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FORMULATION AND EVALUATION OF FAMOTIDINE SUBLINGUAL TABLETS

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فى هذه الدراسة تم عمل أقراص الفاموتدين التحت لسانية السريعة التفكك. وقد تم عمل خمس عشرة صيغة قرصية باستخدام الكبس المباشر وذلك للتوصل للصيغة المناسبة التى يتحقق فيها متطلبات عدم الهشاشة مع زمن تفتت يكون أقل من دقيقة واحدة وقوة صلابة تتراوح ما بين ٢ ٤ كجم/سم^{٢}. ولتحقيق ذلك تم فحص كفاءة مواد الصياغة المختلفة فى تكوين تلك الأقراص ذات الخصائص المبينة. وقد تم التوصل إلى الصيغة المناسبة لصياغة أقراص الفاموتدين التحت لسانية. أوضحت النتائج أن الصيغة التى تضم المانيتول والأفيسيل ب.هـ ١٠١ والآك دى صول والسكارين صوديوم واستيارات الماغنسيوم بالإضافة إلى العقار كانت لها الخصائص المقبولة من حيث الصلابة والهشاشة وزمن التفتت بالإضافة إلى أنها أعطت أعلى معدل إذابة للعقار ومن ثم فقد وقع الاختيار على أقراص هذه الصيغة للتقويم الحيوى. وقد تم دراسة التوافر الحيوى على أقراص تحتوى على ٢٠ مجم من العقار حيث تم إعطاؤها إلى خمسة متطوعين بالغين. وقد استخدمت بيانات الإخراج البولى كطريقة لقياس التوافر الحيوى للعقار بإستخدام جهاز الكروماتوجرافيا السائلة ذات الكفاءة العالية. كما تم عمل مقارنة بين الأقراص المصاغة تحت اللسانية والأقراص الفموية المتوفرة فى السوق (الببسيد). وقد تم حساب معدل الإخراج البولى والكمية الجمعية الكلية لكل متطوع على حدة والمتوسط للمتطوعين معا لكل من شكلى الدواء. وتم إجراء تحليل إحصائى للنتائج عند حد ثقة ٩٥% لتحديد المعنى الإحصائى للاختلاف بين شكلى الدواء. وبالتحليل الإحصائى وبالإختلاف بين الحالتين أتضح أنه يوجد فرقا إحصائيا معنويا للإختلاف بين الكمية الجمعية الكلية للفاموتدين المخرجة بعد ساعتين وبعد ستة ساعات من تناول الدواء. كما أوضحت النتائج وجود اختلاف غير معنوى فى المساحة تحت منحنى معدل الإخراج من - ١٢ ساعة بين شكلى الدواء ، مما يدل على أن الأقراص التحت لسانية هى على الأقل متكافئة حيويا لأقراص الببسيد الفموية تحت ظروف التقويم الحيوى فى المتطوعين الأصحاء.

Formulation of famotidine, rapidly disintegrated sublingual tablets, by direct compression was carried out. Fifteen tablets formulae were made in order to obtain suitable non-friable formulae, with disintegration time less than one minute and average crushing strength of 2-4 kg/cm^2. The excipients used in the different formulae are Avicel pH101, sorbitol, mannitol, lactose anhydrous, Ac-Di-Sol, magnesium strearate and saccharin sodium. The formulae prepared were tested for the effect of certain excipients on the hardness, friability and disintegration time. Tablets of 20 mg famotidine from the formulated and commercial oral dosage forms were administered to five healthy volunteers participated in the study using a balanced cross-over design. Comparison of the mean urinary excretion rate obtained after administration of both dosage forms indicated that in both cases, the time taken to reach peak occurred at a mid point of 1.5 hours. Comparison of the cumulative amounts excreted in the urine after administration of famotidine in the two different dosage forms revealed that about 5.49±1.06 mg of the administered dose (20 mg) was recovered unchanged in the urine during 12 hours following sublingual tablets administration. This value was found to be higher than that excreted after administration of Pepcid® oral tablets (4.61±0.65 mg) during the same period of time. Statistical analysis of the difference at P= 0.05, revealed non-significant difference in the urinary excretion rate obtained of the two different dosage forms. On the other hand, a significant difference was found to exist in the total cumulative amount of famotidine excreted in the urine at 2 and 6 hours from both dosage forms. The results also indicated that there was no significant difference in AUC_{0-12} between the two dosage forms.

