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Invitro chrecterization: pulsatile drug delivery system with plantago ovata seed mucilage and natural gums

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ABSTRACT

Chrono therapeutic drug delivery basically refers to the release of drug based on biological needs of the patients; it is purely related to the circadian rhythm of individuals. Aceclofenac is a first line and safest NSAID used for Rheumatoid arthritis (RA) which is poorly water soluble used by elders/ Rheumatoid arthritis patients, who may get morning stiffness and joint pains early in the morning. It generally affects the joints and their synovial membranes, cartilages, capsules and the muscles supplying them. Pulsatile Drug Delivery System is administered at bed time but drug is going to be released after a lag time in a burst manner.

In present study Aceclofenac with natural super disintegrants like Plantago ovata seed mucilage &modified agar in inner fast release core tablet and natural polymers like xanthum gum, Guar gum in different ratios as a compression coating. The prepared tablets were evaluated for various precompression and post compression parameters all the results were within the limit. Out of all formulationsF6 &F12 are the best formulations based on pre-and post-compression parameters and Invitro drug release is 95.7±0.10 & 93.7±0.15 respectively at 10 hrs. Which contains 8% of psyllium mucilage and 10% of modified agar with 1:1 ratio of Xanthum gum and guar gum as a coating material.

Keywords: Pulsatile Drug Delivery, Lag Time, Plantago Ovata Seed, Modified Agar, Xanthum Gum, Guar gum

INTRODUCTION

Pulsatile Drug Delivery Systems (PDDS) are time-controlled drug delivery systems in which the drug is released over a definite pause time which is independent of environmental factors like pH, enzymes, gastrointestinal mobility, etc. Circadian

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rhythms are controlled by an inbred master clock network composed of the paired suprachiasmatic nuclei (SCN) that are sited in the hypothalamus and the pineal gland. This master clock network arranges the period and phase of the multitude of submissive peripheral circadian clocks located in cells, tissues, and organ-systems. The end effect is a rather exquisite temporal organization of biological processes and functions.

Compression coating is the absolute dry coating without solvent and heat use. The compression coated tablet dosage form (tablet –in-tablet design) is a time and rate controlled drug delivery device, which consist of a core tablet and an outer layer that is considerably thicker than typical tablet core tablet and which completely, surrounds the core tablet. This method has no limitation for the cores & coating. This method can be used to protect hygroscopic, light sensitive, oxygen –labile or acid labile drugs, to combine and separate different drugs and to modify drug release pattern.

Polymers have been successfully investigated and employed in the formulation of various dosage forms and are specifically useful in the design of novel drug delivery systems. Synthetic polymers are toxic, expensive, have environmental related issues, need long development time for synthesis and freely available comparison to naturally available polymers. However, the use of natural Excipients is safe, nontoxic, and biodegradable. In present study the natural polymers that were selected as suitable for PDDS are xanthum gum (XG, guar gum (GG).

MATERIALS AND METHODS

Materials

Aceclofenac was purchased from BMR pharma &chemicals, Hyderabad. Remaining all laboratory grade chemicals.

Isolation of mucillage from psyllium seed

Psyllium seeds were soaked in distilled water for 48 hr and then boiled for 10min the resulting, mass was squeezed through the muslin cloths to the filtrate equal volume of acetone was added to precipitate mucilage. The isolated mucilage was dried in an oven at 40 0C for 2hr, powdered through sieve no.80 and stored in a desecrator.

Preparation of modified agar

Modification of natural agar was done by suspending 5 g of Agar agar in 100ml distilled water. The suspension is stirred at 500rpm using, magnetic stirrer for 24 hrs obtained swollen mass is dried at 40 o C for 72 h. Dried product is collected and crushed in pestle motor and passed through sieve no 100.

Preparation of core tablet

Core Tablets were made by direct compression method. All ingredients were weighed accurately and blended homogeneously for 15 minutes by trituration using glass mortar and pestle. Microcrystalline cellulose was used as direct compressing agent. Psyllium seed mucilage and modified agar were used as disintegrating agents. Magnesium stearate and Talc were used as lubricants. Tablets were compressed in Mini Press Tablet Compression Machine using 6 mm round concave punches.

