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Formulation and In-Vitro Evaluation of sustained release Matrix Tabelts of Aceclofenac by using different natural polymars

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ABSTRACT

The objective of this study was to develop a sustained release matrix tablet of aceclofenac using different natural polymers (Guargum, Xanthine gum, Chitosan) in various proportions as release controlling factor by direct compression method. The powders for tableting were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and hausner rato etc. The drug polymer interaction was studied by FTIR and DSC thermal analysis. The tablets were subjected to thickness, weight variation test, drug content, hardness, friability and *in vitro* release studies. The *in vitro* dissolution study was carried out for 11 hours using United States Pharmacopoeia (USP) 1 Basket-type dissolution apparatus in 0.1N hydrochloric acid for first 2 hours and phosphate buffer pH 7.4 for 9 hours. The powder blend showed satisfactory flow properties. All the tablets complied with pharmacopoeial specifications. The in vitro release study shows that only F9 formulation was releases the drug in a sustained manner for 11 hours. From this study, a decrease in release kinetics of the drug was observed when the polymer concentration was increased. The drug release from these formulations was satisfactory after 3 months storage in 40C and 75% RH. Besides, this study explored the optimum concentration and effect of polymer(s) on acelofenac release pattern from the tablet matrix for 11 hour period.

Key words: Aceclofenac, Sustained Release, Hydrophillic Matrix, Direct Compression.

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INTRODUCTION

Aceclofenac is an orally administered phenyl acetic acid derivatives with effects on a variety of inflammatory mediators. Aceclofenac contains not less than 99.0% and not more than the equivalent of 101.0 percent of 2-[[2-[2-[(2, 6-dichlorophenyl) amino] phenyl] acetyl] oxy] acetic acid. It is an effective analgesic and anti-inflammatory agent with a good tolerability profile. Through its analgesic and anti-inflammatory properties, aceclofenac provides symptomatic relief in a variety of painful conditions.

A reduction in the stimulated generation of reactive oxygen species, which may play a role in joint damage, was observed after 15 days in these patients. At day 180, O_2 release was similar to that seen in a group of 41 healthy untreated individuals. The successful treatment of arthritis depends on the maintenance of effective drug concentration level in the body for which a constant and uniform supply of drug is desired. The shorter biological half life (about 4 hours) and the dosage frequency more than one per day make aceclofenac an ideal candidate for sustained release formulations, which reduce the frequency of dose in order to improve patient compliance. The most common method of modulating drug release is to include it in a matrix system. Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. Among the natural polymers, cellulose and gum derivatives are frequently used because of its nontoxic nature, easy compression, swelling properties and accommodation to high levels of drug loading.

Oral sustained release dosage form by direct compression technique is a very simple approach in the pharmaceutical area for its ease, compliance, faster production, avoids hydrolytic or oxidative reactions occurred during processing of dosage forms. Sustained or controlled drug delivery occurs while a drug embedded within a polymer that may be natural or semi-synthetic or synthetic in nature. The polymer is judiciously combined with the drug or other active ingredients in such a way that the active agent is released from the material in a predetermined fashion and released drug at constant rate for desired time period. There are number of techniques applied in the formulation and manufacturing of sustained release dosage form. However, the matrix tablet by direct compression has attracted much attention due to its technological simplicity in comparison with other controlled release systems.

MATERIALS AND METHODS

Materials

Aceclofenac was obtained from Lupin Research Park, (Pune India). Chitosan were purchesed from Paras Chem suppliers (Pune, India). Other materials Xanthan Gum, Guar gum Lactose, Polyvinylpyrolidone, Methyl paraben Talc and Magnesium Stearate were purchased from Qualigens fine chemicals, (Mumbai, India).

Methods

Preparation of sustained release tablets

The composition of different formulations of Aceclofenac SR matrix tablets is shown in Table 1. Different tablet formulations were prepared by direct compression technique. All the powders passed through 40/60 mesh sieve. The required quantity of drug, various polymers and other ingredients were mixed thoroughly. Talc and magnesium stearate were finally added as a glidant and lubricant respectively. The blend was directly compressed (10 mm diameter, round flat faced punches) using multiple punch tablet compression machine (Cad mach Machinery Ltd., Ahmedabad, India). Each tablet contained 200 mg of Aceclofenac.

Characterization of powder blend

The tablet blend were evaluated for their bulk density, tapped density, compressibility index, angle of repose and Hausner ratio. The tapping method was used to determine the bulk density, tapped density, percent compressibility index and Hausner ratio.

