Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 9[7] June 2020 : 74-85

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD
Global Impact Factor 0.876
Universal Impact Factor 0.9804
NAAS Rating 4.95

ORIGINAL ARTICLE **OPEN ACCESS**

Formulation and Evaluation of Bilayer Tablet of Combination of Verapamil Hydrochloride and Ramipril for the Treatment of Hypertension by using Hydrophilic polymer

S.T. Tambe*, P.B. Dangat, S.M. Dhobale, S. L. Jadhav, D.D. Gaikwad
VJSM's Vishal Institute of Pharmaceutical Education and Research Ale, Tal – Junnar Dist-Pune (412411)
E-mail: dangatpranali5@gmail.com

ABSTRACT
The objective of present study is to develop a sustained release bilayer tablet of combination of verapamil hydrochloride and ramipril in the doses 50 mg and 10 mg respectively for to maintain constant levels of the drug for over 12 hrs. The both drugs possess antihypertensive effect; this combination is useful for severe cardiovascular disease such as angina pectoris, hypertension or conjective heart failure, heart attack, strokes, kidney problems. This bilayer tablet prepared by using superdisintigrant such as cross carmilose sodium which is for immediate release of ramipril and carbapol, xanthum gum , HPMC ,for sustained release layer of verapamil . All the formulations were possess preformulation parameters like solubility, compatibility (FTIR)study , melting point , precompression parameters such as angle of repose, bulk density, tapped density hausner's ratio and post compression parameters such as drug contained , friability, thickness, diameter were found to be within limits. In vitro studies of all formulated tablets were performed in acid buffer pH 1.2 for 30 min and phosphate buffer pH 6.8 for the remaining 12 hrs. The dissolution data were subjected to various release kinetic model to recognize the mechanism of drug release. The optimized formulation based on all the parameter R3 (cross carmellose sodium) is selected for immediate release layer and V3 (carbapol and HPMC) was selected for controlled release layer so it can be concluded that tablets were particularly suitable for sustained release action.
KEYWORDS: *Verapamil HCl, Ramipril, Bilayer, Sustained release, Hydrophilic Polymer.*

Received 18.03.2020 Revised 09.05.2020 Accepted 19.06.2020

INTRODUCTION

Oral rout is the most frequently used route of drug administration and is the most convenient. Although solid-dose forms such as tablets and capsules have a high degree of drug stability in body and provide accurate dosage. Bilayer tablet is appropriate oral dosage form for continuous release of two drugs in which one layer is immediate release and second layer is controlled release, the aim is to maintain plasma drug concentrations for extended periods of effective concentration. Verapamil is a calcium channel blocker [3]. Verapamil is used to treat hypertension, angina , and certain heart rhythm disorders. Verapamil inhibits the Trans membrane influx of extracellular calcium ions which causing dilatation of the main coronary and systemic arteries and decreasing myocardial contractility and help to reduce the hypertension. More than 90% of verapamil is absorbed when given orally, but due to high first-pass metabolism, bioavailability is much lower (10–35%).The half-life of verapamil is 2.8-7.4 hours. second drug is ramipril. Ramipril is an ACE inhibitor and it's used to treat or congestive heart failure, and to improve survival after a heart attack. Ramipril prevent conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. Ramipril reduced formation of angiotensin II decreases peripheral arterial resistance and, in turn, decreases aldosterone secretion, reduces sodium and water retention, and lowers blood pressure. Ramipril also has antihypertensive activity in patients with low-renin hypertension [1-2]. The half-life of ramipril is 13 to 17 hrs. The combination therapy of verapamil and ramipril may be useful in cardiovascular disease such as angina pectoris, hypertension or conjective heart failure, heart attack, strokes, kidney problems [4]. The combination therapy of both drug produce desire therapeutic effect for prolong period of time and thus dose fluctuation and missing dose chances are reduced.

MATERIAL AND METHOD (5-6)

Materials

Verapamil HCL and ramipril was obtained gifted sample from Flamingo pharmaceutical, HPMCK100M, Cross Carmellose sodium,Carbapol, Talc (Thermosil fine chem),sodium saccharin (research Lab) lactose,(sahyadri scientific supply) magnesium stearate (Hilab chemicals) were sample is analytical grade.

Table 1: Formulation of Sustained Release Tablets

Sr. No	Ingredients	V1	V2	V3	V4	V5	V6
1	Verapamil HCL	50	50	50	50	50	50
2	Carbapol	80	70	60	80	70	60
3	Xanthum gum	-	-	-	40	60	80
4	Hpmc k100M	40	60	80	-	-	-
5	Talc	6	6	6	6	6	6
6	Mag. Stearate	2	2	2	2	2	2
7	Lactose	72	62	52	72	62	52

Average weight of each tablet is 250 mg

Table 2: Formulation of Immediate Release Tablets

Sr. No	Ingredients	R1	R2	R3
1	Ramipril	10	10	10
2	Crosscarmellose sodium	5	10	15
3	Starch	7.5	12.5	14.5
4	Lactose	84	85.5	88.5
5	Talc	35.5	25.5	15.5
6	Aerosil	1.5	1.5	1.5
7	Na. Saccharin	5	5	5
8	Colour	q.s	q.s	q.s
9	Ethanol	q.s	q.s	q.s

Average weight of each tablet is 150 mg

Preparation of bi-layer tablet:

Formulation of bilayer tablet was prepared by direct compression method. Immediate release layer was prepared by using wet granulation method. First weighed all ingredients accurately, then Ramipril, crosscarmellose sodium (superdisintigrant),lactose and other ingredients shifted sieve of mesh size 30, then the bulk of above mixture was granulated with the binder solution of starch and ethanol. Then passed the wet mass through mesh size 16 and dried the wet granules in oven at 60-65ºC. After that passed the dried granules through were passed through mesh size 22 and then 40. Then granules were mixed with the aerosil and magnesium state.

Sustained release layer was also prepared by direct compression, drug and polymer (HPMCk100M, carbapol, xanthum gum) were pass through the 40# sieve , Other excipients were mixed well and finally added Magnesium Stearate in above blend and were mixed for 2 min [7]. Finally above blends were compressed by rotary tablet compression machine (Make-Create Industries, Model-Lp-8gmp).

EVALUATION PARAMETERS (8-13)

Preformulation Study:

Melting point

In determining the melting point range of the verapamil and ramipril, a capillary tube (sealed at one end) was one-third-filled with the dried respective drug. The capillary tube and a thermometer were immersed in an oil bath. The temperature at which the solid started to melt and the temperature when the entire sample was completely liquefied this point called melting point of that sample.

