

FORMULATION OF BIOADHESIVE HYDROPHILIC MATRIX TABLETS WITH FAMOTIDINE USING DIFFERENT COMBINATIONS OF POLYMERS

ADELA E. PEREANU*, IOAN TOMUȚA, SORIN E. LEUCUȚA

University of Medicine and Pharmacy „Iuliu Hațieganu”, Faculty of Pharmacy, Department of Pharmaceutical Technology and Biopharmaceutics, 400023, Cluj-Napoca, Romania

**corresponding author: elena.pereanu@umfcluj.ro*

Abstract

The aim of this work was to prepare bioadhesive matrix tablets with famotidine (FAMO) using different polymer and filler combinations in order to determine the best combination regarding the water uptake properties, the drug release profile and the bioadhesive properties. The employed bioadhesive polymers were: hydroxypropyl-methylcellulose (HPMC), polyacrylic acid (Carbopol, CP) 71G, acrylic acid polymer crosslinked with divinyl glycol (Polycarbophil, PC) and sodium carboxymethylcellulose (SCMC). The employed fillers were: isomaltose (ISO) and dicalcium phosphate (DCP). For this purpose an experimental design with 5 variables and 3 levels was used. The tablets were analyzed regarding the *in vitro* water uptake properties, the drug release behavior and the bioadhesive properties.

From the obtained results it was concluded that the formulations containing three bioadhesive polymers in the highest used concentration (HPMC, CP/PC and SCMC) have advantages in comparison to the formulations with two or just one bioadhesive polymer in regard to water uptake and dissolution profiles. The bioadhesive properties of the tablets were positively influenced by the combination of CP and SCMC in the same formulation.

Rezumat

Obiectivul acestei lucrări a fost de a prepara comprimate bioadezive de tip matriță cu famotidină (FAMO), utilizând diferite combinații de polimeri și diluanți cu scopul de a determina combinația cea mai potrivită și de a evalua posibilul avantaj al unei combinații binare sau ternare de polimeri bioadezivi asupra retenției de apă, a profilului de eliberare a substanței active și asupra proprietăților bioadezive. Polimerii utilizați în studiu au fost: hidroxipropilmetilceluloză (HPMC), acid poliacrilic (Carbopol 71G, CP), acid poliacrilic reticulat cu divinilglicol (Polycarbophil, PC) și carboximetilceluloză sodică (SCMC). Excipienții utilizați au fost: isomaltoză (ISO) și fosfat dicalcic (DCP). În acest scop a fost realizat un plan experimental cu 5 variabile și 3 nivele. Comprimatele au fost caracterizate în ceea ce privește proprietățile de îmbibare cu apă, profilul de cedare *in vitro* și proprietățile bioadezive.

Din rezultatele obținute putem concluziona că formulările conținând cei trei polimeri bioadezivi în concentrația cea mai mare (HPMC, CP sau PC și SCMC) prezintă avantaje în comparație cu formulările cu doi sau doar un polimer bioadeziv, în ceea ce privește îmbibarea cu apă și profilul de eliberare a substanței active. Proprietățile bioadezive ale tabletelor sunt influențate pozitiv de combinația CP alături de SCMC în aceeași formulare.

Keywords: famotidine, matrix tablets, hydrophilic polymers, experimental design, bioadhesion.

Introduction

Various approaches have been proposed to control the gastric residence of drug delivery systems (DDS) in the upper part of the gastrointestinal tract including floating drug delivery systems (FDDS) [10, 25, 26, 30], mucoadhesive systems [5, 9, 29], swelling and expanding DDS [7, 8, 16] and other delayed gastric devices [4, 6, 11, 15, 21, 22].

The mucoadhesive/bioadhesive systems are designed in order to retain the drug in the stomach for a longer period of time and thereby improve the bioavailability of drugs on site.

Anionic polymers are the most widely employed mucoadhesive polymers within pharmaceutical formulation due to their high mucoadhesive functionality and low toxicity. Such polymers are characterised by the presence of carboxyl and sulphate functional groups that give rise to a net overall negative charge at pH values exceeding the pKa of the polymer. Typical examples include poly(-acrylic acid) (PAA) and its weakly cross-linked derivatives and sodium carboxymethylcellulose (NaCMC). PAA and NaCMC possess excellent mucoadhesive characteristics due to the formation of strong hydrogen bonding interactions with mucin. Polycarbophil and carbomer (Carbopol), PAA derivatives, have been studied extensively as mucoadhesive platforms for drug delivery to the gastro-intestinal (GI) tract. One clear distinction between carbomer and polycarbophil is the level of cross-linking and the crosslinking agent itself. Carbomers are cross-linked with allyl sucrose or allylpentaerythritol, whereas polycarbophil polymers are cross-linked with divinyl glycol. Both compounds have the same acrylic backbone but vary in their cross-link density. Non-ionic polymers like cellulose derivatives contain carboxylic side groups as well. A typical example of cellulose derivative is hydroxypropylmethylcellulose (HPMC) also used extensively as mucoadhesive polymer [1, 2].

Famotidine (FAMO) was chosen as the model drug because its characteristics: prolonged antisecretory effect in the therapy of duodenal, gastric, and peptic ulcer, and it has a low solubility (25 µg per mL) with a relatively short elimination half-life time (about 2.5 - 4 h) [19].

The aim of this work was to prepare bioadhesive matrix tablets with famotidine using either a single polymer, binary or ternary polymer combinations along different fillers in order to determine which composition is best suited in terms of bioadhesive properties and release profile. The goal

was to determine if there is a synergistic effect of a particular combination of polymers which determines better properties in comparison with the matrix tablets formulated with only one polymer.

Materials and Methods

Materials

Famotidine (FAMO) (SMS Pharmaceuticals Ltd., India), was used as model drug. Four hydrophilic polymers with bioadhesive properties were used in this study: HPMC K15M (Colorcon, UK), Sodium Carboxymethylcellulose (SCMC, Fluka, Germany), Carbopol 71G (CP, Carbopol® 71G NF, Lubrizol, Belgium) and Polycarbophil (PC, Noveon® AA-1, Lubrizol, Belgium). Microcrystalline cellulose (MCC) (JRS Pharma, Germany), dicalcium phosphate (DCP) (Di-Tab, Rhodia Chemie, Belgium) and isomaltose (ISO) (galenIQ Palatinit GmbH, Germany) were used as fillers. In all tablets formulations fumed silica – Aerosil® (Degussa, Germany) and Magnesium stearate (Merck, Germany) were used as glidants and lubricants. The release profiles were evaluated using several release models such as Baker-Lonsdale, Korsmeyer-Peppas, Hixson-Crowell, Higuchi first order and zero order. The Akaike criterion was chosen for distinguishing among competing models.

