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Formulation and Optimisation of Mouth Dissolving Tablet of Diclofenac Using 3^2 Factorial Design

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ABSTRACT

The objective of the study deals with the Formulation and Optimization of Mouth dissolving tablets of Diclofenac with the application of Factorial Design. Prolonged-release of the drug and increased bioavailability leads to a significant reduction in dose and hence dose-related side effects. For the formulation development, Camphor and Crosspovidone were selected as variable to formulate MDT of a drug. A 3^2 factorial design was used to optimize the effect of the amounts of Camphor (subliming agent), X1 Crosspovidone (super-disintegrant), X2 which were independent variables. The direct compression method is used for tablet Preparation. From the experimental design, the drug release rate and profile are obtained. The relation between the dependent and independent variables are drawn out from the Mathematical equations and response surface plots. The result shows that the dissolution rate found to be increased.

1. INTRODUCTION:

Over the past three decades, Mouth Dissolving Tablets (MDTs) have gained much attention as a preferred alternative to conventional oral dosage forms such as tablets and capsules. An MDT is a solid dosage form that disintegrates and dissolves in the mouth (either on or beneath the tongue or in the buccal cavity) without water within 60 seconds or less and absorption is systemic without first-pass metabolism For people who are having the problem in the swallowing or chewing can take it easily as the disintegrated mass can slide down smoothly with the help of saliva. An MDT is formulated as a bioequivalent line extension of an existing oral dosage form[1]. These dosage forms rapidly disintegrate and/or dissolve to release the drug as soon as they come in contact with saliva, thus obviating the need for water during administration, an attribute that makes them highly attractive for pediatric and geriatric patients[2,3]. Superdisintigrants are used for the rapid dissolution and sublimating agents are used to increase porosity[4,5]. The fast-dissolving tablets usually dissolve in the oral cavity within 15 to 60 s. The faster the drug goes into solution, the quicker the absorption and onset of clinical effects[6].

1.1. FACTORIAL DESIGN

Factorial designs are typically used for variable screening or response surface optimization. These designs set each of the predictor variables at one of several levels, usually a low, center, and high levels are denoted by 1, 0, and + 1, respectively. When the number of inputs is small, factorial designs can use a relatively small number of runs to explore the predictor space and allow the estimation of simple linear or quadratic models, which can in turn be used to identify the regions of the space corresponding to optimal response values. Factorial experiment is an experiment whose design consists of two or more factors each with different possible values or “levels”. Factorial design technique was introduced by “Fisher” in 1926. Factors can be “Quantitative”(numerical number) or they are “Qualitative”.

1.2. OPTIMISATION OF MOUTH DISSOLVING TABLET FORMULATION BY USING 3^2 FULL FACTORIAL DESIGNS:-

It is desirable to develop an acceptable pharmaceutical formulation in the shortest possible time using the minimum number of man-hours and raw material. Traditionally pharmaceutical formulation after developed by changing one variable at a time approach. The method is time-consuming & requires a lot of imaginative efforts. It is thereof very essential

to understand the complexity of pharmaceutical formulation by using statistical tools such as Factorial Design.

The technique of factorial design is an effective method of indicating the relative significance of several variables and their interactions. The number of experiments required for these studies is dependent on the number of independent variables selected. With the application of A 32 full factorial design and Response Surface Methodology (RSM) effect of formulation variables on the performance of these tablets was studied[7,8]. The response (Y) is measured for each trial.

$$Y= b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_{12} + b_{22}X_{22}$$

Where,

Y= dependent variable

B0= Arithmetic mean response of the nine runs

B1= Estimated coefficient for the factor X_1.

The interaction terms (X_1X_2) shows how the response changes when two factors simultaneously change.

2. MATERIALS AND METHODS:

MATERIALS:

Diclofenac was obtained as a gift sample from Calyx Chemicals and Pharmaceuticals Ltd., Tarapur. Camphor, Crospovidone, Aspartame, Aerosil was procured from Loba. Talc, Microcrystalline cellulose was purchased from SD Fine Chemicals, Mumbai.

METHODS:

1) The tablets were prepared as follows according to the proportion given in table 1.

