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Research Article

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Studies on Formulation Development of Mucoadhesive Sustained Release Itraconazole Tablet Using Response Surface Methodology

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Abstract. The purpose of this research was to prepare and evaluate sustained release mucoadhesive tablets of Itraconazole. It is practically insoluble in aqueous fluids hence its solid dispersion with Eudragit E100 was prepared by spray drying. This was formulated in matrix of hydrophilic mucoadhesive polymers Carbopol 934P (CP) and Methocel K4M (HPMC). The formulation was optimized using a 3^2 factorial design. Amounts of CP and HPMC were taken as formulation variables for optimizing response variables i.e. mucoadhesion and dissolution parameters. The optimized mucoadhesive formulation was orally administered to albino rabbits, and blood samples collected were used to determine pharmacokinetic parameters. The solid dispersion markedly enhanced the dissolution rate of itraconazole. The bioadhesive strength of formulation was found to vary linearly with increasing amount of both polymers. Formulations exhibited drug release fitting Peppas model with value of *n* ranging from 0.61 to 1.18. Optimum combination of polymers was arrived at which provided adequate bioadhesive strength and fairly regulated release profile. The experimental and predicted results for optimum formulations were found to be in close agreement. The formulation showed C_{max} 1898± 75.23 ng/ml, t_{max} of the formulation was 2 h and AUC was observed to be 28604.9 ng h/ml

KEYWORDS: factorial design; itraconazole; mucoadhesion; optimization; response surface methodology.

INTRODUCTION

Itraconazole is an oral antifungal agent with a broad spectrum of activity. Itraconazole is weakly basic (pK_a=3.7) and highly hydrophobic (octanol/water partition coefficient at pH=8.1, log *P*=5.66) (1). Itraconazole is most effective when drug concentration is maintained above the minimum effective concentration (MEC) Studies in immuno-compromised patients have shown that plasma concentration below the MEC not only results in poor clinical response but may cause relapse of disease (2). Itraconazole belongs to Biopharmaceutical Classification Systems Class II drugs categorized with low water solubility and high permeability (3). Because of poor dissolution in the gastrointestinal tract, its oral administration is faced with large interindividual variations in bioavailability; therefore enhancing the dissolution rate of itraconazole is an important task for its formulation development (4). Itraconazole has been formulated with various carriers such as Eudragit E100, HPMC, phosphoric acid and hydroxypropyl-β-cyclodextrin to improve dissolution (5–8).

Mucoadhesive drug delivery system by virtue of prolong the retention time in the stomach, by improves the oral bioavailability of the drug. The application of an optimization technique consisting of statistical design to pharmaceutical formulation development provides an efficient and economical method to acquire the necessary information to understand the relationship between controllable (independent) variables and performance dependent variables or responses (9). The technique of optimization is well reported in the literature for the development of tablet formulations (10–12).

This study aimed at developing mucoadhesive dosage forms containing a solid dispersion of itraconazole with Eudragit E100 investigate the effect of two independent variables i.e. amount of two swellable polymer: Methocel K4M (HPMC) and Carbopol 934P (CP) on *in vitro* release at the end of 8 h and adhesive strength (f) of mucoadhesive drug delivery system. The mucoadhesive tablets involves relatively more economical and less complicated technology *vis-à-vis* many other drug delivery devices such as osmotic and transdermal delivery systems using (computer-aided optimization technique incorporating 3^2 full factorial design).

MATERIALS AND METHODS

Itraconazole was a gift sample from Ranbaxy Pharmaceuticals, Jejury, India, Methocel K4M by Colorcon Asia Pvt. Ltd. (Goa, India), Carbopol 934P from M/s Loba Chemie Ltd. (Mumbai, India), Eudragit E100 was a gift sample from Degussa, India. Lactose from M/s Loba Chemie Ltd. (Mumbai, India) were procured from commercial sources. All other chemicals used in the study were of analytical grade.

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Preparation of Solid Dispersion

Solid dispersion of itraconazole with Eudragit® E100 was prepared by spray drying technique (13). Drug and carrier were dissolved in dichloromethane in different ratios and spray dried on Labultima laboratory spray dryer model LU 222. Following parameters were employed aspiration speed: 60, feed rate: 10 ml/min, inlet temperature: 80°C, outlet temperature: 40°C.

