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Der Pharmacia Lettre, 2016, 8 (8):227-238
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ISSN 0975-5071
USA CODEN: DPLEB4

Formulation and evaluation of diclofenac sodium oro dispersible tablets using different superdisintegrants by direct compression technique

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ABSTRACT

Aim of the present work was to formulate a tablet which disintegrates and dissolves rapidly to show a rapid onset of action. Diclofenac sodium, a non steroidal anti inflammatory drug with analgesic and anti inflammatory properties was selected as a model drug. In the present study, attempt has been made to prepare fast dissolving tablets of diclofenac sodium using 3 different superdisintegrants like Sodium starch glycolate, croscarmellose sodium, and cros povidone by direct compression technique using 3 different concentrations of each superdisintegrant. The pre compression parameters of the prepared tablet blend like angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio and the post compression parameters of the tablet like hardness, friability, weight variation, in vitro dispersion time, wetting time, water absorption ratio, in vitro disintegration time and in vitro drug dissolution were evaluated. It was concluded that formulation F10 showed better release characteristics of the drug.

Keywords: oro dispersible tablets, Diclofenac sodium, Croscarmellose sodium, cros povidone, sodium starch glycolate

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INTRODUCTION

For decades, oral drug delivery has been known as the most widely used route of drug administration when compared to all the other routes that have been explored for delivery of different dosage forms to systemic circulation. The reason for such popularity of oral route may be attributed to its ease of administration [1]. Recent advances in novel drug delivery systems (NDDS) aim at formulating a convenient dosage form for administration and to achieve better patient compliance to enhance safety and efficacy of drug molecules. One such approach is oro-dispersible tablet [2]. An oral fast dissolving drug delivery system is a novel tablet dosage form which dissolves or disintegrates in the oral cavity with a good taste and flavor increasing the acceptability of bitter drugs without the need of water or chewing and hence called melt in mouth tablets or oro-dispersible or rapid disintegrating or quick dissolving tablets [3]. The drugs may be absorbed from mouth, pharynx or esophagus while the saliva passes down into the stomach. Advantages of the fast dissolving tablets include rapid onset of action, ease of swallowing without the aid of water, enhanced dissolution rate, increased gastric absorption, minimized first pass metabolism, improved oral bioavailability and improved patient compliance [4]. ODT formulation combines the advantages of both conventional tablets and liquid formulations. It provides the convenience of a tablet dosage form and also allows the ease of swallowing provided by the liquid formulation [5].

In the present study it was proposed to formulate fast dissolving tablets of diclofenac sodium by using direct compression technique, with the aim of reaching a high serum concentration of the drug in a short time period. In this study, effort has been made to formulate the fast dissolving tablets using super disintegrants like Sodium Starch Glycolate, Croscarmellose sodium and Crospovidone.

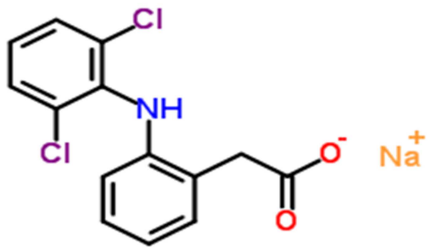

Fig.1: Structure of diclofenac sodium

MATERIALS AND METHODS

Materials

All the materials used in this present work were commercial samples. Diclofenac sodium (Yarrow chem. Products, Mumbai), Sodium starch glycolate (Yarrow chem. Products, Mumbai), Crospovidone (Yarrow chem. Products, Mumbai), Croscarmellose sodium (Yarrow chem. Products, Mumbai), Micro crystalline cellulose (Yarrow chem. Products, Mumbai), Magnesium stearate (Molychem Products, Mumbai), Talc (Lobichem, Mumbai). All the reagents used were of analytical grade. Freshly prepared distilled water was used in the work.

Methods

Identification of drug:

The drug was identified by melting point determination and Ultra Violet spectroscopy (UV)

Melting point determination

Melting point of Diclofenac was determined by capillary tube method. Fine powder of the drug was filled into a glass capillary tube which was previously sealed at one end. The capillary tube tied to a thermometer was subjected to increasing temperatures and the temperature at which Diclofenac melts was recorded.

Ultraviolet spectroscopy

The samples were subjected to UV spectrophotometric analysis and were scanned for absorption maxima (λ_{max}) in the range of 200-400nm using UV-Vis spectrophotometer in an appropriate medium. The obtained data was compared with that of reference values in literature [6].

