Baratta F, Zingarelli C, Felismè F, Lamy E, Cajuste R, Saint-Jean PH, Ambreck E, Di Lascio G, Brusa P. Spironolactone suspension for paediatric use: formulation, quality and stability. Pharmacy Practice. 2024 Jul-Sep;22(3):2987.
https://doi.org/10.18549/PharmPract.2024.3.2987

Original Research

Spironolactone suspension for paediatric use: formulation, quality and stability

Francesca Baratta, Chiara Zingarelli, Fedor Felismè, Editson Lamy, Romel Cajuste, Pierre Hugues Saint-Jean, Emanuela Ambreck, Gaetano Di Lascio, Paola Brusa

Received (first version): 28-Sep-2023 Accepted: 02-Dec-2023 Published online: 14-Jul-2024

Abstract

Background: The compounding of extemporaneous preparations has historically been an essential part of the pharmacist's role, and, even today, its importance is recognized in all regulatory frameworks worldwide. The paediatric age group is known to be a therapeutic orphan, due to the low availability of formulations adapted to this population. There are potential dangers involved in treating paediatric patients with drugs approved for adults, or, more generally, off-label prescription medicines, since the excipients may be not suitable for children. As a result, the prescription of extemporaneous preparations is a common practice among paediatricians. **Objective:** Knowing cardiovascular diseases are currently the main cause of mortality in Haiti, the objective of this study was to develop a suitable paediatric oral liquid formulation of spironolactone with simple and low-cost excipients, and with an easy set-up method. This is in order to make the preparation suitable for the preparation in hospital or community pharmacies in those countries - even with limited resources- where it is necessary to administer spironolactone to paediatric patients. **Methods:** For the formulation being studied, in addition to the quality according to the directives set out in the European Pharmacopoeia, the stability was evaluated to assure adequate validity for therapeutic uses. For the evaluation of the uniformity of the suspension content, a standard procedure was developed through a HPLC method. The suspension samples were also analysed with a spectrophotometric assay. **Results:** The uniformity of content results confirmed that the concentration of the active molecule in each suspension was consistent. In addition, no variation in the expected concentration greater than 10% was detected after 90 days. Concerning pH, from the data, it can be observed that no sample underwent a significant variation in pH over time. **Conclusion:** We chose to focus our research on the development of a suspension with a very simple composition and a simple preparation procedure, while bearing in mind the quality of the finished product must be guaranteed. The preparation procedures should always be congruous with the equipment usually available in a community or hospital pharmacy's compounding laboratory, in whatever part of the world it is located.

Keywords: spironolactone; paediatric; compounding; Haiti; quality

Francesca BARATTA*. Department of Drug Science and Technology, University of Turin, Aid Progress Pharmacist Agreement onlus non-profit association, Via Pietro Giuria 9, 10125 Turin, Italy.
Chiara ZINGARELLI. Department of Drug Science and Technology, University of Turin, Via Pietro Giuria 9, 10125 Turin, Italy.
FEDOR FELISMÈ. Pharmacy service, Saint Damien Paediatric Hospital, Boulevard du 15 Octobre, Tabarre 27, Port-au-Prince, Haiti.
Editson LAMY. Pharmacy service, Foyer Saint Camille Hospital, Marin, Arrondissement de Croix-des-Bouquets, Port-au-Prince, Haiti.
Romel CAJUSTE. Pharmacy service, Saint Damien Paediatric Hospital, Boulevard du 15 Octobre, Tabarre 27, Port-au-Prince, Haiti.
Pierre Hugues SAINT-JEAN. Pharmacy service, Saint Damien Paediatric Hospital, Boulevard du 15 Octobre, Tabarre 27, Port-au-Prince, Haiti.
Emanuela AMBRECK. Fondazione Francesca Rava - NPH Italia ETS, Viale Premuda 38/A, 20129 Milan, Italy.
Gaetano Di LASCIO. Aid Progress Pharmacist Agreement onlus non-profit association, Via Pietro Giuria 9, 10125 Turin, Italy.
Paola BRUSA. Department of Drug Science and Technology, University of Turin, Aid Progress Pharmacist Agreement onlus non-profit association, Via Pietro Giuria 9, 10125 Turin, Italy

