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ORIGINAL ARTICLE

Formulation of immediate release pellets containing famotidine solid dispersions

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Abstract Famotidine (FM) is a potent H2-receptor antagonist used for the treatment of peptic ulcer. It has a low and variable bioavailability which is attributed to its low water solubility. In this study, the dissolution of the drug was enhanced by a preparation of solid dispersion using two hydrophilic carriers, namely Gelucire 50/13 and Pluronic F-127. The prepared solid dispersions were characterized by differential scanning calorimetry (DSC), which indicated that there were no signs of interaction of the drug with the carriers used in the case of solid dispersions containing higher polymeric contents (1:3 and 1:5). FM solid dispersions in the matrices of Gelucire 50/13 and Pluronic F-127 (1:3) were used to prepare pellets. The scanning electron microscope (SEM) images of pellets showed that the pellets have spherical shape and their size depends on the carrier used. The dissolution of the drug from either solid dispersion or pellets was performed. The dissolution study depicted that, the presence of the drug in solid dispersion enhanced its dissolution in comparison with the drug itself. Also, the drug release from the manufactured pellets was found to be improved in the case of solid dispersions (drug:carrier 1:3). A complete drug release occurred after 30 min from pellets containing solid dispersions, while only about 30% of the loaded FM was released from pellets containing untreated drug after 2 h.

1. Introduction

Solid dispersion technique was selected as it was utilized in a limited number of researches to increase the solubility of famotidine. Solid dispersion (SD) is defined as the dispersion of one or more active ingredients in inert carriers at solid state prepared by fusion, solvent, or solvent-fusion methods (Chiou and Riegelman, 1971; Ford and Rubinstein, 1978). It has been widely used to improve the dissolution rate, solubility and oral absorption of poorly water-soluble drugs (El-Badry and Fathy, 2005; El-Badry and Fathy, 2006; Douroumis et al., 2007; Thybo et al., 2007). In solid dispersions, the particle size

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of the drugs is reduced, the wetability and the dispersibility are enhanced; therefore, drug dissolution is improved markedly (Craig, 2002; Abdul-Fattah and Bhargava, 2002; Sethia and Squillante, 2004). Gelucire 50/13 and poloxamer 407 are among the several carriers which have been employed in preparing solid dispersions (Newa et al., 2008; Yassin et al., 2009). Gelucire is a family of vehicles derived from the mixtures of mono-, di- and triglycerides with polyethylene glycol (PEG) esters of fatty acids. These Gelucires are available with a range of properties depending on their hydrophilic-lipophilic balance (HLB) and melting point range (33–65 °C) (Sutananta et al., 1994; Ainaoui and Vergnaud, 1998). They have a wide variety of applications in pharmaceutical formulations as in the preparation of fast release and sustained release formulations (Ainaoui et al., 1997; Cavallari et al., 2005). Poloxamer 407 (P407), also known as Lutrol or Pluronic F127, belongs to the category of non-ionic surface active agent. It is polyoxyethylene–polyoxypropylene–polyoxyethylene block copolymer (Pluronics). It is used in the formulation of dosage forms owing to their low toxicity and ability to form a clear solution or gel in aqueous media (Alexandridis and Hatton, 1995). Pluronic F127 is also useful in the preparation of topical, rectal and ocular formulations (Dumortier et al., 2006; Chiappetta and Sosnik, 2007; Zhang et al., 2002; Ricci et al., 2005).

Famotidine (FM) is indicated for active and maintenance therapy of different types of ulcers and hypersecretory conditions. The mechanism of action, pharmacological effects, site of action, and clinical uses are the same as for the other H2-receptor antagonists, but on equimolar bases, it is reported to be about 7.5 and 20 times more potent than ranitidine and cimetidine, respectively, in inhibiting gastric acid secretion. However, it is relatively free of side effects despite its high potency (Burks, 1995; Page et al., 1997; Kadar, 1998). Famotidine reportedly undergoes minimal first-pass metabolism and its oral bioavailability in man has been reported to be low and variable (ranging from 40% to 50%) due to its poor aqueous solubility, high polarity, and gastric degradation (Hassan et al., 1990; Islam and Narurkar, 1993). Since for poorly water-soluble drugs (like famotidine) the dissolution rate is often the rate-limiting step for bioavailability, the dissolution rate is a function of the solubility and the surface area of the drug. Thus, dissolution rate will increase if the solubility of the drug is increased, and it will also increase with an increase in the surface area of the drug.

