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Formulation and *In-Vitro* Evaluation of Sustained Release Tablets Using Natural Polymers

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ABSTRACT

The current work deals with the formulation and development of sustained release tablets of Aceclofenac using natural polymers. *Anacardium Occidentale* (Cashew) gum and xanthan gum were used as a sustained release polymers. Literature survey has revealed that *Anacardium Occidentale* (Cashew) gum has been used as a pharmaceutical excipient, namely: as a binding agent in tablet formulations, emulsifying agent in emulsions, suspending agent in suspensions and mucoadhesive in mucoadhesive tablet. In this present study we tried to explore its drug release control properties. Aceclofenac drug was used as model drug and xanthan gum was used alone and in combination with cashew gum. Collected cashew gum was purified and checked for its purity by determination of microbial load. Different formulations were set by taking different concentrations of cashew gum, xanthan gum and combinations of both the gums. Tablets were prepared using wet (non-aqueous) granulation method. The flow properties of the granules were evaluated (angle of repose, bulk density, taped density, Car's index, Hausner's ratio) and the physical properties of the compressed tablets, namely dimensions, uniformity of weight, hardness, friability and dissolution rate were determined. All results obtained from these tests were found to be within permissible limit. The granules had good flow properties as evidenced by their Hausner's ratio and Carr's index values. From the overall result obtained and drug release profile we can conclude that cashew gum can be used as sustained release polymer in sustained release tablet.

Keywords: Aceclofenac, *Anacardium Occidentale,* sustained release.

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INTRODUCTION

Tablet is one of the most challenging dosage form. It is most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing. Some drugs have short half-life so frequency of dosing is more. Increase in dosing frequency increases patient non-compliance. The goal in designing sustained release drug delivery system (SRDDS) is to reduce the frequency of dosing and to increase effectiveness of drug by local action by the site of action, reducing the dose required or providing uniform drug delivery[1]. Sustained release dosage forms are designed to achieve prolonged therapeutic effect by continuously release of medication over an extended period of time after administration of a single dose. Sustained release constitutes any dosage forms that provide medication over an extended period of time as shown in figure 1. This figure shows Plasma concentration-time curves obtained following per oral administration of one modified release (MR) dosage form containing the same drug. In case of oral administration dosage forms effective period is measured in hours and critically depends on the residence time of the dosage form in gastro-intestinal track (GIT) [2, 28].

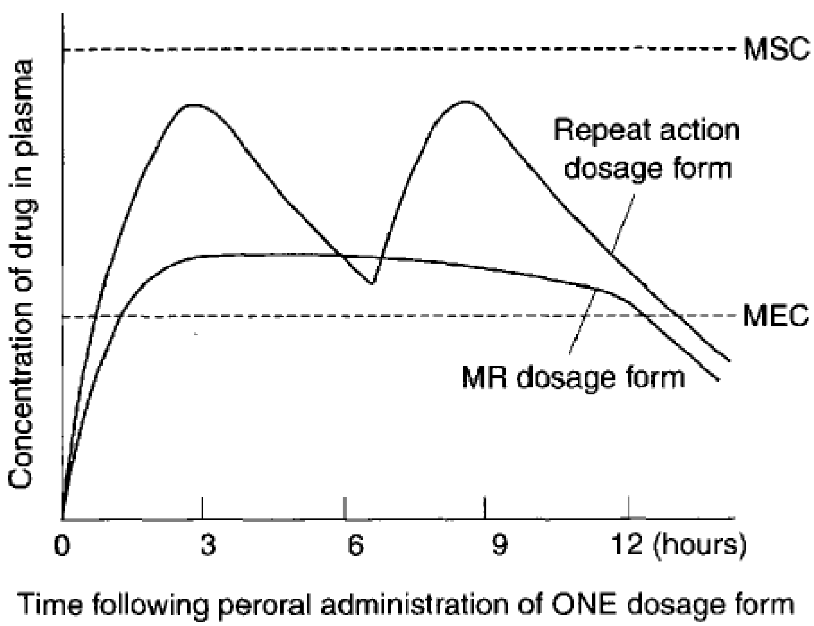

Figure 1: Plasma concentration-time curves obtained following peroral administration of one modified release (MR) dosage form containing the same drug. MSC = maximum safe concentration, MEC = minimum effective concentration[28]

Literature survey has revealed that *Anacardium Occidentale*(Cashew) gum has been used as a pharmaceutical excipient, namely: as a binding agent in tablet formulations, emulsifying agent in emulsions, suspending agent in suspensions and mucoadhesive in mucoadhesive tablet.

