

Formulation design and optimization of taste-masked mouth-dissolving tablets of Tramadol hydrochloride

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The aim of the present study was to mask the extremely bitter taste of Tramadol HCL, an opioid analgesic, and to formulate a tablet which can rapidly disintegrate in saliva (rapidly disintegrating tablet). The crucial aspect in the formulation of mouth-dissolving tablets is to mask the bitter taste and to minimize the disintegration time. Taste masking was done using sweetening agent and D-mannitol and taste-masked pellets were prepared by extrusion spherulization technique. Prepared pellets were tested for drug content, taste evaluation in oral cavity and molecular property. Pellet shows significant taste masking, confirmed by *in vitro* taste evaluation; therefore, it was selected for further study. Pellets were evaluated for density, angle of repose, Carr's index, Hausner's ratio and sphericity while tablets were evaluated for disintegration and *in vitro* dissolution. A 3² full factorial design and statistical models were applied to optimize the effect of two factors, i.e. superdisintegrant sodium starch glycolate and taste-masking agent (D-mannitol). In this study, response surface methodology was used for designing of the experiment, generation of mathematical models and optimization study. Taste evaluation of pellets in human volunteers revealed considerable taste masking with a degree of bitterness below threshold value (2.0) within 10 s, whereas Tramadol HCl was rated intensely bitter with a score of +4 for 10 s. The size of the pellets varied from 0.895 to 1.423 mm for different batch and found to be a spherical. Disintegration time of different formulations varied from 30 to 60 s. It was observed that the responses, i.e. disintegration time and sphericity 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 disintegration and shape.

Key words: 3² factorial design, rapidly disintegrating tablet, response surface methodology, taste-masked granule, Tramadol HCL

INTRODUCTION

Recently, pharmaceutical preparations used for elderly patients have been investigated to improve the treatment compliance and quality of life of such patients. A tablet which can rapidly disintegrate in saliva (rapidly disintegrating tablet) is an attractive dosage form^[1] and a patient-oriented pharmaceutical preparation. The concept of rapid disintegrating drug delivery system emerged from the desire to provide patients with conventional mean of taking their medication. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially elderly and pediatrics, because of the physiological changes associated with these

groups of patients.^[2] Other categories that experience problems using conventional oral dosage forms includes the mentally ill, uncooperative and nauseated patients, those with conditions of motion sickness, sudden episodes of allergic attack or coughing during the common cold and bronchitis where an ultra-rapid onset of action required.^[3] Mouth-dissolving tablet improved compliance in patients.^[4] For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention.^[5]

Mouth-dissolving tablet disintegrate or dissolve quickly in a few seconds in saliva after placing in the oral cavity.^[6] For some APIs, a portion of the medicament is also absorbed through the mouth, pharynx and esophagus as the medicated saliva mixtures descends into the stomach. In this way it provides the rapid onset of action and prevent hepatic first pass metabolism, thus enhancing the bioavailability of the API.^[7] The bioavailability of drugs may be increased compared with the conventional oral dosage forms^[8] as a result of reduced dosage and improved clinical performance through a reduction of unwanted effects.

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The mechanisms of the taste-masking methods may be summarized as following. Mask the distasteful sensation by the addition of flavors, sweeteners, effervescent agents, ion exchange resin, microencapsulation, solid dispersion, multiple emulsions and using inclusion complex. The second is to avoid the bitter drugs coming into direct contact with patients' taste buds by coating or granulation.^[9] The disintegrating property of the tablet is attributable to a quick ingress of water into the tablet matrix, which creates porous structure and results in rapid disintegration. Hence, the basic approaches to develop mouth-dissolving tablet include taste-masked tablet with maximizing the porous structure, incorporating the appropriate disintegrating agent and using highly water-soluble excipients in the formulation. Various techniques such as freeze drying, sublimation, spray drying, moulding, mass extrusion and direct compression have been reported for preparation of mouth-dissolving tablets.

