



Original article

Optimized furosemide taste masked orally disintegrating tablets

Mohamed Abbas Ibrahim^{a,b,*}, Amal El Sayeh F. Abou El Ela^{a,c}^a Department of Pharmaceutics, College of Pharmacy, King Saud University, Saudi Arabia^b Department of Pharmaceutics and Industrial Pharmacy, College of Pharmacy, Al-Azhar University, Assiut, Egypt^c Department of Pharmaceutics, College of Pharmacy, Assiut University, 71526 Assiut, Egypt

ARTICLE INFO

Article history:

Received 16 January 2017

Accepted 10 April 2017

Available online 13 April 2017

Keywords:

Furosemide

Orally disintegrating tablets (ODTs)

Eudragit E100

Optimization

Taste masking

Superdisintegrant

ABSTRACT

Optimized orally disintegrating tablets (ODTs) containing furosemide (FUR) were prepared by direct compression method. Two factors, three levels (3^2) full factorial design was used to optimize the effect of taste masking agent (Eudragit E100; X1) and superdisintegrant; croscarmellose sodium (CCS; X2) on tablet properties. A composite was prepared by mixing ethanolic solution of FUR and Eudragit E100 with mannitol prior to mixing with other tablet ingredients. The prepared ODTs were characterized for their FUR content, hardness, friability and wetting time. The optimized ODT formulation (F1) was evaluated in term of palatability parameters and the in vivo disintegration. The manufactured ODTs were complying with the pharmacopeia guidelines regarding hardness, friability, weight variation and content. Eudragit E100 had a very slightly enhancing effect on tablets disintegration. However, the effects of both Eudragit E100 (X1) and CCS (X2) on ODTs disintegration time (Y1) were insignificant ($p > 0.05$). Moreover, X1 exhibited antagonistic effect on the dissolution after 5 and 30 min (D5 and D30, respectively), but only its effect on D30 is significant ($p = 0.0004$). Furthermore, the optimized ODTs formula showed good to acceptable taste in term of palatability, and in vivo disintegration time of this formula was about 10 s. © 2017 The Authors. Production and hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Patient inconvenience due to swallowing difficulty (dysphagia) may minimize the drug treatment efficacy. Dysphagia is common in elderly patients and those with dementia, whereas patient rejection is frequently perceived. Formulation of drugs as orally disintegrating tablets (ODTs) is one of the approaches to achieve enhanced patient acceptance toward orally solid dosage forms (Ito et al., 2016; Nishiyama et al., 2016). Orally disintegrating tablets are solid dosage forms that disintegrate rapidly when placed upon the tongue, usually within a matter of seconds (FDA, 2008). ODTs are intended to disperse, dissolve, or disintegrate quickly in the mouth cavity due to saliva, which results in release of the drug due to rapid absorption of the medium into the tablet core followed by prompt tablet disintegration under the effect of

superdisintegrant. Thereafter, dissolving of the water-soluble tablet's components causes enhanced drug dissolution from tablets. The dissolved drug molecules are either swallowed or subjected to pregastric absorption, which increases the rate and extent of drug absorption and decreased hepatic metabolism (Van Arnum, 2000). Several formulation and drug delivery advantages in certain patient groups as pediatric, geriatric, and psychiatric patients could be achieved by using ODTs (Sasthy et al., 2000; Suresh et al., 2008). Rapid onset of action could be achieved from the rapid dissolution and absorption of some drugs from ODTs formulations (Ciper and Bodmeier, 2005; Abdelbary et al., 2009). Moreover, when pregastric absorption takes place, bioavailability of drugs that are subjected to hepatic metabolism (first pass elimination route), can be improved (Desai et al., 2016; Samprasit et al., 2010). Wang et al. (2013) showed that formulation of perphenazine/hydroxypropyl-beta-cyclodextrin solid dispersion by inclusion complex as ODTs can enhance pharmacokinetic properties of such drugs. C_{max} of ODTs of the drug was found higher than the reference tablets. In addition, short T_{max} value was recorded in case of ODTs compared to longer T_{max} in case of reference tablets, indicating rapid onset in case of ODTs.

Orally disintegrating tablets of antihypertensive agents have been anticipated to present several therapeutic benefits over the conventional tablets. These expected advantages include

* Corresponding author at: Department of Pharmaceutics, College of Pharmacy, King Saud University, Saudi Arabia.

E-mail address: abbma71@gmail.com (M.A. Ibrahim).

Peer review under responsibility of King Saud University.



Production and hosting by Elsevier

Improvement of drug bioavailability, ease of administration and patient compliance, in addition to the fast onset of action, as it is a major concern in the treatment of hypertension (Shazly and Ibrahim, 2016).

Orally dispersible tablets of the antihypertensive drug (atenolol) developed by including different ratios of crospovidone, croscarmellose sodium and sodium starch glycolate as super disintegrants (Chandrasekhar et al., 2013). The results revealed that the prepared ODTs showed rapid drug dissolution, acceptable mouth feel and improved drug bioavailability with better patient compliance. Also, Shazly and Ibrahim (2016) prepared taste masked ODTs of losartan potassium for hypertensive patients using Eudragit E 100 as taste masking agent. They showed that the drug dissolution rate has been enhanced by addition of superdisintegrant, and the taste masked ODTs showed acceptable taste and mouth feel. The results obtained conclusively demonstrated successful rapid disintegration of the formulated tablets and acceptable in vivo patient palatability.

Furosemide (FUR), 5-(aminosulphonyl)-4-chloro-2-[(2-fuanylmethyl) amino] benzoic acid, is a potent loop (high ceiling) diuretic used mainly in the management of hypertension (Murray et al., 1997). According to the biopharmaceutical classification system (BCS), FUR is classified as a class IV drug due to its low solubility (5–20 µg/ml) and low permeability (Lindenberg et al., 2004). Therefore, low oral bioavailability of FUR has been reported (Nielsen et al., 2015; Ozdmir and Ordu, 1998).

Kawano et al. (2010), masked the undesirable taste of furosemide by granulation with maltitol by mixing and coating methods prior to compression into ODTs. They observed that increasing the amount of maltitol resulted in increasing tablet disintegration time.

