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Research Article

FORMULATION AND *IN VITRO* EVALUATION OF BILAYER FLOATING TABLETS OF ACECLOFENAC AND RANITIDINE HCL

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Abstract: The objective of the present investigation was to develop bilayer floating tablets of Aceclofenac and Ranitidine HCL. OTC analgesics like NSAID are widely used, are frequently taken inappropriately and potentially dangerously, and users are generally unaware of the potential for adverse side effects. Approximately 10-20% of patients taking NSAID'S suffer from Gastric ulcers. This bilayer floating tablets of Aceclofenac and Ranitidine HCL is ideal to treat pain and inflammation and also to control NSAID'S induced ulcer. It consists of an immediate release layer of Ranitidine hcl and a floating sustained release layer of Aceclofenac formulated using direct compression technique. Nine formulations of immediate release layer containing Ranitidine hcl (FR1 – FR9) were prepared by using three different superdisintegrants (Crospovidone, Croscarmellose sodium, Sodium starch glycolate) at three different concentrations. Nine formulations of Floating sustained release layer containing Aceclofenac (FA1 – FA9) were prepared by using 3 different release retarding polymers (Chitosan, Xanthangum, HPMC E15) at three different concentrations along with other additives. The immediate release layer formula (FR3) was found to be optimum and released 98.45% of Ranitidine HCL in 10min. The floating sustained release formulation (FA9) released 98.44% of Aceclofenac in 12hrs while thebuoyancy lag time was 29 sec and the tablet remained floatable throughout the studies. The drug release was inversely proportional to the polymer concentration. FTIR study revealed the absence of any chemical interaction between drug and polymers used.

Key**words:** Bilayer floating tablet, Aceclofenac, Ranitidine hcl, NSAIDs induced ulcer

INTRODUCTION

Gastro-retentive Dosage Form (GRDF)is the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract by controlling the gastric residence time (GRT)[1]. Buoyant/floating systems is one of the approaches used to increase the GRT. Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. Intra Gastric Bilayer Floating Tablets is one type of floating drug delivery system it consist two layers -Immediate release layer, 2. Sustained release layer[2].

Orally administered NSAIDs are among the most commonly prescribed drugs worldwide and play an important role in symptomatic management of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis and other chronic pain conditions. NSAIDs are frequently taken inappropriately and potentially dangerously, and users are generally unaware of the potential adverse side effects. It is a well-known phenomenon that NSAIDs cause gastric mucosal damage resulting in outcomes ranging from nonspecific dyspepsia to ulceration, upper gastrointestinal (GI) bleeding and death – summarized by the term 'NSAID gastropathy'[3]. NSAIDs work by inhibiting two enzymes, substances that cause chemical changes in the body, called COX-1 and COX-2. Both enzymes produce prostaglandins—chemicals produced in the body's cells—that promote pain, inflammation, and fever. COX-1 protects the stomach lining from stomach acid and helps control bleeding. By inhibiting COX-1, NSAIDs increase the risk of a peptic ulcer developing and bleeding[4].

The current investigation aims at the development of gastro retentive bilayer floating tablets with different release patterns of Aceclofenac and Ranitidine HCL. Aceclofenac is a newer non-steroidal anti-inflammatory drug (NSAID) it is a phenyl acetic acid derivative showing potent anti inflammatory and analgesic properties. Aceclofenac is rapidly and efficiently absorbed after oral administration but has a short half life of 3-4 h and requires multiple dosing for maintaining therapeutic effect throughout the day[5]. 9 different formulations of aceclofenac is formulated as sustained release floating layer to maintain the therapeutic effect by using release retarding polymers (Chitosan, Xanthangum, HPMC E15) at 3 different concentrations. The most frequent adverse side effects occurring with aceclofenac are gastrointestinal (GI) disturbances, peptic ulceration and GI bleeding. Ranitidine being a H2 antagonist, helps in nullifying the gastric side effects of acelofenac. 9 different formulations of immediate release layer by using different super disintegrants (Sodium starch glycolate, Croscarmellose sodium, Crospovidone) at 3 different concentrations. The bilayer floating tablet of aceclofenac and ranitidine hcl free of gastric side effects is ideal to treat chronic inflammatory conditions.

