Journal of Pharmaceutical and Scientific Innovation
www.jpsionline.com
Research Article

FORMULATION AND EVALUATION OF EFFERVESCENT FLOATING TABLET OF AMLODIPINE BESILATE WITH NATURAL POLYMER CHITOSAN

Dubey Vivek[1]*, Arora Vandana[2]
[1]M.pharma (pharmaceutics), Lloyd Institute Of Management & Technology, Greater Noida, U.P, Mahamaya technical university
[2]Head of Department, Lloyd Institute Of Management & Technology. Greater Noida, U.P., Mahamaya technical university
*Email: vivekdubey08@gmail.com

Received on: 14/04/12 Revised on: 20/05/12 Accepted on: 15/06/12

ABSTRACT
Amlodipine Besilate effervescent floating tablets were developed in nine different formulations (F1 to F9) by employing natural polymer (Chitosan) and some other different grades of polymers and effervescent agents such as sodium bicarbonate and citric acid. Direct compression was the technique used for preparing tablets. The formulations were evaluated for various physical parameters, buoyancy studies, dissolution parameters and drug released mechanisms. F5 formulation showed maximum floating time of 12 hours and gave slow and maximum drug release of amlodipine Besilate spread over 12 hours. So the composition of the batch 5 should be optimized, to achieve the goal of formulation and evaluation of effervescent floating tablet of amlodipine Besilate.
KEY WORDS Amlodipine Besilate, Chitosan, Effervescent floating tablet, Direct compression, Buoyancy studies.

INTRODUCTION:

Floating drug delivery systems were first described by Davis in 1968.[1,2] It is possible to prolong the gastric residence time of drugs using these systems. Several techniques are used to design gastro retentive dosage forms. These include, floating drug delivery systems (FDDS), high-density DDS, muco-adhesive systems, swelling and expanding DDS, modified shape systems, and other delayed gastric devices.[3,4,] Floating drug delivery systems, also called as hydrodynamically balanced system, is an effective technology to prolong the gastric residence time in order to improve the bioavailability of the drug.[5] This technology is suitable for drugs with an absorption window in the stomach or in the upper part of small intestine,[6] drugs acting locally in the stomach [7] and for the drugs that are poorly soluble or unstable in the intestinal fluid.[8]

Effervescent floating drug delivery systems generate gas (CO2), thus reduce the density of the system and remain buoyant in the stomach for a prolonged period of time and released the drug slowly at a desired rate.[9,10,11] Amlodipine is long acting calcium channel blocker and used in the treatment of hypertension, and chronic stable angina. In hypertension or angina, initially 5 mg. one daily and adjusted to maximum dose 10 mg one daily dose of Amlodipine is given orally[12] Amlodipine has maximum solubility in acidic pH. Amlodipine has some adverse effect such as nausea, abdominal pain. Effervescent floating tablet of Amlodipine besylate retain in stomach improves solubility, bioavailability, reduces drug waste and decrease side effect such as gastric irritation and nausea.[13, 14] In present work, effervescent floating tablets of different formulation were developed with an objective of achieving maximum floating and drug release time .

EXPERIMENTAL

Materials

Amlodipine Besilate was procured from Glenmark Pharmaceuticals Limited Baddi .Chitosan, HPMC K100 M, Carbapol 934 p, Sodium bicarbonate, Citric acid, poly vinyl pyrrolidine and Talc were obtained from Colorcon Asia Pvt. Ltd and Loba chemicals.

Methods

Effervescent Floating tablets containing Amlodipine Besilate were prepared by direct compression technique using varying concentrations of different grades of polymers with Sodium bicarbonate and citric acid. All the ingredients were accurately weighed and passed through different mesh sieves accordingly. Then, except Magnesium stearate all other ingredients were blended uniformly in glass mortar After sufficient mixing of drug as well as other components, Magnesium stearate was added, as post lubricant, and further mixed for additional 2-3 minutes. The tablets were compressed using rotary tablet machine. The weights of the tablets were kept constant for all formulation.

