

RESEARCH ARTICLE



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Development of Directly Compressible Mucoadhesive Fast Disintegrating Sublingual Tablet System of Piroxicam Using 3 factor, 3 Level Box Behnken Design

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Abstract

Piroxicam is a non steroidal anti-inflammatory drug with analgesic properties. The purpose of this study was to develop a mucoadhesive fast disintegrating tablet of poorly soluble Piroxicam by direct compression technique using superdisintegrant sodium starch glycolate and interactive mixture was characterized by physicochemical parameters. A Box Behnken design was applied to systematically optimize the drug disintegration time. Independent variables studied were the amount of Disintegrant (X_1), amount of Bioadhesive (X_2) and amount of Binder (X_3). The dependent variables were Hardness (Kg/cm^2) (Y_1), Disintegration time (sec), (Y_2) friability (%) (Y_3) and wetting time (sec) (Y_4). The prepared tablets were evaluated physical properties hardness, friability, disintegration time, wetting time and In-vitro drug release.

Keywords: Interactive mixture, direct compression, piroxicam, box behnken design.

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INTRODUCTION

Recent developments in the technology have prompted scientists to develop orally disintegrating tablets with improved patient compliance and convenience. ODTs are solid unit dosage forms, which disintegrate or dissolve rapidly in the mouth without chewing and water. Orally disintegrating tablets provide an advantage particularly for paediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules because paediatric patients may suffer from ingestion problems as a result of underdeveloped muscular and nervous control. They are also suitable for bed-ridden, psychotics, developmentally disabled and the patients with persistent nausea during travelling or who have little access to water. Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action. Moreover, drug candidates that undergo pregastric absorption when formulated as ODTs may show increased oral bioavailability. It provides good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients¹. Box Behnken experimental design is one of the best tools for studying the effect of different variables on the quality determinant parameters of any formulation. Multiple regression analysis of results gives an equation that adequately describes the influence of the independent formulation variables on the selected responses². Piroxicam (PIRO) is a nonsteroidal anti-inflammatory drug (NSAID) of the oxicam family that has been recognized for its value as a chemopreventative, anti-tumor agent, acute and chronic musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, rheumatoid arthritis, dysmenorrhoea and sometimes for pain associated with it. Oxicams derive their anti inflammatory effect from inhibition of cyclooxygenase (COX) activity and subsequent repression of prostaglandin synthesis. Two forms of COX are currently recognized. Cyclooxygenase-1 is found in the stomach, gastrointestinal tract, platelets and kidney. It is this form that is responsible for most of the side effects associated with NSAIDs³. Cyclooxygenase-2(COX-2) predominates at areas of inflammation, immune reaction, and increased cellular activity. Although the precise anti-tumor mechanisms of PIRO and other NSAIDs are unknown, some have suggested that they may be secondary to the aforementioned COX and PG inhibition⁴.

The studies described in this work were designed to evaluate a new sublingual tablet system using low doses of piroxicam. In this system, water-soluble carrier particles are covered with piroxicam and a bioadhesive material during dry mixing. In principle,

the tablet quickly disintegrates into the ordered units consisting of carrier, piroxicam and bioadhesive component. These units initially adhere to the mucosa. The water-soluble carrier particles gradually dissolve and piroxicam dissolves along with them. With this approach, optimal exposure of active substance to the dissolving fluids is combined with bioadhesive retention of the drug in the oral cavity^{5,6}.

For poorly soluble, highly permeable (class II) drugs (like piroxicam), the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal (GI) tract. Therefore, together with permeability, solubility and dissolution behaviour of a drug are key determinants of its oral bioavailability. This undesired property, may also increase the amount of GI damage, due to long contact of drug with the mucous of GI.

MATERIALS AND METHODS

Reagents and samples

All the Analytical grade materials were used. Piroxicam reference standard was collected from Asoj Soft Caps. Pvt. Ltd., India. Mucoadhesive fast disintegrating tablets were formulated using mannitol, sodium croscarmellose (SCC), microcrystalline cellulose (MCC), dicalcium phosphate (DCP), magnesium stearate and mango flavor as an excipients. Acetonitrile (HPLC grade), Distilled water (HPLC grade) were used as analytical grade solvent for analysis purpose^{7,8,9}. All the excipients and solvents were purchased from Loba Cheme, Mumbai. The reagents 0.1 N Sodium Hydroxide, Phosphate buffer solution pH 7.2, simulated salivary fluid (pH 6.8) was prepared according to compendial procedure¹⁰.

Formulation of piroxicam fast disintegrating mucoadhesive tablets

Preparation of mixtures/powder blend

Coarse mannitol particles were covered with piroxicam by dry mixing. This material was mixed in a teflonized metal jar of All Purpose Mixer (Shakti corp., Mumbai) at 90 rpm for 24 hrs. SCC and MCC were added to the interactive mixture and mixed at 30 rpm for an additional 48 hrs. The DCP and mango flavour was added in interactive mixture and mixed for 1 hr at 30 rpm¹¹.

Determination of mixture homogeneity

The content of piroxicam was used to express the quality (i.e. heterogeneity) of the mixtures. Samples of each mixture weighing 120 mg were withdrawn with the aid of sample thieves/Spatula^{11,12}. The amount of piroxicam in the samples was measured spectrophotometrically (Shimadzu corp. Japan) at a wavelength of 354 nm.

