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Design and development of immediate release tablets of terbutaline sulfate using 3^2 full factorial statistical design

Prabhjot Singh Bajwa[1]*, Jaya Sharma[2], Anurag Bhargava[1], Shailesh Sharma[3], Abhimanyu Rai Sharma[1], Binu Raina[1]

[1]Ch. Devi Lal College of Pharmacy, Jagadhri, Yamuna Nagar, Haryana, India, [2]School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India, [3]Department of Pharmaceutics, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Ropar, Punjab, India

ABSTRACT

Aim: Present study was aimed at developing an immediate release tablets (IRT) of Terbutaline sulphate (TS) that can be used forquick relief from asthma attacks.

Method: IRT's were formulated using Ac-Di-Sol and Sodium starch glycolate as superdisintegrants. There concentrations were optimized using a 32 full-factorial design to produce tablets able to disintegrate within 30 s with minimum friability. Then the tablets were evaluated for physical evaluation and drug release studies.

Results: The optimizedIRT formulation (OIRT1) showed a disintegration time of 31.67 ± 0.577 s and friability value of 0.58 ± 0.021 %. The accelerated stability studies showed no significant changes in physicochemical properties and release behaviour.

Conclusions: It can be concluded from the study that the IRT of TS can be successfully formulated to get a fast release and these tablets can be used to get quick relief from asthma attacks.

Key words: Ac-Di-Sol, Asthma, immediate release tablet, sodium starch glycolate, terbutaline sulfate

INTRODUCTION

The national asthma education and prevention program defines asthma as a chronic disorder of the airways that are complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyper-responsiveness, and an underlying inflammation.[1] Asthma is a reversible airways disease since the abnormally low airflow rates can be partially or fully restored by prescription bronchodilator and anti-inflammatory medications.[2,3] The immediate release preparations can be used for faster onset of action for relief from asthma.

In this study, terbutaline sulfate (TS) 5-[2-[(1, l-dimethylethyl) amino]-1-hydroxyethyl]1,3-benzenediol sulfate which is a selective β_2 adrenergic agonist has been used as a model drug. It is an effective bronchodilator following peroral administration. TS is having half-life of 3.6 h and a peroral dose of 5 mg 3 times a day.[4-6]

In the present study, immediate release tablets (IRTs) are designed to disintegrate and release drug quickly for a rapid action. Direct compression technique has been employed for formulating immediate release formulations as it does not require granulation which can lengthen the process of tablet making. For formulating IRTs using direct compression directly, compressible excipients such as Avicel PH-101 and superdisintegrants are required to achieve tablets of suitable hardness without compromising the rapid disintegration characteristics.[7]

In this work, we attempted to formulate and optimize IRTs of TS for quick relief from asthma. The IRTs were formulated using sodium starch glycolate (SSG) and Ac-Di-Sol (croscarmellose sodium) as superdisintegrants.

MATERIALS AND METHODS

Materials

TS and Avicel PH-101(Microcrystalline cellulose) were obtained from Oscar remedies Ltd., Yamuna Nagar, India, as a gift sample. Ac-Di-Sol (croscarmellose sodium) was procured from Optica pharmaceuticals, Haryana, India. Other materials were purchased from commercial sources: SSG, lactose and talc (Nice Chemicals, Mumbai, India), and magnesium stearate (Loba Chemicals, Mumbai, India).

Methods

Formulation of IRT

The direct compression technique was used for tablet preparation. All the raw materials [Table 1] were passed through a #60 sieve before mixing. All the ingredients except talc and magnesium stearate were blended using a laboratory mortar and pestle. The powder blend was then lubricated with 2% talc and 2% magnesium stearate. The powder blend was then compressed using a 6-mm tooling punch on a single punch tablet machine, (Rolex Eng. Work, Ambala, India) to get tablets weighing 100 mg.

Experimental design for IRT

A three-level full factorial design (3^2) was employed.[7-9] According to the model, nine experiments were conducted in total. This

Address for correspondence:
Mr. Prabhjot Singh Bajwa, Ch. Devilal College of Pharmacy, Jagadhri, Yamuna Nagar, Haryana, India. Phone: +91-9991974709.
E-mail: Prabhjot.bajwa1@gmail.com

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design consists of dependent variables Y and independent or controlled variables X_1 and X_2. The two independent formulation variables selected for this study were X_1, amount of Ac-Di-Sol; and X_2, amount of SSG. The independent variables were varied at three levels. The levels for these three parameters were determined from the preliminary trials. The three levels (−1, 0, and +1) for both the independent variables are 2, 4, and 6% w/w. The dependent variables were Y_1, disintegration time in seconds; Y_2, friability in % weight. Table 2 summarizes the factors, the levels tested, and the responses. Response surfaces were constructed using the software package Design Expert software (version 10.1, Stat-Ease Inc., Minneapolis, USA).