Tramadol is an opioid analgesic used for the treatment of moderate to severe pain. Tramadol HCL is Class 1 drug which get rapidly absorbed after oral administration. The mean bioavailability of a 100 mg oral dose is approximately 75%. It is an extremely bitter drug. It undergoes metabolism and its half life is about 6 h. Its onset of action is accrued during 30 to 60 min. Hence, it was selected as a model drug for preparation of taste-masked mouth-dissolving tablet. The usual dosage of Tramadol HCL is 50 to 100 mg three times daily orally.^[10,11]

Rational behind the selection of drug is patient's convenience, because in the present scenario and due to ever increasing competition every individual has to travel frequently including patients of rheumatoid arthritis. In such instances, 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 use of superdisintegrant (generally 2-5%) provides instant disintegration of tablet after putting on tongue, thereby releasing the drug in saliva.^[12] In general, croscarmellose sodium, sodium starch glycolate (SSG) and crospovidone are some of the few superdisintegrants used frequently for such applications.^[13]

Previously Randale *et al.*, prepared rapidly disintegrating tablet, which masked the intensely bitter taste of Metoclopramide HCL.^[14] The major objective of the present study was to develop taste-masked mouth-dissolving tablet of Tramadol HCL using sucrose and D-mannitol and by formulating taste-masked pellets using industrially feasible extrusion spherionization technique. Sodium starch glycolate was used to enhance disintegration and dissolution rate of the prepared formulation. In this case, 3² factorial design was used to optimize the formulation in which sphericity and disintegration parameter were dependent variables.

MATERIALS AND METHODS

Tramadol HCL was procured as a gift sample from Cadila Pharma, Ahmedabad, India. Sodium starch glycolate was obtained from Hi-Media Laboratories Pvt. Ltd., Mumbai, India. Sucrose, D-mannitol and lactose were gifted by JRS Pharma, Mumbai, India. All other solvents and chemicals used were of analytical grade.

Experimental factorial design for the preparation of pellets

A full factorial 3² design was used for optimization procedure. It is suitable for investigating the quadratic response surfaces and for constructing a second-order polynomial model, thus enabling optimization of the pellets. Mathematical modeling and response surface modeling were performed by employing Design-Expert[®] software (Version 8.0.1.0, State-Ease Inc., Minneapolis, MN). Pellets containing Tramadol HCL were prepared based on 3² factorial designs. Quantity of SSG (X_1) and D-mannitol (X_2) were selected as two independent variables. Three levels determined from preliminary studies of each variable were selected and nine possible batches were prepared using different levels of variables [Table 1].

Preparation of taste-masked pellet

The pellets were prepared by extruder spheronizer as per the previously reported method.^[15,16]

Preparation of wet mass

The drug, sucrose, D-mannitol and lactose were accurately weighed and mixed for 5 min in a glass mortar pestle. The appropriate quantity of PVP 10% w/v was slowly added, and was mixed for a further 10 min. Formulation composition of the pellets are shown in Table 2.

Preparation of pellets using extrusion/spherionization process

The drug, sucrose, D-mannitol, lactose and appropriate quantity of binder liquid (PVP, 10% w/v) were premixed using glass mortar pestle for 5 min. The kneaded mass was subjected to extrusion. Extrudates were obtained by using an extruder, extruding at a constant extruder speed of 100 rpm, through a screen having die of 1mm in diameter.

Table 1: Different batches with their respective compositions as per 3² factorial design

Batch code	SSG (X_1)	D-mannitol (X_2)
1	-1	-1
2	-1	0
3	-1	+1
4	0	-1
5	0	0
6	0	+1
7	+1	-1
8	+1	0
9	+1	+1

X1 levels [12 mg (-1), 18 mg (0), 24 mg (+1)]; X2 levels [38 mg (-1), 44 mg (0), 50 mg (+1)]; SSG, sodium starch glycolate

A spheronizer (UICE Lab, Umang Pharma Tech, Mumbai, India) equipped with a radial chequered plate was used for the spheronization stage. Extrudates were processed for 10 min at a speed of 1000-1200 rpm. Pellets were dried at 50°C for 30 min in a hot air oven.

Preparation of taste-masked tablet

For tablet preparation, Tramadol HCl taste-masked pellets equivalent to 50 mg was weighed accurately. Superdisintegrant and diluents were added to obtain final weight of 300 mg. The powder blend was compressed into tablets on a ten-station rotary punch-tableting machine (Rimek Mini Press-1, Ahmedabad, India) using 6-mm-flat punch set. Formulation compositions of tablet are shown in Table 3.

