented scientific evidence on the efficacy and safety of the off-label use of the drug (not very common in the literature), and must obtain informed consent. Then, a licensed physician or pharmacist, and not a nurse or another HCP, must perform compounding, assuring minimal API loss and the correctness of the dose in the compounded form.

Since the problem of oral therapy in geriatric dysphagic patients is not new, reputable

institutions have issued guidelines on marketed product compounding.[88–91] In the absence of published studies on the manipulation of a specific medicinal product, prescribers and pharmacists should refer to the general principles reported in them. Unfortunately, this issue receives minimal attention by the stakeholders and, only recently, regulatory agencies and academics are taking the first steps toward the development of age-appropriate geriatric medicinal products.[59,92] In May 2011, the European Medical Agency's Committee for Medicinal Products for Human Use established the Geriatric Expert Group to provide scientific advice on different matters related to geriatric medicines and gerontology. Among others, the Group has to provide advice on 'specific geriatric aspects of medicine development, assessment of products or pharmacovigilance issues'.[93]

We sincerely hope that these actions will improve the quality aspects of medicines for older people and reduce the risks linked to the manipulation of marketed medicinal products.

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2. Current Clinical Practice

2.1. Prescription errors

2.1.1. INAPPROPRIATE PRESCRIBING OF SOLID ORAL DOSAGE FORMS IN ELDERLY DYSPHAGIC PATIENTS

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ABSTRACT

Objectives

Pharmaceutical formulations suitable for dysphagic patients are not always commercially available and caregivers are forced to manipulate solid oral dosage forms to facilitate swallowing. In many cases, medicine manipulations have to be avoided and these prescriptions are considered inappropriate. This paper reports for the first time the effect of the hospitalization on the rate of the inappropriate prescriptions (IPs) and the incidence of dosage form related IPs on elderly patients with dysphagia.

Methods

Data collection was performed in the Italian National Research Center on Aging through the review of patient medical records. The therapy at admission and discharge was analysed by considering: inappropriate drug associations, inappropriate drugs for dysphagic patients, inappropriate dosage forms and inappropriate dosage form manipulations.

Key findings

Forty-one dysphagic patients with an average age of 88.3 years were included in the study and 451 prescriptions were analysed. IPs were widespread at admission and the hospitalization did not improve the situation in a statistically significant manner. The most common IPs identified (> 80%) were related to dosage forms selection and manipulation.

Conclusions

This study highlights a clear need of continuous education about the appropriate prescription of solid oral dosage forms in patients with dysphagia.

Keywords: Dysphagia, old-old patients, inappropriate prescriptions, solid oral dosage form, compounding.

INTRODUCTION

Dysphagia, defined as swallowing difficulty, is a common issue in the elderly population. Although the exact prevalence of dysphagia is difficult to determine, deglutition disorders affect around 55% of patients in aged care settings [1] and it is expected to increase in the near future due to the gradual aging of the population [2].

The spread of swallowing disorders in the elderly is associated with physiologic deficits in the mouth, pharynx, larynx and oesophagus, connected to aging, as well as to central nervous system diseases (e.g., stroke, Parkinson and dementia) [3–5] and to drug treatment [6,7]. Swallowing difficulty affects the ingestion of food and solid oral dosage forms (SODFs) [8]. In the last case, pharmaceutical formulations suitable for patients with dysphagia (PWD) are not always commercially available and the prescription of tablets or capsules determines low adherence and/or treatment failures [9]. For this reason, tablets or capsules have to be manipulated by crushing or opening them (i.e., compounding) to allow an easier swallowing [10]. This practice can compromise the effectiveness of the medicinal product and might increase its toxicity [11,12]. Since SODFs manipulation is not immune from risks, different resources on the precautions to undertake during medicinal product manipulation are now available [13,14]. For instance, modified release formulations, such as prolonged-release or enteric-coated forms, should not be crushed to avoid adverse events due to changes in pharmacokinetics [14,15]. However, guidelines issued from reputable institutions advocate this practice in specific clinical circumstances [16,17].

The comorbidity of elderly people with dysphagia makes these patients a tough challenge for the healthcare professionals. They are more prone to medication errors due to the presence of comorbidity and polypharmacy, two factors that increase the use of medicines and consequently all the possible errors related to them. Medication errors have been defined

> *'any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer'* [18].

These errors can happen at any stage of the medication management and they are usually classified in: ordering/prescribing, transcribing and verifying, dispensing and delivering, administering, monitoring and reporting errors [19].

Among the various classes of medication errors, medicine administration errors (MAEs), defined as

'deviation from the prescriber's order as written on the patient's drug chart' [20],

have been largely investigated in elderly. In the specific case of elderly PWD, the most recent studies highlight a higher MAE frequency in PWD with respect to the control group [21,22]. Similar findings were reported by Haw et al [23], by comparing MAE frequency in psychiatric inpatients with and without swallowing difficulties.

Inappropriate prescriptions (IPs) represent another type of medication errors with a high frequency in the elderly population. A review of 11 studies published from 1997 to 2001 showed an IP rate ranging from 21% to 40%, as a function of polypharmacy, health status, and gender [24]. A more recent collection of studies on IPs in the elderly reported comparable values, even though large differences were recorded as a function of the Country considered [25]. Although these studies used different criteria to detect IPs, all can be considered as inappropriately prescribed drugs.

The high incidence of IPs in elderly PWD is a common knowledge but only few reports investigated their incidence in elderly with and without dysphagia [22].

A multidisciplinary team (e.g., doctors, nurses, pharmacists, speech and language therapists) of INRCA geriatric hospital drafted and disseminated among healthcare professionals medical review guidelines for PWD with the purpose of helping hospital physicians in assessing the medication regimen of these patients to avoid IPs.

The aim of this study is to evaluate the effect of hospitalization on the rate of IPs in elderly PWD through a retrospective analysis of the medication lists at admission and discharge in INRCA geriatric hospital. According to the categories as defined by Beers, our study is focused on the third category:

> *'medications that should not be used in persons known to have specific medical conditions, even though their use in the general population of elders might be appropriate'* [26].

Emphasis was given to active pharmaceutical ingredients (APIs) and dosage forms that should not be used in dysphagic patients. IPs were subdivided in: inappropriate drug association (IDA); inappropriate drug for dysphagic patient (IDDP), inappropriate dosage form for dysphagic patient (IDF), and inappropriate dosage form manipulation (IDM).

METHODS

Sample and data collection

The medication lists at admission and the discharge letters (attached to the medical records) of patients hospitalized between January and April 2015 in the Italian National Research Center on Aging (INRCA) in two elderly care units (geriatric unit 1 and 2) and one neurological unit were analysed. All the patients involved in the study were selected according to the following criteria:

- Age > 79 years (categorized as old-old [27]);
- Diagnosis of dysphagia carried out by the speech and language therapists before the hospital admission or during the hospitalization. No patients involved in this study were able to swallow SODFs.

The data collection was carried out through the review of medical records in collaboration with caregivers and the medical and nursing staff of the wards involved.

Age, gender, the presence of previous hospitalizations during the last year, the inpatient ward, any suspicion of aspiration pneumonia at admission, the drugs prescribed before (with respect to admission) and after the hospitalization (discharge) were recorded for all the patients.

Inappropriate prescriptions (IPs) were grouped according to the following criteria:

- Inappropriate drug association (IDA): simultaneous prescription of APIs that should not be associated according to Lexicomp® database (x grade) [28].
- Inappropriate drug for dysphagic patients (IDDP): prescription of a drug which can induce dysphagia (Drug-Induced Dysphagia) identified according to the following criteria [6,7]:
  - ✓ Dysphagia is a side effect of the drug;
  - ✓ Dysphagia is a complication of the drug therapeutic action;
  - ✓ Medication-induced oesophageal injury.

Only drugs having these side effects reported as ‘common’ (≥1/100 and < 1/10) or ‘very common’ (≥1/10) have been considered. Examples of drug that can induce dysphagia are substances with anticholinergic, anti-muscarinic activity, or associated with dry mouth (xerostomia) [5,7,29,30].

- Inappropriate dosage form (IDF): prescription of a medicine having an inappropriate dosage form for PWD (e.g. tablets or capsules) when more suitable

formulations are commercially available (e.g., trans-dermal patches and oral solutions) [31,32].

- Inappropriate dosage form manipulation (IDM): prescription of SODFs that cannot be crushed, such as enteric-coated tablets or modified-release formulations [14,33,34].

Sample size

Assuming an incidence of the IP rate in elderly population around 30% [24,25], 323 prescriptions and 144 prescriptions are required to obtain a 95% interval of confidence (CI) of ±5% and ±7.5%, respectively. With average prescriptions for patients of 7.4 in elderly Italians between 80-84 years [35], 44 patients and 19 patients represent an adequate sample size to obtain the 95% CI ±5% and ±7.5%.

Data analysis

All the collected data were summarized using descriptive statistics. Hypothesis testing were performed to analyse the effects of hospitalization. The number of prescriptions for each patient and the number of inappropriate prescriptions for each patient at admission (n=29) and discharge (n=29) were compared using the paired t-test (significance level $p<0.05$; normality of mean difference data evaluated using the Anderson-Darling test). The proportions of the inappropriate and appropriate prescriptions at admission (n=41) and discharge (n=29) were instead compared using the Fisher's Exact test (significance level $p<0.05$). Data along the text are reported as mean ± standard deviation if not differently specified.

RESULTS

This study analysed the appropriateness of prescriptions in 'old-old' PWD hospitalized at the INRCA. The general characteristics of the population are summarized in Table 1. The number of patients considered in this study varied comparing the admission and the discharge, due to the exitus and to the transfer to other wards of 12 patients (29.3%). A diagnosis of dysphagia was present at the admission in 91.7% of the patients, while at the discharge such percentage reached 100%. Around 27% of the patients were in enteral feeding when admitted. This percentage increased to around 28% when the patients

were discharged. Such a variation was exclusively related to the reduction of the number of patients at the end of the study: none of the hospitalized patients was switched to the enteral feeding.

Table 1: General characteristics of the patients.

	Admission	Discharge
N° of patients entered in the study	41	29*
Geriatric 1 unit	17	13
Geriatric 2 unit	16	12
Neurological unit	8	4
Age (y), mean (SD)	88.3 (5.4)	88.5 (5.6)
Males, no (%)	19 (46.3)	13 (44.8)
N° of patients with dysphagia diagnosis at admission (%)	38 (91.7)	29 (100)
N° of patients with enteral feeding tubes at admission (%)	11 (26.8)	8 (27.6)
Nasogastric tube (%)	7 (17.1)	6 (20.7)
Percutaneous endoscopic gastrostomy tube (%)	4 (9.8)	2 (6.9)
N° patients with suspicious of aspiration pneumonia (%)	13 (31.7)	
N° patients with previous hospitalizations during the last year (%)	25 (61.0)	
Hospitalization (days), mean (SD)	15.2 (7.2)	

*The reduction of patients at discharge is due to the absence of the discharge letter due to exitus (n=7) or transfer to another hospital ward (n=5).

The hospitalization (mean length 15 days) determined a slight increase of the total prescriptions (TPs) of around 10.3%. The mean TPs for patient at admission and at discharge were not statistically different (95% CI for the mean differences -0.3 to 1.6) when tested with the paired t-test on the 29 patients admitted and discharged. The distribution of the number of prescription at admission and discharge is reported in Figure 1A.

The presence of IPs was widespread; only 4.9% of the patients at admission (n=41)

showed a medication list without IPs and the mean IPs for patient was 2.4±1.5. At discharge (n=29), the percentage of patients without IPs raised to 6.9%, while the mean IPs for patient remained similar (2.3±1.6). A summary of the number and mean values of appropriate and inappropriate prescriptions at admission and discharge is reported in Table 2.

The mean IPs for patient at admission and discharge (taking into account only the 29 patients discharged) was not statistically different (95% CI for the mean differences -0.6 – 0.8, paired t-test). The same results were found comparing the proportions of appropriate and inappropriate prescriptions (p-value =0.142, Fisher's Exact test) between the two groups (n=41 *versus* n=29). The distribution of the number of IPs at admission and discharge is reported in Figure 1B.

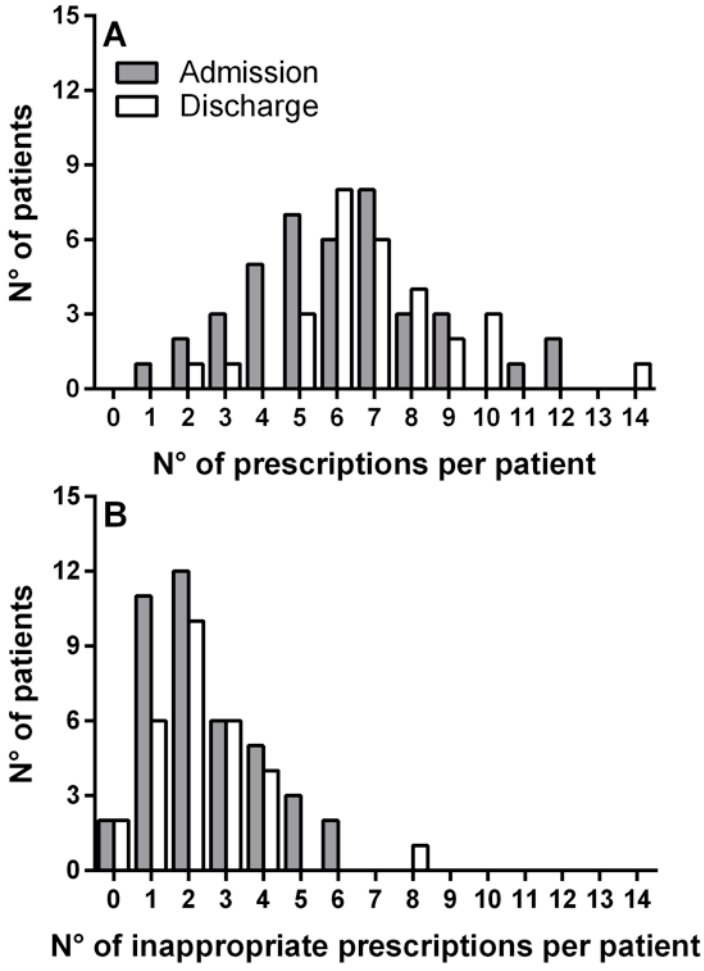

Figure 1: Distribution of A) number of prescriptions for patient and B) number of inappropriate prescriptions for patient at admission and discharge.

Table 2: Number and mean values of appropriate and inappropriate prescriptions at admission and discharge.

	Admission	Discharge
Total n° of prescriptions	247 185*	204
Mean n° of prescriptions for patients (95% CI)	6.0 (5.2-6.8) 6.4 (5.4-7.4)*	7.0 (5.8-7.8)
Total n° of IPs (%)	100 (40.5) 64 (34.6)*	68 (33.3)
IDA (%)	5 (5) 5 (8)*	0 (0)
IDDP (%)	20 (20) 15 (23)*	7 (10)
IDF (%)	38 (38) 23 (36)*	40 (59)
IDM (%)	37 (37) 21 (33)*	21 (31)
Mean n° of IPs for patients (95% CI)	2.4 (2.0-2.9) 2.2 (1.6-2.8)*	2.3 (1.7-2.9)
N° of patients without IPs (%)	2 (4.9) 2 (6.9)*	2 (6.9)

*The datum refers only to the admitted patients that were also discharged (n=29).

The frequency percentage of the different types of inappropriate prescriptions at the admission and discharge is reported in Figure 2A. For the 29 patients admitted and discharged, the most diffused IP was IDF (around 48% of all the IPs) followed by the IDM (32%), IDDP (17%), and IDA (4%). The most common IDF was associated with the diuretic

furosemide (around 40%), prescribed as tablets while a liquid oral formulation was available. The compounding of gastro-resistance tablets containing acetylsalicylic acid, pantoprazole, and lansoprazole was the most diffuse IDM, followed by the manipulation of extended release oral dosage forms of trazodone and tamsulosine. Quetiapine and olanzapine were instead the most common IDDP prescribed [7,36], while the most frequent IDA was the association of omeprazole-clopidogrel (bearing in mind that the number of IDA detected was 5). All the prescriptions considered inappropriate, together with the inappropriateness reasons are reported in the supplementary Table 1 (Table ST1).

For a better understanding, data of prescriptions at admission (n=41) and discharge (n=29) were grouped into drug related (IDA+IDDP) and dosage forms related (IDF+IDM) IPs. The frequency percentage at the admission and discharge of each group IPs is reported in Figure 2B. Comparing the proportions of the grouped IPs, statistically significant differences were observed (p-value=0.018, Fisher's Exact test). The analysis of the adjusted standardized residues [37,38] indicates that both the increase of the IPs related to the dosage forms and the decrease of the IPs related to drug were wider than would be expected by chance.

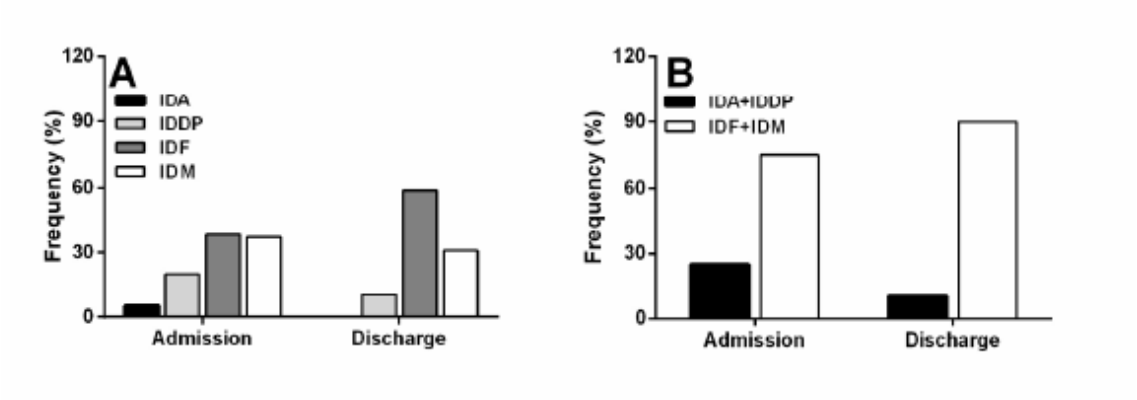

Figure 2: Percentage distribution of A) the 4 different IPs at admission and discharge and B) the IPs grouped (API related IDA+IDDP and dosage forms related IDF+IDM) at admission and discharge.

DISCUSSION

Starting from 1990's, different criteria to individuate and quantify IPs have been defined and implemented [26,39–45]. Despite their wide use in the elderly, these criteria do not

consider specific issues of elderly dysphagic patients.

The present study evaluates for the first time the rate of IPs in elderly PWD by considering, not only the appropriateness of the APIs prescribed but also the suitability of the dosage form. The major role of the IPs related to the dosage form is evident from the analysis of the collected data. Most of the prescriptions were considered inappropriate for dosage form selection and manipulation (Table 2). Dosage form related to IPs were higher when compared to the API related IPs.

Interesting results come from the effect of the hospitalization on prescription appropriateness. Hospitalization was responsible for a non-statistically significant reduction of the number of patients without IPs and of the proportions of the total IPs. However, by analysing the variation of proportions of the clustered IPs, Fisher's Exact test revealed statistically significant changes between admission and discharge. At discharge, APIs related to IPs decreased while dosage forms related to IPs increased. The analysis of the adjusted standardized residues indicated that both changes were wider than those expected by chance. Therefore, the errors related to dosage forms persisted and even increased after hospitalization.

It is important to highlight that this work is a retrospective study and the drug related IPs can be considered as such only from a general point of view. In fact, it is likely that the physicians evaluated every single case and decided the prescriptions according to risk/benefit criteria. The same consideration may not be valid for the dosage forms related to IPs. Another obvious limitation of the study is the impossibility to analyse to what extent clinical problems have occurred in consequence of the identified IPs.

Since the problem is not new, different clinical governing bodies and associations in Europe and United States of America have suggested the use of a collaborative, multidisciplinary team approach for the management of dysphagia. For instance the British geriatrics society issued a Best Practice Guide entitled 'Dysphagia Management for Older People Towards the End of Life' recommending, among others 'A holistic patient-centred multidisciplinary team approach to dysphagia management' [2]. Recently, also the Scottish Intercollegiate Guidelines Network (SIGN) issued a national clinical guideline entitled 'Management of patients with stroke: identification and management of dysphagia', where it is suggested to evaluate the availability of alternative formulations or routes of administration, since to crush tablets to allow easier swallowing it is not always

appropriate. In SIGN guidelines is also reported:

> *'Hospital and community pharmacists or medicines information centres should be consulted by the professional managing the patient's dysphagia, on the most appropriate method of administering medication'* [3].

It is evident that the scientific community is moving toward the correct management of pharmacological therapy in PWD. However, the present study, albeit performed on a limited number of patients, underlines the need of a greater awareness when prescribing SODFs to dysphagic patients. Special attention has to be paid to modified-release formulations where an unsuitable manipulation can seriously compromise the pharmacokinetics and/or the pharmacodynamics features of the medicinal product with the insurgence of severe side effects. The introduction of a 'do not crush' label [46–48] could represent a useful tool to improve prescription and administration of oral therapies to dysphagic patients.

CONCLUSION

The appropriateness of oral therapy in patients with dysphagia represents a special challenge. Previous studies have already highlighted the importance of the close collaboration between doctors, nurses, and pharmacists to reduce inappropriate prescriptions and the administration of solid oral dosage forms in patients with dysphagia.

The results of this study show a high number of inappropriate prescriptions in elderly patients with dysphagia, mainly due to the selection of wrong dosage forms or to the compounding of unsuitable medicines. According to our data, hospitalization determines only a slight reduction of the inappropriate prescriptions, which was not statistically significant. Due to the high frequency with which medication errors are still reported in the literature, the application of a multidisciplinary approach, introducing corrective measures to reduce the inappropriate prescriptions rate, is now mandatory.

PATIENT CONSENT

Informed consent for data treatment was obtained from all individual participants included in the study according to the national privacy standard.

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Table ST 1: Complete list of all the prescriptions considered inappropriate. N° represents the number of patients having this prescription, API is the active pharmaceutical ingredient, DF is the dosage forms, and Note report the reason of inappropriateness.

IPs at admission				IPs at discharge			
N°	API	DF	Note	N°	API	DF	Note
IDA				IDA			
1	Olanzapine-Alprazolam		X grade Lexicomp® database	No inappropriate drug association detected			
2	Clopidogrel-Esomeprazole		X grade Lexicomp® database				
2	Quetiapine-Tetrabenazine		X grade Lexicomp® database				
IDDP				IDDP			
5	Olanzapine	Orodispersible tablets	A + B + C + D	4	Quetiapine	Conventional tablets	A + B + C +D
4	Quetiapine	Conventional tablets	A +B + C + D	1	Fentanyl	Transdermal patch	A + D
2	Doxazosine	Conventional tablets	A	1	Glycopyrronium	Dry powder inhaler	A
1	Alprazolam	liquid dosage form	A + B	1	Risperidone	Liquid dosage form	A + B + C + D
1	Fentanyl	Transdermal patch	A + D	A = Dry mouth. B = Detrimental effects on consciousness or oropharyngeal swallow response. C = Hyperfunctional involuntary movements (dyskinesia) of the oral pharyngeal musculature, rigidity and spasm of the pharyngeal musculature. D = Sedation.			
1	Glycopyrronium	Dry powder inhaler	A				
1	Mirtazapine	Orodispersible tablets	A + B + D				
1	Paroxetine	Liquid dosage form	A + B				
1	Perindopril and Indapamide	Conventional tablets	A				
1	Risperidone	Liquid dosage form	A + B + C + D				
1	Donperidone	Liquid dosage form	A + C				
1	Clonidine	Transdermal patch	A				
IDF				IDF			
16	Furosemide	Conventional tablets or Injection	Available as liquid oral dosage form.	14	Furosemide	Conventional tablets or Injection	Available as liquid dosage form.
3	Lansoprazole	Enteric tablets	Available as orodispersible tablets.	7	Lansoprazolo	Enteric tablets	Available as orodispersible tablets.
3	Levothyroxine	Conventional tablets	Available as liquid dosage form.	3	Losartan	Conventional tablets	Available as liquid dosage form.
2	Polyethylene Glycol 3350	Powder for water dispersion*	Available as liquid dosage form.	2	Ciprofloxacine	Conventional tablets	Available as liquid dosage form.
2	Valproate	Conventional tablets	Available as liquid dosage form.	2	Levodopa/carbidopa	Conventional tablets	Water dispersible tablets
1	Codeine and Acetaminophen	Conventional tablets	Available as granules for oral Suspension.	2	Levothyroxine	Conventional tablets	Available as liquid dosage form.

1	Domperidone	Conventional tablets	Available as liquid dosage form.	2	Polyethylene Glycol 3350	Powder for water dispersion*	Available as liquid dosage form.
1	Esomeprazole	Water dispersible tablets**	Available as water dispersible powder dosage form.	1	Esomeprazole	Water dispersible tablets**	Available as water dispersible powder dosage form.
1	Phenobarbital	Conventional tablets	Available as injection	1	Phenobarbital	Conventional tablets	Available as injection
1	Lormetazepam	Conventional tablets	Available as liquid dosage form.	1	Lormetazepam	Conventional tablets	Available as liquid dosage form.
1	Losartan	Conventional tablets	Available as liquid dosage form.	1	Mirtazapine	Conventional tablets	Available as orodispersible tablets.
1	Acetaminophen	Conventional tablets	Available as granules for oral Suspension and effervescent tablets.	1	Olanzapine	Conventional Tablets	Available as orodispersible tablets.
1	Digoxin	Conventional tablets	Available as liquid dosage form.	1	Acetaminophen	Injection	Available as granules for oral Suspension and effervescent tablets.
1	Promazine	Injection	Available as liquid dosage form.	1	Paroxetine	Conventional Tablets	Available as liquid dosage form.
1	Cefixime	Conventional tablets	Available as orodispersible tablets.	1	Trazodone	Conventional Tablets	Available as liquid dosage form.
1	Levodopa and Benserazide	Conventional tablets	Water dispersible tablets				
1	Torasemide	Conventional tablets	Available as injection				
IDM				**IDM**			
10	Pantoprazole	Enteric tablets	Unstable in the gastric environment.	5	Lansoprazole	Enteric tablets	Unstable in the gastric environment.
8	Acetylsalicylic acid	Enteric tablets	harmful for gastric mucosa.	4	Pantoprazole	Enteric tablets	Unstable in the gastric environment.
4	Lansoprazole	Enteric tablets	Unstable in the gastric environment	3	Tamsulosin	Extended release capsules	Drug overdose
4	Trazodone	Extended release tablets	Drug overdose	2	Acetylsalicylic acid	Enteric tablets	Unstable in the gastric environment.
3	Iron sulfate	Enteric tablets	harmful for gastric mucosa.	2	Oxycodone /Naloxone	Extended release tablets	Drug overdose
2	Tamsulosin	Extended release capsules	Drug overdose	1	Valproate	Extended release tablets	Drug overdose
2	Isosorbide	Extended release tablets	Drug overdose	1	Biperiden	Extended release tablets	Drug overdose
1	Nifedipine	Extended release tablets	Drug overdose	1	Dabigatran	Capsules	Drug overdose
1	Biperiden	Extended release tablets	Drug overdose	1	Nifedipine	Extended release tablets	Drug overdose
1	Oxycodone / Naloxone	Extended release tablets	Drug overdose	1	Trazodone	Extended release tablets	Drug overdose
1	Venlafaxine	Extended release tablets	Drug overdose				

* Polyethylene glycol 3350 dispersible powder is not suggested for PWD due the high water amount necessary for the reconstitution (> 100 mL). The concentrated liquid formulation is strongly suggested for PWD.
** In PWD requiring jellified vehicles, Nexium® granules is the most suitable formulation; while Nexium® tablets are appropriate for patients under enteral nutrition (see manufacturer information).

2.2. Manipulation and compounding of solid oral dosage forms (SODFs)

2.2.1. QUETIAPINE TABLET SPLITTING IN ELDERLY PATIENTS WITH DEMENTIA

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ABSTRACT

Quetiapine is an atypical antipsychotic approved for treating schizophrenia, bipolar depression, and mania but is frequently used in an off-label manner to control behavioral and psychological symptoms of dementia in elderly patients. Due to the necessity of dose personalization in elderly patients with dementia, quetiapine tablet manipulation is widespread in hospital settings, long-term care facilities, and patient home. The aim of this study was to assess the impact of the different splitting techniques on quetiapine tablet quality. Data showed that split tablets, independently of the dose strength and the technique employed, produced masses with weight and drug content highly scattered with respect to the nominal value. Thus, such a common practice could have potential effects on treatment efficacy and toxicity, also considering the fragility of the target population (age, polytherapy). These results evidence the compelling needs of flexible quetiapine formulations assuring a more accurate dose personalization.

KEYWORDS

Dysphagia; Behavioral and psychological symptoms of dementia, BSPD; Tablet Splitter; Compounding; Quetiapine Fumarate.

INTRODUCTION

Patients with Alzheimer's disease, vascular dementia, Parkinson's dementia, frontotemporal dementia and Lewy body dementia can develop changes in behavior and personality. The frequency and nature of these symptoms might vary over the course of disease [1]. In the majority of patients, lack of insight occurs even in early stages of disease representing an important predictive factor for the occurrence of neuropsychiatric symptoms, including apathy, agitation, irritability, psychosis, or behavioral symptoms in general [2].

Atypical antipsychotic medications are the only class of drugs which have shown consistent benefit in the control of behavioral and psychological symptoms of dementia (BPSD) for short-term treatment [3,4]. BPSD include agitation, verbal aggression, sleep disturbances, hallucinations, persecutory delirium, psychosis and mood disorders and are associated with high levels of distress both in patients and caregivers [5]. BPSD represent a relevant clinical target for intervention [6] even if the use of antipsychotics must be balanced against their serious adverse effect profile [7].

On the market are available mainly solid oral dosage forms (SODFs) of psychotropic drugs that do not cover all the patient needs, so tablet manipulation (splitting and/or crushing) is often needed and becomes a common practice [8]. Tablet manipulation, on the one hand, allows dose flexibility and facilitates swallowing, often compromised in advanced phases of dementia, while, on the other hand, it can compromise the dosage form performance [9–11]. Tablet splitting may be particularly difficult if tablets do not have break marks and an inappropriate manipulation can compromise dose accuracy with administration of an imprecise dose [12,13].

Since the global prevalence of dementia (5-7% of world population in 2010) is expected to increase due to the ageing of population, the clinical needs of suitable dosage forms will increase as well [14,15].

In Italy, the neurologists of Alzheimer Evaluation Centers can prescribe atypical antipsychotics to patients with diagnosis of dementia for treatment of BPSD by *ad hoc* 'treatment plan' to be updated each two months. The treatment plan contains the diagnosis of BPSD, personal data, patient primary disease as well as prescribed therapy and dosage regimen. Atypical antipsychotics are dispensed by hospital pharmacies after the submission of the treatment plan to the pharmacist. Quetiapine (2-(2-(4-

Dibenzo(b,f)(1,4)thiazepine-11-yl-1-piperazinyl)ethoxy)ethanol) is an atypical antipsychotic with higher affinity for serotonin 5-HT_{2A} receptor than for the D_2 receptor in the brain and with minimal extrapyramidal side effects [16]. It is approved by the European Medicine Agency for treating schizophrenia, bipolar depression, and mania [17–19], however, due to its favorable properties, it is very frequently used in an off-label manner to control BPSD in elderly patients with dementia.

Taking into account the large prescription of quetiapine fumarate tablets for BPSD treatment in elderly patients with dementia and the specific necessity of dose adjustment as a function of clinical response, quetiapine tablet manipulation is widespread in hospital settings, long-term care facilities, and patient home. Thus, the aim of this study was to assess the impact of the different splitting techniques on quetiapine fumarate tablet quality, intended as the uniformity of dosage units (i.e., content uniformity and weight variation).

METHODS

Data collection on splitting techniques

During summer 2016, hospital pharmacists of the Italian National Research Centers on Aging (INRCA) collected data of patients with BPSD diagnosis treated with quetiapine fumarate (n=155). Some indications were derived from treatment plans of these patients. Specifically, a subgroup that has a prescribed dose requiring the split of 25 or 100 mg tablets were identified (n=52). The characteristics of the sample population (n=52) are reported in Table 1.

During drug dispensing, the hospital pharmacists collected information about the technique adopted by patients or family caregivers for tablet splitting.

Table 1: Characteristics of the sample population (n=52) diagnosed with BPSD and needing tablet splitting to adjust the prescribed dose.

	Number	Percentage
All	52	100
Sex	F = 30	57.7
Mean Age ± SD (years)	85.5 ± 7.2	-
• **65 - 80**	13	25
• **> 80**	39	75
Diagnosis of Dementia		
• **Alzheimer's**	36	69.2
• **Vascular**	8	15.4
• **Parkinson's**	4	7.7
• **Frontotemporal**	3	5.8
• **Mixed**	1	1.9

Effect of splitting technique on tablets weight and dose

Materials

Standard quetiapine fumarate was purchased from Sigma-Aldrich (Darmstadt, Germany batch number 2501103). 25 and 100 mg of quetiapine fumarate tablets (Quetiapina Teva) were from Teva Pharmaceutical Industries Ltd (Teva Italia S.r.l. Milan, Italy). Analytical grade potassium dihydrogen phosphate and hydrochloric acid 37% were purchased from AppliChem GmbH (Darmstadt, Germany) and Sigma-Aldrich (Seelze, Germany), respectively.

Sample size

The actual mean weight and standard deviation of 25 and 100 mg quetiapine fumarate tablets were preliminarily determined (Gibertini E42S, sensitivity 0.1 mg; Gibertini, Italy).

To perform weight and drug content analysis of variance, sample size was determined for whole and split tablets. Power analysis was carried out setting the effect size at 5%, a standard deviation equal to the double of that preliminarily measured and a power of 0.8. In the case of drug content power analysis, the standard deviation was derived from the coefficient of variation of tablets weight by hypothesizing a homogeneous distribution of the active pharmaceutical ingredient in the tablet mass.

The sample size obtained was 5 tablets for the weight and 6 tablets for the drug content. For caution, the sample size was increased to 12 tablets for group, obtaining a theoretical power around 0.9.

Sample preparation and data collection

The actual weight of twelve tablets of each dose strength was determined using an analytical balance (Gibertini E42S) and the calculated half weight of each tablet was used as control.

Twelve tablets of quetiapine fumarate were taken at random, split by kitchen knife or tablet cutter (Ultra pill splitter, Apex, USA), and positioned inside a specific grid (Figure SF1). For each tablet only one half (right or left alternatively, Figure SF1) was collected and used for the analysis. The same procedure was applied to 25 and 100 mg quetiapine tablets. The weight of each half tablet obtained after splitting was determined using the analytical balance.

The drug content for each half tablet or whole tablet was determined by UV-Vis analysis (spectrophotometer Shimadzu UV-1800, software UV-Probe 2.43) following the procedure reported by Pucci et al [20]. Each single dose was dissolved in a suitable amount of phosphate buffer pH 2.5 to obtain a nominal concentration of 50 µg/mL, and the absorbance measured at 246nm. The drug content was determined through a calibration curve obtained analyzing standard solutions of quetiapine fumarate in phosphate buffer pH 2.5 in the concentration range 8.13-65.00 µg/ml (r^2 >0.999). All analysis were performed in triplicate.

Statistical analysis

Descriptive statistics for the two measured parameters (i.e. weight and drug content) was calculated for all the groups.

Differences between the two different splitting techniques were evaluated using the t-test, setting minimum level of significance at 5%. The normality of the data distributions was evaluated with the Shapiro-Wilk normality test setting the α level of 0.05, while the homoscedasticity (equality of variance) of two compared groups was evaluated using the F-test at 95% confidence interval (α=0.05).

Pearson's correlation test was performed to determine any correlation between weight and drug content for each group. The correlation coefficients and associated probability values were calculated, and a minimum level of significance of $p<0.05$ was used.

RESULTS

Data about splitting techniques

During the summer 2016, the hospital pharmacy identified 155 patients with prescription of 25 and 100 mg quetiapine fumarate tablets. Among all, 34% of patients (n=52) had prescriptions requiring tablet splitting. Most of these patients (75%) were aged > 80 years and Alzheimer's disease was the main cause of dementia (≈69%) (Table 1).

The use of 25 mg split tablets occurred in 16 patients, instead, the use of 100 mg split tablets occurred in 36 patients (for 10 of them the caregiver split and crushed the tablet).

In both cases kitchen knife and tablet cutter were the two most common techniques for tablet splitting, with a frequency higher than 88% (Figure 1).

The 23% of all patients crumbled tablets and dispersed the powder in liquid or semisolid vehicle to facilitate swallowing, and, among them, 30% (11 patients) carried out this operation on half tablets.

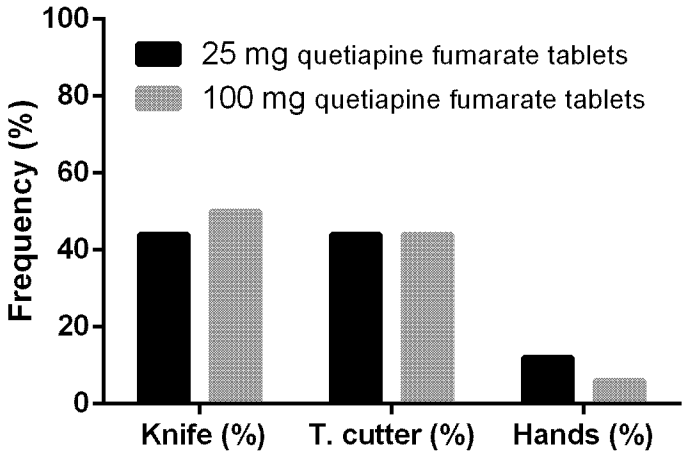

Figure 1: Frequency of tablet splitting techniques reported by patients and/or family caregivers.