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INTRODUCTION

Famotidine is a histamine H_2-receptor antagonist drug. Four H_2-receptor antagonistic drugs are known which include cimetidine, ranitidine, famotidine and nizatidine.[1] Famotidine is usually administered orally in the form of tablets, suspensions or orally disintegrated tablets (wafers). The drug may also be given as a slow intravenous infusion in hospitalized patients with pathologic hypersecretory conditions, intractable douodenal ulcers, or when oral therapy is not feasible.[2] Orally administered famotidine is incompletely absrobed. The bioavailability of oral doses is 40-45%. Gastric degradation, and poor aqueous solubility are believed to contribute to its low oral bioavailability.[3]

There has been much interest expressed in the use of oral cavity membranes as sites of drug administration. Both the buccal and sublingual sites has advantages compared with other routes, including rapid onset of action, high blood levels, avoidance of the first-pass effect and possible degradation of drugs as a result of its exposure to the gastrointestinal tract. In addition, there is excellent accessibility and the drug can be applied, localized and removed easily.[4,5]

The bioavailability of a drug is determined by its absorption, distribution, metabolism, and excretion. Some of these factors are determined by the drug as such, and some are modified by either the route of administration or particular dosage form. The properties of the dosage form influence the dissolution and, hence, the absorption of drug. A recently proposed drug classification scheme recognizes that there are two main rate-limiting processes during absorption namely dissolution and membrane permeability.[6] The buccal mucosa is an easily accessible and convenient site for drug delivery. It is routinely exposed to food and other "foreign substances" and thus it is robust. This makes tablets sublingual / buccal drug delivery widely acceptable. After administration to the oral cavity, the drug must dissolve in the aqueous saliva, however the drug molecules must be lipophilic to be able to pass the mucosal barrier into the blood circulation.[7]

The aim of the this study was to develop a sublingual, rapidly disintegrating famotidine tablet with a taste and texture acceptable to patients. In-vitro and in-vivo evaluation of these tablets was carried out. The bioavailability of famotidine after administration of sublingual and oral tablets was determined. Statistical analysis of the results was carried out (at P= 0.05) to evaluate the significane of difference between the two dosage forms.

EXPERIMENTAL

Materials

Famotidine (Merck and Co. Inc.), Famotidine 20 mg tablets (Pepcid®, Merck Sharp & Dohme Limited UK), famotidine and cimetidine were purchased from USPC, incorporated (Rockville, MD), Avicel PH101 (Seppic, France), sorbitol, mannitol, Ac-Di-Sol and magnesium stearate (Cooperation Pharmaceutique Francaise, France), lactose anhydrous (Prolabo, France) and saccharin sodium (Sinochem Imp. Exp. Corp., China), acetonitrile HPLC grade (Labscan Ltd., Ireland), methanol HPLC grade (Riedel-de-Haën AG.D.30926 Sleez, Germany), sodium acetate and concentrated hydrochloric acid (Prolabo, France), 1-heptane-sulphonic acid sodium salt (Sigma Chemical Co., USA).

Different formulae were made without active ingredients and the best formulae which give, the least disintegration time, with suitable hardness and the highest dissolution rate were chosen and then the active ingredient was added. For all formulations; powders were blended for 10 min and then magnesium stearate was added, followed by 5 min mixing.

Equipment

Single punch tablet machine (Shang Hai; Hua Mao Industrial and Commercial Co., China), hardness tester (Dr-Schleuniger Pharmaton Model 60), disintegration apparatus and friabilator (Veego, India), dissolution apparatus (Erweka, Apparatebau-GmbH, Germany) and spectrophotometer (Shimadzu UV-150-02, Japan).

HPLC analysis was performed on Gilson instrument equipped with a model 307 Piston Pump and Gilson 118 UV/Vis detector. Separation was performed on SynChropack RP-P (250x4.6 mm I.D.) HPLC column, preceded by SynChropack RP-P (50x4.6 mm

I.D.) guard column (MIRCA Scientific, Inc.). Chromatographic peaks were electronically recorded and integrated using HP 3395 integrator (Hewlett Packard).

