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Original Article

Formulation and Evaluation of Gastro-Retentive Floating Bilayer Tablets of Nifedipine

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ABSTRACT

Nifedipine is a calcium channel blocker of the dihydropyridine type, mainly used for the treatment of hypertension and angina pectoris. Nifedipine is a suitable candidate for Controlled Release administration due to its short elimination time 2-4 hrs.

The aim of present investigation is to increase the gastric residence time by preparing gastro retentive floating bilayered tablet thereby improving bioavailability. A simple UV spectro photometric method has been employed for the estimation of nifedipine at 238 nm with a Beer's range of 0-10µg/ml. Fourier transform Infrared spectroscopy confirmed the absence of any drug/polymers interactions.

Ten formulations (F_1 to F_{10}) were prepared using various polymers such as HPMC K4 HPMC K15, Carbopol and Sodium Carboxy methyl cellulose in different ratios. Direct compression method was adapted to compress bilayer floating tablet.

The prepared floating bilayer tablets were evaluated for hardness, weight variation, thickness, friability, drug content uniformity, buoyancy lag time, total floating time, water uptake (swelling index) and *in-vitro* dissolution studies. All the formulation showed drug release ranging from 89.19% to 98.08 and drug content ranging from 96.10 to 101.2%. Formulation F_7 has shown maximum drug release with good physical integrity upto 16hr in pH 1.2. Kinetic study shown F_7 release exponent (n) value is within permissible limits. It indicated that, the release mechanism for F_7 may by diffusion mechanism followed by non-fickian transport. F_7 selected as best formulation which contains HPMC K4M and Carbopol.

Accelerarated Stability studies revealed that F_7 were stable when stored at room temperature as well as different accelerated temperature and humidity conditions for a period of six months. The values were within permissible limits.

Keywords: Bilayered floating tablets, Buoyancy lag time, Controlled release, Flotation, Nifedipine, Total floating time, Water uptake study.

INTRODUCTION

Biopharmaceutics Classification System (BCS) class II drugs exhibit low solubility and high permeability characteristics. Their oral absorption is mostly governed by *in vivo* dissolution; the solubility and the dissolution rate are therefore key determinants for the oral bioavailability of these drugs. This implies that a small increase in the dissolution rate will result in a multifold increase in bioavailability[1]. Nifedipine is a calcium channel blocker of the dihydropyridine type which is mainly used for the treatment of hypertension and angina pectoris. Nifedipine is a suitable candidate for CR administration due to its short elimination half-life of 2-4 hrs, its rapid and complete drug absorption over the entire gastrointestinal tract, despite its low water solubility and the relationship between drug plasma concentrations and blood pressure reduction[2,3]. Conventional tablets need to be administered three to four times a day and controlled release formulations of nifedipine would be effective in overcoming the dissolution limitation by slowing supplying the drug from the intact matrix base during its sojourn in the gastrointestinal tract and is thus expected to decrease side effects and improve patient compliance[1].

Nifedipine bilayer floating Tablets were formulated as a once-a-day immediate release and Controlled-release tablet for oral administration designed to deliver the drug at gastric region for treatment of hypertension.

MATERIALS

Nifedipine was gift sample from micro labs, hosur. Hydroxy propyl methyl cellulose(K4 and K15), Sodium Carboxy methyl cellulose, Croscarmellose sodium, Lake Sunset Yellow, NaHCO3, Starch, Magnesium Stearate and Talc was gift samples of Unilink pharma (P) Ltd Chennai. Nellore.

METHODS

Preparation of standard calibration curve of Nifedipine

Principle

The nifedipine exhibits peak absorbance at 238nm in 1.2 pH buffer[6].

Instrument used

UV Spectrophotometer (shimadzu UV 1800)

Procedure

Preparation of standard solution

Standard stock solution of Nifedipine was prepared in 1.2 pH buffer. 100mg of nifedipine was accurately weighed and transferred into 100 ml volumetric flask and dissolved in small quantity of 1.2 pH buffer. The volume was made up to 100 ml to get a concentration of 1000µg/ml (SS-I). From this 25 ml solution was withdrawn and diluted to 100 ml to get a concentration of 250µg/ml (SS-II).

Preparation of working standard solutions

Further, from (SS-II) aliquots of 0.1 ml, 0.2 ml, 0.3, 0.4 up to 1 were pipetted into 25 ml volumetric flasks. The volume was made up to with 1.2 pH buffer to get the final concentrations of 1,2,3,4 up to 10µg/ml

respectively. The absorbance of each concentration was measured at 238nm.

Formulation design

Formulation of Bilayer floating tablet

Immediate release layer was formed by using Croscarmellose sodium as a super disintegrant. Starch (binder) used to promote cohesive compacts for directly compressed tablets. Magnesium stearate (Lubricant) intended to reduce the friction during tablet ejection between the walls of tablet and walls of the die cavity in which the tablet was formed. Talc (Glidant) intended to promote flow of the tablet granulation. Sunset yellow used to distinquising of off-colour layers. Lactose (diluent-filler) designed to make up the required bulk of the tablet[4].

Controlled release layer of effervescent layer tablets are designed to produce a solution, rapidly with simultaneous release of carbon- dioxide. The tablets are typically prepared by compressing the active ingredients with mixture of organic acid and sodium-bicarbonate. Polymers used to prolong the drug release by forming matrix tablets. Finally lactose (Diluent – Filler) used to design required bulk tablet[5].

a) Preparation of Immediate release layer

The Immediate release layer contains uniform mixture of Nifedipine, Cross Carmillose sodium, starch, lactose, sunset yellow were weighed.(Table 2) followed by shifting through 40# sieve and mixed well for 10min. finally prepared powder lubricated with magnesium stearate, the well mixed powder were used as upper layer[8,11].

b) Preparation of controlled release layer

The controlled release matrix tablet containing uniform mixture of drug, polymers and excipients including gas - generating agent. Nifedipine was mixed using variable amount of SCMC,Carbopol p 934 and HPMC(K4M, K15M) properly in a mortar with weighed amount of excipients as shown in table 3. The well-mixed powder was compressed by direct compression technique and used as controlled release layer[15,16].

c) Preparation of Bilayer tablet

Bilayer tablets were prepared by combining of fast release layer and various formulations of controlled release layer. After the compression upper punch was lifted and the blend of powder for immediate release layer was poured into the die, containing initially compressed matrix tablet on CADMAC multi station punching machine using 12.5 mm flat punches, with the hardness of 6.5kg/cm^2.