Aceclofenac drug was used as model drug and xanthan gum was used alone and in combination with cashew gum. Collected cashew gum was purified and checked for its purity by doing tests[11, 12, 21, 23, 24, 13]. In SRDDS release of drug is over an extended period of time at non-specific site. They show first order kinetics. Release of drug is concentration dependent. This SRDDS have lot of advantages and very few disadvantages as compared to conventional dosage forms. There are so many methods to achieve sustained release of drug from the dosage form. One of them is hydrophilic matrix tablets[3]. Details about hydrophilic matrix tablets are given below.

Hydrophilic matrix tablets[4]

Principles of Formulation and Release Mechanisms

Hydrophilic matrix tablets are composed of an active substance, a hydrophilic polymer release modifiers, lubricants, and glidant. The release mechanism for this type of formulation starts with isolations of hydrophilic matrix polymers and the formation of a highly viscous polymer layer around the tablet (Figure2).

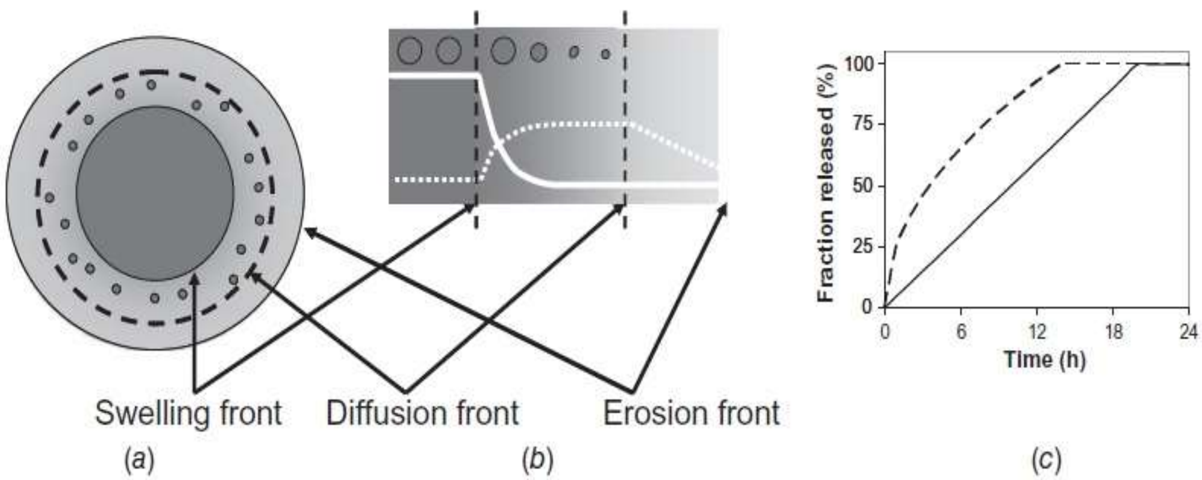

Figure 2: Hydrophilic matrix system

a) Hydrophilic matrix system shown with core (dark gray) and drug particles (small dark gray particles). The swelling, diffusion, and erosion fronts are depicted. (b) Dependencies of volume fraction polymer (solid line) and dissolved drug (broken line) as function of position in matrix system together with swelling, diffusion, and erosion fronts. Top shows how the solid drug particles diminish in size. (c) Examples of drug release as function of time for erosion - controlled (n = 1, solid line) and diffusion - controlled systems (broken line, n = 0.5)[4](cut see-shayne cox gad, ph.d., d.a.b.t., pharmaceutical manufacturing handbook production and processes, a john Wiley & sons, inc., publication,2008,1191-1214)

