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FORMULATION AND EVALUATION OF DISPERSIBLE TABLETS OF DICLOFENAC SODIUM

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ABSTRACT

The objective of this research was to develop dispersible tablets of Diclofenac sodium in order to attain the instantaneous pregastric release of the drug in upper gastrointestinal tract which resulted enhanced bioavailability of drug bypassing the first pass metabolism.

Nine batches of dispersible tablets of Diclofenac sodium was prepared by adopting superdisintegrant addition method. The superdisintegrants used in the study were crospovidone, croscarmellose sodium and sodium starch glycolate with other excipients such as microcrystalline cellulose & mannitol as diluents, sucralose as sweetening agent, clove oil as flavoring & mild local anesthetic agent and talc & magnesium stearate as glidant and lubricant respectively. Each batch consisted of varying concentrations (3%-7%) of individual superdisintegrant incorporated in the formulation process.

Various pre-compression physicochemical parameters of formulation blends were analyzed and obtained results were: angle of repose (23.5-30.1), bulk density (0.49-0.53 gm/ml), tapped density (0.59-0.65 gm/ml) and compressibility index (15.25%-20.6%).

The prepared tablets were evaluated for various post-compression parameters and results depicted weight variation (193.68-204.1 mg), friability (0.58-0.71 %), hardness (2.5-3.5 kg/cm^2), in-vitro disintegration time (17 to 42 seconds) and percent drug content (98.77-100.6). In-vitro release study of each formulation was carried out on dissolution apparatus (TDT 06L, Electro lab) in pH 7.2 phosphate buffer solution which gave the amounts of drug released as ranging 97.3%-99.7% while in simulated salivary fluid it ranged 97.4%-99.9%. The best drug release profile was seen with formulation F_3 (containing 7% crospovidone) in pH 7.2 phosphate buffer solution and simulated salivary fluid 99.7% & 99.9% respectively. Results of accelerated stability testing revealed no physical and chemical changes in the tablets during 3 months study.

INTRODUCTION

Dispersible tablets offer advantage for patients who have difficulty in swallowing. It has been reported that disphagia is common among all age groups of patients but is more specific to pediatrics, geriatrics along with institutionalized patients and patients with nausea, vomiting and motion sickness complications. Dispersible tablets with good taste and flavour increase the acceptability of bitter drugs by various groups of population. Although chewable tablets have been on the market for some time, they are not the same as the new dispersible tablets. Patients for whom chewing is difficult or painful can use these new tablets easily. Dispersible tablets can be used easily for pediatric patients who have lost their primary teeth but do not have full use of their permanent teeth. The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing.

MATERALS AND METHODS:

Material: All the chemicals used in this work were procured from industry of repute. The drug Diclofenac sodium was procured by the institute itself.

Methods:

Preparation of standard stock solution (stock-1):

10 mg of Diclofenac sodium was dissolved in 100 ml pH 7.2 phosphate buffer to prepare (100µg /ml) stock solution.

Estimation of λmax:

The sample solution (100µg /ml) was scanned at the range of 200-400 nm to access the λmax value for Diclofenac sodium which was reported and confirmed by obtaining the overlain UV spectra of the drug with different concentrations between 4-12 µg/ml. The standard calibration curve was obtained with the samples of same concentrations as opted in the process.

Preparation of Aliquots:

From the stock solution (stock I), serial dilutions were prepared (4-12 µg/ml) and the absorbances were estimated at 276 nm. The standard curve was obtained by plotting absorbance v/s concentration (µg/ml).

Preparation of Standard Calibration Curve in simulated salivary fluid:

Preparation of Simulated Salivary Fluid:

To prepare simulated salivary fluid, a 5 % mucin solution was first prepared by adding 200 ml of deionized water to 10 g. of mucin and stirring the mixture until dissolved completely. Then following ingredients ($NaNO_2$, $MgCl_2$, $CaCl_2.2H_2O$, NaCl, KH_2PO_4, K_2HPO_4, KCl, $NaHCO_3$, Thimerosol, Amylase and Antipain 50µg/ml) were mixed, in the order, in about 800 ml of deionized water with slow stirring.

