AAPS PharmSciTech, Vol. 11, No. 2, June 2010 (© 2010)
DOI: 10.1208/s12249-010-9425-9

Research Article

Formulation of Ketotifen Fumarate Fast-Melt Granulation Sublingual Tablet

Saadia A. Tayel,[1] Iman I. Soliman,[1] and Dina Louis[2,3]

Received 2 December 2009; accepted 5 April 2010; published online 21 April 2010

Abstract. The purpose of this study was to prepare sublingual tablets, containing the antiasthmatic drug ketotifen fumarate which suffers an extensive first-pass effect, using the fast-melt granulation technique. The powder mixtures containing the drug were agglomerated using a blend of polyethylene glycol 400 and 6000 as meltable hydrophilic binders. Granular mannitol or granular mannitol/sucrose mixture were used as fillers. A mechanical mixer was used to prepare the granules at 40°C. The method involved no water or organic solvents, which are used in conventional granulation, and hence no drying step was included, which saved time. Twelve formulations were prepared and characterized using official and non official tests. Three formulations showed the best results and were subjected to an ex vivo permeation study using excised chicken cheek pouches. The formulation F4I possessed the highest permeation coefficient due to the presence of the permeation enhancer (polyethylene glycol) in an amount which allowed maximum drug permeation, and was subjected to a pharmacokinetic study using rabbits as an animal model. The bioavailability of F4I was significantly higher than that of a commercially available dosage form (Zaditen® solution-Novartis Pharma-Egypt) ($p>0.05$). Thus, fast-melt granulation allowed for rapid tablet disintegration and an enhanced permeation of the drug through the sublingual mucosa, resulting in increased bioavailabililty.

KEY WORDS: chicken pouches; fast-melt granulation; ketotifen fumarate; permeation; sublingual tablet; Zaditen®.

INTRODUCTION

The melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by the use of a low melting point binder which is added to the other components of the powder. Once in a molten state, the binder acts as a granulating liquid. The temperature of the mixture is raised to above the melting point of the binder, either by a heating jacket, or by the heat of friction generated by the impeller blades if the impeller speed is high enough (1). Sustained-release dosage forms can be prepared by this process through using a lipophilic binder as glyceryl monostearate (2), stearic acid (3), or a combination of hydroxypropyl methyl cellulose and hydrophobic polymers (4). It also can be used to prepare fast-release formulations by using a water soluble binder as polyethylene glycol (PEG) (5) and Gelucire® (6).

Several advantages are offered by such technique over conventional wet granulation process (7) including omitting the step of eliminating water or organic solvents used as granulating agents, and hence there is no risk of residual solvents, no need to the drying step and less consumption of time and energy.

A fast dissolving tablet has been prepared by combining a low melting point compound that melts or softens at or below 37°C, with a water soluble excipient, preferably a saccharide. The heat generated by mixing in a high shear mixer can result in melting the compound, and hence binding of the components together. This combination makes up a fast dissolving granulation. Also, preparation can take place by melting the low melting point compound, then, the water soluble excipient is added. The combination is mixed until congealing takes place to make granules (8).

Many drugs were formulated as tablets using the melt granulation technique as carbamazepine (9) which was formulated as fast-release tablets. Also Gelucire, through this technique, was employed to improve the solubility of griseofulvin (10). Theophylline, through the melt granulation was formulated into a sustained-release matrix (10,11).

The objective of this work was to prepare a sublingual tablet containing the antiasthmatic and antiallergic drug ketotifen fumarate (12), so as to improve its bioavailability, which was only 50% following oral ingestion (13). The sublingual tablets were prepared using the fast-melt granulation technique, where the tablet base was a mixture of a saccharide and a polyethylene glycol blend which melted around the body temperature (8). Upon tablet insertion in the sublingual vicinity, rapid disintegration occurs within 3–5 min (14) to release the drug to be available for absorption.

The work involved mixing polyethylene glycol blends with sugars (granular mannitol and sucrose) at 60°C to produce the granules, which were combined with the drug

[1] Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, Cairo, Egypt.
[2] Faculty of Pharmacy, Cairo University, Kasr El Eini Street, Cairo, Egypt.
[3] To whom correspondence should be addressed. (e-mail: dinalouis@hotmail.com)

and other tablet additives to prepare twelve tablet formulations. The successfully tableted formulations were tested for the drug permeation through ex vivo chicken cheek pouches (15). The tablet formulation with the highest permeation showed significantly higher pharmacokinetic parameters in rabbits compared to the commercially available Zaditen® Novartis Pharma solution (each 5 ml of Zaditen® solution contains the equivalent of 1 mg ketotifen base).

MATERIALS AND METHODS

Materials

Ketotifen fumarate (KF), Wuhan Yuancheng Co., China; PEG 400, and 6000, Morgan Co., Egypt; magnesium stearate, silicon dioxide, orange flavor; sucrose, ADWIC, Egypt; Pearlitol® 500 DC granular mannitol (G.mannitol), was provided as a generous gifts from Roquette Co., France; Croscarmellose sodium (Ac-di-sol®) FCM corp., Pennsylvania, USA; Scilicified microcrystalline cellulose Prosolv® SMCC, Microcrystalline cellulose Avicel PH 102, provided as generous gifts from JRS, Germany; Zaditen® solution (the equivalent of 1 mg ketotifen/5 ml solution equivalent to 1.38 mg ketotifen fumarate), Novartis Pharma, Egypt.

