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Design and Evaluation of Sustained Release Matrix Tablets of Antihyperlipidemic Drug

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ABSTRACT

The aim of present work was to design and evaluate sustained release matrix tablets of antihyperlipidemic drug. In the present investigation, polymers used in different combinations such as Eudragit RL100 and HPMC E5 in the ratio of 1:1, 1:2, 1:3 and vice versa with PVP K25 using direct compression technique were prepared. The tablets were evaluated for physical parameters like thickness, hardness, friability, weight variation, and in vitro release studies. The FTIR study indicated that the drug is stable in formulation. The maximum drug release was found to be 94.41% over a period for 12 hours for F4 batch, thus concluded that as the concentration of Eudragit RL100 is increased the drug release decreased. The drug release mechanism followed non-fickian transport from both polymer matrices. All the formulations were stored at 25⁰C/60% RH and 45⁰C/75% RH for 3 months. It showed that all the formulations were physically and chemically stable.

Keywords: Sustained release, direct compression, Matrix tablets, Simvastatin, EudragitRL100, HPMC E5.

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INTRODUCTION

For any drug therapy to be successful, the drug must reach to the target site or tissue or must reach to the systemic circulation in optimum concentration which should be maintained for desired time. Matrix tablets composed of drug and polymer as release retarding material offer the simplest approach in developing sustained release drug delivery system. Sustained release and controlled release will represent separate delivery process sustained release constitutes any dosage form that provides medication over an extended period of time.^{1,2} Controlled release however, denotes that, system is able to provide same actual therapeutic control, whether this be temporal nature, spatial nature, or both. Primary objective of sustained release drug delivery is to ensure safety and to improve efficiency of drugs as well as patient compliance.^{3,4} This can be achieved by better control of plasma drug levels and frequent dosing. Hyperlipidemia is an important risk factor in the initiation and progression of atherosclerosis and coronary heart disease. These are the most common form of heart disease of lipoprotein disorder and single most important cause of premature death in the developed world. In the UK one in four men and one in five women die from this disease. It is necessary to find a new formulation which is produced and have specific sustained or prolonged action without producing side effects.^{5,6}

Simvastatin is the antihyperlipidemic used to controlled elevated cholesterol, or hypercholesterolemia. Simvastatin is a member of the statin class of pharmaceuticals, is a synthetic derivate of a fermentation product of as per gillusterreus. It is structural analog of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme). Like other agents, it inhibits the enzyme hydroxymethylglutaryl-CoA (HMG-CoA) reductase. It has an extremely high affinity for this enzyme and was considered the most potent agent of the HMG-CoA class. Simvastatin is inactive lactone prodrug and hydrolyzed in the gastrointestinal track to the active β - hydroxyl derivative. It decreases total cholesterol, LDL cholesterol, triglycerides, and apolipoprotein B, while increasing HDL.⁷

MATERIALS AND METHOD

Simvastatin was obtained gift sample from Flemingo Pharma, Navi Mumbai, Maharashtra. PVP K25 and HPMC E5 were purchased from Analab fine Chemicals, Mumbai. Eudragit RL100 purchased from Evonik, Mumbai. Magnesium stearate, Talc, Lactose and other chemicals purchased from Research-lab fine chem industries, Mumbai.

PREFORMULATION STUDIES:

Solubility studies of drug:

The solubility of Simvastatin was determined at 0.1 N HCL and pH 6.8 Phosphate buffer to observe suitability of solution as a dissolution medium. Excess amount of drug were taken and dissolve in 5 ml of 0.1 N HCL and pH 6.8 Phosphate buffer at $37\pm 0.5^{\circ}\text{C}$ for 24 hours. After suitable dilutions, concentration were determined spectrophotometrically at 238 nm.⁸

Method of preparing the standard curve of Simvastatin in pH 6.8 Phosphate buffer: Solution

1st: 100 mg of Simvastatin was accurately weighed and dissolved in Methanol in 100 ml volumetric flask, then the volume was made up to 100 ml with pH 6.8 phosphate buffer. This was 1st stock solution containing 100 $\mu\text{g}/\text{ml}$.

Solution 2nd: From this 1st stock solution, 1 ml was pipetted out and transferred in to a 100 ml volumetric flask and volume was made up to 100 ml with 6.8 pH phosphate buffer which contained the concentration of 100 $\mu\text{g}/\text{ml}$. From 2nd stock solution aliquots equivalent to 2-10 μg (2,4,6,8,10) were pipette out in to a series of 10 ml volumetric flask with pH 6.8 phosphate buffer. The absorbance of these solutions was measured against the pH 6.8 phosphate buffer as a blank at 238 nm using UV-Visible double beam spectrophotometer. Then a calibration curve was plotted concentration in $\mu\text{g}/\text{ml}$ on X-axis and absorbance on Y-axis.⁹

Fourier Transport Infrared Spectroscopy:

The sample was crushed with KBr to make pellets under hydraulic pressure of 10 tons, and then the FTIR spectra were recorded between 600 and 4000 cm^{-1} . It was used to study the interaction between the drug and polymer. The drug and polymer must be compatible with one another to produce a stable product. Drug and polymer interaction were studied by using FTIR IR spectral analysis of pure Simvastatin and mixture of Simvastatin with HPMC E5, Eudragit RL100 and optimized batch F4 was carried out.¹⁰