Experimental design

An experimental design with 5 factors and 3 variables was developed using Modde 9 statistical software (Umetrics, Sweden) [18, 28, 31]. The independent variables, the matrix of the experimental design and the dependent variables are presented in table I, II and table III, respectively.

The coefficient calculation, the statistic parameter calculation and the evaluation of the quality of fit were performed using the same software.

Table I
Independent variables

Formulation variables	Symbol	Levels		
		-1	0	1
Percentage of HPMC K15	X ₁	20	35	50
Percentage of Carbopol or Polycarbophil	X ₂	0	7.5	15
Type of bioadhesive polymer	X ₃	Carbopol	-	Polycarbophil
Type of filler	X ₄	Dicalcium phosphate	-	Isomaltose
Percentage of SCMC	X ₅	0	7.5	15

Table II
The matrix of experimental design

Exp. Name	Run Order	X ₁	X ₂	X ₃	X ₄	X ₅
N1	9	20	0	Carbopol	Dicalcium phosphate	15
N2	14	50	0	Carbopol	Dicalcium phosphate	0
N3	6	20	15	Carbopol	Dicalcium phosphate	0
N4	17	50	15	Carbopol	Dicalcium phosphate	15
N5	18	20	0	Polycarbophil	Dicalcium phosphate	0
N6	15	50	0	Polycarbophil	Dicalcium phosphate	15
N7	11	20	15	Polycarbophil	Dicalcium phosphate	15
N8	5	50	15	Polycarbophil	Dicalcium phosphate	0
N9	1	20	0	Carbopol	Isomaltose	0
N10	2	50	0	Carbopol	Isomaltose	15
N11	13	20	15	Carbopol	Isomaltose	15
N12	12	50	15	Carbopol	Isomaltose	0
N13	7	20	0	Polycarbophil	Isomaltose	15
N14	16	50	0	Polycarbophil	Isomaltose	0
N15	8	20	15	Polycarbophil	Isomaltose	0
N16	4	50	15	Polycarbophil	Isomaltose	15
N17	19	35	7.5	Carbopol	Dicalcium phosphate	7.5
N18	3	35	7.5	Carbopol	Dicalcium phosphate	7.5
N19	10	35	7.5	Carbopol	Dicalcium phosphate	7.5

X₁ – percentage of HPMC K15M, X₂ – percentage of Carbopol or Polycarbophil, X₃ – Type of bioadhesive polymer, X₄ - Type of filler, X₅ – Percentage of SCMC

Table III
Responses (dependent variables)

Nr. Crt.	Responses	Symbols
1	% release after 0.25 h	Y ₁
2	% release after 0.5 h	Y ₂
3	% release after 1.0 h	Y ₃
4	% release after 1.5 h	Y ₄
5	% release after 2.0 h	Y ₅
6	% release after 2.5 h	Y ₆
7	% release after 3.0 h	Y ₇
8	% release after 3.5 h	Y ₈
9	% release after 4.0 h	Y ₉
10	% release after 4.5 h	Y ₁₀
11	% release after 5.0 h	Y ₁₁
12	% release after 5.5 h	Y ₁₂
13	% release after 6.0 h	Y ₁₃
14	% release after 6.5 h	Y ₁₄
15	% release after 7.0 h	Y ₁₅
16	% release after 7.5 h	Y ₁₆
17	% release after 8.0 h	Y ₁₇

Nr. Crt.	Responses	Symbols
18	% release after 8.5 h	Y ₁₈
19	% release after 9.0 h	Y ₁₉
20	% release after 9.5 h	Y ₂₀
21	% release after 10.0 h	Y ₂₁
22	% release after 10.5 h	Y ₂₂
23	% release after 11.0 h	Y ₂₃
24	% release after 11.5 h	Y ₂₄
25	% release after 12.0 h	Y ₂₅
26	k Peppas	Y ₂₆
27	n Peppas	Y ₂₇
28	Bioadhesion	Y ₂₈
29	% water uptake after 0.5h	Y ₂₉
30	% water uptake after 1.0 h	Y ₃₀
31	% water uptake after 2.0 h	Y ₃₁
32	% water uptake after 4.0 h	Y ₃₂
33	% water uptake after 8.0 h	Y ₃₃
34	% water uptake after 12.0 h	Y ₃₄

Tablet preparation

All the materials for the tablet preparation - FAMO 10 mg/tablet, HPMC polymer between 20% and 50%, Carbopol, Polycarbophil and SCMC between 0%-15% (as shown in Table II), excipients (MCC 15%) and other excipients as difference (isomaltose, dicalcium phosphate), glidant 0.25% and lubricant 0.5%, were mixed in planetary mixer for 10 minutes (Erweka, Germany). The powder mix was sieved through a 400- μ m sieve and then mixed again for 5 minutes in the same apparatus. Tablets with 600 mg weight were prepared by direct compression using an EK-0 Tablet press (Korsch, Germany) equipped with 16 mm diameter punch and dies. The tablet hardness was between 9-10 kg force and the friability under 1%.

Water uptake

The water uptake study was performed in triplicate in the same conditions as the dissolution study (at $37\pm0.5^\circ$) in USP no. 1 apparatus (basket), (HCl 0.1 M, 100 rpm). A tablet was weighed together with the basket (W1) and placed in the dissolution medium. At regular time intervals (0.5, 1, 2, 4, 8 and 12 hours) the tablet and basket were removed, excess surface liquid was carefully removed by a filter paper and weighed again (W2). The swelling index (SI) was calculated using the formula: $SI = (W2 - W1)/W1$.

In vitro release study

The *in vitro* dissolution tests were conducted in the PharmaTest PT-DT7 device, which was equipped with the USP no. 1 apparatus (with basket), at 100 rpm rotation speed. The dissolution media used was 900 mL HCl 0.1 M (pH=2) at $37\pm0.5^\circ$. A 5 mL sample was collected after 15 minutes for the first half hour and then for every 30 minutes until 12 hours. Each sample was immediately filtered through a 0.45 μ m filter and replaced by fresh media to maintain a constant volume across the experiment. The sample solutions were analyzed at 265 nm by UV spectrophotometry (Jasco, V530. Japan).