EVALUATION STUDIES OF BILAYER FLOATING TABLETS

All the prepared bilayer floating tablets were evaluated for following official and unofficial parameters[2,3,4].

Thickness

Thickness was measured using a calibrated vernier calliper. Five tablets of the formulation were picked randomly and thickness was measured individually[4]. Other technique employed in production control involves placing 5 or 10 tablets in a holding tray, where their total crown thickness may be measured with a sliding caliper scale. The tablet thickness was measured using screw gauge. (Table 4)

Hardness

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. Hardness of the tablet is an indication of its strength. Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping[7]. The hardness of the tablets was determined using

Monsanto Hardness tester. "Hardness factor", the average of six determinations, was measured and reported. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated. (Table 4)

Friability

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition[6].

Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions, the tablets were dedusted and weighed again. The percentage friability was measured using formula,

$$\%F = \{1 - (Wt/W)\} \times 100$$

$$Where, \%F = Friability\ in\ percentage$$

$$W = Initial\ weight\ of\ tablets$$

$$Wt = Weight\ of\ tablets\ after\ revolution$$

Weight variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated[1]. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight. (Table 4)

Drug content uniformity

Ten tablets equivalent to 30mg weighed and diluted with 1.2 pH buffer. An ultraviolet UV spectro photometric method based on the measurement of absorbance at 238nm in 1.2 pH was used for the estimation of Nifedipine. The method obeyed Beer's law in the concentration range 0-10µg/ml[6].

Floating property study

The time taken for dosage forms to emerge on surface of medium called buoyancy lag time (BLT). Duration of time by which the dosage forms constantly emerge on surface of medium called Total floating time (TFT)[11,12]. Tablets were placed in a 400 ml flask of pH 1.2 buffer, time needed to go upward and float on surface of the liquid and floating duration were determined.

Water uptake study

The swelling of the polymers can be measured by their ability to absorb water and swell. The swelling property of the formulation was determined by various techniques[11]. The water uptake study of the tablet was done using USP dissolution apparatus II. The medium used was distilled water, 900 ml rotated at 50 rpm. The medium was maintained at 37±0.5°C throughout the study. After a selected time intervals, the tablets were withdrawn, blotted to remove excess water and weighed. Swelling characteristics of the tablets were expressed in terms of water uptake (WU) as:

$$\mathbf{WU\ (\%)} = = \frac{weight\ of\ swollen\ tablet - Initial\ weight\ of\ the\ tablet}{\text{Initial weight of tablet}} \text{ x } 100$$

In vitro dissolution studies

Dissolution of the tablets was carried out on USP XXIII dissolution type II apparatus using paddle. The tablet was fixed to the paddle by hydration mechanism. 900 ml of pH 1.2 as dissolution medium was filled in a dissolution vessel and the temperature of the medium was set at 37 ± 0.5^0C. The rotational speed of the paddle was set at 100 rpm[7,13]. 1 ml of sample was withdrawn at predetermined time interval of 1 hr up to 12 hr and same volume of fresh medium was replaced. The withdrawn samples were diluted to 10 ml with 1.2 pH buffer, filtered

and analyzed on UV spectrophotometer at 238nm using 1.2 pH buffer as a blank. Percentage cumulative drug release was calculated. Values are represented in table 7 & Figure 5.

Data analysis

To analyze the mechanism of release and release rate kinetics of the best formulation, the data obtained were fitted into Zero order, First order, Higuchi matrix, and Peppa's model. Based on the r-value, the best-fit model was selected[8].

Stability study

Accelerated stability study for best formulation was carried out as per ICH guideline 'Q1E Evaluation for stability Data' using Ostwald stability chamber for best formulation the stability study was carried out at room temperature as well as different accelerated temperature and humidity conditions for a period of six months[18,19]. The conditions were modified as 25°C/60%RH, 40°C/70%RH, 60°C/80%RH for every months i.e. 2nd, 4th and 6th month respectively[20].

RESULTS & DISCUSSION

Determination of λ max

Drug was identified by UV scanning method which showed a λmax at 238nm as reported in the literature.

The linear regression analysis for standard curve

The linear regression analysis was done on absorbance data points. (Figure-1)The results are as follows:

The slope = 0.0545

The intercept = 0.0036

The correlation coefficient = 0.9993

A straight-line equation (Y = mx + c) was generated for the calculation

Absorbance = 0.0545 × Concentration + 0.0036

Formulation design

Ten formulations (F_1 to F_{10}) were prepared using various polymers such as HPMC K4 HPMC K15, Carbopol and Sodium Carboxy methyl cellulose in different ratios. The detailed composition of each formulation is given in the Table 2 & 3 the prepared tablets are shown in the figure Figure 2.

Formulation of the of controlled release layer

For floating drug delivery system, the polymers used must be highly swellable in shortest time. Hence HPMC (HPMC K4M and HPMC K15M) was preferred because it is widely used as low-density hydrocolloid system; upon contact with water, a hydrogel layer would be formed to act as a gel boundary for the release of drug, but it would fail to retard the release of drug through the matrix because of its solubility in stomach pH Various grades of HPMC were reported to have duration of buoyancy of more than 8 hours in the simulated meal medium, as well as in distilled water. Polymer with lower viscosity was shown to be beneficial than higher viscosity polymer in retarding drug release at same concentration of SCMC.

In order to retain the dosage form in the stomach for a long period of time and to avoid erosion and dissolution Carbopol p 934/SCMC was used in combination with HPMC to retard the drug release due to the low solubility at pH 1.2 to 3.