Differential Scanning Calorimetry of drug:

The physical state of Simvastatin was characterized by the Differential Scanning Colorimetry thermogram analysis. The sample (about 3 mg) was placed in standard aluminium pans, and dry nitrogen was used as effluent gas. Sample was scanned at temperature speed of $10^{\circ}\text{C}/\text{min}$ and heat flow 50 to 350°C using Mettler Toledo DSC Thermal analyser.¹¹

X-ray Diffraction study of simvastatin:

The internal physical state of simvastatin was determined by X-Ray diffraction study and carried out using Broker, D5. The measuring condition was followed $\text{CuK}\alpha$ Radiation, nickel filtered, graphite monochromator, 45 kV voltage 40 mA current, sample run at $1^{\circ}(2\theta)$ min^{-1} from 0 to $60^{\circ}(2\theta)$.

Pre-compression evaluation parameter of powder:

Angle of Repose: Angle of repose was determined using funnel method. The height of the funnel was adjusted in such a way the tip of the funnel just touches the heap of the blends. Accurately weighed blend is allowed to pass through the funnel freely on to the surface.¹² The height and diameter of the of the powder cone was measured and angle of repose was calculated using the following equation,

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

Where, h= Height if pile,

θ = Angle of repose,

r= Radius of pile

Table 1: Relationship between Angle of repose (θ) and Powder flow

Angle of repose (θ) (degree)	Degree of flow
<25	Excellent
25-35	Good
30-40	Passable
>40	Very poor

Bulk density:

The sample under test was screened through sieve no. 60, the sample equivalent to 3gm was weighed accurately and filled in 100 ml of graduated cylinder, initial volume was measured and calculated according to formula,

$$\text{Bulk density} = M/V_0$$

Where,

M= mass of powder taken,

V_0 = apparent unstirred volume

Tapped density:

Tapped density was determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached minimum volume, the tapped density may be computed.

$$\text{Tapped density} = M/ V_t$$

Where, M=weight of powder taken,

V_t = tapped volume.

Hausner's Ratio:

Hausner's Ratio is an indication of the flow ability of powder and the ratio is greater than 1.25 is considered to be an indication of poor flowability.¹³Hausner's Ratio was determined by the

following equation,

Hausner's Ratio= Tapped density/ Bulk density

Carr's Index:

The compressibility of sample blend was determined from their apparent bulk density and tapped densities by using following formula,

Table 2: Grading of powder for their flow properties

Carr's index (%)	Degree of flow
5-15	Excellent
12-16	Good
18-21	Fair
23-35	Poor
35-38	Very poor
<40	Extremely poor

% compressibility index= Tapped density – Bulk density / Tapped density × 100

Preparation of Sustained release matrix tablets of Simvastatin:

The sustained release matrix tablets were prepared by direct compression technique. First accurately weighed quantity of Simvastatin, HPMC E5, Eudragit RL100 and PVP K25 were mixed for 5 minutes in mortar with pestle, except magnesium stearate which was added at last and mixed before passing the mixture through sieve no: 60. Finally the mixture was compressed using 8 mm concave shaped punches in 12 station rotary tablet punching machine. The resulting matrix tablets were subjected to various evaluation parameters.¹⁴The composition of sustained release matrix tablets are shown in table 3.

Table 3: Composition of Sustained Release Matrix Tablets of Simvastatin

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7
Simvastatin	40	40	40	40	40	40	40
PVP K25	30	30	30	30	30	30	30
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Eudragit RL100	-	40	20	20	20	40	60
HPMC E5	40	-	20	40	60	20	20
Lactose	135	135	135	115	95	115	95
Total weight	250	250	250	250	250	250	250

Post compression parameters:

Weight variation: Twenty tablets were randomly selected weighed and the average weight of standard deviation of 20 tablets calculated.

Thickness: The thickness of tablets was measured by using digital vernier caliper, twenty tablets from each batch were randomly selected and thickness was measured.

Hardness; Hardness was measured using Pfizer hardness tester, for each batch three tablets were tested.

Friability: Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 min, after revolution the tablets were dusted and weighed and friability calculated by using formula.¹⁵

$$\text{Friability} = \frac{W1 - W2}{W1} \times 100$$

Where, W1 = Weight of the tablets before friability test (mg)

W2 = Weight of the tablets after friability test (mg)

Drug content uniformity: Ten tablets were randomly selected and allowed to equilibrate with HCL acid buffer of pH 1.2 overnight and the solution was filtered (0.22 μ , Millipore) after 24 hours. Suitable dilution made with HCL acid buffer of pH 1.2 to get the concentration in beer's range. Absorbance of the solution was analysed spectrophotometrically at 238 nm against suitable blank using UV-visible Spectrophotometer (1800, Shimadzu, Kyoto, Japan) and drug content per tablet was calculated.¹⁶

