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Optimization of a metformin effervescent floating tablet containing hydroxypropylmethylcellulose and stearic acid

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This study optimizes the composition of an effervescent floating tablet (EFT) containing metformin hydrochloride (M) regarding tablet hardness (H), time to dissolve 60% of the embedded drug ($t_{60\%}$), and buoyancy, the floating lag time (FLT). A simplex lattice experimental design has been used comprising different levels of hydroxypropylmethylcellulose (HPMC), stearic acid (SA), sodium bicarbonate (SB) as tablet matrix components, and hardness (H), $t_{60\%}$, FLT as response variables. Two models have been applied to decide which composition will result in Fickian diffusion or in overlapping of two dissolution mechanisms, diffusion and matrix erosion. Three of EFT showed the two dissolution mechanisms but most of EFT showed Fickian diffusion only. Checking the experimental response by a linear, quadratic, special cubic and cubic model using multivariate regression analysis resulted in best fit for the cubic model. Overlaying the results for the cubic model under constraints defined shows the domain of accepted values of response variables. The optimized EFT shall have been included HPMC between 15.6% and 24.2%, SA between 12.8 and 15.6% and SB between 16.1% and 17.5%. The result of this study has been critically evaluated considering analogous EFT described in literature.

1. Introduction

A dosage form that floats immediately upon contact with gastric fluids may increase the bioavailability of drugs with absorption windows in the upper small intestine (Streubel et al. 2006). Metformin (M) absorption after oral administration is likely site dependent, with an absorption window predominantly present in the small intestine (Balan et al. 2001). Effervescent matrix tablets based on hydrophilic polymers such as hydroxypropylmethylcellulose (HPMC, e.g. Methocel K4M), further components as lipophilic matrix formers (e.g. stearic acid, SA, beeswax), and an effervescent compound, e.g. sodium bicarbonate (SB), have been shown to have floatable characteristics (Arora et al. 2005; Basak et al. 2007).

Developing such an effervescent floating tablet (EFT), one has to optimize the composition with regard to at least two dependent variables, drug dissolution and buoyancy. Numerous articles dealt with an optimization of EFT resulting in compositions containing 10 to 79%

HPMC, 9 to 26% SA, and a time to dissolve 60% of the embedded drug ($t_{60\%}$) between 2 and 10 hours (Table 1). A 3^2 full experimental design has been used for optimization predominantly. To examine *in vitro* buoyancy, the method described by Rosa et al. (1994) has been commonly used (Basak et al. 2007; Prajapati et al. 2008) to determine the floating lag time (**FLT**).

The objective of the present investigation was to optimize the composition of **EFT** showing acceptable hardness ($\mathbf{H} > 10\,kg/cm^2$) containing 500 mg **M** per tablet whereas the total mass should not exceed 1000 mg. In addition, the initial burst dissolution of **M** as a drug showing high water solubility (>300 mg/ml at 25 ° C) should be avoided ($t_{60\%} > 4.5$ hours). To avoid sinking of the tablet in the stomach **FLT** should be shorter than 120 s.

Since the pH of the stomach under fed conditions is elevated (3.5 to 4.0), citric acid (**CA**) should be used to provide an acidic environment for **SA** to ensure CO_2 generation. A simplex lattice experimental design was used as an optimization technique (Table 2).

Using a hydrophilic compound (**HPMC**) and a lipophilic compound (**SA**) together in one matrix requires two models to decide which composition will result in Fickian diffusion or in overlapping of two dissolution mechanisms, diffusion and matrix erosion. The relative contribution of each of these two mechanisms, diffusion or matrix erosion, was quantified by applying the two terms dissolution equation, Eq. (1), as proposed by Catellani et al. (1988), and applied by Efentakis et al. (2007) in drug dissolution studies from hydrophilic matrices loaded with drugs of different solubility.

