RESEARCH

Response surface method for optimization of prepared satranidazole powder layered pellets

Rana Mazumder[1,2*], Beduin Mahanti[1], Subhabrota Majumdar[3], Rabindranath Pal[3] and Ashok Dhar Chowdhury[3]

Abstract

Background: The purpose of the present study was to evaluate layered of satranidazole powder using natural polysaccharides as coating materials for colon targeting that were inexpensive and natural with a non-toxic nature using a composite response design of 3 levels and 2 factors for each of the four responses in the quadratic model. The independent variables were the ratio of coating consistency % (X1) and coating level % (X2) in the pellet. The dependent factors were % release of drug at 2 h. (Y1), % release of drug at 6 h. (Y2), % release of drug difference in presence & absence of colonic enzyme (Y3) and mean dissolution time (Y4). The various models were fitted for the responses with an explanation of suitable statistical methods. Variance analysis and different factor levels of responses were constructed by response surface plots.

Results: Satranidazole pellets were efficiently prepared by the variable amount of ingredients that showed compatibility with possible pellet characterization and drug dissolution profiles to optimize the formulation.

Conclusions: The strategy of response surface can be a successful tool for improving the prepared satranidazole pellets which can be an appropriate replacement of regular one.

Keywords: Central composite design, Response surface method, Pellets, Satranidazole, Powder layering

Background

Satranidazole is a 5-nitroimidazole compound substituted in position number two and chemically designated by 1-methylsulfonyl-3-(1-methyl-5-nitro-2-imidazolyl)-2-imidazolidinone [1] with possible activity against bacterial and protozoal diseases for the management of amebiasis [2]. Satranidazole (STZ) is reported to show higher plasma absorption than metronidazole [3] and when introduced directly to the colonic region, the highest drug concentration reaches with increasing drug residence time. Therefore, it was found to be useful against infection by protozoa, particularly *Entamoeba histolytica* [4]. Also, satranidazole has better patient compliance and

nonappearance of neurological responses which favored in patients with susceptible neurological side effects [5].

Statistical experimental design technique is a classical tool useful for the optimization and characterization of pharmaceutical processes by studying the effects of variables with their interaction [6]. The exploratory design gives an economical method to get the best measure of data by expending the least amount of experimental effort which can produce a high-quality and low-cost pharmaceutical product. Quality by design [7] has been implemented by the US FDA authorities who maintain drug quality management. The experimental models can be optimized by considering independent and dependent variables to keep the process in a systemic and rapid mode [8]. Pellets in the form of tablets are affected by various parameters of their formulation. Therefore, a suitable method design can be useful for the optimization of pellets instead of the conventional optimization

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Mazumder *et al. Futur J Pharm Sci*   (2021) 7:190

Page 2 of 11

method where unpredictable records and inappropriate waste of chemicals are required to run the process. Thus, optimization by statistical design could be a suitable way to address the aforementioned situation [9].

The central composite design is a valuable framework for the response surface methodology that has factorial, central and axial focuses [10]. The response surface technique dependent on a measurable and numerical design with a polynomial connection to the research data [11]. The statistical design generally leads to a regression linear model or quadratic composite design. This allows prediction of the properties of the system using the response surface method within a variable space. In the experimental procedure, one or more of the process factors may be changed to study the impact of alterations on the selected responses. The purpose is to get statistical information that can analyze a valid conclusion to find the ideal configuration of all factors and responses. Therefore, the response surface method [12] is an exceptionally valuable model for designing the core compound to influence formulation through the use of variables.

The present research work was based on the use of natural polysaccharides as a coating material provided with microbial degradation and enzymatically degradable for the release directed to the colon, triggered by physiological characteristics of the colonic environment that were inexpensive and of natural and non-toxic origin. The pellets were efficiently organized by single unit that were associated with uniform distribution and drug release throughout the gastrointestinal tract, including minimal variability. The powder coating technology was also given a heterogeneous pellet shape with uniform particle size. The purpose of the present study was to apply a central composite model followed by a response surface technique for the advancement of satranidazole pellets. As an element of the improvement method, the independent

effects with dependable factors of the formulation were investigated by the central quadratic composite model. The consistency of the coating was evaluated with its percentage of coating levels to find its result in the dissolution profile at various time intervals in different media. This allows dissolution studies to be validated as an important tool for characterizing pellet formulations through a minimal number of experiments within the statistical design. Therefore, the technique for response surface can optimize the pellets formulation as a substitute for conventional products.

Materials

Satranidazole was gifted by Alkem Laboratories Ltd., Sikkim, India. Locust bean gum, xanthan gum and chitosan gum were obtained from Merck Specialities Pvt. Ltd., Mumbai, India. Non-pareil sugar seeds (25/30 #) were gifted by Anthem Biosciences Pvt. Ltd., Ramanagara District, Karnataka, India. Hydroxypropyl methylcellulose (HPMC-K10) and polyvinyl pyrrolidone K 30 (PVP-K30) were obtained from Loba Chemie Pvt. Ltd., Mumbai, India. Any remaining solvents and compounds were of analytical grade.

Methods
Statistical design of experiments

A 3-level, 2-factor composite response surface design among four responses in the quadratic model was used for optimization [13]. The experiments were operated by the software of Design-Expert (Version 8.0.3 Stat Ease Inc., Minneapolis, MN). The study was done through the two independent factors during their adequate range as shown in Table 1, together among the dependent factors. The resulting formulations are explained in Table 2.

