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Design and Characterisation of Bi-layer Tablets Containing Simvastatin as Sustained Release and Labetalol HCl as Immediate Release

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ABSTRACT

The objective of present investigation is to design and characterise sustained release Simvastatin and immediate release of Labetalol HCl, a bi-layer tablet. The combination therapy of Simvastatin and Labetalol HCl can be useful in severe cardiovascular disease such as hypertension, angina pectoris, congestive heart failure which may occur along with increasing cholesterol level in the blood, while this combination remain preferable choice to the patient as compared to single dosage form. The bi-layer tablet is suitable for sequential release of two drugs in combination which are compatible with each other. Objective of present investigation is to prepare bi-layer tablet in which one layer is sustained while another one is immediate release. For the preparation of bi-layer tablet, different super disintegrants like cross carmellose cellulose, micro crystalline cellulose is used for immediate release and HPMC and Carbapol as controlled release polymer. The pre-formulation parameter such as solubility, melting point, compatibility study (FTIR) were studied. Pre-compression parameter such as angle of repose, bulk density, tapped density, hausner's ratio and compressibility index were studied. The tablets were evaluated by physical and chemical parameters such as weight uniformity, hardness, thickness, diameter, friability, drug content, disintegration time and in-vitro drug release. The dissolution data were subjected to various release kinetic model to recognize the mechanism of drug release.

Keyword: sustained release tablet, bi-layer tablet, Simvastatin, Labetalol HCl.

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1. INTRODUCTION

Oral rout is most convenient route for administration of dosage form. Tablet is the convenient oral dosage form and acceptable by patients and physicians. Bi-layer tablet is suitable for sequential release of two drugs in which one is immediate release and another is sustained release. Sustained release drug delivery is the important approaches to achieve the controlled release of drug to obtained sufficient bioavailability. Hypertension and hypercholesterolemia frequently coexist and may require concomitant drug treatment.[1, 2]

Simvastatin is the lipid lowering agent which is use to decrease the bad cholesterol level. It is potent inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme, [HMG-CoA] reductase which catalyzes the conversion of HMG-CoA to Mevalonate, an early rate determining step in cholesterol biosynthesis. Absorption of Simvastatin is about 85% of an oral administration. However because of Simvastatin is undergo extensive first pass metabolism and hence bioavailability is low is about 5%.peaak plasma concentration found to be 1.3-2.4 hours after administration. So sustained release drug delivery system is suitable for Simvastatin.[3] Labetalol HCl. is a third generation selective alpha-1-aderenergic agonist and non selective beta-adrenergic antagonist with vasodilatory and antihypertensive properties. Labetalol competitively bind to alpha-1-adrenergic receptor in vascular smooth muscle, thereby inhibiting the adrenergic stimulation of endothelial cell function and vasoconstriction and peripheral blood vessels. The result is a decrease in resting and exercise heart rate cardiac output and both systolic and diastolic blood pressure thereby resulting vasodilation and hence reduce the hypertension. Labetalol is completely absorbed (100%) from gastrointestinal tract. The half-life of Labetalol HCl. is approximately 4-6 hrs.[4]

The combination therapy of Simvastatin and Labetalol HCl. may be useful and effective in serious cardiovascular disease such as hypertension, angina pectoris, congestive heart failure which may occur along with increasing cholesterol level in the blood, while this combination remain preferable choice to the patient as compared to single dosage form. The statin combine with antihypertensive drugs may improve the B.P. control in patients having obesity and hypertension.[2]

2. MATERIAL AND METHOD

2.1. Materials:

Simvastatin and Labetalol HCl. gifted sample (Flamingo pharmaceutical), HPMCK4M, Cross Carmellose Cellulose, Carbapol, Talc (Thermosil fine chem.) Microcrystalline Cellulose, Sodium Saccharine, PVPk30 (research lab) Lactose, (Sahyadri scientific supply) Magnesium Stearate (Hilab chemicals) were sample is analytical grade.[5, 6]

2.2. Preparation of bi-layer tablet:

Formulation of bilayer tablet was prepared by direct compression method. Immediate release layer was prepared by using different super disintegrants (Microcrystalline Cellulose, Crosscarmellose Cellulose).

