Saudi Pharmaceutical Journal (2014) **22**, 53–61

King Saud University

Saudi Pharmaceutical Journal

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Formulation and optimization of orodispersible tablets of flutamide

Kadria A. Elkhodairy [a,b,*], **Maha A. Hassan** [a,c], **Samar A. Afifi** [a,d]

[a] *Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia*
[b] *Department of Industrial Pharmacy, Faculty of Pharmacy, Alexandria University, Alexandria, Egypt*
[c] *Department of Pharmaceutics, Faculty of Pharmacy, Assiut University, Assiut, Egypt*
[d] *Department of Pharmaceutics, National Organization for Drug Control and Research, Giza, Egypt*

Received 8 December 2012; accepted 25 January 2013
Available online 10 February 2013

KEYWORDS

Flutamide;
Orodispersible tablets;
Superdisintegrant-addition;
Sublimation;
Effervescence

Abstract The present study aimed to formulate orodispersible tablets of flutamide (FTM) to increase its bioavailability. Orodispersible tablets were prepared by direct compression technique using three different approaches namely; super-disintegration, effervescence and sublimation. Different combined approaches were proposed and evaluated to optimize tablet characteristics. Sodium starch glycolate (SSG) was used as the superdisintegrant. The prepared powder mixtures were subjected to both pre and post compression evaluation parameters including; IR spectroscopy, micromeritics properties, tablet hardness, friability, wetting time, disintegration time and in-vitro drug release. IR studies indicated that there was no interaction between the drug and the excipients used except Ludipress. The results of micromeritics studies revealed that all formulations were of acceptable to good flowability. Tablet hardness and friability indicated good mechanical strength. Wetting and dispersion times decreased from 46 to 38 s by increasing the SSG concentration from 3.33 to 6.66% w/w in tablets prepared by superdisintegration method. The F8 formulation which was prepared by combined approaches of effervescence and superdisintegrant addition gave promising results for tablet disintegration and wetting times but failed to give faster dissolution rate. The incorporation of 1:5 solid dispersion of FTM: PEG 6000 instead of the pure drug in the same formulation increased the drug release rate from 73.12 to 96.99% after 15 min. This increase in the dissolution rate may be due to the amorphization of the drug during the solid dispersion preparation. The presence of the amorphous form of the drug was shown in the IR spectra.

1. Introduction

Flutamide (FTM) is an oral, non-steroidal antiandrogen drug primarily used to treat prostate cancer. It competes with testosterone and its powerful metabolite, dihydro-testosterone (DHT) for binding to androgen receptors in the prostate gland. By doing so, it prevents them from stimulating the prostate cancer cells to grow. Flutamide may also be used to

* Corresponding author. Address: Department of Pharmaceutics, King Saud University, P.O. Box 22452, Riyadh 11495, Saudi Arabia. Tel.: +00 96 6543791270; fax: +0096612913735.
E-mail address: elkhodairy53@yahoo.com (K.A. Elkhodairy).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

1319-0164 © 2013 Production and hosting by Elsevier B.V. on behalf of King Saud University.
http://dx.doi.org/10.1016/j.jsps.2013.01.009

treat excess androgen levels in women – especially those with Polycystic Ovarian Syndrome (PCOS) George et al., 2001. It is a poorly water-soluble drug; its dissolution is the rate-limiting step in the process of drug absorption that in turns dependent on disintegration. The low bioavailability of FTM after oral formulations may be due to poor wettability, low aqueous solubility, poor permeability, rapid first pass hepatic metabolism and low concentration at the absorption surface (Zuo et al., 2000). FTM undergoes a rapid first pass hepatic metabolism after oral administration resulting in a relatively short half-life of 5–6 h, thus it is usually given 250 mg three doses per day (Zuo et al., 2000). Therefore, developing novel formulations that mitigate solubility and dissolution will produce higher concentrations of FTM in solution at the absorption site and may overcome the first pass effect-mediated poor bioavailability.

The dissolution rate and bioavailability of a poorly soluble drug from solid dosage form depend much on formulation additives and formulation characteristics. On the basis of these considerations, in the present study it was proposed to formulate an oral delivery system, in the form of orodispersible tablet of flutamide to increase its bioavailability.

Orodispersible tablets were prepared by direct compression technique using three different approaches namely; superdisintegrant addition, effervescence and sublimation. In addition combination between different approaches was proposed and evaluated to optimize tablet characteristics. The prepared tablets were subjected to both pre and post compression parameters' evaluation, including; IR spectroscopy, Carr's index, angle of repose, Hausner ratio, hardness, friability, wetting time, disintegration time and dissolution rate. Solid dispersions in the ratios of 1:2 and 1:5 (FTM: PEG 6000) were prepared to increase the solubility and hence the dissolution rate of the drug from the orodispersible tablets.

2. Experimental

2.1. Materials

FTM was kindly donated by Archimica (Origgio, Italy). Sodium starch glycolate (Explotab), spray dried lactose (Ludipress) (El-Amreya Pharmaceutical Co., Alexandria, Egypt). Microcrystalline-cellulose (Avicel pH 102) (FMC Co., USA). Mannitol (Pearlitol SD 200) (BDH, United Poole, England). Polyethylene glycol (PEG 6000) (Pharaonia Pharmaceuticals, Alexandria, Egypt). Sucralose (McNeil Nutritional, LLC, Washington, PA, USA). Sodium bicarbonate, citric acid, sodium tribasic phosphate and camphor (WINLAB, UK). All other chemicals were of analytical reagent grades.

