Original Research

STUDIES ON THE EFFECT OF MIXING TIME, SPEED AND CONCENTRATION OF ONE COMPONENT ON MIXING INDEX

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ABSTRACT:
Mixing process is widely used in pharmaceutical industry to blend different API as well as additives to prepare solid dosage formulations. If mixing is not done properly there is always chance of dose variation and content uniformity variations. Due to this, the present paper deals with the study of the effect of mixing time, speed and % of one compound in another on the effectiveness of the process. Statistical analysis technique was used to understand the interaction effect of variables instead of one factor at a time. A 2^3 factorial design was applied to investigate the combined effect of three formulation variables, time (A), mixing speed (B) of and the % amount of diclofenac sodium (C) used. The mixing index (MI) taken as responses (Y). Polynomial equations were used to relate each response to the factors affecting it. Counter plots and response surface plots were drawn and an optimum formulation was selected using the desirability function.

KEYWORDS: Powder mixing, Mixing index, Response surface plots, Contour plots.

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1. INTRODUCTION

Mixing may be defined as the process in which two or more than two components in a separate or roughly mixed condition are treated in such a way so that each particle of any one ingredient lies as nearly as possible to the adjacent particles of other ingredients[1]. This process ensures that there is uniformity of composition between the mixed ingredients which may be determined by taking samples from the bulk material and analyzing them, which should represent overall composition of the mixture[2]. Mainly, the object of mixing operation is to produce a bulk mixture which when divided into different doses, every unit of dose must contain the correct proportion of each ingredient. The degree of mixing will increased with the length of time for which mixing is done[3]. It is one of the most common operations employed in pharmaceutical industries for the preparation of different types of formulations, e.g. powders, capsules and tablets. When grinding and mixing of different substances is to be done simultaneously then two or more than two substances are fed to the mill one at the same time. To obtain good results of powder mixing the Nature of the product and physical properties of drugs must be taken into consideration before undertaking any kind of powder mixing[4,5]. It has been generally accepted that in all the mixtures, solid mixing is achieved by a combination of one or more of the following mechanisms: (i) Convective mixing, i.e., transfer of groups of particles takes place from one location to another by means of blades or paddles of the machine; (ii) Shear mixing, in which slip planes are set up within the mass of material; and (iii) Diffusive mixing, where mixing occurs by diffusion process by random movement of particles within a powder bed and cause them to change their relative positions[2]. Generally the process of mixing is critically affected by a multitude of parameters like mixing time, mechanism of mixing, type of mixer and batch size. For each mixing method a characteristic mechanism determines the rate and the attainable degree of mixing. The mixing quality, i.e. the degree of homogeneity is especially important when a relatively small amount of an active ingredient is to be distributed in a large quantity of bulk solids or powders[3].There is always some variation in the composition of the samples drawn from a random mixture and the standard deviation in the composition of large number of such samples can be determined, provided an accurate assay method is available[6]. A random mix gives samples with low standard deviation as compared to mixture of the same components that have not reached the random state. Mixing process involves many interacting variables and operating conditions, experimental design methods are suitably being used in the mixing studies. To understand the variables and their interactions, many statistical experimental designs have been recognized as useful techniques. Optimization through experimental design (including factorial design) and response surface methodology is a common practice [7,8]. Factorial designs are used in experiments where the effects of different factors or conditions on choice for simultaneous determination of the effect of several factors and their interaction. Factorial design is used to study the effect of different variables on the dependent variables of any formulation. Based on the principle of design of experiments, factorial design is employed to investigate the effect of two independent factors. Design of experiments encompasses the use of various types of experimental designs, generation of polynomial equations, and responses over the experimental domain to determine the optimum formulation. Contour plots and response surface plots describe the influence of the independent variables on the selected responses [9,10].

