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Optimizing Fast Dissolving Dosage Form of Diclofenac Sodium by Rapidly Disintegrating Agents

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ABSTRACT

The present work was focused on optimizing fast dissolving dosage form of diclofenac sodium by rapidly disintegrating agents. Fast-dissolving tablets of diclofenac sodium was prepared by using different superdisintegrants like carboxymethyl cellulose, crospovidone and sodium starch glycolate by direct compression method. Preformulation studies have been performed for the active pharmaceutical ingredients. Tablets have been prepared in ten different formulations (control, F1- F9) with change in the concentration of superdisintegrants. These tablets are evaluated for various parameters like weight variation test, hardness, thickness, in-vitro dissolution studies. Tablets containing carboxymethyl cellulose (mainly F3) showed better-disintegrating character along with rapid release (95% release in 15 mins). The concentration of the super disintegrants had also an effect on disintegration time and in-vitro dissolution. Higher levels of supersdisintegrants producing rapid disintegration and faster dissolution.

INTRODUCTION:

Fast-dissolving tablets (FDTs) are solid single-unit dosage forms that are placed in the mouth, allowed to disperse/dissolve in the saliva and then swallowed without the need for water[1]. Fast dissolving tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapimelts, porous tablets, quick dissolving etc. The basic approach in development of FDT is the use of superdisintegrants like cross linked carboxymethylcellulose (croscarmellose), sodium starch glycolate (primogel, explotab), polyvinylpyrrolidone (polyplasdone) etc, which provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva[2].Masking is compatible with taste and feeling pleasant to the mouth. Paediatric, elderly and mentally handicapped patients can be readily administered. Accurate dose as compared to liquids may be provided[3].

MATERIALS AND METHOD:

Materials

Diclofenac sodium was gifted from Mundra Enterprises, carboxymethyl cellulose, mannitol, magnesium sterate and talc was purchased from S D fine chemicals Ltd, crospovidone from Shreeji chemicals, sodium starch glycolate from Aditya Chemicals and microcrystalline cellulose from LOBA chemie. Phosphate buffer pH 6.8 was prepared as described in the Indian pharmacopoeia.

Methods[4]

Diclofenac sodium fast dissolving tablets were prepared by Direct compression method. Drug, mannitol and micro crystalline cellulose were mixed thoroughly Superdisintegrants were incorporated in the powder mix. Add magnesium stearate and talc to the powder mix. Weigh individually and punched into tablets using rotary punch tableting machine. The compressed tablets were evaluated for various parameters viz, appearance, thickness, hardness, weight variation, friability, drug content, disintegration test and in-vitro drug release studies.

Table NO. 1: Composition of Diclofenac sodium fast-dissolving tablets.

Formulations (mg)	Drug (mg)	Mannitol (mg)	MCC (mg)	Ac-di-sol (mg)	Explotab (mg)	Polyplasdone XL (mg)
Control	25	47	36	-	-	-
F_1	25	41	36	6	-	-
F_2	25	38	36	9	-	-
F_3	25	35	36	12	-	-
F_4	25	41	36	-	6	-
F_5	25	38	36	-	9	-
F_6	25	35	36	-	12	-
F_7	25	41	36	-	-	6
F_8	25	38	36	-	-	9
F_9	25	35	36	-	-	12

EVALUATION PARAMETER

Pre Compression parameters:

- **Angle of repose:**[5]

The friction forces in a loose powder can be measured by the angle of repose (θ). It is indicative of the flow properties of the powder. It is defined as the maximum angle possible between the surface of the pile of powder and the horizontal plane.

$$\tan (\theta) = h / r$$

$$\boldsymbol{\theta = \tan\text{-}1 (h / r)}$$

Where, ɵ is the angle of repose

h is the height in cm

r is the radius in cm

- **Bulk density:[6]**

Bulk density was determined by pouring the blend into a Graduated cylinder. The bulk volume (V) and weight of the powder (M) were determined. The bulk density was calculated by using the below mentioned formula,

Bulk density = mass of granules/volume of granules

- **Tapped density:**

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density was calculated using the following formula,

Tapped density = weight of the blend/ volume occupied in cylinder (V_t).

- **Carr's compressibility index:[7]**

The simplest way of measuring of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow. The compressibility index is determined by Carr's index, which is calculated by using the following formula,

$$C= 100(1-B/T)$$

Where B is the freely settled bulk density, and T is tapped bulk density.