MATERIALS AND METHODS

Materials used:

Aceclofenac, ranitidine hcl gifted by MICRO Labs (Bangalore) ,HPMC E15, HPMC K4M, , PEG – 4000 gifted from COLORCON Asia Pvt Ltd, lactose, crospovidone, croscarmellose sodium, aerosol, sodium starechglycolate, Aspartame, sodium bicarbonate, magnesium stearate obtained as gift sample from SD fine chemical Ltd., chitosan, xanthangum, starch cornm , MCC pH 101 gifted by NICE chemicals laboratory.

Preparation of bilayer floating tablets:

Formulation of Immediate release layer:

The immediate release granules were prepared by blending the drug with different super disintegrants(Sodium starch glycolate, Croscarmellose sodium, Crospovidone) at different concentrations and along with other excipients. The granules so obtained were used to obtain immediate release layer of drug in bilayer floating tablets. For preliminary studies to optimize the IR formulations, a weighed quantity of above lubricated drug mixture blend was fed manually into the die and directly compressed using 8 mm flat faced punch of 10 station Rimek compression machine to get IR tablets. Nine formulation batches were made in order to achieve desired disintegration time and drug release. Formulation compositions of different immediate release batches are given in the Table 1.

Formulation of floating sustained release layer:

Required quantity of drug , and polymers (HPMC k4m(12%), Chitosan,Xanthangum, HPMC E15) gas generating agent (Sodium bi carbonate) , and other excipients (Magnesium stearate, lactose ,aerosol) were weighed and blended. Then drug mixture blend was fed manually in to the die and direct compressed. Nine formulation batches were made by different polymers at different concentrations to achieve sustained drug release. Formulation compositions of different floating sustained release batches are given in the Table 2.

Formulation of bilayer floating tablets:

Bilayer floating tablets were prepared by direct compression method using 12 mm flat faced punch of 10 station Rimek compression machine. First the granules of floating sustained release layer were poured in the die cavity and the granules were compressed. After the compression, the upper punch was then lifted and the immediate release granules of drug were poured in the die, containing initially compressed sustained release layer and compressed to form bilayer.

Drug excipients compatibility study[6]:

Pure drug, polymer, excipients, drug – excipients mixture and optimized formulation were subjected to FTIR studies to investigate the drug – excipients interaction.

Hardness[5]:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using monsanto hardness tester. it is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

Friability Test [5]:

The friability of tablets was determined using rochefriabilator. It is expressed in percentage (%). Ten tablets were initially weighed (w_0 initial) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. the tablets were weighed again (w final). The % friability was then calculated by

Percentage Of Friability= 100 (1-w_0/w)

Percentage friability of tablets less than 1% is considered acceptable.

Tablet Density[7]:

Tablet density is an important parameter for floating tablets. The tablet will float when its density is less than that of gastric fluid (1.004g/cc). The density was determined using following formula.

$v = \pi r^2 h$

d = m/v

v = volume of tablet (cc)

r = radius of tablet (cm)

h = crown thickness of tablet (mm)

m = mass of tablet

Buoyancy / Floating Test[8]:

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

Disintegration studies[9]:

The IR tablets were placed in each of six tubes of the basket and the assembly is suspended in water maintained at a temperature of 37 ± 0.5°C. The time taken to disintegrate the tablets completely was determined.

Drug content[10]:

Simultaneous estimation of Aceclofenac and Ranitidine HCL was carried out using UV spectrophotometric method. Twenty tablets were accurately weighed and the average weight was calculated. The tablets were then ground to a fine powder. The powder was dissolved, diluted suitably and analyzed by UV method at 275 nm and 315nm.

In-Vitro Drug Release Study[7,9]:

In-vitro release studies were carried out using USP XXIII, paddle dissolution test apparatus. 900ml of simulated gastric fluid (pH 1.2) was taken in dissolution vessel and the temperature of the medium was maintained at $37^0c \pm 0.5^0c$. The speed was 100 rpm. 1ml of sample was withdrawn at predetermined time intervals and same volume of fresh medium was replaced. The samples were analyzed for drug

content against 0.1N HCl as a blank at □max 274 nm and 315nm using U.V. Spectrophotometer.

