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Research Article

Optimization of mouth dissolving meloxicam tablets prepared by sublimation technique

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ABSTRACT

The aim of this investigation was to develop mouth dissolving tablets of Meloxicam. Granules containing Meloxicam, menthol, crospovidone and mannitol were prepared by wet granulation technique. Menthol was sublimed from the granules by exposing the granules to vacuum. The porous granules were then compressed in to tablets. Alternatively, tablets were first prepared and later exposed to vacuum. The tablets were evaluated for percentage friability and disintegration time. A 3^2 full factorial design was applied to investigate the combined effect of two formulation variables: amount of menthol and crospovidone. The results of multiple regression analysis indicated that for obtaining mouth dissolving tablets; optimum amount of menthol and higher percentage of crospovidone should be used. Surface response plots are also presented to graphically represent the effect of the independent variables on the percentage friability and disintegration time. The validity of a generated mathematical model was tested by preparing a checkpoint batch. Sublimation of menthol from tablets resulted in rapid disintegration as compared with the tablets prepared from granules that were exposed to vacuum. Hence, it was concluded that mouth dissolving tablets with improved meloxicam dissolution could be prepared by sublimation of tablets containing suitable subliming agent.

Keywords: Mouth dissolving tablets, meloxicam, sublimation, menthol, factorial design, response surface plot

INTRODUCTION

Many patients express difficulty in swallowing tablets tending to non-compliance and ineffective therapy.[1] Recent advances in novel drug delivery system aim to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is mouth-dissolving tablets. Advantages of this drug delivery system include administration without water, accuracy of dosage, easy portability, alternative to liquid dosage forms, ideal to pediatric and geriatric patients and rapid onset of action. [2-3]

The fundamental difference used in the development of the mouth dissolving tablets is to maximize its pore structure. Researchers have evaluated spray dried materials [4] and plastic materials [5] for the development of such tablets. Vacuum drying[6-8] and freeze-drying[9-11] techniques have been tried by researchers to maximize the pore structure of tablet matrix. Freeze drying is cumbersome and yields a fragile and hygroscopic product. Therefore, a vacuum drying technique was adopted in the present investigation after addition of subliming agent to increase porosity of the tablets. It is likely that porous hydrophilic matrix will easily pick up the disintegration medium and break quickly.

Meloxicam (MXM) is an oxicam or enol carboxamide derivative. It is non-steroidal anti-inflammatory drug (NSAID) with highly selective cyclo-oxigenase - 2 inhibitory action. It is used in the treatment of rheumatoid arthritis, osteoarthritis, dental pain and in the management of acute post operative pain.[12] It was selected as model drug in present investigation.

MATERIAL AND METHODS

Meloxicam (MXM) was received as a gift sample from Sun Pharmaceuticals Ltd., Vadodara, India. Croscarmellose sodium (CCS), crospovidone (CRP), sodium starch glycolate (SSG), Polyvinyl pyrrolidone K25 (PVP) were purchased from Loba Chemicals, Mumbai, India. All other chemicals used were of analytical grade.

Preparation of Meloxicam tablets

The raw materials were passed through a sieve number 80 prior to mixing. MXM, subliming material, intragranular fraction of disintegrant and mannitol were mixed using a glass mortar and pestle. All the ingredients were dry blended for 10 min and alcoholic solution of PVP was added to the mixture in a quantity just enough to bind the

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mass. The wet mass was passed through 30 mesh and resulting granules were vacuum dried at 65ºC for 24 hrs to facilitate sublimation of subliming materials. The granules were mixed with the extragranular fraction of crospovidone and the required proportion of fines (10%). The granules were lubricated with a blend containing talc (2%), magnesium stearate (1%) and sodium lauryl sulfate (0.5%). The uniformly mixed blend was compressed into tablets using normal concave punches on single compressed tablet machine (Cadmach). Sublimation was performed from tablets instead of granules at 65ºC in selected batches (A7 and F1 to F9 and check point). The composition of the preliminary and factorial batches is shown in Table 1 and 2, respectively.

Evaluation of formulated tablets

Prepared tablets were evaluated for friability (EF-2, Electrolab) and crushing strength using Erweka Hardness tester (TBH20, Electrolab). For the determination of disintegration time, one tablet was placed in each tube of disintegration apparatus (ED-2, Electrolab). Disintegration test was carried out using distilled water as a disintegration media at 24±2ºC. the evaluation results of the preliminary and factorial batches are shown in Table 1 and 2, respectively.

