RESEARCH ARTICLE

Formulation design and optimization of orodispersible tablets of Etoricoxib by response surface methodology

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The purpose of the present investigation was to design a formulation of orodispersible tablets of Etoricoxib by adopting a systematic approach of 3^2 factorial design and to evaluate various quality control parameters. Etoricoxib is a novel, selective second-generation cyclooxygenase-2 inhibitor administered orally as an analgesic and antiinflammatory drug that is used for the treatment of osteoarthritis, rheumatoid arthritis and gouty arthritis. The poor aqueous solubility of the drug leads to variable dissolution rates. In the present investigation, an attempt has been made to prepare orodispersible tablets of Etoricoxib using three different directly compressible fillers to improve mouthfeel with an enhanced dissolution rate. In the study, a 3^2 full factorial design was adopted to investigate the joint influence of two formulation variables: amount of mannitol and crospovidone and the evaluation thereof. Response surface plots were also presented to represent graphically the effect of the independent variables on the disintegration time and drug percent dissolved in 60 s. The statistical model is mathematically valid as the experimental (actual) values and predicted values suggested by the full model were relatively close to each other. This systematic formulation approach will help in understanding the effect of formulation variables and permits the arbitrary selection of a batch of tablets with improved dissolution profile after oral administration of the selective COX-2 inhibitor.

Key words: *Etoricoxib, response surface methodology, orodispersible tablet, 3^2 factorial design*

INTRODUCTION

Recently, European Pharmacopoeia (5.0, 2005) adopted the term "orodispersible tablet" as a tablet to be placed in the mouth where it disappears rapidly before swallowing, stating a maximum disintegration time (DT) of 3 min as determined in a conventional disintegration test apparatus.[1] Orodispersible tablets are also known as quick dissolves, fast melts, fast dissolving, fast disintegrating, rapid dissolve or orally dissolving tablets. 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.[2]

Etoricoxib (5-chloro-2-[6-methyl pyridin-3-yl]-3-[4-methylsulfonylphenyl] pyridine) is a novel, selective second-generation cyclooxygenase-2 inhibitor administered orally as an analgesic and antiinflammatory drug that is used for the treatment of osteoarthritis, rheumatoid arthritis and gouty arthritis. Etoricoxib can be categorized as a class II drug according to the Biopharmaceutics Classification System. These drugs are poorly water soluble but once dissolved, they are easily absorbed over the gastrointestinal membrane.[3]

Optimization techniques provide both a depth of understanding and an ability to explore and defend ranges for formulation and processing factors. With a rational approach to the selection of the several excipients and manufacturing steps for a given product, one quantitatively selects a formulation. It is at this point that optimization can become a useful tool to quantitate a formulation that has been qualitatively determined.

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The present investigation deals with an attempt of systematic formulation approach for optimization of orodispersible tablets by adopting a 3^2 full factorial design to investigate the joint influence of two formulation variables and the evaluation thereof to find the formula with the least time of disintegration and friability and eventually the best hardness and to permit the arbitrary selection of a batch of tablets with improved dissolution profile after oral administration of the selective COX-2 inhibitor.

MATERIALS AND METHODS

Materials

Etoricoxib was procured as a gift sample from Torrent Research Center, Ahmedabad, India. Aspartame, microcrystalline cellulose (PH102), mannitol (granular), crospovidone, colloidal silicon dioxide, mixed fruit flavor and magnesium stearate were procured as gift samples from Concept Pharmaceuticals Ltd., Aurangabad, India, and all other chemicals and reagents were of analytical grade.

Methods

Preparation of orodispersible tablets of Etoricoxib

Etoricoxib, aspartame, microcrystalline cellulose (PH102), mannitol (granular) and the mixture thereof, crospovidone, colloidal silicon dioxide and mixed fruit flavor were sifted through the sieve #44 and admixed for about 15 min to make a uniform blend. Magnesium stearate was passed through sieve #100 and mixed with the above blend for sufficient time, usually 5-7 min. The powder blend was evaluated for various flow properties[4,5] as follows and observations were reported in Table 1. The resulting uniform blends of composition per tablet as mentioned in Tables 2 and 3 were directly compressed using a 10 mm, round, flat-faced tooling to make the tablets of said compression specifications as mentioned in Tables 4 and 5, using a 12 station LABPRESS compression machine (Cemach Machineries Ltd, Ahmedabad, Gujarat, India.). The tablet press setting was kept constant across all formulations.

Optimization by the 3^2 factorial design

A 3^2 randomized full factorial design was used in the present study. In this design, two factors each were evaluated at three levels and experimental trials were performed at all nine possible combinations,[2] as reflected from Table 3. The amount of directly compressible filler, mannitol (X_1), and the amount of superdisintegrant, crospovidone (X_2), were selected as independent variables. *in vitro* DT and drug percent dissolved in 60 s (DP_{60}) were selected as dependent variables and their respective responses are presented in Table 3.

Tablet weight was not constant because that would require the use of diluents for weight adjustment, which in turn may have caused variation in the release profile. Thus, additional diluent was not added in the formulation to nullify any effect due to change in the proportion of diluents.

Evaluation of tablets

The following standards or quality control tests were carried out on compressed tablets and observations were reported in Table 4 for tablets as per the formulation design [Table 2] and in Table 5 for tablets as per the 3^2 full factorial design layout [Table 3], respectively.