Kinetic release evaluation

To evaluate the release profiles, several release models (Table VII) were tested, such as Baker-Lonsdale [3], Korsmeyer-Peppas [17, 23], Hixson-Crowell [14], Higuchi [12, 13] first order and zero order [24]. The

mathematical models, shown in Table IV, were fitted to individual dissolution data with the regression module of Kinetica 4.4 for Windows.

Table IV
Release models tested

Baker-Lonsdale	$(3/2)[1-(1-(Q_t/Q_\infty)^{2/3})-(Q_t/Q_\infty)]=K_b t$
Peppas - Korsmeyer	$Q_t/Q_\infty = K_p t^n$
Hixson-Crowell	$Q_0^{1/3} - Q_t^{1/3} = K_h t$
Higuchi	$Q_t/Q_\infty = K_h t^{0.5}$
First order	$Q_t/Q_\infty = K_1 t$
Zero order	$Q_t = Q_0 + K_0 t$

Regression analyses were used to obtain the release constant k , correlation coefficients R and Akaike Information Criterion (AIC) for each model. The Akaike criterion was chosen for distinguishing among competing models. Considering this criterion a lower value of the indicator means a better fit. On the basis of the Akaike indicator we selected the mathematical model, which describes the release profile for all the analyzed samples with the greatest accuracy. The equation with the lower value of the indicator was judged to be the most appropriate model for each system. The mechanism of drug release was analyzed using the Peppas equation in which k is the release rate constant and n is the release exponent indicating the mechanism of drug release [17].

Bioadhesive properties

The measurement of the bioadhesive forces of the formulations was performed on a modified two arms balance using cellophane as a synthetic membrane. The tablets were pre-hydrated for 3 minutes with 50 μ L of HCl 0.1M and brought in contact with the synthetic membrane for 5 minutes to allow interaction between the hydrated polymer and the cellophane. The force necessary to detach the tablets from the synthetic membrane was calculated by using the below formula: Detachment force (N) = [Weight (g) • 9.8]/1000.

All measurements were repeated 10 times.

Results and Discussion

Experimental design analysis. Quality of fit

The statistical module from the Modde 9 software was used in order to fit the experimental data with the chosen experimental design and to calculate the statistical parameters, with the Partial Least Squares method.

To check the validity of the experimental design the following statistical parameters were calculated: R^2 , Q^2 and the ANOVA test where R^2 represents the fraction of the variation of the response explained by the model and Q^2 represents the fraction of the variation of the response that can be predicted by the model [18, 24, 31].

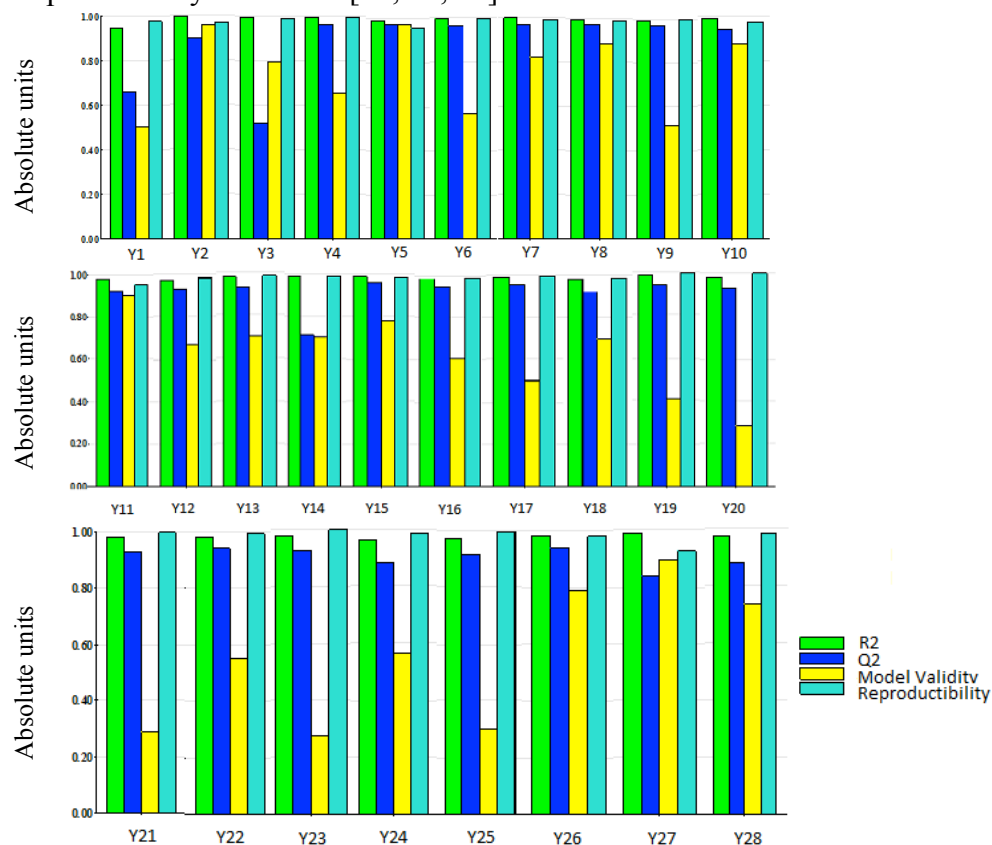


Figure 1

R^2 , Q^2 , Model Validity and Reproducibility for responses:

Y₁ - % release after 0.25 h, Y₂ - % release after 0.5 h, Y₃ - % release after 1.0 h, Y₄ - % release after 1.5 h, Y₅ - % release after 2.0 h, Y₆ - % release after 2.5 h, Y₇ - % release after 3.0 h, Y₈ - % release after 3.5 h, Y₉ - % release after 4.0 h, Y₁₀ - % release after 4.5 h, Y₁₁ - % release after 5.0 h, Y₁₂ - % release after 5.5 h, Y₁₃ - % release after 6.0 h, Y₁₄ - % release after 6.5 h, Y₁₅ - % release after 7.0 h, Y₁₆ - % release after 7.5 h, Y₁₇ - % release after 8.0 h, Y₁₈ - % release after 8.5 h, Y₁₉ - % release after 9.0 h, Y₂₀ - % release after 9.5 h, Y₂₁ - % release after 10.0 h, Y₂₂ - % release after 10.5 h, Y₂₃ - % release after 11.0 h, Y₂₄ - % release after 11.5 h, Y₂₅ - % release after 12.0 h, Y₂₆ - k Peppas, Y₂₇ - n Peppas, Y₂₈ - bioadhesion

Values close to 1 for both R^2 and Q^2 indicate a very good model with an excellent predictive power. The values of R^2 , Q^2 were good, indicating a good quality of fit.