This was added to the mucin solution with continuous stirring until complete dissolution occurred. The final volume was adjusted with deionized water to 1000 ml.

The solution was filtered once through 0.45 µm (commercially available micropore) and then passed through 0.2 µm micropore filters. Due to

the viscous nature of the solution, filters became clogged so it was necessary to change filters oftenly.

A 25 ml of sample solution was pipetted out and pH (6.5± 0.2) was determined.

Preparation of standard stock solution (stock-2):

10 mg of Diclofenac sodium was dissolved in 100 ml (including adjustment of final volume) simulated salivary fluid to prepare (100 µg/ml) stock solution.

DRUG-EXCIPIENT COMPATIBILITY STUDY:

Compatibility study using FTIR technique:

Drug-excipient interaction study was carried out by FTIR (Shimadzu, Affinity-1) spectrophotometry. The mixture of drug and KBr (potassium bromide) was ground in to fine powder using mortar pestle and then compressed into discs in a hydraulic press at a pressure of 75 kg/cm^2. Each KBr disc was scanned 45 times at a resolution of 2 cm^{-1}. The characteristic peaks were recorded and compared with that obtained with individual formulation.

Thin layer chromatographic method:

The drug-excipient compatibility was also studied by densiometric TLC evaluation using UV spectrophotometer at 254 nm wavelength. The spots of drug and different excipients were obtained on pre-coated (silica gel F_{254}) plates using ammonia: methanol: ethyl acetate: methylene chloride in the ratio 2:40:50:90 (v/v) as mobile phase.

FORMULATION DESIGN

The dispersible tablet formulations of Diclofenac sodium were divided in to nine batches prepared with clove oil (mild local anesthetic agent), sucralose (burst sweetener) and different concentrations of three superdisintegrants as depicted in the table below:

Table 1 Formulation composition chart for DTs of Diclofenac sodium.

S. N.	INGREDIENTS	QUANTITY (in mg)								
		F_1	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**
1.	Diclofenac sodium	50	**50**	**50**	**50**	**50**	**50**	**50**	**50**	**50**
2.	Crospovidone	7.5	12.5	17.5	-	-	-	-	-	-
3.	Croscarmellose sodium	-	-	-	7.5	12.5	17.5	-	-	-
4.	Sodium starch glycolate	-	-	-	-	-	-	7.5	12.5	17.5
5.	Sucralose	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
6.	Clove oil	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
7.	Talc	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
8.	Magnesium stearate	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
9.	Mannitol	89	84	79	89	84	79	89	84	79
10.	MCC	86	86	86	86	86	86	86	86	86
	Total	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Preparation of formulation blend:

- All the ingredients were sifted individually through sieve no. 40 to ensure the absence of any unwanted particulate matter and to break up the lumps, if present, for the ease of mixing and to ensure the proper flow.
- All the sifted ingredients were then weighed individually for each batch using electronic weighing balance.
- The weighed ingredients were then transferred to a laboratory mixer in a sequential manner. First the drug was mixed with the bulking agent i.e. 1/2 portion each of mannitol and MCC to ensure the uniformity of active medicament throughout the blend and then other excipients were added.
  Talc and magnesium stearate were added few minutes before the start of compression.

Pre-compression evaluation of formulation blend:

The prepared formulation blend was evaluated for angle of repose, bulk density, tapped density, percent compressibility and flowability.

Angle of repose:

The frictional forces in a loose powder can be measured by the angle of repose, 'θ' regarded as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

$$tan\ \theta = \frac{h}{r}$$

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

True density:

The true density of a substance is the average mass of the particles divided by the solid volume, exclusive of all the voids that are not a fundamental part of the molecular packing arrangement. The true density (ρ) was calculated using the following equation:

$$\rho = \frac{w}{V}$$

where, 'w' is the weight of the sample and 'V' is the powder volume.