- **Hausner's Ratio:**

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner's Ratio}= \rho_t / \rho_o$$

Where ρ_t is tapped density and ρ_o is bulk density.

Lower Hausner's ratio (< 1.25) indicates better flow properties than higher ones (> 1.25).

Post-compression parameters:

- **Tablet hardness and thickness:[8]**

This test was applied with a tablet hardness tester (Monsanto, tablet hardness tester) on 10 tablets for each formulation. It is usually expressed in Kg/cm^3. The thickness of the tablet is calculated by using screw gauge which indicates the strength of withstand the compression force applied.

- **Friability test:[9]**

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these are placed in the Roche friability, rotating at 100 rpm for 4 min. The tablets are then taken out, dedusted and were weighed. The difference in the weight is noted and expressed as a percentage.

$$\% F = (1 - W/W^*) 10$$

Where,

W* is the original weight of tablet.

W is the final weight of tablet after test.

Acceptance limit of friability is: 0.5 – 1%[13]

- **Drug content uniformity:**

Twenty tablets were crushed and powder equivalent to the weight of one tablet was dissolved in phosphate buffer 6.8. Then suitable dilutions were made and absorbance at 276 nm wavelength was taken by using a UV visible spectrophotometer.

- **Weight variation:[10]**

The formulated tablets were tested for weight uniformity. For this 20 tablets were weighed collectively and individually. From the collective weight, the average weight was calculated. Each tablet's weight was then compared with the average weight to ascertain whether it was within permissible limits or not.

% Weight variation = Average weight-Individual weight/average weight ×100.

- **wetting time and water absorption ratio:**

A double-folded tissue paper was placed in a Petri dish. 6 mL of water containing a water-soluble dye (eosin) was added to the Petri dish. A tablet (pre-weighed) was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablet was noted as the wetting time. The wetted tablet was then weighed and the water absorption ratio (R) was determined by using the equation:

$$R=100\ (W_b-W_a)/W_b$$

Where W_a and W_b are the weights of the tablet before (dry weight) and after water absorption (wet weight) respectively.

- ***In-vitro* Disintegration test**:[11]

The disintegration time for the batches of tablets was determined using the BP tablet disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus. Phosphate buffer of P^H 6.8, used as the disintegration medium was maintained at 37 ± 0.5 ºC and the time taken for the entire tablet to disintegrate completely was measured in seconds.

- ***In-vitro* Dissolution studies:[12]**

An in-vitro dissolution rate study was done by using USP Type II apparatus which was rotated at 75 rpm. Phosphate buffer pH 6.8 (900 ml) was taken as a dissolution medium. The temperature of the dissolution medium was maintained at 37±0.5°c. Aliquots of dissolution medium were withdrawn at specific time interval and it was filtered. Absorbance of the filtered solution was determined by Spectrophotometer (SYSTRONICS-UV Double beam spectrophotometer-2101) at 276 nm and drug concentration was determined from standard calibration curve**.**

RESULT AND DISCUSSION

The melting point of the obtained drug sample (diclofenac sodium) was found to be 279-289ºC, which complied with IP standards, thus indicating the purity of the drug. Solubility analysis of Diclofenac sodium was done in different solvent and it is observed that the drug is sparingly soluble in water, soluble in ethanol, freely soluble in methanol and practically soluble in phosphate buffer P^H 6.8. The DSC thermogram of pure Diclofenac sodium showed sharp endothermic peaks at 285.35ºC. The λmax of the Diclofenac sodium in Phosphate

buffer pH 6.8 was found to be 275.4 nm. The blended powder of different formulations was evaluated for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. Angle of repose ranged from 25.3 to 29.3. The results were found to be below 30° and hence blend was found to have good flowability. (Table NO 3) Bulk and tapped densities are used for the measured for the measurement of Compressibility index. (Table NO 3) The compressibility index (%) ranged from 13.63 to 14.90(table NO 3). The blend was found to have excellent flowing property as the results were found be below 15%. The Hausner's ratio ranged from 1.11 to 1.20 (Table NO 3). The result indicates the free-flowing properties of powder.

The tablets were observed visually and did not show any defect such as capping, chipping and lamination. The physical characteristics of Diclofenac sodium fast-dissolving tablet (control, F1-F9) such as thickness, hardness, friability, weight variation and drug content were determined and results of the formulation (control, F1-F9) found within the limits specified in official books.

