Formulation and evaluation of bilayer floating tablets of simvastatin and lovastatin

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ABSTRACT

This study was performed to design bilayer floating tablets of simvastatin and lovastatin to give sustained release of simvastatin and immediate release of lovastatin. Bilayer floating tablets comprised of two layers i.e, immediate and sustained release layers. Bilayer floating tablets of simvastatin and lovastatin was formulated by using HPMCK 100M and super disintegrants like sodium alginate, sodium starch glycolate, croscarmellose sodium, L-HPC and polyox WSR 303 which offers a suitable and practical approach in management of hypolipidemia. Sodium bicarbonate was used as gas generating agent. Accelerated stability studies were carried out as per ICH guidelines. Moreover 90% of lovastatin was released within 30 minutes. Simvastatin from controlled release layer for 12 hours. The release of simvastatin was found to follow a mixed pattern of Korsmeyer-Peppas, Hixson-Crowell and zero order release models. Therefore, biphasic drug release pattern was successfully achieved through bilayer floating tablets in this study.

Keywords: Simvastatin, Lovastatin, Bilayer tablets, Floating
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INTRODUCTION

Floating drug delivery systems are low density systems that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying for a prolonged period of time by remaining in the gastric region for several hours significantly which improves bioavailability and solubility for drugs that are less soluble in pH environment [1-2] It has also local drug delivery to the stomach and proximal small intestines. Hence to achieve controlled drug drug delivery gastro retentive drug delivery system is used to provide drug release at a predetermined, controlled and predictable rate [3-4]. Some drugs are absorbed at a particular portion of GIT only such drugs are said to have a absorption window, for the administration of these types of drugs gastro retentive drug delivery systems are used. Bilayer floating tablets of simvastatin and lovastatin was formulated by using HPMCK 100M and super disintegrants like sodium alginate, sodium starch glycolate, croscarmellose sodium, L-HPC and polyox WSR 303 which offers a suitable and practical approach in management of hypolipidemia. Simvastatin was planned to design as the sustained release by wet granulation method, and lovastatin as the immediate release by direct compression method.

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EXPERIMENTAL SECTION

Materials: simvastatin, sodium starch glycolate, croscarmellose sodium, L-HPC, microcrystalline cellulose, sodium bicarbonate, HPMCK100, PVPK-30, sodium bicarbonate, magnesium sterate, iso propyl alcohol.

1. Preparation of immediate layer of simvastatin by Direct compression method:
1. Drug and super disintegrants (Sodium starch glycolate, Croscarmellose sodium and L-HPC) pass through 40 # mesh separately and then transfer it to poly bag and mix it for 3 minutes.

2. Add other excipients to the above mixture. Finally add the Glidant (Magnesium Stearate) to the above blend mix it for 2min.[Refer table 1,]

Table 1, Composition of Immediate Layer Containing Simvastatin

S.NO.	INGREDIENTS	S1 (mg)	S2 (mg)	S3 (mg)	S4 (mg)	S5 (mg)	S6 (mg)
1	Simvastatin	20	20	20	20	20	20
2	Sodium starch glycolate	5	10	--	--	--	--
3	Croscarmellose sodium	--	--	5	10	--	--
4	L-HPC	--	--	--	--	5	10
5	Microcrystalline Cellulose	72	67	72	67	72	67
6	yellow iron oxide	0.25	0.25	0.25	0.25	0.25	0.25
7	Aerosil-200	0.75	0.75	0.75	0.75	0.75	0.75
8	Magnesium stearate	2	2	2	2	2	2
	Total wt	100	100	100	100	100	100

2. Preparation of floating matrix layer of lovastatin by wet granulation method:
1. Drug and polymer (HPMC K100M, Sodium Alginate and Polyox WSR 303) pass through 40 # mesh separately and then transfer it to poly bag and mix it for 3 minutes.
2. Binder (PVPK-30) dissolved in isopropyl alcohol which is used as a granulating agent.
3. Above drug-polymer blend is granulated by using binder solution.
4. Dry the prepared granules in the tray dryer for not more than 20 min at 60^0C.
5. Add other excipients to the above mixture. Finally add the Glidant (Magnesium Stearate) to the above blend mix it for 2min.
6. Compressed the above lubricated blend by using suitable punches.[Refer table 2,]

Table 2, Composition of Floating matrix Layer Containing Lovastatin

S.NO.	INGREDIENTS	L1	L2	L3	L4	L5	L6	L7	L8	L9
1	Lovastatin	50	50	50	50	50	50	50	50	50
2	HPMC K100M	20	40	-	-	-	-	20	20	-
3	POLY0X WSR 303	-	-	20	40	-	-	20	-	20
4	Sodium alginate	-	-	-	-	20	40	-	20	20
5	Sodium bicarbonate	30	30	30	30	30	30	30	30	30
6	Microcrystalline Cellulose	140	120	140	120	140	120	120	120	120
7	PVP K-30	5	5	5	5	5	5	5	5	5
8	Iso Propyl Alchol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
9	Magnesium Stearate	3	3	3	3	3	3	3	3	3
10	Talc	2	2	2	2	2	2	2	2	2
	Total Wt	250	250	250	250	250	250	250	250	250