2.2. Preparation of FTM orodispersible tablets

Orodispersible tablets of FTM were prepared by direct compression method using three different approaches; superdisintegrant addition, effervescence, and sublimation, in addition to combined approaches according to the formulae given in Table 1. FTM 300 mg tablets each containing 125 mg of drug were prepared. In all formulations spray dried lactose (Ludipress) and mannitol were used as diluents. The specified quantity of the drug and the other excipients were weighed accurately and passed through 100 # screen prior to mixing. All the materials were transferred to mortar in geometrical order and co-grounded for 15 min. The resulting powder mixture was compressed into tablets using single punch tablet machine (Erweka, Germany) using 8 mm flat surface punches (Nayak and Gopalkumar, 2004). The compression force was adjusted to give tablet hardness in the pharmacopeial range of orodispersible tablets (2–4 kg/cm^3). For tablets prepared by sublimation technique using camphor as a sublimating agent, the tablets were dried at 60 °C in an oven till constant weight was obtained (Gohel et al., 2004). For tablets prepared by the effervescence method, sodium bicarbonate and citric acid were accurately weighed and preheated at a temperature of 80 °C. In all formulations the weighed amounts of drug and Ludipress were mixed first then other excipients were mixed thoroughly to load the drug on the surface of water soluble carriers. Ten formulations were designed, one of which is a control and two others were prepared using solid dispersions of FTM (Table 1).

2.3. Preparation of FTM solid dispersions

FTM solid dispersions (SDs) were prepared by fusion method using PEG 6000 as the polymeric carrier in drug to polymer ratios of 1:2 and 1:5. The weighed amount of the polymer was melted in a porcelain dish placed in a water bath at 60 °C, and then the calculated amount of the drug was added while stirring till homogeneity. The melted mixtures were left to con-

Table 1 Formulations of orodispersible tablets of flutamide.

Ingredients (mg)	Formulation code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug	125	125	125	125	125	125	125	125	SD # 125	SD #125
Mannitol		15	15	15	15	15	15	15	15	15
Avicel 102	45	45	45	45	45	45	45	45	45	45
SSG		10	15	20		20		20	20	20
Sodium bicarbonate							30	30	30	30
Citric acid							24	24	24	24
Camphor					60	60				
Sucralose	3	3	3	3	3	3	3	3	3	3
PEG 6000	6	6	6	6	6	6	6	6	6	6
Ludipress qs	121	96	91	86	26	96	52	32	32	32
TW* (mg)	300	300	300	300	300	300	300	300	550	800

TW* = Total weight of tablet in mg.

geal and then passed through 100 # screen. The powdered solid products were kept in a desiccator to dry. An amount of solid dispersion equivalent to 125 mg of the drug was formulated as fast dissolving tablets for comparison between the drug (F8) and its SD efficacy (F9 and F10) (Table 1). The total weight of tablets in case of 1:2 and 1:5 SDs was 550 and 800 mg, respectively.

2.4. Pre-compression evaluation

2.4.1. IR study

IR spectra of physical mixtures (1:1) of FTM and various excipients, as well as the drug solid dispersions were performed to find out any possible drug-excipient interaction by KBr pellet method using Perkin–Elmer FTIR series (model-1615) spectrophotometer.

2.4.2. Micromeritics study

2.4.2.1. Angle of repose (θ°). The angle of repose of powder blends was determined by the funnel method. Accurately weighed powder blends were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder blends (2 cm). The powder blends were allowed to flow through the funnel freely onto its surface. The diameter of the powder cone was measured and angle of repose was calculated (Cooper and Gunn, 1986). Three determinations were performed.

2.4.2.2. Bulk density. Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 mL measuring cylinder. After the initial volume was determined, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 s intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated (Shah et al., 1997). The determination was carried out in triplicate.

2.4.2.3. Compressibility index and Hausner ratio. The compressibility index of the powder blends was determined by Carr's compressibility index or Carr's index (CI) Aulton and Wells, 1988. Hausner ratio (HR) was also determined for each powder blend (United States Pharmacopeia 24/NF19, 2000). Three determinations were done for each formula.

2.5. Post-compression evaluation

2.5.1. Hardness

The tablet hardness is the force required to break a tablet in a diametric compression force. Erweka hardness tester (Erweka, Germany) was used in this study. This tester applies force to the tablet diametrically (Banker and Anderson, 1987). The test was performed on six tablets and the average was calculated.

2.5.2. Friability

The friability (F) of a sample of 20 tablets was measured using Roche friabilator ((ERWEKA, Germany). Twenty tablets were weighed, rotated at 25 rpm for 4 min. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated. Friability below 1% was considered acceptable (Banker and Anderson, 1987).

2.5.3. Weight variation test

Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average weight (Banker and Anderson, 1987).

2.5.4. In-vitro disintegration time

Tablet was placed in a beaker containing 20 ml of distilled water at 37 ± 0.5 °C. Time for complete disintegration of the tablet was measured in triplicate (Banker and Anderson, 1987; Khan, 1975).

2.5.5. Wetting time

The wetting time of the tablets can be measured using a simple procedure. A filter paper of 10 cm diameter was placed in a Petri dish with a 10 cm diameter. One milliliter of water containing amaranth, a water soluble dye, was added to Petri dish. A tablet was carefully placed on the surface of the filter paper. The time required for water to reach the upper surface of the tablet was noted as a wetting time (Tejvir et al., 2011). Three determinations were performed.

