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Formulation Design and Optimization of Mouth Dissolve Tablets of Nimesulide Using Vacuum Drying Technique

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Mukesh Gohel,[1] Madhabhai Patel,[2] Avani Amin,[2] Ruchi Agrawal,[1] Rikita Dave,[1] and Nehal Bariya[1]

[1]L. M. College of Pharmacy, Navrangpura, Ahmedabad – 380 009, India
[2]Shree S.K. Patel College of Pharmaceutical Education & Research, Ganpat Vidyanagar, Kherva, Mehsana – 382 711, India

ABSTRACT

The purpose of this research was to develop mouth dissolve tablets of nimesulide. Granules containing nimesulide, camphor, crospovidone, and lactose were prepared by wet granulation technique. Camphor was sublimed from the dried granules by exposure to vacuum. The porous granules were then compressed. Alternatively, tablets were first prepared and later exposed to vacuum. The tablets were evaluated for percentage friability, wetting time, and disintegration time. In the investigation, a 3^2 full factorial design was used to investigate the joint influence of 2 formulation variables: amount of camphor and crospovidone. The results of multiple linear regression analysis revealed that for obtaining a rapidly disintegrating dosage form, tablets should be prepared using an optimum concentration of camphor and a higher percentage of crospovidone. A contour plot is also presented to graphically represent the effect of the independent variables on the disintegration time and percentage friability. A checkpoint batch was also prepared to prove the validity of the evolved mathematical model. Sublimation of camphor from tablets resulted in superior tablets as compared with the tablets prepared from granules that were exposed to vacuum. The systematic formulation approach helped in understanding the effect of formulation processing variables.

KEYWORDS: mouth dissolve tablet, nimesulide, camphor, factorial design, contour plot

INTRODUCTION

The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome this weakness, scientists have developed innovative drug delivery systems known as "melt in mouth" or "mouth dissolve (MD)" tablets. These are novel types of tablets that disintegrate/dissolve/disperse in saliva. Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients. They are also suitable for the mentally ill, the bedridden, and patients who do not have easy access to water. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice in the current market.[1,2]

The basic approach used in the development of the fast-dissolving tablet is the use of superdisintegrants. Croscarmellose sodium, sodium starch glycolate, and crospovidone were screened in the present study, and the best one was used for further studies. Another approach used in developing MD tablets is maximizing pore structure of the tablets. Freeze-drying[3,4] and vacuum-drying[5-7] techniques have been tried by researchers to maximize the pore structure of tablet matrix. Freeze drying is cumbersome and it yields a fragile and hygroscopic product. Therefore, it was decided to adopt the vacuum-drying technique in the present investigation. Vacuum drying was adopted after addition of a subliming agent to increase porosity of the tablets. It is likely that a porous hydrophilic matrix will easily pick up the disintegrating medium and break quickly.

Clinically, nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed by physicians for inflammatory disorders. NSAIDs exert their effect through inhibition of cyclooxygenase-II, the main form of isozyme associated with inflammation. But the simultaneous inhibition of cyclooxygenase-I and the resulting gastric and renal dysfunction limit their frequent use.[8] Nimesulide, a model active pharmaceutical ingredient acts specifically on cyclooxygenase-II and does not affect cyclooxygenase–I.[9] Hence, nimesulide exerts its anti-inflammatory action while showing a marked increase in gastrointestinal tolerability and minimal incidences of renal dysfunction. Because of its additional action of inhibiting respiratory burst of phagocytosing neutrophils, nimesulide is also well tolerated by asthmatic patients.[10] Thus, it is one of the most commonly prescribed NSAIDs for the treatment of various inflammatory conditions such as tonsillitis, pharyngitis, stomatitis, rheumatoid arthritis, osteoarthritis, low back pain, etc. Nimesulide results in poor bioavailability when administered in the form of conventional tablets because of its high hydrophobicity and poor aqueous solubility.[11] Complexation and cosolvency techniques have been useful in improving the dissolution characteristics of nimesulide.[12,13]

Corresponding Author: Mukesh Gohel, L M. College of Pharmacy, PO Box 4011, Navrangpura, Ahmedabad - 380 009 India; Tel: 91-79-26302746; Fax: 91-79-26304865; Email: mukeshgohel@hotmail.com.