The aim of this study is to optimize and formulate ODTs containing FUR. The effects of the taste masking agent (X1; Eudragit E 100) and superdisintegrant (X2; croscarmellose sodium, CCS) on the tablets disintegration and dissolution will be investigated.

2. Materials and methods

2.1. Materials

Furosemide (FUR) was purchased from Synopharm (Barsbüttel, Germany), croscarmellose sodium (CCS) was kindly supplied by (SPIMACO, Qassem, KSA). Microcrystalline cellulose, MCC (Avicel® PH101) was purchased from Serva Feinbiochemica (Heidelberg, Germany). Spray dried mannitol; Mannogem™ EZ was kindly supplied by SPI (Grand Haven, USA). Magnesium stearate was purchased from Riedel-de Haën (Seelze, Germany). Eudragit E100 was obtained from Evonik Rohm GmbH (Germany).

2.2. Experimental design

Two factors, three levels (3²) full factorial design was used to optimize FUR orally disintegrating tablets, namely Eudragit E 100 (X1) and croscarmellose sodium, CCS (X2) concentrations using a statistical package (Statgraphics Plus, version 5). Statistical models with interaction terms were derived to evaluate the effect of the two factors on the disintegration time in seconds (Y1), percentage of FUR dissolved within 5 min (Y2), percentage of FUR dissolved within 30 min (Y3) of the manufactured orally disintegrating tablets.

The selected two factors as well as their levels and analyzed response are shown in Table 1 and the matrix of the factorial design is represented in Table 2. Each row in the matrix identifies an experiment and each experiment provides a result (response). This design provided an empirical second order polynomial model.

Table 1
Variables in 3² full factorial design.

Independent variable, Factor	Low (-1)	Middle (0)	High (1)
X1: Eudragit E100 (%)	2.5	6.25	10.0
X2: Croscarmellose Sodium, CCS (%)	2	5	8
Dependent variable, Response			
Y1: Disintegration time (sec)			
Y2: Dissolution after 5 min, D5 (%)			
Y3: Dissolution after 30 min, D30 (%)			

Table 2
Matrix of 3² full factorial design for FUR oral disintegrating tablet formulations.

Experiment no.	Eudragit E100 (X ₁)	Croscarmellose Sodium, CCS (X ₂)
1	2.5	8.0
2	10.0	2.0
3	10.0	5.0
4	10.0	8.0
5	6.25	5.0
6	2.5	2.0
7	2.5	5.0
8	6.25	2.0
9	6.25	8.0

In this mathematical approach, each experimental response (Y) can be represented by a quadratic equation of the response surface:

$$Y = B_0 + B_1X_1 + B_2X_2 + B_3X_1X_2 + B_4X_1^2 + B_5X_2^2$$

2.3. Furosemide taste masking and tablet compression

To mask the undesirable taste of FUR, Eudragit E100 and spray dried mannitol were used to prepare taste masked composite containing the drug. The composition of FUR ODTs is displayed in Table 3. The formula weight of FUR and Eudragit E100 were dissolved with 10 ml acetone to form a clear solution, which was then mixed with mannitol in a mortar to form a wet mass, and the solvent was allowed to evaporate. Thereafter, the powder mass was allowed to dry overnight at 50–60 °C. The resulting solid mass was then pulverized and sieved (350 µm). The formula weights of MCC and CCS were added and the powders were mixed in Turbula mixer (type S27, Erweka, Apparatebau, Germany) for 5 min. At the end, magnesium stearate amount was incorporated and the mixture was mixed for further 2 min. The powder was compressed into tablets weighing 200 mg using Korsh single punch machine (Erweka, EKO, Germany) with 9 mm shallow concave punches.

2.4. Evaluation of tablets

2.4.1. Dosage unit uniformity

FUR uniformity of content in the ODTs was evaluated according USP 30-NF 25 guidelines (USP 30-NF 25) using UV spectrophotometer (Labomed, Inc, USA) at a wavelength of 276 nm (Quinteros et al., 2008). In brief, ten individual tablets were placed in 100 ml volumetric flask, and 10 ml methanol and 50 ml of phosphate buffer pH 6.8 were added. The dispersion was then sonicated for 15 min to dissolve the tablets. The volume was completed with the buffer. The dispersion was then filtered and the drug concentration was measured.

2.4.2. Weight variation

Twenty tablets were chosen randomly from each ODT formulation and individually weighed. The average weight and standard deviation were calculated.

Table 3
Composition of different FUR oral disintegrating tablet formulations.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Furosemide	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
Eudragit E100	5 mg	20 mg	20 mg	20 mg	12.5 mg	5 mg	5 mg	12.5 mg	12.5 mg
CCS	16 mg	4.0 mg	10 mg	16 mg	10 mg	4.0 mg	10 mg	4.0 mg	16 mg
Mg stearate	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
MCC	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg
Mannitol	117 mg	114 mg	108 mg	102 mg	115.5 mg	129 mg	123 mg	121.5 mg	109.5 mg
	To 200 mg								

2.4.3. Thickness

Tablet thickness measurements were performed on 10 tablets of each ODT formula using a micrometer (Starrett, Athol MA, USA), and the average thickness, standard deviation were determined.

2.4.4. Hardness

The hardness of the ODT formula was determined using hardness tester (Pharma test GmbH, Hainburg, Germany) for 10 tablets of each formula with known weight and thickness. The average hardness and standard deviation were calculated.

2.4.5. Friability

Tablet friability was determined according to USP30-NF25. In brief, twenty tablets were weighed (W_1) and placed into the friabilator (Erweka, TA3R, Heusenstamm, Germany) that was rotated at 25 rpm for 4 min. The tablets then were reweighed after removal of fines (W_2), and the friability was calculated as:

$$\% \text{ Friability} = 100 \times (W_1 - W_2)/W_1$$

2.4.6. In vitro disintegration time

Tablet disintegration experiment was carried out using tablet disintegration test apparatus (Electrolab, ED-21, Mumbai, India) on six tablets according to the pharmacopoeial guidelines (USP 30-NF 25) for immediate release tablets. One tablet was placed in each of six tubes of the basket containing phosphate buffer (pH 6.8), maintained at $37 \pm 1 \text{ }^\circ\text{C}$. The tablet was considered disintegrated completely when all the particles passed through the screen. The disintegration time and standard deviation of 6 individual tablets were recorded.