Water uptake study

The release profile from the bioadhesive matrix tablets depends also on the water uptake properties of the polymers (Figure 2). Most of the formulations have a water uptake between 12 and 18%. Formulations N5 (R18) and N9 (R9) which have only HPMC K15M in a low concentration (20%) in their composition present also a high erosion profile as the formed gel layer at the surface of the tablets is not strong enough and begins to erode after only 2 hours. On the other hand formulations like N4 (R17) and N16 (R4) which contain three bioadhesive polymers in the highest concentration or formulations like N6 (R15), N10 (R2) and N12 (R12) containing HPMC and SCMC or CP in the highest concentration present the highest water uptake profile and no significant erosion profiles after 12 hours.

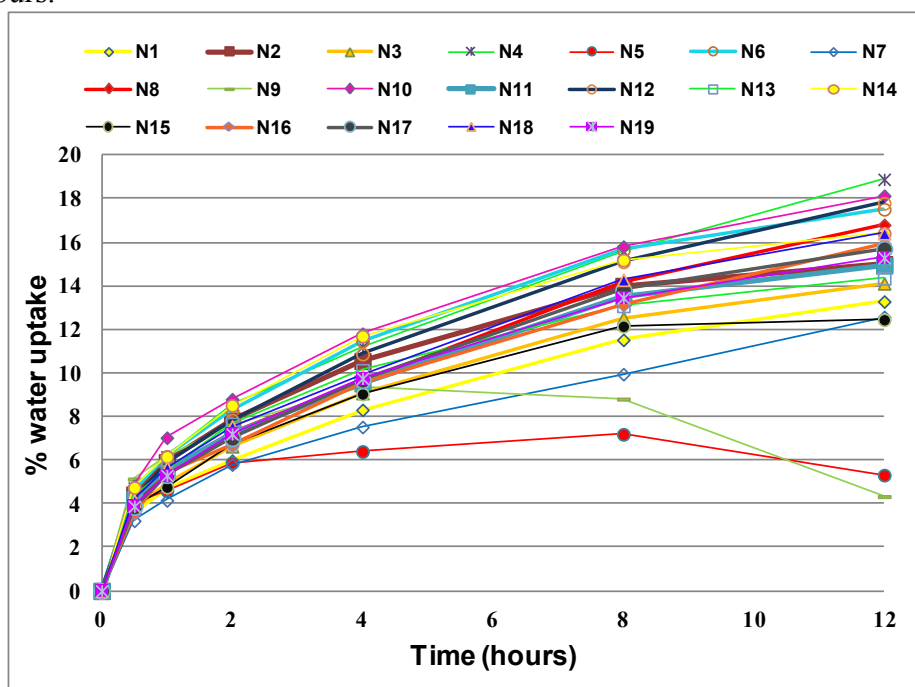
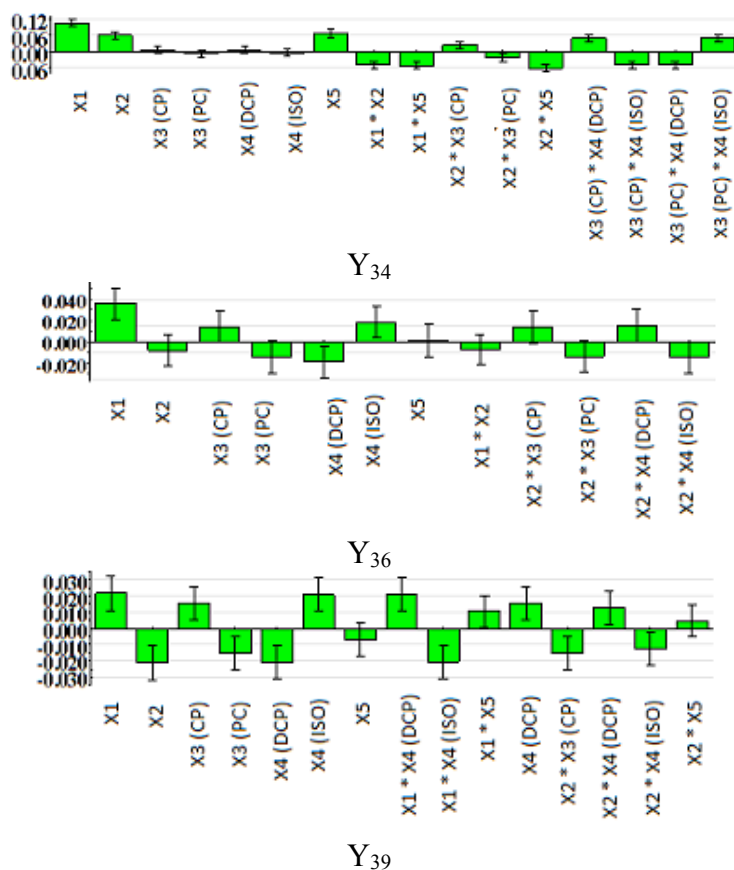


Figure 2
Water uptake of the experimental formulations

**Figure 3**

Influence of the formulation factors on the Y_{34} , Y_{36} and Y_{39} responses.

Y_{34} - Percent released after 0.5 hours, Y_{36} - Percent released after 2.0 hours, Y_{39} - Percent released after 12.0 hours, X_1 – percentage of HPMC K15M, X_2 – percentage of Carbopol or Polycarbophil, X_3 – Type of bioadhesive polymer, X_4 – Type of filler, X_5 – Percentage of SCMC

Figure 3 shows that the most important formulation variables influencing the release are the percent of HPMC (X_1). By increasing the percent of HPMC the water uptake of the tablet is favored.

This result is comparable to the results obtained by S. Sonar *et al* [27]. They state that the percentage of water uptake is increased by rising of the concentration of HPMC in the formulations. Drug diffusion in matrix tablets depends significantly on the water content of the tablet. This may be because the mobility of the polymer chains is very dependent on the water content of the system. In the case of high water content, polymer chain

relaxation takes place with volume expansion resulting in the swelling of the system.