Table 1. Results of Preliminary Batches of Mouth Dissolve Nimesulide Tablets*

Formulation	A1	A2	A3	A4	A5
Nimesulide (mg)	100	100	100	100	100
Camphor (mg)	-	10	20	20	20
Crospovidone (mg) †	8	8	8	8	8
Colloidal silicon dioxide (mg)	-	-	-	2	2
Lactose..q.s.....to.....(mg)	200	200	200	200	200
Friability (%)	0.3	0.5	0.6	0.4	0.5
Wetting time (seconds)	140	105	90	80	40
Disintegration time (seconds)	154 ± 0.71	138	110	100	50

*All batches contained 10% polyvinylpyrrolidone in ethyl alcohol as a binder and 2% talc and 1% magnesium stearate.
Camphor was sublimed from granules in Batches A1 to A4 and from tablets in Batch A5.
†Intragranular 50%; extragranular 50%.

An attempt was made in the present investigation to prepare MD tablets of nimesulide using various sublimable materials.

Materials and Methods

Materials

Nimesulide and crospovidone were obtained from Redson Pharmaceuticals (Ahmedabad, India) and BASF Chemicals (Mount Olive, NJ), respectively. Croscarmellose sodium, sodium starch glycolate, and lactose IP were obtained as gift samples from Zydus Cadila Healthcare Ltd (Ahmedabad, India). Polyvinylpyrrolidone (PVP-K40) and colloidal silicon dioxide were obtained from Laser Industries (Ahmedabad, India) and Cabot Sanmar Ltd (Ahmedabad, India), respectively. Camphor, menthol, and thymol were obtained from a local ayurvedic pharmacy. Magnesium stearate was purchased from Apex Chemicals (Ahmedabad, India).

Methods

Preparation of Nimesulide Tablets (Preliminary Trials and Factorial Design)

The raw materials were passed through a no. 100 screen prior to mixing. Nimesulide, camphor, intragranular fraction of crospovidone, and lactose were mixed using a glass mortar and pestle. Alcoholic solution of PVP (10% wt/vol) was added to the mixture in a quantity just enough to bind the mass. The granules (50 g) of 44/no. 100 mesh screen were collected and vacuum dried at 60°C for 24 hours to facilitate sublimation of camphor. The granules were mixed with the extragranular fraction of crospovidone and the required proportion of fines (10%). The granules were lubricated with 2% wt/wt talc and 1% wt/wt magnesium stearate. The granules ready for compression were converted into tablets using a single-punch tablet machine (Cadmach, Ahmedabad, India). Sublimation was performed from tablets instead of granules at 60°C in selected batches (A5 and F1 to F9 and check point). The composition of the preliminary and factorial design batches is shown in Tables 1 and 2, respectively.

Evaluation of Tablet Properties

The crushing strength of the tablets was measured using a Monsanto hardness tester (Sheetal Scientific Industries, Mumbai, India). The friability of a sample of 10 tablets was measured using a Roche Friabilator (Electrolab). Twenty preweighed tablets were rotated at 25 rpm for 4 minutes. The tablets were then reweighed after removal of fines (using no. 60 mesh screen), and the percentage of weight loss was calculated. The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10-cm diameter were placed in a petri dish with a 10-cm diameter. Ten milliliters of water containing eosin, a water-soluble dye, was added to the petri dish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time. The disintegration time was measured using a modified disintegration method (n = 5). For this purpose, a petri dish (10-cm diameter) was filled with 10 mL of water. The tablet was carefully put in the center of the petri dish and the time for the tablet to completely disintegrate into fine particles was noted.

Full Factorial Design

A 3^2 randomized full factorial design was used in the present study. In this design 2 factors are evaluated, each at 3 levels, and experimental trials are performed at all 9 possible combinations.[14,15] The amount of subliming agent, camphor (X_1), and the amount of superdisintegrant, crospovidone (X_2), were selected as independent variables. The disintegration time and percentage friability were selected as dependent variables.

Results and Discussion

Water insoluble diluents such as microcrystalline cellulose and dicalcium phosphate were omitted from the study as they are expected to cause an unacceptable feeling of grittiness in the mouth. Among the soluble diluents, lactose was selected