Determination of solubility:

Qualitative Solubility

Qualitative solubility analysis of drugs were done by dissolving 5 mg of drug in 5 ml solvent such as distilled water, methanol, ethanol, chloroform, phosphate buffer(7.4),ether.

Identification test by U.V vis. Spectrophotometer:

For Verapamil HCl:

25mg of pure drug was accurately weighed and transferred to well cleaned and dried 25ml volumetric flask. To this 25ml of methanol was added and agitated well until the drug dissolves completely. Then 10 ml withdraw from stock solution and make up the volume up to 100 ml by using water. Further dilutions were made with this stock solution and scanned in the range of 400-200 nm using respective blank in UV spectrophotometer.

For Ramipril:
25mg of pure drug was accurately weighed and transferred to well cleaned and dried 25ml volumetric flask. To this 25ml of methanol was added and agitated well until the drug dissolves completely. This was considered as stock solution (1000 mcg/ml).Then 10 ml withdraw from stock solution and make up the volume up to 100 ml by using water. Further dilutions were made with this stock solution and scanned in the range of 400-200 nm using respective blank in UV spectrophotometer.

Compatibility study (FT-IR spectroscopy)
The compatibility study was done by using FT-IR spectroscopy tech. The Ramipril pellets were with all the formulation combinations were subjected to FTIR comparative studies along with potassium bromide was used for FTIR (Fourier Transform Infra-Red) studies. The I.R spectra were recorded using I.R spectra photometer (Perkin-Elmer FTIR, Perkin Elmer, and USA). The sample kbr pellet was prepared by using ratio 1:100 i.e. 1mg sample: 100mg KBr are compressed to form transparent pellets. The sample was scanned from 4000 to 400 cm^{-1} at ambient temperature.

Pre-compression Evaluation

Bulk density
The bulk density of a powder is the ratio of the mass of an untapped powder of drug sample and bulk volume. The bulk density is expressed in grams per mL (g/mL) and the bulk density was calculated by using formula.

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

Tapped density
The tapped density is obtained by tapping a graduated measuring cylinder containing the powder sample. The cylinder tapped up to 100 times and then measures the tapped volume and calculates the tapped density by using formula.

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

Hausner's ratio:
The Hausner ratio is a number that is correlated to the flow ability of a powder or granular material of that sample or drug. The Hausner ratio is calculated by the formula

Hausner's ratio = tapped density / bulk density.

Compressibility index:
Compressibility index was calculated by formula,

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

Angle of repose:
Angle of repose is defined as the maximum angle viable between the surface of a pile of the powder and horizontal aircraft. The frictional pressure in an unfastened powder or granules can be measured by using angle of repose.

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

Post compression evaluation:

Friability:
Twenty tablets have been initially weighed and transferred into friabilator. The friabilator run as much as 100 revolutions. The tablets were weighed again. The percentage friability was then calculated by

F = Initial weight – Final Weight/ Initial weight X 100

Hardness:
The hardness of the tablet was measured by using of Monsanto Hardness tester. It's far expressed in Kg/cm2.

Thickness and diameter
The thickness and diameter were measured to determine the uniformity of size and shape. Thickness and diameter of the tablets was measured using Vernier calliper.

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

Content Uniformity:

For verapamil HCl:
Five tablets were weighed and crushed in a motor with pestle. The crushed powder equivalent to 50mg of verapamil was weighed accurately and transferred to a clean, dried 100ml volumetric flask. 100 ml of 0.1N HCl was added and agitated vigorously for 10 minutes and sonicated for 30 minutes. The final sample was filtered through 0.45µm whatmann filter paper. 1 ml of the filtered sample was pipetted out and transferred to a 10ml volumetric flask and the volume was made up to 10ml with 0.1N HCl and the flask was shaking for 5 minutes. The sample was then analysed for the drug content at 278 nm using UV Spectrophotometer.

For Ramipril:
Five tablets were weighed and crushed in a motor with pestle. The crushed powder equivalent to 50mg of ramipril was weighed accurately and transferred to a clean, dried 100ml volumetric flask. 100 ml of 0.1N HCl was added and agitated vigorously for 10 minutes and sonicated for 30 minutes. The final sample was filtered through 0.45µm whatmann filter paper. 1 ml of the filtered sample was pipetted out and transferred to a 10ml volumetric flask and the volume was made up to 10ml with 0.1N HCl and the flask was shaking for 5 minutes. The sample was then analysed for the drug content at 210 nm using UV Spectrophotometer.

***In vitro* Drug Dissolution Studies:**

***In vitro* drug release was study for immediate release tablet (Ramipril)**

In vitro dissolution studies were carried out according to the USP paddle method. The dissolution medium was 900 mL of 0.1N HCl (pH 1.2), at 37.0 + 0.5 °C for 30min and a stirring speed of 50 rpm was used. 5 ml of the sample was withdrawn every 5 min interval filtered and again 5ml sample fluid was replaced. Then the samples were suitably diluted and analyzed by UV- Visible Spectrophotometer using appropriate blank solution for every sample at a wavelength of about 210 nm.

***In vitro* drug release was study for sustained release tablet (verapamil HCL)**

In vitro dissolution studies were carried out according to the USP paddle method. The dissolution medium was 900 mL of pH 6.8 phosphate buffer, at 37.0 + 0.5 ° 12 hrs.And a stirring speed of 50 rpm was used. 5 ml of the sample was withdrawn with specific time then filtered and again 5ml sample fluid was replaced. Then the samples were suitably diluted and analyzed by UV- Visible Spectrophotometer using appropriate blank solution for every sample at a wavelength of about 278 nm.

***In vitro* drug release was study for bilayer tablet:**

The release of bilayer tablets was determined using USP Type II (Paddle) dissolution apparatus under sink condition. The dissolution medium was 900 ml of a 0.1N HCl solution (pH=1.2), at 37^0c±0.2^0c for 30 min. Then dissolution media replace by phosphate buffer (6.8pH). The stirring speed was 50 rpm. The solution was collected at specific interval and maintained sink condition. The verapamil HCL and Ramipril were analysed spectrophotometrically at 278 nm and 210 nm respectively using simultaneous equation method.

Kinetic Release Models:

This kinetic model describes in-vitro drug release rate of pharmaceutical dosage forms, Zero order kinetics refers that the constant drug release from a drug delivery device.

The first order kinetic describes the release rate of drug is concentration dependent. Higuchi model is based on Fickian diffusion and it describes the release of drugs from matrix as a square root of time dependent. Korsmeyer - Peppas Model describe drug release from a polymeric system.