Characterization of Solid Dispersion

Solubility

The solubility of itraconazole in solid dispersion was investigated by a dispersion method using 0.1 N HCl. One hundred milligrams of a solid dispersion was added into a test tube containing 10 mL of the 0.1 N HCl (pH 1.2±0.1). The mixture was vortexed to disperse homogeneously and then centrifuged at 15,000×*g* for 20 min. The content of intraconazole in the supernatant, defined as the degree of solubility in this study, was measured by the UV spectrophotometric method at 254 nm.

Fourier Transform-Infrared Study. Fourier transform-infrared (FT-IR) spectra were measured using an IR spectrophotometer (Jasco). FT-IR spectra over the scanning range 400–3,600 cm^{-1} were obtained with the resolution of 2 cm^{-1}.

Diffferential Scanning Calorimetric Study of Solid Dispersion. Diffferential scanning calorimetric (DSC) study was done on solid dispersion, itraconazole and Eudragit E100 on Mettler Toledo Diffferential scanning calorimeter.

Preparation of Mucoadhesive Compressed Matrices

The composition of different mucoadhesive formulations prepared using varying amounts of CP (33–100 mg), HPMC (33–100 mg), with fixed quantity of micro crystalline cellulose (15 mg) and lactose (85 mg). Solid dispersion (300 mg) containing Itraconazole equivalent to 100 mg and excipients were homogeneously blended and subsequently compressed into flat-faced tablets (12 mm diameter) to achieve tablet hardness 7 to 8 kg/cm^2.

Factorial Design

A 3^2 full FD was constructed where the amounts of CP (X_1) and HPMC (X_2) were selected as the factors. The levels of the two factors were selected on the basis of the preliminary studies carried out before implementing the experimental design. All other formulation and processing variables were kept invariant throughout the study.

Tablet Evaluation

Tablet Assay

Twenty tablets were powdered individually and a quantity equivalent to 100 mg of itraconazole was accurately weighed and extracted with a suitable volume of 0.1 N HCl. Each extract was suitably diluted and analyzed spectrophotometrically (Jasco V-530 UV/VIS Spectrophotometer) at 254 nm.

Physical Evaluation

Tablets were evaluated for uniformity in weight and thickness. Friability was measured using a Roche-type friabilator (Tropical Equipment Pvt. Ltd., Mumbai, India) and hardness using a Monsanto-type hardness tester (Campbell, Mumbai, India).

Ex vivo Bioadhesion Studies

The *ex vivo* adhesion studies were conducted using a modification of a test assembly described by Gupta *et al.* (14). The porcine stomach mucosa was kept frozen in 0.1 N HCl and thawed to room temperature before use. The membrane was excised by removing the underlying connective and adipose tissue and was equilibrated at 37±0.5°C for 30 min in 0.1 N HCl before the study. The tablet was placed on mucosa under constant weight of 5 g for a total contact period of 1min. Bioadhesive strength was assessed in terms of weight (grams) required for detaching the tablet from the membrane.

In Vitro Release Study

Drug release studies (n=5) were conducted for all the formulation combinations using dissolution test apparatus (DA-6D USP Standard); 0.1 N HCl (900 ml) was taken as the release medium at 100 rpm and 37±0.5°C employing USP II paddle method (Apparatus II).

Data Analysis

The data obtained from dissolution kinetic studies were analyzed using PCP disso software (Poona College of Pharmacy, Pune, India.). The computed values of kinetic constant (k) and diffusional release exponent (n) were calculated using logarithmic transformation of the relationship proposed by Korsmeyer *et al.* as in Eq. 1 (15).

$$\mathrm{Log}\,(M_t/M_\infty) = \mathrm{Log}k + n\mathrm{Log}t \quad (1)$$

Where M_t/M_∞ is the fraction of drug released at time t. The values of $t_{50\%}$ were calculated.

The influence of polymers on bioadhesive strength and *in vitro* release from tablet at the end of 8 h was investigated by two-way analysis of variance (ANOVA)-based factorial analysis followed by several one-way ANOVA.

Various computations for the current optimization study using Response Surface Methodology (RSM) were carried out, employing software, State Ease Design Expert Version 7. Statistical second-order model including interaction and polynomial terms were generated for all the response variables.