Table 2. 3^2 Full Factorial Design Layout*

Batch Code	Variable Levels in Coded Form		Disintegration Time	% Friability
	X_1 (mg)	X_2 (mg)	**DT ± SD** (seconds)	**% F ± SD**
F1	-1	-1	120 ± 2.5	0.235 ± 0.018
F2	-1	0	90 ± 4.8	0.168 ± 0.020
F3	-1	+1	60 ± 3.51	0.137 ± 0.013
F4	0	-1	50 ± 2.52	0.266 ± 0.012
F5	0	0	32 ± 1.53	0.213 ± 0.013
F6	0	+1	25 ± 1.53	0.203 ± 0.012
F7	+1	-1	40 ± 2.65	0.400 ± 0.016
F8	+1	0	30 ± 2.08	0.257 ± 0.012
F9	+1	+1	20 ± 1.15	0.223 ± 0.013
Check point	-0.2	+0.8	28 ± 2.0	0.183 ± 0.010

Coded values	Actual Values	
	X_1	X_2
-1	0	4
0	5	8
1	10	12

*X_1 indicates amount of camphor (mg); X_2, amount of crospovidone (mg); DT, disintegration time; and F, friability. Camphor was sublimed by heating tablets in a vacuum oven.

as a model soluble diluent considering its advantages in terms of easy availability, cost-effectiveness, and relative moisture insensitivity.

The preliminary trials were conducted by using 2% superdisintegrants (croscarmellose sodium, sodium starch glycolate, and crospovidone) intragranularly and 2% extragranularly. Three batches were prepared using a single superdisintegrant, while the other 3 batches were prepared using an equal proportion of 2 disintegrants. Granules of lactose and superdisintegrants were prepared by using wet granulation technique (PVP K40, 10% wt/wt alcoholic solution as a binder). The granules were lubricated and compressed into tablets on a single-punch tablet machine. On the basis of the results obtained in the preliminary screening studies, the batch containing crospovidone showed the fastest disintegration. Hence, it was selected for further studies. Polyvinylpyrrolidone was used as a binder at a concentration of 10% wt/vol, considering its widespread applicability in the industry. The crushing strength of the tablets was adjusted to 5 kilopond (kp) (49 N). Subliming agents such as menthol, camphor, and thymol were used to increase porosity of the tablets in the preliminary tablet formulations. Camphor-containing tablets exhibited faster disintegration as compared with tablets containing menthol and thymol.

The batches A2 and A3 were prepared using camphor at different concentrations to study its effect on disintegration time. The sublimation time (5-10 hours) depended on the amount of camphor present initially (0%, 10%, or 20%). Batch A3, containing 20% camphor, showed the least disintegrating time. The results shown in Table 1 indicate that concentration-dependent disintegration was observed in batches prepared using camphor as a subliming agent. The porous structure is responsible for faster water uptake, hence it facilitates wicking action of crospovidone in bringing about faster disintegration.[16,17] It is worthwhile to note that as the concentration of camphor increased, the wetting decreased.

Tablets with lower friability (≤0.5%) may not break during handling on machines and/or shipping. The use of a sublimation agent resulted in increased friability probably due to increased porosity. It was decided to incorporate colloidal silicon dioxide, extragranularly, at a level of 1% to decrease the friability of the tablets (batches A4 and A5). Addition of colloidal silicon dioxide resulted in appreciable decrease in friability and marginal decrease in disintegration time. Colloidal silicon dioxide helps to restore the bonding properties of the excipients.[18]

In the first few attempts (A1-A4), sublimation of camphor was performed from granules prior to compression into tablets. Batches A1 to A4 showed good mechanical integrity, but the disintegration time was a little longer than the arbitrarily chosen value of less than 50 seconds. In Batch A5, sublimation was performed after compression rather than directly from granules. The results shown in Table 1 reveal that sublimation of camphor from tablets resulted in faster disintegration. The compaction process might have caused breakage of porous granules and subsequent reduction in porosity. The low value of wetting time and disintegration time indicate that the porosity of tablets of batch A5 would be greater than batches A1 to A4. The granules required 2 hours of vacuum

Table 3. Summary of Results of Regression Analysis*

For Disintegration Time						
Response (disintegration time)	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}
FM	34.44	-30	-17.5	24.33	1.833	10
RM	35.667	-30	-17.5	24.333	-	10
For Percentage Friability						
Response (percentage friability)	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}
FM	0.2064	0.0567	-0.0563	0.0093	0.0313	0.0198
RM	0.2335	0.0567	-0.0563	-	-	-

*FM indicates full model; and RM, reduced model.

drying, whereas the tablets required 10 hours of vacuum drying. The longer drying time was required in the case of tablets probably because of the decreased surface area and porosity. In order to investigate the factors systematically, a factorial design was employed in the present investigation.

