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DESIGN, FORMULATION AND EVALUATION OF FLOATING MATRIX BILAYER TABLET OF RAMIPRIL HYDROCHLORIDE

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ABSTRACT

The Aim of this research work was to develop a bilayer tablet of Antihypertensive drug having sustained release layer (SR) and immediate release layer (IR) of Ramipril. The combination of these two layers in a single dosage form will reduce the frequency of drug administration and increase patient compliance.

The floating matrix release layer was prepared by using swallable polymer HPMC K100, carbapol and immediate release layer was prepared by using superdisintegrant i.e. Sodium Starch Glycolate (SSG) by wet granulation. All physicochemical properties were evaluated for tablets. And all the values were found within limit.

The optimized batches F6 and I3 by taking biphasic drug release pattern. In-vitro drug release study was carried out using USP Type-2 paddle apparatus, In-vitro drug dissolution study indicate that increasing concentration of polymers which decrease the rate of drug release. And result showed that carbapol 934P in floating matrix layer can control the drug release up to 8hrs. The mechanism and rate release of Ramipril from the prepared floating tablets were analyzed by fitting the dissolution data into the zero order, First order, Higuchi and Korsmeyer-Peppas equation. The Bilayer tablet of optimized batch fitted in to zero order release which show linear equation with (r^2 value 1) and release pattern which indicate by diffusion.

Keyword: Ramipril, Bilayer Tablet, Immediate Release, floating matrix delivery system

1. INTRODUCTION

The oral route of drug administration is the most convenient and commonly used method for drug delivery system. There are various route of administration utilize for the drug delivery. Oral route remains most preferable route of administration. Tablet is conventional dosage form acceptable by patient and physician because of ease of administration, accurate dosing, cost effective manufacturing method and generally improved shelf-life of the product **[1]**. Bilayer tablet is use for sequential release of two drugs in combination in which one layer floating matrix release and another layer is immediate release or sometimes single drug also used in bilayer tablet by approach of loading dose and maintenance dose. Immediate release act as loading dose and the floating matrix release act as maintenance dose. Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability **[2]**.

Present investigation is formulation and evaluation of bilayer tablet of Ramipril. Ramipril is long acting angiotensin converting enzyme inhibitor. Ramipril is a pro-drug of Ramiprilat which is 6 times active than Ramipril. It reduces the blood pressure by relaxing the blood vessel by causing vasodilation which helps to prevent heart attacks and strokes **[3]**. On oral administration of Ramipril the peak plasma concentrations of Ramipril are reached within one hour. The oral

Administration of Ramipril is absorbed through upper part of GI tract and absolute bioavailability of Ramipril is approximately 50- 60%. Due to presence of food in gastrointestinal track affects the absorption of Ramipril. The absolute bioavailability of Ramipril is 28%. Elimination half-life of Ramipril is about 2-4 hours **[3, 4]**.

There is a need to formulate Ramipril floating matrix bilayer tablet dosage is because, the developed floating matrix layer help in reduction of frequency of administration by maintaining prolonged therapeutic concentrations of dose of drug in plasma, while immediate release layer act as loading dose which is release immediately within one hour to achieve peak plasma concentration loading dose of the drug. Thereby patient compliance can be improved by improving availability of dose of drug through formulation of floating matrix bilayer tablets of Ramipril.

The proposed work involve the development of floating matrix tablet of Ramipril by using Hydrophilic polymers such as HPMC K100

and carbapol 934P and gas generating agents sodium bicarbonate and citric acid. Floating matrix layer compressed by direct compression. In immediate release layer prepared by using superdisintegrant i.e. Sodium starch glycolate (SSG) which is compressed by wet granulation. To evaluate blends in terms of Angle of repose, Bulk and tapped density, Carr's index, Hausner's Ratio and to evaluate Bi-layer matrix tablets in terms of hardness, weight variation, friability, thickness, drug content uniformity, *In-vitro* dissolution studies in 0.1 N HCl.

2. MATERIAL AND METHOD

2.1 Materials: [5]

Ramipril HCl. gifted sample (Flamingo pharmaceutical), HPMCK100, Carbapol 934P, Talc, sodium bicarbonate, citric acid (Thermosil fine chem.) sodium starch glycolate, Sodium Saccharine, PVPk30 (research lab) Lactose, (Sahyadri scientific supply) Magnesium Stearate (Hilab chemicals) were sample is analytical grade.