Table no -1 FORMULATION OF CORE TABLET

Ingredients(mg)	CT_1	CT_2	CT_3	CT_4	CT_5	CT_6	CT_7	CT_8	CT_9	CT_{10}	CT_{11}	CT_{12}
Drug	100	100	100	100	100	100	100	100	100	100	100	100
Microcrystalline cellulose	10	10	10	10	10	20	10	10	10	10	10	20
Modified Agar	10	12	15	15	15	15	-	-	-	-	-	-
Psyllium gum	-	-	-	-	-	-	10	12	15	12	12	12
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1
Starch	12	12	10	07	7	-	10	12	10	07	7	-
Lactose	19	17	17	20	20	17	21	1	17	20	10	07
Total wt.	150	150	150	150	150	150	150	150	150	150	150	150

METHOD OF COMPRESSION COATING

The accurate quantity of natural polysaccharides was weighed half quantity of weighted coating material was placed in the die cavity. Than the core tablet was placed over this remaining half part of coating polymer was poured. Than at optimum speed the tablet was compressed using 9 mm punch.

Table no 2 FORMULATION OF COMPRESSION COATED TABLET

Ingredients(mg)	F_1	F_2	F_3	F_4	F5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
Core tablet	CT1	CT2	CT3	CT4	CT5	CT6	CT7	CT8	CT9	CT10	CT11	CT12
Xanthum gum	50	50	50	100	75	75	50	50	50	100	75	75
Guar gum	100	100	10	50	75	75	100	100	10	50	75	75
Total weight	300	300	300	300	300	300	300	300	300	300	300	300

Saturation solubility studies

Saturation solubility was determined by the shake-flask method. Plain Aceclofenac in excess quantity were placed in glass-stoppered flasks containing 10 ml of distilled water, pH1.2, pH6.8, pH7.4 respectively. The samples were placed in a mechanical shaker (Technico, thirumudivakam) at 37 °C and 100 rpm until equilibrium was achieved (24 h). The aliquots were filtered through Whatman No. 41 filter paper. The filtrates were diluted appropriately in distilled water and assayed spectrophotometric ally at 273 nm. The results were shown in figure no. 1

Drug- excipient compatibility studies [9]

The compatibility between drug and polymers was evaluated using Fourier Transmitted Infrared spectroscopy (FTIR). Physical mixtures were prepared to study the effect of sample manipulation. In addition the samples of physical mixture were heated at 55°C for three weeks to obtain more reliable conclusions [70]. The IR shows that all peaks are present in Aceclofenac spectra are present in the physical mixture. The result were shown in figure no 2, 3 & 4.

METHODS OF PRE FORMULATION STUDIES

Bulk density

Apparent bulk density was determined by placing prepared powders into a graduated cylinder and measuring the volume and weight as it is Db = W/ Vb

Tapped density

The accurately weighed blend was filled in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum. The result was shown in Table no 3. That was calculated by formula.

Dt= W/Vt

Compressibility index

Carr's index = (Tapped density – Bulk density / Tapped density) X 100

Hausner's Ratio

Hausner 's ratio = Do/ Dt

Where, Dt = tapped density

Do = bulk density

Angle of Repose

$\Phi = \tan^{-1} h/r$

Hardness test

The crushing strength kg/cm^2 of prepared tablets was determined for tablets by using Monsanto hardness tester. A tablet is placed between the anvils and the crushing strength, which causes the tablet to break, is recorded. Average of three readings was taken and noted. The result was shown in Table no 3.

Thickness of coated tablet

Tablet thickness is an important characteristic in reproducing appearance; average thickness of coated tablet is calculated and presented with

deviation using vernier caliper. The result was shown in Table no 3

Weight variation

Individually coated tablets were weighed and average weight was calculated, not more than 2 tablets from this average weight should not be deviate. The test was performed according to the Indian Pharmacopoeia 2010. Weight variation was calculated by using following formula. The result was shown in Table no 3

$$\text{Percentage weight variation} = \frac{\text{Weight of single tablet – average tablet}}{\text{Average weight of tablet}} \times 100$$

Friability testing

20 tablets were taken, it is weighed and initial weight was noted then it was placed into the Roche friabilator and test was performed for 4 min by using 25 rpm after that tablets were weighed and friability was calculated by using following formula. The result was shown in Table no 3

$$\text{Percentage loss} = \frac{\text{Initial Weight of tablet – final weight of tablet}}{\text{Initial weight of tablet}} \times 100$$

Disintgration test for compressed coated tablet

Disintegration test on coated tablet of Aceclofenac was performed by using phosphate buffer pH-7.4, the tablets of simvastatin were taken and placed in 6 respective tubes of disintegration apparatus and disintegration time of the tablet was measured.