Characterization of pellets

The pellets were characterized for particle size, tapped density, compressibility index and flow properties.^[14,15]

Density

The loose bulk density (LBD) and tapped bulk density (TBD) of pellet was determined by USP II tap density tester (Electrolab, Mumbai, India). The pellets (2 g) were poured into calibrated cylinder (100 ml) and initial volume was noted. Then the cylinder was allowed to fall under its own weight on to the hard surface from the height of 2.5 cm at 2-s-interval. The tapping was then continued until no further change in volume was noted. LBD and TBD were calculated using the following equations:

$$\text{LBD} = \frac{\text{Weight of the pellet}}{\text{Volume of the packing}}$$

$$\text{TBD} = \frac{\text{Weight of the pellets}}{\text{Tapped volume of the packing}}$$

Compressibility

Compressibility index (Carr's index) was determined using the following equation:

$$\text{Carr's Index (\%)} = \frac{[(\text{TBD} - \text{LBD}) \times 100]}{\text{TBD}}$$

Angle of repose

The angle of repose was determined by the funnel method. The accurately weighed pellets were taken in a funnel. The height of a funnel was adjusted in such a way that its tip just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely on to the surface. The diameter of the powder heap was measured and angle of repose was calculated using the following equation:

$$\tan(\theta) = h/r$$

where, h = height of powder heap

r = radius of powder heap.

Size analysis of pellets

Size analysis was carried out for all above-mentioned

Table 2: Formulation composition of pellets

Composition	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pellets material									
Tramadol HCl*	50	50	50	50	50	50	50	50	50
Sucrose*	150	150	150	150	150	150	150	150	150
D-mannitol*	38	50	50	44	38	38	44	50	44
Lactose*	50	26	38	38	38	47	44	32	32
PVP (10%)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

*Represents values in mg; q.s., Quantity sufficient

Table 3: Formulation composition of tablet

Composition	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pellets (Equivalent to 50 mg Tramadol HCL)	276	276	276	276	276	276	276	276	276
SSG*	12	24	12	18	24	15	12	18	24

*Represents values in mg

formulations using Motic microscopy. In Motic microscopy randomly selected 50 pellets of these formulations were observed under Motic DMWB2-223 digital microscope fitted with 1/3 CCD camera imaging accessory and using Motic Images 2000 (1.3 Version) image analysis software Motic Instruments Inc., Richmond, British Columbia, Canada. The images of pellets were analyzed for their average diameter such as roundness and shape factors.^[15,16] The software reported roundness values, generated using the following expression:

$$\text{Roundness} = \frac{0.9399P^2}{4\pi A}$$

$$\text{Shape factor} = 4\pi A/P^2$$

where, P is the perimeter of the pellet image and A is the area determined by the total number of pixels within the feature. The factor 0.9399 corrects the perimeter for the effect of the corners produced by digitization of the image. A roundness value of 1 corresponds to the image of a perfect sphere, and higher values correspond to less spherical images.

Determination of yield

The yield of formulated pellets was calculated using the weight of final product after drying with respect to the initial total weight of the drug and polymer used for preparation of pellets and percentage of yields was calculated as per the formula mentioned below,

$$\% \text{ Yield} = \frac{P_m}{T_m} \times 100$$

where, P_m and T_m are practical and theoretical mass of the pellets, respectively.

Bitterness evaluation by taste panel

To know the mouth feel of the tablets, six human volunteers having an average age of 24 years were administered the formulated taste-masked tablet and asked to hold the disintegrated particles in the mouth for 30 s and the taste sensation felt was recorded. After the test was over,

volunteers were asked to spit out the contents and rinse mouth using water. The method reported by Kimura *et al.*, was followed with slight modification.^[17]

In vitro drug release studies

In vitro drug release studies were performed in a USP dissolution apparatus (TDT-08L, Electrolab) with paddle speed at 50 rpm. Dissolution studies were performed using pH 6.8 phosphate buffer for complete release of drug. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper, concentration of Tramadol HCl was determined in samples spectrophotometrically (UV-1700, Shimadzu, Tokyo Japan) at 272 nm. Volume of dissolution medium (900 ml), stirring speed (50 rpm) and temperature of medium ($37\pm 0.2^\circ\text{C}$) were kept same for all dissolution studies.

Statistical analysis of the data and validation of the model
Response surface modeling and evaluation of the quality of fit of the model for the current study were performed using Design-Expert software.^[18] Polynomial models including interaction and quadratic terms were generated for all the response variables using multiple linear regression analysis. Three-dimensional response plots were constructed using Design-Expert software. One final formulation corresponding to the predicted optimum amount of SSG and D-mannitol were carried out to determine the validity of the model generated. Subsequently, the resultant experimental data of the response properties were quantitatively compared with those to the predicted values by percentage prediction error.

