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DESIGN, FORMULATION AND *IN-VITRO* EVALUATION OF ACECLOFENAC FAST DISINTEGRATING TABLETS USING NATURAL POLYMERS

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ABSTRACT

Aceclofenac is a Non-steroidal anti-inflammatory drug (NSAID) with marked anti-inflammatory and analgesic properties. The aim of the present work is to formulate a tablet which disintegrate and dissolve rapidly and give its rapid onset of action. The present study was to formulate and *in-vitro* evaluation of fast disintegrating tablets of Aceclofenac by using Natural polymer such as Pithecellobium dulce seed gum and Guar gum by direct compression technique using 3 different concentrations of 2%W/W, 4%W/W & 6%W/W. Each formulation was evaluate for various pre and post compression parameters such as Flow property, Bulk density, Tapped density, Weight variation, Hardness, Friability, Wetting time, Disintegration time, Assay, *in-vitro* dissolution. Among the 06 formulations, "F3" formulation Aceclofenac with 6%w/w of Pithecellobium dulce seed gum showed excellent disintegration time and best dissolution rate studies. *In-Vitro* dissolution studies showed (99.96%) release of drug within 20 minutes It was concluded that the fast disintegrating tablets are prepared by Natural polymer Pithecellobium dulce seed gum and Guar gum acts as a Fast disintegrant and the Pithecellobium dulce seed gum showed excellent disintegration time and enhance the dissolution rate compared to Guar gum.

KEYWORDS: Aceclofenac, NSAID, Pithecellobium dulce gum, Guar gum, Fast disintegrant.

INTRODUCTION

Drug delivery is the most desirable and preferred method of administering therapeutic agents to attain systemic effects mainly because of patient acceptance, convenience in administration and cost-effective manufacturing process.[1] Fast disintegrating tablets release tablets are those which disintegrate rapidly and get dissolved to release the medicaments. Immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption. A disintegrant is an excipient, which is added to a tablet or capsule blend to aid in the break up of the compacted mass when it is put into a fluid environment. In many cases disintegrants have the major role in the disintegration and dissolution process of rapidly disintegrating tablets made by direct compression these are agents added to tablets and some encapsulated formulations to promote breakup of tablets and capsules slugs into smaller fragments in the aqueous environment thereby increasing the available surface area and promote more rapid release of drug substance.[2,3]

METHODOLOGY

Isolation of mucilage from Pithecellobium dulce seeds[4]

The Pithecellobium dulce seeds were collected and cleaned. The seeds were crushed and boiled in water with stirring for 30minutes and left to stand for 24hrs to allow complete release of the mucilage into the water. The mucilage was extracted using a multi-layer muslin cloth bag to remove the marc from the solution. Acetone (three times the volume of filtrate) was added to precipitate the mucilage (PDM). The mucilage was separated, dried in an oven at 40°C, collected grounded, passed through a mesh #80and stored in desiccators at 30°C.

Preformulation study[5-14]

Definition

Preformulation studies describes as the process of optimizing the delivery of drug through the determination of physic-chemical properties of the new compound that could affect the drug performance and development of an efficacy, stable and safe dosage form.

Scope
Use of preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacy and stable product and at the same time provides the basis for optimization of drug product quality.

Organoleptic properties of drug
Colour: A small amount of powder was taken in butter paper and Aceclofenac was viewed in well illuminated place.

Odour& taste: very less quantity of drug was used to get taste with the help of tongue as well as smelled to get the odour.

Determination of melting point: Melting point was determined by taking small amount of drug in a capillary tube closed at one end. The capillary tube was placed in an electrically operated melting point and the temperature at which the drug melts was recorded. This was performed thrice and average values were noted.

Solubility Analysis
To Prepare supersaturated solutions of Aceclofenac drug with water, 0.1N HCl, Phosphate buffer-pH 6.4, Phosphate buffer- pH -6.8, Phosphate buffer- pH -7.2 separately. All the solution kept a side for 24 hrs and filter the solution. Collect the filtrate and measure the absorbance at 273 nm.

The solubility of the drug can be calculated by using the following formula.
Solubility = (At/As) ×Cs× (Dt/Wd×1000) ×100
Where At is the Sample (test) absorbance.
As is the Standard absorbance
Cs is the standard concentration of drug.
Dt is the dilution factor.
Wd is the Weight of the drug.

Pre Compression Evaluation Parameters
Bulk density
Bulk density was determined by pouring the powder into a graduated cylinder. The bulk volume (Vb) and mass (m) of the powder was determined. The bulk density was calculated by using the following formula

Bulk density (eb) = Mass of the powder (M) / Bulk volume of powder (Vb)
Tapped Density
The measuring cylinder containing known mass of powder blend was tapped 1000 times for a fixed time. The minimum volume occupied in the cylinder (Vt) and mass of the powder (m) was measured. The tapped density was measured by using the following formula
Tapped density (et) = Mass of powder (M) / Tapped volume of powder (Vt)

Carr's compressibility Index
The compressibility index determines the flow property characterstics of powder developed by Carr's. The percentage compressibility of powder is a direct measure of the potential powder arc and stability. The Carr's index can be calculated by the following formula.
%Carr's index = et – eb / et ×100

Where et is the tapped density of powder
eb is bulk density of powder.

