Indian Journal of Pharmaceutical Education and Research | Association of Pharmaceutical Teachers of India

Taste Masking of Tramadol Hydrochloride by Polymer Carrier System and Formulation of Rapidly Disintegrating Tablets using Factorial Design.

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ABSTRACT

Submitted: 20/02/2012 Revised: 13/07/2012 Accepted: 08/10/2012

The objective of this study was to formulate and optimize taste masked rapidly disintegrating tablet of intensely bitter drug tramadol hydrochloride by 3^2 factorial design. The drug polymer complex was prepared by coacervation method using aminoalkyl methacrylate copolymer (Eudragit EPO) as polymer and sodium hydroxide as precipitant and characterized for molecular properties, drug content, *in vitro* dissolution and taste evaluation. Drug polymer complex with a ratio of 1:8 was selected based on no release in phosphate buffer pH 6.8 showing successful taste masking of drug. Bitterness score was evaluated by human gustatory sensation test. The bitterness score of drug polymer complex was decreased as compared to tramadol hydrochloride. Optimized drug polymer complex was characterized and used for preparation of rapidly disintegrating tablet using menthol as subliming agent and crospovidone as superdisintegrant by applying 3^2 factorial design. Rapidly disintegrating tablet were evaluated for disintegration time, weight variation, friability and dissolution studies. Best fit equations for optimization purposes of disintegration time (Y_1), % cumulative drug release in 5 min in pH 1.2 (Q_5 min pH 1.2) (Y_2) and % cumulative release after 5 min in phosphate buffer pH 6.8 (Q_5min pH 6.8) (Y_3) were obtained. Findings of this study demonstrated successful masking of taste by DPC. Experimental design study revealed that the dependent variables strongly depended ($p<0.05$) on the independent variables. It is thus concluded that by adopting a systematic formulation approach, an optimum point can be reached in the shortest time with minimum efforts.

Keywords: Tramadol HCl, Eudragit EPO, Drug polymer complex, factorial design, taste masking.

INTRODUCTION

The taste-masking of bitterness in pharmaceutical medicines is an important component in the move to improve patient compliance. Among the dosage forms developed to facilitate ease of medication, the rapidly disintegrating tablet (RDT) is one of the most widely employed commercial products.[1-3] RDTs are useful in pediatric, geriatric or bedridden patients who may face difficulty in swallowing conventional tablets or capsules leading to ineffective therapy. RDTs are expected to disintegrate in oral cavity and the disintegrated mass can slide down smoothly along the oesophagus with the help of saliva. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability and good stability make RDTs popular in the current market.[4-7] The fundamental principle used in the development of the rapidly disintegrating tablet is to maximize its pore structure for rapid uptake of water and rapid disintegration of tablet. Researchers have evaluated spray dried materials for development of such tablets. Vacuum-drying and freeze-drying techniques have been tried by researchers to maximize the pore structure of tablet matrix. Freeze drying is cumbersome and yields a fragile and hygroscopic product. Therefore, a vacuum-drying technique was adopted in the present investigation after addition of a subliming agent to increase porosity of the tablets. It is likely that a porous hydrophilic matrix will easily pick up the disintegrating medium and break quickly.[8-10]

Tramadol HCl is a centrally acting synthetic opioid analgesic used for treating moderate to severe pain.[11-13] Tramadol HCl has been proved to be effective in both experimental and clinical pain without causing serious cardiovascular or respiratory side effects. It has been reported that tramadol HCl posseses bitter taste. The primary objective of the present investigation was to mask the intensely bitter taste of tramadol HCl and 3^2 factorial design was applied to achieve optimal point in formulation of rapidly disintegrating tablets resulting in quick onset of action.

MATERIALS AND METHODS

Materials:

Tramadol HCl was obtained as a gift from Emcure Pharmaceuticals (Pune, India). Aminoalkyl methacrylate copolymer (Eudragit EPO) was received as a gift sample from Degussa India Private Ltd. (Mumbai, India). Menthol, sodium saccharin, mannitol, crospovidone were received as gift samples from Nulife Pharmaceuticals (Pune, India). All other chemicals used in the study were of analytical grade.