Drug and above super disintegrants were passed though the 40# sieve and transfer into poly bag and mix up to 3 min. Then, other excipients added to the above mixture. Finally added (lubricants), Magnesium Stearate into the blend.[7]

Another layer was also prepared by direct compression; drug and polymer (HPMCk4M, carbapol) were pass through the 40# sieve transfer into poly bag and mixed properly up to 3 min. Other excipients were mixed well and finally added Magnesium Stearate in above blend and were mixed for 2 min.

Finally above blends were compressed by rotary tablet compression machine (Make-CREATE INDUSTRIES, MODEL-LP-8GMP).[1, 2, 7]

Table 1: Formulation of Immediate Release of Labetalol HCl.

Sr.No	Ingredients	L1	L2	L3
1	Labetalol HCl	50	50	50
2	Lactose	20	40	60
3	Crosscarmellose cellulose	50	40	30
4	Microcrystalline cellulose	60	50	40
5	Sodium saccharine	3	3	3
6	Talc	9	9	9
7	PVPk0	6	6	6
8	Magnesium stearate	2	2	2

Average weight of each tablet = 200 mg.

Table 2: Formulation of Sustained Release of Simvastatin.

Sr.No	Ingredients	S1	S2	S3	S4	S5	S6
1	Simvastatin	20	20	20	20	20	20
2	Lactose	130	100	70	130	100	70
3	HPMCk4M	40	70	100	-	-	-
4	Carbapol	-	-	-	40	70	100
5	Talc	7.5	7.5	7.5	7.5	7.5	7.5
6	Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5
7	Colour	q.s	q.s	q.s	q.s	q.s	q.s

Average weight of each tablet = 200 mg.

2.3. Preformulation Study :

2.3.1 Identification test by U.V vis. Spectrophotometer:

a) For Labetalol HCl:

50 mg of Labetalol 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 mcg/ml). further dilutions were made with this stock solution and scanned in the range of 400-200 nm using respective blank in UV spectrophotometer.

b) For Simvastatin:

50 mg of Simvastatin was weighed accurately and transferred it to 50 ml volumetric flask. Dissolved it in Phosphate buffer (6.8pH) and make the volume up to 50 ml with respective solvent. This was considered as stock solution (1000 mcg/ml). further dilutions were made with this stock solution and scanned in the range of 400-200 nm using respective blank in UV spectrophotometer.

2.3.2 Melting Point determination:

The melting points of Simvastatin and Labetalol were determined by Melting point apparatus. The melting point was determined by introducing small amount of substance in the capillary attached to graduated thermometer.

2.3.3 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.

2.3.4 Compatibility study, by FT-IR spectroscopy:

The powdered substance of the tablet were mix, dried potassium bromide (IR grade) ratio of sample is should be 1:100 mg, 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. [8, 9]

2.4. Pre-compression Evaluation:

2.4.1 Bulk density:

Bulk density was determined by placing the power blend into measuring cylinder and total volume was measured and also total powder weight was measured. The bulk density was calculated by using formula.

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

2.4.1 Tapped density:

Tapped density was obtained by tapping the cylinder by 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.

$$\text{Tapped Density (TD)} == \frac{\text{weight of powder}}{\text{tapped volume}}$$

2.4.3 Hausner's ratio:

Hausner's ratio is the number that is correlated to the flowability of a powder or powder blend. it is calculated using formula,

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

2.4.4 Compressibility index:

Compressibility index was calculated by formula,

$$\text{Carr's index (\%)} = \frac{\text{Tapped density - bulk density}}{\text{tapped density}} \times 100$$

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 through funnel separately until apex of pile so formed just touch the tip of the funnel. The angle of repose was calculated by using formula

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

h is height of pile; r is radius of pile.

2.5 Post compression evaluation:[9, 10, 11]

2.5.1. 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.

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 thickness was measured in (mm).