INTRODUCTION

The compounding of extemporaneous preparations has historically been an essential part of the pharmacist's role, and, even today, its importance is recognized in all regulatory frameworks worldwide. The capability of preparing customised medicines in a hospital or community pharmacy, is indeed very beneficial to satisfying therapeutic needs unmet by industrially manufactured medicinal products. For example, it is possible to vary the quantity of each active ingredient within a preparation, as well as to combine substances which are more efficacious when acting in concert.[1] Finally, and no less importantly, pharmaceutical compounding is a convenient way to obtain suitable medicines even when there are no options available on the market. Active pharmaceutical ingredients can be incorporated into a wide range of products including liquid, semi-solid or solid formulations in various dosage forms, including sterile ones.[2]

The paediatric age group is known to be a therapeutic orphan, due to the low availability of formulations adapted to this population.[3] For example, it has been reported that approximately 35% of medicines for endocrinal, metabolic, and CNS disorders, as well as infections and infestations, did not have paediatric dosage forms available even though they had documented dosage information for children. Moreover, more than 40% of approved products for the treatment of paediatric

www.pharmacypractice.org (eISSN: 1886-3655 ISSN: 1885-642X)

cardiovascular disease did not have a suitable paediatric dosage form.[4] The paediatric population is a heterogeneous group ranging from preterm, new-born and infants to adolescents with a vast range of physiological and developmental differences regarding organ maturation, metabolism, and other factors that impact on the pharmacokinetics and pharmacodynamics of a drug.[5] There are potential dangers involved in treating paediatric patients with drugs approved for adults, or, more generally, off-label prescription medicines, since the excipients may be not suitable for children, even in small amounts. As a result, the prescription of extemporaneous preparations is a common practice among paediatricians.[6]

The development of formulations appropriate for children can present significant challenges. In the first place, it must be considered that the use of a formulation in solid form for oral use is not preferable for paediatric patients; instead, among the adult population, oral solid dosage forms are generally more accepted by the majority of patients. This is certainly an important factor given that a solid formulation for oral use is normally easier and cheaper to develop, manufacture, transport, store and dispense than liquid medicines. Despite that, liquid formulations for oral use are recommended in that they ensure easier administration to children, especially younger children, as well as facilitating the adjustment of the dosage according to the bodyweight of the patient. However, some disadvantages have been reported. In particular, the dose and volume of liquid medicines may be limited by the solubility of drug substances; thus, requiring the addition of cosolvents or surfactants. Moreover, assuring the stability of the formulation may require buffering agents, antioxidants and preservatives.[7] Another aspect which must not be neglected is the palatability of the formulation, which must be ensured by adding suitable flavours or aromas. Furthermore, in a formulation of this type, there may be greater difficulties in ensuring stability or, in any case, may be a reduced availability of relevant reference data.[3]

In this context, several studies have shown that extemporaneous formulations are widely used, as there is a lack of suitable industrial dosage forms for children, especially for medicines of the cardiovascular pharmacological group.[8] Spironolactone is an antagonist of the mineralocorticoid receptor widely used in paediatric medicine. It is a synthetic steroid which competitively inhibits binding between aldosterone and its receptor in the distal nephron (collecting tubule) with the consequent excretion of sodium and the sparing of potassium. The diuretic power of spironolactone is relatively limited, but its potassium-sparing effect has made it an important pharmaceutical. Spironolactone is available for sale in a range of strengths in tablet form for oral use for adults and older children. However, administering the required dosage for the treatment of neonatal and paediatric patients requires the use of a liquid formulation, which is not commercially available at present.[8-9]

Cardiovascular diseases are currently the main cause of mortality in Haiti, having overtaken HIV (Human immunodeficiency virus) in the last decade. The paediatric population is also affected by pathologies of this type, and, indeed, it is estimated that 2,000 children are born every year with some type of coronary condition; of these 50% require active treatment. However, given the limited access to paediatric cardiac care, hundreds of Haitian children die every year from treatable cardiac conditions. That said, the true incidence of cardiovascular diseases in Haiti is still unknown in large part due to the lack of screening, record-keeping and data.[10]