Compaction of tablets

Prior to compaction, all tablet masses were mixed with magnesium stearate in the tumbling mixer at 30 rpm for 2min. Tablets were made in 8 station Rota press (Karnavati, Ahmadabad) using 5mm flat edged punches; the powder was filled into the die with a feed frame. The tablets contained piroxicam 20 mg in bases. Each batch comprised 100 tablets. Piroxicam fast disintegrating mucoadhesive tablets were prepared by direct compression method ^{11,12}. A total number of fifteen formulations (F1 to F15) of piroxicam tablets were prepared. Before tablet preparation, the mixture blend of the formulations were subjected to precompression study parameters like Angle of repose, bulk density, tapped density, compressibility index and hausner's ratio ^{13,14,15,16}.

Optimization of mucoadhesive fast disintegrating tablet by box-behnken design

The objective functions for the present study was selected as maximizing the hardness while controlling the disintegration time. Hence, a Box-Behnken statistical design with 3 factors, 3 levels, and 15 runs was selected to statistically optimize the formulation parameters and evaluate the main effects, interaction effects and quadratic effects of the formulation ingredients on the hardness, disintegration time, % friability and wetting time of fast disintegrating tablet. 3-factor, 3-level design was used to explore the quadratic response surfaces and for constructing polynomial models thus helping in optimizing a process using a small number of experimental runs. The experimental design consists of a set of points lying at the midpoint of each edge and the replicated center point of the multidimensional cube ¹⁷. The independent and dependent variables are listed in table 1. The polynomial equation generated by this experimental design (using Reliasoft DOE) is as follows:

$$Y_i = b_0 + b_1 X_1 + b_2 X_2 + b_3 X_3 + b_4 X_1 X_2 + b_5 X_1 X_3 + b_6 X_2 X_3 + b_7 X_{12} + b_8 X_{22} + b_9 X_{32}$$

Where; Y_i is the dependent variable; b_0 is the intercept; b_1 to b_9 are the regression coefficients computed from the observed experimental values of Y from experimental runs; X_1 , X_2 and X_3 are the independent variables that were selected from the preliminary experiments. $X_1 = (A - X_0) / \Delta X$; X_1 = coded value of the variable A; X_0 = value of A at the center point, ΔX = Step change and so on where A, B etc. are the input variables. The terms AB and AA_i ($i = 1, 2$ or 3) represent the interaction and quadratic terms, respectively.

Statistical analysis

Statistical analysis of the Box-Behnken design batches was performed by multiple regression analysis using Microsoft Excel. To evaluate the contribution of each factor with different levels to the response, the two-

way analysis of variance (ANOVA) was performed using the @Reliasoft Office DOE software. To graphically demonstrate the influence of each factor on the response, the response surface plots were generated using the @Reliasoft Office DOE software ¹⁸.

Checkpoint analysis

A checkpoint analysis was performed to confirm the role of the derived polynomial equation and contour plots in predicting the responses. Values of independent variables were taken at 3 points, 1 from each contour plot, and the theoretical values of hardness and disintegration time were calculated by substituting the values in the polynomial equation. Mucoadhesive Fast disintegrating tablets were prepared experimentally at 3 checkpoints and evaluated for the responses ¹⁸.

Run order/ Batch No.	Independent Variables			
	(X1) Superdisintegrant (mg)	(X2) Binder (mg)	(X3) Bioadhesive (mg)	
1	0	-1	1	
2	0	1	-1	
3	1	1	0	
4	0	-1	-1	
5	0	1	1	
6	1	0	1	
7	-1	1	0	
8	-1	0	1	
9	0	0	0	
10	1	-1	0	
11	0	0	0	
12	-1	-1	0	
13	1	0	-1	
14	0	0	0	
15	-1	0	-1	
Independent variables		Low	Medium	High
A= Amount of Disintegrant (mg) (Croscarmellose sodium)		5	10	15
B= Amount of Bioadhesive (mg) (Mannitol)		50	55	60
C= Amount of Binder (mg) (Microcrystalline cellulose)		10	15	20
Dependent variables (Factors)				
Y ₁ = Hardness (Kg/cm ²)				
Y ₂ = Disintegration time (Sec)				
Y ₃ = Friability (%)				
Y ₄ = Wetting time (Sec)				

Table 1: Box Behnken experimental design

Optimization data analysis

The optimized formulation was obtained by applying constraints (goals) on dependent (response) and independent variables (factors).

The models were evaluated in terms of statistically significant coefficients and R^2 values. Various feasibility and grid searches were conducted to find the optimum parameters. Various 3-D response surface graphs were provided by the @Reliasoft Office

DOE software¹⁸. The optimized checkpoint formulation factors were evaluated for various response properties. The resultant experimental values of the responses were quantitatively compared with the predicted values to calculate the prediction error.

Characterization of formulations

Physical characterization of tablet

General appearance, thickness, diameter and volume, tablet hardness, weight variation, uniformity of content and friability.¹⁹⁻²³

The physicochemical evaluation was performed according to European Pharmacopoeia (1997).

The tablet thickness is expressed as averages of 5 measurements made at 5 different points between the 2 surfaces of the compact.

Hardness of the tablet of each formulation was determined using Pfizer hardness tester. Three tablets from each formulation batch were tested randomly and the average reading was noted.

Randomly selected 20 tablets were weighed individually and together in a single pan balance. As per Indian Pharmacopoeia this method is satisfactory to determine the drug content uniformity. The average weight was noted and standard deviation was calculated.

