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Research Article

Formulation Design and Optimization of Novel Taste Masked Mouth-Dissolving Tablets of Tramadol Having Adequate Mechanical Strength

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Abstract. The purpose of this work was to develop novel taste masked mouth-dissolving tablets of tramadol that overcomes principle drawback of such formulation which is inadequate mechanical strength. Tramadol is an opioid analgesic used for the treatment of moderate to severe pain. Mouth-dissolving tablets offer substantial advantages like rapid onset of action, beneficial for patients having difficulties in swallowing and in conditions where access to water is difficult. The crucial aspect in the formulation of mouth-dissolving tablets is to mask the bitter taste and to minimize the disintegration time while maintaining a good mechanical strength of the tablet. Mouth-dissolving tablets of tramadol are not yet reported in the literature because of its extreme bitter taste. In this work, the bitter taste of Tramadol HCl was masked by forming a complex with an ion exchange resin Tulsion335. The novel combination of a superdisintegrant and a binder that melts near the body temperature was used to formulate mechanically strong tablets that showed fast disintegration. A 3^2 full factorial design and statistical models were applied to optimize the effect of two factors, i.e., superdisintegrant (crospovidone) and a mouth-melting binder (Gelucire 39/01). It was observed that the responses, i.e., disintegration time and percent friability were affected by both the factors. The statistical models were validated and can be successfully used to prepare optimized taste masked mouth-dissolving tablets of Tramadol HCl with adequate mechanical strength and rapid disintegration.

KEY WORDS: tramadol; taste masking; mechanical strength; mouth-dissolving tablets; optimization.

INTRODUCTION

Tramadol is a centrally acting opioid analgesic structurally related to codeine and morphine used in the treatment of moderate to severe pain in diverse conditions. Combined with low dependence/abuse potential, it has proven to be of significant advantage over other agents, especially in the elderly (1). Routes other than oral, like intravenous, which are used to administer tramadol are used in acute conditions like postoperative neuralgia or situations when the patient is hospitalized. Unlike insulin, tramadol must be injected under the supervision of a physician only. Patients suffering from arthritis or neuralgia have to take the therapy for longer duration of time. In such cases, oral route is the preferred route. Thus, the problems like bitter taste and ease of swallowing need to be solved for tramadol therapy. Mouth-dissolving tablets (MDT) are very beneficial for patients with difficulties in swallowing and in conditions where access to water is difficult. MDT dissolves fast and exerts rapid onset of action (2).

MDT can be formulated using various methods. Some of them involve increasing the porosity of the tablet and decreasing the disintegration time (DT) (3). Superdisintegrants are used that swell or absorb water rapidly to disintegrate the tablet (4). Technologies like Zydis based on lyophilization yield tablets that dissolve in a few seconds. Most of the techniques aim at lowering the DT, but doing this always compromises the mechanical strength. Zydis tablets need special packaging and patient counseling for removing the tablets from the strip (5). Hence, the objective of this work was to formulate and optimize mouth-dissolving tablets of Tramadol HCl that disintegrate in a few seconds and still have good mechanical strength. Mouth-dissolving tablet of tramadol is not reported yet because of its extreme bitter taste. Currently, very few methods have been reported for taste masking of tramadol and very few literature are available for the same. Methods like polymer coating increase drug particle size and are not useful for formulation into mouth-dissolving tablets, as they affect the mouth feel. Commonly used resins for taste masking like Indion 234 or Amberlite IRP 64 fail to mask the bitter taste of tramadol. This work describes an optimized method of masking the bitter taste of tramadol by ion exchange process.

Generally, a binder increases the mechanical strength but delays DT. Hence, in the present work, a novel approach is used which combines a binder having melting point near to body temperature with a superdisintegrant. Initial screening of various materials like polyethylene glycols, hydrogenated vegetable oils, and combinations of various glycerides showed that Gelucire 39/01 is the binder that fits for this purpose. Crospovidone, which acts by very rapid water wicking

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mechanism, was used as a superdisintegrant. Effects of crospovidone and Gelucire on DT and percent friability of the tablets were optimized using a 32 factorial design, and the mathematical models were validated.