For a given time t, the first term of the right part of Eq. (1) represents the Fickian diffusion and the second term refers to matrix erosion. If this term becomes negative, there is obviously no contribution of that mechanism to the drug dissolution, and Eq. (1) could be reduced to Eq. (2).

$$M_t/M_\infty = k_1 * t^{1/2} + k_2 * t \quad (1)$$

$$M_t/M_\infty = k_1 * t^{1/2} \quad (2)$$

Starting this investigation, we did know the design of a floatable gastroretentive tablet of **M** and its *in vitro* testing (Basak et al. 2007). Two reasons precluded us from reproducing this approach:

Table 1: Review on EFT based on HPMC, drugs embedded, content of drugs, HPMC, SA and CA, experimental design so far as used to optimize the EFT, and some of the resulting dependent variables: FLT, and the time to dissolve 60% of the drug ($t_{60\%}$)

Drug	Content (mg/ tablet)	Exp. design	HPMC (%)	SA (%)	CA (%)	FLT (s)	$t_{60\%}$ (h)	Ref.
Atenolol	50	-	53–79	0	0.8−4.3	90–900	4–9	(Srivastava et al. 2005)
Carbamazepine	200	simplex	27–34	15*	-	153–255	7–10	(Patel DM et al. 2007)
Domperidone	30	BB**	10–30	-	-	2–33	>9.5	(Prajapati et al. 2008)
Dipyridamol	150	3^2	20–40	-	-	<180	6.5–10	(Patel VF 2007a; 2007b)
Diltiazem	240	3^2	25–35	15–25$	10–19#	240–1800	7.5–13	(Gambhire et al. 2007)
Metformin	500	-	18–22	-	1.8–2.4	15–42	2.5–3.5	(Basak et al. 2007)
Metformin	500	simplex	13–29	10–27	2	0–120	2–6.8	here
Ranitidine	336	3^2	17	0–2	1.8–3.7	65–695	>5	(Dave et al. 2004)

* beeswax
** Box-Behnken
$ Compritol 888 ATO
# succinic acid

Table 2: Simplex lattice experimental design

Formulation variables		Levels (mg)		Response variables (Y)	Constraints	
		Low	High		Min.	Max.
X_1	SA	100	270	H (Kg/cm^2)	10.2	20.3
X_2	HPMC	130	300	FLT (sec)	0	120
X_3	SB	75	245	$t_{60\%}$ (hours)	3	4.5

Table 3: EFT compositions and experimental results of hardness (H), floating lag time (FLT) and the time to dissolve 60% of the drug ($t_{60\%}$)

No.	X_1	X_2	X_3	**H** ± SD (kg/cm^2)	**FLT** ± SD (s)	$t_{60\%}$ ± SD (h)
T1	270	130	75	13 ± 1.7	135.5 ± 11.3	1.9 ± 0.03
T2	100	300	75	6.9 ± 0.7	347.4 ± 88.1	3.5 ± 0.04
T3	100	130	245	5.4 ± 0.7	66.7 ± 6.8	2.5 ± 0.07
T4	213.4	186.6	75	10.3 ± 0.6	175.8 ± 22.3	6.1 ± 0.92
T5	213.4	130	131.6	11.7 ± 0.9	209.8 ± 59.9	3.4 ± 0.18
T6	100	243.4	131.6	6 ± 1.1	41 ± 11.5	6.2 ± 0.26
T7	156.6	243.4	75	13 ± 0.6	304.3 ± 44.5	3.1 ± 0.03
T8	156.6	130	188.4	11.2 ± 0.7	165.3 ± 19.1	2.6 ± 0.20
T9	100	186.6	188.4	5.6 ± 0.9	37.2 ± 6.2	2.0 ± 0.04
T10	156.6	186.6	131.6	13.9 ± 1.2	99.6 ± 18.9	3.5 ± 0.07
T11	128.2	243.2	103.2	7.2 ± 1.2	39 ± 3.5	3.2 ± 0.08
T12	128.2	158.2	188.2	6.7 ± 0.6	131.7 ± 7.1	4.4 ± 0.20
T13	213.2	158.2	103.2	13 ± 0.3	213 ± 42.4	6.8 ± 0

SD, standard deviation (n = 6)

- The manufacturing method, a conventional wet granulation using poly (vinyl-pyrrolidone, PVP K90) in isopropyl alcohol,
- The excipient lactose as defined in the experimental part.

The disadvantage of using wet granulation is, that it has to be processed with organic solvents in particular during the granulation process, the organic solvent having to be removed again as completely as possible before the granulate is processed further.

For the excipient lactose, DTA and DSC thermal data showed incompatibility with **M** (Santos et al. 2008).

2. Investigations and results

EFT in all the batches prepared (Table 3) contained **M** within 100 ± 5% of the labeled content (500 mg), and complied with pharmacopoeia specifications for weight variation (less than ±1%) and friability (less than 0.3%).