2.5.3. Hardness:

Hardness is important parameter of evaluation of tablet. The resistance of the tablet to break under condition of handling, transportation and storage depend upon hardness. The hardness of tablet was 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, cap or break. 20 tablets are weighed and placed in the roche friabilator apparatus they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of 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;[7]

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

2.5.5. Content Uniformity:

2.5.5.1. For Labetalol HCl:

Tablets were taken and crushed into morter to form powder. From that, sample equivalent to 50 mg of drug was taken and transferred to 100ml volumetric flask. Methanol (20ml) was added and gently heated on water bath to dissolve the drug, cool to room temperature and volume was made up to mark with methanol, this was filtered. From the filterate 1ml was taken and diluted with pH 6.8 phosphate buffer and absorbance of this solution was measured by using U.V-spectrophotometer at 302nm (SHIMADZU; U.V1800).

2.5.5.2. For Simvastatin:

In this test, 5 tablets were randomly selected and crushed into morter to form powder; sample equivalent to 20 mg was dissolved in 100ml of phosphate buffer pH 6.8, followed by stirring. The solution was filtered through a whattman filter paper, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 247 nm using phosphate buffer pH 6.8 as blank. Then absorbance of this solution was measured by using U.V-spectrophotometer (SHIMADZU; U.V1800).

2.5.6. In Vitro Drug Dissolution Studies:

2.5.6.1. In vitro drug release was study for immediate release tablet (Labetalol HCl)

In vitro drug release was studied using USP II (paddle) apparatus, with 900 ml of dissolution medium maintained at 37±1°C for 15 h, at 50 rpm. 0.1 N HCl (pH 1.2). 5ml of sample was withdrawn in 10 min time intervals. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. Collected samples were analyzed by U.V spectrophotometrically at 302 nm, and cumulative percent drug release was calculate

2.5.6.2. In vitro drug release was study for sustained release tablet (Simvastatin)

The In-vitro dissolution study for the Simvastatin sustained release tablets were carried out in USP type-II dissolution test apparatus (Paddle type) using 900 ml of phosphate buffer pH 6.8 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 247 nm using UV Visible spectrophotometer and calculate the percentage drug release.

2.5.6.3. 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 370c±0.20c for 1hour. Then dissolution media replace by phosphate buffer (6.8pH). The stirring speed was 50 rpm. Aliquot of the solution was collected at specific interval were replaced with fresh dissolution medium. The Labetalol and Simvastatin were analyzed spectrophotometrically at 302 nm and 247 nm respectively using simultaneous equation method.

3. RESULT AND DISCUSSION

Pre-formulation studies:

The UV absorption of 10 µg/ ml in 0.1N HCl (pH-1.2) for Labetalol HCl is 302nm 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 drug are carried out and result is include in table 4 and 5.

Table 4: Preformulation study of Labetalol HCl

Sr.No	Parameters	Observation
1	Identification by U.V Vis spectrophotometer.	302 nm (ʎ max)
2	Melting Point	187^{0}c
3	Solubility	Sparingly soluble in Water and Ethanol, soluble in phosphate buffer, practically insoluble in ether and chloroform.
4	Compatibility study (FTIR)	Compatible.

Table 5: Preformulation study of Simvastatin.

Sr.No	Parameters	Observation
1	Identification by U.V Vis spectrophotometer.	247 nm (ʎ max)
2	Melting Point	136^{0}c
3	Solubility	Very soluble in dichloromethane, freely soluble in ethanol, soluble in phosphate buffer.
4	Compatibility study (FTIR)	Compatible.

