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Research paper

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

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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

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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

Spireas et al. [4] used the flowable liquid retention potentials (Φ-values) of powder excipients to calculate the required ingredient quantities, Hence, the powder excipients ratios R and liquid load factors L_f of the formulations are related as follows:

$$L_f = \Phi + \Phi(1/R) \quad (3)$$

So in order to calculate the required weights of the excipients used, first, from Eq. (3), Φ and Φ are constants, therefore, according to the ratio of the carrier/ coat materials (R), L_f was calculated from the linear relationship of L_f versus $1/R$. next, according to the used liquid vehicle concentration, different weights of the liquid drug solution (W) will be used. So, by knowing both L_f and W, the appropriate quantities of carrier (Q_o) and coating (q_o) powder materials required to convert a given amount of liquid medication (W) into an acceptably flowing and compressible liquisolid system, could be calculated from Eqs. (1) and (2).

2.3. Preparation of liquisolid systems

The desired quantities previously weighed of the solid drug and the liquid vehicle (PG) were mixed and heated to 80–90 °C with constant stirring, the solution was then sonicated for 15 min, until a homogenous drug solution was obtained. Next, the calculated weights (W) of the resulting hot liquid medications were incorporated into the calculated quantities of the carrier material (Avicel® PH 102) (Q), after mixing, the resulting wet mixture was then blended with the calculated amount of the coating material (Aerosil® 200) (q) using a standard mixing process that was previously described by Spireas and Bolton [1] and Spireas [2] to form simple admixture. Later on, each selected liquisolid formula was blended with 5% of the disintegrant, Explotab (sodium starch glycolate) and the prepared liquisolid systems that were proven to have simultaneous acceptable flowability and compressibility were compressed into cylindrical tablets of desired weight using a single punch tablet press machine [1,2].

2.4. Precompression studies of the prepared liquisolid powder systems

Prior to the compression of the formulations into tablets, in order to ensure the suitability of the selected excipients, various studies were performed including differential scanning calorimetry (DSC), X-ray diffraction (XRD), and scanning electron microscope (SEM). In addition, so as to select the optimal formulae for compression, flowability studies were also carried out.

Differential scanning calorimetry (*DSC*) was performed using Shimadzu differential scanning calorimeter, DSC-50 (Shimadzu, Kyoto, Japan), in order to assess the thermotropic properties and the thermal behaviors of the drug (famotidine), Avicel® PH 102, Aerosil® 200, as well as the liquisolid system prepared. Samples of 3–4 mg of the pure famotidine or the above-mentioned samples were sealed in a 50-μl aluminum pans at a constant heating rate of 5 °C/min. in the scanning temperature range of 0 to 500 °C. Empty aluminum pans were used as references and the whole thermal behaviors were studied under a nitrogen purge.

For further characterization of the crystalline state, the *X-ray diffraction* (*XRD*) patterns were determined for famotidine, Avicel® PH 102, physical mixtures (1:1) of famotidine: Avicel® PH 102 and famotidine: Aerosil® 200, and finally for the liquisolid system prepared. On the other hand, there was no need to carry out X- ray diffraction for Aerosil® 200 alone as it was previously proven to be a non-gritty amorphous powder [20]. The X- ray powder diffraction was obtained using Scintag XGEN-4000 X-ray diffractometer (Advanced Diffraction system, Scintag Inc., USA). The samples were exposed to Cu-K_α radiation (45 kV × 40 mA) at a scan rate of 2°/min over the 2θ range of 3–60°, the results were then obtained as peak height (intensity) versus 2θ.

Scanning electron microscopy (*SEM*) was utilized in order to assess the morphological characteristics of the row materials and the drug–carrier systems using a JEOL (JXA-840A) scanning electron microscope (Japan Electron Optical Laboratory, Tokyo, Japan). The samples were fixed on aluminum stubs with double-sided tape, gold-coated sputter and examined in the microscope using an accelerating voltage of 15 kV, at a working distance of 8 mm.

The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to get a uniform feed as well as reproducible filling of tablet dies, otherwise, high dose variations will occur. In order to ensure the *flow properties* of the liquisolid systems that will be selected to be compressed into tablets and further evaluated, angle of repose measurements, Carr's index and Hausner's ratios were adopted [19–22]. *In the angle of repose method*, the fixed height cone method was adopted [19,20]. The procedure was done in triplicate and the average angle of repose was calculated for each powder.

In the bulk density measurements, fixed weight of each of the liquisolid powder formulae prepared were placed in a graduated cylinder and the volume occupied was measured and the initial bulk density D_{Bmin} was calculated. The cylindrical graduate was then tapped at a constant velocity till a constant volume is obtained when the powder is considered to reach the most stable arrangement, the volume of the powder was then recorded as the final bulk volume, then the final bulk density D_{Bmax} was calculated. Carr's compressibility index was then calculated according to the equation [19,20]

$$\text{Carr's index } \% = \frac{D_{B\,max} - D_{B\,min}}{D_{B\,max}} \times 100 \quad (4)$$

in addition, Hausner's ratio was calculated from the equation

$$\text{Hausner's ratio} = \frac{D_{\text{B max}}}{D_{\text{B min}}} \quad (5)$$

The experiments and calculations were done in triplicate and Carr's compressibility index and Hausner's ratio with the corresponding standard deviations for each of the prepared formulae were then calculated.