Drug content

The tablet was tested for their drug content; randomly 10 tablets were weighed and powered. The powder equivalent to 100mg was weighed accurately and transferred to 100ml of volumetric flask then dissolved with 5ml of methanol then the flask is sonicated for 5 min. The Volume was then made up to 100ml with phosphate buffer pH 7.4. Above solution was filtered through whatman paper and absorbance was measured at 273 nm. The result was shown in Table no.3

In- vitro dissolution studies of core tablet

The in vitro release pattern of core tablets was studied as visually by taking images of the core tablets in a petri dish containing dissolution medium (Phosphate buffer pH7.4) at the specific time intervals of 10 min up to 1hr.

In- vitro dissolution studies [21]

Dissolution test of coated tablet of aceclofenac was performed by using pH1.2, 6.8 and 7.4 phosphate buffers for 10 hrs, 2hrs in pH-1.2 (HCL) followed by 3hrs in 6.8 pH and 5 hrs. in pH-7.4, The Dissolution study was carried out at 37^0C and 50 rpm by using USP type II apparatus. 1ml sample were withdrawn from dissolution medium at every 1 hr up to 10hr and diluted to 10ml with respective pH medium, the absorbance was measured by using UV spectroscopy at the range of 273-275 nm. The withdrawn sample was immediately replaced by equal volume of fresh buffer. The dissolution data obtained were plotted as percentage drug release versus time. The result was shown in Table no3. and Figure no.5&6

Rupture test [10]

The rupture test on coated tablets was carried out using USP paddle 2 apparatus. Here all other Parameters were same as *In-Vitro* dissolution method. The rupture time was carried out in pH 1.2 6.8 and 7.4.The time at which the outer coating layer starts to rupture is called as lag time. This was determined by rupture test. The results are shown in Figure no.7.

Swelling studies [10]

The percentage swelling capacity of tablets was determined in the containers filled with 10 ml of pH 1.2 and pH 7.4 phosphate buffers. Tablets were removed from containers at predetermined regular intervals, blotted with tissue paper, weighed and again placed in medium till the outer coating of tablet started to rupture. The % swelling was calculated using the formula. The result was shown in Table no.4.

% swelling = ((Wt -Wo)/Wo) ×100

Where, Wt is weight of wet tablet at time

Wo is weight of dry tablet.