Physical characterization of the tablets

The control of general appearance, uniformity of weight ($n = 20$), hardness (Monsanto hardness tester), thickness (Vernier caliper) and % friability (Roche Friabilator) was essential from the general evaluation point of view for the tablets.[4,5]

Drug content and content uniformity

The amount of active ingredient(s) is determined by the method described in assay and the amount of active ingredient is calculated.[6] Because the active ingredient of the present investigation is not official in any pharmacopoeia, the following method was used for determination of the drug content. Twenty tablets were weighed and powdered. The blend equivalent to 60 mg of Etoricoxib was weighed and dissolved in a sufficient quantity of 0.1N HCl. The solution was filtered through a Whatmann filter paper (no. 41), suitably diluted with 0.1N HCl and assayed at 233 nm using a UV-Visible double beam spectrophotometer (PharmaSpec UV-1700, Shimadzu Scientific Instruments, Kyoto, Japan).

One tablet was transferred and dissolved in 0.1N HCl. The solution was filtered through a Whatmann filter paper (no.41), suitably diluted with 0.1N HCl and analyzed at 233 nm using a UV-Visible double beam spectrophotometer. Each sample was analyzed in triplicate. The same procedure was repeated for the remaining nine tablets.

Water absorption ratio and wetting time

Water absorption ratio was determined by the method described by Chaudhari *et al*.[7] and wetting time was determined by the method described by Schiermeier and Schmidt.[8]

Table 1: Characterization of powder blends of API and excipients

Formulation code	Evaluation parameters*					
	Angle of repose	Bulk density (g/cm³)	Tapped density (g/cm³)	Compressibility index (%)	Hausner's ratio	Flowability
ETR-2	36.22 ± 0.547	0.301 ± 0.010	0.331 ± 0.010	9.05 ± 0.272	1.09 ± 0.003	Excellent
ETR-5	32.17 ± 0.708	0.447 ± 0.001	0.510 ± 0.006	12.40 ± 1.113	1.14 ± 0.014	Excellent
ETR-8	26.28 ± 0.477	0.585 ± 0.003	0.683 ± 0.003	14.29 ± 0.296	1.16 ± 0.004	Excellent

*All values are mean ± SD, n = 3

In vitro and in vivo DT

Disintegration or, more specifically, dispersion times, was measured in 900 ml purified water according to the I.P. method without using a disc at room temperature (25 ± 2°C).[4] *In vivo* DT was determined by the method described by Vijaya and Mishra.[4]

In vitro dissolution study

Dissolution profiles of Etoricoxib tablets were determined using the USP 24 method II with a paddle speed at 50 rpm. Dissolution was performed in 900 ml 0.1N HCl maintained at 37 ± 0.5°C according to recommendations from the SUPAC-IR guidance.[9] Five milliliters of the samples were withdrawn at specified time intervals. The volume of dissolution fluid was adjusted to 900 ml by replacing each 5 ml aliquot withdrawn with 5 ml of 0.1N HCl prewarmed at 37 ± 0.5°C. Samples withdrawn were filtered through a Whatmann filter paper (no.41), suitably diluted with 0.1N HCl and analyzed at 233 nm using a UV-Visible double beam spectrophotometer.

RESULTS AND DISCUSSION

Before formulation, blends of API and excipients were prepared and evaluated for various parameters, as explained earlier [Table 1]. Bulk density was found in the range of 0.301-0.585 g/cm^3 and the tapped density between 0.331 and 0.683 g/cm^3. Using the above two-density data, Hausner's ratio and compressibility index were calculated. The powder blends of all formulations with Hausner's ratio < 1.25 indicated better flow properties. The compressibility index was found to be between 9.05 and 14.29% and the compressibility–flowabilty correlation data indicated an excellent flowability of all powder blends. The better flowability of all powder blends

Table 2: Formulation design of the orodispersible tablets of the COX-2 inhibitor

Tablet ingredients (mg)/ formulation code	ETR-1	ETR-2	ETR-3
Etoricoxib	60	60	60
Aspartame	4	4	4
Microcrystalline cellulose (PH102)	320	-	-
Microcrystalline cellulose (PH102): mannitol (granular) (1:1)	-	320	-
Mannitol (granular)	-	-	320
Crospovidone	8	8	8
Colloidal silicon dioxide	2	2	2
Mixed fruit flavor	2	2	2
Magnesium stearate	4	4	4
Total weight	400	400	400

Table 3: Full factorial design (3^2) layout

Formulation code	Variable level		Total weight (mg)	*In vitro* disintegration time (s) ± SD	Drug percent dissolved in 60 s (%) ± SD
	X_1	X_2			
F1	−1	−1	356	18.44 ± 0.091	90.5 ± 0.156
F2	−1	0	360	16.34 ± 0.045	91.52 ± 0.542
F3	−1	+1	364	15.19 ± 0.078	92.47 ± 0.129
F4	0	−1	396	35.5 ± 0.317	46.90 ± 0.634
F5	0	0	400	19.93 ± 0.240	89.25 ± 0.342
F6	0	+1	404	18.53 ± 0.168	91.4 ± 0.346
F7	+1	−1	436	58.46 ± 0.155	26.27 ± 0.369
F8	+1	0	440	49.67 ± 0.130	35.68 ± 0.525
F9	+1	+1	444	46.79 ± 0.358	38.13 ± 0.959

Coded values	Actual values (% w/w)		Actual values (mg)	
	X_1	X_2	X_1	X_2
−1	70	1	280	4
0	80	2	320	8
+1	90	3	360	12