2.5. Evaluation of famotidine liquisolid tables

To each of the selected formulae, 5% of Explotab was added and then, the tablets were compressed using a single-punch tablet press machine with 12 mm punch and die (Shanghai Tiane pharmaceutical machinery, Shanghai, China).The prepared famotidine liquisolid tablets of the selected formulae were further evaluated. *Famotidine content* in different liquisolid tablet formulations was determined by accurately weighing 10 tablets of each formula individually. Each tablet was then crushed and dissolved in 100 ml 0.1 N HCl, then, the solution was filtered, properly diluted, and then measured spectrophotometrically using Spectrophotometer UV-1601 PC (Shimadzu, Kyoto, Japan) at λ_{max} of famotidine (265 nm), thereafter, the famotidine content of each tablet was determined. *The friability* of the prepared formulae was measured using Digital tablet friability tester, Model DFI-1 (Veego, Bombay, India), and the percentage loss in weights were calculated and taken as a measure of friability. *The hardness* of the liquisolid tablets prepared was evaluated using Stoke's hardness tester (F.J. Stokes Machine Company, Philadelphia, US), the mean hardness of each formula was determined. *The disintegration time* was performed using USP disintegration tester, VTD-3 (Progressive Incorp., Bombay, India) and following its procedure. Finally, the *in vitro dissolution studies* were carried out and the dissolution rate of famotidine from liquisolid tablets was determined using USP Dissolution Test Apparatus II (Pharma Test, Germany) containing 400 ml of 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C. This was done by placing a tablet of each formula, containing an equivalent of 20 mg famotidine in the basket fitted with stainless steel screen of pore size 100 μm. to prevent fine particles from emerging. The basket was then rotated at 50 rpm, then, 3-ml aliquots from the dissolution medium were withdrawn at predetermined time intervals, the aliquots withdrawn were filtered through 0.45 μm Millipore® membrane filter (Versapor, German Sciences), adequately diluted and analyzed spectrophotometrically for their famotidine content at λ_{max} 265 nm against a blank of 0.1 N HCl. The experiments were done in triplicates for each of the selected liquisolid formulae and for conventional directly-compressed famotidine tablets containing also an equivalent of 20 mg famotidine for comparison.

2.6. In vivo evaluation of famotidine liquisolid tablets

2.6.1. Volunteers

The *in vivo* study was carried out on six healthy male volunteers aged between 20 and 40 years; the health status of the volunteers was confirmed by complete medical history, physical examination, and laboratory analysis for complete hematological and biochemical examination, all these were carried out at baseline. The study protocol was approved by the Ethical Committee of Cairo University (Cairo, Egypt) and each volunteer signed an informed form of consent before starting the trial. All the volunteers were active, ambulatory adults with no history of drug or alcohol abuse, nor did any of them have acute or chronic gastrointestinal, cardiac, vascular, hepatic or renal disease The subjects were instructed to take no drugs for 1 week prior to and during the course of the study; i.e., no concurrent medication was allowed during the course of the study. No consumption of nicotine was permitted 12 h before and 8 h after drug intake, moreover, on each test day, coffee, tee, and cola beverages were withheld from subjects 12 h before the administration and till the blood sampling was completed [23,24].

2.6.2. Dosage schedule and blood sampling

The study was performed on two dosage forms each containing an equivalent of 20 mg of famotidine

- Commercial famotidine tablets.
- Formula 14 of the liquisolid tablets. Each liquisolid tablet weighed 0.571 g and composed of 0.458 g Avicel® PH 102 and 0.009 g Aerosil® 200 prepared using 20% famotidine in PG (equivalent to 20 mg famotidine).

The dosage forms were administered following a single-dose, randomized, cross-over design. The volunteers were divided into two groups each containing three volunteers: Phase I: the first group received F1 while the second group received F14 LST. Phase II: the first group received F14 LST while the second group received F1. A 14-days washout period was left between the two phases.

In the experimental setup, the drug was administered after overnight fasting. At 7:00 am on the treatment day, the subjects received 400 ml of water, at 8:00 am they received the drug, with 300 ml of water. A standard breakfast was taken 3 h after the administration of the dosage form. Heparinized venous blood samples were collected in glass tubes before administration of the dosage form, and at 20, 40 min and 1, 1.5, 2, 3, 4, 6, and 8 h after drug administration. All samples were collected and serum was immediately separated from the blood cells by centrifugation at 3000 rpm for 10 min and stored frozen at −20 °C until analysis.

2.6.3. HPLC assay of plasma samples

Chromatographic separation was performed on C-18 reversed-phase column (10 μm, 250 × 4.6 mm) (Nucleosil, Germany) with an isocratic pump, model LC-10 AS (Shimadzu, Japan) using Rheodyne injector, Model 7161, Cotati (California, USA) equipped with 20 μl injector loop and Ultra-violet variable wavelength detector, Model SPD-10A (Shimadzu, Japan). The internal standard used was

cimetidine and the mobile phase consisted of acetonitrile: 0.02 M aqueous phosphoric acid (5:95, v/v) and was delivered to the system at a flow-rate of 1.0 ml/min, the detection wavelength 267 nm and the sensitivity was set at 0.0001 AUFS. All assays were performed at ambient conditions [25,26].