Table 4: Results from fitting the dissolution data following Eq. (1)

Tablet formulation	Release constant k_1	Release constant k_2	R^2	Diffusion at t60% (%)	Erosion at t60% (%)
T4	0.217	0.011	0.997	89	11
T6	0.189	0.021	0.999	78	22
T13	0.218	0.005	1.000	94	6

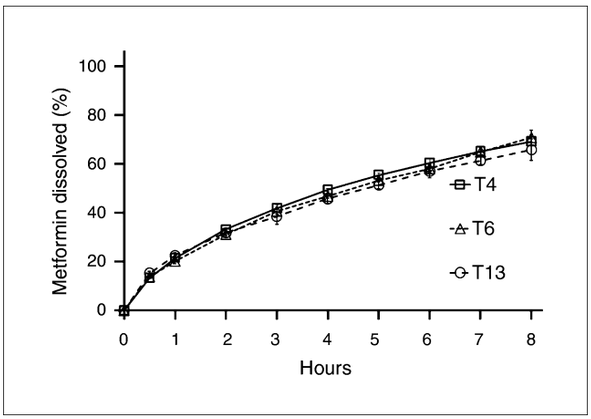

Fig. 1: Percent of cumulative dissolution of **M** from **EFT** T4, T6, T13 (fitting data see Table 4)

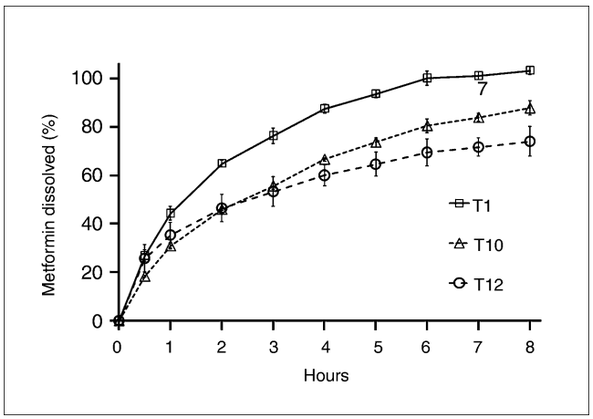

Fig. 2: Percent of cumulative dissolution of **M** from **EFT** T1, T10 and T12 (fitting data see Table 5)

Table 5: Results from fitting the dissolution data following Eq. (2)

Tablet formulation	Release constant k_1	R^2
T1	0.434	0.997
T2	0.322	0.998
T3	0.381	0.989
T5	0.326	0.964
T7	0.343	0.999
T8	0.375	0.925
T9	0.429	0.994
T10	0.322	0.995
T11	0.334	0.991
T12	0.287	0.973

The hardness (**H**) of the **EFT** was between 5.4 and 13 kg/cm^2, and the floating lag time (**FLT**) was found between 37.2 and 347 s (Table 3).

Three of **EFT's** (T4, T6, T13) have shown an overlapping of two dissolution mechanisms, drug diffusion and matrix erosion ($R^2 > 0.997$, Table 4). The dissolution profiles of T4, T6 and T13 are quite similar (Fig. 1).

Most of **EFT** released the drug following a simple Fickian diffusion mechanism ($R^2 > 0.924$, Table 5), and the dissolution profiles of these **EFT's** are quite different (Fig. 2).

Checking the experimental response for hardness (**H**), floating lag time (**FLT**), and $t_{60\%}$ by a linear, Eq. (3) quadratic, Eq. (4) special cubic, Eq. (5), and cubic model, Eq. (6) using multivariate regression analysis resulted in best fit for the cubic model (Table 6).

$$Y = X_1 + X_2 + X_3 \tag{3}$$

$$Y = X_1 + X_2 + X_3 + X_1X_2 + X_2X_3 + X_1X_3 \tag{4}$$

$$Y = X_1 + X_2 + X_3 + X_1X_2 + X_2X_3 + X_1X_3 + X_1X_2X_3 \tag{5}$$

$$Y = X_1 + X_2 + X_3 + X_1X_2 + X_2X_3 + X_1X_3 + X_1X_2X_3 + X_1X_2(X_1 - X_2) + X_2X_3(X_2 - X_3) + X_1X_3(X_1 - X_3) \tag{6}$$

Overlaying the results for the cubic model under constraints shown in Table 2 shows the domain of accepted values of response variables (Fig. 3).

3. Discussion

It was concluded from previous investigations of **EFT** containing **HPMC** (Table 1), to test a wide range of **HPMC** content between 130 and 300 mg per tablet (26 to 60% related to drug) to precise the optimum percentage of that consistency performing excipient.