Table-1 Composition of floating tablets of Amlodipine besylate

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Amlodipine	10	10	10	10	10	10	10	10	10
Chitosan	15	15	15	30	30	30	45	45	45
HPMC K100M	15	30	45	15	30	45	15	30	45
Carbapol 934P	45	45	45	30	30	30	15	15	15
MCC	45	30	15	45	30	15	45	30	15
Sodium Bicarbonate	30	30	30	30	30	30	30	30	30
Citric Acid	25	25	25	25	25	25	25	25	25
PVP K30	5	5	5	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Talc	3	3	3	3	3	3	3	3	3
Aerosil	2	2	2	2	2	2	2	2	2
Total weight	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

*All the quantities are in mg

EVALUATION PARAMETERS

Pre-compression parameter

Prior to the compression, the formulation powder blends were evaluated for their bulk and tapped density and from these values compressibility index and Hausner's ratio were calculated. While the flow properties of the powder bled were accessed from the angle of repose.

Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weighed powder blend was taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$\tan\theta = h/r$ (2.3)

$\theta = \tan^{-1}(h/r)$ (2.4)

Where,

θ = angle of repose

h = height of pile

r = radius of the base of pile

Different ranges of flowability in terms of angle of repose are given below in Table 2

Table 2: Effect of Angle of repose (ϕ) on Flow property

Angle of Repose (Φ)	Type of Flow
< 25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density

Bulk density was determined by pouring mass of powder into 25ml graduated measuring cylinder and the bulk volume was noted down. The method was repeated three times and the mean of the values exhibited as final volume was calculated as a result of bulk volume. Bulk density of the powder was determined by applying following formula:

$$\text{Bulk density (poured)} = \frac{\text{Weight of powder}}{\text{Bulk volume of powder}}$$

Tapped density

Tapped density was determined by poured mass of complex and excipients into 25ml graduated measuring cylinder and graduated cylinder was then subjected to 100 tappings, using tapped density apparatus, until the change in the volume approached constant value. The method was repeated three times and the mean of the values exhibited as final volume was calculated as a result of tapped volume. Tapped density of the powder was determined by applying following formula:

$$\text{Tapped density (tapped)} = \frac{\text{Weight of powder}}{\text{Tapped volume of powder}}$$

Compressibility index

The simplest way of measurement of free flow property of powder is compressibility, an indication of ease with which a material can be induced to flow given by % compressibility index (% CI) which was calculated as follows:

$$\%\ CI = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio

Hausner's ratio is an index of ease of powder flow, it is related to interparticulate friction as such, could be used to predict powder flow properties. It is calculated by following formula:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table 3: Effect of Carr's Index and Hausner's Ratio on flow property

Carr's Index (%)	Flow Character	Hausner's Ratio
≤10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very very poor	>1.60

EVALUATION OF FLOATING TABLETS

Post- Compression Parameters

The prepared tablets were evaluated for quality control tests like weight variation, hardness, thickness, friability and content uniformity.

Appearance:

The tablet should be free from cracks, depressions, pinholes etc. The color and the polish of the tablet should be uniform on whole surface. The surface of the tablets should be smooth. Tablets were subjected to evaluation of properties including drug content uniformity, weight variation, tablet hardness, friability, and thickness, and in-vitro drug release with different media.

Weight variation

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit. USP official limits of percentage deviation of tablet are presented in the table-4.

Table no-4: Tablet weight variation

Sr. No.	Average weight of tablet (mg)	Maximum % difference allowed
1	130 or less	10
2	130-324	7.5
3	324<	5

Tablet hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm2. six tablets were chosen randomly and tested for hardness. The average hardness of six determinations was recorded.

Friability

Friability determines the resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage. Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients. If there is any chipping,

capping, cracking or breaking of tablet; then the batch should be rejected.

$$\%F = (1 - W/W_o) \times 100$$

Where, W_o = weight of tablet before test

W = weight of tablet after test.

Method

20 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded.

Dimensions:

The dimensions of the tablets are thickness and diameter. The tablets should have uniform thickness and diameter. The manufacturer normally states these. Thickness and diameter of a tablet were measured using vernier calipers. These values were checked and used to adjust the initial stages of compression.

Content Uniformity:

Ten tablets were individually weighed and crushed. A quantity of powder equivalent to the mass of one tablet (200mg) was extracted in 100 mL of 0.1N HCl. The solution was filtered through a cellulose acetate membrane (0.45 µm). The drug content was determined by UV spectrometer at a wavelength of 365 nm after a suitable dilution with 0.1 N HCl.