RESULTS

Saturation solubility studies

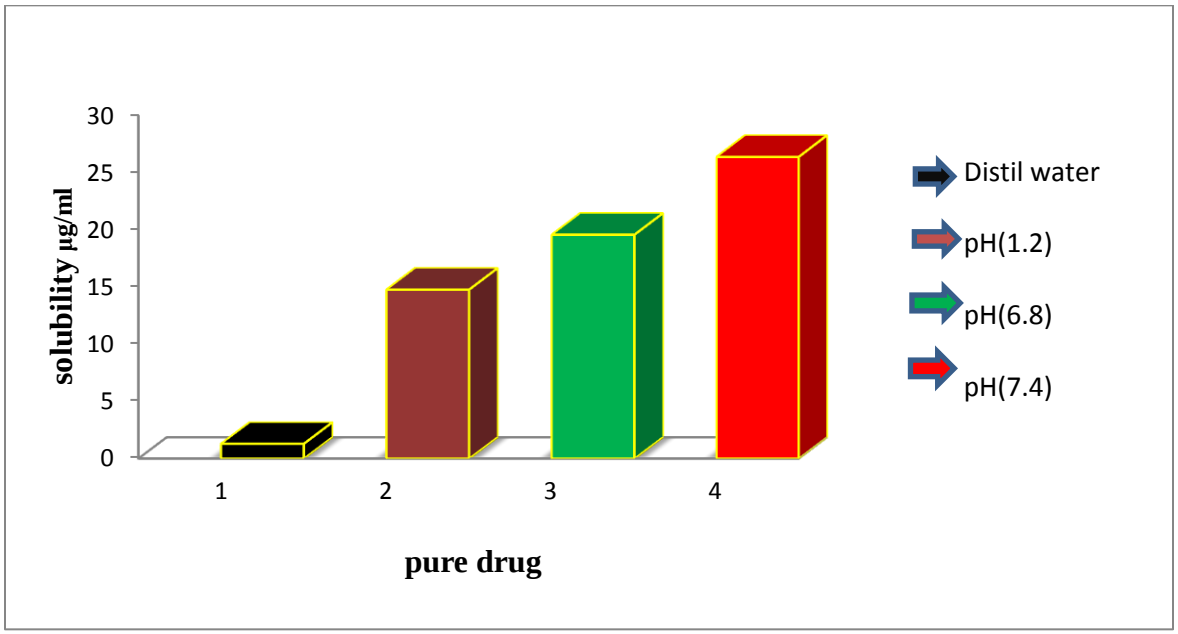

Fig no 1: solubility studies of pure drug in different pH

Drug- excipient compatibility studies

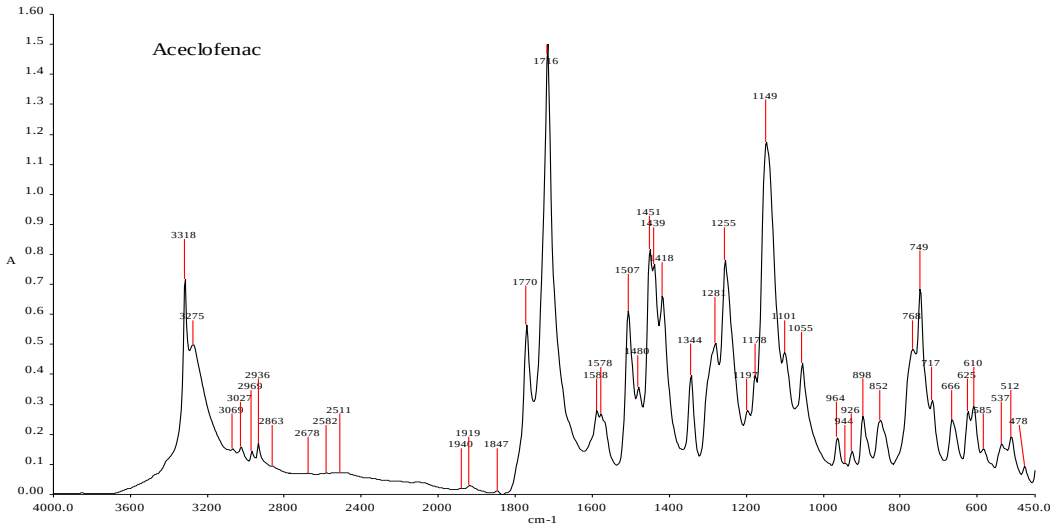

Fig-2 FTIR spectrum of drug Aceclofenac

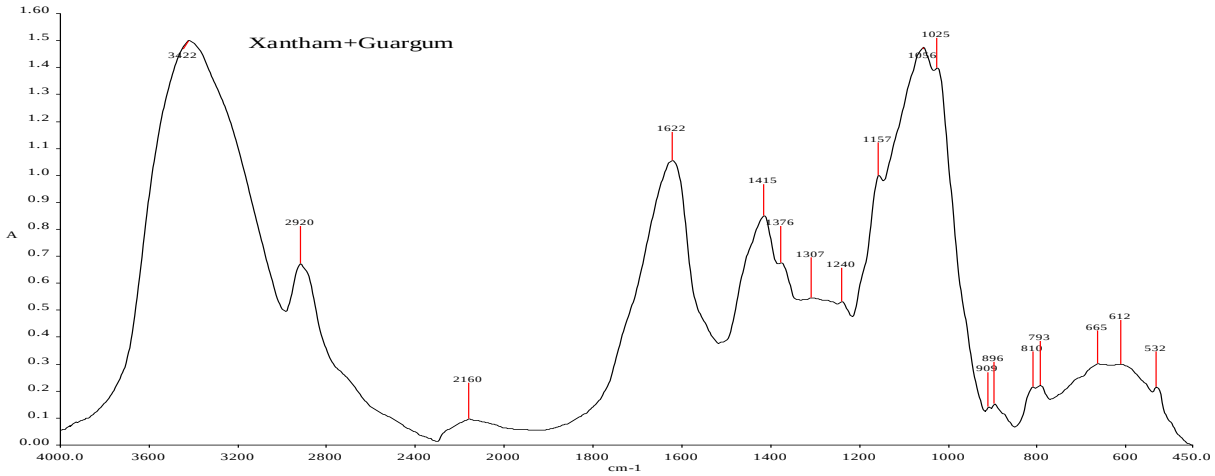

Fig-3 FTIR SPECTRUM OF XANTAM GUM+ GUAR GUM

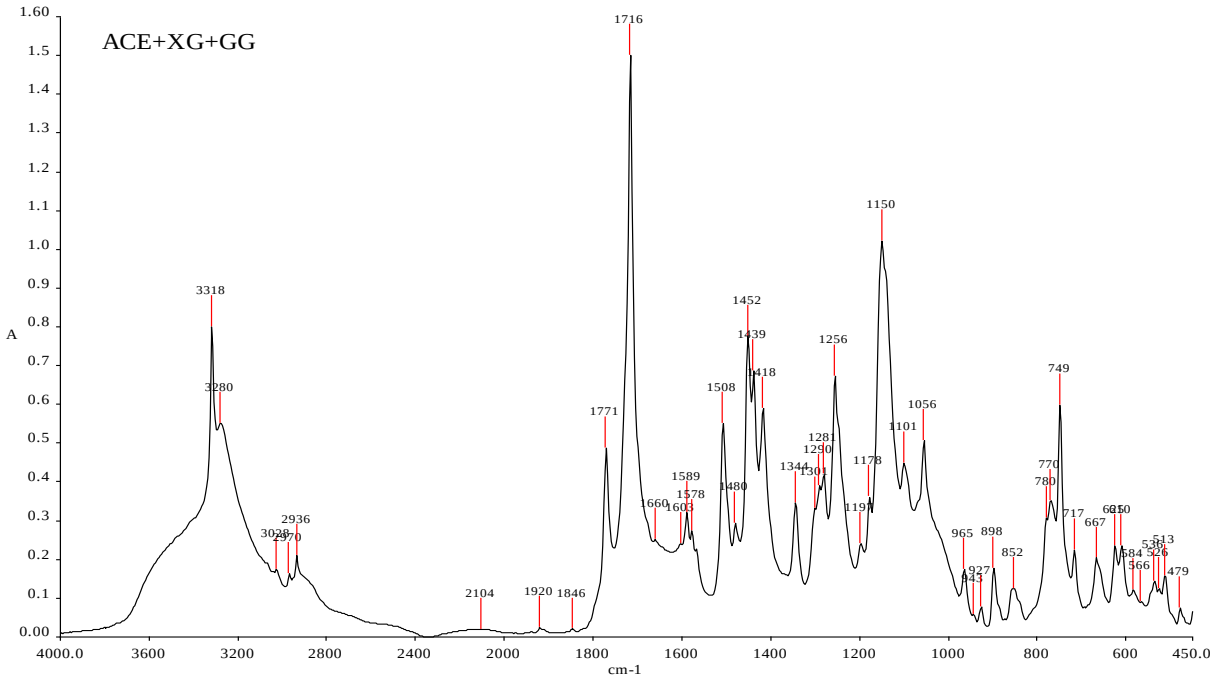

Fig-4 FTIR SPECTRUM OF ACECLOFENAC+ XANTAM GUM+ GUAR GUM

