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Comparative effects of different cellulosic-based directly compressed orodispersable tablets on oral bioavailability of famotidine

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ABSTRACT

Famotidine is a potent H_2-receptor antagonist most commonly used by elderly patients. Orodispersible tablets (ODT) are gaining popularity over conventional tablets due to their convenience and suitability for patients having dysphagia. The purpose of this study is to prepare famotidine ODT using the economic direct-compression method.

A 3^2 full factorial design was used to evaluate the influence of different excipients on the properties and *in vitro* dissolution of famotidine ODT. Two factors were studied for their qualitative effects, namely, disintegrants and diluents. Disintegrants were studied in three levels viz. Ac-Di-Sol, sodium starch glycolate (Primojel) and low-substituted hydroxypropyl cellulose (L-HPC). Fillers were studied in three levels viz. mannitol, spray dried lactose and Avicel PH 101. The ODTs were prepared by direct compression and were evaluated for hardness, drug content, uniformity of weight, *in vitro* disintegration time, oral disintegration time, wetting time and *in vitro* dissolution. Maximum dissolution and minimum oral disintegration time (11.4 s) were observed in F7 prepared using L-HPC and mannitol. Furthermore, in human volunteers it showed significant increase in bioavailability compared to Servipep® with mean $AUC_{(0-\infty)}$ 117.1 ng/ml and 82.71 ng/ml, respectively, and its relative bioavailability was 141.57%. Hence, ODT (F7) could possibly be used to overcome the drawbacks of conventional famotidine tablets in elderly patients with significant increase in oral bioavailability.

1. Introduction

Due to impaired swallowing ability, many elderly patients find it difficult to take some conventional dosage forms such as tablets and capsules. In order to solve this problem, the development of solid dosage forms that disintegrate rapidly or dissolve even when taken orally without water is being undertaken. Many attempts having rapidly disintegrating behavior have been reported like lyophilizing (Green & Kearney, 1999), molding (Myers, Battist, & Fuisz, 1995) and compressing wet powders to construct highly porous structure (Verley & Yarwood, 1990). However, these methods require particular machines and are time consuming techniques; moreover, the hardness of the products was not enough to stand the process of packaging and transportation. Therefore, direct compression is the simplest, most convenient and easiest way to produce rapidly disintegrating tablets with sufficient structural integrity.

To develop a rapidly disintegrating tablet with direct-compression method, it was necessary to find suitable excipients with good compactability and disintegrating ability. Although the superdisintegrants primarily affect the rate of disintegration, when used at high levels, they can also affect mouth feel, tablet hardness, and friability. Thus, several factors must be considered when selecting a superdisintegrant.

The direct-compression tablet's disintegration and dissolution are based on the single or combined action of disintegrants and water-soluble excipients. In many cases, the disintegrants have a major role in the disintegration/dissolution process of rapidly disintegrating tablets made by direct compression. The choice of a suitable type and an optimal amount of disintegrants is paramount for ensuring a high disintegration rate. The simultaneous presence of a disintegrant with a high swelling (or disintegrating) force, defined as "disintegrating agent" and a substance with a low swelling force, defined as "swelling agent," was claimed as the key factor for the rapid disintegration of a tablet, also offering satisfactory physical resistance (Cousin, Bruna, & Gendrot, 1995).

Famotidine is a histamine H2-receptor antagonist used to treat peptic ulcer; gastroesophageal reflux; and conditions where the stomach produces too much acid, such as Zollinger-Ellison syndrome (Dollery, 1999). Over-the-counter famotidine is used to prevent and treat heartburn due to acid indigestion and sour stomach caused by eating or drinking certain foods or drinks. It is reported that famotidine is 30–60 times more potent than cimetidine

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(Dollery, 1999). Clinically famotidine is beneficial for elderly patients. Therefore a new famotidine preparation that is useful for swallow function deficient patient would be advantageous.

Previous workers (Mizumoto, Tamura, Kawai, Kajiyama, & Itai, 2008; Xu, Bovet, & Zhao, 2008) prepared fast disintegrating famotidne granules and microspheres, respectively, using spray drying method, however this method is time consuming and inconvenient.

The aim of this study was to formulate famotidine ODTs using direct-compression technique and to clarify the effect of different excipients on the disintegrating and dissolution properties of tablets. The *in vivo* behavior of the prepared ODT was assessed by studying its bioavailability compared to commercial conventional tablets in human volunteers.

2. Materials and methods

2.1. Materials

Famotidine (kindly supplied by Amoun Company, Cairo, Egypt), Lactose monohydrate (spray dried NF, Fast Flo; Foremost Farms, Baraboo, WI), Crosscarmellose sodium (Ac-Di-Sol; FMC BioPolymer, Philadelphia, PA), Sodium starch glycolate (Primojel; DMV International, Veghel, The Netherlands), Microcrystalline cellulose (Avicel PH101) and Mint flavor were kindly supplied by Chemical Industries Development Company (CID) Company, Giza, Egypt), Mannitol, Magnesium stearate and talc (El-Nasr pharmaceutical chemical company, Abu-Zaabal, Cairo, Egypt), Low-substituted hydroxypropylcellulose (L-HPC) (L-11 grade was kindly supplied by Shin-Etsu Chemical Co., Ltd., Japan).