In-vitro Dissolution studies

In vitro release studies of F1 to F9 formulations and one brand of Amlodipine besylate were carried out in the dissolution test apparatus (USP Type II). The tests were carried out in 900 ml of dissolution media 7.4 pH buffers for 24 hrs at 50 rpm at 37±0.5°C 10 ml of the aliquot were withdrawn at different predetermined time intervals (0, 1, 2, 3, 4, 5, 6, 7,.8, 9, 10, 11, 12 hr) and filtered. The required dilutions were made with and the solution was analyzed for the drug content by using UV detector detecting at λ max 365 nm 10 ml of sample was replaced in the vessel after each withdrawal to maintain sink condition. From this percentage drug release was calculated and this was plotted against function of time to study the pattern of drug release. The in-vitro drug release profiles of tablet from each batch (F1 to F9) were shown in Table 8. The plot of cumulative percentage drug release versus time (hr) was plotted and depicted as shown in Figure 1 and Figure 2.

Release kinetics:

Data obtained from *in-vitro* release studied was evaluated to check the goodness of fit to various kinetics equations for quantifying the phenomena controlling the release from tablets. The kinetic models used were zero order, first order, and Higuchi and Korsmeyer-Peppas model. The goodness of fit was evaluated using the correlation coefficient values (R2).

In vitro buoyancy studies

The prepared tablets were subjected to in vitro buoyancy test by placing them in 250 ml beaker containing 200 ml 0.1 N HCl (pH 1.2, temp. 37±0.5 C). The time between introduction of the dosage form and its buoyancy in the medium and the floating durations of tablets was calculated for the determination of lag time and total buoyancy time by visual observation. 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). the results of the buoyancy lag time (BLT) and total floating time (TFT) were shown in Table 7.

Stability studies:

The optimized formulation of Amlodipine besilate were packed in strips of 0.04 mm thick aluminium foil laminated with poly vinyl chloride by strip packing and these packed formulations were stored in ICH certified stability chambers (Thermo labs, Mumbai) maintained at 40°C and 75% RH for 1 month (zone III conditions as per ICH Q1 guidelines). The samples were withdrawn periodically and evaluated for their hardness, content uniformity and for *in vitro* drug release.

RESULTS AND DISCUSSION:

Amlodipine Besilate is a potent drug for the treatment of angina, hypertension and also suitable in the treatment diabetic hypertension. Amlodipine had maximum solubility in acidic pH. Amlodipine has some adverse effect such as headache, nausea, abdominal pain. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in high pH environment. Effervescence production, decrease the several local GIT side effect, such as gastric irritation, nausea and gastritis. The effervescent floating tablets of Amlodipine besylate were formulated in ten different batches F1 toF9 by using natural polymer Chitosan and hydrophilic polymers HPMC K100M and hydrophobic polymer Carbapol 934P along with effervescing agent sodium bicarbonate and citric acid. It was found that Carbapol has a negative effect on floating behavior but it was used only for the drug release retardant characteristics. All the formulations were prepared by direct compression method. The prepared tablets of all the formulations were evaluated for physical characters like tablet hardness, friability, weight variation buoyancy lag time, total floating time, assay, in-vitro drug release. The main aim was to optimize the formulation for 12 hours in-vitro release and total floating time to more than 12 hours. The measured hardness of tablets of each formulation ranged between 5.9 to 6.15 kg/cm2. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits of ±5% of the weight. Buoyancy lag time (BLT) and total floating time (TFT) of different formulation were noted, where F1 BLT of 110 sec and TFT of >10 hours, F2 BLT of 120 sec and TFT of >11 hours, F3 BLT of 130 sec and TFT of >12hours, F4 BLT of 133sec and TFT of >11 hours, F5 BLT of 110sec and TFT of >12 hours, F6 BLT of 141 sec and TFT of >11 hours, F7 BLT of 140 sec and TFT of >12hours, F8 BLT of 138 sec and TFT of >12 hours, F9 BLT of 110 sec and TFT of >10 hours,. Formulation F5 containing Chitosan, HPMC K100M and carbopol 934P showed good BLT of 110 sec and TFT of more than 12 hrs. Amlodipine besylate release from the effervescent floating tablets was studied in phosphate buffer pH 7.4. The release profile of various formulations are shown in table no. Figure no. 1 and 2.

Formulation F1 released 96.44% of the drug in 10 hours.
Formulation F2 released 96.70% of the drug in 12 hours.
Formulation F3 released 95.53% of the drug in 12 hours.
Formulation F4 released 97.27% of the drug in 12hours.
Formulation F5 released 98.52% of the drug in 12 hours.
Formulation F6 released 94.04% of the drug in 12hours.
Formulation F7 released 88.75% of the drug in 12 hours.
Formulation F8 released 97.75% of the drug in 11 hours.