RESULTS AND DISCUSSION

Excipients compatability study:

All the excipients used in the formulation were compatible.(Fig 1 , 2, 3)

Micromeritic studies:

Bulk density, tapped density, compressibility index, hausner's ratio, and angle of repose of the granules were determined. The precompression study of the formulation showed satisfactory flow properties. (Table 3,5)

Physical parameters:

The physical parameters of the compressed tablets were determined. The friability was with in the limit. Hardness of the formulation was found to be 5.1 to 6 kg/cm^2 and the hardness was sufficient to prevent all chipping and breaking during transportation. The drug content of all the formulations was within the limits.(Table 4,6)

Floating characteristics:

From that nine formulations more than three formulations floated for more than 12h with a floating lag time up to 29 sec. During the floating, formulations maintains the matrix integrity. The optimum concentration of Sodium bi carbonate was found to be 6% for obtaining low floating lag time and prolonged floatation. Floating duration and floating lag time were found to be dependent on the amount of the polymers incorporated in formulations.

Dissolution study of immediate release layer:

The immediate release tablets of Ranitidine HCL were formulated with three different superdisintegrants (Crospovidone, Croscarmellose sodium, Sodium starch glycolate) at three different concentration (3%, 6%, 9%). Crospovidone at 9% concentration was found to be optimum (The release of the Ranitidine HCL was with in 10min and the tablets disintegrated in 121 sec). The immediate release formulation FR3 was found to be optimum.(Fig 4)

Dissolution study of Floating sustained Release layer:

The floating sustain release layer of Aceclofenac(FA1 – FA9) was formulated using 3 different release retarding polymers. First three formulations (FA1,FA2,FA3) consists Chitosan at the concentration of 5%, 10%, 15%. The FA1,FA2 and FA3 were unable to retard the release of the drug from the floating matrix layer and the formulations and release the entire drug at the end of 7, 8, and 10hrs respectively.Next three formulations (FA4 , FA5 , FA6) consists Xanthangum at the concentration of 5%, 10%, 15%. The FA4 , FA5 and FA6 were unable to retard the release of the drug from the floating matrix layer and the formulations and release the entire drug at the end of 5, 6, and 7hrs respectively. The final three formulations (FA7, FA8, FA9) consists HPMC E15 at the concentration of 5%, 10%, 15% . These formulations retard the drug release more than the previous formulations. The formulations release the drug at the end of 5, 7, and 12hrs respectively. The formulation FA9 retard the release of the drug from the polymer matrix for 12h (Fig 5). FA9 floating matrix tablet of Aceclofenac containing HPMC K4m and HPMC E15 had satisfactory sustained release.

CONCLUSION

The bilayer floating tablet of acelofenac and ranitidine was successfully formulated and evaluated. The immediate release formulation FR3 and floating matrix tablet of AceclofenacFA9 exhibited satisfactory results. The study demonstrated that the formulated bilayer floating tablet of aceclofenac and ranitidine is capable of treating chronic inflammatory conditions like arthritis and is also free of gastric side effects.

Table 1- Layer 1(immediate release) Ranitidine Hcl

INGREDIENTS	FR1	FR2	FR3	FR4	FR5	FR6	FR7	FR8	FR9
Ranitidine HCl	75	75	75	75	75	75	75	75	75
Starch corn	30	30	30	30	30	30	30	30	30
MCC pH101	64	58	52	64	58	52	64	58	52
Crospovidone	6	12	18	-	-	-	-	-	
Croscarmellose sodium	-	-	-	6	12	18	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	6	12	18
Aspartame	15	15	15	15	15	15	15	15	15
PEG-4000	5	5	5	5	5	5	5	5	5
Aerosil	5	5	5	5	5	5	5	5	5
Total tablet weight	200	200	200	200	200	200	200	200	200

Table 2 -Layer 2(floating tablet) Aceclofenac

INGREDIENTS	FA1	FA2	FA3	FA4	FA5	FA6	FA7	FA8	FA9
Drug (ACF)	100	100	100	100	100	100	100	100	100
Lactose	76.5	64	51.5	76.5	64	51.5	76.5	64	51.5
HPMC k4m (12%)	30	30	30	30	30	30	30	30	30
Chitosan	12.5	25	37.5	-	-	-	-	-	-
Xanthangum	-	-	-	12.5	25	37.5	-	-	-
HPMC E15	-	-	-	-	-	-	12.5	25	37.5
NaHCO3	15	15	15	15	15	15	15	15	15
Magnesium stearate	10	10	10	10	10	10	10	10	10
aerosil	6	6	6	6	6	6	6	6	6
Total tablet weight	250	250	250	250	250	250	250	250	250