2.2. Methods

2.2.1. Experimental design

A 3^2 full factorial design was applied for tablets preparation in which two factors were studied each at three levels. The two factors were the disintegrants and the diluents. Three disintegrants were used, each in its optimum concentration as tested before in preliminary studies, Ac-Di-Sol in a concentration of 3%, Primojel in a concentration of 8% and L-HPC in a concentration of 15%. The three diluents evaluated were mannitol, spray dried lactose and Avicel PH101. The compatibility of the chosen excipients was tested using DSC in a preliminary study. The compositions of the prepared formulae are presented in Table 1.

2.2.2. Preparation of famotidine ODTs

Famotidine ODTs were prepared by direct-compression technique. Each tablet was composed of 20 mg famotidine, 0.5 mg of magnesium stearate as a lubricant, 1 mg citric acid as an acidifying agent, 0.5 mg mint flavor and various concentrations of the excipients as follows: either 3% Ac-Di-Sol, 8% Primojel or 15% L-HPC as disintegrants; either mannitol, spray dried lactose or Avicel PH101 as diluents to complete the final weight of the tablet to 100 mg. Before compression, the previously sieved drug, diluent, acidifying agent and disintegrant were mixed in a glass mortar, followed by tumbling for 15 min in a turbula mixer, then the lubricant was added and mixing was continued for further 5 min. One hundred milligrams of powder mixture was manually filled into the 7 mm die and compressed into flat-faced tablets at pressure ranging from 400 to 500 kg using a single punch tablet machine (Manesty Single Punch Machine, Liverpool, England).

Table 1
Composition of the different famotidine ODT prepared by direct compression using 3^2 full factorial design.

Disintegrant	Diluent	Formula
Ac-Di-Sol (3%)	Mannitol	F1
	Spray dried lactose	F2
	Avicel PH101	F3
Primojel (8%)	Mannitol	F4
	Spray dried lactose	F5
	Avicel PH101	F6
L-HPC (15%)	Mannitol	F7
	Spray dried lactose	F8
	Avicel PH101	F9

2.2.3. Evaluation of prepared famotidine ODTs

The prepared famotidine ODTs were subjected to the common quality control tests viz. weight uniformity, drug content, hardness, friability, as well as *in vitro* disintegration test.

2.2.4. Determination of the wetting time and water absorption ratio of the prepared tablets

The wetting time of the tablets in 6 ml of water replaces the disintegration time determination. This experiment mimics the action of saliva in contact with tablet (Schiermeier & Schmidt, 2002). A conventional method was used to measure wetting time and capillarity of the ODTs. A piece of tissue paper (10.75 × 12 cm) folded twice was placed in a small culture dish, of 6.5 cm in diameter, containing six milliliters of water. A weighed tablet was put on the paper and the time for complete wetting was measured. The wetted tablet was again weighed. To check reproducibility, the measurements were carried out six times and the mean value was calculated. Three replicates were made for each tablet batch. Water absorption ratio (R) was calculated by:

$$R = \frac{100(W_a - W_b)}{W_b}$$

where W_b and W_a denote the weight of the tablet before and after wetting, respectively (Bi et al., 1996).

2.2.5. In-vivo oral disintegration time

The disintegration time of ODTs is measured utilizing the conventional tests for tablets that are described in the Pharmacopoeias. However, it is difficult to assess the disintegration rate for the ODT with these tests due to its rapid disintegration rate even in a small amount of water. Thus, the disintegration rate obtained from the conventional disintegration tests appears not to be reflective of the disintegration rate in the human mouth. Nevertheless, this standard compendial test faces many limitations in the discrimination between different ODTs as their disintegration time is very short and also because of the strong agitation and large volume of water used during this test (Watanabe et al., 1995). So measurements of disintegration time in the oral cavity were carried out in five healthy volunteers (mean age = 22 ± 3.2), who were randomly administered the nine formulae at 24 h intervals (Fukami, Ozawa, Yoshihashi, Yonemochi, & Terada, 2005). Prior to the test, all volunteers got a detailed briefing on purpose of this test and gave informed consent. Then they were asked to rinse their mouth with a cup of water (200 ml). The ODT was placed on the subject's tongue and immediately a stopwatch was started as soon as the tablet contacts the tongue. The subjects were instructed to gently move the tablet against the upper part of the mouth with their tongue and to cause a gentle tumbling action on the tablet. It was emphasized to the subjects that this is a gentle motion without biting on the tablet or tumbling it from side to side. Immediately after the last noticeable granule had disintegrated, the time was recorded. The swallowing of saliva was prohibited during the test, and also saliva was rinsed from the mouth after each measurement.

2.2.6. In vitro dissolution studies

The drug release was determined using USP standard dissolution tester, Apparatus II (rotating paddle) (Pharma Test, Germany). Dissolution was carried out in 300 ml simulated saliva fluid (SSF) pH 6.75. The paddle was rotated at 50 rpm at 37 ± 0.5 °C. Aliquots of 3 ml were withdrawn and replaced with equal volumes of fresh SSF at specified time intervals (0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 15, 20, 25 and 30 min). Samples were adequately diluted and analyzed spectrophotometrically for their famotidine in SSF at 279 nm (UV-1601 PC, Shimadzu, Kyoto, Japan). The experiments were done in triplicates for each of the selected ODT formula.