Table 4: Evaluation of the compressed tablets for the formulation batches

Evaluation parameters*/ formulation code	ETR-1	ETR-2	ETR-3
Appearance	400 mg, off-white color, 10 mm, round flat faced	400 mg, off-white color, 10 mm, round flat faced	400 mg, off-white color, 10 mm, round flat faced
Weight variation (± %)	0.692 ± 2.78	0.774 ± 3.105	0.823 ± 3.30
Hardness (kg/cm^2)	4.5 ± 0.1	4.43 ± 0.115	4.43 ± 0.057
Thickness (mm)	4.25 ± 0.025	4.33 ± 0.043	4.46 ± 0.05
Friability (%)	0.57 ± 0.026	0.696 ± 0.020	0.713 ± 0.025
Drug content (%)	101.69 ± 0.987	101.58 ± 1.527	101.99 ± 0.614
Content uniformity** (%)	101.891 ± 1.324	101.909 ± 1.248	101.183 ± 1.336
Water absorption ratio (%)	73.42 ± 1.729	79.74 ± 0.877	84.42 ± 0.653
Wetting time (s)	21.85 ± 0.460	19.21 ± 0.313	15.36 ± 0.384
In vitro DT (s)	25.49 ± 0.638	24.97 ± 0.310	19.93 ± 0.240
In vivo DT (s)	35.13 ± 0.328	34.53 ± 0.376	28.89 ± 0.425
DP_{60} (%)	73.49 ± 0.102	77.55 ± 0.343	89.25 ± 0.342

*All values are mean ± SD, *n* = 3 and **values are mean ± SD, *n* = 10; DP_{60} = drug percent dissolved in 60 s

Table 5: Evaluation of the compressed tablets for the factorial design batches

Evaluation parameters*/ formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Appearance	356 mg, off-white color, 10 mm, round flat faced	360 mg, off-white color, 10 mm, round flat faced	364 mg, off-white color, 10 mm, round flat faced	396 mg, off-white color, 10 mm, round flat faced	400 mg, off-white color, 10 mm, round flat faced	404 mg, off-white color, 10 mm, round flat faced	436 mg, off-white color, 10 mm, round flat faced	440 mg, off-white color, 10 mm, round flat faced	444 mg, off-white color, 10 mm, round flat faced
Weight variation (± %)	0.713` ± 2.539	0.739 ± 2.661	0.718 ± 2.615	0.608 ± 2.412	0.714 ± 2.856	0.532 ± 2.149	0.558 ± 2.433	0.443 ± 1.954	0.570 ± 2.536
Hardness (kg/cm^2)	3.83 ± 0.057	3.86 ± 0.057	4.03 ± 0.057	4.4 ± 0.1	4.46 ± 0.057	4.56 ± 0.057	4.86 ± 0.057	5.03 ± 0.057	5.16 ± 0.057
Thickness (mm)	3.23 ± 0.065	3.45 ± 0.030	3.63 ± 0.037	3.98 ± 0.017	4.19 ± 0.015	4.37 ± 0.015	4.43 ± 0.032	4.48 ± 0.060	4.52 ± 0.036
Friability (%)	1.289 ± 0.007	1.173 ± 0.005	1.057 ± 0.003	0.663 ± 0.037	0.623 ± 0.015	0.59 ± 0.01	0.366 ± 0.020	0.35 ± 0.01	0.326 ± 0.020
Drug content (%)	100.58 ± 0.890	101.24 ± 1.453	101.15 ± 1.924	101.34 ± 1.527	101.58 ± 1.527	100.75 ± 0.856	100.33 ± 1.273	101.99 ± 0.614	101.59 ± 1.026
Content uniformity** (%)	101.51 ± 1.392	101.89 ± 1.324	101.04 ± 1.350	100.96 ± 1.073	101.90 ± 1.248	100.90 ± 1.024	101.72 ± 1.173	101.10 ± 1.283	101.14 ± 1.075
Water absorption ratio (%)	86.60 ± 0.256	88.75 ± 0.098	91.00 ± 0.073	74.37 ± 1.263	84.42 ± 0.653	85.05 ± 0.151	57.48 ± 1.099	62.03 ± 0.665	66.46 ± 0.466
Wetting time (s)	13.49 ± 0.117	11.44 ± 0.604	10.46 ± 0.105	30.35 ± 0.525	15.36 ± 0.384	14.54 ± 0.173	53.32 ± 0.642	43.56 ± 0.274	41.73 ± 0.149
In vitro DT (s)	18.44 ± 0.091	16.34 ± 0.045	15.19 ± 0.078	35.5 ± 0.317	19.93 ± 0.240	18.53 ± 0.168	58.46 ± 0.155	49.67 ± 0.130	46.79 ± 0.358
In vivo DT (s)	29.2 ± 0.165	25.13 ± 0.328	24.21 ± 0.262	45.47 ± 0.610	28.89 ± 0.425	27.36 ± 0.503	68.44 ± 0.695	58.89 ± 0.425	55.89 ± 0.770
DP_{60}(%)	90.5 ± 0.156	91.52 ± 0.542	92.47 ± 0.129	46.90 ± 0.634	89.25 ± 0.342	91.4 ± 0.346	26.27 ± 0.369	35.68 ± 0.525	38.13 ± 0.959

*All values are mean ± SD; *n* = 3 and **values are mean ± SD, *n* = 10, DP_{60} = drug percent dissolved in 60 s

was also evidenced from the angle of repose (in the range of 26.28-36.22°), which is below 40°, indicating good flowability.[5]

Orodispersible tablets of Etoricoxib were prepared by the direct compression technique, with preliminary focus on *in vitro* DT and dissolution profile, although other quality control parameters were also evaluated.