Compressibility index = $[\rho_t - \rho_b / \rho_t] \times 100$

Hausner ratio= ρ_t / ρ_b

Where ρ_t = tapped density

ρ_b = initial bulk density of tablet blend.

Angle of repose θ of the tablet blend measures the resistance to particle flow and was determined by fixed funnel method.

Differential scanning calorimetry (DSC)

The DSC analysis of pure drug, drug+ Guar gum, drug+ Chitosan and drug+ Xanthan gum were carried out using a Shimadzu DSC 60, (Japan) to evaluate any possible drug-polymer interaction. The 2 mg sample were heated in a hermetically sealed aluminum pans in the temperature range of 25-300ºc at heating rate of 10ºc /min under nitrogen flow of 30ml/min.

Fourier transform infra-red (FTIR) spectrum

FTIR study was carried out to check compatibility of drug with excipients. Infrared spectrum of aceclofenac was determined on fourier transform infrared spectrometer using KBR dispersion method. The base line correction done using dried potassium bromide, then the spectrum of dried mixture of drug and potassium bromide was run followed by drug with various polymers.

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Evaluation of sustain release tablets

The prepared SR tablets were evaluated for Dimension (Diameter and Thickness) using 6 tablets (vernier calipers), uniformity of weight using 20 tablets (Shimadzu BL-220H analytical balance), hardness using 6 tablets (Monsanto hardness tester), friability using 20 tablets (Roche type friabilator).

Drug content

An accurately weighed amount of powdered aceclofenac (100 mg) was extracted with water and the solution was filtered through 0.45-µ membrane filter paper. The absorbance was measured at 275 nm after suitable dilution by using Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer.

In vitro release studies

The release rate of aceclofenac from sustained release tablets was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus 1 (paddle method; Veego Scientific VDA-8DR, Mumbai, India). The dissolution test was performed using 900 ml of 0.1N hydrochloric acid for first 2 hours and phosphate buffer pH 7.4 for 9 hours, at 37 ± 0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with dissolution medium. Absorbance of these solutions was measured at 275 nm using a Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer. For each formulation, the experiments were carried out in triplicate. The percentage release was calculated by using PCP disso V3 software.

Stability study

Sustained release Aceclofenac tablets formulated and accelerated stability studies were carried out as per ICH guidelines. The prepared Aceclofenac Sustained release tablets containing guar gum, Xanthan gum, Chitosan. The formulation (F9) was selected for stability study on the basis of in vitro drug dissolution studies. The Sustained release tablets were stored at 40°C/75% RH in closed high density polyethylene bottles for 3 months. The samples were withdrawn after periods of 1 month, 2 month and 3 month. The samples were analyzed for its hardness, drug content and In vitro drug release.

RESULT AND DISCUSSION

The prepared sustained release tablets were evaluated for thickness, weight variation, hardness, friability, drug content, in vitro drug dissolution studies and stability studies. All the studies were performed in triplicate, and results are expressed as mean ± SD.

Characterization of powder blend

The powders prepared for compression of sustained release tablets were evaluated for their flow properties, the results were shown in Table 2. Angle of repose was in the range of 20.30±0.49º to 22.37±0.30 which indicates excellent flow of the powder for all formulations. The bulk density of the powder formulation was in the range of 0.672±0.009 to 0.697±0.005 gm/ml; the tapped density was in the range of 0.777±0.011 to 0.790±0.06 gm/ml, which indicates that the powder was not bulky. The Carr's index was found to be in the range of 10.85±0.94 to 13.44±1.71, the Hausner ratio was found to be in the range of 1.11±0.02 to 1.15±0.011, indicating compressibility of the tablet blend is good. These values indicate that the prepared powdered exhibited good flow properties.

Differential scanning calorimetry (DSC)

Any possible drug polymer interaction can be studied by thermal analysis. Aceclofenac exhibits a sharp endothermic peak at 158.3 °C shown in figure 1a, which corresponds to its melting point. The Aceclofenac+Guar gum exhibit a sharp endothermic peak at 158.7ºC, Aceclofenac+Chitosan exhibit a sharp endothermic peak at 152ºC and Aceclofenac+ Xanthan gum exhibit a sharp endothermic peak at 155.3ºC shown in figure 1b, 1c and 1d respectively. Hence DSC study shows that there is no any drug polymer interaction.