Bulk density:

It is the ratio of total mass to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml given by

$$D_b = \frac{M}{V_o}$$

Tapped density:

It is the ratio of total mass to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume and expressed in gm/ml.

$$Dt = \frac{M}{V_t}$$

Carr's index (compressibility index):

It indicated the ease with which a material could be induced to flow and expressed in percentage as given by

$$I = \frac{D_{t-D_b}}{D_t} \times 100$$

Hausner's ratio:

Hausners ratio is closely related to C.I and it was calculated using the following equation:

$$C.I = \frac{D_b}{D_t}$$

where, D_b and D_t were bulk and tapped density respectively.

PREPARATION AND EVALUATION OF THE DT's:

The oral dispersible tablets of Diclofenac sodium were prepared by compressing the powdered formulation blend by direct compression method using single punch hand operated tablet punching machine. The prepared tablets were then evaluated for the following post-compression parameters:

Tablet weight variation:

From each batch 20 tablets were randomly selected and their average weight was calculated. The individual weight of each tablet was compared with the average weight of 20 tablets. The tablets were said to pass the weight variation test if they complied with the weight variation specifications as per I.P.

Tablet thickness:

The crown thickness of individual tablet was measured with a digital vernier calipers. Tablet thickness should be controlled within a ±5 % variation of the standard value of predetermined thickness.

Hardness:

The hardness of the tablet was measured using the Monsanto hardness tester. Tablet was placed between two anvils and force (kg/cm^2) was applied, the crushing strength that just causes the tablet to break was recorded.

Friability:

The friability of the tablets was measured using the laboratory friability apparatus known as Roche friabilator. A preweighed sample of tablets was placed in the friabilator and operated for 100 revolutions at the rate of 25rpm. The tablets were dusted, reweighed and the percent friability was calculated using the following formulae:

$$F = \frac{W_{initial} - W_{final}}{W_{inital}} \, x \, 100$$

where, W_{final} = final weight of tablets after 100 rotations and $W_{initial}$ = initial weight of tablets.

The acceptance value for the tablets to pass friability is not more than 1%.

In-vitro dispersion time:

Tablet was added to 10 ml Phosphate buffer solution, pH 7.2 at 37± 2ºC. Time required for complete dispersion of a tablet was measured.

Drug content uniformity:

Ten tablets from each formulation of DT's were powdered finely. An amount equivalent to 50mg of Diclofenac sodium was weighed and dissolved in pH6.8 phosphate buffer in 100 ml volumetric flasks. The solution was filtered and diluted appropriately and analyzed spectrophotometrically at 276nm using pH6.8 buffer as blank.

Wetting time and water absorption ratio:

A double folded piece of tissue paper was placed in a petridish (internal diameter is 6.5 cm) containing 10ml of water maintained at 37ºC. A tablet was placed on the paper and the

time for complete wetting of the tablet was measured in seconds.

Water absorption ratio (R) was determined using following equation:

$$R = 10 \times \frac{W_a}{W_b}$$

where, W_b and W_a are the weight of tablet before & after water absorption respectively.

In vitro dissolution study:

In vitro dissolution study was performed using USP type II apparatus (paddle type) at 50 rpm using pH 7.2 phosphate buffer and simulated salivary fluid as dissolution media maintained at temperature of 37± 0.5 ºC. Aliquots of dissolution media were withdrawn at specific time intervals replacing with fresh media and filtered. The amount of drug dissolved was determined by U.V spectrophotometric analysis of withdrawn sample at 276 nm. The experiments were conducted in triplicate.

Stability study:

The optimized formulation was packed suitably and kept in stability chamber at accelerated conditions (40°C ± 2 °C/ 75%±5% RH) for a period of three months. The samples were analyzed at 30, 60 and 90 days for different physicochemical parameters and in-vitro drug release.