The thickness of the tablet indicates that die fill was uniform. The thickness depends upon punch and the weight of the tablet (108 mg). The thickness of the batch from control-F_9 was found to be in the range of 3.14 to 3.22 mm (Table NO 4). The hardness was uniformly maintained for all formulation and it was found to be 3.0 to 3.5 kg/cm^2(Table NO 4). Thus, tablets were having good mechanical strength. Friability is needed for tablets to withstand force of compression applied during the manufacture of tablets. The friability of all the formulated tablets was found to be in the range0.82 to 0.94. (Table NO 4) All the formulated tablets were shown the % friability within the official limits (i.e., not more than 1%). Prepared tablets were evaluated for weight variation and percentage deviation from the average weight was reported in Table NO 4. The values were found to be within the prescribed official limits. The drug content of all the formulations of oral disintegrating tablets was found to be within the range of 98.00 to 99.80 % which was within the limits of IP specifications. (Table NO 4) The wetting time of all the formulations (control-F_9) was found to be within 15 to 58sec, which complies with the official specifications. (Table NO 5) The tablets were evaluated for In-vitro disintegration studies in pH 6.8 buffer were found to be in the range 13 to 72 seconds. (Table NO 5) The In-vitro dissolution studies for formulations (control-F_9) was conducted using the USP paddle type II dissolution apparatus with phosphate buffer pH 6.8 and the result was shown in Table NO 6 and in the Figures 3 and 4. Formulation control showed the drug release of 83.45%, formulations F_1, F_2, F_3 (with

6%, 9% and 12% concentration of carboxymethyl cellulose) showed drug release of 95.63%, 97.77%, 99.81% respectively. Formulations F_4, F_5, F_6 (with 6%, 9% and 12% concentration of crospovidone) showed drug release of 92.03%, 94.29% and 98.14% respectively. Formulations F_7, F_8, F_9 (with 6%, 9% and 12% concentration of sodium starch glycolate) showed drug release of 85.23%, 89.44% and 90.66% respectively.

Table NO. 2: Standard calibration curve of Diclofenac sodium in phosphate buffer pH 6.8

SL NO	Concentration in µg/ml	Absorbance at 275.4 nm			Standard Deviation (SD)
		Trail-1	Trail-2	Trail-3	
1.	0	0	0	0	0
2.	2	0.136	0.134	0.138	0.136±0.002
3.	4	0.251	0.253	0.249	0.251±0.002
4.	6	0.363	0.365	0.367	0.365±0.002
5.	8	0.488	0.486	0.490	0.488±0.002
6.	10	0.643	0.647	0.645	0.645±0.002
7.	12	0.755	0.753	0.751	0.753±0.002
8.	14	0.819	0.821	0.817	0.819±0.002

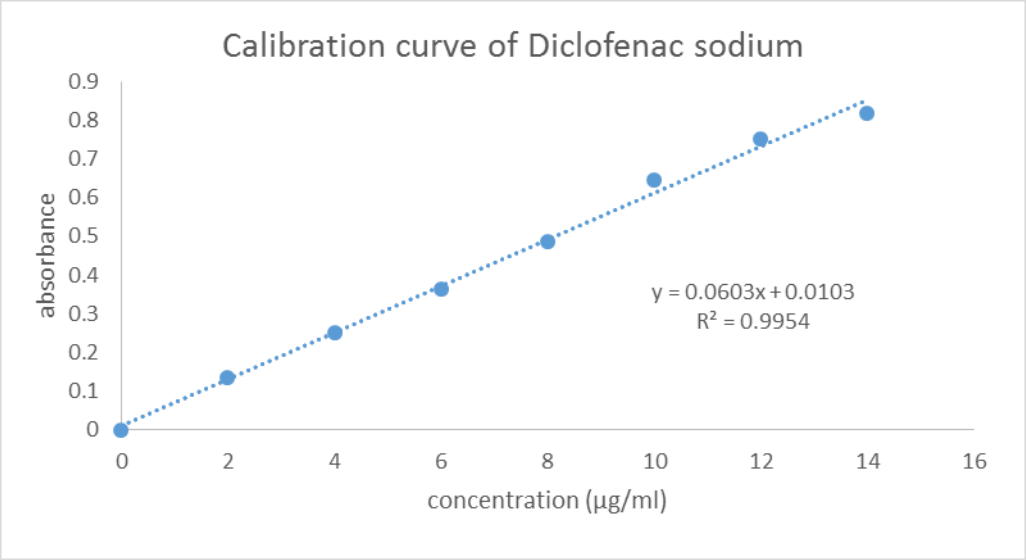


Figure 1: Standard calibration curve of Diclofenac sodium

Table NO 3: Flow properties of the blended powder.