Hausner Ratio
It is the measurement of frictional resistance of the drug. It was determined by the ratio of tapped density and bulk density.
Hausner's ratio = et / eb

Angle of repose (θ)
Angle of repose is the maximum angle that can be obtained between the freestanding surface of the powder heap and the horizontal plane. It is a characteristic related to the inter particulate friction or resistance to movement between particles.

Angle of repose of different formulations was measured according to fixed height funnel standing method. The method used to find the angle of response is to pour the powder in the form of a conical heap on a flat surface and measure the inclined angled with the horizontal pile.
Tan θ = h / r
$\theta = \tan^{-1}(h / r)$

Where h = height of pile r = radius of the base of the pile θ = angle of repose

Procedure
Weighed quantity of Powder was passed through a funnel kept at a height of 2 cm for the base. The powder is passed till it forms heap and touches the tip of the funnel. The radius was measured and angle of repose was calculated by using the above mentioned formula.

Table 1: Flow Properties and Corresponding Angle of Repose, Compressibility index, Hausner ratio.

Flow characters	Compressibility index (%)	Hausner ratio	Angle of repose (θ)
Excellent	< 10	1.00 – 1.12	25-30
Good	11-15	1.12 – 1.18	31-35
Fair	16-20	1.19 – 1.25	36-40
Passable	21-25	1.26 – 1.34	41-45
Poor	26-31	1.35 – 1.45	46-55
Very poor	32-37	1.46 – 1.59	56-65
Very Very poor	> 38	> 1.60	> 66

Drug Excipient Compatibility Studies

Fourier Transform Infrared Spectroscopy (FT-IR)

The objective of drug/excipient compatibility considerations and practical studies was to delineate, as quickly as possible, real ad possible interactions between potential formulation excipients and the API. Homogenous mixtures of drug and excipients were prepared and filled in glass vials. Samples packed in glass vials were maintained at 60± 2°C for 2 weeks.

Potassium bromide was mixed with drug and/or polymer in 9:1 ratio and the spectra were taken. FT-IR spectrum of Aceclofenac was compared with FT-IR spectrum of Aceclofenac with polymer. Disappearance of Aceclofenac peaks or shifting of peaks in any of the spectra was studied.

Calibration curve of Aceclofenac

Preparation Of Dissolution Medium (Phosphate buffer at p^H 6.8)

Dissolve 28.80gm Disodium hydrogen phosphate and 11.45gm of Potassium dihydrogen phosphate in sufficient amount of water and to produce upto 1000ml.

Preparation of standard stock solution:

The I stock solution was prepared by dissolving 100mg of Aceclofenac in 100ml of phosphate buffer at p^H 6.8 solution(1mg/1ml). From stock I solution, pipetted out 10ml of solution into a 100ml volumetric flask and make up the volume with Phosphate buffer p^H 6.8 solution and it is consider as stock II solution(100µg/1ml).

Sample Preparation

From the secondary stock solution(II) various concentrations such as 1-10 µg/mL were prepared by using Phosphate buffer p^H 6.8 solution for calibration curve. Standard Calibration curve was plotted by taking absorbance of secondary stock solutions in UV double beam spectrophotometer at 273 nm.

Formulation and Development of Aceclofenac fast disintegrating tablets by using Direct Compression method

Step 1: All the ingredients- Aceclofenac Disintegrating agents and lactose have been weighed individually into separate poly bags.

Step 2: These ingredients are then sifted through sieve no. 40 and blended together in a poly bag for 10 min.

Step 3: Lubrication-Weighed amount Magnesium Stearate sieved through mesh sieve no. 60 were added to the above blend and blending was carried out for 5 more min.

Step 4: Compression-The lubricated blend is compressed using punch toolings.

Upper punch: Plain

Lower punch: Plain.

Step 5: Description of core tablets:

White and Oblong biconvex tablet plain on both sides

Table 2: List of Formulations.

S.NO	Name of the Ingredient	F1	F2	F3	F4	F5	F6
1.	Aceclofenac	100	100	100	100	100	100
2.	Pithecellobium Dulce seed gum	4	8	12	-	-	-
3.	Guar gum	-	-	-	4	8	12
4.	Magnesium Stearate	3	3	3	3	3	3
5.	Talc	3	3	3	3	3	3
6.	Lactose	90	86	82	90	86	82
7.	Total weight (mg)	200	200	200	200	200	200

***In-Vitro* Evaluation tests for Fast Disintegrating tablets**

General appearance

The formulated tablets were assessed for its general appearance and observations were made for shape, colour, texture and odour.

Thickness

Thickness mainly depends up on die filling, physical properties of material to be compressed under compression force. The thickness of the tablets was measured by using Digital Vernier Calipers.