Methods

Tablet Formulation

Sublingual tablets containing diluents, disintegrants and lubricants of different concentrations were formulated. The amount of each ingredient in the formualtion was shown as a percentage per tablet weight. The total weights of the tablets were kept constant in all formulations. Ingredients of each formula were mixed using geometric dilution method for 10 minutes. The produced mixture was finally mixed with magnesium stearate for 5 minutes. The tablets were then compressed using single punch tablet machine with 5 mm flat-faced punch. Tablet's weight was monitored during processing to be 70±3 mg. The formulae were subjected to evaluation of hardness, friability and disintegration time, drug content, and the dissolution rate. The formula which showed the best results was used in the in-vivo evaluation and compared with the commercial famotidine oral tablet (Pepcid®). Each formula contained 20 mg of famotidine.

Measurement of the Crushing Strength (Hardness)

Tablet crushing strength (the force required to break a tablet by compression on the radial direction) was measured using tablet hardness tester. Ten tablets of each formula were selected randomly and placed individually in the hardness tester. The total hardness of the ten tablets was calculated and the average hardness was determined.

Measurement of Tablet Friability

Twenty tablets were selected randomly, weighed and transfered to the friability tester. The apparatus was adjusted at constant rotation speed of 25 rotations per minute for 15 minutes. Tablets were removed and cleaned from any loose dust and reweighed. The friability percent was calculated using the equation:

$$\% \text{ Friability} = \frac{\textit{Weight before rotation - weight after rotation}}{\textit{Weight before rotation}} \textit{ x 100}$$

Tablets considered not friable when the % friability is not more than 0.8%.

Measurement of Disintegration Time

Six tablets of each formula were introduced individually into each tube of a basket-rack assembly of the disintegration apparatus. The assembly was then immersed in 900 ml distilled water maintained at 37±0.5°. A disc was added to each tube to prevent tablet floating. The disintegration time of the last disintegrated tablet was determined and the average of two determinations was then calculated.

Dissolution Study

The dissolution rate study was carried out on six tablets, each containing 20 mg of famotidine. The dissolution was carried out in 900 ml phosphate buffer (pH 6.8), at 50 rpm and maintained at 37°±0.5°. An aliquot of 5 ml was withdrawn at different time intervals for 30 minutes, filtered and measured at 267 nm. The withdarwn samples were replaced by equivalent volumes of phosphate buffer (pH 6.8).

Bioavailability Study

Subjects

Five healthy volunteers, aged between 25-30 years and weighing 60-70 kg, participated in the study that compared the bioavailability of famotidine 20 mg oral tablets with sublingual tablets containing the same dose of the drug. All the volunteers had no history of gastrointestinal, renal or hepatic disorders, and not taking any other medications during the period of the study.

Drug administration

Commerical tablet of 20 mg famotidine were administered orally (Pepcid® 20 mg) or the proposed sublingual tablets containing the same dose were administered to each volunteer in the study using a balanced cross-over design, with at least 72 hours washout period between each drug administration. After an overnight fast, oral tablets were given with 200 ml of water. For sublingual tablets the volunteers drink 200 ml water before its administration and keep the tablet beneath the tongue for 5 minutes.

Urine collection

The volunteers emptied their bladders completely and immediately before dosing. An aliquot of the blank urine was collected. After dosing, urine was collected by complete voiding at 0.5, 1, 2, 4, 6, 9 and 12 hours. The volumes were measured at each collection time, an aliquot was taken and stored at 4° for analysis.

Drug analysis

The analysis of famotidine in urine was carried out according to the method developed by Dowling and Frye[8] by HPLC using cimetidine hydrochloride as an internal standard. The mobile phase consisted of a mixture of acetonitrile and a solution of 1-heptane-sulphonic acid sodium salt (2.8 g/L) in 20 mM sodium acetate buffer (20:70). The pH of the mixture was adjusted to pH 5 with concentrated HCl, followed by filtration through 0.45 um filter (Whatman-sterile membrane filter) and degassing by sonication for about 5 minutes. The mobile phase was delivered at a rate of 1 ml/min with 100 bar pressure. The detector wave length was set at 267 nm.

Six concentrations (5, 10, 15, 20, 25 and 30 µg/ml) were made by dilution of famotidine stock solution (100 µg/ml) with urine. Two milliliters of each concentration were transferred into 10 ml volumetric flask and 2 ml of internal standard (1 µg/ml cimetidine HCl) were added and the volume was completed with the mobile phase. The standard calibration curve was constructed from the different concentrations that were run in treplicate. Urine samples were prepared by adding 1 ml urine and 2 ml internal standard (1 µg/ml cimetidine HCl) to 10 ml volumetric flask. The volume was then completed with the mobile phase. An aliquot of 25 µl of each sample was withdrawn and 20 µl was injected in the HPLC system.

