ORIGINAL ARTICLE

Formulation development and optimization of sustained release matrix tablet of Itopride HCl by response surface methodology and its evaluation of release kinetics

Anirbandeep Bose [a,b,*], **Tin Wui Wong** [a,b], **Navjot Singh** [c]

[a] *Particle Design Research Group, Universiti Teknologi MARA, 42300 Puncak Alam, Selangor, Malaysia*
[b] *Non-Destructive Biomedical and Pharmaceutical Research Centre, Universiti Teknologi MARA, 42300 Puncak Alam, Selangor, Malaysia*
[c] *NRI Institute of Pharmacy, Bhopal 462021, India*

Abstract   The objective of this present investigation was to develop and formulate sustained release (SR) matrix tablets of Itopride HCl, by using different polymer combinations and fillers, to optimize by Central Composite Design response surface methodology for different drug release variables and to evaluate drug release pattern of the optimized product. Sustained release matrix tablets of various combinations were prepared with cellulose-based polymers: hydroxy propyl methyl cellulose (HPMC) and polyvinyl pyrolidine (pvp) and lactose as fillers. Study of pre-compression and post-compression parameters facilitated the screening of a formulation with best characteristics that underwent here optimization study by response surface methodology (Central Composite Design). The optimized tablet was further subjected to scanning electron microscopy to reveal its release pattern. The in vitro study revealed that combining of HPMC K100M (24.65 MG) with pvp(20 mg) and use of LACTOSE as filler sustained the action more than 12 h. The developed sustained release matrix tablet of improved efficacy can perform therapeutically better than a conventional tablet.

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* Corresponding author at: Particle Design Research Group, Universiti Teknologi MARA, 42300 Puncak Alam, Selangor, Malaysia; Non-Destructive Biomedical and Pharmaceutical Research Centre, Universiti Teknologi MARA, 42300 Puncak Alam, Selangor, Malaysia.
  E-mail address: anirbandeep@gmail.com (A. Bose).

1. Introduction

Matrix tablet is one of the most convenient approaches for the preparation of the sustained release dosage forms. In actual practice direct compression of drug, retardant material, additives is done to form a tablet in which drug particles are embedded in the matrix core of the retardant. Dry or wet granulation technique may also be employed for the preparation of

this type of tablets. Among the different strategies to prolong the drug action, formulation of matrix tablet has gained immense popularity now a days because it has the advantage of simple processing and a low cost of fabrication (Reddy et al., 2003).The loading dose is most convenient to include in a separate layer or in a coating applied to the tablet. An equation was developed by Higuchi (1961, 1963) to explain the drug release from the matrix base, which was later on extrapolated to the diffusion of solid drug dispersed in homogenous polymer matrices. Sustained release matrix tablet can be prepared in two ways, one is direct compression of the powder blend containing the drug, polymer and other additives, and another one involves granulation prior to compression. Selection of the proper method depends on the properties of the drug, polymer and other ingredients.

There are three primary mechanisms by which active agents can be released from a delivery system: diffusion, degradation, and swelling followed by diffusion. Any or all of these mechanisms may occur in a given release system. Diffusion occurs when a drug or other active agent passes through the polymer that forms the controlled-release device. The diffusion can occur on a macroscopic scale as through pores in the polymer matrix or on a molecular level, by passing between polymer chains.

Development of a sustained release tablet dosage form is based on many statistical experiments which are recognized as useful techniques to design an optimized formulation with an appropriate dissolution rate in a short time period and a minimum number of trials. For this reason, a computer based optimization technique with a response surface methodology (RSM) utilizing a polynomial equation and artificial neural network (ANN) has been widely used (Ghosh et al., 2008; Mandal et al., 2007; Nazzal et al., 2002; Hamed and Sakr, 2001; Fassihi and Ritschel, 1993; Takayama et al., 2003; Sastry and Khan, 1998; Huang et al., 2004; Bozic et al., 1997). Different types of screening designs have been used for preformulation evaluation. On oral administration, Itopride is rapidly and extensively absorbed and peak serum concentrations are achieved within 35 min after oral dosing. Thus it has a rapid onset of action, unlike cisapride and mosapride, which take around 60 min to reach peak plasma concentrations . The half life of Itopride is about 6 h (Banka, 2003). It is excreted mainly by the kidneys as metabolites and unchanged drug. Due to its short half life it is excellent for the formulation of matrix tablet sustained release formulation.

2. Materials and methods

2.1. Materials

2.1.1. Materials used in the preparation 50 mg Itopride SR

I) Itopride HCl:	Provided by Theon Pharmaceuticals Pvt. Ltd., HP
III) HPMC K100 M/K15M/K4M:	Provided by Stadmed Pvt. Ltd., Kolkata
IV) PVPK 30:	-Do-
VI) Talcum powder:	-Do-
IX) Magnesium stearate:	-Do-
X) Lactose:	-Do-
XII) Isopropyl alcohol:	Merck, Germany.

2.2. Development of sustained release formulation of Itopride 50 mg

The most effective method of modulating drug release is to include it in a matrix system. The matrix tablet was prepared via wet granulation method. Many polymers have been used in the formulation of matrix based controlled released drug delivery system. Reports are found on the use of hydrophilic polymers like HPMC for the preparation of SR formulation of different drugs. Different viscosity grades of polymers are widely used for designing oral controlled drug delivery system because their flexibility to provide a desired drug release profile and cost effectiveness and broad regulatory acceptance. However, the use of hydrophilic matrix alone for extending drug release for the highly water soluble drug is restricted due to rapid diffusion of dissolved drug through the hydrophilic gel network, for such drug inclusion of the binder like PVP K30 becomes essential in the matrix systems. Hence, in the present work, an attempt has been made to formulate the extended release matrix tablets of Itopride using different ratios of three different viscosity grades of HPMC polymer with and without binder (PVP K30). Fourteen formulations of Itopride was developed as shown in Table 1 . The granules were formulated according to wet granulation method .All the raw drugs and excipients were passed through a 40 mesh size sieve separately. Active drugs, the polymers and lactose were mixed thoroughly. The PVP K30 paste was formed using granulating fluid IPA .The PVP paste was thoroughly mixed with the mixture of drugs and polymers. The mixing product was passed through the 20 mesh size sieve. The granules were dried at 40 °C in an oven dryer for 30 min .The granules thus formed were also passed through a 18 mesh size sieve. The granules were then mixed with lubricating agent talcum and magnesium state before final compression.

2.3. Micromeritic properties of granules for 50 mg Itopride HCl SR formulation

2.3.1. Angle of repose
Angle f repose can be determined by the fixed funnel and free standing cone methods, the method employed a funnel that was secured with its tip at a given height, H above the graph paper that was placed on a flat horizontal surface. Powder or granules were carefully poured through the funnel until the apex at the conical pile just touched the tip of the funnel .Thus, with R being the radius of the base of the conical pile $\tan \infty = H/R$. Where, H and R are the height and radius of the powder cone.

2.3.2. Bulk density of Itopride HCl granules
The term bulk density refers to a measure used to describe a packing of particles of granules. A quantity of 5 g powder for each formulation, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed the cylinder was allowed to fall under its own weight onto a hard surface from a height of 25 cm at 2 s intervals.