In vitro drug release studies: In vitro dissolution of Simvastatin sustained release formulation were studied in USP type-2 dissolution apparatus employing a paddle stirrer at 50 rpm using 900 ml of phosphate buffer solution at pH 1.2, 6.8 as dissolution medium maintain at temperature of $37 \pm 0.5^\circ\text{C}$. One tablet was used in each test. Aliquots of dissolution medium (1 ml) were withdrawn at the regular intervals of time (1 hour) and equivalent amount of fresh medium was replaced to maintain a constant volume. After each sampling suitably was diluted up to 10 ml with suitable buffer solution. Then 1 ml of the resulting solution was diluted up to 10ml with suitable buffer solution medium and the resolution was filtered. The amount of drug dissolved was determined by UV-visible spectrophotometer by measuring the absorbance at 238nm. Average percentage of drug release with standard deviation were calculated and recorded. Cumulative percentage of Simvastatin released was plotted against time.¹⁷

Kinetic analysis:

To analyse the mechanism of drug release rate kinetics of all the formulations, the results of in vitro release profiles were fitted into first order kinetic models, Higuchi model, zero order kinetic model and Korsmeyer peppas model.¹⁸ The results of invitro release profiles were plotted in models of data as follows:

1. Log cumulative percent drug remaining versus time (first order kinetic model)
2. Cumulative percent drug release versus square root of time (Higuchi model)
3. Log Cumulative percent drug release versus time (Zero order kinetic model)

4. Log Cumulative percent drug release versus log time (Korsmeyer model)
5. Cube root of % drug release versus time (Hixson crowell)

Stability studies:

Stability studies were carried out to assess the stability of all formulated sustained release matrix tablets. The prepared tablets were kept at 25⁰C/60%RH and 40⁰C/75%RH for 3 months. At 30 days intervals the tablets were evaluated for all physical parameter and in vitro release studies were also determined.¹⁹

RESULTS AND DISCUSSION

Table 4: Solubility of Simvastatin in various media

Sr no.	Media	Solubility (mg/ml)
1	0.1 N HCL	19.48
2	pH 6.8 Phosphate buffer	42.42