Table no- 3 POST COMPRESSION PARAMETERS

Formulation Code	Thickness (mm)	Weight variation(mg)	Hardness (Kg/cm²)	Friability (%)	%drug content	Disintegration Time(min)
F1	4.39±0.12	299± 0.12	5.80±0.12	0.69±0.015	99.2±0.12	15.6± 0.12
F2	4.36±0.08	298±0.1	5.56±0.24	0.51±0.017	100.2±0.1	18.26± 0.1
F3	4.33±0.2	301±0.14	5.63±0.08	0.48±0.014	100.6.8±0.7	14.38± 0.2

F4	4.29±0.1	299±0.1	4.93±0.15	0.64±0.015	99.4±0.32	11.48± 0.15
F5	4.35±0.3	299±0.2	5.73±0.25	0.71±0.016	99.6±0.2	19.32± 0.1
F6	4.38±0.13	302±0.18	5.66±0.17	0.54 ± 0.02	99.7±0.16	20.54± 0.2
F7	4.38±0.11	297±0.17	5.6 ± 0.24	0.49 ± 0.2	100.5±0.18	23.12± 0.1
F8	4.32±0.1	300±0.12	4.38±0.11	4.38±0.11	100.5±0.18	23.12± 0.1
F9	4.31±0.12	299±0.17	5.52 ± 0.14	0.71±0.016	99.6±0.2	11.12± 0.1
F10	4.35±0.11	296±0.2	6.01± 0.17	0.54 ± 0.02	99.7±0.16	19.60± 0.2
F11	4.38±0.11	297±0.12	6.1 ± 0.13	0.49 ± 0.2	100.5±0.18	21.2± 0.17
F12	4.28±0.11	300±0.12	6.2 ± 0.14	4.38±0.11	4.38±0.11	20.12± 0.18