RESULTS & DISCUSSION

Spectrophotometric scan of Diclofenac Sodium:

The stock solution (10µg/ml) of Diclofenac Sodium was prepared by dissolving 10mg of diclofenac Sodium in 100 ml of pH 7.2 phosphate buffer and a particular sample containing a definite concentration (10µg/ml) was scanned between 200-400 nm.

Serial dilutions were made from the stock solution and an overlain spectrum was obtained which confirmed λ_{max} of 276 nm and validated the process.

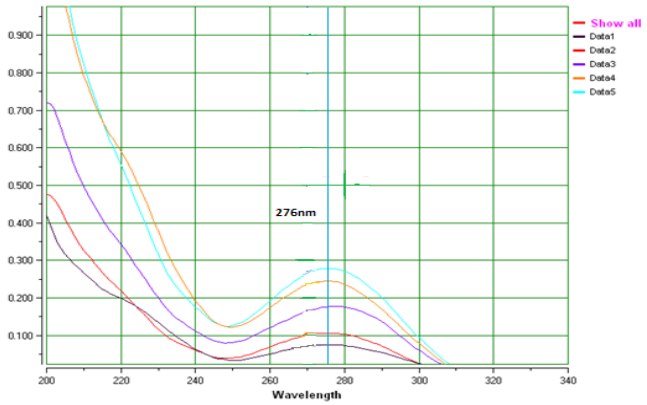

Figure no. 1: Overlain spectra of diclofenac Sodium.

Preparation of calibration curve in simulated salivary fluid:

Various samples with different concentrations were loaded on the UV spectrophotometer and respective absorbances were obtained at 276nm. A graph was plotted (concentration Vs Absorbance) which resulted a straight line concluding that the drug followed Beer Lambert's Law at the concentration range of 5-25µg/ml.

The regression analysis was carried out on these experimental data & Y and r^2 values were calculated. The obtained values were Y= 0.029x & r^2= 0.999 in simulated salivary fluid.

Table no. 2 Concentration Vs Absorbance data of Diclofenac Sodium in pH 7.2 phosphate buffer.

Sr. no.	Concentration (mcg/ml)	Absorbance in buffer	Absorbance in SSF
1	5	0.125	0.127
2	10	0.225	0.235
3	15	0.355	0.365
4	20	0.481	0.498
5	25	0.593	0.627

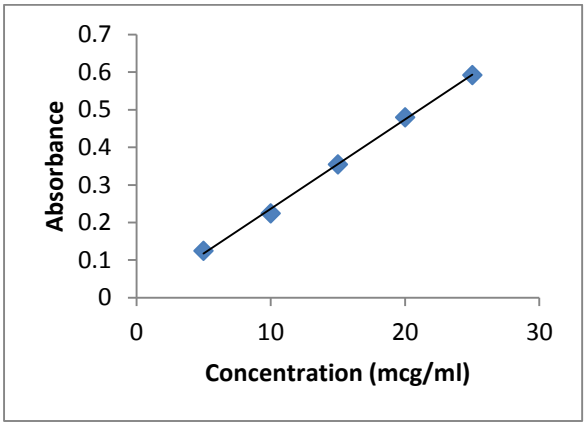

Figure no. 2: Standard calibration curve of Diclofenac Sodium in pH 7.2 phosphate buffer.

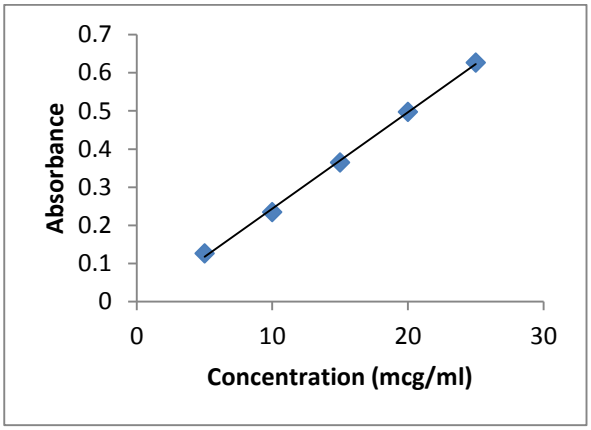

Figure no 3.Standard calibration curve of Diclofenac Sodium in simulated salivary fluid.