METHODS

Preparation of the Polyethylene Glycol Blend

PEG 400 was mixed with PEG 6000 at ratios of 1:9; 2:8; 3:7; 4:6; 5:5; 6:4; 7:3; 8:2; and 9:1 weight ratios. These blends were melted on a water bath until homogeneous, then removed from the bath and triturated until congealed. The resulting mixtures had their melting points determined using electrothermal melting point apparatus (UK). The mixtures which produced a melting point around 37° and 35°C were being used for granulation preparation.

Preparation of Fast-Melt Granulation

The two PEG blends: Blend 1 with a melting point of 37°C and Blend 2 with a melting point of 35°C, were mixed with the sugar at the following weight ratios: 4:1; 4:0.75; 4:0.5; 4:0.25; and 4:0.1 of sugar: PEG blend, respectively. Preparation took place by raising the temperature of the PEG blend to 40°C in using a water bath. The sugar was added to the melted mass and stirred at 100 rpm for 5 min using a mixer (Mechanika high speed mixer, Poland). Afterwards, the water bath was removed while the mixture continued to be stirred until complete cooling. The sugars used to prepare the granules were G.mannitol, and 1:1 sucrose/G.mannitol.

Preparation of Fast-Melt Granulation Tablets

The granules were mixed with other tablet additives geometrically. All formulations were to contain 1.38 mg ketotifen fumarate (16) per tablet, 1.2% *w/w* orange flavor, 5% *w/w* Ac-di-sol as disintegrant, 20% *w/w* Avicel pH 102 and 30% *w/w* Prosolv®, 0.5% *w/w* silicon dioxide as glidant, except for the formulation which contained Prosolv® (being scilicified microcrystalline cellulose, thus no need for silicon dioxide). Magnesium stearate was used as a lubricant at 0.5% and 1.5% *w/w* (17) and was added finally to the mixture followed by mixing for two minutes.

The final tablet weight was designed to be 100 mg. Twelve formulations were suggested, whose compositions are given in Table I.

Before compression, the powders were evaluated by determination of the angle of repose, initial bulk and tapped bulk densities (18), and percentage compressibility (19).

The formulations with optimal flow properties were compressed into tablets using a single punch machine, 7 mm flat punch (Veego/MaticMD, India).

Evaluation of Ketotifen Fumarate Sublingual Tablets

The formulations which were successfully compressed into tablets were evaluated by physical tests: determination of tablet hardness (20) (Monsanto hardness tester, USA), percentage loss in weight (% friability; USP Tablet friability test apparatus, India) (18).

Humidity content was determined using Karl Fisher method (19) (Veego Karl Fisher apparatus, India), and disintegration time (Logan Instruments Corp.-Disintegration tester, USA) was determined in distilled water at 37±2°C (21)

Drug content of the tablets was determined following the USP test for drug content (19) using six tablets.

Tablets should not contain less than 85% and not more than 115% of the labeled potency (18).

Table I. Composition of Tablets Prepared by Fast-Melt Granulation

	F1		F2		F3		F4		F5		F6		F7		F8	F9	F10	F11	F12
	I	II	I	II	I	II	I	II	I	II	I	II	I	II					
Sugar	G.M[a]		G.M		G.M		G.M		G.M		G.M		G.M		S/G.M[b]	S/G.M	S/G.M	S/G.M	S/G.M
PEG Blend[c]	1		1		1		1		2		2		2		1	1	1	1	1
Sugar: PEG	4:1		4: 0.75		4: 0.5		4: 0.25		4: 0.75		4: 0.5		4: 0.25		4:1	4: 0.75	4: 0.5	4: 0.25	4: 0.25
% Mg stearate	L[d]	H[e]	L	H	L	H	L	H	L	H	L	H	L	H	H	H	H	H	H
Binder	20% Avicel PH 102																		30% Prosolv

[a] Granular mannitol
[b] Sucrose/ Granular mannitol 1:1 mixture
[c] PEG blend 1of melting point 37^{o} C and blend 2 of melting point 35^{o} C
[d] Low concentration of Mg stearatein formulations I (0.5%)
[e] High concentration of Mg stearate in formulations II(1.5%)