Physicochemical evaluation of sustained release tablets

The sustained release Aceclofenac tablets were off-white, smooth, and flat shaped in appearance. The results of physicochemical characterizations are shown in Table 3. The thickness of sustained release tablets was measured by vernier caliper and was ranged between 3.2±0.05 and 3.3±0.05 mm. The weight variation for different formulations (F1 to F9) was found to be ±1.90% to ±2.40%, showing satisfactory results as per Indian Pharmacopoeia (IP) limit. The hardness of the Sustained release tablets was measured by Monsanto tester and was controlled between 5.66±0.44 and 5.83±0.25 kg/cm2. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The percentage of drug content for F1 to F9 was found to be in between 97.89±6.56 to 100.59±6.09 of aceclofenac it complies with official specifications.

In vitro release study

In vitro dissolution studies of all the formulations of aceclofenac sustained release tablets were carried out in 0.1 N HCl and phosphate buffer (pH 7.4). The study was performed for 11 hours, and percentage drug release was calculated at 1 hours time intervals. The results of in vitro dissolution studies of all formulations were shown in Figure 2. The higher initial drug dissolution was observed in tablets containing guar gum (F1 and F2) and xanthan gum (F4, F5 and F6). This showed that in less concentration guar gum and xanthan gum hydrated more rapidly in the presence of phosphate buffer pH 7.4. The formulation containing chitosan (F9)

was sustained the drug release for 11 hours. The variation in drug release was due to different types of polymers and different concentrations of polymer in all the nine formulations. When % drug release was plotted versus time (figure 2), it was observed that for three of the polymers used, an increase in polymer concentration from 15%-45%, induces a decrease in the release rate. The drug release rate from chitosan matrix was found to be less as compared to guar gum and xanthan gum. This might be due to slow hydration of matrix and its property to from a thick gel layer, which retard the drug release from the tablet.

It is expected that the developed formulation should have the following theoretical drug release profile, *i.e*., 20 to 25 % in 1 h, 25 to 45 % in 2 h, 55 to 75 % in 4 h, 65 to 85 % in 6 h and 85 % after 8 h. Formulations F1 to F8 failed to meet the needed theoretical drug release profile. Formulation F9 meet the needed theoretical drug release profile for these reasons, it was considered that the formulation F9 was best formulation among all the nine formulations of this series. The percentage drug release data of formulation F9 were shown in table 4.

Stability study

The stability study results obtained were shown in Table 6. The aceclofenac sustained release tablets did not show any significant change in physicochemical parameters and other tests (Table 6). Thus, it was found that the sustained release tablets aceclofenac of (F9) were stable under these storage conditions for at least 3 months [1-15].

CONCLUSION

The aim of the study was to study the effect of various hydrophilic polymers on in vitro release rate from sustained release tablet of Aceclofenac based on a low density polymer. The sustained release drug delivery was a promising approach to achieve a prolonged therapeutic action of drug. Different types of matrix forming polymers guar gum, Xanthan gum and chitosan were studied. Formulation F9 containing chitosan polymer showed sustained drug release for 11 hours. The Aceclofenac sustained release tablets were stable at 40°C/75% RH up to 3 months.

ACKNOWLEDGEMENTS

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Table 1: Composition of Aceclofenac Sustained Release tablet

Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Aceclofnac	200	200	200	200	200	200	200	200	200
Guar gum	30	60	90	-	-	-	-	-	-
Xanthan gum	-	-	-	30	60	90	-	-	-
Chitosan	-	-	-	-	-	-	30	60	90
Lactose	84	54	24	84	54	24	84	54	24
Polyvinylpyrolidone	14	14	14	14	14	14	14	14	14
Methyl paraben	6	6	6	6	6	6	6	6	6
Talc	10	10	10	10	10	10	10	10	10
Magnesium Stearate	6	6	6	6	6	6	6	6	6
Total weight	350	350	350	350	350	350	350	350	350