EVALUATION OF FAST DISSOLVING TABLETS

Pre Compression Parameters:

Angle of repose

Angle of repose was determined using funnel method. The blend was poured through funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap was measured and angle of repose was calculated using the formula,

$\theta = tan^{-1}\, h/r$

Where,

θ is the angle of repose

h is height of pile

r is radius of the base of pile [7]

Table 1: Limits of angle of repose

Angle of repose (θ)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density

Bulk density of a powder is defined as the ratio of the mass of the powder and its bulk volume. It is used to describe packing of particles. For bulk density determination, a weighed quantity of the powder material was introduced into a graduated measuring cylinder and volume of powder was determined.

Bulk Density = Mass of the powder/ bulk volume

Tapped density

For determination of the bulk density, a weighed quantity of the powder was introduced into a graduated measuring cylinder and was tapped mechanically either manually or using a tapping device till a constant volume was obtained [8]

Tapped density = Mass of the powder/ Tapped volume

Carr's compressibility index

The simplest way of measurement 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,

$$C = 100(1 - \frac{B}{T})$$

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.

Hausner's Ratio= ρ_t / ρ_o

Where $\rho_t$is tapped density and ρ_o is bulk density

Lower Hausner's ratio (< 1.25) indicates better flow properties than higher ones (> 1.25) [9]

Table 2: Flow characteristics

Carr's index	Flow character	Hausner's ratio
<10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
>38	Very very Poor	>1.60

Post Compression Parameters:

Weight variation

Tablets are designed to contain a specific amount of drug in a specific amount of tablet formula. The weight of the tablet is measured to help ensure that a tablet contains the proper amount of drug. 20 tablets were selected randomly from each formulation were individually weighed using an electronic balance. Average weight of the tablets was calculated. The individual weight o the tablets was compared with average weight. The tablets meet the USP specifications if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit [10].

Percentage Deviation= (W_{avg})- $(W_{initial})$/ (W_{avg}) × 100

Where
W_{avg}= Average weight of tablet,
$W_{initial}$ = Individual weight of tablet

Table 3: Weight variation

Average weight of tablets (IP)	Average weight of tablets (USP)	Maximum % Difference allowed
Less than 80 mg	Less than 130 mg	10
80 mg-250 mg	130 mg-324 mg	7.5
More than 250 mg	More than 324 mg	5

Hardness
The hardness of the tablet indicates its tensile strength and is measured in terms of load/pressure required to crush it when placed on its edge. Hardness has influence on disintegration and dissolution times and may affect bioavailability. Monsanto hardness tester was used to measure the hardness of the formulated tablets. The tester consists of a barrel containing a compressed spring held between two plungers. The lower plunger was then forced against a spring by turning a threaded bolt until the tablet fractures. As the spring was compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture was record and the zero force reading was deducted from it. It is expressed in kg/cm^2.

Friability
This test evaluates ability of tablet to withstand abrasion and edge damage during packing, handling and shipping. Friability generally reflects poor cohesion of tablet ingredients. Friability was measured by the help of Roche friabilator. 10 tablets were weighed and placed in plastic chamber that revolves at 25 rpm for 4minutes. Tablets were re-weighed after removal of fines (de-dusted). The friability was calculated by the formula [11].

$F = (1 - w/w^*)100$
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%

Wetting Time
This was carried out to measure the time required for the complete wetting of tablet formulations. A piece of tissue paper folded twice was placed in small petridish containing 6ml of water in which amaranth, a water-soluble dye was added. A tablet was placed on this paper. The time required for water to reach the upper surface of the tablet was noted as wetting time.

Water Absorption Ratio
A piece of tissue paper folded twice was placed in small Petridish containing 6ml of water in which amaranth, a water-soluble dye was added. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio R, was determined using the equation [12].

$R=10\ (W_a/W_b)$
Where,
W_b is the weight of the tablet before water absorption,
W_a is the weight of the tablet after water absorption.

***In vitro* dispersion time**
Two tablets were placed in a 100 mL beaker containing pH 6.8 phosphate buffer solution at 37°C. Time required for complete dispersion of tablet was observed [13].

***In vitro* disintegration time**
The process of breakdown of a tablet into smaller particles is known as disintegration. One tablet was placed in each of the 6 tubes of the basket. A disc was added to each tube and the apparatus was run using 6.8 pH phosphate buffer maintained at 37 °C as the immersion liquid. The assembly was raised and lowered between 30 cycles per

minute in the 6.8 pH phosphate buffer. The time in seconds taken for complete disintegration of the tablet with no mass remaining in the apparatus was measured and recorded. The tablet must be disintegrated within 3 minutes [14].

