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Research Article

Pharmaceutics for better Drug formulation

Formulation and *In Vitro* Evaluation of Fast Disintegrating Tablets of an Anti-Inflammatory Drug using Natural Super Disintegrating Agents

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Abstract: Fast disintegrating tablets are defined as solid dosage forms containing medicinal substances which disintegrate rapidly usuall within seconds when placed upon the tongue. The present work is concerned with the formulation and *in vitro* evaluation of fas disintegrating tablets of an inflammatory drug using natural super disintegrating agents like jackfruit seed powder and oats powder. The objective of this study was to develop the aceclofenac tablets with rapid disintegration employing natural super disintegrants and to enhance the patient compliance by providing rapid therapy in the inflammation conditions. Natural super disintegrants were employed in the study as they are devoid of toxic effects. The tablets were prepared by direct compression method. Ten formulations were developed with different concentrations (2%, 4%, 6%, 8%, 10%) of natural disintegrants like jackfruit seed powder and oats powder. FTIR and DSC studies showed no evidence of interaction of drugs with natural super disintegrating agents and other excipients. Precompression parameters were evaluated for all the formulations and were in the acceptance limits. The results of flow properties such as angle o repose, carr's index and hausners ratio ensured that all the formulations exhibited good flow. Post compression parameters like hardness friability, disintegration test and dissolution test were evaluated. Among all the formulations, tablets developed using jackfruit seed powder showed best results with respect to disintegration and drug release. The *in vitro* drug release profile shows that formulation F5 which contains jack fruit seed powder exhibited 98.7% of drug release at the end of 30 min and the disintegration time was found to be 3 seconds. The drug release from F5 formulation follows first order kinetics. F5 formulation is considered as the promising formulation which ensures the patient compliance by providing rapid disintegration.

Keywords: Aceclofenac, Fast disintegrating, Natural superdisintegrants, Jackfruit seed powder and Oats powder.

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1. INTRODUCTION

The oral delivery of drugs is considered the most accepted route for the administration of drugs because of the convenience of self-administration and patient compliance. Oral administration remains to be the suitable route for the administration of active pharmaceutical ingredients despite the numerous advancements in drug delivery.[1] However, the oral administration of drugs also has several drawbacks especially while administering the dosage forms such as tablets and capsules, which can lead to difficulty in swallowing and administration of unpalatable drugs which lead to patient noncompliance especially among pediatric and geriatric patients. This is also observed in people who are ill in bed or who are busy or travelling, especially those who have no access to drinking water.[2] Therefore, to improve patient compliance especially among pediatric and geriatric patients emphasis is given on the development of novel formulations .One such approach is development of fast disintegrating tablets(FDTs). These FDTs are synonymous with orally dispersible tablets (ODTs), fast and rapidly disintegrating tablets, rapid dissolve, fast melts, quick disintegrating, melt in mouth tablets, porous tablets, and freeze dried wafers.[3] When these formulations are placed in the mouth, saliva quickly penetrates in the pores to cause rapid tablet disintegration without any chewing by the patients. Aceclofenac, is a non-steroidal anti-inflammatory drug(NSAID) widely used in various painful indications.[4] Natural super disintegrants are devoid of side effects as they are obtained from the natural source and are mainly preferred by the patients as they are more safe and efficacious as compared to the synthetic super disintegrants and have more patient compliance.[5] In the present research an attempt was made to formulate the FDT of aceclofenac using natural super disintegrants like jackfruit seed powder(JFSP) and oats powder (OP) to provide rapid disintegration of the tablet and to afford therapy to the patients.

2. MATERIALS AND METHODS

Aceclofenac was received as a gift sample from Micro labs, Bangalore, India. Mannitol was purchased from Thermo fisher scientific India Pvt. limited Mumbai. saccharin sodium, magnesium stearate, talc from Loba chemie, Mumbai. Every one of the synthetic compounds utilized were of analytical grade.

2.1 FT-IR studies

Small amount of drugs and superdisintegrants (JSP, OP) were mixed with potassium bromide and separately made into small and thin pellets.[6] The pellets were analyzed using a Fourier transform infrared spectrophotometer and were scanned in the range of 4000cm^{-1} to400cm^{-1}.

2.2 DSC Analysis

A small amount of drugs and superdisintegrants were loaded into an aluminum pan, followed by crimping to seal the pan. The sample was analyzed using DSC instrument with heating rate of 10°C/min and nitrogen pure gas at a flow rate of 20ml/min.[7]

2.3 Analytical method development

2.3.1 Preparation of phosphate buffer 7.4

Dissolve 6.8g of potassium dihydrogen phosphate and 1.56g of sodium hydroxide in sufficient water to produce 1000ml.[8]