The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formula:

Table 1 Composition of 14 Itopride formulations with different ratios and different grades of HPMC polymer.

Composition	Formulation code													
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
Itopride HCl	50	50	50	50	50	50	50	50	50	50	50	50	50	50
HPMCK100M	0	0	0	0	30	30	0	0	15	15	15	15	10	10
HPMC K 15M	0	0	30	30	0	0	15	15	15	15	0	0	10	10
HPMC K 4M	30	30	0	0	0	0	15	15	0	0	15	15	10	10
PVP K30	0	30	0	30	0	30	0	30	0	30	0	30	0	30
Lactose	110	80	110	80	110	80	110	80	110	80	110	80	110	80
Talcum	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5	5	5
IPA	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml
Total	200	200	200	200	200	200	200	200	200	200	200	200	200	200

LBD = Weight of the powder/volume of the packing
TBD = Weight of the powder/tapped volume of the packing

2.3.3. Compressibility index for sustained release Granulation
The compressibility was calculated by Carr's compressibility index caution and wells, 1088.

$$Carr's\ index(\%) = [(TBD - LBD) \times 100]/TBD$$

2.3.4. Total porosity of granules for 50 mg Itopride HCl SR matrix tablet
Total porosity was determined by measuring the volume occupied by a selected weight of a powder (V_{bulk}) and the true volume of granules (the space occupied by the powder exclusive of spaces greater than the intermolecular space, V):

$$Porosity(\%) = V_{bulk} - V/V_{bulk} \times 100$$

2.4. Tablet compression and Characterization of the compressed tablet

Granules of both SR layers were prepared separately and dried. These dried granules were lubricated separately with talc and Mg-stearate. Two hundred milligrams of Itopride HCl SR granules per each tablet was taken and compressed on a 10 station lab press compression machine (CIP Machineries Pvt. Ltd., Ahmedabad) using D tooling concave punches.

2.5. Physical properties of sustained release tablets

The tablets were characterized immediately after the formulation. The weight variation of the 20 tablets was accomplished according to guidelines mentioned in I.P. 1996 using an electronic balance. Friability of 10 tablets was evaluated by Roche type friabilator for 4 min at the rate of 25 rpm. For each formulation the hardness of 10 tablets was evaluated using Monsanto hardness tester (chambell electronics, India). The thickness of the 10 tablets was measured by electronic Vernier caliper (mitutoyo) japan. As the formulations one sustained release matrix tablet so there is no scope for disintegration test.

2.6. Assay of Itopride HCl matrix tablet

Twenty tablets of the sustained formulation were crushed into a fine powder by mortar and pestle, 100 mg of the crushed powders was weighed in 100 ml volumetric and diluted in a flask with methanol. After sonication for 15 min the diluted solution was filtered. The total amount of drug for each tablet was analyzed. After the proper dilution of test solution by using the HPLC method as described in the section against the reference solution of pure drug powder prepared in the same procedure. As we have chosen the HPLC so there is no chance of detection of any degradation products.

2.7. Dissolution study of matrix tablet

Drug release of individually six tablets were measured using USP 1 (basket type) apparatus (Electrolab, TDPOGP, USPxxiii) using media of 900 ml 0.1 (N) HCl for first 2 h and the rest of hours at pH 6.8 phosphate buffer. The dissolution media were maintained at a temp of 37 °C. The sample was withdrawn at the internal of 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 h according to preprogrammed manner. At every withdrawal the sample was replaced with 5 ml of fresh media. All the solutions of samples were analyzed by using high performance liquid chromatography (HPLC) method as described later.

2.8. Optimization of sustained release formulation by response surface methodology (RSM)

2.8.1. Experimental design
The optimization of Sustained release formulation of both Itopride HCl was done by using the design expert software (Design Expert trial version 7.0.3 State Inc, Minneapolis, MN). A central composite design (CCD) with α = 1 was employed as per the standard protocol Based on preformulation study the amounts of HPMC K 100M (X_1) and PVP K30 (X_2) were selected as the independent factors, studied at three levels each. The central point (0, 0) was studied in quintuplicate. All other formulation and processing variables were kept invariant throughout the study. Table 2 summarizes an account of the 13 experimental runs studied, their factor combinations, and the translation of the coded levels to the experimental units employed during the study. % of drug released in 1 h (rel$_{1\ h}$) (Y_1), % of drug released in 8 h (rel$_{8\ h}$)

(Y_2), time to 50% drug release ($t_{50\%}$) (Y_3) were taken as the response variables.

2.8.2. Data analysis and validation of optimization model for matrix tablet

Various RSM computations for the current optimization study were performed employing Design Expert software (Design Expert trial version 7.0.3 State-Ease Inc, Minneapolis, MN). Polynomial models including interaction and quadratic terms were generated for all the response variables using multiple linear regression analysis (MLRA) approach. The general form of the MLRA model is represented as the following equation:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2 + \beta_6 X_1 X_2^2 + \beta_7 X_1^2 X_2$$

here, β_0 is the intercept representing the arithmetic average of all quantitative outcomes of 13 runs; β_1 to β_7 are the coefficients computed from the observed experimental response values of Y; and X_1 and X_2 are the coded levels of the independent variable(s). The terms $X_1 X_2$ and X_i^2 ($i = 1$–2) represent the interaction and quadratic terms, respectively. Statistical validity of the polynomials was established on the basis of ANOVA provision in the Design expert Software. Subsequently, the feasibility and grid searches were performed to locate the composition of optimum formulations (Singh and Ahuja, 2002; 2004) Three-dimensional (3D) response surface plots and two dimensional (2-D) contour plots were constructed based on the model polynomial functions using Design Expert software. These plots are very useful to see interaction effects on the factors on the responses. Seven optimum checkpoints for Itopride were selected by intensive grid search, performed over the entire experimental domain, to validate the chosen experimental design and polynomial equations. The formulations corresponding to these checkpoints were prepared and evaluated for various response properties. Subsequently, the resultant experimental data of response properties were quantitatively compared with those of their predicted values. Also, linear regression plots between observed and predicted values of the response properties were drawn using MS-Excel, forcing the line through origin.

2.9. Computation of release kinetics of 50 mg Itopride HCl matrix tablet

To study the mechanism of drug release from the optimized formulation of matrix tablets, the release data were fitted to the following equations:

Zero-order equation : $Q_t = Q_0 + k_0 t$

Where, Q_t is the amount of drug release in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and k_0 is the zero order release rate.

First-order equation : $\ln Q_t = \ln Q_0 + k_1 t$

Where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution and k_1 is the first order release rate constant.

Higuchi's equation : $Q = k_H t^{1/2}$

Where, Q is the amount of drug release at time t, and k_H is the Higuchi diffusion rate constant.

Korsmeyer et al.'s equation (16) : $M_t/M_\infty = Kt^n$

Where, M_t is the amount of drug released at time t, M_∞ is the amount of drug released after infinite time, and k is a kinetic constant incorporating structural and geometric characteristics of the tablet and n is the diffusion exponent indicative of the drug release mechanism. The mechanism of drug release was dependent on the value of 'n'.