Factorial Design

The amount of subliming agent (camphor, X_1) and the superdisintegrant (crospovidone, X_2) were chosen as independent variables in a 3^2 full factorial design. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2, \quad (1)$$

where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_i is the estimated coefficient for the factor X_i. The main effects (X_1 and X_2) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when 2 factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The disintegration time and percentage friability for the 9 batches (F1 to F9) showed a wide variation (ie, 20-120 seconds and 0.137%-0.4%, respectively). The data clearly indicate that the disintegration time and percentage friability values are strongly dependent on the selected independent variables. The fitted equations (full and reduced) relating the responses disintegration time and percentage friability to the transformed factor are shown in Table 3. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (ie, positive or negative). Table 4 shows the results of the analysis of variance (ANOVA), which was performed to identify insignificant factors.[19]

The high values of correlation coefficient for disintegration time and percentage friability (Table 4) indicate a good fit. The equations may be used to obtain estimates of the response as a small error of variance was noticed in the replicates. The significance test for regression coefficients was performed by applying the Student t test. A coefficient is significant if the calculated t value is greater than the critical value of t.

Table 4. Calculations for Testing the Model in Portions*

For Disintegration Time						
	DF	**SS**	**MS**	**F**		***Fcalc* = 0.2280**
Regression						*Ftable* = 10.13
FM	5	8828	1765	59	0.9900	DF = (1,3)
RM	4	8821	2205	92	0.9893	
Error						
FM	3	88	29			
RM	4	95	23			
For % Friability						
	DF	**SS**	**MS**	**F**		***Fcalc* = 1.5467**
Regression						*Ftable* = 9.28
FM	5	0.0420	0.0084	10.5415	0.946	DF = (3,3)
RM	2	0.0383	0.0192	18.8741	0.86	
Error						
FM	3	0.0024	0.0007			
RM	6	0.0061	0.0010			

*DF indicates: degrees of freedom; SS, sum of squares; MS, mean of squares; F, Fischer's ratio; R^2, regression coefficient; FM, full model; and RM, reduced model. Details of calculations are shown in Mendenhall W and Sincich T.[19]

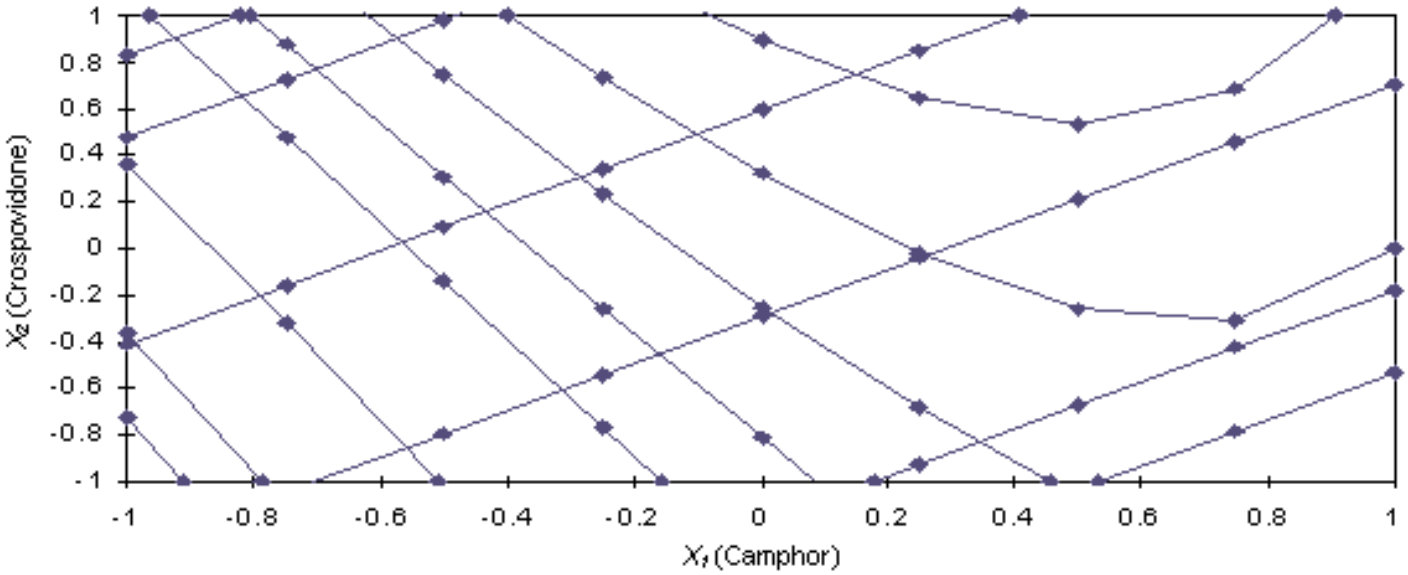

Figure 1. Combined contour plot for disintegration time and percentage friability.