The general form of the model is represented as in Eq. 2.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2 + \beta_6 X_1^2 X_2 + \beta_7 X_1 X_2^2 + \beta_8 X_1^2 X_2^2 \quad (2)$$

Where β_0 the intercept, is the arithmetic average of all quantitative outcomes of nine runs, β_1 to β_8 are the

coefficients computed from the observed experimental values of Y, and X_1 and X_2 are the coded levels of the independent variable(s). The terms X_1X_2 and $X_i^2 (i = 1,2)$ are the interaction and polynomial terms, respectively. The statistical validity of the polynomials was established on the basis of Yates' ANOVA. Subsequently, feasibility as well as grid search was performed to locate the composition of optimum formulations. Also, three-dimensional response surface graphs and contour plots were drawn in MS-Excel using the output files generated by the State Ease Design Expert Version-7 software.

Validation of Optimization Model

Five optimum formulations were selected by intensive search, performed over the entire experimental domain, to validate the chosen experimental design and polynomial equations. The criterion for selection of optimum was primarily based on the highest possible values of the two response parameters namely percent drug released in 8 h and bioadhesive strength. The formulations corresponding to this optimum were prepared and evaluated for various response properties. The resultant experimental data of response properties were subsequently quantitatively compared with predicted values. Also, linear regression plots between observed and predicted values were prepared.

In Vivo Study of Optimized Formulation

In vivo evaluation was carried out in rabbits of the optimized formulation of itraconazole tablets to establish the bioavailability of the formulation (16).

Five rabbits of either sex weighing (2.2–2.6 kg) were taken for *in vivo* studies of the optimum formulation. Food was withdrawn 72 h before drug administration. All rabbits had free access to water throughout the study. The institutional animal ethical committee approved the protocol for this study. Blood samples 1–2 ml (with anticoagulants) was collected by means of cannula from marginal ear vein at different intervals for 36 h. Plasma was immediately separated by centrifugation at 300–400 rpm for 10 min. This was then transferred to labeled tubes and was stored at −20°C until subsequent high performance liquid chromatography (HPLC) analysis.

At the end of study the animal was sacrificed and the stomach was opened to investigate the position of tablet in rabbit stomach.

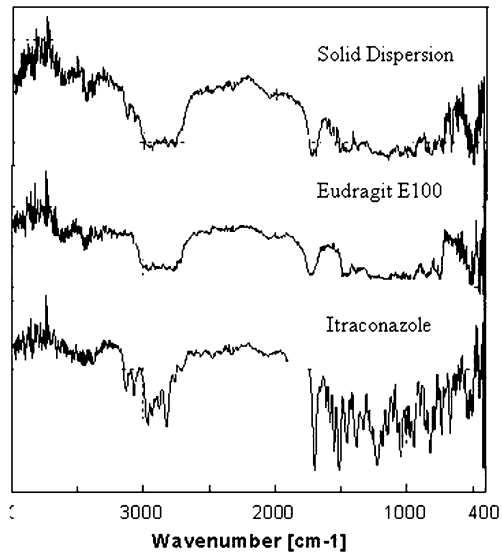

Fig. 1. FT-IR spectra of itraconazole, eudragit E100 and solid dispersion of itraconazole: eudragit E100 (1:2)

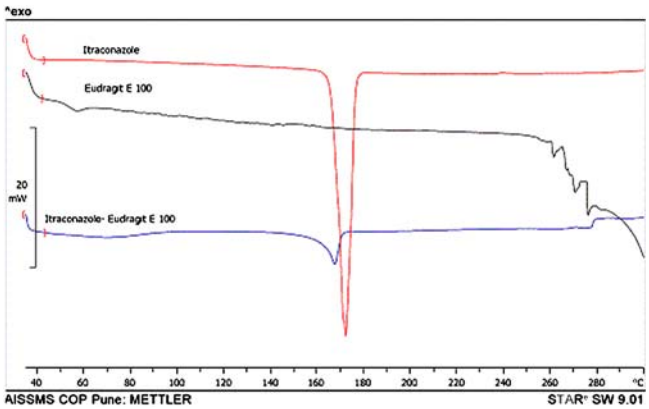

Fig. 2. DSC study for itraconazole, eudragit E100, and solid dispersion (1:2)

High Performance Liquid Chromatography Analysis

High Performance Liquid Chromatography Instrumentation and Chromatographic Conditions

Jasco HPLC system, consisting of Jasco PU-2080 plus HPLC pump and Jasco UV-2075 plus UV/VIS detector and HiQ SiL C_{18} (250×4.6 mm i.d.) column was used in analysis. A Rheodyne injector with 20 µl loop was used for injecting the sample. All weighing were done on Shimadzu balance (Model AY-120).

