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FORMULATION AND EVALUATION OF ACECLOFENAC FAST DISINTEGRATING TABLETS USING NATURAL POLYMER EXTRACTED FROM "*PHYLLOPHORA RIBIS*"

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ABSTRACT

Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory and analgesic properties. The aim of the present work is to design and formulate a tablet which disintegrate and dissolve rapidly, give its rapid onset of action. The present study was to Formulate and evaluation of fast disintegrating tablet of Aceclofenac by using Natural polymer extracted from "***Phyllophora Ribis***" mushroom by direct compression technique in 05 different concentrations of 2%W/W, 4%W/W, 6%W/W, 8%W/W & 12%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 05 formulations, F5 formulation Aceclofenac with 12%w/w of mushroom extract powder showed the best dissolution rate studies. In-Vitro dissolution studies showed (99.98%) release of drug within 25 minutes and the mechanism of drug release from the tablets was followed to be first order kinetics. It was concluded that the fast disintegrating tablets are prepared by Natural polymer extracted from P.Ribis mushroom acts as a Fast disintegrant and the mushroom polymer powder showed excellent disintegration time.

KEYWORDS: Aceclofenac, NSAID, Phyllophora Ribis, Mushroom extract powder, Superdisintegrant.

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. For many drug substances, conventional fast disintegrating tablets provide clinically effective therapy, by maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patient. These agents are formulated to produce maximum stability, activity and bioavailability.[1]

Isolation of polymer from P.Ribis

Fruit bodies of mushroom samples were washed and dried in an oven at 50 °C for 10 days. Samples were ground into powder in a mixer before polymer extraction. Twenty gram milled mushroom samples were weighted for the polymer extraction. The mushroom samples were treated with 250 ml 2M HCl solution to remove the minerals. The demineralization step took 15 hr at 60 °C. By the end of this time, the samples were filtered through a filter paper with the pore size of 2 µm by rinsing with distilled water. Then, the filtrates were treated with 2M NaOH solution at 85°C for removal of protein residues in the structure. After NaOH treatment of 24 hours, samples washed with distilled water until a neutral pH. This step was followed by a decolourization process using hydrogen peroxide.

Bleaching the samples took one hour. Finally, the samples were rinsed again with distilled water and kept in an oven at 50°C until drying.[2]

METHODOLOGY

Preformulation Studies[3-13]

A Preformulation activity ranges from supporting discovery's identification of new active agents to characterizing physicochemical properties of the new compound that could affect the drug performance and development of an efficacious dosage form. A thorough understanding of these properties may ultimately provide a rationale for the formulation design, or support the need for molecular modification.

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
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 273nm.

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.

Supersaturated solutions of Aceclofenac drug with water, 0.1N HCl, Phosphate buffer-p^H6.4,Phosphate buffer-p^H-6.8, Phosphate buffer-p^H-7.2 were prepared and absorbance was measured at 273nm.

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

Bulk density (ρ_b) = Mass of the powder (M) / Bulk volume of powder (V_b)

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

Carr's compressibility Index
The compressibility index determines the flow property characteristics 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 = $\rho_t - \rho_b / \rho_t \times 100$

Where ρ_t is the tapped density of powder
ρ_b 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 Ratio was measured by using formula,

Hausner Ratio = V_i/ Vo
Where, Vo = Bulk density
V_i = Tapped density

Angle of repose (θ)
The angle of repose of powder blend was determined by the fixed funnel method. The accurately weighed quantity of powder was taken in a funnel. The height of funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of powder cone was measured and angle of repose was calculated using the following equation.

Tan θ = h/r
θ = tan-1 (h/r)
Where θ is the angle of repose
h is the height of cone in cm
r is the radius of the cone base in cm.

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	2.00 - 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 and 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/excipients. Disappearance of Aceclofenac peaks or shifting of peaks in any of the spectra was studied.