Effect of splitting technique on tablets weight and dose

The effect of tablets splitting on the weight is reported in Figure 2. Independently by quetiapine dose, split tablets showed very scattered weights with respect to the control groups. The coefficient of variation for the weight of control tablets is around 18 and 15 times lower with respect to those obtained for the split tablets for quetiapine 25 mg and 100 mg, respectively (Table 2).

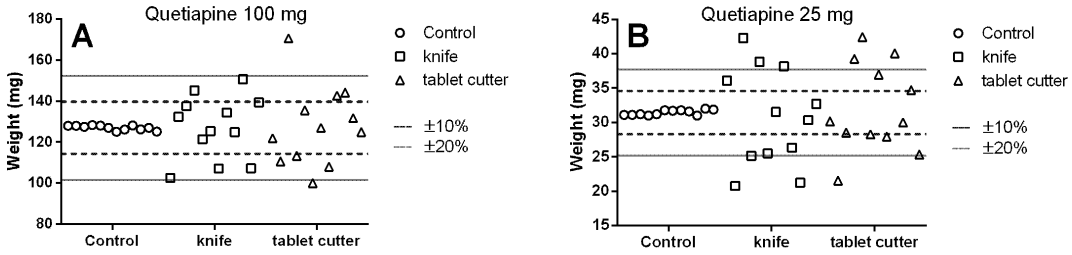

Figure 2: Effect of tablet splitting on weight for 100 mg (A) and 25 mg (B) quetiapine tablets. The control groups are represented by the half weight of whole tablets. The solid lines and the dash lines represent the EP limits for the uniformity of mass of single-dose preparations.

Table 2: Descriptive statistics of all groups analysed, F-test and t-test results, and results of Pearson correlation analysis.

		Tablets quetiapine 100 mg			Tablets quetiapine 25 mg		
		Control	Knife	T. cutter	Control	Knife	T. cutter
Weight comparison	Mean (mg)[1]	127.0	127.3	127.5	31.5	30.8	32.1
	SD[2]	1.2	15.6	19.3	0.4	7.1	6.5
	CV (%)[3]	0.9	12.2	15.2	1.2	23.1	20.2
	SEM[4]	0.3	4.5	5.6	0.1	2.1	1.9
	Normal distribution[5]	Yes	Yes	Yes	Yes	Yes	Yes
	Homoscedasticity[6]	/	Yes		/	Yes	
	T test	/	P-value=0.977		/	P-value=0.633	
Drug content comparison	Mean (mg)[1]	51.2	51.8	52.0	13.2	12.8	13.6
	SD[2]	0.8	5.4	8.0	0.2	2.9	2.9
	CV (%)[3]	1.6	10.3	15.4	1.7	22.5	21.2
	SEM[4]	0.2	1.5	2.3	0.1	0.8	0.8
	Normal distribution[5]	Yes	Yes	Yes	Yes	Yes	Yes
	Homoscedasticity[6]	/	Yes		/	Yes	
	T test	/	P-value=0.962		/	P-value=0.530	
Pearson correlation	Correlation coefficient (r)	0.470	0.947	0.996	0.046	0.997	0.994
	P_value	0.123	< 0.001	< 0.001	0.886	< 0.001	< 0.001

1 Mean weigth of half tablet (for control group the mean value refers to the half weight of a whole tablet).

2 Standard deviation.

3 Coefficient of variation (relative standard deviation RSD %).

4 Standard error of mean.

5 The normality of distributions has been tested using the Shapiro-Wilk normality test with a α level of 0.05.

6 The homoscedasticity (equality of variance) of the two distributions compared with the t test has been evaluated using the F test with a α level of 0.05.

The comparison among control, knife and tablet cutter groups by Anova, as initially planned, did not make sense and statistical comparison was performed only between the weight of two groups including tablets split with different techniques (kitchen knife and

tablet cutter) by t-test. The results of statistical analysis highlighted the absence of any significant differences between the weigth of half tablets obtained with knife and tablets cutter for the two type of tablets (Table 2).

Similar results were obtained for the drug content (Figure 3). In the group of half-tablets (split by knife or cutter), where masses were strongly scattered, the drug amount was highly variable: the coefficient of variation for the drug content of control tablets is around 13 and 8 times lower with respect to those obtained for the split tablets for quetiapine 25 mg and 100 mg, respectively (Table 2).

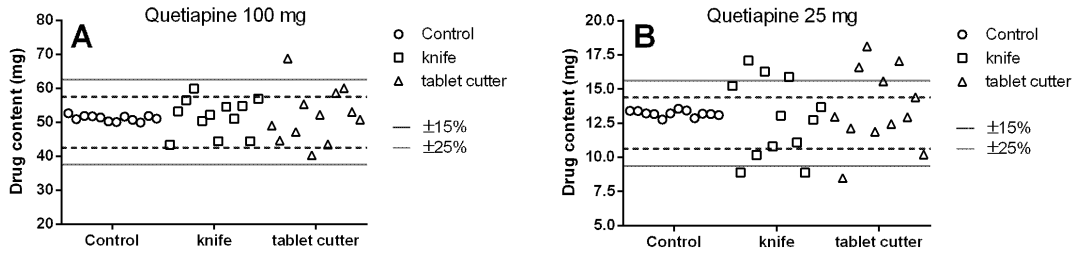

Figura 3: Effect of tablet splitting on drug content for 100 mg (A) and 25 mg (B) quetiapine tablets. The control groups are represented by the half drug content of whole tablets. The solid lines and the dash lines represent the EP limits for the uniformity of content of single-dose preparations.

The relationship between weight and drug content was analysed by Pearson correlation analysis (Figure 4). In the groups of half tablets (split by knife or cutter) a strong positive ($r \geq 0.947$), highly significant ($p<0.001$) correlation was found between weight and drug content. It can be stated that a variation of the tablets mass determines a change in the drug content. From the other side, in the whole tablets groups, the correlation was weak and never statistically significant. Consequently, any correlation is due only by chance.

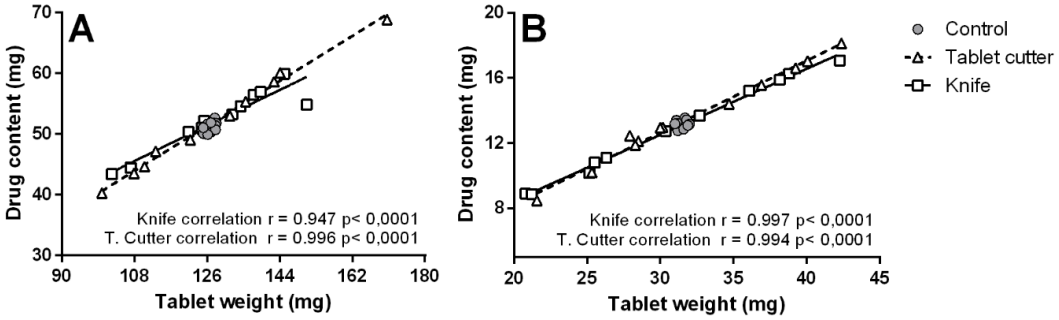

Figura 4: Pearson correlation analysis between weight and drug content for all the groups of half and whole tablets: A) nominal dose 100 mg, B) nominal dose 25 mg, of quetiapine fumarate.

DISCUSSION

Quetiapine prescriptions for the control of BPSD, requiring tablets splitting, are common among elderly patients. In fact, the highest frequency of prescribed doses achievable through tablets splitting is found on psychotropic drugs in old patients [21,22]. Nevertheless, limited information are available on tecniques exploited by patients or family caregivers to split tablets. Data show that tablet splitters are rarely used by patients [23,24]. When patient experiences problems with hand or teeth splitting, knives or other sharp objects are preferred to tablet splitter [25]. In the present study, the results are overturned since almost half of the patients use a tablet splitter and only a marginal fraction split tablets by hand.

The analysis of the weigth and drug content of the split tablets highlighted high dispersion of the measuerd values around the mean. All the groups of half-tablets were not compliant with the European Pharmacopoeia (EP) specifications (2.9.5. uniformity of mass of single-dose preparations), which state that no more than two of the individual masses may deviate from the average mass by more than 10% and none by more than 20% (for the specific class of tablet weigth considered) [26]. In addition, they were not compliant with European Pharmacopeia standard for scored tablets-subdivision of tablets, stating that no more than 1 individual mass (on 30 half tablets) can be outside the limit of 85-115% of the average mass [27].

Interestingly, such results were obtained analysing only twelve tablets against the 20 or 30 tablets required by the EP, indicating how far are the split tablets in terms of quality

requirements with respect to an industrial medicinal product. It has also to be bear in mind that these results were obtained operating in ideal conditions by lab experienced personnel. Greater variations in quetiapine content are expected in real-life situation since patients and/or caregivers perform tablet splitting in a more approximative way and not in a suitable environment.

The issue of weigth and drug content accuracy on split tablets has been first arised between the 80's and 90's [28,29] and extensively studied in the last 15 years. Published results are very different, probably due to the specific features of the analysed tablets. In fact, it has been reported as the presence of scoring lines [12,30,31], tablet shape and hardness [30,32], tablet size [31,32], splitting techniques [13,31,33], and patient training [34] affect the accuracy of the splitting procedure. In the specific case of quetapine fumarate tablets, the marked weigth variation could be related to the absence of score lines and the small tablet size. The latter point appears particularly relevant, in fact, the 25 mg tablets (diameter and thickness about 5.1 mm and 2.8 mm, respectively) show a variability almost twice (on the CV values) with respect to that of 100 mg tablets (diameter and thickness about 8.7 mm and 4.4 mm, respectively). This is in agreement with previous findings that tablets with a diameter smaller than 7/8 mm are difficult to handle and break [35,36]. Contrary to published results, the use of a tablet cutter does not assure a higher accuracy with respect to the use of a kitchen knife [33].

Tablet splitting is a quite common practice but its effect on medicinal product quality has been largely overlooked [33]. Here we demonstrate that quetiapine split tablets are no more compliant with the EP quality requirements, with potential effects on treatment efficacy and toxicity.

Several new atypical antipsychotic drugs, including quetiapine, risperidone, olanzapine and ziprasidone, have become available in the short-term treatment of BPSD. Long-term use of antipsychotics in individuals with dementia is frequent and not in line with guidelines recommandations about time-limited use in treatment [37]. Available data also showed that antipsychotics are often used in patients for sustained periods (> 6 months) with limited monitoring of their effects [38]. Atypical antipsychotics are considered to have a favourable adverse effect profile compared to traditional antipsychotics although, in rare cases, therapeutic and supratherapeutic doses have lead to the death of the patients [39]. Even if quetiapine is reportedly well tolerated in therapeutic doses,

overdoses are characterized by hypotension, sinus tachycardia, and somnolence due to central nervous system depression [40]. These adverse effects could be increased by coingestion of other drugs with similar metabolic pathways, in particular by inhibiting cytochrome P450 isoenzyme CYP3A4 and CYP3A5 [41]. On the other hand, underdosages may compromise quetiapine efficacy.

CONCLUSION

Patients treated for BSPD with quetiapine are often obliged to subdivide tablets to adjust the prescribed dose. Probably, due to the small tablets size, most interviewed patients divide tablets by using kitchen knife or tablets cutter. The splitting of quetiapine tablets, independently of the dose strength and the technique employed, compromise the dose accuracy since the variation of weight and drug content uniformity fall outside the limites established by the European Pharmacopoeia.

We therefore consider that in elderly patients with dementia, a population which tends to be in polypharmacotherapy, the avoidance of potential side effect by correct dosing is a priority. To this aim, formulations (e.g., liquid forms), allowing a more precise dose personalization, is an unmet need.

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Supplementary figure 1

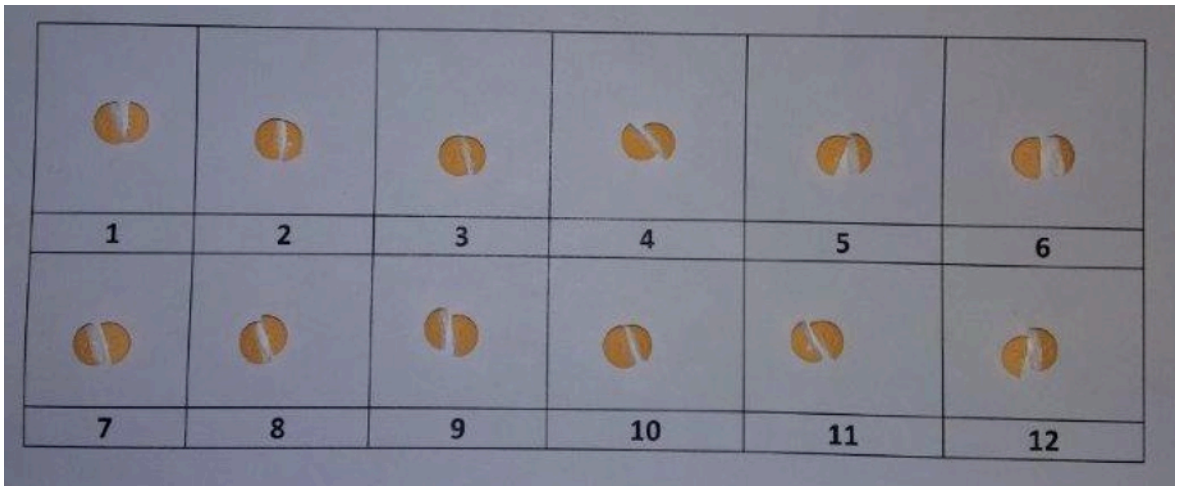

Figure SF1: Quetiapine fumarate split tablets by kitchen knife.

2.3. Occupational risks

GENERAL CONSIDERATIONS

The daily practice of extemporaneous compounding to facilitate drug administration to dysphagic patients creates risks not only for the patients but also for the health care providers (HCPs), especially nurses and hospital pharmacists[1]. Other workers, such as shipping-receiving staff, or housekeeping and laundry service staff are involved in the potentially dangerous hospital-working environment. Sometimes, manipulation process of the original drugs to make easier their administration to dysphagic people may include indifferently handling activities or compounding proceedings. The main risk comes from the inhalation or ingestion of drug aerosol generated during the manipulation and from contact with skin and mucosae. Allergic contact dermatitis has been described for different therapeutic classes of APIs, such as benzodiazepines[2-4], β-blocking agents[5], angiotensin converting enzyme (ACE) inhibitors[6-8], NSAIDs[9] and antineoplastic drugs[10-13]. The occupational risks reported for these drugs are discussed below.

Benzodiazepines

Benzodiazepines are frequently prescribed to geriatric patients. In the USA, benzodiazepines represent about 3% of all drugs prescribed in ambulatory care visits, and similar values have been reported for Europe[3]. Tetrazepam is one of the most frequent benzodiazepine prescribed as a muscle relaxant in hospital geriatric units. Neurological and gastrointestinal effects have been reported in patients treated with tetrazepam, while cutaneous reactions are quite rare[14-20]. However, this drug was identified as the cause of allergic airborne contact dermatitis among nursing staff in hospital geriatric units, who were regularly exposed to these drugs for compounding reasons. In a recent study[3], 10 HCPs of a geriatric unit were patch tested with tetrazepam and diazepam as allergens after crushing tablets for their patients. Tetrazepam revealed strong positive reactions in all workers, while diazepam sensitization was observed just in three subjects.
In another study[1], it has been proved that even if diazepam and tetrazepam have a similar chemical structure, diverse moieties could be responsible for the differences observed in the patch tests. In fact, tetrazepam contains a non-aromatic cyclohexene ring, while diazepam has an aromatic ring (Figure 1) that could be more stable toward skin

metabolism. In other words, cyclohexene could enhance the selectivity for T cell receptors[1].

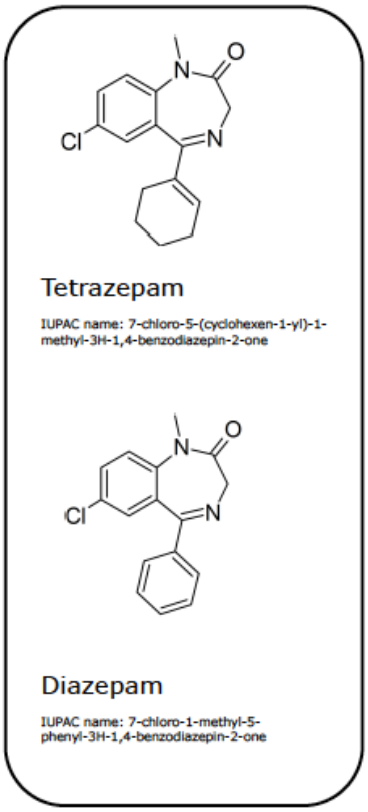

Figure 1: Molecular structure and IUPAC name of diazepam and tetrazepam

In addition, diazepam produces a less-reactive benzophenone metabolite that may induce a weaker reaction when patch tested. Benzodiazepines should be taken into account and assayed in suspected allergic contact dermatitis in HCPs involved in benzodiazepines compounding[1,3].

β-blocking agents

β-blocking agents, in particular propranolol[21,22], carvedilol and levobunolol[5] have been reported as occupational allergens in the pharmaceutical industry. In this regard, literature refers some cases of risk related to the manipulation of β-blocking agents in the workplace even though not in a hospital environment[21,22]. Cutaneous lesions localized on hands, forearms and thighs have been reported in workers employed in chemical-

pharmaceutical company (i.e., drug synthesis) and exposed mainly to propranolol[22]. Structurally, β-blockers are comparable to the endogenous neurotransmitter noradrenaline: they present an aromatic ring and a side aliphatic chain important for receptor binding (Figure 2). This aliphatic group can have a role as antigenic determinant[5]. However, an alternative explanation could be that the cross-sensitivity is due to a common metabolite and not to their aliphatic chains[23].

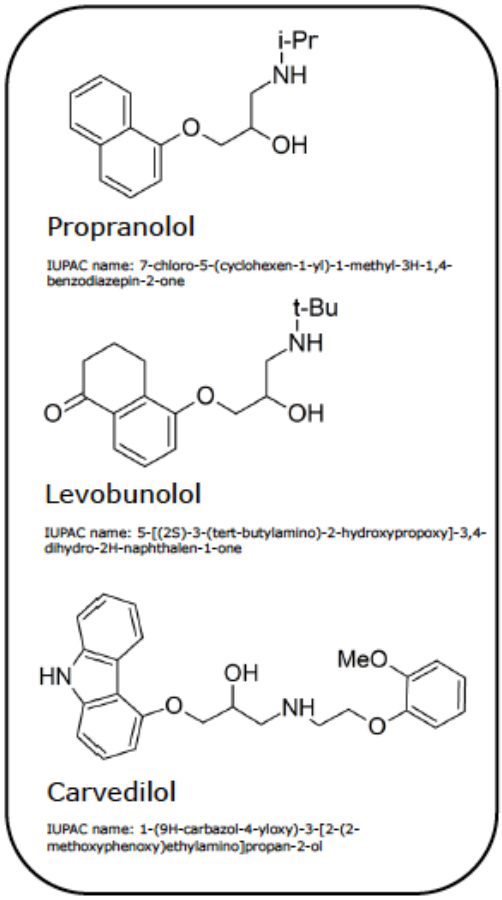

Figure 2: Molecular structure and IUPAC name of propranolol, levobunolol and carvedilol

Although there are no clear evidences of adverse reactions derived from β-blocking agents compounding in the hospital environment, the possible occupational risk should be considered; even because the reaction can have a latency period and false-negative results in patch tests have been reported[24,25].

ACE inhibitors

Contact sensitization and other adverse reactions have been reported in HCPs after manipulation of tablets containing ACE inhibitors[1,6-7].

The different adverse reactions observed, have been attributed to the differences in ACE inhibitors chemical structures[1] which can be divided into sulfur-containing compounds, for example, captopril and zofenopril, and non-sulfur-containing compounds, for example enalapril and lisinopril[1] (Figure 3). The characteristic thiol group in the captopril structure could be responsible for some reactions. As this molecule is excreted in the urine, genital pruritus or local dermatitis could appear in patients that suffer from contact allergy to captopril. Furthermore sometimes, reactions induced after captopril manipulation could be similar to those induced by other sulfhydryl-containing drugs, for instance tiopronin[8,26].

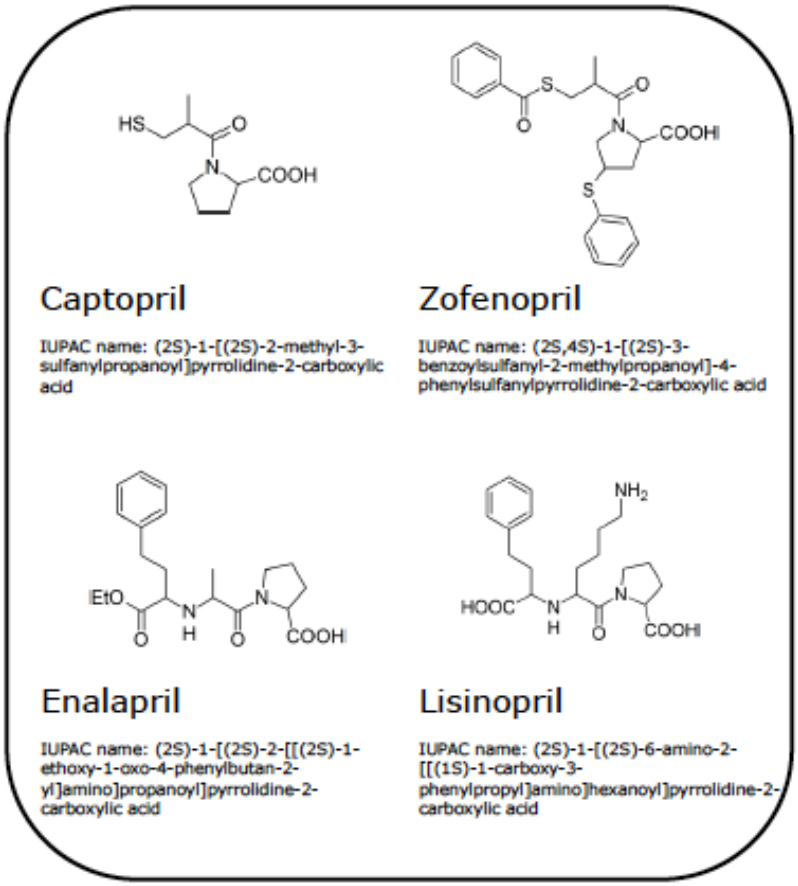

Figure 3: Molecular structure and IUPAC name of captopril, zofenopril, lisinopril and enalapril

Angioedema may be observed in patients taking lisinopril and enalapril. However, the side effects of ACE inhibitors could be caused by their chemical group, which was considered the responsible of allergic reactions[8].

NSAIDs (piroxicam)

The cutaneous reactions, specifically, fixed drug eruptions (FDEs), have been registered after handling of NSAIDs. FDEs are drug-induced exanthemas typically of acute onset, marked by lesions that recur on the same site and that appear as annular, edematous, reddish-brown to violaceous macules or plaques[27], but the pathogenetic mechanism of which is still unknown. Even if not very common, FDEs have been reported in patients treated with piroxicam[28,29]. Lamchahab et al.[9] reported the first case of FDE in an occupational context, in particular the case of a nurse in an orthopaedic department, involved in piroxicam extemporaneous compounding to ease the administration to geriatric patients.

Antineoplastic drugs

The extemporaneous compounding of anticancer drugs and the related occupational exposure increase the risk of dermatitis, liver damage, spontaneous abortion or respiratory tissue damage[10-12]. Antineoplastic drug toxicity is well known since 1940s, the decade they were introduced in therapy. Toxicity comes from the lack of selectivity of most anticancer therapeutics that are non selective for cancer cells and damage healthy tissues[30].

Falck et al. provided one of the first reports of occupational exposure in HCPs. They found that nurses, who handled cytostatic drugs, had higher indicators of mutagenic substances in their urine when compared with non-exposed workers, for example, psychologists and office clerks as control[31].

Investigations on workplace exposures to antineoplastic drugs show acute health effects primarily in nurses, such as: hair loss, headache, acute irritation, and/or hypersensitivity, reproductive damage, mainly, in female HCPs[32], including infertility[33], spontaneous abortions[34,35], and congenital malformations[30].

Selevan et al.[34] studied the connection between the fetal loss and the occupational exposure to the antineoplastic drugs in female nurses employed in oncologist

departments of 17 Finnish hospitals and noted a two times higher risks of miscarriage after exposure to cyclophosphamide, doxorubicin, and vincristine. The first trimester of pregnancy was the most critical period because a statistically significant relationship between spontaneous abortion and anticancer exposure could be established. However, the authors concluded that the effects caused by the manipulation of the mentioned drugs could not be associated with a single molecule because the most of nurses manipulated more than one drug at the same time.

Early studies on occupational exposure have reported the importance of the use of hoods in the manipulation of anticancer therapeutics. In fact, detectable levels of antineoplastic drugs were revealed in hospital environments with no hoods[34]. However, the use of hoods *per se* does not always guarantee reduced HCP exposure to airborne particles: horizontal laminar flow hoods do not always prevent from antineoplastic contamination[36]. Vertical laminar-flow hoods seem to be effective in decreasing worker exposure. In fact, mutagenic agents were found in the urine of HCPs who handled anticancer drugs in areas provided with horizontal laminar-flow hoods, but traces of them were not found when vertical laminar-flow cabinets were used[31,36].

Training and skills in proper antineoplastic drug handling are fundamental and the HCPs have to protect themselves from contamination during compounding. In fact, Staiano et al.[37] analysed urine samples of pharmacists, administering cancer chemotherapeutic agents at the National Institutes of Health (NIH), collected 2 days before and after exposure. No mutagenic activity was detected in the urine of the pharmacists.

Antineoplastic drug compounding and administration are not the only activities that present risks for HCPs. A number of routine activities in oncology wards or in the service of oncology patients in other settings can be responsible for exposure through inhalation, skin contact, ingestion, or injection, for HCPs and non-HCPs alike. HCPs very frequently perform the following activities: i) handling drug-contaminated vials, ii) reconstituting powdered or lyophilized products, and iii) expelling air from syringes. Non-HCPs are exposed to occupational risks coming from activities such as i) handling body fluids or body-fluid-contaminated clothing, dressing, and linens, ii) handling contaminated wastes, iii) decontaminating and cleaning drug preparation or clinical areas, and iv) performing maintenance on biological safety cabinets or isolators used to prepare antineoplastic drugs[30].

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3. Compounding of water-soluble drugs

3.1. Liquid forms of two model drugs: pravastatin sodium and potassium canrenoate

PRAVASTATIN SODIUM (ATC classification: C10AA03)

Pravastatin sodium (Figure 1), sodium;(3R,5R)-7-[(1S,2S,6S,8S,8aR)-6-hydroxy-2-methyl-8-[(2S)-2-methylbutanoyl]oxy-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]-3,5-dihydroxyheptanoate, belongs to statins group, a class of pharmaceutical compounds.[1]

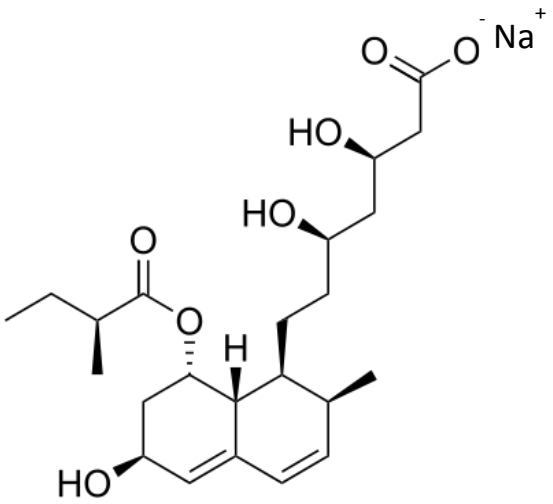

Figure 1: Chemical structure of pravastatin sodium.

Statins are very effective molecules to reduce blood cholesterol levels in patients with hypercholesteremia. In addition to lower cholesterol, pravastatin is prescribed for primary and secondary prevention of cardiovascular diseases.

The increasing life expectancy, the growth of aged people, and the large diffusion of cardiovascular pathologies in the developed Countries make statins, and in particular pravastatin, a widely prescribed drug. Currently, pravastatin is traded on the Italian

pharmaceutical market just as immediate-release tablets. Due to its wide and diffuse prescription, pravastatin was chosen as model drug to elaborate a part of the doctoral thesis.

Pravastatin competitively inhibits hepatic hydroxy-methyl-glutaryl coenzyme A (HMG-CoA) reductase, the enzyme that catalyses the conversion of HMG-CoA in mevalonate, a key step in cholesterol synthesis.[2] Pravastatin, like other statins, shows pro-apoptotic, growth inhibitor, and pro-differentiation activities in several cancer cells.[3]

The pure drug appears as a white crystalline powder, odourless, freely water-soluble (1:3). It absorbs in the UV range and presents a characteristic peak at 238 nm.[4]

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POTASSIUM CANRENOATE (ATC classification: C03DA02)

Potassium canrenoate (Figure 1), potassium;3-[(8R,9S,10R,13S,14S,17R)-17-hydroxy-10,13-dimethyl-3-oxo-2,8,9,11,12,14,15,16-octahydro-1H-cyclopenta[a]phenanthren-17-yl]propanoate, is a diuretic drug belonging to potassium-sparing agents.

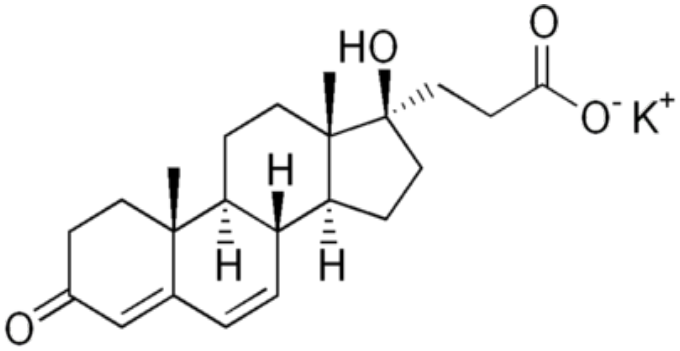

Figure 1: Chemical structure of potassium canrenoate.

It is an aldosterone antagonist of the spirolactone group. It is a pro-drug, and is metabolized to active canrenone in the body. Potassium canrenoate has been used in several illnesses, including hepatic cirrhosis associated with ascites. It has a direct positive inotropic effect on the human heart, therefore it may used in the treatment of congestive heart failure.[1]

In addition to tablets, potassium canrenoate is the only one clinically used anti-mineralocorticoid, available for parenteral administration (specifically intravenous route). The intravenous administration of potassium canrenoate is generally performed in the intensive care units for an acute pharmacological treatment. Parenteral administration requires qualified persons, like nurses, that are able to administer the drug via parental injection. In the chronic administration, intravenous route is not the preferable one; thus, providing a liquid form through enteral intake for long-term diuretic treatment might offer some advantages. Moreover, the prescription of diuretic drugs is common among people as well as statin treatment, so these reasons have been the driving-force to choose potassium canrenoate as model drug.

The pure drug appears as a white crystalline powder, odourless, freely water-soluble. It absorbs in the UV range and presents a characteristic peak at 293nm.[2]

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3.1.1. Chemical and microbiological stability studies of an aqueous solution of pravastatin sodium salt for drug therapy of the dysphagic patients

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ABSTRACT

Objective This study is aimed to improve dysphagic patient compliance under therapy with cholesterol-lowering drugs. Patients suffering from severe dysphagia, who do not feed independently, receive enteral nutrition through feeding tube and they need alternative oral route also for the administration of pharmacological therapy. This research deals with the development and stability (chemical and microbiological) of an aqueous solution of pravastatin sodium salt that will be administered orally directly in the feeding tube starting from commercial tablets. Tablets formulation is the only pharmaceutical dosage form available on the market for this type of drug.

Methods Pravastatin sodium salt tablets are dissolved in a preserved sodium bicarbonate solution at the final concentration of 4 mg/mL. Samples are stored in two different conditions until 60 days. The samples are prepared for high-performance liquid chromatography analysis coupled to a diode array detector (HPLC-DAD), microbiological analysis and pH measurements.

Results The chemical stability of the solution performed with HPLC-DAD analysis shows peaks' overlapping, which are characteristic of pravastatin, and correspondence of the concentration of the active ingredient in the solution. The detected values are analysed by one-way analysis of variance showing no statistically significant differences. Microbiological analyses proved that there is not microbial growth. By considering the dilution factor applied, it was possible to express the result as <10 CFU/mL in the two different culture media.

Conclusion This study demonstrated the possibility to reformulate pravastatin tablets as liquid pharmaceutical formulation for enteral administration with the aim of improving drug therapy in dysphagic patients.

KEYWORDS: Pravastatin tablets, dysphagia, compliance, management drug therapy.

INTRODUCTION

Swallowing is a complex function involving several nerves and muscles that act in reflected and synchronised way after an initial volunteer swallowing. Dysphagia is defined as difficult swallowing; more specifically, a sensation causing one to perceive an impairment in the passage of food from mouth to stomach.[1] The main consequences of dysphagia are different and can imply a social aspect as patient's isolation due to difficulty in swallowing or medical aspect such as respiratory problems, due to penetration of bolus in the airway, suction by tracheobronchial tree, choking and *ab-ingestis* pneumonia.[2–4] Another implication regards the nutritional problem, which means reduction of spontaneous feeding with progressive weight loss until protein-calorie malnutrition, dehydration, electrolyte unbalances, reduction of immune defences that might require enteral nutrition (EN) administered through a feeding tube (nose-gastric, nose-duodenal, nose-jejunal or orogastric) or Percutaneous Endoscopy Gastrostomy.[5–8]

There are various causes of dysphagia and both geriatric and paediatric patients are affected by it. This manuscript mainly focuses on geriatrics, but the studied preparation can be addressed to paediatric population after correct dosage revision. In fact, it is possible to distinguish between 'presbifagia', mainly due to patient's age, and dysphagia that is the term used when additional pathological conditions are also present. Dysphagia is common in patients having pathologies which involve the central nervous system, as for example, neurodegenerative pathologies, such as Alzheimer's or Parkinson' diseases, or in presence of strokes due to damages in specific brain areas. Specifically, it has been reported that swallowing difficulties are found in 60%–80% of patients with moderate to severe cognitive impairment[9]; moreover, dysphagia affects 40%–80% of patients in the first week post stroke[10] and persists in the 3%–17% of the cases after 1 month from vascular event.[11]

Swallowing deficits can be related also to pharmacological or radiotherapic treatments. For example, molecules having antipsychotic activity, with their extrapyramidal side effects, reduce pharyngeal muscle tone interfering with dopaminergic and adrenergic receptors causing dysphagia.[12] In addition, radiotherapy, alone or together with chemotherapy, can affect swallowing ability when the oropharyngeal area is treated.[1]

Finally, dysphagia could be also a consequence of head, neck and thoracic area's surgery,

due to the potential damaging of the nervous, muscular and cartilaginous structures involved in swallowing process.[1]

When patients are unable to swallow common solid dosage forms, different formulations need to be used and often an alternative route is chosen.

A common practice is to crush tablets or open capsules prior to the administration[5 13 14] which requires a manipulation of original pharmaceutical formulation that makes it necessary to consider different issues such as decrease of drug efficacy, increase in toxicity, problems of instability, lowering of palatability and loss of invaluable amount of drugs. Besides, when a solid oral dosage form is administered through a different way with respect to that authorised by pharmaceutical company, the manipulation and administration responsibility is early on the prescriber and then on the person who administers.[15] For example, when an oral liquid formulation is not available, it is common practice to open the capsule or crush the tablet and then mix it with food or beverages to allow administration through a feeding tube.

In this paper, chemical-analytical and microbiological stability of an aqueous solution of pravastatin sodium salt starting from tablets has been investigated with the aim to administer the solution orally by using syringe directly in feeding tube. The work deals with stability studies on pravastatin sodium salt, HMG-CoA (3-hydroxy-3-methyl-glutaryl-Co-enzymeA) reductase inhibitor belonging to the family generically called statin-series compounds. Physicians prescribe this molecule for treating primary disorder such as hypercholesterolaemia or hyperlipidaemia in addition to well-balanced diet, primary and secondary prevention of cardiovascular diseases and post solid-organ transplant. Tablet is the only pharmaceutical dosage form for this type of drug and the formulation of an aqueous solution is performed to improve compliance and pharmacological therapy in dysphagic patients treated with cholesterol-lowering drugs.

METHODS

Materials

- Pravastatin sodium salt 20 mg tablets (Pensa Pharma);
- Sodium bicarbonate 8.4% w/v solution (S.A.L.F. Laboratorio Farmacologico);
- Methyl p-hydroxy benzoate sodium (Sharon Laboratories);
- Propyl p-hydroxy benzoate sodium (Clariant);

► Sterile polypropylene (PP) microtubes 2 mL (Sarstedt AG & Co);

► PP syringes 30 mL plus needle 19G (Rays);

► Culture medium Columbia Agar + 5% sheep blood–COS (Columbia sheep) in Petri plates (BioMerieux);

► Culture medium SABOURAUD gentamicin chloramphenicol—SGC2 in Petri plates (BioMerieux).