This layer is often referred to as a gel layer even though it normally contains only physical entanglements and not chemical cross - linkers, which is traditionally required for gels. However, the gel layer surrounds the inner (more or less dry) part of the tablet and this part is called the core. In traditional hydrophilic tablets, the active substance particles are embedded in the matrix carrier. The dissolution process of the active substance can start when the carrier material has dissolved in water and formed the aqueous gel layer, since without exposure to water the active substance cannot dissolve. Therefore, the "dry" core will shield the active drug from dissolution, which is one reason for the extended drug release from this type of formulation. The release process for hydrophilic matrix tablets can be schematically described as in Figure 2 .The left side of the figure shows a hydrophilic tablet undergoing dissolution, swelling, and release. An interface between the solution and gel layer, here called the erosion front, can be identified, and the polymer chains and drug molecules are released at this front. In the gel layer, the polymer concentration will decrease (Figure 2) from a highly concentrated solution at the swelling front, the interface between the gel layer and more or less dry core, to a diluted polymer solution at the erosion front. At the same time, the water content in the gel layer gradually increases from the center of the tablet toward the erosion front, and thus the dissolution of the active substance particles can start already in the gel layer. However, the volume fraction of dissolved drug depends on the amount of available water, which in turn is a function of the position in the gel layer. Assuming that the drug saturation concentration is equal in water solutions and polymer gels, the volume fraction dissolved drug will correlate with the volume fraction water available, and the volume fraction drug will gradually increase with increasing distance from the core. Far from the core, the variations in the concentration of polymer and water are less pronounced and, as long as solid particles coexist with the saturated drug solution, the volume fraction of the drug will theoretically be almost constant. A third front has also been introduced, the diffusion front, which corresponds to the position in the gel layer where all of the active substance has dissolved. Between the swelling and dissolution front, dissolved and undissolved drug particles will coexist, but between the dissolution and erosion fronts, only dissolved drug molecules occur. In this region, the diffusion of drug out from the matrix will give rise to a decrease in the volume fraction of the drug.

Manufacturing of Hydrophilic Matrix Tablets[4]

The traditional way of producing hydrophilic matrix tablets resembles the production of the core for membrane - coated tablets and insoluble matrix tablets. It includes a mixing step, possibly a granulation step, a compaction step, and sometimes a coating step. However, one large difference between the production of insoluble and soluble matrix systems is notable; the latter matrix type has strong interactions with water, which complicates the production steps when water is present. Therefore, for hydrophilic matrix systems with large fractions of hydrophilic polymers, traditional wet granulation with water as granulation liquid may cause problems with formation of hard lumps. To avoid this problem, a new technique using foam granulation has been suggested[4]. During granulation, the foams will flow on the top of already foam - wetted particles, which may lead to superior distribution of the granulation liquid. An alternative wet granulation method is to use organic solvents such as ethanol as granulation liquid.

MATERIALS AND METHOD

Aceclofenac was obtained from Aarti drugs ltd. MIDC Tarapur. Cashew gum was collected from the bark of cashew tree. Other materials Xanthan Gum, Lactose, Polyvinyl pyrolidone, microcrystalline cellulose, Talc and Magnesium Stearate were purchased from Meher Chemie Pvt. Ltd. Mumbai- 67. And isopropyl alcohol was purchased from SD fine chem. Limited 315-317 TV industrial estate, Warli road Mumbai.

Preparation of Matrix Tablets[7, 10,22]

Matrix tablets, each containing 200 mg Aceclofenac, were prepared by wet granulation technique. The drug polymer ratio was developed to adjust drug release as per theoretical release profile (Table 1) and to keep total weight of tablet constant for all the fabricated batches (F1 to F9) under experimental conditions of preparations. The total weight of the matrix tablets were 600 mg with different drug polymer (cashew gum and xanthan gum) ratio. A batch of 500 tablets was prepared in each formula. The composition of tablets is shown in Table 1.