2.10. Surface topography of bi-layer matrix tablet by scanning electron microscope (SEM)

Scanning electron microscopy (SEM) is a commonly used technique to examine the surface morphology of tablets and to visually support other qualitative and quantitative results (Korsemeyer et al., 1983; Porter and Saraceni, 1988; Poukavoos and Peck, 1993; Lehtola et al., 1995; Felton and Mcginty, 1996). In scanning electron microscope as electrons are employed, a vacuum is maintained inside the microscope column to keep free of air molecules. Generally the column is maintained at a vacuum of about 10 torr. Now when a narrow beam of primary electrons are generated from the electron gun and hits the specimen surface then secondary electrons are emitted from the spot. The yield of the secondary electron depends on the angle between the direction of primary electrons and the specimen surface. A flat surface produces a minimum number of secondary electrons. If the beam is moved to another spot, there also the yields of secondary electrons would depend upon the topographical features of that region and maybe more or less than that of the first spot. Thus, continuous moving or scanning the electron beam over the specimen surface achieves a corresponding signal output. If the secondary electrons are also continuously collected and displayed on a cathode ray tube (CRT), an image appears which is comparable to the topographical detail of the specimen. The SEM study was carried out for SR layer of formulated bi-layer matrix tablet to check the surface texture of the same. A smooth surface gives a uniform drug release

Table 2 Formulation trials of 50 mg Itopride HCl sr matrix tablet as per experimental design.

Trial No.	Coded factor levels	
	X_1	X_2
I	−1	−1
II	−1	0
III	−1	1
IV	0	−1
V	0	0
VI	0	1
VII	1	−1
VIII	1	0
IX	1	1
X	0	0
XI	0	0
XII	0	0
XIII	0	0
Translation of coded levels in actual units		
Coded level for Domperidone	−1	0	1
X_1: HPMC K 100M (mg)	5	10	15
X_2: PVP K30 (mg)	5	10	15
Coded level for Itopride HCl	−1	0	1
X_1: HPMC K 100M (mg)	20	30	40
X_2: PVP K30 (mg)	20	30	40

whereas uneven or cracked surface gives an uncontrolled and non-uniform drug release. The study was carried out by JEOL/JSM/5200.

3. Results and discussion

3.1. Micromeritic properties of granules

Matrix tablets were formulated according to wet granulation method as described in Section 2. Granulation (Table 3) is the key process in the production of matrix tablet sustained release dosage form. The properties of granules which should be evaluated to ensure the proper formulation of the tablet dosage form are an important aspect in matrix tablet formulation.

3.2. Physical properties of matrix tablet

All the formulated tablets containing the active drugs were evaluated to find the physical properties like hardness, thickness, friability and drug contents (Table 4). In a weight variation test, the pharmacopeial limit of percentage deviation for tablets whose weight is more than 250 mg is ± 5%. The average percentage deviation of all the tablets was found within the limit which was less than 1%. Hardness of the tablets was

found acceptable and uniform from batch to batch variation. The drug content was also found uniform and within the prescribed limit.

3.3. Dissolution study of 50 mg Itopride HCl SR matrix tablet

3.3.1. Chromatographic analysis
Dissolution samples were analyzed by HPLC-UV method described in Section 2. Fig. 1 shows the representative chromatogram of a dissolution sample showing separation of Itopride HCl and Domperidone (internal standard) at 2.077 and 4.167, respectively.

3.3.2. In vitro release of Itopride from SR matrix tablet
Mean cumulative % release of Itopride at different time intervals are shown in Fig. 2. The dissolution profile for both the formulations was found to be different from batch to batch. But the formulation of f6 was found to be the most desired release profile for the formulation. The release of formula f6 was most consistent, accurate and complete. After the evaluation of dissolution study it can be concluded that the F6 formulation for the matrix tablet containing HPMC K 100 with PVP K30 possesses excellent drug release kinetics. The formulation of F6 also possesses good micromeritic and physical properties. The f6 formulation was selected for further experiment.

Table 3 Micromeretic properties of granules for different trial formulation of Itopride 50 mg SR matrix tablet.

Formulation trial	Angle of repose	Loose bulk density (gm/ml)	Tapped bulk density (gm/ml)	Compressibility index (%)	Total porosity (%)
1	24.12 ± 0.08	0.42 ± 0.04	0.553 ± 0.10	15.08 ± 0.11	24.01 ± 0.14
2	25.12 ± 0.05	0.442 ± 0.1	0.532 ± 0.11	14.07 ± 0.04	23.09 ± 0.13
3	24.34 ± 0.18	0.412 ± 0.03	0.512 ± 0.09	12.06 ± 0.08	24.05 ± 0.23
4	24.23 ± 0.11	0.453 ± 0.04	0.522 ± 0.08	11.06 ± 0.11	22.02 ± 0.19
5	24.09 ± 0.05	0.432 ± 0.05	0.502 ± 0.14	14.00 ± 0.14	23.13 ± 0.21
6	24.33 ± 0.07	0.422 ± 0.02	0.512 ± 0.20	12.06 ± 0.07	27.21 ± 0.11
7	24.44 ± 0.11	0.411 ± 0.09	0.598 ± 0.09	13.11 ± 0.11	24.12 ± 0.12
8	22.98 ± 0.05	0.443 ± 0.04	0.532 ± 0.10	14.09 ± 0.09	26.09 ± 0.32
9	23.23 ± 0.06	0.422 ± 0.05	0.509 ± 0.08	13.23 ± 0.11	20.54 ± 0.25
10	24.45 ± 0.03	0.411 ± 0.07	0.522 ± 0.06	15.12 ± 0.15	26.32 ± 0.32
11	24.98 ± 0.11	0.422 ± 0.04	0.512 ± 0.14	14.08 ± 0.09	22.29 ± 0.21
12	23.98 ± 0.06	0.410 ± 0.08	0.533 ± 0.09	12.03 ± 0.08	21.19 ± 0.49
13	23.45 ± 0.18	0.397 ± 0.10	0.521 ± 0.07	11.04 ± 0.06	26.75 ± 0.20
14	23.12 ± 0.18	0.432 ± 0.04	0.512 ± 0.15	14.05 ± 0.11	25.09 ± 0.12

Table 4 Physical properties and drug content of Itopride 50 mg SR matrix tablet.

Trial No.	Friability (%)	Hardness (kg/cm^2)	Thickness (mm)	Drug content (%)
	Itopride	Itopride	Itopride	Itopride
0	0.48 ± 0.12	5.2 ± 0.12	4.5 ± 0.15	98.03 ± 0.12
1	0.53 ± .12	4.3 ± 0.04	4.4 ± 0.12	97.09 ± 0.12
2	0.41 ± 0.02	5.2 ± 0.03	4.6 ± 0.08	97.07 ± 0.03
4	0.43 ± 0.05	5.3 ± 0.08	4.4 ± 0.16	98.03 ± 0.12
6	0.61 ± 0.11	4.3 ± 0.06	4.4 ± 0.09	97.09 ± 0.12
8	0.55 ± 0.04	4.3 ± 0.12	4.6 ± 0.28	94.03 ± 0.12
10	0.41 ± 0.12	5.3 ± 0.11	4.4 ± 0.15	95.09 ± 0.12
12	0.43 ± 0.11	5.3 ± 0.09	4.3 ± 0.15	97.03 ± 0.12
13	0.48 ± 0.12	5.1 ± 0.12	4.4 ± 0.17	98.09 ± 0.12
14	0.53 ± 0.02	5.1 ± 0.07	4.6 ± 0.13	99.12 ± 0.12

Now the objective of our study is to evaluate the effect of independent factors i.e. PVP K30 and HPMC on different response variables. And then to find the ratio of two independent variables in that formulation which will possess our desired release kinetics.