RESULTS AND DISCUSSION

Micromeritic properties

Pellets were characterized for bulk density, tapped density, Carr's index and angle of repose. The tapped density values of pellets ranged from 0.725 ± 0.01 to 0.853 ± 0.048 g/ml. The Carr's index values are ranged from 2.47 ± 0.46 to 8.49 ± 0.69 . All formulations showed excellent flowability as expressed in terms of angle of repose ($< 25^\circ$). Results of these studies are shown in Table 4.

Image analysis and morphology of pellets

The pellets of all the batches were spherical with roundness. Results of the physical examination of pellets are shown in Table 5. The size of pellets varied from 0.895 ± 0.025 to 1.423 ± 0.078 mm for different batches.

In vitro drug release

Dissolution studies were performed in phosphate buffer of pH 6.8 for complete drug release and then subsequently the medium was replaced with fresh buffer having maintained a temperature of $37\pm 0.2^\circ\text{C}$. All the batches of pellets showed fast disintegration and drug release in phosphate buffer of pH 6.8. Although the drug release from pellets of all batches was quiet rapid, the composition of pellet shows significant effect on initial drug release in phosphate buffer [Figure 1]. Increase in the D-mannitol caused marked increased in drug release in initial few minutes. Optimized batches prepared pellets showed more than 80% drug release within 10 min.

Table 4: Micromeritic evaluation parameters for pellets

Batch	Bulk density* (g/ml)	Tapped density* (g/ml)	Carr's index* (%)	Angle of repose* (°)
F1	0.6874±0.014	0.7512±0.028	8.49±0.69	17.38±0.56
F2	0.7468±0.01	0.7750±0.042	3.64±0.05	15.58±0.04
F3	0.7219±0.005	0.7402±0.046	2.47±0.46	18.95±0.80
F4	0.6941±0.09	0.7264±0.01	4.44±0.57	17.64±0.07
F5	0.6905±0.03	0.7318±0.078	5.64±0.09	16.53±0.45
F6	0.7748±0.031	0.8174±0.066	5.21±0.12	19.72±0.05
F7	0.7875±0.023	0.8497±0.019	7.32±0.04	15.19±0.01
F8	0.6947±0.052	0.7397±0.006	6.08±0.02	17.22±0.54
F9	0.7814±0.047	0.8530±0.048	8.39±0.61	18.39±0.43

*Value expressed as mean±SD, n = 3

Table 5: Characterization of pellets

Batch	Average diameter*±S.D.	Shape factor*±S.D.	Roundness*±S.D.	Production yield*±S.D. (%)	DT*±S.D.
F1	1.106±0.51	0.829±0.051	1.423±0.078	85.76±3.16	60±0.02
F2	1.125±0.08	0.778±0.027	1.176±0.043	87.76±1.05	33±0.12
F3	1.348±0.76	0.756±0.031	1.041±0.046	88.64±1.26	57±0.05
F4	0.868±0.06	0.858±0.032	0.899±0.045	78.53±4.14	45±0.15
F5	1.074±0.03	0.715±0.032	1.098±0.050	92.68±2.66	30±0.24
F6	1.301±0.50	0.717±0.016	0.895±0.025	85.70±3.46	45±0.03
F7	1.124±0.04	0.726±0.034	0.986±0.058	75.99±5.27	55±0.34
F8	1.075±0.52	0.754±0.045	1.126±0.069	81.84±2.78	48±0.42
F9	1.087±0.07	0.767±0.069	1.324±0.106	96.34±3.95	35±0.2

*Value expressed as mean±SD, n = 3

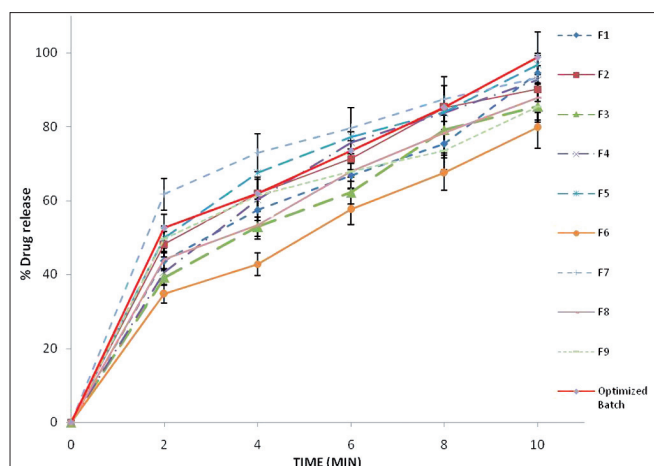


Figure 1: % Drug release profiles of tablet of all the batches and of optimized batch

Bitterness evaluation by taste panel

The result of the bitterness evaluation by taste panel has been summarized in Table 6. All the members of the taste evaluation panel reported the formulation from slightly bitter to tasteless one when compared with pure drug which has a strong bitter taste.

