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STUDIES IN FORMULATION DEVELOPMENT AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM OF METFORMIN HCL

STUDIJA RAZVOJA FORMULACIJE I PROCENA GASTRO-RETENCIONOG (FLOTIRAJUĆEG) SISTEMA PRIMENE METFORMIN HCl

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Metformin hydrochloride, gastro-retentive, floating drug delivery, central composite

Metformin hidrohlorid, gastro-retencioni, plutajući (flotirajući) prenos leka, centralni kompozit.

Abstract

The purpose of this investigation was to prepare a gastro-retentive drug delivery system for metformin hydrochloride, which is incompletely absorbed from the small intestine because of narrow absorption window. Effervescent based approach was used for the development of the formulation. Sodium bicarbonate was incorporated as a gas-generating agent. The effects of amount of HPMC and carbopol on drug release profile and floating properties were investigated. The addition of carbopol reduces the drug dissolution due to its low water uptake property. A central composite design was applied to systematically optimize the drug release. The amount of HPMC (X1) and carbopol (X2) were selected as independent variables. The floating lag time, time required for 50% (t_{50}) and 80% drug dissolution (t_{80}) were selected as dependent variables. The results of the central composite design indicated that amount of HPMC favors sustained release of metformin hydrochloride from a gastro-retentive formulation. A theoretical dissolution profile was generated using pharmacokinetic parameters of metformin hydrochloride. The similarity factor f2 was applied to compare the central composite design batches and the theoretical dissolution profile. Batches F7, F8 and F9-13 (replicate batches) were promising batches as the f2 values were greater than 50. The in-vivo X-ray studies showed that the tablet was intact and remained floated in the gastric content up to 6 hr after administration.

INTRODUCTION

Metformin Hydrochloride (MTF) is an orally administered biguanide derivative widely used in the treatment of non-insulin dependent diabetes mellitus. It improves glycaemic control by enhancing insulin sensitivity in the liver and muscles. The drug has also exhibited beneficial effects on several cardiovascular risk factors such as dyslipidemia, elevated plasma plasminogen activator inhibitors, other fibrinolytic abnormalities, and hyperinsulinemia and insulin resistance [1,2].

The short biological half-life of the drug (~2.5-3 hours) favors the development of a sustained release formulation. In humans, metformin is incompletely absorbed after oral administration because of narrow absorption window in the small intestine [3]. The physicochemical property of metformin demonstrates that it is a strong base (pKa = 11.5) and is protonated under physiological pH conditions. The ionized metformin has a tendency to be absorbed to the negatively charged intestinal epithelium affecting the drug absorption pattern [4]. Thus, the absorption window of metformin is predominantly the small intestine which follows a saturable dose dependent mechanism [1,5]. Metformin absorption after oral absorption is therefore likely to be site specific.

However, a conventional oral sustained release formulation will stay at the site of absorption for a short duration and spend most of the time in the colon where it releases a major portion of the drug content. Thus, an ideal sustained release (SR) formulation should have the drug absorption window either in the colon or throughout the gastrointestinal tract (GIT). Vidon et al. and Marathe et al. have indicated that

metformin has poor colonic absorption in healthy human subjects [5, 6]. Release of metformin after the small intestine is thus, of no therapeutic value. Marathe et al. have also strongly mentioned that the conventional strategies of prolonging the release of metformin from the dosage forms throughout the GIT would not be effective. They have also indicated that the extent of metformin absorption is improved when the gastro intestinal motility is slow [6]. Thus, development of a gastro retentive sustained release formulation for metformin hydrochloride which will slowly release the drug in the stomach for gradual absorption in the intestine would be a better alternative to the conventional sustained release formulations. An in-vivo study conducted by Gusler et al. depicted that the mean bioavailability of gastro retentive metformin tablets was approximately 115% relative to the immediate release metformin product suggesting complete utilization of drug probably with lower side effects [7].

With the above considerations in view, in the present investigation an attempt has been made to develop a gastroretentive floating drug delivery system (GR-FDDS) of metformin hydrochloride for better management of non-insulin dependent diabetes mellitus.

Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices [8,9]. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.

An effervescent approach utilizing a swellable polymer and bicarbonate was applied in the formulation of floating MTF tablets. A hydrophilic swellable polymer like HPMC was investigated because of flexibility and reproducibility. This polymer is also widely used because of its rapid hydration and good compression and gelling properties. The present investigation utilizes a systematic approach for the development of gastro-retentive MTF tablets. The application of central composite design (CCD) for developing pharmaceutical dosage forms are well documented [10-15].

