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FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING TABLET IN TABLET OF ACECLOFENAC

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ABSTRACT

One of the most suitable approach for achieving prolonged and predictable drug delivery profile in GI tract is gastroretentive drug delivery system. Floating pulsatile drug delivery system intended for chronopharmacotherapy is widely used for disease which shows circadian variation. It was applied to increase gastric residence of dosage form having lag phase followed by burst release. Aceclofenac is most suitable model drug for rheumatoid arthritis, osteoarthritis, pain and inflammatory conditions. Excipients were characterized for given specification. Binary mixture of Aceclofenac and polymers were prepared and evaluated for compatibility. Result of DSC thermogram and IR spectra shows drug:polymers are compatible with each other. Triple layer tablet was prepared using hydrophilic polymer as bottom layer and hydrophobic polymer as top layer. Tablet in Tablet of F23, F26 and F30 formulations shows 8 h floating with pulsatile release pattern. These three formulations were evaluated for micromeritics and physicochemical parameters, all parameters were found within acceptable range. Selected formulations of tablet in tablets were evaluated for buoyancy and drug release pattern. The polymer level have significant role for providing buoyancy and pulsatile release pattern.

Keywords: Tablet in tablet, Gastroretentive, floating, Pulsatile, Aceclofenac

INTRODUCTION

The oral route of drug administration is the most important method of administering drugs for systemic effects. Oral solid dosage forms represent the preferred class of product. The reasons for this preference are well known **[5]**. An ideal dosage regimen in the drug therapy of any disease is the one which immediately attain the desired therapeutic concentration of drug in plasma and maintains it's constant for the entire duration of treatment. This is possible through the administration of conventional dosage form but which are associated with number of limitations such as poor patient compliance; typical peak valley plasma concentration and unavoidable fluctuations **[9]**. To overcome above discussed limitations of conventional dosage forms it indicates the need of the development of non conventional dosage forms **[9]**. Oral controlled/sustained release dosage forms are being developed for the past three decades due to their advantages. The design of oral controlled/sustained drug delivery systems should primarily be aimed at achieving more predictable and increased bioavailability of drugs **[1, 36]**. The basic rational for sustained/controlled drug delivery systems is to alter the pharmacokinetics and pharmacodynamic of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and or physiological parameter inherent in a selected route of administration.

Commonly two general approaches for the formulation of controlled drug delivery system, which are drug based and other is dosage form based[25].The inability to restrain and confine these systems to selected regions GI tract has been the principle obstacle to the development of oral controlled release systems. Various approaches have been tried to overcome such an obstacle. They include the control of gastric residence time (GRT), using gastroretentive drug delivery system (GRDDS) that will provide us with new and important therapeutic options **[25]**. To comprehend the consideration taken in the design of the GRDDS and to evaluate their performance, the relevant anatomy and physiology of the GI tract must be fully understood. The GI tract is essentially a tube about 9 m long that run from mouth to the anus **[4]**.

The stomach is a j-shaped dilated portion of the alimentary tract situated in the epigastric, umbilical and left hypochondriac region of the abdominal cavity **[18]**. Fasting gastric pH is specially steady and approximate 2, but there are short periods of 7 ± 6 min characterized by higher values. Food buffers and neutralizes gastric acid,

thus increasing the pH up to 6.5. After meal ingestions completed, the pH rapidly falls back below 5 and then gradually decline to fasting state values over a period of few hour **[7, 18]**. The pyloric sphincter has a diameter of 12.8±7 mm in humans. The duodenal pH is 6.1;and its transit time is relatively short, less than 1 min. The small intestine has a large surface area, which is comparable to the area of basketball, 463 m^2. The pH of the small intestine is 6-7 and its transit time is 3±1 h, is relatively constant and is unaffected by food **[49]**.

Recent scientific and patent literature shows increased interest in academics and industrial research groups regarding the novel dosage forms that can be retained in the stomach for a prolonged and predictable period of time. One of the most feasible approaches is gastroretentive drug delivery system (GRDDS) **[49]**.Gastroretentive system can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits to patients[3].Various approaches have been followed to encourage gastric retention of an oral dosage form in the stomach, including Mucoadhesive, Swelling and expanding, High density system, Modified shape system, Delayed gastric emptying system and Floating drug delivery system (FDDS).The use of passage-delaying excipients has been proposed as an attempt to develop a form that exerts some influence on its own transit. Preliminary *in-vivo* result depicts a major problem related to the highly variable inter-subject reactions. Another analogue approaches consist of using passage delaying drug, for example propantheline, which is generally considered undesirable because of potential side effects **[50]**. The concept of floating drug delivery systems (FDDS) was first described in the literature as early as 1968, when Davis disclosed a method for overcoming the difficulty experienced by some persons of gagging or chocking while swallowing medical pills. The author suggested that such difficulty could be overcome by providing pill having a density less than 1.004 g/cm^3, so that pill will float on water surface. Since several approaches have been used to develop an ideal floating drug delivery system **[35]**.

Recent studies in the area of oral controlled drug delivery include novel approaches, which prolong the gastric retention time and Chronotherapeutic delivery system which release the drug in a pulsatile fashion, is recently gaining much attention worldwide. Pulsatile drug delivery system are characterized by two release phases, a first phase with no or little drug being released,

followed by a second phase, during which the drug is released completely within a short period of time after the lag time. Specifically, symptoms of rheumatoid arthritis and osteoarthritis, dyspnoea and epilepsy appear to have a peak during the night or early in the morning. Aceclofenac was taken as a model drug, which is effective for preventing the time related occurrence of rheumatoid arthritis and osteoarthritis. Aceclofenac was widely accepted as a NSAID agent. So Aceclofenac is a typical example of drug, which is used in the therapy of symptoms or disease as described. However for such cases, conventional drug delivery system are inappropriate for the delivery of Aceclofenac, as they cannot be administered just before the symptoms are worsened, because during this time patient are asleep **[18]**.

However chronobiology has long recognized that biological systems alter with days or seasons taking their clues from the environment. This occurs has led to the development of chronotherapeutics a new branch of therapy. Main objective of chronotherapy is the delivery of drug to the body, to the right site, at the right time, at the optimal dose **[24]**. Applications of Chronopharmacotherapy are to give a competitive edge to a product and enable or accelerate market entry.

MATERIALS AND METHODS

Aceclofenac, Dibasic calcium phosphate and microcrystalline cellulose were obtained from Macleod pharmaceutical, Mumbai. Sodium bicarbonate, Citric acid and Magnesium stearate obtained from Concept Pharmaceutical, Aurangabad. Hypromellose K4M, K15M and K100M supplied by Colorcon, Goa.

Excipient Compatibility study: Here thermal analysis and IR spectroscopy was used to investigate and predict any physicochemical interaction between components **[3]**.

Differential scanning calorimeter (DSC): Differential Scanning Calorimeter (DSC) was performed on drug alone, polymers alone and mixture of drug and polymers. The physical mixtures of drug with polymers for compatibility studies were prepared by triturating drug and polymers (1:1) in a dried mortar for 5 min and kept as it is for 24 h. The samples (drug alone, polymers alone and mixture of drug and polymers (1:1)) were weighed 2 to 5 mg and sealed in aluminum pans. Then sealed aluminum pan was heated at a scanning rate of 15 degrees centigrade/min from 100 to 200 degrees centigrade. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the drug, polymer and drug-polymer mixture **[35]**.

Infrared spectrophotometer (IR): Infrared (IR) spectroscopy was conducted and the spectrum was recorded in the wavelength region of 4000 to 400 cm^{-1}. The procedure consisted of, dispersing a sample (drug alone, polymers alone and mixture of drug and polymers (1:1)) in KBr and compressing into discs by applying a pressure of 7 tons for 5 min in a KBr press. The pellet was placed in the light path and the spectrum was obtained **[28]**.

Drug solubility study: Drug solubility study was performed by taking an excess quantity of aceclofenac and physical mixture of aceclofenac with excipients in 10 ml of different solutions given in **(Table 1)**. Then prepared solutions were kept in a shaking water bath for 24 h with 100 agitations/min at room temperature. Then solution was filtered and the amount of drug dissolved was analyzed by spectrophotometer **[26]**.

Table 1: Solubility of Aceclofenac in Different in Different Solution Media

Drug + Excipients	Medium
Aceclofenac	Distilled Water
Aceclofenac	0.1 N HCl
Aceclofenac	Phosphate buffer pH 6.8
Aceclofenac	Phosphate buffer pH 7.4
ACL+ MCC+DCP+MS	0.1 N HCl
ACL+HPMC+MCC+DCP+SBC+CA+MS	0.1 N HCl

ACL= Aceclofenac, MCC= Microcrystalline cellulose, DCP= Dicalcium phosphate, HPMC= Hydroxypropyl methylcellulose, SBC= Sodium bicarbonate. CA= Citric acid, MS= Magnesium Stearate.

Micromeritic properties: The angle of repose of aceclofenac was determined by fixed funnel method **[37]**. The bulk density (BD) and tapped density (TBD) were determined **[12]**. The Carr's index (%) and the Hausner ratio were calculated using following equatios **[26]**.

$$Carr's\ \ Index = \frac{TBD - LBD}{TBD} \times 100$$

$$Hausner\ Ratio = \frac{TBD}{LBD} \times 100$$

Melting point: The melting point of aceclofenac was determined by capillary method **[21]**.

Loss on drying: LOD was calculated by placing 2 g of drug powder in a Petri dish for drying in an oven at 105 degrees centigrade for 1 h, then weighed after drying and LOD was calculated using below formula **[32]**,

$$\%LOD = \frac{Weight\ \ of\ \ water\ in\ sample}{Weight\ of\ \ dry\ sample} \times 100$$

Analytical method: Analytical method for quantitative determination of pure drug form formulation to assure drug release was developed **[15]**.

UV method: Ultra violet absorption spectrum of aceclofenac was obtained in phosphate buffer pH 6.8 and 0.1 N Hydrochloric acid in the scanning range of 200-400 nm.

Preparation of phosphate buffer (PBS) pH 6.8: A 50 ml of 0.2M potassium dihydrogen phosphate solution was mixed

with 39.5 ml of 0.2M sodium hydroxide solution and final volume made up to 200 ml with distilled water.

Preparation of standard solution: An accurately weighed amount of aceclofenac dissolved in PBS to provide final concentration 100 µg/ml (solution A). An accurately weighed amount of aceclofenac dissolved in 0.1 N Hydrochloric acid to provide final concentration 100 µg/ml (solution B).

Construction of calibration curve: A series of dilutions from solution A and solution B in the range of 10-50 µg/ml were prepared and calibration curve was constructed at wavelength maxima of 274.2 nm and 273.2 nm respectively.

Formulation development: Formulation development study was carried out for the preparation of gastroretentive floating pulsatile release tablet in tablet by using direct compression method **[50]**.

Preparation of triple layer tablets: All excipients shown in **(Table 2)** was weighed properly and passed through 22 mesh sieve. The excipients of first layer, second layer and third layer were mixed separately in mortar and lubricated with magnesium stearate (1% w/w). Powder mixture of first layer was transferred manually into the die and then powder mixture of second layer was transferred over the first layer, finally after addition of the third layer in to the die, the total die content was compressed with 12 mm diameter flat faced punch tooling.

Table 2: Composition of Triple Layer Tablet Formulation

F	Layer	SBC	CA	MCC pH 102	DCP	EC	HPMC K4 M	MS	Aceclofenac
F1	I	10	2	35	126	50	-	2	-
	II	-	-	40	58	-	-	2	100
	III	-	-	40	83	-	100	2	-
F2	I	20	3	35	115	50	-	2	
	II	-	-	40	58	-	-	2	100
	III	-	-	40	83	-	100	2	
F3	I	30	4	35	104	50	-	2	
	II	-	-	40	58	-	-	2	100
	III	-	-	40	83	-	100	2	
F4	I	40	4	35	94	50	-	2	-
	II	-	-	40	58	-	-	2	100
	III	-	-	40	83	-	100	2	-
F5	I	40	4	35	69	75	-	2	-
	II	-	-	40	58	-	-	2	100
	III	-	-	40	83	-	100	2	-
F6	I	40	4	35	44	100	-	2	-
	II	-	-	40	58	-	-	2	100
	III	-	-	40	83	-	100	2	-
F7	I	40	4	35	18.5	125	-	2.5	-
	II	-	-	40	58	-	-	2	100
	III	40	4	40	14	-	125	2	-
F8	I	40	4	35	18.5	-	125	2.5	
	II	-	-	40	58	-	-	2	100
	III	40	4	40	14	-	125	2	-

F= Formulation code, SBC= Sodium bicarbonate, CA= Citric acid, MCC= Microcrystalline cellulose, DCP= Dicalcium phosphate, EC=Ethyl cellulose, HPMC K4M= Hydroxypropyl methylcellulose, MS=Magnesium stearate

Preparation of Tablet in Tablet floating-pulsatile release tablets: Tablet in tablet floating pulsatile release tablet was prepared by using compression coating method.

Initially, core tablet of aceclofenac was prepared further tablet in tablet manually formulated using compression machine.

Preparation of core tablets (CT): All excipients of core tablet given in **(Table 3)** were weighed and passed through 22 mesh sieve. Resultant powder was mixed thoroughly in mortar and lubricated with magnesium stearate (1% w/w). A 200mg powder was weighed and transferred manually in to die and compressed by using 8 mm diameter flat faced punch tooling.

Table 3: Composition of Aceclofenac Core Tablet Formulation

Formulation	Aceclofenac	MCC pH 102	DCP	SSG	Magnesium stearate
Core Tablet 1	100	40	58	0	2
Core Tablet 2	100	40	50	8	2

Tablet in Tablet of core tablets: Formulation compositions of outer polymer layer are shown in **(Table 4)**, containing varying percentage of polymers were weighed and passed through 22 mesh sieves. The excipients of outer polymer layer were mixed in a mortar and lubricated with magnesium stearate (1% w/w). Required weight of outer polymer layer was weighed and used in two steps: first half outer polymer blend was filled into the die then core tablet was placed in the center of die. Core tablet was slightly pressed to fix the polymer blend around and under the core tablet. Then rest of half outer polymer blend was filled and compressed by using 10/12 mm flat faced punch tooling.

Table 4: Composition of Coating Layer

F*	HPMC K4 M	HPMC K15 M	HPMC K100 M	MCC pH 102	DCP	SBC	Citric Acid	Magnesium stearate
F9	50	0	0	60	115	60	12	3
F10	75	0	0	60	90	60	12	3
F11	100	0	0	60	65	60	12	3
F12	225	0	0	0	0	60	12	3
F13	133	0	0	80	87	80	16	4
F14	200	0	0	80	20	80	16	4
F15	300	0	0	0	0	80	16	4
F16	133	0	0	80	87	80	16	4
F17	200	0	0	80	20	80	16	4
F18	300	0	0	0	0	80	16	4
F19	60	0	0	80	160	80	16	4
F20	80	0	0	80	140	80	16	4
F21	100	0	0	80	120	80	16	4
F22	120	0	0	80	100	80	16	4
F23	110	0	0	80	110	80	16	4
F24	0	60	0	80	160	80	16	4
F25	0	80	0	80	140	80	16	4
F26	0	100	0	80	120	80	16	4
F27	0	0	40	80	180	80	16	4
F28	0	0	60	80	160	80	16	4
F29	0	0	80	80	140	80	16	4
F30	0	0	100	80	120	80	16	4

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. *F9-F12 compressed on 10 mm punch and F13-F30 compressed on 12 mm punch.