2.6.4. Calculation and statistical analysis

The plasma concentration–time data of the dosage forms were evaluated through the following pharmacokinetic parameters:

- $AUC_{(0-8)}$ and $AUC_{(0-\infty)}$ were determined as the area under the plasma concentration–time curve calculated by trapezoidal rule from time 0 up to the last measured time point (8 h) and from time 0 to infinity, respectively.
- C_{max} (ng/ml) was determined for each formula as the highest observed famotidine concentration during the 8-h study period.
- t_{max} (h) is the time taken to reach C_{max} for each formula.

For statistical evaluation, One-way analysis of variance (one-way ANOVA) was used to assess the significance of the difference between the pharmacokinetic parameters obtained for the tested formulations.

3. Results and discussion

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

Spireas et al. [27] clarified that the liquisolid hypothesis suggests that when the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibers in its interior as cellulose, both absorption and adsorption take place; i.e., the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive properties and large specific surface area gives the liquisolid system the desirable flow characteristics [1,2,27,28].

In order to calculate the required ingredient quantities, the flowable liquid retention potentials (Φ-values) of powder excipients were utilized. In propylene glycol, the Φ-value of Avicel® PH 102 was found to be 0.16, while for Aerosil® 200 the Φ-value used was equal to that of Cab-O-Sil® M5 as they both possessed the same specific surface area and density, and according to Spireas et al. [27], the Φ-value of a powder material is a function of its specific surface, thus, Aerosil® 200 and Cab-O-Sil® M5 are expected to have similar adsorptive power [1,2,27–29], Therefore, the Φ-value used for Aerosil® 200 in PG was 3.31. This relatively high Φ-value is advantageous as it results in smaller sizes of the formulated tablets according to Spireas et al. [27].

Using "the new formulation mathematical model", the straight line equation for Avicel® PH 102 and Aerosil® 200 in PG will be

$$L_f = 0.16 + 3.31(1/R)$$

For each R-value used, the corresponding L_f value can be calculated. As soon as the optimum liquid load factor L_f of a given excipients ratio is established for each formula and W is calculated according to famotidine concentration in PG, the appropriate quantities of Avicel® PH 102 (Q_o) and Aerosil® 200 (q_o) required to convert a given amount of liquid medication (W) into an acceptably flowing and compressible liquisolid system, were calculated using Eqs. (1) and (2). Table 2 represents the exact qualitative and quantitative composition for each formula.

3.2. Precompression studies of the prepared liquisolid powder systems

One of the most classic applications of *DSC* analysis is the determination of the possible interactions between a drug entity and the excipients in its formulation; it is very important to establish the existence of any incompatibilities during the preformulation stage to ensure the success of the subsequent stability studies [30]. Fig. 1 reveals the thermal behaviors of the pure components together with the thermal behavior of the final liquisolid system prepared. Famotidine peaks are clear in its DSC thermogram (Fig. 1a) demonstrating a sharp characteristic endothermic peak at 166.58 °C corresponding to its melting temperature (T_m); such sharp endothermic peak signifies that famotidine used

Table 2
Composition of different famotidine liquisolid formulae prepared using PG as a liquid vehicle according to the mathematical model

Formula	Famotidine conc. in PG	R	L_f	Avicel® ($Q = W/L_f$)	Aerosil® ($q = Q/R$)	Unit dose weight
F1	10%	5	0.822	0.252	0.050	0.510
F2		10	0.491	0.422	0.042	0.671
F3		15	0.381	0.544	0.036	0.787
F4		20	0.326	0.636	0.032	0.875
F5		30	0.270	0.767	0.026	1.000
F6		40	0.243	0.853	0.021	1.081
F7		50	0.226	0.917	0.018	1.142
F8	20%	5	0.822	0.126	0.025	0.255
F9		10	0.491	0.211	0.021	0.336
F10		15	0.381	0.272	0.018	0.394
F11		20	0.326	0.318	0.016	0.437
F12		30	0.270	0.384	0.013	0.500
F13		40	0.243	0.426	0.011	0.541
F14		50	0.226	0.458	0.009	0.571
F15	30%	5	0.822	0.084	0.017	0.170
F16		10	0.491	0.141	0.014	0.224
F17		15	0.381	0.181	0.012	0.262
F18		20	0.326	0.212	0.011	0.291
F19		30	0.270	0.256	0.009	0.333
F20		40	0.243	0.284	0.007	0.360
F21		50	0.226	0.305	0.006	0.380

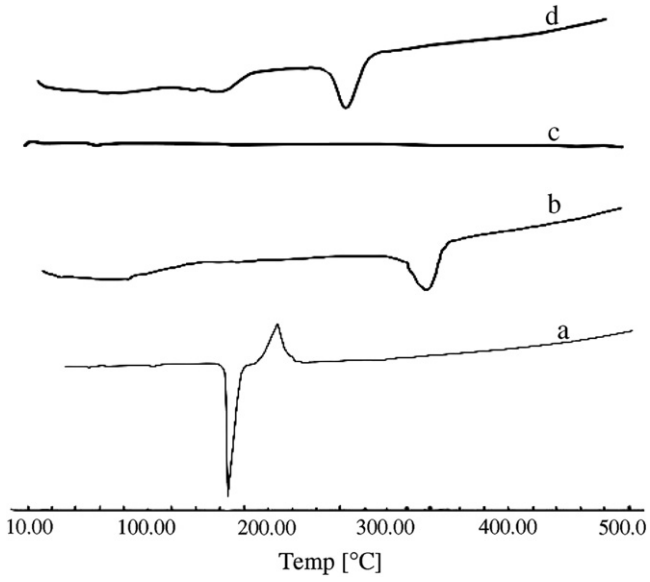

Fig. 1. DSC thermograms of (a) famotidine, (b) Avicel® PH 102, (c) Aerosil® 200, and (d) the liquisolid system. The curves have been displaced vertically for better visualization.