Aid Progress Pharmacist Agreement (*A.P.P.A.*®) is a non-profit association established inside the University of Turin whose main activity is the *A.P.P.A.*® Project. The Project focuses on establishing laboratories for the compounding of personalized medicines in medical structures located in developing countries in accordance with the principles of International Health Cooperation. The Project complies with both European and guest Country legislation, while safeguarding the quality of medicinal products. After almost twenty years of work, several Projects have been established in Angola, Cameroun, Chad, Haiti and Madagascar.[1,11-13] The first *A.P.P.A.*® galenic lab in Haiti was established in 2012 at the NPH Saint Damien Paediatric Hospital in the Tabarre district, one of the poorest neighbourhoods of Port-Au-Prince, thanks to the request and support of the Francesca Rava Foundation.[14] The NPH Saint Damien is the only paediatric hospital on the island, and it treats about 80,000 children every year.[15] In the Haiti lab, it was therefore necessary to introduce several formulations for paediatric use because the number of young patients is high, and the availability of preparations designed for them is limited.

Given the high incidence of cardio pathologies among the Haitian population, it was recently recognised that there was a need for a liquid formulation for oral use based on spironolactone. In this context, the objective of this study was to develop a suitable oral liquid formulation of spironolactone with simple and low-cost excipients, and with an easy set-up method. A formulation that could be prepared in the hospital pharmacy in NPH Saint Damien in Haiti, and, more generally, in hospital pharmacies or community pharmacies in those countries - even with limited resources- where it is necessary to administer spironolactone in liquid form for oral use to paediatric patients.

METHODS

Active compound and excipients

The materials used for the galenic preparations were purchased from a pharmaceutical supplies company (Farmalabor s.r.l, Canosa di Puglia, Bari, Italy) and complied with the relevant monograph of the European Pharmacopoeia.

Suspension preparation

For the preparation of the 5 mg/ml spironolactone suspension (the exact composition in reported in table 1): first, the spironolactone is added to the mixture of glycerol and propylene glycol, and then the carboxymethylcellulose is mixed in. In a separate container, the sodium methyl parahydroxybenzoate, the citric acid and the sodium citrate are dissolved in depured

Table 1. Suspension composition for 100 ml	
Ingredients	**Quantity (g)**
Spironolactone	0,50
Propylene glycol	5,00
Glycerol	10,00
Sodium citrate	1,34
Citric acid	1,05
Sodium carboxymethyl cellulose	1,00
Sodium methyl parahydroxybenzoate	0,085
Depured water	85,00

water and this solution is added to the mixture above. The solution is mixed until it is homogenous.

All suspensions were prepared manually. After preparation, a sample of each solution was also mixed with a mechanical homogenizer (IKA-T18 digital Ultraturrax).

Quantitative analysis

For the evaluation of the uniformity of the suspension content according to the directives set out in the European Pharmacopeia[16] a standard procedure was developed. In particular, the concentration of spironolactone was quantified through a HPLC (high performance liquid chromatography) method using a UV (UltraViolet) detector (YL9300 liquid chromatograph, Younglin Instruments Co., Korea). Furthermore, the amount of spironolactone was also evaluated by spectrophotometric analysis (V-730 UV-Visible Spectrophotometer, Jasko Inc., Japan) in order to compare the results obtained from the two analytical techniques.

All chemicals were analytical grade (Sigma–Aldrich, Milan, Italy). Experiments were performed at room temperature (15–25 °C).