***In vitro* dissolution studies**

In-vitro dissolution studies of the tablets were carried out in USP dissolution apparatus type II by employing a paddle stirrer at 50 rpm using 900 mL of pH 6.8 phosphate buffer at 37 ± 0.5 °C as a dissolution medium. One tablet was used in each test. Aliquots of 5 mL each were withdrawn at specified time intervals (1, 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 minutes) and replaced with equal volume of fresh medium. The withdrawn aliquots were analyzed for drug content spectrophotometrically at λmax 275 nm. Drug concentration was calculated and expressed as cumulative percent of the drug released [15].

DRUG EXCIPIENT COMPATIBILITY STUDIES

Fourier Transform Infrared Spectroscopy (FTIR)

Identification of pure drug as well as interaction between drugs and excipients were investigated with the help of FT-IR spectrophotometer (IR- Prestige-21 Shimatzu, Japan). Test samples were placed in the side KBr discs (with a ratio of 1: 100 of test sample within KBr was maintained) and compressed at applied hydrostatic pressure of 5.2 N/m^2 for about 180 seconds. The range of scanning was between 400-4000 cm^{-1}. For both pure drug and excipient mixture, spectra were generated.

Differential Scanning Calorimetry (DSC)

A differential scanning calorimetry was performed to find out the thermal behaviour of the pure drug and drug-excipient mixture. Approximately 5 mg of sample was placed inside an aluminium pan with perforations (50 µm). A temperature range of 5 to 300 ^{0}C, at a rate of 10 ^{0}C per minute was applied to the samples present inside a nitrogen atmosphere (used as purging gas with 25 mL per minute of flow rate) [16].

Preparation of fast dissolving tablets of Diclofenac sodium using direct compression technique

Direct compression is used to define the process by which tablets are compressed directly from the powder blends of active ingredients and suitable excipients. No pre-treatment of the powder blends by wet or dry granulation is involved. Direct compression technique does not require the use of water or heat during the formulation procedure and is the ideal method for moisture and heat-labile medications. This is a process of compressing mixed powders into tablets without the need of intermediate granulating step. This technique involves conventional equipment, commonly available excipients and a limited number of processing steps. High doses can also be accommodated and the final weight of tablet can easily exceed than that of other production methods.

Fast dissolving tablets of Diclofenac sodium were prepared by Direct Compression Method. All the ingredients were passed through #60mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 200mg by using 10-station Rotary mini press tablet machine [17, 18].

Table 4: FORMULATION CODE

S.NO	INGREDIENTS (mg/tablet)	FORMULATION CODE									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Diclofenac sodium	50	50	50	50	50	50	50	50	50	50
2	Lactose	126	122	121	120	122	121	120	122	121	120
3	Micro Crystalline Cellulose	12	12	12	12	12	12	12	12	12	12
4	PEG 4000	5	5	5	5	5	5	5	5	5	5
5	Sodium starch glycolate	-	4	5	6	-	-	-	-	-	-
6	Crospovidone	-	-	-	-	-	-	-	4	5	6
7	Croscarmellose sodium	-	-	-	-	4	5	6	-	-	-
8	Magnesium stearate	3	3	3	3	3	3	3	3	3	3
9	Talc	4	4	4	4	4	4	4	4	4	4
10	Total weight	200	200	200	200	200	200	200	200	200	200

RESULTS AND DISCUSSION

Diclofenac fast dissolving tablets were prepared by direct compression method. Sodium starch glycolate, crosscarmellose sodium and crospovidone were used as superdisintegrants which help in rapid breakdown and fast drug dissolution.

UV Spectroscopy:
The drug sample when subjected to UV spectrophotometric analysis, showed absorption maxima (λ_{max}) at a wavelength of 275nm. The obtained peak was as per the reference values in literature.