2.3.2 Preparation of standard stock solution

100 mg of aceclofenac pure drug was weighed and dissolved in 10 ml of methanol and then made up with phosphate buffer 7.4 up to mark in 100 ml volumetric flask (stock solution-1000µg/ml). From this 10 ml of solution was taken and adjusted to 100 ml with phosphate buffer 7.4(100µg/ml). The obtained solution was diluted serially to get the concentrations in the range of 2 to 10 µg/ml. The absorbance of above dilutions was measured at 215 nm by using UV-Spectroscopy using phosphate buffer 7.4 as blank solution.[9]

2.4 Extraction of starch from jackfruit seeds

About 5gm of JFSP was added to 0.1N NaOH and set aside for 6-8 hrs with constant stirring. Slurry was filtered through sieve no #212 and the remaining sediment was washed with distilled water for 3 times. The filtrates were collected and precipitated overnight at 4°C. Then supernatant was discarded and the crude starch was washed with distilled water.[10] This step was repeated 3 times and starch cake obtained was dried at 40°C for 24 hrs in a tray drier. Starch was ground with mortar pestle and obtained starch was packed in an airtight container at room temperature for further use.

2.5 Extraction of starch from oats powder

250 gm of oats powder was taken in a beaker with sufficient water to form thick suspension. Filter using strainer into 100ml beaker and kept aside for 1hr by addition of water. Supernatant was removed and starch was collected at the bottom and again filled with water.[11] Repeat the procedure for 4 to 5 times. Obtained starch was kept in a hot air oven at temperature 50°C and Packed in an airtight container.

2.6 Preparation of aceclofenac fast disintegrating tablets

FDTs containing aceclofenac were prepared by direct compression method using varying concentrations of natural Superdisintegrants like JFSP and OP with mannitol as diluent. Sodium saccharin was used as a sweetening agent. All the ingredients were weighed as per the batch formula mentioned in Table 1. The drug and excipients were initially passed through sieve no. 40. and were mixed with other ingredients homogeneously using mortar and pestle. The above mixture was lubricated with magnesium stearate and talc prior to the compression. The tablets were compressed by using Rimek tablet compression machine.[12]

Table 1. Composition of Aceclofenac Fast Disintegrating Tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Aceclofenac	100	100	100	100	100	100	100	100	100	100
Jackfruit seed powder	6	12	18	24	30	-	-	-	-	-

Oats powder	-	-	-	-	-	6	12	18	24	30
Mannitol	185	179	173	167	161	185	179	173	167	161
Saccharin sodium	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3
Total weight (mg)	300	300	300	300	300	300	300	300	300	300

2.7 Evaluation of precompression parameters

2.7.1 Bulk Density

t is the ratio of total mass of powder to the bulk volume. It was measured by pouring the weighted powder into a measuring cylinder and volume was noted.[13]

Bulk density = Mass of powder(w) / bulk volume

2.7.2 Tapped Density

It is the total mass powder to the tapped volume of powder. It was determined by placing a graduated cylinder, containing a known mass of drug excipient blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted.[14]
Tapped density = mass of powder / tapped volume.

2.7.3 Carr's consolidation index

Carr's index was used to show the relationship between the bulk density and tapped density of the powder, by using the above equation.[15]
Carr's index = Tapped density – Bulk density/Tapped density × 100

2.7.4 Angle of repose

It is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose is determined by the following formula.[16]

$$\text{Angle of repose } (\Theta) = \tan^{-1}(h/r)$$

h = Height of pile
r = Radius of base of pile

2.7.5 Hausner's ratio

It is the ratio of tapped density to the bulk density and can be calculated using the following equation.[17]
Hausner's ratio = Tapped density/Bulk density

2.8 Evaluation of post compression parameters

2.8.1 Hardness

Hardness of a tablet determines its crushing strength.[18] Monsanto hardness tester was used to measure the hardness of the tablets and is expressed as kg/cm^2.

2.8.2 Thickness

Thickness was measured by using Vernier calipers. Randomly tablets were taken and placed between the two upper jaws and thickness was measured.[19]

2.8.3 Uniformity of weight

20 tablets were selected at random and weighed individually and calculated the average weight and compared the individual weight to the average weight followed by estimation of percentage deviation.[20]

2.8.4 Drug content

10 tablets were selected randomly and were crushed in a mortar and from the blend accurately weighed an amount of tablet powder was taken and transferred to 100ml volumetric flask and diluted with phosphate buffer of pH 7.4. Then the solution was filtered using Whatman filter paper and absorbance was measured at 215nm and the drug content in each tablet was calculated.[21]

2.8.5 In vitro Disintegration test

The disintegration time was measured using disintegration test apparatus (Electrolab). One tablet was placed in each tube of the basket containing purified water as medium, maintained at 37±2°C. The time required for complete disintegration of the tablet was noted.[22]

2.8.6 Wetting time

For measurement of wetting time a piece of tissue paper folded twice was placed in a petri dish with a 10 cm diameter containing 6 mL of purified water. A previously weighed tablet was placed on the surface of the tissue paper and the time to wet the tablet completely was noted as the wetting time.[23]

2.8.7 Water absorption ratio

A piece of tissue paper folded twice was placed in a small petri dish containing 6ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighed. Water absorption ratio, R was determined using following equation.[24]

$$R = 100 \times (Wa - Wb)/Wa$$

Where, Wa = Weight of tablet after water absorption
Wb = Weight of tablet before water absorption.