MATERIALS AND METHODS

Materials

Tramadol HCl (Lupin Labs, Pune), Tulsion 335 (Thermax India Ltd., Pune), crospovidone (ISP Corp, Hong Kong), Gelucire 39/01(Gattefosse, France), orange flavor(Keva Flavors, Mumbai), Aerosil, and sodium saccharine(Iatros Pharma, Pune) were received as gift samples. Menthol, mannitol, and citric acid (reagent grade) were purchased from Loba Chemie.

Methods

Taste Masking of Tramadol HCl

Determination of threshold bitterness concentration of Tramadol HCl (6). A panel of ten healthy human volunteers (age 20–25) was selected. 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 were asked to hold 10 mL of each solution in oral cavity for 30 s 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). Rinsing the mouth by distilled water and a gap of 30 min were applied between successive tests. Based on the opinion of the volunteers, threshold bitterness concentration of Tramadol HCl was judged.

Preparation of DRC (7,8). Batch method was used to prepare drug–resin complex (DRC). Five grams of Tulsion 335 was allowed to swell for 90 min in a beaker containing 200 mL of deionized water of conductivity less than 2. Then, 5 g of Tramadol HCl was added to it and stirred for 300 min. The mixture was filtered through Whatman filter paper no. 41. The residue was washed with 100 mL of deionized water and dried.

Optimization of various parameters for maximum drug loading (9,10). Drug loading process was optimized for maximum drug loading considering parameters like effect of activation, resin swelling time, and pH. The effect of activation of resin on drug loading was studied as follows. Five grams of Tulsion 335, placed on a Whatman filter paper in a funnel, was washed with deionized water and subsequently with 1 N HCl (100 mL). The resin was rewashed with water until neutral pH was reached. DRC was prepared in the same way as discussed earlier using 5 g each of Tramadol HCl and acid-activated resin. Similarly, alkali activation of Tulsion 335 was done, replacing 1 N HCl with 1 N NaOH. Finally, Tulsion 335 was also activated with combined treatment of 1 N HCl and 1 N NaOH solutions. Drug loading efficiency in each case was determined.

To study the effect of other parameters, activated resin was used.

Optimization of resin swelling time was carried out by keeping 5 g of Tulsion 335 in each of the five beakers containing 200 mL of deionized water for 30, 60, 90, 120, and 180 min, respectively. DRC was prepared as described above using 5 g of Tramadol HCl and percent drug loading was estimated. To assess the effect of pH on drug loading, drug solution was prepared in deionized water and pH was adjusted to 2, 3, 4, 5, 6, 7, and 8 using standard solutions of hydrochloride and sodium hydroxide. Equal quantity of resin was swollen separately and added to drug solution and loading efficiency determined at these conditions.

Characterization of DRC

In vitro taste evaluation (6,8). A quantity of DRC equivalent to 50 mg of Tramadol was added to each of the six volumetric flasks containing 10 mL of phosphate buffer of pH 6.8. The mixtures were shaken for 0, 15, 30, 60, 120, and 300 s and filtered. Content of Tramadol in each filtrate was determined. For satisfactory taste masking, the amount of drug dissolved at the end of 120 s should not be more than the threshold bitterness concentration of the drug.

Confirmation of Complexation (9,11,12)

FTIR studies. Tramadol HCl, Tulsion 335, and physical mixture of both and DRC were subjected to Fourier transform infrared spectroscopy (FTIR) studies. Samples were prepared using KBr disc method and spectra were recorded over the range 400 to 4,000 cm^{-1}. Spectra were analyzed for drug–resin interactions and functional groups involved in the complexation process.

Powder X-ray diffraction studies. X-ray diffractograms of Tramadol HCl, Tulsion 335, and DRC were recorded using Philips PW 3710 deffractometer and analyzed for interactions between drug and resin and confirmation of complexation.

Thermal analysis. Differential scanning calorimetry (DSC) was carried out using Mettler Toledo 823e instrument equipped with intracooler. Indium zinc standards were used to calibrate the temperature and enthalpy scale. The samples were hermetically sealed in aluminum pans and heated over the temperature range 30°C to 300°C with heating rate of 10°C/min. Inert atmosphere was provided by purging nitrogen gas flowing at 40 mL/min.

Estimation of drug content. One hundred milligrams of DRC was stirred with 100 mL of 0.1 N HCl for 60 min so as to release the entire drug from DRC. The mixture was filtered and 1 mL of the filtrate was diluted to 100 mL using 0.1 N HCl. The absorbance of this solution was measured at 272.3 nm using 0.1 N HCl as blank and the content of Tramadol estimated.