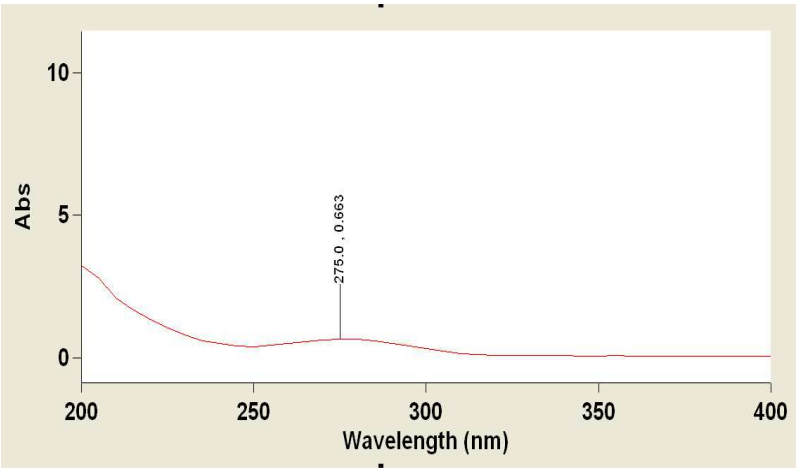

Fig. 2: UV Spectra of diclofenac sodium

PRE-COMPRESSION EVALUATION
FTIR spectroscopy
FTIR analysis of pure drug, crospovidone and optimized formulation (F10) containing diclofenac sodium and crospovidone were obtained. IR spectra of Diclofenac sodium exhibited a characteristic peak at 3384.80 cm^{-1} due to NH stretching of the secondary amine, 1575.75 cm^{-1} owing to –C=O stretching of the carboxyl ion and at 747.66 cm^{-1} because of C-Cl stretching. Infrared spectra of optimized formulation showed the characteristic peaks of the pure drug diclofenac sodium. From the above interpretation, it was found that there is no shifting in the frequencies of above said functional groups. Hence no interaction between drug and excipients was found.

