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Preparation and characterization of spironolactone-loaded nano-emulsions for extemporaneous applications

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ABSTRACT

In neonates as well as in adults having swallowing difficulty, oral medication is given through a nasogastric tube making liquid formulations preferable. In this study, we present the high potential of nanometric emulsions formulated by spontaneous surfactant diffusion, as extemporaneous formulations of hydrophobic drug. Spironolactone used as hydrophobic drug model, was incorporated in oil before formulation at a concentration of 13.5 mg/g oil. Then, all formulations were evaluated from pharmacotechnical and clinical standpoints, for their use in hospital or community pharmacy. The strength of this new liquid formulation lies on the simplicity, efficiency and reproducibility of their low energy process as on clinical aspects: high dose uniformity, facility to be administered through in nasogastric tube without any retention and a stability of 2 months at least compatible for an extemporaneous use. Moreover, this emulsion presented spironolactone content of 3.75 mg/ml among the most concentrated formulations published.

1. Introduction

Spironolactone is a specific aldosterone antagonist which is used as a potassium sparing diuretic (Sweetman, 2009). Spironolactone is therefore interesting in the treatment of primary hyperaldosteronism or for the management of heart failure in both adults and infants. This drug is also used to treat refractory edema reducing, for example, lung congestion in premature infants (Atkinson et al., 1988). In neonates like in adult having swallowing difficulty (mostly in neurology, gastroenterology, geriatric and reanimation departments), oral medication is given through a nasogastric tube making liquid formulations preferable. These liquid formulations should preferably have a minimal spironolactone content of 3 mg/ml to minimize the extra water-load to kidneys (Kaukonen et al., 1997). However, this drug content should be lower than 5 mg/ml to be handled during patient dosing adjustment. Therefore, the spironolactone-loaded preparation volume is between 5 and 100 ml.

Currently, there is no commercially available oral liquid preparation (Agence nationale de sécurité du médicament et des produits de santé (ANSM)) (ANSM, 2014) due to the poor water-solubility of spironolactone (28 μg/ml at 25 °C) (Sutter and Lau, 1975). Various extemporaneous preparations were therefore developed. Poor water solubility has been firstly solved by using high osmolality syrups as suspending agents (Allen and Erickson, 1996; Mathur and Wickman, 1989; Nahata et al., 1993) or high amount of cosolvents (Pramar et al., 1992) both approaches being not recommended especially for neonates (Leff and Roberts, 1987). In addition, suspensions like tablets showed incomplete oral behavior, slow dissolution rate and a risk of degradation during storage (Clarke et al., 1977; Laouini et al., 2011; Levy, 1962). Then, approaches using cyclodextrins (Kaukonen et al., 1997; Soliman et al., 1997), nanocapsules (Limayem Blouza et al., 2006), nanoparticles (Dong et al., 2009) or liposomes (Laouini et al., 2011) were developed. Spironolactone solubilization into nanoparticles may be particularly interesting by improving the dissolution rate and protecting the drug from degradation by confining it within these

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particles or oil droplets (Couvreur et al., 2002; Laouini et al., 2011). In addition, it is worth noting that nanometric particles or oil droplets also induce stabilization against sedimentation or creaming and so prevent from heterogeneous preparation, in so far as the particles/droplets are solely under the influence of the Brownian motion (Anton et al., 2008).

In hospital or community pharmacy, formulation process have to be simple, quick, reproducible, requiring few personal/materials and compatible to the good manufacturing practices (GMP) or adapted GMP according to the considering state. Besides, storage stability beyond the month is not necessary for extemporaneous preparation due to treatment personalization and the frequent prescription changes.

A promising technology lies to formulate liquid preparation of hydrophobic drugs is in the low-energy nano-emulsification of drug loaded oils (Anton et al., 2008; Li et al., 2013). The nano-emulsions are generated through a spontaneous emulsification method, which is a simple, quick, and efficient alternative to obtain extemporaneous liquid preparation.

The purpose of the present study is to investigate the potential of emulsification process to develop liquid preparation of hydrophobic drugs for hospital applications. For this purpose, we developed new formulations of spironolactone-loaded nano-emulsions made by low-energy emulsification process. Spironolactone was chosen as common hydrophobic drug model. Then, all formulations were evaluated from pharmacotechnical and clinical standpoints, for their use in hospital applications.