Experiments of 3² full factorial design

To develop taste-masked mouth-dissolving tablet, amount of SSG and D-mannitol are important parameters affecting the DT and sphericity. The optimization strategy was carried out with the aim of finding optimum amount of SSG and D-mannitol to achieve taste-masked mouth-dissolving tablet.

Multiple regression and mathematical model building

The targeted response parameters were statistically analyzed by applying one-way ANOVA (analysis of variance), at 5% significance level and the significance of the model was estimated using the statistical Design-Expert. The individual parameters were evaluated using F-test and mathematical relationship was generated between the factors (independent variables) and responses (dependent variables) using multiple linear regression analysis, for determining the levels of factors which yield optimum DT and sphericity [Table 7].

A polynomial equation was used to study the effect of variables on different evaluation responses (Y), where the coefficients in the equation ($\beta_0, \beta_1, \beta_2$ and β_{12}) were related to the effects and interactions of the factors. A second-order polynomial regression equation that fitted to the data is as follows:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + \beta_{12} X_1 X_2$$

where, β_0 is the arithmetic mean response of nine batches, β_1 and β_2 coefficients of factor X_1 and X_2 and β_{12} the coefficient of interaction of X_1 and X_2 . The interaction ($X_1 X_2$) shows how the dependent variable changes when two or more factors are simultaneously changed. Design-Expert was used to obtain values of coefficients in the equation and f-statistics were

Table 6: Bitterness evaluation by taste panel

	Volunteers					
	1	2	3	4	5	6
Pure drug	4.0	4.0	4.0	4.0	4.0	4.0
Adsorbate (5 sec.)	2.0	0.0	0.0	1.0	1.0	0.0
Adsorbate (10 sec.)	1.0	0.0	1.0	2.0	2.0	0.0

0.0 = tasteless; 1.0 = acceptable bitterness; 2.0 = slight bitterness; 3.0 = moderate bitterness; 4.0 = strong bitterness.

Table 7: Estimation of regression coefficients for different response variables

Coefficient	Response	
	DT (Y1)	Sphericity (Y2)
β_0 (Intercept)	45.33	0.9332
β_1	-12.33	0.0246
β_2	0.5	-0.0121
β_{12}	0.0000	0.115
β_{11}	0.0000	0.2026
β_{22}	0.0000	0.0581
R^2	0.9663	0.5607
F	86.15	0.77
P*	0.0001	0.6305

β_0 , arithmetic mean response of nine batches; β_1 and β_2 coefficients of factor X_1 and X_2 ; $\beta_{12}, \beta_{11}, \beta_{22}$, coefficient of interaction of X_1 and X_2 . *Significant level is set at 5%. A bold value has P-value less than 0.05, hence the corresponding factors are considered to significantly influence the response

used to identify statistically significant terms. In Table 7, factor effects of 3² full factorial design model and associated P-values for the responses Y_1 and Y_2 are presented. A factor is considered to influence the response if the P-value is less than 0.05. The final equations of the responses are given below:

$$DT (Y_1) = 0.48 - 0.031 * X_1 + 0.010 * X_2 - 0.000024 * X_1 * X_2 + 0.012 * X_1^2 + 0.001133 * X_2^2$$

$$Sphericity (Y_2) = 5.00 + 1.85 * X_1 - 0.042 * X_2 - 0.20 * X_1 * X_2 - 0.10 * X_1^2 - 1.09 * X_2^2$$

The equations represent the quantitative effect of factors (X_1 and X_2) upon the responses (Y_1 and Y_2). Coefficients with one factor represent the effect of that particular factor while the coefficients with more than one factor and those with second-order terms represent the interaction between those factors and the quadratic nature of the phenomena, respectively. Positive sign in front of the terms indicates synergistic effect while negative sign indicates antagonistic effect of the factors.