The **EFT** developed contain the highest amount of drug, 500 mg (Table 1), compared with previous studies and as before also achieved for **M** (Basak et al. 2007) but wet granulation and the excipient lactose have been avoided. The simplex lattice experimental design based on constraints of **H** between 10.2 and 20.3 kg/cm^2, of **FLT** between 0 and 120 s and of drug dissolution ($t_{60\%}$) between 3 and 4.5 h (Table 1) resulted in 13 compositions of **EFT** (Table 3).

The data of drug dissolution have been fitted following Eq. (1) (Table 4) and/or Eq. (2) (Table 5). For T4, T6, T13, Eq. (1) comprising Fickian diffusion and matrix erosion showed the best fit, and the dissolution profiles of the **EFT** were quite similar (Fig. 1). For the most **EFT**, Eq. (2) based on Fickian diffusion only gave the best fit, and the dissolution profiles of these **EFT** were disparate (Fig. 3). Since Fickian diffusion was the dominant dissolution mechanism, the time to release 60% of the drug was below 4.38 h (Table 3). If the tablets resisted the erosion

Table 6: Values of regression coefficients (R^2) and predicted residual sums of squares (PRESS) for different models

Responses (Y)	Models							
	Linear		Quadratic		Special Cubic		Cubic	
	R^2	PRESS	R^2	PRESS	R^2	PRESS	R^2	PRESS
H	0.963	54.392	0.978	31.622	0.980	27.471	0.980	18.864
FLT	0.805	809.230	0.922	311.875	0.924	296.530	0.957	129.339
$t_{60\%}$	0.867	334	0.889	263	0.889	256	0.954	63

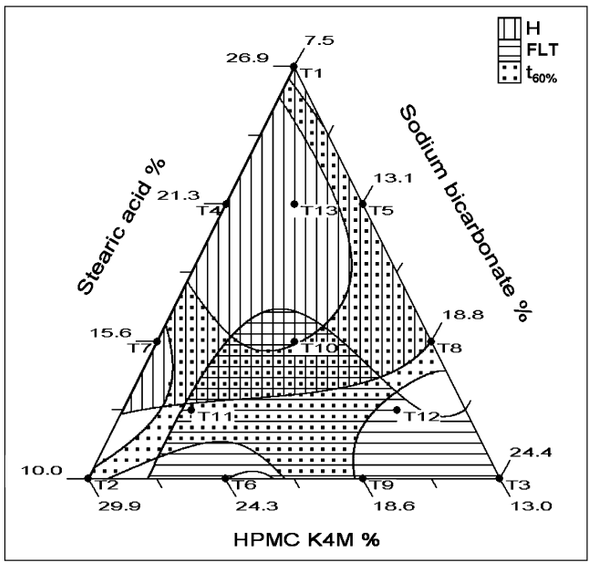

Fig. 3: Under constraints (Table 2) accepted values of Hardness (**H**), floating lag time (**FLT**) and $t_{60\%}$ as functions to percentages of stearic acid (**SA**), hydroxypropylmethylcellulose (**HPMC**) and sodium bicarbonate (**SB**)

and, consequently, in this case, **M** molecules had to travel a bigger distance before being released into the surrounding liquid, $t_{60\%}$ was higher than 6.01 h up to 6.76 h (Table 3).
Analyzing the domains of accepted values of response variables (Fig. 3) one can draw the following conclusions:

- **H** is more influenced by the percentage of **SA** than by that of **HPMC** or **SB**, and the acceptable **EFT** hardness resulted for the minimum percentage of **SA** (12.8%). Also **FLT** is more influenced by the percentage of **SA** and **SB** than by that of **HPMC**, and there is a minimum percentage of **SB** (10.4%) and a maximum percentage of **SA** (17%) to accomplish acceptable values for both **H** and **FLT** at the same time.
- The domain of accepted values of $t_{60\%}$ is associated with **SA** percentages between 11.8% to 18.9% and percentages between 14.2% to 21.3% for both **HPMC** and **SB**.
- Finally, the optimized **EFT** contains between 15.6% and 24.2% **HPMC**, between 12.8 and 15.6% **SA**, and between 16.1% and 17.5% **SB**.