2.5.6. In-vitro dissolution studies

In-vitro dissolution of the fast disintegrating tablets was studied in USP XXIV dissolution apparatus II (Pharmatest, Germany) employing a paddle stirrer at 100 rpm using 900 ml of pH 6.8 phosphate buffer containing 1% sodium lauryl sulfate at 37 ± 0.5 °C as a dissolution medium. One tablet was used in each test. Aliquots of 5 ml each were withdrawn at specified time intervals (1, 2, 3, 4, 5, 6, 8, 10, 15, 20, 30, 45 and 60 min.) and replaced with equal volume of fresh medium. The withdrawn aliquots were analyzed for drug content spectrophotometrically at λ_{max} 302 nm. Drug concentration was calculated and expressed as cumulative percent of the drug released. The dissolution tests were carried out in triplicate.

2.6. Statistical analysis

All the results were expressed as mean value ± standard deviation (SD). One way analysis of variance (ANOVA) with Turkey's multiple comparison post hoc was used to test for significance, at a 5% significance level. Statistical difference dealing ($P < 0.05$) was considered significant (Bolton and Bon, 2004).

3. Results and discussion

FTM orodispersible tablets were prepared by direct compression method being the most simplest and economic technique. Three different approaches; superdisintegrant addition, effervescence and sublimation as well as combined approaches were used. Avicel PH102 was used as directly compressible material to facilitate powder mixture compression into tablets. Mannitol was used as it imparts multidimensional benefits as it has good aqueous solubility and good wetting properties facilitating tablet breakdown as well as negative heats of solution

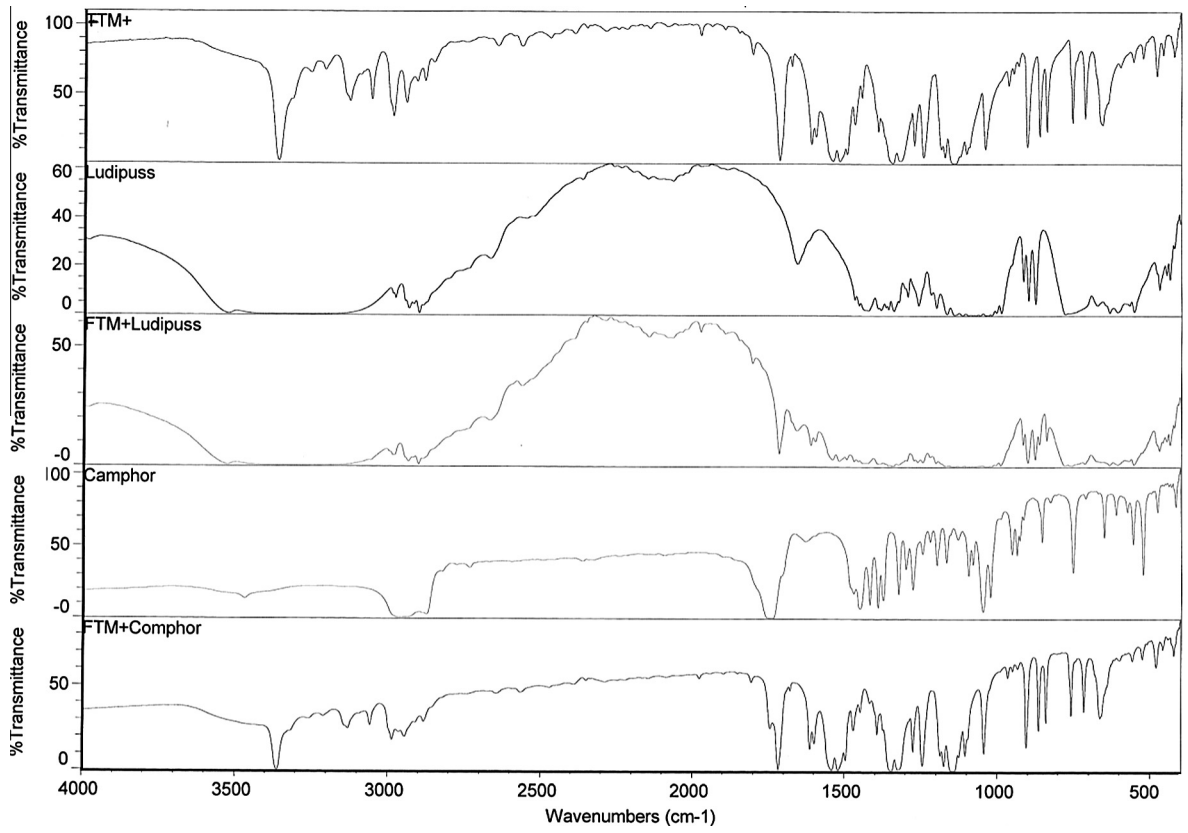

Figure 1a IR spectra of FTM, Ludipress, Camphor and physical mixtures of 1:1 drug-excipient (Ludipress or Camphor).