Table 1 Variables of response surface design

Independent variables	Levels used		
	Low (− 1)	Medium (0)	High (+ 1)
Design of experiment			
X_1: Ratio of coating mixture % (Locust bean gum: Xanthan gum & Locust bean gum: Chitosan gum)	1:2 or 33.3%	*1:1 or 50%*	2:1 or 66.7%
X_2: Coating level %	10	20	30
Numerical optimization			
Dependent variables	Constraints Range	Goal	
Y_1: Drug release at 2 h. (%)	In the range	Minimize	
Y_2: Drug release at 6 h. (%)	In the range	Minimize	
Y_3: Drug release difference in presence & absence of colonic enzyme at 10 h. (%)	In the range	Maximize	
Y_4: Mean dissolution time	In the range	Minimize	

Mazumder *et al. Futur J Pharm Sci* (2021) 7:190

Page 3 of 11

Table 2 Experimental formulation (Runs) and observed results from response surface design

Batch no	Batch code [a]	Independent variables		Dependent variables			
		X_1: Ratio of coating mixture (Locust bean gum: Xanthan gum & Locust bean gum: Chitosan gum) (%)	X_2: Coating level (%)	Y_1: Drug release at 2 h (%)	Y_2: Drug release at 6 h (%)	Y_3: Drug release difference in presence & absence of colonic enzyme at 10 h (%)	Y_4: Mean dissolution time (MDT)
1(F1)	LX	50	20	1.124	17.254	18.872	9.016
2(F2)	LX	50	10	1.441	20.761	40.801	8.706
3(F3)	LX	33.3	30	0.086	3.784	3.896	10.508
4(F4)	LX	33.3	10	1.989	11.908	30.392	7.471
5(F5)	LX	66.7	10	1.124	20.011	68.396	8.601
6(F6)	LX	66.7	30	0.547	12.096	9.146	9.669
7(F7)	LX	50	30	0.001	0.0281	25.936	7.471
8(F8)	LX	33.3	20	1.960	6.655	8.409	9.784
9(F9)	LX	66.7	20	0.720	10.584	25.308	9.593
10(F10)	LC	50	20	0.324	5.616	15.227	10.360
11(F11)	LC	33.3	20	1.103	24.107	5.560	9.048
12(F12)	LC	66.7	20	0.121	4	14.935	7.627
13(F13)	LC	50	10	2.407	16.234	11.952	9.675
14(F14)	LC	50	30	0.426	4.897	14.285	10.342
15(F15)	LC	33.3	10	1.038	8.001	11.908	9.298
16(F16)	LC	33.3	30	0.037	0.500	6.957	10.032
17(F17)	LC	66.7	10	2.998	39.835	40.412	6.437
18(F18)	LC	66.7	30	0.278	12.022	12.745	9.424

[a] Batch no 1 to 9 (LX) = Locust bean gum: Xanthan gum as a coating mixture with 10 to 30% coating level and batch no 10 to 18 (LC) = Locust bean gum: Chitosan gum as a coating mixture with 10 to 30% coating level

Preparation of satranidazole pellets
Preparation of drug containing pellets by powder layering technique
Satranidazole layered pellets were prepared using coating pan equipment maintaining all instrument parameters. The optimal characteristics of the pellets were considered by a number of parameters, such as primary core load, powder application rate, plate speed, type, position of atomizers, atomization pressure, the type of air cap and the bed temperature. Non-pareil sugar seeds were placed into the coating pan and then treated with a nebulizer binder solution which is prepared by polyvinyl pyrrolidone (K 30) as a binder with isopropyl alcohol and demineralized water mixed in 70:30 proportions using a mechanical stirrer at 200 rpm. It was applied by spray guns and with a dispersed powdered drug applied by a particularly designed powder feed unit [14]. The sphere bed was dried to completely remove the solvent and finally, drug-containing pellets were formed.

Coating of layered pellets
Satranidazole layered pellets were coated using coating pan equipment maintaining all instrument parameters.

The coating solution was applied by spraying through spray nozzle, and the process parameters were optimized. The level of coating was determined from the increase in weight after drying using the following equation:

1.

$$\%\text{of the coating level} = (\text{weight of coated pellets} - \text{weight of uncoated pellets})/\text{weight of coated pellets}$$

(1)

2.

$$\text{The efficiency of the coating process}(\%) = (\text{Mass of the coated particle} - \text{Mass of the uncoated particle})/\Sigma \text{ Mass of drug, binder and excipients}$$

(2)

Various mixtures of locust bean gum (LBG) and xanthan gum (XG) were applied in a ratio of 2: 1 and a mixture of locust bean gum (LBG) and chitosan gum (CG) biopolymers in a ratio of 1: 2 by different levels of coating.

Before film coating, a seal coating was performed to restrict the migration of the drug layer in drug form before and after functional coating, respectively [15]. The

Mazumder *et al. Futur J Pharm Sci* (2021) 7:190

Page 4 of 11

seal coat was performed using HPMC as a film former in a concentration of 5–15%. A total of 18 batches of coating were developed according to the response surface software model described in Table 2. The composition of the coating formulation was revealed with the corresponding batch in Table 3.

Dissolution studies of formulations
In vitro dissolution studies
Dissolution methods were determined by paddle-type USP XXIII dissolution apparatus using 900 ml of dissolution fluid with 50 rpm speed at 37 °C ± 0.5 °C. The perfect sink conditions prevailed during the drug dissolution study period. The release of the drug simulating to the gastrointestinal transit time was accomplished by varying the pH of the liquid at various time intervals. The pellets (300 mg) were weighed accurately and gently spread over the surface of 900 mL of dissolution medium. The dissolution fluid pH was kept at pH 1.2 during 2 h in gastric simulated liquid using 0.1 (N) HCl, pH 4.5 during the third to fourth hour in a mix of gastric and simulated intestinal liquid using NaH_2PO_4 (1.7 g) and $Na_2HPO_4.3H_2O$ (2.35 g) were added to the dissolution medium, adjusting the pH to 4.5 with NaOH 1.0 M and pH 7.4 in a ratio of 39:61 throughout fifth to sixth hour in simulated intestinal liquid (SIF) and pH 7 for the seventh hour onwards in simulated colonic liquid [16].