In vitro dissolution studies (11). A quantity of DRC equivalent to 50 mg of Tramadol was subjected to dissolution studies using USP type II dissolution test apparatus at 37±2°C at 50-rpm speed. Nine hundred milliliters of 0.1 N HCl was used as dissolution medium. Aliquot equal to 5 mL was

withdrawn at specific time intervals and amount of Tramadol released from DRC was determined.

Formulation development. DRC was used to prepare MDT by direct compression technique. Composition of tablets is mentioned in Table I. All materials except Gelucire 39/01 were passed through sieve number 85. Crospovidone was divided into two equal parts by weight. DRC, one part of crospovidone, sodium saccharine, citric acid, and mannitol were mixed uniformly and heated to 40°C. Gelucire 39/01 was melted separately at the same temperature and added to this powder blend with continuous mixing. The mass was passed through a sieve number 18 to form granules and cooled. After cooling, the granules were mixed with remaining crospovidone, menthol, orange flavor, and lubricated with aerosil. Tablets were compressed using 8-mm flat punch on Minipres II MT Rimek 16 station compression machine. Tablet weight was maintained at 250 mg. Target tablet hardness was between 3 and 4 kg/cm^2.

Optimization of Formulation (13–16)

Selection of suitable experimental design. In a full factorial design, all the factors are studied in all the possible combinations, as it is considered to be most efficient in estimating the influence of individual variables (main effects) and their interactions using minimum experimentation. In the present study, fitting a cubic model is considered to be better as the values of the response surfaces are not known from the previous findings. Hence, 32 factorial design was chosen for the current formulation optimization study. Amounts of crospovidone and Gelucire 39/01 were selected as independent factors, whereas DT and percent friability (%F) were measured as responses. Based on initial trials, levels of crospovidone were selected as 7.5, 15, and 22.5 mg, whereas Gelucire 39/01 levels were 10, 15, and 20 mg. Nine formulations were prepared according to 32 factorial design and evaluated. The responses were analyzed for analysis of variance (ANOVA) using Design Expert version 7.1.5 software. Statistical models were generated for each response parameter. The models were tested for significance.

Validation of statistical model. Levels of crospovidone and Gelucire 39/01 were selected at six different points and responses predicted by the statistical models were calculated. Mouth-dissolving tablets were prepared using these levels and responses were measured practically. The predicted responses were compared against observed responses and closeness between them was checked.

Response surface plots. Response surface plots were generated for each response to study the effect of both factors on each response.

Evaluation of Tablets

General parameters (17,18). Tablets were evaluated for hardness (Monsanto hardness tester), friability (Roche friabilator), and weight variation.

Uniformity of content. Five tablets were selected randomly and dissolved in 100 mL of 0.1 N HCl, stirred for 60 min, and filtered. One milliliter of the filtrate was diluted to 100 mL with 0.1 N HCl. Absorbance of this solution was measured at 272.3 nm using 0.1 N HCl as blank and content of Tramadol was estimated.

Disintegration time. Many reports suggest that conventional DT apparatus may not give correct values of DT for MDTs (19–21). The amount of saliva available in the oral cavity is very limited (usually less than 6 mL), whereas the conventional DT apparatus uses a large amount of water with very rapid up and down movements. MDT is required to disintegrate in such small amounts of saliva within a minute without chewing the tablet. In a simplest method to overcome these problems, 6 mL of phosphate buffer of pH 6.8 was taken in a 25-mL measuring cylinder. Temperature was maintained at 37±2°C. A MDT was put into it and time required for complete disintegration of the tablet was noted.

Wetting time (22). A Petri dish containing 6 mL of distilled water was used. A tissue paper folded twice was kept in the dish and a tablet was placed on it. A small quantity of amaranth red color was put on the upper surface of the tablet. Time required for the upper surface of the tablet to become red was noted as the wetting time of the tablet.