COMPATIBILITY STUDIES:

FTIR ANALYSIS:

FTIR spectra of Diclofenac Sodium (pure drug):

The IR absorption spectra of Diclofenac Sodium were obtained using KBR pellet technique and characteristic peaks obtained were recorded. The IR spectra of Diclofenac Sodium exhibited distinctive peaks at 3259.84 cm^{-1} due to NH stretching of the secondary amine, 1587.48 cm^{-1} owing to –C = O stretching of the carboxyl ion and at 746.48 cm^{-1} because of C-Cl stretching.

FTIR spectra of formulation:

Drug polymer compatibility was studied by obtaining FTIR spectra of different formulations and detecting the characteristic peaks. The retention of such peaks of the pure drug in formulations confirmed that it was compatible with all excipients incorporated therein.

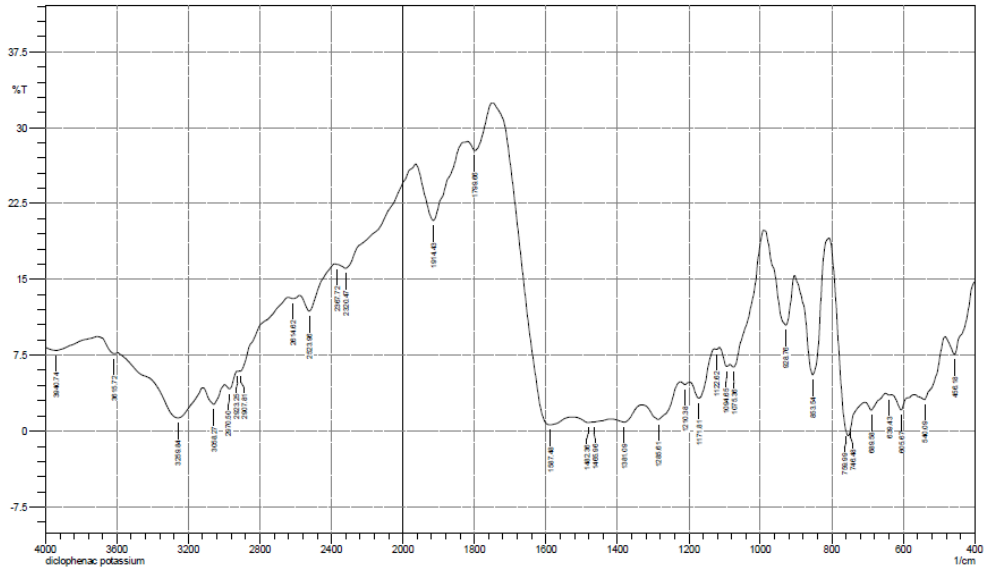

Figure no. 4: FTIR Spectra of Pure drug

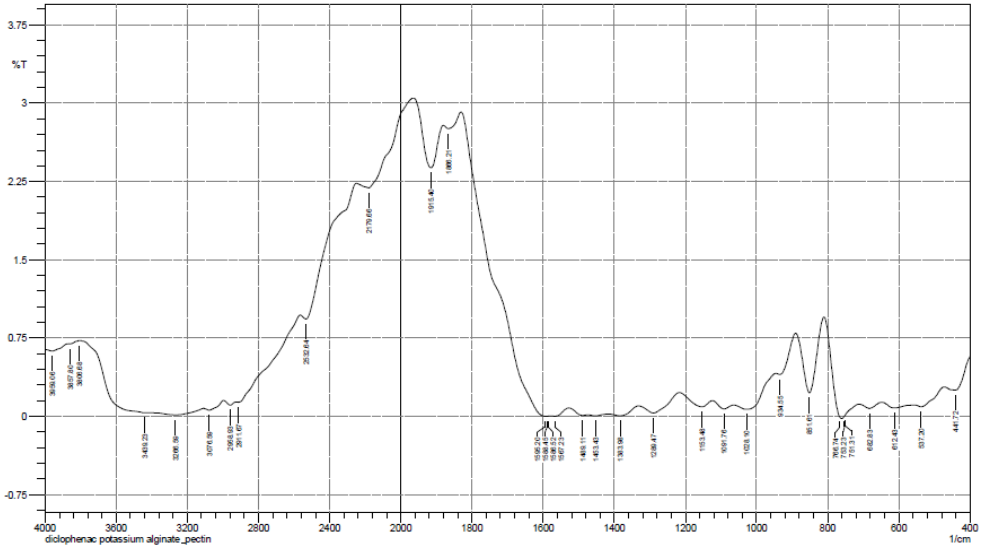

Figure no. 5: FTIR of Formulation

Thin Layer Chromatography (TLC) method:

The R_f value of Diclofenac sodium (in batches F_1-F_9) was 0.85 (similar with pure drug) thus confirmed compatibility between drug and excipients used.

EVALUATION PARAMETERS:

Pre-compression parameters:

Pre-compression parameters like bulk density, tapped density, carr's index and angle of repose for samples of formulation blend (F_1-F_9) were determined and found in the range of 0.49-0.53

gm/ml, 0.59-0.65 gm/ml, 15.25-20.60 % & 23.5-30.1 respectively.

Table 3 Results of pre-compression parameters.