2.2.7. Pharmacokinetic study in healthy volunteers

2.2.7.1. Subjects selection. Six healthy volunteers aged between 20 and 40 years were chosen. None of the volunteers had any history of drug or alcohol abuse, nor did they have any acute or chronic gastrointestinal, cardiac, vascular, hepatic or renal disease. The protocol of the study was reviewed and approved by the Ethical Committee of the Faculty of Pharmacy, Center of Applied Research and Advanced Studies (CARAS), Cairo University. The purpose of the study was fully explained and volunteers had given their written consent. The subjects were instructed to take no drugs for one week prior to and during the course of the study. No consumption of nicotine was permitted 12 h before and 24 h after drug intake, moreover, on each test day, coffee, tea and cola beverages were withheld from subjects 12 h before the administration and till the blood sampling was completed.

2.2.7.2. Study design. Randomized, single dose, three-way crossover open-label study was performed using three famotidine formulae viz. the conventional market product Servipep® 20 mg Tablets (NOVARTIS), the prepared F2 and F7 ODTs. In all phases, the drug was administered after overnight fasting. At 7:00 a.m. on the treatment day, the subjects received 200 ml. of water, at 8:00 a.m. they received the drug with no water taken except with Servipep® tablets, which was taken with 200 ml water. After 30 min, 200 ml. of water was taken. Afterwards, no more restriction on water was made. A standard breakfast was taken 3 h after administration of the dosage form.

2.2.7.3. Sample collection. Venous blood samples were collected in glass tubes before administration of the dosage form, and at 0.25, 0.5, 0.75, 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. The volunteer's blood pressure, heart rate and adverse reactions were routinely monitored.

2.2.7.4. Determination of famotidine in human plasma. A Shimadzu prominence HPLC system was used (Kyoto, Japan), consisting of an HPLC pump (LC-10ADVP), a degasser (DGU-14A), an autosampler (SIL-20A), connected to a Shimadzu UV detector. For separation, Symmetry® C18–75 × 4.6 mm, 3.5 μm (Waters, Milford, MA) column was used. 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 was 267 nm using cimetidine as an internal standard and the sensitivity was set at 0.0001 AUFS. All assays were performed at ambient conditions. Famotidine stock solution (100 μg/ml) was prepared by dissolving 10 mg famotidine in 100 ml methanol. The working standard solution was prepared by further dilution of 10 ml of the stock solution to 100 ml with methanol (10 μg/ml). These solutions were stable at 4 °C for at least one month. The working standard solutions chosen to make the standard calibration curve were at concentrations ranging from (4–60 ng /ml).

For sample preparation, aliquots of 500 μl plasma samples spiked with 250 μl of cimetidine solution containing 80 ng cimetidine as an internal standard were placed into 7 ml glass centrifuge tubes. The samples were deproteinized with 2 ml acetonitrile and extracted with 4 ml 2-butanol. After centrifugation, the organic layer was evaporated to dryness using Eppendorf® Vacufuge Concentrator 5301 at 40 °C for 2 h. The residue was reconstituted with 250 μl mobile phase and 50 μl of the samples were injected.

2.2.7.5. Pharmacokinetic data analysis. Plasma concentration–time data of famotidine was analyzed for each volunteer by non compartmental pharmacokinetic models using kinetica® software (version 4.4.1). The peak plasma concentrations (C_{max}) and the time of its occurrence (t_{max}) were directly obtained from the concentration–time data. The area under the plasma concentration–time curve (AUC) from time zero to last measured concentration (AUC_{0-t}) was calculated according to the linear trapezoidal rule. The terminal elimination rate constant (λz) was estimated by linear regression of the terminal portion of the ln (concentration)–time curve, and the elimination half-life was calculated. $AUC_{0-\infty}$ was the corresponding area extrapolated to infinity by $AUC_{0-t} + C_t/\lambda z$, where C_t was the last measurable drug concentration.

2.2.7.6. Statistical analysis of the pharmacokinetic parameters. All statistical analysis was undertaken using ANOVA test to assess the significance of the difference between the pharmacokinetic parameters obtained for the three formulations.

3. Results and discussion

3.1. Evaluation of the prepared famotidine ODTs

All the prepared tablet formulations met the USP 27 requirements for weight variation. Content uniformity was found to be good where the percentage of drug content was more than 98%.

ODT should disintegrate rapidly upon placement in the mouth, yet possess sufficient structural integrity to withstand handling without substantial breakage. Thus, tablet properties such as hardness, and friability are closely linked to causing rapid tablet disintegration. The preferable strength of the orally disintegrating tablet is usually about 2–15 kg, and more preferably between 3 and 8 kg (Liu et al., 2002).

The hardness of all the prepared tablets was in the range of 4.66–12.31 kg with the highest hardness values observed in F3, F6, F8 and F9 with mean hardness values of 9.196, 10.293, 10.8 and 12.31 kg, respectively. The increase in hardness of F3, F6 and F9 might be due to the strong inter-particle force between Avicel PH101 particles used as diluent in these formulae (Sunada & Bi, 2002).