The present study, therefore, deals with the optimization of different variables to design the best mixing condition of competitive objectives, because interactive effects via a trial-and-error approach are time consuming and often unsuccessful. Mathematical optimization by means of an experimental design is most helpful in shortening the experimental time [11,12]. The objective of the present work was to apply 2^3factorial design with desirability function for understanding the quality and optimization of mixing process. A 2^3 factorial design was applied to investigate the combined effect of

three formulation variables, time (A), mixing speed (B) of and the % amount of diclofenac sodium (C) used. The mixing index (MI) taken as responses (Y). Polynomial equations were used to relate each response to the factors affecting it. Contour plots and response surface plots were drawn and an optimum formulation was selected using the desirability function (fig. 1).

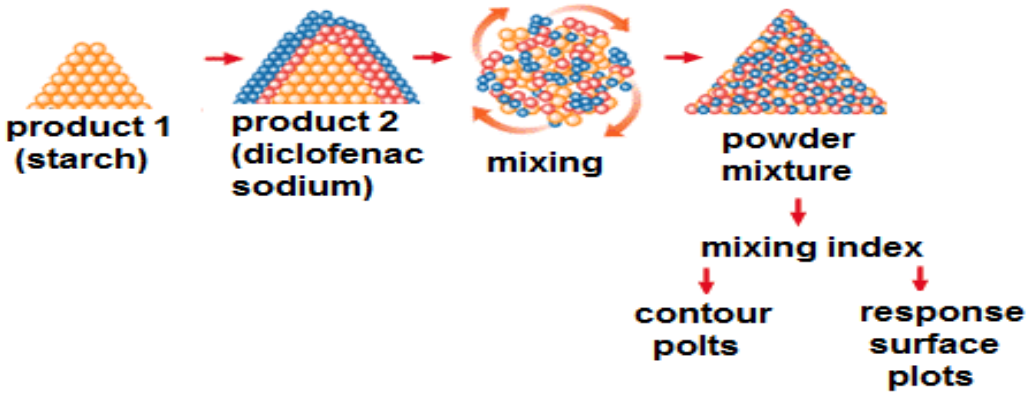

Fig.1. Basic principle of mixing function.

2. MATERIALS AND METHODS

2.1. Materials

Diclofenac sodium was a gift sample from Cipla Pharmaceuticals, Sikkim, India; Starch (soluble extra pure) was obtained from Merck Specialities Pvt. Ltd., India. All other reagents and chemicals used in this study were of analytical grade.

2.2. Blend Preparation

The different blends were prepared at ambient condition. The starch was taken and blended with model drug and mixture was prepared using "cone blender". Mixture was pre-mix with spatula before blending of drug. The blender was operated at 700 to 3000 revolutions per minutes for 2 to 10 minutes. Data from different mixing time and speed was obtained from same batch and vice versa. The batch size and contents are represented in table1.

Table 1. Batch size and blending formulations

Formulation code	A (Time)	B (Speed)	C (Ratio)
F1	+1	+1	+1
F2	+1	+1	−1
F3	+1	−1	+1
F4	−1	+1	+1
F5	−1	−1	+1
F6	−1	+1	−1
F7	+1	−1	−1
F8	−1	−1	−1

A (Time): −1 (2 min), +1 (10 min);
B (Speed): −1 (low speed), +1 (high speed);
C (Ratio): −1 (1% Drug **:** 20% Excipient), +1 (1% Drug **:** 10% Excipient),

2.3. Blending Content uniformity test

After blending, the drug content of the different formulations was determined by performing the assay method of model drug diclofenac sodium using spectophotomeric analysis. 10 mg of powder sample from each batch was accurately weighed and was dissolved in 20 ml methanol in 100 ml volumetric flask. Then volume was adjusted up to 100 ml with water. Then the solution was filtered through Whatman® filter paper (No. 40). The drug content in the filtrate was determined using a UV–vis spectrophotometer (Shimadzu, Japan) by measuring absorbance at λ_{max} of 276 nm.