2.4.7. Wetting time

A piece of tissue paper folded twice was placed in a small petri dish containing ten milliliters of distilled water and water-soluble die. A tablet was placed on the paper and the time required for complete tablet wetting was measured. Complete wetting can be taken as the time at which colored water covered the entire tablet (Mostafa et al., 2013). The test results were presented as mean value of three determinations \pm SD.

2.4.8. In vitro dissolution studies

In vitro release study for FUR orally disintegrating tablets was performed in USP type II dissolution tester (Erweka DT-600 GmbH, Germany). The study was conducted in 500 ml of pH 6.8 as a dissolution medium with paddle speed of 50 rpm at a temperature of $37 \pm 0.5 \text{ }^\circ\text{C}$. Aliquots of dissolution medium (5 ml) were withdrawn at specified intervals, 1, 5, 6, 8, 10, 15, 20, 25 and 30 min and replaced with an equal volume of fresh medium. Dissolution studies were performed in replicates of six. The concentration of drug in samples was analyzed using UV spectrophotometer (GenesysTM 5, Thermospectronic, USA) at a wavelength of 276 nm. Cumulative % of drug release was calculated and plotted against time.

2.4.9. Differential scanning calorimetry (DSC)

Thermal analysis has been carried out for selected ODT tablet formulation containing FUR compared with the individual tablet excipients. The powder sample (weighing about 5 mg) was sealed in aluminum pans hermetically, and subjected to a heating rate of $10 \text{ }^\circ\text{C}/\text{min}$, at temperature range of $30\text{--}300 \text{ }^\circ\text{C}$. In addition, N_2 was used as purging gas at rate of 40 ml/min. DSC scans of the samples have been recorded using differential scanning calorimeter (DSC-60, Shimadzu, Japan) with Shimadzu software programs. Indium standard was utilized to calibrate the DSC temperature and enthalpy scale.

2.4.10. Evaluation of palatability and in vivo disintegration time in human volunteers

The optimized formulation (F1) was selected to assess palatability parameters as taste, mouth feel, after taste, and also the in vivo disintegration time in 9 healthy human volunteers at the age group of 23–30 years. The study protocol was approved by the Ethics Committee of Faculty of Medicine, King Saud University. The purpose and protocol of the study were given to all volunteers and each one gave the written consent for participating in the study. The tablet was placed on the tongue and allowed to move without biting on it until disintegration, and then disgorged. The taste, mouth feel, and after taste were evaluated after the tablet was placed in the mouth, moreover after 3–4 min and rated on a scale of 1 through 4 as shown in Table 4. Time taken for the volunteer to feel that the tablet was completely disintegrated in the oral cavity was considered as the in vivo disintegration time. The swallowing of the saliva of the volunteers was not permitted during the test and the rinsing of their mouth was advised after the end of measurement.

3. Results and discussion

3.1. Evaluation of tablet property

The evaluated properties of FUR ODTs were shown in Table 5. The content uniformity test of the prepared FUR ODTs was found to be within the the pharmacopoeia guidelines (USP 30-NF 25). FUR content in all formulations ranged from $97.36\% \pm 1.5$ to $103.1\% \pm 4.2$ of the theoretical label claim. FUR tablets showed acceptable values for hardness ($5.11 \pm 1.69\text{--}7.98 \pm 1.52 \text{ kp}$). Also, the percentage of friability was found less than 1% in all tablet formulations (0.42–0.75%). In addition, the manufactured tablets exhibited uniform weight ranging from $199.99 \pm 0.007 \text{ mg}$ to $212.1 \pm 0.007 \text{ mg}$, and thickness from 2.42 ± 0.02 to $2.63 \pm 0.01 \text{ mm}$.

3.2. In vitro disintegration time

In the development of ODTs, the disintegration time of tablets is the most important parameter that should to be optimized. The effect of different concentrations of the taste masking agent, Eudragit E100 (2.5, 6.25 and 10%) and superdisintegrant, CCS (2, 5 and 8%) on the in vitro disintegration of FUR ODTs formulations

Table 4
Palatability evaluation parameters.

Scale				
Effect	1	2	3	4
Taste	Bitter	Acceptable	Good	Excellent
Mouth feel	Gritty	Acceptable	Good	Excellent
After taste	No taste	Slight	Moderate	Strong

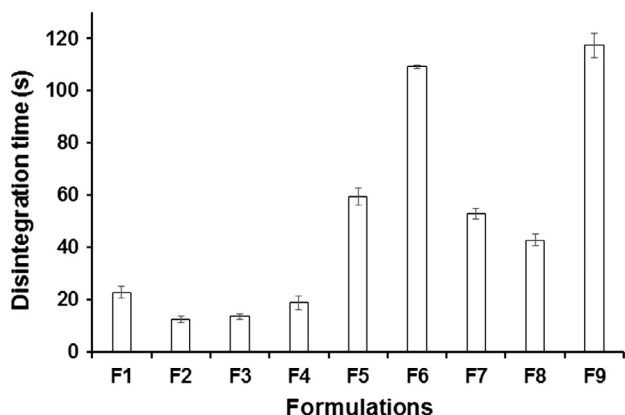
Table 5
Properties of FUR oral disintegrating tablet formulations.

Formula	Weight (mg ± SD)	Drug Content uniformity (% ± SD)	Thickness (mm ± SD)	Friability (%)	Hardness (kp ± SD)	Disintegration time (s ± SD)	Wetting time (s ± SD)
F1	199.99 ± 0.007	97.36 ± 1.5	2.43 ± 0.02	0.42	5.21 ± 1.08	23.00 ± 2.31	14.25 ± 0.96
F2	209.91 ± 0.008	101.2 ± 3.2	2.57 ± 0.03	0.43	7.18 ± 0.95	12.50 ± 1.38	7.67 ± 2.52
F3	212.1 ± 0.007	98.78 ± 2.1	2.59 ± 0.02	0.54	4.94 ± 1.45	13.75 ± 0.96	14.33 ± 0.58
F4	210.3 ± 0.007	99.4 ± 4.5	2.58 ± 0.03	0.51	5.11 ± 1.69	19.00 ± 2.65	16.33 ± 0.58
F5	208.2 ± 0.006	103.1 ± 4.2	2.63 ± 0.01	0.75	5.06 ± 1.32	59.50 ± 3.32	10.75 ± 1.71
F6	211.9 ± 0.011	101.7 ± 1.8	2.44 ± 0.02	0.44	7.65 ± 2.16	109.25 ± 0.50	13.00 ± 1.0
F7	207.3 ± 0.007	98.4 ± 2.8	2.45 ± 0.02	0.75	5.83 ± 0.93	53.00 ± 2.16	13.50 ± 2.08
F8	203.7 ± 0.007	97.8 ± 5.1	2.42 ± 0.02	0.75	6.44 ± 1.80	43.00 ± 2.28	12.00 ± 0.82
F9	206.2 ± 0.005	96.9 ± 4.5	2.42 ± 0.02	0.49	7.98 ± 1.52	117.33 ± 4.62	11.67 ± 0.58