Samples preparation

Aqueous solution of pravastatin sodium salt[16] was prepared according to Good Manufacturing Practice (GMP Ph. Eur. VIII Ed.). Briefly, methyl p-hydroxy benzoate sodium, propyl p-hydroxy benzoate sodium and then, 20 mg tablets of pravastatin sodium salt were added to a sodium bicarbonate 8.4% solution under magnetic stirring[17] up to a final pravastatin concentration of 4 mg/mL. The need to use basic diluent was linked to assure a final pH solution in a specific range of 7–10, according to the suggestion detailed in the last-mentioned reference.

The final aqueous solution formulation contains: (1) pravastatin sodium salt 20 mg tablets, 20 units; (2) methyl p-hydroxy benzoate sodium, 0.150 g; (3) propyl p-hydroxy benzoate sodium, 0.050 g and (4) sodium bicarbonate 8.4% solution q.s. 100 mL.

Chromatography analysis

Chemical stability of the aqueous solution containing pravastatin sodium salt 4 mg/mL was evaluated using a high-performance liquid chromatography system coupled to a diode array detector (HPLC-DAD) method supported by ChemStation for LC 3D system.[18–21] The ultraviolet–visible DAD was set at 210–220–230 nm (Agilent ChemStation for LC 3D System). The active compound pravastatin sodium salt was monitored and quantified at 230 nm (wavelength of maximum absorption). Pravastatin sodium salt was separated isocratically on a C18 reverse phase analytical column (Varian, 5 mm, 4.6Å~250 mm). The mobile phase was prepared from monobasic potassium phosphate and phosphate acid in HPLC grade water. The 0.02M buffer solution was adjusted to pH 3.0 with phosphate acid and mixed with methanol (HPLC-GOLD-Ultragradient Carlo Erba Reagenti) (60:40v/v). The flow rate was set at 1 mL/min. The injection volume was 1 µL and the column temperature was controlled at 30°C. HPLC-DAD studies were performed using an Agilent

technology 1100 series, made of an auto-sampler and a binary solvent pump.

In order to validate analytical HPLC method, the calibration curve is obtained by plotting the peak area against a solution of pravastatin sodium salt at different concentrations (1, 2, 4, 8 mg/mL), with a good correlation $R^2 \geq 0.999$. Limit of detection and limit of quantification values are 0.001 and 0.003 mg/mL, respectively.

With the calibration curve it was possible to check the active compound dosage in the used tablets and to verify the declared amount by the manufacture.

According to section 2.9.6 of the Italian Pharmacopoeia (FUI), 'Uniformity of content of the pharmaceutical forms in single dose',[22] the preparation respected the essay if the declared amount is in the range of 85%–115% compared with mean value. The analysed tablets fall within the required range.

A total of 51 samples listed above are divided into:

- three samples frozen at −20°C at time 0;
- 24 samples stored in the refrigerator (2°C–8°C) without light exposure;
- 24 samples stored at room temperature (22°C–25°C) without light exposure.

Temperature, samples' weight and microtubes' appearance were carefully controlled during 60 days.

Three samples among that stored in refrigerator and three among that stored at room temperature are frozen at −20°C at the days 1, 5, 8, 14, 21, 30, 46, 60 from the beginning.

In order to check any variations in the aqueous solution's composition, not caused by the tablet inside the preparation, 17 reference samples of 1 mL are prepared. They have the same composition of solution with the exception of the tablets.

Also the references were divided into:

- one sample frozen at −20°C at time 0;
- eight samples stored in the refrigerator (2°C–8°C) without light exposure;
- eight samples stored at room temperature (22°C–25°C) without light exposure.

At days 1, 5, 8, 14, 21, 30, 46, 60, the corresponding samples were frozen at −20°C and then, chromatographic analyses were performed only for samples at the days 0, 14, 30, 60.

The number of analysis was reduced because of a good stability of the active ingredient in the solution as confirmed by the samples at 60 days and secondly, also for those at 14 and 30 days. Before analysis, samples' weight was controlled for verifying any variations.

Then, every microtubes were centrifuged at 13300 rpm for 5 min and the content was filtered with 0.22 μm filter and syringed in a vial.

Duplicate HPLC determinations are performed on each analysis time and on each storage condition in order to have variability within the sample and between samples. The results were enough for a suitable statistical interpretation of the obtained outcomes.

At days 0 and 60, the reference samples were tested in order to underline any potential variations not due to the presence of the tablets in the solution.

Stability analysis

An HPLC evaluation for physical and chemical stabilities was evaluated for 60 days at two storage conditions: room temperature (22°C–25°C) and refrigerated (2°C–8°C). Thus, 68 samples were prepared from original aqueous solution of pravastatin sodium salt and packed in PP sterile microtubes 2 mL. In particular, 51 samples of 1 mL for chromatographic analysis and 17 samples of 1.5 mL for pH evaluation were prepared.

Every sample was labelled with a specific name to be identified and the weight of each one was checked to monitor any variations (table 1).

The visual examination of solution colour and the pH values measured through a digital pHmeter (Denver Instrument—BASIC) on days 0, 14, 30, 60 were assessed as a further confirmation of the stability of the liquid solution.

Table 1: Samples' weight of pravastatin sodium salt aqueous solution.

Sample's name	Weight after preparation mean±SD	Weight before freezing mean±SD	Weight after unfreezing mean±SD
0.1	2.59±0.0004	2.60±0.0002	2.61±0.0003
0.2	2.61±0.0001	2.61±0.0003	2.62±0.0004
0.3	2.61±0.0002	2.59±0.0001	2.60±0.0003
Reference 0	2.62±0.0001	2.61±0.0003	2.67±0.0002
14.1 R.T.	2.63±0.0005	2.62±0.0002	2.63±0.0004
14.2 R.T.	2.65±0.0005	2.65±0.0002	2.65±0.0002
14.3 R.T.	2.61±0.0007	2.61±0.0001	2.61±0.0002
14.1 REF.	2.62±0.0003	2.62±0.0000	2.62±0.00006
14.2 REF.	2.62±0.0003	2.62±0.0000	2.62±0.0002
14.3 REF.	2.64±0.0008	2.64±0.0000	2.64±0.0004
30.1 R.T.	2.65±0.0002	2.65±0.0003	2.66±0.0002
30.2 R.T.	2.63±0.0006	2.63±0.0002	2.63±0.0002
30.3 R.T.	2.64±0.00006	2.64±0.0002	2.62±0.0005
30.1 REF.	2.63±0.0005	2.63±0.0002	2.63±0.0001
30.2 REF.	2.62±0.0004	2.65±0.0003	2.63±0.0001
30.3 REF.	2.63±0.0008	2.63±0.0003	2.64±0.0001
60.1 R.T.	2.62±0.0002	2.62±0.0006	2.62±0.0001
60.2 R.T.	2.63±0.0008	2.63±0.0002	2.63±0.0002
60.3 R.T.	2.66±0.0005	2.66±0.0006	2.64±0.0004
Reference 60 R.T.	2.64±0.0005	2.66±0.0003	2.65±0.0001
60.1 REF.	2.67±0.0003	2.67±0.0002	2.67±0.0001
60.2 REF.	2.64±0.0001	2.64±0.0002	2.64±0.0001
60.3 REF.	2.63±0.0003	2.64±0.0002	2.62±0.0002
Reference 60 REF.	2.65±0.0004	2.63±0.0005	2.65±0.0003

X.1 R.T.: day X sample 1 room temperature; X.2 R.T.: day X sample 2 room temperature; X.3 R.T.: day X sample 3 room temperature; X.1 REF.: day X sample 1 refrigerator; X.2 REF.: day X sample 2 refrigerator; X.3 REF.: day X sample 3 refrigerator; Reference X R.T.: reference sample day X room temperature; Reference X REF.: reference sample day X refrigerator.

Microbiological analysis

Four PP syringes, each containing 20 mL of solution, were prepared and protected from light, then, two syringes were preserved at room temperature and two in refrigerator.

According to section 5.14 of FUI, 'with microbiological quality of pharmaceutical preparations and substances for pharmaceutical non sterile use',[22] orally used preparations have to respect these criteria:

1. Total aerobic microbial count (TAMC): maximum acceptable 200 CFU/mL;
2. Total combined yeasts and molds count (TYMC): maximum acceptable 20 CFU/mL.

About 1 mL of pravastatin sodium salt aqueous solution taken at days 0, 1, 5, 8, 14, 21, 30, 46, 60 from the preparation date, from each previous prepared syringe, was sown in duplicate on Petri plates by seeding method on surface. For the TAMC, the used culture medium was Columbia Agar + 5% sheep blood—COS and the plates were incubated, upside down, in a thermostat at 30°C–35°C (34°C) for 3 days.

Instead, for the TYMC, the used culture medium was SABOURAUD gentamicin chloramphenicol—SGC2 and the plates were incubated, upside down, in a thermostat at 20°C–25°C (24°C) for 5 days. The seeding procedures were performed under laminar flow hood. Before the seeding, each sample was diluted 1:10 with sterile water. After incubation period, any microbial colonies grown were estimated in each type of culture medium plates and then, average values were registered. Because of the analysis was carried out on diluted samples, in order to express results, it was necessary to multiply the obtained CFU values by 10. Therefore, the microbial growth was registered as <10 CFU/mL (applied dilution factor).

In order to validate the microbiological method, specific American Type Culture Collection (ATCC) strains were used: *Staphylococcus aureus* ATCC 6538, *Pseudomonas aeruginosa* ATCC 9027, *Escherichia coli* ATCC 8739 and *Candida albicans* ATCC 10231. The only difference in the seeding procedures for the specific microbial strains used was the addition of Tween 80 (1% diluent sterile water) to the diluted sample to neutralise the parabens put in the formulated aqueous solution.

Moreover, to confirm method and in order to carry out 'Microorganisms Recovery Test', positive and negative controls were performed in duplicate. For the positive check, 100 µL suspension of the specific strain ATCC were added to 900 µL diluent and the total was sown on the plates COS and SGC2 with the same seeding procedures and for the same incubation period. Instead, for the negative one, the sterility of diluent (water), culture media and the operating conditions were monitored.

Statistical analysis

Significant differences among the means of the obtained concentrations were determined through one-way analysis of variance using Minitab program (V.15.1.0.0). A p-value less than 0.05 was considered statistically significant. p-Values for aqueous solution are 0.232 at room temperature and 0.117 in the refrigerator.

RESULTS

Chromatography analysis

The identification of pravastatin sodium salt, as active compound, in the solution was assessed by comparison with the retention time of the pravastatin sodium salt standard (retention time 6.94 min). A further confirmation of this qualitative analysis was achieved by comparison with related ultraviolet spectra obtained by DAD detector.

The chromatograms gave a great overlapping of the peaks that identify pravastatin sodium salt in all analysis time (0, 14, 30, 60 days from the preparation) and in both storage conditions (figure 1 A, B).

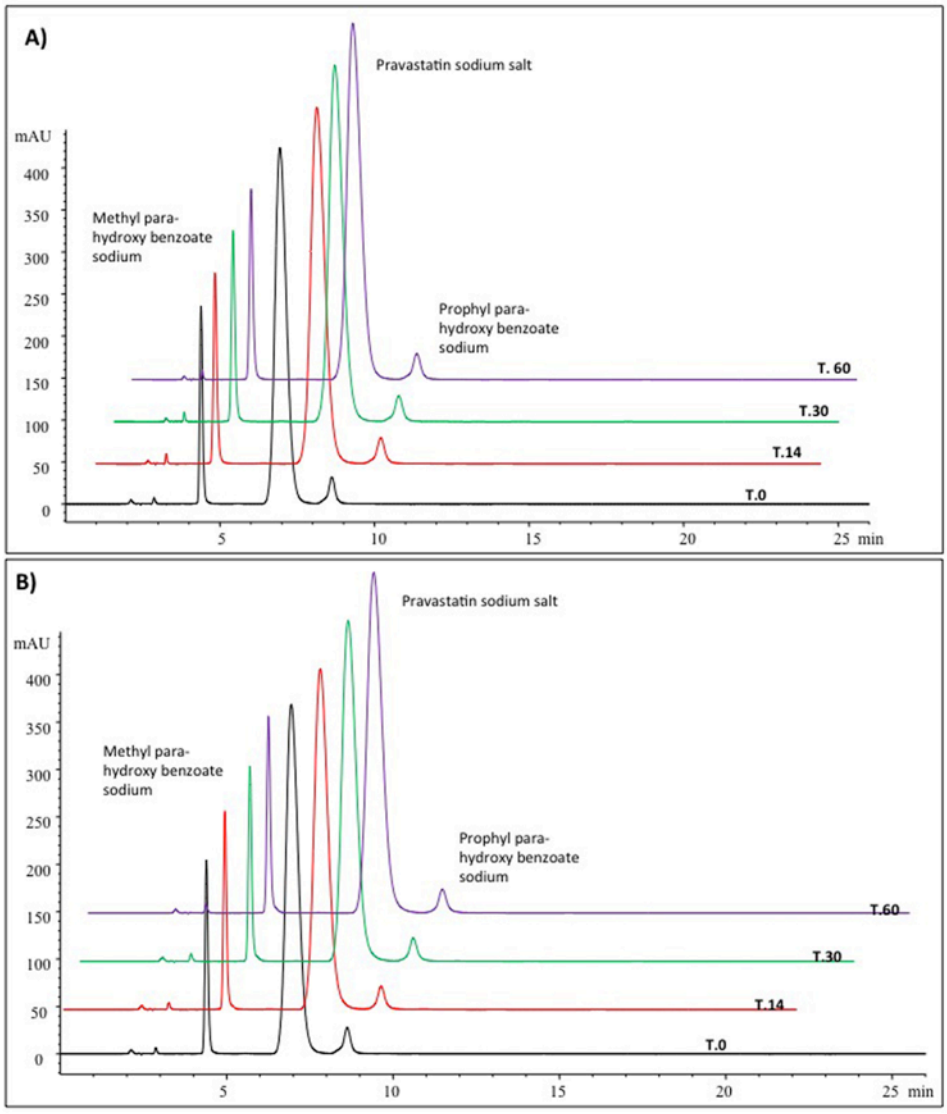

Figure 1: High-performance liquid chromatography analysis coupled to a diode array detector chromatograms showing the aqueous solution of pravastatin sodium salt at time 0–14–30–60 days stored (A) at room temperature and (B) in the refrigerator.

Average peak area was calculated and it was possible to deduce relative concentrations of active compound in the solution through the calibration curve. These values were compared with the amount of pravastatin sodium salt declared by the company. The mean concentration of the active ingredient in the solution was 4.36 (0.076) mg/mL that was equivalent of 21.79 (0.38) mg as dosage of pravastatin sodium salt in each tablet. These values were included in the required range of FUI. The results demonstrated that the molecule was stable because there are no significant changes in the obtained data (figure 2). The analysis performed on the reference samples at days 0 and 60 showed that there were no variations due to the presence of the tablets in the reference solution. The temperature was not a significant parameter because the two different detected storage conditions did not affect the analysis results. This aspect can be important for the management of the drug therapy both in the hospital and at home.

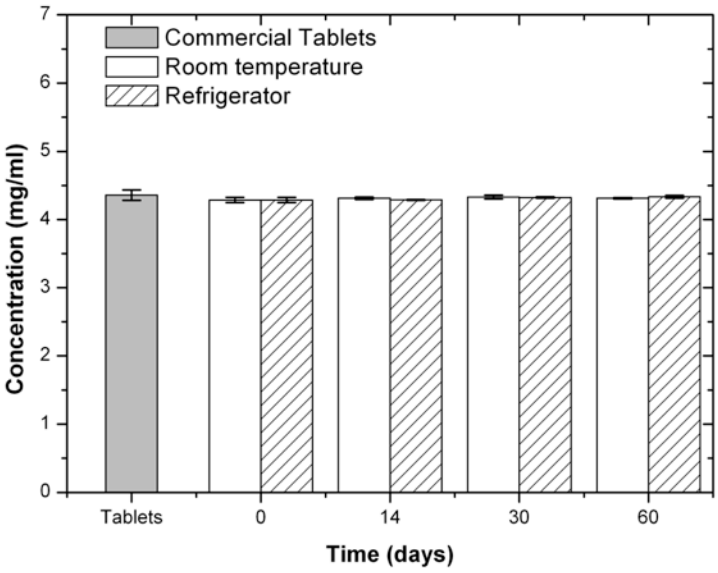

Figure 2: Quantification of active compound pravastatin sodium salt in the aqueous solution stored at room temperature and in the refrigerator.

Microbiological analysis

The microbial tests were carried out on the aqueous samples at every established time in the programme work and in both storage conditions, in order to have a strict monitoring of any microbiological growth. After the incubation periods, 3 CFU/mL of Corynebacterium jeikeium were detected in two samples of Columbia Agar + 5% sheep blood plates used for TAMC evaluation and 3 CFU/mL of Penicillium spp were detected in one sample of SABOURAUD gentamicin chloramphenicol plates used for TYMC evaluation. These results demonstrated that the microorganisms found in the liquid preparation most likely were the result of a contamination during the preparation steps or during analysis although GMP was observed in both cases.

Considering the limited number of CFU/mL in both culture media, it was possible to express the result as <10 CFU/mL (applied dilution factor). Moreover, a complete microbiological stability of pravastatin sodium salt solution 4 mg/mL can be declared, both when it was held at room temperature and when it was preserved in the refrigerator.

The suitability of the analytical method was assessed verifying that the mean value obtained for each microorganism test (ATCC strain) in presence of product was compared with the mean value obtained in the positive control ('Microorganism Recovery Test').

Recovery percentage for each microorganism used was calculated according to this formula:

$$Recovery\ \% = \frac{mean\ value\ obtained\ in\ presence\ of\ product}{mean\ value\ in\ positive\ control} * 100$$

This percentage has to be in the range of 50%–200% (factor of 2) and this criterion has to be respected by the four specific microorganisms selected for this study and by all batches of products used in the analytical method's validation (tables 2 and 3).

Table 2: Recovery test of aqueous solution of pravastatin sodium salt stored at room temperature

Recovery Test aqueous solution - room temperature	Mean value obtained in presence of product CFU/plates	Mean value in positive control CFU/plates	Recovery %
Staphylococcus aureus **ATCC 6358 (Agar COS)**	42	38	110.5
Pseudomonas aeruginosa **ATCC 9027 (Agar COS)**	55	45	122.2
Escherichia coli **ATCC 8739 (Agar COS)**	29	28	103.5
Candida albicans **ATCC 10231 (Agar SGC2)**	19	16	118.7
ATCC, American Type Culture Collection.			

Table 3: Recovery test of aqueous solution of pravastatin sodium salt stored at room temperature

Recovery Test aqueous solution - refrigerator	Mean value obtained in presence of product CFU/plates	Mean value in positive control CFU/plates	Recovery %
Staphylococcus aureus **ATCC 6358 (Agar COS)**	22	38	57.8
Pseudomonas aeruginosa **ATCC 9027 (Agar COS)**	66	45	146.6
Escherichia coli **ATCC (Agar COS)**	24	28	85.7
Candida albicans **ATCC (Agar SGC2)**	18	16	112.5
ATCC, American Type Culture Collection.			

pH stability

The pH measurements of the aqueous solution showed a substantial stability of the preparation and respected the stability range of the active ingredient (table 4). These results confirmed the stability of new aqueous pravastatin formulation.

Table 4: pH values of aqueous solution of pravastatin sodium salt

Aqueous solution samples (day)	Room temperature pH mean±SD	Refrigerator pH mean±SD
0	8.52±0.026	
14	8.57±0.020	8.53±0.052
30	8.63±0.089	8.58±0.050
60	8.72±0.040	8.60±0.260

DISCUSSION

This study offers an alternative treatment for the management of drug therapy in dysphagic patient who cannot take solid oral dosage forms such as tablets or capsules. The topic about improving the administration of drugs in patients with swallowing difficulties is discussed every day in the hospitals, in the nursing homes and at home among relatives who have to manage the intake of therapy by the member of their family.

Therefore, the development of this liquid pharmaceutical form, safe and exact in the dosage, can help nurses and caregivers in the administration of medication in patients who cannot swallow. The analytical HPLC-DAD method used allows an exact quantification of each injected sample in the instrument and a right amount of drug administered to patient. Microbiological tests assure a high grade of microbial stability until 60 days. This period allows organising the management of the galenic preparations of the aqueous solution according to the necessities of the clinical pharmacy.

CONCLUSION

The stability study performed through chemical-analytical and microbiological analyses and the pH measurements show that the active compound is stable for all the considered period of 60 days. Moreover, it is possible to administer the aqueous solution of pravastatin sodium salt to dysphagic patients in order to improve their drug therapy even when they are in EN.

Key messages

What is already known on this subject

- Patients with swallowing difficulty require the correct management of drug therapy, especially because of solid oral dosage forms (e.g. tablets and capsules), may cause choking, or can remain in patient's mouth or oesophagus.
- In this contest, those who administer medication have to manipulate the original pharmaceutical formulation, despite this procedure being not safe and can cause a lot of risks for prescriber and patient.

- Currently, some practises such as chopping and mixing tablets with water or food are followed, but it is necessary to consider the introduction of a medication review to improve the management of drug therapy in dysphagic patient.

What this study adds

- This study demonstrated the possibility to formulate and administer an aqueous solution of pravastatin sodium salt to dysphagic patients in order to improve their drug therapy even when they are in enteral nutrition.
- This new preparation can be administered through feeding tube in order to obtain exact dosage of the drug, avoiding risks for patient and medical-legal implications for those who administer or prescribe the therapy.

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3.1.2. Enteral delivery of pravastatin sodium liquid form

1. INTRODUCTION

Pharmaceutical market provides a large number of formulations even though sometimes these cannot totally cover the necessities of the population. In fact, despite of the dosage forms are mainly solid (e.g., tablets, capsules, powders, or granules for oral use) due to the fact that present many advantages either for the pharmaceutical industries or for the majority of the patients, some people prefer or need different dosage forms. Other routes of administration may be taken into account (e.g., intravenous, intramuscular, transdermal, orodispersible) but, sometimes, an active pharmaceutical ingredient (API) is not accessible as different formulation with respect to the solid one.

In particular, paediatric, geriatric, bedridden, non-compliant patients, or people who manifest swallowing complications may benefit from not solid oral formulations. Currently, a common practice is handling or compounding of the solid oral dosage form crushing tablet or opening capsule and dispersing the obtained powder or content in a suitable vehicle. Occasionally, powders are dispersed in food or beverages, sometimes are solved in water and thus, patients can assume their drug therapy.

A crucial focus regards patient who are completely unable to swallow due to physiological ageing process, or several primary pathologies (e.g., post-stroke, central nervous system disorders, temporary disability) and they are supplied through enteral nutrition (EN).[1] Therefore, tubes are used to feed and administer drug therapy. In these cases, it is challenging to find out a suitable option to make sure and efficient drug administration and therapy. Patients fed through EN, have to undergo an enteral intubation (e.g., naso-gastric tube, NGT) generally performed by medical doctor and nursing staff for oral nutritional and drug intake.

In this work we wanted to carefully explore the delivery of a model drug Pravastatin sodium through feeding tube to evaluate and, consequently, arrange, modify, or refine all manual operations that should be applied in case of the drug enteral administration via feeding tube. To perform enteral intake of the drug Pravastatin, some actions should be realized to switch from original solid form (tablet) to liquid form able to be flushed in the tube. In addition, we were interested in understanding the influence that nutritional formulas have on the drug intake into the same tube.[2] The market offers numerous nutritional formulas presenting a large number of nutritional compositions to satisfy every patient demand. Characteristics of feed ranged from standard formulas to low-

protein, or low-fat, or low-fiber, or low-sugar content products according to personal dietary intake. To delimitate investigational field, we chose to select two alimentary formulas: standard and low-fiber content and to evaluate influence of alimentary bolus on drug intake in case of enteral tube delivery.[3]

A number of factors may affect the drug delivery via feeding tube: either health care providers responsible for compounding or patients due to their state of health. In fact, the health care providers experience and ability during manipulation or handling may affect the final product quality. In addition, the compliance of the patient may contribute in effective drug taking.

All these parameters and characteristics play a significant role on drug therapy via feeding tube. In this study only some aspects will be investigated in order to understand and evaluate the management of therapy in dysphagic patients fed and treated through enteral tube.

2. MATERIALS AND METHODS

2.1 Materials

Pravastatin sodium (PraNa) immediate-release tablets 20mg produced by Pensa s.p.a. were bought in local pharmacies; PraNa raw material was kindly offered by Teva Pharmaceutical Industries Ltd., Hungary through Angelini A.C.R.A.F. s.p.a., Ancona; polyurethane feeding tubes (i.e., length 120cm, inner and outer diameters were 5.4mm and 4mm, respectively) size 12 French, were purchased from Teleflex Medical s.r.l.; enterally used polypropylene syringes were bought from Pentaferte Italia s.r.l..

Enteral nutrition Nutricomp® Standard Fiber was purchased from B. Braun (Melsungen AG, Germany), and nutrition Nutrison® 1Kcal/mol from Nutricia Advanced Medical Nutrition, Danone Group (Milano, Italy). Preservative agents, methyl para hydroxy benzoate sodium and propyl para hydroxy benzoate sodium, were bought from Galeno s.r.l. (Italy), sodium bicarbonate was purchased from Sigma Aldrich (Steinheim, Germany). They were all pharmaceutical grade and widely employed in pharmaceutical field.

2.2 Methods – *in vitro* model study

The experimental design was based on two main working phases: firstly, arrangement of three liquid formulations to investigate differences in setting up and to choose the proper

method to obtain a liquid form. The purpose was to compare the results obtained either regarding the compounding of original tablet or operating with PraNa raw material.

Secondly, one of the three liquid forms was chosen and the work was completed by studying the delivery of two nutritional formulas followed by drug administration via feeding tube and by observing diet influence in the assumed drug amount.

The project has been planned as an *in vitro* model study where enteral administration via feeding tube of all three liquid formulations was simulated. Three independent tubes for each type of the liquid preparation were placed and fixed on a support at 45° to respect the physiological angle of the tube insertion in a patient. This set was to simulate three dysphagic patients in enteral nutrition. Ten successive administrations of the liquid preparations were delivered in any tube. Additionally, it was possible to evaluate if repeated administrations of liquid PraNa into the same tube may affect the drug amount assumed by the patient in a specific time interval. Afterwards, the same setting was reproduced to investigate nutritional formulas influence on drug delivery.

2.3 Samples preparation

Three different liquid preparations containing PraNa were set up to compare three different liquid form of the drug. In all preparations, the initial concentration of the molecule was 2mg/mL.

In the detail, extemporaneous preparation (EXT) was prepared crushing one by one PraNa tablet 20mg in a mortar, then 10mL of distilled water were added to the powder and a suspension was obtained. The single-dose dispersion was withdrawn into an enteral syringe and flushed in the tube.

Galenic preparation (GAL) was made dissolving tablets of PraNa 20mg in a sodium bicarbonate 8.4% preserved aqueous solution[4,5] in a volumetric flask. A single-dose was sampled from the bulk and administered in the tube.

Standard solution (STD) was obtained solubilising PraNa as raw material in a sodium bicarbonate 8.4% preserved aqueous solution[5] in a volumetric flask. The single-dose was delivered in the tube.

In GAL and STD preparations, parabens (methyl para-hydroxy benzoate sodium and propyl para-hydroxy benzoate sodium) were employed as preservative agents to assure

microbiological stability in bulk aqueous products. In all three preparations, delivery of a single-dose was repeated ten times for every single tube.

Gravimetric and spectrophotometric evaluations were performed for all three liquid formulations.

2.4 Gravimetric determinations

In the detail, gravimetric quantification was referred to assess the weight losses during each working step in EXT, GAL and STD formulations.[6] In the EXT, the sequence of the recorded weights was as follows: one tablet in the previously calibrated mortar, the crushed tablet, the suspension obtained after the water addition (10mL), the empty syringe used for the administration, and then, the full syringe (containing the suspension withdrawn from the mortar to be administered) were registered. The content of the syringe was called upstream weight.

Once administered, the liquid form was collected at the tip of the tube in a calibrated burette and, weight (downstream weight) and volume were registered after each administration. Then, 10mL of additional water were flushed in the same tube for washing it and added to the previous volume. The final weight and volume were again recorded to monitor each step of the manipulation process.

In the GAL and STD, the working phases were similar to EXT, with the exception of the initial procedure. In fact, GAL and STD were prepared in bulk, thus each single-dose (equivalent of 10mL) was withdrawn from the stock and, the weights were registered (upstream weight). Then, similarly for both preparations, the quantities were administered in the tubes and the downstream collections were measured in the burettes (weights and volumes). Therefore, tube washing with water was carried out and the weights and volumes were again annotated after the flushing of 10mL of water.

All collected liquids were stored for spectrophotometric analysis.

2.5 Spectrophotometric determinations

Spectrophotometric quantifications (Shimadzu UV-1800, software UV-Probe 2.43) of the drug were detected at the specific wavelength of PraNa 238nm, and the upstream and downstream concentrations of the active ingredient in the three different preparations were revealed. To validate analytical method, calibration curve of PraNa was plotted

correlating absorbance values to PraNa solutions at different concentrations (22.5-5µg/mL) with a good correlation coefficient $R^2 \geq 0.999$.

First of all, in order to verify the accuracy of the tablet drug content declared by the manufacturer in the commercial product, random tablets belonging to the same batch were quantitatively analysed.

Afterwards, upstream and downstream concentrations of the samples were measured through spectrophotometer after proper dilutions: 1:100 (for upstream concentration) and 1:50 (for downstream concentration), respectively.

Parabens had to be contemplated in drug amount determinations because they showed an absorbance peak at 256nm, close to UV peak of PraNa. Therefore, the presence of the preservative agents in GAL and STD formulations had to be considered to detect the correct value of PraNa in upstream and downstream concentrations. Specifically, the absorbance values of parabens at 238nm should be detracted to the total absorbance to calculate the absorbance exclusively related to the PraNa.

The theoretical upstream concentration of PraNa in EXT, GAL and STD formulations was 2mg/mL, instead, the final downstream concentration was 1mg/mL due to the tube flushing with 10mL of water. Analytical upstream determinations allowed establishing if, the preparations set up in bulk, had a right initial concentration. The ending values allowed knowing the quantitative variations due to the delivery of PraNa.

2.6 Nutritional formulas influence on drug delivery

Furthermore, GAL formulation was chosen as PraNa liquid form to perform this additional investigation. The influence of two common nutritional formulas on the drug assumption was explored to evaluate the effective amount of the drug assumed by patient after enteral intake of the meal. Two common, daily-used enteral nutritional formulas were chosen: standard nutrition Nutricomp® to give an equilibrate intake of all nutrients, and Nutrison® 1Kcal/mol to provide a low-fiber diet. Statin administration occurs after evening mealtime and, generally, drug administration occurs after flushing the tube with water.

The study aimed to evaluate if a specific nutritional composition may affect the systematic drug uptake reducing the dose. Additionally, every difference between two alimentary supplies was assessed in the delivered drug quantity.

The specific selection of these two types of feedings arises to understand if the different compositions (standard or low-fiber diet) may influence the quantity of the drug passing into the tube and/or if some components (e.g.: fibers) may vary the drug dose because of the absorption of the active molecule onto the dietary matrix.

The same previous *in vitro* model study was set up and three independent tubes were placed to represent three ideal patients for both of nutritional formulas. The drug administrations through enteral syringe after feed were repeated ten times into each tube to simulate a bedridden patient in an acute pathological condition.

Specifically, a 300mL nutritional bolus corresponding to a meal was pumped into the tube by a syringe and the tube was washed with 10mL of water.[7] Then, 10mL of GAL preparation, (upstream drug concentration 2mg/mL) withdrawn from the bulk, were administered into the tube and collected into the burette. Finally, a further tube washing was performed with 10mL water and collected into the same burette, thus the final theoretical PraNa concentration was around 1mg/mL. The volumes of the liquid content into the burette were registered to calculate the relative and real concentrations of the PraNa. Each collected sample was maintained in a proper vial before performing spectrophotometric analysis and determining the drug content ideally administered to the patient.

Obviously, in order to determine the drug amount, an estimation of the absorbance values of the nutritional formulas at 238nm was verified. These absorbance values of both formulas were taken into account to be contemplated when the determination of the downstream drug content was calculated.

3 RESULTS

3.1 Gravimetric determinations

The weight losses expressed as percentages and calculated after determination between upstream and downstream weights gave the following results: 2.45% ± 1.99%, 2.53% ± 2.11% and 1.74% ± 2.11%.

The weight losses were expressed as mean values ± standard deviations (SDs) for EXT, GAL, STD preparations, respectively.

The simulation about the delivery of the novel liquid forms into the feeding tubes and the collection into a burette to simulate an ideal gastric district represented a rather realistic setting of the administration of the liquid product via enteral tube.

The results obtained after the gravimetric determinations revealed that some differences might be referred to the different preparation procedures executed to arrange the three liquid products.

Obviously, in EXT setting, a greater number of operations were necessary to optimize the liquid medicinal product. EXT single-dose took more time for preparing it before delivery, with respect to GAL and STD that may be made in bulk.

A precise sequence of actions needed to be followed in order to obtain every EXT dose. Alternatively, GAL and STD may appear quicker in preparation time because they may set up in bulk and distributed on demand. The fewer number of operations may reduce the risks to make some errors and to deliver a proper drug amount via tube.

3.2 Spectrophotometric determinations

Spectrophotometric determinations performed to verify the nominal drug content in the tablets, revealed that the average content of PraNa in the tablet was 21.17 ± 0.22mg. The assay of content uniformity for solid oral dosage forms reported in the Italian Official Pharmacopoeia 12th edition[8] (IOP) states that drug content in a solid forms like tablets may range within the limit of 85-115% with respect to the average drug amount declared by the manufacturer. In this specific contest, the determined variation corresponds to 5.85% with respect to the nominal drug content 20mg. This value respects the limit imposed by IOP. This evaluation was to further assess the tablet drug content and to confirm the accuracy of the starting point. In fact, EXT and GAL liquid forms derived from tablet compounding.

Afterwards, the upstream concentrations of PraNa were measured in all three liquid preparations and mean values ± SD were reported: 2.15 ± 0.04mg/mL, 2.11 ± 0.04mg/mL, 2.03 ± 0.04mg/mL for EXT, GAL and STD, respectively. These values were close to the theoretical upstream concentration of 2mg/mL. The concentrations values at the starting point, before administration, corresponded to the following milligrams ± SDs of PraNa: 21.59 ± 0.59mg, 21.11 ± 0.46mg, and 20.30 ± 0.38mg.

After administration, downstream concentrations of PraNa were determined spectrophotometrically and mean values, calculated for the three tubes, were here reported: 1.05 ± 0.03mg/mL, 0.98 ± 0.04mg/mL, and 0.94 ± 0.05mg/mL for EXT, GAL, and STD preparations (theoretical downstream concentration was 1mg/mL). Instead, the respective milligrams calculated as overall mean ± SDs and collected in the burettes, were: 20.16 ± 0.46mg, 18.93 ± 0.95mg, and 19.02 ± 0.84mg for EXT, GAL, and STD compared liquid systems. The graphs (Figure 1) showed values referred to any tube and not just the overall average.

Although the slight differences between the administered doses and the collected ones, patients resulted correctly treated. The lower detected drug quantities at the tip of the tubes with respect to the upper ones, respected the limit of 85-115% with respect to declared mean value (20 mg) as required by Pharmacopeia in the assay about drug content uniformity for solid oral dosage forms (Figure 1). Reference value 20 mg was represented in the graphs by the red straight lines, instead, the upper and lower dotted ones were the limits of acceptance.

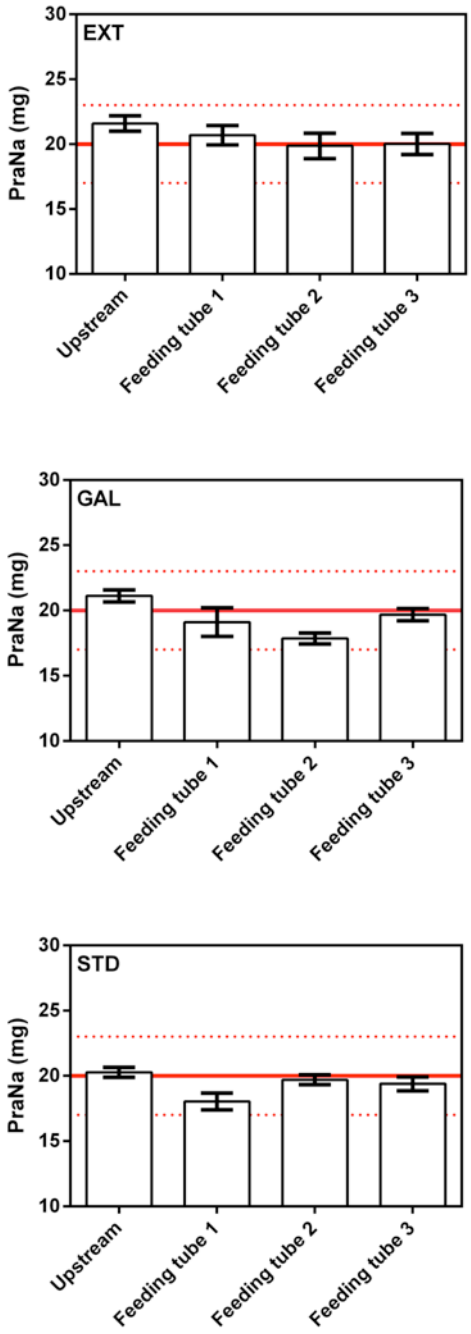

Figure 1: Mean values of PraNa administration after ten administrations for each tube. Three liquid forms (EXT, GAL, STD) of PraNa compared. 20mg represent the reference value. The upper and lower dotted red lines represent the limits of acceptance allowed by the Italian Official Pharmacopoeia.