The mobile phase used was Acetonitrile: 10 mM KH_2PO_4 (60:40) with pH adjusted to 7.8 with *o*-phosphoric acid with flow rate of 2.5 mL min^{-1}. UV detection was carried out at 263 nm.

Procedure

One hundred milligrams of Itraconazole was initially mixed with 100 µL of chloroform and then dissolved in 10 mL of dimethyl sulfoxide to yield stock solution of 10 mg mL^{-1}. Various working solutions of Itraconazole were prepared by dissolving stock solution in methanol. One milliliter of Acetonitrile was added to the tubes containing 250 µL aliquots of plasma and mixtures were agitated on a vortex mixer for 1 min and then centrifuged for 5 min. The supernatant fluid was decanted and dried in air for 30 min. The residues were redissolved in 100 µL aliquots of mobile phase, which were then injected into the HPLC apparatus. In order to construct standard curve, drug-free sample of plasma were each spiked with Itraconazole at a concentration 0.1, 0.5, 1.0, 2.0, 5.0, 10.0 and 20.0 µg mL^{-1}.

Table I. 3^2 Full Factorial Experimental Design Layout Translation of Coded Levels in Actual Units

Trial no.	Coded factor levels X_1	X_2	Coded level	−1	0	1
F1	−1	−1	X_1: CP (mg)	33	67	100
F2	−1	0	X_2: HPMC (mg)	33	67	100
F3	−1	1				
F4	0	−1				
F5	0	0				
F6	0	1				
F7	1	−1				
F8	1	0				
F9	1	1				

CP Carbopol 934P, *HPMC* hydroxy propyl methyl cellulose K4M

Precision and Recovery Studies

Recovery studies were carried out to check accuracy of the method. Three replicate assays over three concentrations were performed containing known amounts of the analyte added to biological matrix sample. Precision was assessed at three concentration levels (n=3) on the same day as well as on three different days.

RESULTS

The spray dried solid dispersions of itraconazole and eudragit produced free flowing product, the ratio of itraconazole: eudragit was selected on basis of solubility study.

Solubility Study for Solid Dispersion

The solubility of itraconazole from solid dispersion containing 1:2 itraconazole: eudrajit enhanced to was 4 mg/ml in aqueous medium; the reported solubility of itraconazole at pH 1.2 was 0.57 mg/mL (6). The prepared solid dispersion was used in formulation of mucoadhesive tablet.

Fourier Transform-Infrared Analysis

FT-IR analysis of itraconazole, eudragit and solid dispersion was carried out in order to detect any interactions between itraconazole and Eudragit E100 (Fig. 1) in the range 400–4000 cm^{-1}. Major, specific FT-IR spectra of itraconazole powders were noticed at 400–1800 cm^{-1}. They might have arisen from the stretching and vibration of functional groups such as –C=C– of aromatic groups. A peak observed at 1600–1800 cm^{-1} is attributed to –C=O stretching and vibration, whereas peaks for alkane and amine groups were noticed at 2800–3200 cm^{-1}.

Diffferential Scanning Calorimetric Studies

In DSC the pure drug shows sharp endotherm at 167°C indicating the melting point of the pure drug. Same endotherm is seen in solid dispersion (Fig. 2).

Factorial Design

Preliminary studies carried out prior to the experimental design revealed that the tablet formed with low polymer content exhibited 100% drug release, but was vulnerable to fragmentation. On the other hand, the tablet formed with very high polymer content possessed good structural integrity, but showed undesirably slow release. Accordingly, a suitable range for each of the polymer amounts was selected.

Design of experiment has been widely used in pharmaceutical field to study the effect of formulation variables and their interactions on response variables. Table I summarizes the experimental runs, their factor combinations, and the translation of the coded levels to the experimental units used in the study.

Tablet Evaluation

The assay content of itraconazole varied between 98.2% and 99.8%.

Physical Evaluation. Tablet weights varied between 595 and 605 mg, thickness between 3 to 4 mm, and hardness between 6.5 and 7.5 kg/cm^2 and the friability ranged between 0.3% and 0.6%.