are displayed in Table 5 and Fig. 1. For ODTs containing high concentration (10%) of Eudragit 100, (F2, F3 and F4), the addition of different concentrations of CCS (2, 5 and 8%) resulted in an increase in the in vitro disintegration time from 12.50 ± 1.38 s to 13.75 s ± 0.96 and further to 19.00 ± 2.65 s, respectively. The same results were obtained using medium concentration (6.25%) of Eudragit E 100, (F5, F8 and F9). The increase in the concentration of CCS from 2% (F8) to 5% (F5) and further to 8% (F9) led to a pronounced increase in the disintegration time of the tablets from 43.00 ± 2.28 s to 59.50 ± 3.32 s and further to 117.33 ± 4.62 s, respectively.

Moreover, the increase in the concentration of CCS had a positive antagonistic effect on the in vitro disintegration time of tablets using low concentration (2.5%) of Eudragit E100. Increasing the concentration of CCS (from 2%, 5% and 8%), F6, F5 and F8 respectively, resulted in a noticeable increasing in tablets disintegration. Therefore, the disintegration time has been shortened from 109.25 ± 0.50 s, to 53.00 ± 2.16 s and further to 23.00 ± 2.31 s, respectively for F6, F5 and F8. This may be due to the enhancing effects of both Eudragit E 100 and CCS at low concentration of Eudragit E100 (2.5%) on tablet disintegration as shown in Fig. 6.

Effect of Eudragit E100 (X1) and CCS (X2) concentrations on the disintegration time in seconds (Y1) of the manufactured ODTs is displayed in Table 6a. The equation that describes the effect of X1 and X2 on tablet disintegration is:

**Fig. 1.** Effect of Eudragit E100 (X1) and croscarmellose sodium (X2) on disintegration time (Y3) of FUR oral disintegrating tablet formulations.

$$\text{Disintegration (Y1)} = 106.43 + 14.4589X1 - 26.44X2 - 2.48X1^2 + 2.06X1X2 + 1.33X2^2$$

It is clearly from the equation that X1 was found to exert enhancing effect on disintegration, while X2 was found to prolong the disintegration time. The effect of X1 on tablet disintegration was found to be prominent in comparison to that of X2 due to the higher value of sum of squares obtained upon analyzing the effect of X1 (Eudragit E100). In addition, each variable effect on Y1 is noticeable at the low concentration of the other variable, as seen from the response surface plots in Fig. 2. However, the effects of both X1 and X2 on tablet disintegration are statistically insignificant ($p > 0.05$).

This unexpected behavior of CCS on the in vitro disintegration time may be attributed to the formation of a viscous gel layer by CCS which may impede further penetration of the disintegration medium and hinder the disintegration of tablet content (Swamy et al., 2007; Setty et al., 2008). Moreover, Ferrero et al. (1997) showed that at high levels of CCS (>8%), the decrease in disintegration time not only is less remarkable but also can increase. Jagdale et al. (2010) described that the disintegrating effect of CCS in its low levels might be due to a fact that its fibrous nature permits water wicking into ODTs matrices. Thereafter, tablet swelling results in a smoothing of the edges of the particle, leading to decreasing the length of particle's perimeter per unit area. Therefore, the fibrous nature is more noticeable and smoothens gradually with time at lower superdisintegrant concentrations. Similar findings were recorded with Mostafa et al. (2013), who studied the effect of different superdisintegrants on the dexamethorphan hydrobromide orally disintegrating tablets. They found that the disintegration time decreased by increasing the concentration of CCS up to a certain level, after which disintegration time increased by increasing CCS level.