RESULT AND DISCUSSION

Pre-formulation studies:

UV Spectroscopy

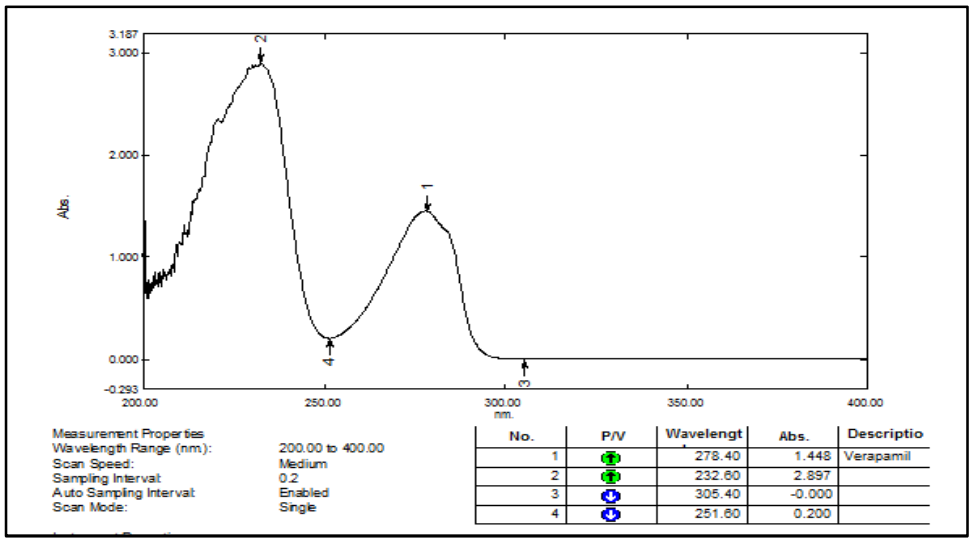


Figure 1: Lambda max of verapamil

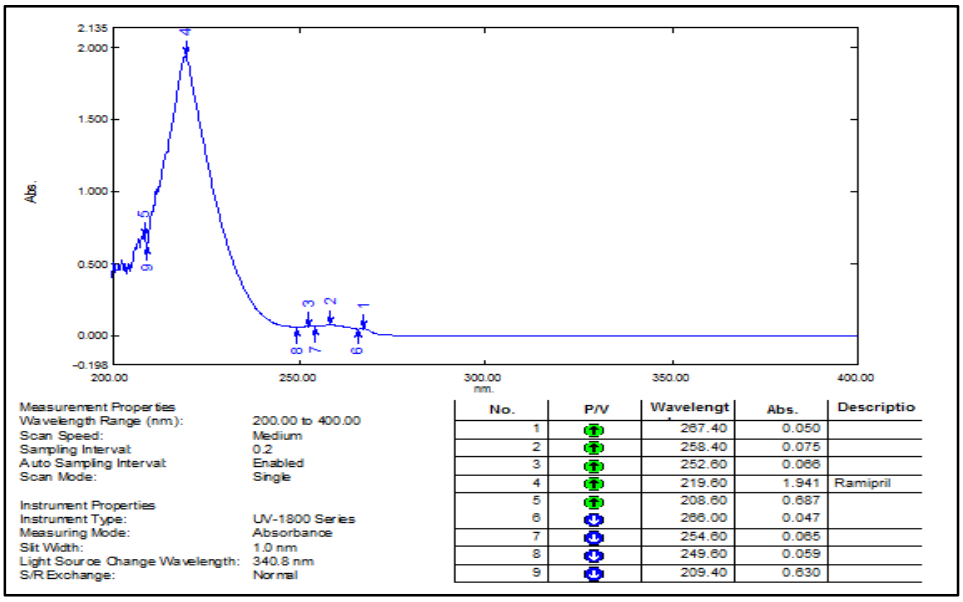


Figure 2: Lambda max of Ramipril

Chemical compatibility

Compatibility study of drug with polymer

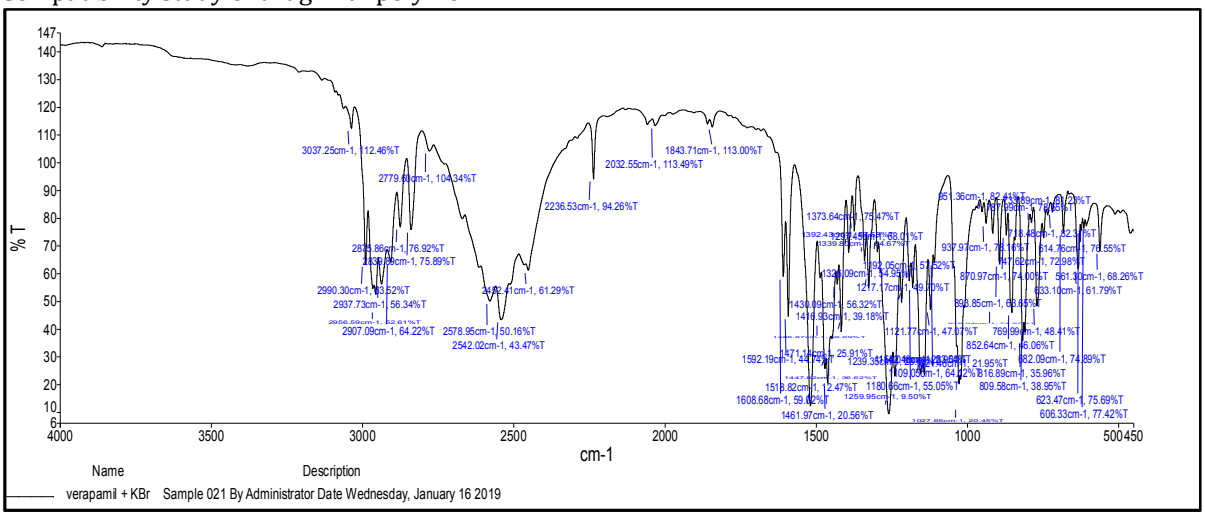


Figure 3: FT-IR spectrum of Verapamil hydrochloride

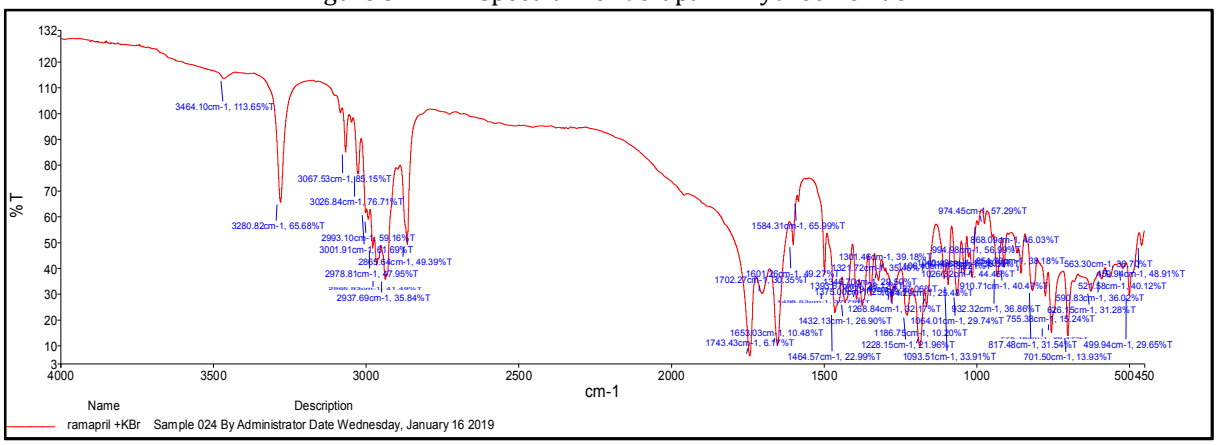


Figure 4: FT-IR spectrum of Ramipril

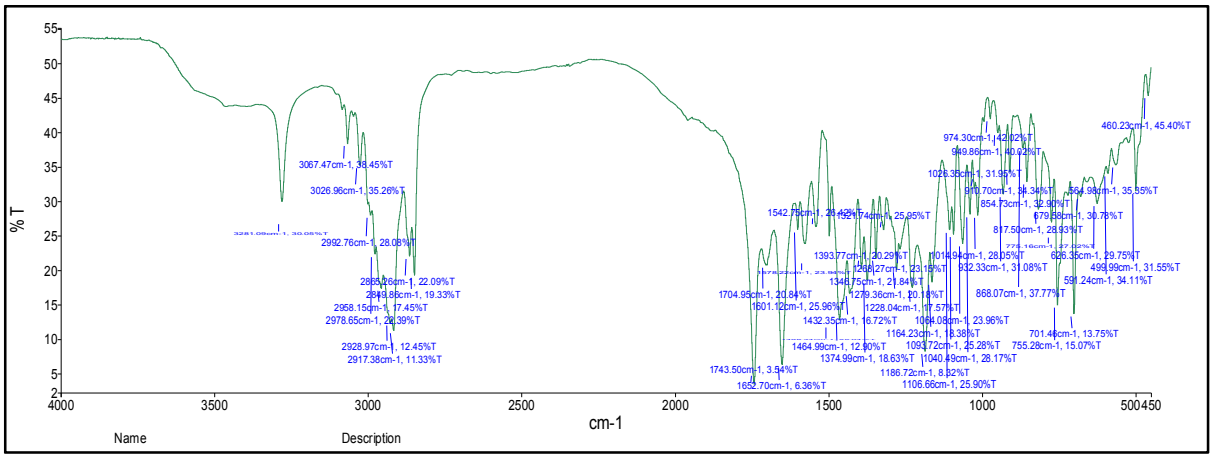


Figure 5: FT-IR spectrum of Verapamil HCL powder blend

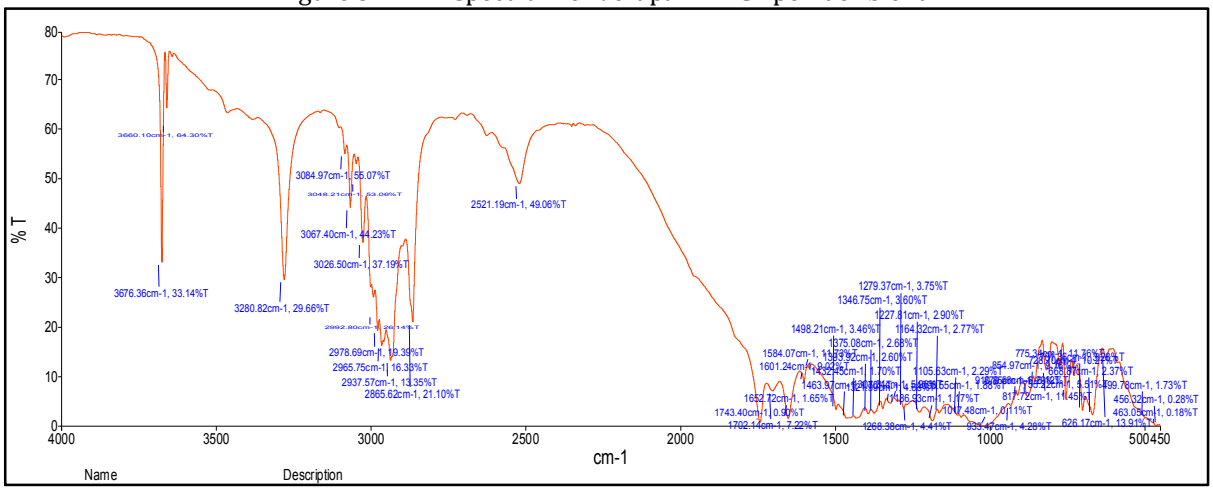


Figure 6: FT-IR spectrum of Ramipril powder blend

Melting point, solubility and compatibility study of both drugs are carried out and result is including in table 3.

Table No 3: Preformulation study of verapamil HCL and Ramipril

Sr. No	Parameters	Observations	
		Verapamil	Ramipril
1	Identification by U.V Vis Spectrophotometer	278 nm	219 nm
2	Melting point	245^{0}c	110^{0}c
3	Solubility	Soluble in ethanol, methanol. Sparingly soluble in chloroform, acetone.	Soluble in methanol.
4	Compatibility study (FTIR)	Compatible	Compatible

Pre-compression Evaluation:

Pre-compression Parameters such as angle of repose, bulk density (i.e. Lose bulk density, tapped bulk density), compressible- It index, and Hausner's ratio. Results showed that all Parameters were within limits. Hausner's ratio ⬍1.25 For both optimized batches indicated good flow prop- erties.

All the formulations of Verapamil and Ramipril were evaluated for various micromeritics properties. The Compressibility Index values of all the formulations were found to be less than 30. The angle of repose was found to be in between 27.0 to 30.0^0. These values indicate that the granules possess good flow properties. The results are tabulated in Table 4 and 5.

Pre-compression Parameters such as angle of repose, bulk density (i.e. Lose bulk density, tapped bulk density), compressible- It index, and Hausner's ratio. Results showed that all Parameters were within limits. Hausner's ratio ⬍1.25 for both optimized batches indicated good flow properties. pre-compression parameters such as angle of repose, bulk density (i.e.,

lose bulk density, tapped bulk density), compressibility index, and Hausner's ratio. Results showed that all
parameters were within limits. Hausner's ratio ⬍1.25 for both optimized batches indicated good flow properties.