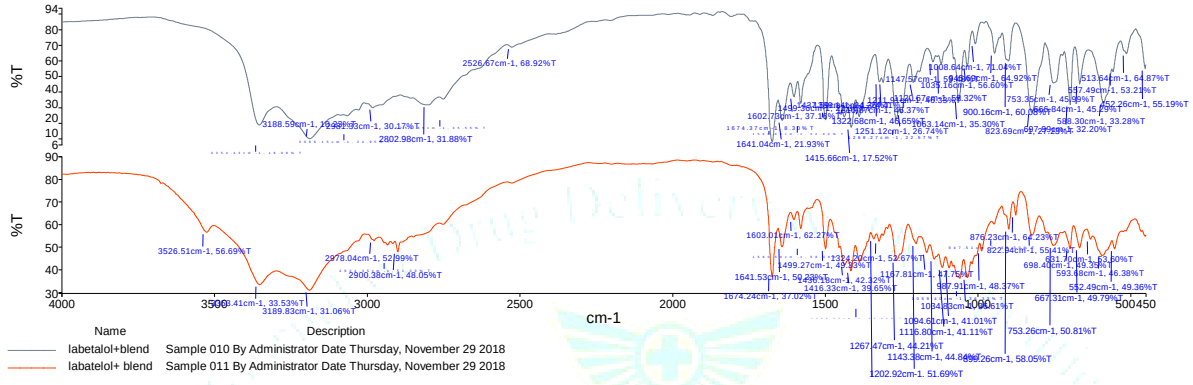


Figure 1: FTIR of Labetalol HCl + Excepients

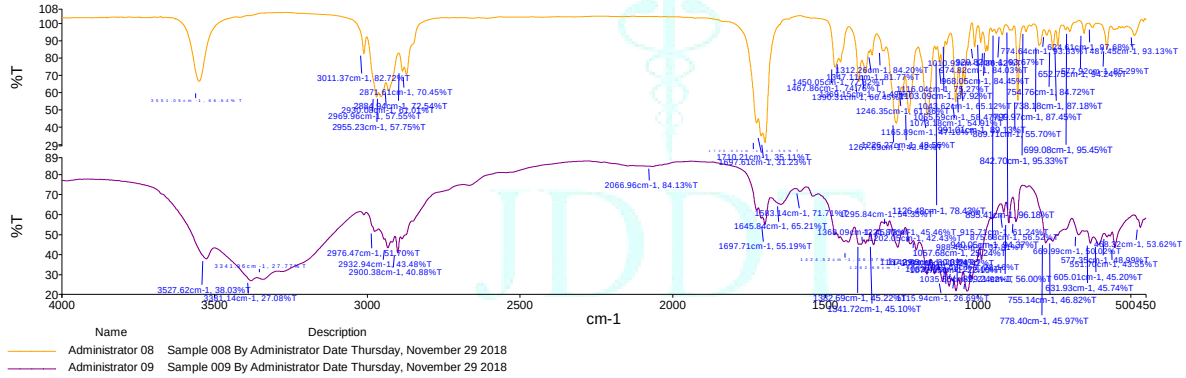


Figure 2: FTIR of Simvastatin + Excipients

Pre-compression Evaluation:

The micromeritic properties such as of bulk density, tapped density, Angle of repose, compressibility index, Hausner's ratio and particle size distribution of Labetalol HCl immediate release layer blend and Simvastatin sustained release layer were studied. The overall results were shown in Table No. 6 and 7. 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 46^0 to 55^0 which indicates poor flow properties.

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

Sr. No	Parameter	L1	L2	L3
1	Bulk density (g/ml)	0.3529	0.3529	0.3388
2	Tapped density (g/ml)	0.5454	0.5454	0.6100
3	Compressibility index (%)	35.29%	35.29%	44.54%
4	Hausner's ratio	1.54	1.54	1.80
5	Angle of repose (degree)	51.11^0	48.99^0	47.20^0

Table 7: Pre-compression evaluation of sustained release powder blend (Simvastatin)

S.N.	Parameter	S1	S2	S3	S4	S5	S6
1	Bulk density(g/ml)	0.30	0.36	0.34	0.35	0.32	0.30
2	Tapped density(g/ml)	0.75	0.70	0.73	0.64	0.62	0.60
3	Compressibility Index (%)	60	57.14	53.42	45.31	48.38	50
4	Hausner's ratio	2.5	1.94	2.14	1.82	1.9	2
5	Angle of repose(degree)	50.19	50.65	47.20	47.64	45.34	42.61

Post-compression Evaluation of Tablet:

The prepared tablets were evaluated for weight variation, dissolution test, thickness, hardness uniformity of dosage units and friability. The weight variation test is done 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 hardness of 6 tablets was determined using

The Friability was determined by first weighing 10 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 test value are include in table no 8

Drug content uniformity determined according to the USP requirements. Test values are include in table no 9 and 10.

***In vitro* Dissolution Study**

The *in-vitro* dissolution characteristics of Labetalol HCl and Simvastatin bilayer tablets are shown Table No.11and 12. Based on the *in-vitro* release profile of drug formulations of L1 to L3, for Labetalol. The formulation of sustained release layer Simvastatin S6 showed better drug release, which was achieved by increasing the polymer concentration of carbapol increase the release rate.