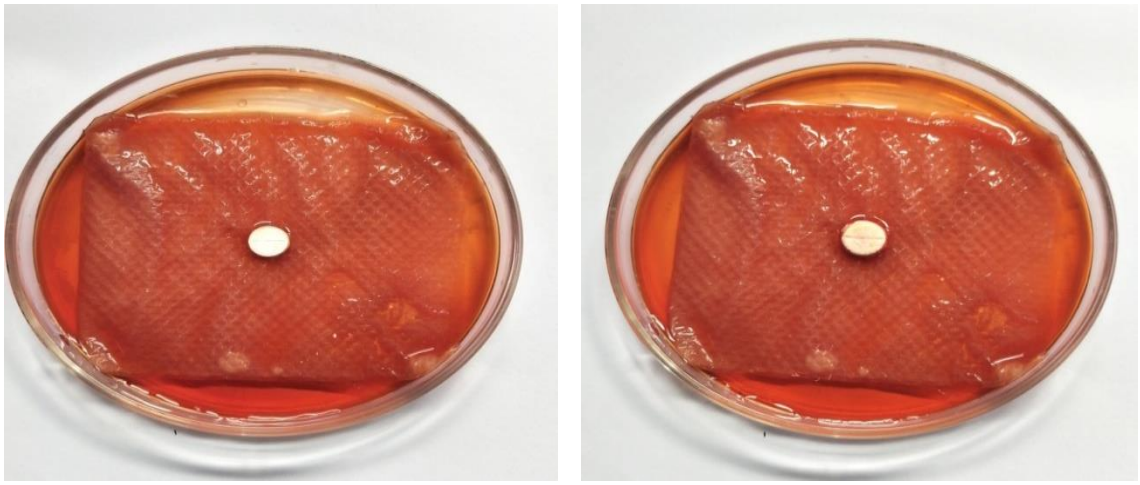
Code	Bulk density (g/cm^3)	tapped density (g/cm^3)	Hauser's ratio	Carr's index (%)	Angle of repose (^{o})
Control	0.59	0.60	1.20	16.12	28.1
F_1	0.51	0.69	1.18	14.04	25.3
F_2	0.50	0.68	1.14	13.63	26.2
F_3	0.48	0.67	1.13	14.50	27.3
F_4	0.57	0.66	1.17	14.90	28.1
F_5	0.53	0.65	1.16	14.70	29.2
F_6	0.52	0.64	1.15	13.80	27.7
F_7	0.58	0.68	1.12	14.60	28.6
F_8	0.56	0.66	1.11	14.40	29.3
F_9	0.55	0.65	1.17	13.67	27.9

Table NO 4: Post-compression parameters of Diclofenac sodium fast-dissolving tablets

Formulation batches	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight Variation(%)	% Drug Content
Control	3.19	3.0	0.87	0.3	99.24
F_1	3.14	3.2	0.91	0.3	98.99
F_2	3.18	3.4	0.89	0.2	99.51
F_3	3.19	3.1	0.88	0.4	99.11
F_4	3.21	3.2	0.89	0.3	98.98
F_5	3.19	3.1	0.94	0..2	99.36
F_6	3.15	3.4	0.82	0.2	99.79
F_7	3.22	3.4	0.89	0.4	99.75
F_8	3.21	3.2	0.88	0.3	99.66
F_9	3.20	3.4	0.91	0.3	99.48

Table NO 5: Results of wetting time and disintegration time.