Sodium bicarbonate (NaHCO3) was incorporated in the formulation in such a way that when in contact with the acidic gastric contents, CO2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage form.

Lactose was included in formulation as hydrophilic agent, with assumption that capillary action of lactose may facilitate higher drug release without affecting the matrix (floating ability), the incorporation of

lactose showed appropriate release and floating time.

Formulation of immediate release layer

The immediate release layer was formed by using cross Carmellose sodium as a disintegrant that was widely used in tablet formulation due to its effectiveness at concentrations of 1 to 6%. CCS gives the maximum disintegration at 6%. In all the prepared formulations concentration of CCS, Starch, lactose and lake sunset yellow were kept constant. In all formulations designed weight of controlled release layers and immediate release layers were kept constant at 300 mg and 200mg respectively giving a total weight of each tablet at 500mg.

Evaluation

1. The prepared tablets were subjected to preliminary characterization such as hardness, thickness, % weight variation, friability and drug content. The evaluated parameters were within acceptable range for all the ten formulations. The values are indicated in Table 4

2. Floating property study reveals that all formulations had good floating property.Floating lag time varied from 43 to 82 seconds. So it concluded, as the polymer concentration increase, floating lag time also increases. (Table 5 & Figure 3)

3. All the ten formulations showed increases in weight indicating that, the polymer employed in the present investigation were having a capacity to swell the tablets. The percentage water uptake ranged from 93.4 to 120.3% after 10 hrs for formulation F_1 and F_{10} respectively. The values are shown in Table 6 and Figure 2.

4. *In vitro* drug release studies were carried out on dissolution test apparatus USP XXIII with paddles in 900 ml of 0.1N HCl. (Table 7 and Figure 5) these release studies revealed that, the order of release was found to be:

Rank order; F7>F5>F1>F2>F4>F9>F10 >F3>F8>F6

Criteria for selection of optimized formulation

All the formulation showed good tablet characteristics for floating drug delivery. The criteria for selection of optimum formulation were floating lag time, total floating time, and maintenance of integrity of tablet for longer time and *in vitro* drug release. Among the all formulation, F_7 selected as optimized formulation which contains combination of HPMP K4 + Carbopol. (Table 9)

Data analysis

The curve fitting results of the release rate profiles for the optimized F_7 formulation was subjected for data analysis. It was found that all the formulations were fitted into Krosmeyers-Peppas model which is the best fitted model. The values are shown in Table 8 and depicted in figures 7 & 8.

These results indicated that, the release mechanism for Nifedipine may by diffusion mechanism followed by non-fickian transport.

Stability study

Stability studies were carried out for formulation (F7) as per ICH guidelines. F_7 the formulation showed good stability and the values were within permissible limits and the values are tabulated in Table 10 & 11. Estimated shelf life of F_7 was 20 months. (Figure 9)

CONCLUSION

From the experimental results, it can be concluded that, Sodium bicarbonate has shown a predominant effect on the buoyancy lag time, while HPMC K4M and HPMC K15M have the predominant effect on total floating time and drug release. SCMC and CARBOPOL p934 have given extra gelling property and helped to maintain the integrity

of the tablet. Floating matrix tablets has given good floating and a controlled release. In-vitro release rate studies showed that the maximum drug release was observed in F_7 formulation upto 12 hrs. Kinetic study shown F_7 release exponent (n) value is within permissible limits. It indicated that, the release mechanism for F_7 may by diffusion mechanism followed by non-fickian transport. F_7 selected as best formulation which contains HPMC K4M and Carbopol.

Accelerarated Stability studies revealed that F_7 were stable when stored at room temperature as well as different accelerated temperature and humidity conditions for a period of six months. The values were within permissible limits. Estimated shelf life of best formulation was 20 months.

From the study, it is evident that a promising controlled release bilayer floating tablets of nifedipine can be developed. Further detailed investigations are required to establish efficacy of these formulations.

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Table 1. Absorbance at 238 nm of Nifedipine in 1.2 pH

Flask No.	Conc. µg/ml	Absorbance at 238nm
1	1	0.06
2	2	0.118
3	3	0.172
4	4	0.223
5	5	0.271
6	6	0.323
7	7	0.379
8	8	0.44
9	9	0.498
10	10	0.552

Table 2. Formulation development for immediate release layer*

S. NO	Ingredients	Quantity/tablet	Amt. in (%)
1	Nifedipine	20mg	10
2	Cross Carmillose sodium	10mg	5
3	Starch	40mg	20
4	Sun set yellow	0.15mg	0.07
5	Magnesium stearate	4mg	2
6	Talc	2mg	1
7	Lactose	To produce 200 mg layer	To produce 100% layer

*Total weight of immediate release layer: 200mg

Table 3. Formulation development for the controlled release layer of Bilayer floating tablets*

Ingredients in mg	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
Nifedipine	20	20	20	20	20	20	20	20	20	20
HPMC K4M	100	120	140	--	--	--	50	--	50	--
HPMC K15M	--	--	--	100	120	140	--	50	--	50
Carbopol	--	--	--	--	--	--	50	50	--	--
SCMC	--	--	--	--	--	--	--	--	50	50
$NaHCO_3$	80	80	80	80	80	80	80	80	80	80
Citric acid	10	10	10	10	10	10	10	10	10	10
Magnesium stearate	2 %	2 %	2 %	2 %	2 %	2 %	2 %	2 %	2 %	2 %
Talc	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
Lactose	To produce 300mg of layer									