2.8.8 In vitro dissolution studies

The *in vitro* dissolution studies were performed using USP paddle apparatus for 30 min at 50 rpm employing phosphate buffer of pH 7.4 as dissolution medium(900ml) and was maintained at 37±0.5°C. Samples of 5ml were withdrawn at predetermined intervals, filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitable diluted with dissolution fluid, where ever necessary and were analyzed for the drug at 215 nm by using UV spectrophotometer.[25]

2.8.9 Drug release kinetics

The *in vitro* dissolution test data were fitted into mathematical models representing zero order, first order in order to determine the order of drug release.[26]

3. STATISTICAL ANALYSIS

The result facts were provided as mean ± standard deviation (SD). All data were produced in three independent experiments. Statistical analysis was performed using XL STAT version 2019.1 with One-way analysis of variance (ANOVA). Differences were considered to be significant at a level of P<0.5.

4. RESULTS AND DISCUSSION

4.1 FTIR and DSC studies

FT-IR studies revealed that there is no change in nature and position of the characteristic bands of drug and excipients used in formulations which ensures that there is no interaction between drug and excipients and was illustrated in Fig.1 and 2. DSC studies were performed on pure drugs and blends which revealed that there is no major change in the melting point of the drug in both thermograms which ensures that the drug is compatible with all excipients used. The thermograms were shown in Fig.3 and 4.

