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FORMULATION AND EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS OF SIMVASTATIN

M.Ravali [*1], K.Navaneetha[2], B.Venkateswara Reddy[2], N.Karthik[3]

[1]Department of Pharmaceutics, Vaagdevi College of Pharmacy, Warangal, A.P, India.

[2]Department of Pharmaceutics, St.Pauls College of Pharmacy, Turkayamjal (V), Hayathnagar (M), R.R, A.P, India.

[3]Department of Pharmacology, Aurobindo College of pharmaceutical sciences, Warangal, A.P, India.

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***Author for Correspondence**
Navaneetha Reddy
Department of Pharmaceutics, St.Pauls college of Pharmaceutics.
Turkayamjal (V) Hayathnagar (M), R.R.Dist- 501510, A.P, INDIA

ABSTRACT

The purpose of this study is to formulate a controlled release matrix tablet of simvastatin a drug which is used in the treatment of dyslipidemia. Simvastatin has a short biological half life of 3 hours which necessitates multiple daily dosing hence a controlled release formulation of simvastatin is developed. Controlled release tablets of simvastatin are prepared by direct compression method by using various polymers such as Eudragit RLPO and Eudragit RSPO. FTIR studies revealed that drug and the excipients used were compatible with each other. The precompression studies revealed that the powder blend has good flow properties, and the post compression studies shows that the results were within the limits. Matrix tablet of Simvastatin that contained a blend of drug and Eudragit RLPO in 1:1.5 showed 99.41% of drug release in a period of 24 hours. The drug release mechanisms for formulations were best described by Higuchi's and Krosmeyer Peppas. The drug release of optimised formula followed non fickian type of diffusion. Thus, concluded that the control release matrix tablets prepared by using Eudragit RLPO were more promising than the Eudragit RLPO.

KEYWORDS: Control Release; Simvastatin; Dyslipidemia; Eudragit RLPO; Eudragit RSPO; Non fickian Diffusion.

INTRODUCTION

Oral controlled release delivery systems are programmed to deliver the drug in predictable time frame that will increase the efficacy, minimize the adverse effects and increase the bioavailability of drugs. Oral drug delivery is the most widely utilized route of administration among all alternatives that have been explored for systemic delivery of drug via various pharmaceutical products of different dosage forms[1].

Availability of wide variety of polymers and frequent dosing intervals help the formulation scientist to develop controlled /sustained release products. Popularity of the route may be ease of administration as well as due to traditional belief that by oral administration the drug is well absorbed into the food stuff ingested daily[2]. Oral controlled release (C. R) / sustained release (S. R) products provide an advantage over conventional dosage forms by optimizing bio-pharmaceutical, pharmacokinetic and pharmacodynamic properties of drugs.

Controlled release (C.R) / Sustained release (S. R) pharmaceutical products have gradually gained medical acceptance and popularity. Regulatory approval for marketing and their pharmaceutics superiority and clinical benefits over immediate release pharmaceutical products have been increasingly recognized[3, 4]. Modified release oral dosage forms have brought new lease of life into drugs that have lost market potential due to requirement of frequent dosing, dose related toxic effects and gastrointestinal disturbances.

The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments or promptly dissolving dosage forms as presently recognized[5, 6].

Controlled release dosage forms cover a wide range of prolonged action formulations which provide continuous release of their active ingredients at a predetermined rate and for a predetermined time. The majority of these formulations are designed for oral administration; however, recently such devices have also been introduced for parenteral administration, ocular insertion and for transdermal application[7]. The most important objective for the development of these systems is to furnish an extended duration of action and thus assure greater patient compliance.

The basic rationale for controlled drug delivery is to alter the pharmacokinetic and pharmacokinetics of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and or physiological parameters inherent in a selected route of administration[8]. It is desirable that the duration of drug action become more to design properly. Rate controlled dosage form, and less, or not at all a property of the drug molecules inherent kinetic properties.

The aim of this present work is to formulate a controlled release matrix tablet of simvastatin using various polymers such as Eudragit RLPO and Eudragit RSPO. Simvastatin has a short biological half life of 3 hours which necessitates multiple daily dosing hence the present study was aimed to develop a controlled release formulation of simvastatin[9].