Pre formulation studies:
Compatibility Studies by FTIR:
Compatibility must be established between the active ingredient and other excipients to produce a stable, efficacious, attractive and safe product. So before producing the actual formulation, compatibility of Simvastatin and Lovastatin with polymers and other excipients were tested using the Fourier Transform Infrared Spectroscopy(FT-IR).For this study, potassium bromide (KBr) pellet method was employed. The samples were thoroughly mixed with dry powdered potassium bromide. The mixture was compressed to form a disc. The disc was placed in the spectrophotometer and the spectrum was recorded. The application of infra-red spectroscopy lies more in the qualitative identification of substances either in pure form or in the mixtures and as a tool in establishment

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of the structure. Since I.R. is related to covalent bonds, the spectra can provide detailed information about the structure of molecular compounds. [Refer fig, 3, 4, 5, 6]

Evaluation:
1. Pre-compression parameters:
(a) Angle of Repose:
Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. The angle of repose is calculated by using equation

Angle of repose (θ) = Tan^{-1} (h/r)

Where, h=height of pile, r=radius of the base of the pile, θ =angle of repose

(b)Bulk density determination:
Weighed quantity of the powder (W) is taken in a graduated measuring cylinder and volume (V_0) is measured and bulk density is calculated using the formula.

Bulk density (BD) = Weight of the powder/Volume of powder

(C) Tapped density determination:
The graduated cylinder was fixed in the 'Tapped Densitometer' and tapped for 500, 750 and 1250 times until the difference in the volume after consecutive tappings was less than 2%. The final reading was denoted by (V_f).

Tapped density (TD) = W/V_f g/ml

(d) Carr's Index or Compressibility index:
It is simple, fast and popular method of predicting powder flow characteristics**.**

Carr's index (%)   = [(Tapped Density-Bulk Density) / Tapped Density] X 100

e) Hausner's ratio:
 It indicates the flow properties of powder and is measured by the ratio of tap density to bulk density.

2. Post compression parameters:
a. Weight variation:
The weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average.[Refer table ,6]

b. Hardness Test:
The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were picked randomly and   analyzed for hardness. The mean values were then calculated. [Refer table, 6]

c. Friability: It is usually measured by the use of the Roche friabilator.
Method: A number of tablets were weighed and placed in apparatus as they fall 6 inches in each turn within the apparatus. After treatment of 4 minutes or 100 revolutions, the tablets are weighed and the weighed tablets are compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. Its value is expressed by the percentage. The percentage friability was determined by the formula:

% friability = (W_1-W_2) / W_1 X 100

W_1 = Weight of tablets before test, W_2 = Weight of tablets after test [Refer table, 6]

d. Drug Content:
 Standard graph of Simvastatin in 0.1N HCl (1.2 pH buffer):-
The construction of standard calibration curve of Simvastatin was done by using 0.1N HCl as the medium. Simvastatin was found to have the maximum absorbance at 238 nm. The standard graph of Simvastatin in 0.1N HCl

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was constructed by making the concentrations of 2µg/ml, 4µg/ml, 6 µg/ml, 8 µg/ml and 10 µg/ml solutions. The absorbance of solutions was examined under UV- spectrophotometer at an absorption maximum of 238 nm. The standard graph of Simvastatin was constructed by taking the absorbance on Y-axis and concentrations on X-axis.[Refer table1,fig,1]

Standard graph of Lovastatin in 0.1N HCl (1.2 pH buffer):-
The construction of standard calibration curve of Lovastatin was done by using 0.1N HCl (1.2 pH buffer) as the medium. Lovastatin was found to have the maximum absorbance at 245 nm. The standard graph of Lovastatin in 0.1N HCl (1.2pH buffer) was constructed by making the concentrations of 2µg/ml, 4µg/ml, 6 µg/ml, 8 µg/ml and 10 µg/ml solutions. The absorbance of solutions was examined under UV- spectrophotometer at an absorption maximum of 245 nm. The standard graph of Lovastatin was constructed by taking the absorbance on Y-axis and concentrations on X-axis. [Refer table2, fig, 2]

Ten tablets were selected randomly and crushed, from that average weight of one tablet was dissolved using 20ml methanol and 20ml of 0.1N HCl until drugs get dissolved then added the dissolution media (0.1N HCl) to make volume 100ml, 0.45µ membrane filter. Standard also performed with the same concentration then this would read at 238 nm, 245 nm by UV spectroscopy.

$$\text{Amount of drug} = \frac{\text{Sample absorbance}}{\text{Std.absorbance}} \times \frac{\text{Std.dilution}}{\text{Sample dilution}} \times \text{Conversion factor} \times 100$$

Conversion factor for Simvastatin = Molecular wt of Simvastatin

Conversion factor Lovastatin = Molecular wt of Lovastatin

$$\% \text{ Purity} = \frac{\text{Amount}}{\text{Label claim}} \times 100$$

Label Claim = 40 mg (Simvastatin) and 50 mg (Lovastatin)

e. In-Vitro Dissolution Studies:

The drug release from floating bilayer tablets can be studied by the invitro dissolution studies using USP II paddle apparatus at a speed of 5 rpm using 0.1N HCl (1.2 pH) with a volume of 900ml at a temperature of 37 ± 0.5^0c . The samples were withdrawn at predetermined time points, and were analyzed spectrophotometrically at 245 nm and 238 nm. [Refer table, 3 fig, 7 8]

Table 3, speed of usp apparatus

Apparatus	USP apparatus II (Paddle)
Agitation speed (rpm)	50rpm
Medium	0.1N HCl (1.2 pH)
Volume	900 ml
Temperature	$37.0 \pm 0.5\,^0$C
Time:	5, 10, 15, 30, 45, 60 min (for immediate layer of Simvastatin) and 1, 2, 4, 6, 8 and 12 hrs (for Floating matrix layer of Lovastatin).
Wavelengths	238 nm and 245 nm

f. In-vitro drug release Kinetics studies for optimized formulation:
 The results of in-vitro drug profiles obtained for all the formulations were fitted into four models of data treatment as follows.
1. Cumulative percent drug released versus time (zero-order kinetic model).
2. Log cumulative percent drug remaining versus time. (First-order kinetic model).
3. Cumulative percent drug released versus square root of time (Higuchi's model).
4. Log cumulative percent drug released versus log time (Korsmeyer-Peppasequation).
[Refer table, 9 fig, 9 10 11 12 13]

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g. Accelerated stability study of optimized formulations:
Accelerated stability study was carried out for optimized formulations, to assess its stability as per ICH guidelines. The optimized formulation were wrapped in the laminated aluminum foils and was placed in the accelerated stability chamber (6CHM-GMP, Remy Instrument Lit, Mumbai) at elevated temperature and humidity condition of 40^0C/ 75%RH and a control sample was placed at an ambient condition for a period of months. Sampling was done at a predetermined time in days of initial 1, 30, 60 and 90 interval respectively. At the end of study, samples were analyzed for the drug content, in vitro drug release profile and other physicochemical parameters.[Refer table ,10]

RESULTS AND DISCUSSION

Calibration curves of simvastatin and lovastatin:

Table 4, Standard graph values for Simvastatin

S. NO.	CONCENTRATION (µg/ml)	ABSORBANCE
1	0	0
2	2	0.156
3	4	0.307
4	6	0.452
5	8	0.607
6	10	0.732

Fig 1, Calibration curve of Simvastatin in 0.1N HCl (1.2 pH buffer)
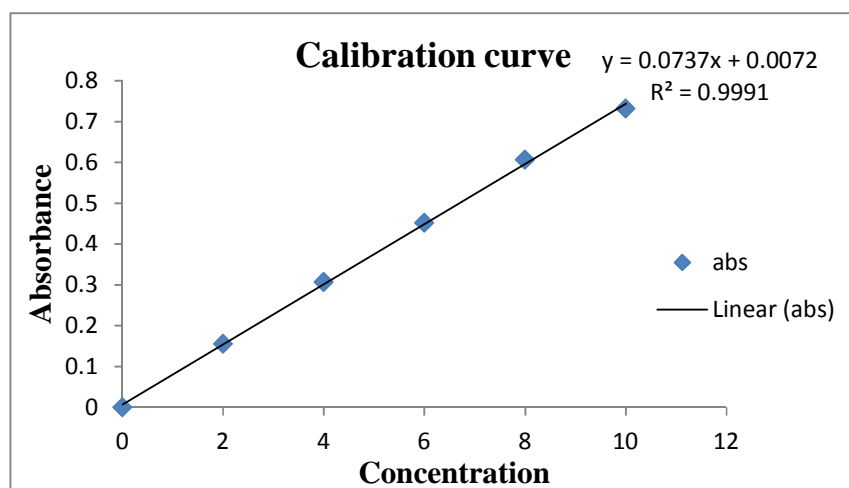
Table 5, Standard graph of Lovastatin

S. NO.	CONCENTRATION (µg/ml)	ABSORBANCE
1	0	0
2	2	0.185
3	4	0.345
4	6	0.526
5	8	0.722
6	10	0.907

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Fig 2, Calibration curve of Lovastatin in 0.1N HCl (1.2 pH buffer)
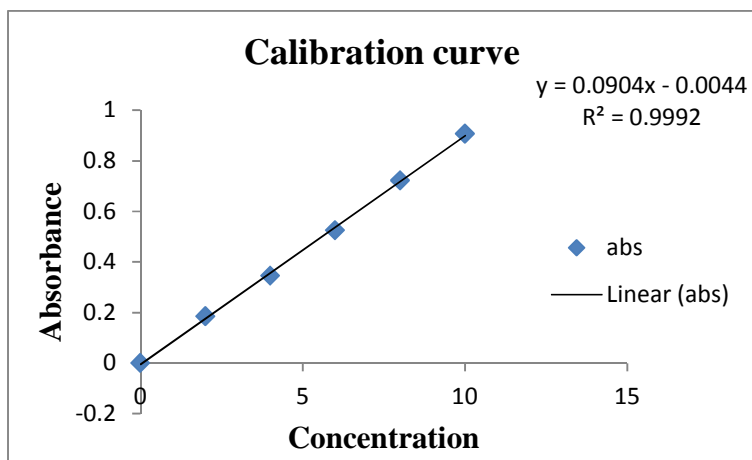
Calibration curve of simvastatin and lovastatin was constructed using using 0.1 N HCl as the medium. Graph was plotted by taking concentration on x-axis and absorbance on y-axis.