Analytical method

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 25mg of Aceclofenac in 25ml of phosphate buffer at P^H 6.8 solution(1mg/1ml). From stock I solution, pipetted out 1ml of solution into a 10 ml 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 tooling's. 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
1	Aceclofenac	100	100	100	100	100
2	***P.Ribis*** extract polymer	2	4	6	8	12
3	Magnesium stearate	4	4	4	4	4
4	Talc	4	4	4	4	4
5	Lactose	90	88	86	84	80
	Total weigh(mg)	200	200	200	200	200

***In-vitro* Evaluation tests for Aceclofenac Fast Disintegrating Tablets[11-19]**

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 Callipers.

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. At a constant compression force (fixed distance between upper and lower punches), hardness increases with increasing die fills and decreases with lower die fills.

Desired hardness: **4-12 Kg/cm^2**

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
Limit: Friability should be less than **1%**

Weight Variation
Individually weighed 20 tablets and calculate 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.

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

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 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± 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
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 273nm.

$$\text{Assay} = (A_t/A_s) \times C_s\,(D_t/W_d) \times 100$$

Where A_t is the Sample(test) absorbance.
A_s is the Standard absorbance.
C_s is the standard concentration of drug.
D_t is the dilution factor.
W_d 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 dissolved in 1Lt of distilled water and sonicated for 10-15 min. The drug release rate of Aceclofenac fast disintegrating tablets was determined using United States Pharmacopeia (USP) dissolution testing apparatus type 2 (paddle method).The dissolution test was performed by using 900 ml of Phosphate buffer pH- 6.8, at 37^0± 0.5^0 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

$$\% \text{ Drug release} = (A_t/A_s) \times C_s\ (D_t \times V_m/W_d \times 1000) \times 100$$

Where A_t is the Sample(test) absorbance.
A_s is the Standard absorbance.
C_s is the standard concentration of drug.
D_t is the dilution factor.
$W_d$is the Weight of the drug.
V_m is the volume of the dissolution medium

Table 4: Dissolution Parameters.

Dissolution medium	Phosphate buffer p^H- 6.8
Dissolution medium volume	900ml
Apparatus	USP-II(Paddle type)
Speed of paddle rotation	50 rpm
Temperature	37^0± 0.50 C
Volume of samples withdrawn	5 ml
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 fast disintegrating tablets 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.

$Q=k_o$ 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

$$\log C = \log C_o - \frac{kt}{2.303}$$

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

Preformulation Studies
API Characteristics
Table 5: API Characteristics.

S. No	Characteristics	Results
1	Description	White
2	Melting Point	149±0.23^{0}c
3	Bulk Density	0.586±0.17 gm/ml
4	Tapped Density	0.668±0.09 gm/ml
5	Carr's Index	12.27±0.22%
6	Hausner's Ratio	1.13±0.05
7	Angle of Repose	33.75^0±0.11

Solubility Analysis

Table 6: Solubility Analysis of Aceclofenac sodium with different solvents.

S. No	Type of Solvent	Solubility(mg/ml)
1.	Water	0.070±0.019
2.	0.1N HCl	0.645±0.006
3.	Phosphate buffer p^H-6.4	0.924±0.028
4.	Phosphate buffer p^H-6.8	0.981±0.554
5.	Phosphate buffer p^H-7.2	0.931±0.035

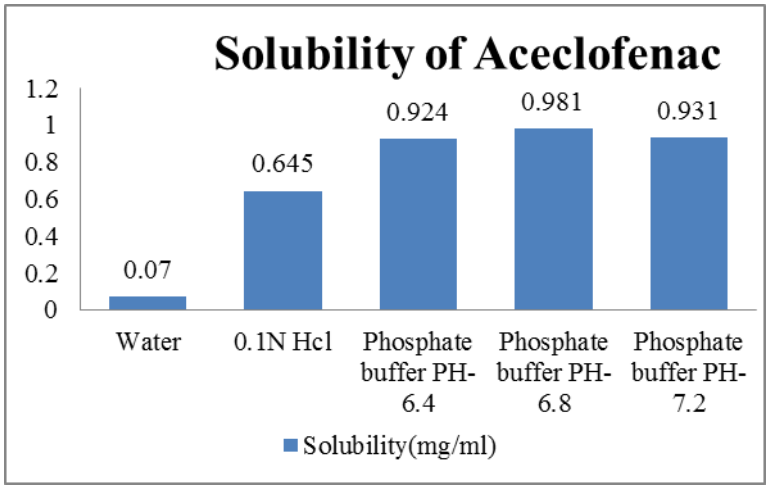

Figure-1: Solubility Analysis of Aceclofenac with different solvents.