2.2 Method:

2.2.1 Preparation of immediate release tablet of Ramipril by wet granulation:

Weighing all ingredients and pass through sieve no 40 #. The drug and powder blend are mix and then add into it binder solution to produce wet mass. This wet mass passes though the sieve no 20 # size to produce uniform granules. The wet granules are dried into try dryer up to evaporation of solvent. The dried granules mixed with extra granulating agent such as superdisintegrant, glident and lubricants. Finally the tablets were compressed using 8 station tablet compression machine (Make-CREATE INDUSTRIES, MODEL-LP-8GMP).

2.2.2 Preparation of floating matrix tablet of Ramipril by direct compression:

Floating matrix tablet of Ramipril is prepared by direct compression method; drug and polymer (HPMC k100, carbapol 934P) were pass through the 40# sieve, transfer into cone blender and mixed properly up to 5 min. Other excipients (citric acid, sodium bicarbonate, Lactose and talc) were mixed well 3 min and then added Magnesium Stearate in above blend and were mixed for 5 min. Finally above blends were compressed by rotary tablet compression machine (Make-CREATE INDUSTRIES, MODEL-LP-8GMP).

2.2.3 Preparation of Bilayer Tablet:

Tablets were prepared by floating matrix layer by direct compression and immediate release by wet granulation using 8 stations tablet punch machine. Bilayer tablets were prepared in two stages. Both the layers were prepared and evaluated separately and optimized the batches separately. Then the

optimized batches are selected for the preparation of Bilayer tablets. Bilayer Tablets were prepared by double compression technique. In this, immediate release Ramipril granules (100mg) were introduced first in to the die cavity and a gently compressed to form uniform layer. Then floating matrix release layer of Ramipril (100 mg) were added and a final compression was made. After final compression, total weight of bilayer tablet was 200mg **[1]**.

2.3 Pre-formulation parameters:

2.3.1 Melting point: [8, 9]

Melting point of drug sample was determined by capillary method using melting point apparatus. Small quantity of drug sample was taken transferred in a thin walled capillary tube. The tube was approximately 10-12 cm in length with 1mm in diameter and closed at one end. The capillary which contain sample was placed in melting point apparatus and heated and when drug sample was melted the melting point of sample powder was noted.

2.3.2. Solubility: [9]

Qualitative Solubility

Qualitative solubility was determined by drug was dissolving 5 mg of drug in 5 ml solvent such as distilled water, methanol, 0.1 N HCl.

2.3.3. Identification method by spectrophotometer: [10, 11]

1. **Identification test by U.V vis. Spectrophotometer:**

   50 mg of Ramipril HCl was weighed accurately and transferred it to 50 ml volumetric flask. Dissolved it in 0.1N HCl and make the volume up to 50 ml with respective solvent. This was considered as stock solution (1000 mg/ml). Further dilutions were made by withdrawing 1ml from this stock solution and dilute up to 10 ml to produce 100 mg/ml. above solution was scanned in the range of 400-200 nm using respective blank in UV spectrophotometer (Shimadzu UV 1800).

2. **FTIR Spectroscopy [11]**

   The drug was identified by FTIR spectroscopy by using KBr press pellet technique. Sample for analysis and KBr were taken in 1:100 ratio and ground in motor for even distribution of sample in KBr. The pellet was prepared in the form of disk by applying pressure of 100 PSI for 1min using hydraulic press and subjected to FTIR. The pellet Scanned at 400 to 4000cm-1 IR range (Perkin Elmer).

2.3.4 Drug-Excipient compatibility study:

The drug-excipients interaction was studied by FTIR spectroscopy by KBr press pellet method. Sample for analysis and KBr were taken in 1:1:100 ratio and ground in motor for even distribution of sample Drug-Excipient in KBr. The pellet was prepared in the form of disk by applying pressure of 100 PSI for 1min using hydraulic press and subjected to FTIR. The pellet Scanned at 400 to 4000cm^{-1} IR range.

2.4 Pre-compression parameters: [6, 11]

2.4.1. Bulk Density:

Bulk density was determined by the pre-weighed power blend introduced into measuring cylinder and measures the volume of powder. The bulk density was calculated by using formula.

Bulk density (BD) = weight of powder /bulk volume.

2.4.2 Tapped density:

Tapped density was determined by tapping the cylinder using tapped density apparatus. Tapped the cylinder up to 100 times and then measure the tapped volume and calculate the tapped density by using formula.

Tapped Density (TD) = weight of powder /tapped volume.