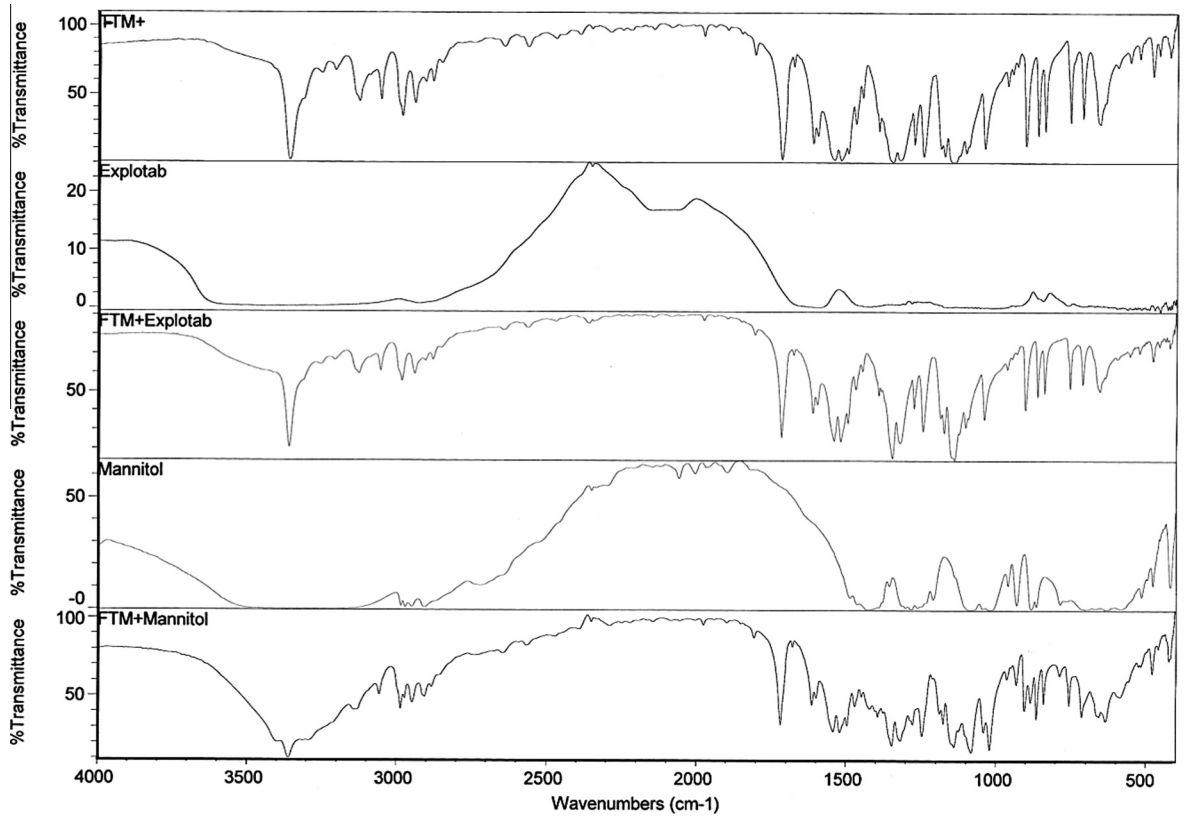

Figure 1b IR spectra of FTM, Explotab, Mannitol and physical mixtures of 1:1 drug-excipient (Explotab or Mannitol).

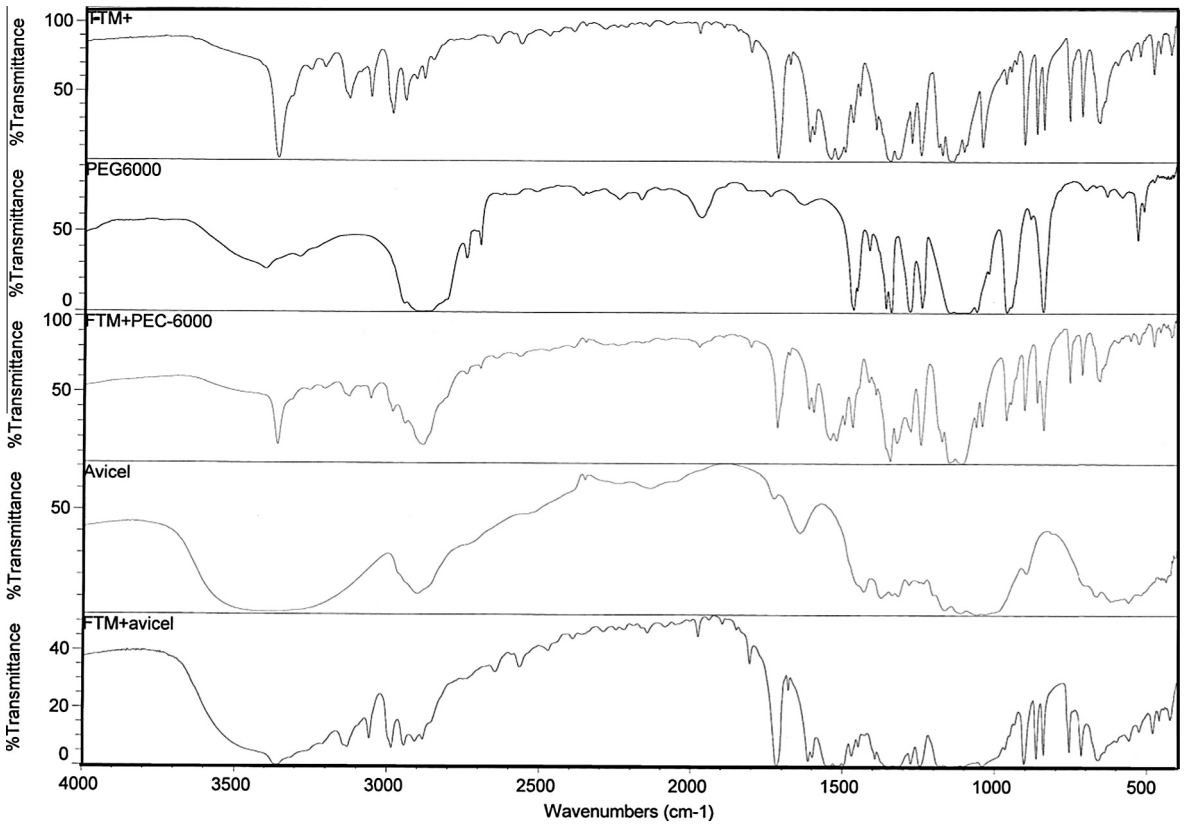

Figure 1c IR spectra of FTM, Avicel, PEG 6000 and physical mixtures of 1:1 drug-excipient (Avicel or PEG 6000).