MATERIALS AND METHODS

Materials

Metformin hydrochloride was received as a gift sample from Wallace Pharmaceuticals Pvt. Ltd., Mumbai, India. Hydroxypropyl methylcellulose (HPMC K4 M and K100 M) were received as gift samples from Colorcon Asia Pvt. Ltd., Goa, India. Carbopol was received as gift sample from Corel Pharma, Ahmedabad, India. Guar gum was purchased from National Chemicals, Vadodara, India and sodium bicarbonate and stearic acid were purchased from S.D. Fine-Chem Ltd, Vadodara, India. All other chemicals were of laboratory reagent grade.

Methods

Preparation of Metformin hydrochloride Floating Tablets

Metformin hydrochloride (500 mg) was mixed with the required quantities of the matrix forming polymers (HPMC K4 M, K100 M, guar gum or carbopol) and dicalcium phosphate dihydrate by geometric mixing. In batches A5-A8, various carbonates were tried as gas-generating agents, among the batches A5-A8, tablets with sodium bicarbonate exhibited the least floating lag time. Thus, in batches A9-A11, sodium bicarbonate was tried at different concentrations (40, 60, 80 mg). The tablets containing 60 mg sodium bicarbonate showed the least floating lag time (3 sec) and thus it was used for further trials. In batches A12-A14, MTF HCl was dispersed in chloroformic solution of different concentration of stearic acid (release retarding agent). The dispersion was stirred and chloroform was evaporated to form a MTF-stearic acid mixture. This mixture was then blended with other ingredients as described previously. In batches A15-A16, different grades of carbopol (release retarding agent) were tried along with HPMC K100M. The powder blend was then lubricated with magnesium stearate (1% w/w) and purified talc (1% w/w) and compressed on a rotary tablet machine (Rimek, Ahmedabad, India). The tablets were round and flat with an average diameter of 13 ± 0.1 mm, thickness of 5 ± 0.2 mm and average weight of 800 mg. The formulations of the preliminary trial batches (A1 to A16) are shown in Table 1. The formulations of the central composite design batches (F1to F13) are shown in Table 2.

Table 1 Formulation of Metformin floating Tablets: Preliminary Trials*

Ingredients (mg)	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12	A13	A14	A15	A16
HPMC K100 M	125	250	--	--	125	125	125	125	125	125	125	125	125	125	125	125
HPMC K4 M	--	--	125	250	--	--	--	--	--	--	--	--	--	--	--	--
Sodium bicarbonate	--	--	--	--	60	--	--	--	40	60	80	60	60	60	60	60
Sodium carbonate	--	--	--	--	--	60	--	--	--	--	--	--	--	--	--	--
Potassium carbonate	--	--	--	--	--	--	60	--	--	--	--	--	--	--	--	--
Calcium carbonate	--	--	--	--	--	--	--	60	--	--	--	--	--	--	--	--
Stearic acid	--	--	--	--	--	--	--	--	--	--	--	8	16	24	--	--
Carbopol 934 P	--	--	--	--	--	--	--	--	--	--	--	--	--	--	40	--
Carbopol 940 P	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	40
Dicalcium phosphate dehydrate	159	34	159	34	99	99	99	99	119	99	79	91	83	75	59	59
Floating lag time, seconds	NF#	NF	NF	NF	3	49	23	57	12	3	2	3	8	3	2	3

*All batches contained 500 mg metformin hydrochloride, 1% w/w talc and 1% w/w magnesium stearate. All values are in ....

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All values are in milligrams
NF: No floating observed

In Vitro Buoyancy Studies

The in vitro buoyancy (floating lag time) was determined as per the method described by Rosa et al. [16]. The tablets were placed in a 100-ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. The floating lag time for preliminary trial batches and central composite design batches are shown in Table 1 and Table 2, respectively.

In Vitro Dissolution Studies

The in vitro dissolution studies of MTF floating tablets (n = 3) was determined using USP 24, dissolution testing apparatus (Electrolab, India) type II (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl, at 37 ± 0.5°C and 75 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus every hour for 12 hours, and the test was replaced with fresh dissolution medium. The samples were filtered through a 0.45-μ membrane filter and diluted to a suitable concentration with pH 6.8 phosphate buffer. Absorbance of these solutions was measured at 233 nm using an Elico SL-164–Double beam UV/VIS Spectrophotometer (India). The cumulative percentage drug release was calculated using an equation obtained from a standard curve. The time for 50% and 80% drug release was calculated based on the Korsemeyer and Peppas model for central composite design batches [17].