Calculation

The area under the urinary excretion rate-time curve was determined up to the end of the data collection period (AUC_{0-12}) from the cumulative amount excreted in the urine, and the relative bioavailability (F rel) of famotidine sublingual tablets was determined by comparing its AUC with that of the standard commercial oral tablets (Pepcid®). The two tailed paired student t-test[9] was used to detect any possible difference in the bioavailability, $P< 0.05$ was considered significant.

RESULTS AND DISCUSSION

For the formulation of famotidine sublingual tablets many trials were done to obtain suitable formula with suitable friability, hardness, disintegration time and dissolution rate.

Table (1) represents the three formulae of the sublingual tablets prepared with different excipients and the percentage of each excipient used. Sorbitol, mannitol, and lactose anhydrous were used as diluents, Ac-Di-Sol as a disintegrant, saccharin sodium as a sweeting agent and magnesium stearate as a lubricant.

Table 1: Formulations of famotidine sublingual tablets.

Material	Percentages of materials in different formulae		
	I	II	III
Lactose anhydrous	44		
Mannitol		44	
Sorbitol			44
Avicel PH 101	43.7	43.7	43.7
Ac-Di-Sol	10	10	10
Magnesium stearate	1	1	1
Saccharin sodium	1.3	1.3	1.3

The three formulae were subjected to evaluation of hardness, friability and disintegration time. Table (2) represents these parameters. From the table it is observed that formula **I** which contains sorbitol had the highest hardness (3.4 kg) and also the highest disintegration time (50 sec.). Formula **II** showed the lowest hardness (2.9 kg), and suitable disintegration time (30 sec.). Formula **III** showed higher hardness (3.2 kg) than formula **II** and the lowest disintegration time (25 sec.). The friability values of all formulae were within the limits as shown in Table (2).

Determination of tablet content uniformity indicated that all the three formulae contain the claimed amount of famotidine (not less than

90% and not more than 110% of the specified amount).

Table 2: Hardness, disintegration time and % friability of the final formulations.

Formula number	Hardness (kg/cm^2)	% Friability	Disintegration time (sec)
I	3.9	0.28	50
II	3.3	0.55	40
III	2.4	0.45	30
I + Famotidine	3.4	0.36	50
II + Famotidine	2.9	0.56	30
III + Famotidine	3.2	0.42	25

Figure (1) shows the dissolution rate profiles of the three formulae. From the figure it can be observed that about 96% of the drug content of formula **II** has been dissolved in the first 5 minutes, while only 88% of the drug content of formula **I** was dissolved at the same time. The lowest percent dissolved in the first 5 minutes have been shown with formula **III**, which was only 83%.

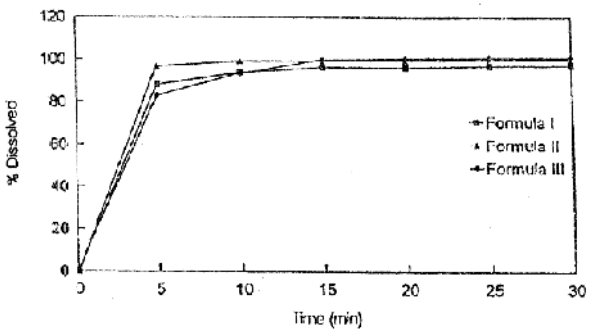

Fig. 1: The dissolution rate profile of different famotidine sublingual tablets formulae

On conclusion, formula **II** which consists of combination of mannitol, Avicel PH101, Ac-Di-Sol, saccharin sodium and magnesium stearate has an acceptable hardness, friability and disintegration time values. It also has the highest dissolution rate among the three formulae under investigation. The above results indicated that formula **II** could be the most suitable formula to be used in the in-vivo evaluation of famotidine sublingual tablets.