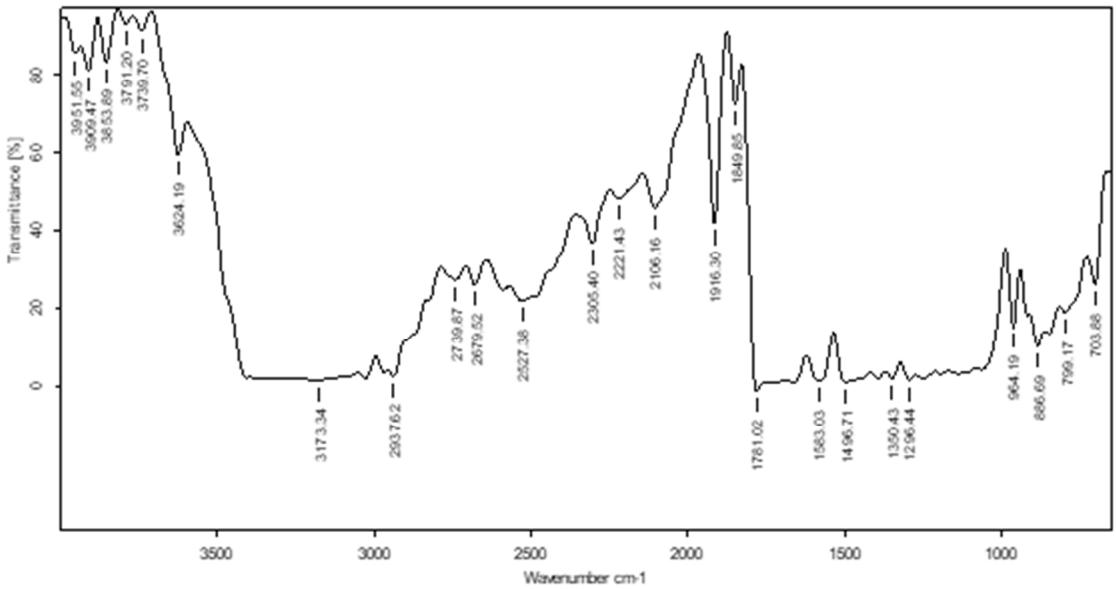

Fig 1. FT-IR spectrum of Aceclofenac

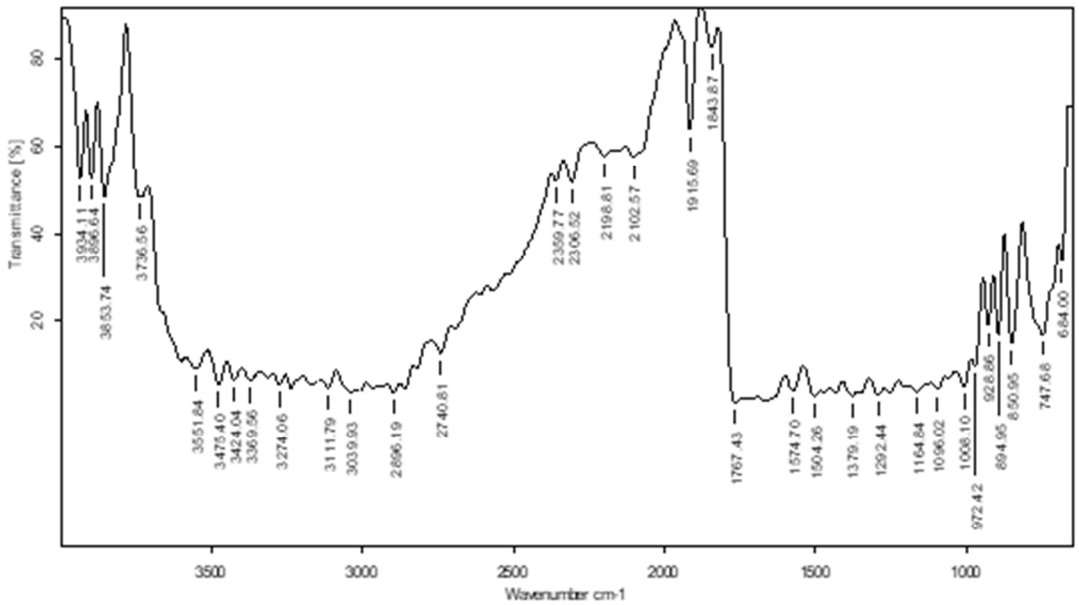

Fig 2. FT-IR spectrum of blend

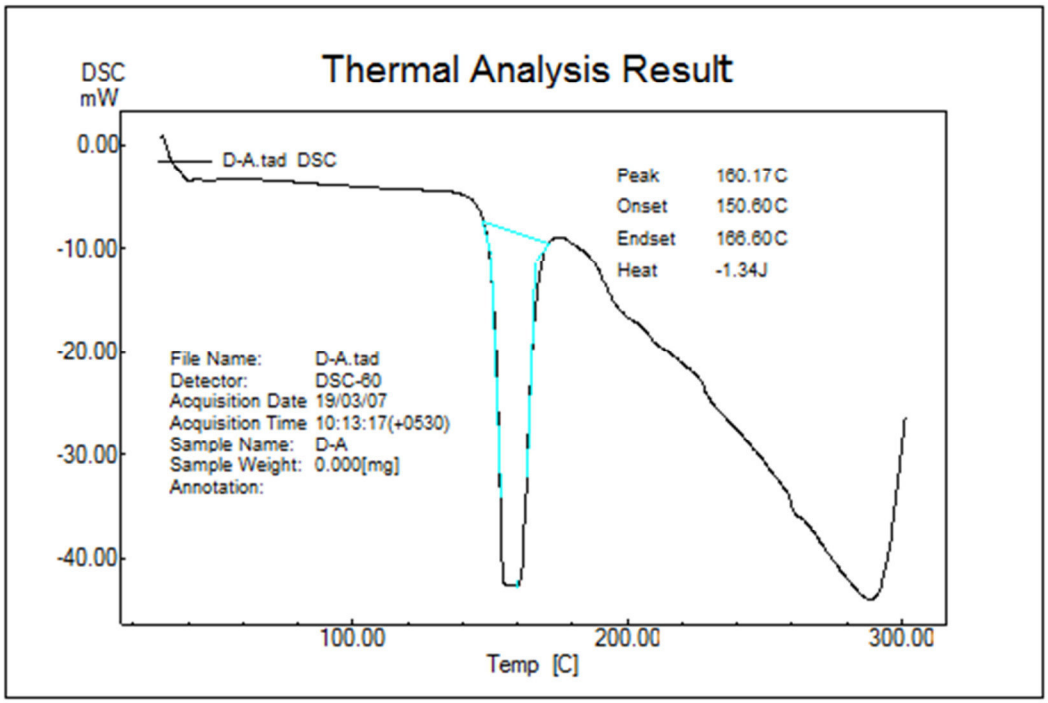

Fig 3. DSC thermogram of Aceclofenac drug

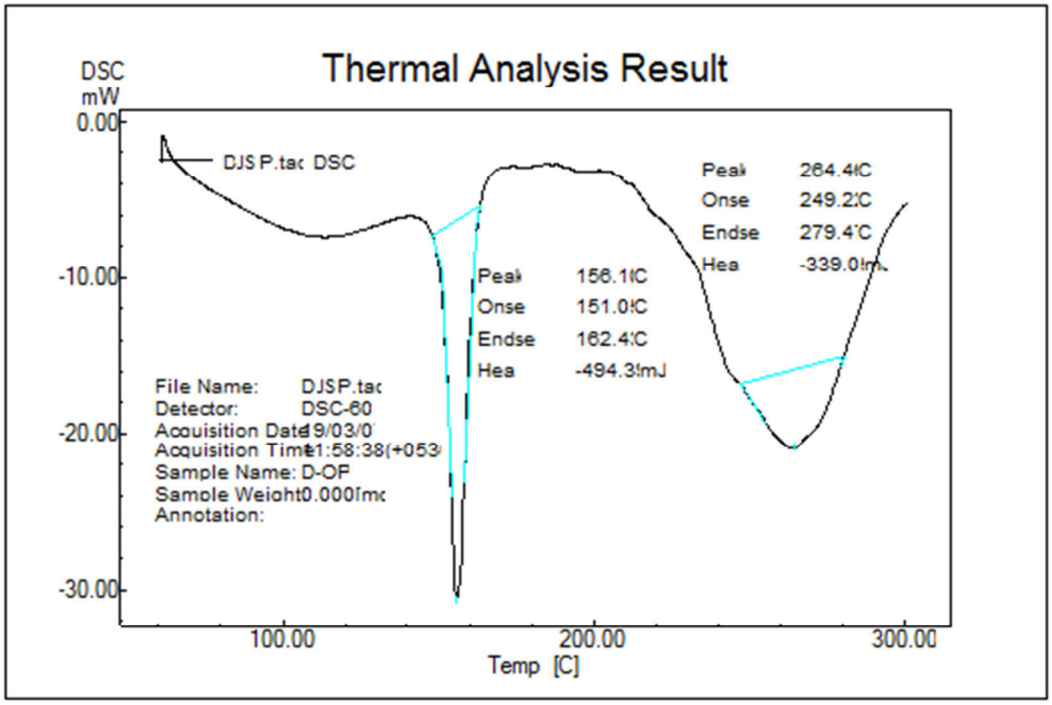

Fig 4. DSC thermogram of Aceclofenac + blend

4.2 Evaluation of precompression parameters

The bulk density of all the formulations F1 to F10 were found to be in the range of 0.50±0.03 to 0.65±0.05 gm/ml and tapped density was found in between the range of 0.59±0.02 to 0.74±0.01 gm/ml. The angle of repose of all formulations was found to be in the range of 22.1±0.06-25.6±0.05. The formulation F5 showed an angle of repose of 22.1±0.06 which indicates that flow property was good. Carr's index of all formulations was found to be in the range of 10.16±0.03-12.90±0.02. The formulation F5 showed 10.70±0.03which ensures that the flow property is good. Hausner ratio of all formulations was found to be in the range of 1.11±0.02-1.15±0.01. The formulation F5 showed 1.1 it indicates that flow property was good and was tabulated in Table 2.

Table 2. *Evaluation of precompression parameters of formulations F1-F10*

Formulation	Bulk Density (gm/ml) ±SD*	Tapped density (gm/ml) ±SD*	Carr's index (%) ±SD*	Hausner's ratio±SD*	Angle of repose (˚) ±SD*
F1	0.54±0.03	0.61±0.03	11.40±0.01	1.13±0.02	23.3±0.05

F2	0.53±0.05	0.60±0.02	11.66±0.04	1.13±0.03	22.5±0.13
F3	0.64±0.02	0.73±0.05	12.90±0.02	1.15±0.01	24.2±0.08
F4	0.63±0.04	0.72±0.01	12.50±0.05	1.14±0.04	22.8±0.15
F5	0.50±0.03	0.56±0.05	10.70±0.03	1.12±0.05	22.1±0.06