3.4. RSM optimization results of Itopride HCl

For optimization of the Itopride formulation we had selected central composite design. In central composite design the three response variables and two independent variables were taken for Itopride 50 mg SR .The response variables are Release in 1 h, $t_{50\%}$ and Release in 8 h .The independent variables are
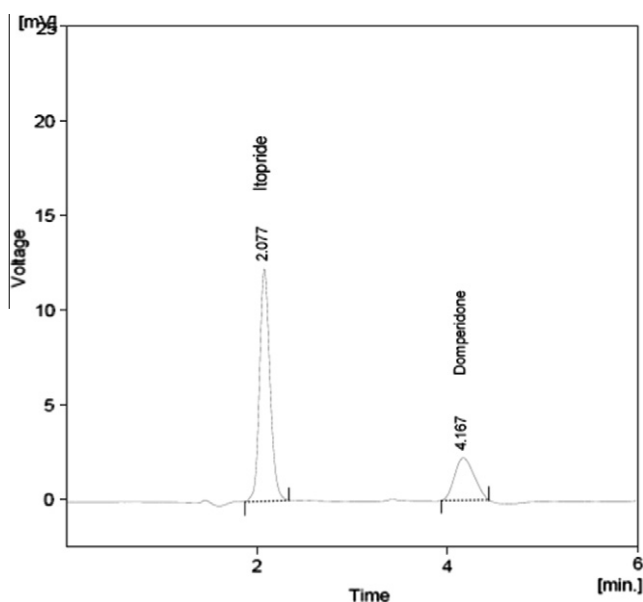

Figure 1 Representative chromatogram showing separation of Itopride at 2.077 and Domperidone at 3.09 min.
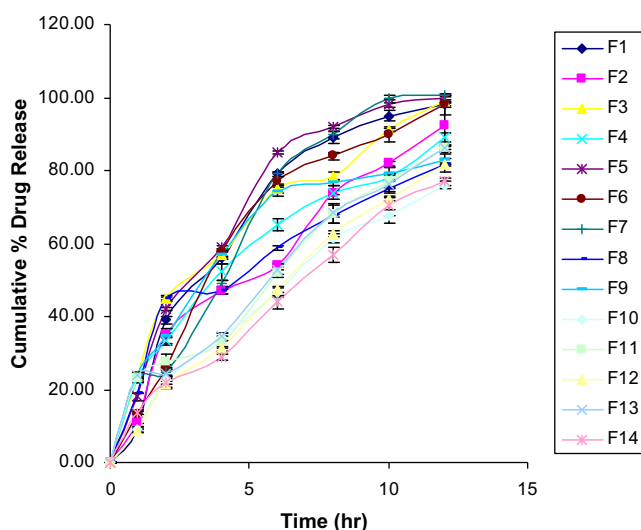

Figure 2 Mean cumulative % drug release profiles of Itopride HCl matrix formulations prepared as per the experimental design.

HPMC K100 (A) and PVP K30 (B) all the in vitro release kinetic properties of Itopride for 13 formulations are shown in Table 5. Three different concentrations of HPMC K100 and PVP K30 were used to evaluate different independent release kinetics.

3.4.1. Mathematical modeling of RSM optimization of Itopride HCl
Mathematical relationships in the form of polynomial equation for the measured response (Release in 1 h, $t_{50\%}$ and release in 8 h) were obtained with the stat-ease software. The polynomial equation relating the different response and independent variable is given below:

$$R1(\text{rel}_{1\,h}) = +10.93 - 1.43A + 0.17B + 1.46AB + 5.517\text{E}^{-003}\text{A}^2 - 0.054B^2$$

$$R2(t_{50}\%) = +5.30 + 0.66A + 0.057B - 0.19AB - 0.16A^2 + 0.26B^2$$

$$R3(rel_{8\,h}) = +0.80 - 0.041A - 0.083B + 0.060AB + 0.042A^2 + 0.048B^2$$

The above equation represents the quantitative effect of process variables and their interaction on the response. For estimation of the significance of the model, the analysis of variance (ANOVA) was determined as per the provision of design expert software as shown in Tables 6–8. Using 5% significance level, a model is considered significant if the p-value (significance probability value) is less then 0.05.

3.4.2. Response surface analysis (release in 1 h)
Figs. 3 and 4 represent the contour plot and three dimensional analysis for the studied response properties of release in 1 h. From the contour plot it can be concluded that the release in 1 h decreases with augmentation of both the variables. The response changes the variables in a nonlinear and descending manner. But the contour plot shows that HPMC has a completely greater influence on the response variables than PVP K30. From the contour plot it was evident that the declining trend was obtained with ascending order of HPMC. However very little effect was observed until the intermediate levels of PVP K30 were reached, after which a declining trend was observed at increasing the concentration of PVP K30.

3.4.3. Response surface analysis ($t_{50\%}$)
Figs. 5 and 6 demonstrate the relation of $t_{50\%}$ (Time to 50% drug release) with PVP K30 and HPMC. The effect of PVP and HPMC was found to be in an ascending manner i.e. increasing the amount of both increases the response. The effect of PVP was found to be little throughout different concentrations. The effects of HPMC were found to be linear at low concentrations but at high concentrations it shows non linear response. From the contour and 3D plot it is quite evident that HPMC has a comparatively grater influence on the response variables than PVP-K30.

3.4.4. Response surface analysis (release in 8 h)
Figs. 7 and 8 represent the contour plot and three dimensional analysis for the studied response properties of release in 8 h. From the contour plot it can be concluded that release in 8 h

Table 5 Response variables (R1–R3) obtained from various trial formulations of Itopride HCl 50 mg SR tablets[a].

Run	Factor 1 HPMC K100, mg (A)	PVP K30 (B)	Release at 1 h % (R1)	$t_{50\%}$ (R2)	Release at 8 h % (R3)
1	30.00	30.00	10.96	5.18	69.07
2	20.00	30.00	11.93	4.78	72.38
3	20.00	20.00	14.54	4.13	78.3
4	20.00	40.00	10.54	5.06	69.58
5	40.00	20.00	8.84	6.07	63.73
6	30.00	30.00	11.36	5.12	69.43
7	30.00	40.00	11.96	5.25	67.46
8	40.00	30.00	8.9	5.63	67.53
9	40.00	40.00	10.67	6.23	61.42
10	30.00	30.00	11.02	5.39	66.89
11	30.00	30.00	11.17	5.34	68.09
12	30.00	20.00	8.75	6	62.7
13	30.00	30.00	11.21	5.36	68.39

[a] A: HPMC K 100M; B: PVP K30; $rel_{1\ h}$: release in 1 h; $rel_{8\ h}$: release in 8 h; $t_{50\%}$: time to 50% drug release.