Table 2: Flow properties of powder

Formulation Code	Angle of repose (θ)*	Bulk density (gm/cm3)*	Tapped density (gm/cm3)*	Hausner ratio (HR)*	Carr's index (IC)*
F1	21.30±0.19	0.690±0.006	0.779±0.008	1.12±0.011	11.41±0.94
F2	20.99±0.28	0.693±0.010	0.786±0.011	1.13±0.02	11.99±2.07
F3	20.3±0.49	0.697±0.0005	0.788±0.008	1.12±0.011	11.95±1.60
F4	22.37±0.30	0.695±0.01	0.779±0.002	1.12±0.015	10.85±0.94
F5	22.11±0.24	0.684±0.009	0.786±0.01	1.14±0.001	12.92±0.88
F6	21.07±0.29	0.692±0.004	0.777±0.011	1.11±0.02	12.02±1.75
F7	20.88±0.60	0.682±0.004	0.773±0.01	1.13±0.02	11.78±1.65
F8	20.84±0.72	0.672±0.009	0.790±0.06	1.15±0.011	12.87±0.84
F9	21.15±1.00	0.683±0.005	0.789±0.05	1.15±0.02	13.44±1.71

*All the values are expressed as mean± SE, n=3.

Table 3: Physico-Chemical Characterization of Aceclofenac SR Tablets

Code	Thickness (mm)*	Weight variation test (%)	Hardness (kg/cm^2)*	Friability (%)*	Drug content (%)*
F1	3.2±0.14	±2.30	5.83±0.25	0.42±0.03	97.89±6.65
F2	3.2±0.10	±2.40	5.66±0.40	0.48±0.08	100.59±6.09
F3	3.3±0.07	±1.90	5.58±0.37	0.49±0.08	96.32±5.92
F4	3.2±0.07	±2.19	5.75±0.41	0.45±0.02	97.02±5.79
F5	3.2±0.05	±2.12	5.66±0.40	0.47±0.05	97.99±5.18
F6	3.3±0.054	±1.92	5.66±0.40	0.54±0.04	100.11±2.38
F7	3.3±0.089	±2.09	5.83±025	0.53±0.09	99.14±5.37
F8	3.3±0.075	±2.12	5.66±0.40	0.49±0.04	99.15±4.680
F9	3.2±0.075	±2.03	5.57±0.37	0.46±0.05	100.11±2.65

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*All the values are expressed as mean± SE, n=3.

Table 4: In vitro release of optimized formulation F9

Time (hours)	Cumulative % Drug release (%)*
0	0
0.5	2.93±0.48
1.0	5.07±0.14
1.5	8.32±0.36
2.0	11.03±0.68
2.5	19.63±0.35
3	33.91±0.97
4	45.57±0.13
5	54.57±1.26
6	67.60±1.50
7	72.30±0.48
8	80.51±0.93
9	86.32±1.32
10	91.79±0.91
11	95.88±1.19

*All the values are expressed as mean± SE, n=3.

Table 5: Stability studies of optimized formulation (F9) of sustained release Aceclofenac tablet

Characteristic	Initials	1 Month	2 Month	3 Month
Hardness (kg/cm2)*	5.57±0.37	5.33±0.76	5.16±0.422	5.00±0.00
Drug content (mg/tablet)*	101.11±2.65	98.07.04±0.79	96.96.±0.13	95.17±0.70
In vitro drug release at 11 hour*	95.58±1.11	94.62±1.11	93.35±0.32	91.26±1.61

*All the values are expressed as mean± SE, n=3.

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Fig 1a: IR spectra of Aceclofenac