The quadratic equation for model is of the following form:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{12}X_1^2 + b_{22}X_2^2$$

Where, Y is the selected response; b_0 is the arithmetic mean response of the nine runs; and b_1 and b_2 are the estimated coefficients for the independent factors X_1 and X_2, respectively.

Evaluation of IRT

The tablets were evaluated for thickness, weight variation, hardness, friability, and drug content uniformity. The thickness of the tablets (n = 3) was determined using a Vernier caliper. The weight variation was estimated by weighing 20 tablets of each formulation using an electronic weighing balance (AW 120, Shimadzu Corporation, Japan). The hardness of three tablets was measured using Pfizer tablet hardness tester. Friability was determined on sample of whole tablets corresponding to about 6.5 g in a Roche friabilator (Electro lab, Mumbai, India) at 25 rpm for 4 min (100 revolutions). For estimation of drug content, randomly selected 10 tablets were crushed, and the aliquot of powder equivalent to 5 mg of drug was dissolved in suitable quantity of pH 1.2 HCl buffer solution. Solution was filtered and diluted and drug content was determined spectrophotometrically (water's 2487) at 276 nm. Assessment of *in vitro* disintegration time for was carried out using United State Pharmacopeia (USP)-27/NF-22 disintegration test apparatus. Disintegration time of all the batches was measured by placing one tablet in each tube and the basket assembly was positioned in 900 ml of water maintained at 37 ± 2°C. The endpoint of disintegration was manifested as the disappearance of the last tablet fragment from the tube.[7-9]

Table 1: Composition of TS fast-release tablet formulations (batches F1-F9 in mg)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
TS	2	2	2	2	2	2	2	2	2
Ac-Di-Sol	2	2	2	4	4	4	6	6	6
SSG	2	4	6	2	4	6	2	4	6
Avicel PH-101	30	30	30	30	30	30	30	30	30
Lactose	60	58	56	58	56	54	56	54	52
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2

TS: Terbutaline sulfate, SSG: Sodium starch glycolate

Table 2: Factors combinations as per the chosen experimental design for formulating IR tablets and responses obtained

Batches	Variable levels in coded form		Responses	
			Y_1	Y_2
	X_1	X_2	Disintegration time (s)	% friability
F1	−1	−1	75.33±2.517	0.65±0.041
F2	−1	0	54.33±1.528	0.6±0.024
F3	−1	+1	43.33±2.517	0.25±0.017
F4	0	−1	63.67±3.055	0.68±0.07
F5	0	0	42.33±2.517	0.56±0.039
F6	0	+1	24.33±1.528	0.36±0.017
F7	+1	−1	59.00±1.00	0.78±0.065
F8	+1	0	35.33±2.517	0.67±0.027
F9	+1	+1	18.00±1.00	0.46±0.03

Results are average of three determinations (Mean±SD), X_1: Amount of Ac-Di-Sol, X_2: Amount of SSG. IR: Immediate release, SSG: Sodium starch glycolate, SD: Standard deviation

In vitro release studies of IRT

Dissolution studies were performed using USP dissolution apparatus II (Rolex Scientific Eng. Ambala, India) at 100 rpm. The dissolution studies were carried in 900 mL of 0.1N HCl (pH 1.2) as dissolution medium at 37 ± 0.5°C. Samples of 5 mL were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through 0.2 µm Whatman filter paper and analyzed spectrophotometrically at 276 nm (Water's 2487 ultraviolet detector). The release studies were conducted in triplicate. Drug release data were appropriately corrected for loss of drug and receptor medium volume during sampling by replacement using the following equation:

$$C_i = A_i + \left(\frac{V_s}{V_t}\right).\sum_{t=1}^{n-1} A_i\left(\frac{V_t}{V_t - V_s}\right)$$

Where, C_i is the corrected absorbance of ith observation, A_i is the observed specific absorbance, V_s is the sample volume, and V_t is the total volume of dissolution medium.[10,11]

Optimization of IRT

The optimization process was used to generate a model equation that provides a means of evaluating changes in response due to changes in the independent variable levels. After application of full factorial design and with help of polynomial terms, the optimized tablet batch (optimized IRT [OIRT1]) was produced which were targeted to the disintegration time of 30 s and friability 0.42–0.96%.