Evaluation study:

Dry mixed powder characteristic study- Pure aceclofenac and its binary mixture with different excipients as given in **(Table 5)** were evaluated for angle of repose, bulk density, tapped density, Hausner ratio, Carr's index and degree of blend homogeneity.

Table 5: Aceclofenac and its Physical Mixtures with Excipients

Excipients
Pure Aceclofenac
ACL+MCC
ACL+MCC+DCP
ACL+MCC+DCP+MS
HPMC K4M+MCC+DCP+SBC+CA+MS
HPMC K15M+MCC+DCP+SBC+CA+MS
HPMC K100M+MCC+DCP+SBC+CA+MS

ACL= Aceclofenac, MCC= Microcrystalline cellulose, DCP= Dicalcium phosphate, MS= Magnesium stearate, HPMC K4M= Hydroxypropyl methylcellulose K4M, SBC= Sodium bicarbonate, CA= Citric acid, HPMC K15M= Hydroxypropyl methylcellulose K15M, HPMC K100M= Hydroxypropyl methylcellulose K100M.

Angle of repose-An angle of repose of pure aceclofenac and prepared mixture was determined by fixed funnel method **[45]**.

$$\theta = \tan^{-1}\frac{h}{r}$$

Where,

θ - Angle of repose

h - Height of granules above the flat surface

r - Radius of the circle formed by the granule heap.

Bulk density-Bulk density of pure aceclofenac and prepared mixture **(Table 5)**. Bulk density was determined by measuring poured volume of powder and mass of powder used **[44]**.

$$\rho_b = \frac{V_b}{M}$$

Where,

ρ_b - Bulk density

V_b - Volume of

M – Mass of powder.

Tapped density-Tapped density was determined by using the below mentioned formula **[44]**,

$$\rho_t = \frac{V_t}{M}$$

Where,

ρ_t - Tapped density

V_t - Tapped volume

M – Mass of powder

Compressibility (%)-Compressibility is a characteristic of mixed powder flow properties. It was calculated by using the formula **[44]**,

$$I = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

Where

I – index

ρ_t - Tapped density

ρ_b - Bulk density

Hausner ratio-Hausner ratio was calculated by using following formula **[44]**,

$$Housners\ Ratio = \frac{TBD}{LBD} \times 100$$

Carr's index (CI) (%)-CI was calculated by using following formula **[44]**,

$$Carr's\ Index = \frac{TBD - LBD}{TBD} \times 100$$

Degree of homogeneity of blend: Quantity of dry mixed powder equivalent to 100 mg of drug was taken and dissolved in alkaline phosphate buffer (pH 6.8), filtered and analyzed by spectrophotometer at 274.2 nm **[44]**.

Evaluation of Tablets:

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 **[24]**.

Hardness-Tablet hardness was recorded in kg/cm.

Friability-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 **[13]**.

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

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 upto 50 µg/ml and analyzed spectrophotometrically at 274.2nm. The concentration of drug was determined using standard calibration curve **[10]**.

Buoyancy determination-The buoyancy test of triple layer tablet and FPRT was studied by placing them in 500 ml beaker containing 0.1 N HCl, then tablet from same batches were placed in dissolution test apparatus containing 0.1 N HCl, maintained at 37±0.5 degrees centigrade and agitated at 100 rpm. 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 **[24]**.

***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 0.1 N HCl for initial 8 h, followed by in phosphate buffer pH 6.8 for 2 h, each 900 ml of dissolution media, maintained at 37±0.5 degrees centigrade and agitated at 100 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 273.2 and 274.2 nm for acidic and basic media, respectively.

Swelling Characteristics-To evaluate the water penetration characteristics, the tablets were exposed to 500 ml distilled water in three different beakers for 6 h and then evolution of tablet surface area was carried out by recording the change in diameter and thickness of the tablets. Change in surface area of the tablets was calculated by using formula **[18]**.

$$SA = 2\pi r$$

Where,

SA – Surface area

r – Radius of tablet

Stability Study-The fabricated floating pulsatile tablet formulations were subjected for stability study at room temperature and 50 degrees centigrade for three week. Then product evaluated for, buoyancy, drug content and *in-vitro* dissolution test **[34]**.

RESULTS AND DISCUSSION

Preformulation study:

Excipient Compatibility study-The possible interaction between the drug and the polymers was studied by Differential Scanning Calorimeter (DSC) and IR spectroscopy.

Differential Scanning Calorimeter-There was no considerable change in the DSC endotherm values, when aceclofenac was mixed with Hypromellose K4M, Hypromellose K15M and Hypromellose K100M, compared to that of pure aceclofenac **(Figure 1, 2, 3, 4, 5, 6 and 7)**.

Infrared spectroscopy-The IR spectra's of pure aceclofenac, Hypromellose K4M, Hypromellose K15M, Hypromellose K100M and physical mixture of aceclofenac with Hypromellose K4M, Hypromellose K15M and Hypromellose K100M (figs. 8, 9, 10, 11, 12, 13 and 14). Pure aceclofenac showed 3319.10, 2936.81, 2359.47, 1771.56, 1716.83 and 750.01 cm^{-1} wave number as major peaks. The results revealed no considerable changes in the IR peaks of aceclofenac when mixed with polymers compared to pure aceclofenac, Shown in **(Table 6)**.