*Total weight of controlled release layer 300mg

Table 4. Evaluation parameters

Evaluation parameters					
Formulation code	Thickness ± S.D.(mm) (n= 5)	Hardness ± S.D. (Kg/cm^2) (n =5)	Friability (%)	Average weight variation (n=10)	Drug content (%)
F_1	3.60 ± 0.043	6.5 ± 0.4	0.291	0.525 ± 0.011	97.72
F_2	3.54 ± 0.055	6.2 ± 0.2	0.308	0.520 ± 0.010	98.7
F_3	3.72 ± 0.085	6.1 ± 0.2	0.415	0.521 ± 0.010	98.16
F_4	3.70 ± 0.067	6.6 ± 0.1	0.152	0.518 ± 0.135	101.1
F_5	3.64 ± 0.054	6.4 ± 0.6	0.419	0.501 ± 0.009	97.17
F_6	3.76 ± 0.048	6.6 ± 0.3	0.244	0.511 ± 0.010	97.24
F_7	3.78 ± 0.028	6.2 ± 0.2	0.298	0.526 ± 0.008	97.92
F_8	3.83 ± 0.039	6.7 ± 0.3	0.205	0.515 ± 0.008	99.5
F_9	3.58 ± 0.026	6.3 ± 0.4	0.393	0.523 ± 0.008	101.2
F_{10}	3.66 ± 0.016	6.5 ± 0.2	0.351	0.521 ± 0.009	97.30

Each value represents the mean ± standard deviation

Table 5. Results of floating property of the bilayered floating formulations

Formulation code	Floating lag time (sec)	Total floating time (hr)
F_1	45±0.4	>12
F_2	52±0.3	>12
F_3	64±1.5	>12
F_4	43±1	>12
F_5	58±0.1	>12
F_6	68±0.3	>12
F_7	56±0.1	>12
F_8	82±0.2	>12
F_9	55±0.4	>12
F_{10}	68±0.5	>12

Table 6. % Water uptake study of formulations

Time in Hrs	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
1	57.5	56.9	55.7	59.2	60.2	93.50	94.65	94.62	96.9	95.8
2	84.82	87.2	83.5	89.7	94.9	100.87	101.6	104.6	104.2	107.14
3	98.3	96.4	102.7	103.1	113.4	115.73	115.2	119.3	121.6	122.34
4	102.62	106.3	107.4	108	126.7	140.1	141.8	168.8	194.6	211.85
5	111.2	110.5	112.8	118.3	135.5	146.56	166.66	160.2	176.6	193.91
6	108.2	110.9	113.3	118.5	143.2	128.5	139.37	146.3	161.4	164.8
7	95.4	99.2	101.6	101.5	124.8	114.6	118.71	118.6	122.7	142.5
8	77.4	82.7	89.8	96.2	119.4	94.6	101.16	99.4	102	125.1
9	57.2	62.6	69.2	80.3	109.9	84.6	89.71	90.6	101.5	122.4
10	27.2	31.4	36.7	64.7	93.4	61.9	63.69	82.12	87.53	120.3

Table 7. *In vitro* % Cumulative drug release (F_1-F_{10})

Time in min	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
1	34.15	50.59	39.16	28.77	38.47	35.53	34.32	31.37	31.20	32.93
2	41.63	60.35	53.75	39.02	47.69	45.44	46.66	39.19	42.49	42.15
3	48.95	66.82	62.64	58.29	58.13	52.94	58.31	47.72	50.67	51.72
4	57.66	74.00	70.33	66.84	66.51	64.60	69.80	53.14	66.83	59.57
5	65.69	78.58	77.33	76.78	72.30	71.08	77.50	66.54	71.24	68.12
6	71.31	82.65	79.32	82.93	81.04	76.87	81.22	70.25	78.93	71.31
7	77.97	86.38	83.74	86.13	85.80	79.38	88.07	75.69	84.56	76.58
8	81.17	89.59	84.87	88.13	89.01	81.20	90.59	78.72	86.21	80.82
9	85.07	92.80	87.39	91.17	91.54	83.89	92.25	84.17	89.25	84.37
10	89.84	95.50	88.70	92.14	93.71	85.88	94.77	86.34	91.26	86.37
11	94.78	96.99	90.01	93.45	96.59	87.88	96.26	89.21	93.43	89.24
12	97.31	97.01	92.01	96.67	97.56	89.19	98.08	91.39	96.13	91.76

Table 8. Fitting data of the release rate profile of F_7 formulation

Formulation	Zero order	Higuchi's	Peppa's(n)
F_7	0.8204	0.9716	0.5381

Table 9. Selection of Optimized Formulation

Formulation	F_7
Floating Lag Time	56 ± 0.1 sec
Total Floating Time	>12 hrs
Integrity of Tablet for longer time	Yes
In vitro drug release	98.08%

Table 10. F_7 formulation physical parameters subjected to stability study

Time In months	Visual appearance	Hardness Kg/cm^2	Thickness mm	Weight variation	% Friability
2	Pink/ Yellow	6.4	3.6	515	0.496
4	Pink/ Yellow	6.3	3.6	513	0.557
6	Pink/Yellow	6.3	3.5	510	0.590

Table 11. Comparison of observed with calculated assay of best formulation subjected to stability study

Time in months	Observed Assay (%) Mean ± SD	Calculated Assay (%) Mean ± SD
0	99.80 ± 0.32	99.35 ± 0.44
1	98.76 ± 0.48	98.92 ± 0.71
2	98.47 ± 1.03	98.50 ± 0.71
3	97.68 ± 1.13	98.07 ± 0.71
4	97.39 ± 1.05	97.65 ± 0.71
5	97.02 ± 0.49	97.22 ± 0.71
6	96.89 ± 0.78	96.80 ± 0.71

Each value represents the mean ± standard deviation (n=3)