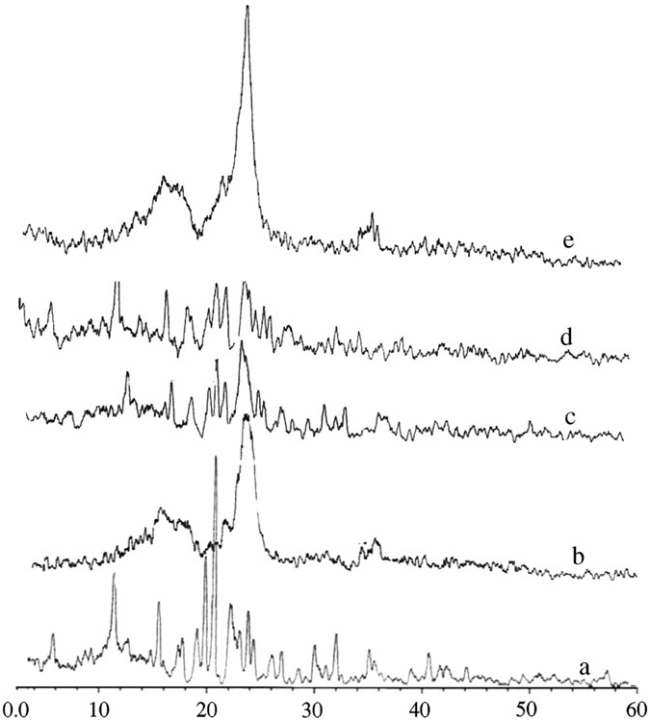

Fig. 2. X-ray diffractograms of (a) pure famotidine, (b) Avicel® PH 102, (c) Famotidine: Avicel®PH 102 (1:1) physical mixture, (d) famotidine: Aerosil®200 (1:1) physical mixture, and (e) liquisolid powder system. The curves have been displaced vertically for better visualization.

was in pure crystalline state. There was also an exothermic peak at 204.92 °C which might be due to boiling or vaporization probably following drug decomposition [31]. The thermograms of Avicel® PH 102 in Fig. 1b displayed two broad endothermic peaks at 90.18 and 342.78 °C that might correspond to the volatilization of adsorbed water followed by melting decomposition with charring of the crystalline cellulosic material. The thermal behavior of Aerosil® 200 in Fig. 1c did not show any sharp peaks; proving that the coating material was almost in an amorphous state. On the other hand, the liquisolid system thermogram in Fig. 1d displayed complete disappearance of both characteristic peaks of famotidine; a fact that agrees with the formation of drug solution in the liquisolid powdered system, i.e., the drug was molecularly dispersed within the liquisolid matrix. That was accompanied by the formation of a new endothermic peak at 285.87 °C that might correspond to the melting and decomposition of the whole liquisolid system. Such disappearance of the drug peaks upon formulation of the liquisolid system was in agreement with McCauley and Brittain [30] who declared that the complete suppression of all drug thermal features, undoubtedly indicate the formation of an amorphous solid solution. Additionally, Mura et al. [32] found out that the total disappearance of the drug melting peak indicates that drug amorphization was obtained.

The *XRD* results were in good agreement with the thermal analysis data. X-ray diffraction patterns in Fig. 2 revealed that pure famotidine was clearly in crystalline state as it showed sharp distinct peaks notably at 2θ diffraction angles of 11.5°, 15.5°, 19.5°, and 20.5°. The liquisolid powder X-ray diffraction pattern (Fig. 2e) showed only one sharp diffraction peak at 2θ angle of 22.5° belonging to Avicel® PH 102, indicating that only Avicel® PH 102 maintained its crystalline state. Such absence of famotidine constructive reflections (specific peaks) in the liquisolid X-ray diffractogram indicates that famotidine has almost entirely converted from crystalline to amorphous or solubilized form, such lack of crystallinity in the liquisolid system was understood to be as a result of famotidine solubilization in the liquid vehicle that was absorbed into and adsorbed onto the carrier material (Avicel® PH 102) and coated with the coating (Aerosil® 200); i.e., this X-ray data supported the conclusion that the famotidine formed a solid solution within the carrier matrix.

On the other hand, famotidine characteristic peaks were observed in the physical mixtures (Fig. 2c and d), demonstrating that its crystalline structure remained unchanged during the physical mixing, and that the loss of crystallinity was due to liquisolid system formation. This amorphization or solubilization of famotidine in the liquisolid system may contribute to the consequent improvement in the dissolution rate, apparent solubility and therefore the bioavailability of famotidine. Such results were also in good agreement with Mura et al. [32] and Ghebremeskel et al. [33].