The test for uniformity of drug content is carried out by collecting a sample of 10 tablets from a batch and determining their individual amount of drugs in each tablet. As per Indian Pharmacopoeia this method is satisfactory to determine the average drug content and the content of individual tablets should fall within specified limits in terms of the percentage deviation from the mean.

The Roche friabilator was used for determination of friability²⁴.

Drug content

Ten tablets from each formulation were weighed individually and powdered. The Powder equivalent to 20mg of Piroxicam was weighed and dissolved in 10ml of methanol and volume was adjusted to 100ml with pH 6.8 simulated salivary fluid. From this solution 1 ml was taken and made up to 100 ml using same dilution media, solution was filtered, and analyzed at 354 nm by UV-visible spectrophotometer using simulated salivary fluid as the blank. Each sample was analyzed in triplicate^{25,26}.

Disintegration time

Nine hundred millilitres of water maintained at 37°C. DT was determined at the point at which the tablet disintegrated and passed through the screen of the sinker completely (opening of mesh of the sinker: 3-3.5 mm in height and 3.5-4 mm in width)²⁷.

In vitro dispersion time

In vitro dispersion time i.e. time required to

breakdown the tablet into small particles and make dispersion was measured by dropping a tablet in a beaker containing 50 ml of simulated salivary fluid pH 6.8^{27,29}.

Wetting time and water absorption ratio

Although a wetting test is not a standard test, it is useful for quality control and provides supportive evaluation of sublingual tablets. A piece of tissue paper folded twice was kept in a Petri dish containing 6 ml of purified water. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue paper. The time required to develop a red colour on the upper surface of the tablet was recorded as the wetting time. The same procedure without amaranth was followed for determining the water absorption ratio. The wetted tablet was weighed and the water absorption ratio, R, was determined²⁹.

Measurement of tablet tensile strength

A diametral compression test was performed according to European Pharmacopoeia (resistance to crushing of tablets) (n = 35)³⁰. The tablet crushing load, which is the force required to break a flat-faced tablet into halves by compression in the radial direction, was measured using a tablet hardness tester. Tensile strength for crushing (Ts) was calculated using the following equation:

$$T_s = \frac{2F}{\pi \cdot dt}$$

Where F is the crushing load, and d and t denote the diameter and thickness of the tablet, respectively.

Measurement of tablet porosity

The tablet porosity was calculated from the dimensions and weight of the tablet and the apparent particle density of the mixture. The apparent density (ρ_{app}) of the compact, were calculated from the ratio of the tablet mass to the volume of the compact³¹.

$$(\rho_{app}) \text{ of compacts} = \frac{\text{Mass of tablet}}{\text{Volume of compact}} = \frac{gm}{\pi r^2 h}$$

The porosity of the compacts was calculated using the relationship

$$\text{Porosity } (\epsilon) = 1 - \frac{\rho_{app} \text{ density of compacts}}{\rho \text{ true density of particles}}$$

Where, ϵ is the porosity of the compacts, ρ_{app} is the apparent density of the compact, and ρ true is the true density of the particles. The ratio of ρ_{app}/ρ_{true} is a measure of the relative density or the solid fraction of the compact.

In vitro dissolution test

The release rate of piroxicam from mucoadhesive fast disintegrating tablets was determined using USP dissolution testing apparatus II (paddle method, Electrolab, TDT-06T, Mumbai, India). The dissolution

test were performed using 900 ml of simulated salivary fluid (pH=6.8), at 37 ± 0.5°C and 50 rpm. A sample (1ml) of the solution was withdrawn from the dissolution vessel at 1, 2, 3, 4, 5, 10 and 20 min time intervals. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through a whatman filter. Absorbance of these solutions was measured at 354 nm using a Shimadzu UV-1700 UV/Vis double beam spectrophotometer^{32,33}. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

RESULT AND DISCUSSION

Box-Behnken experimental design

The use of experimental design allows for testing a large number of factors simultaneously and precludes the use of a huge number of independent runs when the traditional step-by-step approach is used. Systematic optimization procedures are carried out by selecting an objective function, finding the most important or contributing factors and investigating the relationship between responses and factors. A Box Behnken experimental design has the advantages of requiring fewer experiments (15 batches) than would a 3² full factorial design (27 batches). Transformed values of all the batches were shown in table 1. The all selected dependent variables obtained at various levels of the 3 independent variables (X1, X2 and X3) were subjected to multiple regression to yield a second order polynomial equation.

$$Y1 = 4.9667 - 0.9125 X_1 - 0.400X_2 - 0.4125 X_3 + 0.625 X_1X_2 + 0.30 X_1 X_3 + 0.125X_2X_3 + 0.1417 X_{11} - 1.083 X_{22} - 0.7533X_{33}$$

$$Y2 = 57.66 - 4.25 X_1 + 0.875 X_2 + 1.875 X_3 - 8.00X_1X_2 + 1.5 X_1 X_3 + 3.25 X_2X_3 - 6.4583 X_{11} - 10.2083X_{22} - 10.2083X_{33}$$

$$Y3 = 0.5933 + 0.0975 X_1 + 0.775X_2 + 0.0525 X_3 - 0.0675X_1X_2 - 0.0225 X_1 X_3 - 0.0125 X_2X_3 - 0.0454 X_{11} + 1.3463X_{22} + 1.446X_{33}$$

$$Y4 = 98.667 - 33.87 X_1 - 14.750X_2 - 6.125 X_3 + 21X_1X_2 + 3.750 X_1 X_3 + 6 X_2X_3 - 4.0417 X_{11} - 37.20X_{22} - 17.45X_{33}$$