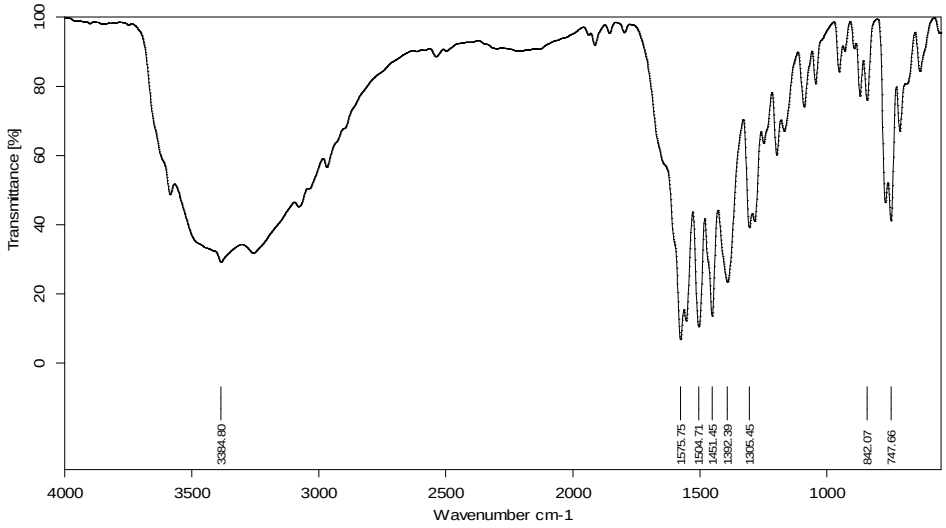

Fig. 3: FTIR spectra of Diclofenac sodium

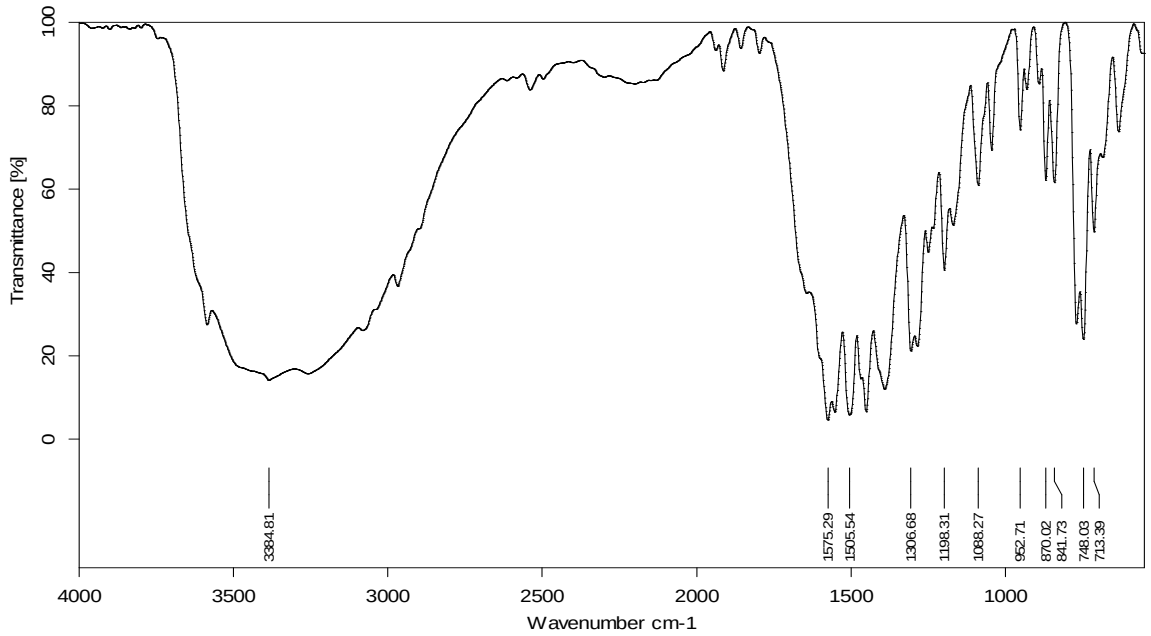

Fig. 4: FTIR spectra of F10 mixture

Differential Scanning Calorimetry

The DSC thermogram of the drug depicts a sharp endothermic peak at 281.28°C corresponding to the melting transition temperature of Diclofenac sodium. DSC thermogram of the optimized tablet formulation showed peak at 281.78ºC. This shows that there is no interaction between the drug and excipients and hence they are compatible.