S. No.	Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Angle of repose (θ)
1.	F_1	0.50	0.63	20.60	30.1
2.	F_2	0.51	0.61	16.40	25.2
3.	F_3	0.53	0.65	18.46	28.1
4.	F_4	0.50	0.59	15.25	23.5
5.	F_5	0.49	0.60	18.33	28.6
6.	F_6	0.52	0.62	16.12	25.0
7.	F_7	0.53	0.64	17.18	27.7
8.	F_8	0.50	0.61	18.03	28.9
9.	F_9	0.52	0.63	17.46	26.8

Post-compression parameters:

The samples from each batch of tablet formulation were evaluated for post compression parameters such as weight variation, thickness, hardness, friability, wetting time, In-vitro disintegration time & percent drug content. The results inferred weight-variation, thickness, hardness, friability, wetting time, disintegration time & percent drug content in the range of 193.68-204.1 mg, 2.18-2.25 mm, 2.5-3.5 kg/cm^2, 0.58-0.71%, 13-30 seconds, 17-42 seconds & 98.77-100.6% respectively.

Table 4 Results of post-compression parameters for batches F_1-F_3.

S. No.	Post-compression parameters	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
1.	Weight variation (mg)	198.6 ±2.48%	199 ±2.45%	200.1 ±2.0%	198.5 ±2.23%	199.6 ±2.01%	198.5 ±1.75%	199.5 ±1.5%	199.8 ±2.23%	199 ±2.45%
2.	Thickness (mm)	2.25	2.23	2.20	2.18	2.19	2.20	2.22	2.21	2.20
3.	Hardness (kg/cm^2)	2.5	3.0	3.0	2.5	2.5	3.0	3.5	2.5	3.0
4.	Friability (%)	0 .63	0.65	0.65	0.71	0.68	0.66	0 .62	0.58	0.60
5.	Wetting time (seconds)	19	17	13	22	19	15	30	26	18
6.	In-vitro disintegration time (seconds)	30	23	17	35	30	23	42	35	29
7.	Percent drug content (%)	99.43	100.31	98.91	98.77	100.5	100.6	99.10	98.8	99.5