F6	0.52±0.02	0.59±0.02	11.86±0.04	1.13±0.01	23.62±0.18
F7	0.53±0.01	0.59±0.04	10.16±0.03	1.11±0.02	22.9±0.12
F8	0.65±0.05	0.74±0.01	12.16±0.01	1.13±0.04	25.6±0.05
F9	0.62±0.04	0.71±0.03	12.67±0.05	1.14±0.03	24.3±0.06
F10	0.61±0.01	0.70±0.05	12.85±0.02	1.14±0.05	24.7±0.01

n=3 All values are expressed as mean±SD

4.3 Evaluation of post compression parameters

The results of post compression parameters such as hardness, thickness, average weight, friability, drug content was shown in Table 3. The friability of all the formulations was found to be less than 0.5% which indicated that the prepared tablets were mechanically stable. The weight variation of all the tablets was found to be within ±5% deviation and were in the acceptable limits as per IP which ascertains that the tablets does not have any differences in terms of weight. The drug content of F5 formulation was found to be 99.7±0.03.

Table 3. Post compression parameters of formulations F1-F10

Formulation	Hardness (kg/cm^2)±SD* (*n=5)	Friability (%)±SD* (*n=10)	Average weight (mg) ±SD* (*n=20)	Thickness (mm)	Drug Content ±SD* (*n= 10)
F1	3.5±0.05	0.45±0.02	299±0.65	4.35	97.1±0.10
F2	3.8±0.10	0.39±0.08	300±0.14	4.37	96.4±0.04
F3	3.6±0.08	0.42±0.05	300±0.86	4.35	98.2±0.06
F4	3.0±0.03	0.49±0.13	299±0.72	4.40	96.5±0.02
F5	3.4±0.06	0.41±0.04	298±0.18	4.35	99.7±0.03
F6	4.2±0.02	0.48±0.09	298±0.17	4.45	98.5±0.12
F7	3.8±0.07	0.35±0.15	300±0.46	4.47	98.3±0.08
F8	4.2±0.01	0.44±0.06	298±0.24	4.49	95.5±0.04
F9	4.0±0.05	0.38±0.01	299±0.05	4.44	97.2±0.06
F10	4.2±0.09	0.36±0.12	300±0.64	4.45	99.3±0.08