Looking at the general trends of PraNa single-dose distribution into the tubes in all three compared liquid forms, PraNa contents assumed by the patients, showed a random profile, with respect to the upstream concentrations (Up) taken as reference. Trends

were not dependent on repeated administrations. No accumulation of drug into the tubes was registered and eventual burst effect should be avoided for the patients. Variability may be due to the chance of the operations related to preparation and administration (Figure 2). All detected values ranged within the limits of acceptance imposed by the Pharmacopeia. In fact, drug content varied between 17-23 mg. In the following graphs, the straight red lines represented the reference value 20 mg, instead, the dotted red lines reported the limits of acceptance 85-115%.

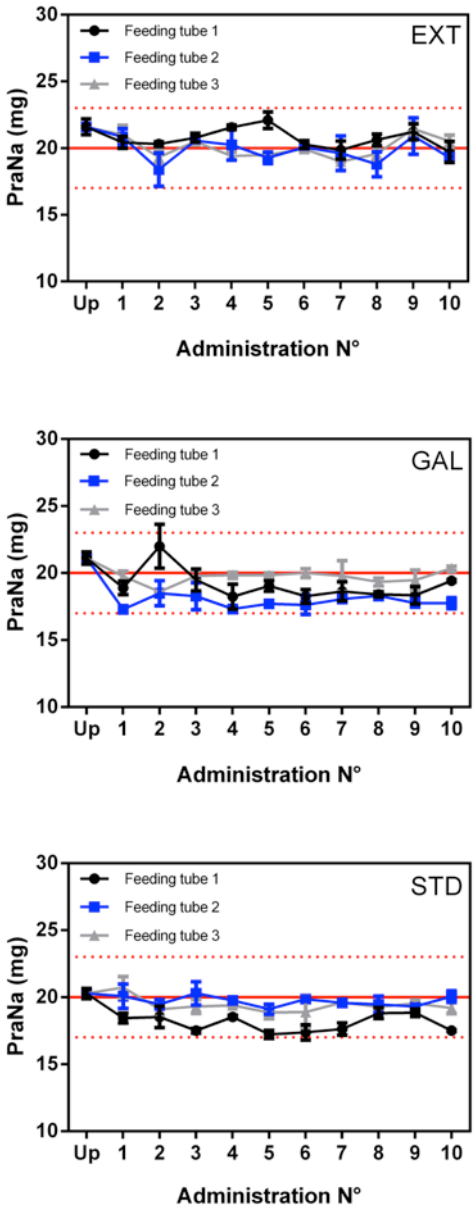

Figure 2: Random effect of PraNa administrations in the feeding tubes. 20mg represent the reference value. The upper and lower dotted red lines represent the limits of acceptance of IOP.

3.3 Nutritional formulas influence on drug delivery

To understand the effect of nutritional formulas on the drug amount delivered via enteral feeding tube, spectrophotometric assessments of feed were performed. In fact, the absorbance values of both nutritional formulas were check at 238nm. Detection revealed that Nutrison® 1Kcal/mol, low-fiber diet, had an influence of 6% on absorbance value of PraNa; instead standard nutrition Nutricomp® had an influence of 4%.

Fixed these two values, the measurements of the drug downstream concentrations were carried out after flushing alimentary bolus, 10mL of water to wash the tube and the PraNa single-dose to mimic a realistic care setting. Evaluations gave final PraNa concentration of 1.01 ± 0.01mg/mL and 1.00 ± 0.02mg/mL for low-fiber diet and standard nutrition, respectively. These concentrations, converted in milligrams ± SDs, revealed 19.77 ± 0.07mg and 19.63 ± 0.25mg of PraNa content. As shown in the graphs (Figure 3) and previously explained, the red straight and dotted lines showed the reference values (20 mg) and the limits of acceptance 85-115% of IOP. Instead, the green straight and dotted lines represented the influence of nutritional formulas, + 6% and + 4%, respectively, with respect to the absorbance value strictly detected for PraNa.

Although an influence due to the type of diet may be detected in both nutritional formulas, the patient assumed the correct dose of PraNa either with Nutrison® 1Kcal/mol low-fiber diet, or with standard nutrition Nutricomp®. Theoretically, patients assumed a drug amount comprised with the IOP limits of acceptance although limits were *ad hoc* adjusted and adapted in order to take into account the presence of nutritional boli. Even though, the patients assumed a slightly lower drug amount, the differences were irrelevant in order to make compliant cholesterol-lowering drug treatment for patients receiving enteral support.

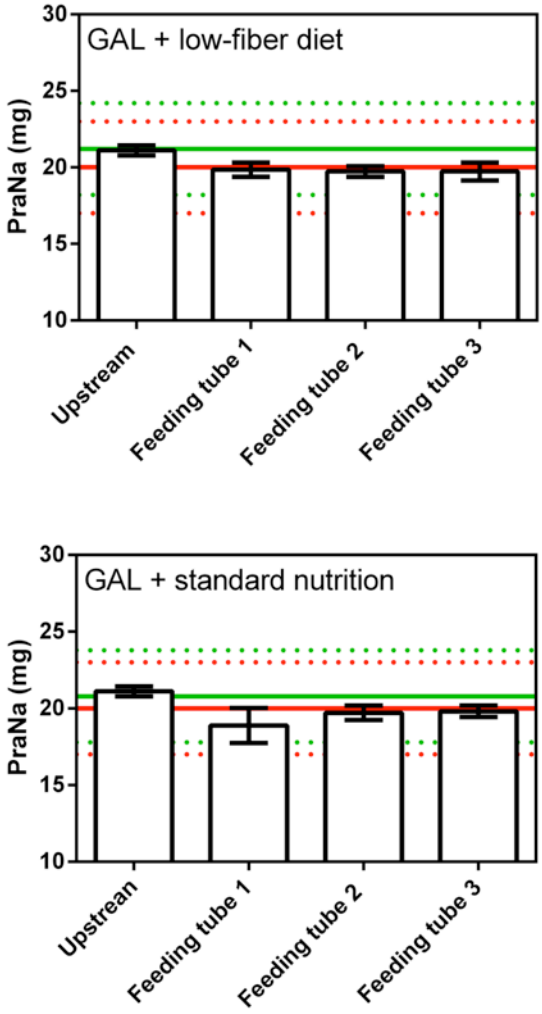

Figure 3: Influence of nutritional formulas on enteral intake of PraNa liquid form. 20mg represent the reference value (straight red line). The upper and lower dotted red lines represent the limits of acceptance of IOP. The green straight and dotted lines represent the influence of nutritional formulas.

4 CONCLUSIONS

The study has demonstrated that the optimization of several liquid forms of PraNa was an interesting initial point to evaluate the enteral delivery of the drug via feeding tube.

Starting from tablet crushing until the administration of the liquid form into the feeding tube, EXT preparation required a precise procedure to limit any errors and assure an accurate drug dosage to patient. Nevertheless, drug manipulation and compounding to produce a customized medicinal product might cause risks for patients. If a licensed pharmacist or physician or a qualified person under the supervision of a pharmacist did

not perform these procedures in a precise and standardized way more dangerous complications might occur. GAL and STD required a sort of simplified procedure to arrange the liquid form even though proper working steps were required to produce a compounded final formulation.

GAL preparation was chosen for the second part of the work for evaluating nutritional influence on drug delivery. It was considered a right balance between the use of EXT preparation or STD solution. On the one hand, compounding of any single tablet of PraNa was a laborious work and the final quality might not be always assured. On the other hand, the use of raw material was very expensive in the future perspective of a personalized drug therapy. In addition, high costs did not correspond to as much as possible improvements in terms of assumed drug amount. GAL liquid form was obtained by dissolving tablets in an aqueous medium; therefore actually, just a partial manipulation of the original tablets was performed.

This kind of arrangement of liquid form (GAL) may limit possible risks and adverse events linked to modifications of the original dosage form not only for patients, but also for health care providers. Sometimes, they alter drugs without the specific knowledge and awareness of the technology practised to formulate a dosage form. Simultaneously, patients in enteral nutrition may receive drug therapy even though enteral support was required.

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3.1.3. Potassium canrenoate compounding for administration via enteral feeding tubes: a physical and microbiological stability study

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ABSTRACT

Background Swallowing difficulties are arising in an increasing number of patients, especially in elderly people. When deglutition ability is completely compromised, enteral administration of a drug via feeding tubes is used. Licensed pharmacists have to compound the original solid forms to enable this drug therapy.

Objectives To evaluate the possibility of compounding original commercial tablets to produce a liquid formulation suitable for administering via a feeding tube.

Methods Two liquid formulations containing potassium canrenoate 5 mg/mL were prepared: a standard solution obtained by solubilising raw material and an extemporaneous preparation obtained by dissolving film-coated 100 mg tablets. Spectrophotometric determinations (UV range) of the drug established chemical stability of the analyte up to 60 days. Samples were tested for microbial growth. Gravimetric quantifications of liquid formulations were used to check any weight loss during the different steps before enteral administration.

Results UV data confirmed the chemical stability of potassium canrenoate up to 60 days. Samples showed no microbial growth. A higher weight loss was recorded in extemporaneous preparations than in the standard solution (10.7% vs 7.6%) according to the gravimetric quantification.

Conclusion It is possible to compound the original tablets into a liquid formulation suitable for administration via a feeding tube.

KEYWORDS: compounding, potassium canrenoate, dysphagia, solid oral dosage forms, feeding tubes, enteral administration.

INTRODUCTION

Every day, physicians, pharmacists, nurses and caregivers have to deal with problems in the management of pharmacological therapy, especially if patients cannot swallow solid oral dosage forms such as tablets and capsules. Swallowing difficulties, defined as dysphagia, are common in the elderly population and affect around 55% of aged patients in care settings.[1]

Physicians and pharmacists face a challenge when patients with swallowing difficulties need to be treated with drugs that are commercially available only as solid oral dosage forms. Tablets and capsules have to be crushed or opened to allow easier swallowing. However, this procedure may cause coughing, choking and adhesion to mouth and oesophagus' wall in this 'fragile' population, resulting in low adherence to treatment or treatment failures.[2] Moreover, manipulation of tablets and capsules might compromise their effectiveness or increase their toxicity.[3,4]

For these reasons prescribers should assess the medication regimen of patients with dysphagia, to find alternative dosage forms or administration routes, to avoid inappropriate prescriptions which can result in medication administration errors.[5–7]

In patients with severe dysphagia, feeding tubes (eg, nasogastric tubes (NGTs)) are usually placed and used for the administration of enteral nutrition (EN) and pharmacological therapy.[8,9] In these cases, the eligible drug formulations are liquid, but most commercially drugs are available only as solid oral dosage forms since their production is easier and cheaper, and also ensure more stability over time and an accurate dosage.

Therefore, to treat these patients, caregivers (eg, nurses) crush the tablets, disperse the powder obtained in water and administer the drug by a syringe directly into feeding tubes already placed for enteral loadings.

To improve the administration of solid oral dosage forms, where a liquid dosage form is not commercially available, an extemporaneous liquid formulation should be prepared by the pharmacist.[10]

To ensure safety for patients and reassure healthcare providers with concerns about possible adverse effects, one should consider, a decrease in effectiveness, changes of chemical/microbiological stability or pharmacokinetic changes and therefore toxicity of such molecules.[11–14] Not all formulations are suitable for manipulation (eg, enteric-coated forms or modified-release forms).[15,16] On the other hand, if an extemporaneous

preparation is possible, good manufacturing procedures (GMPs) must be respected to guarantee a safe final product.[17] If caregivers crush tablets and suspend them in water before administration, there is a high risk of error, owing to non-standardised preparation procedures of the compounded medicinal product.[18]

In this study, we focused on potassium canrenoate (a potassium-sparing drug and an aldosterone antagonist), which is used in clinical practice as a diuretic for various diseases, including hepatic cirrhosis associated with ascites and treatment of congestive heart failure for its inotropic effect on human heart.[19] We selected potassium canrenoate since it is commercially available only as film-coated tablets and an injectable solution in vials and not as an oral liquid formulation. For this reason, caregivers have to administer this drug by crushing the tablets and 'dispersing/suspending' them in water and finally, injecting the dispersion obtained through the enteral feeding tube.

The first aim of the study was to compare the chemical and microbiological stability of two different liquid formulations of potassium canrenoate prepared according to GMP: (1) a standard solution obtained using raw material (standard powder) and (2) an extemporaneous preparation obtained using tablets dissolved in an aqueous medium.

The second aim of the study was to evaluate, by gravimetric quantification, the difference in weight loss when potassium canrenoate is administered through a feeding tube as a standard solution prepared using raw material (standard powder) or as an extemporaneous preparation obtained by crushing a single tablet. This last procedure is usually adopted by caregivers.

MATERIALS AND METHODS

Materials

- Potassium canrenoate as pharmaceutical grade powder (FARMALABOR – Farmacisti Associati);
- Potassium canrenoate as film-coated 100 mg tablets (Sandoz S.p.A);
- Methyl p-hydroxy benzoate sodium and propyl p-hydroxy benzoate sodium (Sharon Laboratories Ltd, Israel);
- Sterile polypropylene (PP) 2 mL microtubes plus screw caps (Diatech Labline);
- Specific American Type Culture Collection (ATCC) strains: *Staphylococcus aureus* ATCC 6358, *Pseudomonas aeruginosa* ATCC 9027, *Escherichia coli* ATCC 8739, *Candida*

albicans ATCC 10231 (Liofilchem);

- Culture media tryptic soy agar (TSA) and Sabouraud dextrose agar (SDA) (Liofilchem);
- Letheen broth base modified as diluent (Liofilchem);
- Petri dishes of 9 cm diameter (Thermo Scientific);
- 12 French polyurethane nasogastric tubes, length 120 cm, outer diameter 5.4 mm and inner diameter 4 mm (Teleflex S.r.l.);
- 10 mL PP syringes (PentaFerte S.p.A).

Chemical and microbiological stability studies

Sample preparation:

Two different liquid forms of potassium canrenoate (5 mg/mL) were prepared according to GMP of the Italian Official Pharmacopoeia (FUI) 12th edition.[17] A standard solution was obtained by dissolving potassium canrenoate as a pure powder, while an extemporaneous preparation was compounded by dispersing tablets containing 100 mg potassium canrenoate. Two solid oral dosages are available on the Italian market: 25 mg and 100 mg tablets; the 100 mg tablets were used in this study. For both liquid formulations, distilled water was used as solvent and a mixture of methyl p-hydroxy benzoate sodium (1.5 mg/mL) and propyl p-hydroxy benzoate sodium (0.5 mg/mL) was used as preservative agents.

Chemical and microbiological stability of the two formulations, stored in sterile PP 2 mL microtubes, was evaluated up to 60 days under two different storage conditions: (1) at room temperature and (2) in a refrigerator. The samples were not exposed to light: the standard powder was put in an amber container and the microtubes were covered with an aluminium foil.

Spectrophotometric analysis:

The chemical stability of the two preserved aqueous preparations containing potassium canrenoate 5 mg/mL was evaluated by analysis of their absorbance values with a spectrophotometer Shimadzu UV-1800, software UV-probe 2.43, at a wavelength of 293 nm (maximum absorption peak for canrenoate potassium). To validate the spectrophotometric method, a calibration curve was obtained by plotting the absorbance peaks against standard solutions of potassium canrenoate at different concentrations

(from 25 µg/mL to 1.56 µg/mL), with a good correlation R^2 ≥0.999.

For each storage condition and for both formulations, 1.5 mL samples were analysed at day 0, and days 14, 30 and 60. Before testing, each sample was shaken vigorously for approximately 30 seconds and then was diluted 1:200 for spectrophotometric analysis. The real concentrations were expressed multiplying by the applied dilution factor.

The antimicrobial agents contained in the preparations absorb at a shorter wavelength than potassium canrenoate (256 nm *vs* 293 nm). Therefore, it was necessary to subtract their absorbance at 293 nm to the total absorbance value detected to determine the real concentration of the analyte. Reference samples containing only preserved solution were prepared to determine whether any alterations had occurred during the period established for evaluation of the chemical stability. Reference samples were analysed at the same time as the potassium canrenoate formulations.

Spectrophotometric determinations were performed in triplicate for each time and storage conditions.

Chemical stability was evaluated with respect to the concentration value established as 5 mg/mL. Standard solutions and extemporaneous preparations were considered suitable if the measured values differed by ±15%, the interval defined in the FUI for single solid oral dosage forms.[17] In this study, the authors chose this range as reference criterion since the extemporaneous preparation was obtained by compounding the tablets. In order to have a common approach for the evaluation of the results, the same criterion was used for both preparations.

pH measurements:

As a further chemical stability parameter, pH measurements were carried out on samples at different times between 0 and 60 days for the two different storage conditions (room temperature and refrigerator) to assess any variations in pH values of both formulations.

Microbiological analysis:

Standard and extemporaneous solutions were prepared in bulk and stored in sterile PP microtubes. Microbiological stability studies were performed as indicated by the FUI.[17]

According to section 5.1.4 of the FUI, 'Microbiological quality of pharmaceutical preparations and substances for pharmaceutical non-sterile use', orally used preparations

have to respect these criteria:

1. Total aerobic microbial count (TAMC): maximum acceptable 200 colony-forming units (CFU)/mL;

2. Total combined yeasts and moulds count (TYMC): maximum acceptable 20 CFU/mL.

The samples from both formulations were divided into:

I. two samples analysed at time 0;

II. six samples stored at room temperature (22°–25°C) without light exposure;

III. six samples stored in a refrigerator (2°–8°C) without light exposure;

IV. four samples stored for microbiological validation tests, two samples stored at room temperature (22°–25°C) and two stored in a refrigerator (2°–8°C) without light exposure.

At 14, 30, and 60 days, two samples from each storage condition and of each formulation were analysed to evaluate microbial growth. In addition, for the remaining samples, microbiological examinations, using ATCC strains, were performed at 60 days, to validate the method and materials employed.

Reference samples constituted by preserved water were prepared to verify any chemical and microbiological variations independent on the drug. Storage of the reference samples followed the same procedures as all the other samples. Microbiological checks were performed on reference samples at 0, 14, 30 and 60 days. ATCC strains were used to validate the preparation procedures for the references samples stored up to 60 days.

For the TAMC experiments, TSA was used as culture medium and the dishes were incubated, upside down, in a thermostat at 30°–35°C for 3 days.

For the TYMC experiments, SDA was used as medium culture, and the plates were incubated, upside down, in a thermostat at 20°–25°C for 5 days.

The seeding procedures were performed under a vertical laminar-airflow cabinet with a pour-plate method: 1 mL of the sample, diluted 1:10 in Letheen broth, was added to the dish and between 15 mL and 20 mL of each culture medium (TSA or SDA) were poured. Both culture media were previously maintained in a water-bath at a temperature below 45°C.

Specific ATCC strains were used for the validation of the method and materials: *Staphylococcus aureus* ATCC 6358, *Pseudomonas aeruginosa* ATCC 9027, *Escherichia coli* ATCC 8739 and *Candida albicans* ATCC 10231. The same seeding procedure was followed for all specific microorganisms and for the two culture media, but in this case in addition

to 1 mL of the diluted sample (1:10), 100 µL of the ATCC strain suspension was added before pouring the culture medium onto the plate. Incubation and calculation of the CFU/mL were performed as described previously.

Recovery of microorganisms in the presence of product (standard solution or extemporaneous preparation samples) was set up as described in the FUI and duplicate seeding was carried out through positive and negative controls.

For the positive control, 100 µL of each ATCC strain suspension was mixed with 1 mL of Letheen broth and the two different culture media were poured onto the dishes with the same procedure for seeding and incubation.

A negative control was performed to verify testing conditions using the chosen diluent: 1 mL of Letheen broth and then, culture medium (TSA or SDA 15–20 mL) was poured onto each plate. The incubation period was maintained: 3 days at 30–35°C for TSA and 5 days at 20–25°C for SDA. No growth of microorganisms indicated sterility.

Gravimetric quantification study

The two formulations of potassium canrenoate were compared by gravimetric quantification to determine whether any differences could be detected in weight losses during the NGT administration.

The weight loss was determined by evaluating the difference between the initial preparation weight administered through an enteral syringe directly into the feeding tube, and the final weight collected downstream from the tube in a previously calibrated cylinder.

The experiment was performed in an *in vitro* model using a feeding tube fixed at 45° angle degree to mimic the normal position of a bedridden patient.[20]

In the first evaluation, a standard solution of canrenoate potassium 5 mg/mL was prepared and packed in 10 mL syringes, previously calibrated. The net weight of the solution in the syringe (upstream weight) was determined. The collected amount of solution (downstream weight) after passing through the NGT was weighed and then, weights and volumes were recorded for each measurement.

In another evaluation, following the procedure usually adopted by caregivers, an extemporaneous preparation of canrenoate potassium was obtained by crushing a 100 mg tablet in a mortar and adding 10 mL of distilled water to obtain a suspension. The

dispersion was carefully withdrawn through a previously calibrated syringe, and then the upstream weight was recorded.

Then, the syringe contents were passed into the feeding tube after vigorous shaking and collected downstream in a calibrated cylinder. The volume was weighed and recorded to determine the decrease in weight of the injected solution.

The net weights of the standard solution and of the extemporaneous preparation were recorded and the weight of each syringe after administration was measured to evaluate further weight losses of the injected liquid formulation. All steps were repeated in triplicate for both preparations.

RESULTS

Chemical and microbiological stability studies

Spectrophotometric analysis:

Triplicate UV determinations for each sample were carried out at a wavelength of 293 nm to detect the absorbance value of potassium canrenoate. In addition, the influence of parabens was determined to evaluate the proper concentration of the analyte as explained in the 'Method' section. Spectrophotometric data are shown in figure 1.

The spectrophotometric data obtained from analysis of the standard solution and extemporaneous preparation revealed constant concentration values in the range 5 mg/mL±15% for both conditions and from 0 to 60 days, indicating the stability of potassium canrenoate. The analytical results demonstrated that it is possible to crush potassium canrenoate film-coated tablets to obtain a liquid formulation and then administer it through the feeding tubes. The values obtained with the extemporaneous preparation in comparison with the standard solution validated the equality of this preparation in the quantity of the drug delivered.

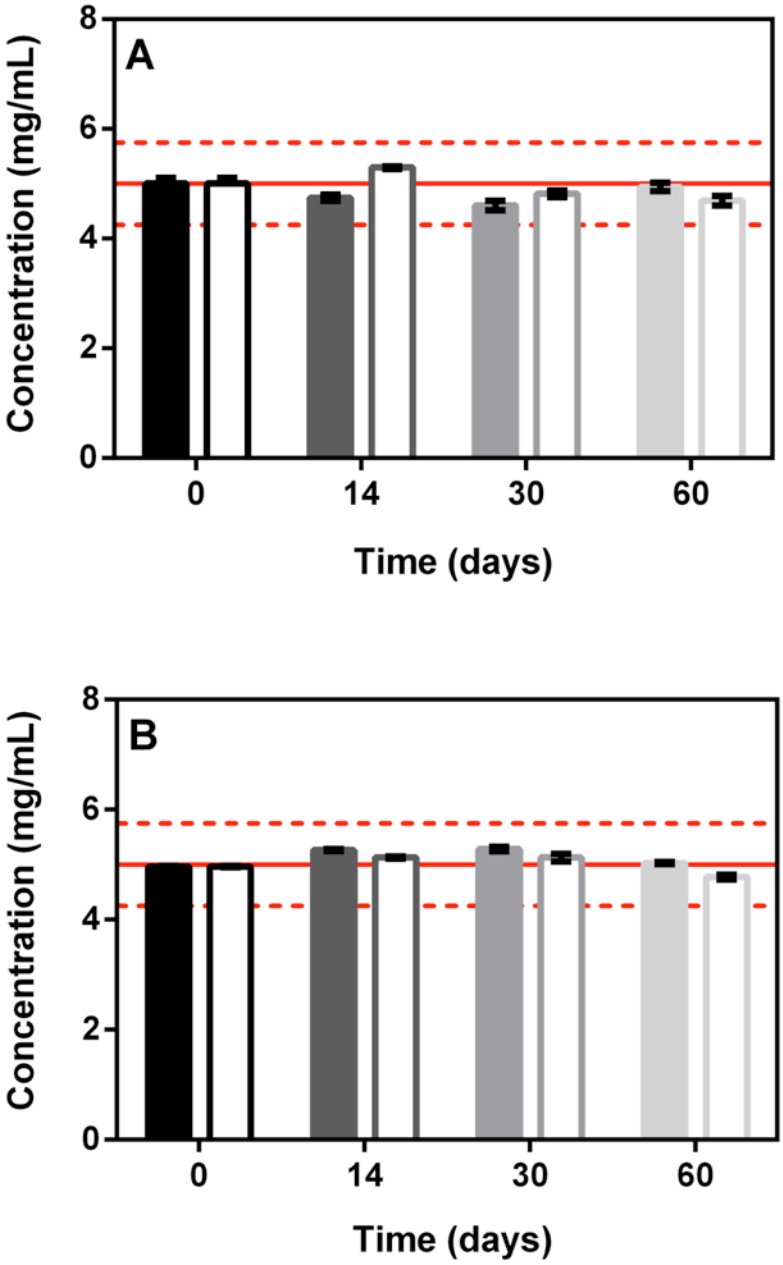

Figure 1: Spectrophotometric determinations in a standard solution (A) and an extemporaneous preparation (B) of potassium canrenoate. Full bars represent samples stored at room temperature (22°–25°C) and empty bars samples stored in refrigerator (2°–8°C). The upper and lower dotted red line levels represent the limits allowed by the Italian Official Pharmacopoeia.

Moreover, the detection of the concentration values of parabens in the reference samples was measured at 256 nm to check for any alterations not related to the analyte. No modifications of the absorbance peak were seen.

pH measurements:

The pH values of potassium canrenoate standard solution and extemporaneous preparation were recorded at the start and after 60 days. The difference was non-significant, indicating acceptable stability of pH values in both storage conditions. The average values determined with a pH meter were 9.6±0.2 and 9.8±0.1 for the standard solution at room temperature and in a refrigerator, respectively. For the extemporaneous preparation, the measurements were 9.2±0.2 and 9.1±0.2 for room temperature and a refrigerator, respectively.

Microbiological analysis:

After the microbiological tests, the TAMC obtained from the standard solution and the extemporaneous preparation of potassium canrenoate demonstrated no microbial growth in both storage conditions. Similarly, the determination of TYMC showed no colonies of fungi or moulds on each dish analysed. Since the analysis was performed on diluted samples (1:10), results may be expressed as <10 CFU/mL (applied dilution factor).

The suitability of the microbiological method was assessed through recovery of microorganisms in the presence of product: the mean value of CFU/plate for each ATCC strain in the presence of product (standard solution or extemporaneous preparation) with respect to the mean value obtained by positive control/plate, ranged between 50% and 200% (factor of 2). The recovery test was calculated according to this formula:

$$\text{Recovery } \% = \frac{\text{Mean value of ATCC strain in presence of product}}{\text{Mean value of ATCC strain in positive control}} * 100$$

This standard had to be observed by each microorganism strain considered, by each batch of product used, and by the reference sample prepared to validate the method applied in this study.

For the negative control, no microbial growth, as determined by the FUI, was detected confirming the sterility of the chosen diluent (Letheen broth) and the used culture media (TSA and SDA).

At the same time, the standard solution and the extemporaneous preparation were microbiologically stable at room temperature and in the refrigerator up to 60 days.

Gravimetric quantifications study

After triplicate administrations of 10 mL standard solution through the NGTs by enteral syringes, the mean±SD weight loss was 7.6±2.1% (table 1). Since the standard solution was a homogeneous system, the decrease in potassium canrenoate in the solution was 3.8±1.1 mg, with respect to the supposed 50 mg delivered in each administration. In table 1, only the main steps are reported. The mean±SD values for the weights of the empty syringe, syringe containing standard solution, net weight of the standard solution and empty graduated cylinder (50 mL) were 8.4±0.0, 18.7±0.0, 10.3±0.0 and 92.6±0.0, respectively.

Table 1: Measured weights relative to the real quantity of the standard solution injected upstream and collected downstream of the NGT

A) Cylinder + downstream standard solution weight (g)			
	Downstream volume (mL)		**Mean ± sd**
Cylinder 1	10		102.0 ± 0.0
Cylinder 2	10		102.6 ± 0.0
Cylinder 3	10		101.6 ± 0.0
B) Downstream standard solution weight (g)			
Solution 1	9.2 ± 0.0		
Solution 2	9.6 ± 0.0		
Solution 3	9.7 ± 0.0		
C) Final weight losses (%)			
	Upstream standard solution net weight (g)	**Downstream standard solution net weight (g)**	**Weight loss (%)**
Solution 1	10.2 ± 0.0	9.2 ± 0.0	**10.0**
Solution 2	10.4 ± 0.0	9.6 ± 0.0	**7.0**
Solution 3	10.4 ± 0.0	9.7 ± 0.0	**5.8**
Mean ± sd			**7.6 ± 2.1**

Administration of the extemporaneous preparation obtained from a single tablet mixed with 10 mL of water was repeated three times. The mean value was calculated and the average weight decrease was 10.7±1.6% (table 2). In table 2, only the main steps are reported. The mean±SD values for the weight of the empty syringe, commercial tablets, syringe plus 10 mL water, syringe containing crushed tablet plus 10 mL water and empty

graduated cylinder (50 mL) were 8.4±0.0, 0.5±0.0, 18.7±0.0, 18.6±0.0 and 92.6±0.0, respectively.

Table 2: Measured weights relative to the real quantity of the extemporaneous preparation injected upstream and collected downstream of the NGT

A) Upstream extemporaneous preparation net weight and weight loss (g)			
Crushed tablet + water 10mL in each syringe (g)		**Weight loss during compounding (%)**	
Dispersion 1	10.4	**5.7**	
Dispersion 2	10.2	**5.3**	
Dispersion 3	10.1	**5.3**	
B) Upstream syringe weight and weight loss in the syringe after administration of extemporaneous preparation (g)			
	Mean ± sd	**Weight loss in syringe (%)**	
Syringe 1	8.5 ± 0.0	**0.5**	
Syringe 2	8.4 ± 0.0	**0.7**	
Syringe 3	8.4 ± 0.0	**0.3**	
C) Cylinder + downstream extemporaneous preparation weight (g)			
	Downstream volume (mL)	**Mean ± sd**	
Cylinder 1	11	103.0	
Cylinder 2	11	101.4	
Cylinder 3	11	102.6	
D) Downstream extemporaneous preparation net weight and weight loss in the tube (g)			
	Extemporaneous preparation upstream weight (g)	**Extemporaneous preparation downstream weight (g)**	**Upstream – Downstream weight loss (%)**
Dispersion 1	10.4	10.1	**2.6**
Dispersion 2	10.2	9.5	**6.1**
Dispersion 3	10.2	9.6	**5.3**
E) Total weight loss (%)			
Weight loss during compounding (%)	**Weight loss in syringe (%)**	**Upstream – Downstream weight loss (%)**	**Total weight loss (%)**
5.7	**0.5**	**2.6**	**8.9**
5.3	**0.7**	**6.1**	**12.1**
5.3	**0.3**	**5.3**	**11.0**
Mean ± sd			
5.5 ± 0.2	**0.5 ± 0.2**	**4.7 ± 1.8**	**10.7 ± 1.6**

The weight decrease might be partially due to excipients used in the original tablet formulation. If the decrease was referred only to potassium canrenoate, the percentage weight loss corresponded to 10.7±1.6 mg with respect to 100 mg—that is, it was within

the range (±15%) established by the FUI for a single solid oral dosage form.

In conclusion, the gravimetric measurements showed a higher weight loss when the drug was administered through nasogastric tubes as an extemporaneous preparation from a single tablet than with a standard solution (10.7% vs 7.6%, respectively). Since potassium canrenoate is a freely water-soluble active ingredient, it should be considered that the weight decrease, observed for the extemporaneous preparation, might have been partially due to the presence of insoluble excipients in the original tablet formulation and may justify the major weight loss of the product collected downstream in the extemporaneous system with respect to the collected standard solution.

DISCUSSION

These results underline the main problem of variability in dosing, when solid oral dosage forms are manipulated immediately before administration. The variability is due to the chemical and physical characteristics of the active compound and excipients, and also to the procedure adopted during the manipulation. This procedure should be standardised and the introduction of intermediate and final checks should ensure the quality and the effectiveness of the final product, as provided by GMP. In addition, the preparation of a bulk solution could reduce the possibility of errors due to compounding.

The manipulation of solid oral dosage forms due to the deficiency of commercially available oral liquid dosage forms remains an on-going problem for patients with deglutition disorders and this study offers an alternative for potassium canrenoate administration through feeding tubes in patients with dysphagia.

CONCLUSIONS

This study showed chemical and microbiological stability of both liquid formulations—the standard solution and the extemporaneous preparation—obtained according to GMP up to 60 days. The outcomes confirm the possibility of compounding potassium canrenoate tablets and thus, offer a liquid formulation that adds to current solid oral dosage forms, already present on the market. The results show stability values in accordance with the FUI target.

To administer potassium canrenoate to dysphagic patients in EN, an extemporaneous preparation of the diuretic molecule made by caregivers is probably the least accurate

method and a standard solution would provide a more accurate dosage.

Evaluation of the weight losses of potassium canrenoate administered via feeding tubes is an investigation that reflects the daily problems faced by caregivers in hospital wards, where an increasing number of patients have been diagnosed with dysphagia. On the one hand, the use of a standard as the raw material assures a higher accuracy than compounding tablets for weight loss of the active molecule when a patient undergoes EN. On the other hand, manipulation of potassium canrenoate tablets allows us to obtain an alternative liquid form that guarantees correct diuretic treatment.

WHAT THIS PAPER ADDS

What is already known about this subject?

- Difficulties exist in the administration of solid oral drug therapy to patients with swallowing inability.
- Compounding of solid oral dosage forms by crushing tablets or opening capsules and mixing with a liquid vehicle is routine in hospitals or care settings.
- Liquid forms have to be prepared for patients using enteral feeding tubes.

What this study adds?

- Investigation of the diuretic drug, potassium canrenoate, showed that it is possible to compound the commercial tablets used in this study in a chemically and microbiologically stable liquid form for up to 60 days.
- When the liquid form was administered via feeding tube, weight loss of drug occurred, but the amount of the delivered diuretic conformed to the specific requirements established in the Italian Pharmacopoeia.
- Comparison of the use of the drug raw material or tablets provides an opportunity to focus on the importance of compounding procedures.

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3.2. Hydrogels

3.2.1. OPTIMIZATION OF A GELIFIED FORM OF PRAVASTATIN SODIUM

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ABSTRACT

The present work aimed to perfect an efficient method to optimize compounding process of commercial tablets of water-soluble active molecules in a semisolid preparation (e.g., hydrogel) for an oral administration, to favourite and help deglutition in patients who develop swallowing inability during their life.

Dysphagia causes are several and it may occur in geriatric or in paediatric patients. Age may be mainly involved in the dysphagia onset, and therefore, this gel formulation could be more exploitable by elderly. At the same time, children could benefit from this new hydrogel.

In order to obtain the gelified formulation, a screening on different polymers used as thickener agents was carried out. Rheological properties, kinetic release profiles, and easiness to assume gel through a teaspoon were investigated.

The objective was to obtain a gelified product having a suitable consistency, so that dysphagic people were able to swallow without choking or pulmonary aspiration risks.

The protocol of this study may be applied to immediate-release tablets containing water-soluble molecule, but this study was performed choosing tablets of pravastatin sodium as model. These solid forms were added to a gelified vehicle described in this work. A wide prescription of pravastatin among elderly people and the availability on the Italian pharmaceutical market just as immediate-release tablet justified the interest in this drug as model to develop this work.

Hydrogels may be packed in a single-dose blister or stickpack, and the switch from tablet to gel may be managed by patient, easily.

Studies on chemical, and rheological stability of hydrogel were performed to present a ready-to-use product for dysphagic patients.

Therefore, the gelified preparation offers an effective dosage form when patients, because of their needs, have to change pharmaceutical formulation.

BACKGROUND ART

Patients having difficulty in swallowing process are not able to assume solid oral dosage forms (SODFs) such as tablets or capsules. Deglutition is a complex function involving several muscles of mouth, throat and oesophagus, which are controlled by several cortical areas and swallowing centre in the brainstem.[1] The brain communicates with the muscles through several cranial nerves. Swallowing requires a high coordination with breathing and the failure of these synchronized movements, results in choking or in pulmonary aspiration of alimentary bolus into the airways.

Therefore, whereas on the market there are not alternative pharmaceutical forms for a specific active pharmaceutical ingredient (API), healthcare providers have to face and solve problems about the manipulation firstly and, secondly, the administration of drug therapy. Currently, swallowing difficulties are a very frequent and common issue among paediatric[2] and geriatric patients.[3,4] In addition, solid forms are by far the most common dosage forms but not the most eligible for children, elderly, bedridden, tube feeding holders and unconscious patients.[5,6] Proper alternative forms may be semisolid preparations, such as gels, because they have a right consistency to facilitate swallowing in this target population.