In Vivo Buoyancy Study

In vivo study was performed by replacing 100 mg of the drug with X-ray grade barium sulphate (this amount was determined experimentally to allow X-ray visibility but not to hinder floatation of the tablet) in the optimized batch. In-vivo study was carried out by administering the floating tablets to male human volunteers. The study was carried out in fasting state. The subjects were asked to swallow the radio opaque floating tablet with 250 ml of water. The subjects were kept under fasting conditions during the study period. Subjects were allowed to drink water after 4 hr of swallowing the tablet. During the experiment the subjects were advised to remain seated in an upright posture. The position of the floating tablet was monitored by X-Ray screening technique. Gastric radiography was done at 2 hours and 6 hours to monitor the tablet position in the gastro intestinal tract.

Central Composite Design

A central composite design was used to systematically study the effect of the independent variables on the dependent variables. In this design 2 factors were evaluated, each at 3 levels and experimental trials were performed at all 9 possible combinations with 5 replication batches. The amount of HPMC K100 M (X1) and carbopol 940P (X2) were selected as independent variables. The time required for 50% and 80% drug dissolution and the floating lag time were selected as dependent variables.

Kinetic of Drug Release

The dissolution profile of batches according to central composite design (F1-13) was fitted to zero-order, first-order[18,19], Higuchi [20-22], Hixon-Crowell [23], Korsemeyer and Peppas [17, 24, 25] and Weibull models [26-29] to ascertain the kinetic modeling of drug release. The method of Bamba et al. was adopted for deciding the most appropriate model [30]. The results of sum square of residuals and F value was used for the selection of the most appropriate model.

Table 2 Formulation and Dissolution Characteristics of Metformin Floating Tablets using a Central Composite Designe

Batch No.	Transformed values X1	X2	Response Floating lag time (min)	t_{50} (min)	t_{80} (min)	f_2 Values
F1	-1	-1	1	158	412	43.57
F2	-1	+1	1	175	436	47.62
F3	+1	-1	5	476	976	37.44
F4	+1	+1	6	506	1024	35.58
F5	-1.41	0	1	139	380	39.21
F6	+1.41	0	7	552	1132	33.32
F7	0	-1.41	2	318	693	56.97
F8	0	+1.41	2	344	723	51.49
F9	0	0	2	332	707	53.85
F10	0	0	2	337	715	52.83
F11	0	0	2	334	707	53.79
F12	0	0	2	336	711	53.24
F13	0	0	2	337	715	52.92

Coded values	Actual values X1	X2
-1.41	79.5	26
-1	100	30
0	150	40
+1	200	50
+1.41	220.5	54

All batches contained 500 mg metformin hydrochloride, 60 mg sodium bicarbonate, 1% w/w talc, and 1% w/w magnesium stearate.
X1 is amount of HPMC K100 M (mg); X2 is amount of Carbopol 940P (mg)
t_{50} – time required for 50% drug dissolution, t_{80}-time required for 80% drug dissolution

RESULTS AND DISCUSSION

In Vitro Buoyancy Studies

Non-effervescent floating drug delivery approach using low density polymer was used to achieve in vitro buoyancy of metformin HCl tablets. In batches A1 to A4, MTF tablets were prepared using low density swellable gel forming polymers such as HPMC K4 M and HPMC K100 M at two ratios of drug: polymer i.e. 2:1 and 4:1, but they did not exhibit sufficient swelling to provide in vitro buoyancy. Batches containing HPMC K4 M failed to form a gel with sufficient strength, while batch A1 with HPMC K100 M (4:1 as Drug: Polymer ratio) produced tablets with good gel strength and was expected that it would entraps CO_2 gas and impart stable and persistent buoyancy. Thus, an effervescent approach was then adopted. The gas generating agent induces CO_2 generation in the presence of dissolution medium (0.1N HCl). The gas generated is trapped and protected within the

hydrocolloid gel, formed by hydration of the polymer, thus decreasing the density of the tablet. As the density of the tablet reduces below 1 g/cc, the tablet becomes buoyant. Whitehead et al. have demonstrated good correlation between in vitro and in vivo buoyancy of floating dosage forms [31]. The effect of different gas generating agent viz. sodium bicarbonate, sodium carbonate, potassium carbonate and calcium carbonate was studied and among which sodium bicarbonate exhibited least floating lag time, thus, was used in further studies. Effect of concentration of sodium bicarbonate on floating lag time was studied and the results depicted that as the amount of sodium bicarbonate increases, the floating lag time decreases. Thus, sodium bicarbonate (~60 mg per tablet) was essential to achieve optimum in vitro buoyancy.