Tablet friability is a measurement of the tablet's physical strength. It was stated that an acceptable friability for dispersible tablets ranges from 0.95% to 1.5% (Mendes & Anaebonam, 1990). All the prepared formulae except F2 complied with the compendia standards as none of them had percentage loss in tablets' weights that exceeded 1%, also; no tablet was cracked, split or broken in either formula. F2 had an acceptable friability which was 1.35%.

According to the compendia standards, ODT should disintegrate within 3 min when examined by the test for disintegration of tablets and capsules (Morita et al., 2002). Although the most suitable disintegration time is not confirmed, we set the desirable disintegration time at 15 s based on information on the disintegration time of commercially available preparations with the characteristic of rapid disintegration. The average disintegration times for formulae F5, F8, and F9 were 28.54, 45.557 and 47.13 s, respectively. On the other hand, all other formulae disintegrated in less than 15 s.

The least disintegration time was observed with F3 having average disintegration time of 8.38 s.

3.2. Wetting time and water absorption ratio for the prepared famotidine ODTs

All the tested formulations were wetted within an acceptable time of less than 1 min, where F1, F2, F3, F4, F5, F6 and F7 were wetted in 24.13, 19.63, 11.53, 32.9, 32.41, 29.76 and 14.5 s, respectively. However, the longest wetting time was taken by F8 and F9 which was 48.1 and 56.7 s, respectively. It was also observed that formula F3 which had the least wetting time also had the minimum disintegration time showing a strong correlation between disintegration time and wetting time.

To test the significance of the difference between the tested factors and their effects on tablet wetting time at 95% confidence limits, ANOVA test was performed and its results are presented in Table 2. From the table, it is clear that all factors under study, namely, disintegrant and diluent types had significant effects on the wetting time of the prepared ODT at $p < 0.0001$.

Figs. 1A and B show in details the main effects of each additive on the tablets' wetting time. Regarding the effect due to disintegrants (Fig. 1A), they can be arranged in ascending order as follows: Ac-Di-Sol < Primojel < L-HPC with mean wetting time values of 18.43, 31.69 and 39.77 s, respectively. The difference between the tested disintegrants was significant at $p < 0.0001$. These results were in compliance with the *in vitro* disintegration test results.

It was observed that the formulae containing Primojel as disintegrant had higher mean water absorption ratio than Ac-Di-Sol and L-HPC, and took more time for wetting of tablets than Ac-Di-Sol this high water uptake lead to less patient convenience while taking the ODTs. Wetting is closely related to the inner structure of the tablets and the hydrophilicity of excipients. Primojel shows its disintegration effect by the mechanism of "swelling". Ac-Di-Sol shows its disintegration action by "wicking" (due to its fibrous structure) and swelling with minimum gelling. It had the minimum wetting time and the minimum water absorption ratio. Increased porosity of Ac-Di-Sol provides pathways for the penetration of fluids into tablets resulting in "wicking" through capillary action causing faster disintegration of tablets (Mishra, Bindal, Singh, & Kumar, 2006).

Coming to diluents, Fig. 1B reveals that the main wetting time effect can be arranged in ascending order as follows: Mannitol < Avicel PH101 < Spray dried lactose with mean wetting time values of 23.85, 32.66 and 33.38 s, respectively. According to Fisher PLSD test that was used to compare between the different pairs, there was a significant difference between mannitol and spray dried lactose and between mannitol and Avicel PH101 $p < 0.0001$. However the difference between spray dried lactose and Avicel PH101 was not significant.

The results obtained from the main effects were not conclusive and had to be completed with the study of the interactions between the different additives. The interaction between disintegrant and diluent (Fig. 1C), showed that Ac-Di-Sol almost had no effect on the disintegration time of tablets containing mannitol, while it significantly decreased the wetting time of spray dried lactose from 33.38 to 19.63 s and of Avicel PH101 from 32.66 to 11.53 s. In case of Primojel, it had almost no effect on the mean wetting time of tablets containing spray dried lactose and Avicel PH101. However, it had a negative effect on the wetting time of tablets containing mannitol where it significantly increased their wetting time from 23.85 to 32.9 s. As for the combined effect of L-HPC with diluents, L-HPC had a very positive effect on tablets containing mannitol where it significantly decreased their wetting time from 23.85 to 14.5 s, while it had a negative effect on the tablets containing spray dried lactose and Avicel PH101 where it significantly increased their wetting times from 33.38 to 48.1 and from 32.66 to 56.7 s, respectively.

3.3. In-vivo oral disintegration time

In general, the disintegration time of tablets in the mouth is related to the penetration rate of water into the tablet. According to literature (Schiermeier & Schmidt, 2002), the oral disintegration time of ODT is 1 min or less, usually about 50 s or less, preferably, about 40 s or less, and more preferably about 30 s or less. Although the most suitable disintegration time is not confirmed, we set the desirable disintegration time as 15 s based on information on the disintegration time of commercially available preparations with the characteristic of rapid disintegration.

F9 showed the longest oral disintegration time of 52.21 s followed by F8 with oral disintegration time of 47.25 s. The oral disintegration time of F1, F3, F4, F5 and F6 were 22.91, 14.63, 17.19, 30.27 and 12.48, respectively. Moreover, F7 and F2 had the shortest disintegration times of 11.42 and 11.69 s, respectively, and this was in agreement with the wetting time test that also revealed that formulae F2 and F7 had the least wetting times of the tested formulae.