Full factorial design

A 3^2 randomized full factorial design was adopted to optimize the variables. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations.[13] The amount of subliming agent, menthol (X_1), and the amount of crospovidone (X_2), were selected as independent variables. The disintegration time (DT) and percentage friability (%F) were selected as dependent variables.

***In vitro* dissolution study**

In vitro dissolution study was conducted using USP dissolution apparatus II (TDT-06T, Electrolab) at 100 rpm; using 0.1 N HCL as dissolution media maintained at 37±5ºC. Samples were withdrawn at various time interval, filtered through 0.45µ membrane filter, diluted and assayed at 363 nm using UV/VIS double beam spectrophotometer (SL-196, Elico).

RESULT AND DISCUSSION

Mannitol was selected as diluent considering its advantages in terms of easy availability and negative heat of dissolution. The preliminary trials were conducted using 2% superdisintegrant (CCS, CRP and SSG) intragranularly and 2% extragranularly. Three batches were prepared using single superdisintegrant, while the other three batches were prepared using an equal proportion of two disintegrants. Granules of mannitol and superdisintegrants were prepared by wet granulation technique using alcoholic solution of PVP (10% w/v) as a binder. The granules were lubricated and compressed into tablets on single punch tablet machine (Cadmach). On the basis of the results obtained in the preliminary screening studies, the batch containing CRP showed the fastest disintegration. Hence it was selected for further studies. PVP was used as a binder, considering the widespread applicability in the industry. Subliming agents such as ammonium bicarbonate, menthol and camphor were used to increase porosity of the tablets in the preliminary tablet formulations (batches A1 to A3). Menthol containing tablets exhibited faster disintegration as compared with tablets containing ammonium bicarbonate and camphor. Batches A4 and A5 were prepared using menthol at different concentrations to study its effect on disintegration time. The sublimation time (5-10 hrs) dependent on the amount of menthol present initially (0%, 5%, or 10%). Batch A5, containing 10% menthol showed the least disintegration time. The results shown in Table 1 indicate that concentration dependent disintegration was observed in batches prepared using menthol as subliming agent. The porous structure is responsible for faster water uptake; hence it facilitates wicking action of crospovidone in bringing about faster disintegration. Tablets with lower friability (=0.5%) may not break during handling on machines and/or shipping. The use of subliming agent resulted in increase in 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 A6 and A7). Addition of colloidal silicon dioxide resulted in appreciable decrease in friability and marginal decrease in disintegration time. Colloidal silicon dioxide helps to restore the binding properties of the excipients.[14] In the first few attempts (A1 to A6), sublimation of subliming material was performed from granules prior to compression into tablets. Batches A1 to A6 showed good mechanical integrity, but the disintegration time was a little longer than the arbitrarily chosen value of less than 40 s. In batch A7, sublimation was performed after compression rather than directly from granules. The results shown in Table 1 reveal that the sublimation of menthol from tablets resulted in faster disintegration. The compaction process (batch A1- A6) might have caused breakage of porous granules and subsequent reduction in porosity. The low value of disintegration time indicates that the porosity of tablets batch A7 would be greater than that of batch A1 to A6. The granules required 3h of vacuum drying, whereas the tablets required 10h 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.

The amount of subliming agent (menthol, X_1) and the superdisintegrant (crospovidone, X_2) were chosen as independent variables in a 3^2 full factorial design. A statistical model, $Y=b_o+b_1X_1+b_2X_2+b_{12}X_1X_2+b_{11}X_1X_1+b_{22}X_2X_2$, incorporating interactive and polynomial terms was used to evaluate responses; where Y is the dependent variable, bo is the arithmetic mean response of the nine runs and b_1 is the estimated coefficient for the factor X_1. The main effect X_1 and X_2 represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors simultaneously changed. The polynomial terms (X_1X_1 and X_2X_2) are included to investigate non-linearity. The DT and %F for the nine batches (F1 to F9) showed a wide variation (i.e., 25 to 234 s and 0.112% to 0.410%, respectively). The data clearly indicate that the DT and %F values are