Desired thickness: 2.0 - 4.0 mm

Hardness

Hardness of the tablet is defined as the force required in breaking a tablet in a diametric compression test. In this test, a tablet was placed between two anvils, force was applied to the anvils and the crushing strength that just causes the tablet to break is recorded. Hence hardness is sometimes referred to as Crushing Strength.

Tablets require certain amount of strength or hardness to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of a tablet, like its thickness, is a function of the die fill and compression force. At a constant die fill, the hardness value increases and thickness decreases as additional compressional force is applied. At a constant compression force (fixed distance between upper and lower punches), hardness

increases with increasing die fills and decreases with lower die fills.

Friability

Friability is defined as the loss in weight of tablet in the container due to removal of fine particle from their surface. It is expressed in percentage (%). A preweighed tablet sample (20 tablets) was placed in the friabilator chamber and rotated for 10 revolutions. In each revolution the tablets are carried up and are allowed to freely fall from a height of 6 inches. After 100 revolutions the tablets are removed from the chamber, dusted and reweighed. When capping is observed during friability test, tablets should not be considered acceptable, regardless of percentage weight loss.

% Friability was then calculated using the following formula:

Friability = [(Initial wt – Final wt)/ Initial wt] X 100

Weight Variation

This test is not applicable to coated tablets other than film coated tablets and to tablets that are required to comply with the test for uniformity of content for all active ingredients. USP and NF provide limits for the permissible variations in the weights of individual tablets expressed as a percentage of the average weight of the sample.

Individually weighed 20 tablets and calculated the average weight not more than two of the individual weights deviate from the average weight by more than the percentage deviation shown in Table 3 and more deviated by more than twice that percentage.

$$\textbf{Percentage deviation} = \frac{\textbf{[Weight of tablet (mg) - Average weight of tablet (mg)]}}{\textbf{Average weight of tablet (mg)}} \times \textbf{100}$$

Table 3: Limits for weight variation.

Average weight of Tablets (mg)		Maximum Percentage deviation(%)
IP	USP	
130 or less	80 or less	10
130 – 324	80-250	7.5
324 or more	250 or more	5.0

Disintegration Test

The process of breakdown of a tablet into smaller particles is called as disintegration. The in vitro disintegration time of a tablet was determined using disintegration test apparatus as per IP specifications.

Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using 0.1 N HCl or Phosphate buffer P^H 6.8 as the immersion liquid and maintained a temperature at $37^o\pm$ 2 ^{o}C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

Content uniformity (Assay)

Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 50mg of Aceclofenac, shake with 60ml of methanol in a 200ml clean, dry volumetric flask and dilute to volume with methanol and sonicate for 30 minutes with intermittent shaking at room temperature. Dilute 5ml of this solution to 100ml with methanol. Centrifuge the solution at 10,000 RPM for 10 minutes. Filter through 0.45µ nylon membrane filter .To measure the absorbance at 273 nm.

Assay = (At/As)×Cs× (Dt/Wd) ×100

Where At is the Sample(test) absorbance.

As is the Standard absorbance.

Cs is the standard concentration of drug.

Dt is the dilution factor.

Wd is the Weight of the drug.

Wetting Time

This test was carried out by 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 10ml 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.

***In-Vitro* drug release study**

Preparation of Dissolution Medium (Phosphate buffer p^H 6.8)

Dissolve 28.80gm of Disodium hydrogen phosphate and 11.45gm of Potassium dihydrogen phosphate in sufficient amount of water to produce 1000 ml and sonicate for 10-15 min. The drug release rate of Aceclofenac fast disintegrating tablets was determined using United States Pharmacopeia (USP) Dissolution Apparatus Type II (paddle method).The dissolution test was performed by using 900 ml of Phosphate buffer p^H 6.8, at $37^0\pm$ 0.50 C and 50 rpm. In specified time intervals an aliquot of 5ml samples of the solution were withdrawn from the dissolution apparatus and with replacement of fresh fluid to dissolution medium. The samples were filtered through filter paper of 0.45 µ m. Absorbance of these solutions were measure data λmax 273 nm using by using UV/Visible Spectrophotometer.

The drug release was plotted against time to determine the release profile of various formulations.

The % drug release of the formulation can be calculated by

% drug release = (At/As)×Cs× (Dt ×Vm/Wd×1000) ×100

Where At is the Sample(test) absorbance.
As is the Standard absorbance.
Cs is the standard concentration of drug.
Dt is the dilution factor.
Wd is the Weight of the drug.
Vm is the volume of the dissolution medium.

Table 4: Dissolution Parameters.

Dissolution medium	Phosphate buffer – pH 6.8
Dissolution medium volume	900ml
Apparatus	USP-II (Paddle type)
Speed of paddle rotation	50 rpm
Temperature	37^{o}± 0.05C
Volume of samples withdrawn	5ML
Sampling time interval (Min)	5,10,15,20,25,30,40,50
Measurement of absorbance	273nm

***In-Vitro* Release Kinetics Studies**

The analysis of drug release mechanism from a pharmaceutical dosage form is Important but complicated process and is practically evident in the case of matrix systems. The order of drug release from FDT was described by using zero order kinetics or first order kinetics.

