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Formulation and Evaluation of Sustained Release Bilayer Tablets of Verapamil Hydrochloride and Enalapril Maleate

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Abstract: ***The present study is aimed to develop a sustained release bilayer tablet of a combination of Verapamil hydrochloride and Enalapril maleate which possess synergistic effect in mild to moderate hypertension in the doses 240 mg and 10 mg respectively. The tablets of both the drugs were formulated by direct compression method individually using different ratios of the controlled release hydrophilic polymers such as HPMC K100 and Carbopol 934.All the tablets were subjected to post-compression evaluation parameters such as hardness, friability, weight variation, thickness and drug content and were found to be within the limits. In vitro studies of the formulated tablets were performed in acid buffer pH 1.2 for first 2 hrs and phosphate buffer pH 6.8 for the remaining hours. The optimised formulations of both the drugs (VH 1 & EM 6) which showed release upto 24 hrs were selected for compression into bilayer tablets and post compression studies were evaluated which were found to be comply with the standards. The in vitro drug release data was fitted into various kinetic models which showed that the drug release follows zero order release and the best fit release kinetics was achieved with the Korsmeyer - Peppas model.***

Keywords: Verapamil hydrochloride, Enalapril maleate, HPMC K100, Carbopol 934

1. Introduction

Hypertension or high blood pressure occurs when the high cardiac output exerts pressure on the arterial wall as the blood flow increases[1]. The present available conventional dosage form for the treatment of hypertension cannot produce the desired therapeutic effect for prolonged period of time and thus dose fluctuation and missing of dose chances are more[2].The rationale for using fixed dose combination therapy is to obtain increased blood pressure control by employing two antihypertensive drugs to enhance the compliance by using single tablet that is taken once a day. The Bilayer layer tablet system allows the incorporation of two drugs into the dosage form. Conventional dosage forms produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing, reducing the dose required and providing uniform drug delivery [3],[4].Different types of sustained release (SR) formulations have been formulated for improving clinical efficacy of active pharmaceutical ingredients (APIs) and patient compliance[5]. Hydroxy propyl methyl cellulose (HPMC) has been extensively considered for the purpose of formulating oral SR formulations. HPMC always finds preference in formulation of hydrophilic matrices due to cost effectiveness, choice of viscosity grades, non-ionic nature, robust mechanism and utilization of existing conventional equipment and methods.

The drugs used in the treatment of hypertension majorly are combination of drugs. Verapamil hydrochloride is a voltage dependent calcium antagonist which has a half-life of 4 -6 hrs and Enalapril maleate is an Angiotensin Converting Enzyme (ACE) inhibitor having an half-life of 2 – 6 hrs. The combination of these drugs possesses the additive effect in mild to moderate hypertension [6]. Hence, the drugs are compressed into bilayer tablets in the form of sustained release formulations since both the drugs have shorter half-life.

2. Literature Survey

The additive effect of the Verapamil hydrochloride and Enalapril maleate is used in the treatment of mild to moderate hypertension. There is no bilayer tablet available utilizing this additive effect. The sustained release formulations of both the drugs using the sustained release polymers HPMC K100 and Carbopol 934, is compressed into bilayer tablet in this study which greatly reduces the dosing frequency and patient compliance.

3. Materials and Methods

Materials

Verapamil hydrochloride was obtained as a gift sample from Apotex Research Pvt. Ltd., Bengaluru and Enalapril maleate was obtained as gift sample from the Hetero drugs Pvt. Ltd., Telangana. Polymers HPMC K100 and Carbopol 934 were obtained from Kniss laboratories.

Preformulation Studies [7]

The Preformulation studies were conducted to establish the physico-chemical characteristics of the drug and its compatibility with the excipients used.

Chemical compatibility study [8][9]

Pure drugs and drug-excipient mixture were subjected to FTIR to investigate the drug-excipient interactions. The IR spectra of test samples are obtained using potassium bromide pellet method.

Bulk Density (ρ_b)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder

into a measuring cylinder and initial weight was noted. This initial volume is the bulk volume. From this, the bulk density was calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$\rho_b = M / V_b$$

Where, **M** and V_b are mass of powder and bulk volume of the powder respectively.