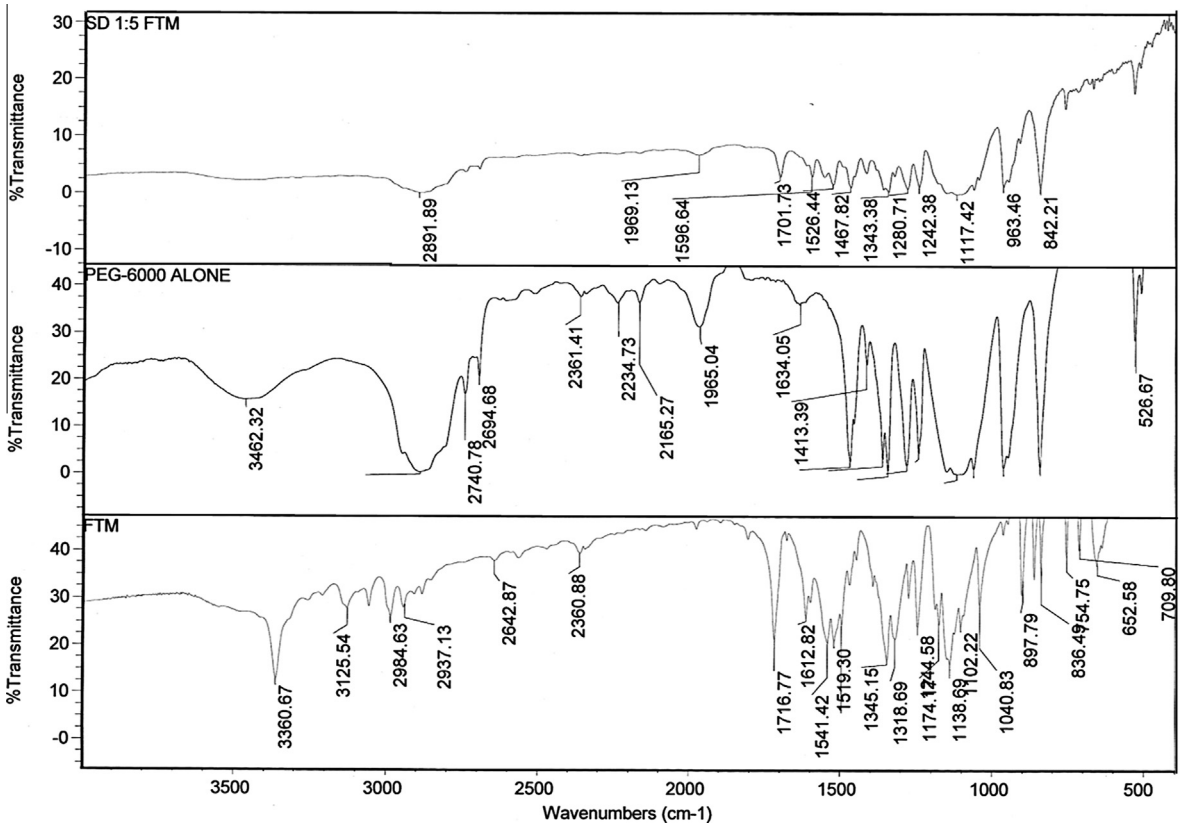

Figure 1d IR spectra of FTM, PEG 6000 and Solid dispersion of 1:5 (drug: PEG 6000).

Table 2 Different properties of FTM orodispersible tablets.

Parameter	Formulation's code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Hardness kg/cm^2	1.83 ± 0.29	2.33 ± 0.49	3.00 ± 0.03	3.19 ± 0.30	2.36 ± 0.26	2.99 ± 0.68	2.49 ± 0.31	3.39 ± 0.35	3.41 ± 0.30	3.42 ± 0.32
Weight variation	298 ± 1.60	299 ± 0.91	298 ± 1.40	300 ± 0.69	296 ± 1.90	297 ± 1.90	300 ± 1.80	300 ± 1.60	549 ± 1.80	798 ± 1.90
% F	0.68	0.85	0.92	0.99	0.81	0.78	0.75	0.81	0.83	0.83
WT (sec)	57.33 ± 1.52	46.00 ± 2.94	42.33 ± 1.69	38.00 ± 1.20	43.00 ± 0.99	32.50 ± 0.83	32.67 ± 1.05	27.33 ± 0.76	30.32 ± 0.89	29.91 ± 0.97
DT (sec)	56 ± 0.82	44.33 ± 1.12	40.67 ± 0.98	37.66 ± 1.23	40.33 ± 1.03	38.33 ± 1.23	28.33 ± 1.99	21.66 ± 2.01	28.79 ± 1.39	21.67 ± 0.87
(θ°)	45.48	39.82	37.34	35.12	34.87	32.53	33.74	30.13	31.5	30.1°
CI	21.18	18.62	18.95	19.81	20.46	19.24	20.48	18.71	18.44	17.88
HR	1.239	1.229	1.234	1.247	1.251	1.238	1.274	1.230	1.212	1.231

% F = % Friability, WT = wetting time, DT = disintegration time, CI = Carr's Index, HR = Hausner Ratio.