The *SEM* outcomes presented in Fig. 3a and b further proved the results of both DSC and XRD. The scanning electron micrographs illustrate that pure famotidine has clearly crystalline nature as previously proven by the DSC and XRD, further, the photomicrographs of the final liquisolid system signify the complete disappearance of famotidine crystals, a fact that indicates that the drug

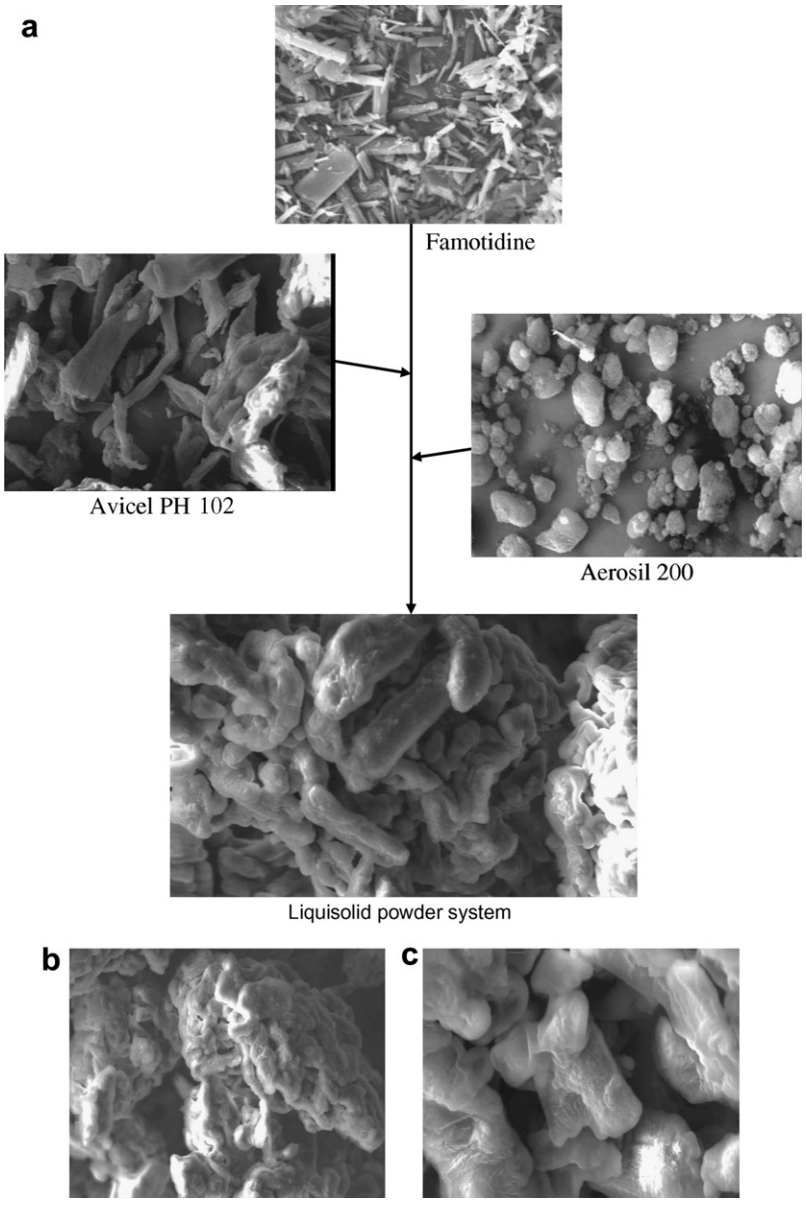

Fig. 3. (a) Scanning electron photomicrograph of famotidine, Avicel® PH 102, Aerosil® 200, and the liquisolid system (500×). (b and c) Scanning electron photomicrographs of liquisolid system prepared magnified 350× (b) and 1300× (c).

was totally solubilized in the liquisolid system. This fact proved the liquisolid formulation hypothesis that even though the drug is in a solid dosage form, it is held within the powder substrate in solution, or in a solubilized, almost molecularly dispersed state, which contributes to the enhanced drug dissolution properties [5–8].

Powder flow is a complicated matter and is influenced by so many interrelated factors; the factors' list is long and includes physical, mechanical as well as environmental factors [22]. Therefore, in our study, because of the subjective nature of the individual types of measurements as indicators of powder flow, three flow measurement types were employed; the angle of repose, Carr's index (compressibility index), and Hausner's ratio and their results are presented in Table 3.

As *the angle of repose* (θ) is a characteristic of the internal friction or cohesion of the particles, the value of the angle of repose will be high if the powder is cohesive and low if the powder is non-cohesive. As presented in Table 3, F7, F12, and F14 showed (θ) values of 35.03°, 35.82°, and 35.54°, respectively, were chosen as liquisolid systems with acceptable flowability according to the angle of repose measurements, while those having higher angles of repose were considered as non-acceptable. Powders showing Carr's index (C_i) up to 21 are considered of acceptable flow properties [20,34]. In addition to Carr's index, Hausner found that the ratio D_{Bmax}/D_{Bmin} was related to the inter particle friction, so, he showed that powders with low interparticle friction, had ratios of approximately 1.25 indicating good flow [20,34]. Therefore, formulae F3, F5, and