As product-reference, a commercial-gelified water (Resource®) was considered in order to obtain a final gelled formulation with similar characteristics in terms of rheological properties. Just for this reason, daily, when there are not available alternative dosage forms, healthcare providers (e.g., nurses or caregivers) are obliged to manipulate original tablets or capsules, crushing or opening them to obtain powders.[7,8] Then, the resulting powders are mixed with food or beverages or gelified commercial water to prepare an extemporaneous product easy to administer to patient and assure compliance.[9]

This practice might be unsafe either for patients or for healthcare workers. In particular, patients risk assuming an improper drug dosage and, consequently, a greater or a lower drug amount intake. In addition to this possible altered efficacy, other issues may occur after crushing or opening original form such as the instability of the active molecule, a lowering of palatability, a loss of invaluable quantity of drug. On the other side, during the manipulation, nurses may inhale powders resulting from crushing or opening. Moreover, cross-contamination issues may verify using the same devices (i.e., mortar or tablet

cutter) to manipulate original dosage forms also in case of different drug therapy. Besides, medication mistakes may occur between nearby bedridden patients.[10]

The manipulation and administration responsibility is on the prescriber (medical doctor) firstly, and then, on the person who administers compounded drug when a solid oral dosage form is delivered through different route or formulation with respect to those authorized by the manufacturing company.

The investigation is aimed to obviate these described difficulties to guarantee suitable alternative pharmaceutical formulations for patients who are unable to swallow.

Other peculiar characteristic of this study was the use of commercial and immediate-release tablet of water-soluble drug to make easy the switch between the tablets to the gelified form in several settings (i.e., hospitals, nursing home, long-term care facilities).

DISCLOSURE OF THE INVESTIGATION

A new, suitable and stable gelified formulation was studied to guarantee and assure the possibility to continue drug therapy even though patient developed swallowing inability. The attention was focused on the development of a stable hydrogel containing water-soluble drug as API.

The study was carried out choosing Pravastatin sodium as model drug that is a hydrophilic molecule, an HMG-CoA reductase inhibitor, and an API belonging to the family generically called statin-series compounds. It is used to treat hyperlipemia or hypercholesterolemia, over several months to several years, or even longer times and is often prescribed to a bedridden patient, a patient with dysphagia, or a tube-feeding patient. In these conditions, the availability of a gel preparation having appropriate features such as viscoelasticity should permit to make easy, safe, and painless the swallowing, and should avoid clogging the throat and reflex vomiting.

Hydrogels have to replace the widespread drug therapy carried out with SODFs, therefore, the formulated gel has to have a drug kinetic release comparable to that of commercial immediate-release tablet. About that, a final gelified formulation was performed after a careful evaluation of several thickener polymers. The polymer selection was made according to rheological and drug kinetic release properties of the gelified system, and was based on easiness of gel administration through a teaspoon.

Actually, no complete disclosure of the investigated polymers was revealed due to the current submission of all data for the release of an Italian patent. For this reason, the name of the all jellifying agents will be replaced with a generic label (i.e., polymer A, polymer B, C1, C2, C3, D1, D2, D3, E, F, G, H, I).

Several thickener agents were tested to achieve a final gelled medical product and, in particular:

- Polymer A
- Polymer B
- Polymer C at different grades (C1, C2, C3, C4, C5)
- Polymer D at different grades (D1, D2, D3)
- Polymer E
- Polymer F
- Polymer G
- Polymer H
- Polymer I

POLYMER SCREENING

The study was firstly focused on which polymer created a semi-solid structural network more comparable to gelified-commercial reference just after a visual examination of the different systems. At the beginning, all polymers were used at the same percentage 1.25% w/w. Distilled water was always used as diluent for the preparation of each vehicle-gel and polymers were gradually added in water. The systems were maintained under constant stirring during the preparation to facilitate polymer dispersion. Gels were prepared at room temperature (22°-25°C) for all selected polymers except to polymer G that generally required a working temperature higher than room temperature to facilitate the polymer dispersion and solvation in water. The products were kept at least 24 hours at room temperature for polymer hydration before any test.

The prepared vehicles were investigated according to three aspects:

1. Easiness to administer gel through a teaspoon (later test called Administrability): gels were brought to trial to 25 anonymous evaluators to judge them (Figure 1).

The evaluators had to express an opinion according to a pre-established score and a visual examination of the appearance: score 0-3 for liquid systems, score 4-6 for viscous liquid products, and score 7-10 for gel systems. Consequently, mark 0 was equivalent to an extreme difficulty to administer system through a teaspoon; instead, mark 10 was equivalent to an excellent formulation easy to deliver by teaspoon to patients with swallowing difficulties.

Evaluator	Administration easiness through teaspoon			
	Liquid (like-water) from 0 to 3	Viscous liquid from 4 to 6	Gel from 7 to 10	NOTE
Formulation A				
Formulation B				
Formulation C				
Formulation D				
Formulation E				

Figure 1: Table extract submitted to the evaluators.

2. Rheological evaluation: rheological tests of oscillation stress sweep were performed on the prepared vehicle-gels by rotational rheometer (Stresstech®, Reologica Instruments) using cone/plate geometry 4/40 at 25°C over the range of stress 0-20 Pa and at 1 Hz constant frequency. In particular, through oscillation stress sweep test, elastic modulus (G') and viscous modulus (G'') were evaluated to know the viscoelastic properties of gels, increasing applied stress.

   The target gel in terms of viscoelastic behaviour was Resource® (Figures 2-3-4) that was compared with vehicle-gels based on different polymers A, B, C1, C2, C3, C4, C5, D1, D2, D3, E, F, H, I. The reference commercial gelled product, Resource®, demonstrated a linear viscoelastic region (LVR) over the all applied stress indicating a non-dependence of the moduli on the applied stress. Over the LVR the material structure was not broken. It behaved as solid-like system over the range of applied stress (0-20 Pa) maintaining constant moduli up to 20 Pa. Resource® exhibited an elastic modulus G' of 64.52 ± 1.76 Pa and a viscous modulus of 21.59 ± 0.13 Pa.

Moreover, all data reported in the graphs derived from triplicate measurements and mean values and standard deviations (SDs) were determined everytime. Actually, SDs were not reported in the graphs just to simply the understanding of the rheological trends in the figures.

Firstly, just polymers that required ambient temperature (22°-25°C) as preparation conditions were considered for the preparation of gelled systems. Afterwards, polymer G was added to the screening.

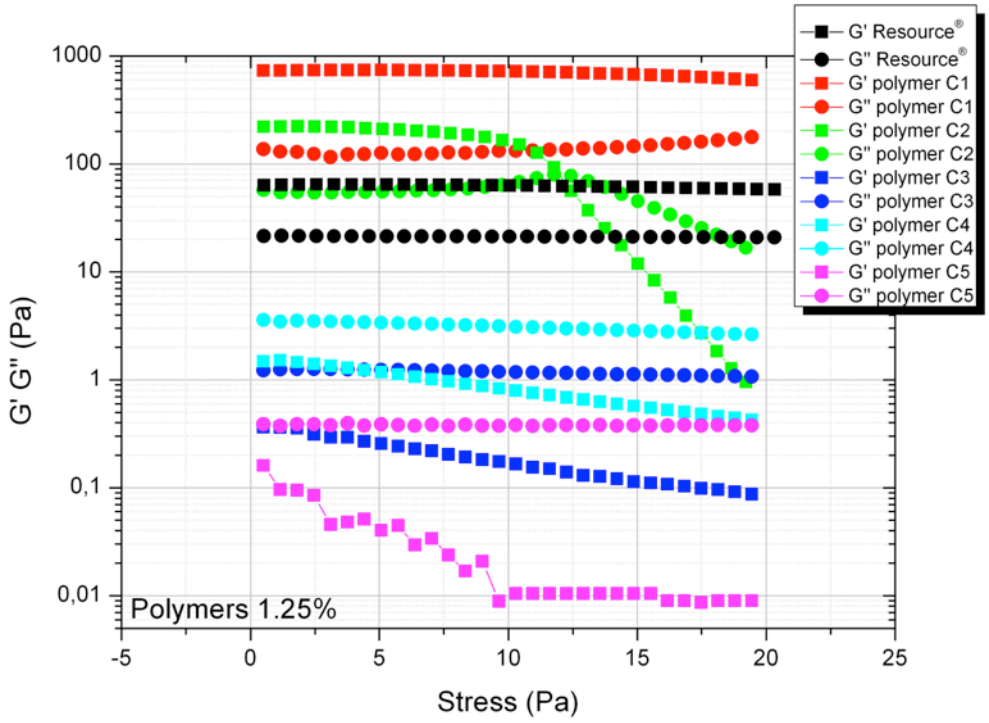

Figure 2: Resource® vs vehicle-gels composed by polymers C1, C2, C3, C4, C5 dispersed in water – oscillation stress sweep test at 25°C.

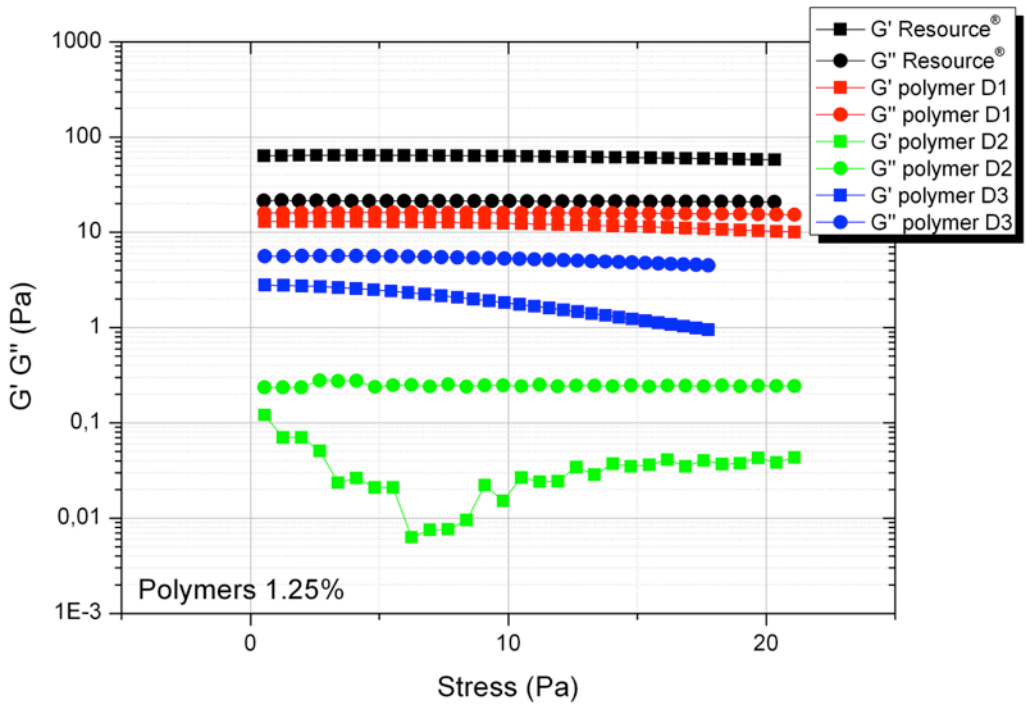

Figure 3: Resource® vs vehicle-gels composed by polymers D1, D2, D3 dispersed in water – oscillation stress sweep test at 25°C.

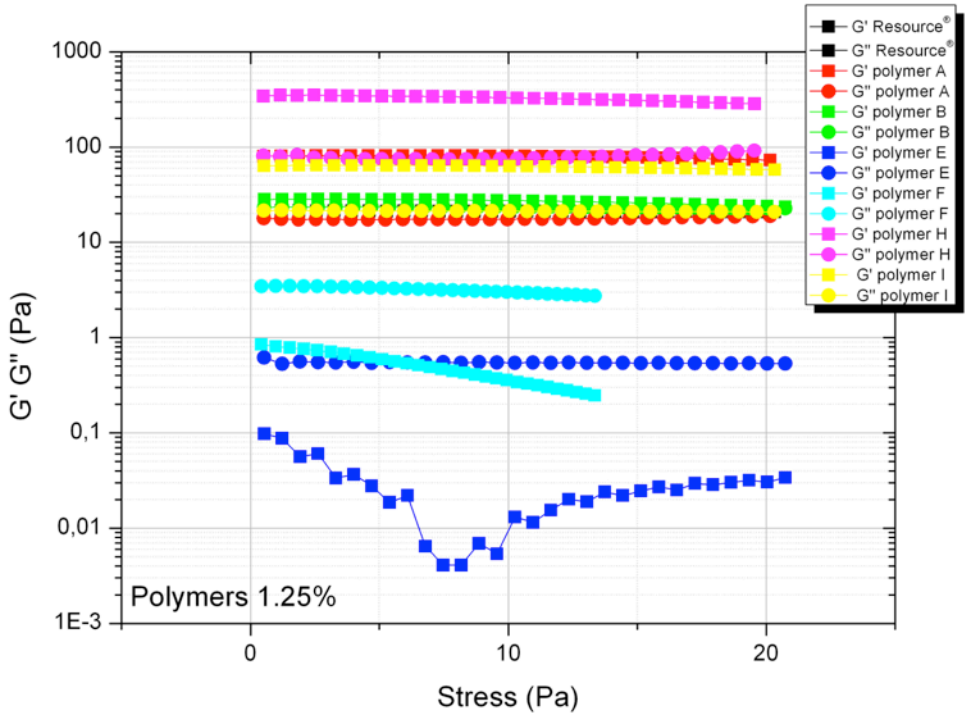

Figure 4: Resource® vs vehicle-gels composed by polymers A, B, E, F, H, I dispersed in water – oscillation stress sweep test at 25°C.

3. Dispersion time (DT) evaluation: dispersion time of each polymeric gelified vehicle or, more accurately, gelled polymer erosion in an aqueous medium was evaluated to select which polymer gave a complete dispersion in order to mimic disintegration time of an immediate-release tablet. Erosion times were registered and used as comparison parameter with respect to erosion time of Resource® (Table 1).

Table 1: Dispersion-erosion time (minutes, min) of each polymer in an aqueous medium.

Polymers 1.25%	Dispersion time (min)
Resource®	30
Polymer C1	10
Polymer C2	15
Polymer C3	2
Polymer C4	2
Polymer C5	2
Polymer D1	20
Polymer D2	2
Polymer D3	2
Polymer B	25
Polymer A	360
Polymer F	2
Polymer E	2
Polymer H	25
Polymer I	70

According to Italian Pharmacopeia XII edition section 2.9.1 'Tablets and capsules disaggregation' section, disaggregation time for an immediate-release tablet is within 15 minutes.[11]

From these first assessments, the obtained results underlined that after the comparison among all vehicle-gels (Figure 5), administrability, elastic modulus G', and dispersion time DT revealed that the best polymers were B, C1, C2, and D1 (Figure 6). The investigation on the other polymers was abandoned because of the unsatisfactory results.

About polymer C2, comparison was acceptable up to applied stress of 10 Pa. At higher stress values, the structure of the system was broken and no longer appropriate polymer.

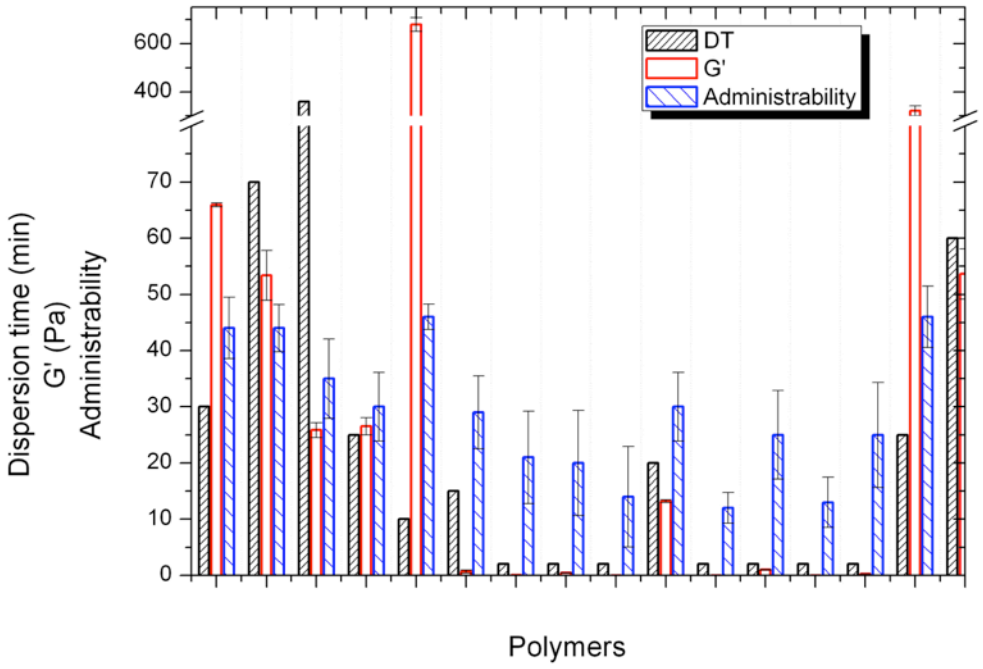

Figure 5: DT, G', administrability comparisons among considered vehicle-gels.

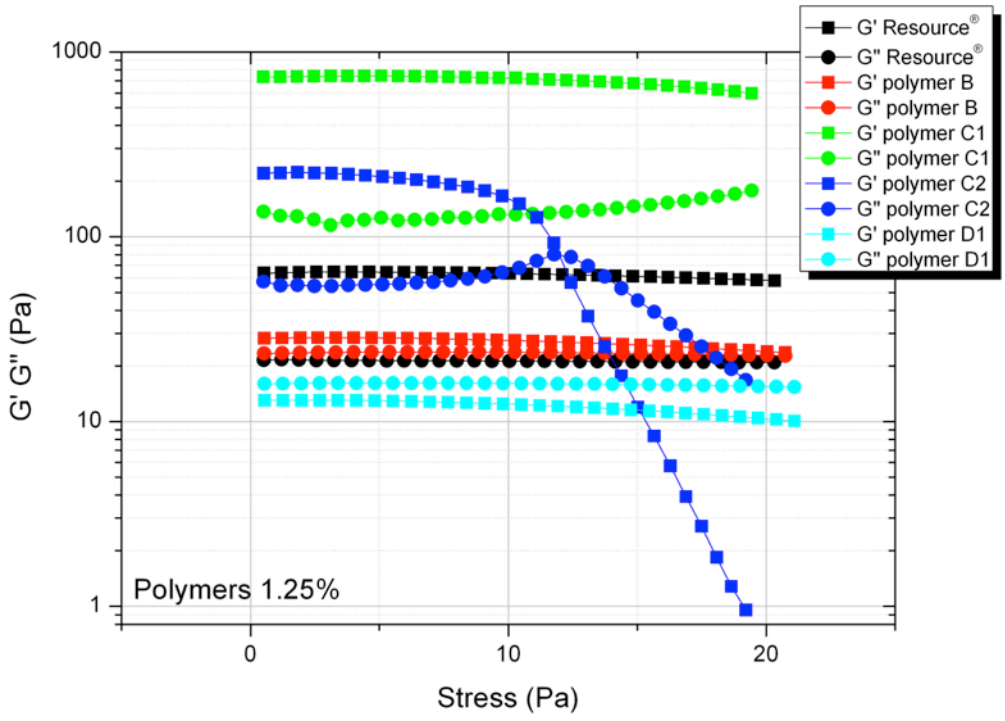

Figure 6: Selected polymers (B, C1, C2, D1) vs Resource® compared by oscillation stress sweep test.

SELECTION OF FOUR POLYMERS

Therefore, for the development of a proper gelified system with desirable characteristics and intended for dysphagic people, a selection of four polymers at the concentration of 1.25% w/w was done. Afterwards, a tuning of a complete gelified formulation was arranged by adding other components. Step by step development of the pharmaceutical formulation required the addition of an active molecule and specifically, as water-soluble drug, pravastatin sodium was considered for the mentioned reasons. Literature reported that pravastatin sodium is stable in a specific pH range: 7-10.[12]

Considering that in the preliminary phases of the work water was used as solvent to dissolve polymers, pH values were checked. pH readings were repeated for the four selected polymeric dispersions to assure a 7-10 pH range in the gelled vehicle suitable for the chosen drug. Then, pH measurements were repeated in the final formulations to ensure appropriate pH conditions in the gels. Moreover, pH levels of 11 or higher may cause adverse reactions such as stomatitis; instead, on the other side, acid pH values may provoke damage to oro-oesophageal mucosae.

Therefore, in this formulation, assuring final pH in the desired gap was fundamental to get optimal oral drug delivery system.

All four pH values were measured and resulted in the required range with the exception of the vehicle formed by the polymer B that, anyway, in the complete final formulation (with dissolved tablets, preservatives, flavouring and sweetener agents) gave a required final pH.

pH values were controlled in order to verify the possibility to use water instead of other diluents as solvents. Therefore, verified last pH results, it was possible to use water as diluent and not a basic diluent in order to simplify the formulation and to ensure a suitable gelified vehicle for pravastatin sodium drug (Table 2).

Table 2: pH values measured in gelified-vehicles.

Polymer concentration 1.25% w/w	pH values
Resource®	7.00
Polymer C1	7.72
Polymer C2	7.61
Polymer D1	7.10
Polymer B	6.41

SELECTION OF SWEETENER AND FLAVOURING AGENTS TO FORMULATE A PALATABLE GEL

To develop a palatable hydrogel for an oral administration, several sweetener agents were evaluated: saccharine, fructose, sorbitol, mannitol, and xylitol. Sucrose shows reference sweetness of 1.

- Saccharine (sweetness 500) was rejected because of a possible incompatibility with iron oxide (excipient present in the tablets used in this study of reformulation). In fact, after 12 hours from the moment of preparation iron oxide precipitation occurred in the system while, in the other cases (other sweeteners) the downfall of components did not verify. Moreover, saccharine is poorly soluble in cold or hot water.
- Fructose (sweetness 1.3-1.7) was a possible sugar. Fructose may be used in paediatric and diabetic population.
- Sorbitol (sweetness 0.6) was a possible sugar. Sorbitol may be used in paediatric and diabetic population.
- Mannitol (sweetness 0.5).
- Xylitol (sweetness 1).

About flavouring agents, the considered components were chosen for masking bitter taste of the active compound. The options were:

- Cherry flavour (liquid form).
- Mandarin-vanilla flavour (powder form).
- Banana flavour (powder form).
- Vanilla flavour (powder form).

Blends of sweetener/flavouring agents in water were prepared in different percentages to evaluate which composition was better of another to give a good palatability in the final oral hydrogel.

The selected sweetener/flavouring blend was sorbitol/mandarin-vanilla, and it was chosen after a panel-test performed during the study. Sorbitol was approved up to 33% for oral administration[13] according to United States Food and Drug Administrations (U.S. FDA).

OPTIMIZATION OF THE FINAL HYDROGEL FORMULATION

A gradual development of the hydrogels was performed.

Gel obtained using polymer C1, liquid or powder flavouring and sweetener agents gave syneresis although different preparations methods were essayed to verify if different methodologies may affect the final product properties. Therefore, this polymer was rejected. Moreover, even though 1.25% w/w was not the correct amount for this polymer, increasing its percentage until 2%, rheological tests did not give comparable properties to reference-gel (rheological data were not reported here). For this reason, dissolution test on this hydrogel was not performed.

Gel obtained using polymer C2 was rejected because even increasing percentage of thickener agent until 2%, the final consistency of hydrogel was not suitable to swallow in dysphagic patients. Rheological tests (not reported here) confirmed the unsuitable product characteristics. Dissolution test on this gel did not perform.

Therefore, two polymers could be still investigated: polymers B and D1.

RHEOLOGICAL CHARACTERIZATION (OSCILLATION STRESS SWEEP TEST)

The rheological investigation was performed on vehicle-gels obtained at different percentages of the chosen polymers B and D1 (1.25%, 1.5%, 1.75% w/w). The evaluations on different percentages offered a wider range of gelled systems to be compared with the commercial gelified water, Resource®.

First of all, some parameters were checked:

- pH values were between 7-10, even increasing polymers percentage (from 1.25% to 1.75%) and using water as diluent.
- Oscillation stress sweep test was carried out at 25°C, 1 Hz constant frequency and an applied stress 0-20 Pa.

Both polymers gave rheological properties depending on the percentage of used polymer. Elastic modulus G' showed a good structural network in the analysed stress range (0-20 Pa) increasing proportionally with respect to growing polymers percentages. From rheological point of view, results about polymer B and D1 systems demonstrated a solid-like behaviour either for B-based systems or for D1-based systems regardless of the percentage of thickener agent employed. Closer percentages to obtain a hydrogel

comparable to the Resource® structure were 1.5% for polymer B (Figure 7) and 1.5% or 1.75% for gelled agent D1 (Figure 8). Currently, both moduli G' and G'' were reported in the following graphs for a complete description of the developed gelified systems. Afterwards, just elastic moduli will be plotted to simplify the graphs. For both systems, gelified forms at 1.25% of polymer were rejected.

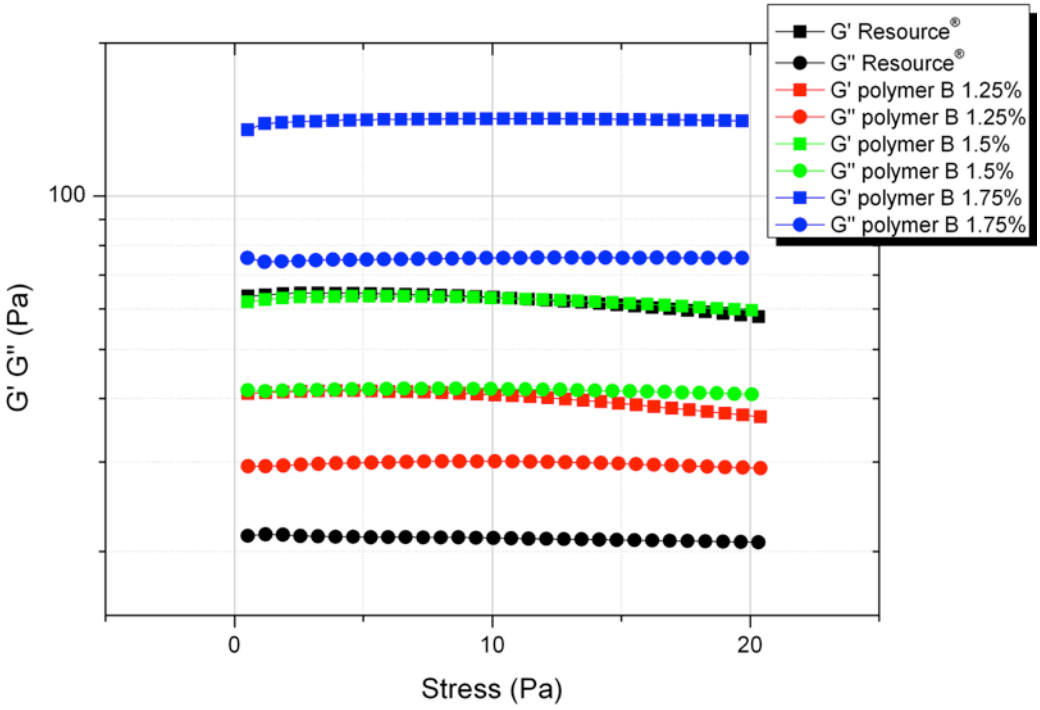

Figure 7: Resource® vs polymer B based vehicle-gels at different concentrations 1.25%-1.5%-1.75% w/w - oscillation stress sweep test 25°C.

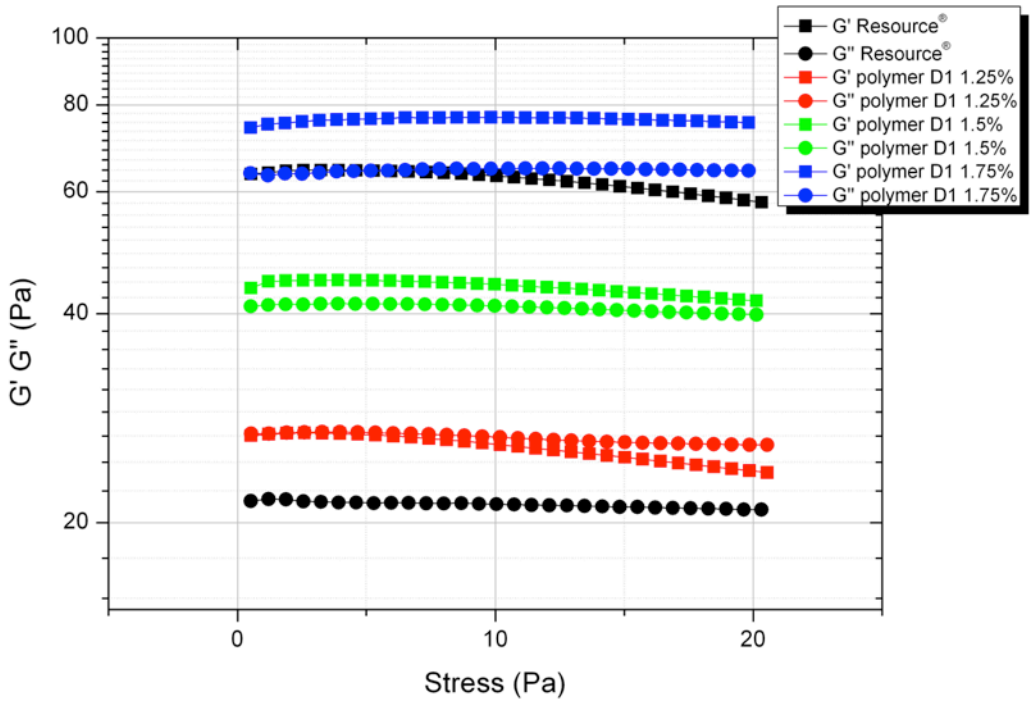

Figure 8: Resource® vs polymer D1 based vehicle-gels at different concentrations 1.25%-1.5%-1.75% w/w - oscillation stress sweep test at 25°C.

DISSOLUTION TESTS

In order to verify the effective use of these two polymers B at 1.5% w/w and D1 at 1.5% and 1.75% w/w, it was necessary to load active compound into the vehicles. As above mentioned, pravastatin sodium tablets were dissolved in the water-based vehicle-gels, and then dissolution tests were performed on hydrogels prepared at different percentages (1.5%, 1.75%).

Studies about pravastatin sodium dissolution tests for hydrogels were performed adapting parameters established by U.S. FDA for pravastatin sodium immediate-release tablets[14]: water as dissolution medium, 900ml as dissolution medium volume, dissolution temperature 37°C, apparatus II (paddle) at 50 rpm specific rate.

Dissolver instrument (Sotax) was coupled with an UV-Vis spectrophotometer (Shimadzu UV-1800, software UV-Probe 2.43) and triplicate analysis were performed (samples were withdrawn from three different vessels, simultaneously). In order to validate spectrophotometer method, a calibration curve of pravastatin sodium, analytical

standard powder, was plotted. A stock solution was prepared in water (22.5 μg/ml) and diluted solutions at various concentrations were also set up. Calibration curve presented a good linearity with a correlation coefficient of 0.9994 (Figure 9).

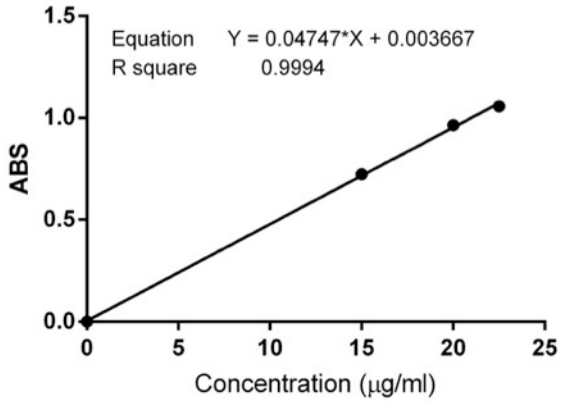

Figure 9: Pravastatin sodium calibration curve.

Withdrawn samples from each vessel were analytically quantified at established times (0-5-15-30-60-90-120-180-240-300-360 minutes) through UV measurements at fixed wavelength 238nm (maximum absorption peak for pravastatin sodium). All obtained kinetic profiles about different gelified polymeric dispersions loaded with pravastatin sodium, were compared with kinetic profile of commercial tablet of pravastatin to elect the proper polymer useful to prepare a right gel able to substitute tablet.

These dissolution parameters and conditions were respected for all dissolution tests carried out during the development of the new hydrogel tuned to replace the tablet.

The work dealt with another aspect regarding the loading method of hydrogels inside the vessel of the dissolver instrument. Each single-dose of hydrogel was thrown into the vessel through a common syringe. It was cut on the top removing the beak where the needle is generally inserted: pushing the plunger, the gel fell into the vessel without undergoing structural modifications and consistency. Then, once in the vessel, hydrogel surface was completely in contact with the water (Figures 10-11-12).

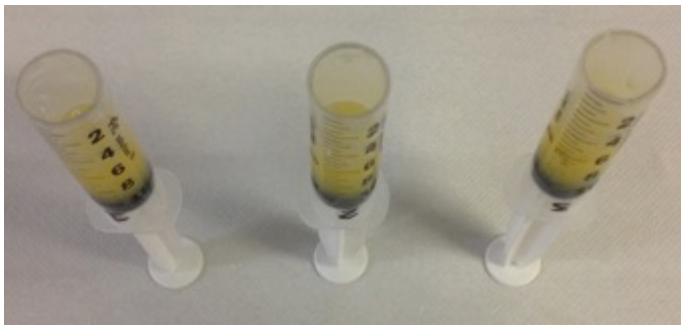

Figure 10: Modified syringes loaded with single-dose hydrogel.

Figure 11: Loading method of hydrogel into the vessel.

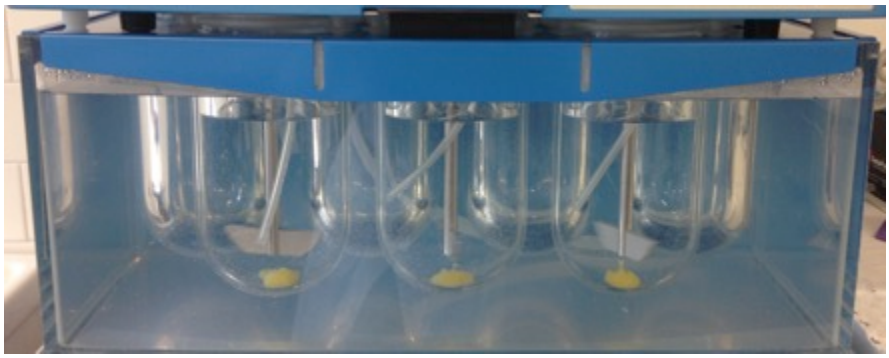

Figure 12: Dissolution test with apparatus II.

Carrying out dissolution test was important to understand which percentage of polymer in the hydrogel showed kinetic release profile more comparable to that of immediate-release tablets to assure the same quantity of active compound delivered in the patient after oral administration of tablet or hydrogel.

Results about dissolution tests performed on pravastatin-loaded hydrogels showed that polymer D1-based gel (only 1.5% w/w) was quicker than polymer B-based system (1.5%) as dissolution time and, dissolution rate was directly proportional to polymer percentage in the formulated hydrogel. The best hydrogel may seem the polymer D1-based hydrogel (Figure 13). Instead, results about dissolution test on polymer D1-based gel at 1.75% w/w were not reported because a slower release profile was obtained.

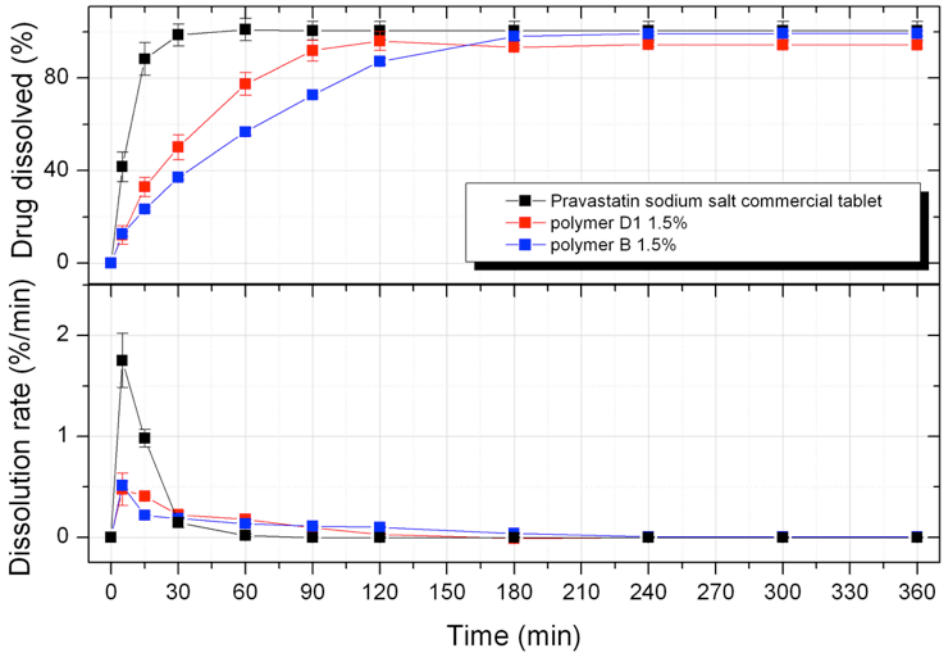

Figure 13: Pravastatin sodium commercial tablet vs polymer B and D1-based hydrogels kinetic release profile.