Determination of Threshold Bitterness Concentration of Tramadol HCl:

A panel comprising of ten healthy human volunteers (age 20-25) were selected for the study. A series of solutions of tramadol HCl in phosphate buffer of pH 6.8 of concentrations 10, 20, 30, 40 and 50 µg/ml was prepared. The volunteers

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were asked to hold 10 ml of each solution in oral cavity for 30s and rate the taste on a scale from 0 to 4 (0: no bitterness, 1: threshold bitterness, 2: bitter, 3: moderate bitterness and 4: strong bitterness). The mouth was rinsed by distilled water and a gap of 30m was allowed between successive tests. Based on the opinion of the volunteers, threshold bitterness concentration of tramadol HCl was judged.[14]

Preparation of Drug-Polymer Complex (DPC):

Tramadol HCl and Eudragit EPO complex was prepared using the precipitation method. Saturated solutions of tramadol HCl and Eudragit EPO were prepared in 1% v/v acetic acid in various ratios (1:1, 1:3, 1:5, 1:7, 1:7.5, 1:8 and 1:8.5) and injected into 0.1 N sodium hydroxide (10 ml) with constant stirring at 700 rpm using a mechanical stirrer for 2.5 h. The droplets were amputated at a flow rate of 5 ml/m into sodium hydroxide solution. The resulting complex was separated by filtration, washed with water to remove uncomplexed drug and other reagents and dried at room temperature for 24 hours under vacuum and pulverized. The sample was stored in a tightly closed container for further studies.[15-19]

Characterization of DPC:

Drug Content:

Drug content was determined by dissolving 10 mg of DPC in 10 ml of methanol and analyzing 1 ml of sample at 272 nm.

***In Vitro* Taste Evaluation:**

To predict release in the human saliva, *in vitro* taste was evaluated by determining drug release in phosphate buffer pH 6.8. DPC, equivalent to 50 mg of tramadol HCl, was placed in 10 ml of phosphate buffer pH 6.8 and shaken for 60 s. The amount of drug released was analyzed at 272 nm.[16]

Gustatory Sensation Test:

Twenty healthy human volunteers of either sex, aged 20–25 years, participated in a gustatory sensation test.[16-18] Formal consent was taken from all human volunteers. DPC equivalent to 1 g of tramadol HCl was dispersed in 50 ml of water for 15 s. Immediately after preparation, each volunteer held about 1 ml of the dispersion in the mouth for 30 s. After expectoration, bitterness was evaluated using bitterness score, classified in eight grades. Comparison of bitterness among the samples was performed on the total number of persons. Tramadol HCl was used as control.

Fourier transform infra red (FTIR) spectroscopic studies:

Fourier transform infrared spectra of tramadol HCl, Eudragit EPO, physical mixture of tramadol HCl and Eudragit EPO (1:8) and DPC (1:8) were obtained by KBr disc method (Perkin Elmer, USA) in the range of 4000 to 400 cm^{-1}. Spectra were analyzed for drug-polymer interactions.

X-ray powder diffraction studies:

The X-ray powder diffractograms of the tramadol HCl, Eudragit EPO and physical mixture of tramadol HCl and Eudragit EPO (1:8), DPC (1:8) were recorded using a x-ray diffractometer (DH Advance- Brukar AXS, Germany) and analyzed for confirmation of drug-polymer complex formation.

Dissolution studies:

In vitro drug release studies of tramadol HCl and selected DPC (1:8) were carried out using USP type II dissolution apparatus (DT 06, Electrolab, Mumbai) at 37±1ºC and 50 rpm speed. Dissolution studies were carried out separately in Phosphate buffer pH 6.8 (900 ml) and acidic buffer pH 1.2 (900 ml). Aliquots of 10 ml were withdrawn at specific time intervals and analyzed at 272 nm for % cumulative drug release using UV-Visible spectrophotometer (JASCO, V-530, Japan).

Physical properties of tablet blend:

Physical properties such as bulk density, tapped density, Hausner's ratio, % compressibility and the angle of repose of blend were determined.

Preparation of rapidly disintegrating tablets:

DPC equivalent to 50 mg of tramadol HCl was used to prepare RDT by using menthol as subliming agent and crospovidone as superdisintegrant. Composition of tablet formulations is mentioned in Table 1. All the materials were weighed accurately and sifted through 40 mesh. Drug and excipients mixed by geometrical mixing for 10 m. Tablet blend was directly compressed (9 mm standard concave punch) using rotary tablet machine (GMC India) at a compression pressure of 13-14 kN. Prepared tablets were vaccum dried at 45°C for 24 h to facilitate sublimation of subliming material.

Full factorial design:

A 3^2 randomized full factorial design was used in development of dosage form. In this design two factors are evaluated, each at 3 levels and experimental trials are performed at all 9 possible combinations. The amount of subliming agent, menthol (X_1) and the superdisintegrant, crospovidone (CRP) (X_2) were chosen as independent variables to investigate the joint influence of two formulation variables.[5,8,20,21] Disintegration time (DT, Y_1), % cumulative drug release in 5m in pH 1.2 (Q_5 min in pH 1.2, Y_2) and % cumulative drug released in 5 m in phosphate buffer pH 6.8 (Q_5 m in pH 6.8, Y_3) were chosen as response variables (Table 1).

Response surface plots:

To study the effect of both factors on response, response surface plots were generated for each response.