Tapped Density (ρ_t)
It is the ratio of weight of the powder to the tapped volume of powder. The powder was introduced into a measuring cylinder with the aid of funnel and tapped for 300 times on a wooden surface at a 2 sec interval and the volume attained is the tapped volume. It is expressed in g/ml and is given by,

$$\rho_t = M / V_t$$

Where, **M** and V_t are mass and tapped volume of the powder respectively.

Carr's Index (or) % Compressibility
It indicates powder flow properties. It is measured for determining the relative importance of inter particulate interactions. It is expressed in percentage and is given by

$$CI = \frac{\rho_t - \rho_b}{\rho_t} X\ 100$$

Where, ρ_t and ρ_b are tapped density and bulk density respectively.

Hausner's ratio
Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$HR = \rho_t / \rho_b$$

Where, ρ_t and ρ_b are tapped density and bulk density respectively.

Angle of Repose (θ)
The flow properties were characterized in terms of angle of repose, Carr's index and Hausner's ratio. For determination of angle of repose (θ), the drug and the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The drug or the blends were poured till the time when the upper tip of the pile surface touched the lower tip of the funnel. Angle of repose was calculated using following equation.

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

Where, **h** = height of pile in cm; **r** = radius of pile in cm.

Formulation of Bilayer tablet

Formulation of Sustained release tablets of Verapamil hydrochloride [10]
The Sustained release tablets of Verapamil hydrochloride (V1, V2, V3 and V4) were prepared by direct compression technique, using various hydrophilic polymers such as HPMC K100 and Carbopol 934. The tablets were prepared by using 10 station tablet compression machine.

Table 1: Formulation of Sustained release tablets of Verapamil hydrochloride

Ingredients	*V1*	*V2*	*V3*	*V4*
Verapamil hydrochloride	240	240	240	240
HPMC K100	120	120	120	120
Carbopol 934	180	150	120	90
Lactose	27	57	87	117
Talc	22	22	22	22
Magnesium stearate	11	11	11	11
Total weight (mg)	600	600	600	600

Total wt. of each sustained release layer is 600 mg

Formulation of sustained release tablets of Enalapril maleate [11][12]
The sustained release tablets of Enalapril maleate were prepared by direct compression technique. Hydrophilic polymers such as HPMC K 100 and Carbopol 934 were used in different ratios from minimum to the maximum. The powder blend was compressed by 10 station tablet compression machine.

Table 2: Formulation table for sustained release Enalapril maleate tablets

Ingredients	*EM 1*	*EM 2*	*EM 3*	*EM 4*	*EM 5*	*EM 6*
Enalapril maleate	10	10	10	10	10	10
HPMC K100	20	20	20	20	50	80
Carbopol 934	30	25	20	15	30	30
Lactose	35	40	45	50	-	-
Talc	3	3	3	3	6	6
Magnesium stearate	2	2	2	2	4	4
Total weight (mg)	100	100	100	100	100	130

The optimized batch of sustained release tablets of Enalapril maleate (EM 6) was then compressed by direct compression technique with the optimized batch of sustained release Verapamil hydrochloride (VH 1) tablets to get bilayer tablets.

Post Compression Studies

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

Hardness
Hardness is defined as the force required for breaking a tablet at diametric compression test and it is termed as tablet crushing strength. Hardness of the prepared formulations were determined using Monsanto hardness tester. It is expressed in Kg/cm^2

Friability
Friability of the prepared formulations was determined by using Roche Friabilator. Pre-weighed sample of tablets was placed in the friability tester, which was then operated for 100 revolutions. Tablets were de-dusted and reweighed. The friability of the tablets was calculated using the formula mentioned below,

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} X\ 100$$

Uniformity of weight

Twenty tablets were selected at random and weighed individually. The average weight was also measured. The percentage deviation of tablets was calculated and compared with standard specifications.