2.4.3 Hausner's ratio:

Hausner's ratio is the ratio of bulk density and tapped density, the number is correlated to the flowability of a powder or powder blend. It is calculated using formula,

Hausner's ratio = tapped density / bulk density.

2.4.4 Compressibility index:

Compressibility index was calculated by formula,

Carr's index (%) = Tapped density – bulk density/ tapped density* 100

2.4.5 Angle of repose:

The angle of repose of powder blend of each layer of each formulation was determined by fix funnel method. The blend was poured into funnel separately until apex of pile is formed up to touch the tip of the funnel. The angle of repose was calculated by using formula

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

h= height of pile

r= is radius of pile.

2.5 Post compression evaluation:

2.5.1. Uniformity weight:

Uniformity weight of the tablet was determined by selecting 20 tablet randomly. This selected tablet weighing individually and the weight of individual tablet was compared with average weight of total tablets.

Table 1: Formulation Table of Floating Matrix Tablet

Ingredients	F1	F2	F3	F4	F5	F6
Dry mix						
Ramipril	5	5	5	5	5	5
HPMC	20	30	40			
Carbapol				20	30	40
citric acid	15	15	15	15	15	15
Sodium. Bicarbonate	30	30	30	30	30	30
lactose	26	16	6	26	16	6
Blending and lubrication						
talc	3	3	3	3	3	3
Magnesium Stearate	1	1	1	1	1	1
total	100	100	100	100	100	100

Table 2: Formulation Table of Immediate Release Tablet

Ingredients	I1	I2	I3
Dry mix			
Ramipril	2.5	2.5	2.5
Lactose	72.5	67.5	62.5
Sodium Saccharin	2	2	2
Wet granulation			
PVP K30	5	5	5
Isopropyl Alcohol	q.s	q.s	q.s
Blending and lubrication			
Sodium Starch Glycolate	10	15	20
Talc	5	5	5
Magnesium stearate	3	3	3
Total	100	100	100

Table 3: Limits for Tablet Weight variation test:

Average weight of tablet (mg)	% Difference allowed
130 or less	10 %
From 130 to 324	7.5 %
> 324	5%

2.5.2 Thickness:

Thickness of the tablet was measured by using vernier calliper. 5 tablets were selected and its thickness was measured in (mm).

2.5.3. Hardness:

Hardness is important factor for evaluation of tablet. The hardness of tablet was done to determine breaking point structural integrity of tablet measured by using Monsanto Hardness Tester. The unit of hardness is expressed in term of kg/cm^2.

2.5. 4. Friability:

Friction and shock are the forces that most often cause tablets to chip, break or cap . 20 tablets are selected and weighed, placed in the roche friabilator apparatus they are exposed to rolling and repeatedly falling sample of tablet from 6 inches over a fix period of time within the apparatus. After 100 revolutions, the tablets are reweighed and the weight compared with the initial weight. The loss due to abrasion is a measure the tablet friability. A maximum weight loss of not more than 1% of the weight of the

tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked. The percentage friability was determined by the formula,

% friability = [initial weight – final weight/initial weight]*100

2.5.5. Disintegration Test:

The disintegration test was carried out as per standard procedure. Take six tablet and placed in each of the six tubes of the basket and the disc was added to each tube. The test was carried out by using 0.1 N HCl as medium. The temperature was maintained at 37 °C + 2°C.The apparatus was operated and note down the disintegration time of the tablet.

2.5.6. In Vitro Buoyancy Studies: [12]

The tablets were placed in a 500 ml beaker, containing 400 ml of 0.1 N HCl. The time required for the tablet to rise up to the surface of water and float was determined as floating lag time (FLT) and the time period up to which the tablet remained buoyant on the surface is determined as total floating time (TFT).

2.5.7. Swelling Study: [6]

The tablets were weighed individually (W_0) and placed separately in Petri dish containing 5 ml of 0.1 N HCl and incubated at 37°C ± 1°C. At regular time interval, the tablets were removed from Petri dish, and the excess surface liquid was removed carefully using the tissue paper. The swollen floating tablets were then reweighed (W_t) and % swelling index (SI) was calculated using the following formula:

$$SI\ (\%) = (W_t - W_0 / W_0) \times 100$$

2.5.8. Drug Content Uniformity:

Take 10 tablet of ramipril and crushed to produce powder form. An accurately weighed amount of powder equivalent to 5 mg of floating matrix release layer and2.5 mg of immediate release layer separately were dissolved in 250ml in 0.1 N HCl separately. Further dilutions were made. Then the drug content was estimated at suitable wavelength of Ramipril against blank reference using UV-Visible Spectrophotometer (Shimadzu 1800).

