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RESEARCH ARTICLE

Evaluation of floating press-coated pulsatile release of Aceclofenac tablets. A solution for Rheumatoid athrites

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ABSTRACT

The objective of this study was to develop and evaluate of a floating press-coated pulsatile drug delivery system intended for treatment of early morning stiffness and symptomatic relief from pain in patients with rheumatoid arthritis with a distinct predetermined lag time of 8 h. Cores containing Aceclofenac as model drug were prepared by direct compression of different Sodium starch glycolate level CT-1 to CT-4) 8 %, 4%, 2% & without disinegrant and Aceclofenac as a model drug by using various proportion of polymers such Hydroxypropyl methylcellulose and Sodium bicarbonate floating layer is prepared. Fifteen formulations were prepared and formulation F15, F18, F22possessed good lag time 8 hr and showed pulsatile drug delivery pattern the tablets *In- vitro* evaluation tests. Results of this study indicated that by using floating-pulsatile release formulations are suitable to optimize pulsatile drug release formulation of Aceclofenac.

Keywords: Floating-pulsatile release formulations, Aceclofenac.

1. INTRODUCTION

Pulsatile drug delivery systems are gaining a lot of interest now days. These systems are designed according to the circadian rhythm of the body. These systems deliver the drug at specific time as per the pathophysiological need of the disease, resulting in improved patient compliance and therapeutic efficacy. Which is meant as the liberation of drugs following programmed lag phases, has drawn increasing interest, especially in view of emerging chronotherapeutic approaches. Pulsatile drug delivery shows rhythms like rheumatoid arthritis, cardiovascular diseases, asthma, peptic ulcer, allergic rhinitis.

The concept of chronotherapeutics originates from the finding of the major disease conditions such as asthma, cardiac disorders, allergic rhinitis, and arthritis following circadian example of symptom outburst. Chronotherapeutics delivery system have been developed to provide the best treatment regimens which revolve around the objective of assuring maximum concentration of the drug at the time of symptom onset.[2,3,4,5,6]

Nowadays, concept of chronopharmaceutics has emerged, wherein, research is devoted to the design and evaluation of drug delivery systems that release a therapeutic agent at a rhythm that ideally matches the biological requirement of a given disease therapy. Future of drug delivery must meet the challenge of future medicine [7]

Aceclofenac, a nonsteroidal anti-inflammatory drug, is used for the symptomatic relief of pain and joint stiffness in patients suffering from rheumatoid arthritis, which is characterized by diurnal variation in circulating levels of proinflammatory cytokines, interleukin-6 and/or tumor necrosis factor-α. Due to this diurnal variation, many symptoms and signs of active rheumatoid arthritis are manifested in the morning.[8] on oral administration at bed-time, releases aceclofenac after a desired lag time of about 8 hr which corresponds with peak levels of proinflammatory mediators. The current study illustrates the formulation, characterization and optimization of a

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Aceclofenac tablets with Press coated floating-pulsatile release.

2. MATERIALS AND METHOD

Cores containing Aceclofenac as model drug were prepared by direct compression of different Sodium starch glycolate level CT-1 to CT-4) 8 %, 4%, 2% & without disinegrant.

Sr.No	Formulation	CT 1	CT 2	CT 3	CT 4
	Ingredients	mg/tablet	mg/tablet	mg/tablet	mg/tablet
1.	Aceclofenac	100.00	100.00	100.00	100.00
2	MCC (Avicel pH102)	40.00	44.00	46.00	48.00
3.	Dicalcium phosphate (DCP)	40.00	44.00	46.00	48.00
4.	Sodium starch glycolate	16.00	8.00	4.00	-
5.	Sunset yellow iron oxide	2.00	2.00	2.00	2.00
6.	Magnesium stearate	2.00	2.00	2.00	2.00

Table No 1: Effect of Sodium starch glycolate level on Drug Release Profile from Uncoated Tablet (CT-1 to CT-4) 8 %, 4%, 2% & without disintegrant

F= Formulation code, CT1= Core tablet 1 with Sodium starch glycolate 8%, CT2= Core tablet 2 with Sodium starch glycolate 4%, CT3= Core tablet 3 with Sodium starch glycolate 2%, CT4= Core tablet 4 with Sodium starch glycolate without disintegran.