3. RESULTS AND DISCUSSION

3.1. Optimization of Formulation using Factorial Design

A Full factorial Design for three factors at two levels each was selected to optimize the response of the variables. In this design, all the factors are evaluated, each at two levels, and experimental trials were performed for all possible combinations. All other formulation variables and processing variables were kept invariant throughout the study. The effect of the three independent variables on the response mixing index (*Y*) was observed. The regression equation for the response (Y) was calculated using the following equation:

$Y= b_0+b_1A+b_2 B+b_3C+b_4AB+b_5BC+ b_6CA+b_7ABC$

Where, the responses (Y) in the above equation are the quantitative effect of the formulation components or independent variables A, B and C; b is the co-efficient of the term A,B,C. The main effects (A,B and C) represent the average result of changing one factor at a time from its low to high value. The interaction term (AB, BC …) shows how the response changes when two factors are simultaneously changed. The polynomial terms are included to investigate non-linearity.

3.2. Results of Mixing Index of various formulations

The mixing indexes of all formulations are found in the range of 0.9762±1.04 to 0.9966±1.26. The highest mixing index was found in case of F2, i.e., prepared with 5%w/w of Diclofenac sodium and process involved maximum mixing time and speed, i.e., 10 min and 3000 rpm respectively. Mixing index of different formuations with corresponding dependent and independent variables was given in Table 2.

Table 2. Mixing index of different formuations with corresponding dependent and independent variables.

Formulation code	A: Time(min)	B: speed (rpm)	C: % of Active agent	Y: Mixing Index
F1	10.00	3000.00	10.00	0.9913±1.78
F2	10.00	3000.00	5.00	0.9966±1.26
F3	10.00	700.00	10.00	0.9762±1.04
F4	2.00	3000.00	10.00	0.9866±1.86
F5	2.00	700.00	10.00	0.9855±2.28
F6	2.00	3000.00	5.00	0.9856±2.14
F7	10.00	700.00	5.00	0.9802±1.64
F8	2.00	700.00	5.00	0.9938±1.92

3.3. Optimization, data Analysis, and desirability function

Various response surface methodology (RSM) computations for the current optimization study were performed employing Design-Expert software (Version 8.0.7.1, Stat-EaseInc., Minneapolis, MN). Polynomial models including quadratic terms were generated for all the response variables. In addition, 2-D contour plots and 3D graphs were constructed using the output files generated by the Design-Expert software. The significance of these parameters on the variables was assessed by analysis of variance (ANOVA, 2-way). After fitting of the mathematical model, the desirability function was used for the

optimization. During optimization of the formulations, the responses were combined to find a product having the desired characteristics. The desirability function combines all the responses into one variable to predict the optimum levels for the independent variables. A desirability value of 0 represents an unacceptable value for the responses, and a value of 1 represents the most desired value for the responses. Further, the optimized formulations as selected by the design were prepared and the parameters were observed and compared to the expected values as given by the design. After analyzing the data by Design Expert software, the results of ANOVA were depicted in Table 3. Statistical analysis was displayed in Table 4 and % contribution of effect on the response was placed in Table 5 respectively. The effect of different variables as main effect and their interaction clearly showed that the model should be reduced. Because only the main effects and the interaction AB are influencing the response. So the equation obtained using the reduced model as follows.

mixing index =+ 0.99 - $9.0*10^{-4}$ * A + $3.050*10^{-3}$ * B - $2.075*10^{-3}$*C + $4.83*10^{-3}$*A* B

Table 3. ANOVA for selected factorial model (analysis of variance table [partial sum of squares -type iii])

Source	Sum of squares	Degree of freedom	Mean square	F value	p-value	Prob> F
Model	3.016E-004	4	7.540E-005	10.03	0.0439	Significant
A-mixing time	6.480E-006	1	6.480E-006	0.86	0.4216	
B-speed	7.442E-005	1	7.442E-005	9.90	0.0514	
C-% of API	3.445E-005	1	3.445E-005	4.58	0.1217	
AB	1.862E-004	1	1.862E-004	24.78	0.0156	
Residual	2.255E-005	3	7.515E-006			
Cor Total	3.241E-004	7				

Table 4. Statistical analysis results.