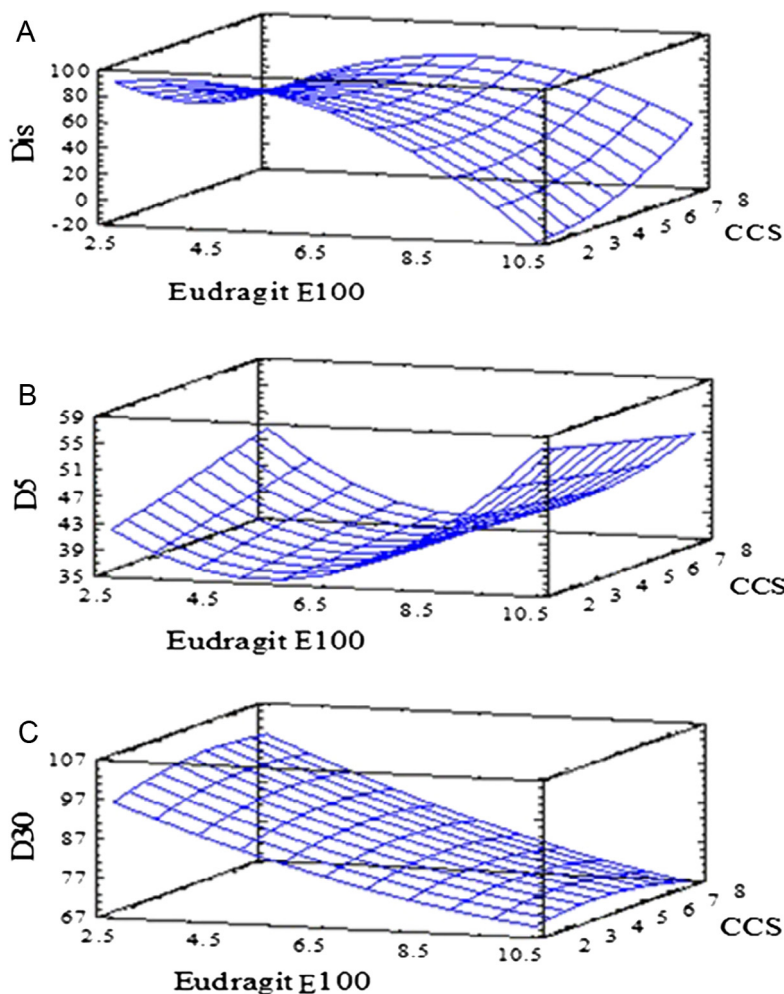
3.3. Wetting time

The wetting time is considered as an important criteria for determining the capacity of disintegrating agents to swell in presence of little amount of water. It was found that the wetting time for all the investigated formulations was less than 20 seconds as shown in Table 5. Formulation F2 showed the lowest wetting time of 7.67 ± 2.52 s while F4 showed the highest one of 16.33 ± 0.58 s. The data revealed that the increase in the concentration of CCS from

Table 6a

Analysis of variance for the disintegration time of FUR ODTs.

Source	Sum of squares	df	Mean square	F-Ratio	P Value
X1: Eudragit E 100	3266.67	1	3266.67	2.19	0.235
X2: CCS	4.89	1	4.89	0.0	0.958
X1 ²	2430.44	1	2430.44	1.63	0.291
X1X2	2150.64	1	2150.64	1.44	0.316
X2 ²	284.65	1	284.65	0.19	0.691
R-squared = 0.73					
Equation: Dis = 106.43 + 14.4589X1 – 26.44X2 – 2.48X1 ² + 2.06X1X2 + 1.33X2 ²					

**Fig. 2.** Response surface plot estimating the effect of Eudragit E100 (X1) and croscarmellose sodium (X2) on the disintegration time (A), the percentage of FUR dissolved after 5 min, D5 (B), and the percentage of FUR dissolved after 30 min, D30 (c) of FUR oral disintegrating tablet formulations.

2 to 8% had synergistic effects on the wetting time of ODTs using high concentration of Eudragit E100 (10%). The wetting time has been increased from 7.67 ± 2.52 s to 14.33 ± 0.58 s and further to 16.33 ± 0.58 s by increasing CCS concentration from 2% to 5% and further to 8%, respectively for F2, F3 and F4. The higher wetting time is correlated with the increased the disintegration time of ODTs as previously mentioned. The medium and low concentrations of Eudragit E100 and CCS did not have a noticeable effect on the ODTs wetting time. These results are in accordance to the data obtained by Jagdale et al. (2010), who studied the effect of different concentrations of CCS on the disintegration time of famotidine rapidly disintegrating tablets. They concluded that at low CCS concentration, the wetting time and consequently the disintegration time were decreased owing to the fibrous nature of CCS at low concentration.

3.4. In vitro dissolution studies

Fig. 3 represents the dissolution profiles of different ODTs formulations containing furosemide. It is clear from the figure that the rate of dissolution was significantly ($p < 0.05$) slowed by increasing the concentration of Eudragit E100 (X1). The formulations F1, F6, and F7 that contain the lowest concentration (2.5%) of Eudragit E100 gave the highest dissolution rate (105.4, 100.3, and 104.1%, respectively after 30 min. Other formulations F5, F8 and F9 that contain medium concentration (6.25%) of Eudragit E100 showed dissolution rate more than 80% after 30 min (89.3, 83.1, and 84.9%, respectively). The remaining formulations F2, F3 and F4 that contain the highest concentration (10%) of Eudragit E100 showed the lowest dissolution rate among the all formulations, 77.3, 78.5 and 73.1%, respectively.

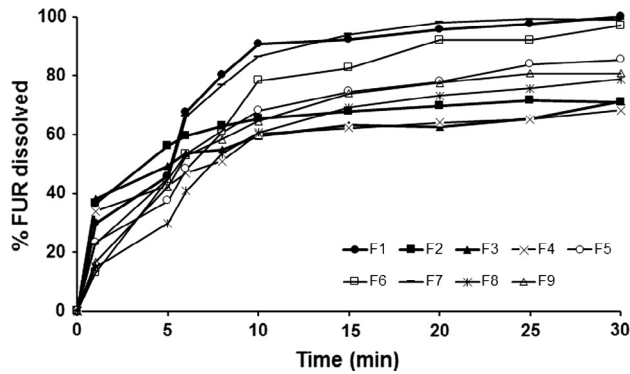


Fig. 3. Effect of Eudragit E100 (X1) and croscarmellose sodium (X2) on dissolution of FUR oral disintegrating tablet formulations.

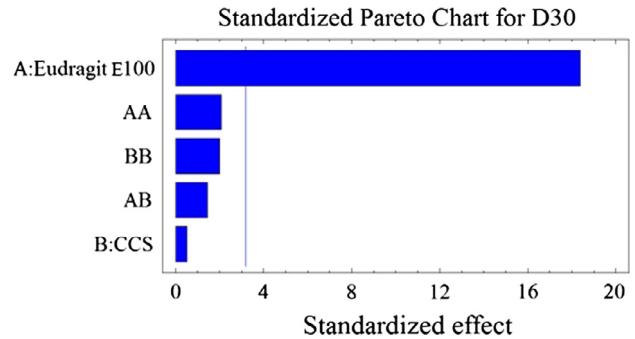


Fig. 4. Standardized Pareto Chart estimating the effect of Eudragit E100 (X1) and croscarmellose sodium (X2) on dissolution of FUR oral disintegrating tablet formulations after 30 min.

Moreover, the results also revealed that the increase in the concentration of CCS (X2) from 2 to 5 and further to 8% led to non-significant ($p > 0.05$) change in the in vitro dissolution rate using Eudragit E100 in different used concentrations.