The analytical chromatographic conditions were: Zorbax Eclipse XDB-C18, 80Å, 4.6 x 250 mm, 5 µm column; a mobile phase consisting of two solvents: a mixture of acetonitrile: water: acetic acid (A) [75 : 23.7 : 1.3 v/v] and acetonitrile (B). Eluent (70%: 30%) was pumped at a flow rate of 1 ml/minute. The detection wavelength UV was 230 nm, and the injection volume was 20 µl. The elution time was approximately 3 minutes. After each analysis the column was washed with 100% acetonitrile for 15 minutes and then brought back to the initial conditions with the mobile phase. The HPLC calibration curve was built using spironolactone analytical standard at concentrations ranging 0,025 and 0,200 mg/ml. All the samples to be analysed were diluted with mobile phase to obtain a final concentration within the range of the calibration curve. In particular, in order to quantify the amount of spironolactone in the suspension, a quantity of 990 µl of mobile phase was added to 10 µl of the preparation to be analysed, the sample was vortexed (Velp Scientific ZX3 vortex machine) for 60 seconds and then filtered (Teknokroma syringe filters nylon 0,45 µm 13 mm ⌀ pk/100). The supernatant thus obtained was separated, suitably diluted to fit within the range of the calibration curves and analysed as described above.

The spironolactone suspension samples were also analysed with a spectrophotometric assay. A calibration curve was built using spironolactone analytical standard at concentrations ranging from 0,00625 to 0,05 mg/ml. All the samples to be analysed were diluted with ethanol to obtain a final concentration fitting the range of the calibration curve. In order to quantify the amount of spironolactone in the suspension, a quantity of 1 ml of ethanol was added to 150 µl of the preparation to be analysed, the sample was vortexed (Velp Scientific ZX3 vortex machine) for 60 seconds and then centrifuged (Beckman Coulter Microfuge 18 Centrifuge) at 6,000 rpm for 6 minutes. The supernatant thus obtained was separated, suitably diluted to fall within the range of the calibration curves and analysed to obtain a spectrophotometric trace between 190 and 600 nm. Two methods were used in the analysis of the spectrophotometric results: the superimposition of the spectra, and the max absorbance of the reference peak for spironolactone according to literature.[17]

Evaluation of suspension stability

Stability tests were carried out on three lots of the 5 mg/ml spironolactone suspensions. Each lot, after preparation, was analysed in order to define the initial state and, then, divided into two parts: the first was stored at room temperature, while the second was stored in a temperature-controlled oven at 40°+/- 2°C.

The samples of the suspension were tested at regular intervals in order to evaluate the stability after storage under different environmental conditions. More specifically, the evaluation of suspension stability was performed immediately after the preparation of the suspension and then repeated every 15 days for 90 days.

For each lot stored at room temperature and in a temperature-controlled oven, the following parameters were assessed: the uniformity of content using the methods described in the previous paragraph 2.3; the pH (Hanna HI 9321 pH meter AC/DC input 110 V), and the evaluation of the dispersion by an optical microscope (LEICA DM 2500 microscope, Leica Microsystems GmbH, Wetzlar, Germany) connected to a digital camera at 630 magnification. In addition, as prescribed by the European Pharmacopoeia, tests were performed to detect any phase separation in the suspension, and whether the suspension could be redispersed by manual agitation.[1]

The tests were performed in triplicate for each batch, and for each of the two conditions of storage temperature. For each parameter the average of the obtained results was evaluated, and the corresponding standard deviation (SD) was calculated. Values were accepted if SD was less than 2%.

The samples under analysis were stored protected from light.

[1] According to the European Pharmacopoeia in the chapter titled "liquid formulations for oral use", suspensions may have some sediment which, however, can be easily dispersed by shaking in order to obtain a suspension that is adequately stable to ensure the correct dosage [16].

RESULTS

Each suspension was analysed immediately after preparation, and successively at regular intervals of time as reported above, using the methods described in paragraph 2.3.

The uniformity of content results confirmed that the concentration of the active molecule in each suspension was consistent. In fact, both the HPLC and spectrophotometric analysis revealed that the variation in concentration of spironolactone in the different suspension batches was less than 10%. In addition, no variation in the expected concentration greater than 10% was detected after 90 days, regardless of the storage temperature and independently of the analytical method employed. The average of the results obtained by HPLC and spectrophotometry at initial conditions, and then at 45 days, and at 90 days are reported in table 2 and table 3 respectively.

Concerning pH, table 4 reports the average pH values of the suspensions. From the data, it can be observed that no sample underwent a significant variation in pH over time.

The microscope examination (table 5) revealed that no significant differences are evident between the suspensions prepared manually and those prepared using the mechanical homogenizer.