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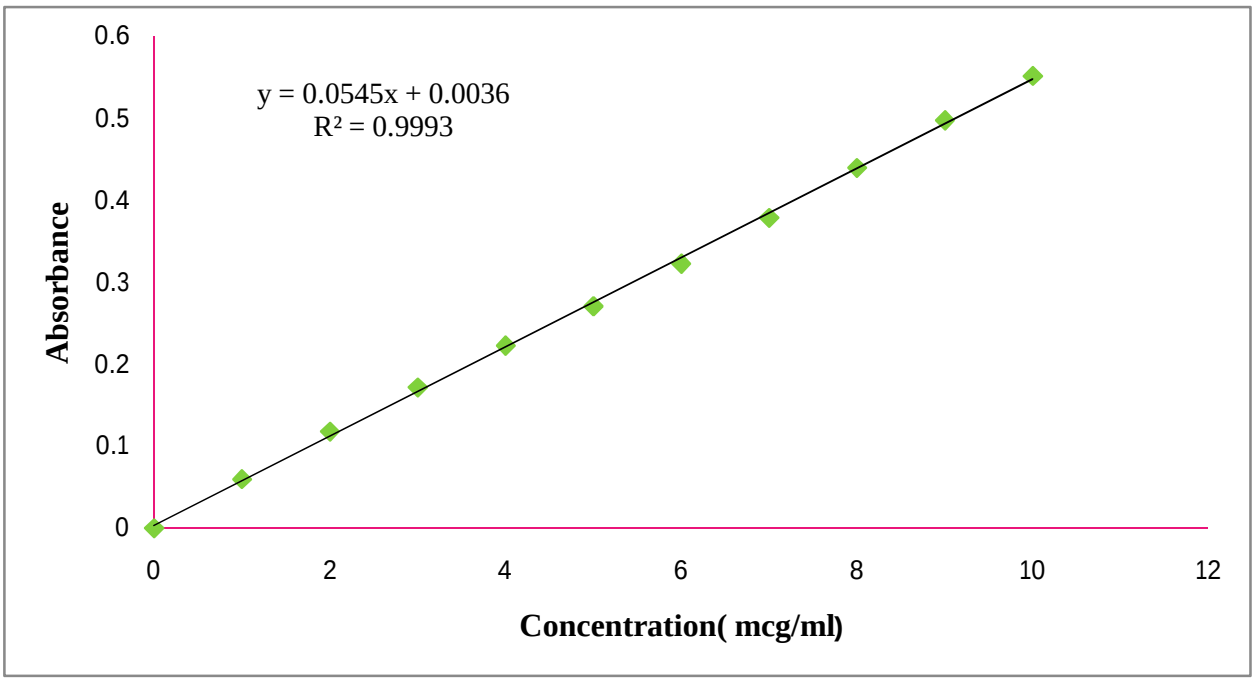