A. Preparation of core tablets (CT):

All ingredients of core tablet given in **Error! Reference source not found.**No 1 were weighed and passed through 30 mesh standard sieve. Resultant powder was mixed thoroughly in mortar and lubricated with magnesium stearate (1 % w/w). A 200 mg powder was weighed and transferred manually in to die and compressed by using 8 mm diameter SC punch tooling.

B. Preparation of Press coated floating-pulsatile release formulation (F 1-F 22)

Formulation compositions of coating layer are shown in **Error! Reference source not found.**No 2, containing varying percentage of polymers were weighed and passed through 30 mesh standard sieve. The ingredients of coating layer were mixed in a mortar and lubricated with magnesium stearate (1% w/w). Required weight of coating powder was weighed and used in two steps: first half coating powder was filled into the die and CT was placed in the center of die. CT was slightly pressed to fix the coating around and under the CT. Then rest of half coating powder was filled and compressed by using 10/12 mm flat faced punch tooling.

Evaluation of Tablet Characteristics:

Physicochemical properties of tablets

Weight variation:

Twenty tablets were selected at random and weighed individually. The average weight of 20 tablets was calculated. Individual weights of the tablets were compared with the average weight.

Hardness:

Tablet hardness has been defined as the force required breaking a tablet in a diametric compression test. A tablet was placed between two anvils of hardness tester, force was applied to the anvils, and the crushing strength that causes the tablet to break was recorded in N.

Friability:

Tablets require certain amount of strength or hardness and resistance to withstand mechanical shock of handling in manufacturing, packaging, and shipping. A pre-weighed sample (20 tablets) were placed in the friabilator, and operated for 100 revolutions, then again weighed the tablets and % friability was calculated using the formula.

$$F = \left(1 - \frac{W_0}{W}\right) \times 100$$

Where

W_0 – Weight of tablet before test

W – Weight of tablet after test

Drugs content:

To evaluate a tablet potential for efficacy, the amount of drug per tablet needs to be monitored from tablet to tablet, and batch to batch. To perform the test, 10 tablets were crushed using mortar pestle. Quantity equivalent to 100 mg of drug was dissolved in 100 ml phosphate buffer pH 6.8, filtered and diluted up to 50µg/ml, and analyzed spectrophotometrically at 274.2nm. The concentration of drug was determined using standard calibration curve.

Buoyancy determination:

The buoyancy test of floating tablets (F 1-F 15) was studied by placing them in 500 ml beaker containing 6.8 phosphate buffer then tablet from same batches were placed in dissolution test. The floating onset time (time period between placing tablet in the medium and buoyancy beginning) and floating duration of tablet was determined by visual observation.

In vitro Dissolution Study:

The in vitro dissolution test was performed using USP type II dissolution test apparatus. The drug release study was carried out in phosphate buffer pH 6.8 900 ml of dissolution media, maintained at 37±0.5°C and agitated at 50 rpm. Periodically 5 ml samples were withdrawn and filtered through whatman filter paper and samples were replaced by its equivalent volume of dissolution media. The concentration of Aceclofenac was measured by spectrophotometrically at 274.2 nm for 6.8 media.

F	HPMC K4 M	HPMC K15 M	HPMC K100 M	MCC pH102	DCP	SBC	Citric Acid	Magnesium stearate	Core tablet
F24	50	0	0	60	115	60	12	3	CT 4
F25	75	0	0	60	90	60	12	3	CT 4
F26	100	0	0	60	65	60	12	3	CT 4
F27	225	0	0	0	0	60	12	3	CT 4
F28	133	0	0	80	87	80	16	4	CT 4
F29	200	0	0	80	20	80	16	4	CT 4
F30	300	0	0	0	0	80	16	4	CT 4
F31	133	0	0	80	87	80	16	4	CT 2
F32	200	0	0	80	20	80	16	4	CT 2
F33	300	0	0	0	0	80	16	4	CT 2
F34	60	0	0	80	160	80	16	4	CT 4
F35	80	0	0	80	140	80	16	4	CT 4
F36	100	0	0	80	120	80	16	4	CT 4
F37	120	0	0	80	100	80	16	4	CT 4
F38	110	0	0	80	110	80	16	4	CT 4
F39	0	60	0	80	160	80	16	4	CT 4
F40	0	80	0	80	140	80	16	4	CT 4
F41	0	100	0	80	120	80	16	4	CT 4
F42	0	0	40	80	180	80	16	4	CT 4
F43	0	0	60	80	160	80	16	4	CT 4
F44	0	0	80	80	140	80	16	4	CT 4
F45	0	0	100	80	120	80	16	4	CT 4