Table II. Dissolution Parameters for All Muccoadhesive Hydrophilic Matrix Formulations (n=3) Prepared as per 3^2 Factorial Design

Trial No.	CP (mg)	HPMC (mg)	n	k	% Drug Rel 8 h	Mucoadhesive strength (mg)
F1	33	33	0.6111	29.67	100.13±0.27	6.22±0.1517
F2	33	67	0.9140	13.18	95.99±0.35	8.04±0.0622
F3	33	100	1.0191	10.17	87.52±0.10	15.08±0.0803
F4	67	33	0.8695	15.28	98.17±0.12	10.72±0.1504
F5	67	67	0.9989	11.55	92.10±0.05	14.44±0.1790
F6	67	100	0.9559	11.47	84.32±0.12	17.73±0.1057
F7	100	33	0.8877	13.41	93.91±0.20	12.55±0.1878
F8	100	67	1.1278	8.31	86.90±0.22	20.28±0.1006
F9	100	100	1.1761	5.99	75.52±0.06	25.52±0.1955

CP Carbopol 934P, *HPMC* hydroxy propyl methyl cellulose K4M, *SD* standard deviation, k kinetic constant, r^2 coefficient of determination, n diffusion coefficient

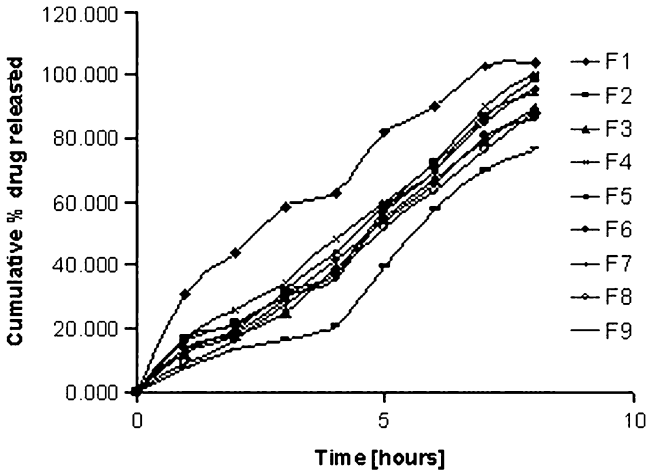

Fig. 3. Drug release profile of mucoadhesive hydrophilic matrix formulations (n=3) prepared as per trial runs in 3^2 factorial design

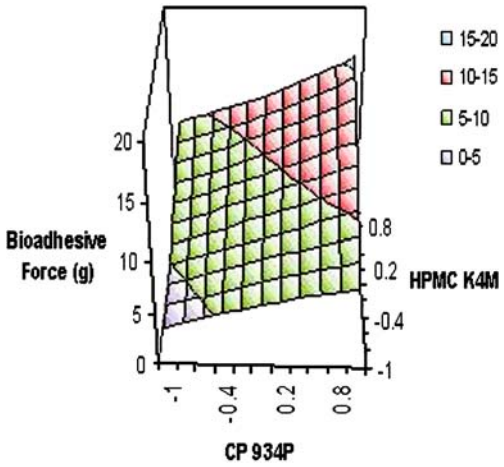

Fig. 5. Response surface plot showing the influence of CP and HPMC on the bioadhesive force for mucoadhesive tablet of itraconazole

Ex Vivo Bioadhesion Strength Determination. Maximum bioadhesive strength (*f*) was seen with the highest level of the two polymers. Application of two-way ANOVA based factorial analysis indicated that the polymers had a significant influence on the bioadhesive properties of the compressed matrices ($\rho<0.001$). Subsequent application of one-way ANOVA, keeping the levels of one of the polymers fixed, also showed a statistically significant difference amongst the observed data of bioadhesive strength ($\rho<0.001$), ratifying the significant positive influence of each polymer on bioadhesion.

Table II lists bioadhesive strength (with procaine mucosa) in gram determined for trial runs in design matrix. The values of bioadhesive strength ranged between 6.22±0.15 and 25.52±0.19 g. The values indicated as polymer content increased from 33.33 to 99.99 mg the bioadhesive strength also increased.

