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Personalised medicine

Permeation studies through porcine small intestine of furosemide solutions for personalised paediatric administration

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ABSTRACT

Personalized medicine is a challenging research area in paediatric drug design since no suitable pharmaceutical forms are currently available. Furosemide is an anthranilic acid derivative used in paediatric practice to treat cardiac and pulmonary disorders in premature infants and neonates. However, it is not commercialized in suitable dosage forms for paediatrics. Elaborating new paediatric formulations when no commercial forms are available is a common practice in pharmacy laboratories; amongst these, oral liquid formulations are the most common. We developed two extemporaneous paediatric oral solutions of furosemide (pure powder). The characterization and stability study were also performed. Parameters such as organoleptic characteristics, rheology, pH, content of active substance, and microbial stability were evaluated at three temperatures for two months. Evaluation of all these parameters showed that both solutions were stable for 60 days at 4 and 25 °C. Moreover, *ex vivo* studies were performed to evaluate the permeation behaviour of developed solutions through porcine small intestine to evaluate the potential paediatric biological parameters influencing the bioavailability and efficacy. A validated spectrofluorometric method was also used for this purpose. Our results guarantee a correct dosification, administration and potential efficacy of furosemide when is formulated in liquid oral forms for the treatment of cardiac and pulmonary disorders in children.

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1. Introduction

Furosemide (FUR) is an anthranilic acid derivative (Smith et al., 1980). It is commonly used as a high-ceiling or loop diuretic(Foye et al., 1995) showing a rapid onset of action and high efficacy (Brazy and Gunn, 1976). It acts on the ascending thick limb of the loop of Henle by inhibiting the co-transporter of sodium, potassium and chloride, and further causes the excretion of calcium, magnesium and bicarbonate ions (Giebisch, 1985). Furosemide is one of the most effective and least toxic diuretics used in paediatric practice to treat cardiac and pulmonary disorders in premature infants and neonates (Agyralides et al., 2004).

In some countries, FUR is only commercially available in tablets. The lack of oral liquid dosage forms on the market is an ongoing problem in many clinical settings. In this context, personalized medicine is a current and challenging research area. Paediatrics are more vulnerable to drug administration errors due to a lack of appropriate dosages forms and strengths for use in this group of patients. Therefore, the community and hospital pharmacists are often challenged with the preparation of a dosage form not commercially available using traditional pharmaceutical compounding techniques as an alternative (Provenza et al., 2014; Santoveña et al., 2012). Only a few products have been designed and tested specifically for paediatric use (Winckler, 2002). Reported studies of medicines commonly prescribed for children with cardiovascular problems concluded that most medicines were unlicensed (Standing and Tuleu, 2005). Unfortunately, many children continue to be treated with unlicensed medicines or adult medicines used "off-label" (Waller, 2007). For this reason, in the design and formulation of dosage forms the physical, chemical and biological properties of the active substance, as well as, the rest of pharmaceutical ingredients used should be seriously considered (Nahata and Allen, 2008).

Orally administered liquids are still considered the standard forms for these patients (Bauters et al., 2012), because a single liquid paediatric preparation may be used for infants and children of all ages, with the dose of the drug varied by the volume administered reducing potential dosage mistakes, and helping the treatment adherence (Allen, 2008).

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Available data on solubility, oral absorption and permeability are sufficiently conclusive to classify FUR as a class IV drug (low solubility, low permeability) according to the biopharmaceutics classification system (Granero et al., 2010). Due to its acidic nature (pK_a 3.9) it is mostly absorbed in stomach and upper small intestine (Karkhile et al., 2010). Several *in vitro* approaches, based on cell cultures were used to estimate the human oral absorption of drugs, being the Caco-2 cell line the most widely employed (Jung et al., 2006). As clinical studies on paediatrics have a special regulation, in the present work, porcine small intestine was used to calculate the effective permeation (P_{eff}) of FUR because of its similarity with the human small intestine (Sanderson and Walker, 1999).

Therefore, the main purpose of the present work was the design of paediatric oral formulations of FUR and the development of a simple and feasible standard operating procedure (SOP) for its use by pharmacist both in community and hospital facilities to guarantee the correct dose administering, the efficiency of the treatment and the formulation stability during its preparation and storage. As second aim, the physicochemical properties, microbiological stability and P_{eff} of apical to basolateral side were evaluated and compared with reported results using Caco-2 cells.