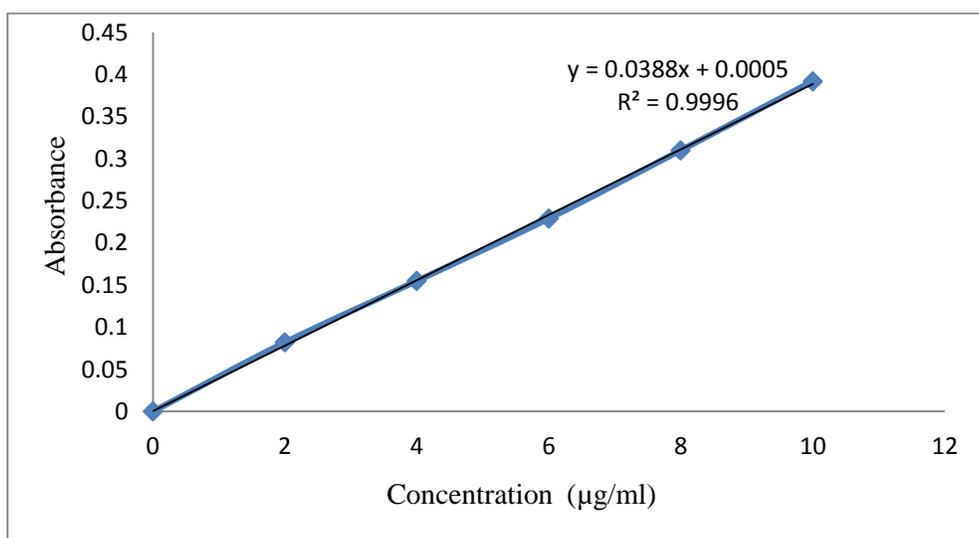


Figure 1: Calibration curve of Simvastatin in pH 6.8 Phosphate buffer

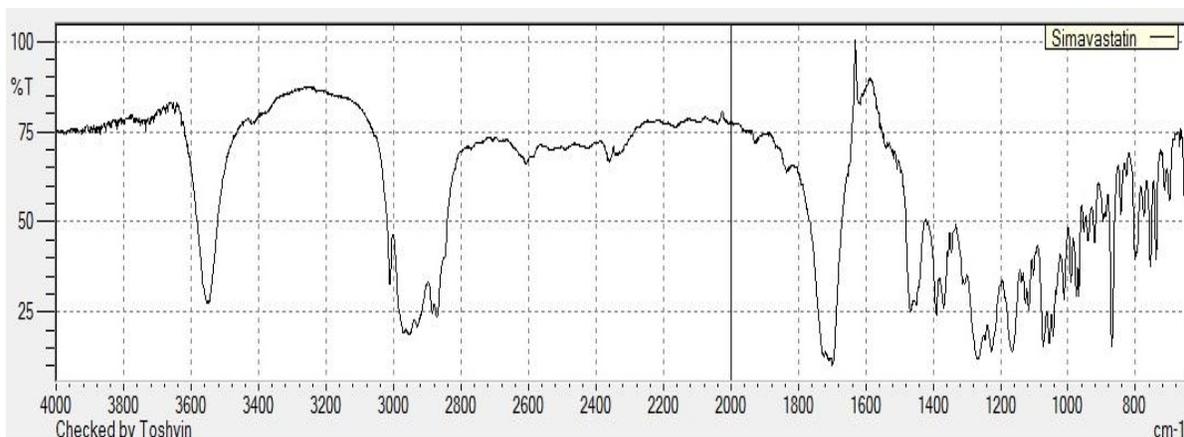
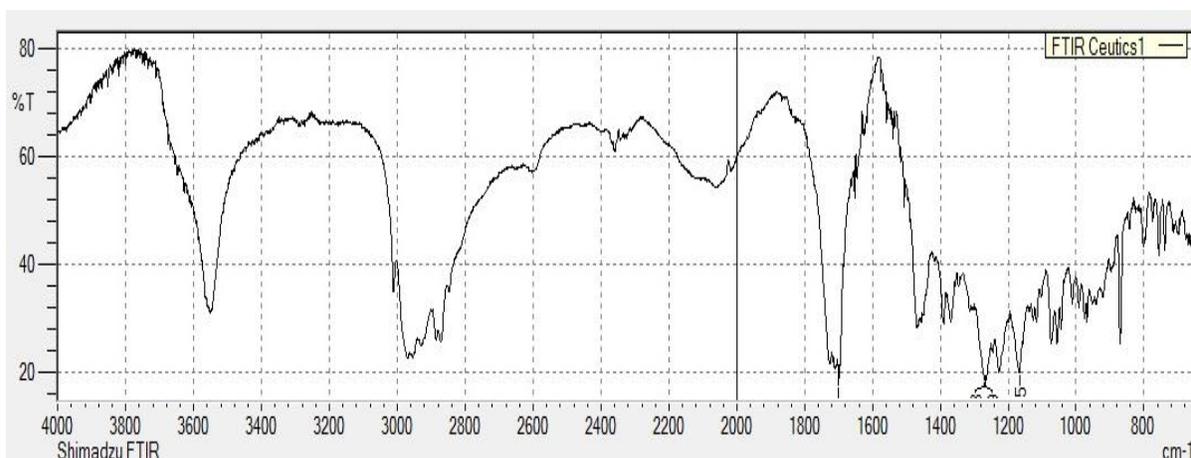
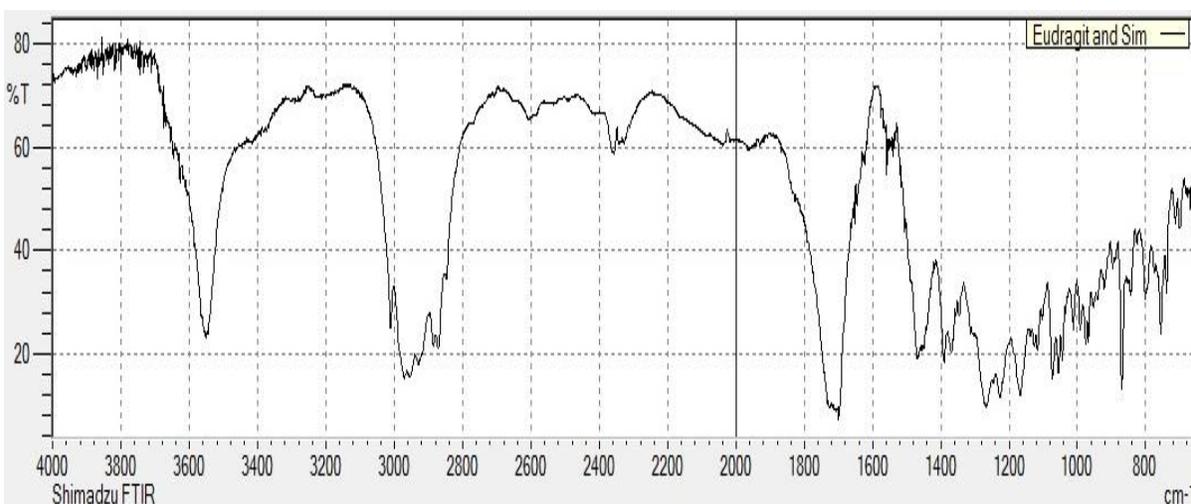
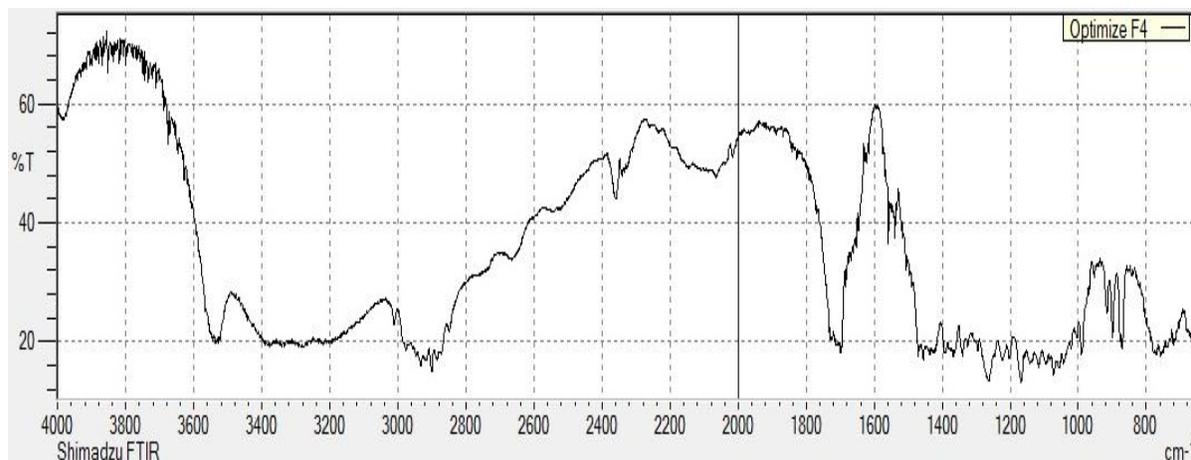


