Acta Pharmaceutica Sinica B 2013;3(2):113–122

Institute of Materia Medica, Chinese Academy of Medical Sciences
Chinese Pharmaceutical Association

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com

ORIGINAL ARTICLE

Improvement in the dissolution rate and tableting properties of cefuroxime axetil by melt-granulated dispersion and surface adsorption

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Received 19 November 2012; revised 29 December 2012; accepted 18 January 2013

KEY WORDS

Molecular modeling;
Gelucire 50/13;
Sylysia 350;
Microbiological assay;
Rapidly dissolving tablet

Abstract A combination of melt-granulated dispersion and surface adsorption techniques was used to enhance the dissolution and tableting properties of cefuroxime axetil (CA). Gelucire 50/13 was used as the melt-dispersion carrier and Sylysia 350 was used to adsorb the melt dispersion. Solubility studies showed an 8-fold increase in solubility at a ratio of 1:1.5 for CA:Gelucire 50/13. The minimum quantity of Sylysia 350 required to achieve the desired flowability and compressibility was 0.5 parts of Sylysia 350 per unit of Gelucire 50/13. Phase solubility studies showed negative ΔG^0_{tr} values for Gelucire 50/13 at various concentrations (2–10%, *w*/*v*), indicating the spontaneous nature of solubilization. FT-IR and DSC spectra exhibited drug-excipient compatibility. Molecular modeling by a computational method employing energy minimization revealed entrapment of CA in Gelucire 50/13. The total potential energy of CA (70.562 kcal/mol) was reduced to 33.578 kcal/mol after solid dispersion with Gelucire 50/13. P-XRD studies indicated that the presence of Sylysia 350 is

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Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.apsb.2013.01.001

less likely to promote the reversion of the amorphous CA to a crystalline state. *In vitro* dissolution studies demonstrated an improved dissolution rate, and drug release at 15 min (Q_{15min}) exhibited a 15-fold improvement. The rapidly dissolving CA tablets showed improved dissolution with improved tableting properties.

1. Introduction

Drugs which belong to class II of the biopharmaceutical classification system (BCS) are characterized by high membrane permeability, slow dissolution rate (due to low aqueous solubility), and high peroral dose[1]. The solubility or dissolution rate of a drug in this category is therefore a key factor in determining the rate and extent of its absorption. Enhancement of the dissolution rate is vital to attain a suitable blood concentration for therapeutic effect, as their dissolution rates are typically the rate-limiting step for bioavailability. Cefuroxime axetil (CA) is an established broad spectrum β-lactamase-stable cephalosporin with poor water solubility. It is used orally for the treatment of mild to moderate respiratory tract infections, acute bacterial otitis, pharyngitis, tonsillitis, mild to moderate uncomplicated skin infections, and uncomplicated urinary tract infections[2].

Several technological methods have been reported for improvement of solubility and dissolution rate of poorly water-soluble drugs, namely (a) reducing particle size to increase surface area; (b) solubilization in surfactant systems; (c) formation of water soluble complexes; (d) use of prodrug and drug derivatization approaches such as strong electrolyte salt forms that usually have higher dissolution rates; (e) lyophilization utilizing skimmed milk as a carrier[3]; (f) manipulation of the solid state of the drug substance to improve drug dissolution, *i.e.,* by decreasing crystallinity of the drug substance through formation of solid dispersions[4]. Solid dispersion can be defined as distribution of active ingredients in molecular, amorphous, and/or crystalline forms surrounded by an inert carrier. The solid state characteristics of solid dispersions have been extensively studied and reported[5,6]. Formulation of poorly water-soluble drugs as solid dispersions leads to a marked improvement in their dissolution rates and is often accompanied by an increase in their relative bioavailability[7,8].

Recently, many researchers reported solid dispersions using Gelucire (polyglycolized glyceride) by fusion and solvent evaporation techniques[9,10]. Gelucire is a varying mixture of mono, di and triglycerides with polyethylene glycol esters of fatty acids. They are inert, semisolid and waxy amphiphilic excipients. A low hydrophilic–lipophilic balance (HLB) value in Gelucire decreases the dissolution rate whereas a high HLB value enhances the dissolution rate. The low HLB compounds are composed of partial glycerides while those with HLB values above 10 are mixtures of partial saturated glycerides and polyethylene glycol (PEG) esters. Gelucire 50/13 is a semisolid excipient with an HLB value of 13 and melting point of 50 °C. Its hydrophilic property makes it a good choice for use as a carrier in preparation of solid dispersions by fusion method[11,12].

Although Gelucire 50/13-based solid dispersions greatly enhance the dissolution rate of poorly water soluble drugs, they have some disadvantages such as poor flow, poor compressibility and difficulty in pulverization[5]. In order to overcome these problems an inert material with good flow and compressibility may be used to adsorb the melt dispersion on its surface. Sylysia is an amorphous SiO_2 with high specific surface area and porosity and is generally recognized as safe (GRAS) under United States FDA (Food and Drug Administration) regulations. Sylysia 350 is a dry, white micronized porous powder having an average particle size of 3.9 μm, and is tasteless and odorless. It has a high specific surface area (300 m^2/g) and a high adsorption capacity (310 mL/100 g), making it a good material for adsorption of a high proportion of drug. It is used primarily as a tablet excipient to improve the ease of powder flow through the tableting process, which provides more accurate dosages. It can be also used for powderizing liquids, to increase the viscosity of liquids and gels, or to protect sensitive compounds from moisture. It is used in research as a drug carrier in solid dispersions to improve dissolution[13]. Spray-drying indomethacin and Sylysia resulted in an amorphous form of indomethacin in a solid dispersion, probably due to its incorporation into mesopores that inhibit crystallization of the drug[14]. This amorphous structure was stable for at least 2 months at elevated temperature and humidity. Similar results (dissolution rate improvement and amorphous drug structure in the dispersion) were also obtained with tolbutamide and spironolactone[15].

Hence, the primary objective of the present research work was to improve the solubility and dissolution rate of CA by melt-dispersion granulation employing Gelucire 50/13 as a meltable hydrophilic carrier. The secondary objective was to convert the melt dispersion into flowable and compressible dispersion granules to yield a rapidly dissolving (more than 85% drug dissolution within 30 min) tablet formulation.

2. Materials and methods

2.1. Materials

Cefuroxime axetil was a generous gift from Aurobindo Pharma Ltd., India. Gelucire 50/13 was a generous gift from Gattefosse India Pvt Ltd., India, and Sylysia 350 was a gift from Fuji Silysia Chemicals, Japan. Crospovidone and Avicel PH 102 were purchased from M/s FMC Biopolymer (Mumbai, India). All other chemicals and reagents used were of analytical grade.