At the beginning of release, the use of DCP has a negative effect on the water uptake while the ISO favors the water uptake. This effect may be attributed to the more hydrophilic nature of ISO. These tendencies disappear at the 12 h sampling point when tablets become fully hydrated.

After 0.5 hours the percentage of CP and PC decreased the water uptake while at time point 12 this factor shifted to a positive influence. As the water penetrates the polymer chains, these become more relaxed and the water uptake is favored.

There are some interactions occurring between bioadhesive polymers. The most important is that of the percentage of HPMC (X1) and the percentage of SMC (X5). At sampling time point 0.5 this interaction works in favor of the water uptake, both polymers having good water uptake properties and working synergic. In time, as these polymers get fully hydrated and start to erode, the influence on the water uptake becomes negative.

***In vitro* release of famotidine**

The results indicate that the percent of famotidine released depends on the formulation factors studied with the experimental design. FAMO was slowly released over 12 hours from all the experimental formulations.

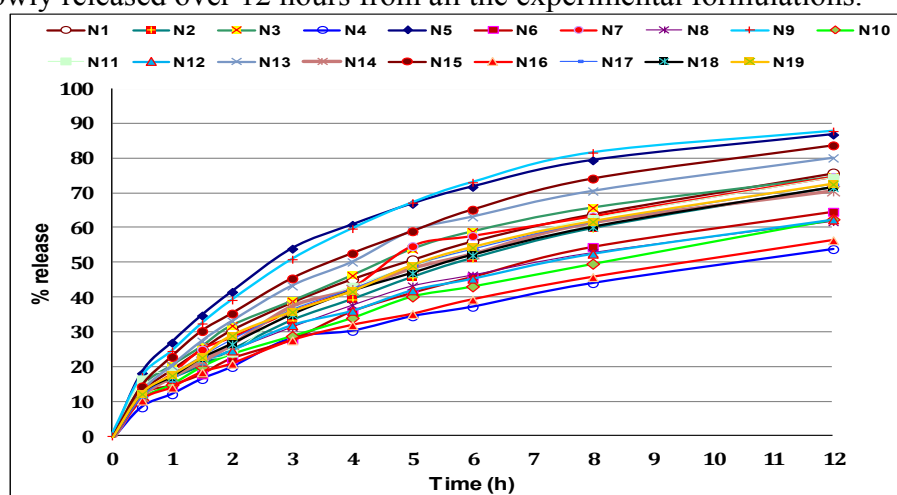
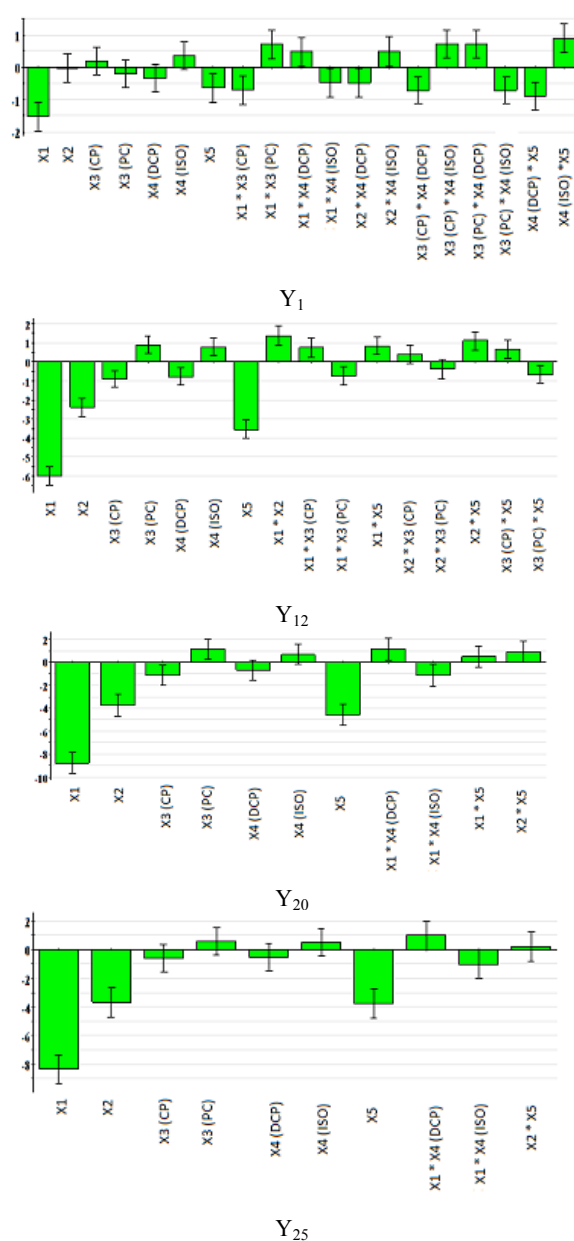


Figure 4

Release profiles of the experimental formulations

The release varied between 52% and 88% depending on the percentage and the combination of the bioadhesive polymers used (Figure 4).

Figure 5 shows the histograms with the influence of the formulation factors on the responses at time points: 0.25 h, 3h, 8h and 12 h.

**Figure 5**

Influence of the formulation factors on the Y_1 , Y_{12} , Y_{20} and Y_{25} responses.

Y_1 - Percent released after 0.25 hours, Y_{12} - Percent released after 3.0 hours,

Y_{20} - Percent released after 7.0 hours, Y_{25} - Percent released after 12.0 hours

X_1 – percentage of HPMC K15M, X_2 – percentage of Carbopol or Polycarbophil,

X_3 – Type of bioadhesive polymer, X_4 - Type of filler, X_5 – Percentage of SCMC

Figure 5 shows that the most important formulation variable influencing the release is the percent of HPMC K15M (X_1); by increasing the percent of HPMC K15M from 20 to 50 % a reduced release of the drug was observed. The same influence, but at a lower intensity, is showed by the percentage of SCMC. Another important formulation variable is the percentage of CP/PC (X_2) and percentage of SCMC (X_5). The increase of the percentage of polymers reduced the release of famotidine. This influence was not observed after 0.25 hours, having no effect on the water uptake.

At the beginning of release, the use of DCP has a delaying effect on the release while the use of ISO favors a fast release. These tendencies disappear at 12 h sampling point when tablets become fully hydrated and start to erode.

Also polymer interactions occur at the beginning of the release study and disappear after some hours. For example, the interaction between the percentage of HPMC and the presence of CP in the formulation has a positive effect after 0.25 hours while the interaction of the percentage of HPMC and PC has an opposite effect. This can be explained by the influence of the PC and CP on the water uptake.