2. Materials and methods

2.1. Chemical and reagents

The active pharmaceutical ingredient (API) FUR, excipient for syrup (sucrose, water, sorbitol, glycerine, flavouring, citric acid, methylparaben, potassium sorbate, sodium phosphate, and colouring) and excipient for syrup sugar free (water, sorbitol, glycerin, flavouring, sodium saccharin, xanthan gum, citric acid, potassium sorbate, methylparaben, sodium citrate, propylparaben, and colouring) were pharmacopoeia grade and provided by Acofarma S.A. (Barcelona, Spain). All other chemicals were all of analytical grade (Sigma–Aldrich, Spain). Double distilled water was used after filtration in a Milli-Q® Gradinet A10 system apparatus (Millipore Iberica S.A.U., Madrid, Spain).

2.2. General SOP

The development of age-appropriate paediatric formulations is paramount to enable child adherence to treatment. It encompasses multi-dimensional considerations including the administration route, the formulation technology, the dosage strength and other parameters such as organoleptic properties, viscosity or pH.

The preparation of extemporaneous formulations often involves commercial dosage forms modification to facilitate an oral administration as liquid forms (Nahata and Allen, 2008); however, the use of the API by modifying a commercially available tablet or capsule could involve clinical and legal implications. Therefore, we used pure powder to prepare the solutions and commercially available excipients for facilitating the elaboration by pharmacists. Solution II is also suitable for the diabetic population as the excipient used is sugar-free.

Table 1
Components of formulations.

Ingredients	Solution I	Solution II
Furosemide (mg)	200	200
Buffer carbonate–bicarbonate (pH 10) (mL)	10	10
Excipient for syrup (mL)	q.s. 100	–
Excipient for syrup sugar free (mL)	–	q.s. 100

Compositions of the developed formulations of FUR are reported in Table 1 and were elaborated according to the following SOP: 200 mg of FUR were added to 10 mL carbonate/bicarbonate buffer solution (pH 10) at room temperature (Budavari, 1989), and sonicated (>20 KHz) in a an ultrasonic bath p-selecta 514 (Vidrafoc, Barcelona, Spain) for 5 min. Subsequently, the vehicle (excipient for syrup in solution I or excipient for syrup sugar free in solution II) was slowly added under stirring using a magnetic stirrer (700 rpm) until a complete solution was achieved. Blank samples were also elaborated in a similar way. All formulations were stored under the same conditions for further analysis.

2.3. Stability test

Further to the preparation of solutions, aliquots of 10 mL were stored in amber glass vials at three temperatures (4, 25 and 40 °C) for 2 months. Measures were performed at 0, 7, 15, 30 and 60 days. Analyses comprised the physicochemical testing of quantifiable parameters considered likely to change during storage, such as appearance, pH, rheological behaviour, microbial growth, and drug content. The acceptance limits established are shown in Table 2.

2.3.1. Appearance

The physical appearance was studied via visual and olfactory examination of the samples stored at each temperature. Thus, parameters such as odour, colour or tendency to spontaneously form precipitates could be appreciated.

2.3.2. pH measurements

pH values ($n = 3$) were measured using a digital pH/mV-meter micro-pH 200 (Crison Instruments S.A., Barcelona, Spain) at three temperatures and pre-selected times. A significant variance of pH over an adequate value per formula was considered to indicate degradation of the pharmaceutical compound or erroneous elaboration.

Table 2
Acceptance limits.

Parameter	Acceptance limits	
Appearance (colour, odour, absence of particles in suspension)	Slightly orange (solution I). Pink (solution II), transparent and with characteristic odour (fruity)	
Furosemide content	±10% of the original amount	
pH	7–10	
Rheological behaviour	Complies (1–250 mPa s)	
Microbiological test [a]	TAMC (CFU/mL)	TYMC (CFU/mL)
	$<10^2$	$<10^1$
	Absence of *Escherichia coli*	

TAMC: total aerobic microbial count; TYMC: total yeast/mould count.
[a] European pharmacopoeia specifications for microbiological quality of non-sterile products for pharmaceutical use.

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