Drug content estimation

Twenty tablets were selected randomly and the average weight was calculated. The tablets were then ground to a fine powder. The powder equivalent to the average weight of tablets was dissolved in 100 ml of 0.1N HCl. 10 ml of the resulting solution was diluted to 100 ml using 0.1N HCl in a separate standard flask. The absorbance of the solution was recorded at 278 nm and 207 nm. The amount of Verapamil hydrochloride and Enalapril maleate were determined by simultaneous estimation method [13][14]

***In vitro* dissolution studies [15]**

The *in vitro* drug release study of optimised bilayer tablets was done by using USP type II (Paddle) dissolution apparatus under sink condition. Stirring rate was maintained at 100 RPM and the temperature was about 37 ± 0.5ºC. The pH of the dissolution medium was kept 1.2 for first 2 hrs using 0.1 N HCl. Then KH_2PO_4 (1.7 g) and $Na_2HPO_4.2\ H_2O$ (2.2 g) were added to the dissolution medium, adjusting the pH to 6.8 with 1.0 M NaOH, release study was continued for the following hours. The samples were withdrawn at various time intervals and the same volume of fresh medium was replaced for each and every sampling. Then the samples were suitably diluted and analyzed by UV- Visible Spectrophotometer using appropriate blank solution for every sample at a maximum wavelength of about 278 nm and 207 nm respectively. The percentage drug release was determined using the simultaneous estimation method.

4. Results and Discussion

Chemical compatibility

Compatibility study of drug with polymers

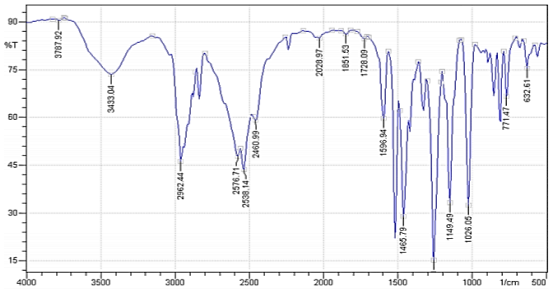

Figure 1: FT-IR spectrum of Verapamil hydrochloride

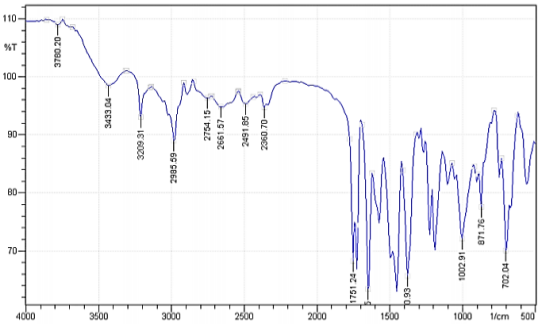

Figure 2: FT-IR spectrum of Enalapril maleate

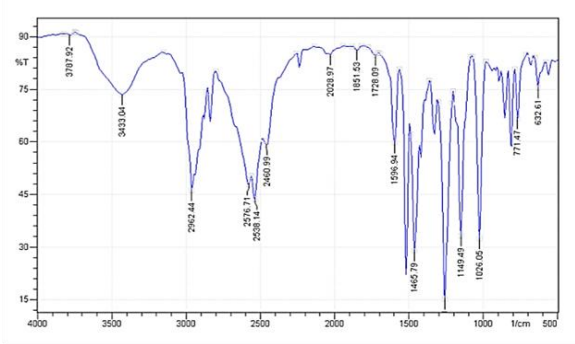

Figure 3: FT-IR spectrum of optimised Verapamil hydrochloride powder blend

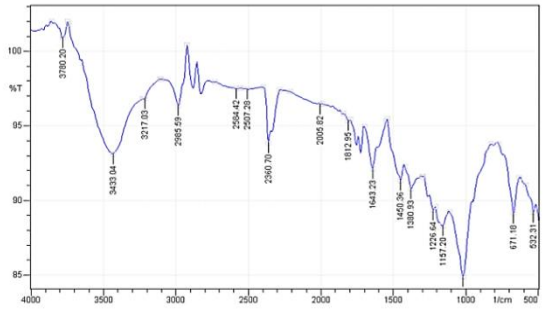

Figure 4: FT-IR spectrum of optimised Enalapril maleate powder blend

FT-IR spectra indicates that there is no interaction between the drug and the polymers.

Pre- compression studies

The powder blends of the sustained release formulations of Verapamil hydrochloride and Enalapril maleate were evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose and results are shown in the tables 3,4 5 and 6.