2.5.9. In-Vitro Dissolution study:

a) For floating sustained released tablet: [13]

The *In-vitro* dissolution study for the Ramipril floating sustained released tablet were carried out in USP type-II dissolution test apparatus (Electrolab TDT-08L) (Paddle type) using 900 ml of 0.1 N HCl at 50 rpm and temperature 37±0.5°C. At predetermined time (1 hr.) intervals up to 12 hrs, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter; the volume

withdrawn at each interval was replaced with same quantity of fresh dissolution medium (0.1 N HCl). The resultant samples were analyzed by measuring the absorbance at 210 nm using UV Visible spectrophotometer and calculate the percentage drug release.

b) For immediate release tablet:

The *In-vitro* dissolution study for the Ramipril immediate release tablets were carried out in USP type-II dissolution test apparatus (Electrolab TDT-08L) (Paddle type) using 900 ml of 0.1 N HCL at 50 rpm and temperature 37±0.5°C. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed by measuring the absorbance at 210 nm using UV Visible spectrophotometer and calculate the percentage drug release.

3. RESULT AND DISCUSSION

3.1. Pre-formulation studies:

The UV absorption of 10 µg/ ml in 0.1N HCl (pH-1.2) for Ramipril HCl is 204 nm in the range of 200-400 nm exhibit maximum and in case of Simvastatin is at 247nm.

Melting point, solubility and compatibility study of both drugs are carried out and result is including in **Table 4, Figure 1, 2**.

3.2. Pre-compression Evaluation:

The micromeritic properties of powder blend such as of bulk density, tapped density, Angle of repose; compressibility index and Hausner's ratio of Ramipril HCl immediate release layer blend and floating matrix layer were studied. The overall results were shown in **Table 5 and 6**. The value of bulk density indicates good packing characteristics. The compressibility index of the formulation Indicating a poor flow properties of powder which were further confirmed by determining the angle of repose, it is in the range of 30 to 35 which indicates good flow properties.

3.3 Post-compression Evaluation of Tablet:

The prepared tablets were evaluated for weight variation, dissolution test, Thickness, Hardness, Drug content uniformity, in-vitro buoyancy and friability. The weight variation test is carried by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average

The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm2. The Friability was determined by first weighing 6 tablets after dusting and placing them in a friability tester (Roche friabilator), which was rotated for 4 min at 25

rpm. After dusting, the total remaining mass of tablet was recorded and the percent friability was calculated. The thickness of the each 10 tablets was measured with the Varnier Caliper. All tests value is included. Drug content uniformity and *In-vitro* drug release determined according to the USP requirements. Test values are including in **Table 7-9, Figure 3-5**.

3.4 Kinetic Models:

The mechanism and rate release of Ramipril from the prepared floating tablets were analyzed by fitting the dissolution data into the zero order, First order, Higuchi and Korsmeyer-Peppas equation. Formulations F1 to F6 show zero order release with linear equation having r^2 near about 0.93 to 0.98 which is indicating drug release followed by diffusion. The Bilayer tablet of optimized batch fitted in to zero order release which show linear equation with (r^2 value 1) and release pattern which indicate by diffusion **(Table 10)**.

Table 4: Preformulation study of Ramipril HCl

Sr. No	Parameters	Observation
1	Identification by U.V Vis spectrophotometer.	204 nm (ƛ max)
2	Melting Point	109^0C
3	Solubility	Slightly soluble in distilled water. Freely soluble in methanol. Soluble in 0.1 N HCl
4	Compatibility study (FTIR)	Compatible.