The In-vivo Study

Measurement of drug in urine is indirect method to ascertain the bioavailability of a drug. The rate and extent of drug excreted in the urine reflects the rate and extent of systemic drug absorption.[10] For drugs excreted primarily unchanged in urine, bioavailability can be estimated by measuring the total amount of drug excreted after a single dose. Ideally urine samples were collected over a period of 7 to 10 elimination half lives for complete urinary recovery of the absorbed drug.[11] One advantage of using the urinary excretion data is the noninvasive nature of such method.[12,13] It is much more convenient to collect urine sample than to draw the blood periodically. Another advantage is that this method allows direct measurement of bioavailability, both absolute and relative, without the necessity of fitting the data to a mathematical model.[13]

Figure 2 represents the mean urinary excretion rate of famotidine of five healthy volunteers after administration of the formulated sublingual tablets and the commercial tablets (Pepcid®). From the figure it can be observed that the urinary excretion rate of the sublingual tablets is higher than that of Pepcid® tablets in the first two hours. The sublingual and oral tablets revealed peak response at 1.5 hr, then a decline in response followed that time. The famotidine kinetics appears that there was a monoexponential decline of the concentration, which can be regarded as reflecting the rate of drug absorption. It is clearly evident that the average rate of urinary excretion of the sublingual tablets in the first six hours is higher than that of the commercial oral tablets (Pepcid®).

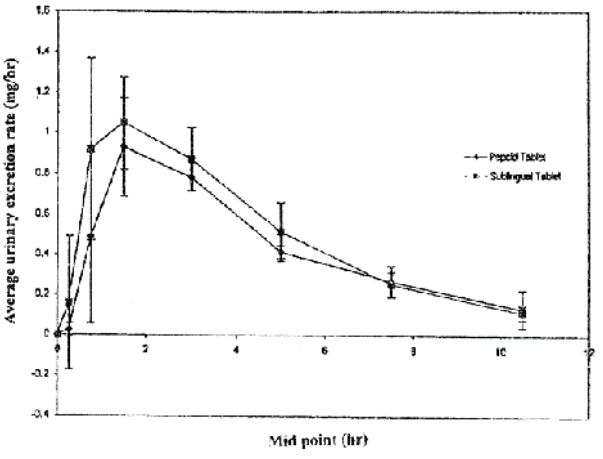

Fig. 2: The mean (±SD) urinary excretion rate of famotidine after administration of sublingual tablets and oral tablets (Pepcid®)

Sublingual absorption is characterized by rapid onset and sharp decline, followed by G.I.T. absorption of the swallowed portion of the dose, which is characterized by delayed onset. These two peaks are not observed which may be due to overlapping of the two absorption phases that results in appearance of one peak and increase in the urinary excretion rate.

Figure 3 shows the logarithmic plot of the urinary excretion rate of famotidine from the two dosage forms under investigation. From the curve, the elimination rate constant as well as the half-life of the drug were calculated. Table (3) represents the difference in the values of the previous two pharmacokinetic parameters between the two different administered tablets. The calculated half-lives were found to be 2.5 hours for sublingual famotidine and 2.8 hours for oral famotidine. These values were in agreement with the reported values (2.5-3.5 hours).[14]

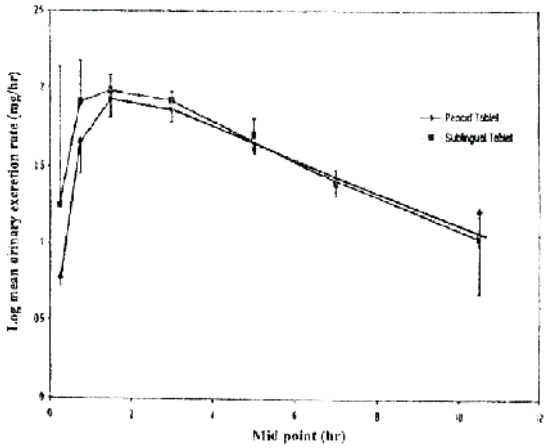

Fig. 3: Logarithmic plot of the average urinary excretion rate of famotidine after administration of sublingual tablets and oral tablets (Pepcid®)

Table 3: Pharmacokinetic parameters of famotidine from sublingual tablets and oral tablets (Pepcid®).

Parameter	Sublingual tablets	Oral tablets (Pepcid®)
Elimination rate contstant (hr^{-1})	0.277	0.247
Half life (hr)	2.5	2.8

The mean cumulative amounts excreted after administration of famotidine in the two different dosage forms (sublingual tablets and oral Pepcid® tablets) were calculated and plotted versus time (Figure 4). The two dosage forms show a similarity in the peak levels, absorption and elimination rate. These results indicated a similarity in the rate of increase in the amount excreted in the two dosage forms but with slight increase in case of the sublingual dosage form.