FT-IR graph for Simvastatin Pure drug and optimized formulation :
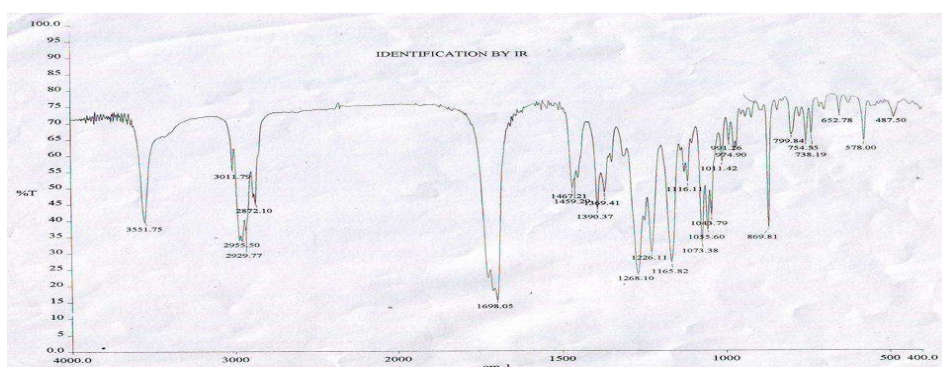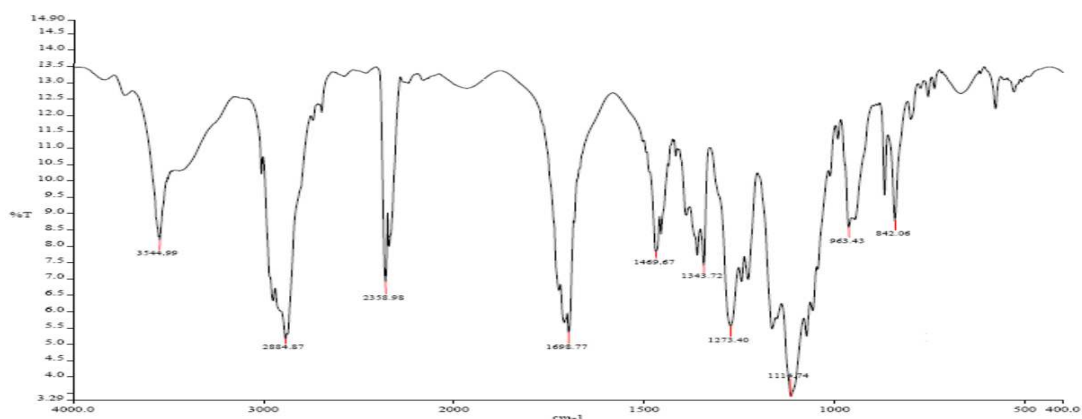
Fig 3, FT-IR graph for Simvastatin Pure drug

Fig 4, FT-IR graph for Simvastatin optimized formulation

FTIR spectroscopy was used to study the possible interactions between Simvastatin and the polymer in the Optimized formulation. All major peaks of Simvastatin were observed at wave numbers 3551 cm^{-1} (free O–H

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stretching vibrations); 3011, 2955, and 2872 cm^{-1} (C–H stretching vibrations); and 1698 cm^{-1} (stretching vibration of ester and lactone carbonyl functional groups) were retained in Optimized formulation, which clearly indicate that no interaction exists between pure drug and polymer in Optimized formulation. [Refer fig, 3, 4]