Evaluation of tablets:

General parameters:[22,23]

Tablets were evaluated for hardness (Monsanto Hardness tester), friability (Roche Friabilator), and weight variation. Tablets were also evaluated for content uniformity.

***In vitro* disintegration time:**

Disintegration time (DT) was evaluated by employing disintegration apparatus (Electrolab TDT) using water (900 ml) as a medium, maintained at 37±0.5ºC. Disintegration time was recorded when all the fragments of the disintegrated tablet passed through the screen of the basket.[24]

Dissolution studies:

In vitro drug release studies of all the formulations were carried out in two different medias *viz* phosphate buffer pH 6.8 (900 ml) and acidic buffer pH 1.2 (900 ml) separately, using USP type II dissolution apparatus (DT 06, Electrolab, Mumbai) at 37±1ºC and 50 rpm speed. Aliquots of 10 ml were withdrawn at specific time intervals and analyzed at 272 nm for cumulative drug release using UV-Visible spectrophotometer (JASCO, V-530, Japan). The optimized formulation was compared with marketed orodispersible tablet for dissolution profile.

RESULTS

Most of the volunteers reported concentration of 20 µg/ml tramadol HCl as threshold bitterness.

Percent drug loading in DPCs was found to be in the range of 82.25% to 92.40% (Table 2). Drug release in phosphate buffer pH 6.8 from DPC was observed in the range of 0 to 1 % (Table 2). Maximum human volunteers rated DPC as tasteless-0 while very few rated as very slightly bitter-0.5 (Table 3).

The IR spectrum of tramadol HCl, Eudragit EPO, physical mixture and selected DPC are shown in Figure 1. The characteristic peak of tramadol HCl at 3306 cm^{-1} is assigned to C-N stretching vibration. In addition peak at 2931 cm^{-1} is assigned to C-H stretching vibration.

The peak at 1387 cm^{-1} is assigned to O-H stretching vibration. The peak at 1247 cm^{-1} is assigned to C-O stretching vibration and peak at around 1579 cm^{-1} corresponds to hydrohalide salt associated with tertiary amine. The spectrum of Eudragit EPO is dominated by the carbonyl C=O stretching vibration at 1732 cm^{-1} and the ester C-O stretching vibration at 1148 cm^{-1}. In addition C-H vibrations can be observed at 1388, 1458 and 2956 cm^{-1}. The absorption at 2771 and 2822 cm^{-1} can be assigned to dimethyl amino groups. In the FTIR spectrum of DPC no peaks of drug was found.

In the XRD studies, tramadol HCl showed number of sharp and intense peaks, the diffractogram of polymer (Eudragit EPO) showed diffused peaks and the diffractogram of the drug polymer physical mixture showed simply the sum of the characteristic peaks of tramadol HCl and the diffused peaks of polymer. However, the diffraction pattern of DPC represents complete disappearance of crystalline peaks of drug (Figure 2).

The tramadol HCl showed complete release within 15-20 m in phosphate buffer pH 6.8 and it showed complete release within 8-10 m in acidic buffer pH 1.2. The selected complex of drug-Eudragit EPO (1:8 ratios) showed more than 90% of drug release in acidic buffer pH 1.2 within 20 m. It showed 5-6% drug release in phosphate buffer pH 6.8 within 60 m (Figure 3).

The values for bulk density were found in the range from 0.6128 ± 0.05 to 0.6812 ± 0.03 for all tablet blends. The values for tapped density for all tablet blends were found in the range from 0.7123 ± 0.02 to 0.7692 ± 0.03. The tablet blend of all the

Table 1: Variables and Experimental Runs for 3^2 factorial design

Batch Code	Variable level in Coded form	
	X_1	X_2
F1	-1	-1
F2	0	-1
F3	1	-1
F4	-1	0
F5	0	0
F6	1	0
F7	-1	1
F8	0	1
F9	1	1
Coded values	**Actual values**	
	X_1 (%)	X_2 (%)
-1	0	3
0	3	6
1	6	9

All batches contains DPC eq. to 50 mg of tramadol HCl, 2 mg of Collidal SiO_2, 2% talc, 1% magnesium stearate and mannitol q.s. to 200 mg.

Table 2: Drug content and in vitro taste evaluation of DPC in phosphate buffer pH 6.8

Sr. No.	Drug polymer ratio in DPC	% drug loading in DPC	% drug dissolved in phosphate buffer (pH 6.8)
1	1:7	82.40± 0.05	0.1%
2	1:7.5	88.43± 0.56	0.4%
3	1:8	92.25± 0.51	Not detected
4	1:8.5	83.64± 0.48	1.0%

*Results are the mean of 3 observations ± SD.

