Development and In vivo Evaluation of Cefdinir Nanosuspension for Improved Oral Bioavailability

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ABSTRACT

Cefdinir belongs to III generation cephalosporins and is an oral extended spectrum antibiotic. It is a BCS class IV drug, with low solubility resulting in a low oral bioavailability of about 21% for capsules and 25% for suspension. The aim of this work was to develop cefdinir nanosuspension to improve the oral bioavailability. Nanosuspensions were prepared by using single stabilizer and combination of two stabilizers by employing high speed homogenization followed by sonication method and the prepared nanosuspensions were characterized. Initially, the drug excipient compatibility was checked by Differential Scanning Calorimeter (DSC). In trial experiments, tween 80 concentration was varied from 0.25 to 0.75% and homogenization time was varied from 2.5 min to 10 min, and 0.5% surfactant concentration was found optimal. Further, trials were conducted with SLS and poloxamer 188 at the same concentration to know the role of stabilizers. Trials were also done by preparing cefdinir nanosuspensions with different techniques for comparative studies and their size and poly dispersity indices (PDI) were found. The mean size and zetapotential (ZP) of nanosuspensions, prepared by high speed homogenization followed by sonication varied from 541.7 to 947.2 nm and -13.7 mV to -22.4 mV respectively. Results of saturation solubility and dissolution studies were used to optimize the nanosuspension. Optimized nanosuspension showed improved saturation solubility, dissolution rate and oral bioavailability by 1.752 fold when compared to marketed suspension and found to be stable at RT for 2 months. The bioavailability improvement was significant at a level of P value < 0.05 when student unpaired t-test was used. Hence, cefdinir nanosuspension formulation holds a great promise in improving dissolution rate and oral bioavailability.

KEYWORDS: Bioavailability; Differential Scanning Calorimetry (DSC); High pressure homogenization; Nanosuspension; Dissolution rate.

Introduction

Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants. Nanosuspension consists of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1µm in size (Arun kumar et al., 2009). To overcome the poor solubility and to enhance the oral bioavailability, nanoparticle based drug delivery systems like nanosuspensions (drug nanoparticles) can be used. These systems enhance the saturation solubility and there by dissolution velocity and increase the drug concentration gradient between lumen of the gut and the blood (Kocbek et al., 2006), thus promote absorption of drug from GIT, resulting in improvement of oral bioavailability (Mittapalli et al., 2007). Formulation as nanosuspensions is a useful technique to all drug compounds belonging to biopharmaceutical classification system (BCS) classes II and IV to increase their solubility and hence partition in to gastrointestinal barrier (Prasanna Lakshmi and Giddam Ashwini Kumar, 2010).

Drugs no longer need to be in the soluble form. High drug loading is achieved as the drug exists in the form of pure solid, and this can significantly reduce the administration volume of high dose. They increase the physical and chemical stability of drugs as they are actually in the solid state (Van Eerdenbrugh et al., 2008). Further, nanosuspensions provide the passive targeting capabilities, when injected intravenously, and represent a very promising targeting carrier system for anti-cancer agents due to enhanced permeability and retention (EPR) effect upon successful surface modification of the drug nanoparticles (Xiaohui et al., 2009).

Different methods and techniques were used to prepare nanosuspensions (Grau M.J et al., 2000), they include Precipitation (Gassmann et al., 1994), High pressure homogenization, Media milling, Dry Co-grinding, Emulsion/Microemulsion method (Trotta et al., 2003). Famous insoluble drugs like Griseofulvin, Albendazole (Mittapalli et al., 2008), Itraconazole, Paclitaxel and Naproxen were investigated for preparing nanosuspensions. Some oral (RAPAMUNE®, EMEND®, TRICOR®, MEGACE®ES and TRIGLIDE™) and parenteral (paclitaxel ABRAXANE®) nanosuspensions are currently available in market (Jiraporn, 2007).