FT-IR graph for Lovastatin Pure drug and optimized formulation :
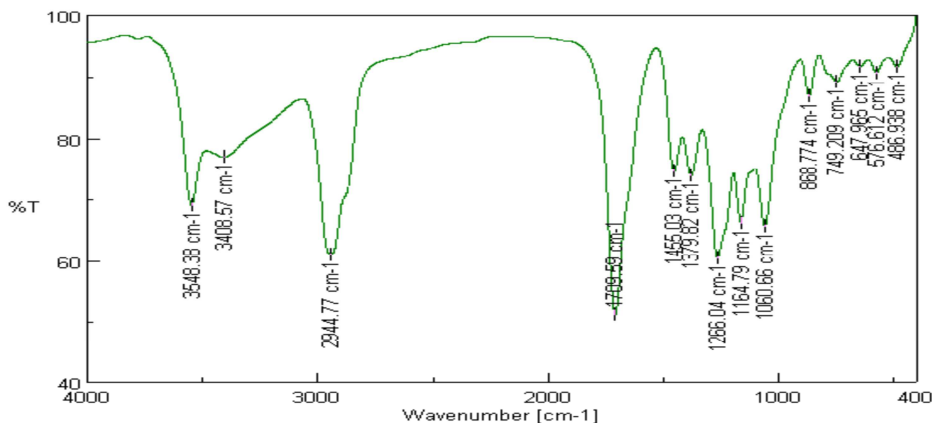
Fig 5, FT-IR graph for Lovastatin Pure drug
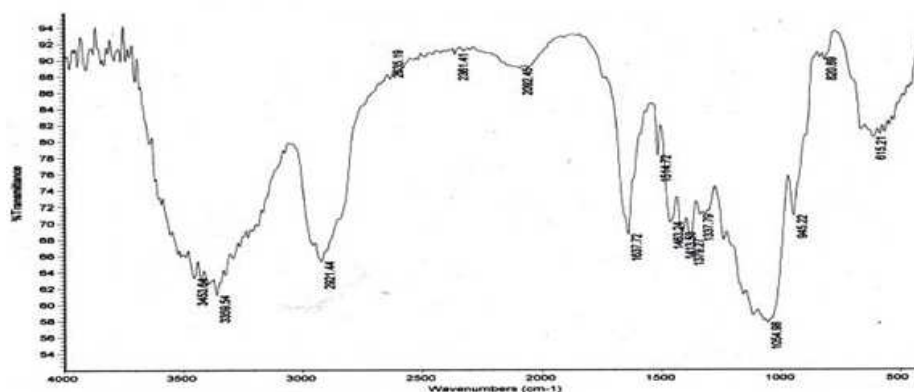

Fig 6, FT-IR graph for Lovastatin optimized formulation

Infrared spectra of Lovastatin as well as its optimized formulation are presented. Pure Lovastatin spectra showed sharp characteristic peaks at 3548.38, 1709.59, and 1266.04cm^{-1}.The FT-IR spectra of optimized formulation showed almost all the bands of pure drug, without affecting its peak position and trends, which indicated the absence of well-defined interactions between the drug and the polymer. [Refer fig, 5, 6]

Evaluation of the Prepared Tablets for Optimized Physical Parameters:

Table 6, Evaluation Parameters for Optimized physical formulation

parameters	SL1	SL2	SL3	SL4	SL5	SL6	SL7	SL8	SL9
Weight variation	350±0.4	349±0.3	348±0.7	350±0.1	349±0.3	350±0.2	349±0.9	350±0.8	350±0.1
Thickness (mm)	2.5±0.4	2.6±0.4	2.3±0.4	2.6±0.4	2.5±0.4	2.5±0.3	2.5±0.2	2.5±0.1	2.5±0.2
Hardness (kg/cm^2)	6.9±1.4	6.4±1.2	6.2±1.2	6.9±0.9	6.4±1.9	6.1±1.7	6.2±1.5	6.3±1.6	6.2±1.4
Friability (%)	0.12±0.2	0.16±0.23	0.15±0.19	0.15±0.26	0.15±0.22	0.12±0.1	0.15±0.4	0.10±0.5	0.13±0.7

All the formulations are tested for physical parameters such as Hardness, Thickness Weight variation, and Friability was found to be within the pharmacopeia limits. The results of the tests were tabulated. The drug content of the

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formulation was determined and was found to be within the permissible limit .This study indicated that all the formulations prepared were good.[Refer table , 6]

In-vitro dissolution Profiles for Simvastatin Immediate layer at 238nm in 0.1N HCl

Table 7, In-vitro dissolution Profiles for Simvastatin Immediate layer at 238nm

Time(Mins)	S1	S2	S3	S4	S5	S6
0	0	0	0	0	0	0
5	25.92	32.67	28.67	34.57	22.61	26.61
10	39.36	57.53	54.91	59.63	49.96	53.56
15	68.21	81.24	74.91	86.35	68.65	78.62
30	87.92	94.72	88.72	96.29	81.44	88.83
45	98.52	98.72	94.78	99.59	92.83	94.26