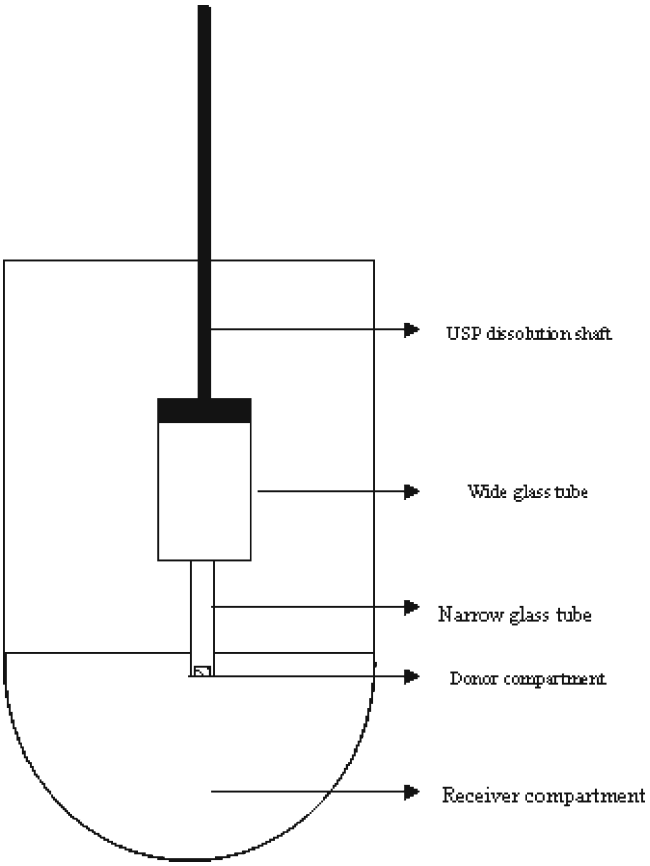

Fig. 1. The apparatus used to test the permeation

Determination of Drug Permeability Coefficient

Formulations which possessed the best results were exposed to permeation testing of the drug through ex vivo chicken cheek pouch of thickness (400–500 um) (15). Figure 1 shows the apparatus used to test the permeation. It consisted of a tube 1.13 cm^2 in area closed from one end using the chicken cheek pouches. The mucosal side of the pouches was directed upward to form the donor side into which a tablet was placed along with 1 ml Sorensen phosphate buffer pH 6.8 to simulate the conditions inside the buccal cavity. The epithelial side was immersed in 50 ml of Sorensen phosphate buffer pH 7.4 to represent the recipient side simulating the blood. This small tube was attached to the shaft of the USP dissolution apparatus. The recipient solution was placed in the USP dissolution apparatus flask. The temperature was maintained at 37±0.5°C, and the apparatus was run at 75 rpm for 2 h. Samples of three milliliters were withdrawn at 10, 15, 30, 45, 60, 75, 90, and 120 min, and were compensated for by equal volume of fresh buffer. The concentrations of the samples were calculated from the absorbance measured at λ 300 nm (22).

The cumulative amount of the permeated drug in milligrams per square centimeter was plotted against the time (in minutes), and the flux (milligrams per square centimeter per minute) was calculated from the slope of the line (23).

The permeability coefficient P was calculated as follows (24):

$$P = \frac{dQ/dt}{AC} = J/C,$$

Where dQ/dt is the permeation rate at steady state slope of the cumulative flux curve; C is the drug concentration in the donor side; A is the surface area of the diffusion membrane (1.13 cm^2); J is the flux.

DETERMINATION OF PHARMACOKINETIC PARAMETERS OF KETOTIFEN FUMARATE FROM FAST-MELT GRANULATION SUBLINGUAL TABLETS

Each of the time to peak concentration T_{max}, peak drug plasma concentration Cp_{max} and the area under the plasma-time curve AUC for ketotifen fumarate were determined after administration of the sublingual tablets to four male albino rabbits weighing 1.75–2 kg which were fasted overnight before the experiment. The animal study followed the rules approved by the ethical committee. A dose of ketotifen fumarate equivalent to 2.5 mg of ketotifen/kg body weight (25) was administered to the animals through the sublingual tablets which were prepared containing this calculated dose. The tablet formulation with the highest permeability coef-

Table II. Characterization of Ketotifen Fumarate Granules

Formulation	Angle of repose θ^0	Initial density (g/ml)	Tapped bulk density (g/ml)	Compressibility (%)
F2 I	33.3 (±0.21)	0.59 (±0.03)	0.69 (±0.01)	14.01
F2 II	33.2 (±0.30)	0.58 (±0.01)	0.69 (±0.02)	16.01
F3 I	30.12 (±0.18)	0.58 (±0.02)	0.64 (±0.01)	10.11
F3 II	30 (±0.15)	0.57 (±0.02)	0.65 (±0.04)	12.31
F4 I	36.2 (±0.25)	0.6 (±0.01)	0.71 (±0.07)	15.49
F4 II	36 (±0.14)	0.6 (± 0.01)	0.72 (±0.01)	16.67
F5 I	35.75 (±0.16)	0.63 (±0.01)	0.76 (±0.03)	16.45
F5 II	34.62 (± 0.21)	0.63 (±0.01)	0.76 (±0.02)	16.71
F6 I	35.42 (±0.17)	0.63 (±0.04)	0.76 (±0.01)	16.75
F6 II	34.46 (± 0.17)	0.64 (±0.01)	0.76 (±0.02)	16.64
F7 I	35.18 (±0.23)	0.63 (±0.01)	0.76 (± 0.01)	16.6
F7 II	36.17 (±0.21)	0.63 (±0.01)	0.76 (± 0.04)	16.58
F10	32.28 (± 0.19)	0.51 (±0.016)	0.57 (±0.03)	11.19
F11	32.28 (±0.18)	0.58 (±0.02)	0.68 (± 0.04)	14.31
F12	29.15 (±0.45)	0.47 (±0.02)	0.54 (±0.01)	11.98