Table 6 ANOVA for response surface quadratic model for release in 1 h. Analysis of variance table [Partial sum of squares - Type III].

Source	Sum of squares	df	Mean square	F value	p-value Prob > F	
Model	21.01	5	4.20	3.74	< 0.0001	Significant
A	12.33	1	12.33	10.97	0.0129	
B-B	0.18	1	0.18	0.16	.7007	
AB	8.50	1	8.50	7.56	0.0285	
A^2	8.407E-005	1	8.407E-005	7.481E-005	0.9933	
B^2	8.198E-003	1	8.198E-003	7.295E-003	0.9343	
Residual	7.87	7	1.12			
Lack of fit	7.77	3	2.59	0.60	0.0003	
Pure error	0.10	4	0.025			
Cor total	28.8812	12				

Table 7 ANOVA for response surface quadratic model for $t_{50\%}$. Analysis of variance table [Partial sum of squares - Type III].

Source	Sum of squares	df	Mean square	F value	p-value Prob > F	
Model	2.98	5	0.60	5.19	0.0262	Significant
A-A	2.61	1	2.61	22.74		
B-B	0.019	1	0.019	0.17	0.6945	
AB	0.15	1	0.15	1.29	0.2935	
A^2	0.070	1	0.070	0.61	0.4595	
B^2	0.19	1	0.19	1.63	0.2426	
Residual	0.80	7	0.11			
Lack of fit	0.75	3	0.25	17.27	0.0094	
Pure error	0.058	4	0.014			
Cor total	3.78	12				

decreases with augmentation of both the variables. The response changes the variables in a linear and descending manner. But the contour plot shows that HPMC has a completely greater influence on the response variables than PVP-K30. From the contour plot it is evident that the declining trend obtained with ascending order of HPMC.

3.4.5. Optimization of the independent variables of Itopride HCl
This was the most important part of response surface methodology. The formulation of the drug which released the drug in

controlled and complete manner was selected for optimum formulation. The criteria for optimum formulation of Itopride HCl are given in Table 9.

3.4.6. Validation of RSM results of Itopride 50 mg SR
Response surface methodology gave us seven solutions where the results of the physical evaluation and tablets assay were found within limits. Table 10 lists the composition, their predicted and experimental values of all response variables and the percentage error. The formulation number T* 6 was
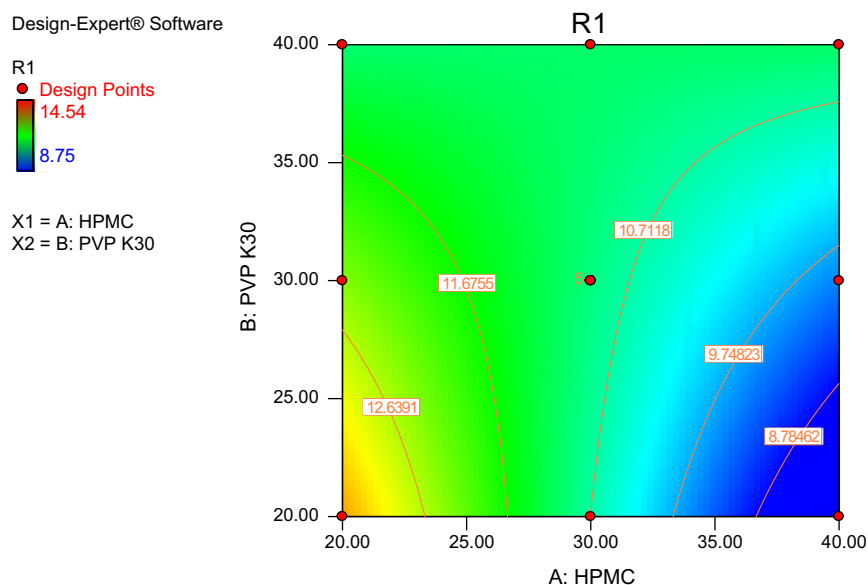
Figure 3 Contour plot showing the effect of the amount of polymer HPMC K 100M and binder (PVP K30) on drug release at 1 h from Itopride SR matrix tablet.
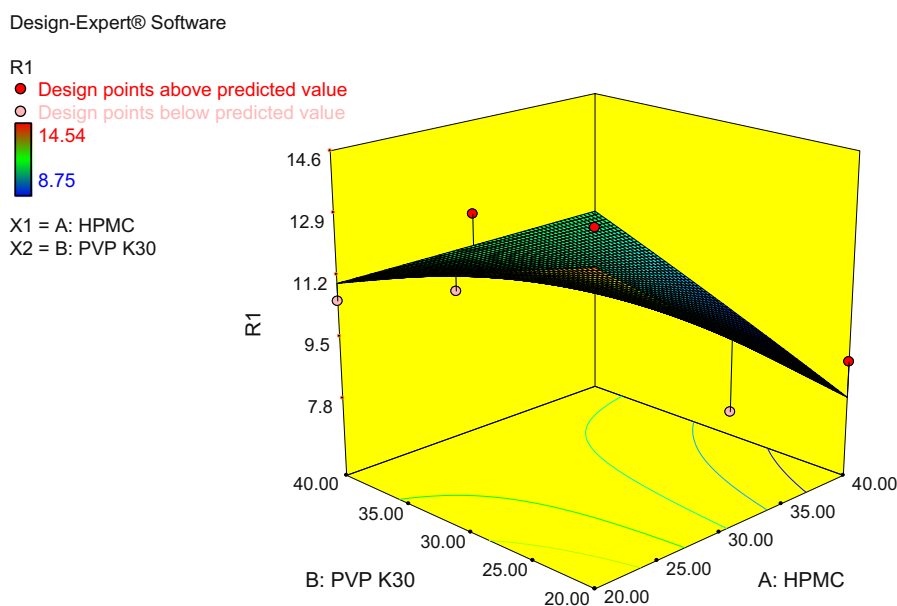

Figure 4 Response surface plot (A) showing the effect of the amount of polymer HPMC K 100M and binder (PVP K30) on drug release at 1 h from Itopride SR matrix tablet.

chosen as the best optimized formula for Itopride SR as the error was minimum for the response of the dependent variables. The composition of the formula is given below (Table 11).