Table 3: Comparative taste evaluation

Volunteers	1	2	3	4	5	6	7	8	9	10
Tramadol HCl	4	4	4	4	4	4	4	4	4	4
DPC	0	0	0.5	0	0	0.5	0	0	0	0

Tasteless = 0,Very slightly bitter = 0.5, Slightly bitter = 1.0, Slight to moderate bitter= 1.5, Moderately bitter = 2.0, Moderate to strong bitter = 2.5,Strongly bitter = 3.0, Very strongly bitter = 4

Fig. 1: FTIR plot of A.Drug, B.EPO, C. Drug-EPO Physical mixture, D. DPC.

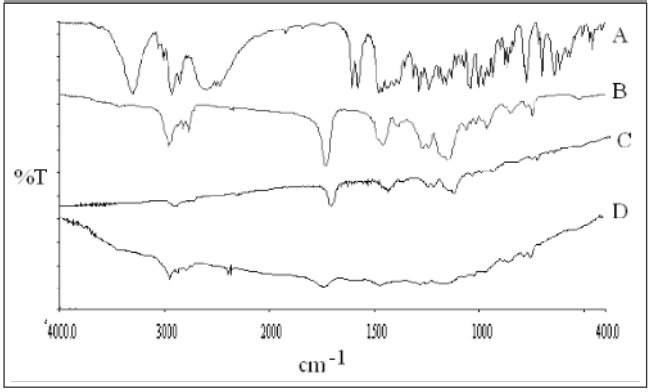


Fig. 2: XRD plot of A. drug, B. EPO, C. drug-EPO physical mixture, D. DPC.

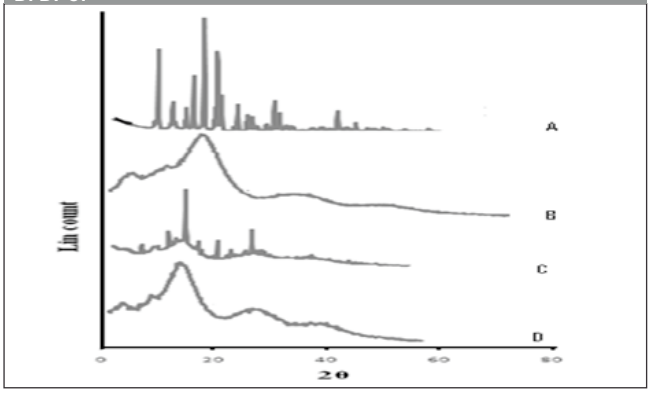
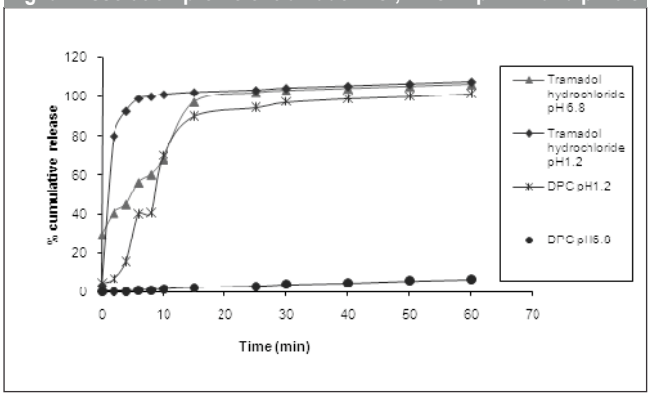


Fig. 3: Dissolution profile of tramadol HCl, DPC in pH 1.2 and pH 6.8.



batches showed good flowability and % compressibility. The values for angle of repose were found <30°. The values for % compressibility were found upto 16%. (Table 4)

The results of weight variation, hardness, friability, content uniformity, disintegration time, Q_5 m in pH 1.2 and Q_5 m in pH 6.8 are revealed in Table 5.

The optimized formulation showed complete release in acidic buffer pH 1.2 within 7 minutes and marketed tablet showed complete release in acidic buffer pH 1.2 within 60 m. (Figure 4)

Based on the 3^2 factorial design, the factor combinations resulted in different drug release rates. Various models, such as Linear, 2FI, Quadratic and Cubic were fitted to the data for three responses simultaneously using Design Expert software and adequacy and best fit of the model was tested using analysis of variance (ANOVA). The multiple correlation coefficient (r^2), adjusted multiple correlation coefficient (adjusted r^2) and the predicted residual sum of square (PRESS), provided by Design-Expert software 7.2, were used as factors for selection of adequate models. The lack of fit analysis shows that a quadratic model is appropriate for the description of all responses.

From the results, the quadratic model was selected as the best fit for the model because its PRESS was the smallest. PRESS is a measure of the fit of the model to the points in design; the smaller the PRESS the better the model fits to the data points.

A statistical model, $Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2$ incorporating interactive and polynomial terms was used to evaluate the responses; where Y is the dependent variable, β_0 is the arithmetic mean response of the nine runs and β_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1X_1 and X_2X_2) are included to investigate nonlinearity.