ANOVA test showed that all factors under study, namely, disintegrant and diluent types had significant effects on the oral disintegration time of the prepared ODTs at $p < 0.0001$.

Figs. 2A and B show in details the main effects of each additive on the tablets' oral disintegration time. The main effect due to disintegrants can be arranged in ascending order as follows: Ac-Di-Sol < Primojel < L-HPC with mean oral disintegration time values of 16.41, 19.98 and 36.96 s, respectively. There was a significant difference between the disintegrants ($p < 0.0001$). The main oral disintegration time effect due to diluents (Fig. 2B) can be arranged in ascending order as follows: Mannitol < Avicel PH101 < Spray dried lactose with mean oral disintegration time values of 17.17, 26.44 and 29.74 s, respectively, according to Fisher PLSD test. There was a significant difference between all the diluents $p < 0.0001$.

The interaction between disintegrant and diluent (Fig. 2C) showed that Ac-Di-Sol had negative effect on the disintegration time of tablets containing mannitol where it significantly increased its oral disintegration time from 17.17 to 22.91 s. On the other hand it significantly decreased the oral disintegration time effect of spray dried lactose from 29.74 to 11.69 and of Avicel PH101 from 26.44 to 14.63 s, respectively. In case of Primojel, it had almost no effect on the mean oral disintegration time of tablets containing mannitol and spray dried lactose, while it significantly

Table 2
ANOVA table for average wetting time of famotidine ODT according to a full factorial design.

Source of variation	DF	Sum of squares	Mean square	*F*-Value	*p*-Value
Disintegrant	2	4178.780	2089.390	177.407	<0.0001(S)
Diluent	2	1014.733	507.366	43.080	<0.0001(S)
Disintegrant * Diluent	4	5474.193	136.548	116.202	<0.0001(S)
Residual	45	529.981	11.777		

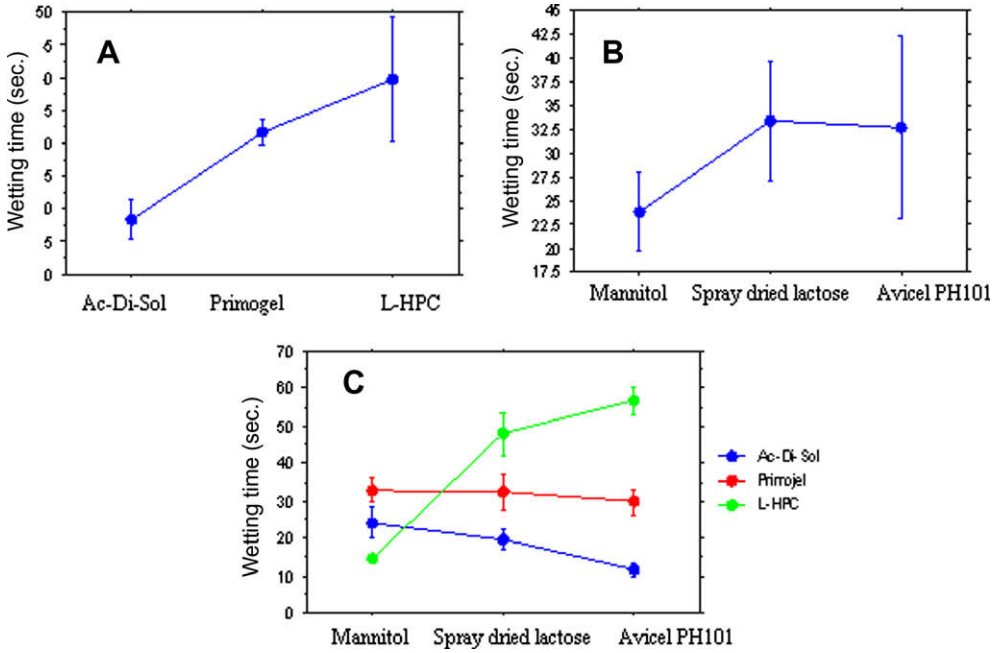

Fig. 1. Effect of different additives on the wetting time of famotidine ODT. (A) Main effect of disintegrants. (B) main effect of diluents. (C) Interaction between disintegrants and diluents.