Table No.2 Press coated floating-pulsatile release formulation. (F1-F22) Dry coating of core tablets

F= Formulation code, HPMC K4M= Hydroxypropyl methylcellulose K4M, HPMC K15M= Hydroxypropyl methylcellulose K15M, HPMC K100M= Hydroxypropyl methylcellulose K100M, MCC= Microcrystalline cellulose, DCP= Dicalcium phosphate, SBC= Sodium bicarbonate. *F24 to F27compressed on 10 mm punch & F28-F45 compressed on 12 m punch.

3. RESULTS AND DISCUSSION:

Evaluation of Tablet characteristics

1. Evaluation of core tablets (CT):

F	Weight Variation (mg) *n=20*	Thickness (mm) *n=10*	Hardness (N) *n=10*	Friability (%)	Drug Content (%) *n=3*
CT 1	200.10±1.24	3.20±0.1	80 N ± 10N	0.21	99.58±1.65
CT 2	200.15±1.11	3.20±0.1	80N ± 12N	0.11	100.25±1.98
CT 3	200.24±1.27	3.20±0.1	80N ± 9 N	0.25	99.98±1.56
CT 4	200.24±1.19	3.20±0.1	80 N ± 11N	0.15	100.58±2.15

Table 3 Evaluation of physical properties of formulation CT1 to CT4

A. Physicochemical properties of tablet:

Tables are evaluated for Weight variation, thickness. hardness, friability and drug content. The results of physicochemical evaluation of tablets are given in table 3.

Press coated floating-pulsatile release formulation.

The final developed Press coated floating tablet F15 were found uniform with respect to thickness (3.25 ± 0.1 mm), diameter (12 mm) and hardness (5.7 - 6.9 kg/cm^2). The friability (0.72 – 0.84%) and weight variation test complies as per I. P. limits. Good and uniform drug content (>100%) was observed within the batches.

Tablets of F18 were found uniform with respect to thickness (3.25 ± 0.1 mm), diameter (12 mm) and hardness (5.6 - 7.0 kg/cm^2). The friability (0.58 – 0.86%) and weight variation test complies as per I. P. limits. Good and uniform drug content (>99%) was observed within the batches.

Tablets F22 were found uniform with respect to thickness (3.20 ± 0.1 mm), diameter (12 mm) and hardness (5.6 - 6.8

F	Weight Variation (mg) n=20	Thickness (mm) n=10	Hardness (kg/cm^2) n=10	Friability (%)	Drug Content (%) n=3
F15	600.96±1.912	3.25 ± 0.1	6.17±0.383	0.77±0.039	100.34±0.198
F15	601.07±1.584	3.25 ± 0.1	6.24±0.441	0.71±0.075	99.36±0.204
F22	600.34±1.379	3.20 ± 0.1	6.19±0.477	0.66±0.066	100.45±0.203

kg/cm^2). The friability (0.55 – 0.78%) and weight variation test complies as per I. P. limits. Good and uniform drug content (>100%) was observed within the batches.

Table No 4 Physicochemical properties of F15, F18 and F22 formulations

All values are expressed as mean ± SD. F= Formulation code, CT4= Core tablet.

All physicochemical properties of F15, F18 and F22 batches were found within limit. Hence, the tablets containing drug, HPMC, DCP, MCC, SBC, CA and magnesium stearate could be prepared satisfactorily by direct compression method.

Time (min)	% Cumulative Drug Release			
	CT-1	CT-2	CT-3	CT-4
5	72.4	46.5	20.2	5.25
10	99.5	62.7	44.2	17.58
15	101.2	84.1	80.5	30.22
30	100.1	100.5	100.1	79.0
45	99.6	99.3	98.7	100.7
60	98.4	98.6	98.2	99.1

Characterization of coating level

Table No 5: % Effect of Sodium starch glycolate level on Drug Release Profile from Uncoated Tablet (CT-1-CT-4)8 %,4%,2% & without disintegrant. in phosphate buffer pH6.8 of different core tablets formulations

To characterize the effect of coating level on floating ability, using HPMC K4M as a coating polymer F1 to F4 batches were prepared, obtained results shown in Figure 1.