Table 8: Post-compression Evaluation of Tablet

Sr.No	Parameter	B1	B2	B3	B4	B5	B6
1	Uniformity weight(mg)	405.7	410.02	399.8	403.1	399.6	405.7
2	Thickness(mm)	3.00	3.00	3.00	3.00	3.00	3.00
3	Hardness(kg/cm^2)	5	5.2	5	5	5.5	5
4	Friability(%)	0.1863	0.2056	0.2032	0.2447	0.2788	0.1977

Table9: Drug content of Immediate Release Layer (Labetalol HCl.)

Sr. No	Parameter	L1%	L2%	L3%
1	Drug Content (%)	99.8	96.50	101.2

Table 10: Drug content of sustained release layer (Simvastatin)

S. No	Parameter	S1 %	S2 %	S3 %	S4 %	S5 %	S6 %
1	Drug Content (%)	99.60	98.20	91.85	97.28	98.52	99.85

Table 11: Percentage drugs release of immediate release layer (Labetalol HCl.)

Time in (min)	L1 % Release	L3 % Release	L3 % Release
10	20.28	19.29	26.76
20	36.96	33.68	47.86
30	46.92	61.7	59.84
40	66.92	81.68	74.64
50	83.53	87.19	91.04
60	97.02	93.38	98.22

Table 12: Percentage drugs release sustained release layer (Simvastatin)

time in hours)	S1 % Release	S2 % Release	S3 % Release	S4 % Release	S5 % Release	S6 % Release
1	29.74	16.8	7.29	8.76	5.17	3.807
2	36.94	20.17	18.27	10.16	5.99	9.097
3	37.26	23.3	19.84	10.69	6.92	11.27
4	37.12	29.89	20.47	11.58	8.45	14.35
5	39.82	40.95	26.73	15.31	13.63	27.11
6	42.43	46.27	35.41	29.47	26.25	40.83
7	47.16	54.18	36.72	40.69	38.6	48.98
8	77.22	85.31	39.91	46.95	43.37	58.09
9	83.33	85.94	52.45	52.45	61.2	70.5
10	87.68	86.35	70.1	61.62	74.94	88.98

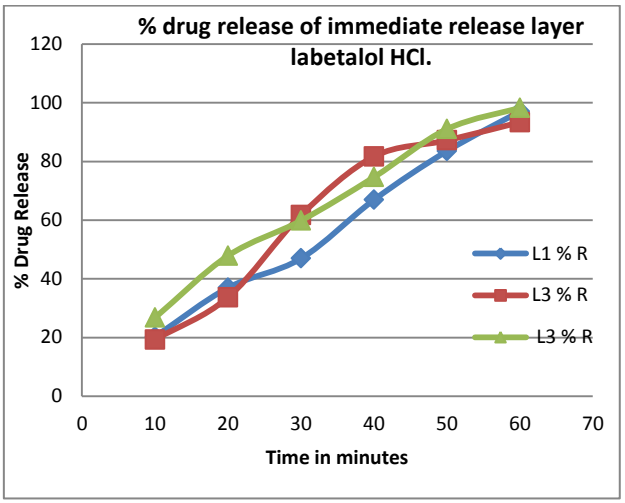


Figure 3: In-vitro dissolution of immediate release layer of Labetalol HCl

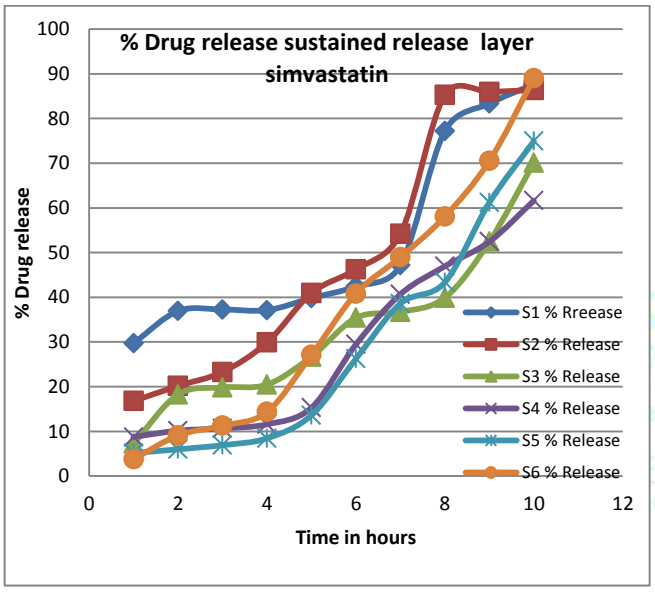


Figure 4: In-vitro dissolution of sustained release layer of Simvastatin

Table13: in-vitro dissolution bi-layered tablet Labetalol HCl and Simvastatin.