In Vitro Dissolution Studies

Among the batches A5 to A8 the batch A5 containing sodium bicarbonate gave least floating lag time. Since the HPMC K100 M alone could not able to release the drug in a sustained manner. Thus, batches A12-A16 were prepared using release retarding ingredients stearic acid and carbopol. However, stearic acid was not sufficient to retard the release of MTF due to high solubility of drug while batches A15 and A16 with carbopol showed considerable retarding effect. Among the two grades of carbopol i.e. 934 P and 940 P the Carbopol 940 P (Batch A16) exhibited the better retardation of drug release (Figure 1). Thus, an experimental design i.e. central composite design was applied for systematic optimization.

The pharmacokinetic parameters of metformin hydrochloride utilized for the calculation of theoretical drug release profile for 12 hr dosage form were bioavailability 55 %, Therapeutic concentration (0.59-1.30 mg/ml), Volume of distribution (1-4 l/kg), Half-life (2.75 hr), Clearance (500-750 ml/min) [32]. The pharmacokinetic advantage relies on the fact that initial drug release from the tablet leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining matrix. [33] The immediate release part for sustained release Metformin hydrochloride was calculated using following equation and was found to be 120.27 mg.

$$\text{Immediate release part} = (C_{ss} * V_d)/F \quad \ldots\ldots\ldots\ldots \quad (1)$$

Where, C_{ss} is steady state plasma concentration, V_d is volume of distribution and F is fraction bioavailable. The total dose of Metformin hydrochloride required for 12 hr. release profiles is calculated by the equation.

$$\text{Dose} = \text{Immediate release part } [1+(0.693 * t/t_{1/2})] \ldots. \quad (2)$$

Where, t is time up to which sustained release is required and $t_{1/2}$ is half-life of the drug.

Dose =120.27 [1+(0.693*12/2.75)] = 485 mg (~500 mg)

Hence, the formulation should release 120.27 mg (24.054%) of drug in 1 hour like conventional tablets and 34.52 mg (6.90%) per hour up to 12 hr. thereafter. The theoretical dissolution profile was compared with the dissolution profiles of the batches of CCD for calculation of similarity factor (f2). The values are shown in Table 2.

Central Composite Design

A 3^2 central composite design was constructed to study the effect of the amount of HPMC K100 M (X1) and the amount of carbopol (X2) on the drug release from gastroretentive MTF tablets. The dependent variables chosen were floating lag time, time required for 50% (t_{50}) and 80% (t_{80}) drug dissolution.

A statistical model shown below incorporating interactive and polynomial terms was utilized to evaluate the response.

$$Y = b0 + b1X1 + b2X2 + b12X1X2 + b11X1^2 + b22X2^2 \ldots \quad (3)$$

where Y is the dependent variable, b_0 is the arithmetic mean response of the 13 runs, and bi is the estimated coefficient for the factor Xi. The main effects ($X1$ and $X2$) represent the average result of changing one factor at a time from its low to high value. The interaction terms ($X1$ and $X2$) show how the response changes when 2 factors are changed simultaneously.

The polynomial terms ($X1^2$ and $X2^2$) are included to investigate nonlinearity. The statistical analysis of the central composite design batches was performed by multiple linear regression analysis using Microsoft Excel. The t_{50}, t_{80}, and floating lag time values for the 13 batches (F1 to F13) showed a wide variation; the results are shown in Table 2. The data clearly indicates the values of t_{50}, t_{80}, and floating lag time are strongly dependent on the independent variables.

The fitted equation relating the response floating lag time to the transformed factors is shown in Eq. 4.

$$\text{Floating lag time} = 1.99 + 2.18X1 + 0.12X2 + 0.25X1X2 + 1.06X1^2 + 0.06X2^2 \ldots\ldots\ldots\ldots \quad (4)$$

The floating lag time for the 13 batches show a variation, that is, the response ranged from a minimum 1 min to a maximum of 7 min. The data clearly indicates that the floating lag time is dependent on the independent factors selected in the study. The value of correlation co-efficient r^2 was found to be 0.994, indicating a good fit. Equation 4 can be used to draw conclusions after considering the magnitude of the coefficient and the mathematical sign it carries (i.e., positive or negative). It may be concluded that at higher levels of X1 (amount of HPMC) and X2 (amount of Carbopol) the floating lag time increases. The level X2 shows less significant effect than X1 on the floating lag time.