Table 3
Flowability parameters of famotidine liquisolid powder systems

Famotidine in PG (%)	Formula No.	Average $\theta \pm$ SD[a]	Average Carr's index (%) ± SD[a]	Average Hausner's ratio ± SD[a]
10%	F1	44.45 ± 1.12	32.61 ± 0.36	1.48 ± 0.01
	F2	38.59 ± 0.26	26.09 ± 0.35	1.35 ± 0.01
	F3	38.00 ± 0.01	*20.61 ± 0.86*	*1.26 ± 0.01*
	F4	41.53 ± 1.14	31.65 ± 0.70	1.46 ± 0.02
	F5	41.59 ± 0.29	*19.96 ± 1.03*	*1.25 ± 0.02*
	F6	39.74 ± 0.50	33.63 ± 0.42	1.51 ± 0.01
	F7	*35.03 ± 0.76*	*21.15 ± 0.40*	*1.27 ± 0.01*
20%	F8	39.04 ± 1.07	27.83 ± 0.34	1.39 ± 0.01
	F9	38.74 ± 0.40	23.58 ± 0.71	1.31 ± 0.01
	F10	39.44 ± 0.95	30.77 ± 0.02	1.44 ± 0.01
	F11	38.40 ± 0.53	27.61 ± 0.97	1.38 ± 0.02
	F12	*35.82 ± 0.94*	28.94 ± 0.52	1.41 ± 0.01
	F13	38.85 ± 0.33	33.94 ± 0.86	1.51 ± 0.02
	F14	*35.54 ± 0.48*	30.00 ± 0.03	1.43 ± 0.01
30%	F15	38.66 ± 0.56	29.83 ± 0.74	1.43 ± 0.02
	F16	37.93 ± 0.31	29.09 ± 0.03	1.41 ± 0.01
	F17	39.04 ± 0.33	32.45 ± 0.44	1.48 ± 0.01
	F18	42.07 ± 0.75	34.62 ± 0.01	1.53 ± 0.01
	F19	41.01 ± 0.01	28.20 ± 0.87	1.39 ± 0.02
	F20	39.62 ± 0.88	26.72 ± 1.22	1.36 ± 0.03
	F21	40.21 ± 0.91	32.28 ± 0.52	1.48 ± 0.01

[a] SD, standard deviation from the mean. Values in italic represent values corresponding to formulae having acceptable flow properties.

F7 were selected as acceptably flowing as they had average C_i of 20.61, 19.96, and 21.15, respectively, and average Hausner's ratios of 1.26, 1.25, and 1.27, in the same order.

Finally, formulae F3, F5, F7, F12, and F14 that were proven to be acceptably flowing according to either the angle of repose or Carr's index and Hausner's ratio were compressed into tablets and subjected for further evaluation while the rest of formulae were nominated as having unacceptable flowability and therefore excluded from further investigation.

3.3. Evaluation of famotidine liquisolid tablets

The collective data concerning famotidine content in the tablet formulations, tablets friabilities, hardness, and disintegration times are presented in Table 4.

A fundamental quality attribute for all pharmaceutical preparations is the requirement for a constant dose of drug between individual tablet; it was observable that formulae F5, F7, F12, and F14 complied with the test of *famotidine content uniformity* according to the European and British pharmacopoeias by having the average famotidine content of 94.63%, 88.42%, 86.08%, and 101.02% w/w, respectively, additionally, in each of the mentioned formulae, no more than one tablet is outside these limits nor one individual is outside the limits of 75–125%. On the other hand, F3 had an average famotidine content of 83.16% w/w. The more uniform famotidine content in the formulae F5, F7, F12, and F14 may be due to the fact that these formulae have high *R*-values of 30, 50, 30, and 50, respectively; such high *R*-values represent higher Avicel® PH 102 (carrier) concentrations that might lead to a more uniform distribution of the drug by either adsorption onto or absorption into the carrier, therefore having more homogeneous distribution throughout the batch. All the selected famotidine liquisolid tablets had acceptable *friability* as none of the tested formulae had percentage loss in tablets' weights that exceed 1%; also, no tablet was cracked, split or broken in either formula. Since all the prepared formulae met the standard friability criteria, they are expected to show acceptable durability and withstand abrasion in handling, packaging and shipment.

In general, formulation should be directed at optimizing tablet *hardness* without applying excessive compression force, while at the same time assuring rapid tablet disintegration and drug dissolution. In other words, tablets should be sufficiently hard to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing [35,36]. The mean hardness of each liquisolid formula was determined and are presented in Table 4 prov-

Table 4
Characteristics of the liquisolid tablet systems

Formula	Average famotidine content (%) ± SD[a]	Friability test		Mean hardness (N) ± SD[a]	Mean disintegration time (min) ± SD[a]
		Fines (%)	Number of broken tablets		
F3	83.16 ± 0.89	0.048	None	71.9 ± 2.31	12.2 ± 0.56
F5	94.63 ± 2.40	0.019	None	32.7 ± 2.31	4.92 ± 0.49
F7	88.42 ± 1.55	0.249	None	33.1 ± 2.12	0.81 ± 0.13
F12	86.08 ± 1.98	0.133	None	36.0 ± 0.85	1.6 ± 0.12
F14	101.02 ± 2.42	0.285	None	28.2 ± 2.12	4.2 ± 0.23

[a] SD, standard deviation from the mean.

ing that all the liquisolid tablet formulae had acceptable hardness. The hydrogen bonds between hydrogen groups on adjacent cellulose molecules in Avicel® PH 102 may account almost exclusively for the strength and cohesiveness of compacts according to Shangraw [36]; the high compressibility and compactness of Avicel® PH 102 can be explained by the nature of the microcrystalline cellulose particles themselves which are held together by hydrogen bonds, when compressed, such particles are deformed plastically and a strong compact is formed due to the extremely large number of surfaces brought in contact during the plastic deformation and the strength of the hydrogen bonds formed [36]. In addition, PG molecule contain two terminal hydroxyl groups, thus there is also a probability of forming hydrogen bonds with Avicel® PH 102.