2. Materials and methods

2.1. Materials

Micronized spironolactone (batch 1104544443) was purchased from Inresa, Bartenheim, France. Oils (oleoyl polyoxyl-6 glycerides, Labrafil M 1944CS®; medium chain triglycerides, Labrafac lipophile WL 1349® and propylene glycol dicaprylate/dicaprate, Labrafac PG®) were kindly gifted from Gattefossé, Saint-Priest, France. Another oil (caprylic/capric triglycerides, Miglyol 812N®) was kindly gifted from Cremer, Witten, Germany. Nonionic surfactants (polyoxyl 35 castor oil, Kolliphor ELP®; polyoxyl 15 hydroxystearate, Kolliphor HS 15® and polyoxyl 40 hydrogenated castor oil, Kolliphor RH 40®), were kindly gifted from BASF, Ludwigshafen, Germany. Chemicals from analytical grade used were as follows: ethanol (99.9%, Fischer Scientific, Leicestershire, UK), ethyl acetate (99.98%, Fischer Scientific, Leicestershire, UK) and acetonitrile (>99.9%, Fischer Scientific, Leicestershire, UK). Radiopaque polyurethane nasogastric tubes (reference AL514, batch 14A27) were purchased by Cair LGL, Civrieux d'azergues, France. Distilled water was obtained using an Autostill 4000x® system (Jencons, Franklin, TN, USA).

2.2. Methods

2.2.1. Emulsion formulation

First, various amounts of oil and nonionic surfactants were magnetically stirred at 50 rpm for 30 s at a controlled temperature of (25 ± 1) °C. Their respective proportion is a critical parameter that allows the precise control of the nano-emulsion size distribution and polydispersity. Once homogeneous, this mixture was added to distilled water and magnetically stirred at 200 rpm until a bluish and translucent suspension was obtained (achieved within a few seconds). We described the mechanism upon which the method is based in our previous work (Hallouard et al., 2011). The formulation parameters were rationalized through (i) the surfactant/oil weight ratio: $SOR = 100 \times w_{surfactant}/(w_{surfactant} + w_{oil})$ and (ii) the surfactant–oil/water weight ratio: $SOWR = 100 \times w_{surfactant+oil}/(w_{surfactant+oil} + w_{water})$. The value of the SOWR was kept constant at 40% throughout this study since its influence on the nano-emulsion formation is negligible (it only influences the droplet concentration (Hallouard et al., 2011). All formulations were prepared in triplicate.

2.2.1.1. Spironolactone solubility studies. The criteria for selecting oil for pharmaceutical use are the lack of toxicity, the absence of drug degradation in the selected oil and a high capacity for the oil to dissolve the drug in question. Thence, a solubility study of

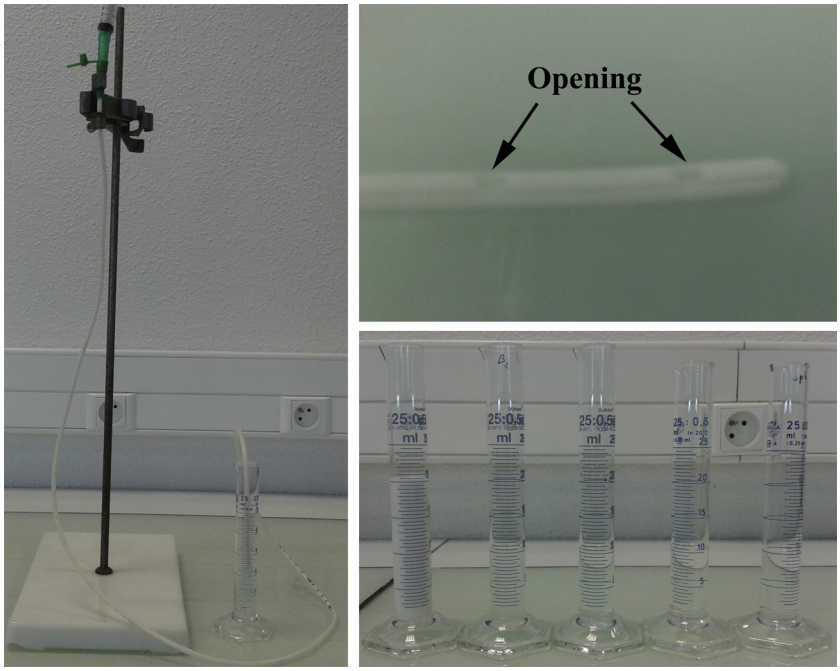

Fig. 1. Montage for emulsion administration study through a nasogastric tube (left). All purges were collected and their volume measured in order to determine their spironolactone content by UV–vis spectrophotometer (bottom right). Distal end of the nasogastric tube presenting lateral openings (top right).