Initially F1 and F2 batches were formulated by taking 16 % and 25 % HPMC K4M and compressed using 10 mm flat faced punch tooling. Here core tablet having mean diameter of 8 mm and final dry coated tablet having diameter of 10 mm means coating of 2 mm thickness. Then buoyancy test was carried out, tablet get float with floating lag time 8 second and all tablets get dispersed within 5 - 10 minutes. Hence F1and F2 formulations unable to float for required period, reason behind this was lower % of polymer that unable to form swollen gel.

Then F3 batch was formulated by increasing the amount of HPMC K4M from 25 % to 33 % using 10 mm flat faced punch tooling. In buoyancy test tablet get separated into layers after 70 min. Here it concluded that, the amount of MCC and DCP in coating mixture was responsible for early separation of layers.

Then F4 was formulated by replacing the concentration of MCC and DCP by HPMC K4M, i.e. 75 % HPMC K4M. Buoyancy test was performed, again tablet float for 100 min and separated into layer.

From Buoyancy study of F1 to F4 batches, it was concluded that core tablet of 8 mm and intact tablet of 10 mm diameter unable to float up to 480 min. It indicates coating thickness of 2 mm get erodes earlier and core tablet get dropped early, hence it need to increase the coating thickness.

Then F5,F6,F7 was formulated by increasing the coating thickness from 2 mm to 4 mm, observed results shown in **Error! Reference source not found.**2 Here final dry coated tablet was compressed on 12 mm flat faced punch tooling, by using polymer concentration 33%, 50%, 75 % respectively. Buoyancy test was performed on F5, F6 and F7, tablet float without separating into layers, but tablet of F5 float for 750 min, F6 for 1100 min and F7 remains float till 1500 min.

Here 4 mm coating level kept the tablet intact, but floating duration was increased beyond limit. Our aim was tablet float for 480 min only, so further study was done by adjusting polymer percentage.

Adjustment of floating duration with HPMC K4M

Here main objective is tablet should have 480 min gastro retention without drug release followed by pulsatile release.

To achieve this objective CT1 (containing super disintegrate SSG) was taken as a core, and F8, F9, and F10 was formulated with 33 %, 50 % and 75 % polymer concentration respectively. Observed results shown in Figure 3. Buoyancy test was carried out for all three formulations, F8 tablet get burst after 90 min, F9 tablet burst at 160 min and F10 tablet remain float till 340 min. This bursting effect was observed because of super disintegrate added to core. Hence further study was done by excluding SSG from core tablet to avoid bursting effect.

Then F11, F12, F13, F14 batches were formulated, by using CT4 as a core tablet, with 15 %, 20%, 25%, 30% HPMC K4M as a coating polymer respectively. Observed effect of polymer concentration on floating duration shown in Figure No 4

Buoyancy test was performed on F11 to F14batches, tablet of F11 batch dispersed within 5 min in dissolution medium. It indicates to increase the HPMC K4M concentration.

Then F12 was formulated by adding 20 % HPMC K4M. Buoyancy test indicates tablet float for 25 min after that get disintegrate. Hence again need to increase the concentration of HPMC K4M.

Further F13 was formulated by using 25 % of HPMC K4M,

tablet get float till 260 min after that core tablet get dropped. Then F14 was formulated by adding 30 % of HPMC K4M, tablet get float till 560 min, after that core tablet get dropped in dissolution media. From this buoyancy pattern of F13 and F14, it concludes that required HPMC K4M concentration should be in between 25 % to 30 %.

Time (min)	% Cumulative Drug Release								
	F5	F6	F7	F13	F14	F15	F18	F19	F22
60	2.14	2.15	0.10	2.35	3.25	2.58	0.20	3.38	2.32
120	3.59	2.78	0.20	3.56	4.52	3.67	0.56	4.56	3.58
180	4.0	3.55	0.56	3.98	4.88	4.12	1.03	5.20	4.40
240	4.52	4.76	1.00	6.0	5.12	4.69		5.59	4.55
300	4.88	5.32	1.78	6.58	5.45	4.98		5.78	5.28
360	4.90	5.98	2.14		5.98	5.55		6.00	5.89
420	5.26	6.12	2.58		6.23	5.96		6.53	6.25
480	6..59	6.98	2.88		7.11	6.89		6.98	6.84
495	7.78	7.52	3.00			68.12		70.00	65.25
510	8.90	7.98	3.25			80.50		80.94	78.87
540	9.85	8.40	3.88			85.76		86.77	84.29
570	10.58	8.89	4.20			92.15		94.02	92.017
600	11.55	9.30	4.70			99.87		100.25	98.22
630	13.88	9.95	5.00						
660	14.8	10.50	5.23						
1440	15.38	11.0	5.59						