The *disintegration time test* revealed that the liquisolid tablet formulae F5, F7, F12, and F14 disintegrated in less than 5 min (4.92, 0.81, 1.6, and 4.2 minutes, respectively), while F3 disintegrated in 12.2 min. Since our aim was to improve famotidine bioavailability via improving the tablets' physical characteristics, the long disintegration time of F3 might retard the drug release and therefore bioavailability; hence, F3 was excluded from further experiments.

The dissolution profiles of the selected famotidine liquisolid tablet formulations together with the dissolution profile of famotidine conventional, directly compressed tablets (DCT) are presented in Fig. 4. It was apparent that formula F14 has the highest dissolution pattern in both the rate and the extent of drug dissolved. The percentage of famotidine dissolved from F14 reached 100.11% after only 30 min, while the DCT had a maximum famotidine content (89.87%) dissolved after 60 min. The percent of drug dissolved from each formula after 10 min (Q_{10}) and the drug release rate (D_R) were taken as a measure of the extent and the rate of drug dissolved from the prepared tablets, respectively, as presented in Table 5. The results in the table clearly affirm that the liquisolid tablet formula F14 had the highest percentage of drug dissolved in 10 minutes;

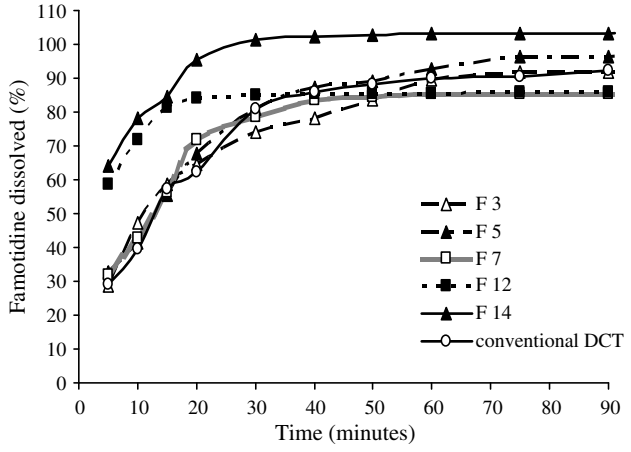

Fig. 4. Dissolution profiles of famotidine from the liquisolid tablet systems and the conventional DCT 0.1 N Hcl (pH 1.2).

Table 5
Percentages of famotidine dissolved after 10 min and 10-min dissolution rates form the conventional directly compressed famotidine tablets and the selected liquisolid tablets

Formula	Q_{10}[a] (%)	D_R[b] (μg/min)
Famotidine conventional DCT[c]	39.34	786.75
F3	47.22	944.35
F5	41.53	830.53
F7	42.84	856.80
F12	71.98	1439.67
F14	78.36	1567.25

[a] Famotidine dissolved after 10 min.
[b] Ten-minute famotidine dissolution rates.
[c] Directly compressed tablet.

it dissolved 78.36% of its famotidine content during the first 10 min. As well, it is clear from the table that F14 had the highest famotidine dissolution rate of all the formulae.

The most important observation is that Table 5 and Fig. 4 signify that all the formulae had higher drug dissolution rates (D_R), and larger amounts of drug dissolved in the first 10 min (Q_{10}) than the conventional, directly compressed famotidine tables. This could be explained according to the "Noyes–Whitney" equation and the "diffusion layer model" dissolution theories, the dissolution rate of a drug (D_R) is equal to

$$D_R = (D/h)S(Cs - C)$$

where h is the thickness of the stagnant diffusion layer formed by the dissolving liquid around the drug particles, D is the diffusion coefficient of the drug molecules transported through it, S is the surface area of the drug available for dissolution, C is the drug concentration in the bulk of the dissolving medium, and finally Cs is the saturation solubility of the drug in the dissolution medium, and thus it is a constant characteristic property related to the drug and dissolving liquid involved. Since all of dissolution tests for formulations were done at a constant rotational paddle speed (50 rpm) and identical dissolution media, we can safely assume that the thickness of the stagnant diffusion layer (h) and the diffusion coefficient of the drug molecules remain almost identical. From the previous equation, the drug dissolution rate is directly proportional not only to the concentration gradient of the drug in the stagnant diffusion layer ($Cs - C$), but also to its surface area (S) available for dissolution [5–8].

Since the liquisolid tablets contain a solution of the drug in suitable solvent (famotidine in PG), the drug surface available for dissolution is tremendously increased. In essence, after tablet disintegration, the liquisolid primary particles suspended in the dissolving medium contain the drug in a state of molecular dispersion, whereas the directly compressed tablets are merely exposing micronized drug particles. In other words, in the case of liquisolid tablets, the surface of drug available for dissolution is related to its specific molecular surface which by any means, is much

greater than that of the famotidine particles delivered by the plain, directly compressed tablets. Therefore, the hypothesis that the significantly increased surface of the molecularly dispersed famotidine in the liquisolid tablets may be chiefly responsible for their observed higher and consistent drug dissolution rates appears to be fundamentally valid [5–8].In addition to the preceding theory, it might be also speculated that Cs, the saturated solubility of the drug at the microenvironment, might be increased in the case of liquisolid system. Admittedly, the relatively small amounts of liquid vehicles (PG) contained per liquisolid compact are not sufficient to increase the overall saturation solubility of famotidine in the aqueous dissolution medium. However, at the local level, the solid/liquid interface between an individual liquisolid primary particle and the dissolving fluid involves minute quantities of aqueous medium clinging onto the particle surface to form the stagnant diffusion layer. At such micro-environment, it is quite possible that the infinite amounts of PG diffusing with the drug molecules out of a single liquisolid particle might be adequate to enhance the solubility of famotidine acting as a co-solvent with the aqueous dissolution medium of the stagnant diffusion layer. Such an increase in Cs will result, of course, in a larger drug concentration gradient ($Cs - C$) thereby increasing the dissolution rate as defined by the Noyes–Whitney equation [5–8].