In this study, **SA**, **HPMC** and **SB** (9–26%, 12–29% and 7–24% successively) used percentages were roughly different from those that were utilized (0–2%, 17% and 10% successively) in the **EFT** of ranitidine hydrochloride (Dave et al. 2004). The authors have used low percentages of stearic acid (0–2%), and they applied chloroform to prepare the ranitidine hydrochloride-stearic acid mixture.
Considering the **EFT** containing carbamazepine (Patel et al. 2007) where the authors have used similar percentages of excipients to this study except beeswax instead of stearic acid, one can see nearly analogous dissolution rates between 6 and 8 h.
The use of hydrophobic components like **SA**, beeswax or compritol 888 in **EFT** did minimize the hydration rate of the matrix and also the variability of the dissolution profiles as shown for diltiazem hydrochloride (Gambhire et al. 2007). In addition, **SA** can enhance the physical properties of the tablets. The hardness (**H**) of the **EFT** selected by this study was greater than 12 kg/cm^2.
Percentages of **HPMC** equal to 20–22% were used in **EFT** of metformin hydrochloride (Basak et al. 2007) which were near the accepted range of **HPMC** resulting in the present study.
Furthermore, it could be stated that the use of similar percentages of **HPMC** to prepare **EFT** resulted in $t_{60\%}$ near to 6 hour which was similar for dipyridamole (Patel and Patel 2007a,b) and for **M** as resulted from this investigation.
It must be noted that metformin hydrochloride and ranitidine hydrochloride are freely soluble in water. In contrast, dipyridamole and carbamazepine are poorly soluble in water. Nerveless similar percentages of **HPMC** have been used to prepare **EFT**, and the resulting dissolution profiles did not differ so much.
Even domperidone have shown a good solubility in acidic pH but the use of 10–30% of **HPMC** resulted in drug dissolution of more than 10 h (Prajapati et al. 2008).
On the other hand, high percentages (59–79%) of **HPMC** K4M as used in the preparation of **EFT** of atenolol, a drug that is sparingly soluble in water, resulted in drug dissolution of more than 60% nearby 6.5 h (Srivastava et al. 2005).
In general the use of sodium bicarbonate (**SB**) in the above references was between 9–19% which is extended to 24% in this study to assure a durable matrix and a rapid floating of the tablet. Compared to wet granulation (Basak et al. 2007), the optimization described here resulted in an analogous composition but solvents and lactose as excipients became redundant by the introduction of **SA** and melt granulation.

4. Experimental

4.1. Materials

M, metformin hydrochloride of Ph Eur. quality; **HPMC** (Methocel K4 M, Dow Europe GmbH, Stade, Germany), **SA**, **SB**, **CA**, magnesium stearate and colloidal silicon dioxide, all of Ph.Eur. quality.

4.2. Preparation of EFT

SA was molten in a beaker and the required quantity of **M** was added to the molten mass. Previously prepared mixture of **CA**, **HPMC**, **SB** was added and the mixture was stirred well to mix. After cooling on room temperature, the mass was passed through a 20-mesh sieve, and the resulting granules were resifted on a 100-mesh sieve to remove the fines. The granules from both the 20- and 100-mesh sieves were collected and mixed with 0.4% wt/wt magnesium stearate and 0.4% wt/wt colloidal silicon dioxide. This lubricated blend was compressed into tablets using 16-mm flat-face round tooling on a SHAKTI rotary tablet machine. Compression force was adjusted to obtain tablets with hardness in range of 5 to 14 kg/cm^2. Tablets weighed 1003 ± 5.2 mg, and showed an average diameter of 16 ± 0.1 mm and thickness of 3.5 ± 0.4 mm.
All **EFT** contained 500 mg **M**, 20 mg **CA**, 4 mg aerosil-200 and 4 mg magnesium stearate. The amount of total excipients was fixed at 503 mg and $X_1 + X_2 + X_3$ (Table 2) = 475 mg.

4.3. Evaluation of EFT

EFT were evaluated for thickness, hardness (**H**), weight variation, friability and drug content. **H** was tested using a hardness tester (ElectroLab, Mumbai, India). The thickness of the tablets was measured by Vernier Caliper. Weight variation test was performed according to USP30.

4.4. In Vitro buoyancy studies

The *in vitro* buoyancy was investigated as described previously (Rosa et al. 1994). Floating lag time (**FLT**) is the time required for the **EFT** to rise to the surface of a beaker containing 100 ml 0.1 N HCl and float.