Some formulations (N5, N9, N13, N15) released famotidine quicker over 12 hours. This consist of a small amount of HPMC K15M (20%) alone or in combination with the other bioadhesive polymers used (CP, PC or SCMC) in low concentrations. The lower the concentration of polymer and the less polymers in the formulation, the faster the release.

Other formulations (N6, N8, N12, N16, N17) consist of a high percentage of HPMC K15M in combination with other bioadhesive polymers. The most delayed profile is the one where there is a ternary combination of polymers in their highest concentration. The higher the amount of bioadhesive polymer the slower the release, as the active substance needs to diffuse through the gel layer formed by the swelling polymer.

Influence of the formulation factors on the kinetics of release

In order to study the release profile of famotidine from bioadhesive matrix tablets six well known kinetic release models where evaluated. Table V provides the summary of the model fitting and statistical parameters for kinetic release characterization of the prepared formulations N1-N19. The best fitting for the drug profile release for all the experiments was obtained with the Peppas equation.

Table V
Results of the kinetic release characterization

Nr. Exp.	Baker and Lonsdale			Peppas				Hixon and Crowell		
	R	AIC	K	R	AIC	K	n	R	AIC	K
N1	0.982	146.13	0.021	0.997	103.24	27.615	0.531	0.971	157.01	0.062
N2	0.988	132.52	0.007	0.999	72.46	15.769	0.559	0.960	163.23	0.027
N3	0.989	139.83	0.010	0.999	87.66	19.030	0.543	0.966	166.71	0.033
N4	0.993	114.62	0.005	0.999	68.57	14.990	0.536	0.944	165.55	0.023
N5	0.996	107.36	0.008	0.997	97.27	18.778	0.490	0.926	177.24	0.028
N6	0.993	128.10	0.013	0.996	117.88	23.459	0.483	0.947	179.64	0.039
N7	0.989	144.62	0.015	0.993	135.25	24.893	0.492	0.962	176.13	0.044
N8	0.991	138.92	0.017	0.997	116.78	25.836	0.496	0.966	172.12	0.048
N9	0.991	137.28	0.012	0.998	101.85	21.646	0.517	0.963	172.02	0.038
N10	0.989	139.09	0.010	0.997	106.61	19.901	0.531	0.963	169.95	0.035
N11	0.987	145.73	0.012	0.994	129.60	21.074	0.521	0.961	173.09	0.037
N12	0.994	115.54	0.007	0.999	73.01	17.733	0.517	0.944	171.63	0.028
N13	0.989	140.00	0.011	0.997	107.57	20.820	0.521	0.959	172.14	0.036
N14	0.983	150.33	0.010	0.998	97.60	17.805	0.572	0.975	159.83	0.033
N15	0.983	145.53	0.008	0.997	101.38	15.862	0.579	0.971	159.06	0.029
N16	0.989	139.30	0.010	0.995	120.92	19.926	0.524	0.958	172.39	0.034
N17	0.993	113.92	0.005	0.998	78.60	14.160	0.540	0.943	164.41	0.022
N18	0.993	128.98	0.021	0.995	123.00	30.171	0.474	0.959	173.02	0.061
N19	0.990	138.53	0.011	0.997	107.17	20.104	0.528	0.963	170.23	0.035

Nr. Exp.	Higuchi			First Order			Zero order		
	R	AIC	k	R	AIC	k	R	AIC	k
N1	0.996	108.31	29.098	0.990	131.50	0.226	0.848	197.15	11.84
N2	0.997	102.48	17.745	0.975	151.47	0.091	0.906	183.87	6.123
N3	0.997	103.98	20.741	0.983	149.22	0.118	0.892	194.67	7.141
N4	0.998	83.20	16.100	0.962	156.19	0.079	0.888	182.19	5.542
N5	0.997	96.12	18.400	0.952	166.78	0.097	0.839	195.48	6.300
N6	0.996	117.46	22.677	0.973	162.82	0.139	0.828	207.36	7.755
N7	0.993	133.48	24.487	0.986	152.51	0.162	0.835	211.40	8.376
N8	0.997	114.85	25.662	0.987	148.96	0.178	0.848	207.91	9.170
N9	0.998	102.49	22.379	0.983	152.87	0.135	0.868	202.24	7.682
N10	0.997	110.87	21.174	0.982	151.83	0.122	0.881	198.09	7.278
N11	0.993	129.00	21.980	0.981	154.63	0.131	0.867	202.25	7.545
N12	0.999	76.56	18.354	0.965	160.10	0.096	0.871	191.47	6.304
N13	0.997	108.50	21.705	0.978	156.88	0.127	0.872	199.42	7.459
N14	0.994	122.39	20.571	0.988	140.89	0.116	0.912	190.43	7.104
N15	0.993	123.51	18.601	0.984	143.61	0.098	0.916	184.64	6.429
N16	0.995	121.13	20.889	0.979	155.32	0.120	0.871	199.17	7.172
N17	0.997	90.54	15.345	0.960	155.48	0.074	0.891	180.04	5.282
N18	0.994	123.92	28.847	0.983	150.70	0.227	0.825	207.51	11.33
N19	0.997	110.44	21.276	0.982	151.83	0.123	0.878	198.67	7.311

In order to analyze the influence of the formulation factors on the kinetic release, the parameters of the Peppas equation (k and n) were introduced as responses ($Y_{26} - k$ and $Y_{27} - n$) in the experimental design. The

coefficients of the equation used to fit the experimental data with the chosen model at kinetic release evaluation are presented as scaled and centred coefficients in figure 6 and figure 7.

The influence of the formulation factors on k parameter is similar with the influence of formulation factors on the *in vitro* release of famotidine at different time point intervals. The percentage of HPMC (X_1), the percentage of CP/PC (X_2) and the percentage of SCMC (X_5) have a negative influence on the k parameter of the Peppas equation, meaning that increasing the concentration of these polymers has a retarding effect on the release profile. This result is in accordance with the data obtained by the statistic parameters of the release profiles. There are no significant interactions between the factors.