Figure.1. Standard calibration curve of Nifedipine at 238nm

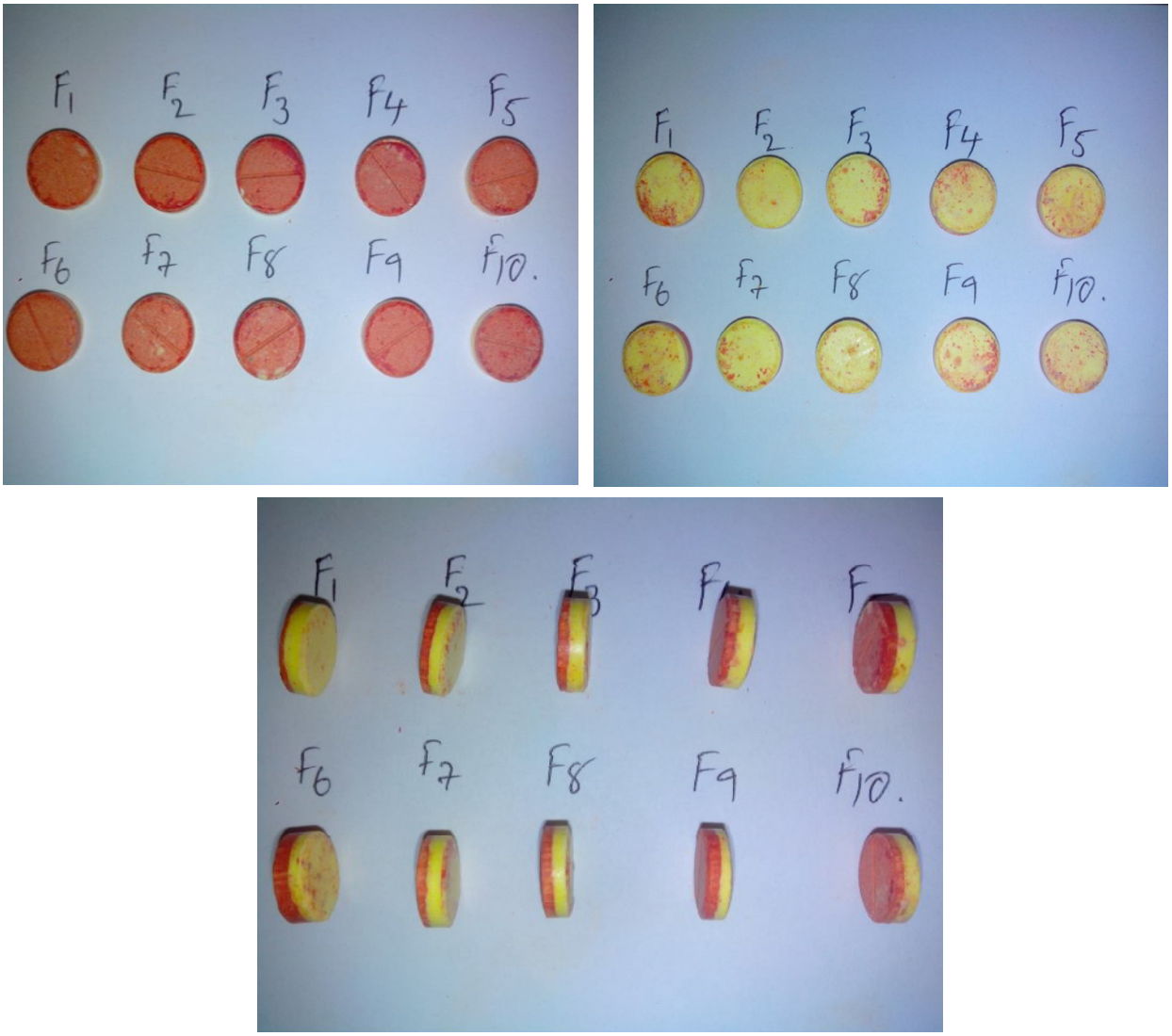

Figure.2. Floating Bilayer Tablets of Nifedipine

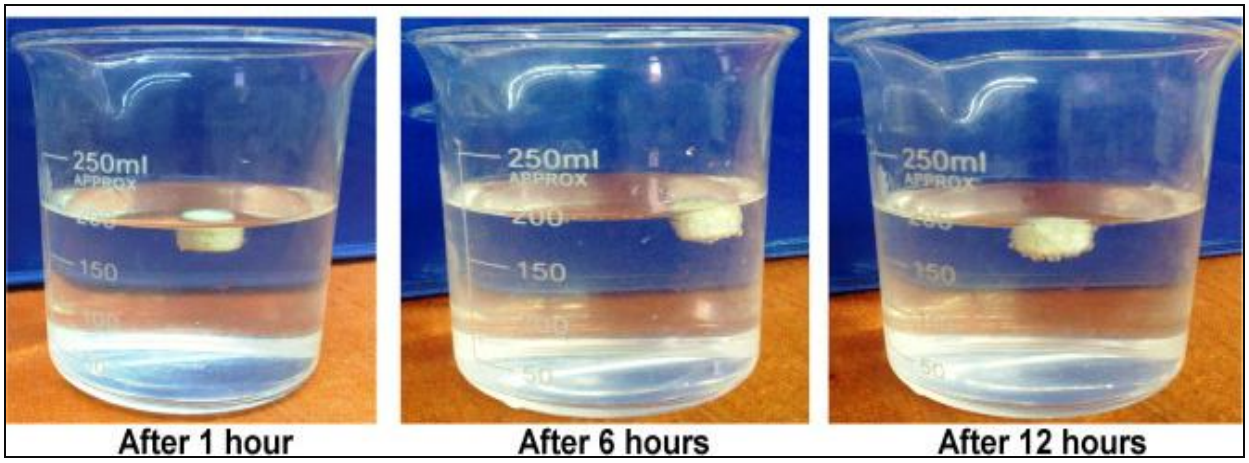

Figure.3. Bilayer floating tablet buoyancy time study

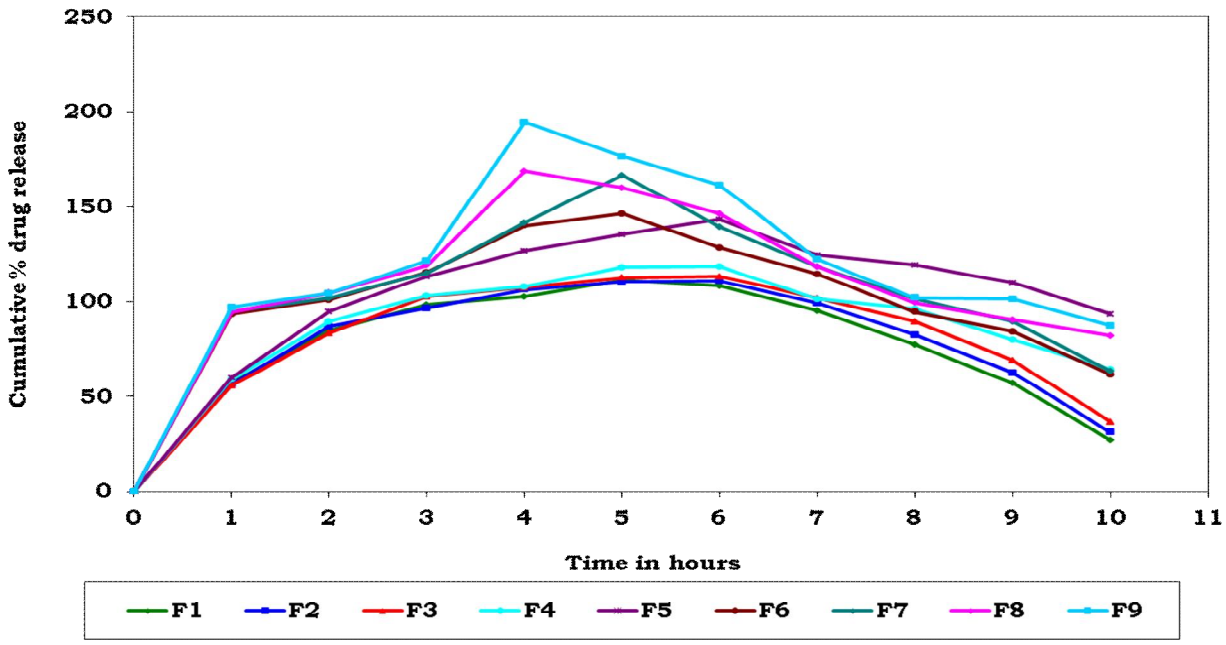