Table I. Composition of Mouth Dissolving Tablets as per 3^2 Factorial Design

	Formulation code								
Ingredient	A1	A2	A3	A4	A5	A6	A7	A8	A9
DRC (eq. to 50 mg of Tramadol)	103.9	103.9	103.9	103.9	103.9	103.9	103.9	103.9	103.9
Crospovidone	7.5	7.5	7.5	15	15	15	22.5	22.5	22.5
Gelucire 39/01	10	15	20	10	15	20	10	15	20
Citric acid	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5
Sodium saccharine	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Menthol	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Orange flavor	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Aerosil	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Mannitol	110.6	105.6	100.6	103.1	98.1	93.1	95.6	90.6	85.6
Total	250	250	250	250	250	250	250	250	250

All quantities in milligrams

Dissolution studies (23). Dissolution test was carried out using USP type II dissolution test apparatus at 37±2°C and 50-rpm speed. Nine hundred milliliters of 0.1 N HCl was used as dissolution medium. Aliquot equal to 5 mL was withdrawn at specific time intervals and amount of Tramadol released from DRC was determined.

RESULTS

Threshold Bitterness

Most of the volunteers reported 20 μg/mL as the threshold bitterness concentration for Tramadol HCl.

Optimization of Parameters for Maximum Drug Loading

The percent drug loading with inactivated resin, treated with acid, alkali, and combination thereof was found to be 88.05±1.2%, 92.54±1.08%, 93.61±1.31%, and 95.78±0.26%, respectively. Highest drug binding on resin was achieved when activated with both acid alkali treatments. It was noted that the resin requires proper swelling time for maximum drug loading. The loading efficiencies for resin swelling time of 30, 60, 90, 120, and 180 min were found to be 80.34± 1.28%, 92.42±1.56%, 95.47±1.19%, 95.89±1.24%, and 95.97 ±1.47%, respectively. It was observed that a swelling time of 90 min was sufficient for maximum drug loading. When Tramadol HCl was loaded in different pH environments like 2, 3, 4, 5, 6, 7, and 8, loading was found to be 81.67±0.89%, 83.12±0.78%, 84.42±1.56%, 91.20±1.15%, 92.62±1.31%, 95.24±1.06%, and 95.36±0.82%, respectively. It was observed that optimum drug loading was achieved at neutral pH and was not much increased at pH higher than this.

Characterization of DRC

In vitro Taste Evaluation

No detectable amount of Tramadol HCl dissolved in the phosphate buffer of pH was detected at the end of 300 s. Thus, the DRC did not release any drug at salivary pH and taste masking of Tramadol HCl by making an ion exchange complex with Tulsion 335 was complete and satisfactory.

Confirmation of Complexation (9,10,24)

FTIR studies. The IR spectrum of Tramadol HCl showed C–N *str* at 3,250 cm^{-1}, C–H *str* at 2,950 cm^{-1}, O–H *str* at 1,380 cm^{-1}, C–O *str* at 1,257 cm^{-1}, and peak around 1,680 cm^{-1} corresponding to hydrohalide salt associated with tertiary amine. The peaks corresponding to C–N *str* and C–H *str* disappeared in the spectrum of DRC. Also, the characteristic peak at 1,680 cm^{-1} representing HCl was not seen in the spectrum of DRC. The spectrum of Tulsion 335 showed distinct C=O *str* of the –COOH functional group of the resin polymer matrix which was not seen in the spectrum of DRC (Fig. 1).

Powder X-ray diffraction studies. The X-ray diffractograms of Tramadol HCl confirmed its crystalline nature, as evidenced from the number of sharp and intense peaks. The diffractograms of Tulsion 335 showed diffused peaks, indicating its amorphous nature, while the diffraction pattern of DRC represents complete disappearance of crystalline peaks of drug (Fig. 2).

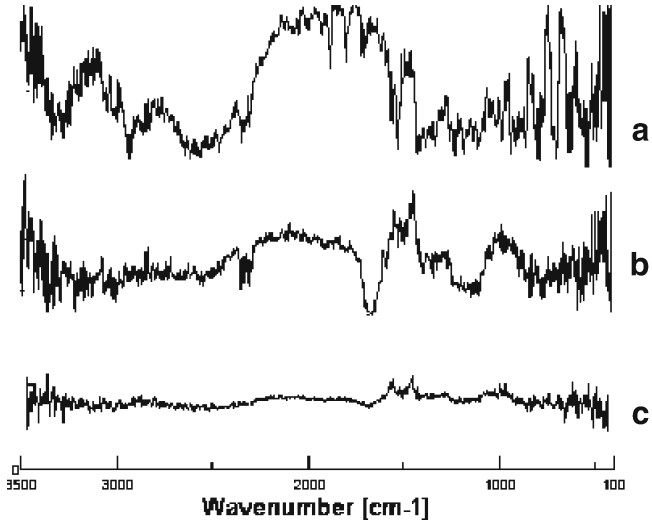

Fig. 1. FTIR spectra of Tramadol HCl (*A*), Tulsion 335 (*B*) and DRC (*C*)

DSC studies. The thermogram of Tramadol HCl shows a sharp endothermic peak at 182.51°C, whereas no sharp peaks were observed in case of Tulsion 335. The endothermic peak of tramadol was absent in the thermogram of DRC (Fig. 3).