Response surface analysis

The quadratic models generated by regression analysis were used to construct 3D response surface plots in which response parameter Y was represented by a curvature surface as a function of X.

Figure 2a show a linear synergistic relationship between the two independent variables on response Y_1 as was also evident from the P-value listed in Table 7. Figure 2 b depicts curvilinear relationship for response Y_2 with ‘a region of maxima’ lying

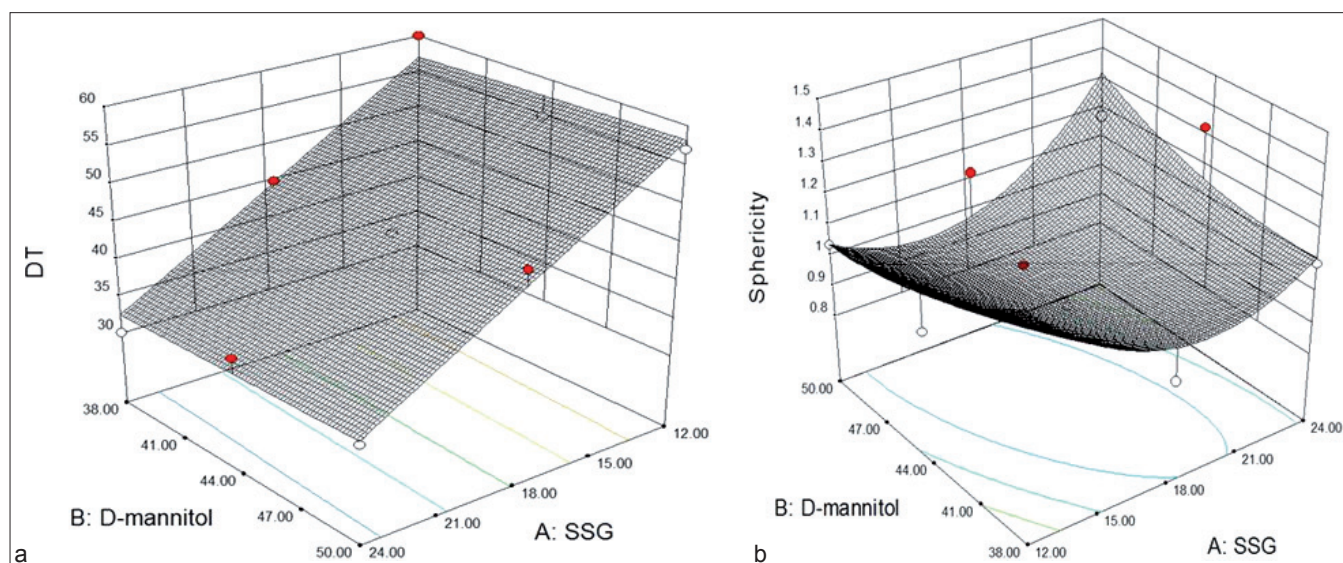


Figure 2: Response surface methodology of DT (a), sphericity (b)

between the lower to higher levels of the factors. A numerical optimization technique using the desirability approach was employed to develop a new formulation with the desired responses.

- SSG, $X_1 = 21.89$ mg
- D-mannitol (mg), $X_2 = 40.33\%$

Validation of response surface methodology

In order to assess the reliability of the developed mathematical model and dissolution test of the formulated pellets corresponding to the predicted optimum SSG and D-mannitol was performed.^[18] For each of these test run, responses were estimated by use of the generated mathematical model and by the experimental procedures. For the optimized batch predicted values for DT Y_1 is 37.35 s while the experimental values for responses Y_1 is 36.53 s, respectively. The pellets prepared according to optimum formulation achieved sphericity Y_2 1.081mm while the experimental values for response Y_2 is 1.080 mm. The release profile of optimized pellet formulation is shown in Figure 2.

CONCLUSION

In conclusion, we have successfully masked the bitter taste of drug using sucrose, D-mannitol and lactose. Concerning statistical analysis, it was shown that appropriate factorial design and optimization technique can be successfully used in the development of the taste-masked mouth-dissolving tablet. Response surface methodology is an important tool for understanding the change of response and locating area of interest. The optimized formula exhibited DT and sphericity which were close to the predicted response. The preparation method designed in this study may be useful for the preparation of rapidly disintegrating tablets containing drugs with strong bitter taste.

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