Based on above results of calculating kinetics of drug release the t_{50} and t_{80} values were calculated, which showed wide variation among all the thirteen batches of CCD. The fitted equations relating the responses, t_{50} and t_{80} to the transformed factor are shown in Equation 5 and Equation 6, respectively. For t_{50} response ranged from a minimum 158 min to a maximum of 552 min, while for t_{80}, it ranged from 380 min to maximum 1132 min.

The value of correlation co-efficient (r^2) was found to be 0.9963 and 0.9969 for t_{50} and t_{80}, respectively, indicating a good fit.

$$t_{50} = 335.22 + 154.37\ X1 + 10.48\ X2 + 3.25\ X1X2 + 2.77\ X1^2 - 4.51\ X2^2 \ldots\ldots\ldots\ldots \quad (5)$$

$$t_{80} = 711.04 + 277.36\ X1 + 14.33\ X2 + 6.0\ X1X2 + 17.54\ X1^2 - 6.59\ X2^2 \ldots\ldots\ldots\ldots \quad (6)$$

Equation 4 and 5 may be used to obtain reasonable estimates of the response since small error of variance was noticed in the replicates

The values of the correlation coefficient indicate a good fit. Figures 2 and 3 show the response surface plot of the amount of HPMC K100 M (*X*1) and amount of carbopol (*X*2) versus t_{50} and t_{80}, respectively. The plot was drawn using Sigma Plot® software (Jandel Scientific Software, San Rafael, CA). The data demonstrates that both *X*1 and *X*2 affect the drug release (t_{50} and t_{80}). It may also be concluded that the high level of *X*1 (amount of HPMC K100 M) and the higher level of *X*2 (amount of carbopol) favor the preparation of gastro-retentive sustained release MTF HCl tablets. The high value of X1X2 coefficient also suggests that the interaction between *X*1 and *X*2 has a significant effect on t_{80}. It can be concluded that the drug release pattern may be changed by appropriate selection of the *X*1 and *X*2 levels.

The similarity factor, f2, given by Scale Up and Post Approval Changes (SUPAC) guidelines for modified release dosage form was used as a basis to compare dissolution profiles [34]. The dissolution profiles are considered to be similar when f2 is between 50 and 100. The method was first reported by Moore and Flanner [35]. On that basis, batches F7, F8 and F9-13 shown f2 values higher than 50. Thus, it fulfills the above criteria and this similarity is also reflected in t_{50} and t_{80} values.

Optimized batch was selected on the basis of the following criteria:

1. Floating lag time should be less than 10-15 min ensuring the tablet starts floating before gastric emptying.
2. Similarity factor to the theoretical release profile

All batches passed the criteria of floating lag time (considering the environment of the stomach and content) with floating lag time within 10-15 min. From the similarity factor, f2 values of batches F7, F8 & F9-13 (replicate batches) considered as promising batches as the f2 value are more than 50.

In Vitro Buoyancy of Central Composite Design Batches

All the central composite design batches showed good in vitro buoyancy. The results of the in vitro buoyancy study of batch F9 are shown in Figure 4. The figure clearly indicates the floating lag time (2 minutes) of the MTF tablets and the floating and swelling tendency of the formulation. The tablet swelled radially and axially. The average radial diameter after 8 hours was 18 ± 0.3 mm, while the thickness was 7 ± 0.4 mm. The figure also indicates that the tablet remained buoyant for 8 hours, but the tablet actually floated throughout the entire study. The in vitro buoyancy study was also conducted at an elevated pH condition (~4.5). The floating tendency remained unaltered at higher pH.

Kinetics of Drug Release

The in-vitro dissolution data of central composite design batches F1 to F13 was fitted to zero-order, first-order, Higuchi, Hixson-Crowell, Korsemeyer and Peppas, and Weibull models. The method of Bamba et al. was adopted for deciding the most appropriate model [30]. The results of sum square of residuals (SSR) and sukservent F test were used to select the most appropriate model. The release profile of the batches of CCD, fitted best to the Korsemeyer and Peppas model and priority should be given to the model with the lowest SSR value. Thus, it may be concluded that drug release from gastro-retentive MTF HCl tablets is best explained by the Korsemeyer and Peppas model. The value of slope for the Korsemeyer and Peppas model is used to find out release type. For most batches, n values lies between 0.45 and 0.89 which represents drug released by diffusion of an anomalous.