Table 3-Precompresion Study of Ranitidine Hcl

Formulation number	Bulk Density	Tapped Density	Carr's Index	Hausner ratio	Angle of repose
FR1	0.52	0.65	20.02	1.25	34.2
FR2	0.55	0.64	26.21	1.16	35.5
FR3	0.49	0.57	14.04	1.163	33.2
FR4	0.48	0.55	12.72	1.14	32.4
FR5	0.5	0.58	13.79	1.16	33
FR6	0.53	0.61	13.11	1.15	32.1
FR7	0.49	0.55	10.9	1.12	33.5
FR8	0.53	0.61	13.11	1.15	32.1
FR9	0.53	0.66	19.69	1.24	31.8

Table 4- Post compression study of Ranitidine Hcl

Formulation	Hardness (Kg / cm^2)	Friability (%)	Thickness (mm)	Disintegration time(sec)	Weight variation(average weight) (mg)	Wetting time(sec)
FR1	3.5	0.41	2.1	112	201	215
FR2	3.8	0.46	2.2	115	204	198
FR3	3.6	0.48	2.1	121	201	184
FR4	4.1	0.42	2.15	124	202	201
FR5	3.8	0.49	2.14	96	198	215
FR6	3.5	0.45	2.14	124	196	214
FR7	3.5	0.44	2.13	98	201	219
FR8	3.6	0.47	2.14	114	201	225
FR9	3.8	0.49	2.13	131	201	183

Table 5-Precompresion Study of Aceclofenac

Formulation	Bulk Density(gm\ml)	Tapped Density (gm\ml)	Compressibility Index (%)	Hausner Ratio	Angle Of Repose
FA1	0.510gm/ml	0.598gm/ml	15.81%	1.17	26.28
FA2	0.512gm/ml	0.597gm/ml	15.38%	1.18	26.85
FA3	0.512gm/ml	0.60gm/ml	14.87%	1.17	27.14
FA4	0.505gm/ml	0.591gm/ml	14.64%	1.17	27.75
FA5	0.507gm/ml	0.595gm/ml	14.72%	1.17	28.07
FA6	0.5076gm/ml	0.597gm/ml	14.97%	1.176	28.07
FA7	0.512gm/ml	0.595gm/ml	13.85%	1.16	29.39
FA8	0.515gm/ml	0.598gm/ml	13.91%	1.161	29.74
FA9	0.515gm/ml	0.602gm/ml	14.43%	1.168	29.02

Table 6- Post compression study of Aceclofenac

Formulation	Weight Variation	Thickness in mm	Diameter in mm	Hardness in Kg/cm^2	Friability	Log float time in seconds	Buoyancy time in hours
FA1	251	2.8	8.7	5.5	0.14	20	<09
FA2	250.4	2.6	8.7	5.4	0.09	16	<09
FA3	248.9	2.5	8.7	5.6	0.12	12	<08
FA4	249.7	2.8	8.7	6	0.07	16	<12
FA5	251.6	2.7	8.7	5.1	0.2	17	<10
FA6	250.1	2.6	8.7	5.4	0.07	16	<10
FA7	249.9	2.6	8.7	5.5	0.12	25	<12
FA8	252.1	2.6	8.7	5.5	0.14	23	<12
FA9	250.4	2.6	8.7	5.4	0.09	29	<12