4.3.1 Disintegration time, wetting time and water absorption ratio

The disintegration time of all the formulations F1 to F10 was found to be 32 sec to 80 sec. The F5 formulation containing 10% of JFSP has shown disintegration time of 32sec and tabulated in Table 4. This may be recommended that an enhancement in the concentration of super disintegrating agents, quicker the disintegration. The cause for reduction in disintegration time is the capability of JFSP to rise water penetration due to a wicking action which elevates the tablet porosity and consequently drops disintegration time.[27] Formulations F1-F5 containing JFSP has shown wetting time of 55,48,41,32,29 seconds & formulations F6-F10 containing OP has shown 64, 58, 52, 48,37 seconds respectively. This clearly suggests that an increase in concentration of disintegrating agents decreases wetting time. Water absorption capacity was found to be elevated with an increase in concentration of both JFSP and OP in the formulations F1-F10 which might be owing to higher water uptake by the natural superdisintegrants.

Table 4. Disintegration, wetting time and water absorption of formulations F1-F10

Formulation	Disintegration time (sec)	Wetting time (sec)	Water absorption ratio (%)
F1	59	55	125.01
F2	52	48	132.15
F3	45	41	139.04
F4	36	32	148.09
F5	32	29	158.12
F6	80	64	116.02
F7	60	58	124.10
F8	55	52	132.07
F9	52	48	136.03
F10	40	37	143.05

4.3.2 *In Vitro dissolution studies*

The dissolution studies were performed for all the formulations and were illustrated in Fig.5 and 6 respectively. Among all the formulations, formulation F5 comprising 10% concentration of JFSP showed highest drug release ie., 98.7% of drug release at the end of 30minutes whereas the formulation F10 comprising OP of 10% concentration showed 94.5% of drug release at the end of 30 minutes. From the dissolution graphs it was observed that gradual increase in the concentration of the superdisintegrant increased the drug release.