Stability Studies

With the help of the ICH guidelines, stability studies were designed to assess the stability of the formulation OIRT1. Three replicates of OIRT1 formulation were sealed in a polyethylene pack with inside aluminum coating and stored at 40 ± 2°C and 75 ± 5% RH in the humidity chamber for 3 months. The samples were taken out of storage after required sampling time. The formulation was subjected to drug assay and *in vitro* dissolution studies. At this point, the data were statistically analyzed using ANOVA to test the significance of difference at the level of significance 0.05. The value of similarity factor F2 was also calculated to compare the dissolution profiles before and after storage.[12-14]

RESULTS AND DISCUSSION

Immediate release formulation is needed to quickly reach minimum effective concentration of drug to relieve patient from the acute asthmatic attacks. Quick disintegration of tablets is needed for rapid dissolution of drug to aid in fast absorption.

Evaluation of IRT Batches F1-F9

The physical evaluation parameters of batches F1-F9 were found to comply with pharmacopoeial limits and all the results were shown in Table 3. The prepared tablets were smooth in appearance and their thickness varied from 2.19 to 2.35 mm and weight varied between 99.30 and 100.92 mg. The thickness and weight of tablets were under passable limits. The hardness was measured to be between 3.5 and 3.7 kg/cm^2. Hardness level between 3.0 and 4.0 kg/cm^2 is required to manufacture tablets having sufficient mechanical strength. Drug assay of all the nine batches was found to be between 99.55 and 100.99% which is under passable limits. *In vitro* release studies were performed for fast release formulations and all the formulations were able to release 100% of the assayed drug content within 5 min [Figure 1a and b].

The values of disintegration time were found to be between 18.00 s and 75.33 s showing quick disintegration properties. Friability was found to be in a range between 0.25% and 0.78%. Friability should be <1.0% and all the batches passed this criterion.

Response Surface and Statistical Analysis of Models for Disintegration Time and Friability

The amount of Ac-Di-Sol and SSG was found to have an important effect on disintegration time and friability. The disintegration time and percent friability for the nine batches (F1–F9) showed a wide variation (i.e., 18–75 s and 0.248–0.771%, respectively). The data clearly indicated that the disintegration time and percent friability values were strongly dependent on the selected independent variables.

Two-dimensional (2-D) contour plots and three-dimensional response surface plots provide information about the effect of independent variables on dependent variables. From the 2-D contour plot [Figure 2a], it can be seen that as the levels of X_1 and X_2 were increased from −1 to 1, the disintegration time decreased from 75 s to 18 s. Response surface plot [Figure 2b] also depicts