Fig 1- FT-IR Spectrum of pure Aceclofenac

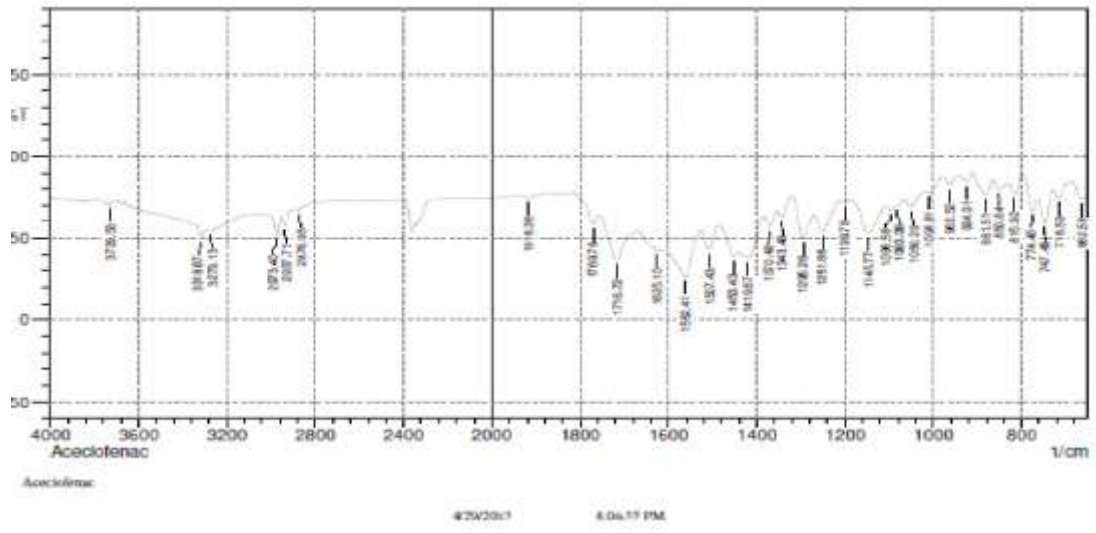


Fig 2- FT-IR Spectrum of pure Ranitidine Hcl

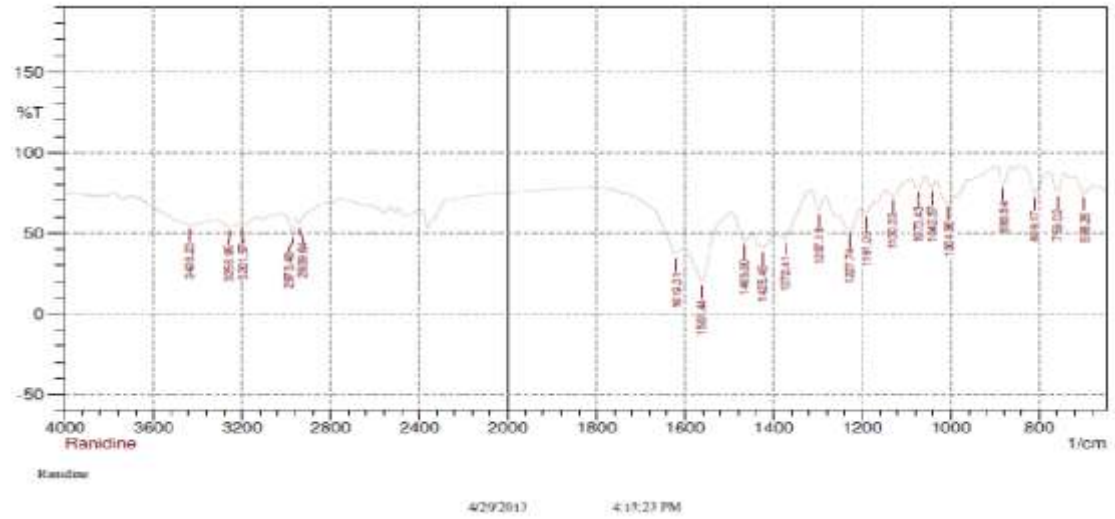


Fig 3- FT-IR Spectrum of Aceclofenac and Ranitidine Hcl after formulation

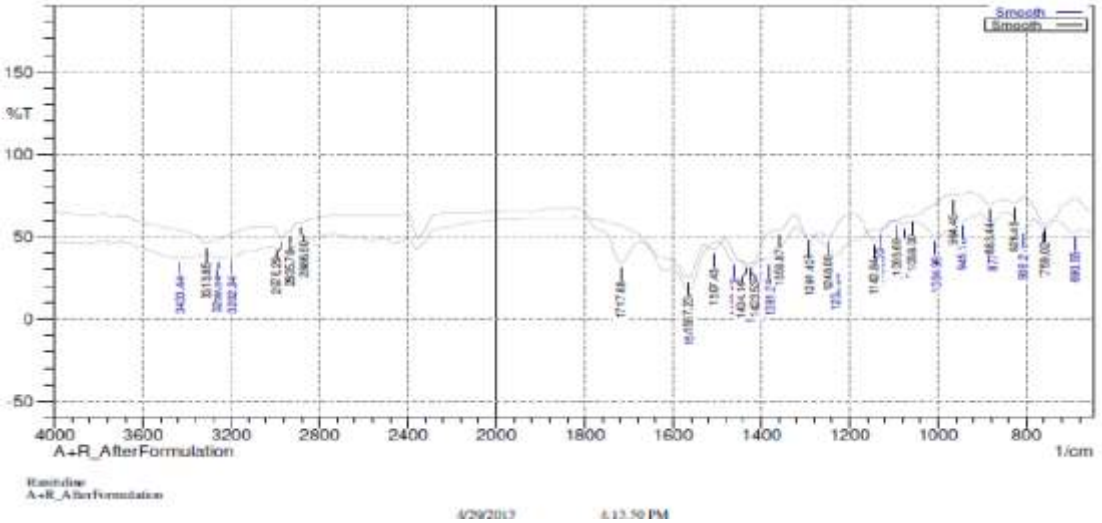