Table no 4: pre-compression evaluation of sustained release powder blend (verapamil)

sr.no	Parameters	V1	V2	V3	V4	V5	V6
1	Bulk density (g/ml)	0.42	0.388	0.406	0.408	0.421	0.388
2	Tapped density (g/ml)	0.504	0.505	0.513	0.486	0.562	0.486
3	Compressibility index (%)	16.66	23.16	20.85	16.04	25.08	20.16
4	Hausnre's ratio	1.2	1.30	1.26	1.19	1.33	1.25
5	Angle of Repose(degree)	30.11	30.02	27.54	27.92	28.54	29.68

Table no 5: pre-compression evaluation of sustained release powder blend (Ramipril)

sr. no	Parameters	R1	R2	R3
1	Bulk density (g/ml)	0.576	0.8	0.615
2	Tapped density (g/ml)	0.72	0.752	0.796
3	Compressibility index (%)	20	23.73	23.73
4	Hausnre's ratio	1.25	1.29	1.29
5	Angle of Repose(degree)	28.5	26.68	28.02

Post-compression Evaluation:

Different formulation codes of Verapamil and Ramipril were subjected to various evaluation tests, such as thickness, hardness, friability, and uniformity of drug content. The results of these parameters are given in Table 7 and 8. All the formulations showed uniform thickness (3 mm), uniform weight. In the weight variation test, the USP pharmacopoeial limit for the percentage deviation for tablets of 130 mg to 324 mg is 7.5% difference and all formulations found to be within the limit as per official requirements. The hardness of the tablets (n = 10) ranged from 5 to 5.2 kg/cm2. The percentage friability of the tablets (n = 10) ranged from 0.23 to 0.65. The percentage friability for all the tablet formulations (Verapamil and Ramipril) were below 1%.Drug content was found to be uniform among different batches of the tablets (n = 20) and verapamil ranged from 95.34% to98.04% and Ramipril ranged from 91.41% to 98.34 %.Test value isincluding in table no 6 and 7.

Table No 6: post-compression parameters of Verapamil HCL sustained release layer tablets

S. N	Parameters	V1	V2	V3	V4	V5	V6
1	Hardness $(Kg/cm)^2$	5	5.2	5	5.2	5	5
2	Thickness (mm)	3.00	3.00	3.00	3.00	3.00	3.00
4	Uniformity of weight (mg)	247.13	246.02	249.34	248.62	249.92	248.33
5	Friability (%)	0.40	0.36	0.28	0.65	0.33	0.23
6	% Drug content	95.34	96.45	98.04	97.5	97.28	96.08

Table No 7: post-compression parameters of Ramipril immedeate release layer tablets

SR. No	Parameters	R1	R2	R3
1	Hardness $(Kg/cm)^2$	5.1	5	5.2
2	Thickness (mm)	3	3	3
4	Uniformity of weight (mg)	149.3	149.5	149.1
5	Friability (%)	0.33	0.40	0.60
6	% Drug content	91.41	98.34	93.81

***In-vitro* Release study of sustained release of Verapamil Hydrochloride**

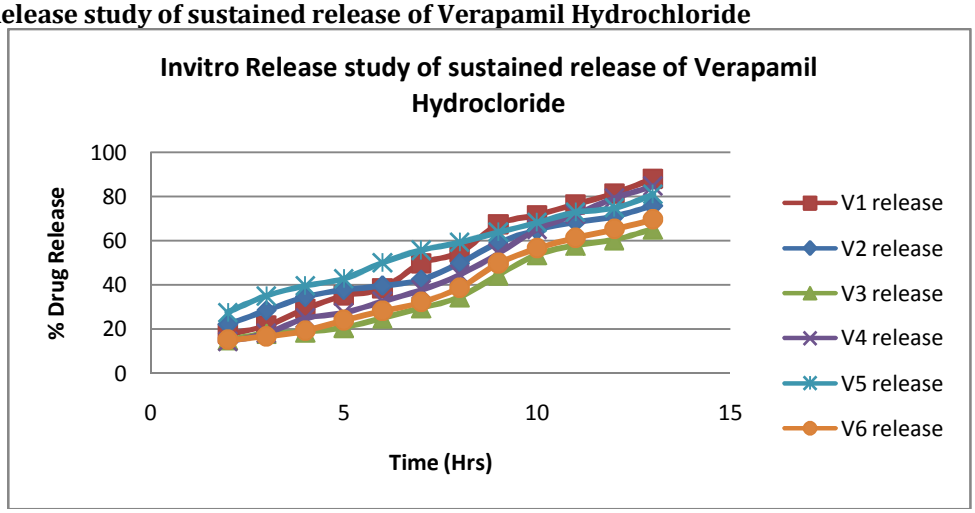


Fig 7: In-vitro dissolution of sustained release layer Verapamil HCl

Figure 7 shows the *In vitro* drug release profile of sustained release tablets containing Verapamil hydrochloride. The rate of drug release from the tablet formulations V1 was highest. Tablets are containing a high concentration of Xanthum gum and HPMC 100M (formulation V6 and V3) exhibited slow release of Verapamil HCl as compared to other formulation. Formulation V3 showed 65.03% and V6 shows 69.62% of the drug release in 12 h whereas other Formulation V1, V2, V4 and V5, showed 87.96%, 75.73%, 84.56% and 80.83% of the drug release respectively in 12 h. When compared with other formulations like V1, V2, V4 and V5, formulation V6 and V3 contained more amounts of Xanthum gum and HPMC which acted as a release retardant. Verapamil formulation containing HPMC 100M alone (V3) shows 65.03% drug release because it exhibited higher water absorption capacity then it swell and form gel outside of the cores. This gel forms a diffusion barrier around the tablet core that's why diffusion path length of drug molecule increases hence reduced drug release from the tablet. From that above data formulation V3 was optimized batch for bilayer tablet as it reflects good release retardant characters.