3.5. Computation of release mechanism of Itopride HCl

The release data were evaluated by applying the equation of zero order, first order, Higuchi and Korsmeyer equation. The regression coefficient values of different release kinetic equations evaluated from the dissolution profile of developed formulation are compared in Table 12. It can be highly postu-

lated that in vitro release profile of all the matrix formulations could be best expressed by the Higuchi model. The plot showed high linearity in comparison to other release kinetic equations. Release of drug from the matrix tablet generally follows diffusion for water soluble drug and erosion or relaxation for water insoluble drug. Diffusion is related to transport drug from the dosage matrix into the in vitro study fluid depending on the concentration gradient between dosage form and in vitro fluid. As gradient varies, the drug is released and the distance for diffusion increases. This could explain why the drug diffuses at a comparatively slower rate. As the dissolution
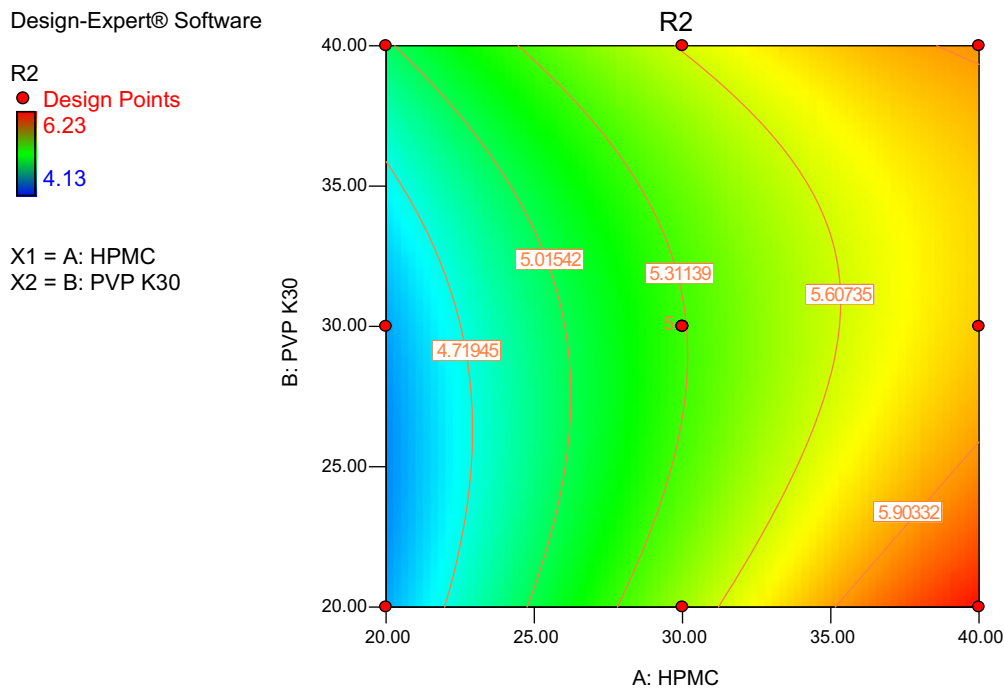
Figure 5 Contour plot showing the effect of the amount of polymer HPMC K 100M and binder (PVP K30) on $t_{50\%}$ from Itopride SR matrix tablet.
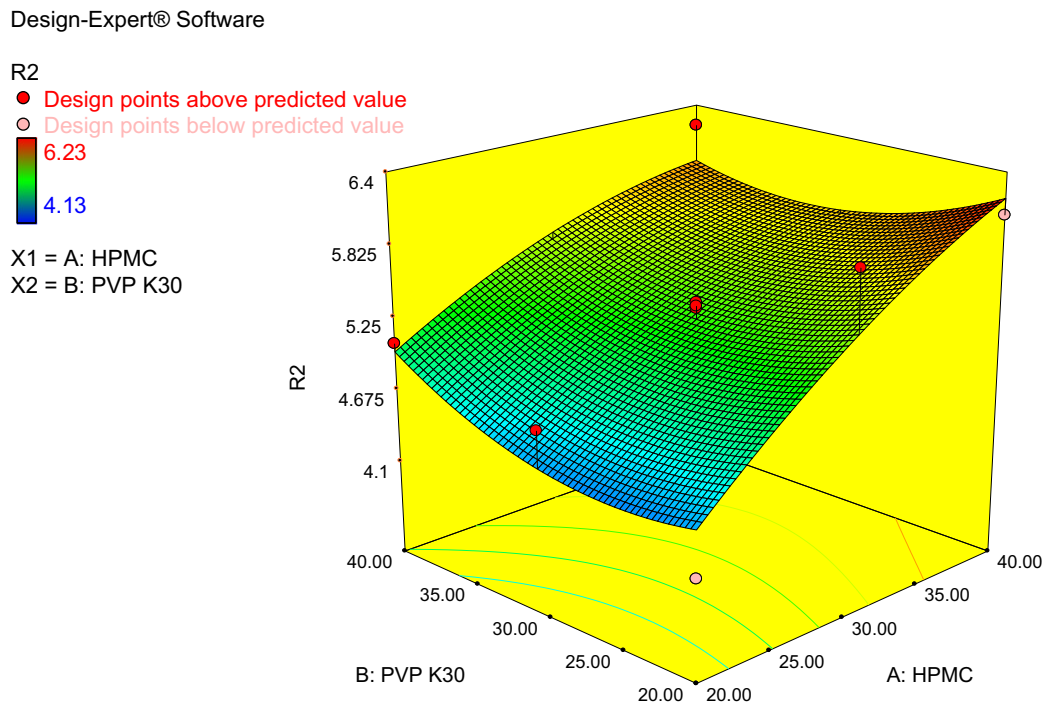

Figure 6 Response surface plot (A) showing the effect of the amount of polymer HPMC K 100M and binder (PVP K30) on drug release at $t_{50\%}$ from Domperidone SR.

time increases which is referred as square root kinetics or Higuchi kinetics. To confirm diffusional mechanism, the data were fitted into Korsmeyer et al.'s equation. For matrix tablet, n value 0.5 indicates diffusion controlled value to near 1.00 indi-