In Vitro Release Studies

Table II lists the dissolution kinetics parameters computed for nine trial runs. The *in vitro* release profiles of the drug for all the formulations could be best expressed by 'Peppas' equation formulations also showed high linearity (R^2= –0.9985), with a comparatively high slope (*n*) value ranging from 0.6111 to 1.1761. The, value of kinetic constant (*k*) ranged from 5.98 to 29.67. Figure 3 shows dissolution profile from all nine formulations prepared as per 3^2 full factorial designs.

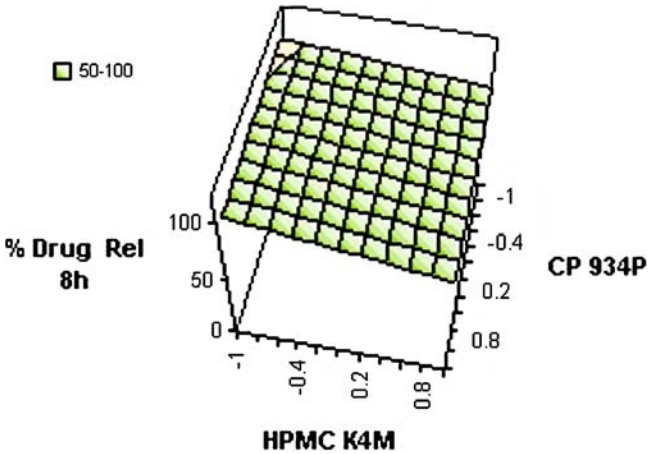

Fig. 4. Response surface plot showing influence of CP and HPMC on the release after 8 h values for mucoadhesive tablet of itraconazole

Optimization Results

The mathematical relationships constructed for the studied response variables are expressed as Eqs. 3–4. All the polynomial equations were found to be highly statistically significant ($\rho<0.001$), as determined by ANOVA,

$$\%\text{Release} = 91.69 - 4.60X_1 - 7.75X_2 - 1.63X_1X_2 \quad (3)$$
$$-0.56X_1^2 - 0.62X_2^2 - 0.27X_1^2X_2$$
$$+0.0033X_1X_2^2 - 0.17X_1^2X_2^2$$

$$\text{Bioadhesion Force} = 8.84 + 2.95X_1 + 2.93X_2$$
$$+ 0.62X_1X_2 + 0.066X_1^2 + 0.073X_2^2$$
$$+ 0.39X_1^2X_2 - 0.40X_1X_2^2$$
$$+ 0.058X_1^2X_2^2 \quad (4)$$

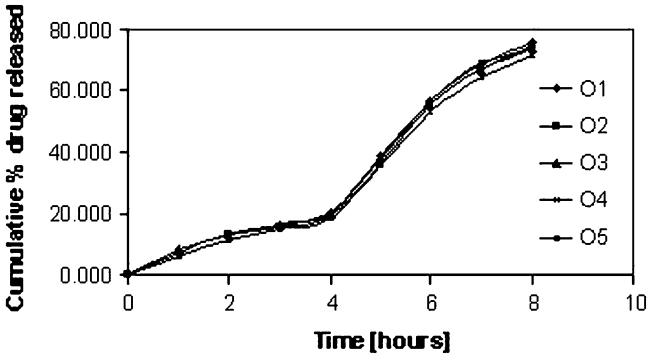

Fig. 6. Drug release profile from optimized mucoadhesive formulations

Table III. Experimentally Observed Response Parameters of Five Optimum Formulation and Comparison with Predicted Values for Validation of Response Surface Methodology

Formulation code	Formulation composition CP/HPMC (mg)	Response property	Experimental value	Predicted value	Percentage error
O1	93.32/93.32	release 8 h	74.31	79.06	6.0080
		f	20.03	23.08	13.2149
O2	94.15/95.82	release 8 h	73.06	78.08	0.02561
		f	20.28	23.66	14.2866
O3	95.82/99.15	release 8 h	72.17	76.97	6.2361
		f	21.68	24.64	12.0129
O4	97.49/96.65	release 8 h	72.08	77.08	6.4867
		f	21.49	24.45	12.1063
O5	99.15/99.99	release 8 h	70.69	75.71	6.6305
			22.48	25.35	11.3214
Mean (± SD) of percent error					8.8329±4.4548

Figure 4, shows that release after 8 h varies in a nearly linear descending pattern with a change in the amount of polymers. The response surface plots for '*f*' values (Fig. 5) reveal that it varies in a somewhat linear fashion with the amount of two polymer(s).