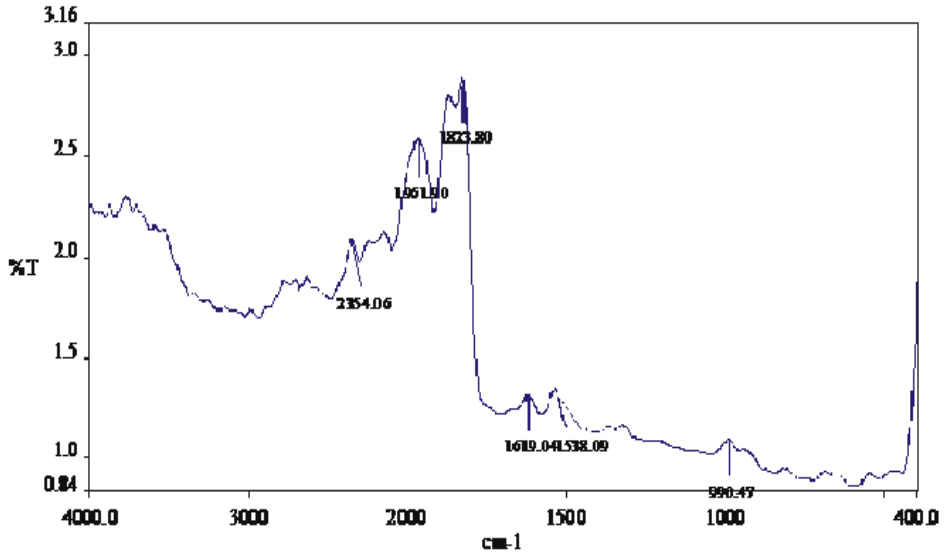

Fig 1b: IR of Aceclofenac and Guar gum

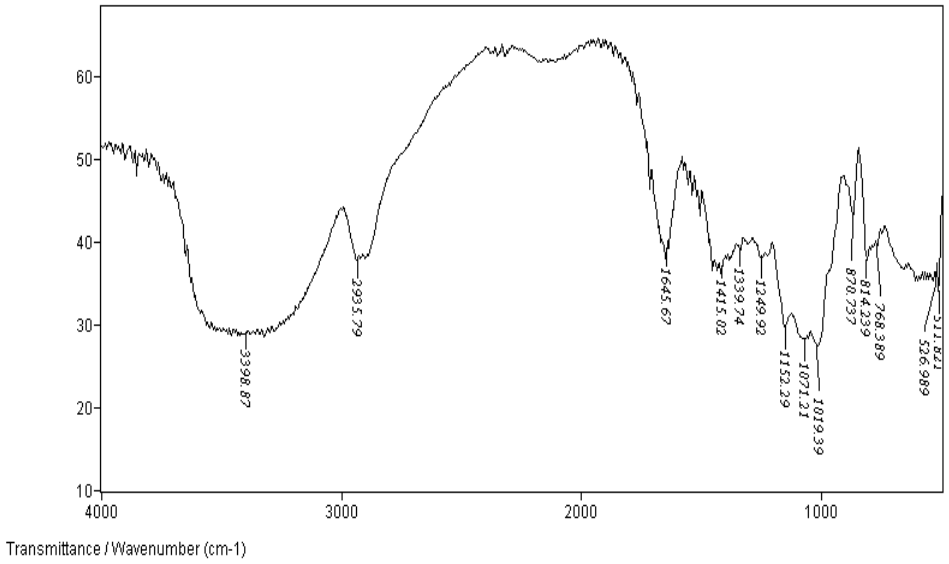

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Fig 1c: IR of Aceclofenac and Xanthan gum