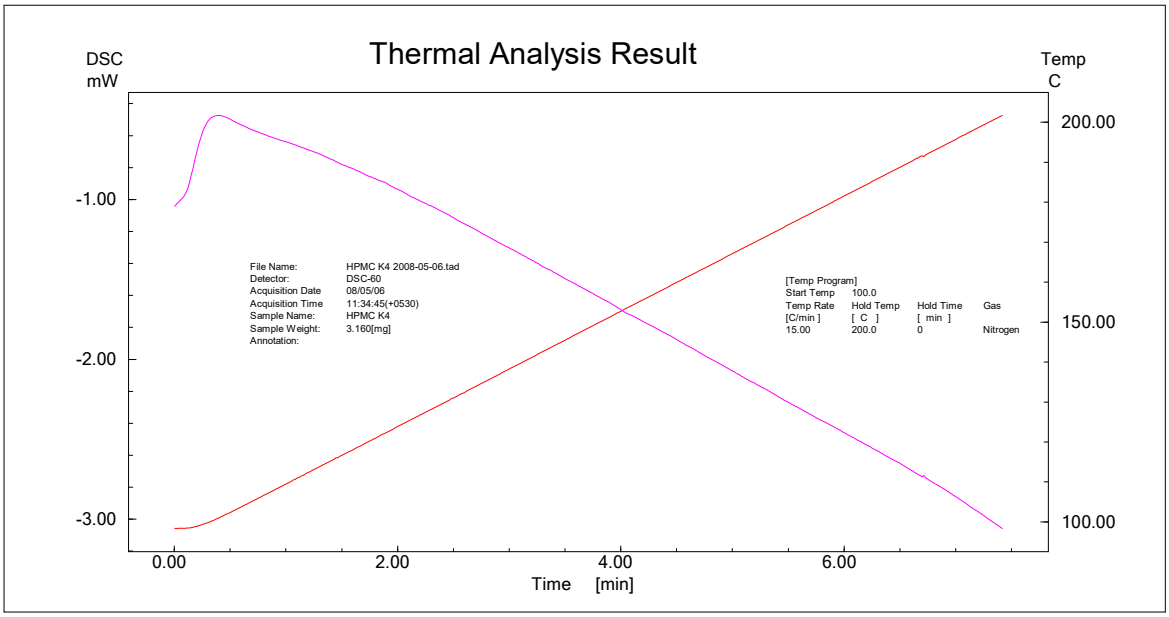


Figure 1: DSC thermogram of plain Aceclofenac

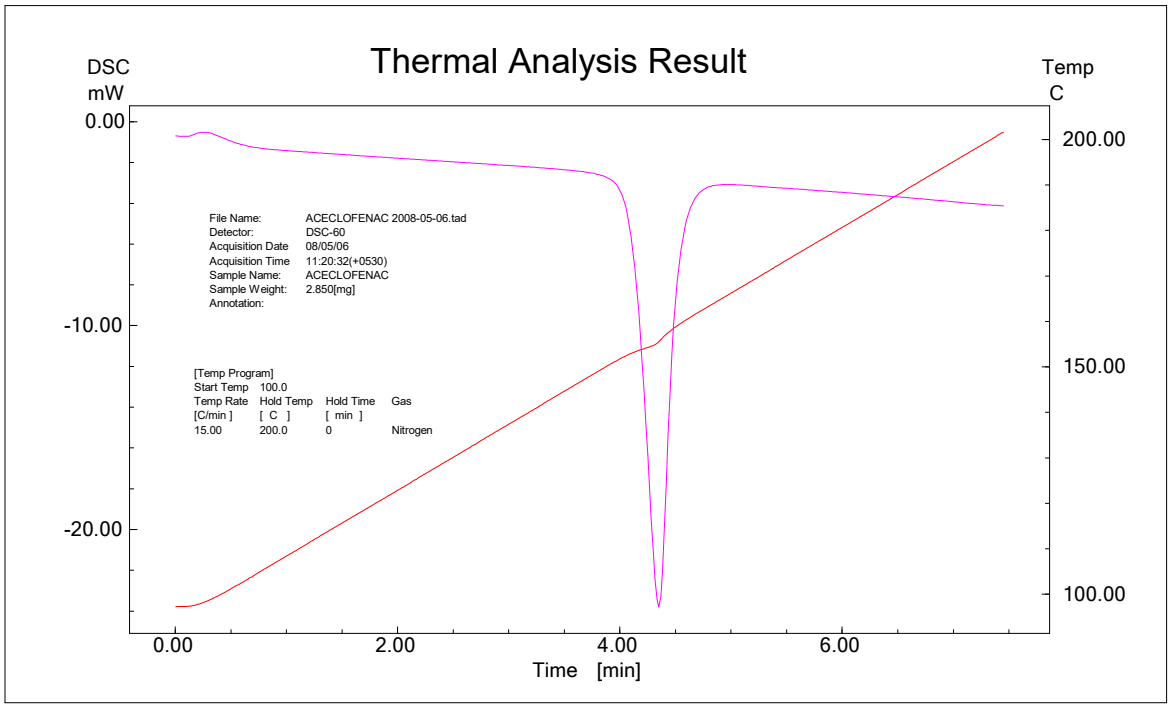


Figure 2: DSC thermogram of plain HPMC K4M

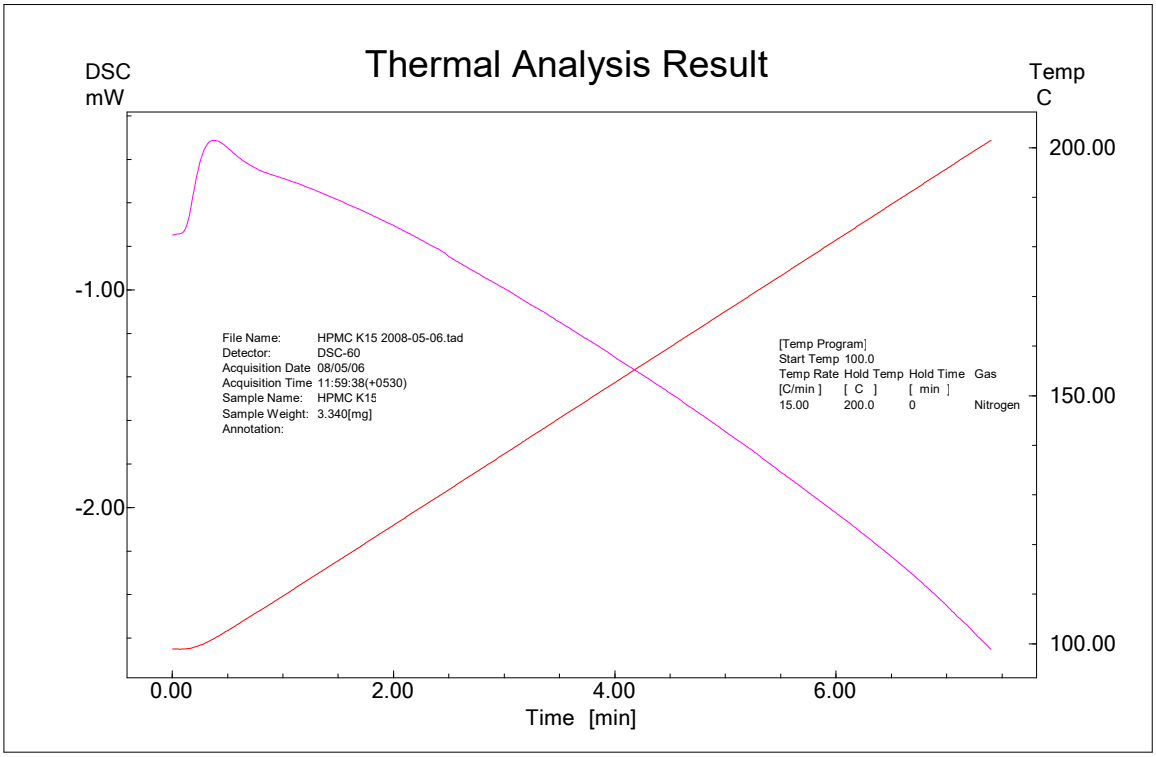


Figure 3: DSC thermogram of plain HPMC K15M

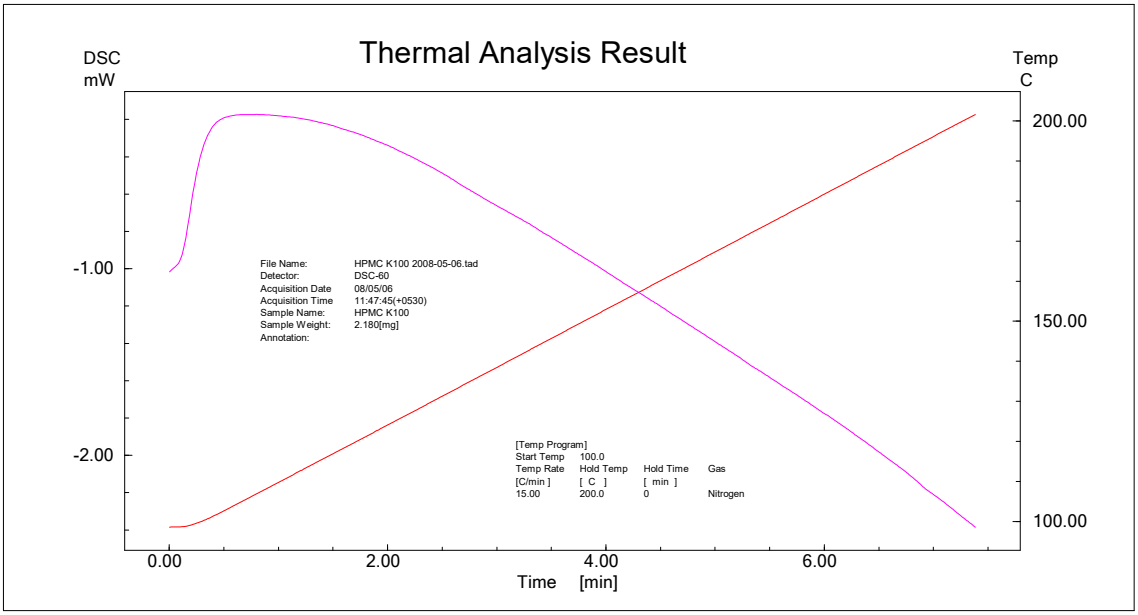


Figure 4: DSC thermogram of plain HPMC K100M

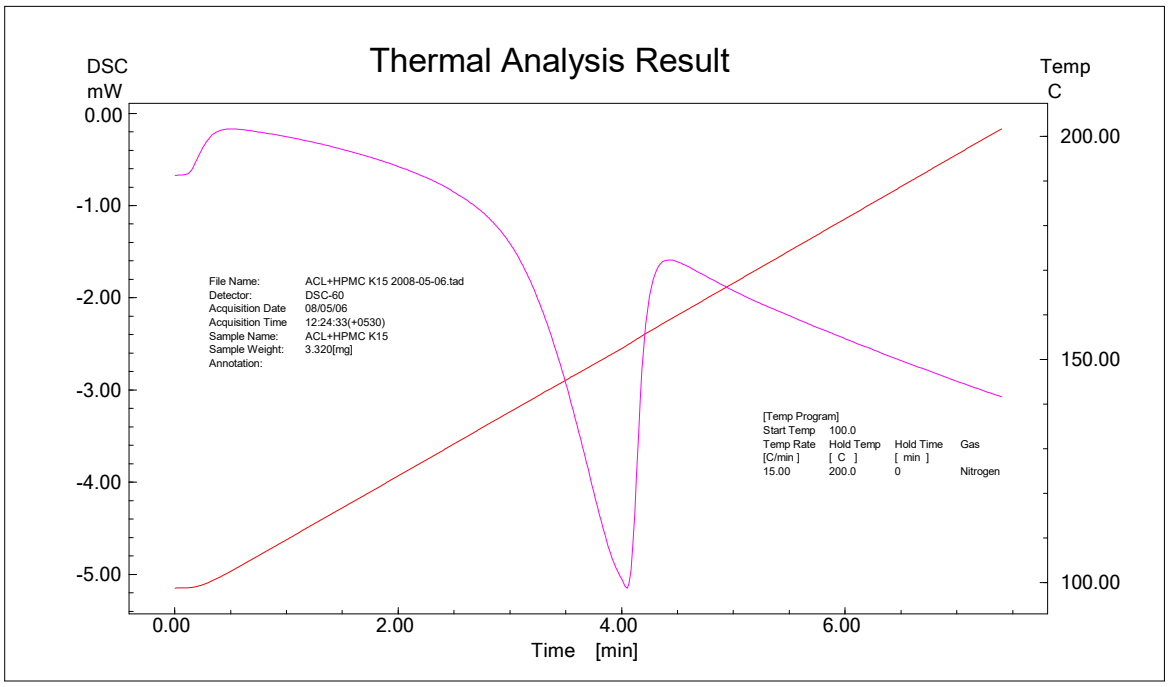


Figure 5: DSC thermogram of mixture of Aceclofenac+ HPMC K4M (1:1)

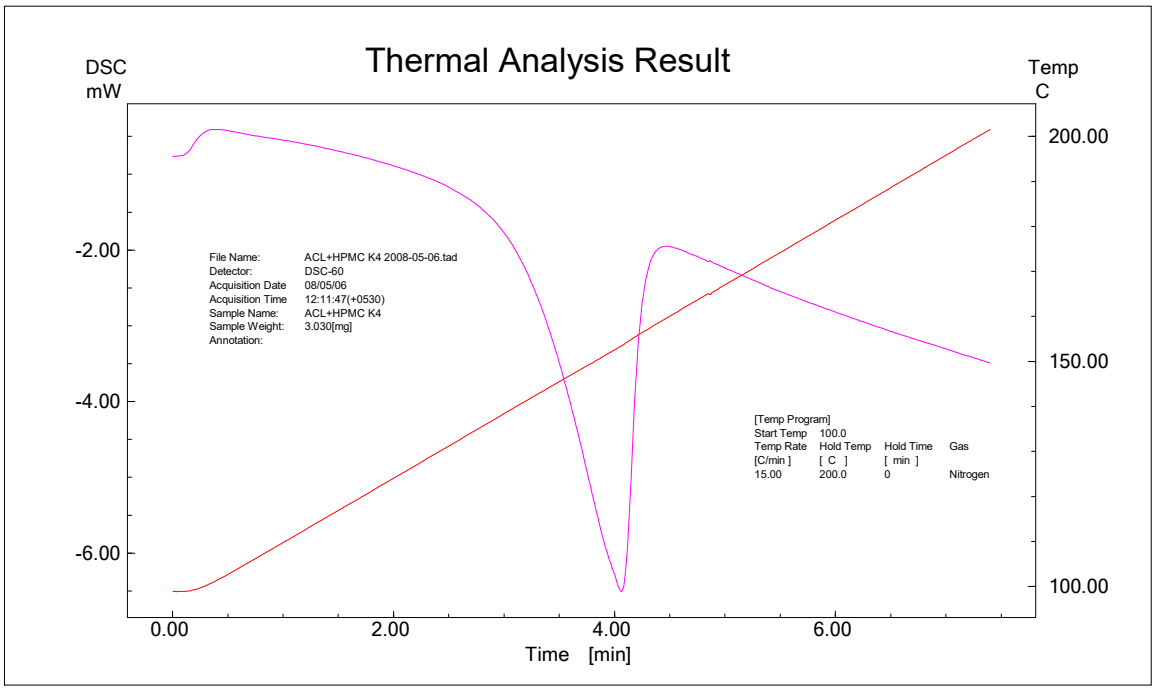


Figure 6: DSC thermogram of mixture of Aceclofenac+ HPMC K15M (1:1)

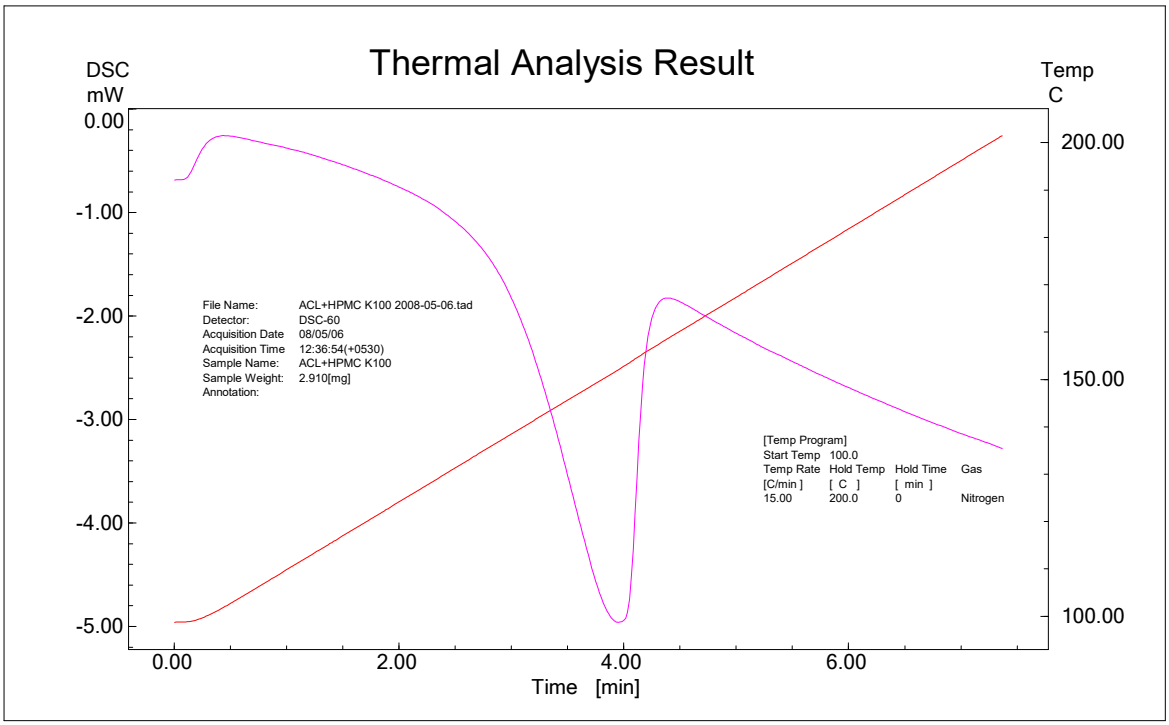


Figure 7: DSC thermogram of mixture of Aceclofenac + HPMC K100M (1:1)

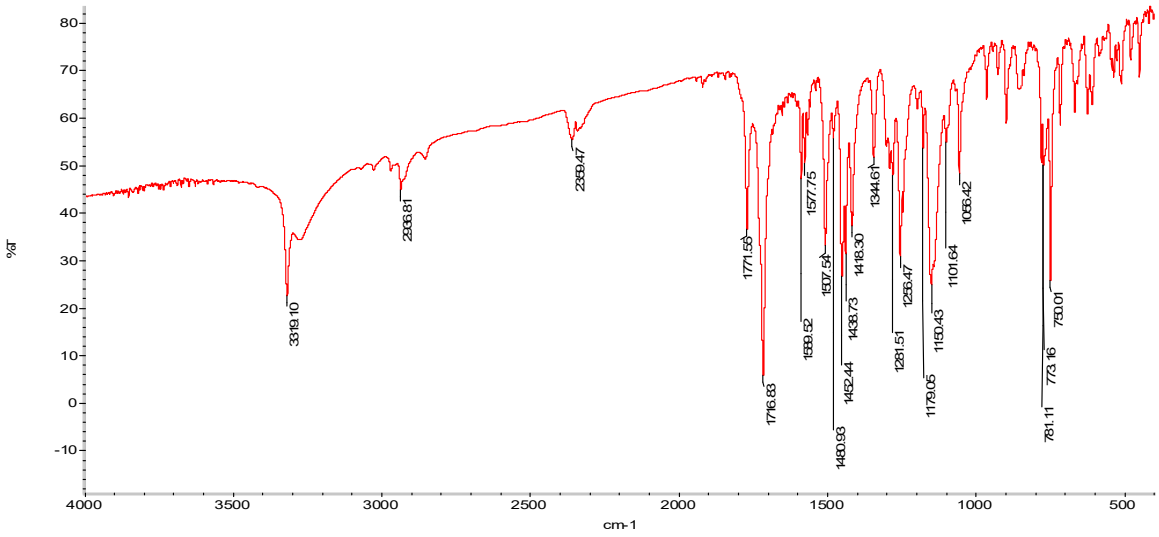
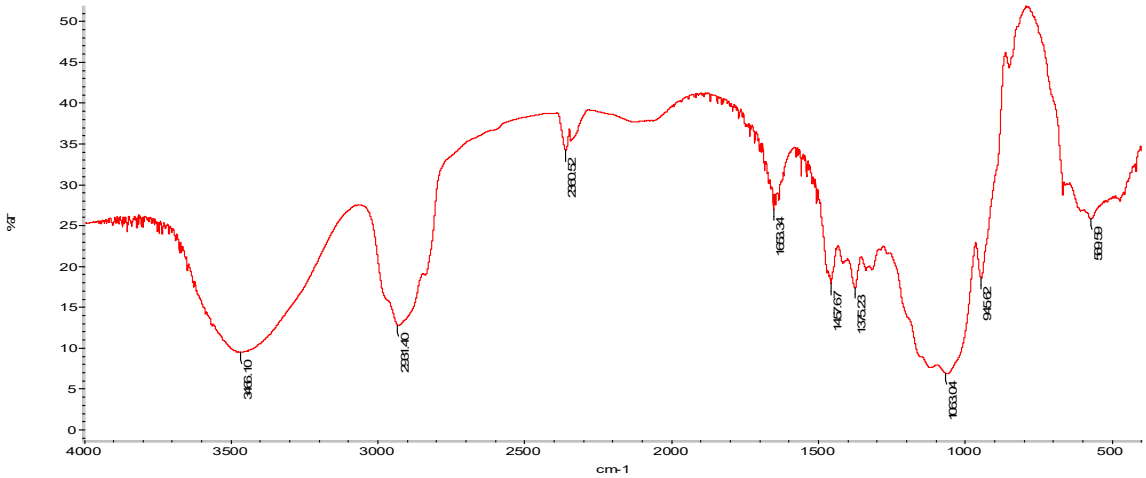