Table 3: Pre-compression parameters of Verapamil hydrochloride sustained release layer blends

Blends	*Bulk Density (g/ml)*	*Tapped Density (g/ml)*	*Carr's Index*	*Hausner's Ratio*
VH 1	0.303	0.384	21.06	1.27
VH 2	0.305	0.386	21.04	1.27
VH 3	0.303	0.411	26.29	1.35
VH 4	0.324	0.487	33.35	1.50

The bulk density of the SR blend of Verapamil hydrochloride (VH) ranged from 0.303 to 0.324 g/ml. The tapped density of the SR blend of Verapamil hydrochloride ranged from 0.384 to 0.487 g/ml. Hausner's Ratio ranged from 1.27 to 1.50 for the SR blend of the Verapamil hydrochloride. Compressibility Index of the SR blend of Verapamil hydrochloride ranged from 21.04 to 33.35.

Table 4: Angle of Repose of Verapamil hydrochloride sustained release layer blends

Blends	*Angle of Repose*
VH 1	39.54
VH 2	44.35
VH 3	43.01
VH 4	42.53

The angle of repose of SR blends of Verapamil hydrochloride after addition of glidant ranged from 39.54 to 44.35. The formulated VH SR blend showed fair to passable flow property.

Table 4: Pre-compression parameters of Enalapril maleate sustained release layer

Blends	*Bulk Density (g/ml)*	*Tapped Density (g/ml)*	*Carr's Index*	*Hausner's Ratio*
EM 1	0.533	0.686	22.22	1.28
EM 2	0.522	0.671	22.22	1.28
EM 3	0.534	0.687	22.22	1.28
EM 4	0.503	0.629	19.99	1.25
EM 5	0.540	0.694	22.19	1.28
EM 6	0.516	0.563	18.34	1.09

The bulk density of the SR blend of Enalapril maleate (EM) ranged from 0.503 to 0.540 g/ml. The tapped density of the SR blend of Enalapril maleate ranged from 0.563 to 0.694 g/ml. Hausner's Ratio ranged from 1.09 to 1.28 for the SR blend of Enalapril maleate. Compressibility Index of the SR blend of Enalapril maleate ranged from 18.34 to 22.22.

Table 5: Angle of Repose of Enalapril maleate sustained release layer

Blends	*Angle of Repose*
EM 1	27.27
EM 2	33.06
EM 3	34.06
EM 4	34.01
EM 5	29.08
EM 6	28.11

The angle of repose of SR blend of Enalapril maleate after addition of glidant ranged from 27.27 to 34.06. The formulated EM SR blend showed excellent to good flow property.

Post Compression Studies were carried out for the VH SR and EM SR layers. The results are furnished in tables 5, 6 and tables 7, 8 respectively.

Table 6: Post-compression parameters of Verapamil hydrochloride sustained release layer tablets

Formulation	*Hardness (Kg/Cm^2)*	*Friability (%)*	*% Drug content*
VH 1	9.25	0.25	101.74
VH 2	9.25	0.25	96.44
VH 3	9.08	0.34	96.67
VH 4	9.08	0.28	103.38

The thickness and diameter of the Verapamil hydrochloride tablets were found in the range of 3.92 to 4.0 mm and 13 mm respectively. The tablets of Verapamil hydrochloride complied with the test for uniformity of weight.

Table 7: Post-compression parameters of Verapamil hydrochloride sustained release layer tablets

Formulation	*Uniformity of weight (mg)*	*Thickness*	*Diameter*
VH 1	606.13	4.0	13.0
VH 2	602.28	4.0	13.0
VH 3	602.98	3.9	13.0
VH 4	600.33	4.0	13.0

The hardness of the Verapamil hydrochloride tablets were found to be between 9.08 kg/cm^2 and 9.25 kg/cm^2. The percentage friability ranged from 0.25 % to 0.34 %. The drug content estimation showed that the drug content of formulated tablets were within the limits.