Zero Order Release Kinetics

It defines a linear relationship between the fractions of drug released versus time.

Q=ko t.

Where, Q is the fraction of drug released at time t.

Ko is the zero order release rate constant.

A plot of the fraction of % of drug released against time (Min) will be linear if the release obeys zero order release kinetics.

First order release kinetics

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that the drug release from most of the slow release tablets could be described adequately by the first-order kinetics. The equation that describes first order kinetics is

Log C= Log C0-kt/2.303

Where C is the amount of drug dissolved at time t,
Co is the amount of drug dissolved at t=0 and
k is the first order rate constant

A graph of log cumulative of log % drug remaining Vs time yields a straight line. It will be linear if the release obeys the first order release kinetics.

RESULTS

Characterization of API

Table 5: API Characteristics.

S. No	Characteristics	Results
1	Description	White
2	Melting Point	156.11 ± 0.23^{0}c
3	Bulk Density	0.592±0.05gm/ml
4	Tapped Density	0.631±0.09gm/ml
5	Carr's Index	9.35±0.22%
6	Hausner's Ratio	1.103±0.05
7	Angle of Repose	23.70^{0}±0.11

Table 6: Solubility Analysis of Aceclofenac with different solvents.

S. NO.	Type of Solvent	Solubility(mg/ml)
1.	Water	0.068±0.019
2.	0.1N HCl	0.691±0.006
3.	Phosphate buffer p^{H}-6.4	0.931±0.028
4.	Phosphate buffer p^{H}-6.8	0.981±0.554
5.	Phosphate buffer p^{H}-7.2	0.926±0.035

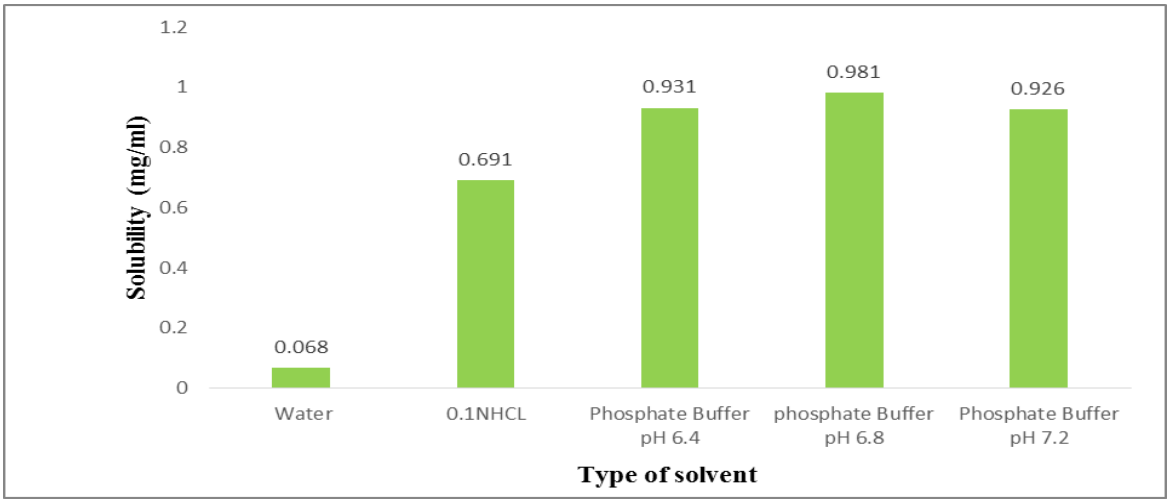

Figure 1: Solubility Analysis of Aceclofenac with different solvents.

Characterization of Natural Polymers

Table 7: Natural Polymers Characteristics.

S. No	Characteristics	Pithecellobiumdulce Seed Gum	Guar gum
1	Description	Yellowish	White gray
2	Bulk Density	0.66±0.06gm/ml	0.541±0.09
3	Tapped Density	0.723±0.11gm/ml	0.631±0.16
4	Carr's Index	8.71±0.11%	14.26±0.23%
5	Hausner's Ratio	1.09±0.052	1.16±0.028
6	Angle of Repose	19.77^0±0.031	28.9^0±0.029

Drug-excipient compatability study

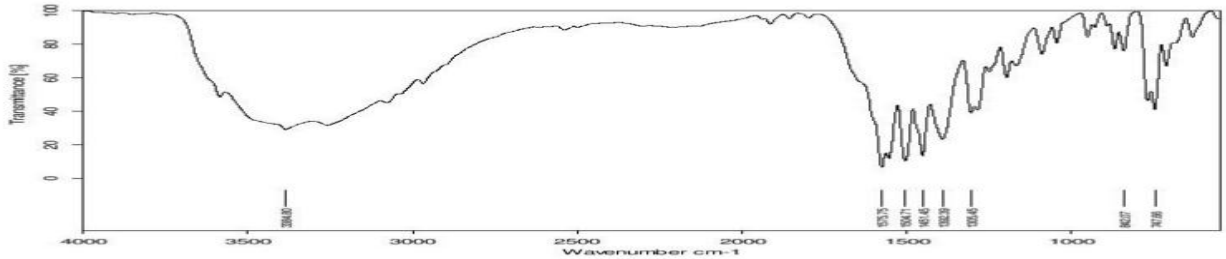

Figure 2: FTIR Spectra of Aceclofenac.