Tables 6b and 6c and Fig. 2 showed the effect of X1 and X2 on the drug dissolution from ODTs after 5 and 30 min, (D5, D30) respectively. It is clearly that X1 exhibited antagonistic effect on the both D5 and D30, but only the effect on D30 is significant ($p = 0.0004$), as shown in Pareto chart, Fig. 4. This could be attributed to the slowing effects of the composite made of Eudragit E100, mannitol and CCS on the drug dissolution during the initial period (5 min). Figs. 5 and 6 showed the estimated main quadratic and interactive effects ($X1X2$, $X1^2$, $X2^2$) of X1 and X2 on D30 at 30 min, respectively. CCS (X2) exerted very slightly agonistic effects on both D5 and D30 especially at the low levels, but these effects are insignificant ($p > 0.05$). Moreover, very slight interactive and quadratic effects on D30 were noticed, as could be seen from the Figs. 5 and 6, and the equations:

$$D5 = 51.23 - 7.23504X1 + 2.70565X2 + 0.7574963X1^2 - 0.333556X1X2 - 0.062037X2^2$$

$$D30 = 103.035 - 5.66733X1 + 3.88694X2 + 0.197689X1^2 - 0.122X1X2 - 0.298889X2^2$$

Table 6b

Analysis of variance for the percentage FUR dissolved from ODTs after 5 min (D5).

Source	Sum of squares	df	Mean square	F-Ratio	P Value
X1: Eudragit E 100	24.08	1	24.08	0.63	0.487
X2: CCS	0.000016	1	0.000016	0.0	0.999
$X1^2$	225.43	1	225.43	6.06	0.094
$X1X2$	56.33	1	56.33	1.47	0.313
$X2^2$	115.54	1	115.54	0.01	0.912

R-squared = 0.73

$$\text{Equation: } D5 = 51.23 - 7.23504X1 + 2.70565X2 + 0.7574963X1^2 - 0.333556X1X2 - 0.062037X2^2$$

Table 6c

Analysis of variance for the percentage FUR dissolved from ODTs after 30 min (D30).

Source	Sum of Squares	df	Mean Square	F-Ratio	P Value
X1: Eudragit E 100	1122.37	1	1122.37	337.35	0.0004
X2: CCS	0.99	1	0.99	0.27	0.6370
$X1^2$	15.46	1	15.46	4.27	0.1308
$X1X2$	7.53	1	7.53	2.08	0.2450
$X2^2$	14.47	1	14.47	3.99	0.1395

R-squared = 0.9915

$$\text{Equation: } D30 = 103.035 - 5.66733X1 + 3.88694X2 + 0.197689X1^2 - 0.122X1X2 - 0.298889X2^2$$

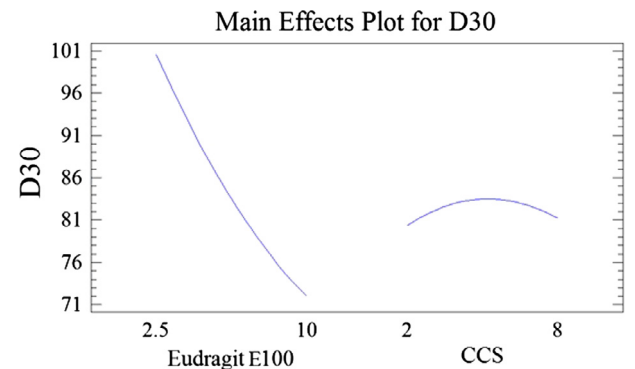


Fig. 5. Main effect plot estimating the effect of Eudragit E100 (X1) and croscarmellose sodium (X2) on dissolution of FUR oral disintegrating tablet formulations after 30 min.

The overall enhanced dissolution rate of the poorly soluble drug (furosemide) in its ODTs containing a composite formed of mannitol and Eudragit E100 might be attributed to the hydrophilic nature of mannitol and its ability to aid the dissolution rate of poorly soluble drugs (McLaughlin et al., 2009). Also, mannitol is readily soluble; it also has the function of improving texture, taste, and mouth feel (McLaughlin et al., 2009). Eudragit E 100 also might participate in enhancing the drug dissolution rate from the manufactured ODTs

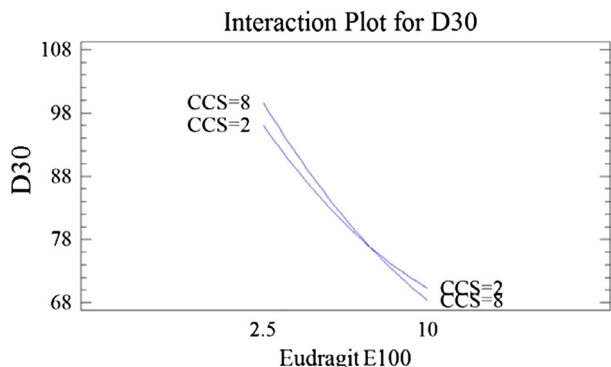


Fig. 6. Interaction effect plot estimating the effect of Eudragit E100 (X1) and croscarmellose sodium (X2) on dissolution of FUR oral disintegrating tablet formulations after 30 min.

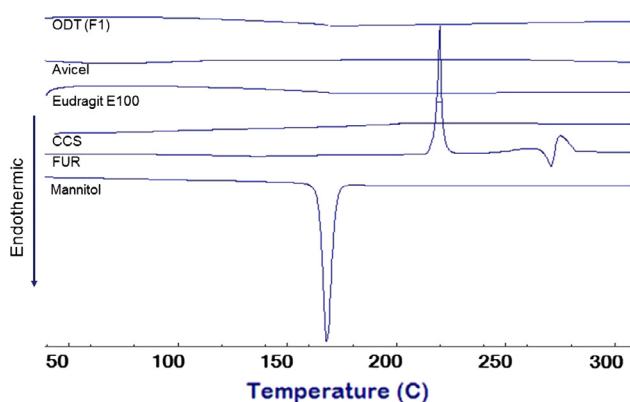


Fig. 7. The DSC scans of ODT tablet formulation (F1) containing FUR compared with the individual tablet excipients.