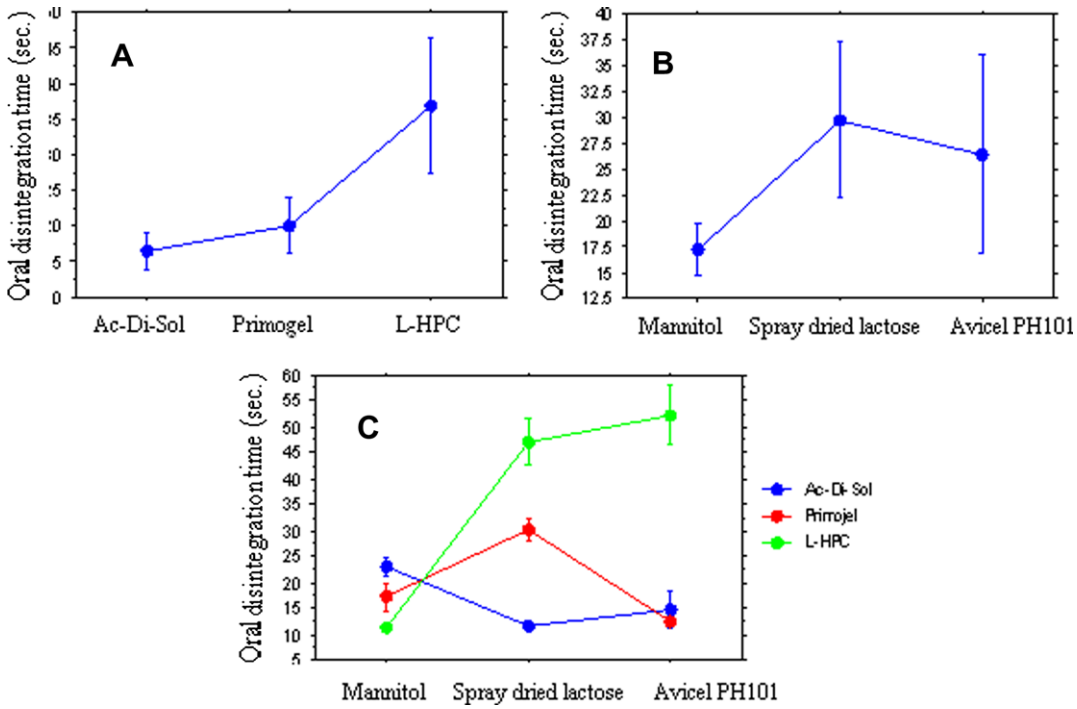

Fig. 2. Effect of different additives on the oral disintegration time of famotidine ODT: (A) Main effect of disintegrants. (B) Main effect of diluents. (C) Interaction between disintegrants and diluents.

decreased the mean oral disintegration time of tablets containing Avicel PH101 from 26.44 to 12.48 s. As for L-HPC it had a very positive effect on tablets containing mannitol where it significantly decreased their oral disintegration time value from 17.17 to 11.42 s, while it had a negative effect on the tablets containing spray dried lactose and Avicel PH101 where their mean oral disintegration time was significantly increased from 29.72 to 47.25 s and from 26.44 to 52.21 s, respectively.

3.4. In vitro dissolution studies

Fig. 3 represents the dissolution profiles of the prepared famotidine ODTs. It is clear that some of the formulations achieved their maximum drug dissolution after only 2 and 3 min of dissolution. F7 dissolved 101.37% of its drug after only 2 min; this might be due to the combined effect of water-soluble mannitol and high concentration of L-HPC which increased the degree of cracking

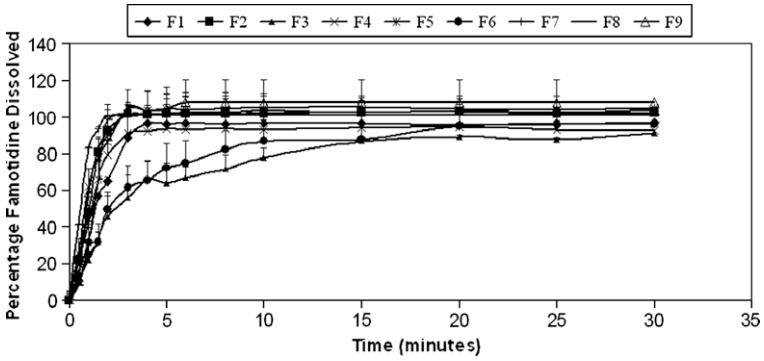

Fig. 3. Dissolution profile of different prepared famotidine ODT in simulated saliva fluid.

and bursting (Shirai, Sogo, Fujioka, & Nakamura, 1994). Also, F2, F5 and F8 achieved their maximum amount of dissolved drug (102.1%, 104.74% and 101.04%, respectively) after 3 min. This might be due to the presence spray dried lactose as diluent which is very soluble in water. F1 exhibited its maximum amount of drug dissolved (96.2%) after 4 min and F4 dissolved 93.3% after 5 min.

F3, F6 and F9 were the formulae that took the longest dissolution time; F3 actually did not reach its maximum concentration within 30 min. F6 and F9 achieved their maximum amount of dissolved drug (95.66% and 107.89%, respectively) after 20 and 8 min, respectively. This might be due to the poor water solubility of avicel which is common in these three formulae.

On comparing the time for 50% of drug to dissolve (t_{50}) of different formulae it was found that the formulae containing Ac-Di-Sol can be arranged in ascending order as follows: F2(spray dried lactose) > F1(mannitol) > F3(Avicel PH101) with (t_{50}) values of 1.02, 1.64 and 2.77 min, respectively, and the t_{50} of famotidine dissolution profile of the different formulae containing Primojel with the different diluents can be arranged in ascending order as follows: F5(spray dried lactose) > F4(mannitol) > F6(Avicel PH101) with (t_{50}) values of 0.8, 1.23 and 2.11 min, respectively. On the other hand, the t_{50} of the dissolution profile of famotidine from the different formulae containing L-HPC with the different diluents can be arranged in ascending order as follows: F7(mannitol) > F9 (Avicel PH101) > F8(spray dried lactose) with (t_{50}) values of 0.64, 0.85 and 1.149 min, respectively, showing that the manner of the famotidine ODT that contained L-HPC differs from the manner of the other tablets having Ac-Di-Sol and Primojel as disintegrants. This dissolution result shows that the combination of L-HPC with spray dried lactose is not favorable, while it is preferable to combine mannitol with L-HPC.