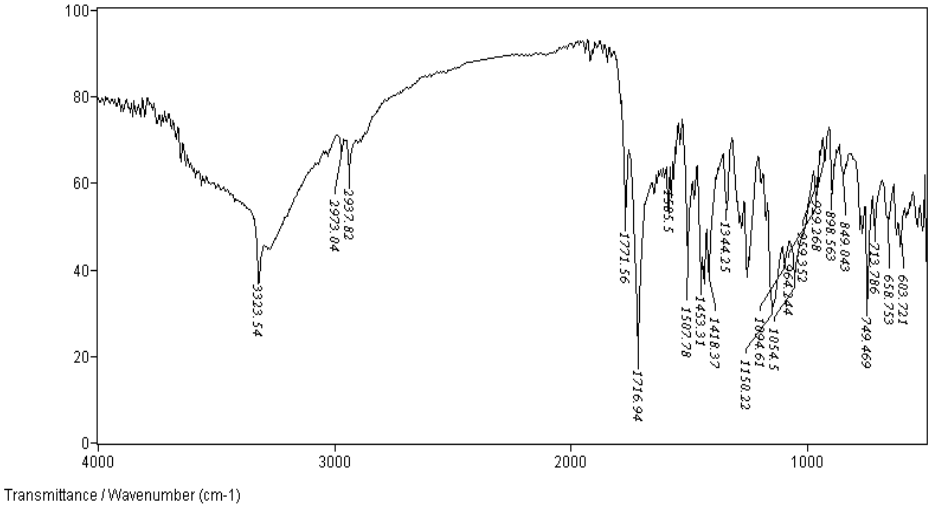

Fig 1d: IR of Aceclofenac and Chitosan

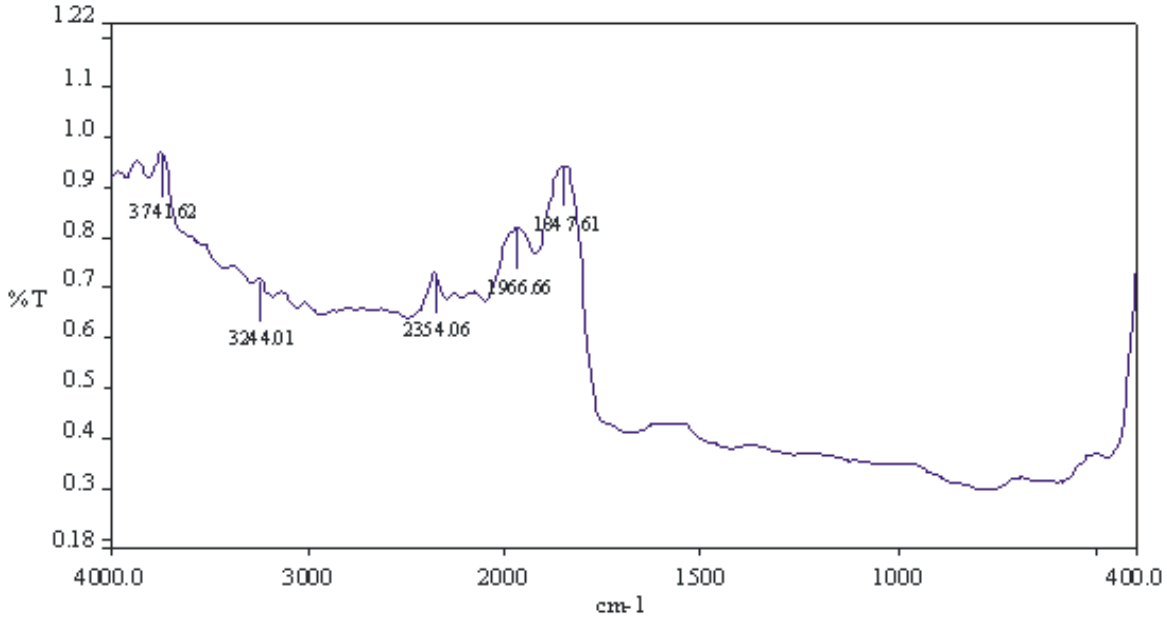

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Fig 2a: DSC of Aceclofenac