Formulation F9 released 95.50% of the drug in 12 hours.
Thus F5 formulation was said to be optimized formulation.
Optimized formulation F5 was subjected to curve fitting analysis, zero order, and first order, Higuhi Kinetics, Korsmeyer and Peppas model. The slope and r2 are shown in Table 9 and graphs in Figure 3. Optimized formulation 5 fitted best foR Korsemeyer – Peppas equation with R2 value of 0.9892**.**

It is, thus concluded that effervescent floating tablet containing Amlodipine Besilate (F5 formulation) gave slow and complete drug release spread over 12hours.

ACKNOWLEDGMENT:
The authors are thankful to H.O.D of LLOYD COLLEGE Prof. Vandana Arora for providing the necessary facilities and help also thankful to Glenmark Pharmaceuticals Limited Baddi for providing gift sample of drug

Table-5: Pre- compression parameters of direct compressed Amlodipine Besilate floating tablet

Batch	Bulk density (g/cm3)	Tap density (g/cm3)	Carr's index	Hausner's ratio	Angle of repose*
F1	0.630	0.735	14.28	1.166	25.19±0.594
F2	0.587	0.722	18.69	1.229	23.89±1.607
F3	0.620	0.720	13.89	1.161	26.68±0.586
F4	0.685	0.865	20.81	1.262	26.53±0.781
F5	0.700	0.849	17.55	1.212	21.28±1.160
F6	0.670	0.843	20.52	1.258	23.77±1.178
F7	0.714	0.833	14.28	1.166	25.62±0.475
F8	0.701	0.851	17.63	1.212	21.28±1.160
F9	0.689	0.869	20.71	1.261	27.61±0.459

*Angle of repose, n=3

Table-6: Post-compression parameters of directly compressed amlodipine besilate floating tablet;

Batch	Weight variation (g)	Hardness Kg/cm2	Thickness (mm)	Diameter (mm)	Friability (%)	Content uniformity (%)
F1	0.200±0.006	6.15±0.187	3.17±0.110	8.00±0.017	0.21	94.29
F2	0.199±0.005	6.15±0.237	3.22±0.085	7.99±0.006	0.40	97.38
F3	0.205±0.008	6.01±0.172	3.02±0.124	7.96±0.04	0.34	103.02
F4	0.200±0.006	6.03±0.186	2.95±0.056	7.99±0.019	0.30	98.15
F5	0.200±0.005	6.14±0.135	3.13±0.067	7.99±0.016	0.16	96.69
F6	0.199±0.05	6.15±0.187	3.05±0.064	7.98±0.039	0.43	99.31
F7	0.200±0.005	6.11±0.116	3.02±0.03	7.97±0.017	0.62	97.04
F8	0.201±0.005	5.91±0.231	2.99±0.085	7.96±0.049	0.51	101.16
F9	0.199±0.007	6.03±0.186	3.00±0.061	7.99±0.021	0.38	98.30

Weight variation, n=20; Thickness, n=6
Hardness, n=6; Diameter, n=6

Table-7: Buoyancy Lag Time, Total Floating Time of formulations (F1toF9)

Formulation	Buoyancy Lag Time (Sec)	Total Floating Time (hrs)
F1	110	>10
F2	120	>11
F3	130	>13
F4	133	>12
F5	101	>11
F6	141	>13
F7	140	>12
F8	138	>13
F9	110	>10