Fig 4 :*In vitro* Dissolution of Ranitidine HCL Immediate release tablet

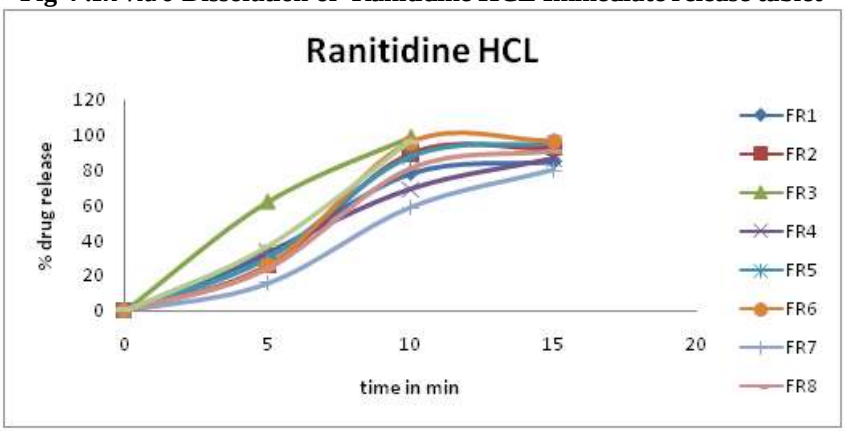
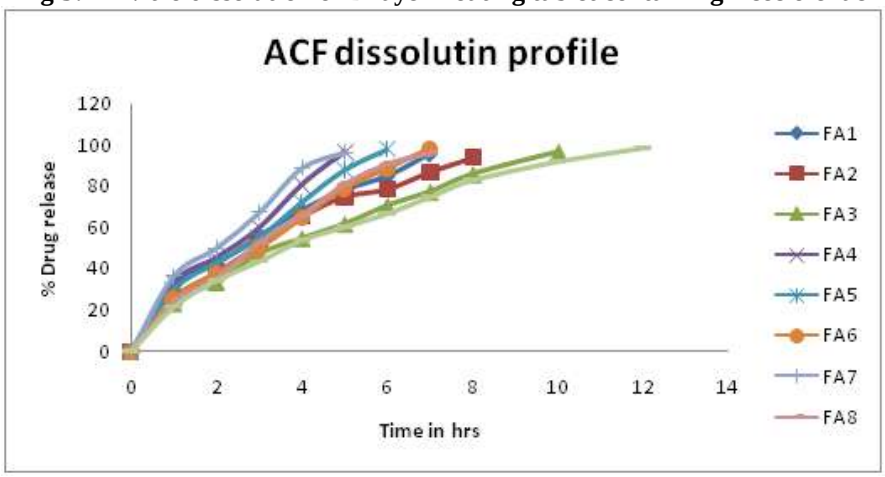


Fig 5: In vitro dissolution of Bilayer floating tablet containing Aceclofenac



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