time (min)	% drug release Labetalol	% release Simvastatin
10	30.3	-
20	47.89	-
30	58.99	-
40	75.94	-
50	93.25	-
60	98.22	-
60	-	2.8
120	-	6.09
180	-	11.27
240	-	15.31
300	-	26.73
360	-	39.91
420	-	61.2
480	-	69.4
540	-	75.2
600	-	87.94

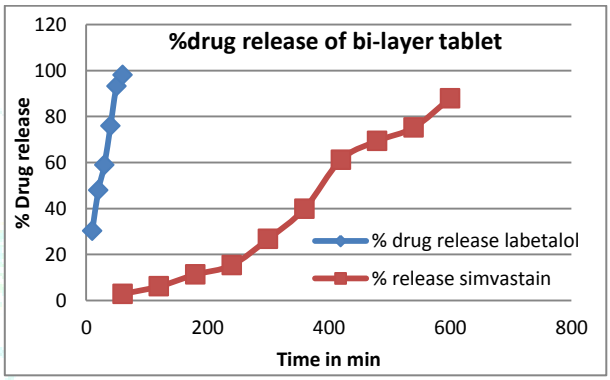


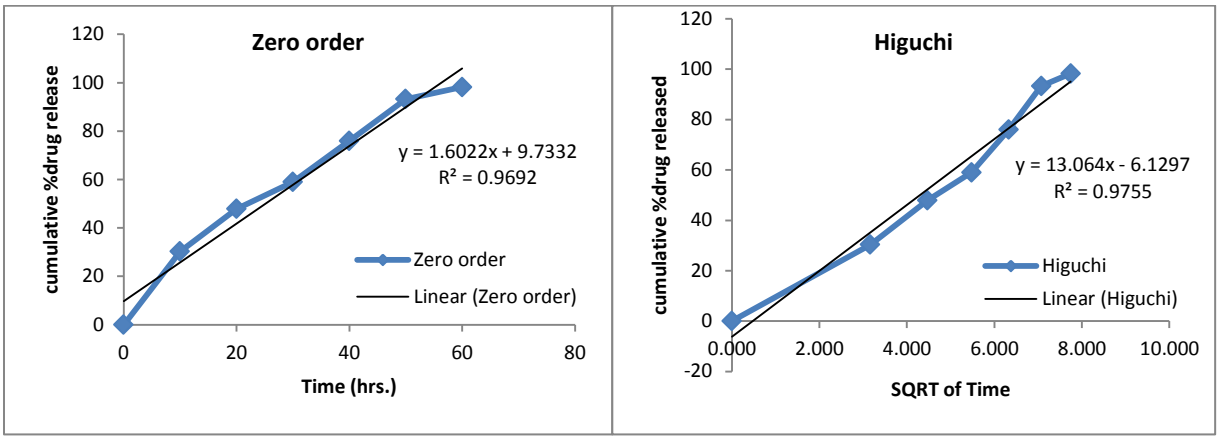
Figure 5: in-vitro dissolution bi-layered tablet Labetalol HCl and Simvastatin.