To provide a drug delivery system for continuous release of drug at controlled rate which increases the patient compliance, effectiveness of therapy and reduces the chances of adverse effect by maintaining the plasma drug concentration at the same level within therapeutic range for the required period of time[10, 11].

MATERIALS AND METHODOLOGY

Materials

Simvastatin was obtained as a gift sample from Aurobindo Pharmaceuticals Hyderabad, India. Eudragit RLPO and Eudragit RSPO from Universal laboratories Hyderabad, India, Aerosil and Microcrystalline cellulose from Loba chemie Pvt. Ltd, Mumbai, PVPK30 and Magnesium stearate from Qualikems Fine chemicals Pvt. Ltd, New Delhi.

Methodology

Drug-Excipient Compatibility Studies

The compatibility studies were performed using Fourier Transform- Infra Red Spectroscopy. The drug and drug- polymer physical mixtures were scanned in the region of 4000-400 cm^{-1}.

Formulation Development

Preparation of simvastatin matrix tablets

All the matrix tablets each containing 20mg of simvastatin were prepared by direct compression method.

Method

Accurately weighed amounts of drug, polymer and diluents were mixed geometrically in a mortar, this mixture was passed through 40 sieve and thoroughly mixed in a polythene bag for 15 minutes. The powder blend was then lubricated by the addition of magnesium stearate and talc and compressed into tablets on a rotary punching machine using 6mm round, flat faced punches. The total weight of the matrix tablets was 100 mg with different drug polymer ratios like 1:0.25, 1:0.5, 1:0.75, 1:1, 1:1.25 and 1:1.5. The polymers used were Eudragit RLPO and Eudragit RSPO. MCC (water-insoluble) was used as a diluent for the preparation of matrix tablets.

Formulations

Table 1: Composition of simvastatin Tablets containing Eudragit RLPO

Formulation code	F1	F2	F3	F4	F5	F6
Simvastatin	20	20	20	20	20	20
Eudragit RLPO	5	10	15	20	25	30
MCC	68.8	63.8	58.8	53.8	48.8	43.8
PVPK30	5	5	5	5	5	5
Magnesium stearate	0.6	0.6	0.6	0.6	0.6	0.6
Aerosil	0.6	0.6	0.6	0.6	0.6	0.6
Total weight(mg)	100	100	100	100	100	100

Table 2: Composition of simvastatin Tablets containing Eudragit RSPO

Formulation code	F7	F8	F9	F10	F11	F12
Simvastatin	20	20	20	20	20	20
Eudragit RSPO	5	10	15	20	25	30
MCC	68.8	63.8	58.8	53.8	48.8	43.8
PVPK30	5	5	5	5	5	5
Magnesium stearate	0.6	0.6	0.6	0.6	0.6	0.6
Aerosil	0.6	0.6	0.6	0.6	0.6	0.6
Total weight(mg)	100	100	100	100	100	100

Characterisation Of Pre-Compression Blend

Angle of repose[12]

The accurately weighed powder blend was taken in the funnel. The angle of repose of powder blend was determined by the funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the powder blend. The powder blend

was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\text{Tan } \theta = h/r$$

Where, h and r are the height and radius of the powder cone.

Bulk density

A quantity of 2 gm of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on continued until no further change in volume was noted. LBD and TDB were following equations.

$$\text{LBD} = \frac{weight\ of\ the\ powder\ blend}{untapped\ volume\ of\ the\ packing}$$

$$\text{TBD} = \frac{weight\ of\ the\ powder\ blend}{tapped\ volume\ of\ the\ packing}$$

Total Porosity

Total porosity was determined by measuring the volume occupied by a selected weight of a powder (Vbulk) and the true volume of the powder blend (The space occupied by the powder exclusive of spaces greater than the intermolecular spaces,v).

$$\text{POROSITY} = \frac{Vbulk - V}{bulk\ density} \times 100$$

Hausner's Ratio

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density.

$$\text{Hausner's Ratio} = \frac{Tapped\ density}{Bulk\ density}$$

Compressibility index (Carr's Index): CI

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material is the more flow able it is. A material having values of less than 20% has good flow property.

$$\text{CI} = \frac{(Tapped\ density - bulk\ density)}{Tapped\ density} \times 100$$

Evaluation Of Simvastatin Tablets

The tablets were evaluated for in process and finished product quality control tests i.e. thickness, weight variation, hardness, friability, assay, drug content and *in-vitro* release studies.