Std. Dev.	2.741E-003	R-Squared: 0.9304
Mean	0.99	Adj R-Squared: 0.8377
C.V. %	0.28	Pred R-Squared: 0.5054
PRESS	1.603E-004	Adeq Precision: 9.182

Table 5. List of effects of different independent variables

Term	Effect	Sum Sqr	% Contribution
Intercept			
A-mixing time	-0.0018	6.48E-006	1.99917
B-speed	0.0061	7.442E-005	22.9596
C-% of API	-0.00415	3.4445E-005	10.6267
AB	0.00965	0.000186245	57.4591
AC	-0.0005	5E-007	0.154257
BC	0.002	8E-006	2.46811
ABC	-0.00265	1.4045E-005	4.33307

3.4. Statistical Analysis of Data

In the RSM analysis, the response (i.e. Mixing Index of all model formulations) was treated by Design-Expert® software. The best fitting mathematical model was selected based on the comparisons of several statistical parameters, including the coefficient of variation (CV), multiple correlation coefficients (R^2) and adjusted multiple correlation coefficients (adjusted R^2). Analysis for both responses showed that quadratic model was the most suitable one *($p < 0.05$)*. The statistical analysis proved that A, B, C, AB, are significant model terms for response.

Fig.2 depicted the interaction of mixing speed and time on the response mixing index. As the two lines are intersecting that indicates a strong interactive effect of these two variables on mixing index. Contour plots and 3D graphs of both responses are demonstrated in Fig. 3 and 4 respectively. By running ANOVA, the final equation of flux in coded values was obtained, while the statistical parameters were as follows: As stated before A, B, C, AB are significant model terms for response. It is concluded that the mixing index has negative relationship with % of API and time as the main effect. The model also introduced speed and AB as positive interaction effect on this response. The values of Prob > F less than 0.05 for all the responses except time are indicating that the models are significant. The response time exhibited Prob > F value 0.0439, which indicating model was significant (Table 3). The lack of fit F value is significant. Similarly 'R-squared' value was also calculated for response. The ideal value is nearer to zero.The "Pred R-Squared" of 0.5054 is not as close to the "Adj R-Squared" of 0.8377 as one might normally expect. This may indicate a large block effect or a possible problem with your model and/or data. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. A ratio of 9.182 indicates an adequate signal. This model can be used to navigate the design space.