Optimization by the 3^2 full factorial design requires that the experimentation should be completed so that a mathematical model can be generated. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses.[2]

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

where, Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs and b_i (b_1, b_2, b_{12}, b_{11} and b_{22}) is the estimated coefficient for the corresponding factor X_i (X_1, X_2, X_{12}, X_{11} and X_{22}), which represents the average results of changing one factor at a time from its low to high value. The interaction term (X_1X_2) depicts the changes in the response when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity.[2]

In vitro DT and drug percent dissolved in 60 s (DP_{60}) for the nine batches (F1-F9) showed a wide variation, i.e. 15.19- 58.46 s and 26.27-92.47%, respectively [Table 5]. The data clearly indicate that *in vitro* DT and drug percent dissolved in 60 s (DP_{60}) values are strongly dependent on the selected independent variables. The fitted equations relating the responses *in vitro* DT and drug percent dissolved in 60 s (DP_{60}) are shown in the following equations, respectively.

Final equations in terms of coded factors

$$DT = 21.46429 + 17.49167\ X_1 - 5.315\ X_2 - 2.105\ X_1X_2 - 10.00643\ X_1^2 + 4.016429\ X_2^{2.} \quad (2)$$

Final equations in terms of actual factors

$$DT = 514.9581 - 13.8401\text{Mannitol} - 4.54071\text{Crospovidone} - 0.2105\text{MannitolCrospovidone} - 0.100064\ \text{Mannitol}^2 + 4.016429\ \text{Crospovidone}^2. \quad (3)$$

($R^2 = 0.9795$)

Final equations in terms of coded factors

$DP_{60} = 84.00929 - 29.063X_1 + 9.721667X_2 + 2.47255X_1X_2 - 15.1686\ X_1^2 - 9.61857\ X_2^2$ (4)

Final equations in terms of actual factors

$DP_{60} = -672.59 + 20.86838\text{Mannitol} + 28.41595\text{Crospovidone} + 0.24725\text{MannitolCrospovidone} - 0.15169\text{Mannitol}^2 - 9.61857\ \text{Crospovidone}^{2.}$ (5)

($R^2 = 0.9075$)

The high values of the correlation coefficient for *in vitro* DT and drug percent dissolved in 60 s (DP_{60}) as shown above indicated a good fit. The polynomial equations can be used to draw conclusions after considering the magnitude of the coefficient and the mathematical sign it carries (i.e., positive or negative).[2] The results of the analysis of variance (ANOVA), which was performed to identify insignificant factors, are shown in Table 6. ANOVA and multiple regression analysis were performed using the *Stat-Ease Design Expert 7.1.4.0* trial software.

The significance levels of coefficient b_{22} and b_{12} were found to be $P = 0.1534$ and 0.2940 and hence they were omitted from the full model. The results of statistical analysis are shown in Table 6. The coefficients b_1, b_2 and b_{11} were found to be significant at $P < 0.05$ and hence they were retained. Hence, it was concluded that the interaction terms b_{22} and b_{12} do not contribute significantly to the prediction of DT and can be omitted from the full model. Therefore, conclusions can be drawn considering the magnitude of the coefficient and the mathematical sign (positive or negative) it carries. The results of the multiple linear regression analysis revealed that on increasing the concentration of mannitol an increase in DT is observed as the coefficient b_1 bears a positive sign whereas on increasing the concentration of crospovidone a decrease in DT is observed as the coefficient b_2 bears a negative sign. When a higher percentage of mannitol is used, lower porosity is expected in the tablet matrix. The water uptake and subsequent disintegration are not thus facilitated. It is obvious that in the presence of a higher percentage of superdisintegrant crospovidone, wicking is facilitated.

The significance level of coefficients b_{11}, b_{22} and b_{12} were found to be greater than $P = 0.05$ and hence they were omitted from the full model. The coefficients b_1 and b_2 was found to be significant at $P < 0.05$ and hence they were retained. Therefore, it was concluded that the interaction term and polynomial terms do not contribute significantly to the prediction of DP_{60}. An increase in the concentration of mannitol leads to a decrease in DP_{60} because the coefficient b_1 bears a negative sign whereas on increasing the concentration of crospovidone an increase in DP_{60} is observed as the coefficient b_2 bears a positive sign. When a higher percentage of mannitol is used, dissolution of poorly soluble drugs is facilitated as mannitol acts as a hydrophilic carrier for these drugs and a higher percentage of crospovidone leads to high DP_{60} due to fast wicking.