Figure 8: IR spectra of plain Aceclofenac

Figure 9: IR spectra of plain HPMC K4M



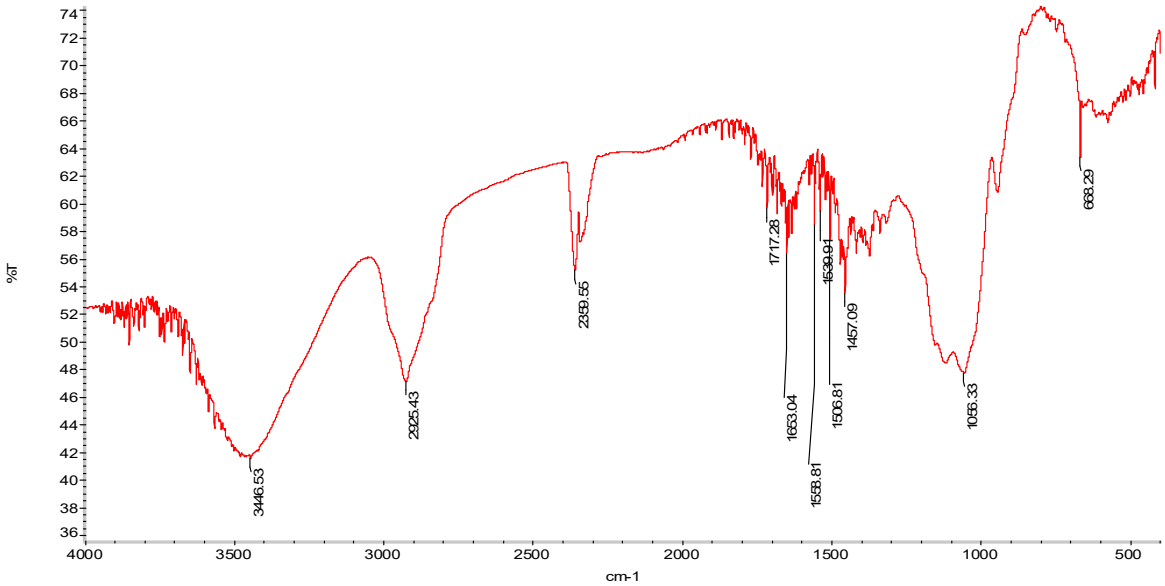


Figure 10: IR spectra of plain HPMC K15M

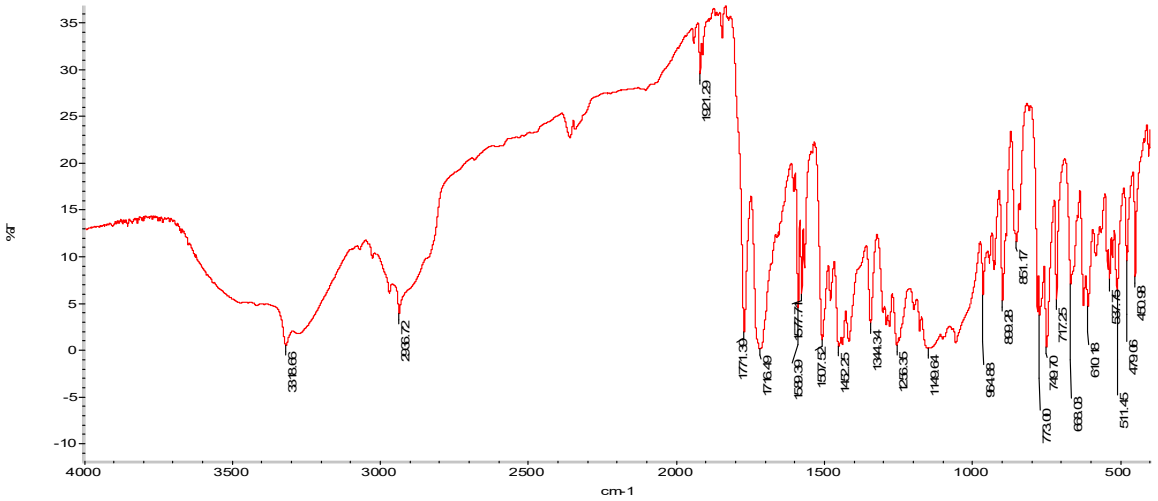


Figure 11: IR spectra of plain HPMC K00M

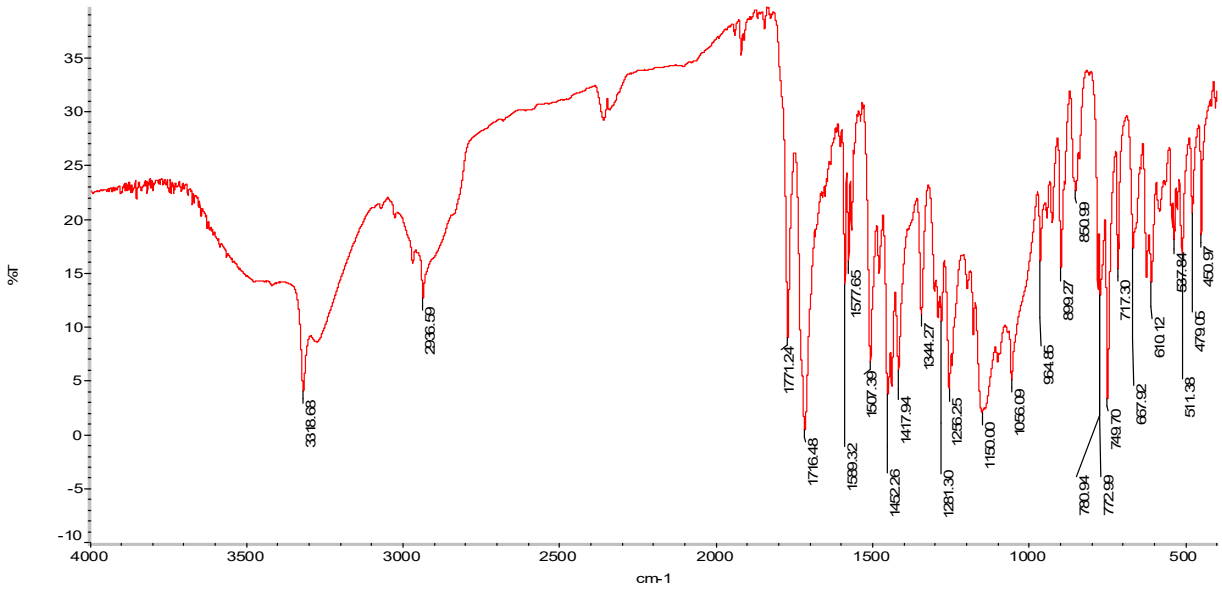


Figure 12: IR spectra of mixture of Aceclofenac + HPMC K4M (1:1)

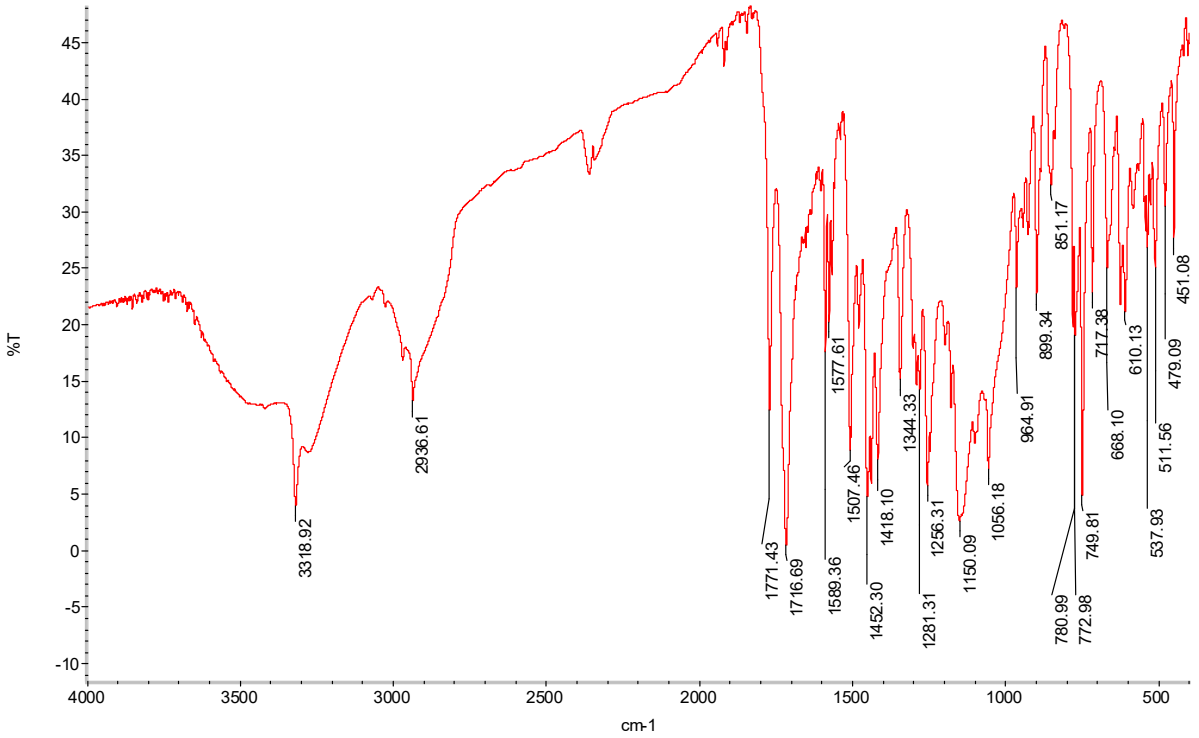


Figure 13: IR spectra of mixture of Aceclofenac + HPMC K15M (1:1)

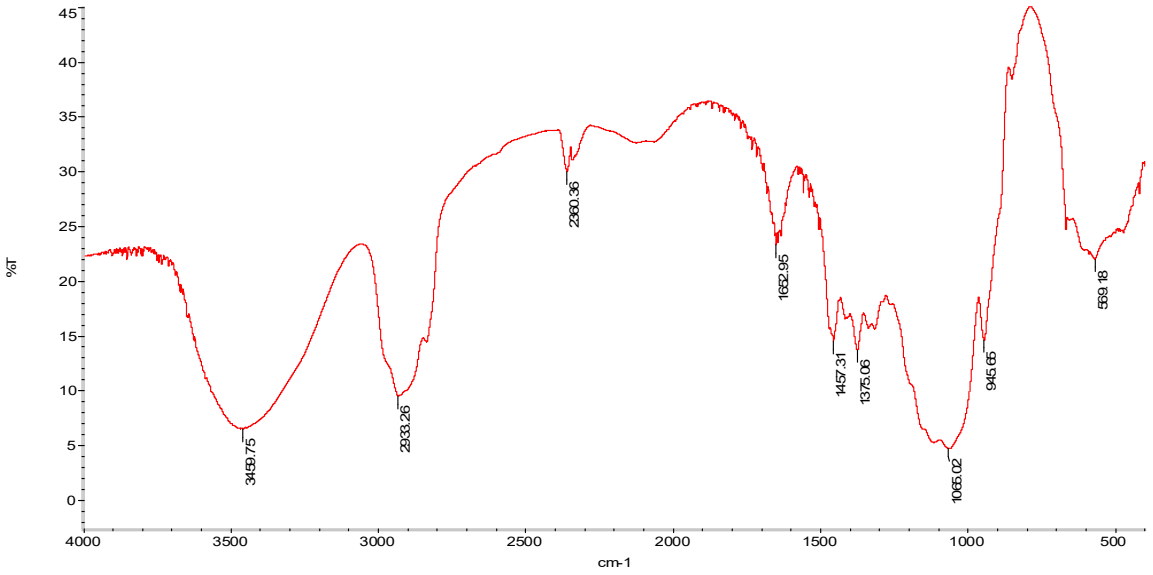


Figure 14: IR spectra of mixture of Aceclofenac + HPMC K100M (1:1)

Table 6: Comparison of Major IR Peaks of Drug Polymer Mixture with Pure Aceclofenac

Major peaks cm^{-1} wave number of			
Aceclofenac	**Aceclofenac: HPMC K4M (1:1)**	**Aceclofenac :HPMC K15M (1:1)**	**Aceclofenac : HPMC 100M (1:1)**
3319.10	**3318.66**	**3318.68**	**3318.92**
2936.81	**2936.72**	**2936.59**	**2936.61**
1771.56	**1771.39**	**1771.24**	**1771.43**
1716.83	**1716.49**	**1716.48**	**1716.69**
750.01	**749.70**	**749.70**	**749.81**

HPMC K4M= Hydroxypropyl methylcellulose K4M, HPMC K15M= Hydroxypropyl methylcellulose K15M, HPMC K100M= Hydroxypropyl methylcellulose K100M.

Drug solubility study-The results of aceclofenac solubility in various media and effect of different excipients are shown in **(Table 7 and 8)**. The solubility of aceclofenac in water was very less. Aceclofenac showed pH dependent solubility. At lower pH, the solubility was less and as the pH was raised from acidic to 6.8 the solubility drastically improved. Further increasing pH from 6.8 to 7.4 the solubility again decreased. Effect of excipients like DCP, MCC, MS does not affect the solubility of Aceclofenac, but further addition of Hypromellose, Sodium bicarbonate and citric acid slightly increased the solubility, but no considerable change were found.

Table 7: Solubility of Aceclofenac in Different Dissolution Media

Medium	Solubility (mg/ml)
Distilled Water	**0.085±0.001**
0.1 N HCl	**0.007±0.001**
Phosphate buffer pH 6.8	**13.183±0.554**
Phosphate buffer pH 7.4	**7.531±0.400**

All values are expressed as mean ± SD, n=3

Table 8: Solubility of Aceclofenac Miture with Different Excipients in 0.1 N HCl

Aceclofenac + Excipients	Solubility (mg/ml)
ACL+ MCC+DCP+MS	**0.007±0.000**
ACL+HPMC K4M+MCC+DCP+SBC+CA+MS	**0.013±0.001**

All values are expressed as mean ± SD, n=3, ACL= Aceclofenac, MCC= Microcrystalline cellulose, DCP= Dicalcium phosphate, MS= Magnesium stearate, HPMC K4M= Hydroxypropyl methylcellulose K4M, SBC= Sodium bicarbonate, CA= Citric acid.

Micromeritic properties-The results of micromeritic properties are presented in **(Table 9)**. Plain aceclofenac exhibited angle of repose value of 51.75º indicating extremely poor flow property. It was further supported by high Carr's index value of 28.51% and Hausner ratio of 1.40. Further addition flow property improving directly compressible vehicles like MCC slightly improve flow property, indicated by decrease in angle of repose value, supported by Carr's index and Hausner ratio value. Further incorporation of DCP considerably improved flow properties as indicated by reduction in the values of angle of repose, Carr's index and Hausner ratio.

Table 9: Micromeritic Properties of Aceclofenac and Mixtures of Aceclofenac with Excipients

Excipients	Angle of Repose	Carr's Index (%)	Hausner Ratio	Flow pattern
Pure Aceclofenac	51.75^0±0.541	28.51±0.212	1.40±0.095	Poor
ACL+MCC	40.92^0±0.292	22.±0.291	1.34±0.067	Poor
ACL+MCC+DCP	22.22^0±0.225	13.10±0.099	1.25±0.002	Very good

All values are expressed as mean ± SD, n=3, ACL= Aceclofenac, MCC= Microcrystalline cellulose, DCP= Dicalcium phosphate, MS= Magnesium stearate

Melting point-Observed melting point of aceclofenac was found in the range of 150-152 degrees centigrade, which comply with given literature value.

Loss on drying-Calculated LOD of aceclofenac was 0.502%.

Analytical method-Spectrum of aceclofenac was obtained in 0.1 N HCl and phosphate buffer pH 6.8 solutions, observed wavelength maxima was 273.2 nm and 274.2 nm respectively. At this particular wavelength absorbance of aceclofenac in 0.1 N HCl and phosphate buffer pH 6.8 solution was taken, a linear curve was obtained with co-relation regression value was 0.99968 and 0.99965 respectively **(Figures 15 and 16)**.