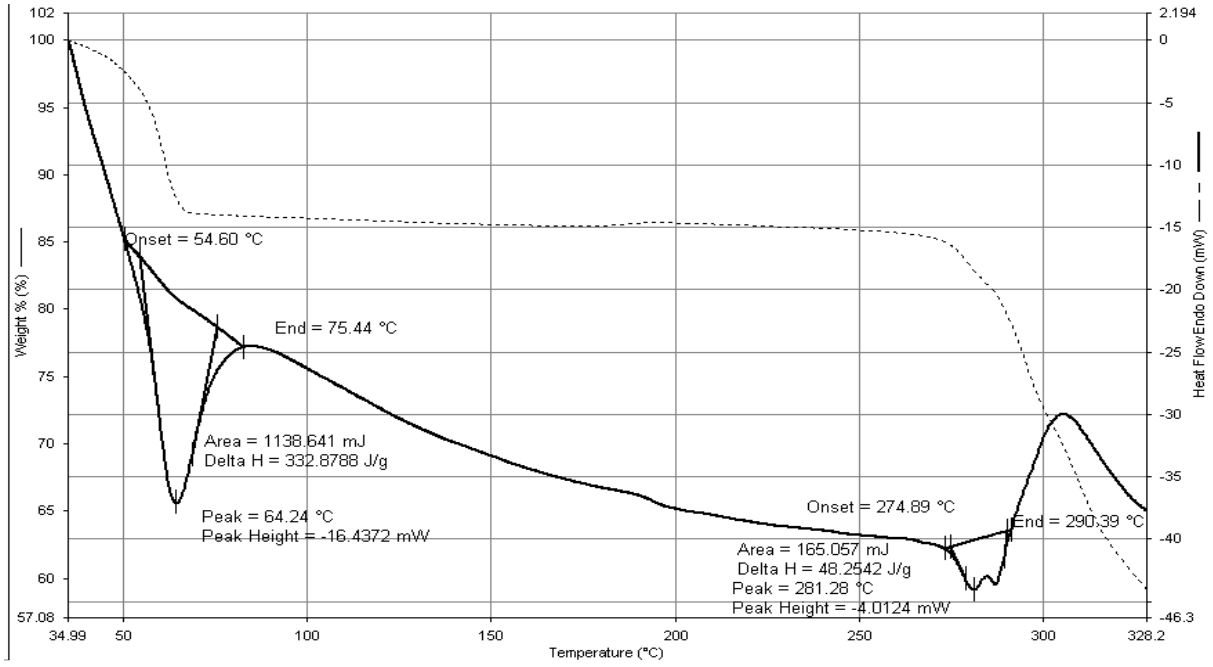

Fig. 5: DSC thermogram of Diclofenac sodium

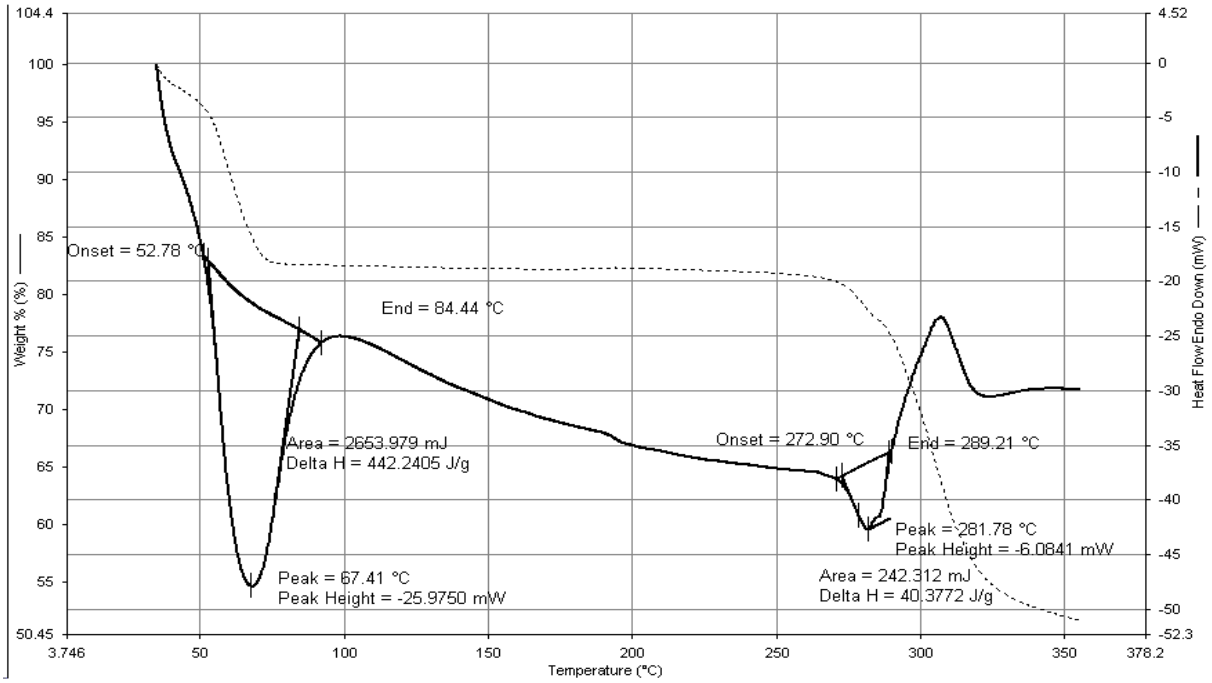

Fig. 6: DSC thermogram of F10 mixture

Micromeretics study

The angle of repose of the formulation blend was in the range of 21.65º-30.45º, which indicates good flow properties of the different blends. The Carr's index, Hausner's ratios were found to be in the range of 11.76-18.45 and 1.16-1.27 indicating good compressibility.

Table 5: Evaluation of pre-compression parameters

Formulations	Angle of repose (Mean±SD)	Bulk density (g/cc) (Mean±SD)	Tapped density (g/cc) (Mean±SD)	Carr's Compressibility index	Hausner's ratio
F1	30.45±0.54	0.55±0.02	0.73±0.05	18.45	1.22
F2	26.43±1.32	0.37±0.04	0.56±0.43	15.43	1.17
F3	24.73±1.04	0.48±0.13	0.52±0.08	14.87	1.12
F4	21.65±1.52	0.42±0.04	0.64±0.14	11.76	1.14
F5	27.32±1.33	0.46±0.14	0.53±0.02	12.01	1.14
F6	26.24±0.67	0.41±0.01	0.64±0.18	13.79	1.19
F7	27.44±0.68	0.44±0.24	0.57±0.09	14.65	1.21
F8	28.62±0.76	0.48±0.16	0.62±0.05	16.44	1.16
F9	26.65±0.42	0.42±0.03	0.62±0.06	13.54	1.27
F10	26.72±0.84	0.44±0.04	0.55±0.06	11.86	1.23

Weight variation

All tablets from each formulation passed weight variation test, as the % weight variation was within the pharmacopeia limits.

Friability

The friability of the formulations was found to be between 0.33-0.75 % and was within the official requirement (i.e. less than 1%).

Hardness

The hardness was maintained to be within 2.8-3.2 kg/cm2, no variation in the hardness was found which clearly indicates that the blending was uniform.