Figure 2: FTIR of Simvastatin (Pure drug)

Compatibility study of drug with excipients by FTIR**Figure 3: FTIR of Simvastatin + HPMC E5****Figure 4: FTIR of Simvastatin + Eudragit RL100****Figure 5: FTIR of optimized Formulation 4****DSC studies of Simvastatin:**

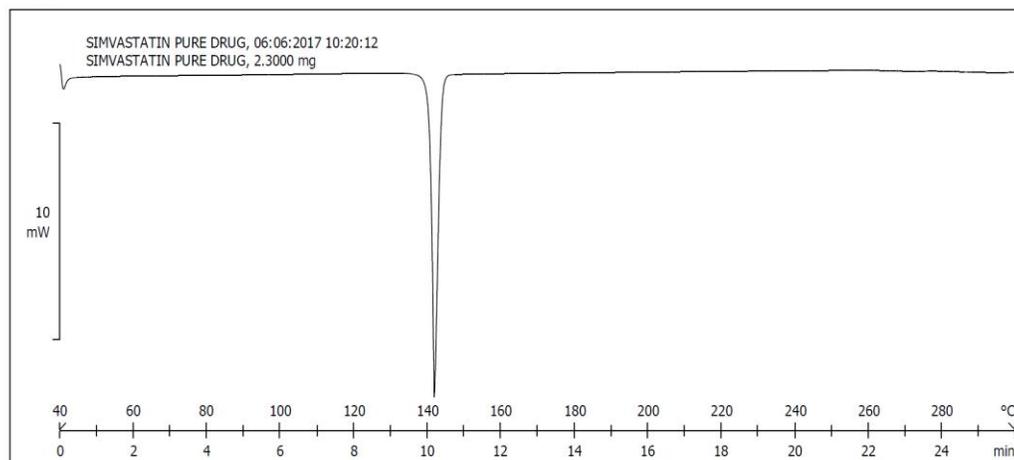


Figure 6: DSC of Simvastatin (Pure drug) DSC image of Simvastatin showed a characteristic endothermic peak at 141°C which corresponds to its melting point.

XRD studies of Simvastatin:

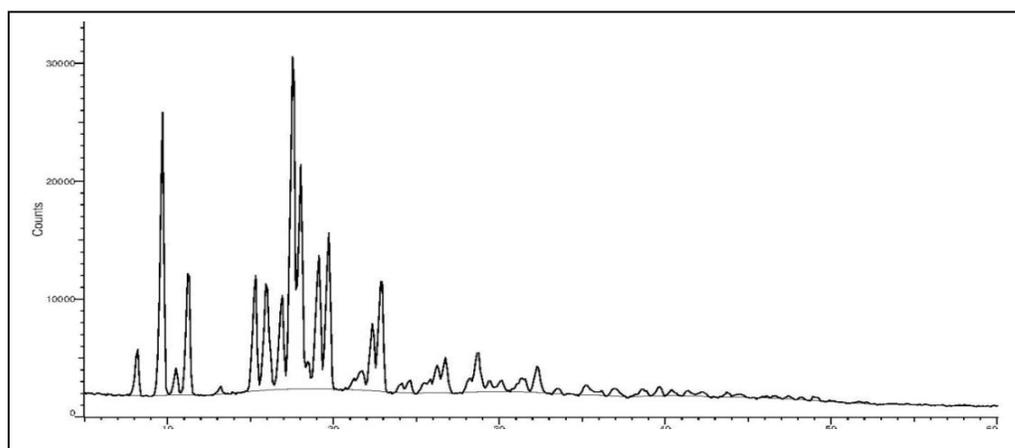


Figure 7: XRD of Simvastatin (Pure drug)

The presence of numerous distinct peaks in X-Ray diffraction spectra indicated Simvastatin was pure drug and peaks appeared at diffraction angle.