Weight variation[13]

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average.

Table 3: Average weight of the Tablets with respect to the % deviation allowed

Average Weight of Tablets(I.P)	Maximum% deviation allowed	Average weight of tablets(U.S.P)
Less than 80 mg	10	Less than 130 mg
80mg-250mg	7.5	130-324mg
More than 250mg	5	More than 324mg

Tablet hardness[13]

The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. Six tablets were chosen randomly and tested for hardness. The average hardness of six determinations was recorded.

Friability[13]

20 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off to remove fines and again weighed and the weight was recorded.

$$\% \text{ of Friability} = \frac{W2 - w1}{w2}$$

Where: w1= weight of the tablet before test; w2 = weight of the tablet after test

Thickness

Thickness of tablets were measured using vernier calipers.

Content uniformity[14]

The tablets were tested for their drug content uniformity. 6tablets were weighed randomly and powdered. The powder equivalent to 100 mg of Simvastatin was weighed accurately and

dissolved in 100ml of pH 6.8 phosphate buffer followed by stirring for 10mins. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured by using UV-Visible spectrophotometer at 239nm using pH 6.8 phosphate buffer.

In-vitro Dissolution studies[15]

In-vitro dissolution study of Simvastatin was carried using USP dissolution test apparatus. Dissolution was carried out for first two hours in 0.1N Hcl and then in 6.8 pH phosphate buffer upto 24 hours. 5 ml samples were withdrawn at pre-determined time intervals and replaced with fresh media. Samples withdrawn were analyzed by UV spectrophotometer at 239nm for estimation of amount of drug released.

Kinetic Analysis of Dissolution Data[16]

To analyze the *In-vitro* release data various kinetic models were used. zero order rate equation describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent. Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson- crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets.

Where, K_0 is zero-order rate constant and t is the time.

$$\text{Log } C = \text{Log}C_0 - Kt/2.303 \quad \text{——————} \quad (2)$$

Where, C0 is the initial concentration of drug and K1 is first order constant.

$$Q = KHt^{1/2} \quad \text{——————} \quad (3)$$

Where, KH is the constant reflecting the design variables of the system.

$$Q_0^{(1/3)} - Qt^{1/3} = KHC\ t \quad \text{——————} \quad (4)$$

Where Qt is the amount of drug remained in time t, Q_0 is the initial amount of the drug in tablet and KHC is the rate constant for Hixson- crowell rate equation.

The following plots were made from the *in-vitro* drug release data

1. Cumulative % drug release vs. time (Zero order kinetic model);
2. Log cumulative of % drug remaining vs. time (First order kinetic model);
3. Cumulative % drug release vs. square root of time (Higuchi model);
4. Log cumulative of % drug release vs. Log time (Korsmeyer peppas);

RESULTS AND DISCUSSION

Drug-Excipient Compatibility Studies

Fourier Transform Infrared Spectroscopic studies: The FTIR Spectra of pure simvastatin drug was compared with the FT-IR spectrum physical mixture of drug and polymer (simvastatin and Eudragit RLPO) and drug with the other excipients used in the optimized formulation.

There was no appearance or disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the, drug and the polymer used