Sr. no.	Term	Hardness	Disintegration time	% Friability	Wetting time
1.	* Intercept	4.97	57.67	0.59	98.67
2.	A: Superdisintegrant (r ²)	-0.91	-4.25	0.10	-33.88
3.	* B: Binder (r ²)	-0.40	0.88	0.08	-14.75
4.	* C: Bioadhesive (r ²)	-0.41	1.88	0.05	-6.13
5.	* AB	0.63	-8.00	-0.07	21.00
6.	* AC	0.30	1.50	-0.02	3.75
7.	* BC	0.13	3.25	-0.01	6.00
8.	* AA	0.14	-6.46	-0.05	4.04
9.	* BB	-1.08	-10.21	0.13	-37.21
10.	* CC	-0.76	-10.21	0.14	-17.46

Table 2: Polynomial Equation values in terms of Actual values

(coefficients)

Quadratic model	(%) R ²	(%) Adjusted R ²
Response Y ₁	71.47	20.10
Response Y ₂	91.29	75.62
Response Y ₃	72.92	24.16
Response Y ₄	75.79	32.22

Table 3: Regression analysis of Y₁, Y₂, Y₃ and Y₄ for fitting to quadratic model

Effect of formulation variables:

The results clearly indicate that the hardness value is strongly affected by the variables selected for the study. This is also affected by the wide range of values for coefficients of the terms of polynomial equation for Y1. The main effects of X1, X2 and X3 represent the average result of changing one variable from its low level to its high level. The interaction terms (X₁X₂, X₁X₃, X₂X₃, X₁₂, X₂₂ and X₃₂) shows how the hardness changes when remained variables are simultaneously changed. The negative coefficients for all 3 independent variables indicate an unfavourable effect on the hardness, while the positive coefficients for the interactions between 2 variables indicate a favourable effect on the hardness. Among the three independent variables, the lowest coefficients value is for X₂, indicating that this variable is insignificant in prediction of hardness.

Y1, Y2, Y3 and Y4 values measured for the different batches showed wide variation (values ranged from 2.1 to 6.4 Kg/cm² for Y1; 28 to 63 second for Y2; 0.51 to 2.90% for Y3 and 32 to 141 second for Y4) which clearly indicate that the Y1, Y2, Y3 and Y4 values is strongly affected by the variables selected for the study. This is also affected by the variables selected for the study. This is also reflected by the wide range of values for coefficients of the terms in equations. The main effects of X1, X2 and X3 represent the average result of changing one variable at a time from its low level to its high level. The negative sign for the coefficients in polynomial equation indicates a negative effect on responses, while the positive sign indicate a positive effect. The statistical analysis of the full model indicates that the independent variables had a significant effect on the responses.

The standardized effect of the independent variables and their interaction on the dependent variable was investigated by preparing a pareto chart (figure 1, 2, 3 and 4) which depicts the main effect of the independent variables and interactions with their relative significance on the Y1, Y2, Y3 and Y4. The length of each bar in the chart indicates the standardized effect of that factor in the responses. Factors remains inside the reference line indicate that these terms contribute the least in prediction of responses.

ANOVA, Pure error and Lack of fit:

The result of ANOVA demonstrates that the model was significant for all dependent variables shown in table 2. Regression analysis was carried out to determine the regression coefficients. All the independent variables were found to be significant for all response variables. The quadratic model was found to be significant for Y2. The linear model was found to be significant for Y3 and Y4. So above result indicates that both the factors play an important role in the formulation of tablet containing piroxicam. The data of pure error and lack of fit can provide a mean response and an estimate of pure experimental uncertainty. The residuals are the difference between observed and predicted values.

The ANOVA for the dependent variables demonstrates that the model was significant for all response variables. The effects are like, the amount of MCC and SCC were found to be significant, along with its quadratic and interaction terms for all the dependent variables.

Hence the above results lead us to believe that concentrations of disintegrant have an important role to play and optimal concentrations in sublingual tablets give rise to rapid disintegration time, good crushing strength values and sufficiently low friability percentages, in order to successfully withstand the mechanical stress, during packing, transportation and handling. The data for pure error and lack of fit provides a mean response and an estimate of pure experimental uncertainty. The residuals values shown represents the differences between the observed and predicted values, given that computed F values were respectively lower than critical F values, which denotes non-significance with regard to lack of fit.

To confirm the omission of non significant terms, F statics was calculated after applying analysis of variance for the full model. The F calculated value 0.80 is less than the tabulated value of 1.39 at 0.05 confidence interval for hardness. Hence it is concluded that the omitted terms do not significantly contribute to predicting the hardness. This implies that the main effect of the amount of binder and the amount of bioadhesive added is significant, as is evident from the high coefficients.

The three replicated center points in the Box Behnken experimental design made it possible to assess the pure error of the experiments and enabled the model's lack of fit to be checked. In this study, the model was checked for lack of fit for all the responses. For lack of fit P values we obtained 0.75, 0.49, 0.36 and 0.872 for Y1, Y2, Y3 and Y4 respectively and hence the current model provided a satisfactory fit to the data and had no lack off fit. The ANOVA studies for Y1, Y2, Y3 and Y4. The statistical significance of each effect was tested by comparing the mean square against an estimate of the experimental error. It was noted that X1, X3 and X4 had p-value greater than 0.05, indicating non significance of these variables in prediction of Y1, Y2, Y3 and Y4.