***In-vitro* Release study of Immediate release Ramipril**

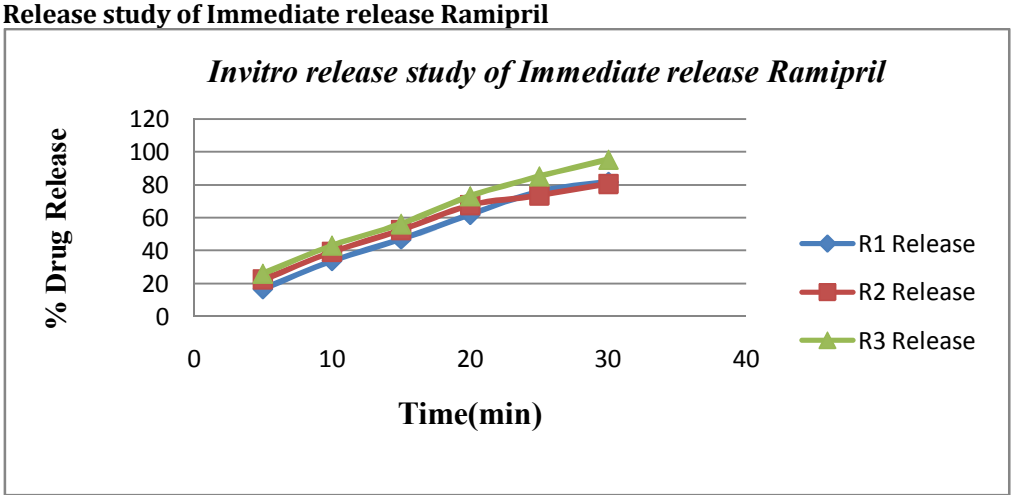


Fig 8: In-vitro dissolution of immediate release layer of Ramipril

Drug Release The release profile of Ramipril from different batches of formulated tablets was represented in Figure 8. In-vitro dissolution testing of all the immediate release layer batches showed the drug release within 20-30 minutes. But the formulation R3 shown maximum amount of drug release i.e. 95.37±0.95 % within 30 minutes in an immediate release manner. Hence it was considered as the R3 is the best batch to get incorporated in bilayer tablet formulation. From the results of in-vitro drug release it was also found that as the concentration of Crosscarmilose sodium was increasing from 5 % to 15 % the release rate of Ramipril was also increased. This is due to the reason that increased concentration of Super-disintigrant lead to decreased disintegration time and thus increased release of Ramipril.

Kinetic Data Analysis:

Table no 8: Kinetic release for SR

Formulation Code	Zero Order R^2	First Order R^2	Higuchi R^2	Korsmeyer n
V1	0.9845	0.9056	0.9465	0.7234
V2	0.9831	0.8954	0.9645	0.7023
V3	0.9962	0.8823	0.9867	0.5123
V4	0.9734	0.9197	0.9634	0.6742
V5	0.9835	0.8936	0.9467	0.6538
V6	0.9867	0.8990	0.9612	0.6845

The *In vitro* release kinetic of sustained release formulation was processed as shown in Table 8.The formulations showed correlation coefficient values (r^2) between 0.9734-0.9962. For zero-order kinetics. Drug release from formulation V3 followed Higuchi model ($r^2$0.9867) and Peppa's model indicates that drug release mechanism was non-fickian (n=0.5123). This reveals that the drug release depends on swelling and diffusion. For remaining formulations, the goodness of best fit were evaluated by regression analysis of the said models.

Table no 9: Kinetic release for IR

Formulation Code	Zero Order R^2	First Order R^2	Higuchi R^2	Korsmeyer n
R1	0.8967	0.9742	0.9464	0.8657
R2	0.8885	0.9934	0.9548	0.8564
R3	0.9366	0.9703	0.9230	0.9586

The values of correlation coefficient (r^2) from different models for the prepared tablets are given in table 9. From the data of correlation coefficient, the drug release from all the formulations, was found to obey the first order release kinetic followed by the Korsmeyer Peppas kinetic model. The formulation R3shows the values of 'n' is more than 0.89 this shown that super case II transport release kinetic.

Post-Compression Study of Bilayer Tablets:

Table No 10: post compression study of bilayer tablets contains verapamil HCL V3 and Ramipril R3 Batch.

Parameters		Bilayer tablets
Uniformity of weight (mg)		397.5
Thickness (mm)		0.2
Hardness (Kg/cm^2)		6.1
Friability (%)		0.15
% drug content	Verapamil	98%
	Ramipril	99%

Table no 11: *in-vitro* dissolution bi-layered tablet Verapamil HCL (V3)and Ramipril (R2)

time (min)	% drug release Ramipril	% release Verapamil HCL
5	28.3	-
10	45.89	-
15	62.99	-
20	76.94	-
25	81.25	-
30	93.67	-
60	-	14.94
120	-	19.69
180	-	25.30
240	-	32.09
300	-	41.09
360	-	49.75
420	-	55.86
480	-	60.9
540	-	68.63
600	-	74.71
660	-	79.81
720	-	89.15

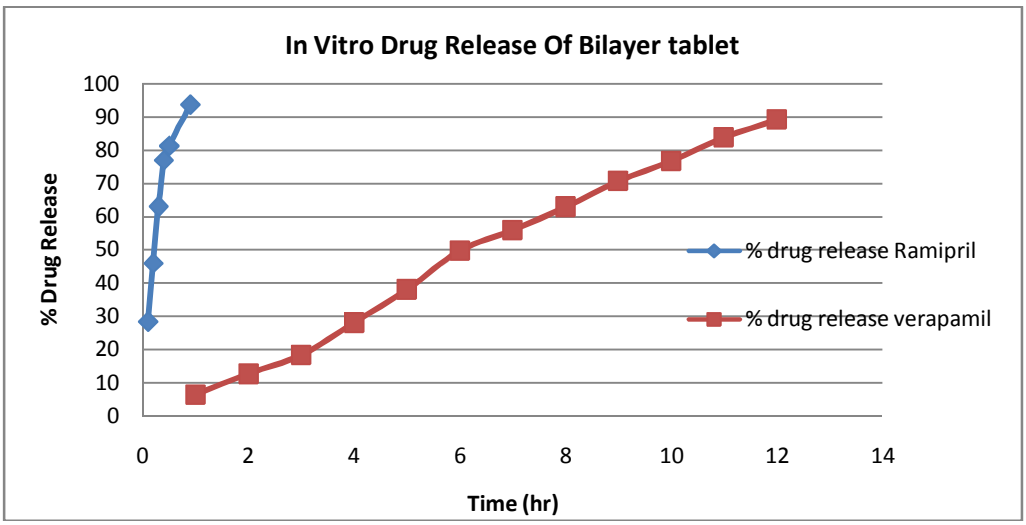
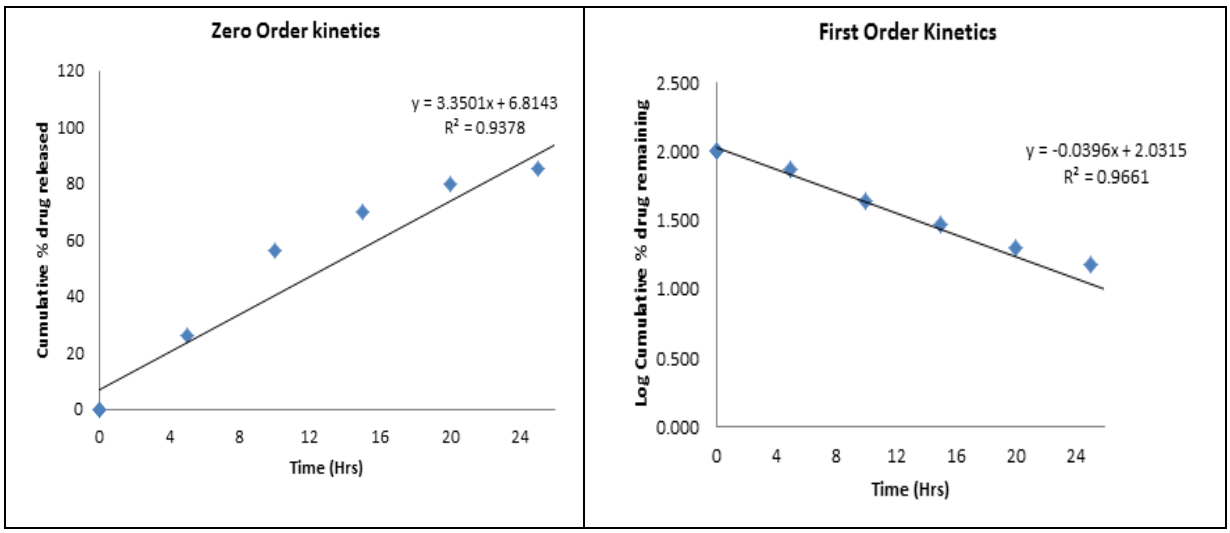