The dissolution parameters of all the five optimum formulations, value of n ranged from 1.13 to 1.21, indicating super class II transport. The value of kinetic constant was varied from 5.07 to 6.15 indicating that Peppas as the best fitting model for all optimized mucoadhesive formulation, % Rel_{8h} ranged between 71% to 77% (Fig. 6).

For all these formulations, the bioadhesive strength ranged between 23.08 to 25.35 g. The hydrogels are known to swell readily when they come in contact with hydrated mucous membrane. The water sorption reduces the glass transition temperature below the ambient conditions and hydrogels become progressively rubbery due to uncoiling of polymer chains and subsequent increased mobility of the polymer chains. This glass-rubbery transition provides hydrogel plasticization resulting in large adhesive surface for maximum contact with mucin and flexibility to the polymer chains for interpenetration with mucin. Increasing the polymer amount may provide more adhesive sites and polymer chains for interpenetration with mucin, resulting consequently in the aggrandization of bioadhesive strength. Although the maximum value of bioadhesive strength is attained at the highest levels of both the polymers, yet the effect of CP 934P is more pronounced than of HPMC K4M.

Validation of Optimization Model

Table III records the values of observed and predicted responses using factorial design along with the percentage predicted errors for these six optimum formulations. The predicted error for the response variables ranged between 2.12% and 0.62%, with the mean ± SD of the percentage error being –0.13±0.7397%.

In-vivo Study

Pharmacokinetic study was conducted on rabbits dosed with optimized itraconazole mucoadhesive tablets.

A chromatogram of Itraconazole is shown in Fig. 7. A linear relationship was established between the peak area and Itraconazole in the concentration range of 0.1 and 20 μg mL^{-1} in plasma. The correlation coefficient was 0.99. Mean percentage recovery range from 87.9% to 94.6% from biological samples, coefficient of variation for intra and interday precision, 10% to 20%.

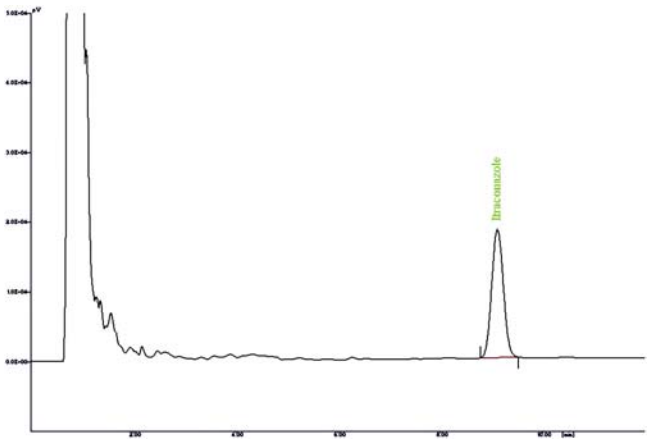

Fig. 7. Chromatogram of itraconazole

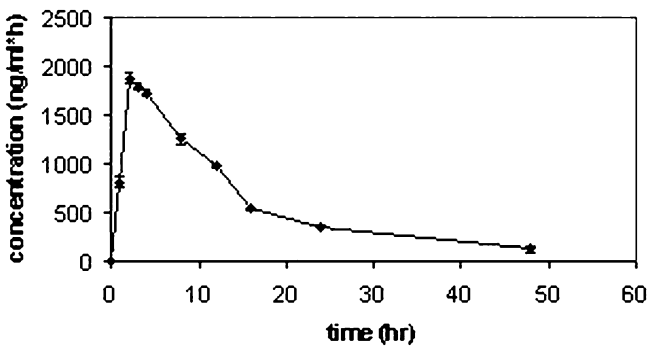

Fig. 8. *In-vivo* pharmacokinetic study for optimized formulation (O1)