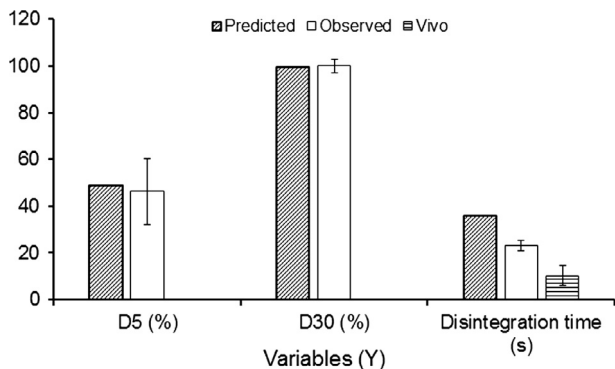


Fig. 8. The predicted and observed variables for the optimized FUR oral disintegrating tablet formulations.

owing to its ability (as a solid dispersion polymer) to enhance FUR dissolution. The use of Eudragit E 100 as dissolution modifier has been investigated, and Eudragit E 100 was used in solid dispersions and in physical mixtures to enhance the solubility and/or dissolution of poorly aqueous solubility drugs. The performance of solid dispersions containing Eudragit and sodium divalproex (Rao et al., 2003), albendazole (Kalaiselvan et al., 2006), piroxicam (Valizadeh et al., 2007) and an experimental anti-inflammatory drug (Horisawa et al., 2000) has been assessed. However, the initial dissolution rate of FUR from ODTs was a slow, which may be due to the time lag to allow dissolution of the composite of mannitol and Eudragit E100 composite containing the drug.

3.5. Differential scanning calorimetry

The DSC scans of ODT of the optimized FUR oral disintegrating tablet formulation (F1) compared with the individual tablet excipients are displayed in Fig. 7. FUR shows an exothermic sharp peak at 219 °C, due to the drug decomposition (Boles Ponto and Schoenwald, 1990). Moreover, the endothermic peak appeared at 268 °C is attributed to the melting of furosemide degradation product (Spamer et al., 2002). The DSC scans of FUR in its ODT tablet formulation (F1) revealed that the drug exothermic characteristic peak disappeared completely. This might be explained on the basis of the solubility and homogeneous dispersion of FUR in the molten polymers (Mahrous et al., 2010). In addition, the disappearance of FUR exothermic peak may indicate thermal stability of FUR in its (mannitol-Eudragit-CCS) composite in the ODTs.

3.6. Model optimization of the formulation parameters

The optimized ODTs formula (F1), a check point of X1 = 2.5% and X2 = 8% was selected. The predicted and observed values of disintegration time, dissolution after 5 min (D5) and dissolution after 30 min (D30) for this checkpoint were highly complying with the values predicted by the model as shown in Fig. 8. At the optimized concentrations of X1 and X2, the predicted disintegration time was 35.88 s, while the observed disintegration time was 23 s. In addition, the predicted D5 and D30 values were 48.85% and 99.62%, respectively, while the observed values were 46.3% and 100%, respectively.

3.7. Evaluation of palatability and in vivo disintegration time in human volunteers

The masking of the unpleasant taste of various bitter drugs is one of the important parameter in developing the ODTs. This study was carried out to test the selected optimized formulation (F1) according to the taste masking, mouth feel, after taste and in-vivo disintegration time. Tables 4 and 7 show the results of the palatability test. According to the taste masking, among the nine

Table 7 Palatability and in vivo disintegration time for the selected formula (F1).

Volunteer No.	Taste				Mouth feel				After taste				Numbness YES/NO	In vivo disintegration time (s) ± S.D
	1	2	3	4	1	2	3	4	1	2	3	4		
1				✓				✓				✓	NO	10.33 ± 4.15
2				✓				✓			✓	NO		
3								✓			✓	NO		
4		✓						✓			✓	NO		
5		✓						✓			✓	NO		
6		✓						✓			✓	NO		
7			✓					✓			✓	NO		
8		✓						✓			✓	NO		
9				✓				✓			✓	NO		

volunteers, 4 volunteers recorded optimized formulation (F1) as '2' indicating an acceptable taste, one volunteer recorded it as '3' indicating that formulation had good taste and 4 volunteers recorded it as '4' indicating an excellent taste of the tablet. Moreover, the optimized formulation (F1) had a good mouth feel without any grittiness as proved from 9 volunteers. The mouth feel was recorded as '2', '3' and '4' for an acceptable, good and an excellent mouth feel respectively. All volunteers recorded that they had no complain of numbness and show only slight feeling after taste. The mean in vivo disintegration time for the 9 volunteers was around $10.33 \text{ s} \pm 4.15$ for the optimized ODT formula (F1) which is noticeably lower than the in vitro disintegration time of F1 ($23 \text{ s} \pm 2.31$).

4. Conclusion

The disintegration time and dissolution rate of the ODTs containing FUR can be optimized by controlling the both the formulation parameters as taste masking agent (Eudragit E100; X1) and superdisintegrant (X2). In addition, palatability of the manufactured ODTs has been improved due to the effects of mannitol and taste masking agent (X1), in addition to the enhanced in vivo disintegration. Moreover, the manufactured FUR orally disintegrating tablets can provide several patient advantages as they disintegrate rapidly (<1 min) in the mouth, no need for water for administration, which might enhance the compliance of the diuretic administering patient. In addition, ODTs provide ease of administration & swallowing, in addition to an acceptable mouth feel.

Acknowledgment

The authors acknowledge financial support from the College of Pharmacy Research Center and the Deanship of Scientific Research, King Saud University, Riyadh, Saudi Arabia.