Table 6: Evaluation of post compression parameters

Formulation Code	Hardness (Kg/cm^2) (Mean±SD)	Friability (%) (Mean±SD)	Weight Variation (mg) (Mean±SD)
F1	3.2±0.24	0.745±0.31	199.6±0.07
F2	2.9±0.11	0.547±0.36	199.2±0.13
F3	3.2±0.15	0.33±0.27	197.6±0.08
F4	2.0±0.04	0.543±0.11	198.4±0.17
F5	2.8±0.17	0.537±0.19	198.2±0.16
F6	2.8±0.03	0.365±0.24	199.5±0.05
F7	2.9±0.03	0.475±0.32	199.5±0.14
F8	2.9±0.08	0.753±0.31	198.6±0.06
F9	2.8±0.21	0.397±0.28	197.2±0.02
F10	2.8±0.06	0.698±0.42	198.7±0.08

Wetting time

The wetting time for all formulations within the range of 14.6- 26.6 seconds. The formulation containing 6 mg of crospovidone (F10) showed lesser wetting time of 14.6 seconds when compared to other formulations.

***In vitro* dispersion time**

The values of the formulations were found to be within the range of 31.2 seconds to 52.6 seconds. The formulation containing 6mg of crospovidone (F10) showed a faster dispersion time of 31.2 seconds when compared with other formulations.

***In vitro* disintegration time**

In vitro disintegration time for all the formulations varied from 23.6-39.3 seconds. The formulation F10 showed better disintegration time of 23.6 seconds.

Table 7: Evaluation of parameters

Formulation Code	Wetting time (sec)	Water absorption ratio	*In vitro* dispersion time (sec)	*In vitro* disintegration time (sec)
F1	72.7	20	31min	20min
F2	24.4	25	45.4	39.3
F3	25.6	26.5	42.7	34.6
F4	23.4	25	36.5	26.8
F5	26.6	24.5	52.6	30.5
F6	24.2	23	44.3	32.4
F7	19.7	23	36.3	26.4
F8	22.4	24.5	38.4	28.4
F9	20.4	27	35.8	25.3
F10	14.6	29.5	31.2	23.6

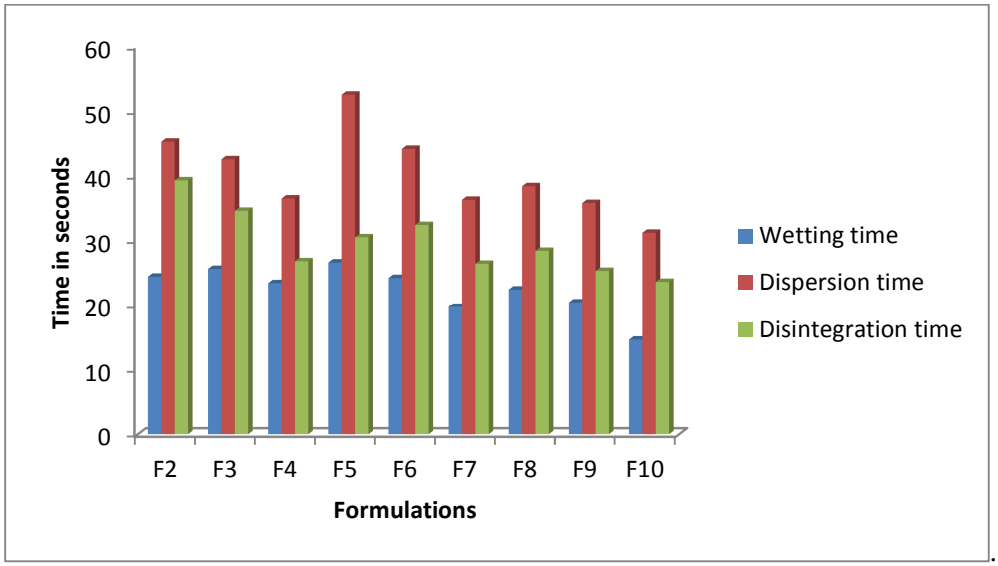

Fig. 7: Wetting time, *in vitro* dispersion time and *in vitro* disintegration time of the formulations

***In vitro* dissolution study**

These fast dissolving tablets are designed to disintegrate in oral cavity and to improve the bioavailability. Remarkable differences in the dissolution profile of different batches were observed. These results indicate that superdisintegrant process used to prepare the oro-dispersible tablets enhanced the rate and extent of dissolution of diclofenac. Control batch was able to give only about 36.74% of drug release within 20minutes. From the *In vitro* dissolution data, it was found that as the concentration of superdisintegrants increased, the drug release also increased. Among the different batches of formulations F10 showed highest dissolution rate where around 97.77% of the label dose was dissolved within 20 minutes.