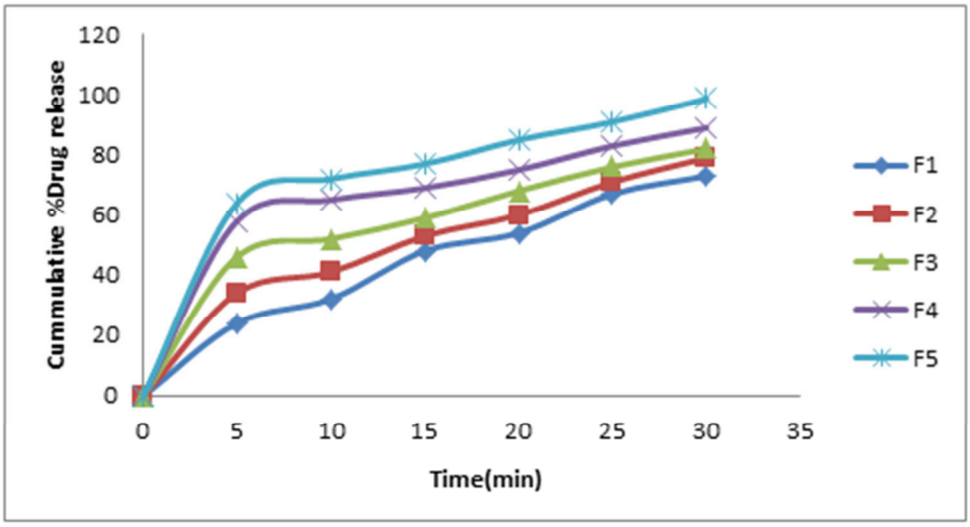

Fig 5. *In vitro* drug release profile of formulations F1-F5

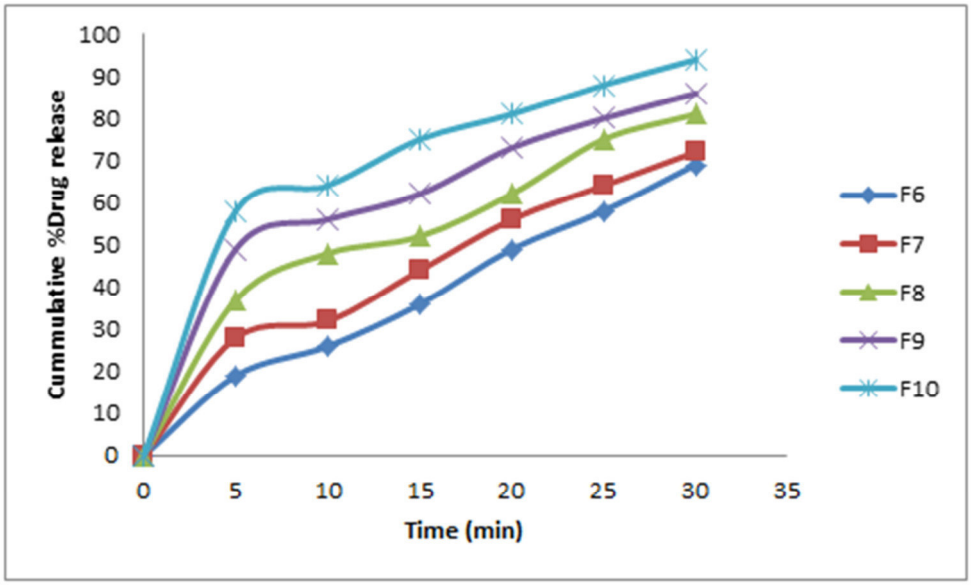

Fig 6. *In vitro* drug release profile of formulations F6-F10

4.3.3 *Drug release kinetic studies*

The dissolution data was fitted to Zero order and First order Kinetics. The R^2 values of Zero order kinetics of F5 formulation showed 0.7234. The R^2 value of first order kinetics of F5 formulation showed 0.8792 and the data was tabulated in Table 5 and illustrated in Fig.7,8,9 and 10. As the R^2 value of first order kinetics is greater than Zero order kinetics, formulation F5 follows first order kinetics.

Table 5. Drug release kinetics for all formulations F1-F10

Formulation	Zero order	First order
	R^2 Values	R^2 Values
F1	0.9643	0.9884
F2	0.9209	0.9787
F3	0.8306	0.9626
F4	0.7261	0.9337
F5	0.7234	0.8792
F6	0.9882	0.9787
F7	0.9509	0.9757