cates erosion. Intermediate value suggests simultaneous diffusion and erosion contribute to overall release mechanism. As the Itopride is water soluble drug diffusion is the main drug release mechanism.
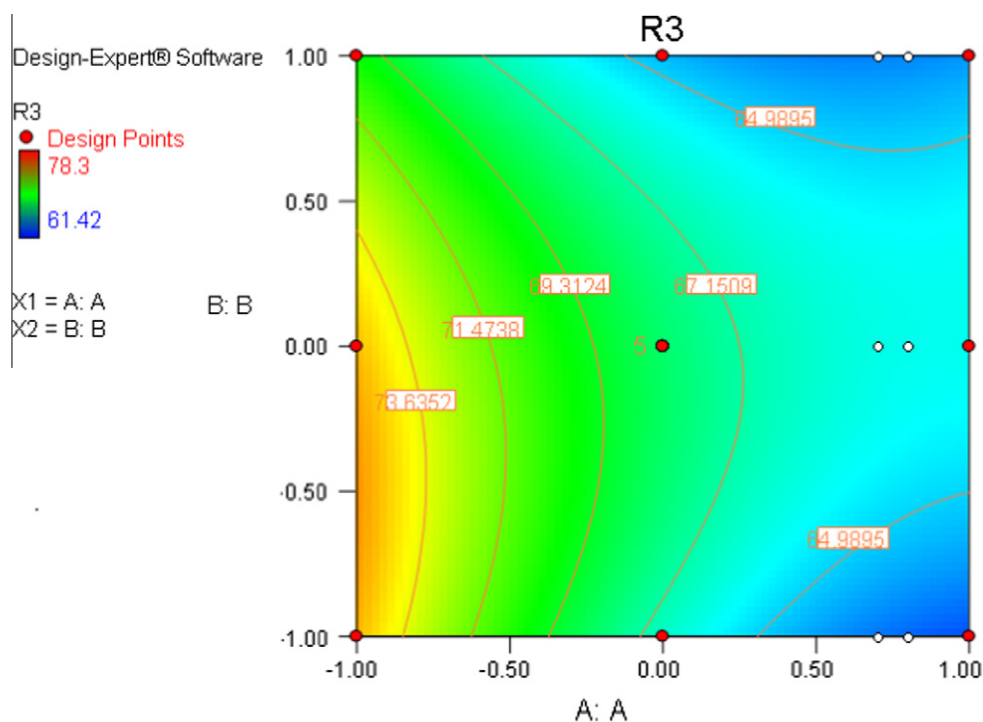
Figure 7 Contour plot showing the effect of the amount of polymer HPMC K 100M and binder (PVP-K30) on release in 8 h from Itopride SR matrix tablet.
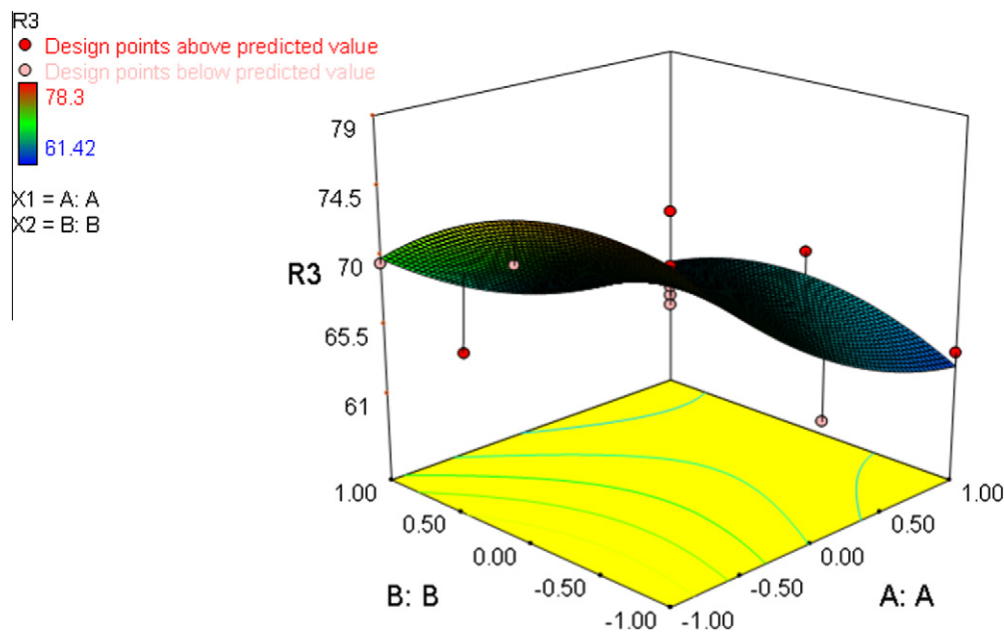

Figure 8 Response surface plot (A) showing the effect of the amount of polymer HPMC K 100M and binder (PVP K30) on drug release in 8 h from Itopride HCl SR matrix tablet.

3.6. Surface topography of bi-layer matrix tablet by scanning electron microscope (SEM)

Scanning electron microscopy (SEM) was performed to determine the surface topography of SR layer of matrix tab-

let. The SEM photographs of intact SR layer of Itopride after 1 h of dissolution study and after 4 h of dissolution study and after 8 h of dissolution study are given in Fig. 9. It showed intact surface only swells without any perforations, channels, or troughs. After dissolution, the solvent front en-

Table 8 Response R3 ANOVA for response surface quadratic model analysis of variance table [Partial sum of squares - Type III].

Source	Sum of squares	df	Mean square	F value	p-value Prob > F	
Model	167.43	5	33.49	4.26	0.0424	Significant
A-A	126.78	1	126.78	16.14	0.0051	
B-B	6.55	1	6.55	0.83	0.3914	
AB	10.27	1	10.27	1.31	0.2904	
A^2	15.28	1	15.28	1.94	0.2058	
B^2	17.58	1	17.58	2.24	0.1782	
Residual	54.98	7	7.85			
Lack of fit	51.10	3	17.03	1.55	0.0091	
Pure error	3.88	4	0.97			
Cor total	222.41	12				

Table 9 Release kinetics of optimum formulation.

Release property	Range
Release in 1st hour	12.2–14.54
Time for 50% release	5–6
Release in 8th hour	70–78.3

Table 11 Final optimized formulation of Itopride 50 mg SR layer.

Particulars	Amount (mg)
Itopride HCl	50
HPMC K100M	24.65
PVP K30	20
Talc	5
Magnesium stearate	5
Lactose	q.s.
IPA	1 ml
Total	200 mg

ters the matrix and moves slowly toward the center of the tablet. The drug diffuses out of the matrix after it comes in contact with dissolution medium. The images of the tablet showed a network in the swollen polymer through which the drug diffused to the surrounding medium. Thus, it was concluded that the drug was released from matrix by diffusion mechanism. During in-vitro dissolution study, the HPMC K100M swells as the dissolution media enter into the polymer matrix. The surface becomes smooth and uniform which results in a slower and controlled drug release. SEM study of Itopride matrix tablets further confirmed both diffusion and erosion mechanisms (Fig. 9) to be operative during drug release from the optimized batch of matrix tablet. SEM photomicrograph of the matrix tablet taken at different time intervals after the dissolution experiment showed that the matrix was intact and pores had formed throughout the matrix. SEM photomicrographs of tablet surface at different time intervals also showed that erosion of matrix increased with respect to time indicated by the photomicrographs at 2, 4 and 8 h revealing pores with increasing diameter. These photomicrograph also revealed the formation of gelling structure indicating the possibility of swelling of matrix tab-

lets (Fig. 9). Hence, the formation of both pores and gelling structure on tablet surface indicates the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of Itopride from formulated matrix tablets.

4. Conclusion

The sustained release matrix tablets of Itopride HCl formulation system includes the drug delivery system that achieves slow and extended release of the drug over an extended period of time. The response variables of the formulation are optimized by Response surface methodology(ccd design).The in vitro dissolution release kinetics and morphology of the matrix tablet analyzed by the SEM indicate the successful sustenance of the matrix tablet for several hours.

Table 10 Composition of the check point formulations, the predicted and experimental values of response variables.

No.	HPMC K 100	PVP K30	Release in 1 h			$T_{50\%}$			Release in 8 h		
			Predicted	Experimental	Error	Predicted	Experimental	Error	Predicted	Experimental	Error
1	24.80	20.18	12.2019	13.25	0.08	5.01351	5.65	0.12	70.59	69.02	0.022
2	24.74	20.08	12.2244	10.25	0.16	5.01111	4.65	0.07	70.61	71.25	0.231
3	24.68	20.22	12.2339	11.32	0.07	5.00002	5.25	0.04	70.70	72.32	0.022
4	24.72	20.32	12.2185	10.32	0.15	5.00039	4.75	0.05	70.70	69.95	0.010
5	24.82	20.08	12.2024	13.25	0.08	5.01896	5.03	0.99	70.54	68.25	0.032
6	24.65	20.06	12.251	14.35	0.17	5.00244	5.02	0.003	70.68	71.25	0.008
7	24.74	20.40	12.208	13.02	0.06	5.00033	5.11	0.021	70.70	69.25	0.020

Table 12 In vitro release kinetics of 50 mg Itopride HCl SR matrix tablet.