Table III. Characterization of Ketotifen Fumarate Tablets

Formulation	Hardness (Kg)	% Loss in tablet weight (% Friability)	Disintegration Time (seconds)
F2 I	1.5 (± 0.02)	0.1	217 (±24.04)
F2 II	1.5 (±0.03)	0.54	201(±15.56)
F3 I	1.5 (±0.04)	0.1	75 (±9.89)
F3 II	1.5 (±0.02)	0.01	36 (±1.4)
F4 I	1.5 (±0.05)	0.8	26 (±0.71)
F4 II	1 (±0.002)	1.13	17 (±0.7)
F5 I	1 (±0.01)	0.94	44 (±7.8)
F5 II	1 (±0.03)	0.62	66 (±4.94)
F6 I	1 (±0.04)	1	13 (±2.12)
F6 II	1 (±0.02)	1.4	35 (±3.54)
F7 I	1 (±0.04)	Tablet breaking	8 (±0.01)
F7 II	1 (±0.01)	Tablet breaking	8 (±0.02)
F10	0.5 (±0.06)	1.6	58 (±12.3)
F11	0.9 (±0.16)	1.4	69 (±23.45)
F12	1.35 (± 0.4)	0.8	122 (±43.31)

ficient was administered as presented in literature (26). The rabbits were anesthetized with pentobarbital (25 mg/kg) and positioned on the table with the lower jaw supported in a horizontal position. The tongue was carefully lifted with tweezers and the tablet was placed under the tongue. Anesthesia maintained tablet below the tongue without escape to the gastrointestinal tract. The plasma samples were collected following tablet administration by 0.5, 1, 1.5, 2, 4, 6, 8, and 24 h. Food and water were supplied to the animals 2 h after tablet administration to minimize drug swallowing. The concentration of ketotifen fumarate in the collected rabbit plasma was determined using the HPLC method of analysis of Chiang *et al.* (27). The pharmacokinetic parameters of the commercially available Zaditen® solution (1 mg ketotifen/5 ml solution, Novartis Pharma, Egypt) were also determined so as to calculate the relative bioavailability of the sublingual tablets. A volume of Zaditen® syrup containing the animal dose was orally administered to rabbits by tube feeding. The study was conducted in a cross-over manner with a wash-out period of 1 week. Both groups were anesthetized before administration of either formulation.

Calculation of the relative bioavailability of the tablet was carried out, where relative bioavailability $= \left(AUC_{(0-t)test}/AUC_{(0-t)reference}\right) \times 100$ (28).

STATISTICAL ANALYSIS

F4I sublingual tablet formulation was compared to Zaditen® solution concerning Cp_{max}, T_{max}, and AUC. Statistical analysis was conducted using the *t* test for paired data using SPSS® 7.5 for windows software.

RESULTS

Choice of the PEG blend. The PEG blend that possessed a melting point of 37°C consisted of a 4:6 weight ratio, whereas, a melting point of 35°C was obtained by using a 1:1 weight ratio (PEG 400: PEG 6000).

Characterization of powders of fast-melt granulation tablets. Table II lists the results of the tests conducted on the powders.

The information concerning F1(I), F1(II), F8, and F9 is not revealed in Table II due to their observed lumpiness and stickiness, thus, failing to acquire a powdery appearance and hence were discarded from further investigation. The other formulations possessed acceptable flow as clear from the small values of the angle of repose and low percentage compressibility (18).

Evaluation of tablets. The powders which were compressed into tablets were evaluated and results are listed in Table III.

From the above-tabulated results, it was possible to reject the following formulations based on unacceptable friability: F4II, F6 II, F7I, F7II, F10, and F11. The remaining formulations had acceptable friability, and the choice among them was based on the short disintegration time and high value for the hardness.

Consequently, F4I (containing PEG blend I), F6I (containing PEG blend II) and F12 (containing PEG blend I and

Table IV. Characterization of Selected Ketotifen Fumarate Tablets

Formulation Test	F4 I	F6 I	F12
Visual Examination	White cylindrical tablets with orange odor		
Thickness (mm)	2.09 (±0.13)	2.12 (±0.12)	2.05 (±0.12)
Diameter (mm)	7.09 (±0.21)	7.87 (±0.03)	7.20 (±0.27)
% Humidity (*w*/*w*)	0.11 (±0.01)	0.11 (±0.03)	0.09 (±0.02)
Average weight (gm)	0.10 (±0.01)	0.11 (±0.02)	0.10 (±0.04)
Content uniformity (mg)	1.39 (±0.09)	1.29 (±0.07)	1.23 (±0.25)
Permeation coefficient (cm^{-2} min^{-1})	54.2 (±4.5)×10^{-5}	38 (± 6.2)×10^{-5}	36.2 (±2.1)×10^{-5}

sucrose/ G. mannitol mixture) were prepared in batches of 100 tablets each and the results of their evaluation are listed in the following Table IV.