Tables 8 and 9 shows the *in vitro* release study of formulated VH SR and EM SR tablets respectively

Table 8: In vitro release study of Verapamil hydrochloride SR tablets

Time (Hours)	*Cumulative percentage drug release*			
	VH 1	*VH 2*	*VH 3*	*VH 4*
1	6.91	5.91	7.35	10.25
2	10.72	9.66	11.67	13.65
3	15.14	13.76	16.37	19.34
4	16.41	14.83	16.99	20.83
5	17.92	15.66	17.84	23.65
6	19.89	16.50	19.65	24.52
7	20.74	18.77	20.99	25.39
8	22.52	21.52	21.41	26.49
9	27.71	23.36	23.70	27.81
10	30.67	25.91	26.26	31.57
11	35.71	28.25	28.60	33.88
12	40.74	30.62	36.12	34.98
16	46.53	58.79	71.72	75.99
17	50.96	68.11	80.56	88.36
18	57.22	75.02	89.91	99.53
19	66.43	82.83	95.42	-
20	69.47	92.31	100.44	-
21	75.43	101.58	-	-
22	82.34	-	-	-
23	88.86	-	-	-
24	92.74	-	-	

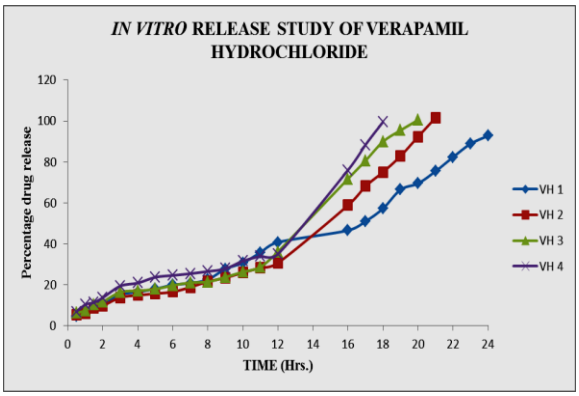

Figure 5: *In vitro* release study of Verapamil hydrochloride SR tablets

The *in vitro* release studies of the formulated tablets of Verapamil hydrochloride showed that the formulation VH 1 is the better formulation as the drug release is extended to the time period of 24 hrs compared to the other formulations. Hence, VH 1 formulation is considered as the optimised formulation.

Table 7: Post - compression parameters of Enalapril maleate sustained release layer

Formulation	*Thickness*	*Diameter*	*Uniformity of weight (mg)*
EM 1	2.1	6.0	101.57
EM 2	2.6	6.0	101.02
EM 3	2.6	6.0	99.0
EM 4	2.6	6.0	103.70
EM 5	2.9	6.0	103.81
EM 6	3.2	6.0	133.02

Table 8: Post - compression parameters of Enalapril maleate sustained release layer

Formulation	*Hardness (Kg/Cm^2)*	*Friability (%)*	*% Drug content*
EM 1	2.5	0.13	98.89
EM 2	2.6	0.11	104.88
EM 3	2.0	0.05	93.67
EM 4	2.3	0.08	102.05
EM 5	2.6	0.28	104.86
EM 6	3.1	0.06	101.37

Table 8: *In vitro* drug release study of Enalapril maleate SR Formulations.

Time (Hours)	*Cumulative percentage drug release*					
	EM 1	*EM 2*	*EM 3*	*EM 4*	*EM 5*	*EM 6*
1	28.7	25.3	34.3	51.6	22.7	15.1
2	41.4	47.0	57.8	64.5	32.0	25.6
3	73.3	58.9	66.2	75.0	39.8	27.8
4	77.2	64.5	69.0	79.8	43.5	29.1
5	81.0	69.1	73.1	82.5	48.8	32.0
6	89.4	77.8	78.2	87.5	51.3	33.6
7	92.3	82.7	88.05	92.5	55.0	36.0
8	99.7	90.1	97.97	99.6	59.4	39.1
9	102.6	98.4	-	-	62.3	43.0
10	-	101.3	-	-	65.2	45.1
11	-	-	-	-	69.8	48.7
12	-	-	-	-	73.9	50.1
13	-	-	-	-	77.3	53.0
14	-	-	-	-	81.2	56.7
15	-	-	-	-	85.3	58.9
16	-	-	-	-	91.2	60.8
17	-	-	-	-	96.0	64.5
18	-	-	-	-	-	69.3
19	-	-	-	-	-	76.3
20	-	-	-	-	-	79.0
21	-	-	-	-	-	85.0
22	-	-	-	-	-	88.8
23	-	-	-	-	-	91.7
24	-	-	-	-	-	99.9