The response surface plots of the percentage of mannitol (X_1) and crospovidone (X_2) versus *in vitro* DT and that versus drug percent dissolved in 60 s (DP_{60}) are shown in Figures 1 and 2,

Table 6: Results of ANOVA for response surface quadratic model

Source	Sum of squares	Degrees of freedom	Mean square	F-value	*P* value	Level of significance
In vitro disintegration time (DT)						
Model	2334.14	5	466.82	38.36	0.0018	Significant
X_1	1835.75	1	1835.75	150.85	0.0003	Significant
X_2	169.49	1	169.42	13.92	0.0203	Significant
X_1X^2	17.72	1	17.72	1.45	0.2940	Nonsignificant
$(X_1)^2$	233.63	1	233.63	19.19	0.0119	Significant
$(X_2)^2$	37.64	1	37.64	3.09	0.1534	Nonsignificant
Residual	48.67	4	12.16	-	-	-
Lack of fit	48.67	3	1622	-	-	-
Pure error	0	1	0	-	-	-
Core total	2382.82	9	-	-	-	-
Drug percent dissolved in 60 s (DP_{60})						
Model	6552.29	5	1310.45	7.857	0.0340	Significant
X_1	5069.80	1	5069.80	30.39	0.0053	Significant
X_2	567.06	1	567.06	3.400	0.0390	Significant
X_1X_2	24.45	1	24.45	0.146	0.7213	Nonsignificant
$(X_1)^2$	536.86	1	536.86	3.219	0.1472	Nonsignificant
$(X_2)^2$	215.87	1	215.87	1.294	0.3188	Nonsignificant
Residual	667.08	4	166.77	-	-	-
Lack of fit	667.08	3	222.36	-	-	-
Pure error	0	1	0	-	-	-
Core total	7219.381	9	-	-	-	-

respectively. The response plots showed that there is a significant effect of both factors on selected responses.

Consequently, the arbitrary selection of a batch of tablets with a desired *in vitro* DT and drug percent dissolved in 60 s (DP_{60}) for appropriate dissolution profile can be achieved considering a suitable composition of directly compressible filler and crospovidone as well as other aspects such as ease of manufacturing, cost etc. When the variable X_1 goes beyond "0" level (80%), porosity of tablets decreased than that for the acceptable dissolution profile.

Thus, we can conclude that the statistical model is mathematically valid as the experimental (actual) values and predicted values suggested by the full model were relatively close to each other. The diagnostic case statistics involving actual and predicted values are given in Table 7. The uniform blends of tablet composition were directly compressed by keeping the tablet press setting constant across all formulations. This is more important especially during nine batches of factorial design as it may be regarded as another process variable affecting the response(s) selected. Proper lubrication of the powder blends was essential for ease of ejection of the compressed tablets as well as for free movement of the lower punch during the compression cycle. This is evident particularly when mannitol (granular) was present as the directly compressible filler in the formulation.

The various standards or quality control tests carried out on compressed tablets [Tables 4 and 5] demonstrated the following:

A tablet shape with more surface area generally has a faster DT than a tablet shape having less surface area, all other factors being equal. Uniform weight due to uniform die fill with acceptable variation as per I.P. standards were obtained because blend of the material was free flowing. The percent deviation in weight variation for all formulation batches, i.e. ETR-1–ETR-3, was found to be between ± 0.692% and ± 0.823% and that for factorial design batches, i.e. F1-F9, was found to be between ±0.443% and ±0.739%. Hence, the weight variation test for all batches of tablets complies with the I.P. specifications.[6] Tablet crushing strength, the critical parameter, was controlled as the resistance of tablets with capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. Hence, hardness for all formulation batches, i.e. ETR-1–ETR-3, was found to be between 4.43 and 4.5 kg/cm^2 and that for the factorial design batches, i.e. F1-F9, showed wide variation in the range of 3.83-5.86 kg/cm^2. The above results were observed due to the constant tablet press setting across all batches of factorial design irrespective of weight variation. Thickness for all formulation batches, i.e. ETR-1–ETR-3, was found to be between 4.25 and 4.46 mm and that for the factorial design batches, i.e. F1-F9, showed a wide variation in the range of 3.23-4.52 mm due to the constant tablet press

Table 7: Diagnostic case statistics involving the actual and the predicted values

Formulation code	*In vitro* disintegration time (s)			Drug percent dissolved in 60 s (%)		
	Actual values	Predicted values	Residual	Actual values	Predicted values	Residual
F1	18.44	19.02	−0.03145336	90.5	89.52	0.010829
F2	16.34	15.96	0.023255814	91.52	92.35	−0.00907
F3	15.19	15.03	0.010533246	92.47	93.01	−0.00584
F4	35.5	35.96	−0.01295775	46.90	46.75	0.003198
F5	19.93	20.35	−0.02107376	89.25	90.52	−0.01423
F6	18.53	19.62	−0.05882353	91.4	92.41	−0.01105
F7	58.46	59.45	−0.01693466	26.27	27.45	−0.04492
F8	49.67	50.62	−0.01912623	35.68	35.89	−0.00589
F9	46.79	47.1	−0.00662535	38.13	39.56	−0.0375