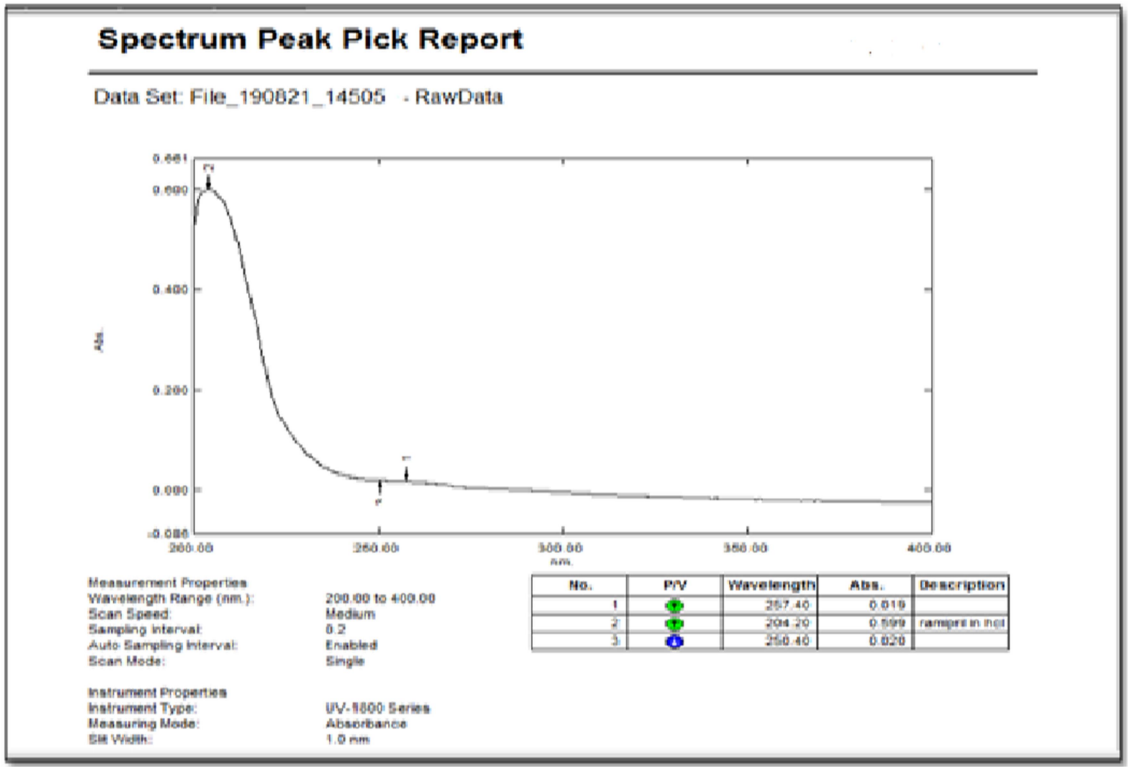

Figure 1: Absorption maxima of Ramipril

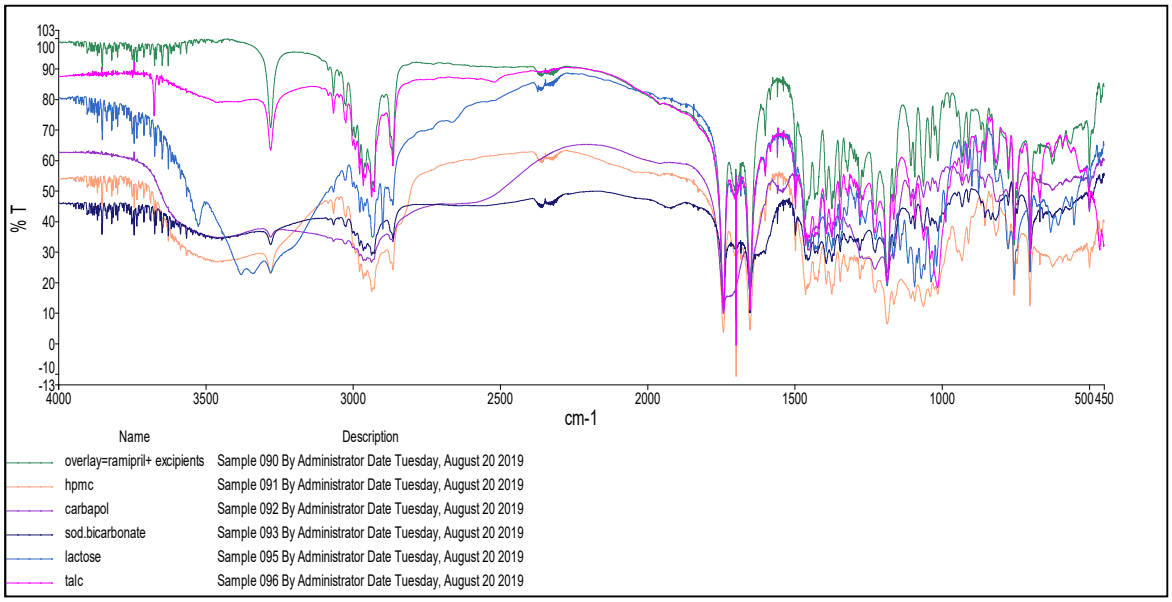

Figure 2: Drug compatibility study

Table 5: Pre-compression evaluation of floating matrix release layer powder blend (Ramipril HCl)