4.5. Estimation of M

An ultraviolet (UV) spectrophotometric (T60 U UV/VIS spectrophotometer, PG instruments Ltd, Alma Park, Woodway Lane, Wibtoft. Leics. United Kingdom LE17 5BH.) method based on measurement of absorption at 233 nm in water was used for the estimation of **M** according to USP 30. The method showed very good linearity ($R^2 > 0.9998$) in the concentration range of 0–30 µg/ml. When a standard drug solution was assayed a number of times (n = 6) the relative error (accuracy) and the relative standard deviation were found to be 0.8% and 0.47% respectively.

4.6. In vitro dissolution studies

Drug dissolution from **EFT** was studied using a dissolution apparatus type 2 (USP 30, ERWEKA dissolution test, Heusenstamm, Germany), in 900 ml 0.1 N HCl at $37 \pm 0.5\,^{\circ}$C and at 100 rpm. Sink condition was maintained for the whole experiment. 10 ml of the dissolution medium were withdrawn at regular intervals and the same volume of pre-warmed ($37 \pm 0.5\,^{\circ}$C) fresh dissolution medium was replaced. The samples withdrawn were filtered through a 0.45 μm membrane filter (Nunc, New Delhi, India) and the drug content in each sample was analyzed after suitable dilution (4.1.2.4).

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References

Arora S, Ali J, Ahuja A, Khar RK, Baboota S (2005) Floating drug delivery systems: A review. AAPS Pharm Sci Tech 6: E372–E390.

Balan G, Timmins P, Greene DS, Marathe PH (2001) *In vitro-in vivo* correlation (IVIVC) models for metformin after administration of modified-release (MR) oral dosage forms to healthy human volunteers. J Pharm Sci 90: 1176–1185.

Basak SC, Rahman J, Ramaligam M (2007) Design and *in vitro* testing of a floatable gastroretentive tablet of metformin hydrochloride. Pharmazie 62: 145–148.

Catellani P, Vaona G, Plazzi P, Colombo P (1988) Compressed matrices: formulation and drug release kinetics. Acta Pharm Technol 34: 38–41.

Dave BS, Amin AF, Patel MM (2004) Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and *in vitro* evaluation. AAPS Pharm Sci Tech 5: 77–82.

Efentakis M, Pagoni I, Vlachou M, Avgoustakis K (2007) Dimensional changes, gel layer evolution and drug release studies in hydrophilic matrices loaded with drugs of different solubility. Int J Pharm 339: 66–75.

Gambhire MN, Ambade KW, Kurmi SD, Kadam VJ, Jadhav KR (2007) Development and *in vitro* evaluation of an oral floating matrix tablet formulation of diltiazem hydrochloride. AAPS Pharm Sci Tech 8: E166–E174.

Patel DM, Patel NM, Pandya NN, Jogani PD (2007) Gastroretentive drug delivery system of carbamazepine: Formulation optimization using simplex lattice design: A technical note. AAPS Pharm Sci Tech 8: E82–E86.

Patel VF, Patel NM (2007a) Statistical evaluation of influence of viscosity and content of polymer on dipyridamole release from floating matrix tablets: A technical note. AAPS Pharm Sci Tech 8: E140–E144.

Patel VF, Patel NM (2007b) Statistical evaluation of influence of xanthan gum and guar gum blends on dipyridamole release from floating matrix tablets. Drug Dev Ind Pharm 33: 327–334.

Prajapati ST, Patel LD, Patel DM (2008) Gastric floating matrix tablets: Design and optimization using combination of polymers. Acta Pharm [Zagreb] 58: 221–229.

Rosa M, Zia H, Rhodes T (1994) Dosing and testing *in-vitro* of a bioadhesive and floating drug delivery system for oral application. Int J Pharm 105: 65–70.

Santos AFO, Basilio ID Jr, de Souza FS, Medeiros AFD, Pinto MF, de Santana DP, Macedo RO et al. (2008) Application of thermal analysis in study of binary mixtures with metformin. J Thermal Anal Calorim 93: 361–364.

Srivastava AK, Wadhwa S, Ridhurkar D, Mishra B (2005) Oral sustained delivery of atenolol from floating matrix tablets - formulation and *in vitro* evaluation. Drug Dev Ind Pharm 31: 367–374.

Streubel A, Siepmann J, Bodmeier R (2006) Drug delivery to the upper small intestine window using gastroretentive technologies. Curr Opin Pharmacol 6: 501–508.