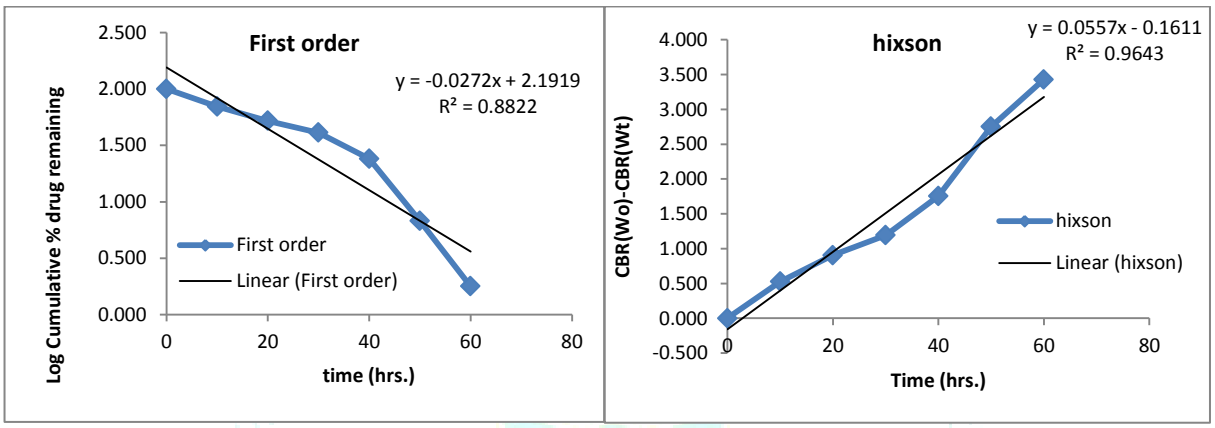
Kinetic Models:

Dissolution data of above bi-layered tablet was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

Table13: Drug release kinetics of Labetalol.

Time (min)	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	30.3	69.7	3.162	1.843	1.000	1.481	30.3	4.115	0.527
20	47.89	52.11	4.472	1.717	1.301	1.680	17.59	3.735	0.907
30	58.99	41.01	5.477	1.613	1.477	1.771	11.1	3.448	1.194
40	75.94	24.06	6.325	1.381	1.602	1.880	16.95	2.887	1.755
50	93.25	6.75	7.071	0.829	1.699	1.970	17.31	1.890	2.752
60	98.22	1.78	7.746	0.250	1.778	1.992	4.97	1.212	3.430





