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.

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

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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-hydroxybenzoate sodium and propyl p-hydroxybenzoate 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-hydroxybenzoate sodium (1.5 mg/mL) and propyl p-hydroxybenzoate 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 $R^2 \geq 0.999$.

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 of 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) was 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 micro-organisms 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 micro-organisms 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 diluents: 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 micro-organisms 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.

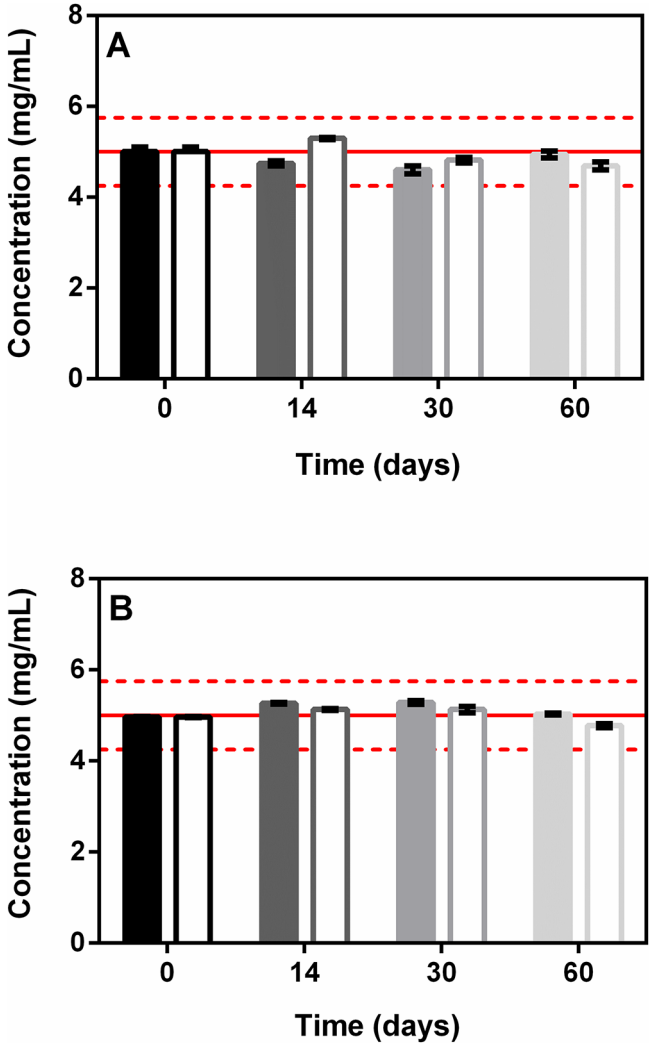

Figure 1 Spectrophotometric determinations in a standard solution (A) and an extemporaneous preparation (B) of potassium canrenoate. Full bars represent samples stored at room temperature (22°–25°C) and empty bars samples stored in refrigerator (2°–8°C). The upper and lower dotted red line levels represent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

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 drug delivered.

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 dishanalysed. 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 micro-organisms 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 :

Recovery % = (Mean value of ATCC strain in presence of product/ Mean value of ATCC strain in positive control) X 100

This standard had to be observed by each micro-organism 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 dispersion, the decrease in potassium canrenoate in the solutions 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

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

(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

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

(A) Upstream extemporaneous preparation net weight and weight loss (g)			
Crushed tablet + water 10 mL 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

(50 mL) were 8.4±0.0, 18.7±0.0, 10.3±0.0 and 92.6±0.0, respectively.

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.

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 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 ongoing 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 allows us to obtain an alternative liquid form that guarantees correct diuretic treatment.

What this paper adds

What is already known on 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 a feeding tube, weight loss of the drug occurred, but the amount of the delivered diuretic agent 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.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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