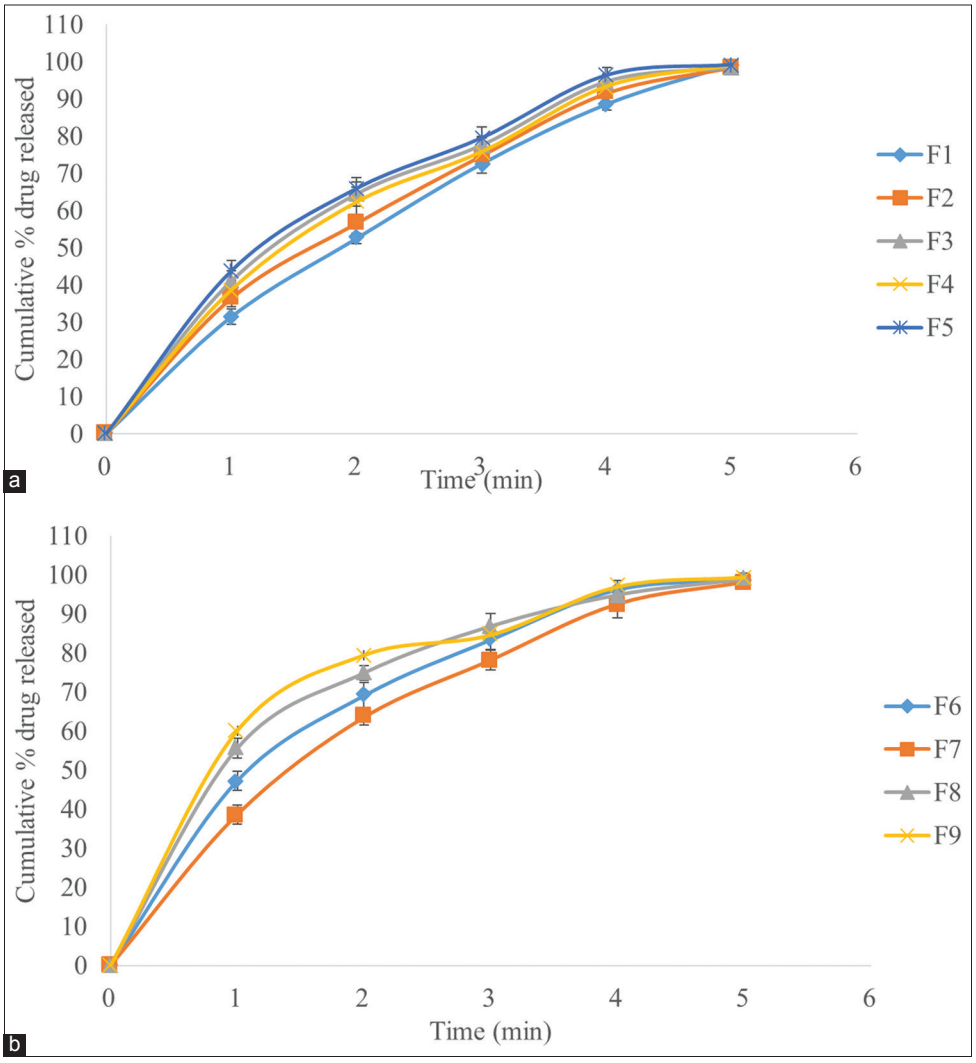

Figure 1: *In vitro* release profile of terbutaline sulfate from fast release tablet formulations; (a) (F1-F5), (b) (F6-F9)

Table 3: Evaluation of IRT

Batches	Thickness[α] (mm)	Average weight[β] (mg)	Hardness[α] (kg/cm^2)	Friability[α] (%)	Disintegration time[α] (s)	Drug content[γ] (% w/w)
F1	2.28±0.07	100.92±1.916	3.67±0.035	0.65±0.041	75.33±2.517	100.34±1.273
F2	2.34±0.165	100.66±2.019	3.59±0.121	0.6±0.024	54.33±1.528	100.31±1.419
F3	2.27±0.051	100.81±2.162	3.64±0.086	0.25±0.017	43.33±2.517	100.11±1.412
F4	2.27±0.145	100.86±1.995	3.62±0.04	0.68±0.07	63.67±3.055	100.35±1.417
F5	2.28±0.217	99.30±1.724	3.7±0.081	0.56±0.039	42.33±2.517	100.16±1.351
F6	2.19±0.068	100.34±1.88	3.65±0.099	0.36±0.017	24.33±1.528	100.31±1.426
F7	2.35±0.24	100.06±2.237	3.58±0.04	0.78±0.065	59.00±1.00	99.55±1.418
F8	2.31±0.195	100.69±2.192	3.56±0.121	0.67±0.027	35.33±2.517	100.99±1.594
F9	2.25±0.113	100.25±2.301	3.59±0.104	0.46±0.03	18.00±1.00	100.5±1.746

All values represent mean ± standard deviation, [α]n=3, [β]n=20, [γ]n=10. IRT: Immediate release tablet

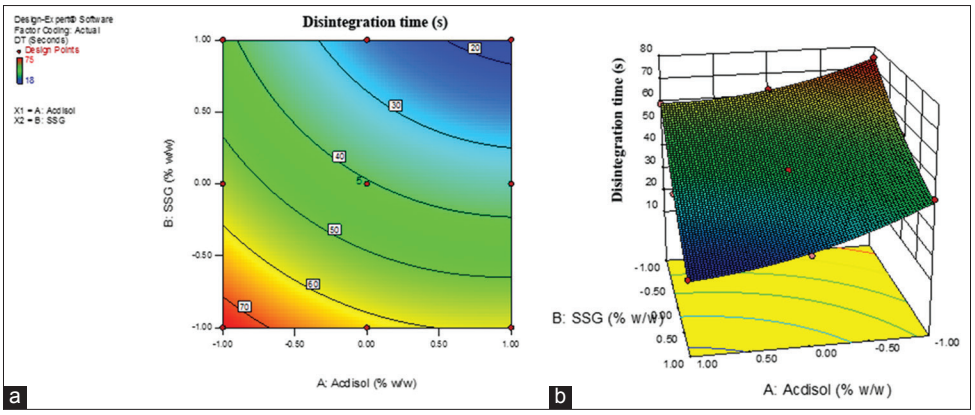

Figure 2: (a) Two-dimensional contour plot and (b) three-dimensional response surface plot showing the effect of independent variables X_1 and X_2 on dependent variable Y_1 (disintegration time)