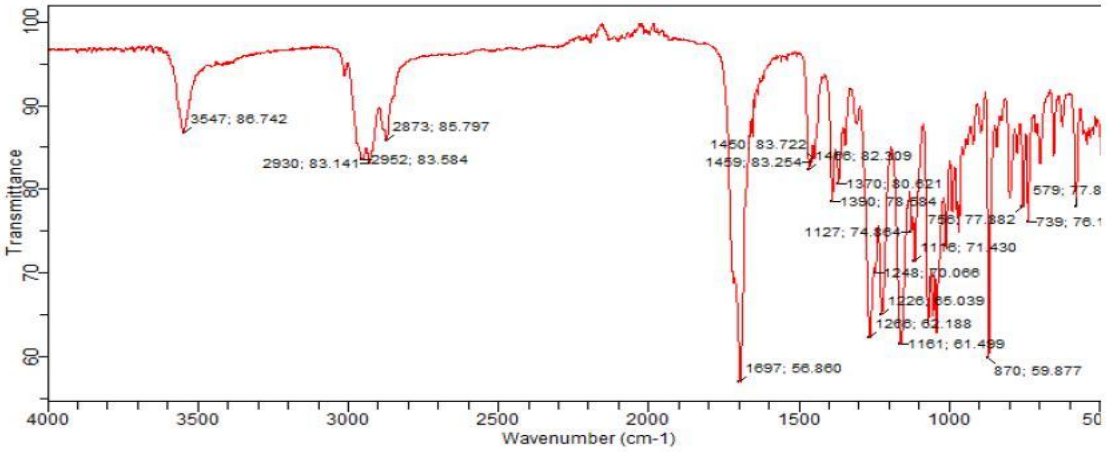

Fig.No.1: FT-IR spectra of simvastatin pure drug

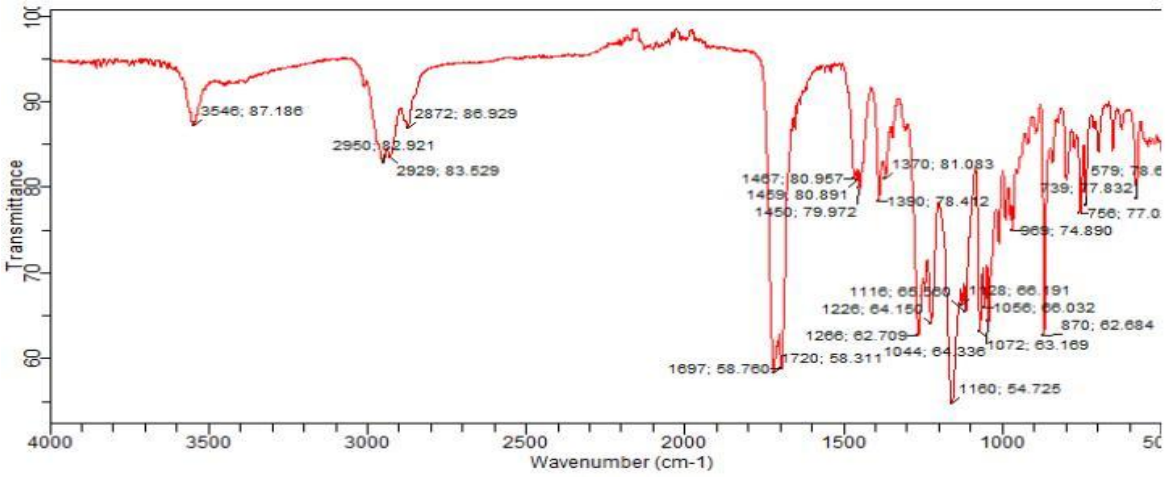

Fig.No.2: FT-IR spectra of Simvastatin with Eudragit RLPO polymer

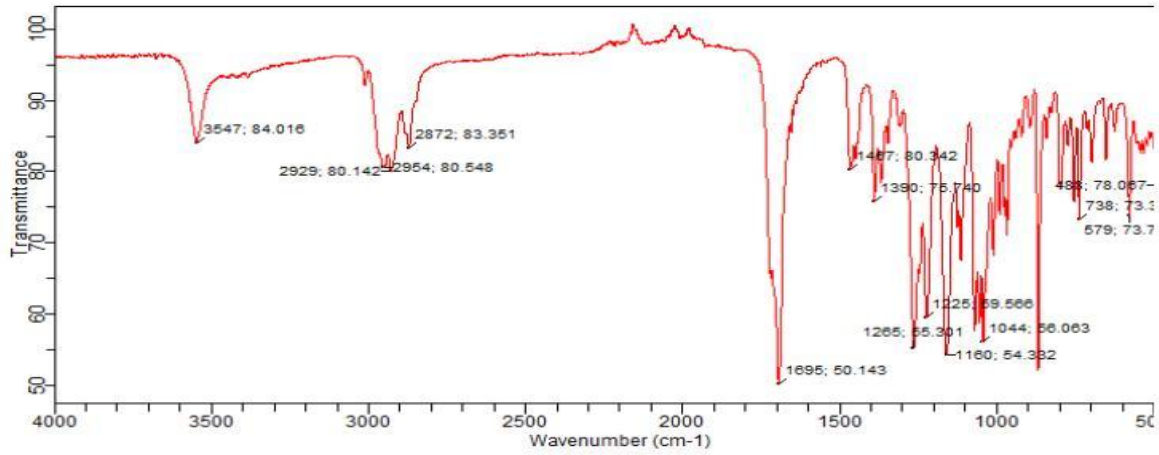

Fig.No.3: FT-IR spectra of simvastatin with PVP

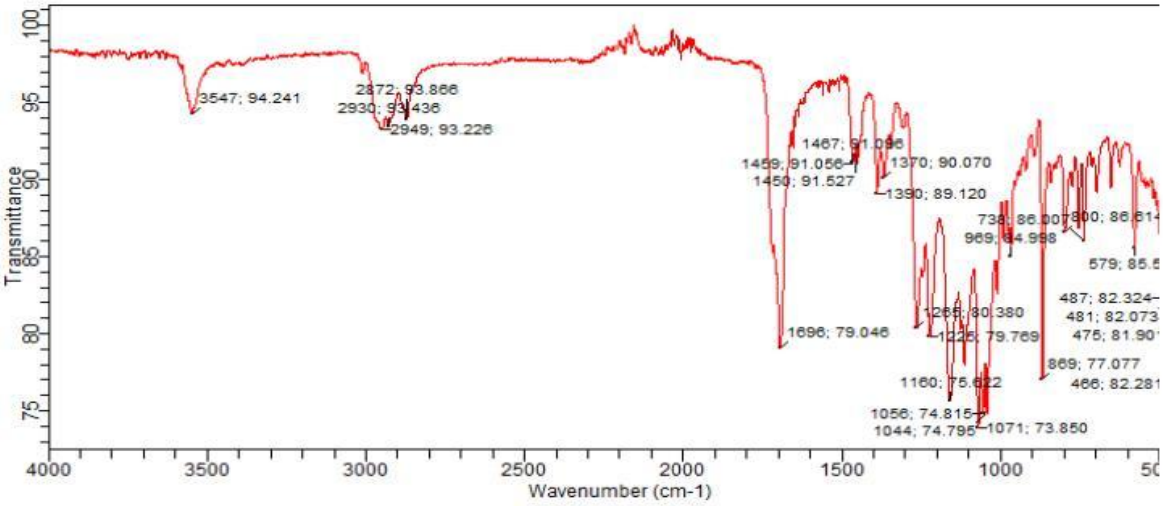

Fig.No.4: FT-IR spectra of Simvastatin with Aerosil

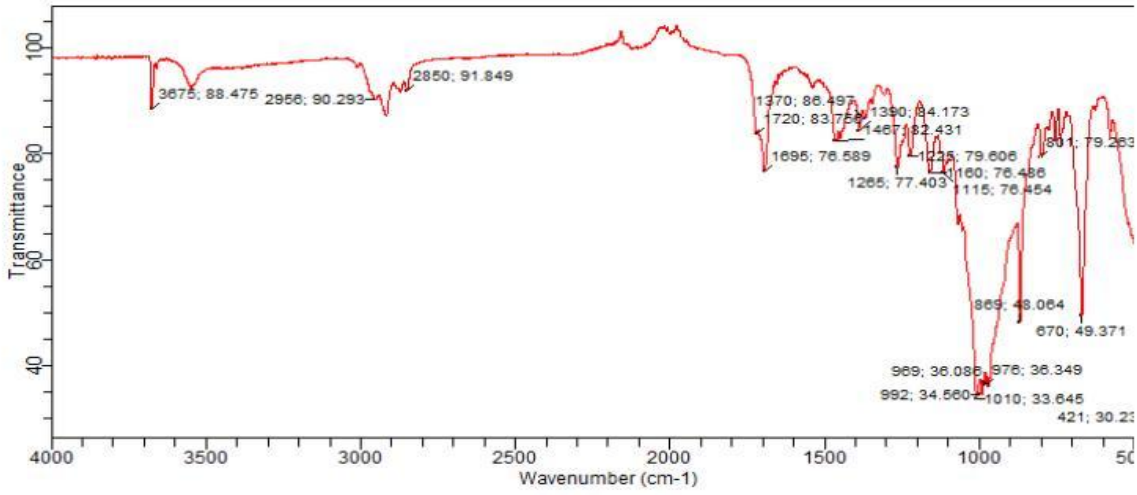

Fig.No.5: FT-IR spectra of simvastatin with Magnesium stearate

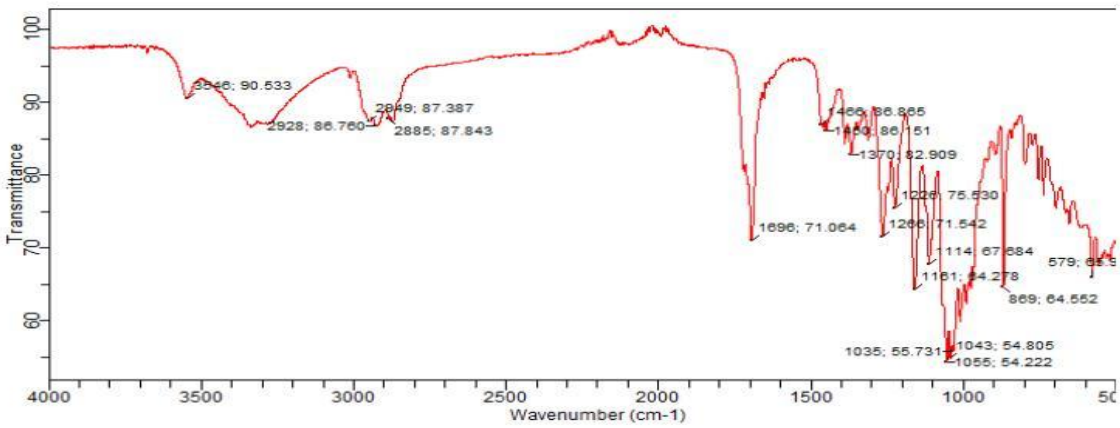