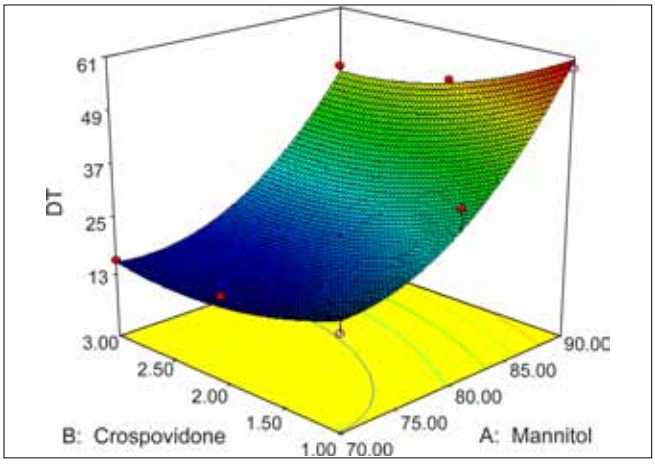

Figure 1: Response surface plot of *in vitro* disintegration time

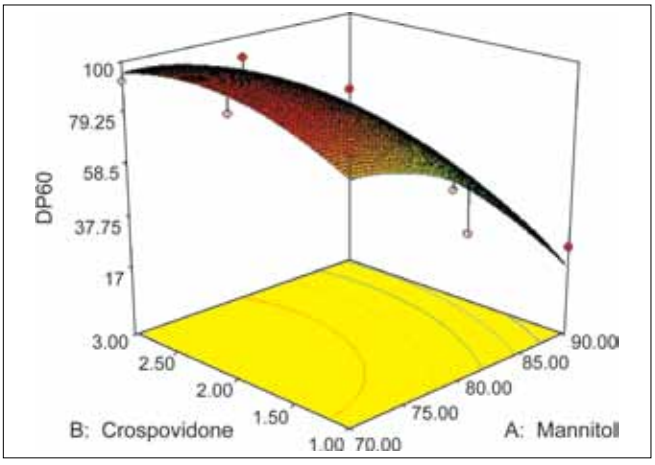

Figure 2: Response surface plot of drug percent dissolved in 60 s

setting across all batches of factorial design irrespective of weight variation. To achieve % friability within limits for an orodispersible tablet is a challenge to the formulator because all methods of manufacturing of the orodispersible tablet are responsible for increasing the % friability values. The % friability values for all formulation batches, i.e. ETR-1–ETR-3, were found to be between 0.57 and 0.716% and that for the factorial design batches, i.e. F1-F9, showed a wide variation in the range of 0.326-1.289%. The above results were observed due to the constant tablet press setting across all batches of factorial design irrespective of weight variation.

Drug content for all formulation batches, i.e. ETR-1–ETR-3, was found to be in the range of 101.59-101.99% and that for the factorial design batches, i.e. F1-F9, showed in the range of 100.33-101.99%. Uniformity of content for all formulation batches, i.e. ETR-1–ETR-3, was found to be in the range of 100.183-101.909% and that for the factorial design batches, i.e. F1-F9, showed in the range of 100.90-101.90%.

To investigate the importance of the total surface area in promoting drug dissolution, a water uptake study was performed on the orodispersible tablets of the COX-2 inhibitor. Because the drug has to dissolve from the interface between drug and water, the maximal water uptake volume can be taken as an estimation of the total surface area available for drug dissolution to take place. Each fiber can act as a hydrophilic channel to facilitate water uptake into the tablet matrix and help increase the total water contact area with the drug.[10] Water absorption ratios for all formulation batches, i.e. ETR-1–ETR-3, showed variation in the range of 73.42-84.42% and that for the factorial design batches, i.e. F1-F9, showed wide variation in the range of 57.48-91.00%. The factorial design batches F1-F3 comprised of 70% w/w mannitol (granular) as the directly compressible filler and 1% w/w, 2% w/w, 3% w/w crospovidone, respectively, water absorption ratios being found between 86.60 and 91.00%. However, the factorial design batches F4-F6 comprised of 80% w/w mannitol (granular) as directly compressible filler and 1% w/w, 2% w/w, 3% w/w crospovidone, respectively, water absorption ratios being found between 74.37 and 85.05%. Moreover, the factorial design batches F7-F9 comprised of 90% w/w mannitol (granular) as directly compressible filler and 1% w/w, 2% w/w, 3% w/w crospovidone, respectively, water absorption ratios being found between 57.48 and 66.46%. Hence, it was evident that the water absorption ratio increased with an increase in the concentration of crospovidone but decreased with an increase in the concentration of mannitol (granular).

Wetting time of the dosage form is related to the contact angle, which needs to be assessed to give an insight into capillarity and, subsequently, the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. Wetting time for all formulation batches, i.e. ETR-1–ETR-3, showed variation in the range of 15.36-21.85 s and that for the factorial design batches, i.e. F1-F9, showed wide variation in the range of 10.46-53.32 s. The factorial design batches F1-F3 comprised of 70% w/w mannitol (granular) as directly compressible filler and 1% w/w, 2% w/w, 3% w/w crospovidone, respectively, wetting time being found between 10.46 and 13.49 s. However, the factorial design batches F4-F6 comprised of 80% w/w mannitol (granular) as directly compressible filler and 1% w/w, 2% w/w, 3% w/w crospovidone, respectively, wetting time being found between 14.54 and 30.34 s. Moreover, the factorial design batches F7-F9 comprised of 90% w/w mannitol (granular) as directly compressible filler and 1% w/w, 2% w/w, 3% w/w crospovidone, respectively, wetting time being found between 41.73 and 53.32 s. Hence, it was evident that the wetting time improved with an increase in the concentration of crospovidone but slowed with an increase in the concentration of mannitol (granular).

Disintegration, the first important step for a drug absorption from a solid dosage form after oral administration, was preliminarily focused. It was reported that tablet disintegration was affected by the particle size, the degree of substitution and the extent of cross-linkage. An important factor affecting the disintegration is the tablet hardness and/or the compaction force used in making the tablet hardness. The hardness of the tablet has an influence on the DT as it affects the porosity of the matrix and, accordingly, the ability of water to penetrate through the matrix.