Run Order	Independent variables			Hardness (Kg/cm ²)	Disintegration time (Sec)	Friability (%)	Wetting time (Sec)
	(A)	(B)	(C)				
1	0	-1	1	3.1	32	0.81	41
2	0	1	-1	2.9	36	0.96	35
3	1	1	0	4.1	28	0.65	48
4	0	-1	-1	4.4	35	0.62	70
5	0	1	1	2.1	46	1.1	30
6	1	0	1	2.9	39	0.85	38
7	-1	1	0	3.6	50	0.71	47
8	-1	0	1	5.2	47	0.58	125
9	0	0	0	5.9	43	0.56	50
10	1	-1	0	3.2	48	0.79	42
11	0	0	0	3.5	54	0.73	46
12	-1	-1	0	5.2	38	0.58	125
13	1	0	-1	2.9	32	0.85	38
14	0	0	0	6.4	56	0.49	140
15	-1	0	-1	6.4	46	0.49	140

Table 4: Response variables (F1-F15) obtained from various trial formulations of piroxicam 120 mg MFD tablets

Run Order	Independent variables			Hardness (Kg/cm ²)		Disintegration time (sec)	
	A	B	C	*Measured	Predicted	*Measured	Predicted
5	0	1	1	2.37±0.40	2.4375	42.33±2.52	43.25
6	1	0	1	2.93±0.21	3.325	39.67±1.53	40.125
7	-1	1	0	3.63±0.15	3.9125	54.33±2.08	54.125

* n=3

Table 4: Checkpoint Analysis:

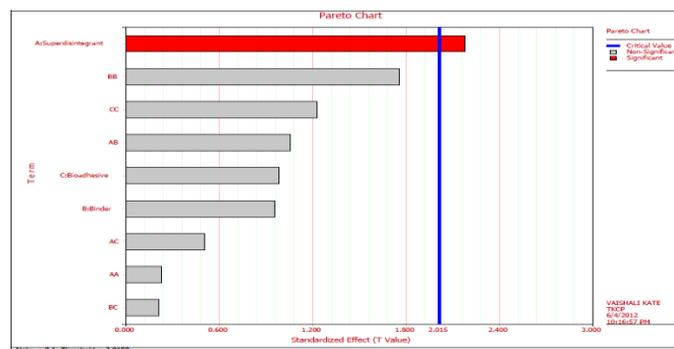


Figure 1: Pareto chart showing the standardized effect of independent variables and their interaction on hardness

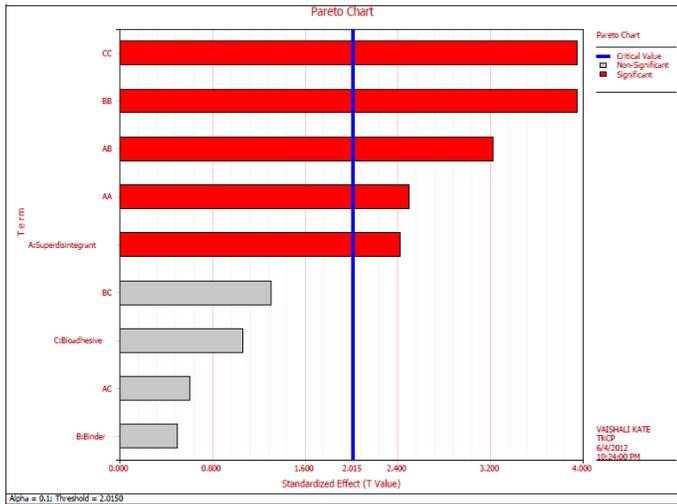


Figure 2: Pareto chart showing the standardized effect of independent variables and their interaction on disintegration time

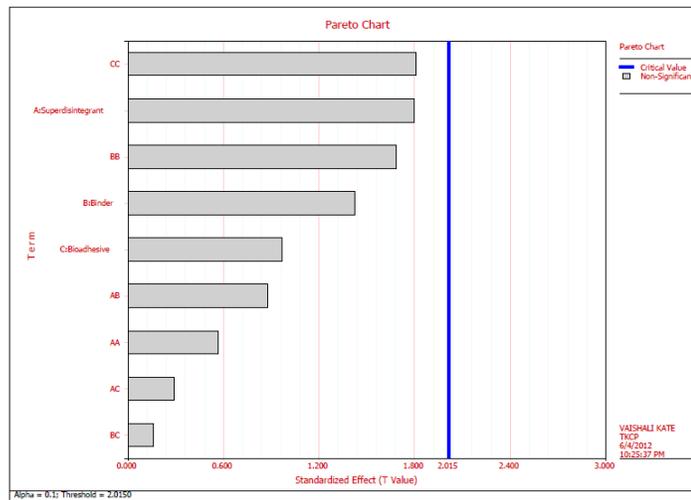


Figure 3: Pareto chart showing the standardized effect of independent variables and their interaction on percentage friability