The permeation coefficients of the tablets were acceptable when compared to the drug in water at 37°C±0.5°C $\left[5.89 \times 10^{-5}(\pm 0.92)\text{cm}^{-2}\ \text{min}^{-1}\right]$. Figure 2 showed the permeation of the drug from the selected tablet formulations. F4I proved to possess the highest drug permeability coefficient, thus it was chosen for the pharmacokinetic study.

Pharmacokinetics of ketotifen fumarate from F4I sublingual tablet. Figure 3 illustrates the mean concentrations of the drug following the administration of each formulation, whereas Table V gives the pharmacokinetic parameters of Zaditen® and F4I.

F4I possessed a 164.15% relative bioavailability compared to Zaditen®, where the AUC of the tablet was significantly different from that of Zaditen®. T_{max} and Cp_{max} of both F4 I and Zaditen® did not significantly differ from one another.

DISCUSSION

Sublingual tablets are intended to dissolve slowly in the oral cavity within 1 to 10 min. Their success lies in their ability to allow the absorption of the major portion of the drug through the oral mucosa (14). Thus, trials were made to obtain tablets with appropriate qualifications allowing maximal drug permeation through the buccal mucosa.

Sucrose is hygroscopic especially at elevated temperatures and high humidity (29). Mannitol, however, has low hygroscopicity and allows a short disintegration time, yet processes low compressibility and results in a soft tablet (30). Granulation of mannitol improves its compressibility (30). Consequently, the tablets were formulated using granular mannitol alone or in combination with sucrose. A mixture of mannitol and sucrose has excellent flow and compression properties: produced tablets are hard, with smooth surfaces and low friability (29). This accounts for the best flow properties of formulations F10, F11, and F12, as indicated by the low values for both the angle of repose and the percent compressibility. Also, inclusion of Prosolv® into formulation

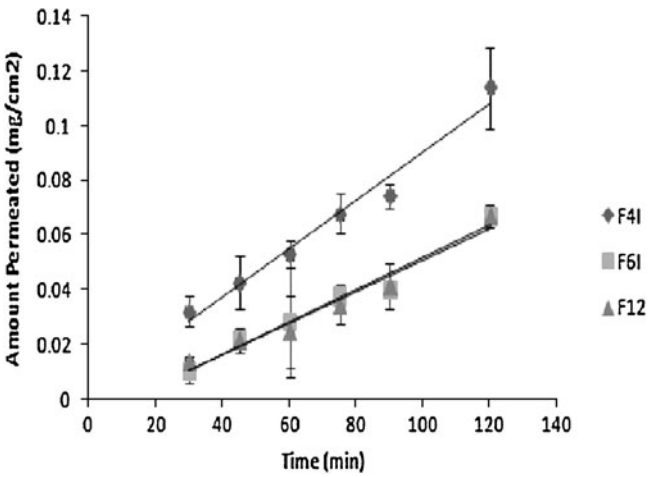

Fig. 2. The permeation of the drug from the selected tablet formulations

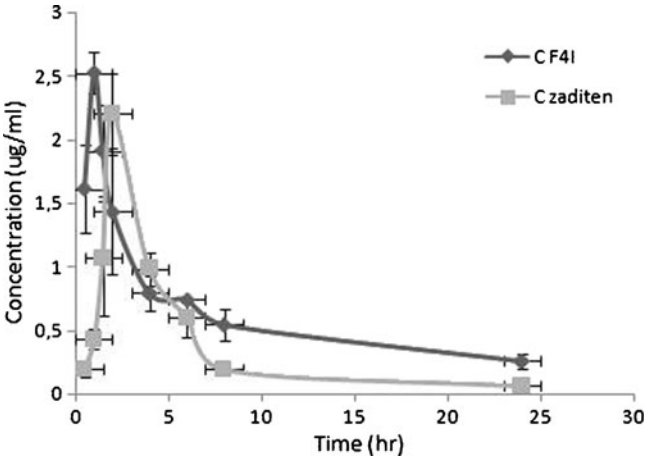

Fig. 3. The mean concentrations of the drug following the administration of each formulation

F12 resulted in further improvement in its flow properties, yet caused an increase in the disintegration time (31).

Formulations F1 (I and II), F8, and F9 were sticky powders despite the presence of granular mannitol which possessed improved flow and compressibility properties (30). The impairment of the flow properties of these powders was due to the high concentration of included PEG blend in the powder (4:1 and 4:0.75 granular mannitol:PEG, respectively). This caused the stickiness and softness of the mixture due to the low melting point (37°C) of the PEG blend.

The rest of the formulations exhibited no significantly different values of the angle of repose and percent compressibility ($P<$ 0.05, one-way ANOVA), due to similarity in their composition.

The use of Avicel PH 102 improves the flow properties of powders due to its granular form, despite its low compressibility resulted from its large particles (32). This poor compressibility is overcome by the use of Prosolv®, which has got better flow and compressibility properties, compared to a physical mixture of microcrystalline cellulose and silicon dioxide. However, it markedly increased the disintegration time (31). This accounts for the long disintegration time recorded for F12 tablet formulation.