HYDROGEL PREPARATION METHODS

Polymer D1 required long time to achieve an optimal polymer solvation and therefore, this thickener agent will not be considered the optimal agent. Although quite acceptable kinetic profile, hydrogel based on polymer D1 was rejected due to the possible large quantity to be produced to satisfy the requirements of a clinical pharmacy either for patients admitted in the hospital (inpatients) or for people in nursing home (outpatients).

On the other side, polymer B-base gel showed preparation times faster than polymer D1, but drug kinetic release profile was not comparable to that of the immediate-release tablet taken as reference. Release prolife showed slower than reference tablet.

Therefore, since unsatisfactory results obtained after gel formulation containing pravastatin sodium tablets and polymers B or D1, another polymer was assessed and investigated: polymer G.

Up to date, all vehicles and specifically vehicle-gels containing polymers B and D1 were prepared at room temperature. Instead, polymer G thickener agent required higher temperature with respect to room temperature, so hot plate stirrer was necessary to prepare such a new-gelled system. This different preparation method favoured polymer solvation process, and then, hydrogel was gradually obtained while the system cooled down.

OPTIMIZATION OF POLYMER G-HYDROGEL FORMULATION

Three different percentages of polymer G were selected 3%, 3.5% and 4% w/w, and on these prepared vehicles rheological studies were carried out.

Preliminary investigations were done through oscillation stress sweep test to measure linear viscoelastic moduli between 0-20 Pa at constant ambient temperature 25°C and frequency 1 Hz. Tests were performed using rotational rheometer with a cone/plate geometry 4/40. Measurements were carried out with the aim to evaluate rheological behaviour of the systems and to distinguish among gelified products obtained with different percentages of polymer G.

First of all, products showed elastic modulus values (G') lower than viscous modulus values (G'') in the range of applied stress. Thus, results demonstrated a liquid-viscous rheological trend and polymer G dissolved in water gave a 'weak gel' at all three

employed percentages, especially when compared with the structure of Resource® (Figure 14).

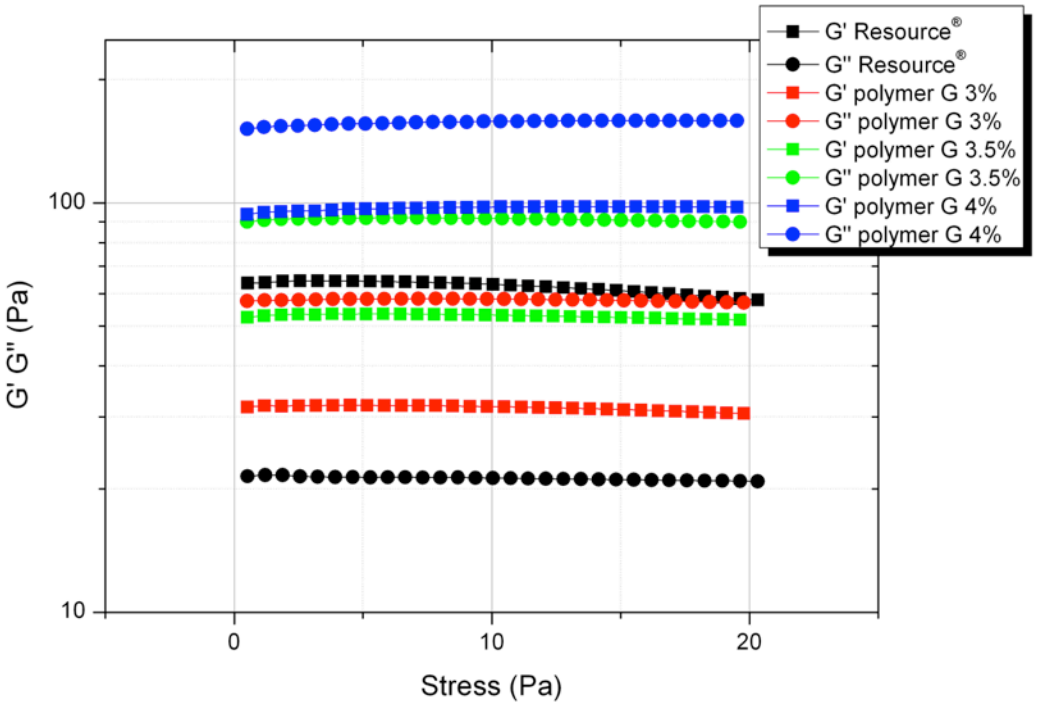

Figure 14: Oscillation stress sweep of polymers G systems at 3%, 3.5%, 4% w/w.

Anyway, despite liquid-viscous performance with respect to solid-gel properties of Resource®, vehicles (preferably 3.5% and 4% of polymer) presented a suitable consistency to encounter the needs of swallowing in dysphagic people.

Therefore, theoretically, the mentioned formulations should be defined liquid-viscous systems, merely, but actually, the terms gel or hydrogel will be named to argue the developed pharmaceutical formula.

However, just comparing G' values, the most suitable and close percentage of polymer G to Resource® gel properties to simulate viscoelastic characteristics was 3.5% w/w (Figure 15). In fact, polymer G based system at 3%, 3.5% and 4% showed G' values (referred to time 0) of 31.58 ± 0.46 Pa, 49.39 ± 0.50 Pa, 92.98 ± 0.77 Pa, respectively. Resource® G' value was 64.52 ± 1.76 Pa.

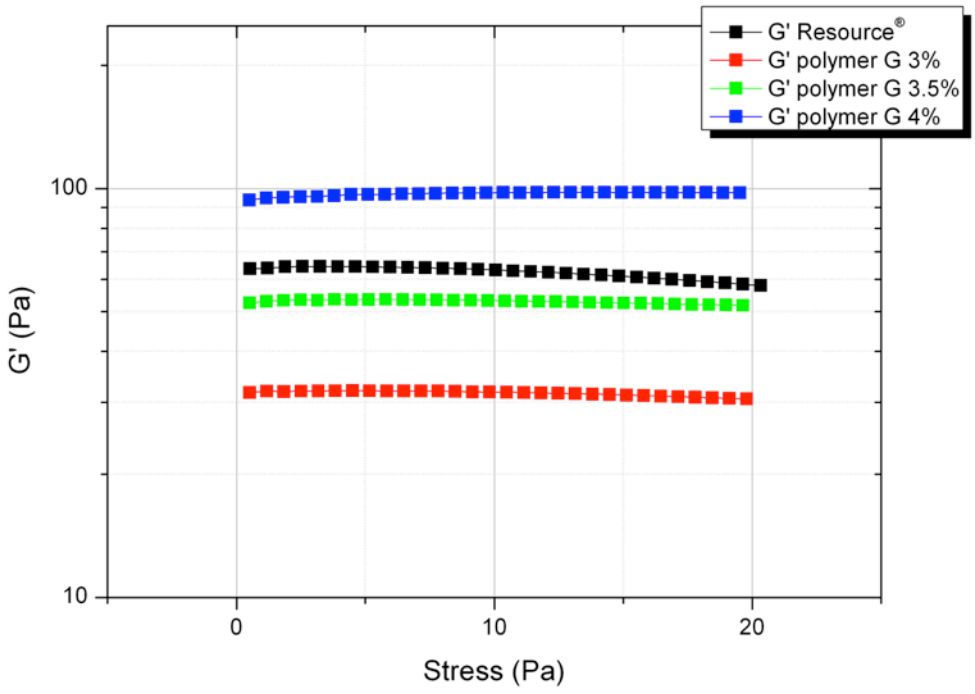

Figure 15: Hydrogels containing polymer G at three different percentages 3%-3.5%-4% - oscillation stress sweep test at 25°C.

Moreover, studies about pravastatin sodium dissolution from hydrogels were performed respecting parameters established for pravastatin sodium tablets by U.S. FDA (dissolution medium water, dissolution medium volume 900ml, dissolution temperature 37°C, apparatus II paddle, rate 50 rpm). Dissolution test results gave better outcomes for the hydrogel containing polymer G 3% demonstrating closer drug release with respect to commercial tablet profile. On the other side, its not fully satisfying rheological characteristics had decreed the choice on the polymer G-based hydrogel at the concentration 3.5% (Figure 16). This percentage respected the established purpose: facilitating and improving deglutition of dysphagic patients reaching a desirable consistency and texture of the product. In fact, a visual examination about consistency of hydrogel 3%, confirmed a poor eligibility of this system seen the targeted-patients to whom gel was intended. On the contrary, even though hydrogel 4% presented a compliant consistency, it showed too slow drug release profile.

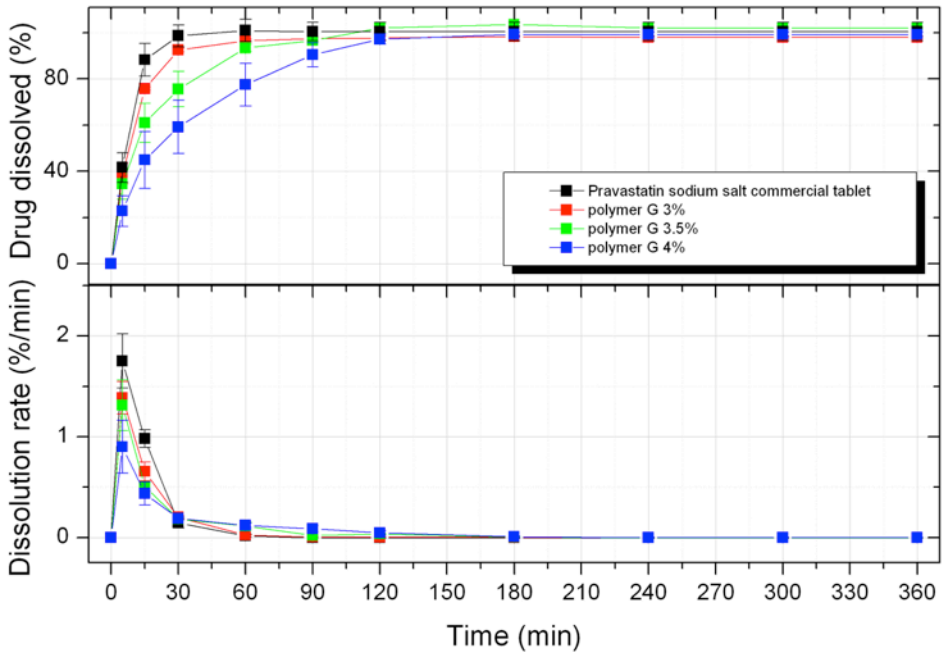

Figure 16: Drug kinetic release profiles on hydrogels based on polymer G 3%-3.5%-4% - comparison among commercial tablet (reference) and hydrogels.

Therefore, combining both results (rheological and kinetic), the ideal hydrogel suitable for dysphagic patients to respond their reduced swallowing ability, was made up by polymer G 3.5% as thickener agent, pravastatin sodium as dissolved tablets in the medium, parabens as preservative agents, mandarin-vanilla powder form as flavouring agent, sorbitol as sweetener agent, and water as diluent.

The aim of the screening was to obtain a hydrogel showing a kinetic release profile of the API from pharmaceutical gelified form more similar to that of commercial tablet because the patient have to receive the same dosage in the same time even modifying the administered dosage form.

Replacing pravastatin tablets with this new gelified formulation, it would be possible to guarantee drug therapy in patients who have developed deglutition inability during their life.

Studies were continued on assessment about the production process reproducibility of hydrogel. Results were reported on figures below (Figures 17-18).

Three batches of the studied formulation were produced. Rheological tests and dissolution proves were repeated to reproducibility evaluation. According to viscoelastic tests, three compared batches showed stable and rather overlapped elastic moduli, G', in the increasing stress range (Figure 17).

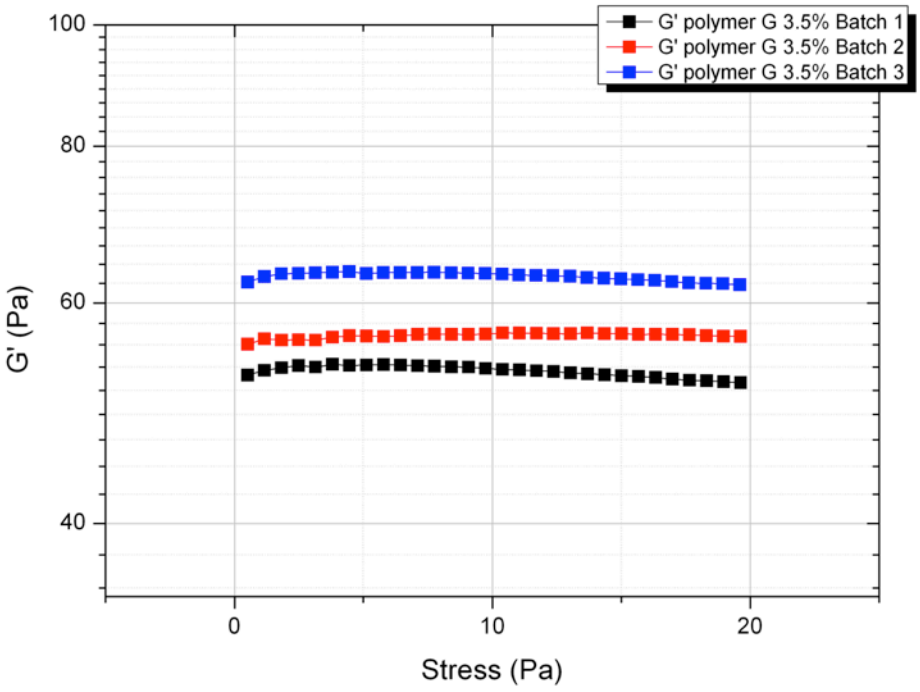

Figure 17: Rheological comparison on different batches of the hydrogel - oscillation stress sweep test.

Instead, observing dissolution results, three batches showed some differences in kinetic profiles that were not significant in order to dissolve pravastatin sodium, completely. In fact, in a reasonable time, each single dose of the drug was dissolved from gelled preparation to dissolution medium (Figure 18). Even though greater differences in release profile were appreciable up to 90 minutes, more than 95% (95.81% ± 5.42%) of the drug dissolved in water within 120 minutes.

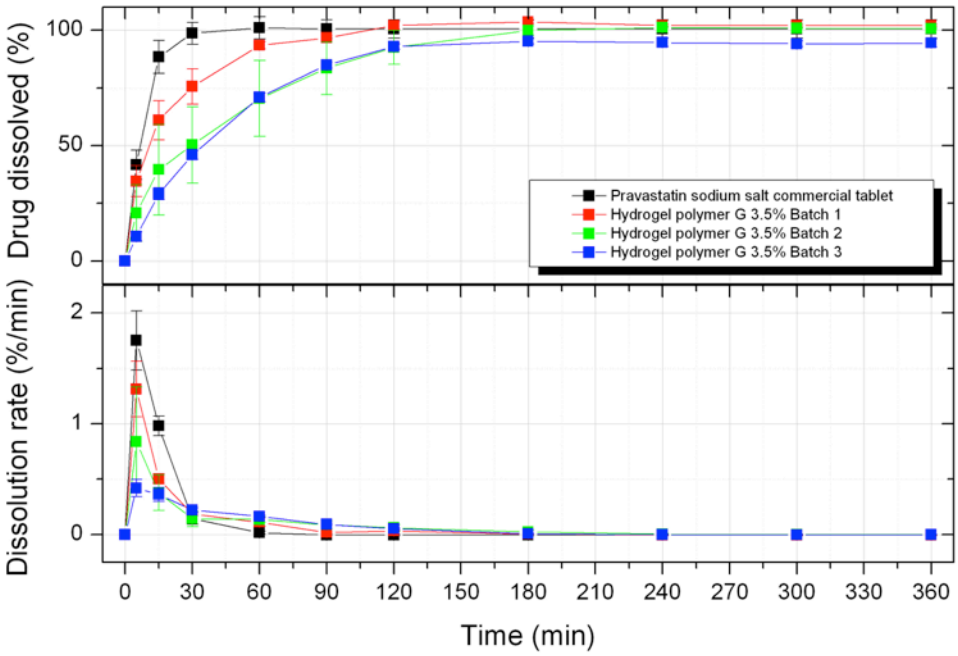

Figure 18: Production process reproducibility about formulated hydrogel.

RHEOLOGICAL STABILITY STUDIES ON DEVELOPED GELIFIED FORMULATION

After defining the gelified formulation, rheological characterization and stability studies on the defined hydrogel (containing polymer G at the concentration of 3.5% w/w, pravastatin sodium added in the vehicle-gel as dissolved tablets and the other excipients), were carried out up to 60 days.

Two different storage conditions were considered to define any temperature influence on sample storage and rheological properties: room temperature (RT, 22°-25°C) and refrigerator (REF, 2°-8°C) without samples light exposure.

Stability investigations were required to ensure an accessible gelled dosage form to dysphagic patients and to all frail population who develop acute or chronic swallowing difficulties.

To verify hydrogel rheological and physicochemical stability, different tests were done during the fixed period. About the rheological investigations, tests of oscillation stress sweep, frequency sweep and viscometry test were performed through a rotational

rheometer at 25°C using a 4/40 cone/plate geometry. Samples were always analysed in triplicate.

In addition to oscillation stress sweep, at 0 time point and after 60 days frequency sweep and viscometry tests were carried out to provide a more exhaustive characterization of the product. Triplicate determinations of frequency sweep test were performed at 25°C at constant stress of 1 Pa and the frequency range 0.01-10 Hz. Moreover, viscometry tests were carried out to obtain flow curves of viscosity. The viscosity values were determined applying the Power Law model to the collected data in order to elaborate the results and to express the system viscosity.

Results about oscillation stress sweep demonstrated that elastic modulus G' maintained constant in all applied stress range, and this feature confirmed a system characterized by a suitable consistency considering the target patient (Figure 19).

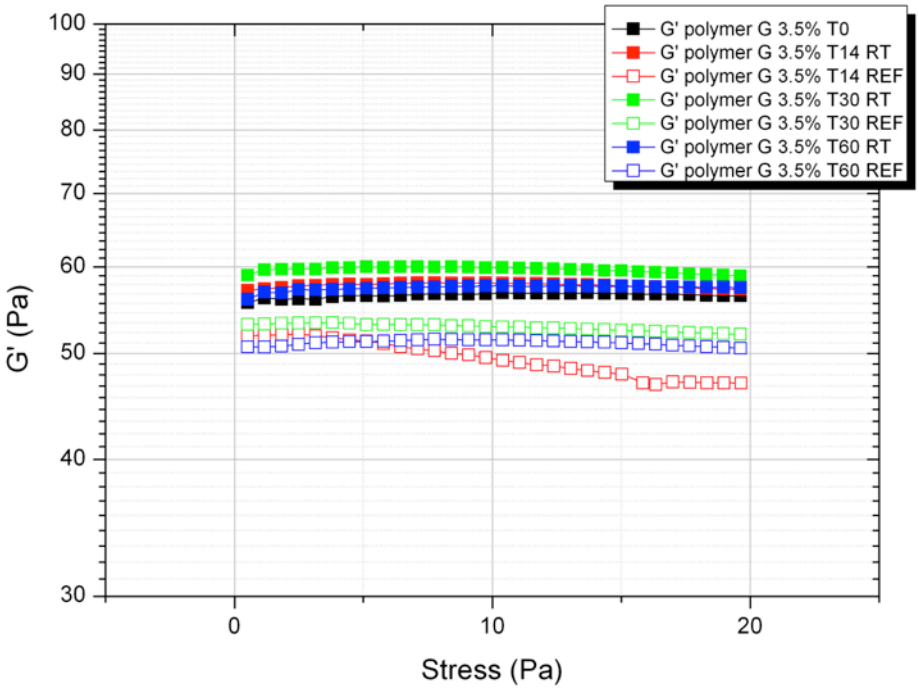

Figure 19: Rheological stability studies on hydrogel formulation.

A more evident decrease of elastic moduli was detected for samples stored at refrigerator temperature; instead, closer values of elastic component to reference Resource® values (64.52 ± 1.76 Pa) were measured in samples kept at room temperature.

Below, a single graph representing a frequency sweep curve at 0 time point was reported to show the behaviour of the gelified system tuned in this study. Trends remained constant and overlapped over the time 60 days (not all data shown) and data revealed through oscillation stress sweep were confirmed in the frequency sweep test. In fact, at 1 Hz fixed frequency, oscillation test gave G' of 49.39 ± 0.50 Pa; G' expressed through frequency test was 53.49 ± 0.84 Pa. Mechanical spectra, showing G' and G'' as a function of the frequency at 25°C, proved a properly viscous fluid system at low frequency where G'' was always higher than G'. Otherwise, at increasing frequency values, moduli tended to encounter and at around 7 Hz cross-over point occurred (Figure 20).

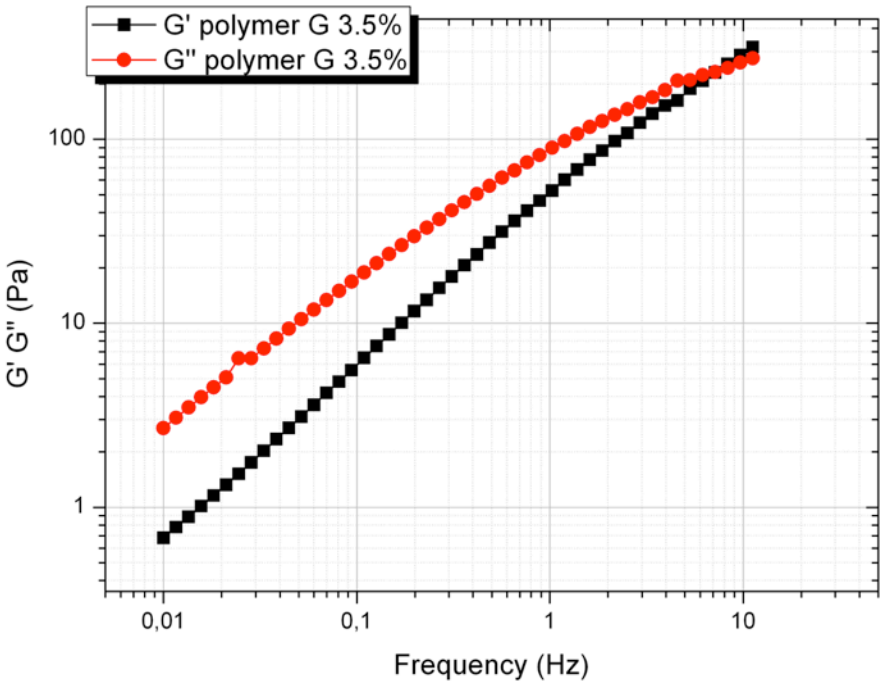

Figure 20: Frequency sweep test on polymer G-based gelified system at 0 time point.

Flow curve of dynamic viscosity at 0 time was reported as example in the graph (Figure 21). Polymer G gelified system was behaving like a viscoplastic fluid. In fact, Power Law

model of measured values gave a power law viscosity (PLV) value of 52.05 ± 0.84 Pa*s, and n (index) =0.48 for samples kept at room temperature. Samples kept in refrigerator showed a slightly lower PLV: 47.13 ± 2.18 Pa*s and n=0.48. Parameters were maintained constant and overlapped up to 60 days.

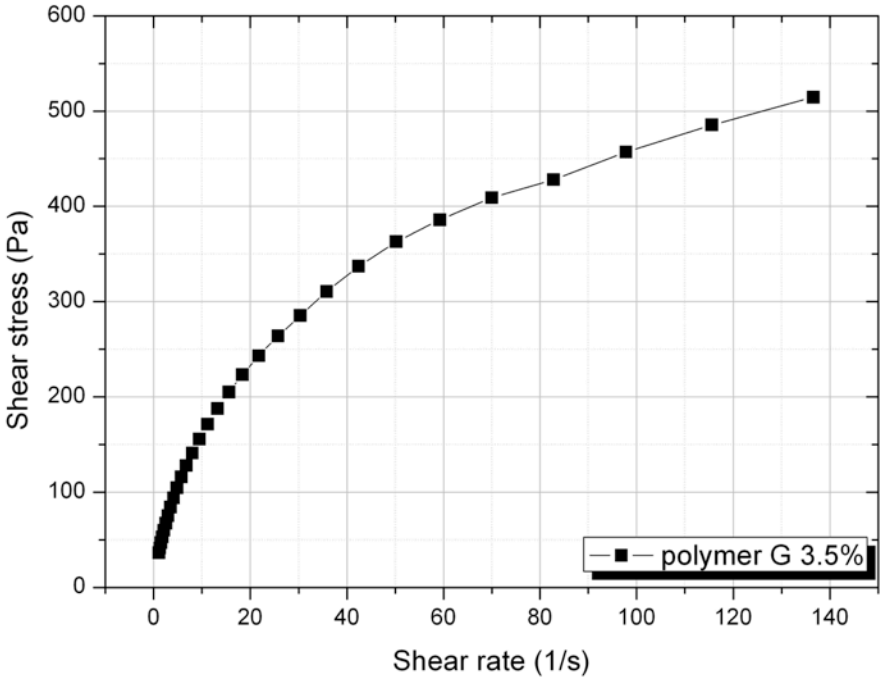

Figure 21: Flow curve of polymer G-based gelified system at 0 time point.

Moreover, through studies on kinetic release profile, it was possible to monitor any variation on kinetic release and chemical stability of pravastatin sodium active molecule, simultaneously. Analytical determinations were collected analysing samples at different timing points 0-14-30-60 days, and detecting samples stored at both temperatures. Data elaboration through statistical methods, establishing 95% confidence interval (CI), indicated that all determinations belonged to CI as reported in the figure below (Figure 22). CI is reported in grey lines in the graph.

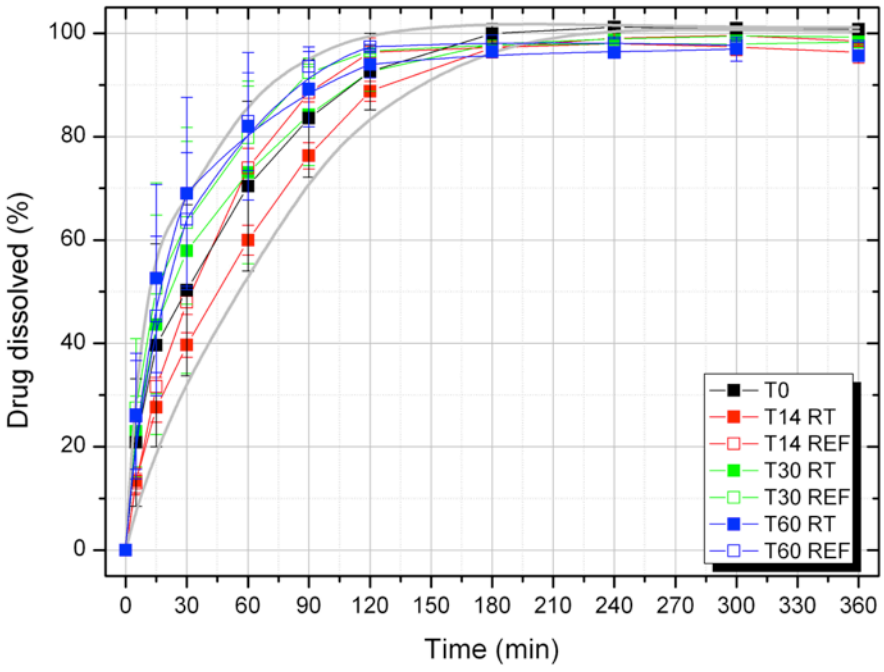

Figure 22: Dissolution tests at 0-14-30-60 days on hydrogel samples stored at two conditions: room temperature (RT) and refrigerator (REF) – CI 95% (grey lines).

Furthermore, a physico-chemical parameter was determined in fact, pH measurements were checked to monitor any pH variation in the final gelified formulation over the time 60 days. In the specific case of pravastatin sodium, changes in pH value outside the required range, 7-10, might mean drug instability.

The pH measurements into the final gelled product gave the following results for the entire monitored period. These collected pH values demonstrated a further stability parameter of the formulated hydrogel able to replace the original SODF with a pharmaceutical formulation suitable to patients unable to swallow (Table 3).

Table 3: pH measurements.

Days	Room temperature pH	Refrigerator pH
0	9.08	
14	9.01	9.05
30	8.86	9.05
60	8.61	8.91

Afterwards, the validity of the study was further compelling through studies, focused on the use of pravastatin sodium as tablet compared to standard powder (STD) dissolved in the gelified medium. These studies have demonstrated the eligible efficacy of tablets employment instead of standard powder (Figure 23). Standard powder of pravastatin sodium was kindly offered by Teva Hungary pharmaceutical company.

The research aimed to propose a pharmaceutical formulation simple to prepare, stable for an enough long-lasting period to guarantee an easy management of the preparative work in a clinical hospital pharmacy laboratory. Indeed, massive quantities of the product could be required in a clinical pharmacy to satisfy requirements from wards, nursing homes, or outpatients.

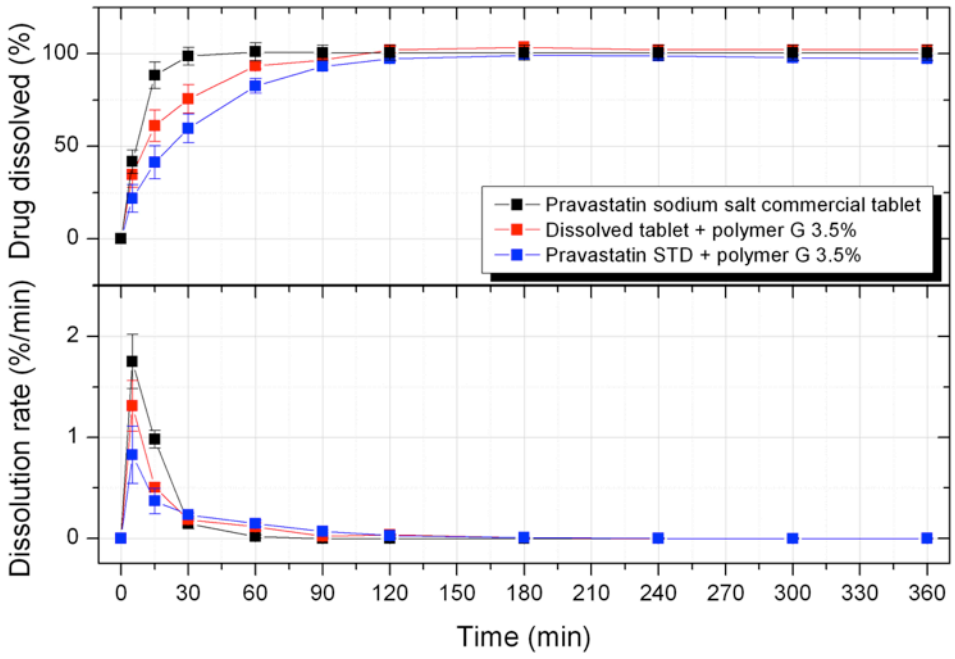

Figure 23: Kinetic release profiles of hydrogels containing dissolved tablets or standard powder (STD) in polymer G 3.5% gelified vehicle.

CONCLUSIONS

To sum up, the study was focused on the development of a semisolid formulation starting from commercial tablets to encounter the need of the clinical hospital pharmacies whenever there were not suitable alternative dosage forms for dysphagic patients on the pharmaceutical market. Patients would not continue drug therapy if pharmacists were not able to set up an alternative formulation.

This protocol provides a gelified vehicle in which the dispersion of immediate-release tablets is possible. Peculiar features have to be: i) a water-soluble active molecule and ii) an immediate-release tablet as original solid form. Therefore, this procedure may be applied whenever pharmacist considers it appropriate. A list of water-soluble drugs is provided in the supplementary material section of this doctoral thesis (SM 1).

In the described context of dysphagic people resident in different care settings, to have a proper formulation, which contemplates the use of dissolved tablets in a gelified vehicle, may be a great advantage for patients. They may continue pharmacological therapy switching from a solid form as tablet to a semisolid one, simply.

Furthermore, generally, hospital pharmacists dispense to the hospitalized patients (inpatients) the commercial products available in the pharmacy for each API prescribed by physician. Anyway, in case of personalized drug therapy, pharmacists may provide compounded product to patients.

In a hospital pharmacy, a greater availability of medicinal products already on the market rather than APIs is present. On the contrary, only the manufacturing company often trades APIs, due to the fact that some drugs are still patented, or are just intended for trading between pharmaceutical companies themselves. In addition, an economic issue makes APIs having higher costs, less enjoyable than commercial formulations considering the large quantities of drugs prescribed to patients in the hospitals.

Due to all these factors, the present work had the peculiar objective to employ commercialized original form instead of raw materials.

The gel preparation for oral administration of the present study takes as model drug pravastatin sodium but the applicability may be extended to other water-soluble molecules. Thus, the described product is administered as daily single-dose (evening) for treating primary disorder such as hypercholesterolemia or hyperlipemia in addition to

well-balanced diet, primary and secondary prevention to cardiovascular disease, and post solid-organ transplant.

The final product is obtained after 24-36h from the beginning of the preparation process. It is necessary to check the pH value in the final hydrogel to assure chemical stability of the included active compound: pH value has to range between 7-10 for the specific case of pravastatin sodium.

Afterwards, bulk-produced hydrogel may be packed in single-dose stickpacks or sealable blisters/sachets, labelled, and delivered to hospital wards, nursing homes, or outpatients in substitution of the SODFs therapy.

From the investigated aspects, the results demonstrated the feasibility of the hydrogel containing as model-active molecule pravastatin sodium tablets, as gelling agent polymer G, as flavour agent mandarin-vanilla powder, and as preservative agents parabens. Data on chemical and rheological stability studies highlighted a stability of hydrogel preferably when stored at room temperature. The maintenance of good consistency of hydrogel over the considered period (60 days) was assured. This time period may permit to organize the preparative work in a clinical hospital pharmacy laboratory to guarantee a proper management of drug therapy of dysphagic patient.

The formulated hydrogel showed overlapping on kinetic release profiles with respect to those of tablets. Therefore, patient might switch pharmacological therapy from original solid form to the gelified formulation and assure compliance to treatment. Patient might improve life quality and safety in drug administration.

The presented work was based on the optimization process of commercial tablets of water-soluble molecules to provide a pharmaceutical product that will replace tablets if patients will be not able to swallow SODFs. Such a research may have a potential industrial applicability if any pharmaceutical company had interest in enlarging production perspectives. The market on a large scale may contribute to improve the therapeutic offering for patients who encounter swallowing inability during their life. The industrial output may cover a market share, which currently, is entrusted to the small-scale production in a pharmacy.

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3.3. Orodispersible films

3.3.1. PRAVASTATIN SODIUM DRUG DELIVERY FILM-SYSTEM (PraNa DDFS) OPTIMIZED THROUGH ELECTROSPINNING TECHNIQUE: A POSSIBLE DOSAGE FORM TO DYSPHAGIC PATIENTS

A part of this work was performed during abroad experience at University of East Anglia, Norwich (UK) under the supervision of Dr. Sheng Qi.

INTRODUCTION

Electrospinning background

During the last decades, electrospinning (ES) process has gained an increasing interest as a potential polymeric processing technique for biological applications like tissue engineering or scaffolds and drug delivery systems. It exploits a high voltage source to inject charge of a certain polarity into a polymeric solution that is then accelerated towards a collector charged with an opposite polarity. The electrostatic forces are able to eject a fiber jet from the so named Taylor cone as the electric field strength overcomes the surface tension of the polymeric solution.[1] In early 1900, some researchers created strong basis to develop a future refined ES technique. Afterward, in 1969, Taylor published a work to explain the behaviour of a polymeric solution droplet if an electric field is applied.[2] Taylor understood that the pendant droplet develops into a cone (Taylor cone) when the surface tension is balanced by the electric field. Moreover, Taylor deduced that the fiber jet is emitted from the apex of the cone and this is the reason why ES technique may be used to generate fibers with diameter significantly smaller than the diameter of the capillary where they are ejected. He found that an angle of 49.3 degrees with respect to the axis of the cone at the cone apex is fundamental to balance the surface tension with the electrostatic forces by examining a variety of viscous fluids.

In order to generate fibers, a number of processing parameters have to be optimized. Actually, the electrospun forms may be mainly fibers or particles depending on the processing parameters. In fibers regard, the optimal dimensions are between 100-500 nm, typically referred to a nanofibers.

A typical ES apparatus (Figure 1) consists of:

- a capillary. A metal needle of a syringe, where the polymeric solution is forced to pass towards to be electrospun, is generally employed;
- a high voltage source. It provides electrical field at opposite polarity. Positive and negative polarities are attached on the one hand to the capillary and, on the other hand to the collector. Thus, liquid polymeric solution is electrically charged;
- a syringe pump. Several sources can be employed as force: syringe pump, gravitational forces, or pressurized gas are used to push the liquid through the capillary up to the tip. The most common used force is a syringe pump;
- a collector. It is used to collect the solid fiber matrix (mat).