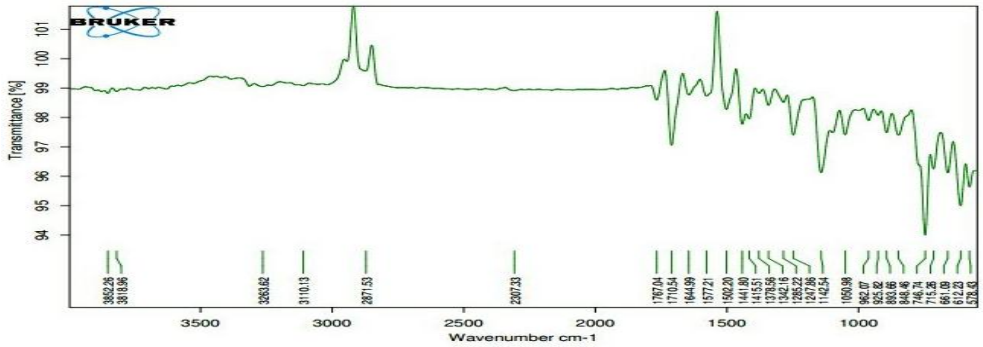

Figure-2: FTIR Spectra of Aceclofenac.

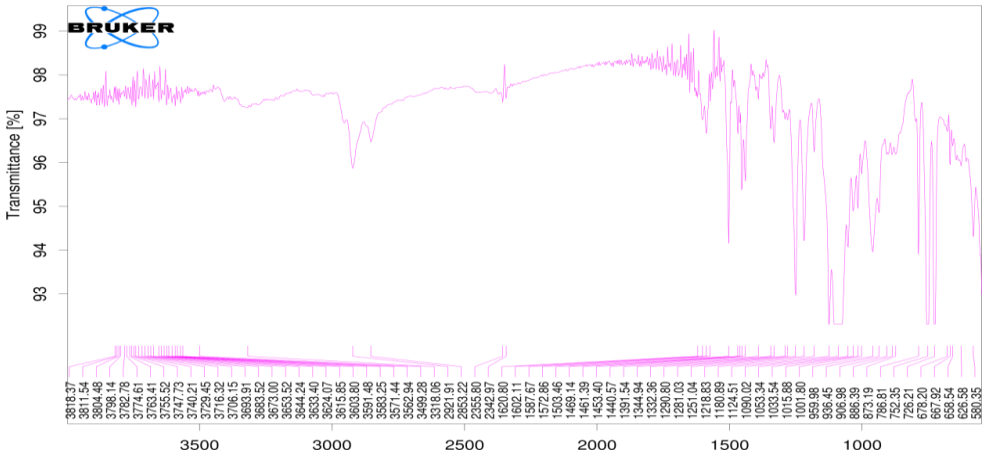

Figure 3: FTIR Spectra of Aceclofenac+Polymer.

Table 7: Standard Calibration Curve Data of Aceclofenac.

S.NO	Concentration (µg/ml)	Absorbance at 273 nm
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

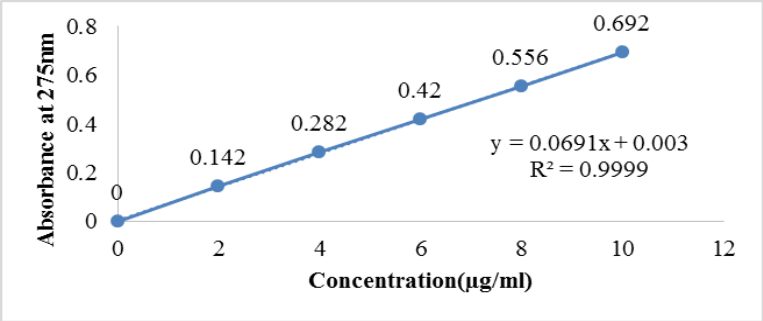

Figure 4: Standard Calibration curve of Aceclofenac.