Figure.4. Swelling index of polymers

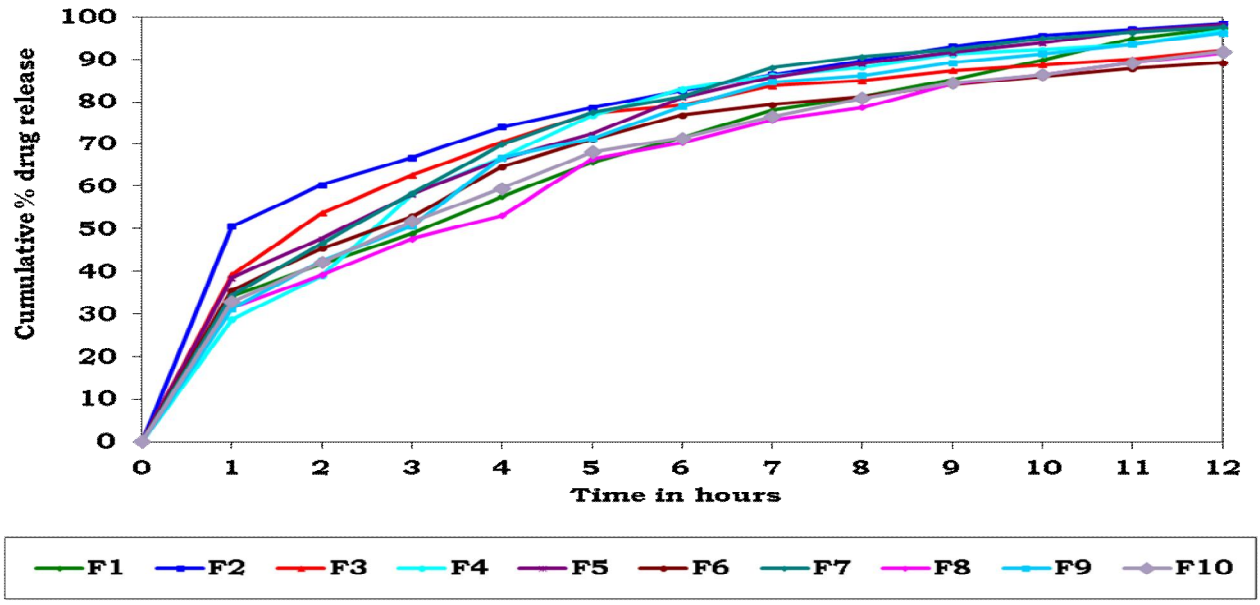

Figure. 5. comparison of drug release pattern

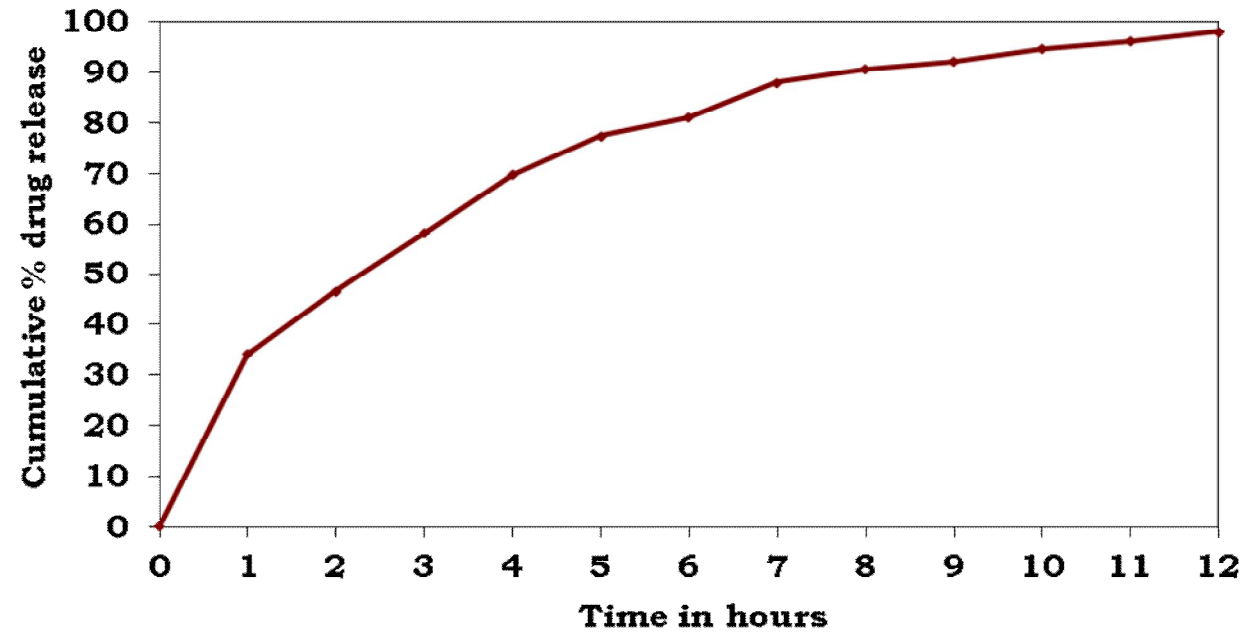

Figure. 6. *In vitro* cumulative % drug release of F_7

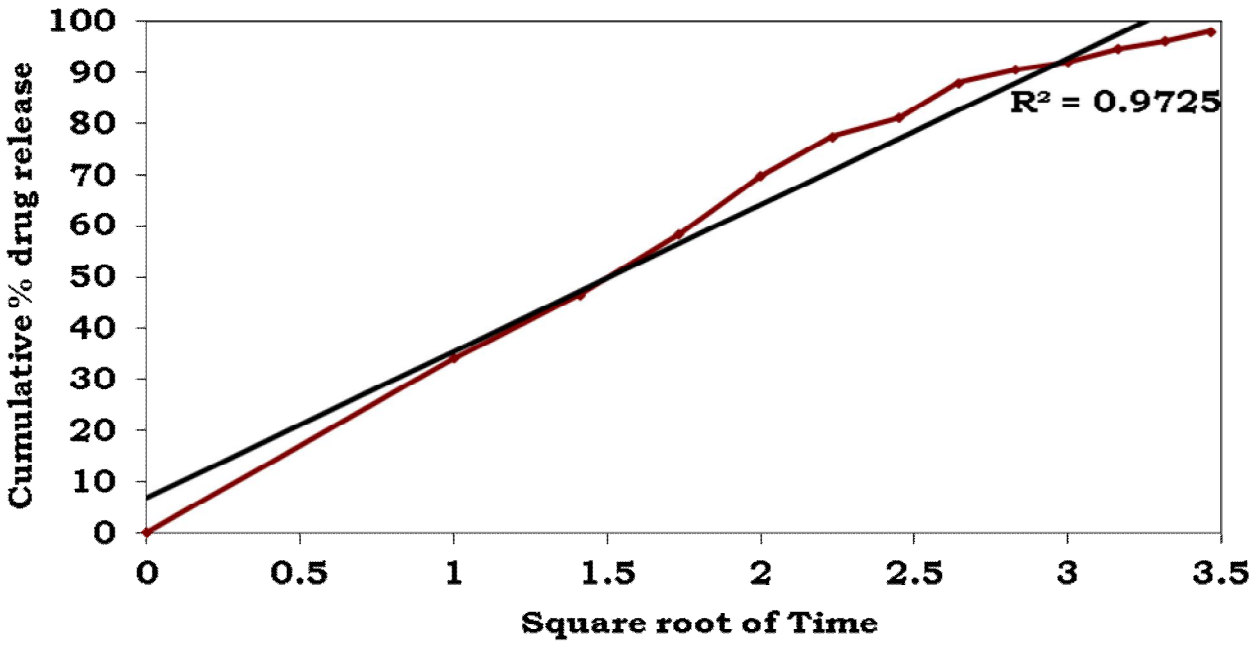