Sr. No	Parameter	S1	S2	S3	S4	S5	S6
1	Bulk density(g/ml)	0.460	0.395	0.436	0.398	0.426	0.432
2	Tapped density(g/ml)	0.640	0.612	0.642	0.569	0.599	0.610
3	Compressibility Index (%)	28.12	35.45	32.08	30.05	28.88	29.18
4	Hausner's ratio	1.39	1.54	1.47	1.42	1.40	1.41
5	Angle of repose(degree)	32.18	28.45	33.04	29.89	30.94	34.23

Table 6: Pre-compression evaluation of immediate release powder blend (Ramipril HCl)

Sr. No	Parameter	I1	I2	I3
1	Bulk density (g/ml)	0.379	0.388	0.420
2	Tapped density (g/ml)	0.505	0.514	0.552
3	Compressibility index (%)	24.95	26.51	23.91
4	Hausner's ratio	1.33	1.32	1.31
5	Angle of repose (degree)	35.10	33.78	30.65

Table 7: Post-compression Evaluation of floating matrix release tablet (Ramipril HCl)

Sr. No	Parameter	F1	F2	F3	F4	F5	F6
1	Uniformity weight(mg)	100	99	102	101	98	101
2	Thickness(mm)	3.5	3.4	3.5	3.6	3.5	3.5
3	Hardness(kg/cm^2)	5	5	5.2	5.5	5.3	5.2
4	Friability (%)	0.54%	0.61%	0.60%	0.64%	0.47%	0.59%
5	Floating lag time (sec)	26	23	25	29	26	30
6	Swelling index (%)	68.93	65.36	71.42	80.23	83.92	87.45
7	Drug content (%)	89.40	93.50	86.92	91.40	90.50	95.92
8	% Drug release	86.21%	82.55%	83.12%	87.21%	83.33%	81.22%

Table 8: Post-compression Evaluation of immediate release tablet (Ramipril HCl)

Sr. No	Parameter	I1	I2	I3
1	Uniformity weight(mg)	100 mg	102 mg	99 mg
2	Thickness(mm)	3.4mm	3.5mm	3.5mm
3	Hardness(kg/cm^2)	3.5kg/cm^2	3kg/cm^2	3.5kg/cm^2
4	Friability (%)	0.54%	0.62%	0.51%
5	Disintegration time (min)	2.41	2.16	1.45
6	Drug content	89.54%	91.15%	90.95%
7	% Drug release	85.51%	83.65%	87.42%

Table 9: Post-compression Evaluation of Bilayer tablet of F6 and I3 Optimized batch

Sr. No	Parameter	F6I3
1	Uniformity weight(mg)	201 mg
2	Thickness(mm)	3.5 mm
3	Hardness(kg/cm^2)	4.5 kg/cm^2
4	Friability (%)	0.642%
5	Drug content (immediate release)	96%
	Drug content (floating matrix release)	92%
6	% drug release (immediate release)	87.29 %
	% drug release (floating matrix release)	81.34%