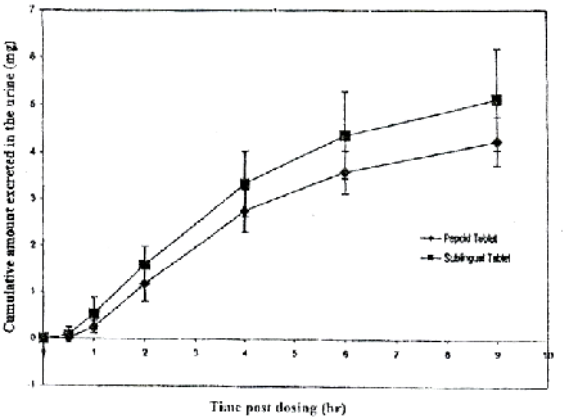

Fig. 4: The mean (±SD) Cumulative amount of famotidine excreted after administration of sublingual tablets and oral tablets (Pepcid®)

Table (4) lists the mean (±SD) of total amount of famotidine excreted in the urine at different time intervals up to 12 hours following dosage. After administration of Pepcid® tablets a mean of 4.61±0.65 mg of famotidine was recovered unchanged in the urine within 12 hours. This amount represents only 23% of the administered dose (20 mg). On the other hand, the total amount excreted in 12 hours after administration of the formulated sublingual tablets was found to be 5.49±1.06 mg, which represents about 27.4% of the administered dose.

Statistical analysis of P= 0.05 of the difference in the urinary excretion rate at different time intervals between the two types of tablets was performed and tabulated (Table 5) and no significant difference was found. On the other hand, statistical analysis of the difference in the total amounts of famotidine excreted in the urine at each time interval shows a significant difference at 2 hours and 6 hours after dosage administration (P< 0.05). This difference was found to be statistically

non significant when the time exceeded 6 hours after dosage administration.

The bioavailability of the drug from each dosage form can be calculated from the total area under the urinary excretion rate-time curve (AUC_{0-12}) which is equal to the total amount excreted in 12 hours following administration of each dose. Statistical analysis of the results indicated a non-significant difference in AUC_{0-12} or bioavailability between the two dosage forms ($P< 0.05$). The pattern of famotidine absorption following sublingual administration resembles that of oral famotidine. In the majority of cases, peak response level, the half life, and the elimination rate constants are nearly similar. Then the absorption of sublingual tablets in comparison with standard oral famotidine tablets was nearly the same. Thus the rate and completeness of famotidine absorption, following sublingual administration are comparable to that following administration of oral tablets on an empty stomach. In clinical terms, sublingual and oral tablets of famotidine are likely to be therapeutically equivalent. Thus famotidine sublingual tablets can be considered bioequivalent to the oral tablets.

Table 4: Mean urinary excretion rate of famotidine after administration of sublingual tablets and oral tablets (Pepcid®) (n= 5).

Time interval (hr)	Urinary excretion rate (mg/hr)		Significance of the difference
	Sublingual tablets	Oral tablets (Pepcid®)	
0 - 0.5	0.158 ± 0.331	0.023 ± 0.032	N.S.
0.5 - 1	0.918 ± 0.448	0.488 ± 0.431	N.S.
1 - 2	1.05 ± 0.227	0.930 ± 0.241	N.S.
2 - 4	0.872 ± 0.152	0.783 ± 0.068	N.S.
4 - 6	0.515 ± 0.146	0.414 ± 0.032	N.S.
6 - 9	0.252 ± 0.061	0.267 ± 0.077	N.S.
9 - 12	0.113 ± 0.036	0.132 ± 0.094	N.S.

N.S. = statistically not significant ($P> 0.05$).

Table 5: Mean cumulative amount of famotidine excreted in the urine after administration of sublingual tablets and oral tablets (Pepcid®) (n= 5).