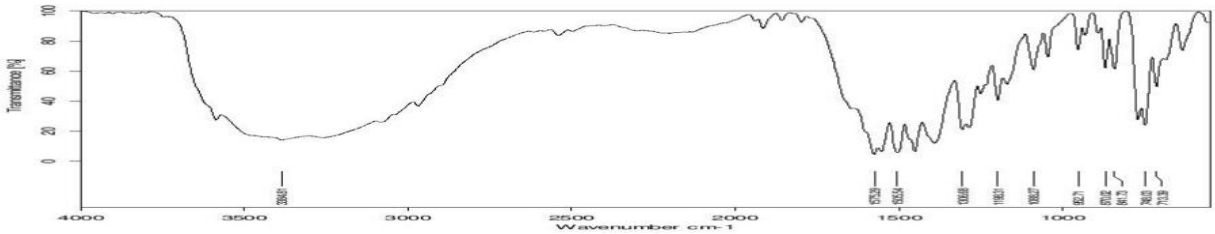

Figure 3: FTIR Spectra of Optimised formulation.

Table 8: Standard Calibration Curve Data of Aceclofenac.

S.NO	Concentration (µg/ml)	Absorbance
1.	0	0
2.	2	0.142±0.018
3.	4	0.282±0.003
4.	6	0.420±0.016
5.	8	0.556±0.025
6.	10	0.692±0.021

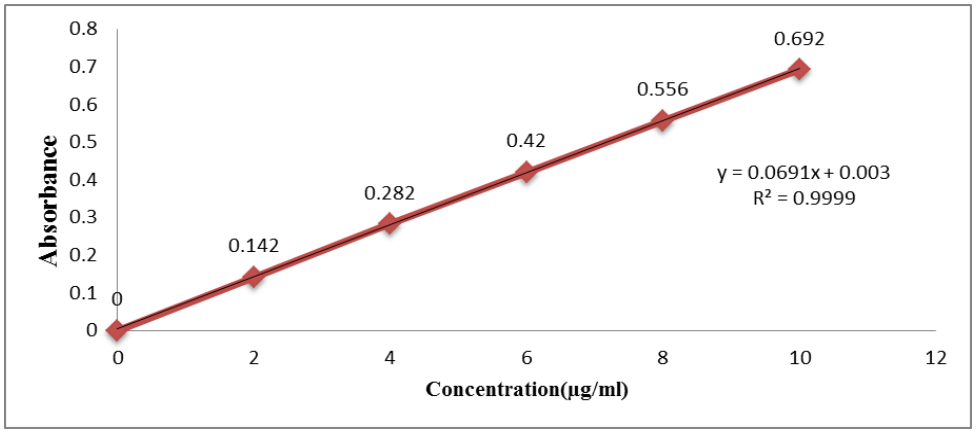

Figure 4: Standard Calibration curve of Aceclofenac.

Table 9: Evaluation of Flow properties of Blends of various trail batches were mean±SD, n=3.

Formulation Code	Angle of repose (Θ)	Bulk Density (gm/cm^3)	Tapped Desity (gm/cm^3)	Compressibility (%)	Hausners ratio
F1	31.1±0.16	0.592±0.12	0.697±0.68	15.06±0.24	1.177±0.07
F2	27.8±0.42	0.590±0.25	0.639±0.42	7.669±0.42	1.08±0.21
F3	26.6±0.25	0.570±0.32	0.620±0.35	8.06±0.24	1.08±0.16
F4	26.7±0.15	0.612±0.10	0.719±0.63	14.88±0.48	1.17±0.14
F5	32.5±0.74	0.602±0.55	0.702±0.52	14.24±0.43	1.166±0.36
F6	29.1±0.18	0.592±0.11	0.654±0.35	9.48±0.32	1.104±0.23

Table 10: Evaluation of Aceclofenac FD Tablets were mean±SD.

Formulations	Weight variation(mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Assay (%)	Disintegration time (sec)	Wetting time (sec)
F1	Pass	2.88±0.22	4.52±0.41	0.62±0.54	99.83±0.43	55±0.52	70±0.43
F2	Pass	2.90±0.36	4.68±0.25	0.73±0.04	98.91±0.09	35±0.43	56±0.16
F3	Pass	2.92±0.28	4.54±0.32	0.66±0.35	99.91±0.17	25±0.12	44±0.09
F4	Pass	2.89±0.87	4.42±0.02	0.64±0.28	99.01±0.01	78±0.68	93±0.47
F5	Pass	2.82±0.49	4.26±0.04	0.68±0.31	97.96±0.36	65±0.47	65±0.21
F6	Pass	2.89±0.38	4.44±0.16	0.75±0.29	99.88±0.53	49±0.26	50±0.06