Table No 6. % Cumulative release of Aceclofenac for in phosphate buffer pH6.8 of different formulations. (F5,F6,F7,F13,F14,F15,F18,F19,F22)

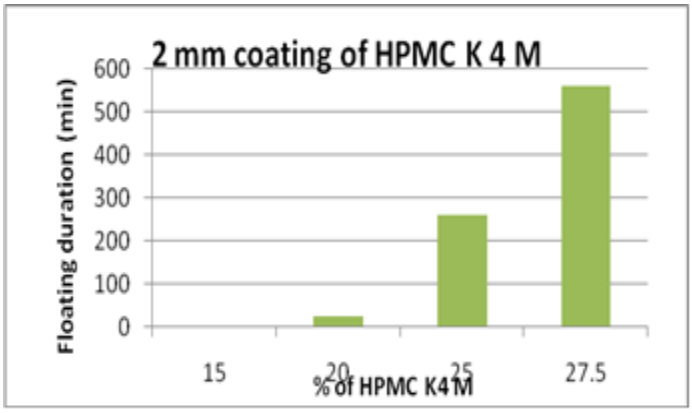

Figure No 1. Effect of polymer concentration and coating level on floating duration. (2 mm coating HPMC K 4 M)

Hence F15 was formulated using 27.5 % HPMC K4M, this formulation float till 473 min and maintains it shape without dropping the inner core tablet. At 480 min all coating get erode and inner core tablet get dropped, here this formulation show required pulsatile release pattern which is required for the treatment of rheumatoid arthritis and osteoarthritis. Hence F15 formulation considered optimized formulation for HPMC K4M polymer.

Here batches F16, F17, and F18 were prepared by using HPMC K15M as a coating polymer with 15%, 20%, and 25% respectively. Obtained results shown in figure 5.

Tablet of F39 formulation get dispersed within 8 min. Then concentration of coating polymer was increased up to 20 % and F40 was formulated, here also tablet gets dispersed after 140 min. After that F18 was formulate with 25% of HPMC K15M, this formulation float till 470 min satisfactorily, after that tablet coating get burst and inner core tablet get dropped. Hence F18 formulation follows the objective of pulsatile fashion and considered optimized formulation for HPMC K15M polymer.

Adjustment of floating duration with HPMC K100M

Here floating duration of formulation was adjusted by using HPMC K100M as a coating polymer. Formulation F19, F20, and F21 was prepared with 10%, 15%, and 20% HPMC K100M respectively. Obtained results provided in Figure 6.

Tablets of F19 to F21 formulations were dispersed within 2 to 20 min because of lower % of polymer. After that F22 was formulated with 25% HPMC K100M, this formulation float till 490 min satisfactorily, after that tablet coating get burst and inner core tablet get dropped. Hence F22 formulation follows the objective of pulsatile fashion and considered optimized formulation for HPMC K100M polymer.

Here dry coated tablet was designed for floating pulsatile release fashion, by using three different grades of HPMC polymer from batch no. F1 – F22. Among this F15, F18 and F21 considered optimized formulation for HPMC K4M, HPMC K15M, and HPMC K100M respectively.

In vitro Dissolution Study:

A. Dissolution of core tablets (CT)

In vitro dissolution test was carried out in phosphate buffer pH 6.8 for 60 min. Results of in vitro dissolution test presented in **Error! Reference source not found.**No 5. In order to perform different release kinetics; depending upon different release mechanism involved, effect of

Sodium starch glycolate level on drug release profile from uncoated tablet (Formulations CT1 to CT4) were determined. As amount of Sodium starch glycolate level decrease from formulations

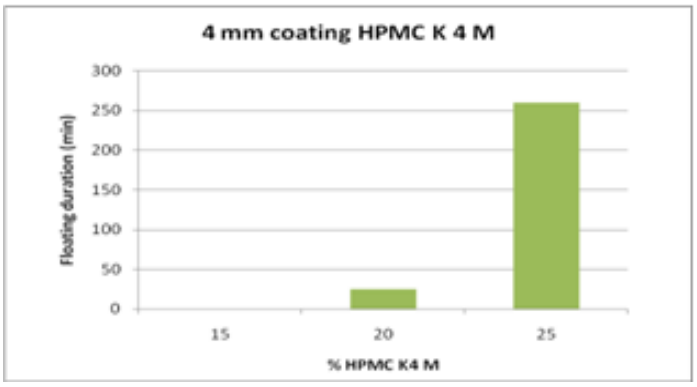

Figure No 2. Effect of polymer concentration 16 %, 33 %, 50 % and coating level on floating duration. (4 mm coating of HPMC K 4 M)