However, F12 exhibited the best flow properties. That resulted from including Prosolv® in that formulation. Prosolv® has improved powder flow properties compared to microcrystalline cellulose (Avicel), thus explaining the lower values for both the angle of repose and the percent compressibility of F12 (33).

Increased tablet hardness results in reduced tablet friability (34). Doubling the quantity of magnesium stearate in a granulation reduces the maximum tablet hardness and

Table V. Summary of Pharmacokinetic Parameters of Zaditen® (Novartis Pharma) and the Prepared F4I Sublingual Tablets

	Ketotifen Fumarate Formulations	
	Zaditen®	F4I
Cp_{max} (μg/ml)	2.21 (± 0.69)	2.53 (±0.16)
T_{max} (h)	2 (±0.01)	1 (±0.9)
AUC_{0-24} (μg h/ml)	9.07 (±1.13)	14.89 (±2.9)
% Relative bioavailability		164.15%

increases friability (35). It was found that the hardness of microcrystalline cellulose tablets was decreased by increasing the percent of magnesium stearate without affecting the disintegration time (35). This decrease in hardness accompanied by increased friability, resulting from increasing the percent of magnesium stearate, was clear in the formulations: F6 II, F7 II, F10, and F11. These formulations contained a high concentration of magnesium stearate (1.5%).

The presence of a mixture of low and high melting point (different melting points) polyethylene glycols has an effect on tablet hardness. As the percent of the low melting point polyethylene glycol increased in the tablet formulation, the tablet hardness was reduced (36). The larger the percent of polyethylene glycol 400 present in the PEG blend 2- which was used to prepare the formulations F5 I, F5 II, F7 I, and F7 II- resulted in low tablet hardness and possibly tablet breaking, evidenced with F7I and F7 II.

Upon compression of the powder formulations into tablets, it was not possible to obtain tablets of acceptable friability from F4 II, F6 II, F7 I, F7 II, F10 and F11. The presence of PEG blend 2 with its low melting point (35°C), resulted in the softness of the tablets, and hence their low hardness and high friability.

The use of PEG 6000 results in prolongation of the disintegration time of tablets due to its binding effects. The higher the amount of polyethylene glycol 6000 incorporated in the tablet formulation, the longer the disintegration time (37). Thus, as the percent of PEG blend in the sugar/PEG mixture decreased from in F2 (containing 4:0.75 sugar: PEG) to in F4 (containing 4: 0.25) the disintegration time decreased from 217 to 26 s. The category including F2, F3, and F4 contained PEG blend1 with a high percent of PEG 6000 (the blend with a high melting point 37°C) had a prolonged disintegration time (37). As for the formulations F5, F6, and F7, they possessed relatively shorter disintegration times due to their softness, yet formulation F5, which had the highest percent of PEG (4: 0.75 sugar: PEG), exhibited the highest disintegration time compared to F7 (4: 0.25) which had the least disintegration time. Thus hardness and disintegration time of the tablet are functions of the amount and melting point of the PEG used as binder.

The presence of PEG increases drug release from tablets (38). PEG is considered to be a co-solvent for the drug favoring its dissolution and penetration through the lipid membrane (39–41).

A high increase in the amount of polyethylene glycol, being a co-solvent, favors the remaining of the drug in the aqueous medium rather than its penetration into the lipid membrane. The most suitable percent of PEG which allowed maximum drug permeability was effected in F4 I which showed the highest permeability coefficient.

The use of the sublingual route allows for improving the drug bioavailability due to avoiding the first-pass effect and prevention of drug exposure to the gastrointestinal tract secretions (42), and the rapid onset of action (43). The sublingual administration of furosemide to patients was associated with a high Cp_{max}, and a high bioavailability (44). Piroxicam sublingual tablets were as effective as the intramuscular injection in the treatment of colic (45). Sublingual tablets of misoprostol (25 μg) for induction of labor were effective in high risk pregnant women (46), and another sublingual formulation of the same drug reduced the frequency of severe postpartum hemorrhage (47). Nicotine 2 mg sublingual tablets had the same pharmacokinetic profile as 2 mg chewing gum (48).

Similarly, F4 I, which had the highest drug permeability in the ex vivo experiments, possessed a 164.15% relative bioavailability compared to Zaditen® Novartis solution. The sublingual mucosa had a high ability to give more uniform and higher rates of transmission, and rabbit anesthesia helped to hold the tablet in its place without swallowing it (49). That allowed a maximum amount of drug to be available for absorption through the sublingual mucosa.

CONCLUSION

It was possible to prepare sublingual tablets of ketotifen fumarate using the fast-melt granulation technique. Inclusion of polyethylene glycol 400 and 6000 in a ratio of 4:6 resulting in a blend with melting point 37°C, which when mixed with granular mannitol at a ratio of 0.25 to 4, respectively, yielded formulation F4I. F4I possessed appropriate tablet hardness, friability, disintegration time, and allowed maximum drug permeation through the buccal mucosa. F4I possessed 164.15% relative bioavailability with respect to Zaditen® Novartis solution, the commercially available form of the drug. That was due to the presence of the permeability enhancer polyethylene glycol, which favored the rapid uptake of the drug through the buccal cavity rather than its swallowing and loss by the first-pass effect.

