Comparative Bioavailability of Cefuroxime Axetil from Tablets and Self-Microemulsifying Drug Delivery Systems in Rats

Satish Puttachari¹, Navanath. V. Kalyane¹, and Sarbani Duttagupta²

¹BLDEA’s College of Pharmacy, Bijapur- 586103, India, and ²Department of Pharmaceutics, Jadavpur University, Kolkata 700032, India.

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ABSTRACT

Cefuroxime axetil has poor bioavailability due to low solubility. This can be surmounted by preparing the drug by self-microemulsifying drug delivery system (SMEDDS). In this study the bioavailability of cefuroxime axetil from SMEDDS and tablets was evaluated in Wistar rats. The optimized SMEDDS formulation was prepared using Labrasol®, Gelucire® 44/14 and Lutrol®E400. The formulation was evaluated for micro-emulsification properties and percent in-vitro dissolution. The HPLC method was developed and optimized to estimate the drug content in the plasma. The method was clearly separating the cefuroxime A and B polymorphs and LOD and LOQ values are satisfactory. Rats were randomized in to two groups - one group of animals were administered with SMEDDS and another with tablet formulation. At frequent intervals the blood samples were withdrawn and analysed for drug content. The pharmacokinetic parameters were calculated using PK Solve software. The calculated bioavailability and tmax from SMEDDS was 1687.06 μg/mL.min and 50 min, respectively, whereas for tablet it was 1219.803 μg/mL.min and 62 minutes, respectively. The bioavailability of SMEDDS formulation was 1.5 times more than the marketed formulation, indicating a significant improvement in oral bioavailability. In conclusion, this study confirms that the SMEDDS formulation is a viable strategy for enhancing the oral bioavailability of cefuroxime axetil.

KEYWORDS: Self-emulsifying; Bioavailability; Pharmacokinetics; PK solver; SMEDDS; Cefuroxime; Antibiotic.

Introduction

Cefuroxime axetil is a selective second generation cephalosporin belonging to BCS class II used against different kinds of bacterial infections. It is reported to have bioavailability of 35 to 50%, maximum drug concentration occurs at 1 to 4 hours and elimination half-life is 1 to 2 hours (Ravindra et al., 2009) exhibiting poor, variable bioavailability. Hence it is difficult to establish optimal oral dosage schedule. Cefuroxime bioavailability after oral and IP administration was nearly 24% and 75%, respectively (Carretero et al., 2004).

Upon oral administration, cefuroxime axetil rapidly hydrolyses in intestinal mucosa with 37–52% of an oral dose reaching to systemic circulation as cefuroxime (Ravindra et al., 2009; Mandell GL and Perti WA, 1996). Peak serum levels occur within 2-3.6 hr following an oral dose; the reported area under the curve is 19.9 mg/mL.h in healthy subjects after administration of a single oral cefuroxime axetil 500 mg dose. Approximately 33–50% of the circulating cefuroxime is protein bound. It is distributed throughout the body tissues and fluids including gall bladder, liver, kidney, bones, uterus, ovary, sputum, bile, peritoneal, pleural and synovial fluids. It penetrates meninges during inflammation and reaches therapeutic levels within the CSF and crosses the placenta (Mandell GL and Perti WA, 1996). It is largely (52%) excreted unchanged in the urine and a small percentage is excreted in breast milk; most of the drug is recovered within the first 6 h after administration. Elimination half-life (T1/2) is 1-2 hr in patients with normal renal functions and increases as renal function declines (Arora et al., 2010; Gudigennavar et al., 2013). The Cefuroxime exhibits good intestinal permeability with poor aqueous solubility. Therefore, absorption is dissolution rate- limited and hence increasing the dissolution of drug shall enhance the bioavailability. Therefore, enhancing the saturation solubility and effective surface area can greatly enhance the bioavailability of Cefuroxime (Kawabata et al., 2011).

SMEDDS are isotropic and thermodynamically stable preparations consisting of oil, surfactants and co-surfactants forms oil-in-water micro emulsions when mixed with water under gentle stirring. On oral administration, digestive motility of stomach and intestine provides agitation required for self-emulsification (Reddy, 2011). SMEDDS technique was chosen for increasing the bioavailability because it provides smaller particle size