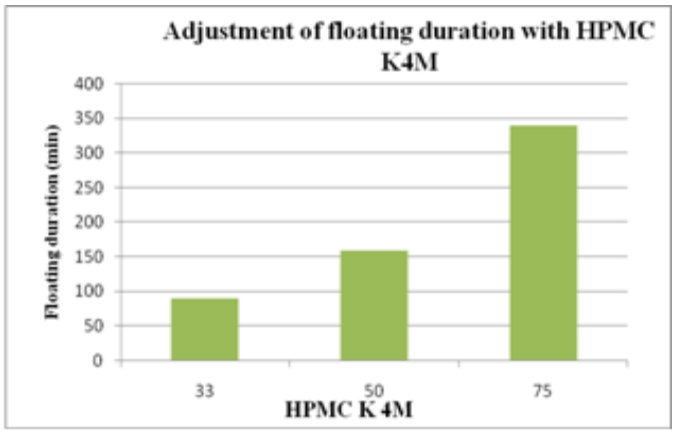

Figure No 3. Effect of polymer concentration 33 %, 50%,75%and coating level on floating duration. (4 mm coating of HPMC K 4 M)

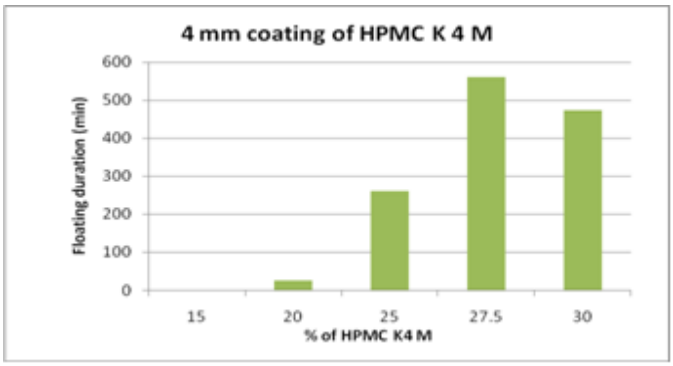

Figure No 4. Effect of polymer concentration 15%, 20%, 25%, 27.5 %, and 30 %, coating level of on floating duration.

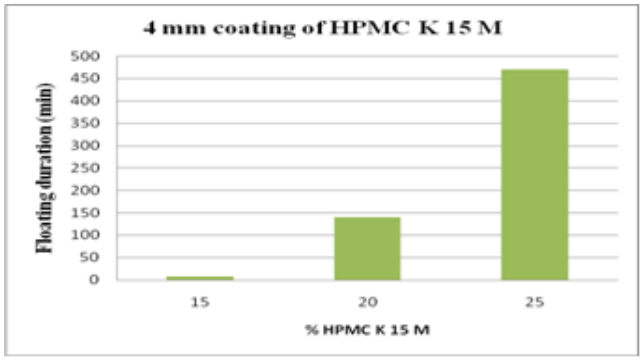

Figure No 5. Effect of polymer concentration 15%, 20%, and 25% coating level on floating duration. (4 mm coating of HPMC K 15 M)

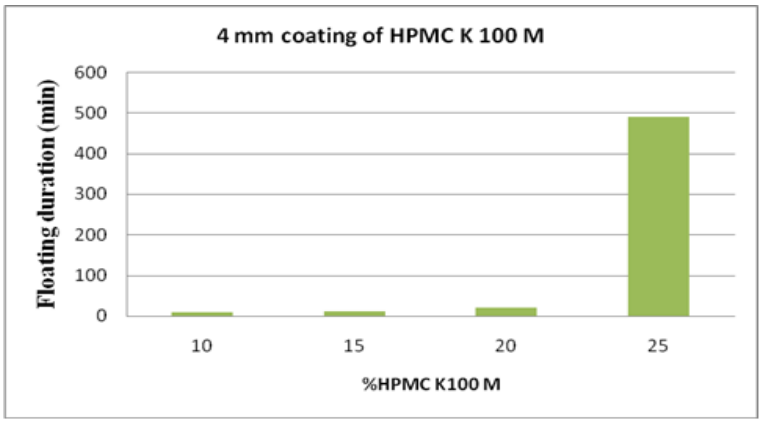

Figure No.6. Effect of polymer concentration and coating level on floating duration