Table 1: Formulations Based on Different Drug Polymer Ratio

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Aceclofenac	200	200	200	200	200	200	200	200	200
Xanthan	100	150	200	-	-	-	75	100	125
Cashew gum	-	-	-	100	150	200	75	100	125
Lactose	236	186	136	236	186	136	186	136	86
Microcrystalline cellulose	10	10	10	10	10	10	10	10	10
PVP (5%)	30	30	30	30	30	30	30	30	30
Talc (2%)	12	12	12	12	12	12	12	12	12
Magnesium stearate (2%)	12	12	12	12	12	12	12	12	12
isopropyl alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Microcrystalline cellulose (MCC) was incorporated as disintegrating agent. Lactose is incorporated as filler to maintain tablet weight constant. Microcrystalline cellulose is water insoluble and lactose is poorly soluble in water. This water insoluble filler was incorporated also to counter balance the faster solubility of the drug in presence of hydrophilic polymer and to provide a stable matrix. The ingredients were passed through sieve no. 100 and thoroughly mixed for 8-10 min in a polythene bag. Granulation was done manually with a solution of calculated quantity of PVP in sufficient isopropyl alcohol. The wet masses were passed through sieve no. 14 and the wet granules produced were air dried. The dried granules were sized by sieve no.22 and mixed with 10% of fines. Talc and magnesium stearate were added as glidant and lubricant. Granules thus obtained were compressed into tablets on 16-station rotary Cadmach machine (Cadmach, Ahmedabad) at a constant compression force.

Identification of Drug[2]

1. The obtained sample was examined by infrared absorption spectral analysis & was compared with the reference standard IR spectrum of Aceclofenac.
2. Preparation of standard curve

The 0.002 per cent w/v solution in methanol shows an absorption maximum at 275 nm when examined in the range 220 nm to 370 nm.

3. Identification test of drug

Dissolve about 10 mg in 10 ml of ethanol. To 1 ml of the solution, add 0.2 ml of a mixture, prepared immediately before use, of equal volumes of a 0.6 per cent solution of potassium ferricyanide and a 0.9 per cent solution of ferric chloride. Allow to stand protected from light for 5 minutes. Add 3 ml of a 1 per cent solution of hydrochloric acid. Allow to stand protected from light for 15 minutes. A blue color develops and a precipitate is formed.

Drug Excipients Compatibility Study

It was studied by using Infra-red Spectrophotometer and Differential Scanning Colorimeter.

Determination of Gel Strength

Gel strength of polymers are determined by preparing gel. Gel is spread on one glass slide and another glass slide is overlap on it. One glass slide is tied and hang on and another glass slide is tied with weight of 5gm. Time require to slide down the glass slide gives us idea about gelling strength. More time require to come down the slide more will be gel strength (figure 8 and 9).

Figure 8: Image showing result of test determination of gel strength of xanthan gum

Figure 9: Image showing result of test determination of gel strength of Cashew gum

Evaluation of Granules[2, 25, 29]

Granules were evaluated for Flow rate, bulk and tapped densities, angle of repose, Carr's index and Hausner's ratio.

Determination of Microbial Load in Extracted Gum[15]

This was carried out using three different media-Mueller Hinton agar (a general purpose medium), Mac Conkey agar (specific for enteric bacteria) and Sabouraud dextrose agar (specific for fungal organisms). One thousand milligrams (1000 mg) of cashew gum was dissolved in 25 mL of sterile water using magnetic stirrer. One milliliter (1 mL) of this stock solution was then used to inoculate 19 mL of the respective media inside a sterile cupboard. The inoculated media were poured into different sterile petri dishes and allowed to solidify within the sterile cupboard. For each culture medium, three replicates and one control were prepared. The inoculated media and their controls were incubated at 37±2°C for 24 h. No growth of any microorganism was found.

Evaluation of Tablets[2, 5, 9,29,30,33]

The prepared matrix core tablets were evaluated for hardness, weight variation, dimension, friability and drug content. Hardness of the tablets was tested using a dolphin Monsanto type hardness tester. Friability of the tablets was determined in a Roche friabilator (Campbell Electronics, Mumbai). The thickness of the tablets was measured by Janta India vernier caliper vernier. Weight variation test was performed according to IP tablet weight variation method. From all F1 to F9 formulation batches F9 gives best results. Assay of best formulation (F9) is carried out by HPLC method.