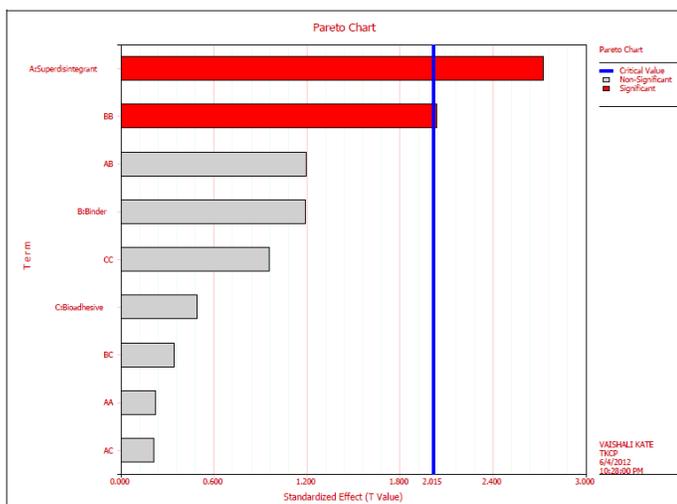


Figure 4: Pareto chart showing the standardized effect of independent variables and their interaction on wetting time

Contour plots and response surface analysis:

Two dimensional contour plots and three dimensional response surface plots are presented in figures 5 to 10,

which are very useful to study the interaction effects of the factors on the responses. These types of plots are useful in study of the effects of two factors on the response at one time. In all the presented figures 5 to 10, the third factor was kept at a constant level. All the relationships among the three variables are non linear, the effects of X1 and X3 with their interaction on hardness at a fixed level of X2. The plots were found to be linear upto 66.78% hardness, but above this value, the plots were found to be non linear indicating a non linear relationship between X1 and X3. Similarly all values for remained dependent variables.

It was determined from the contour plot that a higher value of hardness could be obtained with and X1 level range from 5 to 15 and an X3 level range from 10 to 20. It is evident from the contour plot that the low level of the both X1 and X3 favours the hardness of tablet. When the coefficients values of two key variables, X1 and X3 were compared, the value for variable X1 was found to be higher, indicating that it contributes the most to predicting the hardness. The contours of all the hardness values were found to be curvilinear and indicated that a high value of hardness can be obtained for a combination of the two independent variables, the X1 level in the range of 2.2 to 6.

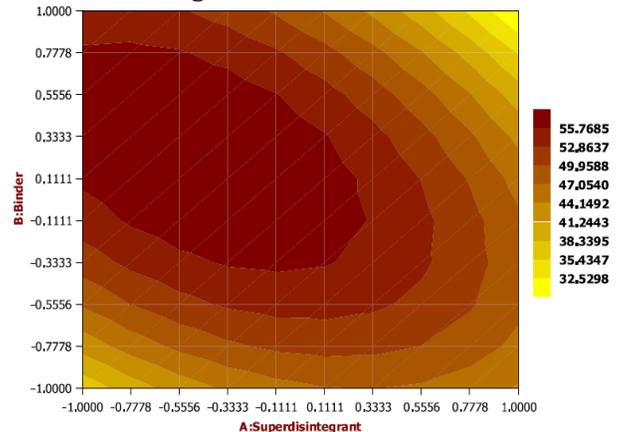


Figure 5: Contour plot showing effect of disintegrant concentration and binder concentration on response Y3

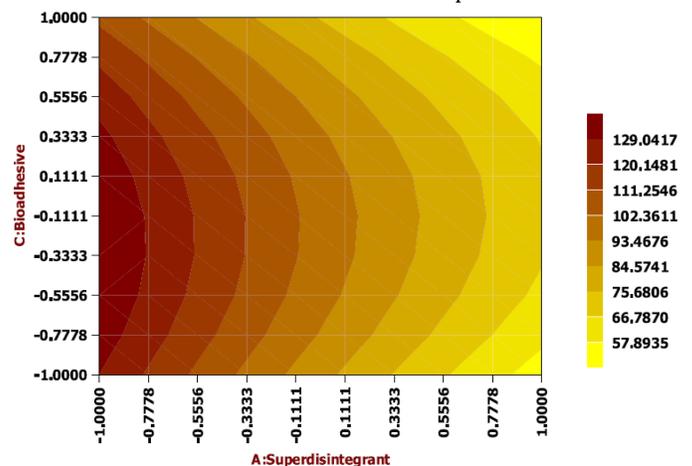


Figure 6: Contour plot showing effect of disintegrant concentration and bioadhesive concentration on response Y3

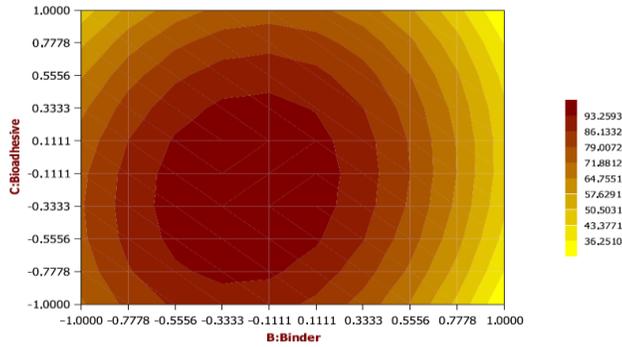


Figure 7: Contour plot showing effect of binder concentration and bioadhesive concentration on response Y3

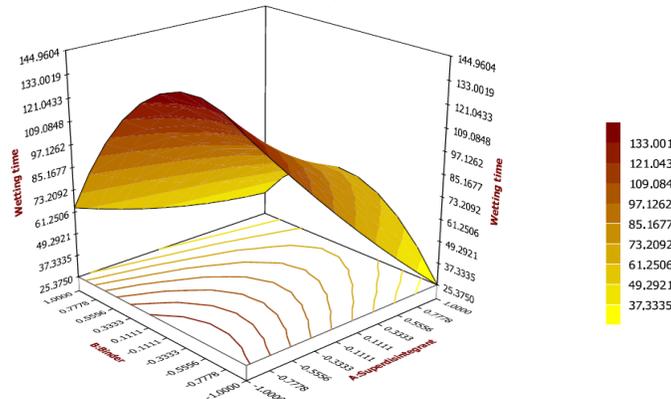


Figure 8: Response surface plot (3D) showing the effect of binder concentration and superdisintegrant concentration on response Y4