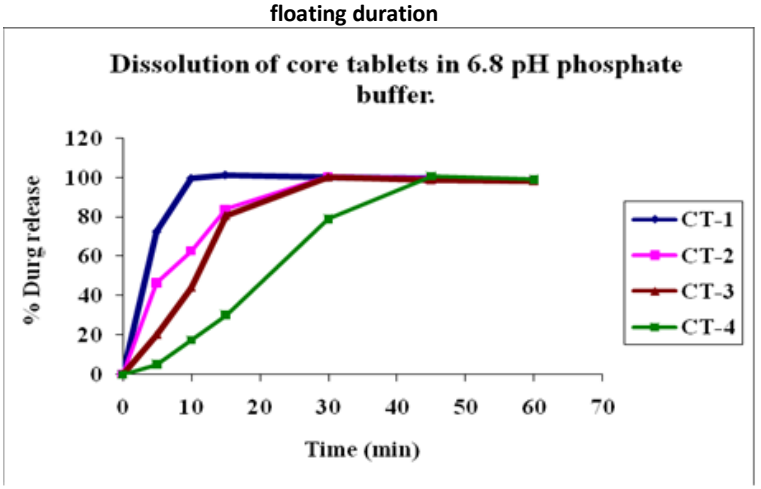

Figure 7:Dissolution of Aceclofenac core tablet formulation with various concentration of disintegrant Sodium starch glycolate 8 %(CT-1),4% (CT-2),2%(CT-3) & without disintegrant (CT-4)

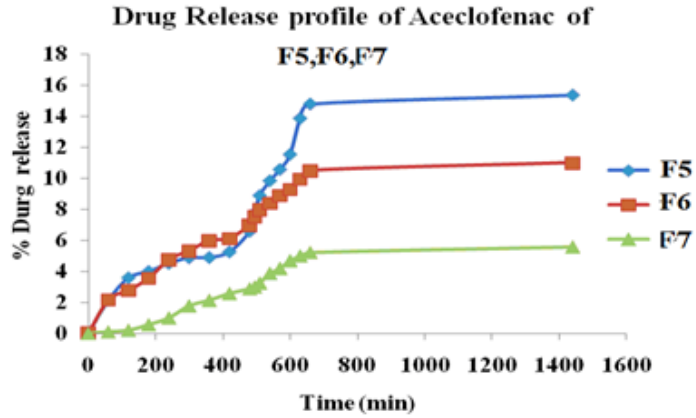

Figure No.8 Drug release profile of Aceclofenac of F5, 6, 7 formulations.

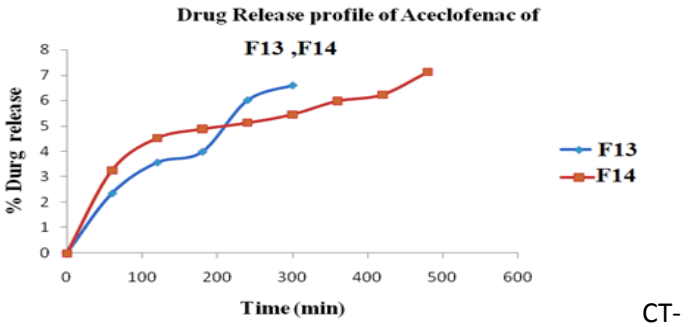

Figure No.9: Drug release profile of Aceclofenac of F13, F14 formulations

CT-1 to CT-4; the formulation containing highest amount of Sodium starch glycolate (CT-1) showed fast disintegration and fast release because of swellable disintegrant present in it. As amount of swellable disintegrant decrease amount of drug release decreased. Without disintegrate Sodium starch glycolate level in formulation CT-4 showing decrease in dintengrant property. As shown in figure7significant change in release profile CT1 shows drug release initially faster compare to CT -4 which without disintegrant.

***In vitro* Dissolution Study Press coated floating-pulsatile release formulation (F 1-F 22)**

In vitro dissolution test was carried out in phosphate buffer pH 6.8. Results of in vitro dissolution test presented in **Error! Reference source not found.**32.