Table 1: Tablet formulation and evaluation of preliminary trials

Formulation ingredients	A1	A2	A3	A4	A5	A6	A7
Meloxicam (mg)	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Ammonium bicarbonate (mg)	10	-	-	-	-	-	-
Camphor (mg)	-	10	-	-	-	-	-
Menthol (mg)	-	-	10	0	20	20	20
Crospovidone (mg)	8	8	8	8	8	8	8
Colloidal silicon dioxide (mg)	-	-	-	-	-	2	2
Mannitol q.s (mg)	200	200	200	200	200	200	200
Disintegration time (s)	176	213	155	228	112	105	380
Friability (%)	0.35	0.20	0.45	0.13	0.50	0.31	0.34

All batches contained 10% polyvinypyrrolidone in ethanol as a binder and 2% talc, 1% magnesium stearate and 0.5% sodium lauryl sulphate. Subliming material was sublimed from granules in batches A1 to A6 and from tablets in batch A7.

Table 2: Formulation and evaluation of batches in full factorial design

BatchCode	Variable levels in coded form[1]		DT ± SD	F ± SD
	X_1	X_2		
F1	-1	-1	234±2.35	0.175±0.015
F2	0	-1	57±1.29	0.295±0.016
F3	1	-1	49±1.50	0.410±0.012
F4	-1	0	222±3.13	0.129±0.015
F5	0	0	41±2.53	0.260±0.011
F6	1	0	35±2.02	0.349±0.013
F7	-1	1	199±3.54	0.112±0.012
F8	0	1	37±2.73	0.252±0.015
F9	1	1	25±1.86	0.273±0.011
Check point	-0.3	0.7	69± 2.67	0.192± 0.017

All batches contained 7.5 mg meloxicam, 2 mg colloidal silicon dioxide, 10% polyvinypyrrolidone in ethanol as a binder and 2% talc, 1% magnesium stearate, 0.5% sodium lauryl sulphate and mannitol q.s. to 200 mg. [1]X_1 is the amount of menthol, where –1=0, 0=10 and 1=20 mg; $X_2$is the amount of crospovidone, where, -1=6, 0=8 and 1=10 mg. DT indicates disintegration time; F, friability; and SD, standard deviation.

Table 3: Summary of results of regression analysis

	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}
Response (disintegration time)/coefficients						
FM	44.44	-91.00	-13.16	2.75	82.33	0.833
RM	45.00	-91.00	-13.16		83.33	
Response (percentage friability)/coefficients						
FM	0.264	0.103	0.040	-0.018	-0.027	0.006
RM	0.251	0.103	0.040			

FM indicate full model; RM, reduced model

Table 4: Calculations for testing the model in portions

	DF	SS	MS	F	R^2	Fcal
For disintegration time regression						
FM	5	644315	12863	510.927	0.999	
RM	3	64283	21427	999.747	0.998	0.628
Error						
FM	3	75.528	25.176			
RM	5	107.167	21.433			
For percentage friability regression						
FM	5	0.0761	0.0152	35.418	0.983	
RM	2	0.0731	0.0365	51.203	0.945	2.5
Error						
FM	3	0.0012	0.0004			
RM	6	0.0042	0.0007			