Formulation batches	Disintegration time (sec)	Wetting time (sec)
Control	72	58
F_1	18	16
F_2	15	17
F_3	13	15
F_4	22	18
F_5	20	17
F_6	17	15
F_7	28	16
F_8	25	15
F_9	21	15



Initial time **After 15 sec**

Figure 2: Wetting time for Optimized formulation F_3

Table NO 6: In vitro drug release study of formulations control, F_1-F_9 in phosphate buffer P^H 6.8

Percentage drug release										
Time (min)	**control**	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**
0	0	0	0	0	0	0	0	0	0	0
1	50.34	60.28	78.02	81.25	69.33	72.58	79.67	56.65	59.5	71.5
3	59.66	75.58	84.62	84.51	74.85	80.28	85.58	69.43	72.44	73.78
6	68.75	84.62	86.23	88.43	81.36	84.62	89.29	73.78	80.89	81.28
9	73.68	91.13	92.55	93.16	85.57	89.99	94.37	78.11	84.23	85.54
12	80.33	93.30	95.45	97.53	90.91	93.30	96.47	83.47	87.85	89.96
15	83.45	95.63	97.77	99.81	92.03	94.29	98.14	85.23	89.44	90.66

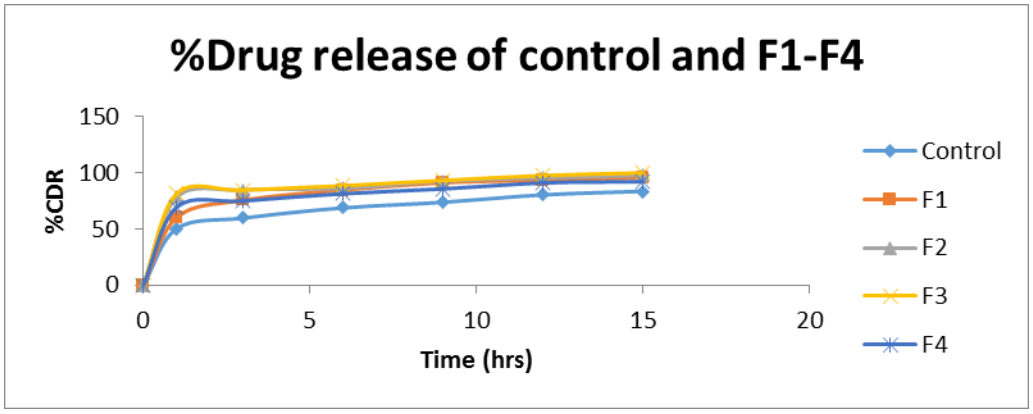


Figure 3: *In vitro* release profile for formulations control and F_1 – F_4

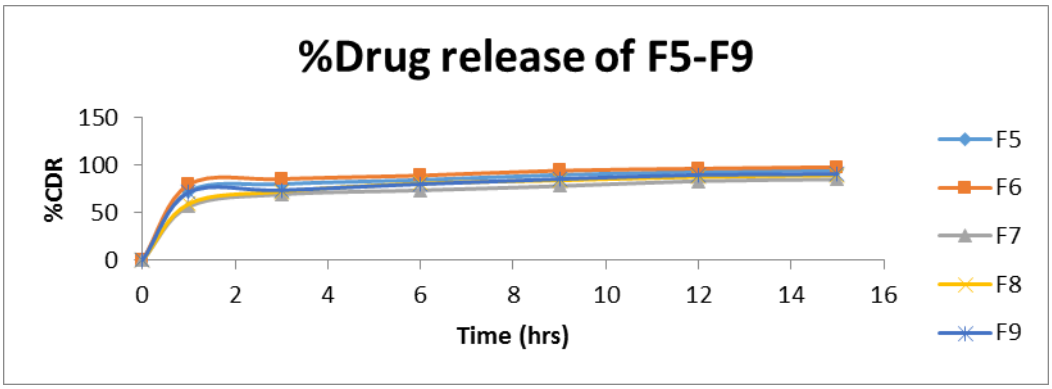


Figure 4: *In vitro* release profile for formulations F_5 –F_9

CONCLUSION:

➢ In conclusion, the super disintegrant such as carboxymethyl cellulose was found to be better suited for the formulation of fast dissolving tablets of Diclofenac sodium when compared to other super disintegrants used in the study. Formulation containing carboxymethyl cellulose have exhibited excellent disintegrating character and consequently the rapid dissolution even at concentration as low as 6 mg.

➢ The optimized formulation is carboxymethyl cellulose containing Diclofenac sodium tablets mainly the F_3 formulation which exhibit the rapid dissolution and less disintegration time. Hence the FDTs which was prepared showed better patient compliance.

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