Time post dose (hr)	Cumulative amount excreted in the urine (mg)		Significance of the Difference
	Sublingual tablets	Oral tablets (Pepcid®)	
0.5	0.079 ± 0.165	0.011 ± 0.016	N.S.
1	0.538 ± 0.354	0.25 ± 0.134	N.S.
2	1.588 ± 0.409	1.186 ± 0.357	S.
4	3.33 ± 0.698	2.753 ± 0.448	N.S.
6	4.365 ± 1.061	3.582 ± 0.460	S.
9	5.123 ± 1.069	4.249 ± 0.518	N.S.
12	5.488 ± 1.069	4.610 ± 0.653	N.S.

N.S. = statistically not significant ($P> 0.05$).
S. = statistically significant ($P< 0.05$).

Table (6) represents the individual relative bioavailability of sublingual famotidine tablets comparable to Pepcid® tablets. The results showed a wide variation in the values ranging from 0.94 to 1.65 with a mean of 1.2±0.27. Individual data variation can be considered normal after sublingual tablets administration because the availability of a drug from the sublingual mucosa is greatly affected by the rate and extent of saliva secretion, which is known to be a variable factor.[15] The relative bioavailability of medazolam from sublingual tablets was evaluated by Fujii *et al.* who considered the area under the drug plasma concentration-time curve in the first four hours following dosage administration is enough for the comparison.[16] Sander *et al.,* also used the AUC in the first six hours for determination of the relative bioavailability of the two sublingual spray formulations of nitroglycerin.[17] In the present study the difference in the area under the urinary excretion-time curve in the first six hours can be used for the determination of the relative bioavailability of famotidine sublingual tablets, based on the fact stating that the urinary excretion rate of a drug is proportional to the amount of the drug in the body.[13] In this case a significant increase in famotidine bioavail-ability after sublingual administration can be observed (Table 7). However, the mean relative bioavailability was found to be 1.21±0.22, which is greatly similar to the value obtained when comparing AUC_{0-12} of the two dosage forms.

Table 6: AUC_{0-12} demonstrated by individual subjects after administration of sublingual tablets and oral tablets (Pepcid®), and the relative bioavailability of the sublingual tablets.

Subject	Sublingual tablets AUC_{0-12} (mg)	Oral tablets (Pepcid®) AUC_{0-12} (mg)	$F_{relative}$
A	5.549	5.042	1.10
B	7.105	4.292	1.65
C	5.464	4.398	1.24
D	5.204	5.488	0.94
E	4.120	3.832	1.07
Mean	5.488	4.610	1.20
± SD	1.069	0.635	0.273

Table 7: AUC_{0-6} demonstrated by individual subjects after administration of sublingual tablets and oral tablets (Pepcid®), and the relative bioavailability of the sublingual tablets.

Subject	Sublingual tablets AUC_{0-6} (mg)	Oral tablets (Pepcid®) AUC_{0-6} (mg)	$F_{relative}$
A	4.437	3.761	1.17
B	5.548	3.482	1.59
C	4.488	3.642	1.23
D	4.383	4.145	1.05
E	2.973	2.884	1.03
Mean	4.365	3.582	1.214
± SD	0.916	0.460	0.226

From the obtained results it can be concluded that administration of famotidine via the sublingual route results in apparently no improvement in time to reach peak plasma concentration compared to the oral tablets. On the other hand, significant increase in the drug bioavailability in the first six hours can be obtained following sublingual administration. Famotidine structure includes several amino group, the ability of binding of oral mucin with amino containing compound was reported.[18] This binding ability can contribute to the delay in time required to reach peak. Moreover, famotidine has a low solubility in both aqueous and organic solvents,[19] which can add to the delayed onset of the sublingual dosage forms.

From the above results we can consider that famotidine sublingual tablets are bioequivalent to famotidine oral tablets. Moreover, the patients who use famotidine oral tablets already suffer from hyperacidity, delayed gastric emptying and impaired absorption, which can greatly affect the rate and extent of drug absorption after oral administration. These factors are completely avoided when the drug is administered as sublingual tablets.

Conclusion

The best in-vitro results were obtained form formula II that consisted of mannitol, Avicel PH101, Ac-Di-Sol, magnesium stearate and saccharin sodium in 44, 43.7, 10, 1 and 1.3% respectively per tablet weight which

showed acceptable hardness, friability, short disintegration time, and high dissolution rate. The bioavailability studies indicated that administration of sublingual famotidine tablets resulted in apparently no change in the time required to reach peak. However, significant increase in the drug bioavailability in the first six hours was observed following sublingual administration in comparison with the results observed after administration of the commercial oral tablets (Pepcid®).

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