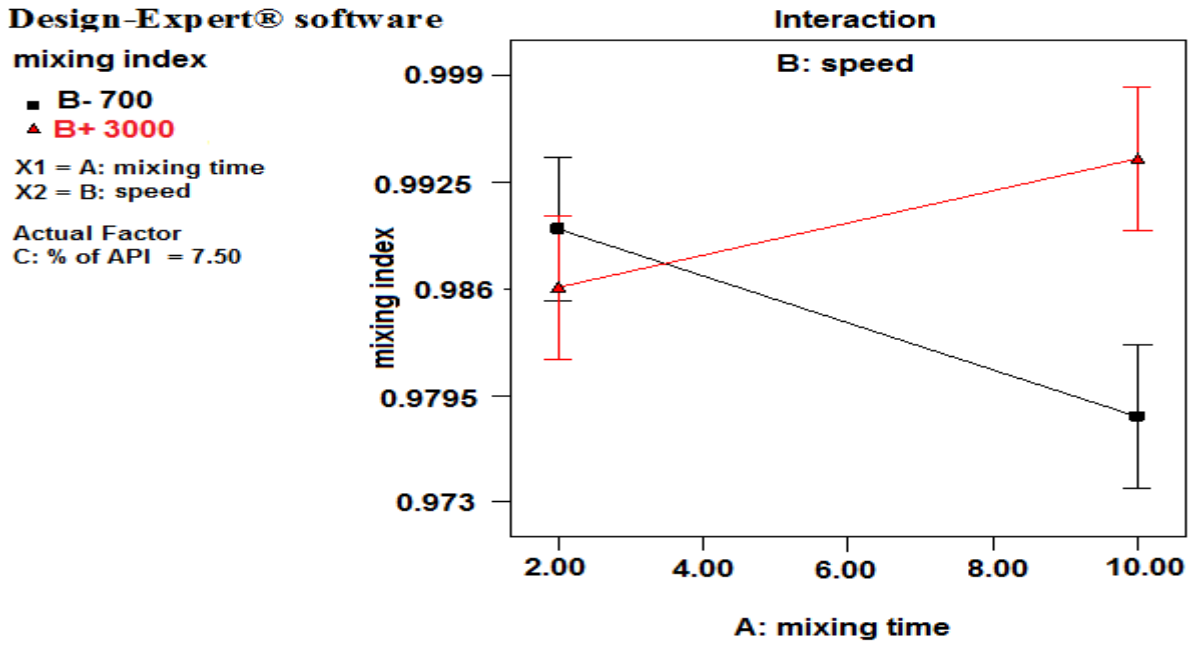

Fig.2. Effect of interaction of mixing speed and time on mixing index.

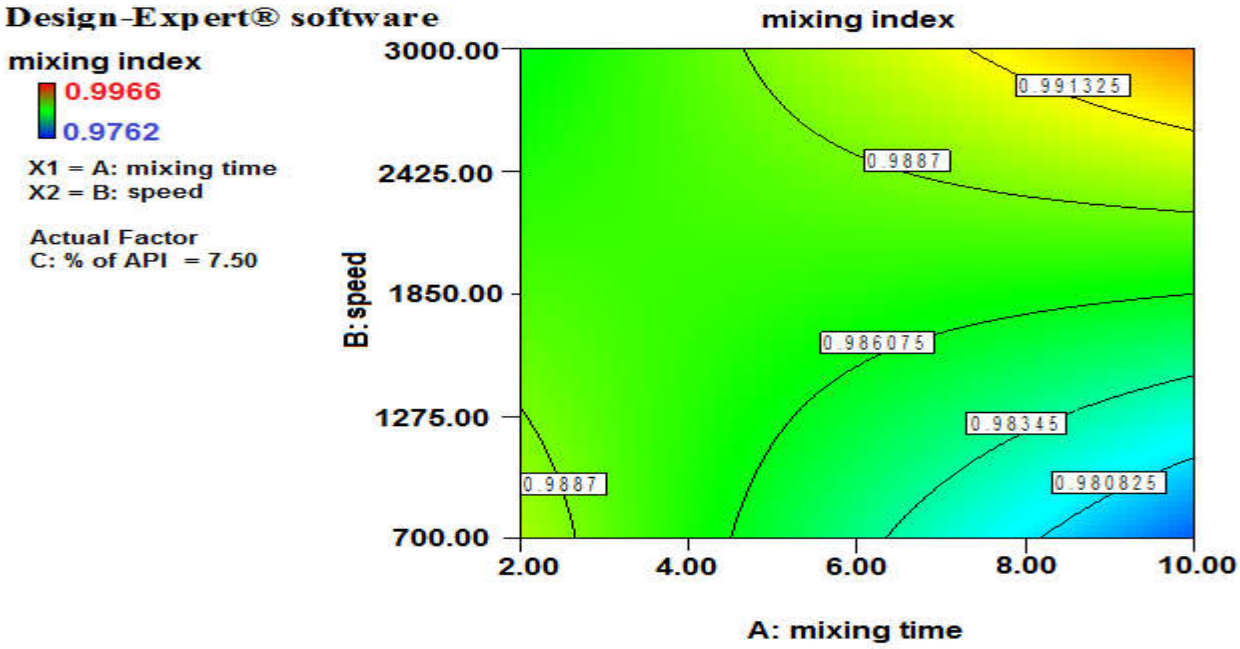

Fig.3. Contour plot showing interaction of mixing speed and time on mixing index.