All of the suspensions displayed a phase separation after one month from the date of preparation, regardless of the storage temperature of the samples. However, as prescribed by the Pharmacopeia, it was possible to easily re-disperse the solid phase again by simple manual agitation.

DISCUSSION

The development of formulations suitable for administration to patients in the paediatric age is a particularly important issue given the lack of availability in general terms, and more specifically regarding formulations in liquid form.

As regards the development of oral use formulations containing spironolactone for paediatric use, it is interesting to note that no approved drugs are currently available in liquid form, and the galenic formulations prepared may vary greatly among hospital and community pharmacies.

With the purpose of standardizing the galenic preparations and the preparation procedure, a number of studies for the development of compounded oral liquid formulations have been published in literature. Many of these formulations specify the use of commercial mixtures of excipients of which the composition may, for commercial reasons, vary over time hence invalidating the stability studies performed.[18] Moreover, these ready-to-use bases, while relatively easy to use, are extremely expensive and, in any case, difficult to source in developing countries.

One of the aims of the present study is to avoid using commercial vectors and, hence, to concentrate on developing formulations based on combinations of readily available, low-cost, and easy to use excipients: conditions that facilitate their use regardless of the geographical region in the world and ensuring equal access to medicines in any part of the world.

In this light, a liquid formulation for oral use was developed with a composition and preparation procedure suitable for any

Table 2. HPLC results

		T0		T 45				T90			
			ROOM TEMPERATURE		THERMOSTATIC OVEN		ROOM TEMPERATURE		THERMOSTATIC OVEN		
		Mean area values	Average	Mean area values	Δ % compared to average value at T0	Mean area values	Δ % compared to average value at T0	Mean area values	Δ % compared to average value at T0	Mean area values	Δ % compared to average value at T0
Sample	1	2518,68	2541,22	2426,74	-4,50	2437,62	-4,08	2424,25	-4,60	2426,68	-4,51
	2	2562,31		2508,12	-1,30	2576,98	1,41	2565,86	0,97	2531,47	-0,38
	3	2542,67		2513,77	-1,08	2430,51	-4,36	2574,74	1,32	2548,74	0,30

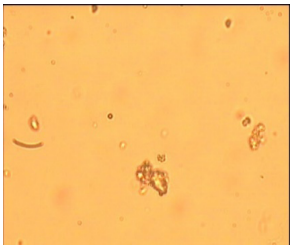
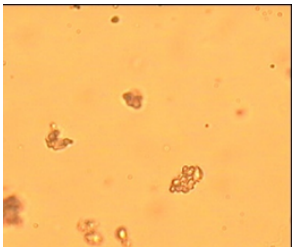
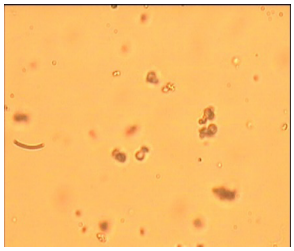
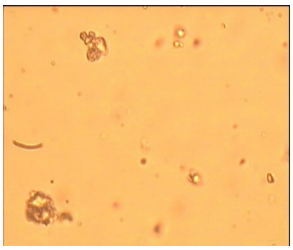
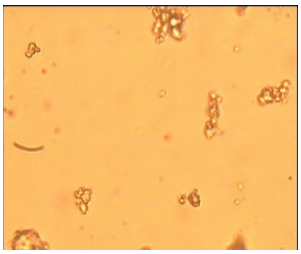
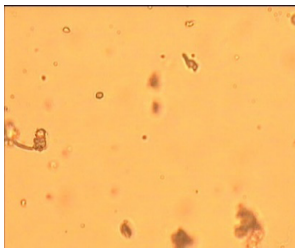
Table 3. Spectrophotometric results

		T0		T 45				T90			
			ROOM TEMPERATURE		THERMOSTATIC OVEN		ROOM TEMPERATURE		THERMOSTATIC OVEN		
		Mean absorbance values	Average	Mean absorbance values	Δ % compared to average value at T0	Mean absorbance values	Δ % compared to average value at T0	Mean absorbance values	Δ % compared to average value at T0	Mean absorbance values	Δ % compared to average value at T0
Sample	1	0,531	0,532	0,523	-1,69	0,499	-6,20	0,521	-1,32	0,535	0,56
	2	0,512		0,515	-3,20	0,494	-7,14	0,558	-6,39	0,520	-2,26
	3	0,552		0,545	2,44	0,540	1,50	0,555	3,01	0,552	3,76