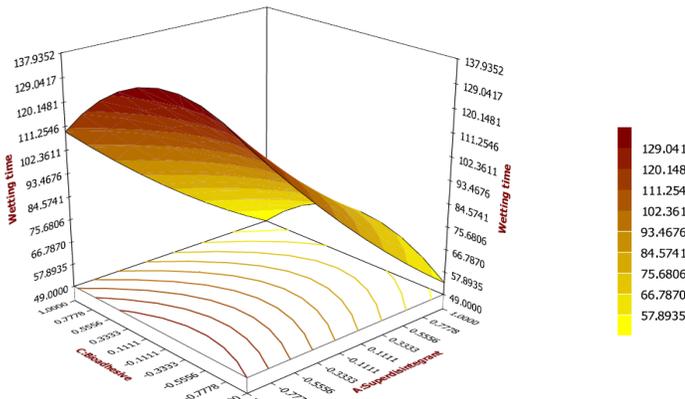


Figure 9: Response surface plot (3D) showing the effect of superdisintegrant and bioadhesive concentration on response Y4

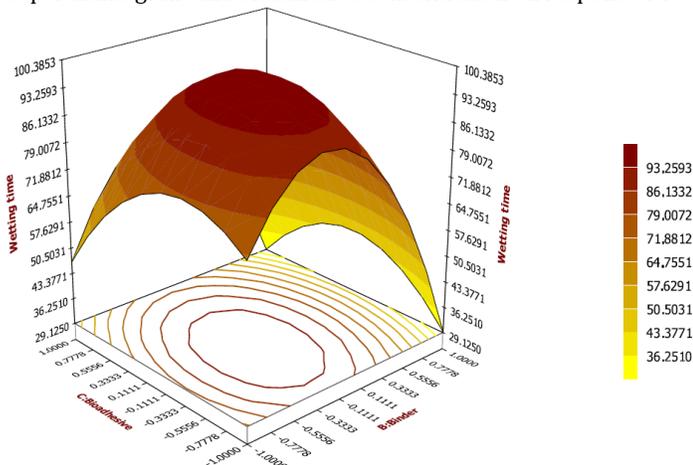


Figure 10: Response surface plot (3D) showing the effect of binder and bioadhesive concentration on response Y4

Checkpoint Analysis:

Besides understanding the main and interaction effects on the responses, the experimental design approach is helpful in obtaining the optimized formula in which the levels of X1, X2 and X3 were decided. In this instance, an optimized formula was theoretically obtained to yield hardness 5, disintegration time 63 min, friability 0.58 % and wetting time 109 seconds.

As a confirmation of this process, a new formulation was prepared at the optimum levels of the independent variables and evaluated. The observed value of responses of Y1, Y2, Y3 and Y4 gave a close agreement with the predicted values.

Three checkpoint batches were prepared and evaluated for hardness and disintegration time table 8. Results indicate that the measured hardness and disintegration time values were as expected. When measured hardness values were compared with predicted hardness values the differences were found to be insignificant. Thus we can conclude that the obtained mathematical equation is valid for predicting the hardness.

Characterization of optimized batch

After studying the effect of the independent variables on the responses, the level of these variables that give the optimum response were determined. The optimum formulation is one that gives high value of hardness and a fast drug release with a low amount of bioadhesive carrier in the resultant tablet. It is evident from the polynomial equation and plots that increasing the amount of superdisintegrant increases in DT and decreases the hardness. It is clear that, medium level was selected as optimum for all the independent variables. Using a computer optimization process and the contour plot, we select the medium level.

Physical characterization of tablet

General appearance, thickness, diameter and volume of tablet

Drug uniformity results were found to be good among different batches of tablets, and the percentage of drug content was more than 98%. The results also showed acceptable and homogenous distribution of drug in tablets.

The weight and thickness of the formulations ranged from 117 to 121 mg and from 2.78 to 3.08 mm, respectively. All tablets prepared in this study meet the USP requirements for weight variation of all formulae was less than 2% (USP 31). In all the formulations, the hardness test indicated good mechanical strength. Tablet hardness is not an absolute indicator of strength. Another measure of a tablet's strength is friability. In the present study, the percentage friability for all the formulations was below 1%, indicating that the friability is within the compendial limits (USP 31) and had a good mechanical resistance.

In vitro disintegration study

In principle, the tablets should disintegrate rapidly, to instantly generate many ordered units consisting of mannitol, piroxicam and SSC. The disintegration time of the all batches of tablets containing piroxicam was 28-63 s. The higher value was probably caused by adhesion of the tablets to the discs (because of the addition of bioadhesive), which fudged the endpoint. It seems reasonable from these results that the tablet will adhere to the mucosa in the mouth. The in vitro data obtained with discs probably better reflects the disintegration time in vivo into ordered units. However, the peristaltic movements that occur in the mouth may contribute to the disintegration of the tablets.