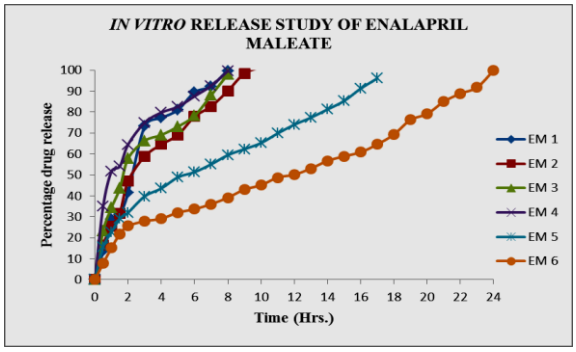

Figure 6: *In vitro* release study of Enalapril maleate SR tablets

The *in vitro* drug release studies of the SR formulations of Enalapril maleate showed that the formulation EM 6 is the optimised formulation, since the drug release of the formulation was found to be extended upto the time period of 24 hrs than the other formulations.

Table 9 shows the post compression study of bilayer tablets.

Table 9: Post compression study of bilayer tablets

Parameters		*Bilayer tablets*
Uniformity of weight (mg)		730.16
Thickness (mm)		4.5
Diameter (mm)		13.00
Hardness (kg/cm2)		10.1
Friability (%)		0.015
% Drug content	Verapamil hydrochloride	99.16
	Enalapril maleate	98.9

The bilayer tablets fulfilled the official requirement of uniformity of weight, thickness, diameter, hardness, friability and the drug content was found to be within the limit.

In vitro dissolution study was carried out for the bilayer tablets and the results are shown in table 10.

Table 10: *In-vitro* dissolution study of bilayer floating tablets

Time (Hours)	*Cumulative % drug release*	
	Verapamil hydrochloride	*Enalapril maleate*
1	10.46	9.26
2	20.68	28.16
3	23.94	33.05
4	26.73	37.63
5	32.61	40.20
6	36.35	44.74
7	40.82	51.10
8	43.84	52.71
9	48.18	56.25
10	54.17	58.79
11	59.43	61.65
12	61.80	67.41
18	84.19	84.62
19	88.58	85.52
20	91.62	88.30
21	93.54	94.77
22	96.94	97.99
23	98.19	98.88
24	99.85	99.45

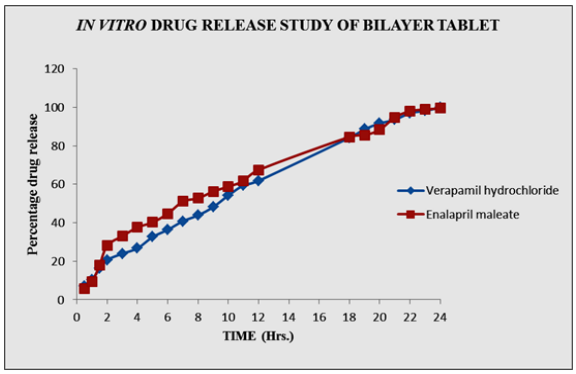

Figure 7: *In vitro* drug release study of Bilayer tablet

The *in vitro drug* release study (Fig.7) of the bilayer tablet indicated that, both the sustained release layers Verapamil hydrochloride and Enalapril maleate showed drug release upto 24 hours of time period which was determined using the simultaneous equation method. Bilayer tablet showed drug release of 99.85 % and 99.45 % of Verapamil hydrochloride and Enalapril maleate respectively at the end of 24 hours.