Table 4. pH values

		T0		T 45			T90			
			ROOM TEMPERATURE		THERMOSTATIC OVEN		ROOM TEMPERATURE		THERMOSTATIC OVEN	
		Mean pH value	Average	Mean pH value	Δ % compared to average value at T0	Mean pH value	Δ % compared to average value at T0	Mean pH value	Δ % compared to average value at T0	Mean pH value	Δ % compared to average value at T0
Sample	1	4,33	4,32	4,37	1,16	4,31	-0,23	4,46	3,24	4,45	3,01
	2	4,31		4,39	1,62	4,31	-0,23	4,44	2,78	4,44	2,78
	3	4,33		4,36	0,93	4,28	-0,93	4,44	2,78	4,44	2,78

Table 5. Microscope examination

	T0	T 90	
		ROOM TEMPERATURE	THERMOSTATIC OVEN
Manually mixed suspension			
Meccanically homogenized suspension			

context. In fact, the preparation method was designed to be as simple as possible, also by providing for manual preparation, considering that the developed standard operating procedure must be easy to replicate in the compounding laboratory of any community or hospital pharmacy.

Given the solubility properties of spironolactone, which is practically insoluble in water, but soluble in ethanol - an excipient that is certainly not suitable for paediatric use, it was decided to develop a suspension-based formulation for oral use. This type of formulation generally has the added advantage of masking the taste of the active ingredients due to their insolubility in the dispersive medium.

The selection of excipients with suitable safety, along with appropriate physicochemical properties, is of paramount importance in paediatric formulation development.[19] In order to evaluate which raw materials to use, it is necessary to refer to the relevant guidelines provided by Regulatory Agencies. On this subject, it is essential to underscore that the propylene glycol, one of the excipients present in the formulation developed in this study, may only be used in concentrations inferior to 50 mg/kg/day in patients between the ages of 4 weeks and 5 years old.[20] Taking account of the dosages generally recommended for spironolactone in paediatric patients (0.5 e 1.5 mg/kg q12h [21]), the present formulation from this study equals a maximum intake of 30 mg/kg/day of propylene glycol.

Instead, concerning the need to ensure the microbiological stability of the formulation, it should be stressed that, according to European Medicines Agency (EMA) guidelines, "The use of preservatives is normally considered acceptable in multidose preparations. However, for many preservatives there is still limited data regarding the levels of safe exposure in children of different ages".[22] The addition of preservatives should therefore be restricted to the minimum amount possible. The parabens, a class that includes sodium methyl parahydroxybenzoate used in the formulation in this study, are however, considered the safest preservatives in paediatrics.[23] Parabens are usually used at concentrations between 0.01 and 0.2% and the maximum recommended daily dose is 10mg/kg/day.[23-24] This is much higher dosage than that used in this study.

For oral liquid formulations, EMA recommends that the administered volume not exceed 5 mL for children under 5 years considering that small volumes are normally better tolerated.[18] the preparation developed in this study is in line with this recommendation.

Once the formulation procedure was defined, it became essential to test the stability. In this case, the tests performed at room temperature were applied to define the stability of samples under storage conditions approved by the European Pharmacopeia. Stability tests carried out at higher temperatures can be used with two objectives. Firstly, they can accelerate the analysis times, as a month of storage in these conditions is the equivalent to four months under standard conditions.[1] Secondly, they reflect the typical climatic conditions of tropical environments and therefore help predict stability in these environments, like those usually present in Haiti, where conservation at controlled temperature cannot be guaranteed.