Table- 8: Cumulative % Drug Release of Amlodipine besilate floating tablets

Time in hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	**0**	**0**	**0**	**0**	**0**	**0**	0	**0**	**0**
1	29.11±0.9	26.63±1.3	22.81±1	25.36±0.8	22.63±1.3	18.25±0.8	19.52±0.7	25.79±1.4	23.40±1.2
2	42.08±1.1	35.72±1	33.44 ±0.8	34.67±0.7	33.82±0.8	26.54±0.7	31.51±0.6	37.53±1.2	33.37±1.5
3	50.55±1.3	40.53±0.9	40.68±0.7	40.73±0.7	39±1	31.57±0.8	36.50±1	44.33±1.3	38.70±0.9
4	59.08±0.8	51.65±0.8	50.61±0.9	48.86±1.8	46.41±1.4	38.64±0.7	45.42±0.6	50.33±0.7	46.24±0.8
5	70.22±1	64.71±1.1	59.63±0.7	57.96±0.9	54.65±1	46.68±1	51.22±0.8	62.67±2.1	51.68±1
6	79.83±0.9	71.14±1.5	69.25±1	65.80±1.4	60.68±1.2	50.57±0.6	56.79±0.9	70.8±2	59.40±0.7
7	89.48±1.6	79.35±1.2	75.17±0.8	71.94±1.1	68.03±1	58.01±0.4	62.03±0.8	82.65±1.5	65.35±0.9
8	92.78±0.7	83.67±0.9	82.45±0.9	80.05±1.3	76.26±1.1	64.88±0.8	67.45±0.7	87.75±1.8	70.39±0.7
9	94.78±0.7	89.76±0.4	87.87±0.5	87.42±1.6	85.17±1.7	70.63±0.8	72.41±1.2	93.62±0.7	76.56±0.9
10	98.44±2.1	92.29±0.7	91.73±0.4	92.10±0.7	92.02±1.1	77.81±0.7	78.27±0.8	95.44±0.8	82.59±1.5
11		94.88±07	93.92±0.8	95.89±0.3	95.65±1	88.61±0.8	83.40±0.8	97.75±1.8	89.68±1.1
12		96.70±07	95.53±1	97.27±1.1	98.52±1.7	94.04±0.3	88.75±0.8		95.50±0.8

Figure 1: In-vitro dissolution profile of formulations F 1 to F 9

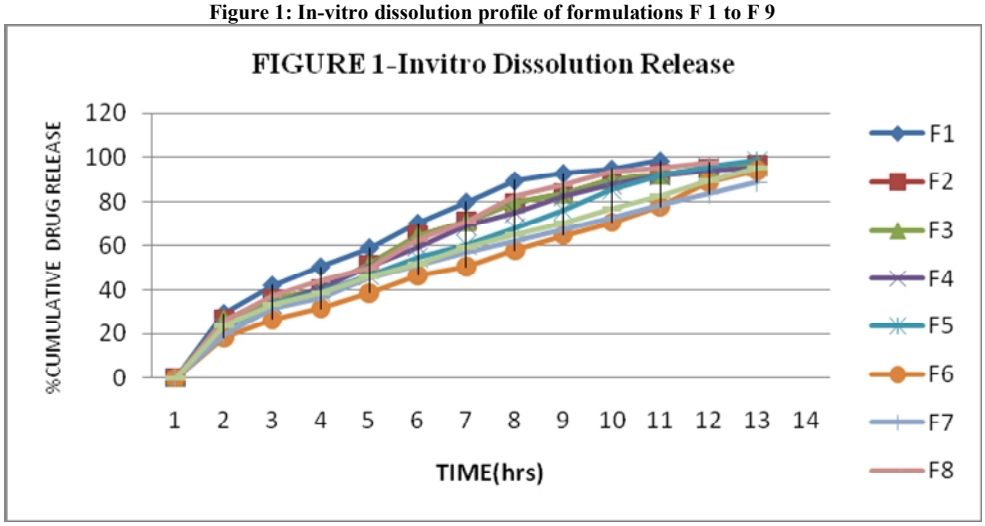


Figure 2: In-vitro dissolution profile of optimized formulation (F 5)