The drug release data of the Verapamil hydrochloride was fitted into various kinetic models as shown in the figures 8 and 9. [16]

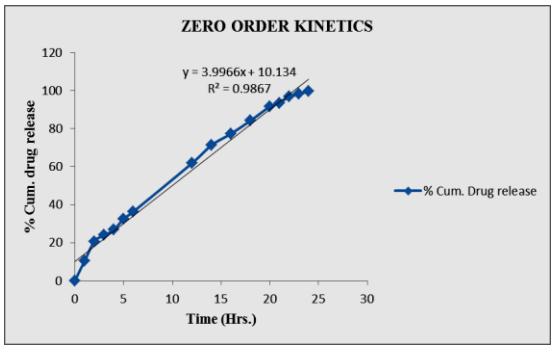

Figure 8: Zero order kinetics

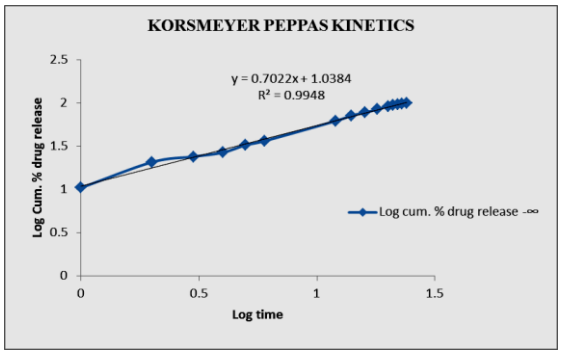

Figure 9: Korsmeyer Peppas Kinetics

The order of release of drug was found to be zero order, in which R^2 value was close to 1. The n value of Korsmeyer Peppas equation was found to be 0.702, thus concluding that the release followed non- Fickian transport. Good correlation coefficients are obtained for Hixson Crowell cube root and Higuchi equation. The results showed that the formulation followed zero order release. The drug release data of the Enalapril maleate was fitted into various kinetic models which as shown in figures 10 and 11. [16]

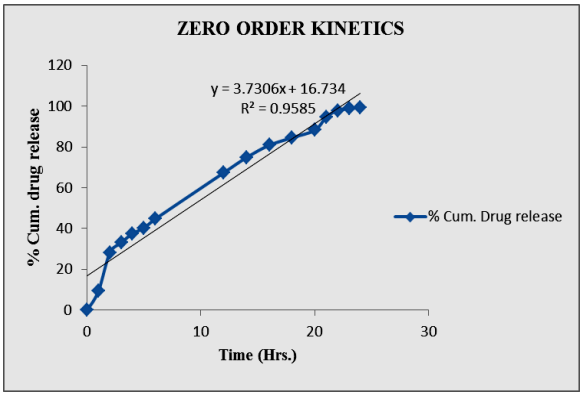

Figure 10: Zero order kinetics

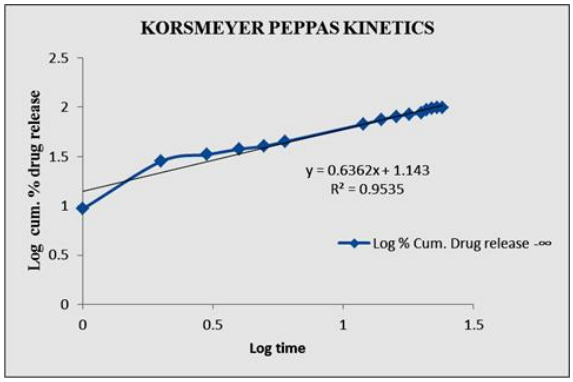

Figure 11: Korsmeyer Peppas Kinetics

The order of release of drug was found to be zero order, in which R^2 value was close to 1. The n value of Korsmeyer Peppas equation was found to be 0.636, thus concluding that the release followed non- Fickian transport. Good correlation coefficients are obtained for Hixson Crowell cube root and Higuchi equation. The results showed that the formulation followed zero order release.

5. Conclusion

The optimised formulations compressed into bilayer tablet showed drug release upto 24 hrs of time in a sustained manner. This combination of Verapamil hydrochloride and Enalapril maleate as sustained release a layer produce additive effect in treatment of hypertension, reduce polytherapy to monotherapy and improves patient compliance by reducing the dosing frequency. The developed formulation proves to be a good alternative to the conventional dosage forms available for the treatment of hypertension in patients.

6. Future Scope

Stability and scale up studies of the optimized formulation. *In-vivo* studies and *in vivo- in vitro* correlation studies has to be done. Bioequivalence studies with the marketed formulations. The Bilayer tablets formulated may replace the conventional polytherapy available in the treatment of mild to moderate hypertension.

7. Acknowledgment

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