F8	0.8945	0.9653
F9	0.8147	0.9644
F10	0.7666	0.9639

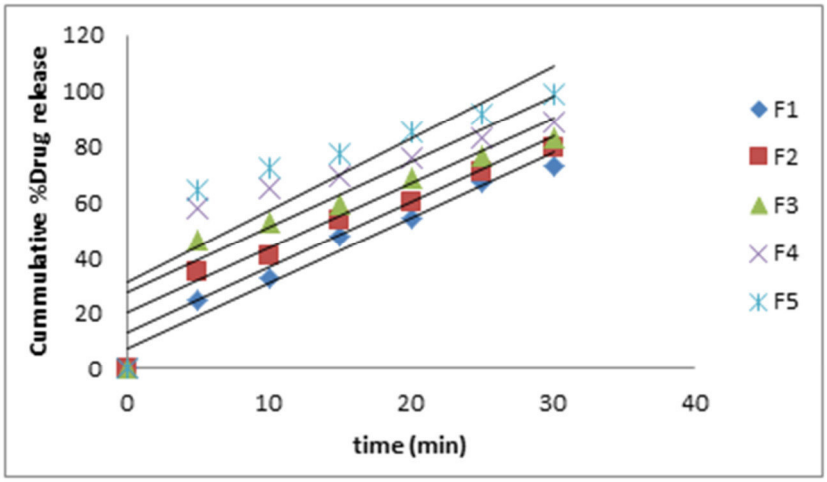

Fig 7. Zero order plots of formulations F1-F5

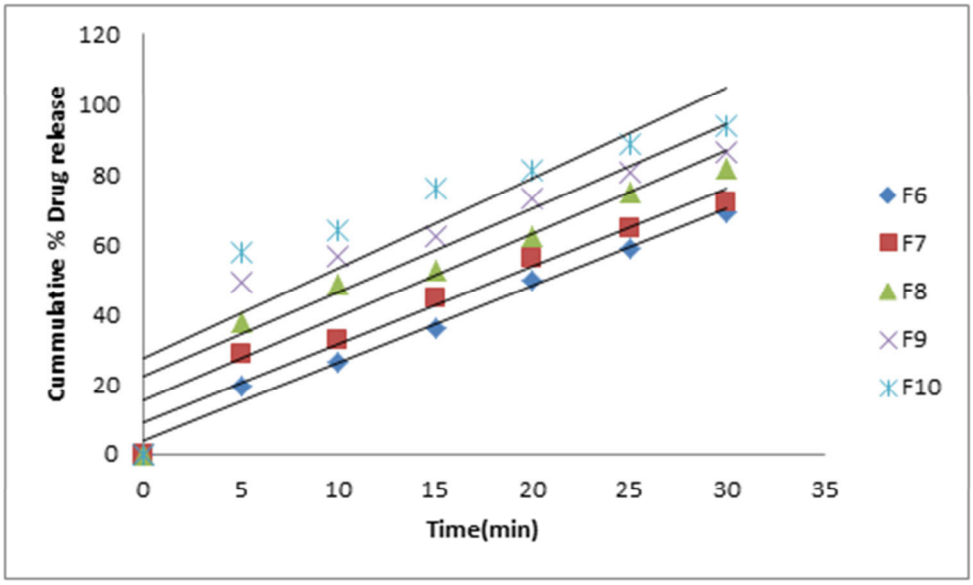

Fig 8. Zero order plots of formulations F6-F10

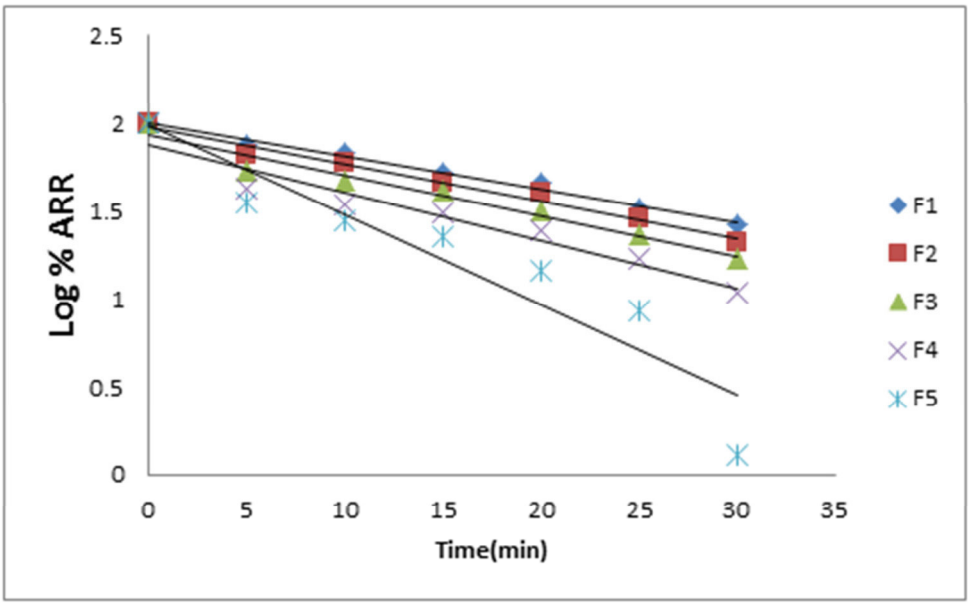

Fig 9. First order plots of formulation F1-F5

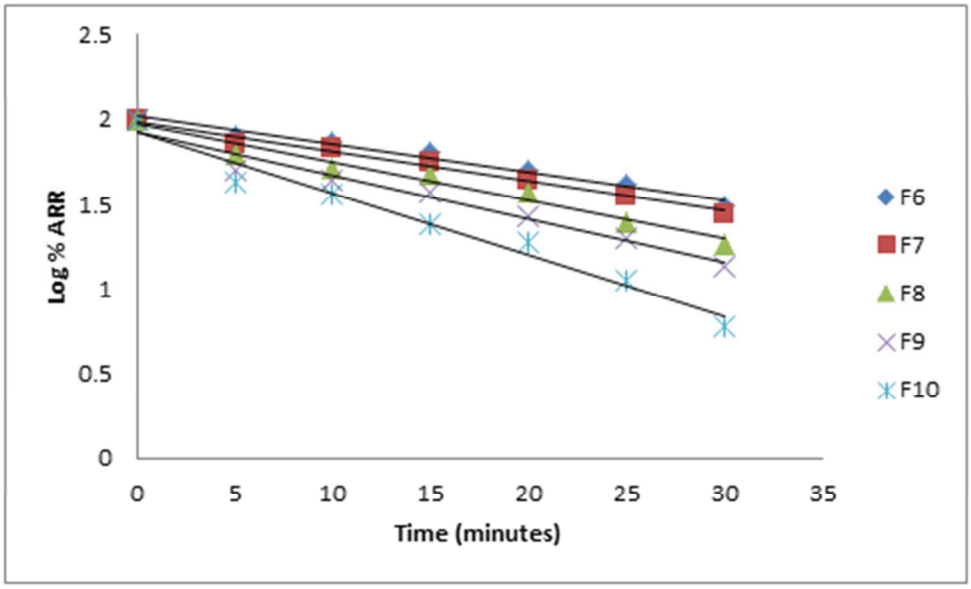

Fig 10. First order plots of formulation F6-F10

5. CONCLUSION

The fast disintegrating tablets of aceclofenac were prepared successfully by using a direct compression method. Among all the formulations, F5 showed better results when compared with other formulations i.e., F5 containing 10% w/w concentration of Jackfruit seed powder showed disintegration time of 32sec and drug release of 98.7% in 30 min and the drug release follows first order kinetics. Finally, it was concluded that the F5 formulation is the most promising formulation in providing faster therapy in the inflammation conditions and will enhance the patient compliance.

6. ACKNOWLEDGEMENT

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7. AUTHORS CONTRIBUTION STATEMENT

Ms. Samhita B, Yasaswini V and Gowthami M conceptualized and collected the data with regard to this work. Dr. Haranath Chinthaginjala and Hindustan Abdul Ahad scrutinized the information and essential ideas were specified in the direction of scheming the manuscript. Ms. Nagajyothi V and Mr. Rahulraghav D contributed to the drug release studies. All the authors conferred the methodology and results and contributed to the final manuscript.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

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