2) The raw material was passed through a sieve no. 60.

3) All the materials mixed in a polybag for 10 min & mixture was lubricated by talc before compression.

4) The tablets were compressed using 12 station rotary tablet compression machine equipped with an 8 mm punch.

5) The tablet weight was adjusted to 250 mg.

6) The sublimation of camphor was done at 60°C[9,10].

Table No. 1: Composition of Mouth Dissolving Tablets

Ingredients	Amounts (Mg)/Tablet
Diclofenac	100 mg
Camphor	25-75 mg
Crosspovidone	12.5-37.5 mg
Aspartame	3 mg
Aerosil	3 mg
Talc	1.5 mg
Microcrystalline Cellulose	q.s

Table No. 2: Design Matrix as per 3^2 Factorial design

	Coded level		Actual Value	
Runs	X1	X2	Camphor	Crospovidone
F1	1	0	75	25
F2	-1	-1	25	12.5
F3	0	0	50	25
F4	0	1	50	37.5
F5	-1	1	25	37.5
F6	-1	0	25	25
F7	0	-1	50	12.5
F8	1	-1	75	12.5
F9	1	1	75	37.5

3. FULL FACTORIAL DESIGN

In this design 2 Factors are evaluated, each at 3 levels and experimental trials is performed at all 9 possible combinations. The amount of subliming agent, camphor (X1), superdisintegrant crospovidone (X2), were selected as independent variables. The design matrix and coded

levels are mentioned in actual values as shown in table 2 and 3.The disintegration time and percentage drug release were selected as dependent Variables. As shown in equation (1), a statistical model incorporating interactive and polynomial terms was used to evaluate the responses. Y = 0– 1 X1 - 2 X12- 3 X2+ 4 X22 + 5 X1 X2- 6 X12 X2+ 7 X1 X22+ 8 X12X22-----(1) Where, Y are the dependent variables, namely, disintegration time (Y1) and percentage friability (Y2); β0 is the arithmetic mean response of the 9 runs; and β1andβ8 are the estimated coefficients for the factors X1 and X2, respectively. The main effects (X1 and X2) represent the average result of changing one factor at a time from its low to high value. The interaction term (X1X2) shows how the response changes when 2 factors are simultaneously changed. The polynomial terms (X12 and X22) are included to investigate nonlinearity. The simplified models were then utilized to produce three-dimensional response surface plots and contour plots to analyze the influence of disintegration time and percentage drug release.

Table No. 3: Coded and actual values of formulations as per 3^2 Factorial Design

Independent Variable			
X1	Camphor (Subliming Agent)		
X2	Crosspovidone (Super disintegrant)		
Levels	Low	Medium	High
Coded levels	-1	0	+1
Dependent Variables (Response Variables)			
Y1	Disintegration Time(Sec)		
Y2	% Drug Release (%)		

4. EVALUATION OF TABLET PROPERTIES[11,12,13,14,15]

4.1. THICKNESS AND CRUSHING STRENGTH:

The thickness of the tablet was measured using Vernier caliper and the crushing strength of the tablets was measured using a Monsanto hardness tester.

4.2. FRIABILITY TEST:

The friability of a sample of 10 tablets was measured using a Roche Friabilator. 10 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.

4.3. DISINTEGRATION TEST:

The disintegration time was measured using a disintegration apparatus.

4.4. DISSOLUTION STUDIES:

Dissolution experiments were performed in triplicate with a dissolution tester (make-Electrolab) in pH 6.8 a simulated gastric fluid (SGF) at 37ºC using the USP XXV paddle method (Type II) at a rotation speed of 50 rpm. At appropriate time intervals, 5 ml of the mixture was withdrawn and filtered. The removed samples that were analyzed at 275 nm by UV-Vis spectrophotometer.