Evaluation of Powder blend:

Table 5: Evaluation parameters of pre-compression study

Batch no.	Angle of repose (θ)	Bulk density (g/ml)	Tapped density (g/ml)	% Carr's Index	Hausner's ratio
F1	27.47±0.84	1.36±0.03	1.53±0.04	11.11±1.45	1.12±0.03
F2	25.17±0.41	1.40±0.02	1.63±0.16	14.11±1.64	1.16±0.04
F3	28.36±0.37	1.55±0.05	1.78±0.06	12.92±1.34	1.14±0.01
F4	30.54±0.54	1.26±0.01	1.42±0.14	11.26±1.62	1.12±0.04
F5	28.10±0.67	1.22±0.05	1.45±0.12	15.86±1.43	1.18±0.02
F6	27.02±0.47	1.51±0.02	1.75±0.09	13.71±1.52	1.15±0.01
F7	28.76±0.31	1.37±0.08	1.57±0.18	12.73±1.16	1.14±0.05

Evaluation of Sustained Release Matrix Tablets of Simvastatin:

Table 6: Evaluation parameters of sustained release matrix tablets of simvastatin

Batch no.	Thickness (mm)	Hardness (kg/cm ²)	% Friability	Weight variation (mg)	Content uniformity
F1	3.52±0.13	4.0±0.17	0.146±0.09	248±5	92.5±0.34
F2	3.76±0.03	4.8±0.24	0.148±0.18	250.7±5.7	94.5±0.26
F3	3.98±0.10	5.0±0.18	0.151±0.43	246±4.2	95.0±0.54
F4	3.61±0.09	5.5±0.15	0.134±0.18	249±5	97.5±0.48
F5	3.78±0.35	4.9±0.22	0.126±0.32	251±6	96.75±0.62
F6	3.96±0.05	5.4±0.19	0.123±0.56	246±5.4	95.25±0.41
F7	3.93±0.09	5.1±0.28	0.141±0.41	249±5.1	94.5±0.65

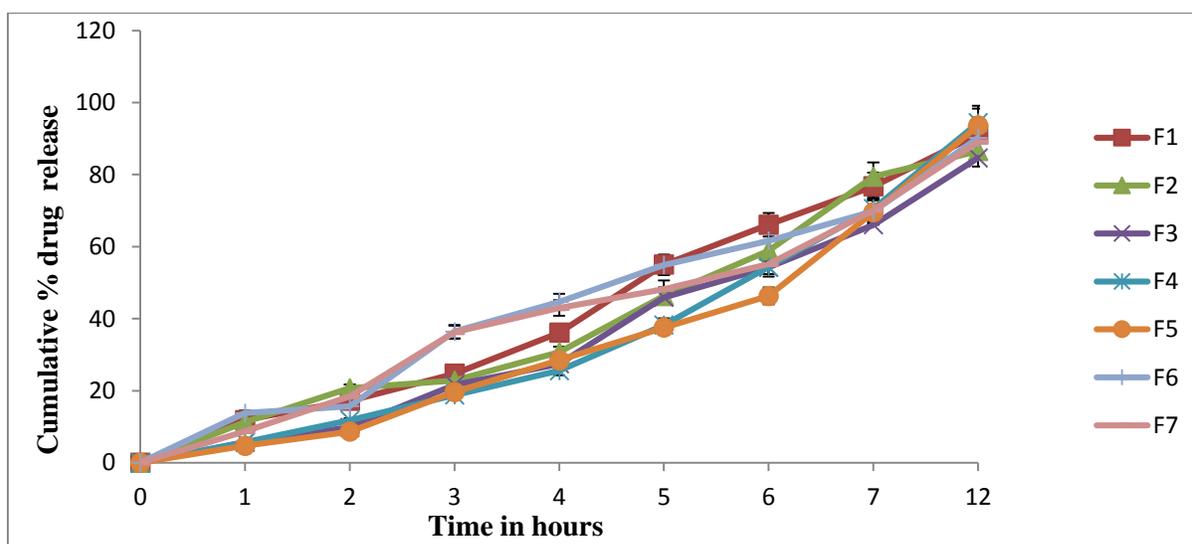


Figure 8: Dissolution profiles of Simvastatin sustained release tablets for all formulations

Kinetic analysis:

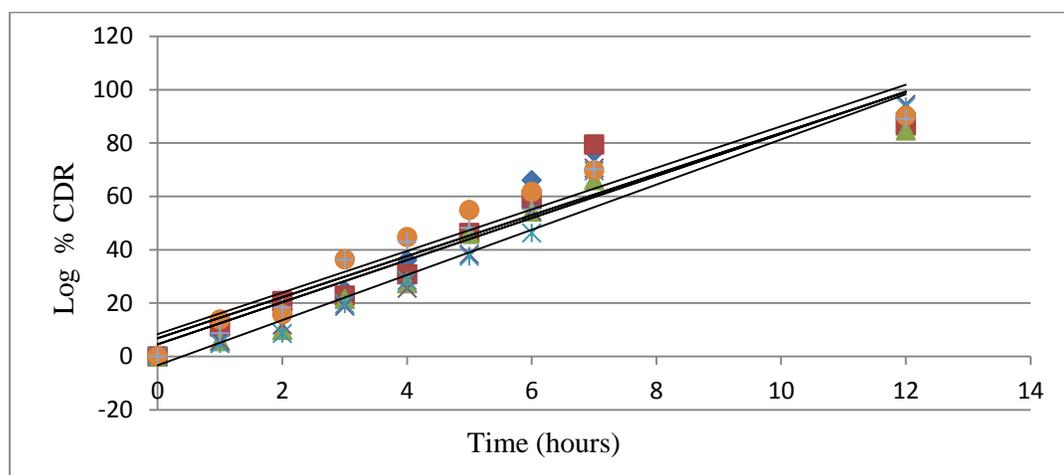


Figure 9: Comparative Zero Order release profile of formulations F1 to F7

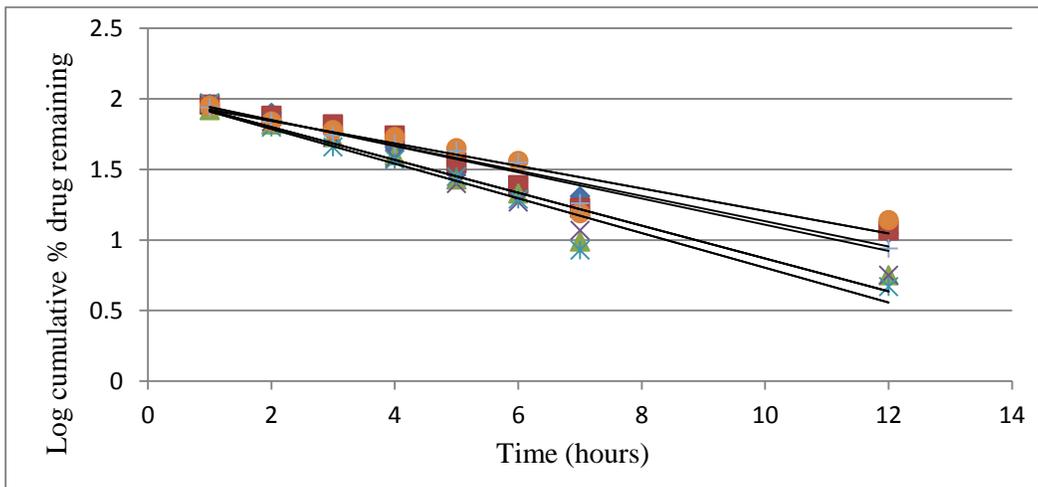


Figure 10: Comparative First Order release profile of formulations F1 to F7

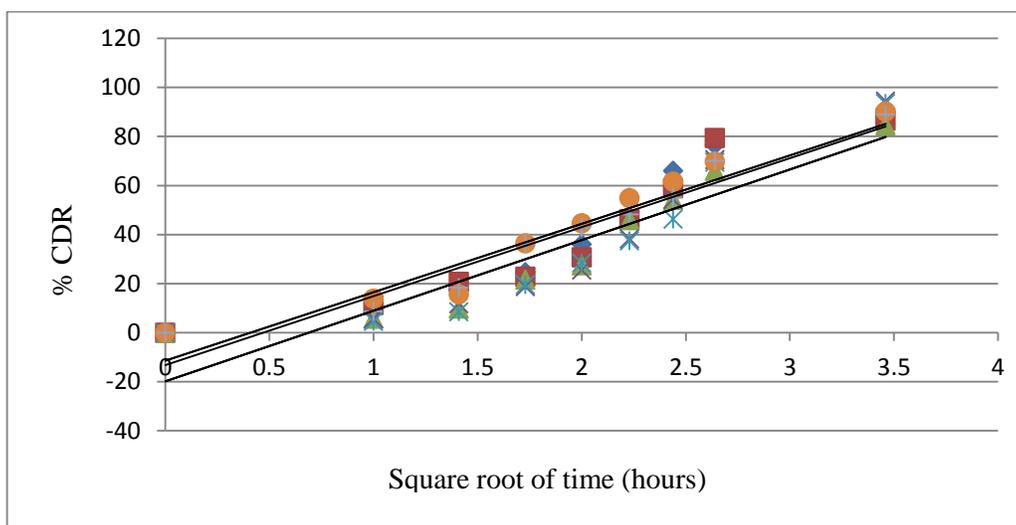


Figure 11: Comparative Higuchi release profile of formulations F1 to F7

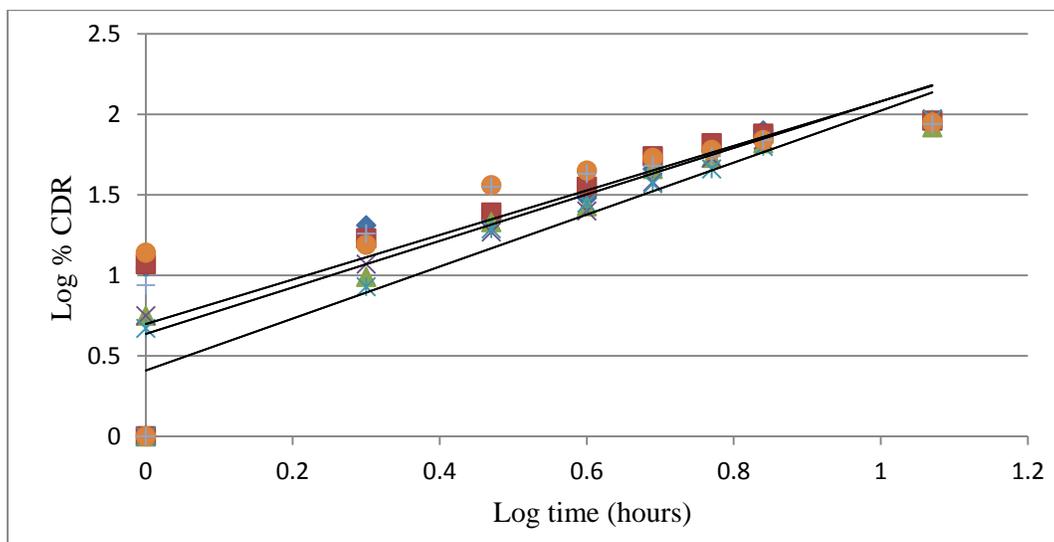


Figure 12: Comparative Korsmeyerpeppas release profile of formulations F1 to F7

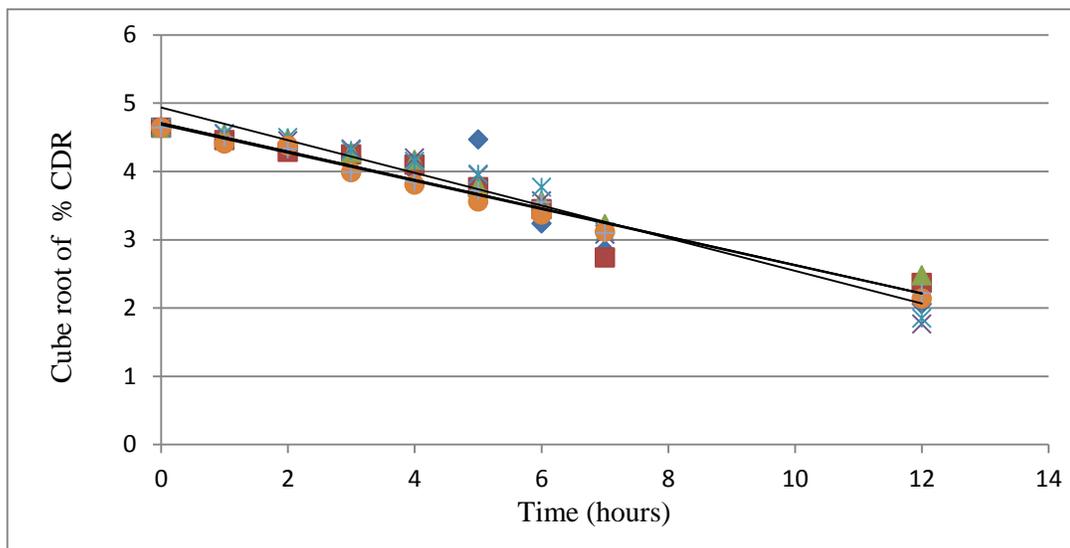


Figure 13: Comparative Hixson crowell profile of formulations F1 to F7

Stability study:

Table 7: Stability study of F4 batch stored at 25°C/60% RH

Storage period	Hardness Kg/cm ²	% Friability	% drug content	% CDR
Initial	5.5±0.15	0.134±0.18	97.5±0.48	94.41±1.44
After 1 month	5.3±0.46	0.136±0.31	97.0±0.12	94.01±1.48
After 2 month	5.1±0.13	0.138±0.21	96.92±0.34	93.48±1.35
After 3 month	5.0±0.09	0.139±0.36	96.02±0.18	92.69±1.96

Table 8: Stability study of F4 batch at stored 45°C/75% RH

Storage period	Hardness Kg/cm ²	% Friability	% drug content	% CDR
Initial	5.5±0.15	0.134±0.18	97.5±0.48	94.41±1.44
After 1 month	5.1±0.47	0.140±0.10	96.95±0.10	92.03±0.24
After 2 month	4.9±0.21	0.143±0.28	96.82±0.28	91.00±0.32
After 3 month	4.8±0.13	0.145±0.36	95.72±0.62	90.35±0.05

CONCLUSION

The present study was undertaken with the aim of design and evaluation of sustained release matrix tablets of antihyperlipidemic drug using different polymers and evaluating the tablets by physical characterization, in-vitro release kinetics and stability studies.

Various sustained release matrix tablet formulations of simvastatin with various polymers, HPMC E5, Eudragit RL100 in different ratios were formulated by direct compression technique. FTIR studies revealed that there was no chemical interaction between drug and excipients. Powder were evaluated for Bulk density, Tapped density, Compressibility index, Angle of repose, Hausner's ratio before being punched as tablets. Results of pre-formulations studies for different batches of Simvastatin prepared using selected excipients, directed for further course of formulation.

Observation of physical characterization for all formulations showed that, all of them comply with the specifications of official pharmacopoeias.

Results of in-vitro release profile study indicated that among all the formulation, F4 was the most promising formulation with 94.41% drug release within 12 hours. The drug release mechanism followed non-fickian transport from both polymer matrices.

The tablets were evaluated for physical parameters, in-vitro release profile and drug content, after one and three months period there was no significant changes observed in any of the studied parameters during the storage period. The matrix tables were evaluated by their appearance, taste, hardness, drug content, in-vitro dissolution release. The studies indicated that no significant change was found in all the above parameters. This indicates that formulation is stable at storage conditions. Based on the observations and results, it was concluded that formulation F4 to be an ideal formulation for 12 hours release as it fulfills all the requirements for sustained release tablet.

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