Redispersible lipid nanoparticles of Spironolactone obtained by three drying methods

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ABSTRACT

This work aimed to prepare a pediatric formulation for Spironolactone a poor water soluble drug characterized by incomplete oral bioavailability, bitter taste, and tendency to destabilize in aqueous media. Regarding to the good solubility of Spironolactone in lipid materials, lipid nanoparticles seemed to be an excellent way to overcome these issues. In an attempt to prevent eventual stability problems linked to lipid nanoparticles, we dried the prepared nanosuspensions into redispersible powder, in association with pediatric adapted drying carriers. A comparison study between drying methods have been conducted. Fluid Bed Drying was introduced as a novel method of drying lipid nanoparticles. This method was compared to usual methods; freeze drying and spray drying. The comparison took into account quality of the obtained powder and its redispersibility, palatability, drug stability during the process and the effect of the drying method on particle size, enntrapment efficiency and dissolution behavior of Spironolactone. The obtained preparations showed size increase of nanoparticles, significant differences about chemical stability and dissolution behavior of same formulas dried with different techniques have been noticed. Thanks to excellent entrapment of drug substance into nanoparticles, the extemporaneous prepared nanosuspensions exhibited a palatable sweety taste adapted to the needs of pediatric patients.

1. Introduction

Development of drug formulations for pediatric use is a common challenging problem for pharmaceutical industry. There is neither ideal formulation nor ideal excipient, all choices taken during formulation have to be justified regarding to special issues linked to this category of ages [1]. In the last decade many regulatory efforts have been conducted to protect children from harmful medications [2,3].

Spironolactone (SP) is a mineralocorticoid widely prescribed in pediatric population. It is considered as receptor antagonist of aldosterone and a potassium sparing diuretic [4]. Primary used to treat edema, and hypertension, many other indications are cited: congestive heart failure, primary aldosteronism, hypokalemia, precocious puberty, etc. This drug is marketed as tablets with the commercial name Aldactone® at 3 strengths 25, 50 and 75 mg [5].

However there is no marketing authorization available worldwide of a pediatric dosage form for this drug. Thus pharmacists or caregivers have to crush or disperse commercially available tablets of Spironolactone in order to make a “sub-formulation” like suspensions or capsules. Due to the lack of data, this operation is often not sufficiently studied and could be risky regarding the drug substance characteristics.

Indeed, this work aimed to prepare a pediatric formulation for Spironolactone, a drug substance characterized by its poor aqueous solubility, slow dissolution rate, incomplete bioavailability, bitter taste and tendency to destabilize in aqueous media. Many attempts to formulate this molecule for adult or pediatric use have been explored in literature [6–13] and many stability issues have been described.

Formulation of aqueous dispersions of lipid nanoparticles is an elegant way to enhance and control drug bioavailability, improve stability, and mask bitterness of some drugs [14–22]. They are interesting carriers for oral delivery of lipophilic and, to a certain extent, hydrophilic substances. Their production can be done without the use of organic solvents, this can make this kind of formulation ideal for pediatric use [23–26]. However, these lipid nanoparticle dispersions can present some instability phenomena (lipid crystallization, particle size increase, gelling, etc.) [27–29]. In order to prevent eventual issues, lipid nanoparticles are dried by spray-drying or freeze-drying techniques into redispersible powders [30,31]. Spray drying (SD) is achieved by atomization of liquid throw a nozzle; this liquid is instantaneously dried by a co-current air flow [33,34].