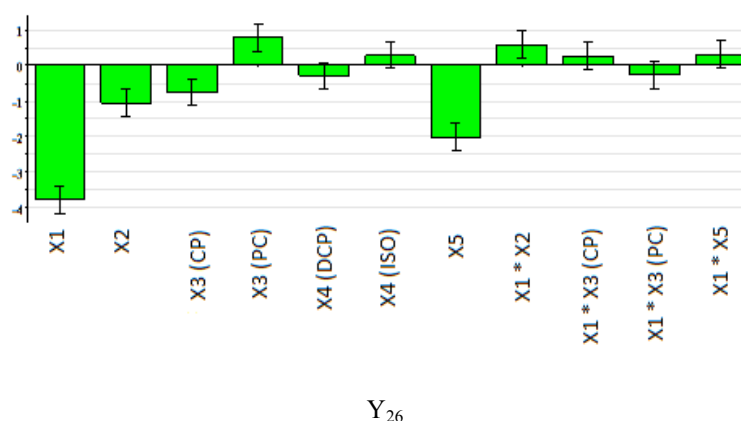
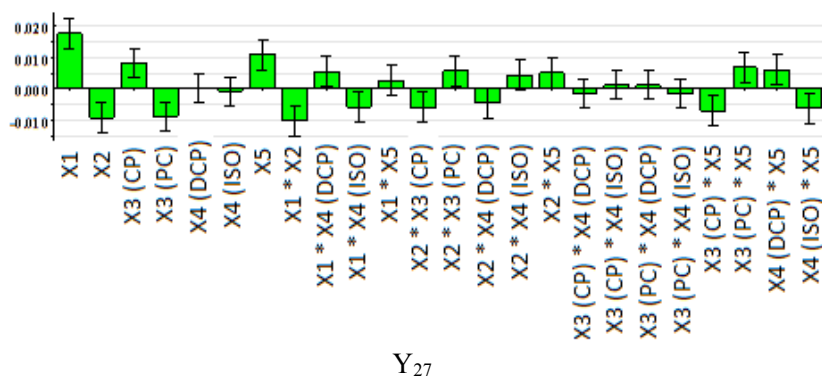


Figure 6

Influence of the formulation factors on the k Peppas (Y_{26}) response.

X_1 – percentage of HPMC K15M, X_2 – percentage of Carbopol or Polycarbophil, X_3 – Type of bioadhesive polymer, X_4 – Type of filler, X_5 – Percentage of SCMC

Regarding the influence of the formulation factors on the n parameter from the Peppas equation, increasing the percentage of HPMC and SCMC in the formulation lead to an increase of the n value and to a more zero order release governed by diffusion through the gel layer. This result is also obtained by using CP in the formulation. Increasing the percentage of CP/PC or using PC in the formulation have a negative effect on n and lead to a system with Higuchi kinetic release behaviour (n close to 0.5), which is governed by diffusion through the gel layer and also by the erosion of it.



Y₂₇
Figure 7

Influence of the formulation factors on the *n* Peppas (Y₂₇) response.

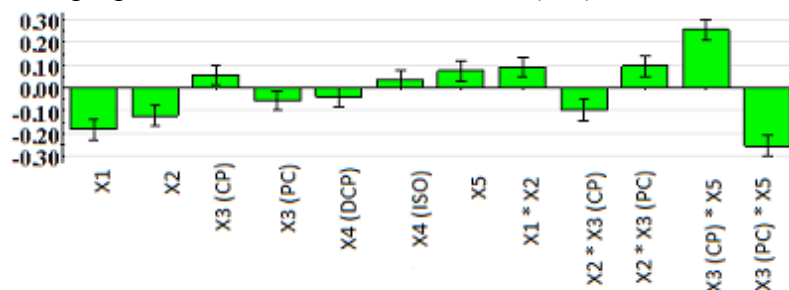
X₁ – percentage of HPMC K15M, X₂ – percentage of Carbopol or Polycarbophil, X₃ – Type of bioadhesive polymer, X₄ – Type of filler, X₅ – Percentage of SCMC

There are some interactions between the polymers which have an influence on *n* Peppas. Increasing the percentage of CP/PC and HPMC (X₁*X₂) and the combination of CP and SCMC in a formulation lead to a more diffusion and erosion controlled release while the use of PC and SCMC in the formulation show a release more governed by diffusion.

The use of DCP or ISO in the formulations has little or no influence on *k* and *n* Peppas.

Influence of the formulation factors on the bioadhesive properties

Figure 8 presents the influence of the formulation factors on the bioadhesive properties of the formulated tablets (Y₂₈).



Y₂₈
Figure 8

Influence of the formulation factors on the bioadhesive properties of matrix tablets.

X₁ – percentage of HPMC K15M, X₂ – percentage of Carbopol or Polycarbophil, X₃ – Type of bioadhesive polymer, X₄ – Type of filler, X₅ – Percentage of SCMC

The factors which have a positive influence on the bioadhesive properties of the tablets, by increasing them, are the concentration of SCMC and the presence of ISO and CP in the formulations. Increasing the percentage of SCMC in the formulations favors the bioadhesive properties. The presence of ISO as a filler permits the penetration of water through the gel layer and thus favoring the faster formation of a gel layer at the surface of the tablets.

The increase of the percentage of HPMC results in lower detachment forces. Also the presence of PC and DCP have the same effect. This fact might be explained by the formation of a strong gel with higher concentrations of HPMC which cannot be easily penetrated by water. The water uptake results confirm this aspect. At first time points, the presence of PC and DCP in the formulations reduces the water uptake of the tablets and thus the formation of the sticky gel layer on the surface.

There are also some interactions between the factors. Of these, the most important is the interaction between the percentage of SCMC (X5) and CP (X3) which is very intense. The two factors work synergic on the bioadhesive properties, increasing them. Another interaction of similar intensity is that of PC (X2) and SCMC (X5). The effect is also synergic and has a negative influence on the bioadhesion.

Conclusions

We have used an experimental design to determine the best combination of different bioadhesive polymers and fillers as well as the possible advantages of binary and ternary combination of bioadhesive polymers on the water uptake properties, the release profile and the bioadhesive properties of matrix tablets with famotidine.

The combination of three polymers (HPMC, SCMC and CP or PC) in the highest concentration used, showed the slowest release of the active substance and the highest water uptake, followed by the formulations containing two polymers in the highest used concentration. The percentage of HPMC and SCMC are the factors with the highest impact as retarding agents, on the release profile of famotidine which was best described by Peppas model.

In terms of bioadhesiveness the combination of CP and SCMC showed a synergic effect of bioadhesive properties increasing the adhesive properties. Also ISO had a positive influence on the bioadhesive properties by favoring the hydration of the polymer surface layer.