similar antagonistic effect of X_1 and X_2 on disintegration time. 2-D contour plot [Figure 3a] and response surface plot [Figure 3b] depict the synergistic effect of independent variables. Plot shows that as the levels of X_1 and X_2 were increased from −1 to 1, the friability increased from 0.25% to 0.78%. A linear behavior was seen between independent and dependent variables.

The fitted equation relating the responses, namely, disintegration time and percent friability to the transformed factor are as follows:

(For disintegration time)

$$Y_1 = +40.59 - 10.00X_1 - 18.67X_2 - 2.25X_1X_2 + 4.45X_1^2 + 3.45X_2^2$$

(For friability)

$$Y_2 = +0.60 + 0.070X_1 - 0.17X_2 + 0.020X_1X_2 + 0.023X_1^2 - 0.085X_2^2$$

Effect of formulation variables on friability

Friability was found to vary between 0.25% and 0.78%. Friability should be <1.0% and all the batches passed this criterion. An increase in the amount of Ac-Di-Sol leads to an increase in friability because the coefficient b_1 bears a positive sign. When a higher amount of Ac-Di-Sol was used, low compressible tablets were produced, which were mechanically weak. The increase in the amount of results in decreased friability values because b_2 bears a positive sign.

Effect of formulation variables on disintegration time

The results of multiple linear regression analysis reveal that on increasing the amount of either Ac-Di-Sol or SSG, a decrease in disintegration time was observed; both the coefficients b_1 and b_2 bear a negative sign. When higher amount of Ac-Di-Sol was used, higher water uptake swelling and deformation of the Ac-Di-Sol take place, which gives internal pressure on tablets to disintegrate. The water uptake and subsequent disintegration were thus facilitated. It was obvious that in the presence of higher amount of SSG, wicking was facilitated. Disintegration time is one of the most important criteria in developing fast release tablets and the disintegration time varied between 18 s and 75 s.

ANOVA and Lack-of-fit Test

ANOVA and lack-of-fit test analysis were done for the model [Tables 4 and 5]. The results of the ANOVA were applied to identify insignificant factors.

The model F = 261.04 and 44.32 with $P < 0.0001$ was significant which implies that the models were significant. Values of "$P > F$" <0.0500 indicate model terms are significant. In this case, X_1 and X_2 are significant model terms. Predicted residual sum of squares (PRESS) is a measure of how well the model fits each point in the design. Value of PRESS was found to be 55.91 and 0.043 for both responses which were small, smaller the PRESS statistic; better the model fits the data points. High R^2 = 0.9947 and 0.9694 for both responses suggested that these models are significant. Lack

of fit is an undesirable characteristic for a model. If the model does not fit the data well, the test will show a significant lack of fit. For a well-fitted model, lack of fit will be insignificant ($P > 0.10$). In our case, *P*-value for the lack of fit of the two models was 0.6722 and 0.2936 and both the values were insignificant, so the model fits the data generated.

Optimization of Sustained Release Tablets

3^2 full factorial design was employed for optimization to predict the formulation showing the targeted release characteristics. Constraints were set to produce tablets targeted to the disintegration time 30 s and friability 0.42–0.96%. Equal importance was given to both responses. The global desirability value was calculated. The suggested optimized formulation was 0.509 and 0.358 for X_1, and X_2, respectively, with the corresponding desirability (D) value of 1.00. This factor level combination predicted the response as Y_1 = 30 s and Y_2 = 0.570%. To confirm the model adequacy for the prediction, three batches of the optimized formulations were prepared and the prepared optimized formulation was evaluated for physical properties and i*n vitro* release studies.

Evaluation of OIRT1

The formulation OIRT1 showed average weight, hardness, and drug content values of 200.99 ± 2.36 mg, 3.19 ± 0.06, and 100.56 ± 1.79, respectively, which were under passable limits. The value of disintegration time and friability was found to be 31.67 ± 0.577 s and 0.58 ± 0.021%, respectively, which were similar to the predicted values. As the observed values [Table 3] of the responses were similar to predicted values, this shows that statistically the model was valid.