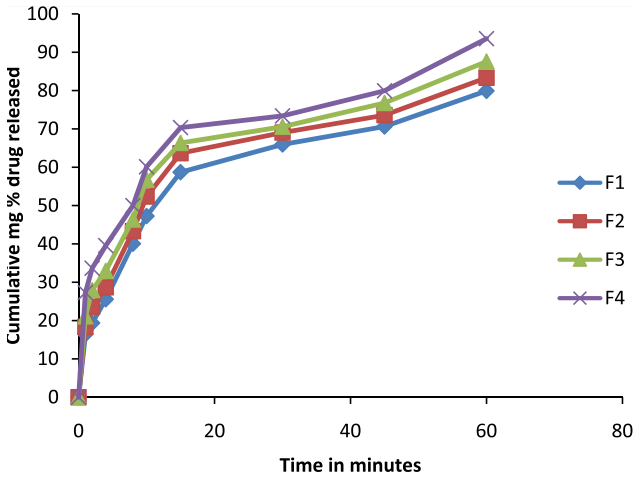

Figure 2 Dissolution rate profiles of FTM orodispersible tablets containing different concentrations of SSG.

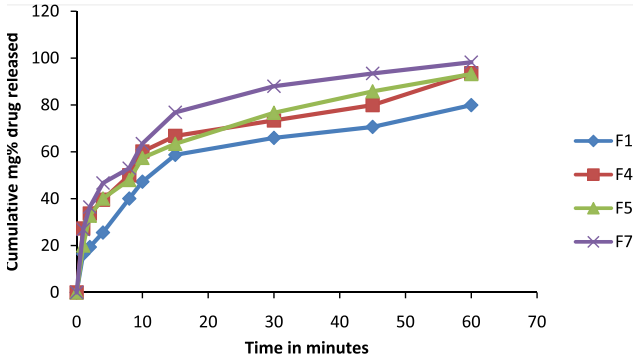

Figure 3 Dissolution rate profiles of FTM orodispersible tablets prepared by superdisintegrant addition (F4), sublimation (F5) and effervescence (F7) techniques compared to control tablet (F1).

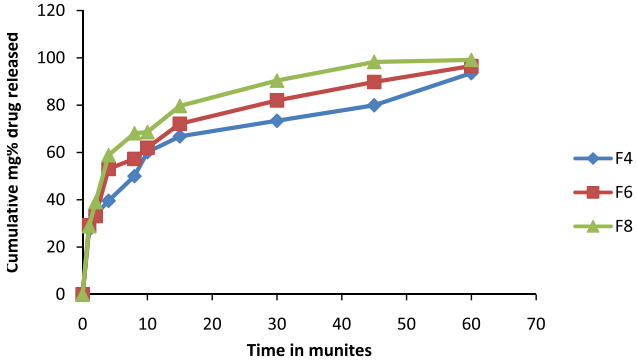

Figure 4 Dissolution rate profiles of FTM orodispersible tablets prepared by combined approaches; sublimation + SSG addition (F6) and by effervescence + SSG addition (F8) compared to tablets prepared by SSG addition (F4).

giving cooling effect in the mouth (Singh and Singh, 2009). Ludipress was used as highly soluble diluent which acted as a water soluble carrier for the drug. PEG 6000 was used as hydrophilic lubricant instead of the hydrophobic magnesium

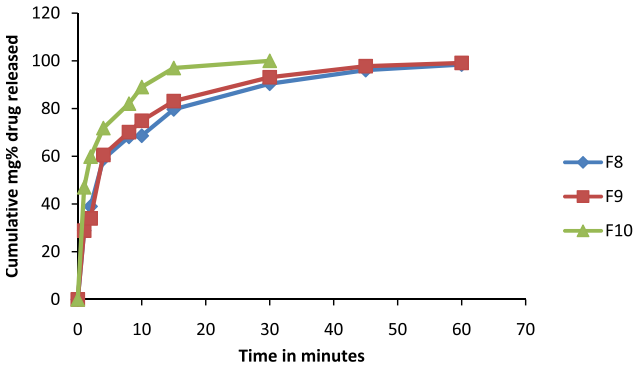

Figure 5 Dissolution rate profiles of FTM orodispersible tablets prepared by effervescence + SSG technique using 1:2 and 1:5 FTM: PEG 6000 solid dispersions (F9, F10) compared to F8.

stearate. The addition of PEG 6000 as lubricant promoted the wettability of the tablets thus accelerating SSG swelling leading to rapid breakdown and fast drug dissolution. The slight bitter taste of the drug has been masked by using 1% w/w of sucralose. Explotab was used as a superdisintegrant. All the excipients used were hydrophilic to obtain orodispersible tablets of fast dissolution rate.

3.1. Pre-compression evaluation

3.1.1. Fourier transform infrared spectroscopy

The pure drug (FTM) and the solid admixture of drug and various excipients used in the preparation of fast dispersible tablet formulations were characterized by FT-IR spectroscopy to test the compatibility. The IR transmission spectra of FTM and its physical mixtures (PMs) with the excipients are demonstrated in Fig. 1a–c. All characteristic peaks of FTM are present in their original position denoting the absence of drug-carrier interaction. The characteristic peak of FTM at 3360 cm^{-1} corresponding to its amino group was detected in all PMs except in case of Ludipress, where the characteristic peak of FTM was completely disappeared that might be due to the adsorption of the FTM onto the surface of the amorphous diluent. It was also observed that the intensity of the peaks in IR spectra of PMs of FTM and excipients (other than Ludipress) was slightly reduced which may be due to the presence of the drug in 1:1 ratio. In case of Avicel and Mannitol it can be noticed that the IR spectra of PMs of FTM and Avicel or Mannitol showed peaks that are superimposed with the characteristic peak of FTM.