***In Vitro* Release Studies**[2, 8, 16, 17]

The release rate of Aceclofenac from sustained release tablets was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus 2(paddle method; LABINDIA DS 8000). The dissolution test was performed using 900 ml of phosphate buffer pH 6.8 for 24 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. From this 1 ml diluted to 50 ml with dissolution medium. Absorbance of these solutions was measured at 275 nm using a UV-visible spectrophotometer. For each formulation, the experiments were carried out in triplicate. The percentage release was calculated.

Kinetic Analysis of Dissolution Data[6, 20, 26]**:**

The release data obtained, for selected batch(s), were treated according to first-order, Higuchi and Korsmeyer-Peppas equation models to determine the release rate and mechanism of drug release from matrices.

RESULTS AND DISCUSSION

Granules were evaluated for Flow rate, bulk and tapped densities, angle of repose, Carr’s index and Hausner’s ratio. The evaluation of granules revealed that granules were freely flow able. The hardness and friability of tablets ranged from10 kg/cm^2 and 0.16% to 0.46% respectively. As such all the batches of tablets were of good quality with regard to hardness, friability (table 2). All tablets complied with Indian pharmacopoeia 2007 specifications for weight variation. Drug content of optimized formulation F9 determined by assay is 102.71% (figure 3).

Table 2: Results of Evaluations of Granules and Tablets

Test	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk density	0.306	0.306	0.306	0.3125	0.306	0.306	0.3125	0.306	0.3
Tapped density	0.34	0.33	0.34	0.34	0.348	0.348	0.348	0.34	0.33
Carr’s index	10	7.27	10	8.08	12.06	12	10.20	10	9
Hausner’s ratio	1.11	1.07	1.11	1.08	1.137	1.137	1.11	1.11	1.1

Angle of repose	19.22	21.15	18.65	18.124	19.8	20.46	21.14	19.8	19.5
Weight (mg)	594.8	595.25	599.15	590.2	594	594.8	622.8	607.95	596.65
Hardness kg/cm2	10	10	10	10	10	10	10	10	10
Thickness (mm)	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3
Diameter	1.24	1.24	1.24	1.24	1.24	1.24	1.24	1.24	1.24
Friability (%)	0.46	0.46	0.16	0.348	0.218	0.218	0.23	0.16	0.16