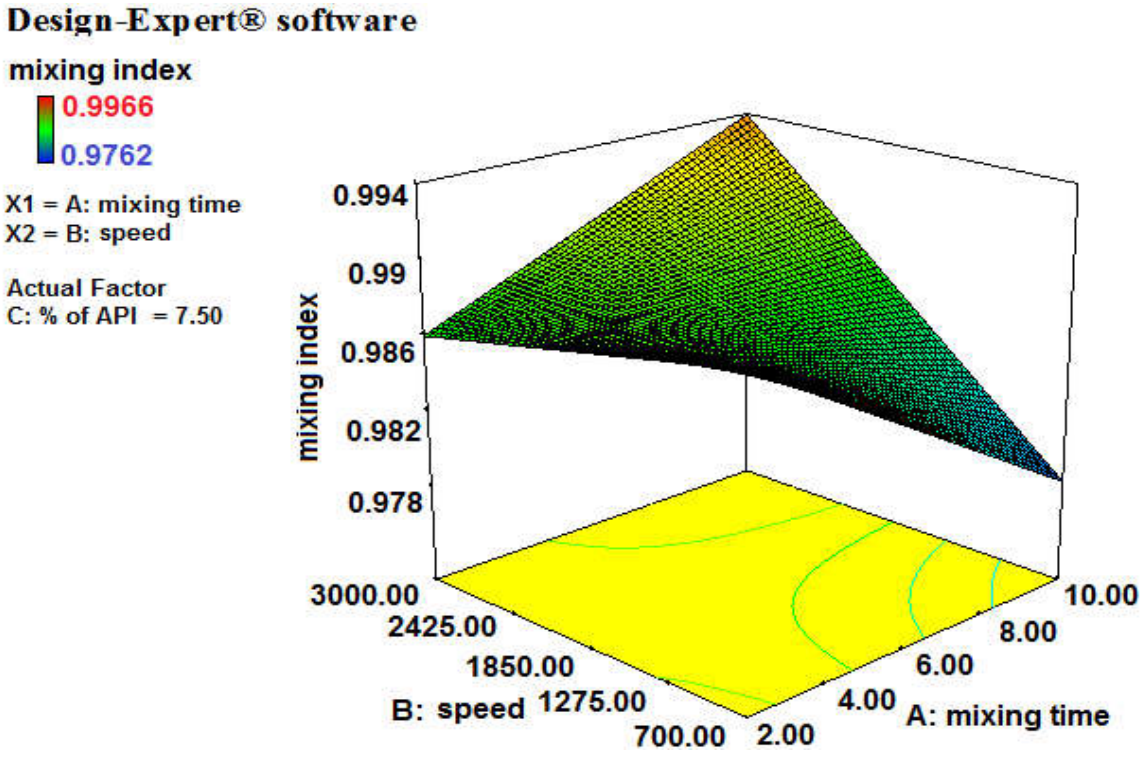

Fig.4. Response surface diagram showing effect of interaction of mixing speed and time on mixing index.

4. CONCLUSIONS

In this experiment we have examined the effect different variables on mixing process. Mixing process is widely used in pharmaceutical industry to blend different API as well as additives to prepare solid dosage formulations. If mixing is not done properly there is always chance of dose variation and content uniformity variations. Due to this we have studied the effect of mixing time, speed and % of one compound in another on the effectiveness of the process. Statistical analysis technique was used to understand the interaction effect of variables instead of one factor at a time. The results have shown that the speed and the % API have strongly influenced the mixing index. Significant influencing factor was the interaction of speed and time. This is again established by 2-D contour plot and 3-D Response Surface Diagram. So it can be concluded that statistical tool can be well utilized for establishment of critical parameter of mixing process.

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