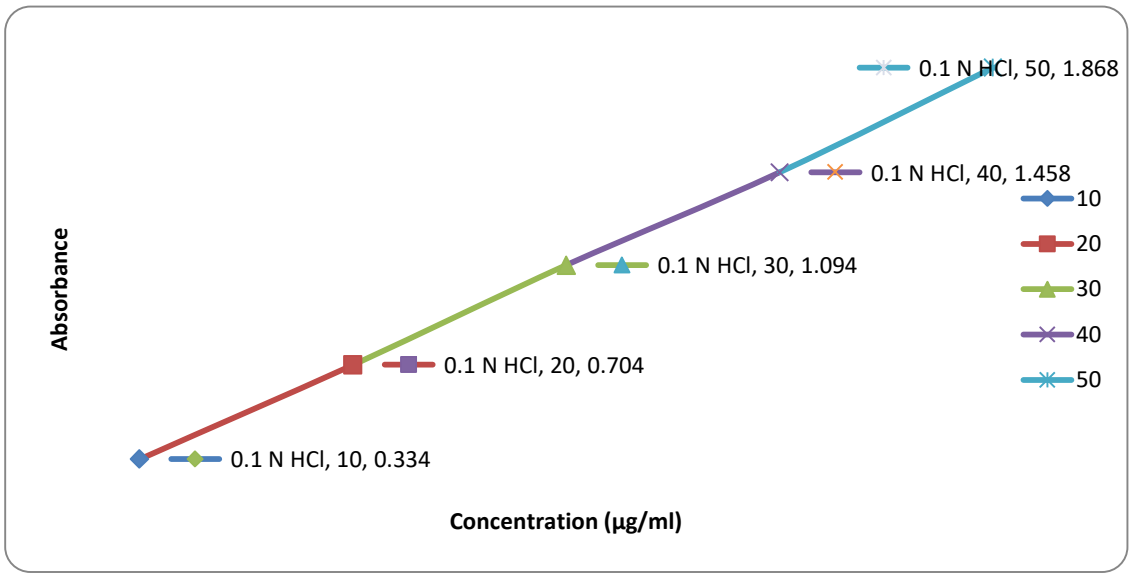


Figure 15: Standard curve of aceclofenac in 0.1 N HCl

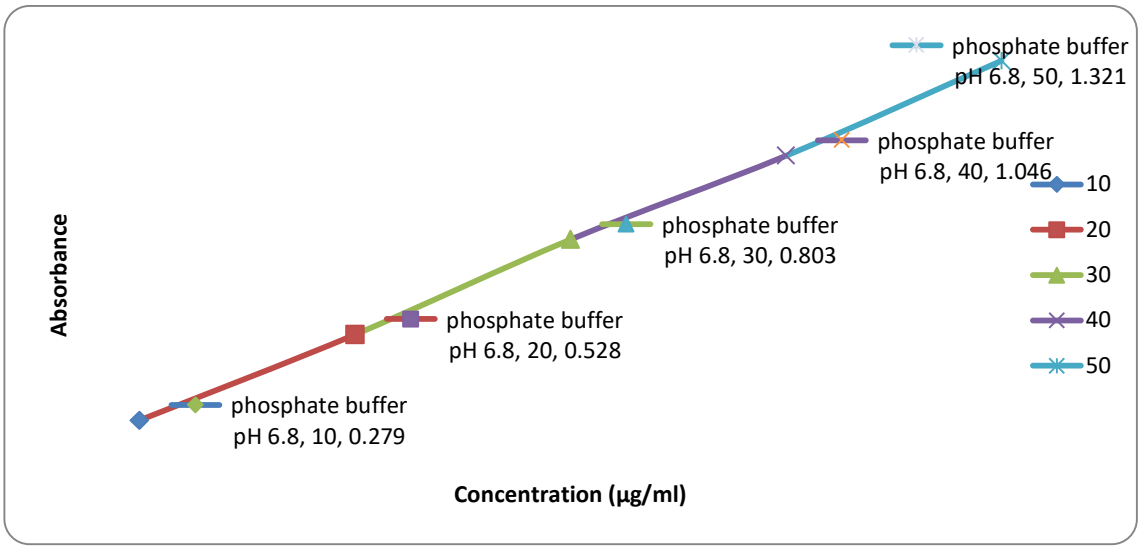


Figure 16: Standard curve of aceclofenac in phosphate buffer pH 6.8

Formulation study: Gastroretentive floating tablet in tablet containing drug and polymer, are one of the simplest approaches for controlled release and pulsatile release for model drug Aceclofenac. Among the different types of hydrophilic polymers reported, Hypromellose was used because of its associated advantages **[4, 10, 27]**. In addition, HPMC is a pH independent material and the drug release rates from Hypromellose matrix formulations are generally independent of processing variables, such as compaction pressure, drug particle size and incorporation of lubricant.

Direct compression-Direct compression approach preferred over wet granulation and dry granulation because of its well known advantages.

Triple layer tablet formulation-For the development of floating pulsatile release triple layer tablet was prepared. Formulated triple layer tablet was composed of three layers, top layer containing hydrophobic polymer (ethyl cellulose) dispersed with various percentage of gas generating agents, middle layer contains active ingredient (Aceclofenac) with other additives and bottom layer composed of hydrophilic polymer (Hypromellose K4M). Initially tablet was characterized for floating ability and result of floating ability provided in **(Table 10)**. Formulations from F1 to F3 get dispersed immediately in the medium without floating; this was due to the lower percentage of gas generating agent and polymer. Then formulation from F5 to F7 was formulated with higher percentage of gas generating agents and polymer. Then

tablets float, but floating lag time was higher with short period of floating and tablet gets separated into layers. During the process of layer separation it was observed that hydrophobic layer get separate initially and hydrophilic layer attached as such to middle layer. Hence it concluded that hydrophobic layer unable to make bonding with the middle layer. From this it decided that top and bottom layer should be of hydrophilic polymer to avoid the problem of layer separation.

Table 10: Floating Ability of Various Triple Layer Tablet Formulation

F. C.	Floating onset time (min)	Floating duration (min)	Integrity
F1	not float	not float	Broken
F2	not float	not float	Broken
F3	not float	not float	Broken
F4	18	30	Separate into layers
F5	6 -8	45	Separate into layers
F6	<3	45	Separate into layers
F7	<3	90	Separate into layers
F8	<1	470	Intact

F. C. = Formulation code.

Then F8 formulation was prepared by replacing Ethyl Cellulose with Hypromellose K4M. F8 formulation shows optimum floating lag time and duration. But during initial 8 h study in 0.1N HCl shows that open surface of middle layer get exposed to dissolution medium. Due to this medium exposure middle layer get erode slowly and this fails to show pulsatile release. From all this study it concluded that, polymer coating to the surrounding surface of middle layer was necessary to avoid the contact of dissolution media.

Tablet in Tablet floating-pulsatile release formulation-Here compression machine was selected because of work feasibility and simplicity. For compression core tablet having suitable 8 mm diameter and thickness less than final intact tablet was compressed.

Core tablet formulation-Core tablet (CT1, CT2) were formulated having diameter 8 mm, average weight 200.01 mg and average thickness 2.07 mm. Here CT1 was formulated without sodium starch glycolate (SSG) and CT2 was compressed by adding 8% sodium starch glycolate (SSG) to show pulsatile release after the complete erosion of polymer coating.

Tablet in Tablet of core tablet-By using CT1 and CT2 as a core tablet floating-pulsatile release tablets was formulated from F9 to F30.

Optimization of Polymer level-To characterize the effect of coating level on floating ability, using Hypromellose K4M as a coating polymer F9 to F12 batches were prepared, obtained results shown in **(Figure 17)**. Initially F9 and F10 batches were formulated by taking 16% and 25% Hypromellose 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 12 s and all tablets get dispersed within 5-10 min. Hence F9 and F10 formulations unable to float for required period, reason behind this was lower % of polymer that unable to form swollen gel.

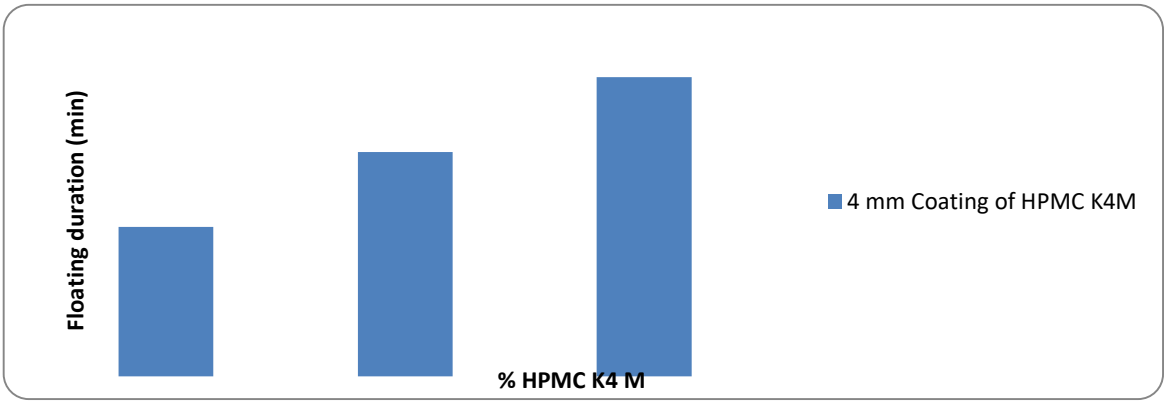


Figure 17: Effect of polymer concentration and coating level on floating duration

Then F11 batch was formulated by increasing the amount of Hypromellose K4M from 25% to 33% using 10 mm flat faced punch tooling. In buoyancy test tablet get separated into layers after 77 min. Here it concluded that, the amount of MCC and DCP in coating mixture was responsible for early separation of layers.

Then F12 was formulated by replacing the concentration of MCC and DCP by Hypromellose K4M, i.e. 75% Hypromellose K4M. Buoyancy test was performed, again tablet float for 94 min and separated into layer.

From *in vitro* buoyancy study of F9 to F12 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 F13, F14, F15 was formulated by increasing the coating thickness from 2 mm to 4 mm, observed results shown in **(Figure 18)**. Here final tablet in tablet was compressed on 12 mm flat faced punch tooling, by using polymer concentration 33%, 50%, 75% respectively. *In-vitro* buoyancy test was performed on F13, F14 and F15, tablet float without separating into layers, but tablet of F13 float for 720 min, F14 for 1080 min and F15 remains float till 1440 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.

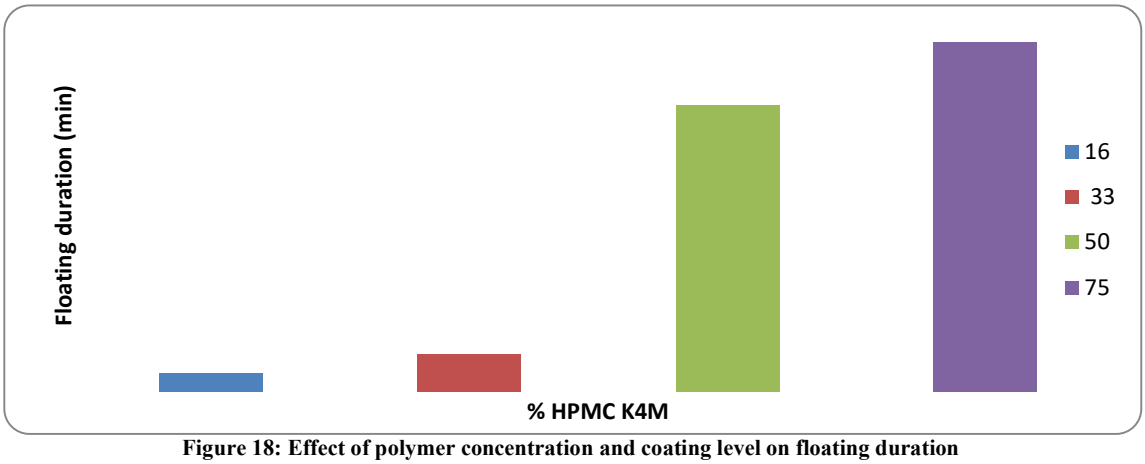


Figure 18: Effect of polymer concentration and coating level on floating duration

Optimization of floating duration with Hypromellose K4M: Here main objective is tablet should have 480 min gastro retention without drug release followed by pulsatile release.

To achieve this objective CT2 (containing super disintegrate SSG) was taken as a core and F16, F17 and F18 was formulated with 33%, 50% and 75% polymer concentration respectively. Observed results shown in **(Figure 19)**. *In vitro* buoyancy test was carried out for all three formulations, F16 tablet get burst after 120 min, F17 tablet burst at 210 min and F18 tablet remain float till 372 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 F19, F20, F21, F22 batches were formulated, by using CT1 as a core tablet, with 15%, 20%, 25%, 30% Hypromellose K4M as a coating polymer respectively. Observed effect of polymer concentration on floating duration shown in **(Figure 20)**.

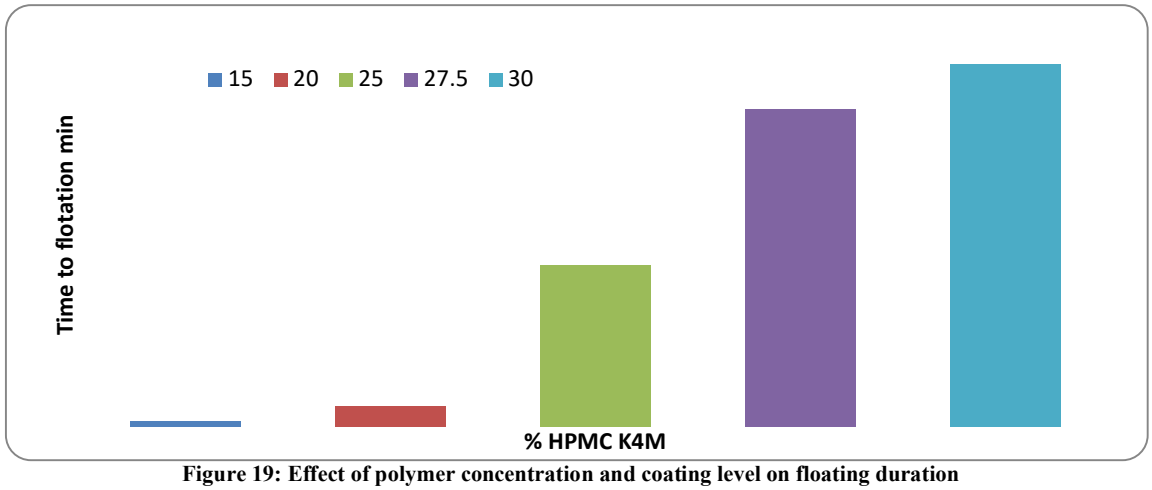


Figure 19: Effect of polymer concentration and coating level on floating duration

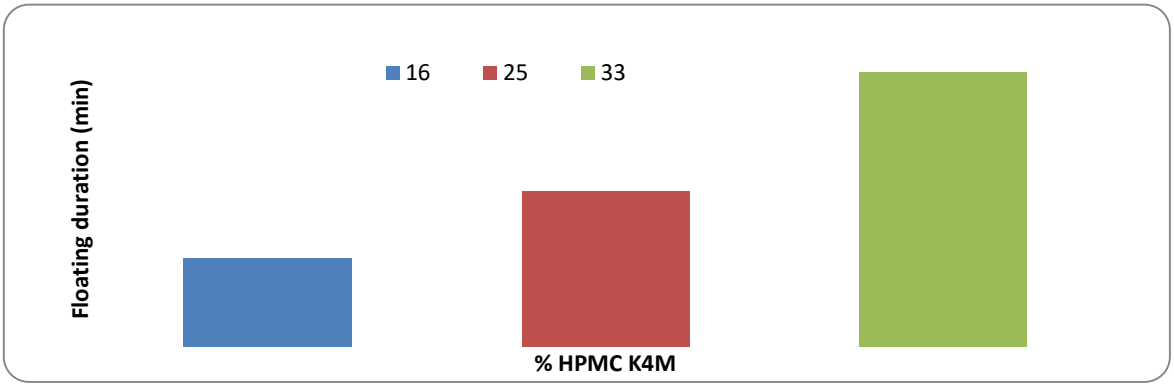


Figure 20: Effect of polymer concentration and coating level on floating duration

In-vitro buoyancy test was performed on F19 to F22 batches, tablet of F19 batch dispersed within 8 min in dissolution medium. It indicates to increase the Hypromellose K4M concentration. Then F20 was formulated by adding 20% Hypromellose K4M. *In vitro* buoyancy test indicates tablet float for 30 min after that get disintegrate. Hence again need to increase the concentration of Hypromellose K4M.

Further F21 was formulated by using 25% of Hypromellose K4M, tablet get float till 240 min after that core tablet get dropped. Then F22 was formulated by adding 30% of Hypromellose K4M, tablet get float till 540 min, after that core tablet get dropped in dissolution media. From this buoyancy pattern of F21 and F22, it concludes that required Hypromellose K4M concentration should be in between 25% to 30%.

Hence F23 was formulated using 27.5% Hypromellose K4M, this formulation float till 473 min and maintains it shape without dropping the inner core tablet. At 473 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 F23 formulation considered optimized formulation for Hypromellose K4M polymer.