In vitro DT for all formulation batches, i.e. ETR-1–ETR-3, showed variation in the range of 19.93-25.49 s and that for the factorial design batches, i.e. F1-F9, showed wide variation in the range of 15.19-58.46 s. The factorial design batches F1-F3 comprised of 70% w/w mannitol (granular) as directly compressible filler and 1% w/w, 2% w/w, 3% w/w crospovidone, respectively, *in vitro* DT being found between 15.19-18.44 s. However, the factorial design batches F4-F6 comprised of 80% w/w mannitol (granular) as directly compressible filler and 1% w/w, 2% w/w, 3% w/w crospovidone, respectively, *in vitro* DT being found between 18.53 and 35.5 s. Moreover, the factorial design batches F7-F9 comprised of 90% w/w mannitol (granular) as directly compressible filler and 1% w/w, 2% w/w, 3% w/w crospovidone, respectively, *in vitro* DT being found between 46.79 and 58.46 s. Hence, it was evident that *in vitro* DT improved with an increase in the concentration of crospovidone but slowed with an increase in the concentration of mannitol (granular).

In vivo DT for all formulation batches, i.e. ETR-1–ETR-3, showed variation in the range of 28.89-35.13 s and that for the factorial design batches, i.e. F1-F9, showed wide variation in the range of 24.21-68.44 s. The factorial design batches F1-F3 comprised of 70% w/w mannitol (granular) as directly compressible filler and 1% w/w, 2% w/w, 3% w/w crospovidone, respectively, *in vivo* DT being found between 24.21 and 29.20 s. However, the factorial design batches F4-F6 comprised of 80% w/w mannitol (granular) as directly

compressible filler and 1% w/w, 2% w/w, 3% w/w crospovidone, respectively, *in vivo* DT being found between 27.36 and 45.47 s. Moreover, the factorial design batches F7-F9 comprised of 90% w/w mannitol (granular) as directly compressible filler and 1% w/w, 2% w/w, 3% w/w crospovidone, respectively, *in vivo* DT being found between 55.89 and 68.44 s. Hence, it was evident that *in vivo* DT improved with an increase in the concentration of crospovidone but slowed with an increase in the concentration of mannitol (granular).

The comparative profiles of wetting time, *in vitro* DT and *in vivo* DT of orodispersible tablets of the COX-2 inhibitor for the factorial design batches are shown in Figure 3.

The differences in the particle size generated in the disintegrated tablets could affect drug dissolution because breaking tablets into finer fragments may promote drug dissolution by providing larger total surface areas for drug dissolution to take place. Drug percent dissolved at 60 s (DP_{60}) for ETR-1–ETR-3 showed variation in the range of 42.16-97.32% and that of F1-F9 showed wide variation in the range of 73.49-89.25%. The factorial design batches F1-F3 comprised of 70% w/w mannitol (granular) as directly compressible filler and 1% w/w, 2% w/w, 3% w/w crospovidone, respectively, DP_{60} being found between 90.5 and 92.47%. However, the factorial design batches F4-F6 comprised of 80% w/w mannitol (granular) as directly compressible filler and 1% w/w, 2% w/w, 3% w/w crospovidone, respectively, DP_{60} being found between 46.90 and 91.40%. Moreover, the factorial design batches F7-F9 comprised of 90% w/w mannitol (granular) as directly compressible filler and 1% w/w, 2% w/w, 3% w/w crospovidone, respectively, DP_{60} being found between 26.27 and 38.13%. Hence, it was evident that DP_{60} improved with an increase in the concentration of crospovidone but again reduced with an increase in the concentration of mannitol (granular). These varied findings of DP_{60} correlate with the apparent differences in particle size generated in the disintegrated tablets. The comparative dissolution profiles of orodispersible tablets of Etoricoxib in 0.1N HCl for the factorial design batches are shown in Figures 4 to 6, respectively.

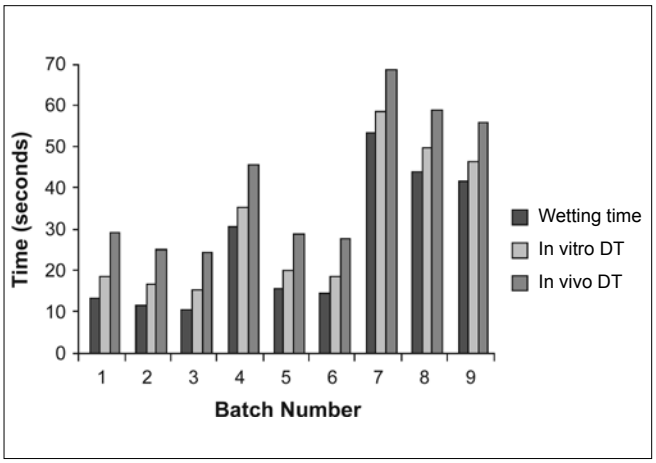

Figure 3: Comparative profiles of wetting time, *in vitro* disintegration time (DT) and *in vivo* DT of all the factorial design batches

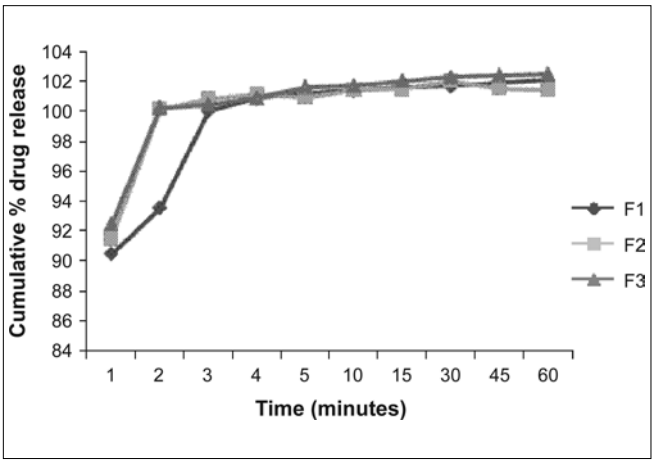

Figure 4: Comparative dissolution profile of orodispersible tablets of Etoricoxib in 0.1N HCl for F1-F3