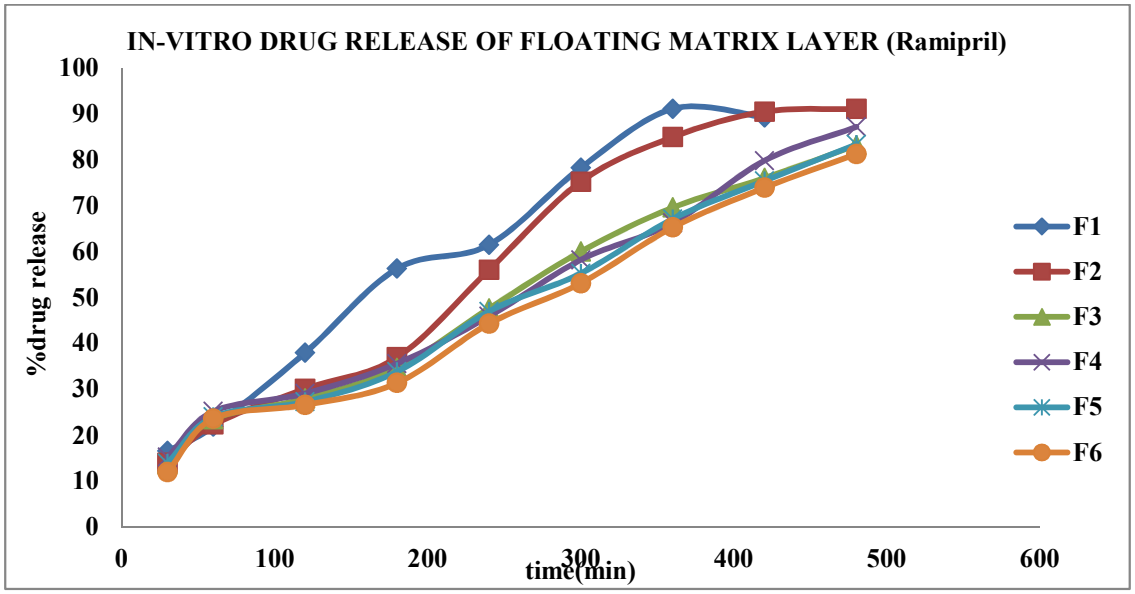

Figure 3: In-Vitro Drug Release Of Floating Matrix Layer (Ramipril)

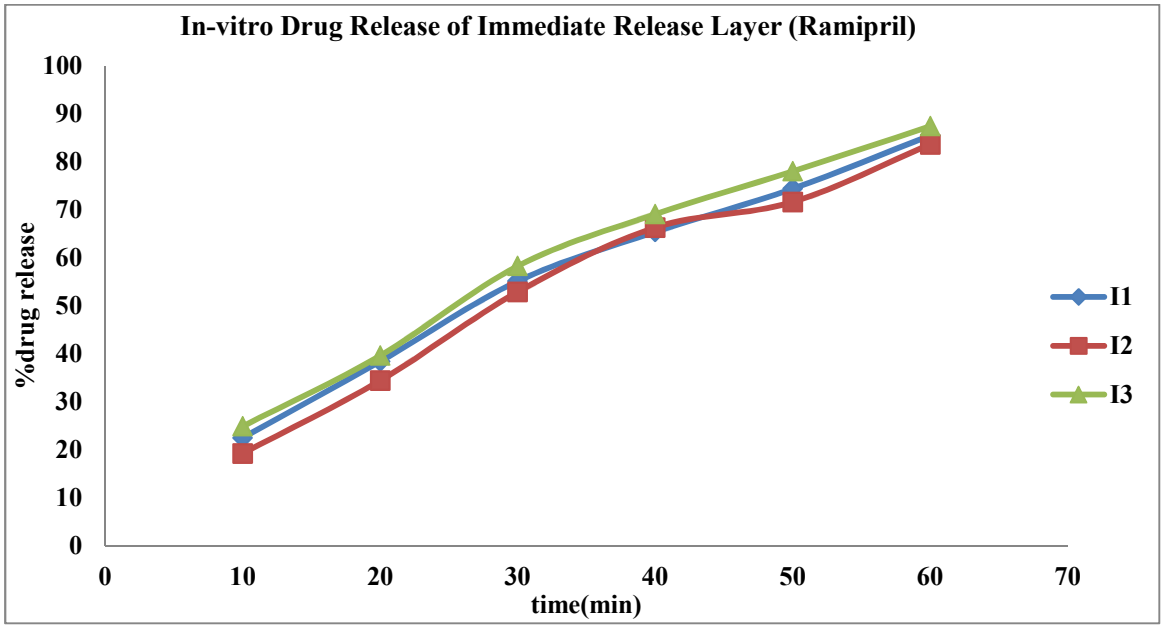

Figure 4: In-vitro Drug Release of Immediate Release Layer (Ramipril)