As regards the quantification of the active molecule both in terms of uniformity of concentration and the stability of the formulation, two analytical techniques were employed: HPLC and spectroscopy. Scientific publications usually propose high performance liquid chromatography (HPLC) as a suitable method for medicinal product analysis.[17] Considering that the Eur. Ph.[16] does not prescribe a specific analytical method to test the concentration of an active principle in a medicinal product (the Ph. Eur. stating that a "suitable analytical method" should be applied), we also applied a spectrophotometric assay. The choice was dictated by the requirement to develop not only a preparation procedure reproducible in any context, but also quantification procedures using instrumentation with a low cost and ease of use. Such instrumentation ensures in fact its use in developing countries. In this light, the results obtained in the present study represent a positive outcome as the data obtained by HPLC and spectrophotometry are substantially equivalent.

As for dispersion by mechanical homogenizer, this step turned out to be unnecessary. In general, however, it would be preferable to include mechanical mixing in protocols for the preparation of suspensions as pharmacies are not usually equipped with a microscope to perform a visual verification. This is an aspect should be considered by the pharmacist when equipping a compounding laboratory: this kind of equipment is not excessively expensive, costing the same as an analytical balance or a capsule filler; equipment usually presents in any galenic laboratory.

CONCLUSIONS

The ability to personalize dosages is particularly useful when treating age groups with different needs like children and the elderly. It is also useful when treating patients suffering from neoplasia or degenerative diseases that can cause a range of conditions, including various pain entities. The possibility to dispose of personalized medicines is also fundamental in the veterinary field where there are often no specific registered products on the market.[1]

The lack of commercially available, approved oral liquid spironolactone-based medication, inevitably means that most of the prescribed therapy must be prepared Galenically. As a consequence, the preparation procedures for this type of medicine should be congruous with the equipment usually available in a community or hospital pharmacy's compounding laboratory, in whatever part of the world it is located. For this reason, we chose to focus our research on the development of a suspension with a very simple composition and a simple preparation procedure, while bearing in mind the quality of the finished product, which must be guaranteed.

To assure the quality of the product prepared in any context, the development of operating procedures for the quantification of the active molecule must be cost-effective and easy to use such as the spectrophotometric method used in this study, which is certainly an important example.

ABBREVIATIONS

SD: standard deviation

T0: initial conditions

T45: 45 days of storage

T90: 90 days of storage

DATA AVAILABILITY STATEMENT

Data is contained within the article

ACKNOWLEDGMENTS

The authors would like to thank Tom O Byrne for the linguistic revision of the text.

AUTHOR CONTRIBUTIONS

Francesca Baratta: conceptualization, investigation, data curation, writing – original draft preparation, writing – review & editing, funding acquisition. Chiara Zingarelli: : investigation, data curation, writing – review & editing

Fedor Felismè: investigation, Editson Lamy: investigation, Romel Cajuste: conceptualization, Pierre Hugues Saint-Jean: conceptualization, Emanuela Ambreck: conceptualization, Gaetano Di Lascio: conceptualization.

Paola Brusa: conceptualization, funding acquisition, writing – review & editing.

DISCLOSURE

The author reports no conflicts of interest in this work.

FUNDING

The study was supported by the fund "Fondi Ricerca Locale" of the University of Turin provided by the MIUR (Ministry of Education, Universities and Research).