Each sample (1 ml) was periodically withdrawn and replaced with an equal amount of fresh dissolution medium (for simulated colonic fluid (SCF), bubbled with carbon dioxide). The volume was made up to 10 ml and centrifuged. The supernatant was filtered through Whatman filter paper, and the drug content was determined spectrophotometrically at 320 nm (UV 1700, Shimadzu, Japan). Each experiment was performed in at least triplicate. All test batches and optimized granules were used for dissolution study for more than 12 h.

Preparation of rat cecal content medium
The simulated colonic fluid for rat cecal content was formed using 20 mM Na_2HPO_4. 12 H_2O, 10 mM $NaHCO_3$, 8 mM NaCl, 0.4 mM $MgCl_2.6 H_2O$ and 0.5 mM $CaCl_2.2H_2O$ in 1000 ml of water and stored in a refrigerator [17]. Here, albino rats weighing around 250 ± 20 g were utilized for the current assessment. Four albino rats each for male and female, weighing 200 g to 250 g, were administered by 2% pectin solution 1 ml per day; microbial enzymes were initiated *in-vivo* during the procedure. The rats were killed by an extreme amount of sodium pentobarbital injected a week later. The abdomens of the rats were opened and the cecum content was isolated and transferred to simulated colonic fluid continuously with a carbon dioxide bubble to uphold anaerobic conditions. Finally, colonic cecum contents were collected and dissolved with 0.1 M isotonic acetate buffer of pH 5 to make a final cecal content (5% w/v) [18, 19].

Release kinetics profile
The drug release kinetics were controlled by the model-independent approach in which the dissolution efficiency (DE) was calculated by the area under the dissolution curve up to a certain time period (*t*). It was calculated by the dissolution efficiency from the dissolution curve using the trapezoidal technique, and it was determined by the percentage of the area of the rectangle through the dissolution time, the average dissolution time and the dissolution efficiency [20], and the mean dissolution time (MDT) was used to interpret the profile differences in a single value. The mean dissolution rate (MDT) was measured as the dissolution rate where the greater the mean dissolution time (MDT), the slower the release rate.

Table 3 Composition of film coating

Sl. no	Batch code	Locust bean gum (LBG) (gm)	Xanthan gum (XG) (gm)	Chitosan gum (CG) (gm)	Glyceryl Mono Stearate (GMS) (gm)	Talc (gm)	Water (gm)
1	LX11[a]	1	1	0	0.1	0.3	100
2	LX12[b]	0.67	0.33	0	0.1	0.3	100
3	LX21[c]	0.33	0.67	0	0.1	0.3	100
4	LC11[d]	1	0	1	0.1	0.3	100
5	LC12[e]	0.67	0	0.33	0.1	0.3	100
6	LC21[f]	0.33	0	0.67	0.1	0.3	100

[a] LX11 (1:1) = Ratio of coating blend (Locust bean gum: Xanthan gum)

[b] LX12 (1:2) = Ratio of coating blend (Locust bean gum: Xanthan gum)

[c] LX21 (2:1) = Ratio of coating blend (Locust bean gum: Xanthan gum)

[d] LC11 (1:1) = Ratio of coating blend (Locust bean gum: Chitosan gum)

[e] LC12 (1:2) = Ratio of coating blend (Locust bean gum: Chitosan gum)

[f] LC21 (2:1) = Ratio of coating blend (Locust bean gum: Chitosan gum)

Mazumder *et al. Futur J Pharm Sci*   (2021) 7:190

Page 5 of 11

It was determined by the following equations:

1.

$$\text{Dissolution efficiency} = \left\{ 0 \int t(y)\,\mathrm{d}t / y * 100 \right\} * t * 100 \tag{3}$$

2.

$$\text{Mean dissolution time} = \sum i = \mathrm{ni} = \mathrm{l}\,\mathrm{tmid} * \Delta M / \\ \sum i = \mathrm{ni} = \mathrm{l}\,\Delta M \tag{4}$$

where i = test number of the dissolution study, n = test time number of the dissolution study, tmid = time of midpoint among i and $i-1$, and M is the quantity of dissolved drug among i and $i-\mathrm{l}$.

The similarities between two dissolution profiles were evaluated using an independent procedure of the pairwise model, similarity factor (f2) [21].

$$\text{Similarity factor}\,(\mathrm{f2}) \\ = 50\,\mathrm{Log}\left\{ \left[1 + 1/n \sum n = \mathrm{In} = 1(Rt - Tt)2 \right]^{1/2} \times 100 \right\} \tag{5}$$

where n = pull points points, Rt = time point for reference profile t, and Tt = test profile at the similar time end.

The assessment of the similarity factor (*f2*) should be between 50 and 100. The similarity factor value (f2) of 100 suggests that the test and reference profiles were identical, and as the value becomes smaller, the dissimilarity between the releases profiles increases.

Scanning electron microscopy (SEM)
Scanning electron analysis was arranged by spraying the pellets on a single side of a piece of adhesive, and pellets were plated with gold (20 Å). The surface morphology of the pellet was observed by a scanning electron microscope (FEI Quanta-200 MK2) [22].