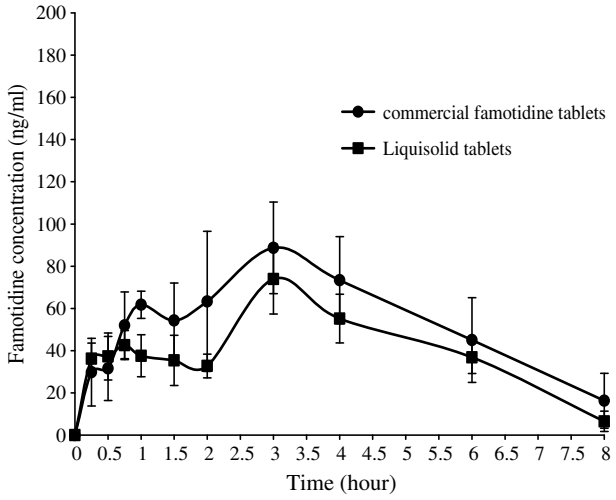

Fig. 5. Mean famotidine plasma profiles following single-dose, crossover bioavailability study comparing famotidine commercial and liquisolid tablets.

Spireas and Bolton [1] and Spireas [2] in their invention proved that comparison between drug dissolution profiles of liquisolid tablets and their commercial counterparts revealed that the prepared liquisolid tablets not only exceeded USP dissolution requirements but often yielded significantly higher drug release rates than those of their commercial counterparts. Also, they observed that the drug release superiority of liquisolid tablets is inversely proportional to the aqueous solubility of the contained drug. Accordingly, since drug dissolution is the rate limiting step in oral drug absorption of non-polar molecules, liquisolid systems might also present substantial *in vivo* superiority over their conventional commercial counterparts. In addition, the study on hydrocortisone liquisolid tablets verified that liquisolid tablets due to their increased wetting properties and surface of drug available for dissolution demonstrated significantly higher drug release rates than those of conventionally made, directly compressed tablets containing micronized hydrocortisone [7].

Moreover, it was previously established that the higher dissolution rates displayed by liquisolid compacts, in comparison with conventional directly compressed tablets, may also imply enhanced oral bioavailability due to increased wetting properties and surface of drug available for dissolution. Therefore, they proved that the liquisolid technique can be a promising alternative for the formulation of water-insoluble drugs into rapid release tablets [1–8].

3.4. In vivo evaluation of famotidine liquisolid tablets

The mean plasma concentration–time profiles of famotidine following the oral administration of the commercial famotidine tablets (F1) and the prepared liquisolid tablets (F14 LST) are shown in Fig. 5 and the calculated pharmacokinetic parameters are presented in Table 6. The administration of famotidine liquisolid tablets resulted in a mean peak plasma concentration (C_{max}) of 77.66 ng/ml, the mean time of peak plasma concentration (t_{max}) was 3.16 h, and the mean $AUC_{(0-8)}$ was found to be 317.80 ng h/ml. It was worthy to note that following the administration of oral famotidine tablets, there was almost a plateau area from 0.5 to 2 h, followed by an increment in plasma concentration of famotidine till reaching C_{max} at 2.67 and 3.16 h for famotidine market formula and liquisolid tablets, respectively. Similar observations were also noted in the results of the sensitive HPLC study on famotidine by Wanwimolruk et al. [37].

Table 6
Mean bioavailability and pharmacokinetic parameters of famotidine following the administration of a single oral dose (20 mg) of the commercial formula and the selected liquisolid formula (F14 LST)

Pharmacokinetic parameter	Market formula (Peptec® tablets)	liquisolid tablets (F14 LST)	*P*-value
C_{max} (ng/ ml)	97.78 ± 40.08	77.66 ± 28.03	0.256
t_{max} (h)	2.67 ± 0.52	3.16 ± 0.40	0.092
$AUC_{(0-8)}$ (ng h/ml)	427.46 ± 165.03	317.80 ± 40.73	0.179
$AUC_{(0-\infty)}$ (ng h/ml)	497.87 ± 216.32	346.05 ± 50.16	0.125

However, one-way analysis of variance (one-way ANOVA) was used to verify whether the differences between the mean pharmacokinetic parameters obtained for the both liquisolid and commercial tablets were significant and the *P*-values calculated were presented in Table 6. It was clear that, according to ANOVA statistical analysis, there were no significant differences ($P < 0.05$) between the mean peak plasma concentrations (C_{max}), the mean times of peak plasma concentrations (t_{max}), nor the mean AUC $_{(0–8)}$ obtained for famotidine liquisolid tablets and commercial famotidine tablets.

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