Fig 9: In-vitro dissolution of Bilayer Tablet

The prepared bilayer tablets were evaluated for post-compression parameters and results were found to be within the satisfactory limits mentioned in the above table no 10.The release profile of bilayer tablet formulation of Verapamil HCL and Ramipril was represented in Figure 9. The optimized immediate release layer (R3) of Ramipril and optimized sustained release layer (V3) of Verapamil HCl was combined to obtain a bilayer tablet formulation. The IR layer released 93.67±0.37 % of Ramipril at the end of 30 minutes whereas the SR layer released 89.15±0.88 % of Verapamil HCl at the end of 12 hours. This reveals that both the IRL and SRL layers were released in immediate and sustained release manner.

Kinetic Data Analysis of Bilayer Tablet:



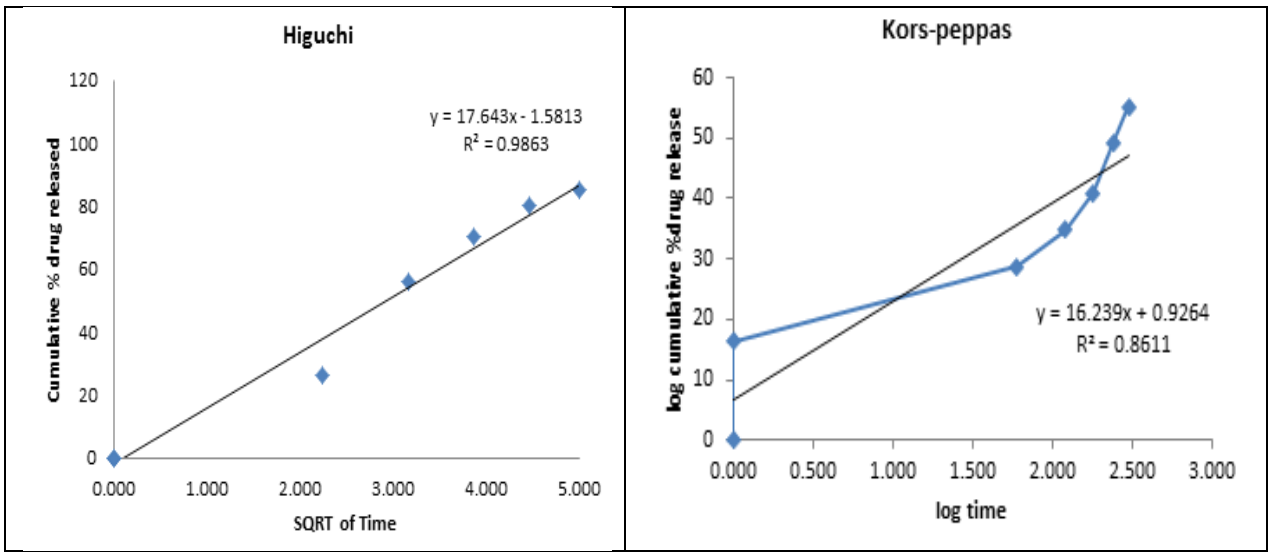


Figure 10: Drug release kinetics of Ramipril (immediate release) layer in bilayer tablet.