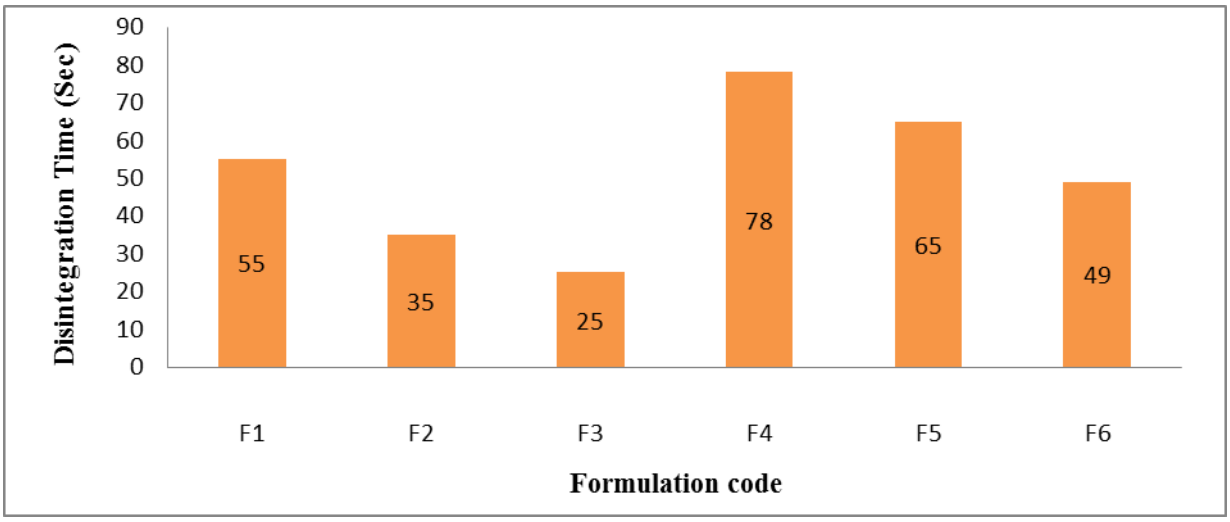

Figure 5: Disintegration time of formulations.

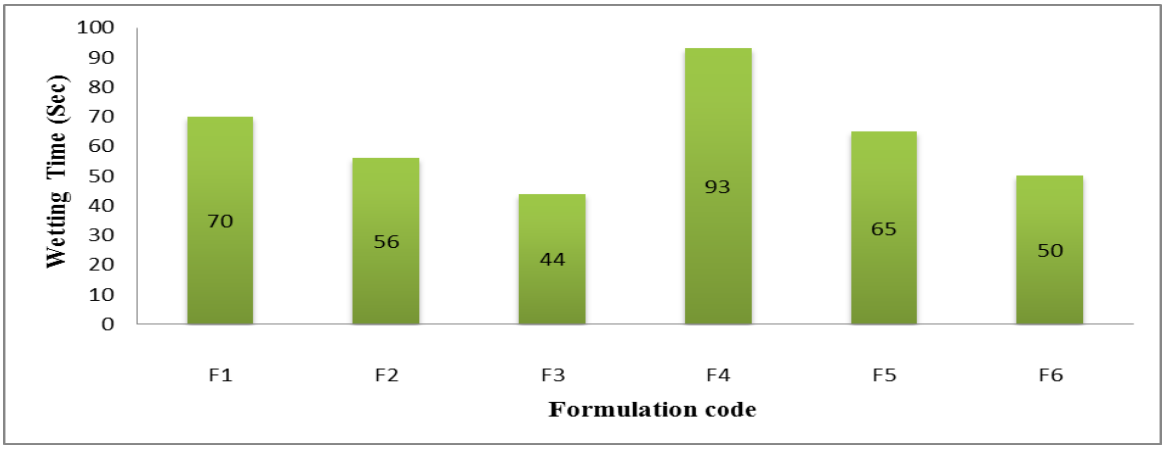

Figure 6: Wetting time of formulations.

***In – Vitro* Dissolution Studies**

Table 11: Dissolution profiles of Aceclofenac with Pithecellobium dulce seed polymer tablets (F1 to F3).

Time (min)	F1	F2	F3
0	0	0	0
5	14.53±0.07	18.97±0.11	24.13±0.13
10	26.13±0.12	34.23±0.08	56.21±0.17
15	49.32±0.19	57.15±0.21	79.32±0.06
20	56.03±0.08	74.20±0.18	99.96±0.15
25	69.35±0.21	86.16±0.22	
30	78.31±0.05	99.83±0.09	
40	99.80±0.13		

Table 12: Dissolution profiles of Aceclofenac with Guar gum polymer tablets (F4 to F6).