Table 8: *In vitro* drug release profile of Diclofenac sodium fast dissolving tablets

S.No	Time in min	Formulation Code (% drug release)									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	2	7.77	13.47	14.80	20.78	7.23	11.75	18.39	12.75	23.87	31.24
2	4	10.23	19.54	21.05	26.63	10.16	17.00	23.51	16.73	26.91	45.97
3	6	13.52	26.52	25.43	31.35	13.54	22.18	27.36	22.84	30.84	52.27
4	8	16.00	27.94	31.68	34.53	18.13	26.23	33.47	24.96	34.42	58.78
5	10	19.53	32.04	34.53	37.52	22.05	31.81	37.39	31.74	37.61	65.29
6	12	21.82	34.84	36.82	40.58	25.77	40.56	38.65	36.22	41.06	72.86
7	14	24.64	36.85	41.79	48.75	28.95	42.11	44.16	46.74	53.37	80.43
8	16	27.62	39.64	44.76	58.71	32.66	47.62	56.63	47.43	62.07	84.81
9	18	31.05	41.85	49.21	67.44	43.65	57.63	74.80	52.77	70.51	90.66
10	20	36.74	48.86	52.65	79.92	51.86	61.15	86.21	64.54	84.65	97.77

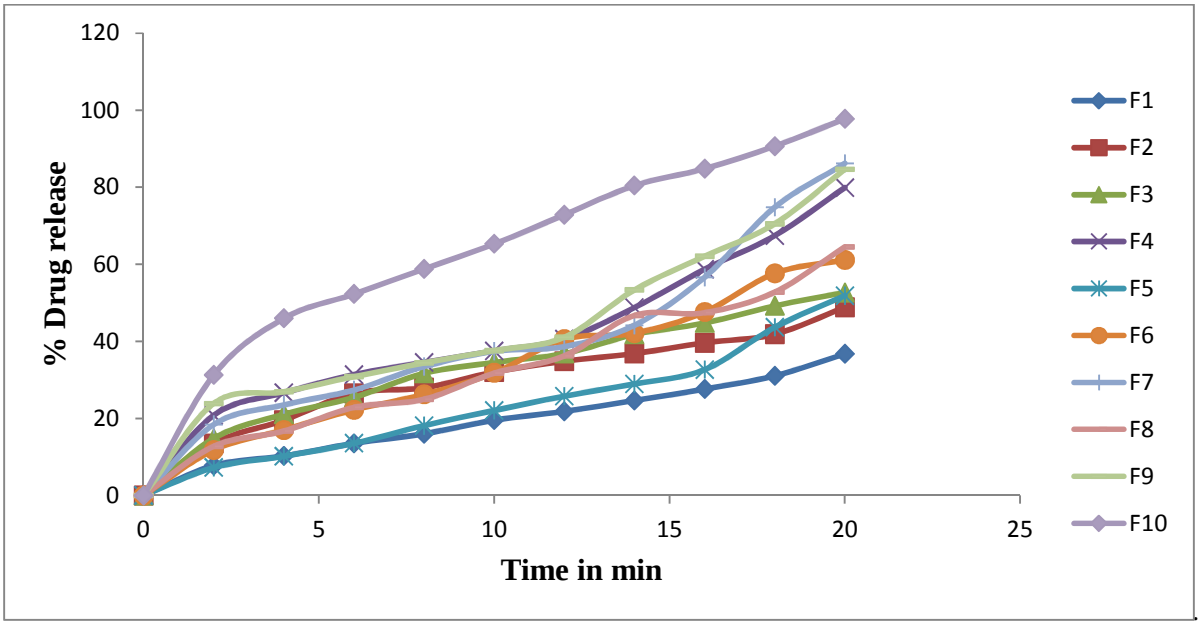

Fig.8: Dissolution rate profiles of different batches of formulation

CONCLUSION

Diclofenac sodium is widely used Non Steroidal Anti-inflammatory drug for rheumatoid arthritis, inflammation and pain relief. Fast dissolving tablets of diclofenac sodium are a useful approach for pain management and a feasible alternative to the available conventional immediate release dosage form. From the results, optimized F10 formulation showed improved drug release characteristics.

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