Numerical optimization for response surface method
The optimization study was determined by expert design software. Polynomial models were used for all response variables that included quadratic terms and interaction through multiple regression analysis technique [23]. The multiple regression analysis models are represented as the following equation:

1.

$$y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 \\ + \beta_5 X_2^2 + \beta_6 X_1 X_2^2 + \beta_7 X_1^2 X_2 \tag{6}$$

β_0 is the intersection that represents the arithmetic average value of every quantitative results of 18 formulations, $\beta_1 - \beta_7$ are the coefficients of dependent response factors of Y and X_1 and X_2 are the independent factors. The quadratic condition and interaction are represented by $X_1 X_2$ and x_i^2, where, $i = 1-2$. The polynomials strength was recognized based on the statistical ANOVA study. Contour plots were determined by the polynomial functions of the model. These graphs were extremely valuable to see the interaction results on the factors of responses. Formulations were organized by different response variables. Consequently, the experimental data resulting from the variable responses were compared with their predicted values.

Results
Statistical design of experiments and preparation of satranidazole pellets
The surface response design was based on the variable factor allocated in the response surface [24] shown in Table 1 and 18 formulations were arranged based on the formulation components within the response surface design shown in Table 2. The design was prepared by using two independent factors with four responses in the quadratic model combined with an efficient role for the pellets [25].

Dissolution studies of formulations
Dissolution studies were determined for each formulation. From the measurement of the dissolution studies, it was hard to conclude, so we chose the implication of the design of the response surface for the dissolution profile [26]. The initial release of satranidazole at 2 h 0–2% was expected and up to the 6th hour below 20% and the maximum drug release at 12 h for optimized batch.

The dissolution profile of the satranidazole [27] pellets (Batch F1–F9) is described in Fig. 1 in simulated gastrointestinal fluid (pH 1.2, pH 4.5 and pH 7) (Fig. 1a) and simulated colonic liquid (pH 7) (Fig. 1b) by locust bean gum with xanthan gum blend as a coating material up to 10 to 30% coating level. The dissolution profile of the satranidazole pellets (Batch F10–F18) is described in Fig. 2 in simulated gastrointestinal fluid (pH 1.2, pH 4.5 and pH 7) (Fig. 2a) and simulated colonic liquid (pH 7) (Fig. 2b) [28] by chitosan with locust bean gum blend as a coating substance up to 10 to 30% coating level.

Scanning electron microscopy (SEM)
An electron microscope study shows that the pellets had a very spherical shape among a smooth surface. Figure 3 shows the scanning electron morphology [29] for optimized batches during the test before dissolution (Fig. 3a,

Fig. 1 Dissolution profiles of satranidazole pellets (Batch F1–F9) (Table 2) at **a** simulated gastrointestinal fluid (pH 1.2, pH 4.5 & pH 7.4) and **b** simulated colonic fluid (pH 7)

Fig. 2 Dissolution profiles of satranidazole pellets (Batch F10–F18) (Table 2) at **a** simulated gastrointestinal fluid (pH 1.2, pH 4.5 & pH 7.4) and **b** simulated colonic fluid (pH 7)
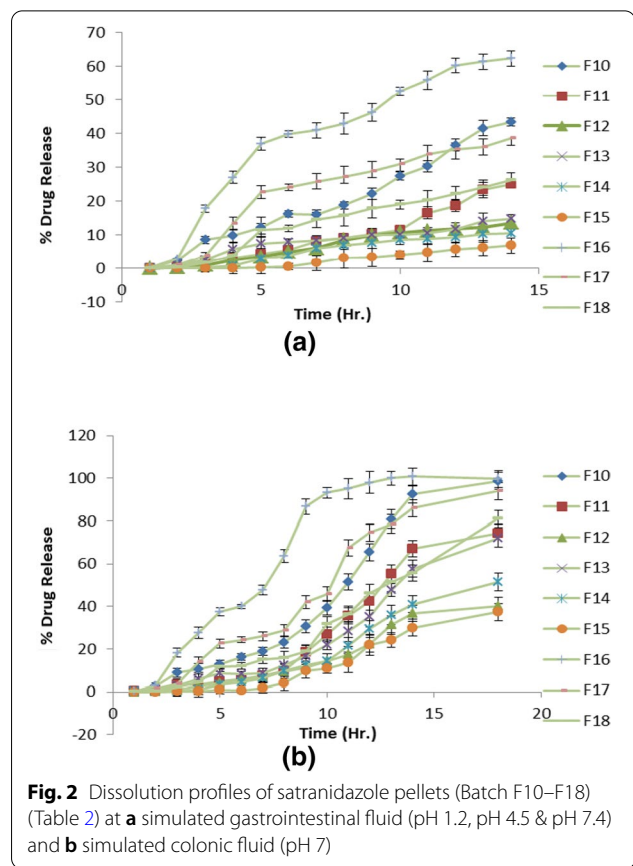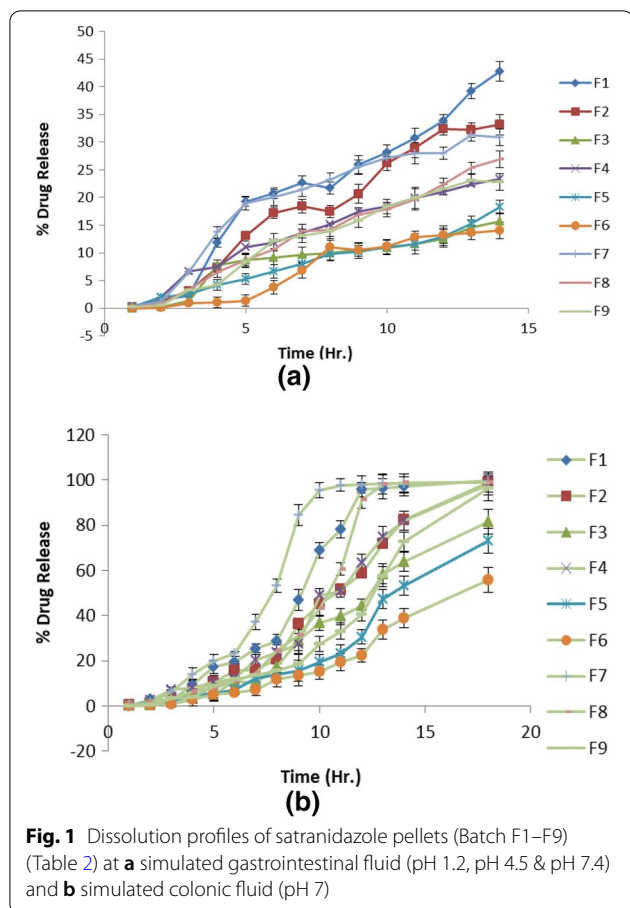
b) and after dissolution (Fig. 3c). At higher resolution, the surface coating layer was visible. The pellets were clearly specified to be of the reservoir type (Fig. 3d).