References

- Abdelbary, A., Elshafeey, H., Zidan, G., 2009. Comparative effects of different cellulosic-based directly compressed orodispersible tablets on oral bioavailability of famotidine. *Carbohydr. Polym.* 77, 799–806.
- Boles Ponto, L.L., Schoenwald, R.D., 1990. Furosemide (furosemide): a pharmacokinetic/pharmacodynamic review. Part I. *Clin. Pharmacokinet.* 18, 381–408.
- Chandrasekhar, P., Shahid, M.S., Niranjana, B.M., 2013. Formulation and evaluation of oral dispersible tablets of anti hypertensive drug atenolol. *Int. J. Pharmacy* 3, 79–84.
- Ciper, M., Bodmeier, R., 2005. Preparation and characterization of novel fast disintegrating capsules (Fastcaps) for administration in the oral cavity. *Int. J. Pharm.* 303, 62–71.
- Desai, S., Poddar, A., Sawant, K., 2016. Formulation of cyclodextrin inclusion complex-based orally disintegrating tablet of eslicarbazepine acetate for improved oral bioavailability. *Mater. Sci. Eng. C* 58, 826–834.
- Spamer, E., Müller, D.G., Wessels, P.L., Venter, J.P., 2002. Characterization of the complexes of furosemide with 2-hydroxypropyl-β-cyclodextrin and sulfobutyl ether-7-β-cyclodextrin. *Eur. J. Pharm. Sci.* 16, 247–253.
- FDA. Guidance for Industry, 2008. 1–6.
- Ferrero, C., Muñoz, N., Velasco, M.V., Jiménez-Castellanos, R., 1997. Disintegrating efficiency of croscarmellose sodium in a direct compression formulation. *Int. J. Pharm.* 147, 11–21.
- Horisawa, E., Danjo, K., Haruna, M., 2000. Physical properties of solid dispersion of a nonsteroidal anti-inflammatory drug (M-5011) with Eudragit E. *Drug Dev. Ind. Pharm.* 26, 1271–1278.
- Ito, Y., Maeda, A., Kondo, H., Iwao, Y., Noguchi, S., Itai, S., 2016. Application of water-insoluble polymers to orally disintegrating tablets treated by high-pressure carbon dioxide gas. *Int. J. Pharm.* 511, 10–22.
- Jagdale, S.C., Fernandes, N.C., Kushekar, B.S., Shah, T.P., Chabukswar, A.R., 2010. Selection of superdisintegrant for famotidine rapidly disintegrating tablets. *J. Chem. Pharm. Res.* 2, 65–72.
- Kalaiselvan, R., Mahanta, G.P., Manna, P.K., Manimekalai, A., 2006. Solid-phase preparation and characterization of albendazole solid dispersion. *Ars Pharm.* 47, 91–107.
- Kawano, Y., Ito, A., Sasatsu, M., Machida, Y., 2010. Preparation of orally disintegrating tablets for masking of unpleasant taste: comparison with corrective-adding methods. *Yakugaku Zasshi* 130, 75–80.
- Lindenberg, M., Kopp, S., Dressman, J.B., 2004. Classification of orally administered drugs on the World Health Organization model list of the essential medicines according to the biopharmaceutics classification system. *Eur. J. Pharm. Biopharm.* 58, 265–278.
- Mahrous, G.M., Ibarhim, M.A., El-Badry, M., Al-Anazi, F.K., 2010. Indomethacin sustained release pellets prepared by extrusion-spheronization. *J. Drug Del. Sci. Tech.* 20, 119–125.
- McLaughlin, R., Banbury, S., Crowley, K., 2009. Orally disintegrating tablets the effect of recent FDA guidance on ODT technologies and applications. *Pharm. Technol. Sept. Supplement*.
- Mostafa, H.F., Ibrahim, M.A., Sakr, A., 2013. Development and optimization of dextromethorphan hydrobromide oral disintegrating tablets: effect of formulation and process variables. *Pharm. Dev. Technol.* 18, 454–463.
- Murray, M.D., Haag, K.M., Black, P.K., Hall, S.D., Brater, D.C., 1997. Variable furosemide absorption and poor predictability of response in elderly patient. *Pharmacother.* 17, 98–106.
- Nielsen, L.H., Rades, T., Müllertz, A., 2015. Stabilisation of amorphous furosemide increases the oral drug bioavailability in rats. *Int. J. Pharm.* 490, 334–340.
- Nishiyama, T., Ogata, T., Ozeki, T., 2016. Preparation of bitter taste-masking granules of lafutidine for orally disintegrating tablets using water-insoluble/soluble polymer combinations. *J. Drug Deliv. Sci. Technol.* 32, 38–42.
- Ozdemir, N., Ordu, S., 1998. Improvement of dissolution properties of furosemide by complexation with β-cyclodextrin. *Drug Dev Ind. Pharm.* 24, 19–25.
- Quinteros, D.A., Rigo, V.R., Jimenez Kairuz, A.F., Olivera, M.E., Manzo, R.H., Allemandi, D.A., 2008. Interaction between a cationic polymethacrylate (Eudragit E100) and anionic drugs. *Eur. J. Pharm. Sci.* 3 (3), 72–79.
- Rao, V.M., Engh, K., Qiu, Y., 2003. Design of pH-independent controlled release matrix tablets for acidic drugs. *Int. J. Pharm.* 252, 81–86.
- Samprasit, W., Opanasopit, P., Akkaramongkolporn, P., Ngawhirunpat, T., Wongsermsin, K., Panomsuk, S., 2010. Preparation and evaluation of taste-masked dextromethorphan oral disintegrating tablet. *Pharm. Dev. Technol.* 17, 315–320.
- Sastry, S.V., Nyshadham, J.R., Fix, J.A., 2000. Recent technological advances in oral drug delivery – a review. *Pharm. Sci. Technol. Today* 3, 138–145.
- Setty, C.M., Prasad, D.V.K., Gupta, V.R.M., Sa, B., 2008. Development of fast dispersible aceclofenac tablets: effect of functionality of superdisintegrants. *Indian J. Pharm. Sci.* 70, 180–185.
- Shazly, G.A., Ibrahim, M.A., 2016. Losartan potassium taste-masked oral disintegrating tablets for hypertensive patients. *Lat. Am. J. Pharm.* 35, 110–117.
- Suresh, B., Kumar, M., Ramesh, G., Rao, Y.M., 2008. Orodispersible tablets: an overview. *Asian J. Pharm.* 2, 2–11.
- Swamy, P.V., Areefulla, S.H., Shirsand, S.B., Gandra, Smitha, Prashanth, B., 2007. Orodispersible tablets of meloxicam using disintegrant blends for improved efficacy. *Ind. J. Pharm. Sci.* 69, 836–840.
- United States Pharmacopoeia 30-NF 25.
- Valizadeh, H., Zakeri-Milani, P., Barzegar-Jalali, M., Mohammadi, G., Danesh-Bahreini, M.A., Adibkia, K., Nokhodchi, A., 2007. Preparation and characterization of solid dispersions of piroxicam with hydrophilic carriers. *Drug Dev. Ind. Pharm.* 33, 45–56.
- Van Arnum, P., 2000. Advancing ODT technology. *Pharm. Technol.* 31, 66–76.
- Wang, L., Xiao, Y.Y., Chen, M.L., Zeng, F., Zong, L., 2013. Pharmacokinetics of orally disintegrating tablets of perphenazine/hydroxypropyl-beta-cyclodextrin inclusion complex in rabbits. *Pharmazie* 68, 800–804.