5. RESULTS & DISCUSSION:

Table No. 4: Design layout of central composite Design & Design summary of experimental Results

		Factor 1	Factor 2	Response 1	Response 2
Std	**Run**	**A: Camphor Conc.**	**B: Cross povidone**	**Disintegration Time**	**Dissolution time**
		Mg	Mg	sec	%
6	1	1	0	80	96.82
1	2	-1	-1	360	79.01
5	3	0	0	90	65.55
8	4	0	1	75	80.33
7	5	-1	1	240	55.51
4	6	-1	0	300	78.44
2	7	0	-1	120	54.18
3	8	1	-1	105	85.07
9	9	1	1	50	149.11

Table No. 5: Physical evaluation parameter of formulation F1-F9

FORMULATIONS	HARDNESS	THICKNESS (mm)	FRIABILITY (%)
F1	3.5	4.23	0.85
F2	3.6	4.12	0.45
F3	3.25	4.1	4.8
F4	3.6	3.98	1.53
F5	2.8	3.6	1.02
F6	3.2	4	0.51
F7	3.4	4.5	0.95
F8	3.7	3.9	1.2
F9	3.2	4.2	5.2

Table No. 6: Disintegration time of formulation F1-F9

FORMULATIONS	DISINTEGRATION TIME
F1	360
F2	300
F3	240
F4	120
F5	90
F6	75
F7	105
F8	80
F9	50

Table No. 7: % drug release of Formulation F1-F9

	F1	F2	F3	F4	F5	F6	F7	F8	F9
5 MIN	19.51	6.25	19.51	1.70	13.83	20.46	15.72	21.41	28.04
10MIN	38.57	19.55	24.90	7.20	32.85	31.37	32.86	28.16	30.09
15MIN	52.04	34.81	39.08	20.70	44.97	52.58	39.11	40.44	52.04
20MIN	63.70	88.56	50.67	35.02	52.80	71.25	71.15	59.80	76.96
25MIN	72.01	93.98	81.83	82.02	86.81	91.71	92.96	94.61	95.39

Final Equation in Terms of Coded Factors:	
Disintegration Time	=
+93.89	
-110.83	* A
-36.67	* B
+16.25	* AB
+94.17	* A^2
+1.67	* B^2

Final Equation in Terms of Actual Factors:	
Disintegration Time	=
+93.88889	
-110.83333	* Camphor Conc.
-36.66667	* Crospovidone
+16.25000	* Camphor Conc. * Crospovidone
+94.16667	* Camphor $Conc.^2$
+1.66667	* Cros $povidone^2$

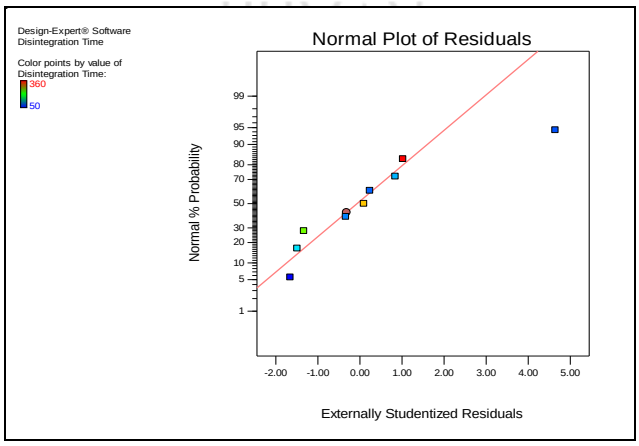

Figure No. 1: Disintegration Time (Predicted Vs Actual Graph)