Fig 7, In-vitro dissolution Profiles for Simvastatin Immediate layer at 238nm in 0.1N HCl
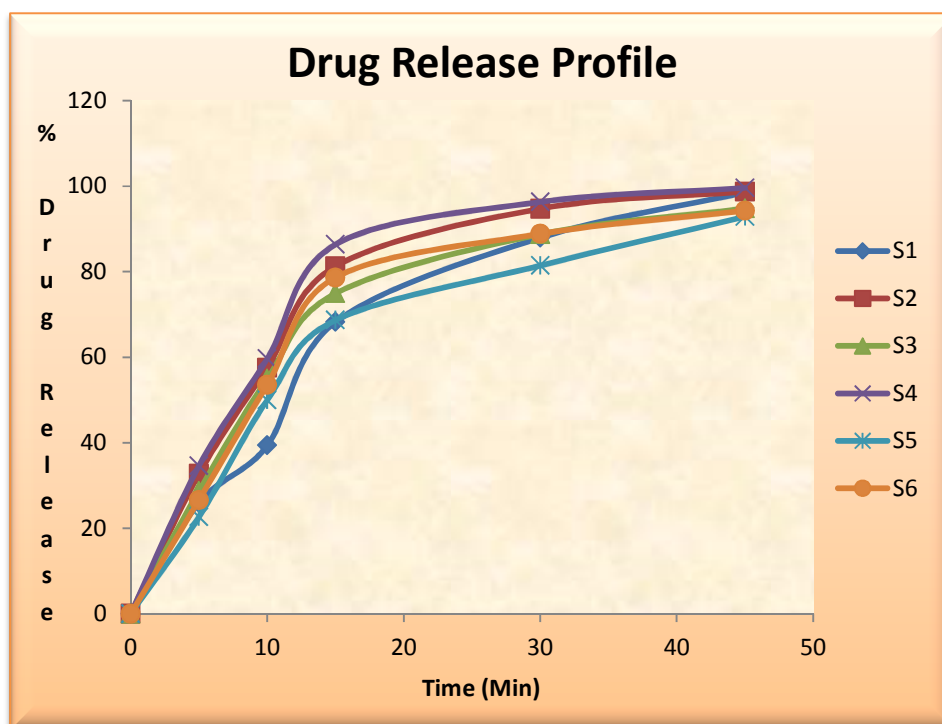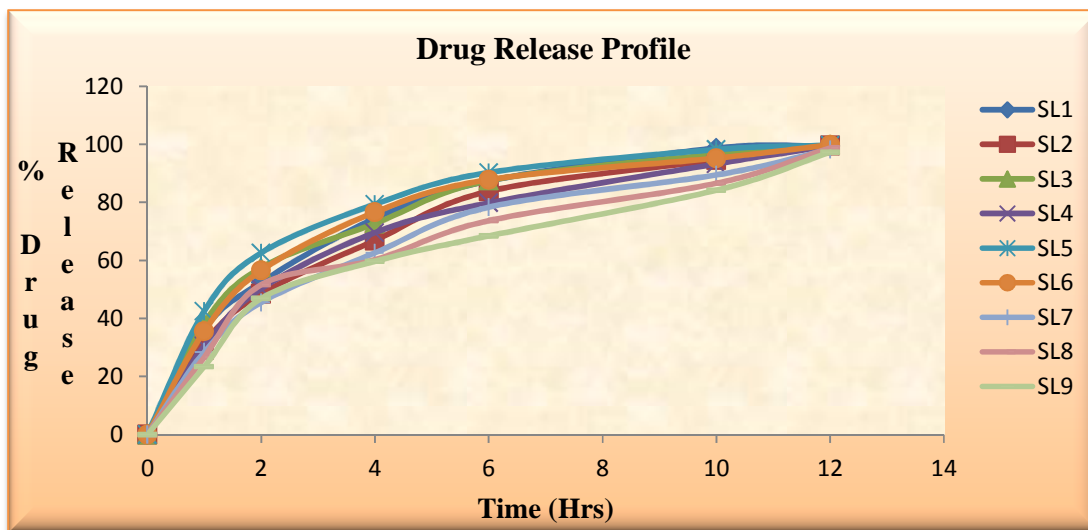

Among all formulations, S4 shows better drug release when compared with all other formulations. So formulation S4 selected as optimized formula consider as "S" in bilayer formulation. [Refer fig, 7]

In-vitro dissolution Profiles for Lovastatin Floating matrix layer in 0.1N Hcl 245nm

Table 8, In-vitro dissolution Profiles for Lovastatin Floating matrix layer at 245nm

Time (Hrs)	SL1	SL2	SL3	SL4	SL5	SL6	SL7	SL8	SL9
0	0	0	0	0	0	0	0	0	0
1	36.28	31.54	38.41	30.61	42.57	35.61	28.43	26.67	23.41
2	52.51	48.51	57.53	50.24	62.63	56.56	45.54	51.67	46.89
4	74.44	66.92	72.73	69.62	79.35	76.62	62.65	60.24	59.72
6	87.38	83.84	87.49	79.83	90.29	87.83	78.37	73.72	68.47
10	98.72	94.58	96.58	93.26	98.21	95.26	89.47	86.61	84.21
12	99.39	99.66	99.82	99.49	99.73	99.87	98.28	98.72	97.29

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Fig 8, In-vitro dissolution Profiles for Lovastatin Floating matrix layer in 0.1N Hcl 245nm

Among all formulations, SL9 shows better drug release when compared with all other formulations. So formulation SL9 selected as optimized formulation. [Refer fig, 8]

In-vitro Drug release kinetic studies of the optimized formulation:

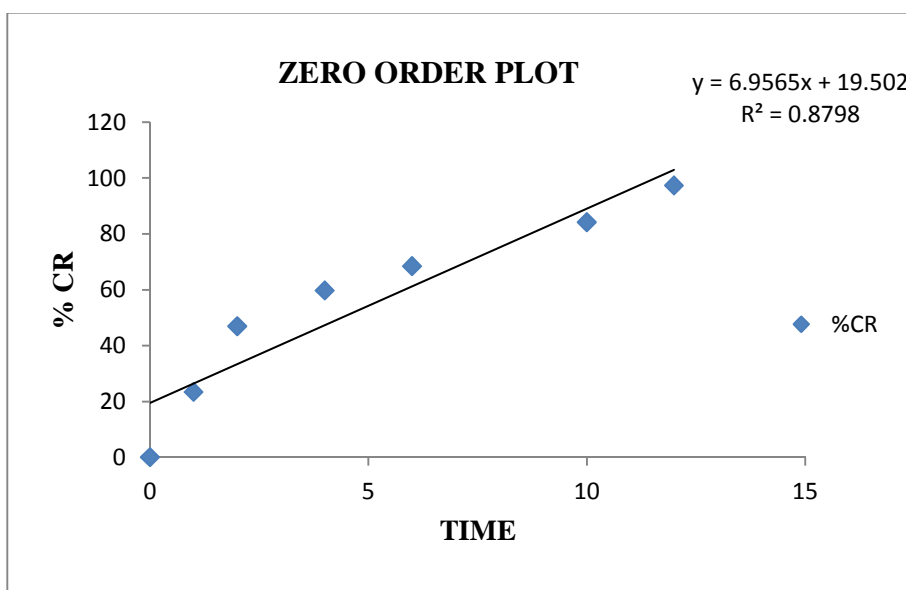**Fig 9, Zero order plot for optimized formulation**

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Table 9, Drug release Kinetic studies for optimized formulation

S.NO	TIME (Hrs)	LOG T	SQUARE ROOT OF TIME	%CR	%DRUG REMAINING	LOG %CR	LOG% DRUG RETAINED	CUBE ROOT OF %DRUG REMAINING
1	0	0	0	0	100	0	2	4.641589
2	1	0	1	23.41	76.59	1.369401	1.884172	4.246756
3	2	0.30103	1.414214	46.89	53.11	1.67108	1.725176	3.758883
4	4	0.60206	2	59.72	40.28	1.77612	1.605089	3.427913
5	6	0.778151	2.44949	68.47	31.53	1.8355	1.498724	3.159182
6	10	1	3.162278	84.21	15.79	1.925364	1.198382	2.508769
7	12	1.079181	3.464102	97.29	2.71	1.988068	0.432969	1.394194

Fig 10, First order plot for optimized formulation
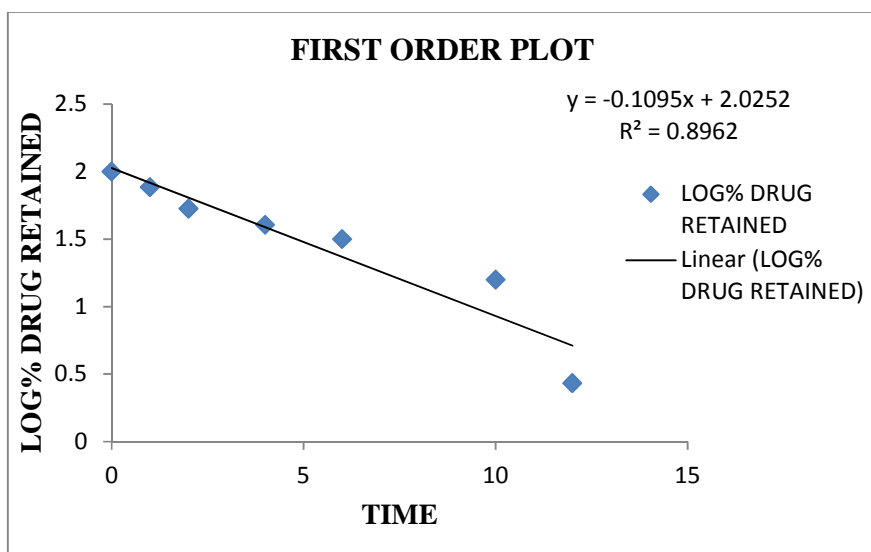
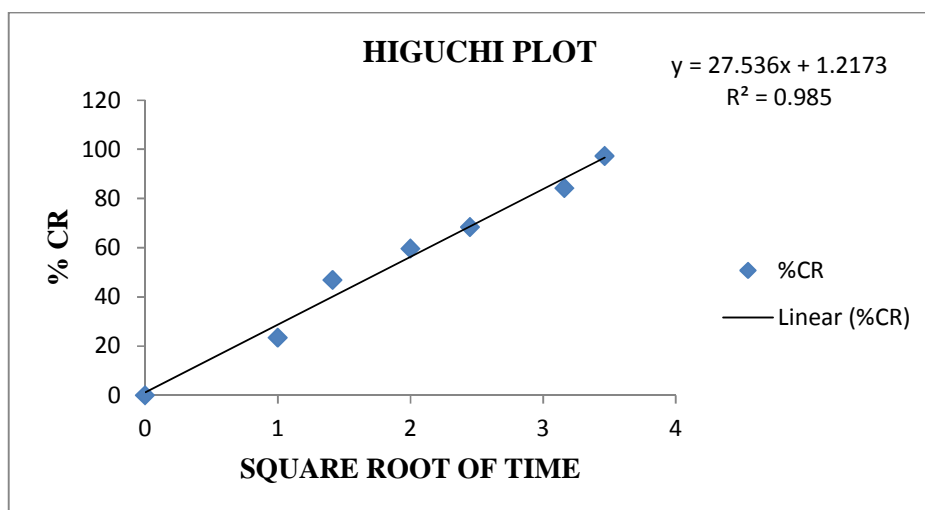**Fig 11, Higuchi plot for optimized formulation**