Time (min)	F4	F5	F6
0	0	0	0
5	10.30±0.06	13.23±0.15	20.13±0.18
10	23.42±0.12	28.00±0.08	35.05±0.09
15	38.13±0.20	43.15±0.19	53.61±0.12
20	55.00±0.16	61.23±0.21	75.32±0.23
25	63.12±0.09	72.08±0.13	86.13±0.16
30	78.52±0.11	80.43±0.05	99.80±0.05
40	90.31±0.18	99.69±0.14	
50	99.70±0.21		

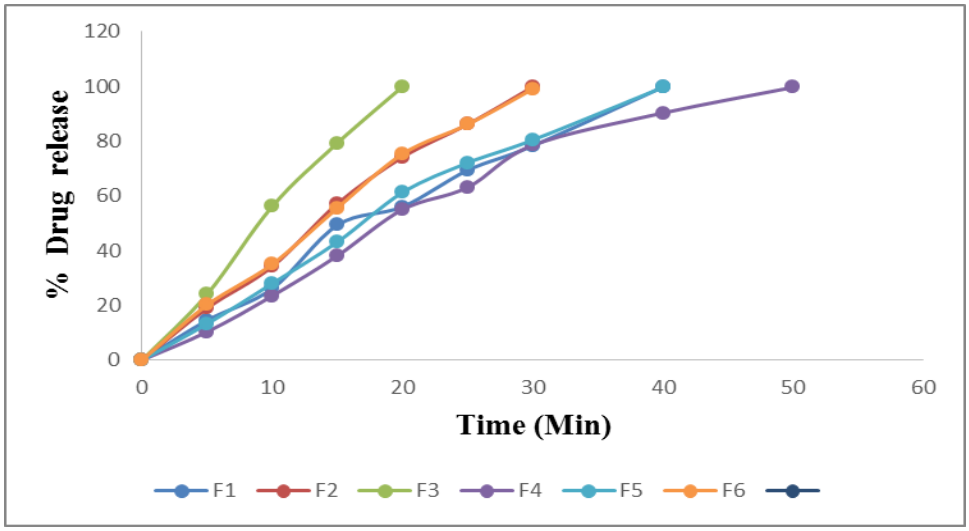

Figure 7: Dissolution graphs of 6 formulations.

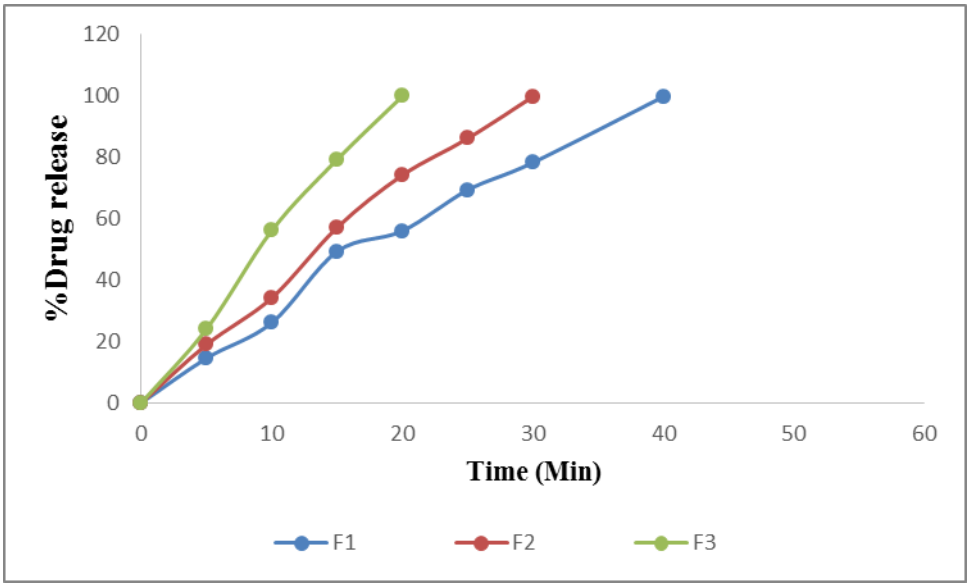

Figure 8: Dissolution graphs of F1-F3 formulations.