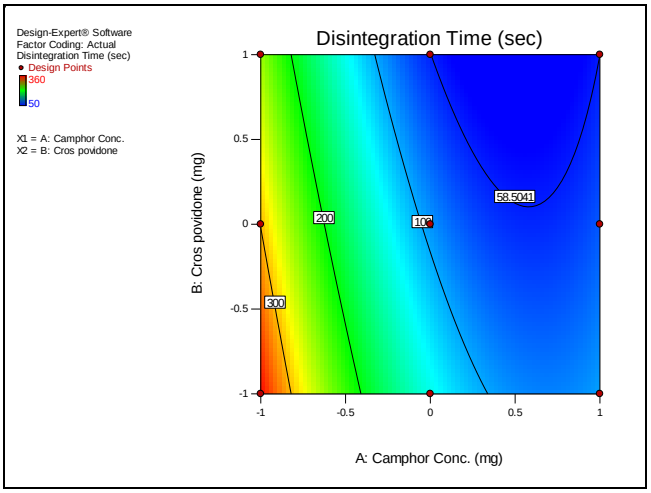

Figure No. 2: Countour Plot of Disintegration Time

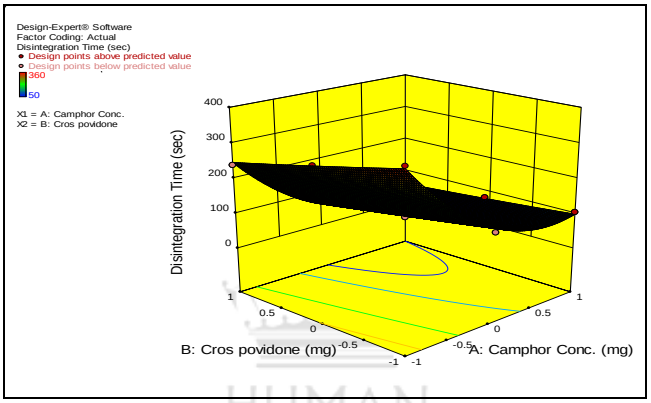

Figure No. 3: 3D Graph of Disintegration Time

Final Equation in Terms of Actual Factors:	
Dissolution time	=
+64.28778	
+19.67333	* Camphor Conc.
+11.11500	* Crospovidone
+21.88500	* Camphor Conc. * Crospovidone
+23.97333	* Camphor Conc.^{2}
+3.59833	* Cros povidone^2

Final Equation in Terms of Coded Factors:	
Dissolution time	=
+64.29	
+19.67	* A
+11.12	* B
+21.89	* AB
+23.97	* A^2
+3.60	* B^2

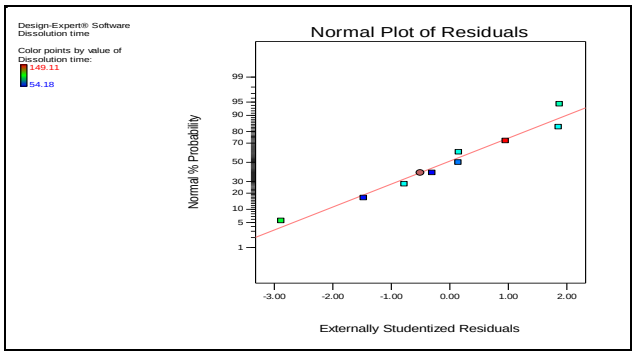

Figure No. 4: Dissolution Time (Predicted Vs Actual Graph)