Trial No.	Zero order R^2	First order R^2	Higuchi R^2	Koresmeyer R^2	Koresmeyer Release exponent (n)
F1	0.9820	0.8500	0.9872	0.9826	0.4452
F2	0.9954	0.8786	0.9875	0.9960	0.4420
F3	0.9851	0.8532	0.9860	0.9858	0.4340
F4	0.9629	0.7885	0.9931	0.9719	0.4400
F5	0.9602	0.7858	0.9926	0.9709	0.4200
F6	0.9462	0.7887	0.9857	0.9696	0.4500
F7	0.9073	0.7807	0.9700	0.9700	0.4900
F8	0.9970	0.8817	0.9855	0.9975	0.4100
F9	0.9608	0.7892	0.9921	0.9716	0.4700
F10	0.9874	0.8325	0.9957	0.9886	0.4400
F11	0.9650	0.8305	0.9956	0.9878	0.4460
F12	0.9914	0.8505	0.9939	0.9929	0.4550
F13	0.9426	0.7997	0.9860	0.9741	0.4440

R^2 = Linear regression coefficient.
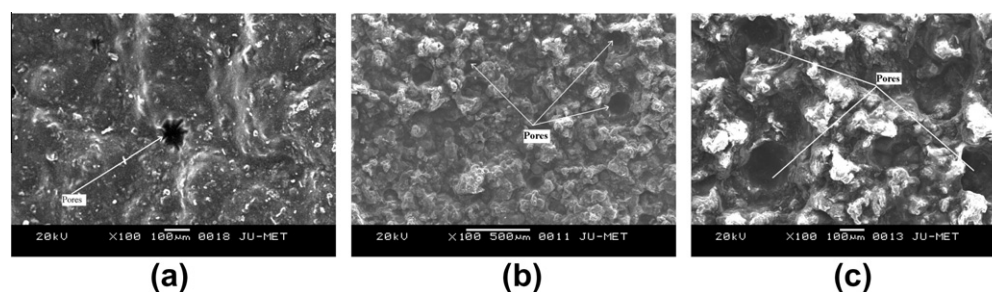
Figure 9 Surface of SR layer of Itopride HCl (a) (after 1 h of dissolution), (b) (after 4 h of dissolution), (c) (after 8 h of dissolution) investigating by scanning electron microscope (SEM).

References

Reddy, K.R., Mutalik, S., Reddy, S., 2003. Once-daily sustained-release matrix tablets of nicorandil: formulation and in vitro evaluation. AAPS PharmSciTech 4 (4), 1–9.

Higuchi, T., 1961. Rate of release of medicaments from ointment bases containing drugs in suspensions. J. Pharm. Sci. 50, 874–875.

Higuchi, T., 1963. Mechanism of sustained action medication: theoritical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci. 52, 1145–1149.

Ghosh, A., Bose, A., Bhaumik, U., Mandal, U., Gowda, V.K., Pal, T.K., 2008. Application of response surface methodology in the formulation of sustained release matrix tablets of metformin hydrochloride. Asian J. Chem. 20 (7), 5541–5556.

Mandal, U., Gowda, V., Ghosh, A., Selvan, S., Soloman, S., Pal, T.K., 2007. Formulation and optimization of sustained release matrix tablet of metformin 500 mg using response surface methodology. Yakugaku Zasshi 127 (8), 1281–1290.

Nazzal, S., Nutan, M., Palamakula, A., Shah, R., Zaghloul, A.A., Khan, M.A., 2002. Optimization of a self-nanoemulsified tablet dosage form of ubiquinone using response surface methodology: effect of formulation ingredients. Int. J. Pharm. 240 (1–2), 103–114.

Hamed, E., Sakr, A., 2001. Application of multiple response optimization technique to extended release formulations design. J. Control Release 73 (2–3), 329–338.

Fassihi, R.A., Ritschel, W.A., 1993. Multiple-layer, direct-compression, controlled-release system: in vitro and in vivo evaluation. J. Pharm. Sci. 82 (7), 750–754.

Takayama, K., Fujikawa, M., Obata, Y., Morishita, M., 2003. Neural network based optimization of drug formulations. Adv. Drug Deliv. Rev. 55 (9), 1217–1231.

Sastry, S.V., Khan, M.A., 1998. Aqueous based polymeric dispersion: Plackett–Burman design for screening of formulation variables of atenolol gastrointestinal therapeutic system. Pharm. Acta Helv. 73 (2), 105–112.

Huang, Y.B., Tsai, Y.H., Yang, W.C., Chang, J.S., Pao-Chu, W.U., 2004. Optimization of sustained-release propranolol dosage form using factorial design and response surface methodology. Biol. Pharm. Bull. 27 (10), 1626–1629.

Bozic, D.Z., Vrecer, F., Kozjek, F., 1997. Optimization of diclofenac sodium dissolution from sustained release formulations using an artificial neural network. Eur. J. Pharm. Sci. 5 (3), 163–169.

Banka, N.H., 2003. Role of prokinetics in dyspepsia. Gastroenterol. Today 7, 1–4.

Singh, B., Ahuja, N., 2002. Development of controlled-release bucco-adhesive hydrophilic matrices of diltiazem hydrochloride: optimization of bioadhesion, dissolution and diffusion parameterhs. Drug. Dev. Ind. Pharm. 28, 431–442.

Singh, B., Ahuja, N., 2004. Response surface optimization of drug delivery system. In: Jain, N.K. (Ed.), Progress in Controlled and Novel Drug Delivery Systems. New Delhi.

Korsemeyer, R.W., Gumy, R., Doelker, E., Buri, P., Peppas, N.A., 1983. Mechanisms of solute release from porous hydrophilic polymers. Int. J. Pharm. 15, 1249–1253.

Porter, S.C., Saraceni, K., 1988. Opportunities for cost containment in aqueous film coating. Pharm. Tech. Sept. 9, 62–76.

Poukavoos, N., Peck, G.E., 1993. The effect of swelling characteristics of superdisintigrants on the aqueous coating solution penetration

into the tablet matrix during the film coating process. Pharm. Res. 10, 1363–1370.

Lehtola, V.M., Heinamaki, J.T., Nikupaavo, P., Yliruusi, J.K., 1995. Effect of some excipients and compression pressure on the adhesion of aqueous-based hydroxypropyl methylcellulose film coating to tablet surface. Drug. Dev. Ind. Pharm. 21, 1365–1375.

Felton, L.A., Mcginty, J.W., 1996. Influence of tablet hardness and hydrophobicity on the adhesive properties of an acrylic resin polymer. Drug Dev. Technol. 1, 381–389.