Table 8: Evaluation of Flow properties of Blends of various trail batches.

Formulation Code	Angle of repose (Θ)	Bulk Density (gm/cm^3)	Tapped Desity (gm/cm^3)	Compressibility (%)	Hausners ratio
F1	32.23±0.59	0.598±0.11	0.692±0.35	15.71±0.45	1.157±0.23
F2	35.38±0.33	0.580±0.20	0.671±0.25	13.56±0.18	1.156±0.08
F3	33.02±0.25	0.525±0.38	0.608±0.59	13.65±0.25	1.158±0.16
F4	34.43±0.14	0.610±0.08	0.720±0.24	15.27±0.72	1.180±0.74
F5	32.34±0.45	0.601±0.67	0.700±0.19	14.14±0.21	1.164±0.58

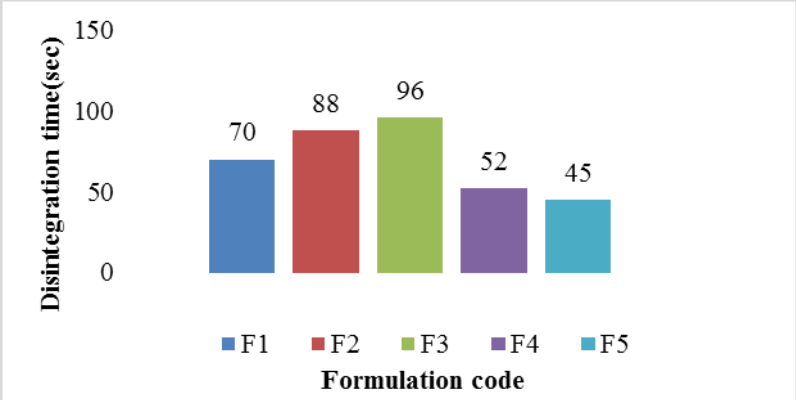

Figure-5: Disintegration time of Formulations (F1-F5).

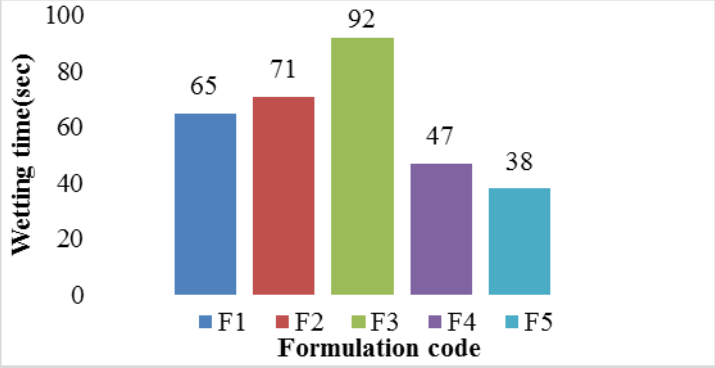

Figure-6: Wetting time of Formulations (F1-F12).

***In - vitro* Dissolution Studies**

Table-9: Dissolution profiles of Aceclofenac with natural polymer tablets.

Time (Min)	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	14.69±0.05	17.58±0.11	21.33±0.24	32.23±0.14	35.54±0.19
10	29.31±0.12	32.42±0.05	38.34±0.37	42.9±0.35	48.32±0.21
15	44.05±0.07	49.09±0.16	52.67±0.28	56.33±0.12	72.43±0.55
20	55.12±0.21	59.10±0.24	64.17±0.26	67.07±0.02	87.33±0.20
25	66.03±0.25	74.23±0.18	76.25±0.22	88.20±0.08	99.9±0.01
30	78.67±0.07	79.34±0.54	80.45±0.64	94.45±0.25	
40	80.02±0.20	82.59±0.45	94.28±0.38	99.85±0.58	
50	85.76±0.09	91.33±0.18	99.6±0.61		
60	99.06±0.4	99.58±0.20			