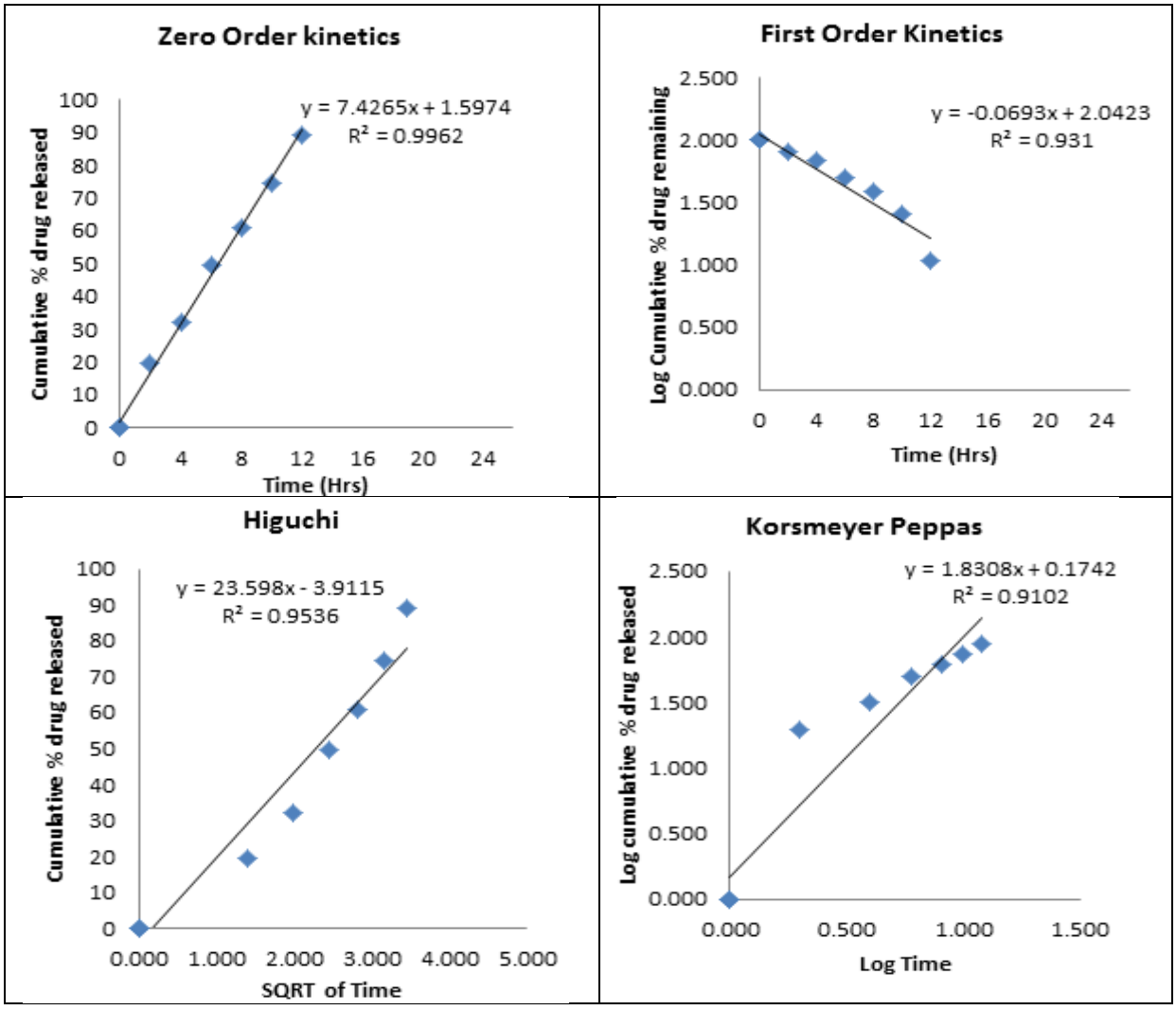


Figure 11: Drug release kinetics of Verapamil HCl (sustain release) layer in bilayer tablet.

The drug release kinetic data of Immediate release layer is best fit in to First order kinetic which had shown a regression coefficient (r^2) of 0.9661.The results of the *In vitro* release data of this layer were fitted to the Korsemeyer-Peppas and the value of "*n*" was found to be more than 0.92, indicating the drug

release follows super case-II transport. The drug release kinetic data of sustained release layer is best fit in to zero order kinetics (r^2 is 0.9962)and higuchi model (r^2 is 0.9535).

CONCLUSION

The present study reveals the successful formulation and evaluation of antihypertensive in a single dosage form as bilayer tablet. In the bilayer tablet, immediate release layer of Ramipril was prepared by wet granulation method using various super disintegrating which optimized formula (R3) contains CrosCarmellose Sodium as super disintigrant and sustain release layer of Verapamil was prepared by direct compression method using different release retarding agents in which optimized formula (V3) contains combination of HPMCK100M and Xanthan gum as release retardants. The drug excipient compatibility studies carried out using FTIR demonstrated that there was no interaction found between drugs and excipients. All the formulations post-compression studies revealed that the results were found to be within the official limits. *In vitro* release studies reveal that Ramipril immediate release layer in bilayer tablet was found to be 93.67% within 30 minutes and Verapamil HCl sustained release layer was 89.15% at the end of 12 hrs. Release kinetics showed good linearity by best fitting in to Higuchi and first order model for IR layer and zero order kinetics and higuchi for SR layer. From the above study, it can be revealed that the prepared bilayer tablets achieve the objective of the research work in treating the hypertension with the sequential release of two drugs.

ACKNOWLEDGEMENT

Authors are thankful to Flamingo pharmaceuticals and Vishal Institute Pharmaceutical Education and Research, Ale for providing the raw materials to carry out this research work successfully.

REFERENCES:

1. Verma R, Devre K, and Gangrade T, (2014). Bi-layer tablets for various drugs: A Review, Scholars Academic Journal of Pharmacy (SAJP), 2014; 3(3): 271-279.
2. https://www.drugbank.ca/drugs/DB00661
3. https://pubchem.ncbi.nlm.nih.gov/compound/ramipril#section=Metabolism-Metabolites
4. Vivek V, Deattu N, Elango K , Dhanalakshmi K , (2015). Formulation and Evaluation of Sustained Release Bilayer Tablets of Verapamil Hydrochloride and Enalapril Maleate, International Journal of Science and Research (IJSR),Value; 6(5) 78.96.
5. Varma KV, (2016). Excipients used in the formulation of tablet. Researchand Reviews Journal of Chemistry, 5(2):143-154.
6. RajawatJ,Ranawat M and Kamble RK, (2015). Formulation and development of Atorvastatin Calcium and Ramipril bilayer tablet,Journal of Chemical and Pharmaceutical Research, 7(2): 979-989.
7. Tambe ST,PadekarHB, Dhobale SM, Dr. Jadhav SL, (2019). Design and Characterisation of Bi-layer Tablets Containing Simvastatin as Sustained Release and Labetalol HCl as Immediate Release, Journal of Drug Delivery and Therapeutics , 9(2):263-270.
8. Kumar SU,Ramu B, Srikanth G, Bigala R, (2016). Formulation and Evaluation of Sustained Release Verapamil Hydrochloride Using Natural Polymers, International Journal of Applied Pharmaceutical Sciences and Research,; 1(2):76-87.
9. Gurdeep R Chatwal and Sham K Anand. (2011). Instrumental methods of Chemical Analysis, 3rded, Himalaya Publishing House, Mumbai. Page no 244.
10. Indian Pharmacopoeia (2010), Govt. of India, Ministry of Health and Family Welfare. Delhi: Indian Pharmacopoeial commission, Ghaziabad, Page no3, 2186,88.
11. Amrutha JV, (2016). Pre and Post Compression Studies of Tablets, Inorganic Chemistry: An Indian Journal, 11(4):100-106.
12. United States Pharmacopoeia, (2007). 30th edition NF 25-2007, The Official Compendia of Standards. 643, Pharmacopoeial forum, 28(2), 618.
13. British Pharmacopoeia.(2009). Medicines and Healthcare products Regulatory Agency. London: The Stationery Office, I, Page no 5872, 7.

CITATION OF THIS ARTICLE

S.T. Tambe, P.B. Dangat, S.M. Dhobale, S. L. Jadhav, D.D. Gaikwad. Formulation and Evaluation of Bilayer Tablet of Combination of Verapamil Hydrochloride and Ramipril for the Treatment of Hypertension by using Hydrophilic polymer. Bull. Env. Pharmacol. Life Sci., Vol 9[7] June 2020 : 74-85