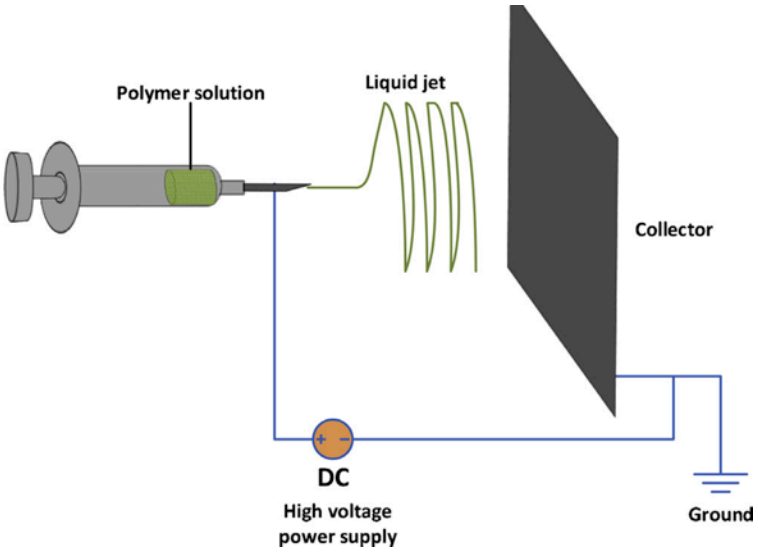

Figure 1: Electrospinning apparatus.

Turning on the electric field, repulsive interactions between charges in the liquid and, simultaneously, attractive forces between the liquid and the collector diffuse determining the elongation of the pendant drop at the tip of the needle. The electric field should be increased until the electrostatic forces balance the surface tension of the liquid leading to Taylor cone formation. The fiber jet is accelerated and moves towards the collector, the non-woven fiber mat is formed and deposited onto a grounded collector (e.g., stationary plate collector giving a randomly oriented fiber, rotating collector giving aligned fibers) thanks to solvent evaporation.[1]

Several different parameters could affect the performance of the final electrospun product (e.g., processing parameters, solution parameters, type of electrospinning apparatus). Applied voltage (AV), polymer flow-rate (PFR) and capillary-collector distance (CCD) are the most interesting processing parameters[3] to set up electrospinning experiments. In fact, the strength of the voltage affects the dimensions of the electrospun fibers from several microns (µm) to tens of nanometres (nm). PFR and CCD influence fibers size, shape and porosity as well.

In addition, solution parameters cover a pivotal role in fiber formation process; in fact, selected polymer or polymeric blend and, solvent or solvent mixture to disperse polymer could influence electrospinnability. Polymer concentration is crucial because is directly

linked to viscosity and surface tension of the system to be electrospun. If the solution is too dilute, fibers do not form because they will tend to break down into droplets before reaching the collector due to the dominant effect of surface tension. On the contrary, if the solution is too concentrated, due to the high solution viscosity, fibers cannot be formed. It is difficult to pump out the solution through the needle of the syringe.

Characteristic of the solvent, for example, volatility is a powerful point in ES arrangement because a proper solvent evaporation may point in one optimal electrospun product or not. Since the fiber jet moves across the atmosphere towards the collector, the importance of CCD is further justified. A sort of phase separation occurs during the solvent evaporation allowing fiber deposition (solid matrix) onto the collector. Any residual solvent may compromise the quality of the final mat. Solution conductivity[4] is significant because a conductive polymeric solution will have free charges to favourite Taylor cone formation and start ES process. Adding a salt to the solution may control the conductivity of the liquid system increasing the numbers of ions in the polymeric solution. Types of ES range within a simpler configuration like a single needle apparatus where a single polymeric solution may be electrospun, to a side-by-side needle where two separate polymeric solution flow into two capillaries even if a single Taylor cone is formed. In addition, another configuration exists (coaxial needle), where a smaller capillary is inserted in a larger one. The smaller fiber will be encapsulated into the bigger one to create a core-shell morphology of the electrospun fibers.[5]

Orodispersible films

Orodispersible films (ODFs) are interesting and quite recent drug delivery systems (DDSs). They are able to rapidly disintegrate in the oral cavity and to facilitate the oral intake of medicinal products.[6] They are attractive forms for paediatric and geriatric patients because they are easy to use and swallow, assure drug stability and are packed in a single-dose. Thus, they may completely replace solid oral dosage forms (SODFs) like tablets. ODFs ability to disintegrate makes them a promising DDS for people unable to swallow. Large-scale production by pharmaceutical companies or small-scale production in pharmacies may be performed according to production volumes. In case of small-scale production, ODFs may receive a specific attention in the future possibility of personalized therapy.

The Food and Drug Administration (FDA) reports the term 'soluble film'[7], as acceptable term to define ODFs. European Medicines Agency (EMA) adopts the terminology 'orodispersible film'. Therefore, oral films are recently introduced in European Pharmacopoeia (Ph. Eur. 7.4), in April 2012, in the 'Oromucosal preparations' monograph, which describes 'orodispersible films'.[8,9]

Actually, ODFs are still heterogeneously defined and labelled both in scientific literature and in regulatory texts including Pharmacopoeias.[10] Miscellaneous terms (e.g., thin-film, oral film, wafer, oral strip, orodispersible film, oral soluble film, buccal soluble film, mucoadhesive film) are actually a limit and create misinterpretation in various contexts. A clear definition of ODFs would be required to give uniformity and clarify regulatory aspects.[11]

As general consideration, ODFs may offer some advantages for patients and for dysphagic patients as well. They do not need additional liquid (e.g., water) to swallow them; they are placed into the tongue and disintegrate with the saliva. They are usually produced by hydrophilic polymers and are able to disintegrate within seconds after contact with saliva. Ph. Eur. only requires that ODFs have to 'disperse' rapidly, but no other information is provided. The crucial points for ODFs are: i) how disintegration should be evaluated, and ii) how long disintegration should last. Disintegration and its duration define the quality of the product. Sometimes, the definition of the disintegration endpoint is difficult to describe, and consequently, the statement 'until the film has completely disintegrated'[9] is considered the final point.

Disintegration behaviour of different film types may differ based on polymer properties. Uncoated tablets should disintegrate within 15 min, according to the Ph. Eur.[12] Orodispersible tablets, taken as reference to be compared with orodispersible films, should disintegrate within 180 seconds (Ph. Eur.); instead FDA establishes 30 seconds as threshold time.

In this work, two hydrophilic film-forming polymers, polyvinylpyrrolidone and polyethylene oxide, were chosen to prepare polymeric dispersion to be electrospun to produce a solid matrix onto the collector. Fiber mat placebo (no drug) and pravastatin sodium loaded films were produced by electrospinning and explored as potential ODFs. An ideal thin, flexible, easy to administer, palatable ODF should be produced.

AIM OF THE WORK

The aim of the study was to optimize orodispersible film by selecting proper polymers in order to produce pravastatin loaded mat able to disintegrate quickly, within 180 seconds in the mouth after the contact with saliva. Films were produced through electrospinning technique. Single-dose film may offer a dosage form useful for elderly and dysphagic patients.

MATERIALS AND METHODS

1. Materials: polyvinylpyrrolidone K90 as amorphous powder (PVP K90, M_w≈360000 g/mol) was purchased from BASF (Germany, batch: 05537575L0). Polyethylene oxide Polyox™ WSR N-750 (PEO 300K, M_w=300K Dalton, batch: DT383916) and Polyox™ WSR 205 (PEO 600K, M_w=600K Dalton, batch: DT382439), semi-crystalline powders were supplied from Colorcon (Kent, UK). Pravastatin sodium (PraNa), raw material, was kindly offered by Teva Pharmaceutical Industries Ltd., Hungary through Angelini A.C.R.A.F. s.p.a., Ancona.

Electrospinning apparatus: electrospinning pump (Cole-Parmer®, USA), syringe 5ml 6% Luer (Terumo®, USA) plus needle Luer 6% (Terumo®, Belgium).

2. Methods

Preparation of polymeric dispersions

Different polymeric dispersions were prepared and labelled as F1 up to F6. Table 1 shows the quantitative compositions of the polymeric dispersions before electrospinning. Distilled water was selected as the spinning solvent because of water-solubility of the designed polymers and PraNa. Polymers were gradually dispersed in water under constant stirring with a magnetic bar at room temperature and up to visual complete polymer dispersion. In PraNa loaded systems, the powder of the drug was gradually added after polymers. The systems were kept at rest for at least 24 hours before electrospinning to reach an optimal polymer solvation. After clear solutions had been obtained and air bubbles disappeared, systems were ready to be electrospun. All polymeric solutions were stored in refrigerator (2°C-8°C) because no preservative agents were used. Before electrospinning process, samples were kept at room temperature to equilibrate system temperature.

Table 1: Composition of different polymeric solutions to be electrospun.

Films		PVP K90 (%, w/w)	PEO 300K Da (%, w/w)	PEO 600K Da (%, w/w)	PraNa (%, w/w)
Progressive number of formulations	Assigned name during the work				
F1	F_10	10	-	-	-
F2	F_96	5	5	-	-
F3	F_36	5	-	5	-
F4	F_58	5	5	-	1
F5	F_52	5	-	5	1
F6	F_94	5	5	-	5

The spinning solutions were loaded into a 5 ml syringe with great care to avoid any air bubbles. A metal needle (18 gauge, 1.2 inner diameter, Terumo®, Belgium) was attached to the syringe. The ES apparatus was organized: on the one side, one electrode from a high voltage power supply was connected to the needle; on the other side, the other electrode was connected to a metal plate collector coated with an Aluminium foil. ES was carried out at room temperature and an electric field of 15 KV was applied maintaining the distance needle tip-collector at 20 cm. The flow-rate of the spinning solutions was 0.5 ml/hour. Methylene blue solution (2-3 droplets) was added to the polymeric solutions before electrospinning to appreciate more easily film disintegration. The net weights of the dry formed matrices were recorded at the end of each run. At least triplicate films were produced for each polymeric system to check repeatability of the process.

Characterization of ODFs

1. Rheological characterization

Viscosity values and viscoelastic properties of the polymeric solutions at the starting point before electrospinning were analysed through a rotational rheometer KINEXUS Lab+ (Malvern Instruments Limited, Worcestershire, UK) with a cone/plate geometry C/P 4/40 at 25°C performing oscillation stress sweep (applied stress 0.01 - 20 Pa at constant frequency of 1 Hz), frequency sweep test (applied frequency 10 - 0.01 Hz at constant shear stress of 1 Pa) and viscometry test (applied shear rate 0.1 - 100 s^{-1}). Tests were

repeated in triplicate and average values and standard deviations (SDs) were reported in the graphs.

Moreover, the viscosity values of electrospun films (placebo and PraNa loaded films) were measured after adding of two different volumes of water. First of all, a single-dose film (squared piece, around 2cm*2cm) was peeled off from the Aluminium foil and placed onto the plate geometry of the rheometer. Afterwards, 1 ml of saliva (water) was added directly onto the dry single-dose film. The film viscous behaviour was simulated during disintegration in a reduced volume of saliva like in case of patients suffering from dry mouth or xerostomia. Alternatively, in a new single-dose film, 5 ml of saliva were added to simulate film disintegration in a normal content of saliva in the mouth (healthy people). Viscometry tests were performed with a cone/plate geometry C/P 2/60 at 25°C and 37°C. They were able to detect any effect in terms of viscosity due to the different PraNa and polymer concentrations in the disintegrating systems and depending on different volumes of the added medium. Distilled water was used as medium instead of artificial saliva for performing the tests. Rheological runs were carried out in triplicate and mean values ± SDs were reported in the graphs.

2. pH values of the polymeric solutions

pH values of each polymeric solution were measure to check if the pH value of the polymeric dispersion was suitable to disperse PraNa. The interval of stability of PraNa molecule ranges between 7-10.[13]

3. Fiber morphology

The structure, dimensions and surface of the electrospun fibers were assessed by scanning electron microscope (SEM, JEOL JSM-5900LV, Tokyo, Japan). Prior to SEM examination, the samples were gold sputter-coated under argon to render them electrically conductive. Images were recorded at an excitation voltage of 20 KV. The mean diameter values ± SDs of the fibers were measured in SEM images using proper software.

4. Thickness of the fiber mat

1ml of each spinning solution was spun onto Aluminium foil. From the entire obtained dry film, squared single-dose (2cm*2cm) was cut by means of a common scissor and peeled

off from the Aluminium foil. The thickness was measured by using an electronic thickness gauge (model ET-3, Createch/Rehder Development Company). The measurements were taken on the corners and in the middle of each piece. The average thickness was reported as mean ± SD.

5. Differential scanning calorimetry – thermal analysis

Differential scanning calorimetry (DSC) analysis was performed using a Perkin-Elmer 8500 calorimeter (Perkin-Elmer, Norwalk, USA) in an inert nitrogen atmosphere. A small amount of the powders (PVP K90, PEO 300K Da, PEO 600K Da, and PraNa raw materials), physical mixtures (PMs), and the produced films (2-4mg) were loaded into a non-hermetically closed Aluminium pan and then analysed. The same thermal program was respected for all samples: heating from 0°C to 200°C at 10°C/min, cooling down from 200°C to 0°C at 10°C/min and second heating from 0°C to 200°C at 10°C/min. All runs were repeated at least in triplicate.

6. Dynamic mechanical analysis – mechanical properties of films

Mechanical behaviour of the dry films was assessed using a dynamic mechanical analyser (DMA 8000, Perkin-Elmer, USA) equipped with a closed furnace. All the tests were performed using tension geometry that is generally employed for thin films.

DMA investigations were done just to the final selected spun films (F2, F4, F6) and, in order to have a deeper characterization and evaluation of the electrospun films, casted matrices were prepared as further comparison. Therefore, polymeric solutions were used both for electrospinning and for casting. The solutions were poured onto plastic Petri dishes and the solvent, water, was gradually evaporated at room temperature. The correspondent names for casted films were: casting F2 (placebo film), casting F4 (drug content 9% in the dry film), casting F6 (drug content 33.3% in the dry film). The resulting foils looked like macroscopically homogeneous and distributed in the dishes without bumps or irregularities. The thickness of the casted films was measured by a digital calliper (Absolute Digimatic, Mitutoyo, USA) and ranged between 110-120 µm.

Spun and casted matrices were cut in rectangular stripes of around 6 mm width and 20 mm length and mounted on the tension geometry (distance between clamps 3 mm). The excess of film length was cut. In addition, spun films were peeled off from the Aluminium

foil before mechanical analysis. A preliminary strain scan test at 25°C was performed on casted films to establish the maximum applicable strain until the samples maintained a linear viscoelastic region (LVR). Therefore, a constant displacement of 0.01 mm (0.3%) was applied for frequency scans performed on all samples (casted and spun) at 25°C in the range of frequency of 0.1 - 15 Hz. All runs were repeated at least in triplicate.

7. Disintegration tests

The European and US Pharmacopoeias do not describe artificial saliva. Several media were generally used to reproduce simulated salivary fluids (SSFs). Some authors chose phosphate buffer at different pH values of 6.0 or 6.8[14]. Moreover, SSFs adjusted at pH 7.4[15] were described as useful medium for orodispersible tablets and therefore, adapted for ODFs. Others preferred purified water at room temperature. Water medium may be acceptable in the preliminary experiments, but media temperature and components may affect the result during the successive evaluations.

There is no a specific disintegration test in the Pharmacopoeias and several methods were introduced in literature for ODFs disintegration. The most used method employs Petri dishes where a single-dose of film is placed in and a small volume (3-5 ml) of water or phosphate buffer or SSF was added.

In this work, 5 ml of phosphate buffer at pH 6.8 was chosen as disintegration medium. A squared piece (2cm*2cm) of each different film was placed into a Petri dish (5 cm as diameter). Disintegration test were performed at 37°C to simulate body temperature and under manual shaking of the dish to simulate the tongue movements. Full disintegration of the films was considered the end-point. Disintegration times were recorded and tests were repeated at least in triplicate.

8. Content uniformity evaluation

Drug content uniformity in the PraNa loaded spun films was checked. Squared pieces of each film representing single-doses were cut from the entire spun matrix, peeled off from the Aluminium foil, and weighted. The PraNa loaded amount was calculated in each single-dose (calculated drug content). The single-dose (2cm*2cm) was dissolved in 5 ml of water (ideal volume of saliva) and relative drug concentration was determined by spectrophotometric method (spectrophotometer Shimadzu UV-1800, software UV-Probe

2.43). PraNa absorbs at a specific wavelength of 238 nm thus, a calibration curve (22.5-5 µg/ml) of PraNa standard solution was plotted with a good correlation coefficient $R^2 \geq 0.9994$. Measurements were repeated at least on three single-doses for each compared film and mean values ± SDs were calculated. Statistical interpretation of drug content uniformity data was carried out through one sample T-test with confidence interval (CI) of 95% (MiniTab software). A p-value < 0.05 was considered statistically significant.

RESULTS

Polymeric solutions were spinnable in the optimized working conditions and dry matrices were obtained with the exception of F1 polymeric dispersion that did not provide a proper mat. Thus, F1 was abandoned for future investigations.

At the same time, pH values of the polymeric solutions were checked to evaluate a compatible pH environment to disperse PraNa and assure stability of the drug (Table 2).

Table 2: pH values of polymeric solutions before electrospinning.

Films	pH value at room temperature
F2	7.60
F3	8.14
F4	9.30
F5	9.11
F6	9.37

These results demonstrated that pH values were compatible with range required by PraNa for all systems. Afterwards, the discriminatory parameter for the selection of good ODFs was disintegration time. Actually, it was possible to distinguish between the disintegration time, properly named, and the complete disappearance of the films in the medium. In fact, disintegration meant the breakdown of the film in small fragments, instead, when the matrix completely disappeared into the Petri dish, endpoint was registered. According to, the recorded times, results were showed in table 3.

Table 3: Disintegration and disappearance of the films.

Films	Disintegration time (≈seconds)	Complete disappearance (≈seconds)
F2	5-7	120
F3	5-7	360
F4	5-7	75
F5	Shrinkage	360 and more – up to 600
F6	5-7	180

Given these preliminary results, the work was further focused on a deeper characterization just for F2, F4, F6 films.

The compositions of the dry films may be described as follows (Table 4).

Table 4: Film compositions.

Films	Compositions of dry films (%)		
	PVP K90	PEO 300K Da	PraNa
F2	50	50	-
F4	45.5	45.5	9
F6	33.3	33.3	33.3

To verify the process efficiency of ES mat production, the yield was calculated taking into account the water content for each prepared batch (Table 5).

Table 5: Recovery and yield of electrospinning process.

Films	Theoretical weights of the entire spun films (mg)	Net weights of the entire spun films (mg)	Water content (mg)*	Net weights of the entire dry spun films (mg)	Yield (%)
F2	100	106.40 ± 4.07	5.32 ± 0.20	101.08 ± 3.87	101.08 ± 3.87
F4	110	108.30 ± 5.48	6.13 ± 0.31	102.17 ± 5.17	92.88 ± 4.70
F6	150	163.02 ± 3.31	8.15 ± 0.17	154.87 ± 3.14	103.24 ± 2.09

* Water content was determined by thermal gravimetric analysis.

Additional parameters in film characterization were film thickness and fiber morphology. Thickness values reported in the following table 6, showed a direct correspondence between the film width and increasing amount of the drug loaded into the matrices. SEM images revealed that fiber dimensions were around 400 nm (Table 6) but the previous relationship (thickness or dimension *versus* PraNa loaded content) was not confirmed. Fiber surface appeared smooth and distribution looked like mainly aligned. Fibers crossed themselves in the mat. No entanglements may be detected from the pictures. In addition, the structure organization was characterized by a high porosity mainly in F2 formulation as the pictures showed (Figure 1). Porosity seemed to decrease, increasing PraNa amount.

Table 6: Mat thickness and fiber dimensions.

Films	Thickness (µm), mean ± SD	Fiber dimensions (nm), mean ± SD
F2	22.40 ± 3.77	445.50 ± 39.68
F4	40.87 ± 15.84	439.60 ± 33.49
F6	223.40 ± 24.70	400.88 ± 60.77

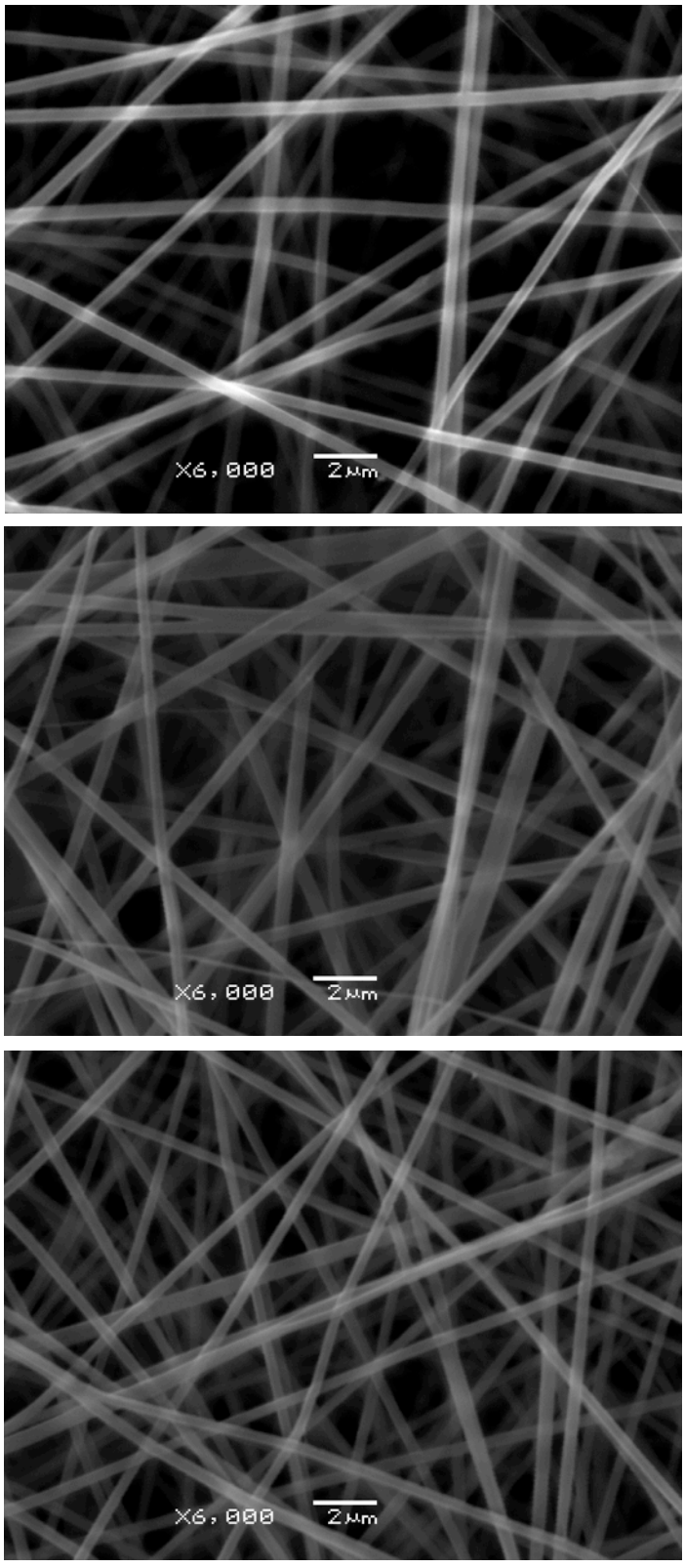

Figure 1: SEM images of F2, F4, F6 (from the top to the bottom) at 6000X of magnification.

Then, a rheological characterization (oscillation stress sweep, frequency sweep and viscometry test) was performed on polymeric solutions F2, F4, F6 before ES. Oscillation stress sweep carried out at 25°C in the applied stress range 0.01 – 20 Pa and at constant 1 Hz frequency showed a clear liquid viscous behaviour for all the three compared systems. Elastic moduli (G') maintained lower than viscous moduli (G'') for all range of stress. At around 12 Pa, systems lost linearity (end of viscoelastic region) (Figure 2).

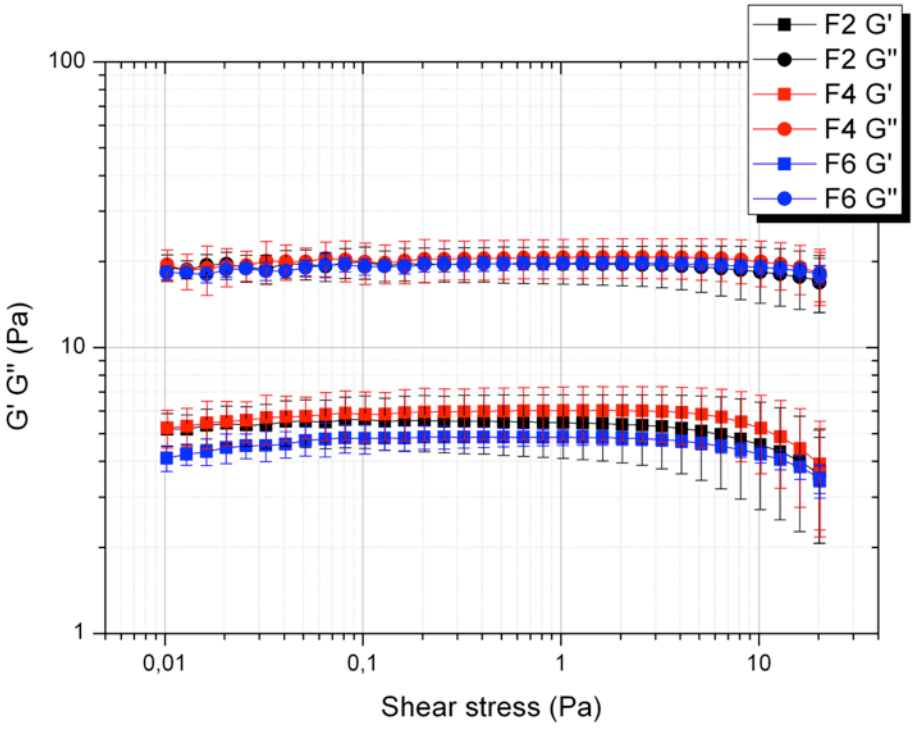

Figure 2: Oscillation stress sweep for three compared polymeric solutions F2, F4, and F6 at 25°C.

Nature of the samples was confirmed through frequency sweep test performed at 25°C at constant applied stress of 1 Pa. G'' higher than G' confirmed the predominant viscous nature over the solid one for the compared systems. Regarding viscous behaviour, the absence or presence of PraNa in two concentrations did not affect the nature of the samples in a significative way (Figure 3).

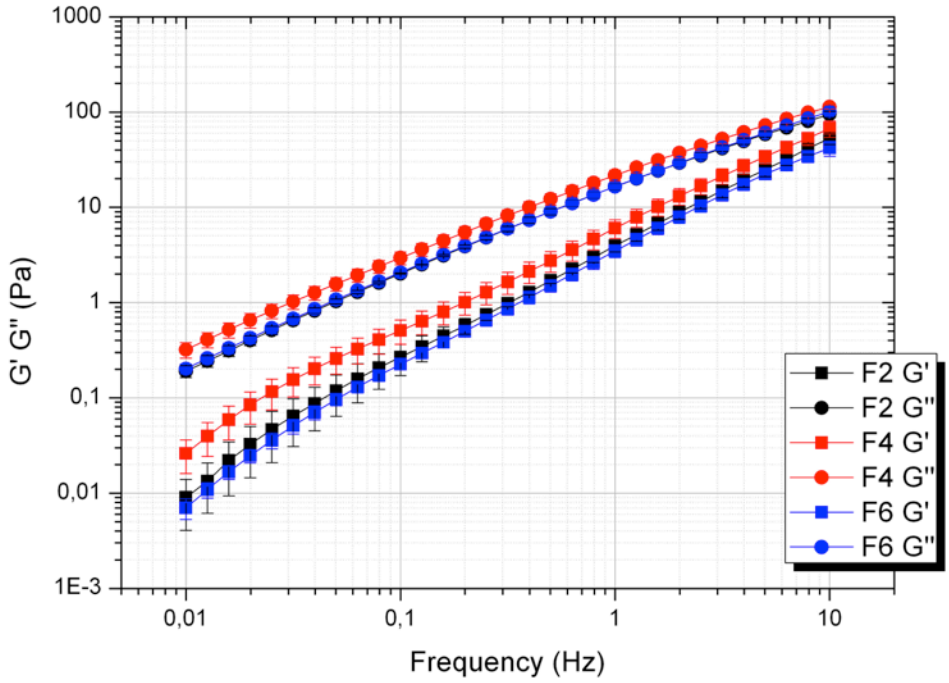

Figure 3: Frequency sweep for three compared polymeric solutions F2, F4, and F6 at 25°C.

Viscosity values on polymeric solutions were determined fitting data through Power Law model and were determined before ES at 25°C under an increasing shear rate 0.1–100 s^{-1}. Flow curves demonstrated an increasing viscosity value starting from placebo dispersion (F2) until F4 and F6 polymeric systems where dispersed PraNa was 1% (F4) and 5% w/w (F6). As general trend, samples appeared shear thinning fluids (Figure 4) and Power Law viscosities (PLVs) were 2.319 ± 0.261 Pa*s, 2.489 ± 0.178 Pa*s, 2.935 ± 0.145 Pa*s, respectively for F2, F4, and F6 viscous fluids. PLV index (n) were < 1 and, in the detail: 0.897, 0.888, and 0.881, respectively for three compared systems.

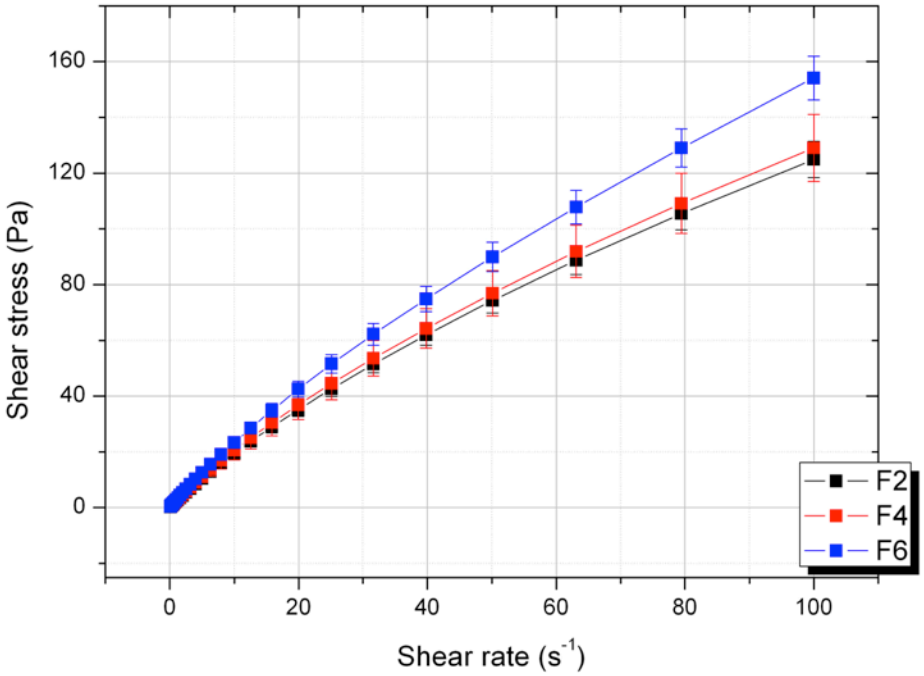

Figure 4: Viscometry test for three compared polymeric solutions F2, F4, and F6 at 25°C.

Another relevant aspect regarded the viscosity value of the systems obtained when different volumes of water (1 ml and 5 ml) were added to the dry films to simulate oral cavity environment. Viscometry tests were performed at the same conditions of the previous ones. As reference, flow curves of distilled water at two temperatures (25°C room temperature and 37°C body temperature) were reported to better understand the behaviour of aqueous fluids (Figure 5).

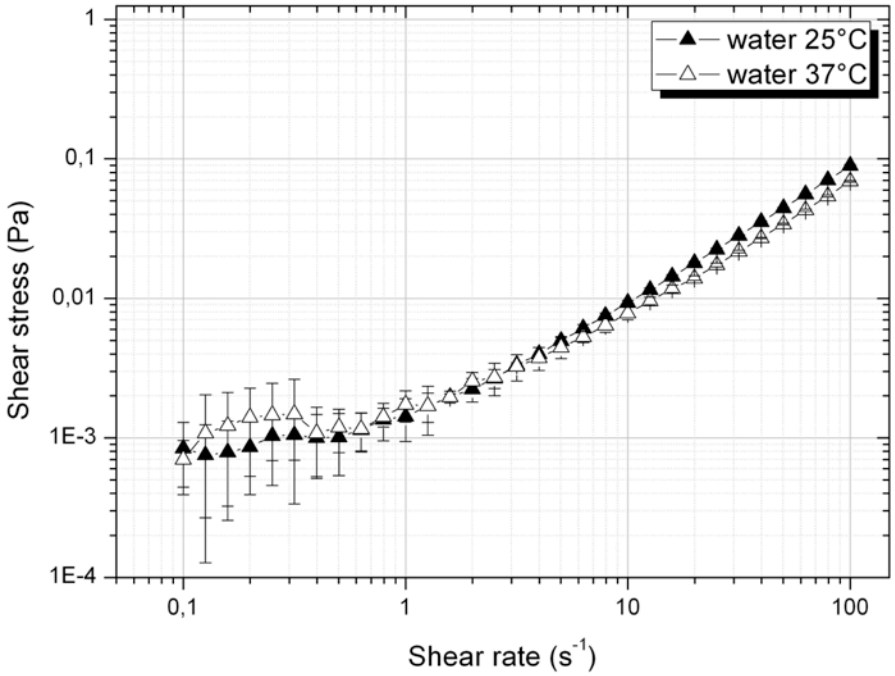

Figure 5: Flow curves of distilled water at 25°C and 37°C.

It is well known the Newtonian behaviour of the water and the theoretical water viscosity of about ≈1*10^{-3} Pa*s. By plotting data on logarithmic scale, and at very low shear rate, (< 1 s^{-1}), water and, generally, low viscous systems having a high surface tension present a characteristic behaviour already known in literature[16]. This typical trend is an artefact due to the influence of surface tension. At upper share rate > than 1, water shows a proper Newtonian trend. Instead, the effect of the temperature did not affect viscosity results of water. Water viscosity was taken into account as reference to compare results obtained for the systems evaluated after addition of 1ml and 5 ml of water.

Some images were reported below to show the used methodology to analyse the samples after addition of 1 ml of water (Figure 6).

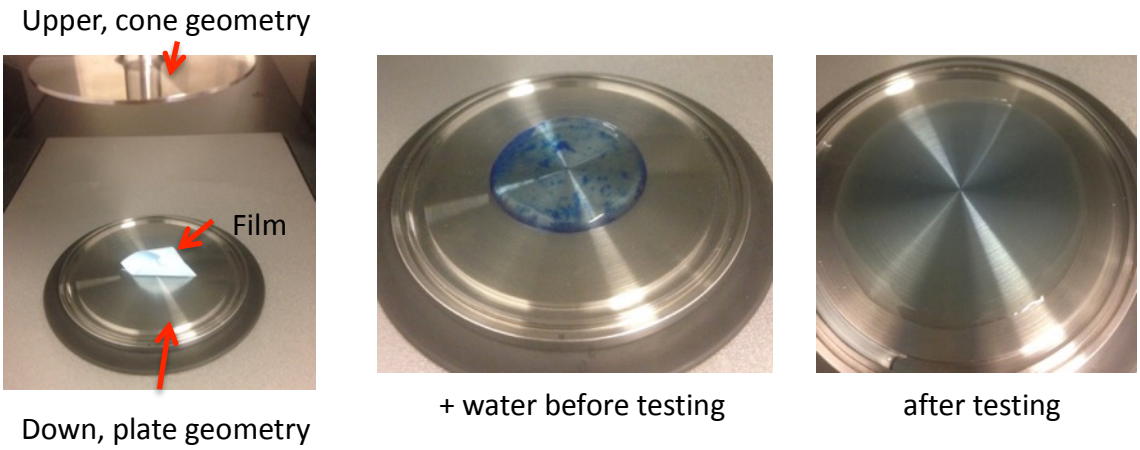

Figure 6: The squared single-dose of the film was directly placed into the plate geometry and then 1 ml of water was added into the sample and analysed.

In case of addition of 5 ml of water, the squared piece of film (2cm*2cm) was dissolved in a becker and then, a proper volume of the aqueous dispersion was loaded onto the plate geometry of the rheometer to analyse the sample.

Results were plotted in the graphs (Figure 7, A and B). Samples were aqueous-like systems and therefore, as seen before, they confirmed a close trend with respect to water behaviour. Also in this case, the Newtonian linearity was lost at low shear rate < than 1 s^{-1} due to the effect of surface tension. Viscosity values similar to those of the reference (water) were reported for the systems obtained after the addition of 5 ml of water where polymeric concentration was lower. On the contrary, slightly higher viscosity values were detected for the samples analysed after addition of 1 ml of water (Figure 8). Full bars are referred to addition of 1 ml of water instead empty bars are referred to addition of 5 ml of water. The dotted dark blue and light blue lines represent the experimental values of water viscosity at 25°C and 37°C, respectively. In any case, the low measured viscosity reflected the poor thickening power of the polymers selected for this study (polymers with high thickening power are not suitable for technological process requiring spinning of solutions through nozzle or needle). Temperature did not affect the performance of the samples in both analysing conditions.