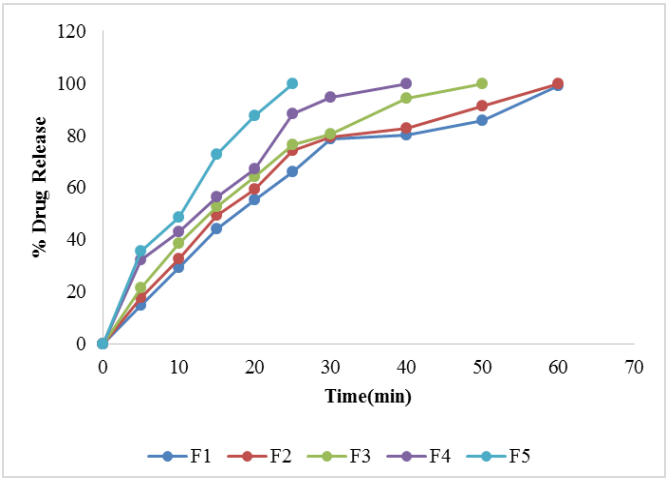

Figure 7: Dissolution graphs of 5 formulation.

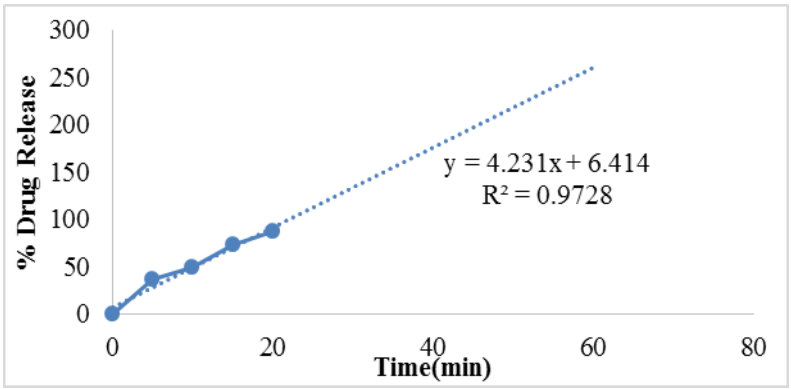

Figure 8: Zero order kinetics of optimized Formulation.

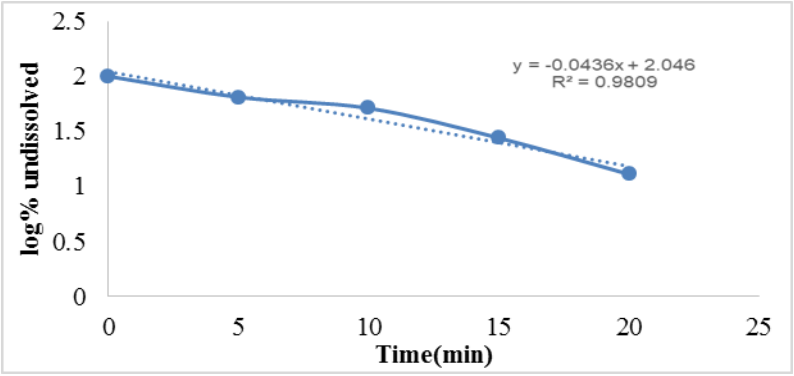

Figure 9: First order kinetics of optimized Formulations.

CONCLUSION

The present study was to formulate and In-vitro evaluation of Aceclofenac Fast disintegrating tablets by using ***Phyllophora Ribis*** as a natural Polymer in the percentage of 2% W/W, 4% W/W, 6% W/W, 8% W/W and 12% W/W.

The powder blendwere evaluated by various physical characteristic tests such as Bulk density, Tapped density, Compressibility index, Hausner's ratio, Angle of repose. So the values were found to be within the limits.

Among all the formulations Assay, Hardness, Friability, Weight variation, Thickness, Disintegration time and Wetting time values were found to be within the limits. As the concentration of Natural polymer increased then the Disintegration time was decreased so selected Natural polymers acts as Fast disintegrating agents. Among all the 05 formulations the optimised formulatioN "F5" (12%W/W) showed better drug release when compared to other formulations. In-Vitro dissolution studies showed 99.98% of drug release within 25 minutes and the mechanism of drug release from the FDT release was followed to be First order kinetics.

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