Numerical optimization for response surface method

A responsive surface design was applied, with the coating consistency (X1) and the coating level (X2) as independent factors, to optimize the formulation with drug release at 2 h. (Y1), drug release at 6 h. (Y2), the release of the drug difference in the presence and absence of colonic content (Y3) and the mean dissolution time (MDT (Y4) as dependent variables shown in Table 1.

Overall 18 experimental formulations based on the response surface design [30], revealed in Table 2 along with the experimental responses. The mathematical relationship was revealed by the subsequent equations generated by the software, shown in Table 4, and all formulations had to be within the satisfactory limit that contains the details of the batch generated by the software (Table 2) with experimental values of the formulations with percentage of error in the forecast. The observed values of each optimized parameter were found to be very close to the target and the

predicted values with less than 5% error. Therefore, the release was finally optimized by a similarity factor value (f2) and the highest similarity factor value was 98.97 to optimize the batch (F9) with a desirability value of 0.478 achieved by the software of design with specified independent variables. The statistical analyses of the models were performed by ANOVA (analysis of variance) [31] shown in Table 5. To estimate the significance of the model, a significance level of 5% was considered for the statistical analysis and the *p* values [32] are represented in Table 5.

Response surface method analysis

The surface response plots with contour plots were graphed with the regression equation [33] and expressed by two independent factors at the same time against each response (Figs. 4, 5, 6, 7). Therefore, the statistical networks between the independent and dependent factors were further interpreted using the response surface method [34].

Figure 4a, b shows the response surface and contour plots for drug release at 2 h (Y1) with a linear shape and a similar pattern of drug release at 6 h (Y2) in Fig. 5a, b continued for other responses for significant *p* values less

Mazumder *et al. Futur J Pharm Sci*   (2021) 7:190

Page 7 of 11
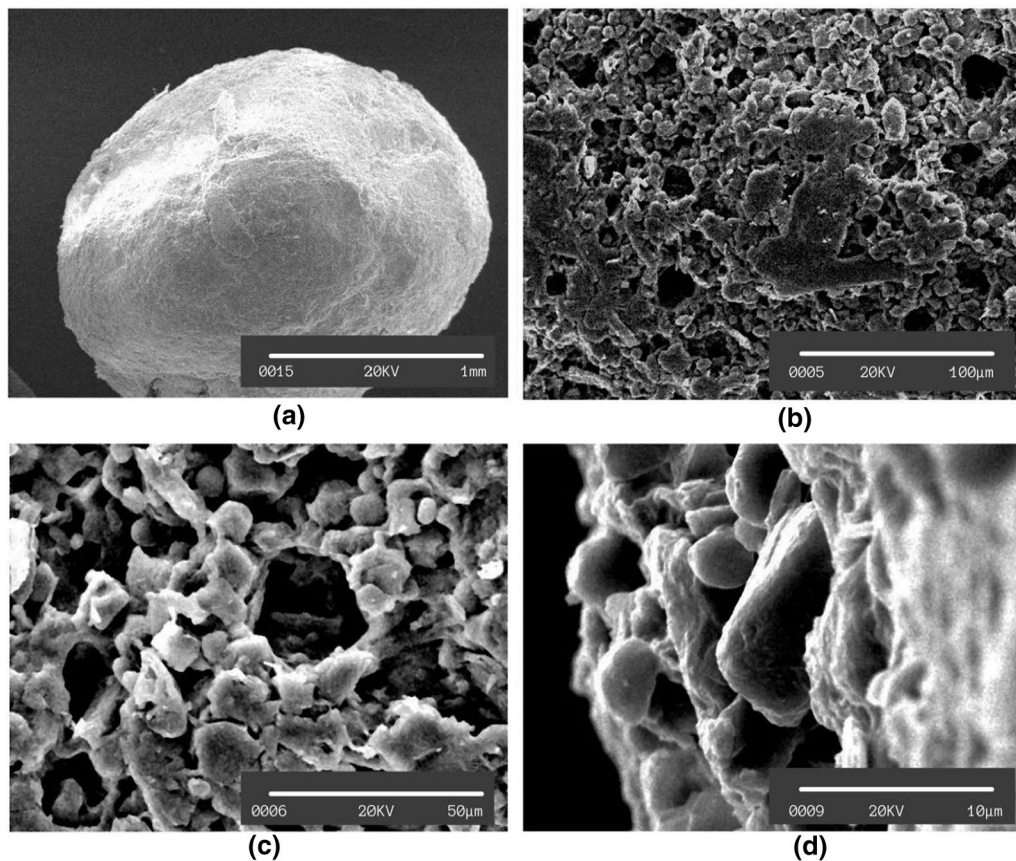
Fig. 3 Scanning electron microscopy (SEM) of optimized satranidazole pellet **a** before dissolution study, **b** surface topology before dissolution study, **c** after dissolution study and **d** cross-section of reservoir pellets (coating layer)