Then in vitro dissolution test was carried out on F5, 6, 7 formulations. Here tablet float until 1440 min and at the end of 1440 min 15.38%, 11.0%, 5.59% drug release was observed respectively (shown in 34). Hence this formulation did not follow the principle
of pulsatile drug release.

Drug release profile of F13, F14 shown in figure No 9. In this F8 shows 6.58 % drug release at the end of 300 min and F14 float for 480 min and at the end of 480 min 7.11 % drug release was observed. Here both formulations did not follow the principle of pulsatile release.

Then F15 F 18, F22 shows 6.89 %, 6.98%, 6.84% drug release at the end of 480 min, drug release profile of F38 provided in figure 10 Which shows optimum drug release profile i.e. initial lag phase of 480 min with 6.89 %,6.98%, 6.84% drug release followed by 99.87 % ,100.25%,98.22% release. F15 F 18, F22 formulations follows the principle of pulsatile release, i.e. initial lag phase followed by instant release

Figure No 10 shows the drug release profile of F15 F 18, F22 shows formulation, which follows the pulsatile release pattern.

4. CONCLUSION:

The objective of this work was to develop and evaluate a floating-pulsatile drug delivery system using hydrophilic polymer for Aceclofenac and to evaluate buoyancy and drug release pattern. Floating pulsatile concept was applied to increase the gastric residence of the dosage form having the lag phase followed by a burst release.

Different batches of dry coated were prepared by varying concentration of HPMC K4M, HPMC K15M and HPMC K100M. All the formulations of dry coated tablets were evaluated for buoyancy and drug release pattern. Formulations from F1 to F4 containing 2 mm coating of HPMC K4M unable to provide floating ability. Formulations from F5 to F7 containing 4 mm coating of HPMC K4M provide floating for >12 h.

Formulations F8 to F15 were formulated by 4 mm coating with HPMC K4M, in which F15 (27.5%) formulation provide floating duration of 8 h with pulsatile release pattern. Formulation F19 to F18 were prepared containing HPMC K15M as a coating polymer. Tablets of F16 to F17 unable to show floating characteristics but F18 (25%) formulation show floating duration of 8 h with pulsatile release pattern. Similarly, F19 to F22 were prepared containing HPMC K100M. Tablets of F22 (25%) formulation shows floating duration of 8 h, with pulsatile release pattern.

Dry coated F15, F18 and F22 formulations shows 8 h floating with pulsatile release pattern. These three formulations were evaluated physicochemical properties; all parameters are found within limits.

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6. REFERENCES

1. Anil K. Anal, Time-Controlled Pulsatile Delivery Systems for Bioactive Compounds, Recent Patents on Drug Delivery & Formulation 2007, 1, 73-79.
2. Javed Ali, Sanjula Baboota, Alka Ahuja, Nitin Saigal., Distinctive features of “chronotherapeutic” and“pulsatile” drug delivery systems negating the practice of their interchangeable terminology. Journal of Drug Targeting; 2010, 18(6), 413–419.
3. Alessandra Maroni, Lucia Zema, Maria Dorly Del Curto, Giulia Loreti, Andrea Gazzaniga., Oral pulsatile delivery: Rationale and

chronopharmaceutical formulations. International Journal of Pharmaceutics, 2010, 398, 1–8.
4. Michael H. Smolensky, Nicholas A. Peppas b., Chronobiology, drug delivery, and chronotherapeutics. Advanced Drug Delivery, Reviews 2007, 59. 828–851.
5. Erhard Haus ,Chronobiology in the endocrine system Advanced Drug Delivery,Reviews 2007. 59 , 985–1014.
6. Asim Sattwa Mandal, Nikhil Biswas, Kazi Masud Karim, Arijit Guha, Sugata Chatterjee, Mamata Behera, Ketousetuo Kuotsu, Drug delivery system based on chronobiology—A review. Journal of Controlled Release, 2010,147 , 314–325.
7. D.D. Breimer, Future challenges for drug delivery. Journal of Controlled Release, 1999,62, 3–6.
8. Arvidson NG, Gudbjörnsson B, Elfman L, Rydén AC, Tötterman TH, Hällgren R., Circadian rhythm of serum interleukin-6 in rheumatoid arthritis. Ann Rheum Dis. 1994, 53,521–524.

Conflict of Interest: None Declared