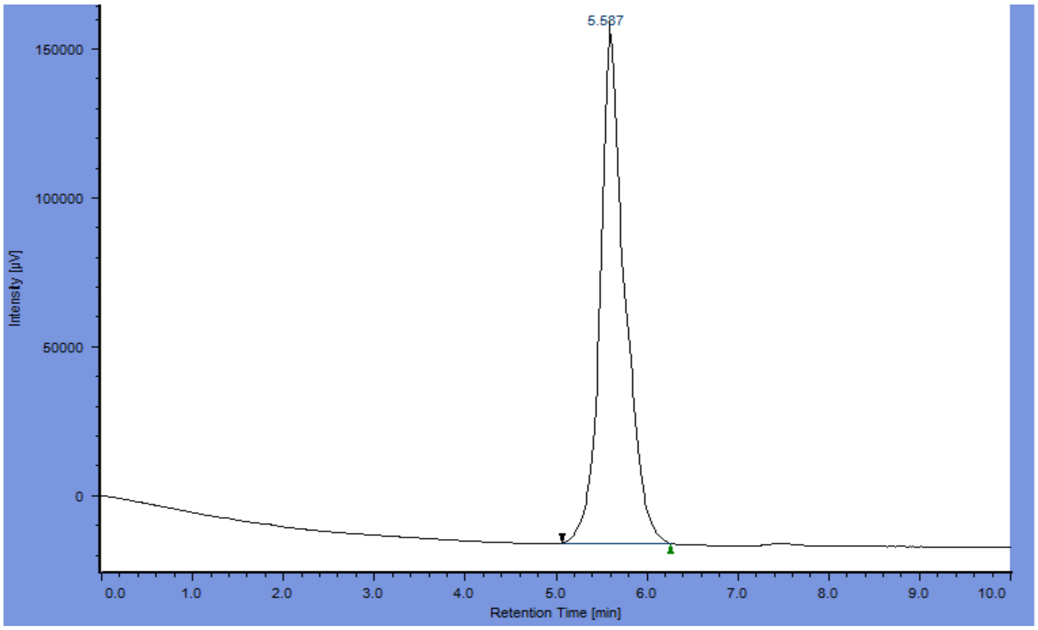

Figure 3: Graph of intensity Vs retention time- result of HPLC showing sharp peak at 5.587 min[33]

Aceclofenac release from tablets was extended from 12 to 24 hours from formulated batches. The results of dissolution studies of formulations F1 to F9 are shown in Figure 4, 5 and 6. Drug release rate from the tablets was found to decrease with increase in drug polymer ratio. Formulation F-1, F2, F3 composed of drug polymer (xanthan gum) ratio of 1:0.5, 1:0.75, 1:1, failed to sustain the drug release beyond 8hr., 9hr and 9hr respectively. On the contrary formulation F-4, F5, F6 composed of drug polymer (cashew gum) ratio of 1:0.5, 1:0.75, and 1:1, sustained release over12hr, 12hr, and 24hr respectively. And combination of both the polymers (xanthan gum and cashew gum) F7, F8, and F9 gave better sustained drug release over 24 hr. (refer table no. 3).All the formulations showed drug release close to theoretical release profile. Formulation F9 was compared with marketed preparation for drug release. F9 gave better results than marketed preparation (table 4 and figure 7). Result of gel strength determination was obtained that cashew gum has more gel strength than xanthan gum.