Determination of drug content. When DRC was prepared using all of the optimized parameters for drug loading, the percent drug loading was found to be 96.24%, and hence, the drug content was 48.14% (*w*/*w*).

In vitro Dissolution Studies

The dissolution profile of DRC showed complete drug release within 20 min. Thus, the loaded drug is quickly released in acidic conditions.

Physical Properties of Tablet Blend

Tablet blends of all formulations showed good flowability (angle of repose <30° and Carr's index ≤12). Bulk densities varied from 0.8 to 0.9 (Table II).

Evaluation of Tablets

The outcomes of various evaluation parameters are shown in Tables III and IV. The dissolution studies indicated 100% drug release within 20 min from all batches (Fig. 4). All batches showed DT less than a minute and friability less than 1.02%.

32 Factorial Design

A statistical model, $Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1X_1 + b_{22}X_2X_2$, incorporating interactive and polynomi-

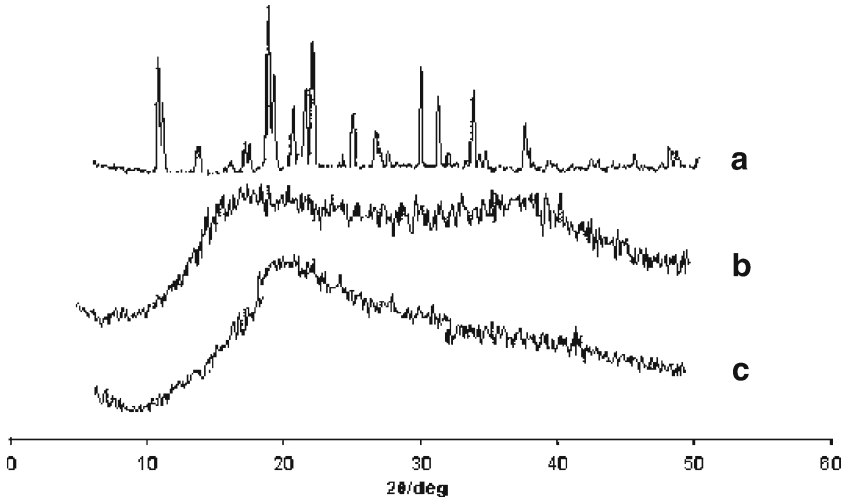

Fig. 2. X-ray diffraction patterns of Tramadol HCl (*A*), Tulsion 335 (*B*), and DRC (*C*)

al terms was used to evaluate the responses, where Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs, and b_i is the estimated coefficient for the factor X_i. 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 DT and $\%F$ for the nine batches (A1 to A9) showed a wide variation (i.e., 12 to 54 s and 0.41% to1.02%, respectively). The data clearly indicate that the DT and $\%F$ values are strongly dependent on the selected independent variables. The fitted full equations relating the responses DT and $\%F$ to the transformed factors are as:

$$DT = 31.56 - 15.83X_1 + 0.61X_1X_1 - 5.33X_2 + 0.11X_2X_2 \quad (1)$$

$$\%F = 0.68 - 0.21X_1 + 0.008333X_1X_1 - 0.08X_2 + 0.003333X_2X_2. \quad (2)$$

Table V shows the results of the ANOVA which was used to generate statistical models.

Response Surface Plots

It was observed that DT and $\%F$ were dependent on both the factors. There was a linear decrease in the disintegration time with increase in the levels of both factors. The same effect was observed with Gelucire 39/01 (Fig. 5).

Validation of Statistical Model

The predicted responses of the six formulations and corresponding actual experimentally observed values were found to be in close agreement as indicated in Table VI. Thus, the models developed to predict the responses were not only significant statistically but also were found to be valid to predict values that were very close to the practical observations.