According to (t_{50}), it was found that the main effect due to disintegrants can be arranged in ascending order as follows: L-HPC < Primojel < Ac-Di-Sol with mean t_{50} values of 0.88, 1.38 and 1.81 min, respectively, with a significant difference between them (Fig. 4A).

It is worthy to note that L-HPC gave the most significant highest dissolution compared to other disintegrants however it gave the lowest wetting and disintegration times. It is reported in literature that, the disintegration time is not always in accordance with the dissolution rate since the latter may be affected by the other factors. Rapid liquid penetration does not ensure good dissolution

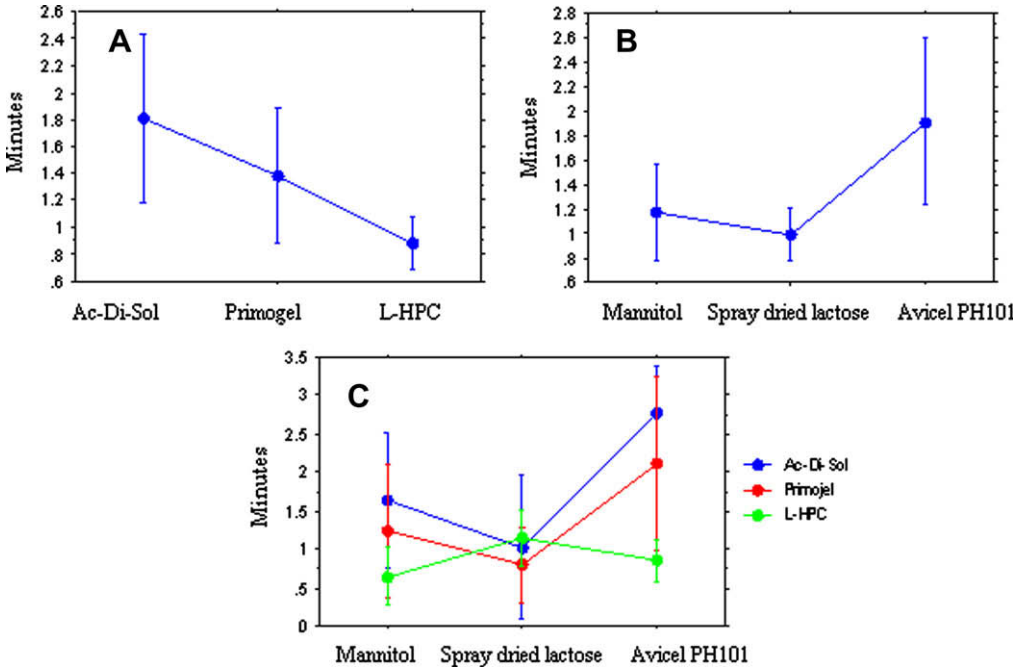

Fig. 4. Effect of different additives on t_{50} of famotidine ODT. (A) Main effect of disintegrants. (B) Main effect of diluents. (C) Interaction between disintegrants and diluents.

characteristics, where the presence of disintegrant readily promotes liquid penetration but does not assist dissolution (Gilbert & Christopher, 2002).

As for the diluents: Spray dried lactose < Mannitol < Avicel PH101 with mean t_{50} values of 0.99, 1.17 and 1.91 min, respectively (Fig. 4B). According to Fisher PLSD test. There was a significant difference between mannitol and Avicel PH101 and spray dried lactose and Avicel PH101 $p < 0.0001$, while there was no significant difference between mannitol and spray dried lactose, this might be due to that both diluents are water soluble while Avicel PH101 is water insoluble.

The interaction between disintegrant and diluent shown in Fig. 4C, showed that Ac-Di-Sol had negative effect on the dissolution rate of ODTs containing mannitol and Avicel PH101. It increased the t_{50} values of tablets containing mannitol from 1.17 to 1.63 min and the t_{50} values of tablets containing Avicel PH101 from 1.91 to 2.77 min. In case of Primojel, it had almost no effect on the mean t_{50} value of tablets containing mannitol and spray dried lactose while it had a negative effect on tablets containing Avicel PH101 increasing their t_{50} value from 1.91 to 2.11 min. As for the combined effect of L-HPC with diluents, L-HPC had positive effect on tablets containing mannitol and Avicel PH101 decreasing their t_{50} values from 1.17 to 0.64 min and from 1.91 to 0.85 min, respectively. While it had a negative effect on tablets containing spray dried lactose increasing their t_{50} value from 0.99 to 1.15 min.

It is worthy to note that the minimum t_{50} values were found in three formulae, F7 formed of L-HPC and mannitol (0.64 min), F5 formed of Primojel with spray dried lactose (0.8 min) and F2 formed of Ac-Di-Sol with spray dried lactose (1.029). F2 and F7 were chosen for further in vivo studies. F5 was not chosen as it had long *in vitro* disintegration time, wetting time and oral disintegration time.