DF indicate degree 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

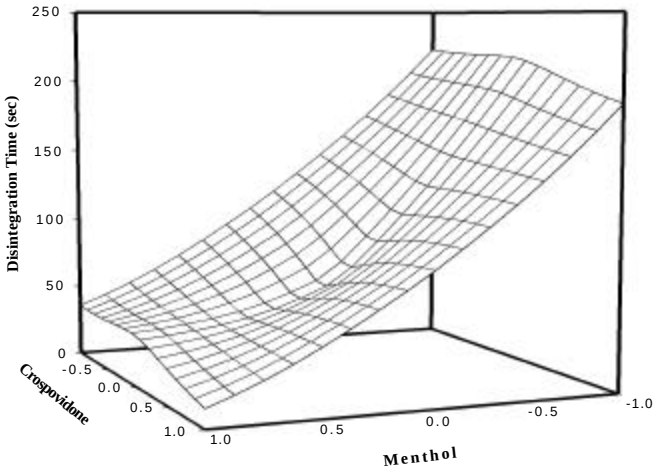

Figure 1. Response surface plot for percentage disintegration time

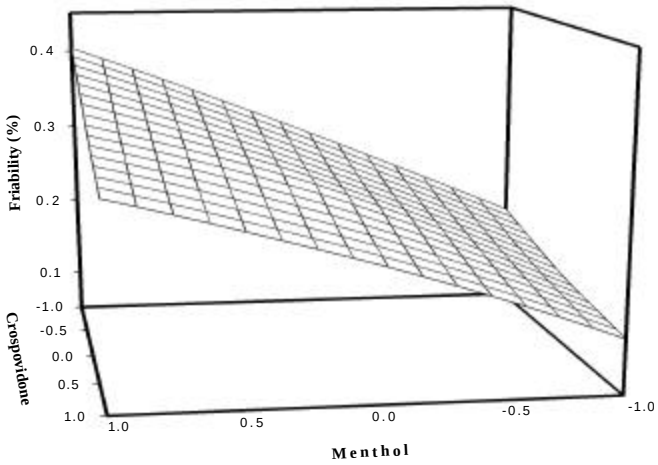

Figure 2. Response surface plot for percentage friability

strongly dependent on the selected independent variables. The fitted equations (full and reduced) relating the responses DT and %F to the transformed factors 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 (i.e. positive and negative). Table 4 shows the results of the analysis of variance (ANOVA), which was performed to identify insignificant factors.[15] The high values of correlation coefficient for DT and %F indicate a good fit i.e., good agreement between the dependent and independent variables. The equation 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 coefficient was performed by applying the student F test. A coefficient is significant if the calculated F value is greater than the critical values of F.

For disintegration, the significance level of coefficient b_{12} and b_{22} were found to be p = 0.353 and 0.829, respectively, hence they

were omitted from the full model to generate the reduced model. The results of statistical analysis are shown in Table 3. The coefficient b_1, b_2 and b_{11} were found to be significant at $p<0.05$; hence they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficient b_{12} and b_{22} contribute significant information for the prediction of DT or not. The results for testing the model in portions are shown in Table 4. The critical value of F for $\mu = 0.05$ is equal to 9.55 (df= 2, 3). Since the calculated value (F= 0.628) is less than the critical value, it may be concluded that the interaction terms b_{12} and polynomial terms b_{22} do not contribute significantly to the prediction of DT and therefore can be omitted from full model. For drawing conclusions, response surface plot (Figure 1 and 2) 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 menthol or crospovidone, a decrease in DT is observed; both the coefficient b_1 and b_2 bear a negative sign. When higher percentage of menthol is used, higher porosity is expected in the tablets. The water uptake and subsequent disintegration is thus facilitated. It is obvious that in the presence of higher percentage of crospovidone, wicking is facilitated.

For friability, the significance level of coefficient b_{12}, b_{11} and b_{22} were found to be p = 0.172, 0.156 and 0.673, respectively, hence they were omitted from the full model to generate reduced model. The coefficient b_1 and b_2 were found to be significant at $p<0.05$; hence they were retained in the reduced model (Table 3). The reduced model was tested in portions to determine whether the coefficient b_{12}, b_{22} and b_{12} contribute significant information for the prediction of %F or not. The results for testing the model in portions are shown in Table 4. The critical value of F for $\mu = 0.05$ is equal to 9.28 (df= 3, 3). Since the calculated value (F= 2.5) is less than the critical value, it may be concluded that the interaction terms and polynomial terms do not contribute significantly to the prediction of %F. 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 menthol leads to an increase in friability because the coefficient b_1 bears a positive sign. When a higher percentage of menthol 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.

Figure 1 and 2 show the plot of the amount of menthol (X_1) and amount of crospovidone (X_2) versus disintegration time and percentage friability, respectively. The plots were drawn using sigma plot software. The plots demonstrate, both X_1 and X_2 affect the disintegration time and percentage friability. It was arbitrarily decided to select a batch of tablets that disintegrate in less than 40 s. Batch F6 (1,0), F8 (0,1) and F9 (1,1) fall in the acceptable criteria. The final selection is done after considering 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 hence batch F8 was selected as best batch. A check point batch was prepared at X_1 =-0.3 level and X_2 =0.7. From the reduced model, it is expected that the friability value of the check point batch should be 0.191% and the value of disintegration time should be 70 sec. Table 2 indicate that the results are as expected and therefore the statistical model is mathematically valid.

The result of a 3^2 full factorial design revealed that the amount of menthol and crosspovidone 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. Sublimation technique would be an effective approach compared with the use of more expensive adjuvant in the formulation of mouth dissolving tablets with improved drug dissolution.

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