In conclusion the screening of bioadhesive polymers and excipients showed an obvious advantage of ternary and binary retarding agents over a single polymer in the studied formulations.

Acknowledgements

The authors wish to thank COLORCON, UK for the Methocel samples and to SMS PHARMACEUTICALS LTD, INDIA for the famotidine sample.

References

1. Andrews G. P., Lavery T. P., Jones D. S., Mucoadhesive polymeric platforms for controlled drug delivery, *Eur J Pharm Biopharm* 2009, 71, 505-518.
2. Asane G. S., Nirmal S. A., Rasal K. B., Naik A. A., Mahadik M. S., Polymers for mucoadhesive drug delivery systems: a current status, *Drug Dev Ind Pharm*, 2008, 34, 1246-1266.
3. Baker R.W., Lonsdale H.S., Controlled release: mechanisms and rates. In *Controlled Release of Biologically Active Agents*, Plenum Press, New York, 1974, 15-71.
4. Bardonnnet P.L., Faivre V., Pugh W.J., Piffaretti J.C., Falson F., Gastroretentive dosage forms: Overview and special case of *Helicobacter pylori*, *J Controlled Release*, 2006, 111, 1-18.
5. Chandira M., Bhowmik D., Jayakar B., Formulation and evaluation of mucoadhesive oral tablet of clarithromycin, *T Pharm Res*, 2009, 2, 30-42.
6. Chavanpatil M., Jain P., Chaudhari S., Development of sustained release gastroretentive drug delivery system of ofloxacin: *in vitro* and *in vivo* evaluation, *Int J Pharm*, 2005, 304, 178-184.
7. Chavanpatil M., Jain P., Chaudhari S., Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin, *Int J Pharm*, 2006, 316, 86-92.
8. Chen R. N., Ho H. O., Yu C. Y., Sheu M. T., Development of swelling/floating gastroretentive drug delivery system based on a combination of hydroxyethyl cellulose and sodium carboxymethyl cellulose for Losartan and its clinical relevance in healthy volunteers with CYP2C9 Polymorphism, *Eur J Pharm Sci*, 2010, 39, 82-89.
9. Dürig T., Fassihi R., Evaluation of floating and sticking extended release delivery systems: an unconventional dissolution test, *J Control Rel*, 2000, 67, 37-44.
10. Gopalakrishnan S., Chentilnathan A., Floating Drug Delivery Systems: A Review, *J Pharm Sci Technol*, 2011, 3, 548-554.
11. Guan J., Zhou L., Nie S., Yan T., Tang X., Pan W., A novel gastric-resident osmotic pump tablet: *In vitro* and *in vivo* evaluation, *Int J Pharm*, 2010, 383, 30-36.
12. Higuchi T., Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices, *J Pharm Sci*, 1963, 52, 1145-1149.
13. Higuchi T., Rate of release of medicaments from ointment bases containing drugs in suspension, *J Pharm Sci*, 1961, 50, 874-875.
14. Hixson A.W., Crowell J.H., Dependence of reaction velocity upon surface and agitation, *Ind Eng Chem*, 1931, 23, 923-931.
15. Hwang S. J., Park H., Park K., Gastric retentive drug delivery systems, *Crit Rev Ther Drug Carrier Syst.*, 1998, 15, 243-284.
16. Klausner E. A., Lavy A., Friedman M., Hoffman A., Expandable gastroretentive dosage forms, *J Controlled Release*, 2003, 90, 143-162.
17. Korsmeyer R.W., Gurny R., Doelker E.M., Buri P., Peppas N.A., Mechanism of solute release from porous hydrophilic polymers, *Int J Pharm*, 1983, 15, 25-35.
18. Leucuța S. E., Tomuța I., Planuri experimentale și optimizarea formulării medicamentelor, Editura RISOPRINT, Cluj-Napoca, 2011, 169-179.

19. M. Jaimini, A.C. Rana, Y.S. Tanwar, Formulation and evaluation of famotidine floating tablets, *Curr Drug Delivery*, 2007, 4, 51-55.
20. Maderuelo C., Zarzuelo A., Lanao J., Critical factors in the release of drugs from sustained release hydrophilic matrices, *J Control Rel*, 2011, 154, 1, 2-19.
21. Möes A. J., Gastroretentive dosage forms, *Crit Rev Ther Drug Carrier Syst*, 1993, 10, 143-159.
22. Mostafavi A., Emamia J., Varshosaza J., Daviesb N. M., Rezazadeha M., Development of a prolonged-release gastroretentive tablet formulation of ciprofloxacin hydrochloride: Pharmacokinetic characterization in healthy human volunteers, *Int J Pharm* 2011, 409, 128-136.
23. Peppas N.A., Analysis of Fickian and non-Fickian drug release from polymers, *Pharm Acta Helv.*, 1985, 60, 110-111.
24. Prasacu I., Mircioiu C., Sandulovici R., Enache F., Release of metoprolol from solid dosage forms. Choice and validation of theoretical model, *Farmacia*, 2009, 57(1), 89-98.
25. Singh B. N., Kim K. H., Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention, *J Control Rel*, 2000, 63, 235-259.
26. Sonar G. S. , Jaina D. K., More D. M., Preparation and *in vitro* evaluation of bilayer and floating-bioadhesive tablets of rosiglitazone maleate, *Asian J Pharm*, 2007, 2 (4), 161-169.
27. Tadros M. I., Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: development, optimization and *in vitro-in vivo* evaluation in healthy human volunteers, *Eur J Pharm Biopharm* 2010, 74, 332-339.
28. Tomuta I., Vlase L., Popa A., Leucuta S.E., *In vitro - in vivo* evaluation of a novel drug delivery system for colonic targeting, *Farmacia*, 2010, 58(3), 368-377.
29. Wang J., Tabata Y., Bi D., Evaluation of gastric mucoadhesive properties of animated gelatine microspheres, *J Control Rel*, 2001, 73, 223-231.
30. Xu X. Q., Sun M. J., Zhi F., Floating matrix dosage form for phenoprolamine hydrochloride based on gas forming agent: *in vivo* and *in vitro* evaluation in health volunteers, *Int J Pharm*, 2006, 310, 139-145.
31. * * MODDE 9, Software for Design of Experiments and Optimization: User's Guide and Tutorial. Umetrics Academy: Umea, 2010, 129-156.

Manuscript received: September 17th 2010