Figure. 7. Higuchi's plot of F_7

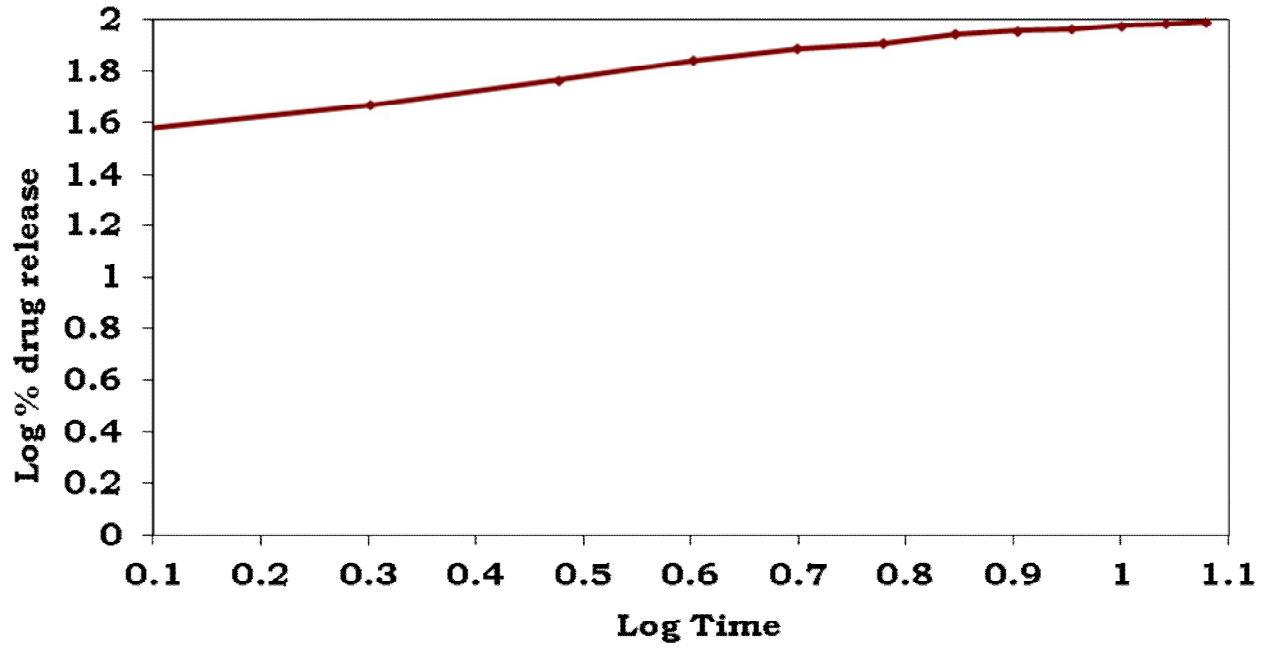

Figure. 8. Peppa's plot of F_7

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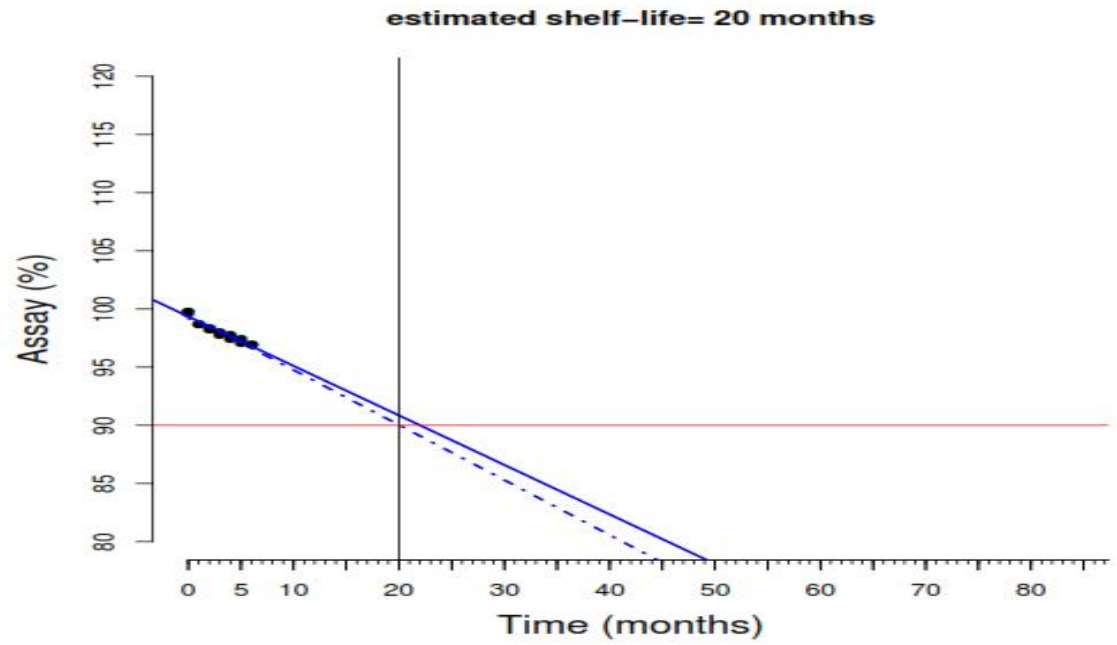

Figure. 9. Graph showing predicted shelf life of best formulation