DISCUSSIONS

Loading of Tramadol HCl on Tulsion 335 was carried out by batch process. Batch process is the preferred method for loading a drug into finely divided ion exchange operations commonly used with ion exchange resins. Due to its fine

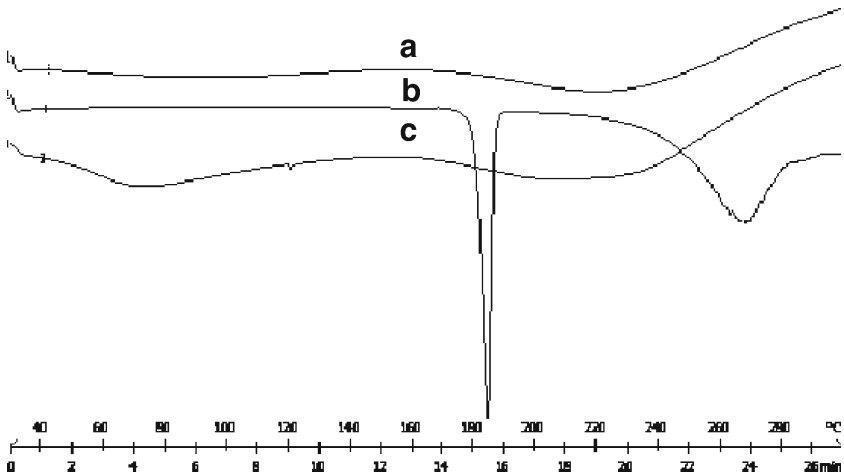

Fig. 3. DSC thermograms of Tulsion335 (*A*), Tramadol HCl (*B*), and DRC (*C*)

Table II. Evaluation of Physical Properties of Tablet Blends

Formulation code	Bulk density	Tapped density	Carr's index	Angle of repose (deg)
A1	0.8294±0.02	0.9296±0.03	12.08	27.78±0.03
A2	0.8626±0.03	0.9036±0.04	4.75	28.08±0.02
A3	0.8439±0.04	0.9156±0.01	8.49	26.06±0.04
A4	0.8321±0.02	0.9221±0.02	10.81	24.67±0.01
A5	0.8284±0.02	0.9286±0.04	11.96	25.55±0.02
A6	0.8675±0.02	0.9135±0.02	5.30	27.08±0.01
A7	0.845±0.02	0.9916±0.01	9.67	25.06±0.01
A8	0.864±0.02	0.9234±0.04	11.73	23.67±0.02
A9	0.8221±0.03	0.9247±0.02	12.48	24.85±0.01

$n=3$

particle size, Tulsion 335 does not lend itself to conventional columnar operations commonly used with ion exchange resins. Higher swelling efficiency in the batch process makes more surface area available for ion exchange. So batch process was selected. Treating an ion exchange resin with combined acid and alkali treatment is considered as rejuvenation of the resin. This ensures removal of the adsorbed impurities associated with industrial scale manufacture or absorbed during storage or handling and activation of the exchangeable groups. The ion exchange process is pH-dependent, and thus, treating the resin at two extremities of pH ensures that more exchangeable groups are available for maximum and rapid drug loading. Hence, activation of the resin is required. Swelling and hydration increases the rate and extent of ion exchange process. In unswollen resin matrix, the exchangeable groups are latent and coiled towards the backbone. Swelling increases the surface area and these groups get oriented towards outside. pH affects the extent of drug loading process. The mobile or exchangeable cation in Tulsion 335 is the hydrogen ion. In acidic environments (generally pH below 4), the resin exists as free acid in an essentially nonionic state. Loading of drug onto Tulsion 335 occurs maximum at pH higher than the acidic range. Thus, it was observed that Tulsion 335 activated by combined acid and alkali treatment, swollen for 90 min in deionized water, showed maximum loading of Tramadol HCl at pH near neutral. The formation of ion exchange complex between Tramadol HCl and Tulsion 335 was confirmed by

Table III. Evaluation of Various Parameters of Tablets

Trial no.	Disintegration time (s)	Friability	% Assay	Wetting time (s)
A1	54±1.02	1.02±0.02	98.64±1.02	40±0.94
A2	48±0.89	0.88±0.01	99.21±1.26	38±0.57
A3	42±1.21	0.8±0.04	99.42±0.85	34±1.21
A4	36±0.67	0.73±0.02	98.41±0.62	28±0.68
A5	30±0.96	0.66±0.03	98.53±1.08	21±0.59
A6	25±0.82	0.60±00.02	98.02±0.96	19±0.74
A7	21±0.69	0.54±0.01	97.93±1.21	16±0.81
A8	16±0.77	0.48±0.03	99.78±1.05	14±0.47
A9	12±0.81	0.41±0.01	97.23±0.85	9±0.52
Broad range	12–54	0.41–1.02	97.23–99.78	9–40