Optimization of floating duration with Hypromellose K15M: Here batches F24, F25 and F26 were prepared by using Hypromellose K15M as a coating polymer with 15%, 20% and 25% respectively. Obtained results shown in **(Figure 21)**. Tablet of F24 formulation get dispersed within 10 min. Then concentration of coating polymer was increased up to 20% and F25 was formulated, here also tablet gets dispersed after 180 min. After that F26 was formulate with 25% of Hypromellose K15M, this formulation float till 472 min satisfactorily, after that tablet get burst and inner core tablet get dropped. Hence F26 formulation follows the objective of pulsatile fashion and considered optimized formulation for Hypromellose K15M polymer.

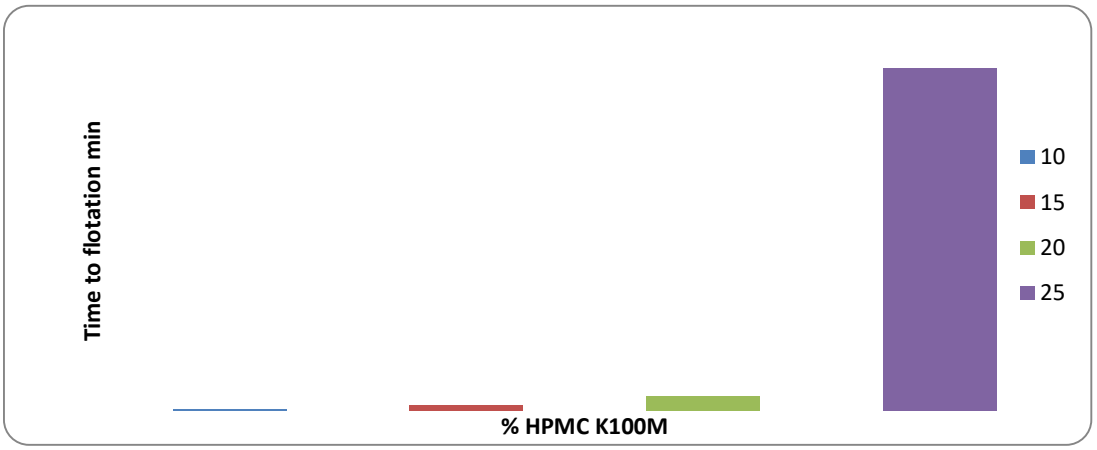


Figure 21: Effect of polymer concentration and coating level on floating duration

Adjustment of floating duration with Hypromellose K100M: Here floating duration of formulation was adjusted by using Hypromellose K100M as a coating polymer. Formulation F27, F28 and F29 was prepared with 10%, 15% and 20% Hypromellose K100M respectively. Obtained results provided in **(Figure 22)**. Tablets of F27 to F29 formulations were dispersed within 2 to 20 min because of lower % of polymer. After that F30 was formulated with 25% Hypromellose K100M, this formulation float till 476 min satisfactorily, after that tablet coating get burst and inner core tablet get dropped. Hence F30 formulation follows the objective of pulsatile fashion and considered optimized formulation for Hypromellose K100M polymer.

Here dry coated tablet was designed for floating pulsatile release fashion, by using three different grades of Hypromellose polymer from batch no. F9-F30. Among this F23, F26 and F30 considered optimized formulation for Hypromellose K4M, Hypromellose K15M and Hypromellose K100M respectively.

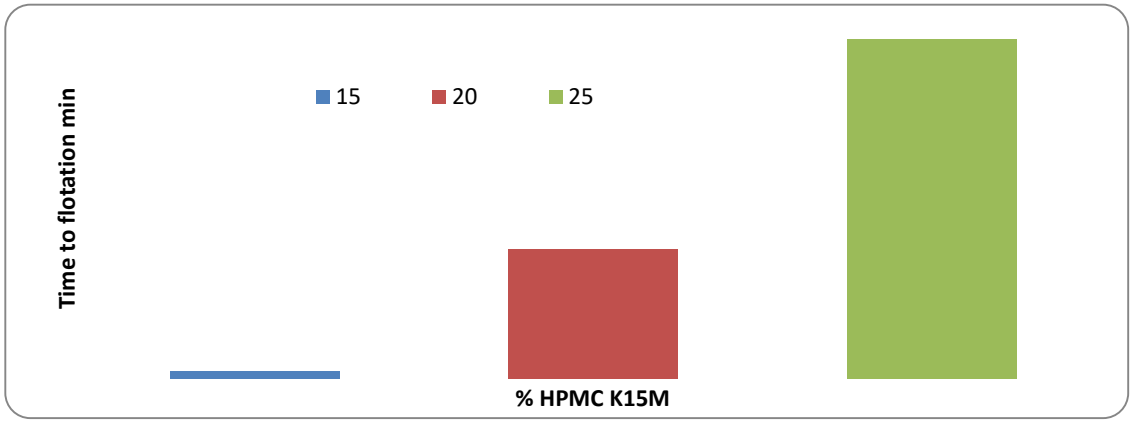


Figure 22: Effect of polymer concentration and coating level on floating duration

Evaluation study:

Evaluation of powder mixture characteristics-The results of micromeritic properties are presented in dry coated material shows excellent flow properties **(Table 11)**.

Table 11: Micromeritic Properties of Aceclofenac with Different Excipients

Excipients	Angle of Repose	Carr's Index (%)	Hausner Ratio	Flow property	Degree of Blend Homogeniety (% w/w)
Pure Aceclofenac	51.75^0±0.541	28.51±0.212	1.40±0.095	Poor	
ACL+MCC	40.92^0±0.292	22.23±0.291	1.37±0.038	Poor	
ACL+MCC+DCP	22.22^0±0.225	13.10±0.099	1.34±0.067	Very good	
ACL+MCC+DCP+MS	21.65^0±0.138	10.28±0.025	1.25±0.002	Very good	98.32±0.325
HPMC K4M+MCC+DCP+SBC +CA+MS	11.28^0±0.292	13.42±0.162	1.13±0.015	Excellent	
HPMC K15M+MCC+DCP+SB C+CA+MS	11.13^0±0.165	13.40±0.165	1.15±0.005	Excellent	
HPMC K100M+MCC+DCP+SB C+CA+MS	11.36^0±0.425	13.43±0.360	1.15±0.001	Excellent	

All values are expressed as mean ± SD, n=3, ACL= Aceclofenac, MCC= Microcrystalline cellulose, DCP= Dicalcium phosphate, MS= Magnesium stearate, HPMC K4M= Hydroxypropyl methylcellulose K4M, SBC= Sodium bicarbonate, CA= Citric acid, HPMC K15M= Hydroxypropyl methylcellulose K15M, HPMC K100M= Hydroxypropyl methylcellulose K100M

The method employed for tabletting in this project was direct compression for which the drug, mixture of drug and excipients, polymers should possess good flow and compacting properties. Plain aceclofenac exhibited angle of repose value of 51.75º indicating extremely poor flow property. It was further supported by high Carr's index value of 28.51% and Hausner ratio of 1.40. Hence it was necessary to use flow property improving directly compressible vehicles like dicalcium phosphate (DCP), microcrystalline cellulose (MCC). The incorporation of these diluents into aceclofenac considerably improved flow properties as indicated by reduction in the values of angle of repose, Carr's index and Hausner ratio. Although both vehicles selected exhibit good flow properties. Degree of homogeneity of blend was studied to characterize the dry mixing process. The observations indicate uniform mixing of blend.

Evaluation of Tablets characteristics:

Physicochemical properties of tablets-The results of physicochemical evaluation of tablets are given in **(Table 12)**.

Table 12: Physicochemical Properties of F8, CT1, F23, F26, F30 Formulation

F	Weight Variation *n=20*	Thickness (mm) *n=20*	Hardness (kg/cm^2) *n=20*	Friability (%) *n=20*	Drug Content (%) *n=3*
F8	650.10±0.641	3.52±0.014	6.28±0.566	0.64±0.085	98.38±0.202
CT1	200.01±1.041	2.07±0.040	5.64±0.412	0.78±0.041	98.39±0.187
F23	600.96±1.912	3.26±0.042	6.17±0.383	0.77±0.039	98.34±0.198
F26	601.07±1.584	3.26±0.056	6.24±0.441	0.71±0.075	98.36±0.204
F30	600.34±1.379	3.25±0.048	6.19±0.477	0.66±0.066	98.45±0.203

All values are expressed as mean ± SD. F= Formulation code, CT1= Core tablet 1

The tablets formulation F8 was found uniform with respect to thickness (3.50-3.56 mm), diameter (12 mm) and hardness (5.4-7.2 kg/cm^2). The friability (0.40–0.73%) and weight variation test complies as per I.P. limits. Good and uniform drug content (>98%) was observed within the batches. The core tablet (CT1, CT2) formulation was found uniform with respect to thickness (2.04–2.17 mm), diameter (8 mm) and hardness (5.1-6.2 kg/cm^2). Friability (0.72-0.86%) and weight variation test complies as per I. P. limits. Good and uniform drug content (>98%) was observed within the batches. Hence, the tablets containing drug, DCP, MCC and magnesium stearate could be prepared satisfactorily by direct compression method. The final dry coated tablets (FPRT) of F23 were found uniform with respect to thickness (3.20-3.35 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 (>98%) was observed within the batches.

Tablets of F26 were found uniform with respect to thickness (3.20-3.36 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 (>98%) was observed within the batches. Tablets F30 were found uniform with respect to thickness (3.18-3.34 mm), diameter (12 mm) and hardness (5.6-6.8 kg/cm^2). The friability (0.55-0.78%) and weight variation test complies as per I. P. limits. Good and uniform drug content (>98%) was observed within the batches.

All physicochemical properties of F23, F26 and F30 batches were found within limit. Hence, the tablets containing drug, Hypromellose, DCP, MCC, SBC, CA and magnesium stearate could be prepared satisfactorily by direct compression method.

Buoyancy determination-*In-vitro* buoyancy study was studied, initially floating lag time and floating duration of tablet was determined simply by placing tablet in 500 ml beaker containing 0.1 N HCl. Observed floating lag time for F8, F23, F26 and F30 was 42, 12, 21, 32 s and floating duration was >1320 min. Then *in-vitro* buoyancy study for the same batch was done in 900 ml dissolution test apparatus at 37.5˚C, 100 rpm. Observed floating lag time for F8, F23, F26 and F30 was 42, 12, 21 and 32 s and floating duration was 470, 473, 472 and 476 min respectively. Here it observed that paddle rotation speed reduce the floating duration.

Floating behavior of tablets of all three formulation were shown in **(Figure 23, 24, 25 and 26)** floating lag time and duration shown by graphically **(Figure 27 and 28)**.

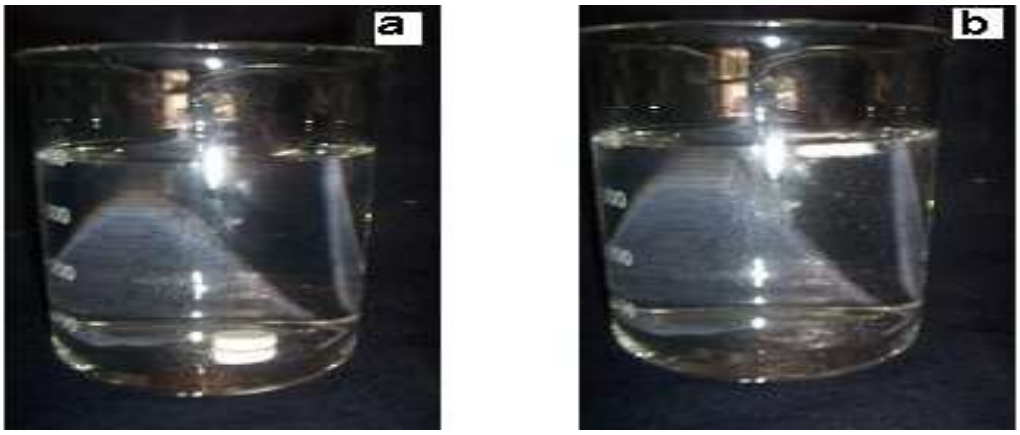


Figure 23: Invitro buoyancy of a) F23 at 0 s, b) F23 at 12 s

Figure 24: *In vitro* buoyancy study of a) F26 at 0 s, b) F26 at 13 s, c) F26 at 21 s