Table 4 Equations for optimization of response surface method

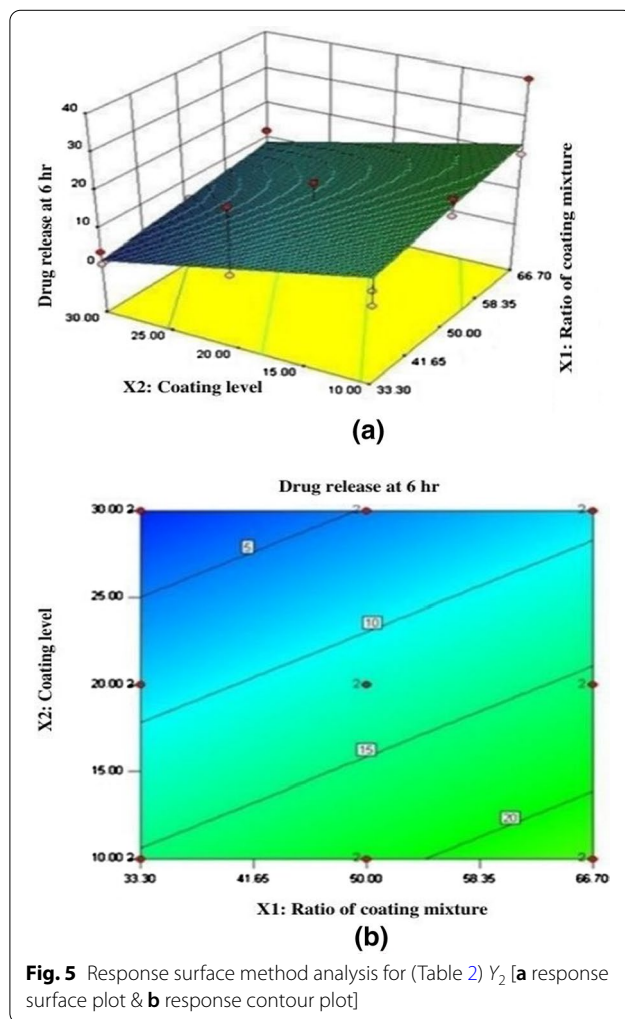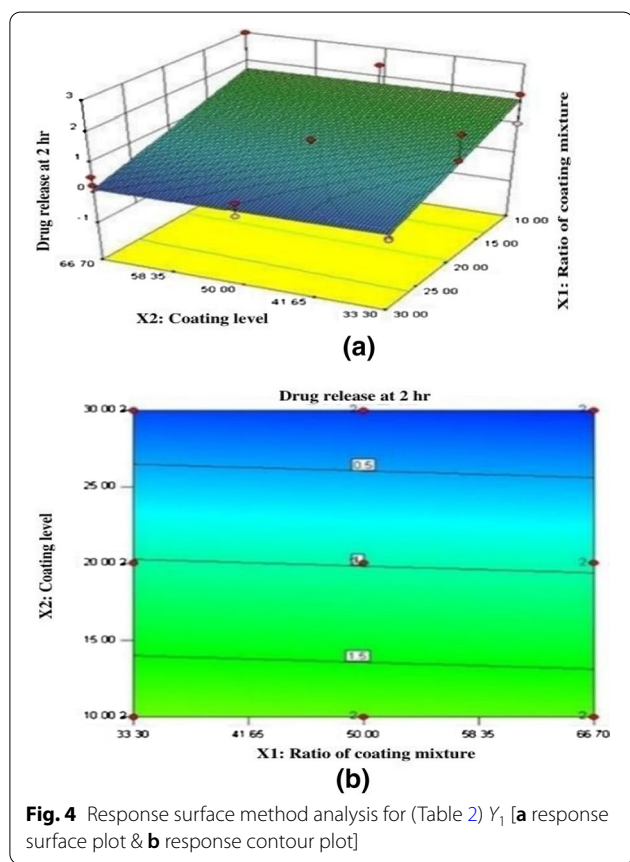| Sl. no	Name of equation	Subsequent equation
1		
a	Final equation in terms of coded factors for drug release at 2 h	Drug release at 2 h $= +0.99 - 0.035 * X_1{}^a - 0.80 * X_2{}^b$
b	Final equation in terms of actual factors for drug release at 2 h	Drug release at 2 h $= +2.694 - 2.114{-}003 * X_1{}^a - 0.080 * X_2{}^b$
2		
a	Final equation in terms of coded factors for drug release at 6 h	Drug release at 6 h $= +12.13 + 3.63 * X_1{}^a - 6.95 * X_2{}^b$
b	Final equation in terms of actual factors for drug release at 6 h	Drug release at 6 h $= +15.155 + 0.217 * X_1{}^a - 0.695 * X_2{}^b$
3		
a	Final equation in terms of coded factors for drug release difference at 10 h	Drug release difference at 10 h $= +20.29 + 8.65 * X_1{}^a - 10.91 * X_2{}^b$
b	Final equation in terms of actual factors for drug release difference at 10 h	Drug release difference at 10 h $= +16.198 + 0.518 * X_1{}^a - 1.090 * X_2{}^b$
4		
a	Final equation in terms of coded factors for mean dissolution time	Mean dissolution time $= +9.06 - 0.40 * X_1{}^a + 0.60 * X_2{}^b$
b	Final equation in terms of actual factors for mean dissolution time	Mean dissolution time $= +9.044 - 0.0239 * X_1{}^a + 0.0604 * X_2{}^b$