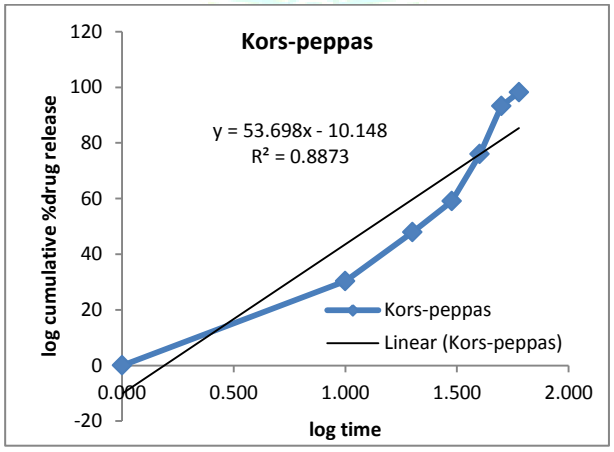
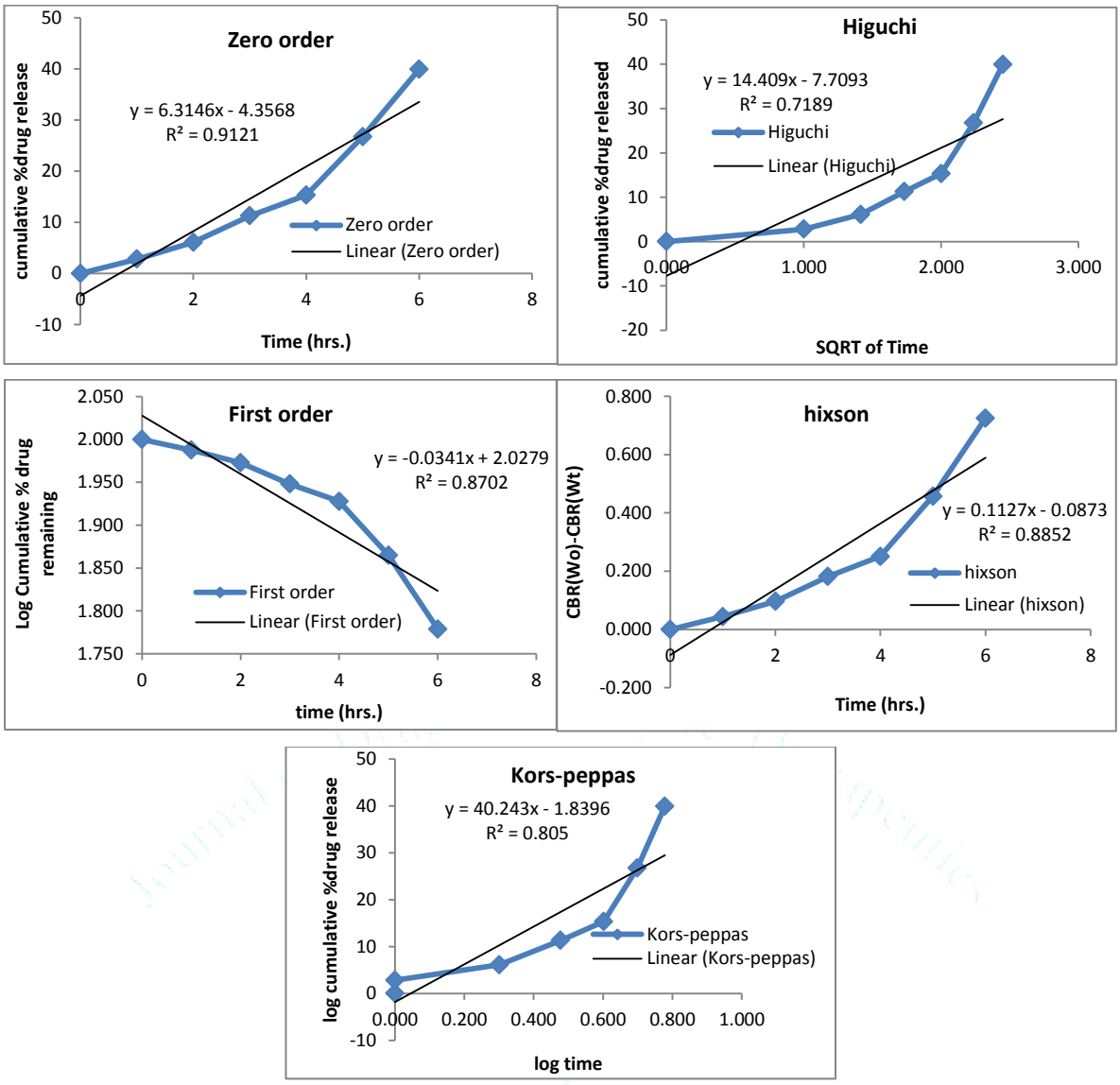


Table 14: Drug release kinetics of Simvastatin.

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
1	2.8	97.2	1.000	1.988	0.000	0.447	2.8	4.598	0.044
2	6.09	93.91	1.414	1.973	0.301	0.785	3.29	4.545	0.097
3	11.27	88.73	1.732	1.948	0.477	1.052	5.18	4.460	0.182
4	15.31	84.69	2.000	1.928	0.602	1.185	4.04	4.391	0.251
5	26.73	73.27	2.236	1.865	0.699	1.427	11.42	4.184	0.458
6	39.91	60.09	2.449	1.779	0.778	1.601	13.18	3.917	0.725
7	61.2	38.8	2.646	1.589	0.845	1.787	21.29	3.385	1.257
8	69.4	30.6	2.828	1.486	0.903	1.841	8.2	3.128	1.514
9	75.2	24.8	3.000	1.394	0.954	1.876	5.8	2.916	1.726
10	87.94	12.06	3.162	1.081	1.000	1.944	12.74	2.293	2.349



4. CONCLUSION

The prepared tablets showed satisfactory results for various evaluation tests such as tablet dimension, hardness, friability, weight uniformity, drug content and in-vitro dissolution study. The optimized formulation based on all the parameter L3 (cross carmellose cellulose) is selected for immediate release layer and S6 (carbapol) was selected for controlled release layer. The drug release mechanism was found to be zero order release; dependent on both drug diffusion and polymer relaxation. The bilayer tablets of Labetalol and Simvastatin may be useful in serious cardiovascular adverse effect such as hypertension, congestive heart failure and exacerbation of angina.

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