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Research paper

Enhancement of famotidine dissolution rate through liquisolid tablets formulation: *In vitro* and *in vivo* evaluation

Rania H. Fahmy *, Mohammed A. Kassem

Department of Pharmaceutics and Industrial Pharmacy, Cairo University, Cairo, Egypt

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Abstract

Although famotidine was reported to be 7.5 and 20 times more potent than ranitidine and cimetidine, respectively, its oral bioavailability is low and variable; due mainly to its poor aqueous solubility. The purpose of this study was to improve famotidine dissolution through its formulation into liquisolid systems and then to investigate the *in vitro* and *in vivo* performance of the prepared liquisolid tablets. The new mathematical model was utilized to formulate various liquisolid powder systems. Both DSC and XRD suggested loss of famotidine crystallinity upon liquisolid formulation which was further confirmed by SEM indicating that even though the drug existed in a solid dosage form, it is held within the powder substrate in a solubilized, almost molecularly dispersed state, which contributed to the enhanced drug dissolution properties. All the tested liquisolid tablet formulations showed higher drug dissolution rates (DR) than the conventional, directly compressed tables. In addition, the selected optimal formula released 78.36% of its content during the first 10 min which is 39% higher than that of the directly compressed tablets. Further, the bioavailability study indicated that the prepared optimal liquisolid formula did not differ significantly from the marketed famotidine tablets concerning C_{max}, t_{max}, and $AUC_{(0-8)}$ at $P < 0.05$.

Keywords: Famotidine; Liquisolid system; New formulation mathematical model; *In vitro* dissolution; Bioavailability study

1. Introduction

Over the years, various techniques have been employed to enhance the dissolution profile and, in turn, the absorption efficiency and bioavailability of water-insoluble drugs and/or liquid lipophilic medications. The use of water-soluble salts and polymorphic forms, the formation of water-soluble molecular complexes, drug micronization, solid dispersion, co-precipitation, lyophilization, microencapsulation, and the inclusion of drug solutions or liquid drugs into soft gelatin capsules are some of the major formulation tools which have been shown to enhance the dissolution characteristics of water-insoluble drugs, however, among them, the technique of "liquisolid compacts" is one of the most promising techniques [1–6].

The liquisolid systems are generally considered as acceptably flowing and compressible powdered forms of liquid medications (that implies liquid lipophilic (oily) drugs, or water-insoluble solid drugs dissolved in suitable water-miscible nonvolatile solvent systems). Such liquid medication may be converted into a dry-looking, non-adherent, free-flowing, and readily compressible powders by a simple admixture with selected powder excipients referred to as the carrier and coating materials. However, even though in the liquisolid and powdered solution systems the drug might be in a solid dosage form, it is held within the powder substrate in solution, or in a solubilized, almost molecularly dispersed state. Therefore, due to their significantly increased wetting properties and surface of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to display

* Corresponding author. Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, 1 Kasr El-Aini Street, 11562 Cairo, Egypt. Tel.: +20 105840256.
E-mail address: raniafahmy@gmail.com (R.H. Fahmy).

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enhanced drug release properties, and consequently, improved bioavailability [4–8].

Famotidine is indicated for active and maintenance therapy of various 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 H_2-receptor antagonists, but on equimolar bases, famotidine is reported to be about 7.5 and 20 times more potent than ranitidine and cimetidine, respectively, in inhibiting gastric acid secretion. However, famotidine is relatively free of side effects despite its high potency [9–13]. Although 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 [14–16]. Since for poorly water-soluble drugs (like famotidine) the dissolution rate is often the rate-limiting step for bioavailability, and 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 [17].

In this study, famotidine was selected as a model drug, since it is a very slightly water-soluble drug, and, thus, it establishes an ideal candidate for testing the potential of rapid-release liquisolid compacts [18]. The flowability and compressibility of liquisolid compacts were addressed simultaneously in the "new formulation mathematical model of liquisolid systems", which was used to calculate the appropriate quantities of the excipients (carrier and coating materials) required to produce acceptably flowing and compressible powders based on new fundamental powder properties called the flowable liquid retention potential (Φ-value) and compressible liquid retention potential (ψ-number) of the constituent powders [1,2,7,8]. The liquisolid powder systems that showed acceptable flowability were then compressed into tablets and evaluated to select the optimal formula; afterwards, a rapid and specific high-performance liquid chromatography (HPLC) method for the determination of famotidine in plasma was used to assess the bioavailability of famotidine from the selected tablet formulation in comparison to commercially available famotidine tablets.

2. Materials and methods

2.1. Materials

Famotidine was obtained from Sigma (St. Louis, MO, USA). Vivapur microcrystalline cellulose 102 (Avicel® PH 102) was obtained from JRS, J. Rettenmaier & Söhne (Rosenberg, Germany). Both colloidal silicone dioxide (Aerosil® 200) and sodium starch glycolate (Explotab) were supplied by FMC Co. (Philadelphia, PA, USA). High-performance liquid chromatography (HPLC)-grade methanol and acetonitrile were obtained from Merck (Darmstadt, Germany). All other reagents and chemicals were of analytical grade.

2.2. Application of the mathematical model for designing the liquisolid systems

In the following study, propylene glycol (PG) was used as liquid vehicle; Avicel® PH 102 and Aerosil® 200 were used as the carrier and coating materials, respectively. In order to attain optimal famotidine solubility in the liquisolid formulations, several factors were varied including the concentration of the liquid vehicle PG (10, 20, and 30 g%), and the carrier: coat ratios (different R-values) (ranging from 5 to 50). The outline of the constituents of each of the formulae prepared from the previously mentioned variables is demonstrated in Table 1.

In order to address the flowability and compressibility of liquisolid compacts, simultaneously, the "new formulation mathematical model of liquisolid systems" was employed as follows to calculate the appropriate quantities of excipients required to produce liquisolid systems of acceptable flowability and compressibility. This mathematical model was based on new fundamental powders properties (constants for each powder material with the liquid vehicle) called the flowable liquid retention potential (Φ-value) and compressible liquid retention potential (ψ-number) of the constituent powders (carrier and coating materials) as previously discussed by Spireas et al. [1,2,7,8]. According to the new theories, the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flow and compression properties. Depending on the excipients ratio (R) or the carrier:coating ratio of the powder system used, where

$$R = Q/q \tag{1}$$

As R represents the ratio between the weights of carrier (Q) and coating (q) materials present in the formulation. An acceptably flowing and compressible liquisolid system can be prepared only if a maximum liquid on the carrier material is not exceeded; such a characteristic amount of liquid is termed the liquid load factor (L_f) and defined as the ratio of the weight of liquid medication (W) over the weight of the carrier powder (Q) in the system, which should be possessed by an acceptably flowing and compressible liquisolid system. i.e.:

$$L_f = W/Q \tag{2}$$

Table 1
The composition of different liquisolid systems

Famotidine concentration in the liquid vehicle (PG) (% w/w)					
10%		20%		30%	
R	Formula No.	R	Formula No.	R	Formula No.
5	F1	5	F8	5	F15
10	F2	10	F9	10	F16
15	F3	15	F10	15	F17
20	F4	20	F11	20	F18
30	F5	30	F12	30	F19
40	F6	40	F13	40	F20
50	F7	50	F14	50	F21