Table 5 Comparative release kinetic data of formulations F_1-F_9 in pH 7.2 phosphate buffer:

S. no.	Time (min.)	% Drug Release								
		F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
1.	1	37.7	41.3	45.0	34.0	37.0	40.0	31.1	33.7	38.0
2.	3	50.5	55.5	59.1	48.5	52.5	56.8	45.5	48.1	54.4
3.	5	67.6	71.3	74.3	65.0	68.6	72.6	62.0	64.9	69.0
4.	10	81.6	85.3	87.0	80.2	83.2	86.0	79.8	81.5	84.2
5.	15	95.3	94.7	97.4	92.2	96.0	96.7	92.8	93.9	96.0
6.	30	97.5	98.5	99.7	97.7	98.1	98.8	97.3	98.0	98.1

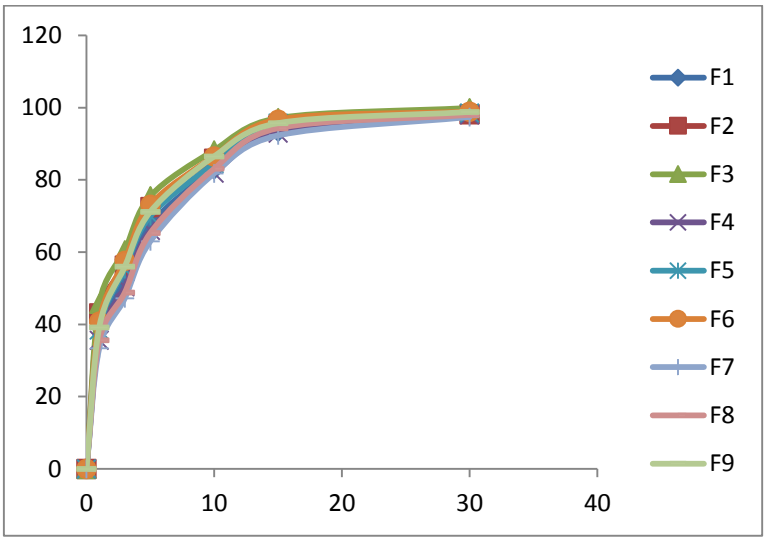

Fig. 6 Comparative release profile of formulations F_1-F_9.

Table 6 Comparative release kinetic data of formulations F_1- F_9 in simulated salivary fluid.

S. no.	Time (min.)	% Drug Release								
		F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
1.	1	39.5	43.1	45.7	35.6	38.5	40.8	33.4	35.6	39.2
2.	3	52.4	56.3	60.5	50.4	55.3	57.6	47.2	48.8	56.0
3.	5	67.6	72.5	75.5	66.0	70.0	73.1	63.0	65.3	71.2
4.	10	82.9	85.9	88.2	81.9	84.5	86.5	81.8	83.1	86.5
5.	15	93.4	95.1	97.1	93.0	95.7	96.7	92.3	94.3	95.7
6.	30	98.1	98.2	99.9	98.0	98.5	98.9	97.4	98.0	98.8