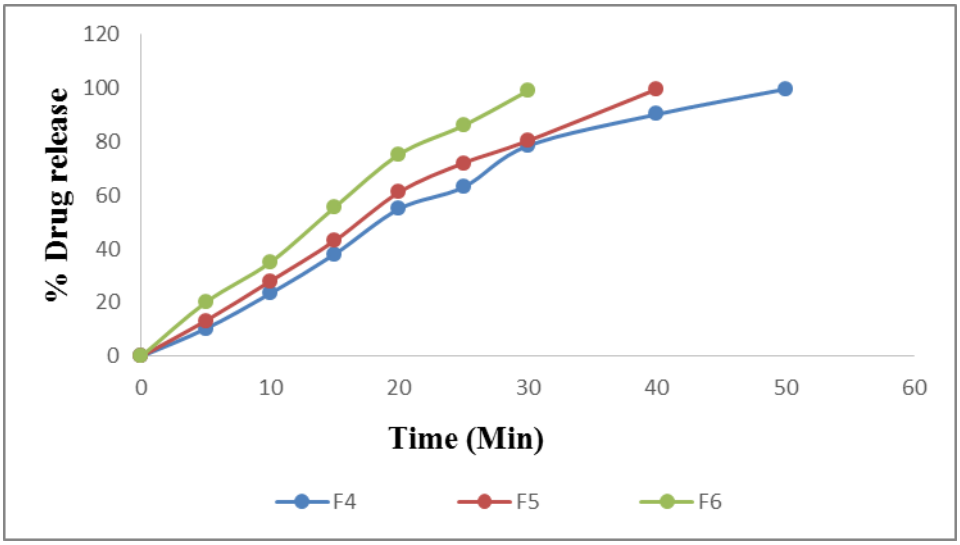

Figure 9: Dissolution graphs of F4-F6 formulations.

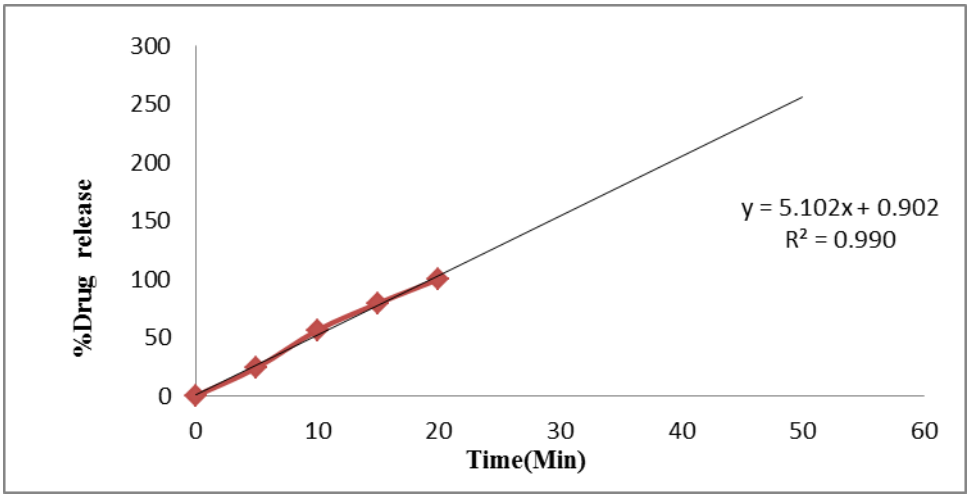

Figure 10: Zero order kinetics of optimized Formulations.

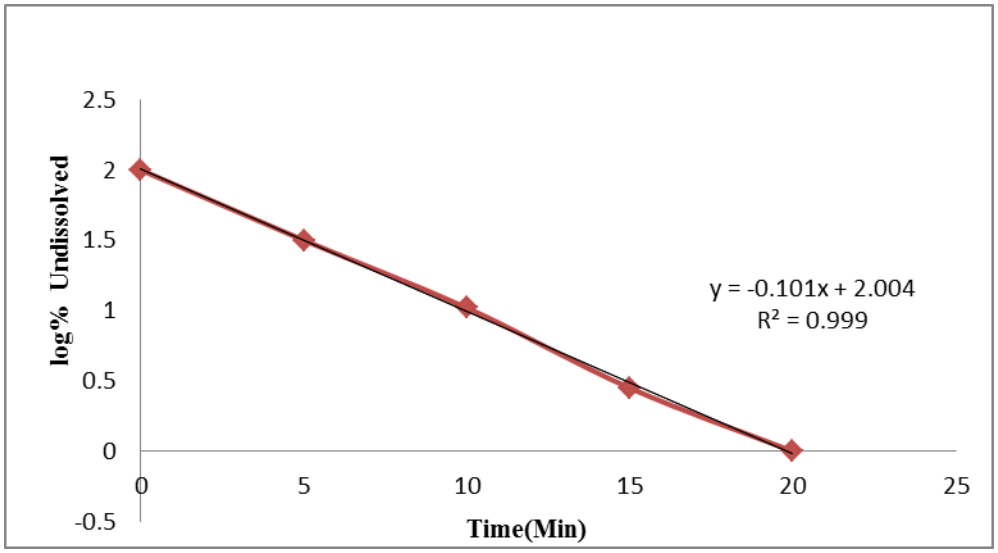

Figure 11: First order kinetics of optimized Formulations.

CONCLUSION

Among the all formulations the Assay, Hardness, Friability, Weight variation, Thickness, Disintegration time and Wetting time result values were found to be within the limits. As the ratio of polymer increased then the Disintegration time was decreased. Among all the 06 formulations the F3 formulation [Aceclofenac: Pithecellobium dulce seed gum] showed better drug release when compared to other formulations. *In-Vitro* dissolution studies showed 99.96% of drug release within 20 minutes. It was concluded that the fast disintegrating tablets are prepared by Natural polymer Pithecellobium dulce seed gum and Guar gum acts as a Fast disintegrant and the Pithecellobium dulce seed gum showed excellent disintegration time and enhance the dissolution rate compared to Guar gum and follows First order kinetics of Drug release.

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