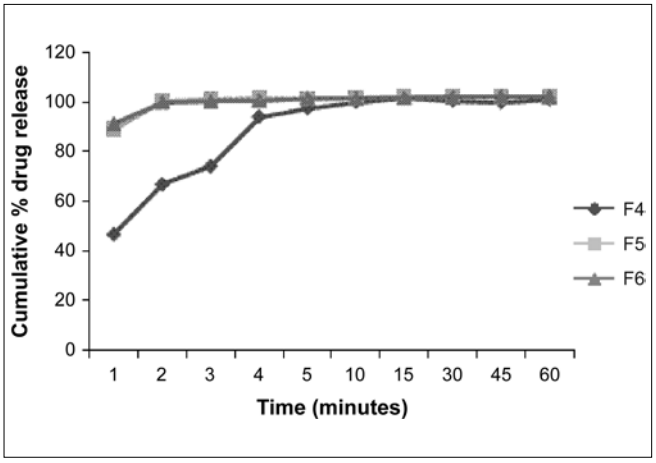

Figure 5: Comparative dissolution profile of orodispersible tablets of Etoricoxib in 0.1N HCl for F4-F6

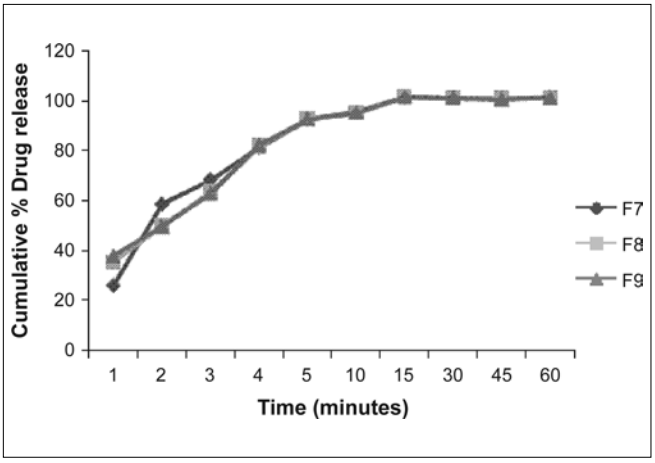

Figure 6: Comparative dissolution profile of orodispersible tablets of Etoricoxib in 0.1N HCl for F7-F9

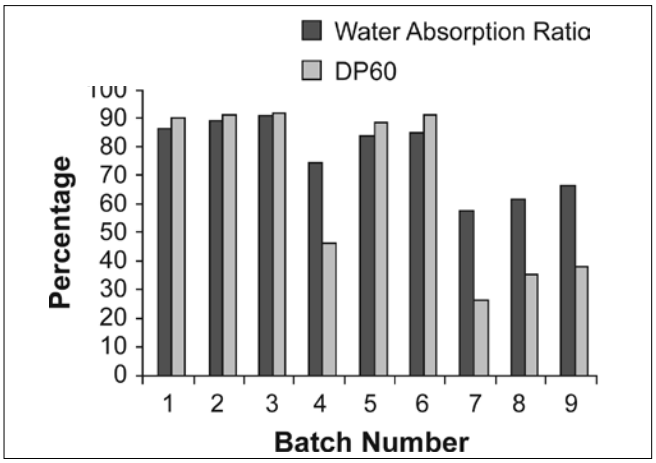

Figure 7: Comparative profiles of water absorption ratios and DP_{60} of orodispersible tablets of the COX-2 inhibitor for the factorial design batches

The improvement in water absorption ratio, wetting time, *in vitro* DT, *in vivo* DT and drug percent dissolved in 60 s was evident in F1-F3 due to the constant tablet press setting across all batches of the factorial design irrespective of weight variation, which might have led to decreased hardness and increased friability. This has further resulted in increased porosity of the tablets and subsequent maximal water uptake volume. If porosity is sufficiently high, water can easily penetrate the tablet. Accordingly, a suitable hardness depends in part on the tablet composition and the desired level of oral disintegration speed.

The comparative profiles of water absorption ratio and drug percent dissolved in 60 s with their interrelationship and of orodispersible tablets of the COX-2 inhibitor for the factorial design batches are shown in Figure 7.

The present work led to the development of orodispersible tablets for oral administration comprising a therapeutically effective amount of selective COX-2 inhibitor as model drug (Etoricoxib) that disintegrates and disperses in the oral cavity in less than 30 s without the need for drinking water, had a pleasant mouth feel and there was no after-taste or grittiness and improved patient compliance, particularly for those who have difficulty in swallowing. The significant effects of the interaction and polynomial variables on the investigated characteristics of the orodispersible tablets of selective COX-2 inhibitor were verified using the 3^2 randomized full-factorial design. This permitted the arbitrary selection of a batch of tablets with a desired and improved dissolution profile after oral administration of the selective COX-2 inhibitor by an appropriate composition of filler and disintegrant. On comparison with the experimental optimized preparation, the observed responses were in close agreement with the predicted values of the optimized one, thereby demonstrating the feasibility of the optimization procedure in developing orodispersible tablets of the selective COX-2 inhibitor.

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