3.5. Pharmacokinetic analysis

The HPLC assay has been validated and has a good linearity from 4 to 60 ng/ml with acceptable within- and between-day reproducibility. The lower limit of famotidine quantification in plasma was 4 ng/ml.

The mean plasma concentration–time data of famotidine following the administration of the market formula (Sevipep® Tablets), F2 and F7 is shown in Fig. 5. Moreover, the pharmacokinetic parameters that were determined from the famotidine plasma concentration–time data are presented in Table 3.

The mean peak plasma concentration (C_{max}) of commercial product was 36.9 ± 1.09 ng/ml with mean t_{max} of 1.17 ± 0.29 h. Additionally, the mean $AUC_{(0-8)}$ was found to be 79.78 ± 6.39 ng h/ml. The $AUC_{(0-\infty)}$ was 82.71 ± 3.43 ng h/ml. The mean elimination half-life ($t_{1/2}$) and elimination rate constant (K) were 1.54 ± 0.68 h and 0.50 ± 0.18 h^{-1}, respectively.

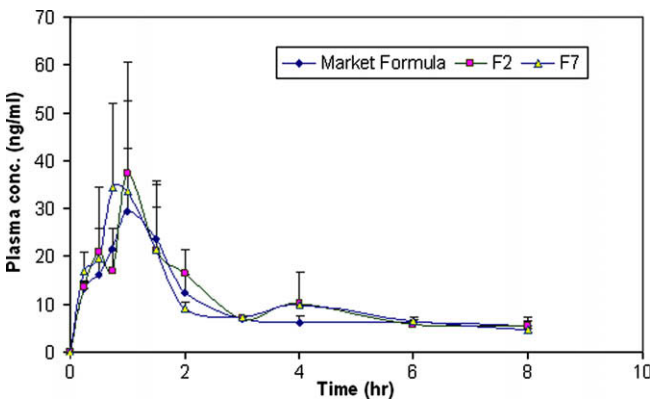

Fig. 5. Mean plasma concentrations–time profiles of famotidine from commercial, F2 and F7 formulae.

Table 3
Mean bioavailability and pharmacokinetic parameters ± SD of famotidine following the administration of a single oral dose (20 mg) of the market formula (Servipep® tablets), the selected ODT formulae F2 and F7.

Pharmacokinetic parameter	Market formula (Servipep® tablets)	F2	F7
C_{max} (ng/ml)	36.90 ± 1.09	42.18 ± 8.71	43.41 ± 8.24
t_{max} (h)	1.17 ± 0.29	0.83 ± 0.29	1.08 ± 0.382
$AUC_{(0-8)}$ (ng h/ml)	79.78 ± 6.39	89.72 ± 5.82	87.47 ± 9.35
$AUC_{(0-\infty)}$ (ng h/ml)	82.71 ± 3.43	106.17 ± 5.38	117.10 ± 5.93
$t_{1/2}$ (h)	1.54 ± 0.68	2.87 ± 0.64	4.55 ± 2.13
K (h^{-1})	0.50 ± 0.18	0.25 ± 0.06	0.19 ± 0.12
Relative bioavailability	–	128.36%	141.57%

The directly compressible formula F2 showed mean peak plasma concentration (C_{max}) of 42.18 ± 8.71 ng/ml, and the mean time of peak plasma concentration (t_{max}) was 0.83 ± 0.29 h. The mean $AUC_{(0-8)}$ was found to be 89.72 ± 5.82 ng h/ml. Similarly, $AUC_{(0-\infty)}$ was found to be 106.17 ± 5.38 ng h/ml. The mean elimination half-life ($t_{1/2}$) and elimination rate constant (K) were 2.87 ± 0.64 h and 0.25 ± 0.06 h^{-1}, respectively.

Concerning the directly compressible formula F7, it was apparent that the mean peak plasma concentration (C_{max}) was 43.41 ± 8.24 ng/ml. The mean time of peak plasma concentration (t_{max}) was 1.08 ± 0.382 h. The mean $AUC_{(0-8)}$ was found to be 87.47 ± 9.35 ng h/ml. Also, $AUC_{(0-\infty)}$ was found to be 117.10 ± 5.93 ng h/ml. In addition, the mean elimination half-life ($t_{1/2}$) and elimination rate constant (K) were 4.55 ± 2.13 h and 0.19 ± 0.12 h^{-1}, respectively.

In order to compare the mean bioavailability and the pharmacokinetic parameters of the tested formulae, the mean C_{max}, t_{max}, $AUC_{(0-8)}$, $AUC_{(0-\infty)}$, $t_{1/2}$, the elimination rate constant (K) were analyzed using ANOVA test, the results revealed that there was no significant difference between the three tested formulae except in the $AUC_{(0-\infty)}$ between F7 and the commercial product with a relative bioavailability of 141.57%.

The increased relative bioavailability of F7 ODT compared to the commercially available conventional tablet might be due to the higher dissolution rate achieved in the ODT formula which reached 100% in 3 min while the commercial formula achieved only 50% dissolution after 10 min.

4. Conclusion

The previous results suggest the superiority of F7 ODT prepared with 15% L-HPC as disintegrant and mannitol as a diluent over the commercially available conventional tablet with relative bioavailability of 141.57%.

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