ACKNOWLEDGMENTS

We are so much obliged to the agents of Roquette, France and JRS, Germany for supplying us with the necessary chemicals as gifts to participate in the field of research.

REFERENCES

1. Schaefer T, Holm P, Kristensen HG. Melt granulation in a laboratory scale high shear mixer. Drug Dev Ind Pharm. 1990;16 (8):1249–77.
2. Thies R, Kleinebudde P. Melt pelletization of a hygroscopic drug in a high shear mixer. Part I: Influence of process variables. Int J Pharm. 1999;188:131–43.
3. Voinovich D, Moneghini M, Perisutti B, Filipovic-Gricic J, Gabnar I. Preparation in a high shear mixer of sustained release pellets by melt pelletization. Int J Pharm. 2000;203:235–44.
4. Ochoa L, Igartua M, Hernandez RM, Gascon AR, Pedraz JL. Preparation of sustained release hydrophilic matrices by melt granulation in a high shear mixer. J Pharm Pharm Sci. 2005;8 (2):132–40.
5. Rodriguez L, Cavallari C, Passerini N, Albertini B, Gonzalez ML. Fini. Preparation and characterization by morphological analysis of diclofenac/PEG 4000 granules obtained using three different techniques. Int J Pharm. 2002;242(1–2):285–9.
6. Damian F, Balton N, Naisens L, Balzarini J, Kinget R, Augustijns P *et al*. Physicochemical characterization of solid dispersions of the antiviral agent UC-781 with polyethylene glycol 6000 and gelucire 44/14. Eur J Pharm Sci. 2000;10:311–22.
7. Passerini N, Albertini B, Gonzalez-Rodriguez ML, Cavallarri C, Rodriguez L. Preparation and characterization of ibuprofen-poloxamer 199 granules obtained by melt granulation. Eur J Pharm Sci. 2002;15:71–8.