Figure 25: *In vitro* buoyancy of a) F30 at 0 s, b) F30 at 32 s

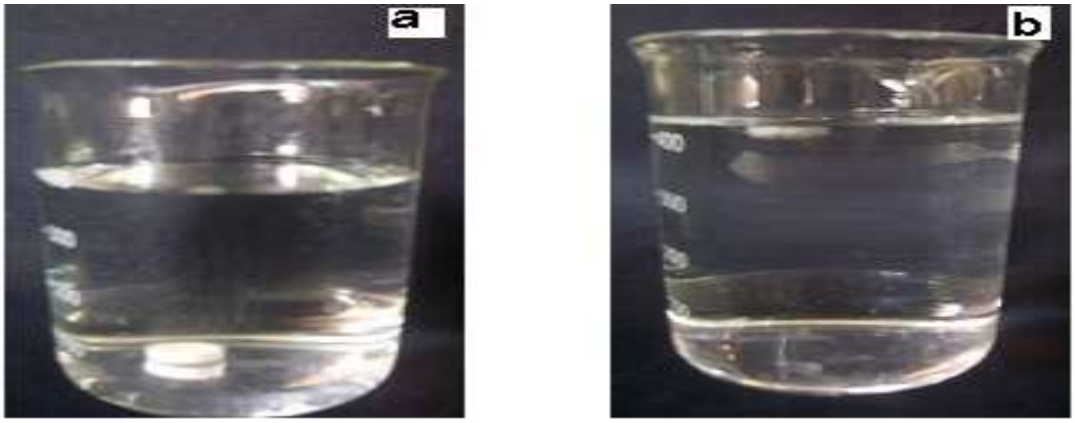


Figure 26: Upper view of *in vitro* buoyancy a) F23, b) F26, c) F30 formulations

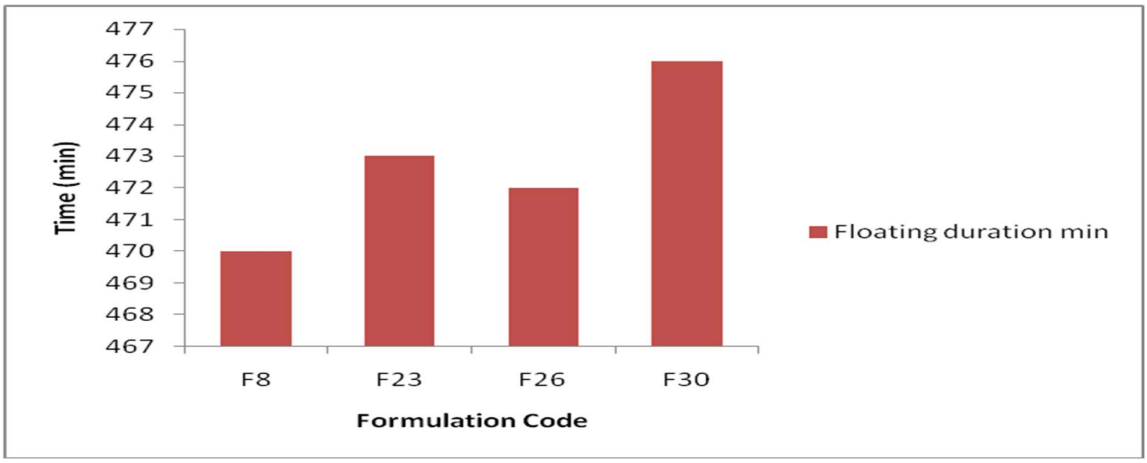


Figure 27: Floating duration of various formulations

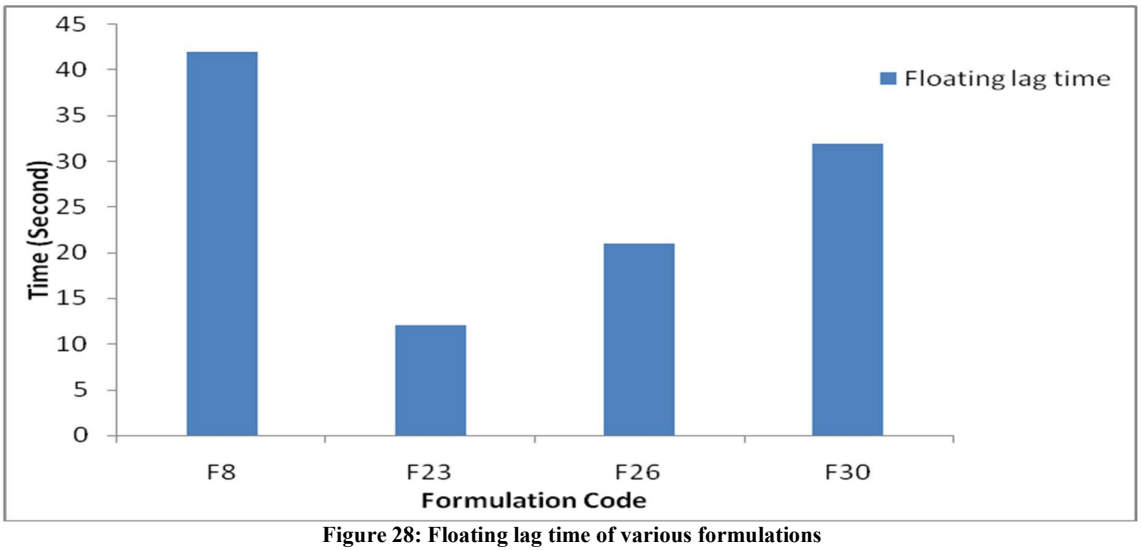


Figure 28: Floating lag time of various formulations

In-vitro* Dissolution Study-In-vitro* dissolution test was carried out in 0.1 N HCl for initial 480 min followed by in phosphate buffer pH 6.8 for 120 min. Result of *in-vitro* dissolution test presented in **(Table 13)**. Initially dissolution test was performed on F8 formulation in 0.1 N HCl for initial 480 min then followed by phosphate buffer pH 6.8 for 180 min. % cumulative drug release of F8 formulation at the end of 660 min was 71.34% only **(Figure 29)**.

Table 13: % Cumulative Release of Aceclofenac for Initial 480 min in 0.1 N HCl Followed by 120 min in Phosphate Buffer pH 6.8 of Different Formulation

Time (min)	% Cumulative Drug Release									
	F8	F13	F14	F15	F21	F22	F23	F25	F26	F30
60	4.28	3.84	4.64	0.20	3.92	4.28	4.56	0.37	4.39	4.48
120	6.28	4.03	4.74	0.60	4.89	5.29	5.14	0.68	5.28	4.50
180	6.58	4.11	5.51	0.86	5.51	5.73	5.33	1.01	5.45	4.77
240	6.62	4.75	6.29	1.27	6.08	5.96	5.85		5.68	5.09
300	6.63	4.94	6.67	2.22		6.56	5.95		5.74	5.25
360	7.42	5.69	6.69	2.29		6.62	6.31		6.14	5.43
420	8.21	5.73	7.01	2.85		6.65	6.96		6.71	5.81

480	10.66	6.70	7.09	3.88		7.96	6.98		6.72	5.88
495	26.21						65.08		70.76	62.87
510	45.07						77.86		77.94	71.91
540	53.02					7.967	82.76		85.78	88.49
570	56.59						93.18		92.05	92.93
600	60.77						97.87		98.18	97.49
630	67.41									
660	71.34									
1440		9.81	7.97	4.06						

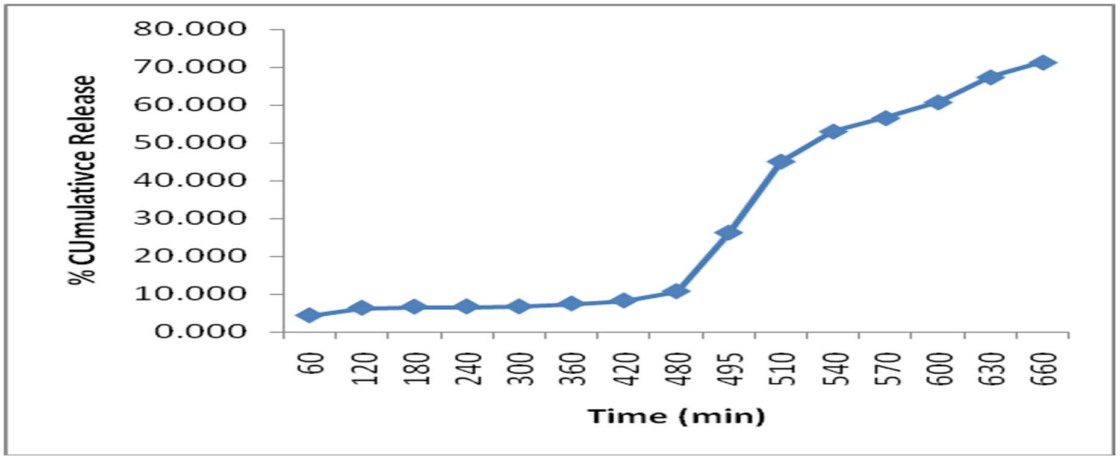


Figure 29: ***In-vitro*** **release profile of Aceclofenac from triple layer floating tablet F8 Formulation for initial 480 min in 0.1 N HCl followed by 120min in phosphate buffer**

Then *in-vitro* dissolution test was carried out on F13, 14, 15 formulations. Here tablet float until 1440 min and at the end of 1440 min 9.81%, 7.97%, 4.06% drug release was observed respectively **(Figure 30)**.

Hence this formulation did not follow the principle of pulsatile release.

Drug release profile of F21, F22 and F23 **(Figure 31)**. In this F21 shows 6.08% drug release at the end of 240 min and F22 float for 540 min and at the end of 540 min 6.96% drug release was observed. Here both formulations did not follow the principle of pulsatile release. Then F23 shows 6.98% drug release at the end of 480 min, drug release profile of F23 provided in **(Figure 32)**. This shows optimum drug release profile i.e. initial lag phase of 480 min with 6.98% drug release followed by 97.87% release within 120 min. Further F25 formulation shows 1.01% drug release at the end of 180 min after that tablet gets burst. Here F25 does not follow the principle of pulsatile release **(Figure 33)**. But F26 formulation shows 6.97% drug release at the end of 480 min followed by 98.18% drug release in phosphate buffer pH 6.8 within 120 min. hence this formulation follows the principle of pulsatile release **(Figure 34)**. F30 formulation follows the principle of pulsatile release, i.e. initial lag phase followed by instant release **(Figure 35)**. Here **(Figure 36)** shows the drug release profile of F23, F26 and F30 formulation, which follows the pulsatile release pattern.

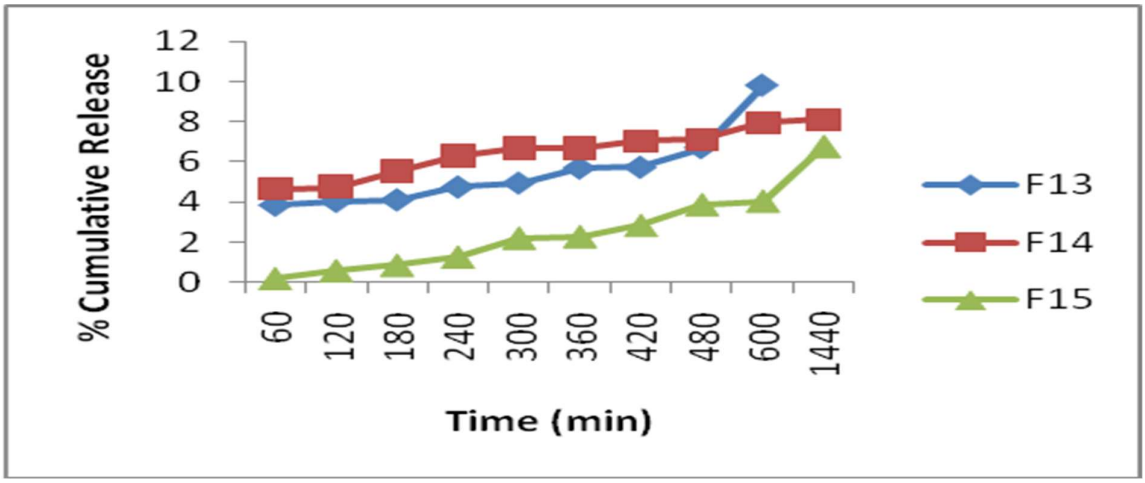


Figure 30: *In-vitro* release profile of Aceclofenac from F13, F14 and F15 Formulation in 0.1 N HCl

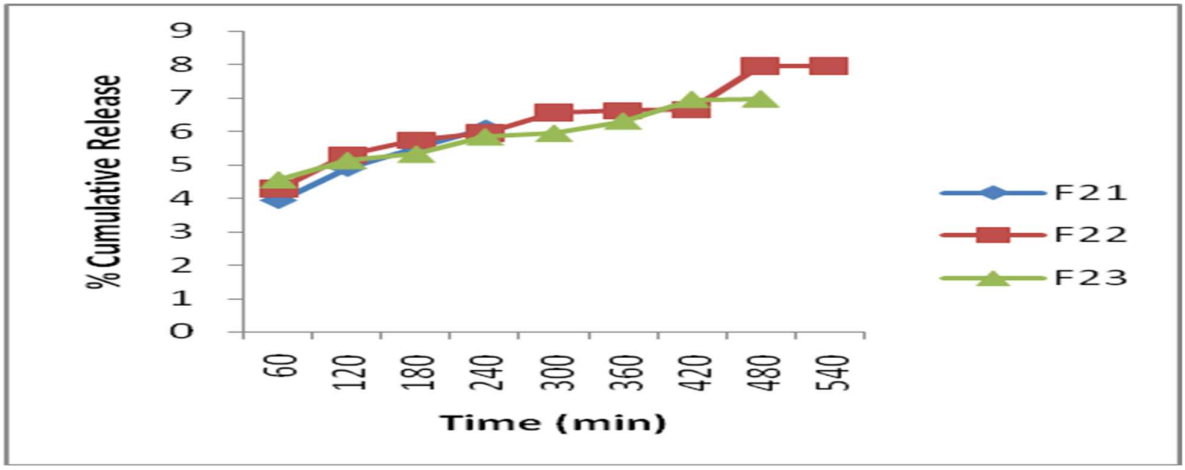


Figure 31: *In-vitro* release profile of Aceclofenac from F21, F22 and F23 Formulation in 0.1 N HCl

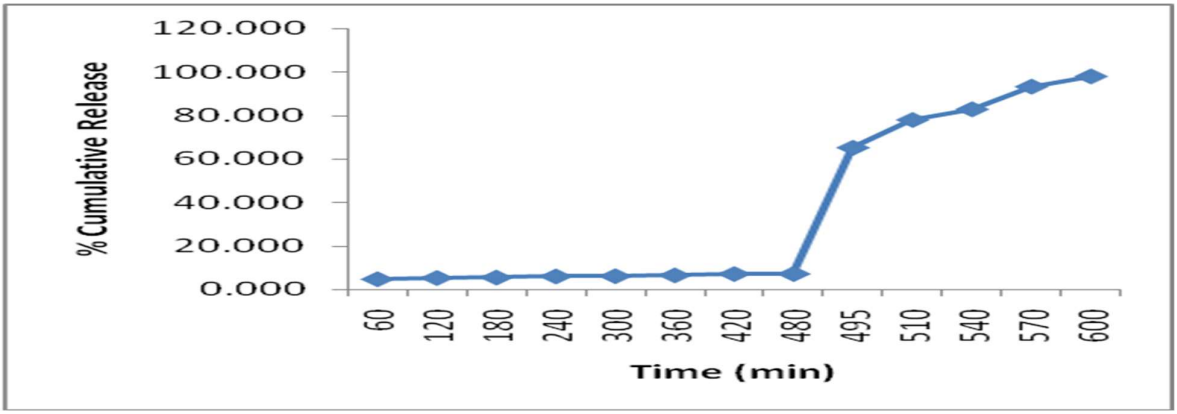


Figure 32: *In-vitro* release profile of Aceclofenac from F23 Formulation for initial 480 min in 0.1 N HCl

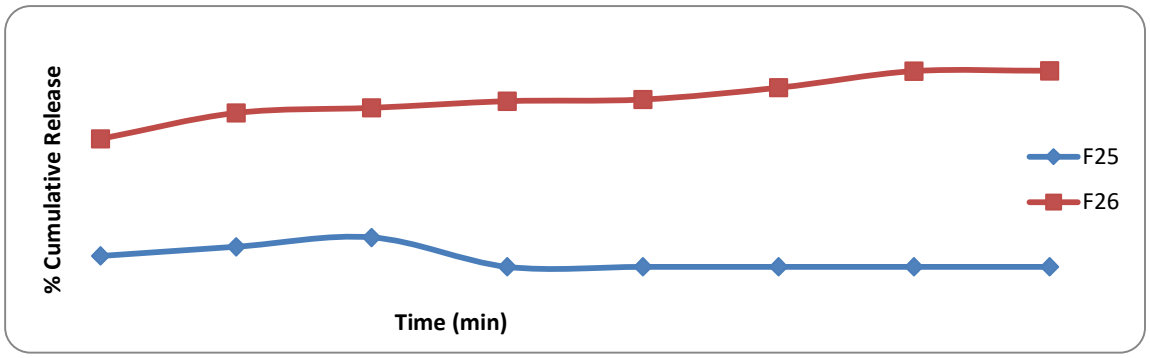


Figure 33: *In-vitro* release profile of Aceclofenac from tablet F25, F26, Formulation in 0.1 N HCl