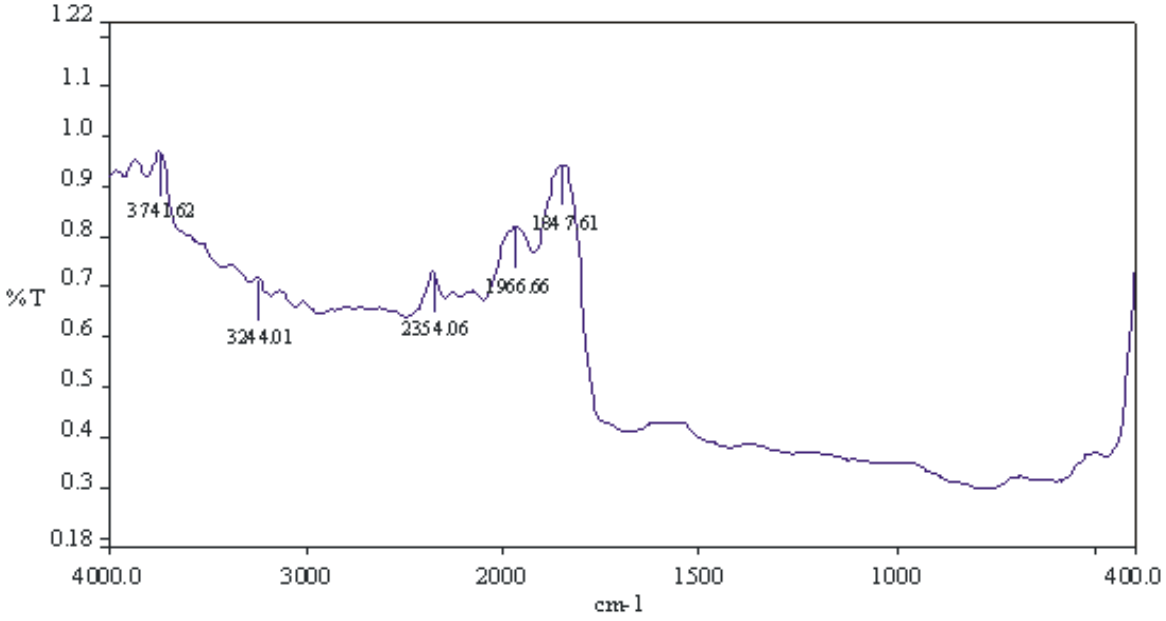

Fig 2b: DSC of Aceclofenac and Guar gum

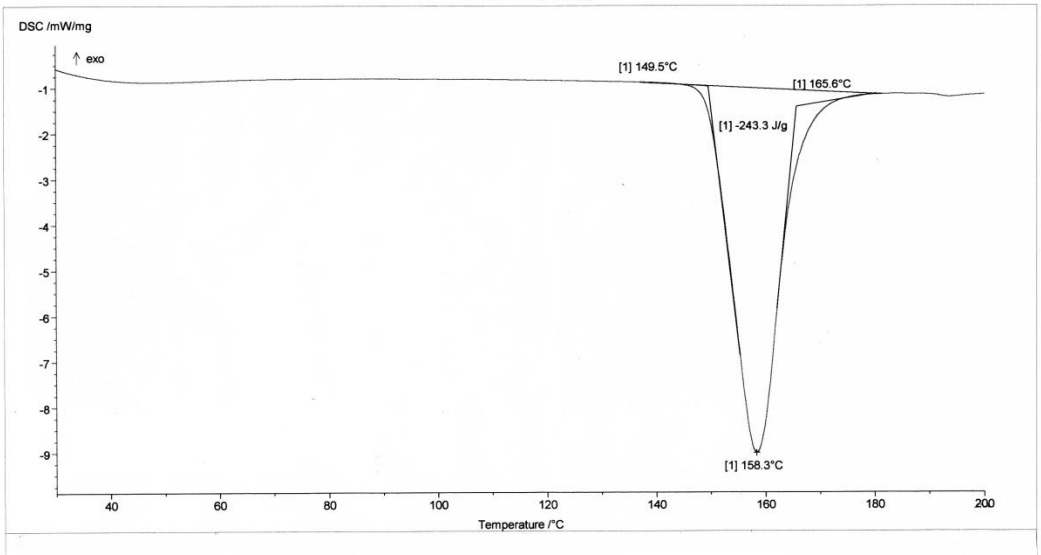

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Fig 2c: DSC of Aceclofenac and Xanthan Gum