$n=3$

Table IV. Evaluation of Tablet Formulations

	Physical evaluation			
Trial no.	Weight variation (mg)±SD	Hardness (kg/cm^2)±SD	Diameter (mm)±SD	Thickness (mm)±SD
A1	250.31±1.61	3.2±0.23	8±0.05	2.5±0.02
A2	250.19±1.32	3.5±0.52	8±0.04	2.7±0.03
A3	250.42±1.47	3.4±0.29	8±0.03	2.8±0.04
A4	249.92±1.46	3.9±0.52	8±0.00	2.7±0.02
A5	250.89±2.11	3.8±0.59	7.9±0.05	2.5±0.01
A6	250.33±1.68	3.3±0.76	8±0.03	2.6±0.02
A7	251.06±1.20	3.7±0.72	8±0.02	2.8±0.05
A8	249.86±1.42	3.2±0.53	8±0.04	2.8±0.03
A9	250.63±1.63	3.1±0.28	8±0.02	2.7±0.04
Broad range	249.86–250.89	3.1–3.9	7.9–8	2.5–2.8

$n=3$

FTIR, X-ray, and DSC studies. It was observed in the FTIR studies that functional groups involved in the complexation process were –COOH of Tulsion 335 and HCl along with the tertiary amine of tramadol HCl. The absence of other peaks of Tramadol HCl discussed earlier in the spectrum of DRC indicated that the drug was completely embedded in the resin polymer matrix. X-ray studies indicated the crystalline nature of tramadol HCl and amorphous nature of Tulsion 335 and DRC. The drug was entrapped in the resin and hence the sharp crystalline peaks of the drug were not observed in the X-ray diffraction pattern of the DRC. The sharp endothermic peak at 182.51°C corresponds to melting of pure drug and its crystalline nature. The thermogram of Tulsion 335 and DRC indicated amorphous nature. The formation of ion exchange complex and entrapment of Tramadol HCl in the polymer matrix of Tulsion 335 was thus confirmed from the findings of these three studies. All tablet blends showed good flow properties. Dissolution studies of DRC and mouth-dissolving tablets showed similar profile of drug release. It was observed that the release of tramadol was controlled by desorption from DRC and independent of formulation. The exchangeable ion for Tulsion 335 is the H^+ ion. Tulsion 335 readily loses the adsorbed species in H^+ ion environment. The tablet formulations were optimized using 32 factorial design. The

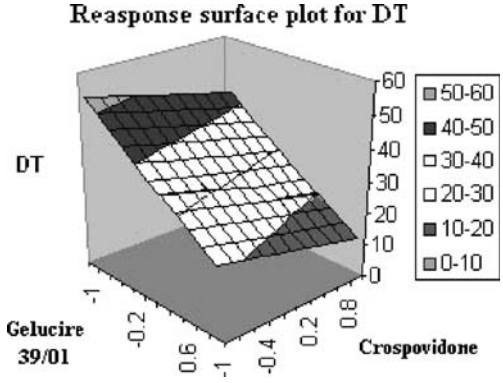

Fig. 4. Release profile of tramadol from tablet formulations

Table V. ANOVA for Selected Statistical Model

Response model	Sum of squares	*df*	Mean square	*F* value	*P* value	R^2	Adeq. precision
DT	1,681.78	4	420.44	688.00	<0.0001	0.9985	72.654
%*F*	0.31	4	0.077	98.51	0.0003	0.9992	27.963