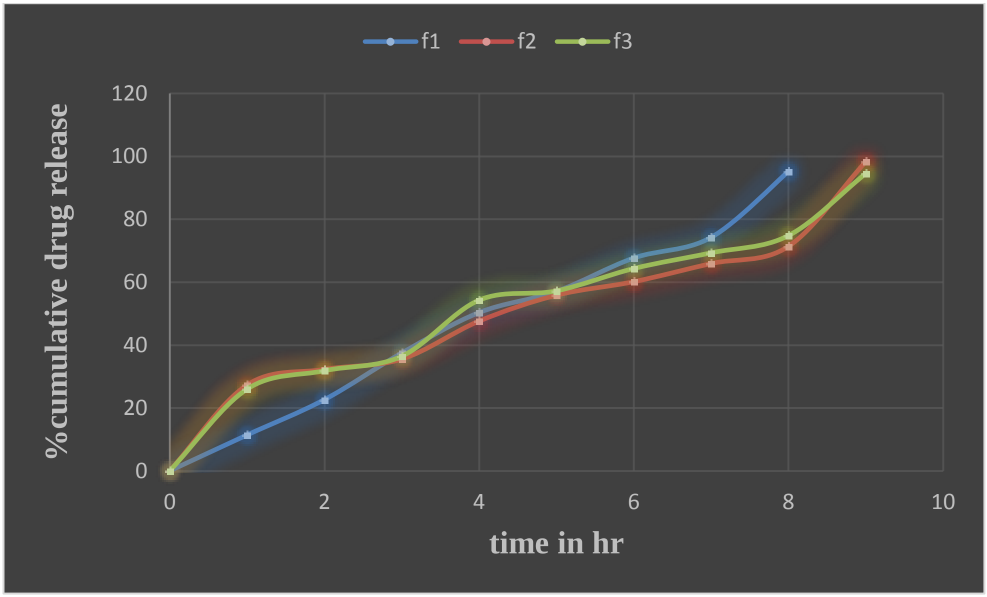

Figure 4: ***In vitro*** **Dissolution of Formulation F1-F3**

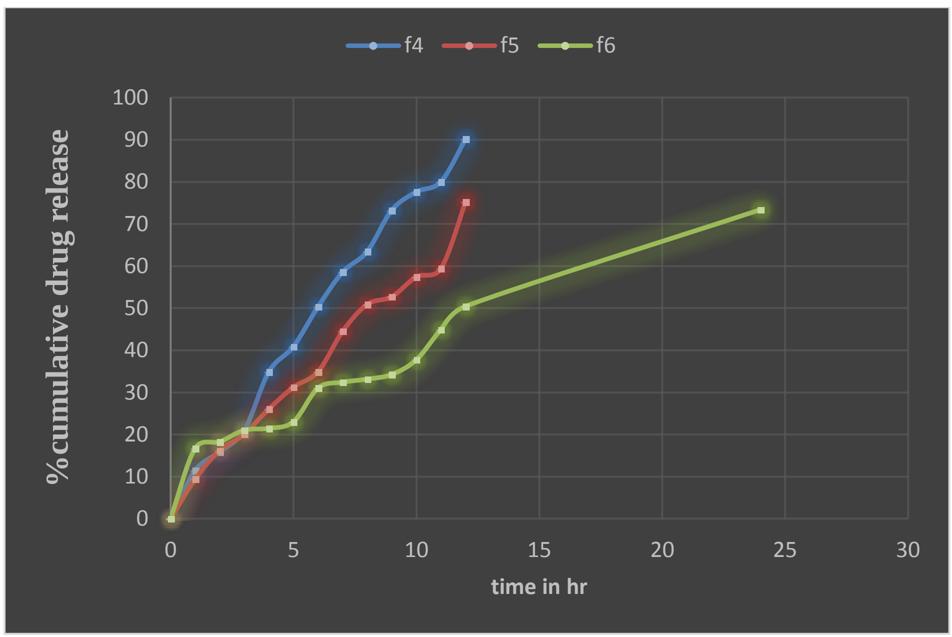

Figure 5: ***In vitro*** **Dissolution of Formulation f4-f6**

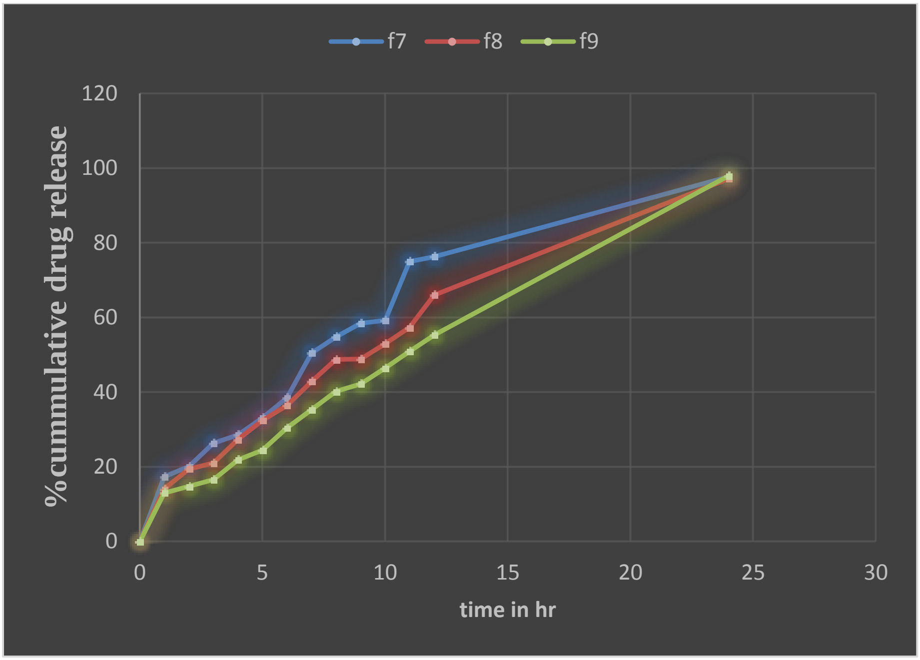

Figure 6: *In vitro* Dissolution of Formulation F7-F9

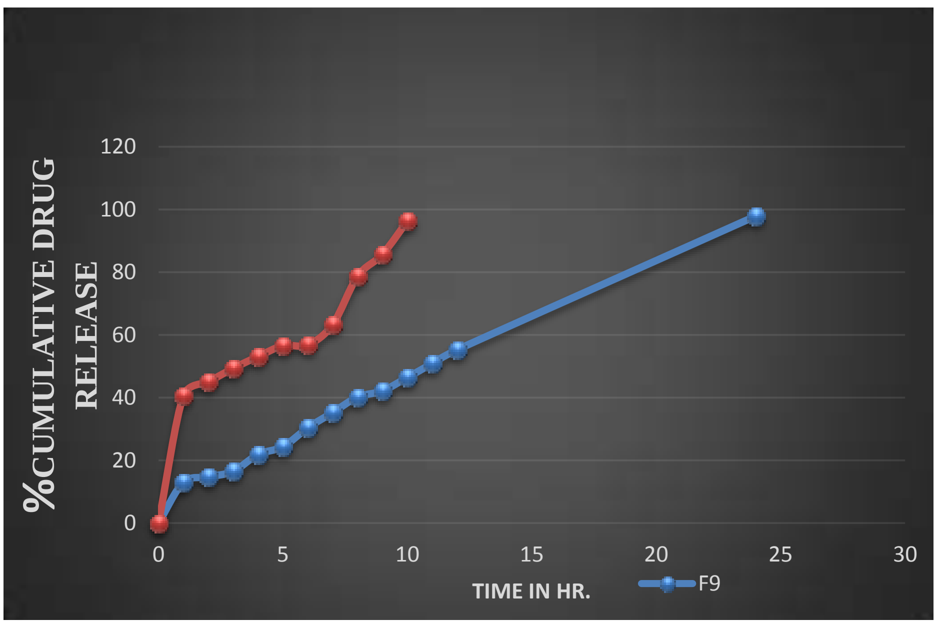

Figure 7: *In vitro* Dissolution of Formulation (f9- MF)

Table 3: *In Vitro* Drug Release Study (Time and % Cumulative Drug Release)

Time (hr.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	11.43	27.315	26.01	11.49	9.39	16.71	17.34	14.07	13
2	22.6535	32.28	31.86	15.9	16.189	18.27	20.04	19.4	14.73
3	37.479	35.56	36.454	21	20.119	21.04	26.33	21	16.56
4	50.346	47.63	54.29	34.9	26.08	21.45	28.57	27.32	21.9
5	57.07	55.86	57.25	40.9	31.23	23.03	33.106	32.43	24.42
6	67.677	60.16	64.35	50.335	34.9	31.04	38.53	36.44	30.42
7	74.2265	65.937	69.341	58.56	44.5	32.42	50.5	42.88	35.29

8	95.208	71.38	74.8	63.45	50.893	33.14	54.8	48.75	40.194
9		98.2725	94.55	73.246	52.699	34.25	58.47	48.84	42.20
10				77.6	57.45	37.75	59.25	53	46.45
11				80	59.38	44.9	75	57.33	50.93
12				90.16	75.215	50.44	76.28	66	55.3
24						73.37	97.7	97.17	97.9

Table 4: *In Vitro* Drug Release Study of F9 and Marketed Preparation

Time in hr	F9	Marketed preparation
1	13	40.54
2	14.73	45.03
3	16.56	49.35
4	21.9	53.16
5	24.42	56.56
6	30.42	56.87
7	35.29	63.34
8	40.194	78.71
9	42.20	85.71
10	46.45	96.34
11	50.93	
12	55.3	
24	97.9	

CONCLUSION

The sustained release drug delivery is a promising approach to achieve a prolonged therapeutic action of drug. In present study the sustained release tablets of Aceclofenac using cashew gum as a sustained release polymer and combination of cashew gum with xanthan gum were successfully formulated by wet granulation method. Cashew gum was successfully employed as sustained release polymer in the preparation of Aceclofenac tablet. The tablets produced demonstrated the requisite physicochemical properties of uniform weight, dimensions, hardness, friability, and dissolution. Cashew gum therefore can be used as sustained release polymer in production of sustained release tablets.

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