Multiple-unit dosage forms have several advantages compared with single-unit dosage forms including more stable plasma profiles and little risk of local side effects (Sandberg et al., 1988). Among the various types of multiple-unit dosage forms, pellets have attracted more attention due to their unique clinical and technical advantages. Pellets as a drug delivery system offer therapeutic advantages such as less irritation of the gastro-intestinal tract and a lowered risk of side effects due to dose dumping (Bechgaard and Nielsen, 1978). In addition, pellets disperse freely in the gastrointestinal (GI) tract, and so, they invariably maximize drug absorption, reduce peak plasma fluctuation, and minimize potential side effects without appreciably lowering drug bioavailability (Eskilson, 1985).

The present study aims to improve FM dissolution rate by the preparation and characterization of FM solid dispersions in the water soluble matrices of Gelucire 50/13 and Pluronic F-127. In addition, immediate release pellets containing FM or FM solid dispersion systems will be formulated so as to study the impact of solid dispersions on the in vitro dissolution rate of the drug from the pellets.

2. Experimental

2.1. Materials

Famotidine (FM) was kindly supplied by Riyadh Pharma (Riyadh, Saudi Arabia). Gelucire 50/13, having a melting point of 50 °C and HLB value of 13, was provided by Gattefosse (Cedex, France). Pluronic F-127 (Lutrol F127) was provided by BASF Aktiengesellschaft (Ludwigshafen, Germany). Microcrystalline cellulose (Avicel® PH101) was purchased from Serva Feinbiochemica (Heidelberg, Germany). Lactose monohydrate was purchased from Winlab (Leicestershire, UK). All other materials and reagents were of analytical grade of purity.

2.2. Preparation of solid dispersion

Solid dispersions at various weight ratios of 1:1, 1:3 and 1:5 of FAM:carriers were prepared by melting method. FM was added to the molten carrier. The drug–polymer blend was heated 10 °C above the melting point of each carrier for 5 min with continuous stirring. The system was placed in a freezer at −20 °C for 24 h. The resulting solid mass was crushed, ground gently with a mortar and pestle and passed through 500-μm sieve. The samples were kept in a desiccator until the next experiments.

2.3. Preparation of physical mixture

Physical mixtures (PM) of Famotidine with Gelucire 50/13, and Pluronic F-127 (at 1:1, 1:3 and 1:5 weight ratios of FM:drug) were prepared by blending them by mixing using a spatula followed with sieving (500 μm).

2.4. Differential scanning calorimetry (DSC)

The samples (3–5 mg) were hermetically sealed in aluminum pans and heated at a constant rate of 10 °C/min, over a temperature range of 25–250 °C. Thermograms of the samples were obtained using differential scanning calorimetry (DSC-60, Shimadzu, Japan). Thermal analysis data were recorded using a TA 50I PC system with Shimadzu software programs. Indium standard was used to calibrate the DSC temperature and enthalpy scale. N_2 was used as purging gas at a rate of 30 ml/min.

2.5. Wet massing studies using a mixer torque rheometer

The mixer torque rheometer was used in the present study to determine the binder ratio required for wet massing during extrusion/spheronization processes for manufacturing pellets. It consists of a 135-ml capacity stainless steel bowl equipped with two mixing blades with rotational speed ranging between 20 and 150 rpm (MTR-3, Caleva, Dorset, England). The data acquisition and analyses were carried out by a personal computer using data acquisition system and software package supplied by the equipment manufacturer.

Powders were mixed in a turbula mixer (type S27, Erweka, Apparatebau, Germany) and 15 g sample of this dry blend was