outcomes for response parameters, i.e., DT and friability, were subjected to regression analysis, and statistical models were found to be significant. The high values of correlation coefficient for DT and %*F* indicate a good fit, i.e., good agreement between the dependent and independent variables. The equations may be used to obtain estimates of the response as a small error of variance was noticed in the replicates. The *F* value in the ANOVA table is the ratio of model mean square to the appropriate error mean square. The larger the ratio, the larger the *F* value and the more likely that the variance contributed by the model is significantly larger than random error. If the *F* ratio—the ratio of variances—lies near the tail of the <*F*> distribution, then the probability of a larger *F* is small and the variance ratio is judged to be significant. Usually, a probability less than 0.05 is considered significant. The *F* distribution is dependent on the degrees of freedom <*df*> for the variance in the numerator and the <*df*> of the variance in the denominator of the *F* ratio. The model *F* value of 688 for DT and 98.51 for friability and high R^2 values suggest that these models are significant. There is only 0.01% chance that a 'model *F* value' this large could occur due to noise. Values of '*p*' less than 0.0500 indicate that model terms are significant. In this case, both the models generated for DT and %*F* are significant. As there are no insignificant terms, model reduction is not required. Adequate precision measures the signal-to-noise ratio. A ratio greater than 4 is desirable. The ratios of 72.654 and 27.963, respectively, for DT and %*F* models indicate an adequate signal for each. These models can be used to navigate the design space. It was observed that disintegration time was dependent on both factors. A linear decrease in the disintegration time was observed with an increase in the levels of both factors. Crospovidone, being a superdisintegrant, enhances faster disintegration. In addition, Gelucire 39/01 also helps in the disintegration process by melting near body temperature. It was observed from the response surface and contour plots that both the factors had influence on the friability of the tablets. There was a linear decrease in the values of friability, as the levels of crospovidone and Gelucire were increased. Gelucire 39/01, being a binder, increases the mechanical strength of the tablet, and crospovidone is also known to produce mechanically strong tablets. Optimum values of friability were observed at high levels of both factors. Thus, it was observed that the novel combination of a super-disintegrant and a binder that melts near body temperature produced mouth-dissolving tablets having adequate mechanical strength and rapid disintegration. Thus, the major problem in formulating mouth-dissolving tablets, i.e., poor mechanical strength, was overcome. A good evaluation of a statistical model is not how well it fits the data but how well it predicts the points. Comparison of predicted responses and observed values for the same showed close agreement, and the models were found to be valid.

CONCLUSION

It was concluded that the bitter taste of tramadol hydrochloride can be masked by forming an ion exchange complex with Tulsion 335. Mouth-dissolving tablets of tramadol having rapid disintegration and good mechanical strength can be prepared using a novel combination of crospovidone and Gelucire 39/01. Thirty-two factorial design and statistical models can be successfully used to optimize the formulations.

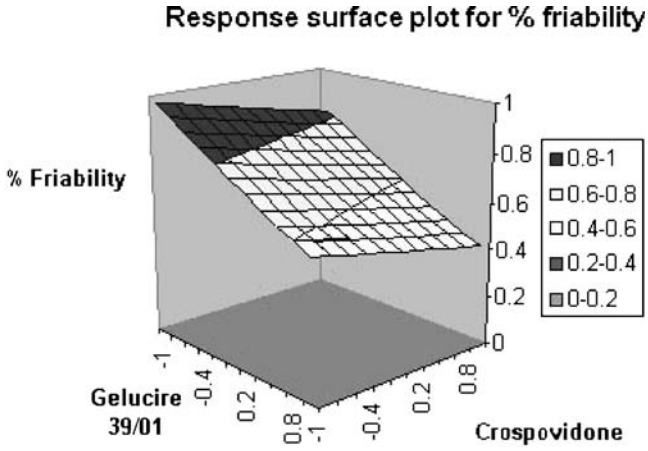

Fig. 5. Response surface plots for DT and % Friability

Table VI. Comparision of Predicted Values and Experimental Values

Formulation code	Predicted values±SD	Experimental values±SD	Residuals
A10	DT 50±0.5	DT 51±0.76	1
	%*F* 0.93±0.02	%*F* 0.91±0.02	0.02
A11	DT 44±1.1	DT 42±1.02	2
	%*F* 0.85±0.01	%*F* 0.82±0.01	0.03
A12	DT 39±0.76	DT 40±0.69	1
	%*F* 0.77±0.04	%*F* 0.74±0.02	0.03
A13	DT 28±0.56	DT 26±0.58	2
	%*F* 0.63±0.03	%*F* 0.61±0.02	0.02
A14	DT 17±0.98	DT 19±0.74	2
	%*F* 0.48±0.01	%*F* 0.50±0.01	0.02
A15	DT 12±0.84	DT 13±0.49	1
	%*F* 0.41±0.02	%*F* 0.43±0.02	0.02

n=3

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