The most important parameter that needs to be optimized in the development of sublingual tablets is the disintegration time of tablets. In the present study, all the tablets disintegrated in the range varied from 28 ± 3.61 to 63 ± 1.53 s. In the USP disintegration test for sublingual tablets, the disintegration apparatus for oral tablets is used without the covering plastic discs, and 2 min is specified as the acceptable time limit for tablet disintegration fulfilling the official requirements (<2 min) for sublingual tablets (USP 31). So all of our formulations meet the requirement for disintegration. The rapid and desired disintegration of tablets is due to the presence and good proportion of Mannitol, MCC and SCC and can be explained with following reasons.

MCC has good wicking and absorbing capacities. Tablets of MCC disintegrated rapidly due to the rapid passage of water into the tablets resulting in the instantaneous rupture of the hydrogen bonds. The ratio of MCC in tablet formulations changes between 10% and 20% and verifies the findings that the optimum concentration of MCC may be less than 15%. MCC accelerates water penetration into tablets can cause easily swelling of SCC, and this reveals readily superdisintegrant property of SCC. But here, there is another important point that must be taken into consideration that the ratio of SCC in sublingual tablet formulation is very important because it was reported that disintegration time increased with increase in the level of SCC in the tablets. It was shown that the increase in the level of SCC had a negative effect on the disintegration of the tablets. At higher levels, formation of a viscous gel layer by SCC might have formed a thick barrier to the further penetration of the disintegration medium and hindered the disintegration or leakage of tablet contents. Thus, tablet disintegration is retarded to some extent with tablets containing SCC. So it can be concluded that the use of SCC in sublingual tablet formulations in 10 mg gives the tablet desired disintegration time. On the other hand, mannitol has a highly water soluble property and this may leave pores

in the tablet matrix after rapid dissolution of it. These pores can accelerate capillary action that may be responsible for penetration of surrounding fluid in the tablet matrix and there after rapid disintegration (James 2003 et al.).

Water absorption, porosity and wetting time

Water uptake increased with increased mannitol content and caused a great deal of swelling. During the manufacture of MCC, accessible amorphous regions of cellulose molecules are hydrolyzed away, so that MCC shows relatively high crystallinity. It can absorb only small amounts of water, and reaches equilibrium rapidly.

Wetting is closely related to the inner structure of tablets and to the hydrophilicity of excipients. According to equation developed from Washburn's, the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of powders which is expressed by contact angle and surface tension. It is obvious that pore size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. Since the hydrophilicity of MCC is lower than Mannitol, wetting time generally decreases with an increased MCC content. When the MCC content exceeded 90%, however, the wetting time showed a reverse tendency. This suggested that the inner structure of these tablets underwent some change at a high MCC concentration. Since MCC particles are of a concave convex shape and their pores are fairly collapsed by compression.

Tablet tensile strength

It was generally recognized that tensile strength was influenced by the number of contact points between the powder particles and the interparticle binding force, such as the surface molecular interaction and mechanical interlocking. The number of contact points was altered by the porosity of the tablet and by the shape and diameter of constituent particles. MCC was easily compressed, when compressed under the same pressure, tablets containing more MCC showed lower porosity.

Both tablet strength and disintegration times were effected by tablet porosity. The porosity of the tablet may affect the action of the disintegrant. A relatively low porosity was most effective action for the action of a disintegrant. However, no general relationship between porosity and disintegration time was seen and it was concluded that the material properties of the tablet components, such as solubility and bounding ability, would also affect disintegration time. The tablet porosity was approximately 25% for all three batches, which appears adequate considering the results for tablet strength.

In vitro dissolution studies

The dissolution tests revealed that piroxicam was dissolved almost instantly from the tablets. In formulated tablets, roughly 50% of the substance was dissolved from the tablet within 1 min, and more than 90% within 10 min. The dissolution profiles for all the tablets are comparable with those obtained for ordered mixtures i.e. compaction of the ordered units did not negatively influence the dissolution rate. After initially rapid disintegration, ordered units are quickly exposed to the solvent and drug dissolution starts more or less instantly. In these studies a large amount of dissolution medium (900 ml, pH 6.8) was used. However the volume of fluid used in *in vivo* was much smaller.

According to the literature, the amount of drug dissolved from sublingual tablets must exceed 80% in 15 min. therefore; the resulted dissolution profile met the above mentioned requirement.

Fast dissolution of the drug from the formulations can be explained with the few comments like; manufacturing method can be one of the most important parameters for the dissolution. As it is known, the tablets prepared by direct compression disintegrate into piroxicam particles instead of granules that directly come into contact with dissolution fluid and exhibits comparatively faster dissolution. It is well known that the addition of mannitol can improve the flow and bond properties of other excipients during direct compression. In particular, mannitol with higher solubility might also facilitate the dissolution of solid dosage forms. When evaluate all formulations, mannitol ratios can give us the chance of preparing sublingual tablets without changing their basic tablet characteristics especially disintegration and dissolution profiles^{34,35}.

CONCLUSION

A Box Behnken design was performed to study the effect of formulation variables on crushing strength, % friability, wetting time and disintegration time by applying the optimization techniques. The results revealed that, the amount of Mannitol, MCC and SCC affected significantly the response variables. An observed response was in close accord with the predicted values of the optimized formulation and consequently demonstrates the feasibility of the optimization procedure in the development of sublingual tablets. It can be concluded that, sublingual tablets provide several advantages especially when administered to children and elderly patients. Rapid absorption into the systemic circulation within a shorter period of time may be achieved. Dosage forms developed in such a way provide therefore, an interesting field for further research given that the results may be extrapolated to other drugs, for which a rapid onset of effect is a desirable objective.

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