In- vitro dissolution studies

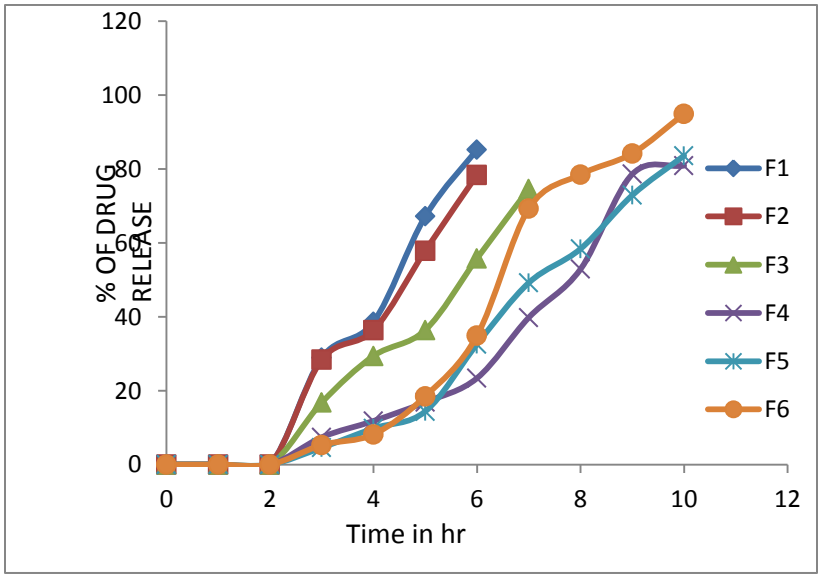

Fig no: 5 Invitro dissolution studies F1-F6

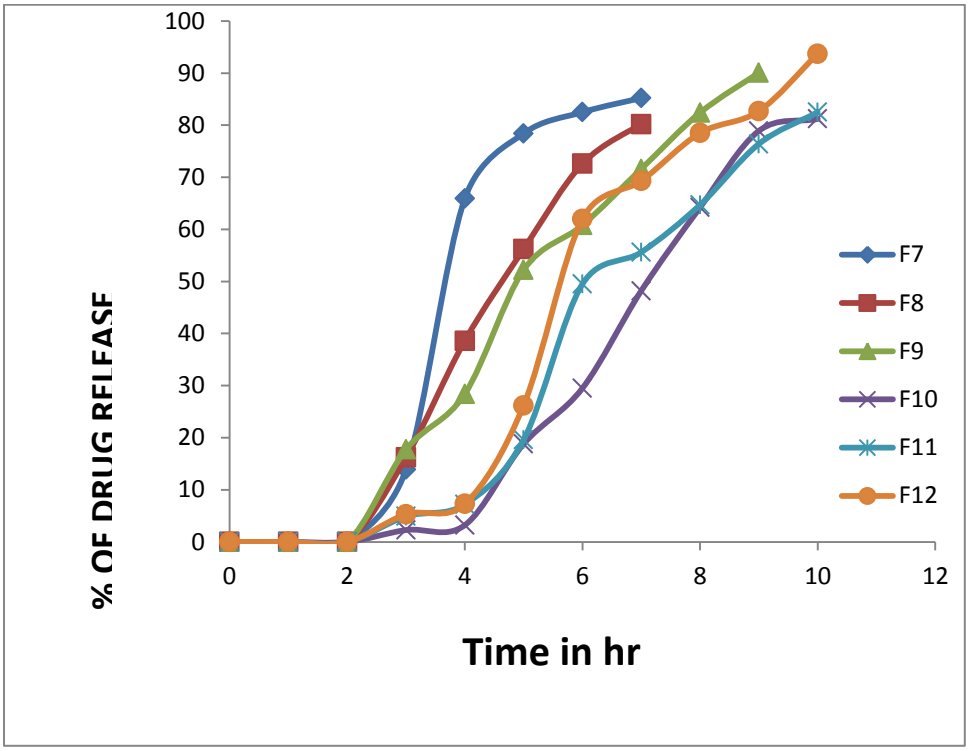

Fig no: 6 Invitro dissolution studies F7-F12

Rupture test

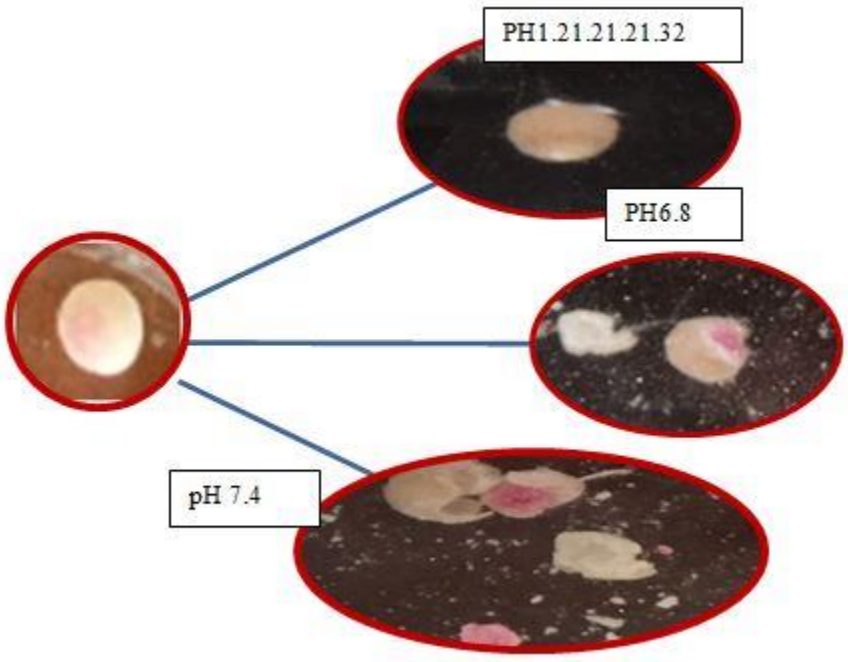

Fig no: 7 Rupture test

Swelling studies

Table no 4 Swelling test

Time (hr)	Formulation code (DF7)	
	pH(1.2)	pH(7.4)
0.5	0	3.3
1	3.3	6.6
1.5	3.3	6.6
2	3.3	10
2.5	3.6	10
3	3.6	13.3
3.5	66	16.6
4	6.6	20
4.5	10	23.3
5	10	23.3