Full and Reduced Model for Disintegration Time

The significance level of coefficient b_{22} was found to be $P = .6656$, hence it was omitted from the full model to generate the reduced model. The results of statistical analysis are shown in Table 3. The coefficients b_1, b_2, b_{11}, and b_{12} were found to be significant at $P < .05$, hence they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficient b_{22} contributes significant information for the prediction of disintegration time or not.[19] The results for testing the model in portions are shown in Table 4. The critical value of F for $\alpha = 0.05$ is equal to 10.13 ($df = 1, 3$). Since the calculated value ($F = 0.2280$) is less than the critical value ($F = 10.13$), it may be concluded that the interaction term b_{22} does not contribute significantly to the prediction of disintegration time and therefore can be omitted from the full model. For drawing conclusions, grid search technique of contour plot should be used since one of the polynomial terms (b_{11}) is also significant.

The results of multiple linear regression analysis (reduced model) reveal that, on increasing the concentration of either camphor or crospovidone, a decrease in disintegration time is observed; both the coefficients b_1 and b_2 bear a negative sign. When higher percentage of camphor is used, higher porosity is expected in the tablets. The water uptake and subsequent disintegration are thus facilitated. It is obvious that in the presence of higher percentage of superdisintegrant crospovidone, wicking is facilitated.

Full and Reduced Model for Percentage Friability

The significance level of coefficients b_{11}, b_{22}, and b_{12} were found to be greater than $P = .05$, hence they were omitted from the full model to generate the reduced model. The results of statistical analysis are shown in Table 3. The coefficients b_1 and b_2 were found to be significant at $P < .05$, hence they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficients b_{11}, b_{22}, and b_{12} contribute significant information for the prediction of disintegration time or not.[19] The results for testing the model in portions are depicted in Table 4. The critical value of F for $\alpha = 0.05$ is equal to 9.28 ($df = 3, 3$). Since the calculated value ($F = 1.5467$) is less than the critical value ($F = 9.28$), it may be concluded that the interaction term and polynomial terms do not contribute significantly to the prediction of disintegration time. Hence, conclusions can be drawn considering the magnitude of the coefficient and the mathematical sign (positive or negative) it carries.

An increase in the concentration of camphor leads to an increase in friability because the coefficient b_1 bears a positive sign. When a higher percentage of camphor is used, more porous tablets are produced, which are mechanically weak. The increase in the concentration of crospovidone results in decreased friability values. Crospovidone is known to produce mechanically strong tablets.

Analysis of contour plot, shown in Figure 1, reveals that the whole of the contour area has acceptable friability values (0.1%-0.35%). It was arbitrarily decided to select a batch of tablets that disintegrate in less than 40 seconds. The area on the right side of the line AE is acceptable. The final selection is done after considering other aspects such as ease of manufacturing, cost, etc. In industry, the total time required for manufacturing a dosage form is of prime concern. When the variable X_1 goes beyond "0" level (5%), vacuum-drying time for complete sublimation increases (5%: 5 hours; 10%: 10 hours). Thus, the working range to get an acceptable product is that on the right side of AE and on the left of BD (ie, area

ABCA). Batches F9 (1,1), F5 (0,0), and F6 (0,1) fall in the acceptable area.

A checkpoint batch F10 was prepared at $X_1 = -0.2$ level and $X_2 = 0.8$. From the reduced model, it is expected that the friability value of the checkpoint batch should be 0.17 and 0.2, and the value of disintegration time should be 28.6 seconds. Table 2 indicates that the results are as expected. Thus, we can conclude that the statistical model is mathematically valid. The factorial design batches were subjected to short-term stability studies at 40°C and 75% RH for 3 months. Studies indicated that no significant change in appearance of the tablets, disintegration time, and percentage friability were observed.

CONCLUSION

The results of a 3^2 full factorial design revealed that the amount of camphor and crospovidone significantly affect the dependent variables, disintegration time, and percentage friability. It is thus concluded that by adopting a systematic formulation approach, an optimum point can be reached in the shortest time with minimum efforts. Vacuum-drying technique would be an effective alternative approach compared with the use of more expensive adjuvants in the formulation of MD tablets.

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