CONCLUSION

The study involves the preparation of gastro-retentive tablets of MTF using an effervescent approach and combination of hydrophilic and hydrophobic polymers. The data reveals that the viscosity of gel forming polymer is a major factor affecting the release and floating properties of the GR-FDDS. The higher viscosity seems to inhibit the initial burst effect of metformin release from the GR-FDDS. The effervescent-based floating drug delivery was found to be a promising approach to achieve in vitro buoyancy. The addition of gel-forming polymer HPMC K100 M and gas-generating agent sodium bicarbonate were essential to achieve in vitro buoyancy. Drug release was retarded by incorporation of carbopol 940P in the formulation thus imparting sustained release property. A systematic study using a 3^2 central composite design revealed that the amount of HPMC K100 M and carbopol 940P had a significant effect on t_{50}, t_{80}, and floating lag time. Thus, by selecting a suitable composition of HPMC K100 M and carbopol 940P, the desired dissolution profile can be achieved. The X-ray studies showed that the tablet was intact and remained floated in the gastric content up to 6 hr of administration.

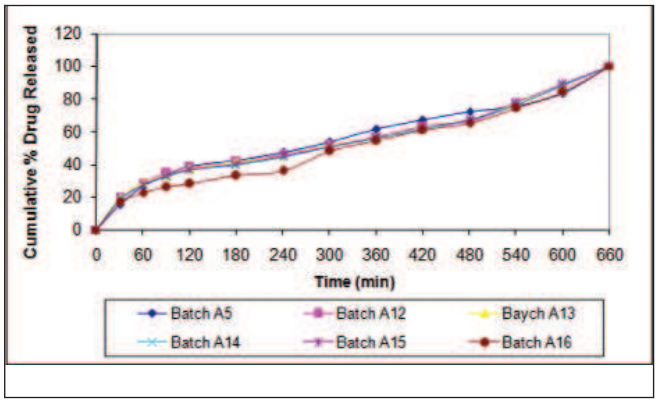

Fig. 1. In vitro release profiles of preliminary batches

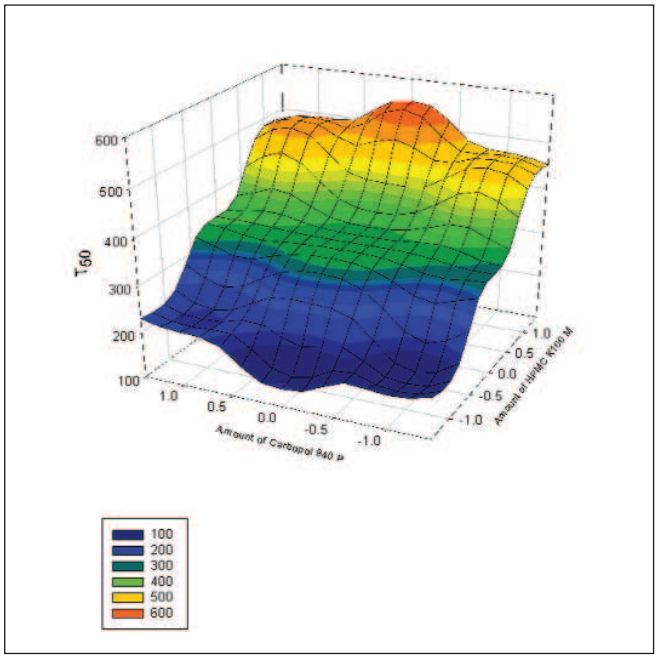

Fig. 2. Response surface plot for t_{50}.