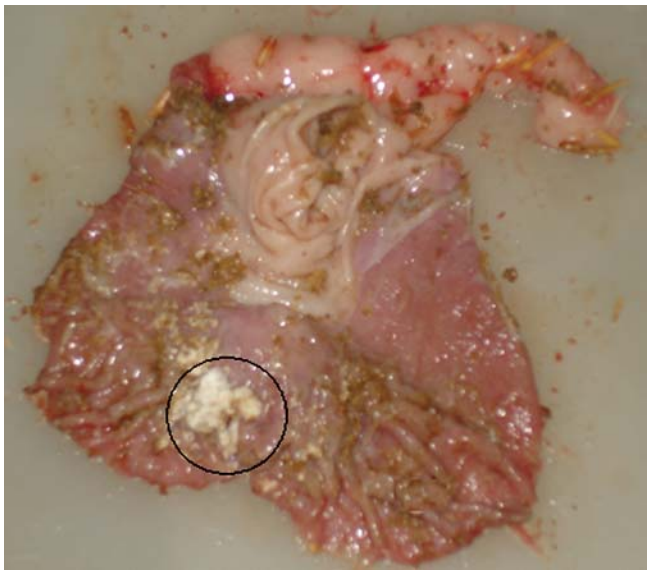

Fig. 9. Photograph of rabbit stomach showing mucoadhesive tablet retained after 8 h

The prepared mucoadhesive formulation exhibited C_{max} 1898±75.23 ng/ml which is comparable to reported value of standard formulation sporanox (16), t_{max} of the formulation was 2 h. The plasma concentrations of itraconazole were followed for 48 h and the AUC was observed to be 28,604.9 ng h/ml (Fig. 8), which is slightly better as compared to reported value for sporanox (23,382.2±6,326). The tablet was found retained in stomach adhering to epithelial lining when animal was sacrificed at the end of experiment (Fig. 9).

DISCUSSION

The itraconazole solubility from solid dispersions was increased by eight times. The state of itraconazole in solid dispersions with eudragit E100 is reported as amorphous and exists as molecular dispersion in eudragit E100 which is responsible for the increase in the solubility (17).

Major peaks observed in Eudragit E100 and itraconazole were also observed in the solid dispersion at 400–4,000 cm^{-1}. Thus FT-IR analysis of itraconazole and solid dispersion with eudragit E100 suggested the absence of any significant interactions. Further DSC studies also indicate absence of significant interactions, as presence of endothermic peak at 167°C in both pure drug and solid dispersion thermograms.

An increase in the amount of polymer will increase the bioadhesive strength; mucoadhesive strength also depends upon molecular weight, contact time and pH (14). Increased mucoadhesive strength is reported when the polymers are used in combination (18).

Although tablets containing hydroxypropyl cellulose and carbopol were shown to have less bioadhesion due to complex formation (19), no complex formation was noticed in present investigation as seen in IR, thus showing additive effect on bioadhesion.

Data Analysis. The dissolution kinetics followed Peppas model. The value of n indicates a coupling of diffusion and erosion mechanisms also called anomalous diffusion. The relative complexity of this formulation and its components may indicate that the drug release is controlled by more than one process. An increase in the amount of polymer will decrease the drug release hence lower value of the drug release constant (k) at high polymer content was obtained. Sustained drug release was seen at highest levels of the two polymers. Application of two-way ANOVA based factorial analysis indicated that the polymers had a significant influence on the release of drug from the compressed matrices ($\rho<0.05$). Subsequent application of one-way ANOVA, keeping the levels of one of the polymers fixed, also showed a statistically significant difference amongst the observed data of dissolution ($\rho<0.05$), ratifying the significant positive influence of each polymer on dissolution. a mixture of HPMC with CP 934P resulted in the reduction of polymer viscosity due to reduced hydration. This reduction of viscosity could facilitate drug diffusion through polymer hydrogel. Evidently, the values of dissolution parameters had a propensity to range optimally between relatively controlled limits rather than those of the original formulations designed as per 3^2 factorial designs. The release profile of optimum formulation is seen in Fig. 6.

The linear plots drawn between the predicted and observed responses demonstrate high r^2 (ranging between 0.9770 and 0.9993), indicating excellent goodness of fit. The low magnitudes of error, as well as the significant values of r^2, designate a high prognostic ability of RSM.

Finally the *in vivo* study indicates a similar t_{max} and C_{max} to that of reported value of immediate release sporanox but subsequently the drug release was prolonged and showed higher AUC.

CONCLUSION

The mucoadhesive polymers carbopol and HPMC are more effective in combination than alone. Suitable combination of the two optimized using 3^2 full factorial design showed good agreement between predicted and observed responses. The *in vitro* drug release was zero order. The *in vivo* studies confirmed sustained drug release and gastric retention for six hours. Thus suitable combination of mucoadhesive polymers can be used to achieve desired gastric retention and drug release profile.

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