8. Abu Izza, Khawla A, Li Vincent H, Look LL, Parr GD, Schineller MK. Fast dissolving tablet. US patent 6733781; 2004.
9. Perissutti B, Rubessa F, Moneghini M, Vocnviich D. Formulation design of carbamazepine fast release tablets prepared by melt granulation technique. Int J Pharm. 2003;329:72–80.
10. Yang D, Kulkami R, Behme RJ, Kotiyan PN. Effect of the melt granulation technique on the dissolution characteristics of griseofulvin. Int J Pharm. 2007;329:72–80.
11. Gelucires: Pharmaceutical Applications. http://www.Pharmainfo.net/reviews/gelucires-pharmaceutical-applications.
12. Grant SM, Goa KL, Fitton A, Sorkin EM. Ketotifen, a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in asthma and allergic disorders. Drugs. 1990;40:412–48.
13. Grahnen A, Lonnebo A, Beck O, Eckernas SA, Dahlstrom B, Lindstrom B. Pharmacokinetis of ketotifen after oral administration to healthy male subjects. Biopharm Drug Dispos. 1992;13 (4):255–62.
14. Gosh TK, Pfister WR. Drug delivery to the oral cavity: molecules to market. Taylor & Francis Gp. (Pub.), USA; 2005.
15. El Samaligy MS, Yehia SA, Basilios EB. Formulation and evaluation of diclofenac sodium buccoabhesive disc. Int J Pharm. 2004;286:27–39.
16. Dollery C. Therapeutic drugs. 2nd ed. U.K: Churchill Livingstone; 1999. p. K25–8.
17. Rowe RC, Sheskey PJ, Owe SC. Handbook of pharmaceutical excipients. 5th ed. Great Britain: Pharmaceutical; 2006. p. 459–263. 466-70.
18. The British Pharmacopoeia. The Stationary Office, UK; 2007, pp. A 207,304, 208, 397, 405.
19. The USP NF. Asian Edn., US pharmacopoeial Convention, NC, Canada, Toronto; 2005, pp. 2677-2700.
20. Lachman L, Leiberman HA, Kanig JK. The theory & practice of industrial pharmacy. Philadelphia, PA: Lee & Frebiger; 1986. p. 36–102. 184, 293, 297.
21. European Pharmacopoeia. 4th Edn, Council of Europe, Strasbourg, France. 2002, pp. 1433–5.
22. Florey K. Analytical profiles of drug substances, vol. 13. USA: Academic; 1984. p. 239–63.
23. Sloan KB, Bcall HD, Weimar WR, Villanueva R. Effect of receptor phase composition on the permeability of hairless mouse skin in diffusion cell experiments. Int J Pharm. 1991;73:97–104.
24. Bird AP, Faltinek JR, Shojaei AH. Transbuccal peptide delivery: stability and *in vitro* permeation studies on endomorphin-1. J Control Release. 2001;73:31–6.
25. Mannila J, Järvinen K, Tarvainen M, Jarho P. Effects of RM-β-CD on sublingual bioavailability of Δ^9-tetrahydrocannabinol in rabbits. Eur J Pharm Sci. 2005;26:71–7.
26. Mannila J, Järvinen K, Tarvainen M, Jarho P. Sublingual administration of Δ^9-tetrahydrocannabinol in rabbits. Life Sci. 2006;78:1911–4.
27. Chiang CH, Lui YL, Chen JR. Therapeutic effect and pharmacokinetics of ketotifen transdermal delivery systems. Drug Dev Ind Pharm. 1998;24(3):213–7.
28. Ndindayino F, Vervaet C, Van Den Mooter G, Remon JP. Bioavailability of hydrochlorothiazide from isomat based moulded tablets. Int J Pharm. 2002;246:199–202.
29. Scwarbrick J., Boylan JC. Encyclopedia of Pharmaceutical Technology. 1991.
30. Shojaei A. Buccal mucosa as a route for systemic drug delivery: a review. J Pharm Pharmaceut Sci. 1998;1:15–30.
31. Gohel MC, Jogani PD. A review of coprocessed directly compressibile excipients. J Pharm Pharmaceut Sci. 2005;8(1):76–93.
32. Bolhius GR, Lerk CF. Comparative evaluation of excipients for direct compression. Part I. Pharm Wkly. 1973;108:469–81.
33. Buckton G, Yonemochi E, Yoon WL, Moffat AC. Water sorption and near IR spectroscopy to study the differences between microcrystalline cellulose and silicified microcrystalline cellulose before and after wet granulation. Int J Pharm. 1999;181:41–7.
34. Gordon MS. Process considerations in reducing tablet friability and their effect on *in-vitro* dissolution. Drug Devel Ind Pharm. 1994;20(1):11–29.
35. Mitrevej A, Sinchaipanid N, Faroongsarng D. Spray dried rice starch: comparative evaluation of direct compression of tablets. Drug Devel Ind Pharm. 1986;12:2091–111.
36. Mesmukl A, Phaechamud T. Indomethacin-polyethylene glycoltablet fabricated with mold technique. J Metals, Materials and Minerals. 2008;18(2):157–67.
37. Leonardi D, Barrera MG, Lamac MC, Salomn CJ. Development of prednisolone PEG 6000 fast release tablets from solid dispersions: solid state characterization, dissolution behavior and formulation parameters. AAPS Pharm Sci Tech. 2007;8(4): Article 108.
38. Verhoeven E, De Beer TRM, Schacht E, Vanden Mooter G, Remon JP, Vervaet C. Influence of PEG/polyethylene oxide on the release characterisitics of sustained release ethylcellulose mini-matrices produced by hot melt extrusion: *in vitro* and *in vivo* evaluations. Eur J Pharm Biopharm. 2009;72:463–70.
39. Herkenne C, Naik A, Kalia YN, Hadgraft I, Guy RH. Effect of propylene glycol on ibuprofen absorption into human skin *in vivo*. J Pharm Sci. 2008;97(1):185–97.
40. Cho YA, Gwak HS. Transdermal delivery of ketorolac tomethamine: effects of vehicles and penetration enhancers. Drug Devel Ind Pharm. 2004;30(6):557–64.
41. Gwak HS, Oh IS, Chum IK. transdermal delivery of ondansetrone hydrochloride: effects of vehicles and penetration enhancers. Drug Devel Ind Pharm. 2004;30(2):187–94.
42. Veuillez FA, Deshusses J, Buri P. Synthesis and characterization of an accylated dipeptide (Myr-Try-Leu) with modified transbuccal properties. Eur J Pharm Biopharm. 1999;48(1):21–6.
43. Rathbone MJ, Hadgraft J. Absorption of drugs from human oral cavity. Int J Pharm. 1991;74:9–24.
44. Haegeli L, Brunner La Rocca HP, Wenk M, Pfisterer M, Drewe J, Kruhenbuhl S. Sublingual administration of furosemide: a new application of an old drug. Br J Clin Pharmacol. 2007;64(6): 804–9.
45. Altay B, Horasanli K, Sarica K, Tanrivereti O, Kendirci M, Miroglu C. Double blind placebo-controlled, randomizied clinical trial of sublingual or intramuscular piroxicam in the treatment of renal colic: a comparative study. Urol Int. 2007;79:73–5.
46. Feitosa FE, de Amorin MM, Alencar Jr CA, Coutinho IC, Sampaio ZS. New formulation of sublingual misoprostol (25 mcg) for induction of labor. Rev Assoc Med Bras. 2006;52:251–5.
47. Hoj L, Cardoso P, Nielsen BB, Hridman L, Nielsen J, Aaby P. The effect of sublingual misoprostol in a primary health centre in Guinia-Bissau: randomizied double blind clinical trial. BMJ. 2005;1(331):723.
48. Molander L, Lunell E. Pharmacokinetic investigation of a nicotine sublingual tablet. Eur J Clin Pharmacol. 2001;56 (11):813–49.
49. Adams D. Penetration of water through human and rabbit oral mucosa *in vitro*. Arch Oral Biol. 1974;19:865–72.