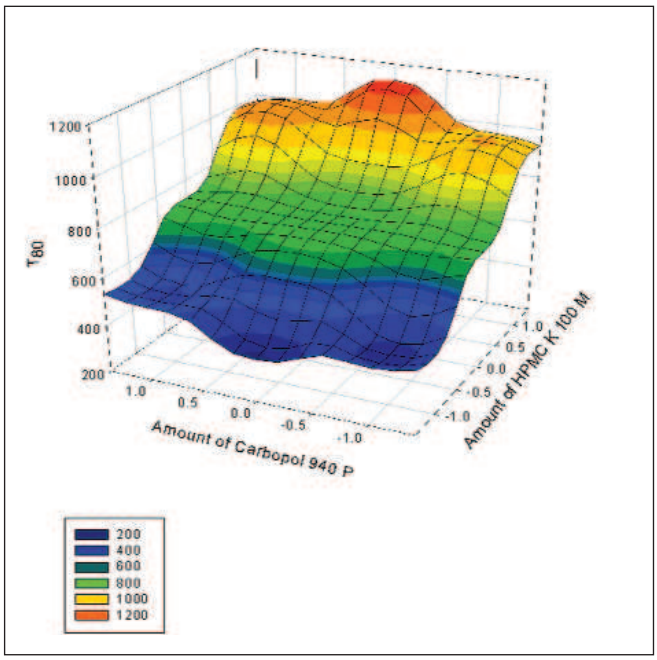

Fig. 3. Response surface plot for t_{80}.

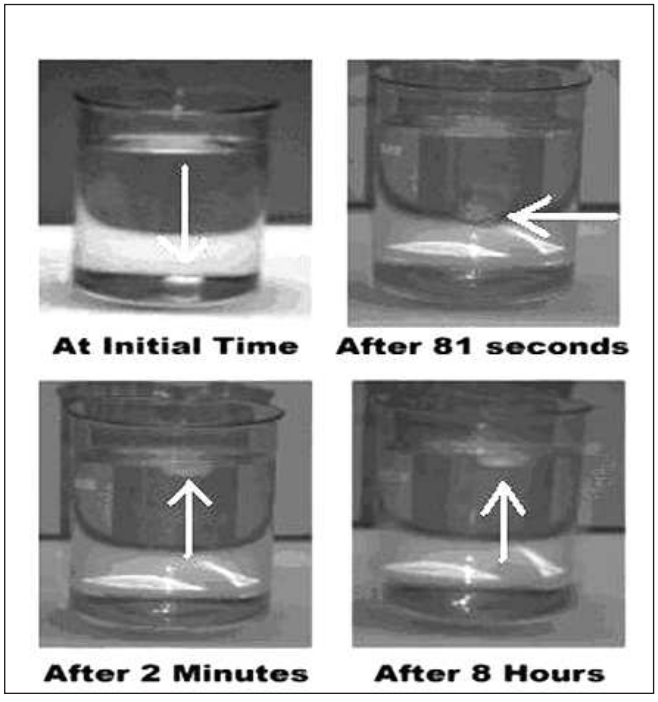

Fig. 4. In vitro buoyancy study of batch F9.

Apstrakt

Cilj ovog istraživanja je bila priprema gastro-retencionog sistema za primenu metformin hidrohlorida koga tanko crevo parcijalno apsorbuje zbog uskog prozora apsorpcije. Pristup je zasnovan na razvoju efervescentne formulacije. Kao agens za generisanje gasa korišćen je natrijum bikarbonat. Istraživani su uticaji količine hidroksipropilmetilceluloze HPMC i karbopola na profil oslobađanja leka i njegova flotirajuća svojstva. Dodavanje karbopola smanjuje rastvorljivost leka zbog njegovog svojstva slabog preuzimanja vode. Za sistematsku optimizaciju oslobađanja leka. primenjen je centralno kompozitni dizajn. Sadržaj HPMC (X1) i karbopola (X2) su određene kao nezavisne promenljive veličine. Vreme potrebno za 50% (t_{50}) i 80% (t_{80}) rastvaranja leka i in-vivo flotacija odabrane su kao zavisne promenljive veličine. Rezultati centralno kompozitnog dizajna ukazuju da količina HPMC favorizuje produženo oslobađanje metformin hidrohlorida iz gastro– retencione formulacije. Teorijski profil rastvorljivosti je generisan upotrebom farmakokinetskih parametara metformin hidrohlorida. Faktor sličnosti f2 je primenjen u cilju poređenja serija centralno kompozitnog dizajna i teorijskog profila rastvorljivosti. Serije F7, F8 i F9-13 (ponovljene serije) su obećavajuće pošto su vrednosti faktora f2 bile veće od 50.
Studije X-ray u uslovima in-vivo pokazale su da je tableta ostala intaktna i flotirajuća u gastričnom sadržaju više od 6 sati nakon primene.

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