The disintegration time, Q_5 m in pH 1.2 and Q_5 m in pH 6.8 for the nine batches (P1 to P9) showed wide variation (i.e. 34 to 232 s, 52 to 96%, 2.45 to 5.75%), (Table 5). The data clearly indicates that disintegration time, Q_5 m in pH 1.2 and Q_5 m in pH 6.8 are strongly dependent on selected independent variables (menthol, CRP).

Quadratic Equations for the Quantitative Effect of Independent Variables (X_1, X_2) on the Responses (Y_1, Y_2, Y_3) are as

$DT = +97.22 - 19.17X_1 - 81.67X_2 + 5.75X_1X_2 - 5.83X_1^2 + 35.67X_2^2$

Q_5 m in pH 1.2 $= +71.03 + 7.03X_1 + 14.34X_2 - 1.32X_1X_2 - 1.17X_1^2 + 5.51X_2^2$

Q_5 m in phosphate buffer pH 6.8 $= +3.64 + 0.55X_1 + 0.87X_2 - 0.13X_1X_2 + 0.31X_1^2 - 0.025X_2^2$

Positive or negative signs before a coefficient in quadratic models indicate a synergistic effect or an antagonistic effect for the factor. Table 6 shows the results of the analysis of variance (ANOVA), which was used to generate statistical model.

Three-dimensional response surface plots of DT, Q_5 m in pH 1.2 and Q_5 m in phosphate buffer pH 6.8 are presented in Figures. 5-7. For drawing conclusions for DT, response

surface plot (Figure 5) should be used since one of the polynomial terms (β_{11}) is significant. The results of multiple linear regression analysis reveal that, on increase in the concentration of either menthol or crospovidone, decrease in DT is observed. There was linear increase in the Q_5 m in pH 1.2 (Figure 6) and Q_5 m in phosphate buffer pH 6.8 (Figure 7) with increase in the concentration of either menthol or crospovidone.

DISCUSSION

Tramadol HCl was found to be strongly bitter in taste from our study. Eudragit EPO is insoluble in salivary pH (pH 6.5 to 7.4) and allows fast release into the gastric fluids (pH 1.0-1.5) so it can retard the release of drug in saliva and mask the bitter taste of drug. Thus Eudragit EPO was selected as taste masking agent in the present study. The pH of the buccal cavity is 6.8. The DPC showing no release in pH 6.8 indicates that the DPC is stable in this pH and taste of the drug will not be sensed in buccal cavity. No drug release was observed in phosphate buffer pH 6.8 from complex with the drug-polymer ratio of 1:8 and maximum loading of drug was also observed in ratio of 1:8, therefore, the ratio 1:8 was considered the optimal DPC with complete masking of bitter taste for further studies. Due to higher concentration of Eudragit EPO in 1:8 ratio, maximum human volunteers rated DPC as tasteless showing good masking of bitter taste of drug. In the FTIR spectrum of DPC no interference from the functional groups of drug was found hence it can be confirmed that the drug particles are completely coated. XRD studies showed crystalline nature of tramadol HCl and amorphous nature of DPC and Eudragit EPO. Drug was completely coated by Eudragit EPO and hence sharp crystalline peaks of drug were not observed in diffractogram of DPC. Thus the formation of drug-polymer complex was confirmed by FTIR and XRD studies. All tablet blends showed good flow properties. The values for angle of repose (<30°) indicated good flow properties of blends and this was further supported by lower compressibility index values. Generally, compressibility index values of up to 16 % result in good to excellent flow properties. 3^2 factorial design was used for optimization of tablet formulations. The outcomes for response variables i.e. DT, Q_5 m in pH 1.2 and Q_5 m in phosphate buffer pH 6.8 were subjected to regression analysis. The model high F value for DT was found to be 592.59, for Q_5 m pH 1.2 was found to be 304.17 and for Q_5 min in pH 6.8 was 34.54. The P values of all three response variables were less than 0.05 thus all three models were found to be significant. From these results, the quadratic model was selected as the best fit for the model because its PRESS was the smallest. After generating the model polynomial equations to relate the dependant and independent variables, the formulation was optimized for all three responses. The final optimal experimental parameters were calculated using the canonical analysis, which allows the compromise among various responses and searches for a combination of factor levels that jointly optimize a set of

Table 4: Evaluation of physical properties of tablet blends.