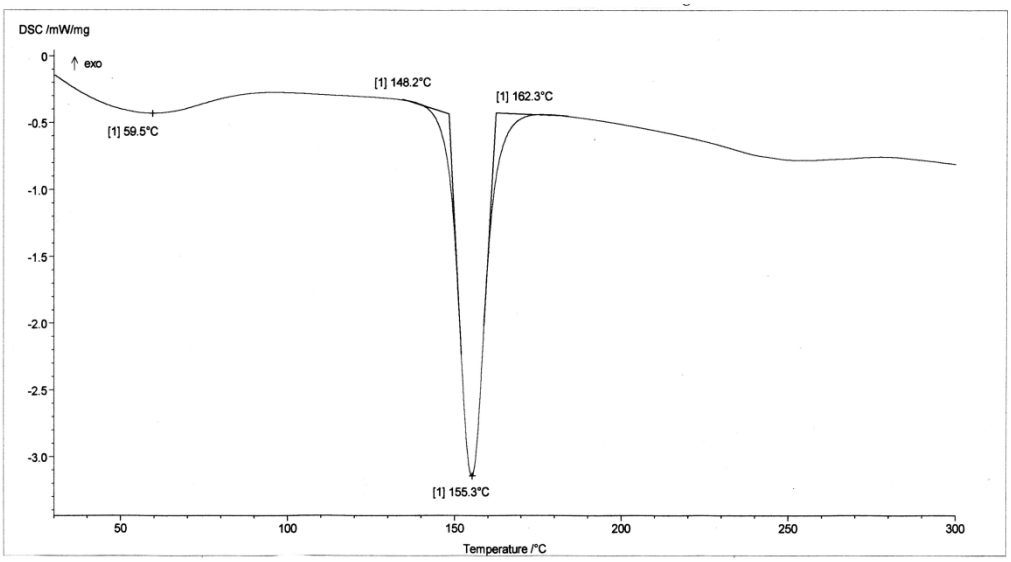

Fig 2d: DSC of Aceclofenac and Chitosan

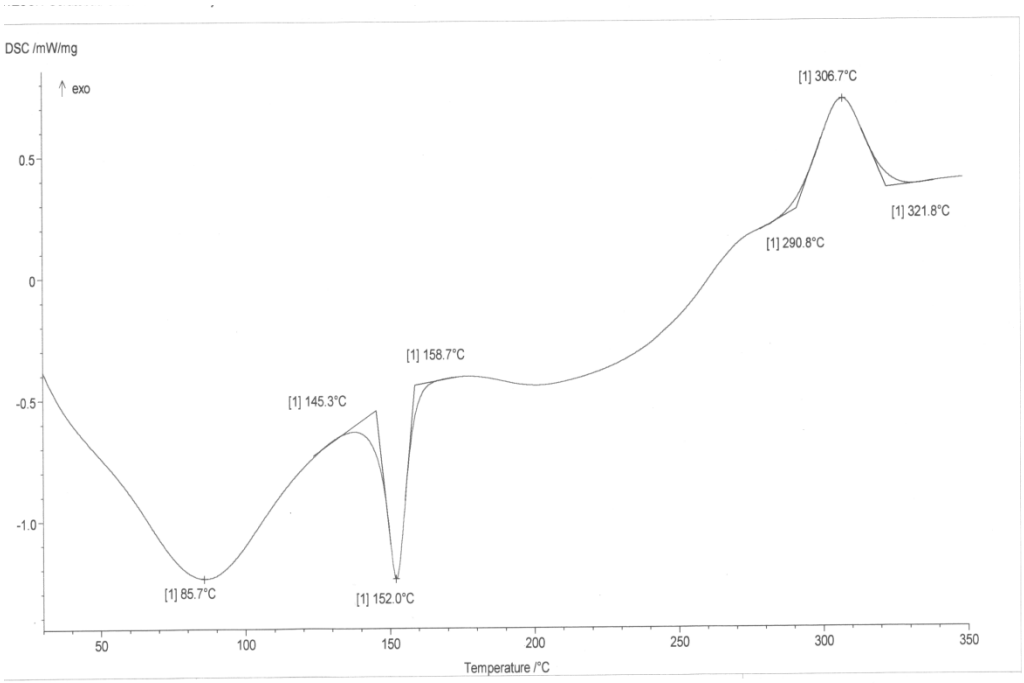

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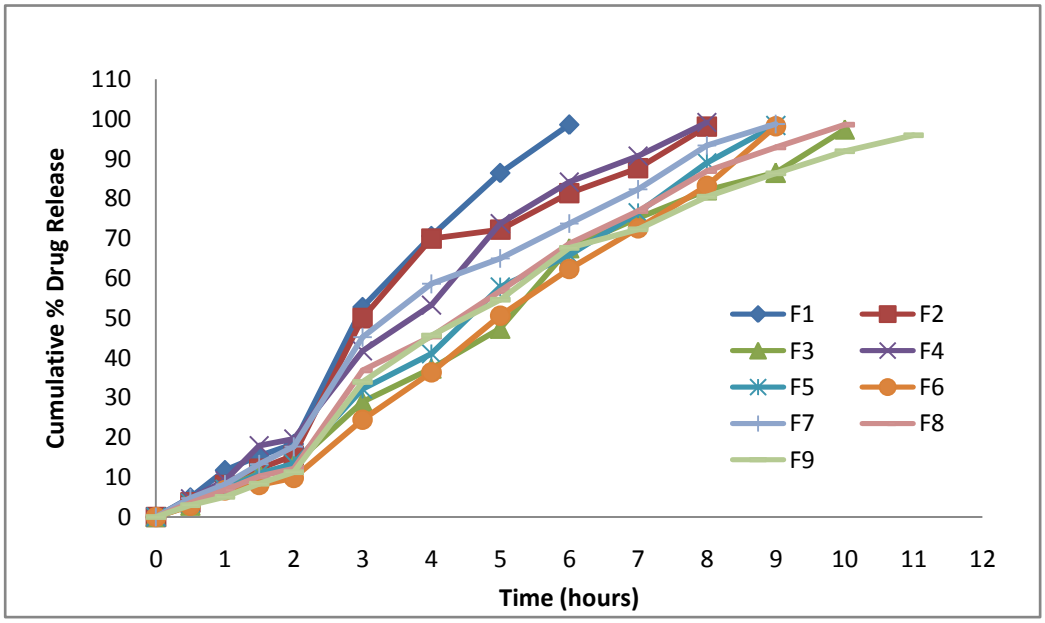
Fig 3: Cumulative Percentage Drug Release



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