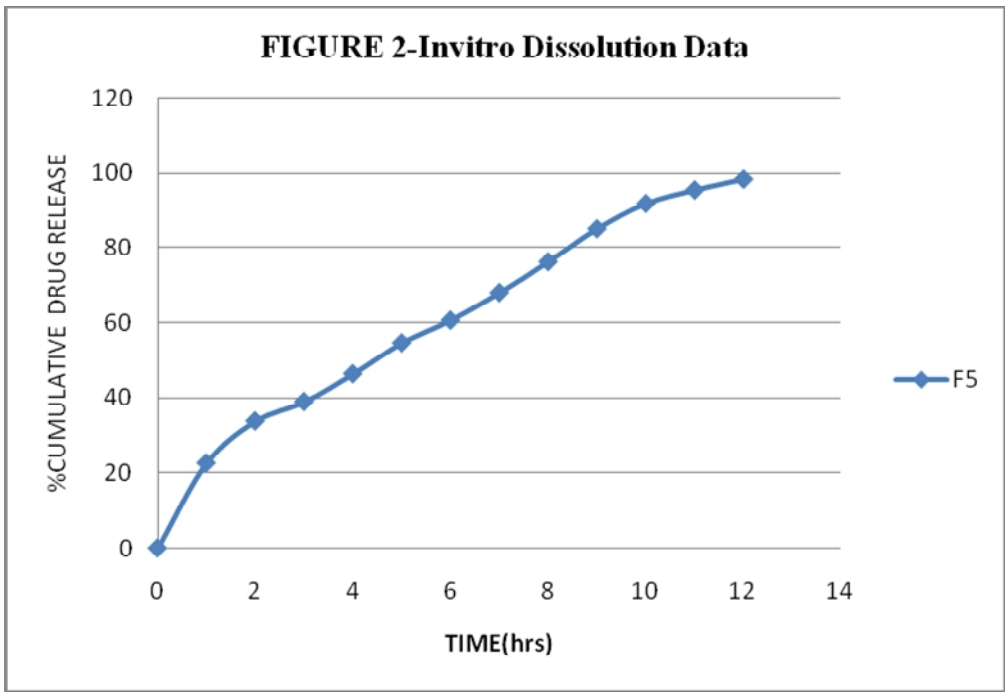
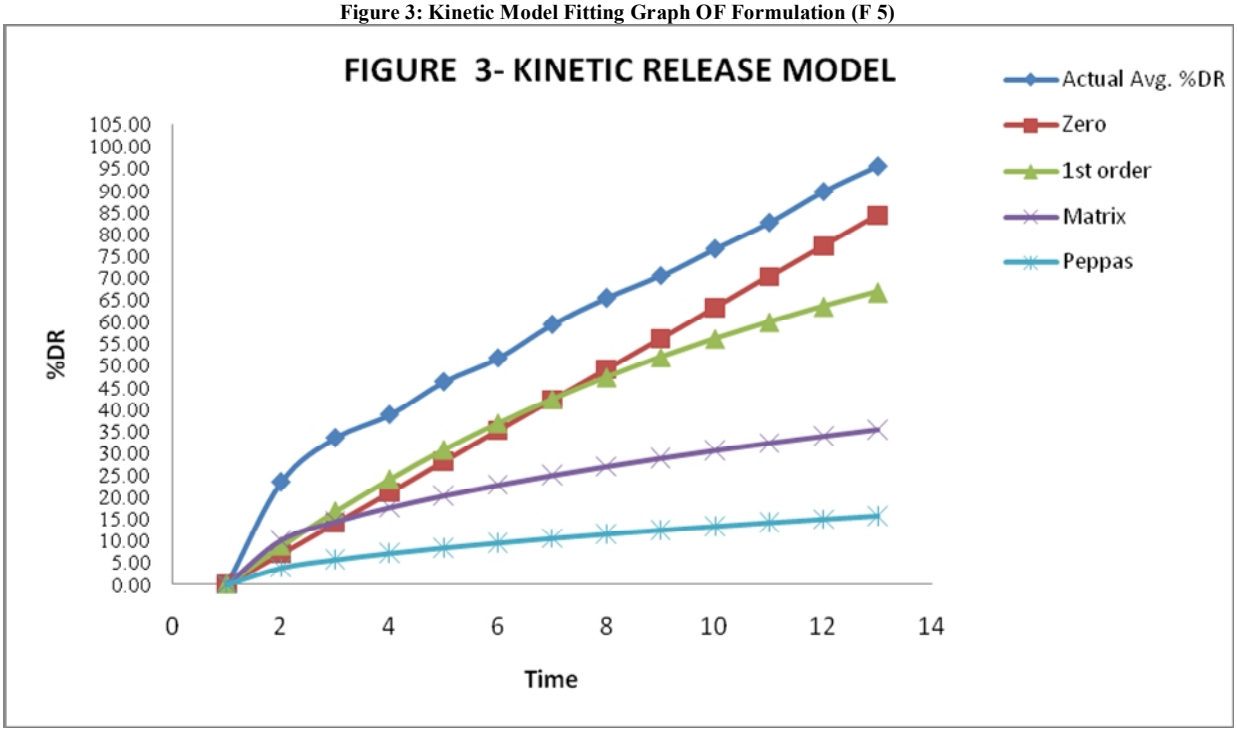


Table9: Kinetic Release Data of Different Model for Optimized Formulation (F5)

Model	R^2 VALUE	slope
Zero order	0.9732	7.6957
1st order	0.8648	-0.2987
Higuchi Matrix	0.9065	10.6502
Peppas	0.9892	3.7729
Hix.Crow.	0.9597	0.0580

Figure 3: Kinetic Model Fitting Graph OF Formulation (F 5)



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Source of support: Nil, Conflict of interest: None Declared