The IR spectra of the SD 1:5 (drug: PEG 6000) compared to the pure drug and PEG 6000 were detected in Fig. 1d. It can be seen that the characteristic peak of FTM at 3360 cm^{-1} was completely disappeared in the SD formulation. This result indicated an interaction between the drug and the polymer leading to the formation of amorphous structure of the drug.

3.1.2. Micromeretics study

Angle of repose (θ) is a characteristic of the internal friction or cohesion of the particles. Its value will be high if the powder is cohesive and low if the powder is non-cohesive. All formulations showed good to acceptable flow properties as indicated by the values of angle of repose (30.13–39.82°). Flow property of FTM was improved in all formulations compared to the control formula (45.48°). Carr's index showed values up 20 denoting that these formulations were of acceptable to good flowability. Hausner showed that powders with low interparticle friction, had ratios of approximately 1.250, indicating good flow properties. All formulations had Hausner ratio values within the stated limit (Table 2).

3.1.3. Post-compression evaluation

Hardness of the tablets was found to vary from 2.327 to 3.394 kg/cm^2 compared to 1.833 kg/cm^2 of control tablet. Percentage friability of all formulations was less than 1% indicating good mechanical characteristics. Wetting dispersion times decreased from 46 to 38 s. by increasing the SSG concentration from 3.33 to 6.66% w/w. Formulation F6 prepared by sublimation approach containing 6.66% w/w SSG showed a decrease in wetting and dispersion times compared to F5 without SSG. The same results were obtained for F7 and F8 prepared using effervescence approach (Table 2), where the presence of SSG in F8 decreased the wetting and dispersion times compared to F7 free from superdisintegrant. It was also observed that all formulations showed deceased values of wetting and dispersion times compared to the control formulation.

The decrease in wetting and dispersion times in all formulations may be attributed to the presence of superdisintegrant which absorbs water and swells causing rupture of the tablets.

Table 3 Dissolution parameters of FTM orodispersible tablets.

Formulation's code	Dissolution Parameters					
	$D_{4\ min}$	$D_{10\ min}$	$D_{15\ min}$	$D_{45\ min}$	$t_{25\%}$ (min)	$t_{50\%}$ (min)
F1	25.550	27.450	58.710	70.630	3.93	10.58
F2	28.670	52.350	63.660	73.590	3.45	9.55
F3	32.940	56.730	66.340	76.770	1.79	8.81
F4	39.560	60.120	70.340	79.940	0.92	8.32
F5	40.060	57.410	63.421	85.810	1.53	8.71
F6	53.040	59.110	68.420	89.790	0.86	8.76
F7	46.700	63.500	76.840	93.450	0.93	7.87
F8	58.840	68.600	79.650	96.110	0.87	7.29
F9	60.550	74.870	78.120	97.760	0.87	6.68
F10	71.820	89.020	96.990	100.00	0.53	1.67

$D_{4\ min}$ = dissolution rate after 4 min. $D_{10\ min}$ = dissolution rate after 10 min.
$D_{15\ min}$ = dissolution rate after 15 min. $D_{45\ min}$ = dissolution rate after 45 min.

Also the presence of camphor in tablets prepared by sublimation approach resulted in the formation of porous tablets which facilitated the diffusion of the wetting medium and led to breakdown of the tablets.

Dispersion time is very important for orodispersible tablets which are desired to be less than one minute for orally disintegrating tablets. This rapid disintegration assists swallowing and also plays a role in drug absorption in buccal cavity, thus promoting bioavailability. Tablet formulations F5, F6, F7 and F8 were found to be promising and displayed an in vitro dispersion time of less than 60 s, which facilitates their dispersion in the mouth (Table 2).

3.1.4. In-vitro dissolution study

The results obtained from the dissolution study are presented in Figs. 2–5. and summarized in Table 3. F1 represents the control formulation to which other formulations were compared. It was observed that the three different approaches used in this study namely; superdisintegrant addition, effervescence and sublimation techniques increased the dissolution rate of the drug compared to the control formula (F1) ($P < 0.001$). The order of increased drug dissolution using the different approaches was as follows; superdisintegrant addition > effervescence > sublimation. In case of superdisintegrant addition approach; increasing the concentration of superdisintegrant from 3.33% w/w in F2 to 6.66% w/w in F4 resulted in an increase in the dissolution rate of the drug after 15 min from 63.66 to 70.34% compared to 58.71% of the control tablet (F1). Tablets prepared by sublimation approach (F5) did not show promising results concerning the dissolution rate compared to that prepared by superdisintegrant addition technique (F4) ($P > 0.05$). Whereas, tablets prepared by effervescence technique F7 showed that the drug release was slightly increased to 46.00 mg% compared to 40.060 mg% in case of F4 after 4 min. of dissolution ($P < 0.05$). The obtained results may be attributed to the rapid disintegration of the tablets F7 due to the evolution of CO2 gas (Table 3). In addition, effervescence technique (F7) showed a significant increase in dissolution rate compared to sublimation technique (F5) with $P < 0.001$.