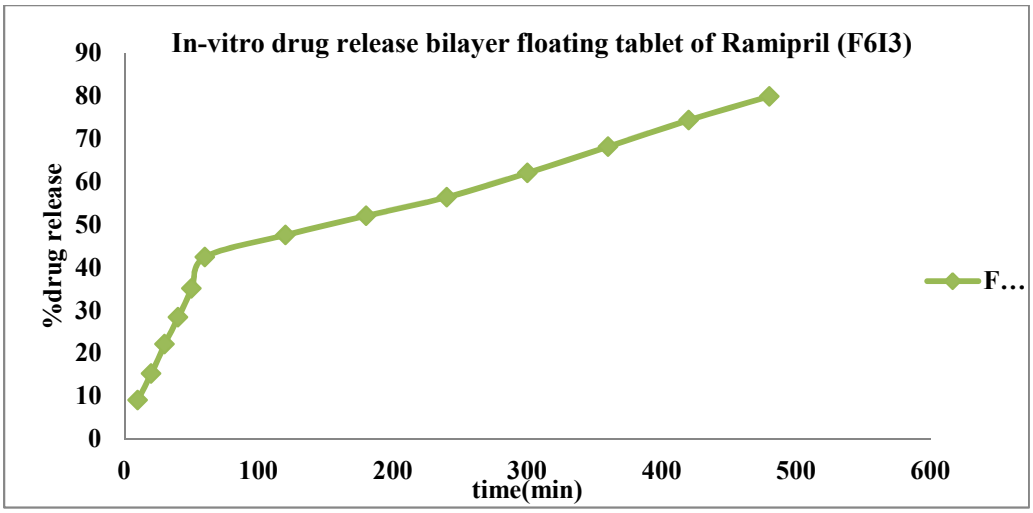

Figure 5: In-vitro drug release bilayer floating tablet of Ramipril (F6I3)

Table 10 kinetic model of bilayer tablet of ramipril

Time (Hr)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remainining	log time	log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
10	10	9.11	3.162	0.960	1.000	1.000	10	2.089	2.553
20	20	15.33	4.472	1.186	1.301	1.301	10	2.484	2.158
30	30	22.15	5.477	1.345	1.477	1.477	10	2.808	1.834
40	40	28.41	6.325	1.453	1.602	1.602	10	3.051	1.591
50	50	35.12	7.071	1.546	1.699	1.699	10	3.275	1.367
60	60	42.5	7.746	1.628	1.778	1.778	10	3.490	1.152
120	120	47.6	10.954	1.678	2.079	2.079	60	3.624	1.018
180	180	52.1	13.416	1.717	2.255	2.255	60	3.735	0.907
240	240	56.42	15.492	1.751	2.380	2.380	60	3.835	0.807
300	300	62.11	17.321	1.793	1.000	2.477	60	3.960	0.682
360	360	68.21	18.974	1.834	2.556	2.556	60	4.086	0.556
420	420	74.4	20.494	1.872	2.623	2.623	60	4.206	0.436
480	480	79.97	21.909	1.903	2.681	2.681	60	4.308	0.334

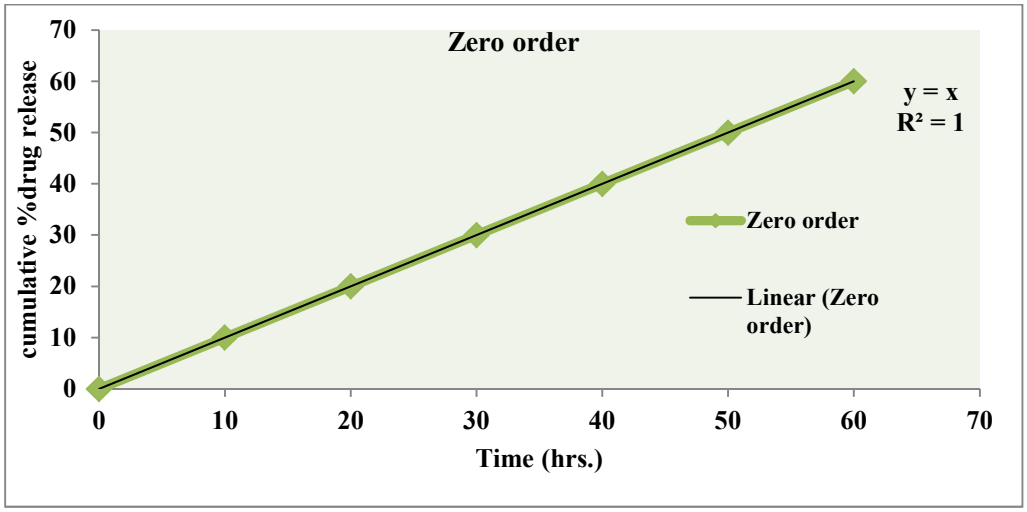

Figure 7: Kinetic model of bilayer tablet of ramipril

4. CONCLUSION

The present study was carried out to formulation development floating matrix Bilayered tablets of Ramipril Immediate release layer by wet granulation method and hydrophilic polymers for floating matrix release layer by direct compression method. It can be concluded that the optimized batches F6 and I3 by taking biphasic drug release pattern in a single unit dosage form could improve patient compliance and give better management of hypertension.

5. ACKNOWLEDGMENT:

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