Stability Studies

Accelerated stability studies data of the formulation OIRT1 showed that there was no significant change in formulation in the sense of drug content and dissolution behavior. From the statistical analysis, it was found that there was no significant difference between before and after storage ($P < 0.05$). The similarity factor F2 was calculated to compare the dissolution profiles of optimized formulation before and after storage, and it was found to be 94 which is more than 50 indicating similarity between the dissolution profile before and after storage.

CONCLUSION

It can be concluded from the present study that IRTs of TS can be successfully formulated using Ac-Di-Sol and SSG as superdisintegrants. The results suggest that concentration of superdisintegrants had a negative effect on disintegration time. The *in vitro* release studies showed that IRTs were able to quickly release drug within 5 min. Thus, the present study shows that IRTs having physical properties under passable limits can be

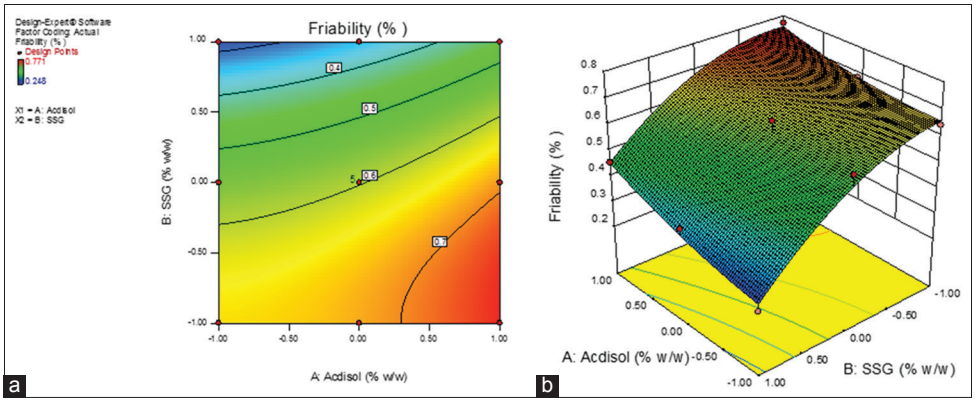

Figure 3: (a) Two-dimensional contour plot and (b) three-dimensional response surface plot showing the effect of independent variables X_1 and X_2 on dependent variable Y_2 (% friability)

Table 4: Analysis of variance and lack-of-fit tests for the response surface model Y_1 (disintegration time)

Source	Sum of squares	df	Mean square	F	*P*-value Prob > F	PRESS	R^2
Model	2851.02	5	570.20	261.04	<0.0001	55.91	0.9947
X_1-acdisol	600.00	1	600.00	274.69	<0.0001		
X_2-SSG	2090.67	1	2090.67	957.13	<0.0001		
X_1X_2	20.25	1	20.25	9.27	0.0187		
X_1^2	54.65	1	54.65	25.02	0.0016		
X_1^2	32.84	1	32.84	15.03	0.0061		
Residual	15.29	7	2.18				
Lack of fit	4.49	3	1.50	0.55	0.6722		
Pure error	10.80	4	2.70				
Corrected total	2866.31	12					

Corrected total: Sum of squares total corrected for mean, df: Degrees of freedom, PRESS: Predicted residual sum of squares. SSG: Sodium starch glycolate

Table 5: Analysis of variance and lack-of-fit tests for the response surface model Y_2 (friability)

Source	Sum of squares	df	Mean square	F	*P*-value Prob>F	PRESS	R^2
Model	0.23	5	0.045	44.32	<0.0001	0.043	0.9694
X_1-acidisol	0.029	1	0.029	28.62	0.0011		
X_2-SSG	0.17	1	0.17	171.78	<0.0001		
X_1X_2	1.600E-003	1	1.600E-003	1.57	0.2501		
X_1^2	1.523E-003	1	1.523E-003	1.50	0.2607		
X_2^2	0.020	1	0.020	19.39	0.0031		
Residual	7.121E-003	7	1.017E-003				
Lack of fit	4.051E-003	3	1.350E-003	1.76	0.2936		
Pure error	0.23	5	0.045	44.32	<0.0001		
Corrected total	0.029	1	0.029	28.62	0.0011		

Corrected total: Sum of squares total corrected for mean, df: Degrees of freedom, PRESS: Predicted residual sum of squares. SSG: Sodium starch glycolate

formulated that can be used to provide quick relief from asthma attacks.

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