Combination of two approaches namely superdisintegrant addition with sublimation or effervescence approach resulted in an increase in the drug dissolution rate. The incorporation of 6.66% w/w superdisintegrant in the formulations F5 prepared by sublimation and F7 prepared by effervescence to get formulations F6 and F8; respectively, increased their dissolution rates compared to tablet formulation F4 prepared by superdisintegrant addition (Fig. 4). The increased dissolution rate of F6 could be explained by, the increased surface porosity of the tablets produced by sublimation of camphor which increased the dissolution medium penetration rate into the tablets thus accelerating the swelling of the SSG and facilitating tablet breakdown. This consequence led to an increase in the tablet dissolution rate ($P < 0.01$). In case of F8, increased dissolution rate could be due to the synergistic effect of SSG and CO2 produced due to the wetting of the tablets. The evolved gas accelerated the breakdown of the tablets as indicated by its dispersion time (Table 2). The highest dissolution rate was obtained on using the effervescence approach combined with superdisintegrant addition (F8) as indicated by the t 25% and t 50% ($P < 0.001$) (Table 3). Although, tablets of F8 formulation showed promising results as orodispersible drug delivery based on its wetting and dispersion times but its dissolution rate was not promising. Therefore, solid dispersions of FTM using PEG 6000 as hydrophilic carrier were prepared and used for the preparation of tablets using the same ingredients in formulation F8. Formulations F9 and F10 were prepared using solid dispersion of drug to polymer ratios 1:2 and 1:5, respectively, instead of the pure drug. Fig. 5 shows the release profiles of tablet formulations F8, F9 and F10. It is obvious that tablets containing the drug in 1:2 SD form (F9) did not show a significant increase in the drug dissolution rate ($P > 0.05$). Whereas, (F10) containing the drug in 1:5 SD form increased the dissolution rate of the drug to 71.82% compared to that released from F8 (58.84%) after 4 min of dissolution test ($P < 0.001$). The best dissolution performance of formulation containing SD was mainly attributed to the almost higher degree of drug amorphization achieved in these systems, as illustrated in IR spectra (Fig. 1d).

In this study, the total weight of F10 was 800 mg which could limit its use as it is too bulk to be administered as orodispersible tablets, but it disintegrated rapidly within 20.66 s. thus traces will remain in the mouth. Thus the bulk weight might not present a problem.

4. Conclusion

Orodispersible tablets of FTM could be considered useful oral delivery systems to increase the drug bioavailability. Among the different approaches studied, effervescence technique was that of choice based on the data from evaluation studies. Combined approaches of effervescence and superdisintegrant addition showed optimum tablet characteristics except their dissolution rate. Therefore, solid dispersion of FTM: PEG 6000 in the ratio of 1:5 was found to improve the dissolution properties of the tablets prepared by the combined approach.

Conflict of interest

The authors have reported no conflict of interest.

Acknowledgements

The authors are greatly thankful to the Research Center of the Female Scientific Section, Riyadh, King Saud University, for financial support by grant.

References

Aulton, M.E., Wells, T.I., 1988. Pharmaceutics: The Science of Dosage Form Design. Churchill Livingstone, London, England.

Banker, G.S., Anderson, N.R.I., 1987. In: Lachman, L., Lieberman, H.A., Kanig, J.L. (Eds.), The Theory and Practice of Industrial Pharmacy, third ed. Varghese Publishing House, Mumbai, pp. 293–299.

Bolton, S., Bon, C., 2004. Pharmaceutical statistics and practical and clinical application. In: Rev and Expanded, 4th ed. Marcel Dekker Inc., New York, pp. 96–146.

Cooper, J., Gunn, C., 1986. Powder flow and compaction. In: Carter, S.J. (Ed.), Tutorial Pharmacy. CBS Publishers and Distributors, New Delhi, India, pp. 211–233.

George, C., Zoumakis, P., Emmanouil, Gravanis, A., 2001. In: Bertram, G., Katzung (Eds.), Basic and Clinical Pharmacology,

8th ed. Lange Medical Books/McGraw-Hill, New York, pp. 704–707.

Gohel, M., Patel, M., Amin, A., Agrwal, R., Dave, R., Bariya, N., 2004. Formulation design and optimization of mouth dissolve tablets of nimesulide using vacuum drying technique. AAPS Pharm. Sci. Tech. 5, 1–6.

Khan, K.A., 1975. The concept of dissolution efficiency. J. Pharm. Pharmacol. 27, 48–49.

Nayak, S.M., Gopalkumar, P., 2004. Design and optimization of fast dissolving tablets for promethazine theoclate. Indian Drugs 41, 554–556.

Shah, D., Shah, Y., Rampradhan, M., 1997. Development and evaluation of controlled release diltiazem hydrochloride microparticles using cross-linked poly (vinyl alcohol). Drug Dev. Ind. Pharm. 23, 567–574.

Singh, J., Singh, R., 2009. Optimization and formulation of orodispersible tablets of meloxicam. Trop. J. Pharm. Res. 8, 153–159.

Tejvir, K., Bhawandeep, G., Sandeep, K., Gupta, G.D., 2011. Mouth dissolving tablets: a novel app to drug delivery. Int. J. Cur. Pharm. Res. 3 (1), 1–7.

United States Pharmacopeia 24/NF19, 2000. The Official Compendia of Standards. Asian Rockville, M.D. (Ed.), United States Pharmacopoeia Convention Inc, pp. 1913–1914.

Zuo, Z., kwon, G., Stevenson, B., Diakur, J., Wiebe, L.I., 2000. Hydroxypropyl-bcyclodextrin flutamide inclusion complex I. Formulation, physical characterization and absorption studies using the Caco-2 in vitro model. J. Pharm. Pharmaceut. Sci. 3, 220–227.