Formulation	Bulk density	Tapped density	Angle of repose (in °)	% compressibility	Hausner ratio
P1	0.6571±0.04	0.7692±0.03	22.56±0.76	14.573	1.17
P2	0.6713±0.02	0.7632±0.16	24.32±0.44	12.041	1.13
P3	0.6314±0.07	0.7123±0.03	27.21±0.45	11.357	1.12
P4	0.6122±0.11	0.7241±0.14	24.21±0.23	15.453	1.18
P5	0.6131±0.06	0.721±0.09	29.78±0.31	14.965	1.17
P6	0.6781±0.1	0.7124±0.04	23.67±0.15	4.8147	1.05
P7	0.6189±0.09	0.7256±0.06	22.92±0.12	14.705	1.17
P8	0.6812±0.03	0.7314±0.08	24.45±0.84	6.8635	1.07
P9	0.6128±0.05	0.7123±0.02	21.09±0.41	13.968	1.16

Table 5: Evaluation of various parameters of tablets.

Formulation	Weight variation (mg)	Hardness (K/cm^2)	Friability (%)	Content uniformity (%)	DT ± SD (s)	Q_5min pH 1.2 (%)	Q_5min phosphate buffer pH 6.8 (%)
P1	200±0.99	3.1±0.86	0.34±0.007	99.2±0.42	232±2.25	52.05±0.45	2.45±0.48
P2	201±1.2	3.8±0.34	0.42±0.09	100±0.32	218±1.30	63.13±0.35	2.57±0.54
P3	201±0.34	3.7±0.81	0.63±0.03	100±0.21	182±2.47	69.08±1.23	3.84±0.469
P4	199±1.43	3.1±0.99	0.51±0.09	100±0.23	110±1.52	63.11±1.35	3.35±0.9
P5	200±0.88	3.5±1.1	0.67±0.42	101±0.45	98±1.03	71.11±1.55	3.84±0.39
P6	200±0.45	3.2±0.61	0.98±0.06	102±0.56	72±1.94	76.52±1.29	4.35±1.42
P7	200±0.35	3.9±0.45	0.71±0.73	101±0.63	61±1.79	84.34±1.48	3.36±0.74
P8	200±0.26	3.1±0.66	0.55±0.12	100±0.23	47±2.37	89.87±0.96	4.46±0.87
P9	199±0.71	3.2±1.2	0.69±0.56	99±0.32	34±1.76	96.09±1.83	5.25±0.83

Table 6: Results of Analysis of Variance for Measured Response

Parameters	df	SS	MS	F	Significance (P)
		For DT			
Regression	54	4965.36	8993.07	592.59	0.0001
Residua	l4	45.53	15.18		
Total	9	45010.89			
		For Q_5 m in pH 1.2			
Regression	5	1600.99	320.20	304.17	0.0003
Residual	4	3.16	1.05		
Total	9	1604.15			
		For Q_5 m in phosphate buffer pH 6.8			
Regression	5	6.57	1.31	34.54	0.0003
Residual	4	0.11	0.038		
Total	9	6.69			

df is degree of freedom; SS is sum of square; MS is mean sum of square; and P is Fischer's ratio.

Table 7: Predicted and Observed Responses of the Optimized Formulation

Responses	Predicted	Observed	Residuals[a]
Y_1	43.922	45	1.078
Y_2	93.234	92.864	-0.37
Y_3	4.738	4.673	-0.065

[a]Residual = observed value - predicted value

Fig. 4: Dissolution profile of marketed tablet and optimized formulation in pH 1.2.

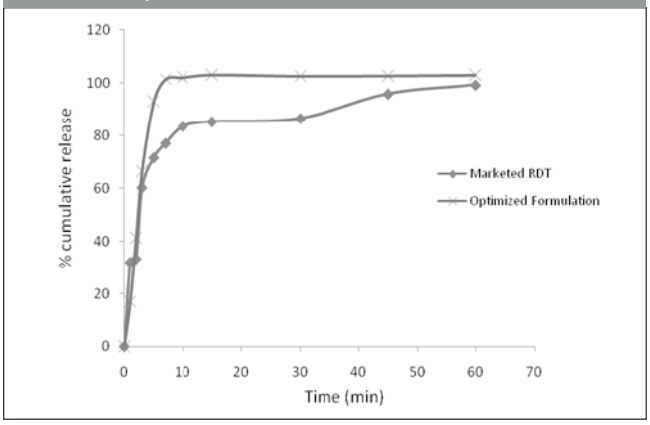


Fig. 5: Response surface plot of DT.

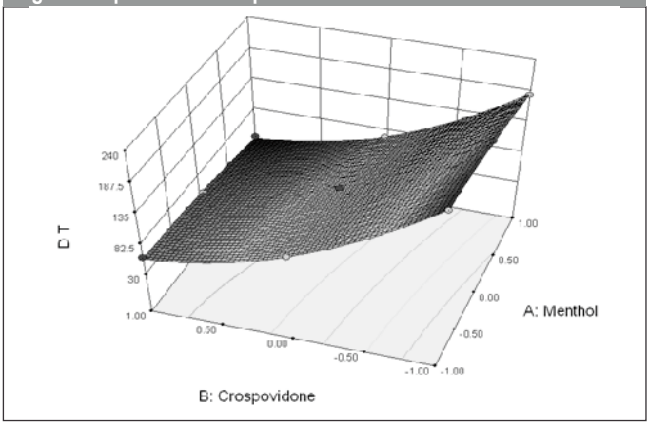


Fig. 6: Response surface plot of Q_5 min in pH 1.2.