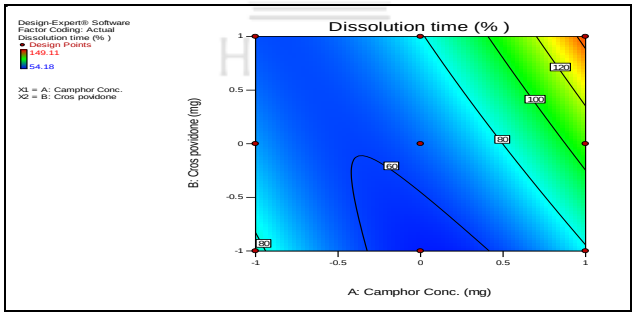

Figure No. 5: Contour Plot of Dissolution Time

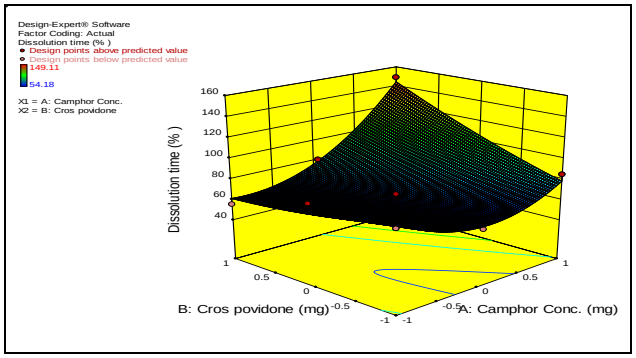

Figure No. 6: 3D Graph of Dissolution Time

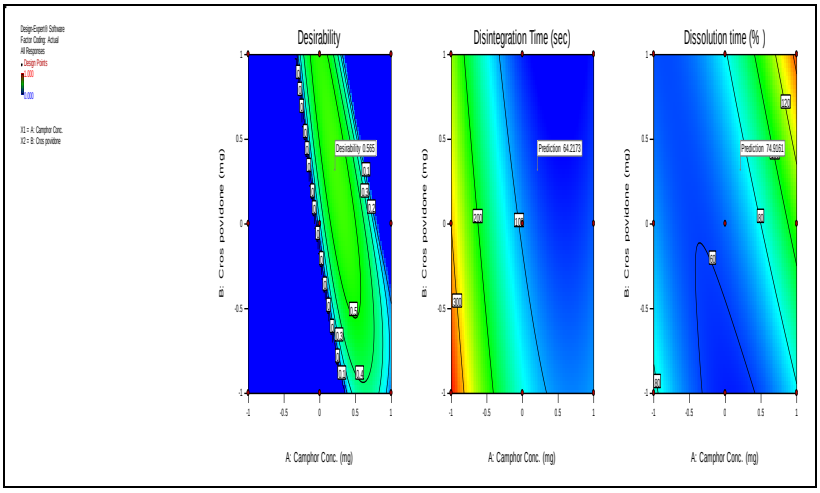

Figure No. 7: Response Graph

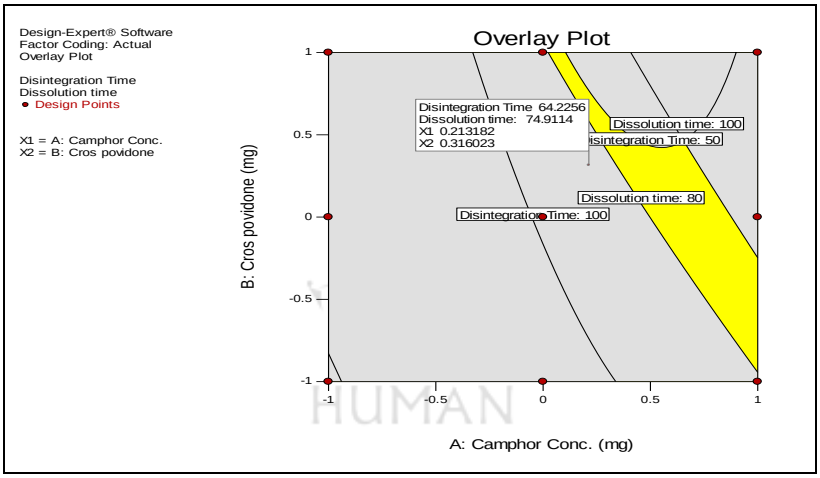

Figure No. 8: Design Space

DISCUSSION:

It should be seen that increasing the % of an incorporated subliming agent had a negative effect on disintegration time. On the other hand.increasing the amount of crospovidone led to a decline in disintegration and wetting time. The result of multiple linear regression analysis showed that both the coefficients X1 & X2 bear a negative sign. Therefore, the concentration of either camphor or cross povidone is expected to decrease disintegration time. The effect of camphor seems to be more pronounced as compared to that of crospovidone, as revealed by the response surface & mathematical model. This is because when higher % of camphor used, higher porosity is expected in the tablet. The content uptake & subsequent disintegration are thus facilitated.

It should be seen that increasing the % of an incorporated subliming agent affected % drug release. On the other hand, the increasing amount of crospovidone led to an increase in the % drug release. The result of multiple linear regression analysis showed that both the coefficients X1 & X2 bear a positive sign. Therefore, the concentration of either camphor or crospovidone is expected to increase the % drug release.

CONCLUSION:

The results of a 3^2 full factorial design revealed that the amount of Crosspovidone and camphor significantly affect the dependent variables, disintegration time, and percentage friability. The significant effects of the interaction and polynomial variables on the investigated characteristics of Diclofenac mouth dissolving tablets were verified.

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