[a] X_1: ratio of coating mixture (%)

[b] X_2: coating level (%)

Mazumder *et al. Futur J Pharm Sci*   (2021) 7:190

Page 8 of 11

Table 5 Statistical summary of ANOVA for response surface design

Response	F-value			p Value			R^2	Adjusted R^2	Predicted R^2
	Model	X_1: Ratio of coating mixture (%)	X_2: Coating level (%)	Model	X_1: Ratio of coating mixture (%)	X_2: Coating level (%)			
% Drug release at 2 h (Y_1)	9.845	0.0381	19.653	0.0021 (S)	0.848 (NS)	0.0006 (S)	0.584	0.525	0.287
% Drug release at 6 h (Y_2)	5.704	2.447	8.962	0.0154 (S)	0.1401 (NS)	0.0097 (S)	0.449	0.370	0.077
% Drug release difference in presence & absence of colonic enzyme at 10 h (Y_3)	9.771	7.547	11.996	0.0022 (S)	0.0157 (S)	0.0038 (S)	0.582	0.523	0.270
Mean dissolution time (Y_4)	2.751	1.669	3.833	0.0982 (S)	0.2172 (NS)	0.0705 (S)	0.282	0.179	0.182

*Significant and non-significant value indicates by S and NS

Fig. 4 Response surface method analysis for (Table 2) Y_1 [**a** response surface plot & **b** response contour plot]

Fig. 5 Response surface method analysis for (Table 2) Y_2 [**a** response surface plot & **b** response contour plot]

than 0.05 which are depicted in Table 5. These were linear for all four responses.

From Fig. 6a, b, we can observe that the drug release difference in presence and absence of colonic enzyme (Y_3) at 10 h from the responses by the predicted R-squared value (0.270) was not close to the R-value adjusted square (0.523) as normally expected. This indicated a large block effect.

Mazumder *et al. Futur J Pharm Sci*   (2021) 7:190

Page 9 of 11

Fig. 6 Response surface method analysis for (Table 2) Y_3 [**a** response surface plot & **b** response contour plot]

Fig. 7 Response surface method analysis for (Table 2) Y_4 [**a** response surface plot & **b** response contour plot]
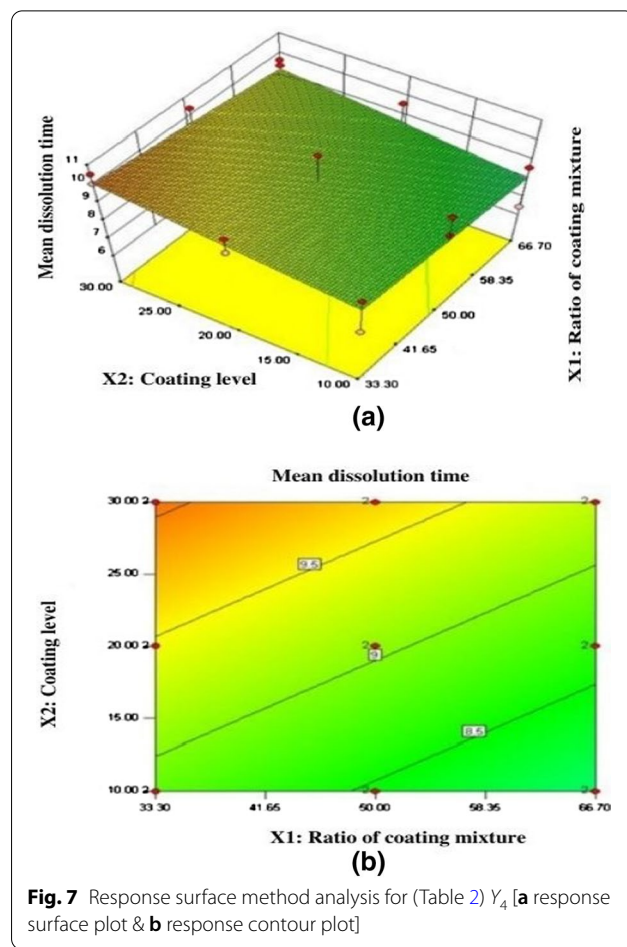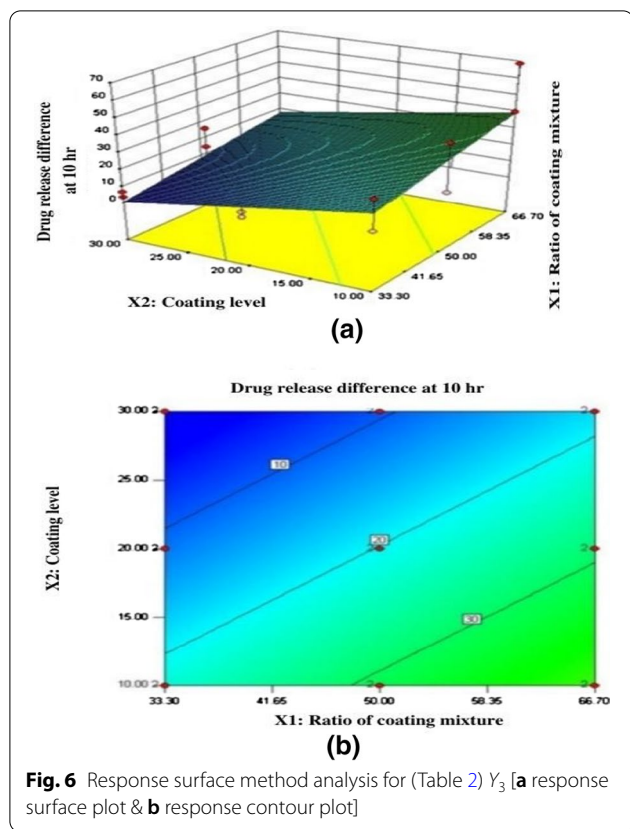
Figure 7a, b shows the surface response and contour graphs were used for the mean dissolution time by an *F* value of 2.75 and an *F* value less than 0.05 indicated that the pattern is significant. In this case, there were no significant model terms. *p* Values greater than 0.100 indicate that the models were not significant and a negative predicted *R*-squared value of the mean dissolution time [35] implies that the overall mean is a superior interpreter of the current model response. The formulations were found during the satisfactory limit in terms of physicochemical evaluations with everything that is represented in Table 2 with experimental and observed results where all the dependent variables result, that was the release of the drug at 2 h. (%), drug release at 6 h. (%), difference in drug release at 10 h. (%) and the mean dissolution time (MDT) were shown. The similarity factor (f2) of the optimized batch F9 was 98.87%. Drug release was also finally optimized by determining the similarity factor (f2) and the similarity value of the optimized batch F9 was 98.87%, achieved by the design software with specified independent variables.