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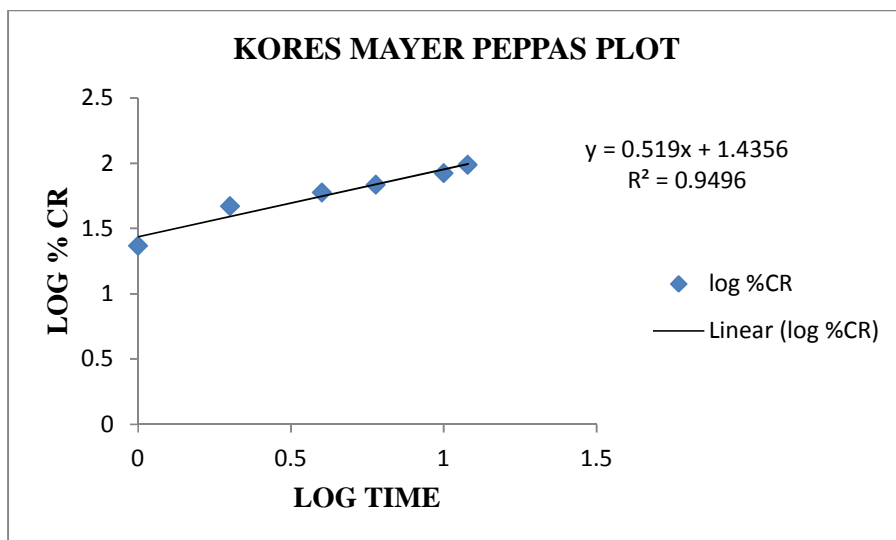**Fig 12, Kores mayer peppas plot for optimized formulation**

KORES MAYER PEPPAS PLOT

y = 0.519x + 1.4356
R² = 0.9496

Fig 13, Hixson Crowell plot for optimized formulation

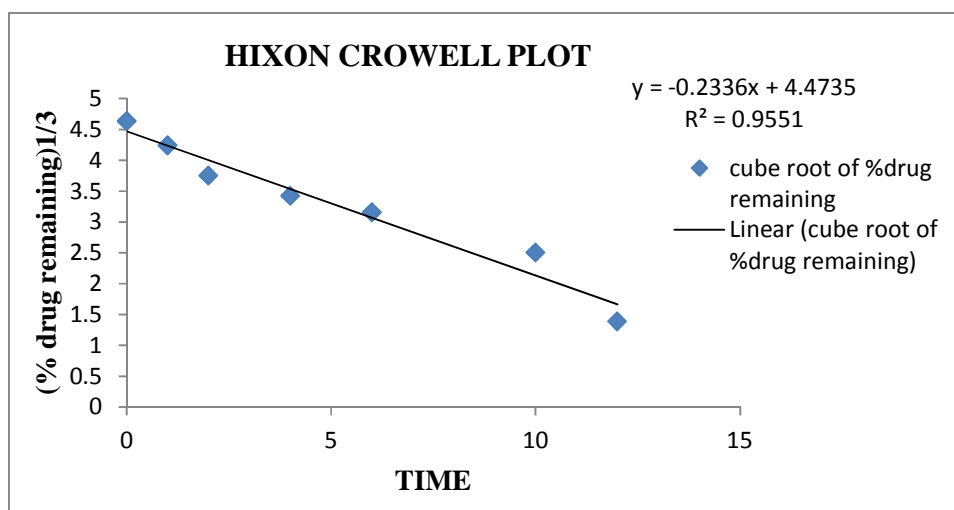**HIXON CROWELL PLOT**

y = -0.2336x + 4.4735
R² = 0.9551

Accelerated stability studies of the optimized formulation:

Table 10, Accelerated Stability Studies of Optimized Formulation

S.NO	Time in days	Physical changes	Mean % drug content ± SD					
			SIMVASTATIN			LOVASTATIN		
			25⁰C/60%	30⁰C/75%	40⁰C/75%	25⁰C/60%	30⁰C/75%	40⁰C/75%
1.	01	No Change	99.58 ±0.49	99.58 ±0.49	99.58 ±0.49	99.74±0.12	99.74±0.12	99.74±0.12
3.	30	No Change	99.32± 0.39	99.47± 0.42	99.46± 0.83	99.31 ±0.37	99.58 ±0.41	99.39 ±0.34
5.	60	No Change	99.21± 0.81	99.32 ±0.80	99.55 ±0.45	99.24 ±0.37	99.46 ±0.32	99.73 ±0.31
7.	90	No Change	99.17 ±0.43	98.94 ±0.73	99.71 ±0.19	99.10 ±0.91	99.21 ±0.43	99.81 ±0.99

In accelerated stability studies of optimized formulation it was observed that there was no change in physical changes even after storage at 40^0c/75% for three months. (Refer table, 10)

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CONCLUSION

It was concluded to prepare lovastatin part by direct compression method and simvastatin by wet granulation method and used for treating hypolipidemia.

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