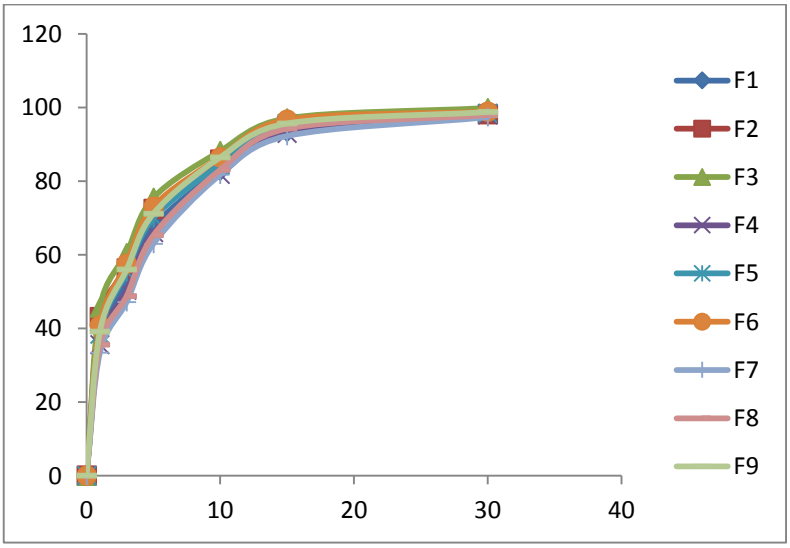

Fig. 7 Comparative release profile of formulations F_1-F_9.

The comparative study of formulations F_1-F_9 showed that F_3 gave the best result as compared to others and hence formulation F_3 was considered as best batch of dispersible tablet and selected for stability studies.

STABILITY STUDY OF OPTIMIZED FORMULATION F_3:

The stability studies were performed on prepared formulations as per ICH guidelines at accelerated condition (40°C ± 2 °C/ 75%±5% RH) which showed that the formulations suffered no physical changes also there was no significant reduction in drug contents.

Table 7 Observations of parameters for stability studies at accelerated conditions (40°C ± 2 °C/ 75%±5% RH).

PARAMETERS	TIME			
	0 Days	30 Days	60 Days	90 Days
Appearance	No change	No change	No change	No change
Average weight (mg)	201	201	203	203
Hardness (Kg/cm^2)	3.0	3.0	2.8	2.5
Disintegration time (seconds)	17	18	15	15
Percent friability	0.65	0.65	0.66	0.70
Percent drug release	99.8	99.3	98.7	98.0

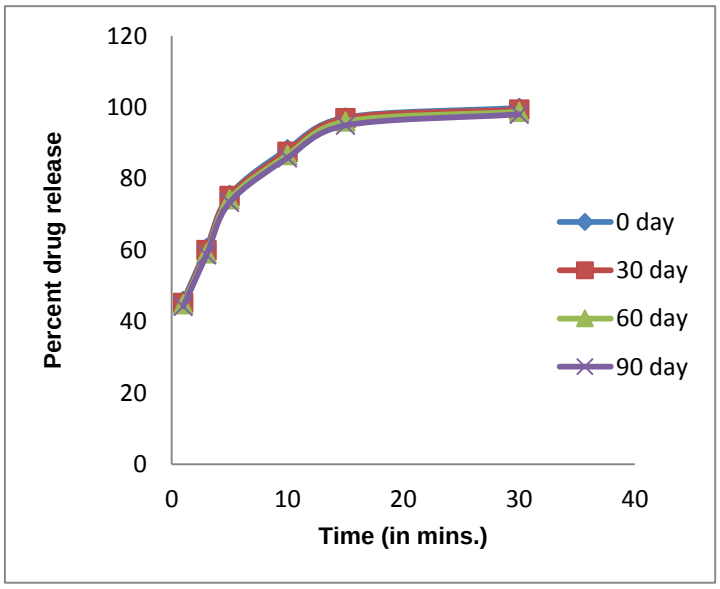

Fig. 8 Comparative release profile of formulation F3 at different time intervals (0, 30, 60 and 90 days) on stability.

CONCLUSION

The present worker conceptualized "The formulation and evaluation of dispersible tablets of Diclofenac sodium" Three batches **(F_1-F_3)** of dispersible tablet using Cross Carmellose Sodium **(3%, 5% & 7%w/w** respectively) and three batches **(F_4-F_6)** using crospovidone **(3%, 5% & 7%w/w** respectively**)** and last three batches **(F_7-F_9)** using sodium starch glycolate **(3%, 5% &**

7%w/w respectively**)** were produced by direct compression method. The formulations increased oral absorption and ultimately the bioavailability would increase.

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