Discussion

The objective of applying the response surface design was to optimize the satranidazole powder layered pellets [36] and the amounts of locust bean gum, xanthan gum,

chitosan gum combination in the pellet for drug release at 2 h., drug release at 6 h., difference in drug release at 10 h. and the mean dissolution time (MDT) showing compliance using possible results as a suitable substitute for the conventional product.

Using the response surface design model, batches F2, F1 and F7 were found to release the drug 42.70%, 33.11% and 14.6% at 14 h, respectively. These batches were maintained with a minimal lag period (> 2% drug release) in simulated gastric fluid. F2 batch was kept in a sustained release at a constant rate and F1, F7 batches were found the release pattern in parallel. Batches F4, F8, and F3 were found to release the drug by 23.32%, 18.34%, and 14.03% at 14 h, respectively, with a minimal amount in gastric fluid and constant drug release throughout the in vitro dissolution study. F5, F9, and F6 did not show much variation in drug release. All formulations were kept up with minimal drug release in the gastric medium and maximal delivery in the colonic part. Locust bean gum [37] with a mixture of xanthan gum was the most effective polymer in controlling the release property in that the increased

Mazumder *et al. Futur J Pharm Sci*   (2021) 7:190

Page 10 of 11

quantity of xanthan gum diminishes the drug discharge rate by decreasing the amount of locust bean gum.

It was found that the release profile of satranidazole pellets mixed by locust bean gum with chitosan with a ratio of 1: 1 (Batch F13, F10 and F14) and a ratio of 1: 2 (Batch F15, F11 and F16) of medication release was within 43.35% and 14.69%, respectively. The release rate was found to decrease in a linear fashion while the amount of chitosan gum [38] was found to increase and the release pattern within batches of fixed mix ratio was found slow as the coating level increased as expected. The release profile of formulations F17, F12 and F18 was found to deliver the medication by 62.3%, 38.6% and 28.65% at 14 h, respectively, and all batches were released by bursts up to the 5th hour followed by maintaining a constant slow release rate.

The response surface study using two central composite design blocks of four responses in the quadratic representation is revealed in a linear model. In these restrictions, the release of drug in the simulated gastric liquid was a minimum quantity and the release triggered in the colon that maximizes the release rate to achieve local application of the medication inside the colonic region [39]. It could be done by the four responses with quadratic models which were significant. The p values were < 0.05 with polynomial equations for the intersection coefficients, first-order effects, interaction conditions, and higher-order effects. The indication and the quantity were the comparative influence of all factors on the response, and it was found that the release of drugs at 2 h and 10 h was more significant, while the mean dissolution time was less important in all the responses.

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It was established that the observed of each parameter was extremely close to the objective and the predicted values with less than 5% error. Drug release was also finally optimized by determining the similarity factor (f2). Here, the highest f2 (98.87% for batch F9) achieved by the design software with specified independent variables. Therefore, the optimized batch was F9 with a 2: 1 ratio of locust bean gum-xanthan gum blends using 20% coating level.

Conclusions

It was revealed that the proper response surface design can be used effectively in enhancing satranidazole pellets to meet colonic release. The surface response graphs and optimization allowed the satranidazole pellets to be layered by a combination of natural polysaccharides with the required release profile. The results suggested that the formulation showed proper evaluations with dissolution profiles directed to the colon under different pH conditions. The coating formulation was shown to consist of locust bean gum-xanthan gum mixtures in a 2:1 (20%) coating ratio to be effective for colonic release of satranidazole pellets. The optimized batch showed release and response profiles close to the predicted response. Therefore, the response surface method can be an effective tool to optimize the pellet as a suitable substitute for conventional products.

Declarations

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Mazumder *et al. Futur J Pharm Sci*   (2021) 7:190

Page 11 of 11

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