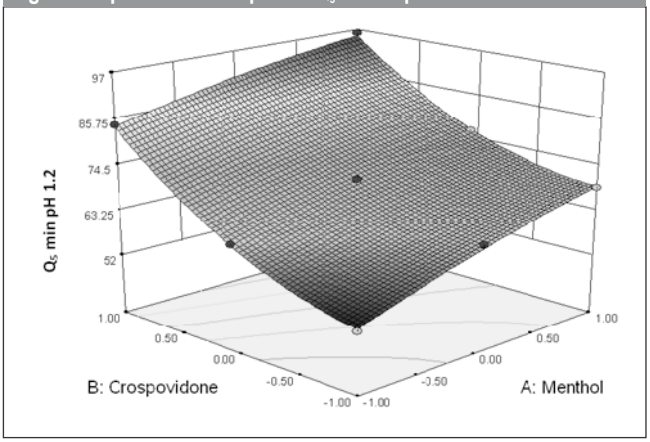
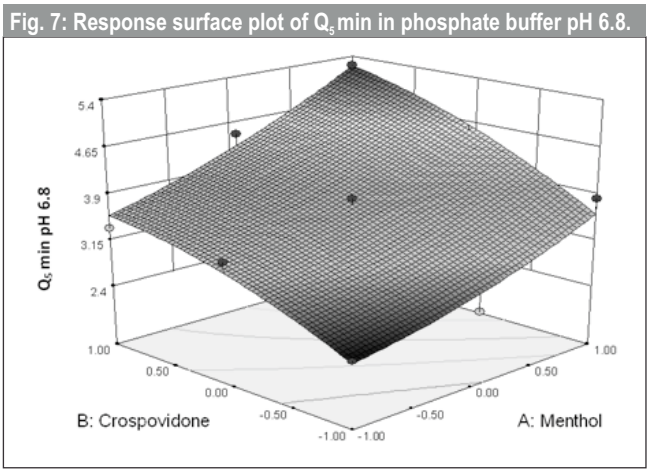


Fig. 7: Response surface plot of Q_5 min in phosphate buffer pH 6.8.



responses by satisfying the requirements for each response in the set. Considering ease of manufacturing and the time required for manufacturing RDT concerned for optimization, the variable X_1 was kept in the range of 0 to 0.5 level because increase beyond that time required for complete sublimation increases time for vaccum drying so that criteria for X_1 is at 0 level. Disintegration time DT (Y_1) criteria was fixed to minimize, Q_5 m in pH 1.2 (Y_2) criteria was fixed for maximize and Q_5 m in phosphate buffer pH 6.8 (Y_3) was kept in range from 2 to 5 %. The optimal calculated parameters were menthol amount (X_1): 4.35%, crospovidone (X_2): 9%. From the results of optimized formulation, it can be concluded that optimized formulation of investigated subliming agent and superdisintegrant ensured the DT and release profile Q_5 m in pH 1.2 and Q_5 m in phosphate buffer pH 6.8, which were very close to the predicted values as shown in Table 7. Higher percentage of menthol results in higher porosity in tablets. As sublimation of menthol creates pores in the tablet structure, the water uptake and subsequent disintegration as well as release of drug are facilitated, while higher percentage of

crospovidone wicking is facilitated. From the above results, it can be concluded that optimization of the RDT was performed in a very short time period and with a small number of experimental runs. All the tablets pass the test for weight variation, hardness, friability, content uniformity, disintegration time as per pharmacopoeial requirements. Dissolution studies of DPC and optimized formulation showed retarded release of drug in pH 6.8 due to higher concentration of polymer. But it showed faster release in pH 1.2 as Eudragit EPO is readily soluble in pH 1.2. This reveals the taste masking of drug in tablets and its suitability for RDT.

CONCLUSION

Thus, results conclusively demonstrated successful masking of taste by polymer carrier system using Eudragit EPO. This may be of value for the pharmaceutical industries dealing with bitter drugs to improve patient compliance and thus effective pharmacotherapy.

The results of a 3^2 full factorial design revealed that the amount of menthol and crospovidone significantly affect the dependent variables viz disintegration time Q_5 m in pH 1.2 and Q_5 m in pH 6.8. It is thus concluded that by adopting a systematic formulation approach, an optimum point can be reached in the shortest time with minimum efforts. Sublimation technique would be an effective alternative approach compared with the use of more expensive adjuvants in the formulation of rapidly disintegrating tablets with improved drug dissolution.