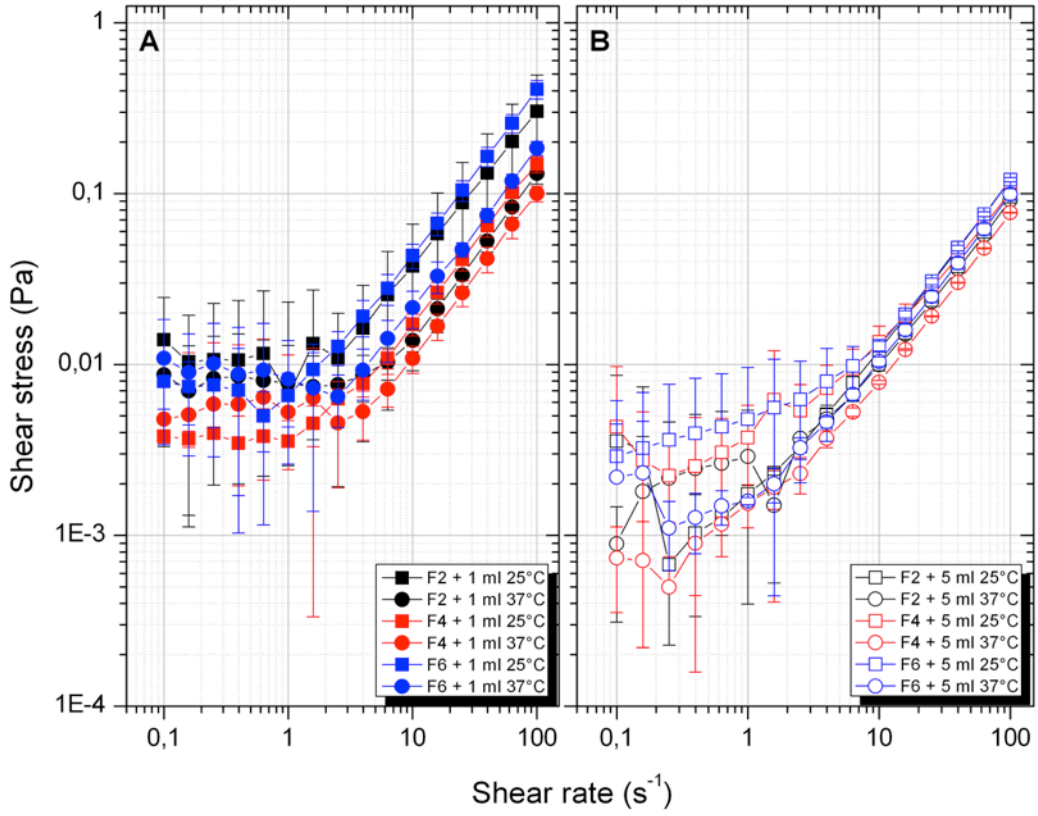

Figure 7: Flow curves of films analysed after addition of 1ml (plot A on the left) or 5 ml (plot B on the right) of water at 25°C and 37°C.

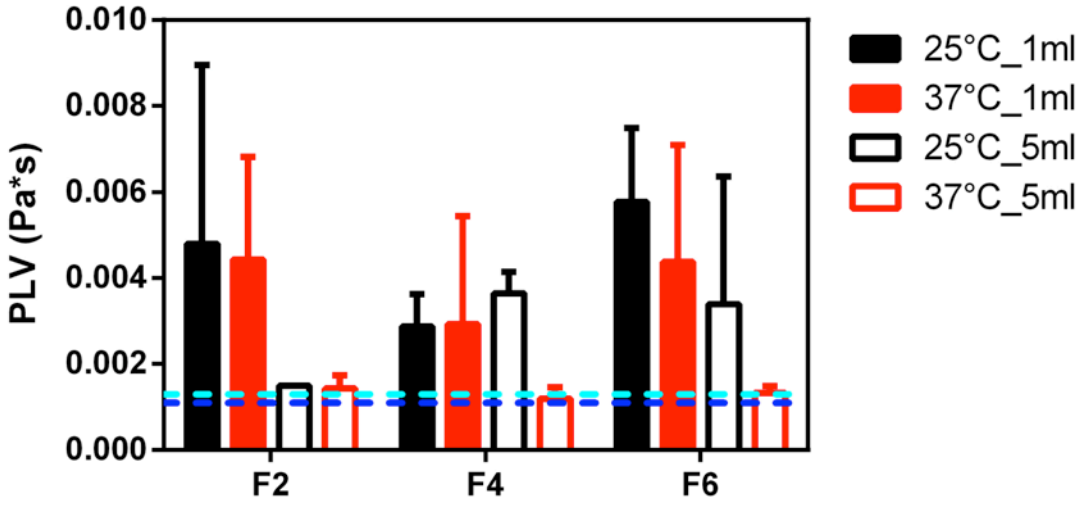

Figure 8: PLV of aqueous dispersions of F2, F4, F6 films.

Going on the thermal characterization of the samples through DSC analysis, raw materials of PraNa, PVP K90, and PEO 300K Da were analysed as received. Then physical mixtures and films F2, F4, and F6 were scanned. The thermograph (endothermic transition was reported as up transition) of PraNa powder (Figure 9) showed a crystalline structure of the drug that presented a melting point peak at 178.15°C and the onset of the transition at 172.24°C. The visible bump between ≈30°-120°C was attributed to the water loss as reported in literature.[17,18] No crystallization peak was detected during cooling down of the thermal program.

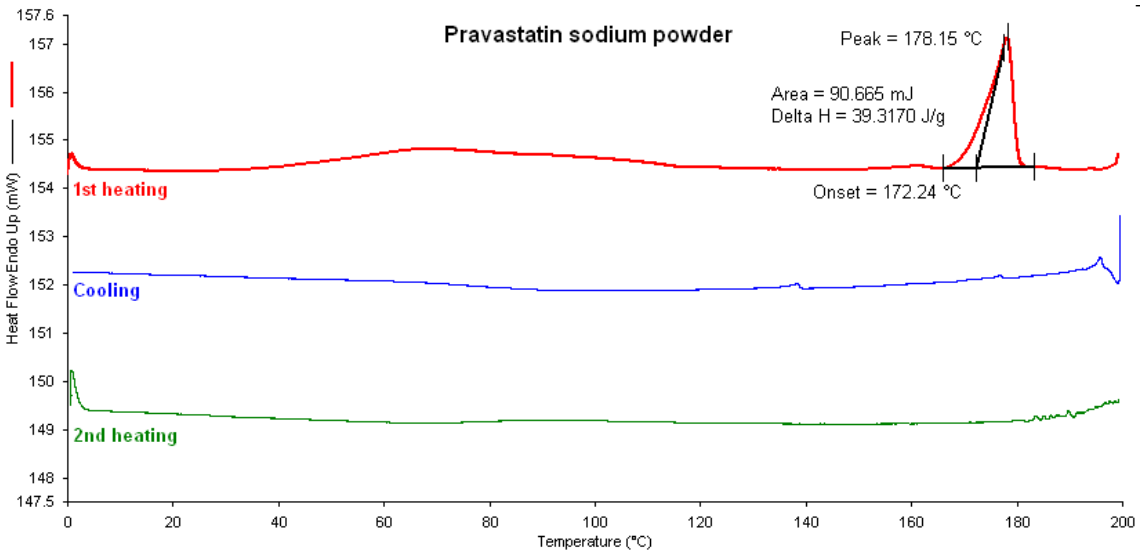

Figure 9: DSC scan of PraNa raw material.

Physical mixtures (PMs) of PVP K90 5% plus PEO 300K Da 5% (1:1), PVP K90 5% plus PEO 300K Da 5% plus PraNa 1% (5:5:1), and PVP K90 5% plus PEO 300K Da 5% plus PraNa 5% (1:1:1) were scanned to evaluate drug behaviour (Figure 10 A, B, and C, respectively).

PM runs showed the characteristic peaks of the polymers: PVP K90 amorphous material presented a glass transition temperature (T_g) in the range of temperature of 160°-163°C, PEO 300K Da semi-crystalline polymer showed a melting point peak at 65°-66°C, a crystallization peak at about 42°C, instead, T_g value at -70 °C known in literature, was not shown in these graphs. In the physical mixture scans, melting peak of PraNa was detected just during the first heating of the applied thermal program.

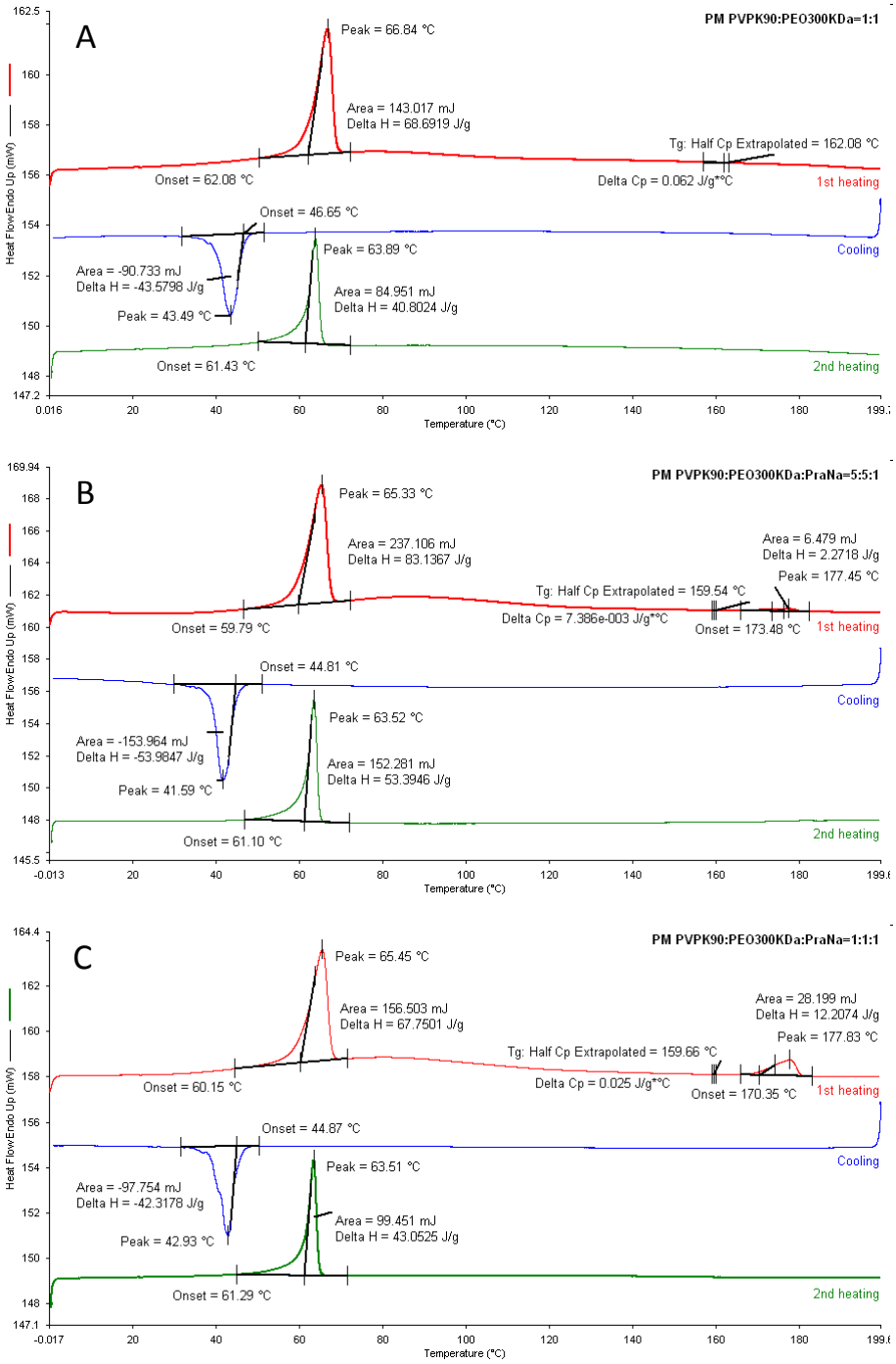

Figure 10: DSC scans of physical mixtures.

To understand PraNa behaviour and to justify the possible arrangement of PraNa in an amorphous state[19] after melting, hot stage microscopy ((HSM), Polarizing Microscope, Meiji Techno, Japan) was carried out on PraNa powder sample. The applied thermal program for HSM was heating from room temperature to 200°C at 2°C/min. Polarized light was used to take the picture at 10X of magnification (Figure 11).

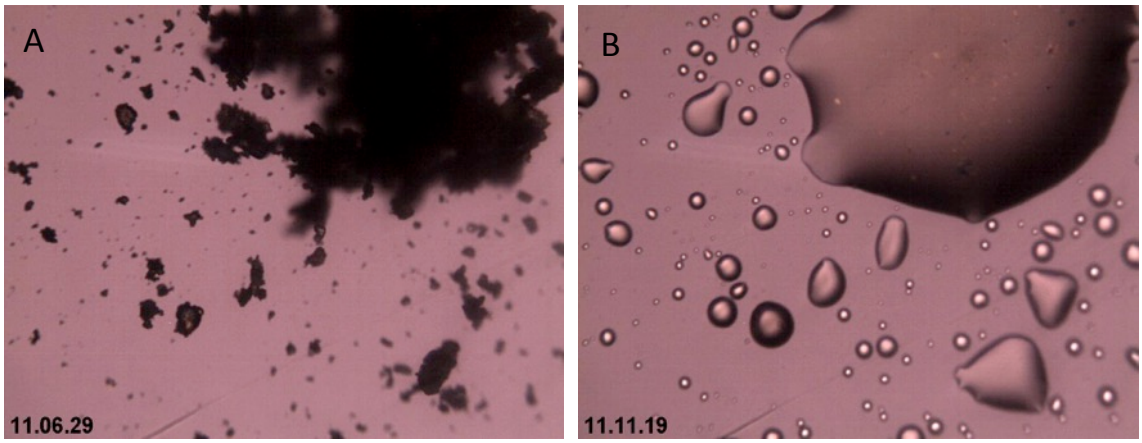

Figure 11: HSM for PraNa before heating (A on the left), and after melting point (B on the right).

PraNa sample was heated up to complete melting and then, it was cooled down on the microscope stage until to room temperature to see drug behaviour. Pictures reported here at 10X of magnification and by using polarized light showed PraNa at 170°C (Figure 12 A on the left) completely melted and at 25°C after cooling (Figure 12 B on the right) still melted. No crystalline structure was again formed after cooling. PraNa did not crystallize immediately. This was the reason because drug peak during DSC cooling run was not detected. Successive pictures taken at different timing points (time 0, after 5, 10, 30, and 60 days, not reported here) revealed that after PraNa melting, drug took long time to trigger re-crystallization process again. PraNa stayed in an amorphous state immediately after melting and it started to crystallize gradually and slowly. These images justified the behaviour of PraNa as raw material and in the physical mixtures.

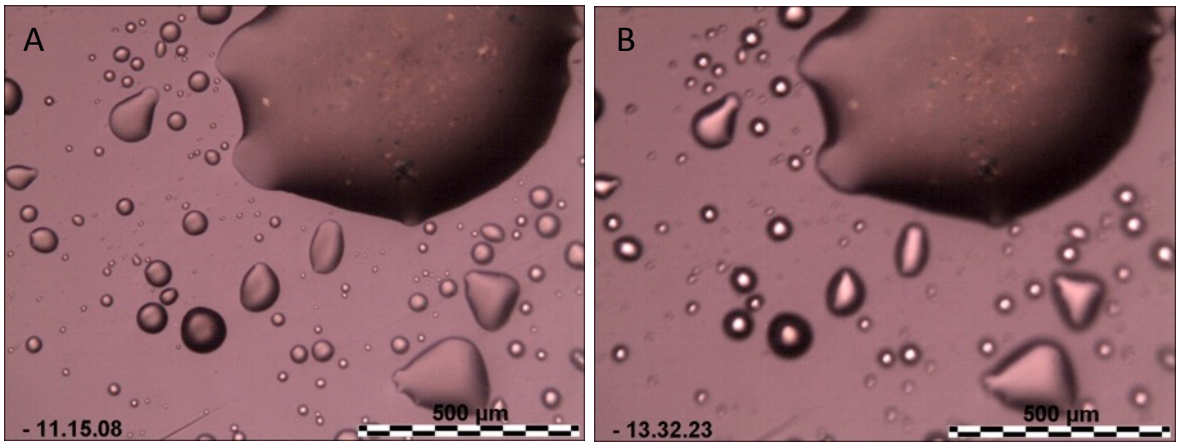

Figure 12: PraNa at 170°C (A) and at 25°C (B).

Moreover, DSC analysis of dry films F4 and F6 containing 9% and 33.3% of PraNa respectively, revealed additional issue about drug detection. Thermograph of F6 was here reported (Figure 13). No PraNa was discovered during the first heating of the DSC run in the film, just thermal transitions directly linked to polymers were scanned.

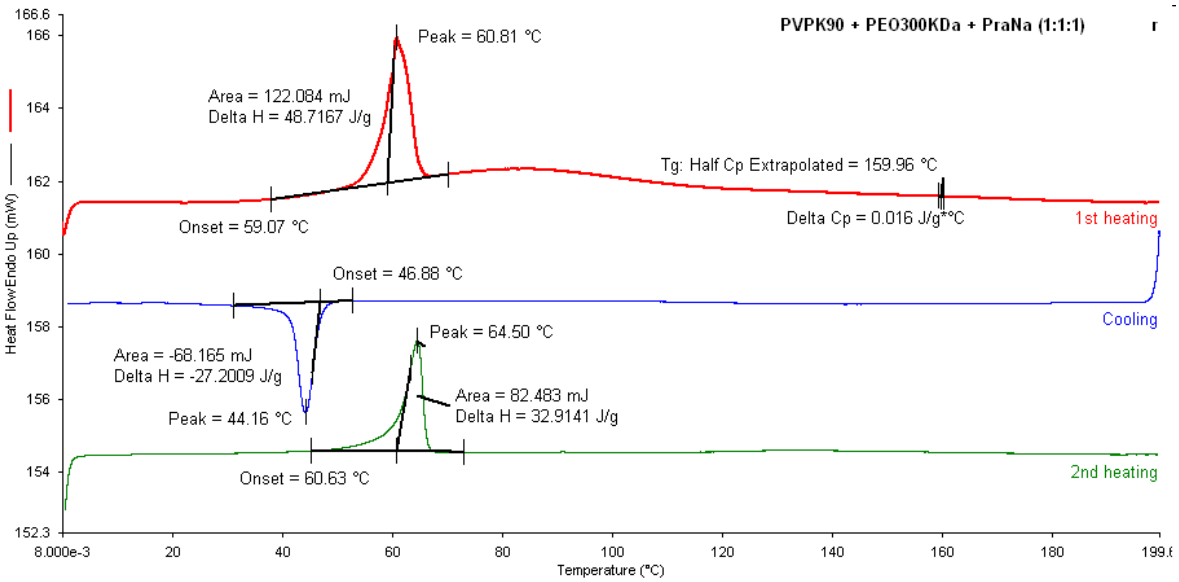

Figure 13: DSC thermograph about F6 spun matrix.

This result was justified simulating what happens during ES process (solvent evaporation). In fact, PraNa powder was solubilized in water and a droplet of the solution was put on a slide to favourite the solvent evaporation at room temperature. After solvent

evaporation, a patina like a 'film' was obtained on the slide instead of getting again a powder. Plasticizing effect of water might cover a role in this result. In addition, PraNa in the polymeric dispersion at the beginning and in a dry film after ES may be stabilized in an amorphous state by polymers themselves.

Afterwards, mechanical characterization of electrospun matrices was performed comparing the stripes with casted films (Figure 14). Results revealed that casted films were generally more stiff samples; the presence of PraNa increase the solid-like behaviour as evident by higher values of the moduli and by the absence of any frequency dependency.

On the contrary, electrospun films exhibited a lower stiffness with respect to casted mats. Anyway, the results of mechanical analysis for ES films were highly variable (SDs were not reported in the graph to improve its interpretation) and no assumption may be made on the PraNa effect. It is only possible to state that the ES process is not able to produce ODFs with homogeneous mechanical features, at least for the selected set up and the used polymers.

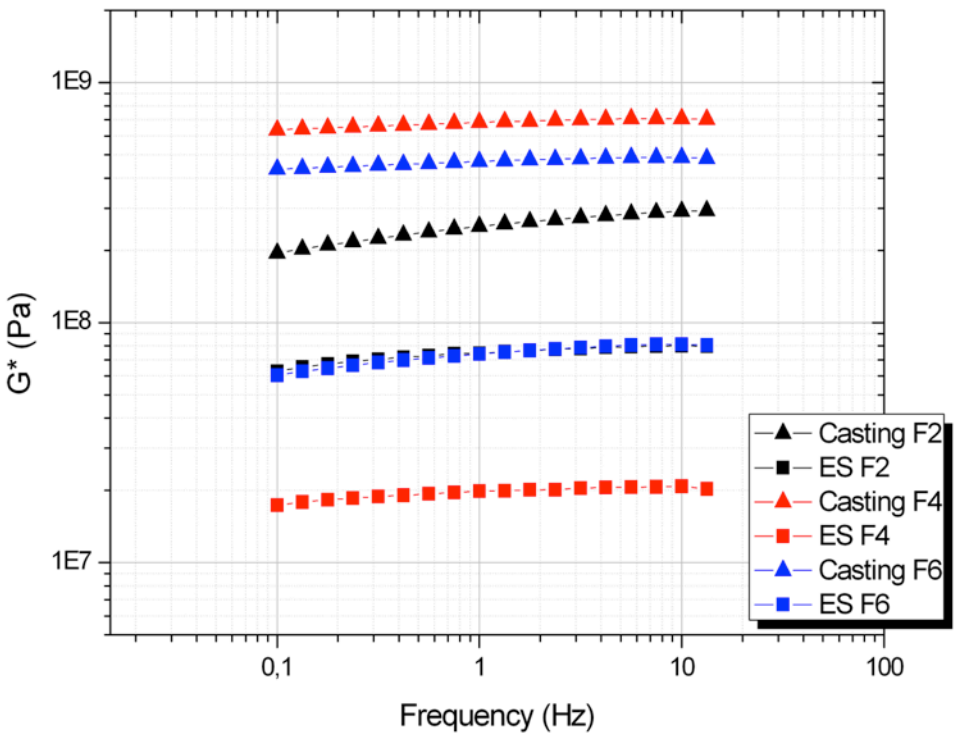

Figure 14: DMA analysis for casted and spun films.

Finally, to check drug content uniformity in a single-dose squared film, PraNa was detected through UV determinations. Results demonstrated that, even though not completely homogeneous samples were obtained from a mechanical point of view, analysed matrices provided uniformity in the PraNa content either in F4 films containing 9% of drug or in F6 films with 33.3% of the active molecule (Figure 15). The dotted lines, black and red, represent the reference values. Respectively, the CI was 8.34% – 12.72% with a p-value of 0.095 for F4 mat; instead, the CI was 30.74% – 43.2% with a p-value of 0.180 for F6 spun films. Statistical results showed that the mean values determined about drug concentrations in the single-doses, were not statistically different from the theoretical concentration of PraNa, 9% and 33.3% respectively.

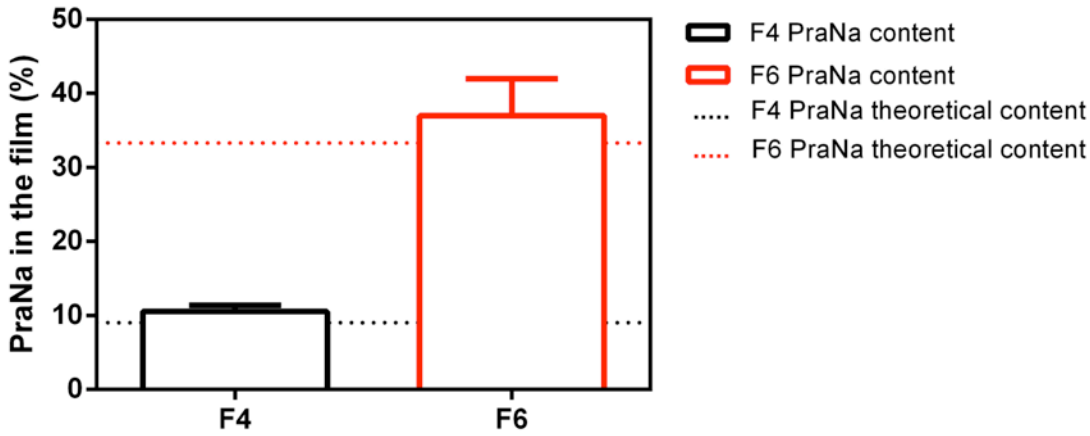

Figure 15: PraNa content uniformity.

CONCLUSIONS

In conclusion, it was shown that ODFs may be prepared choosing proper film-forming polymers like PVP and PEO and setting up suitable ES conditions. ODFs might offer an advantageous delivery system to people unable to swallow and ES may be a potential technique to produce them. In the perspective of a personalized therapy, small-scale

production of electrospun matrices in a hospital pharmacy might provide an opportunity for assuring drug treatment to dysphagic people. Working on ES conditions, same process parameters may be ameliorated in order to make quicker and more efficacious the process. Currently, one the possible limit of the technique regards the duration of the process if specific conditions have to be employed (e.g., use of water as spinning solvent). Alternatively, by combining other ES conditions, parameters, or solvent, process optimization may be tuned and improvements in the production method may be reliable and powerful to enlarge ES technological employment.

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4. Conclusions

This doctoral thesis was focused on the increasing problem of dysphagia among elderly people. The prevalence of dysphagia is expected to grow up rapidly in the next future given the increased life expectancy. Thus, dysphagia is becoming more and more frequent within aged population. Despite physiologic modification in the swallowing due to aging process, dysphagia may not be referred just to aging; in fact, a leading cause should be searched.

The evaluation of dysphagia requires a multidisciplinary approach and several professionals are involved in its management.

Limiting the focus on management of drug therapy in dysphagic patients, the aim of the work was to optimize any manipulation process of solid oral dosage forms, by far the most common dosage forms available on the pharmaceutical market. Solid forms are generally assumed with a glass of water, but this routine operation results too difficult, unsafe, and dangerous for people with swallowing injuries.

Daily, to overcome the problem, crushing tablets or opening capsules are the most frequent practices repeated by nurses in the hospitals. These procedures are referred to manipulation or compounding dosage forms. The crushed tablets or the solid content of capsules are dispersed in water and the obtained systems or solutions are flushed into the feeding tube used for patient in enteral nutrition. Alternatively, nurses may mix the powder in a gelified vehicle, available on the market and ready-to-use, thus patients may assume drug or drugs in a semisolid form, orally. The modified/gelified consistency of feed or medicinal products facilitates their assumption and swallowing in dysphagic patients.

It is a clear evidence that manipulation or compounding may cause a number of errors: crushing coated formulation or controlled-release forms may result in sub-therapeutic (crushing coating) or toxic (controlled-release) blood concentration of the drug causing adverse effects. Moreover, manipulation of cytotoxic medicinal product that should not be crushed, may determine aerosolization of drug small particles that become harming to persons who handle the drug.

Therefore, known this scenario, the aim of the project was to optimize compounding process of solid forms, in the detail of pravastatin sodium immediate-release tablets in

different forms suitable to dysphagic people. The work was mainly focalized on pravastatin sodium due to its diffuse prescription among elderly people to reduce high levels of blood cholesterol and, consequently, to prevent primary and secondary cardiovascular disease. Moreover, the study took into account another active molecule potassium canrenoate, a diuretic drug, largely prescribed. These two model drugs are available on the market as tablets. Thus, the work was finalized to arrange and optimize alternative dosage forms either to patients in enteral nutrition, or to patients not in enteral nutrition. For the first patient group, the investigation has provided liquid forms for both of model drugs and evaluations about enteral delivery of the drugs were performed. Instead, for the second patient category, the study aimed to tune a gelified form compounded from the original commercial tablets of pravastatin sodium, and orodispersible films loaded with pravastatin sodium to offer two alternative dosage forms to people presenting swallowing inability.

The obtained results demonstrated the feasibility of different dosage forms with respect to the most common tablets. The peculiar employment of the commercial tablets instead of active molecule raw material was to simulate the routine hospital settings and to mimic whatever happens as close as possible. The use of raw materials is not convenient either due to expensive costs and hard availability of active molecules, or due to the fact that hospital pharmacies have at their disposal the commercial dosage forms purchased by the pharmaceutical companies.

A proper knowledge in pharmaceutics field should be always considered before any manipulation, handling, or compounding process of dosage forms. Compounding should be performed by qualified persons like pharmacists or people under the supervision of a qualified person because, whatever externally looks like a simple tablet, may imply a really complex formulative technology.

Future perspective of the work might involve studies about other active molecules to enlarge the therapeutic possibility intended for dysphagic people. Currently, studies were performed on water-soluble drugs (pravastatin sodium and potassium canrenoate), but investigations on poorly water-soluble drugs might be of great interest.

In fact, in this regard, re-formulative studies about quetiapine fumarate, antipsychotic and slightly water-soluble drug, are receiving our interest. Medical doctors largely prescribe this molecule to elderly people. Aged persons, in addition to neurologic

disorders like dementia and cognitive impairments, may suffer from dysphagia. The complex status of health generally diffuses among elderly patients (they are in polypharmacotherapy) gets more complicate the management of drug therapy to those who have to treat different pathological conditions. Therefore, tuning suitable forms of quetiapine fumarate is our next objective. Early studies have considered solubility issue of quetiapine, and a possible formulative approach may be to formulate edible oleogels.

Another field of interest will regard the investigation about several thickener agents available on the market and how they are able or unable to modify or influence the kinetic release profile of drugs. It is well known that, in the routine practice in the hospitals, nursing homes, and long-term care facilities, nurses utilize ready-to-use products in order to adjust the consistency and texture of the bolus (nutritional or therapeutic bolus). Studying the interference/influence of thickener agents from a kinetic point of view might be fundamental to enrich background and knowledge whenever compounding process is required. In addition, health care providers should perform a continue education and training to update their experience around the increasing interest in dysphagia.

5. Supplementary material

SM 1 List of water-soluble drugs

Water-soluble drugs listed in the following tables are grouped according to the Anatomical-Therapeutic-Chemical (ATC) classification system that is generally used by the Italian Ministry of Health to classify drugs. It was refined by the Nordic Council for the Scandinavian Countries and then, recognized by World Health Organization.

The active molecules are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Just the first level of the classification is here reported and it comprises fourteen main groups.

	ATC A: alimentary tract and metabolism
1	Sodium Fluoride
2	Benzydamine Hydrochloride
3	Ranitidine Hydrochloride
4	Nizatidine
5	Scopolamine Butylbromide
6	Metoclopramide Monohydrochloride Monohydrate
7	Metoclopramide Hydrochloride
8	Ondansetron Hydrochloride Dihydrate
9	Sodium Picosulphate
10	Lactulose
11	Macrogol 4000
12	Macrogol 4000/Sodium Sulphate Anhydrous/Sodium Bicarbonate/Sodium Chloride/Potassium Chloride
13	Macrogol 3350/Sodium Sulphate Anhydrous/Sodium Bicarbonate/Sodium Chloride/Potassium Chloride
14	Macrogol 3350/Sodium Bicarbonate/Sodium Chloride/Potassium Chloride
15	Macrogol 3350/Sodium Sulphate/Sodium Chloride/Potassium Chloride/Ascorbic Acid/Sodium Ascorbate
16	Paromomycin Sulphate
17	Vancomycin Hydrochloride
18	Chromoglic Acid Disodium
19	Metformin Hydrochloride
20	Glicazide
21	Acarbose

22	Ascorbic Acid
23	Nicotinamide
24	Pyridosine Chloride
25	Pantethine
26	Zinc Sulphate
27	Levocarnitine
28	Cisteamine Bitartrate (Mercaptamine Bitartrate)
29	Zinc Acetate
30	Miglustat

	ATC B: blood and blood forming organs
1	Warfarin Sodium
2	Lysine acetylsalicylate
3	Tranexamic Acid
4	Ferrous Gluconate
5	Cobamamide

	ATC C: cardiovascular system
1	Mexiletine Hydrochloride
2	Propafenone Hydrochloride
3	Flecainide Acetate
4	Etilefrine Hydrochloride
5	Isosorbide Mononitrate
6	Trimetazidine Dihydrochloride
7	Clonidine Hydrochloride
8	Potassium Canrenoate
9	Pentoxifylline
10	Naftidrofuryl Oxalate Acid
11	Troxerutin
12	Propranolol Hydrochloride
13	Timolol Maleate
14	Sotalol Hydrochloride
15	Nadolol
16	Metoprolol Tartrate

17	Celiprolol Hydrochloride
18	Verapamil Hydrochloride
19	Diltiazem Hydrochloride
20	Captopril
21	Lisinopril Dihydrate
22	Perindopril Arginine
23	Perindopril Erbumine (Tert-Butylamine)
24	Perindopril Tosylate
25	Quinalapril Hydrochloride
26	Pravastatin Sodium

ATC D: dermatologicals
No water-soluble drugs

	ATC G: genito-urinary system and sex hormones
1	Oxybutynin Hydrochloride

	ATC H: systemic hormonal preparations, excl. sex hormones and insulins
1	Desmopressin Acetate Hydrate
2	Betamethasone Disodium Phosphate
3	Thiamazole (Methimazole)
4	Thiamazole (Methimazole)/Dibromotyrosine

	ATC J: antiinfectives for systemic use
1	Doxycycline Hyclate
2	Lymecycline (Tetracycline-Levo-Metilenlisine)
3	Tetracycline Hydrochloride
4	Minocycline Dihydrochloride
5	Bacampicillin Hydrochloride
6	Flucloxacillin Sodium
7	Clindamycin Hydrochloride
8	Lincomycin Hydrochloride

9	Ciprofloxacin Hydrochloride Monohydrate
10	Ciprofloxacin Hydrochloride
11	Phosphomycin Tromethamine
12	Isoniazide
13	Ethambutol Hydrochloride
14	Ribavirin
15	Stavudine
16	Telbivudine
17	Metisoprinole

	ATC L: antineoplastic and immunomodulating agents
1	Cyclophosphamide
2	Fludarabine Phosphate
3	Vinorelbine Bitartrate
4	Pocarbazine Hydrochloride
5	Hydroxycarbamide
6	Estramustine Sodium Phosphate

	ATC M: musculo-skeletal system
1	Ketorolac Tromethamine
2	Naproxen Sodium
3	Glucosamine Sulphate Crystalline
4	Cyclobenzaprine Hydrochloride
5	Colchicine
6	Clodronate Disodium
7	Ibandronate Sodium Monohydrate

	ATC N: nervous system
1	Morphine Sulphate
2	Paracetamol/Codeine Phosphate
3	Tramadol Hydrochloride/Paracetamol
4	Oxycodone Hydrochloride/Paracetamol
5	Tramadol Hydrochloride

6	Lysine acetylsalicylate
7	Lysine acetylsalicylate/Metoclopramide Monohydrochloride
8	Paracetamol
9	Paracetamol/Ascorbic Acid
10	Paracetamol/Pseudoephedrine Hydrochloride
11	Paracetamol/Ascorbic Acid/Phenylephrine Hydrochloride
12	Paracetamol/Chlorpheniramine Maleate/Ascorbate Sodium
13	Paracetamol/Chlorpheniramine Maleate
14	Paracetamol/Pseudoephedrine Hydrochloride/Diphenydramine Hydrochloride
15	Phenytoin Sodium
16	Valproate Sodium
17	Buxamina
18	Vigabatrin
19	Levetiracetam
20	Metixene Hydrochloride Monohydrate
21	Amantadine Hydrochloride
22	Selegiline Hydrochloride
23	Chlorpromazine Hydrochloride
24	Trifluoperazine Dihydrochloride
25	Zuclopentixol Dihydrochloride
26	Clorazepate Dipotassium
27	Hydroxyzine Dihydrochloride
28	Flurazepam Monohydrochloride
29	Clomipramine Hydrochloride
30	Amitriptyline Hydrochloride
31	Dothiepin Hydrochloride
32	Oxitriptan
33	Acetyl-L-Carnitine Hydrochloride
34	Amitriptyline Hydrochloride/Chlordiazepoxide Hydrochloride
35	Choline Alfoscerate
36	Naltrexone Hydrochloride
37	Lofexidine Hydrochloride

38	Betahistine Dihydrochloride
39	Tetrabenazine

	ATC P: antiparasitic products, insecticides and repellents
1	Chloroquine Diphosphate
2	Hydroxychloroquine Sulphate

	ATC R: respiratory system
1	Salbutamol Sulphate
2	Clembuterol Hydrochloride
3	Bamifylline Hydrochloride
4	Doxofylline
5	Acetylcysteine
6	Diphenydramine Hydrochloride
7	Chlorpheniramine Maleate
8	Promethazine Hydrochloride

ATC S: sensory organs
No water-soluble drugs

	ATC V: various
1	Deferiprone
2	Folinate Calcium

Colours of Legend
Alternative dosage forms (such as orodispersible tablets, chewable tablets, or suppositories) are available in addition to immediate-release tablets.
Granules or powders for oral use are available in addition to immediate-release tablets.
Oral solutions, syrups, effervescent tablets, vials (dosage and osmolarity adjustment or viscosity increase with thickener agents) are available in addition to immediate-release tablets.
Just tablets are available on the Italian pharmaceutical market.

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1. **S. Logrippo**, G. Bonacucina, M. Cespi, D.R. Perinelli, L. Pavoni, P. Blasi, R. Ganzetti, M. Sestili, G.F. Palmieri. Dysphagia: daily concerns and innovative formulative approaches. 17th Summer School for Italian PhD in Pharmaceutical Technology. Advanced School in Nanomedicine. Sardegna Ricerche Research Park, Pula (CA), Italy, 25-28 September 2017. Book of Abstract p. 61.

Award

1. Best Poster Award 2017 - 11th A.It.U.N. Annual Meeting, 11-12th May 2017, Padova.