References

1. Baratta F,Germano A, Brusa P. Diffusion of counterfeit drugs in developing countries and stability of galenics stored for months under different conditions of temperature and relative humidity. Croat Med J. 2012;53:173-84. https://doi.org/10.3325/cmj.2012.53.173
2. Falconer JR, Steadman KJ. Extemporaneously compounded medicines. Aust Prescr. 2017;40:5-8.
3. Greenhalgh LL, Passos MMBD, Agrizzi AL, Monteiro MSSB. Compounded medications for cardiovascular use in neonatology: an integrative review. Rev Paul Pediatr. 2022;41:2021167. https://doi.org/10.1590/1984-0462/2023/41/2021167
4. Giam JA, McLachlan AJ. Extemporaneous product use in paediatric patients: a systematic review. IJPP. 2008;16:3-10.
5. Lopalco A, Denora N. Paediatric Formulation: Design and Development. Int J Mol Sci. 2020;21;7118. https://doi.org/10.3390/ijms21197118
6. Yuliani SH, Putri DCA,Virginia DM, Gani MR, Riswanto FDO. Prevalence, Risk, and Challenges of Extemporaneous Preparation for Pediatric Patients in Developing Nations: A Review. Pharmaceutics. 2023;15:840. https://doi.org/10.3390/pharmaceutics15030840
7. Nunn T, Williams J. Formulation of medicines for children. Br J Clin Pharmacol. 2005;59:674-6. https://doi.org/10.1111/j.1365-2125.2005.02410.x
8. Ahmed H, VanderPluym C. Medical management of pediatric heart failure. Cardiovasc Diagn Ther. 2021;11:323-335. https://doi.org/10.21037/cdt-20-358
9. Basusarkar A, Kandimalla A, Dudley R. Chemical Stability of Compounded Spironolactone Suspension in Proprietary Oral MixTM Over a 90-day Period at Two Controlled Temperatures in Different Storage Containers. Int J Pharm Sci Rev Res. 2013.
10. Minthor L,Lartigue JW, Vervoort D, Robinson O,Pezzella AT.Cardiac Surgery in Haiti: High Need, Low Support. Int J Pharm Sci Rev Res. 2023. https://doi.org/10.1016/s0140-6736(18)31644-1
11. APPA.® non-profit association website. Available online: www.progettoappa.it (June 2023)
12. Baratta F,Germano A, Di Lascio G,Petieau R,Brusa P. Establishment of galenic laboratories in developing countries to produce high quality medicines: results of Aid Progress Pharmacist Agreement (A.P.P.A.®) Project. Croat Med J. 2014;55(6):662-8. https://doi.org/10.3325/cmj.2014.55.662
13. Baratta F,Di Lascio G, Tarditi F, Petieau R, Brusa P. Galenic formulations to fight the phenomenon of counterfeiting in developing Countries. Journal of Drug Delivery Science and Technology. 2016;32(B):313-315.
14. Francesca Rava Foundation website. Available online: https://www.nph-italia.org/home/ (June 2023)
15. NPH - Saint Damien Hospital website. Available online: https://www.nph.org/stdamien/ (June 2023)
16. European Directorate for the Quality of Medicines and HealthCare. European Pharmacopoeia, 10th edition. Geneva: Council of Europe, 2020
17. Moffat AC, Osselton DM, Widdop B. Clarke's analysis of drugs and poisons. 4th ed. London: Pharmaceutical Press; 2011
18. Cavelier M, Gondé H, Costa D, et al. Development of an Oral Liquid Formulation of Nicardipine Hydrochloride Compounded with Simple Excipients for the Treatment of Pediatric Hypertension. Pharmaceutics. 2023;15:446. https://doi.org/10.3390/pharmaceutics15020446
19. Salunke S, Clapham D, Agrawal A, Hughes K, Nunn T. Best practices for selection of excipients for paediatrics - Workshop reflection. Eur J Pharm Biopharm. 2021;160:77-81. https://doi.org/10.1016/j.ejpb.2020.12.021
20. European medicines agency. Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. 2019. Available online: https://www.ema.europa.eu/en/documents/scientific-guideline/annex-european-commission-guideline-excipients-labelling-package-leaflet-medicinal-products-human_en-1.pdf
21. Masarone D, Valente F, Rubino M, et al. Pediatric Heart Failure: A Practical Guide to Diagnosis and Management. Pediatr Neonatol. 2017;58:303-312. https://doi.org/10.1016/j.pedneo.2017.01.001
22. www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmaceutical-development-medicines-paediatric-use_en.pdf
23. Rouaz K, Chiclana-Rodríguez B, Nardi-Ricart A, Suñé-Pou M, Mercadé-Frutos D, Suñé-Negre JM, Pérez-Lozano P, García-Montoya E. Excipients in the Paediatric Population: A Review. Pharmaceutics. 2021;13:387. https://doi.org/10.3390/pharmaceutics13030387
24. European medicines agency. Reflection paper on the use of methyl- and propylparaben as excipients in human medicinal products for oral use. 2015. Available online: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-use-methyl-propylparaben-excipients-human-medicinal-products-oral-use_en.pdf

www.pharmacypractice.org (eISSN: 1886-3655 ISSN: 1885-642X)