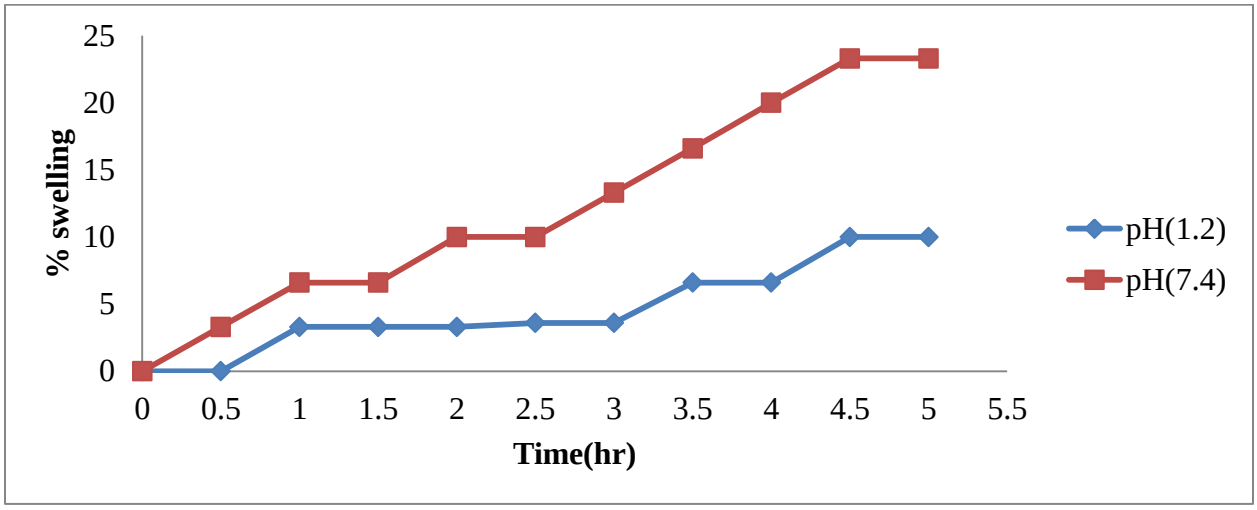

Fig no 8 swelling index

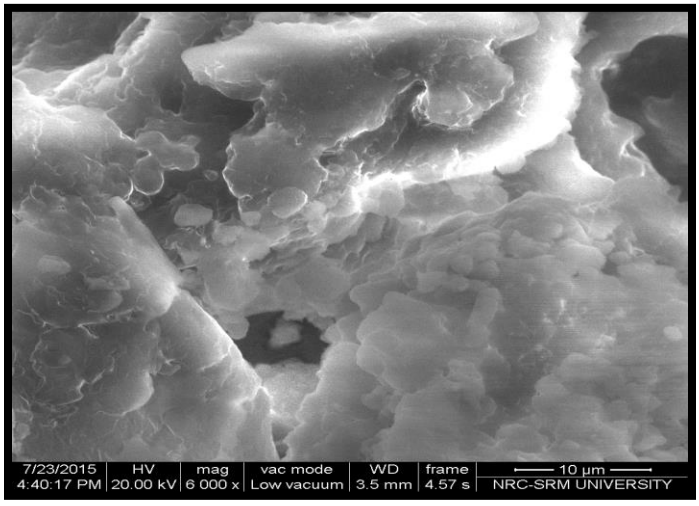

Fig no 9 surface morphology for F6

DISCUSSION

- Pulsatile drug delivery system is the most promising system, to deliver the drug after a pre-determined lag time according to circardian rhythm means drug deliver when the symptoms are more.
- Aceclofenac tablets were prepared by pulsatile drug delivery system, in this study an attempt to increase the lag time by using different pH sensitive natural polymers in different concentration, there by based on the solubility nature of the polymer the drug release will occur after a pre-determined lag time.
- The solubility of Aceclofenac was performed with various solvents like pH 1.2, 6.8&7.4. From the results Compared to pH 1.2 and 6.8 solubility was more in pH 7.4. The micro crystalline cellulose, magnesium stearate and starch was added as the wetting agent, psyllium mucilage & modified agar is added as a super disintegrant, and lactose as a diluents for the preparation of core tablet. xanthum gum , guar gum as a natural polymers are selected as coating polymers .
- The FTIR show no interaction between drug and excipients.
- The pre-compression studies like bulk density, tap density, angle of repose, Hauser's ratio and Carr's index was performed all the formulations shows good flow properties. The post compression evaluation like thickness, hardness, weight variation,, friability was performed.
- In F1,F2&F 3 formulation were prepared with different concentrations of modified agar in this Xanthum gum (XG) and Guar gum (GG)(were taken in the ratio of 1:2 in all these formulations shown less lag time around 3 hrs after coating but the release was fast with 10% modified agar so further formulations were prepared with 10 % of modified agar and different concentrations of Xanthum gum (XG) and Guar gum (GG)to increase the lag time .
- Further formulation F **4** Xanthum gum (XG) and Guar gum (GG) ratio 2:1 was used ,lag time was found to be very high about 8hrs it may be due to increase in the concentration of Xanthum gum (XG) ,so in next formulation F5 the concentration of Xanthum gum (XG) and Guar gum (GG)was taken in equal ratios.
- In F5 lag time was found to be with in hrs but drug release at the end of 10 hrs was found to be 80.5%, so to increase drug release content of Micro Crystalline Cellulose was increased from 10 % to 20 % & drug release was found to be 94.7 % at the end of 10 hrs study.
- From the above results formulation F 6 which is having Xanthum gum (XG) and Guar gum (GG) 1;1 ratio with10%of modified agar & 20% MCC was chosen as a best formulation depend on drug release & lag time by wet lab method
- In F 7,F8& F 9 formulations were prepared with different concentrations of psyllium seed mucilage with 1:2 ratio of Xanthum gum (XG) and Guar gum (GG) as a coating, all this formulations shown less lag time around 3.5 hrs after coating but the release was fast with 8&10 % concentration of psyllium seed mucilage almost the release was same ,so for further formulations in core tablet formulations psyllium seed mucilage concentration is taken as 8%.
- Same like F 4, F5& F6 in F10, F 11& F12 also coating concentrations ratios were changed to achieve desire lag time. Based on the drug release at the end of 10 hrs was 95.7 SF12 was found to be the best formulation among all formulation.

CONCLUSION

In our study natural excipients are playing same role like synthetic additives which are safe to use.

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