ACKNOWLEDGMENT

Authors are thankful to Emcure Pharmaceuticals, Pune, India for providing tramadol HCl, Evonic India Ltd, Mumbai for providing Eudragit EPO. The authors are also thankful to University of Pune, India, for providing financial assistance.

REFERENCES

1. Ishikawa T, Watanabe Y, Utoguchi N, Matsumoto M. Preparation and evaluation of tablets rapidly disintegrating in saliva containing bitter taste masked granules by compression method. Chem Pharm Bull (Tokyo). 1999;47:1451-4.
2. Koizumi K, Watanabe Y, Morita K, Utoguchi N, Matsumoto M. New method for preparing high porosity rapidly saliva soluble compressed tablets using mannitol with camphor, a subliming material. Int J Pharm.1997;152:127-31.
3. Kaushik D, Dureja H, Saini TR. Mouth dissolving tablets: A review. Indian Drugs. 2004;41:187-93.
4. Shu T, Suzuki H, Hironaka K, Ito K. Studies of rapidly disintegrating tablets in oral cavity using coground mixture of mannitol with crospovidone. Chem Pharm Bull (Tokyo). 2002;50:193-8.
5. Bi Y, Sunada H, Yonezawa Y. Evaluation of a compressed tablet rapidly disintegrating in the oral cavity. Chem Pharm Bull 1996;44:2121-7.
6. Chang RK, Guo X, Burnside BA, Couch RA. Fast dissolving tablets. Pharm Technol. 2000;24:52-8.
7. Shimizu T, Sugaya M, Nakano Y. Formulation study for lansoprazol fast disintegrating tablet, III. Design of rapidly disintegrating tablets. Chem Pharm Bull. 2003;51:1121-7.
8. Gohel M, Patel M, Amin A, Agrawal R, Formulation design and optimization of mouth dissolves of nimesulide using vaccum drying technique. AAPS PharmSciTech. 2004;5(3):1-6
9. Ahmed IS, Nafadi MM, Fatahalla FA. Formulation of fast dissolving ketoprofen tablet using freez-drying in blister technique. Drug Dev Ind Pharm 2007;33:505-11.
10. Corveleyn S, Remon JP, Formulation and production of rapidly disintegrating tablets by lyophilization using hydrochlorothiazide as a model drug. Int J Pharm. 1997;152:215-25.
11. Lehmann KA., Tramadol in acute pain. Indian Drugs. 1997;53:25-33.
12. Sweetman S., Martindale: The Complete Drug Reference. 34th edition. Pharmaceutical Press, London; 2005.
13. European Pharmacopoeia. 5th edition. Directorate for the quality of medicines of the council of Europe; 2005.
14. Madgulkar A, Bhalekar M, Padalkar R. Formulation Design and Optimization of Novel Taste Masked Mouth-Dissolving Tablets of Tramadol Having Adequate Mechanical Strength. AAPS PharmSciTech. 2009;10(2):574-81.
15. Sohi H, Sultana Y, Khar R. Taste masking technologies in oral pharmaceuticals: recent development and approaches. Drug Dev. Ind. Pharm. 2004;30:429-48.
16. Khan S, Kataria P, Nakhat P. Taste masking of ondansetron HCl by polymer carrier system and formulation of rapidly disintegrating tablets. AAPS Pham Sci Tech 2007;8(2):38-44.
17. Shah PP, Mashru RC. Effect of chitosan crosslinking on bitterness of artemether using response surface methodology. J Pharm. Pharmcol. 2009;98(2):690-703.
18. Shah PP, Mashru RC. Influence of chitosan crosslinking on bitterness of mefloquine HCl microparticles using central composite design. J Pharm. Sci. 2009;98(2) 690-703.
19. Shah PP., Mashru RC. Development and Evaluation of Artemether Taste Masked Rapid Disintegrating Tablets with Improved Dissolution Using Solid Dispersion Technique. J Pharm. Pharmcol. 2008;60:421-7.
20. United States Pharmacopeia 24/NF 19. The Official Compendia of Standards. Asian ed. Rockville, MD: United States Pharmacopoeial Convention Inc; 2000:1913Y1914.
21. Sammour OA, Hammad MA, Megrab NA, Zidan AS. Formulation and optimization of mouth dissolving tablets containing Rofecoxib solid dispersion. AAPS PharmSciTech. 2006; 7(2), E_1-E_9
22. Bolton S. Pharmaceutical Statics. 2nd edition. marcel decker inc; New York; 1990.
23. Lachmann L, Liberman H and Kanig J. The Theory and Practice of Industrial Pharmacy. 3rd edition. Varghese Publishing House, Mumbai; 1987;296-300.
24. Indian Pharmacopoeia 1996, Vol I. The controller of publications; New Delhi.