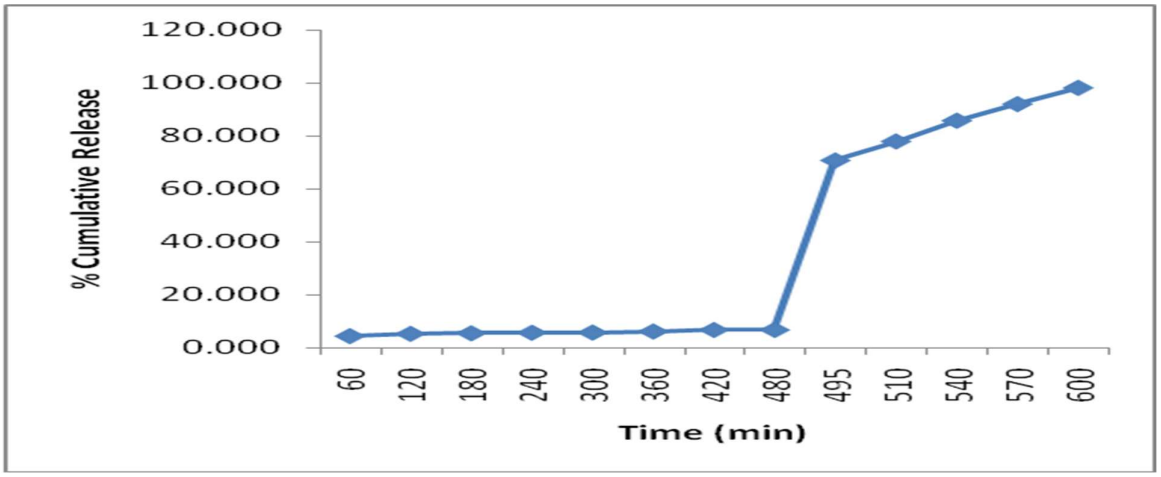


Figure 34: *In-vitro* release profile of Aceclofenac from F26 Formulation for initial 480 min in 0.1 N HCl followed by 120 min in phosphate buffer pH 6.8

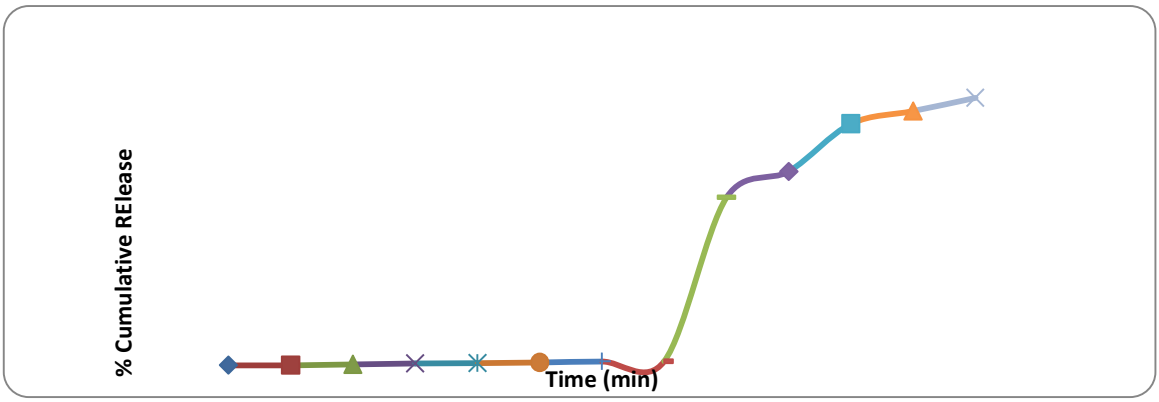


Figure 35: *In-vitro* release profile of Aceclofenac from F30 Formulation for initial 480 min in 0.1 N HCl followed by 120min in phosphate buffer pH 6.8

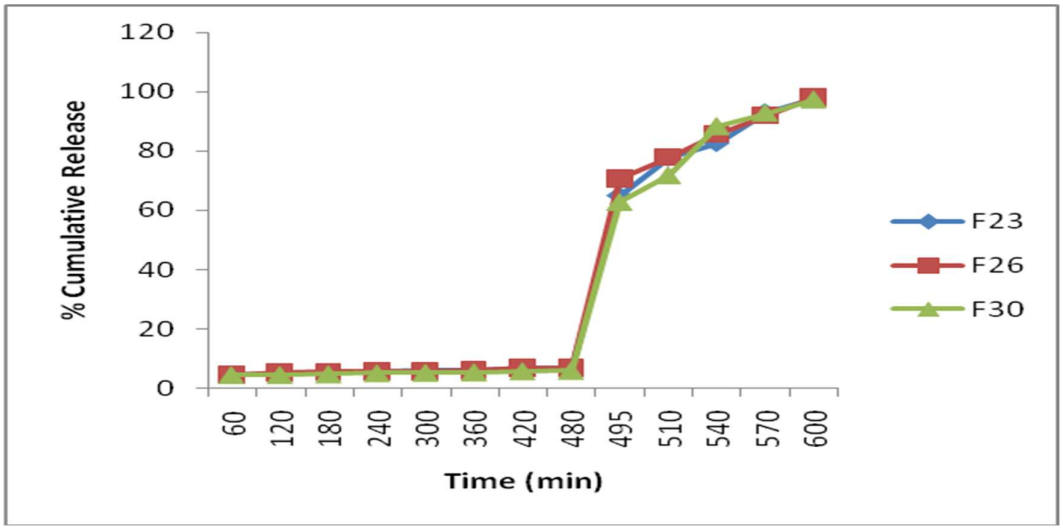


Figure 36: *In-vitro* release profile of Aceclofenac from F23, F26, F30 Formulation for initial 480 min in 0.1 N HCl followed by 120min in phosphate buffer pH 6.8

Swelling Characteristics-Result of swelling characteristics shown in **(Table 14 and 15) (Figure 37)** shows initial tablet without swelling, **(Figure 38)** shows swelled tablet after 180 min. **(Figure 39)** shows swelling after 360 min. **(Figure 40)** shows the increase thickness of tablet after 360 min. Tablet of F30 formulation composed of Hypromellose K100M polymer was shows more swelling than Hypromellose K4M (F23) and Hypromellose K15M (F26).Hypromellose K4M was shown less water uptake capacity than Hypromellose K15M and Hypromellose K100M.Hypromellose K100M polymer was shows more swelling, because Hypromellose K100M having more viscosity than Hypromellose K4M and Hypromellose K15M.

Table 14: Data Collection of Change in Surface Area of F23, F26 and F30 Formulation

Time (min)	Surface area of F23	Surface area of F26	Surface area of F30
0	272.40	272.40	272.40
30	323.70	326.28	344.59
60	347.76	328.70	350.03
120	350.03	341.41	350.94
180	351.40	351.85	364.56
240	352.08	371.37	372.28
300	352.53	372.28	375.00
360	352.99	374.10	375.23

Figure 37: Initial tablet before adding to water a) F23 b) F26 c) F30

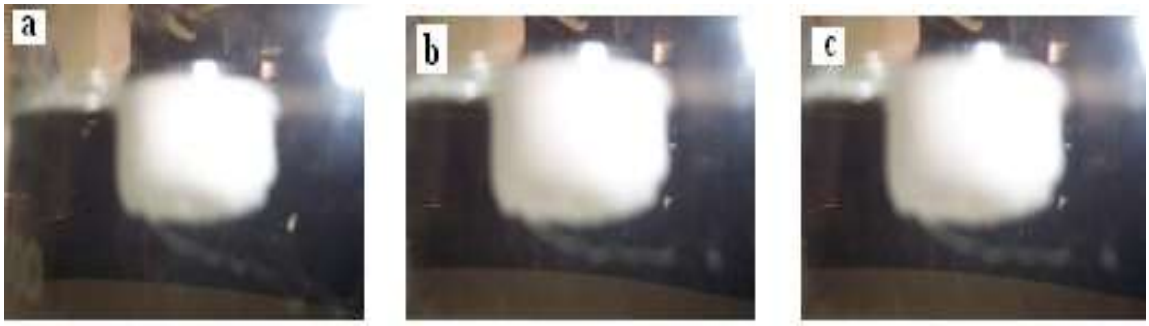


Figure 38: Swelled tablet after 3 h a) F23, b) F26 c) F30

Table 15: Data Collection of Change in Dimeter of F23, F26 and F30 Formulation

Time (min)	Change in diameter of			Change in thickness of		
	F23	F26	F30	F23	F26	F30
0	12	12	12	3.24	3.24	3.26
30	14.26	14.40	15.18	5.18	5.22	6.02
60	15.32	14.48	15.42	6.10	6.24	7.12
120	15.42	15.04	15.46	6.22	6.38	7.16
180	15.48	15.50	16.06	6.42	6.48	7.32
240	15.52	16.36	16.40	6.46	6.52	7.38
300	15.54	16.40	16.52	6.48	6.56	7.40
360	15.56	16.48	16.56	6.52	6.56	7.42

Figure 39: Swelled tablet after 6 h a) F23, b) F26 c) F30

Figure 40: Side view of swelled tablet after 6 h a) F23 b) F26 c) F30 formulations

Stability Study-Subjected formulations for stability study were evaluated for buoyancy (floating lag time, floating duration), drug content and *in-vitro* drug release, obtained results of buoyancy and drug content shown in **(Table 16)**.

Table 16: Results of Buoyancy, Drug Content of Stability Sample

F	Floating lag time (Sec)		Floating duration		Drug content (%), *n=2*	
	37^0C	50^0C	37^0C	50^0C	37^0C	50^0C
F23	15	17	475	471	98.33±0.275	98.27±0.353
F26	22	25	473	472	98.02±0.155	97.95±0.148
F30	36	32	477	473	98.06±0.205	98.05±0.056

CONCLUSION

Results of % cumulative release provided in **(Table 17)** and *in-vitro* drug release pattern shown in **(Figure 41 and 42)**. From above observation it was conclude that there was no significant change in the buoyancy, drug content and *in-vitro* drug release pattern of the tables.

Table 17: % Cumulative Release of Aceclofenac for Initial 480 min in 0.1 N HCl Followed by 120 min in Phophate Buffer pH 6.8 of Different Formulation

Time (Min)	%Cumulative release					
	F23		F26		F30	
	37°C	50°C	37°C	50°C	37°C	50°C
60	4.28	2.62	3.84	4.40	0.20	3.58
12	6.28	4.51	4.03	4.61	0.60	3.72
180	6.58	5.66	4.11	4.87	0.86	4.43
240	6.62	5.87	4.75	5.09	1.27	4.74
300	6.63	6.08	4.94	5.25	2.22	5.14
360	7.42	6.47	5.69	5.45	2.29	5.54
420	8.21	7.13	5.73	5.82	2.85	5.76
480	10.66	7.32	6.70	5.88	3.88	5.91
495	65.08	62.87	70.76	62.87	62.80	62.87
510	77.86	70.38	77.94	71.01	71.91	71.15
540	82.76	88.76	85.78	89.39	88.49	88.76
570	93.18	94.17	92.05	93.83	92.93	93.32
600	97.01	97.60	97.52	97.67	95.98	97.74

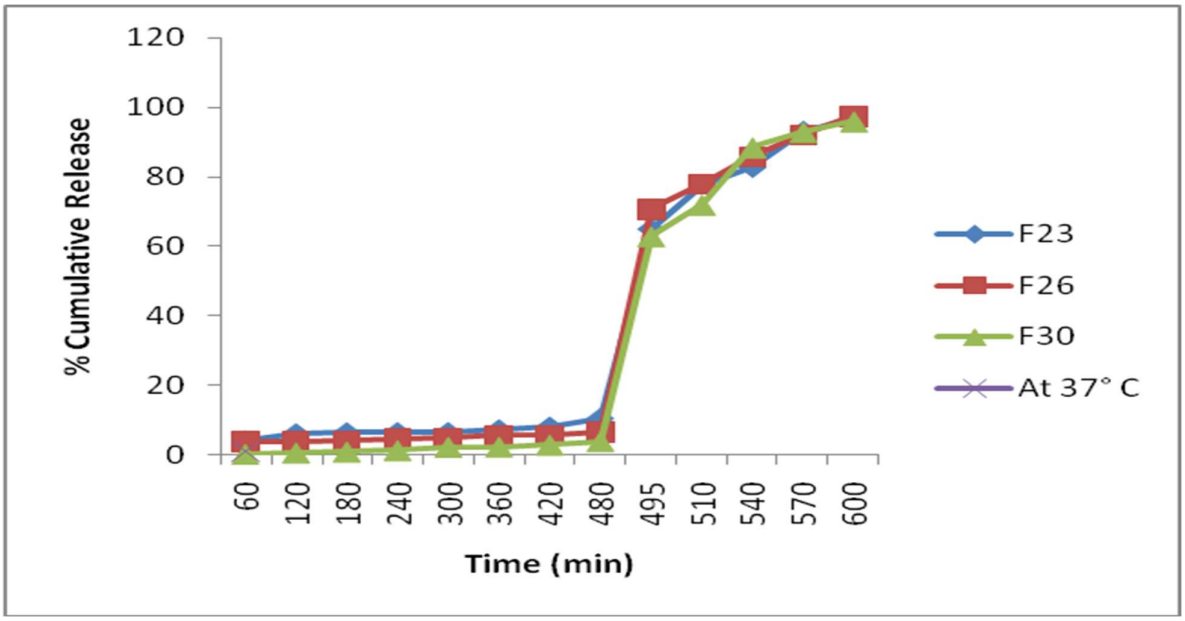


Figure 41: *In-vitro* dissolution study of F23, F26 and F30 formulations for initial 480 min in 0.1 N HCl followed by 120min in phosphate buffer pH 6.8 at 37°C

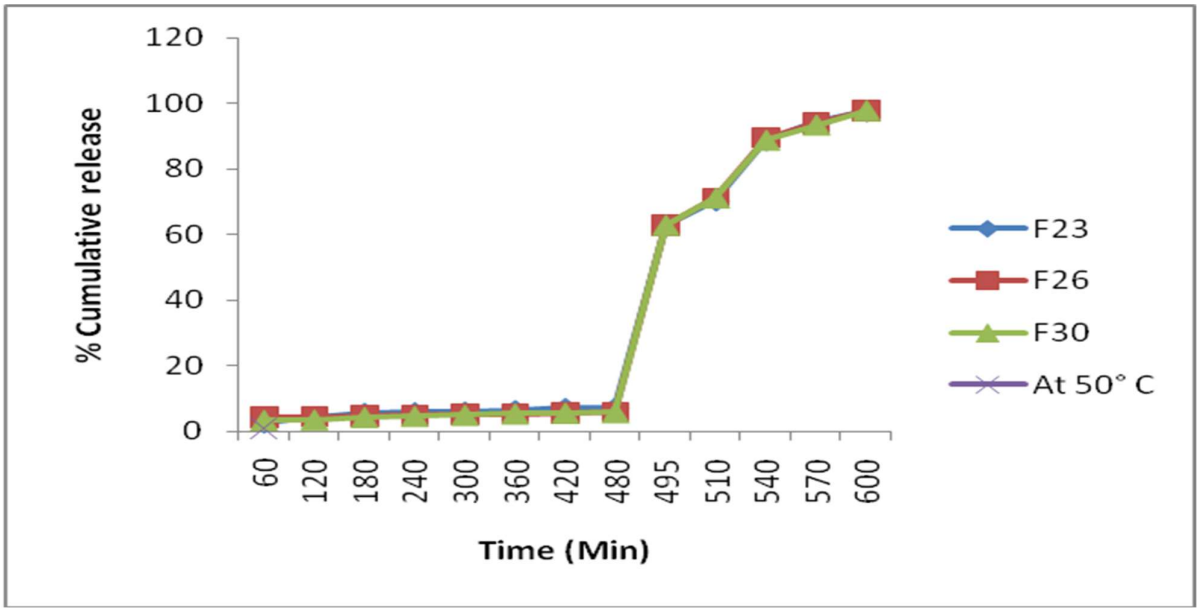


Figure 42: *In-vitro* dissolution study of F23, F26 and F30 formulations for initial 480 min in 0.1 N HCl followed by 120min in phosphate buffer pH 6.8 at 50°C

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