Fig.No.6: FT-IR spectra of Simvastatin with MCC

Charaterisation Of Pre-Compression Blend

Table No. 4: Pre compression parameters

Formulation code	Angle of repose (^{0})	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index(%)	Haunser's ratio
F_1	26.24±1.2	0.521±1.8	0.551±1.6	15.42±0.02	1.057±0.1
F_2	27.42±2.5	0.453±1.2	0.557±1.3	18.18±0.1	1.22±0.05
F_3	25.34±2.5	0.451±1.5	0.565±0.8	20.17±0.08	1.25±0.1
F_4	26.06±1.2	0.462±0.5	0.591±1.2	21.83±0.15	1.19±0.08
F_5	25.42±0.8	0.48±2.5	0.637±1.6	21.39±0.12	1.17±0.5
F_6	28.72±1.2	0.417±2.8	0.472±0.8	24.65±1.8	1.25±0.06
F_7	27.94±0.4	0.392±1.6	0.447±1.4	12.76±2.0	1.14±0.2
F_8	30.48±1.2	0.476±0.9	0.441±2.8	11.36±1.8	1.12±0.1
F_9	29.68±0.1	0.462±1.6	0.547±1.2	12.96±2.5	1.15±0.08
F_{10}	26.82±1.2	0.531±0.5	0.531±1.8	13.20±1.6	1.15±0.05
F_{11}	25.74±0.9	0.538±1.2	0.612±1.4	13.11±2.5	1.18±1.8
F_{12}	26.02±0.8	0.501±1.8	0.584±2.0	13.79±1.8	1.16±1.2

The pre compression blend for matrix tablets were characterized with respect to angle of repose, bulk density, tapped density, carr's index and drug content. Angle of repose was less than 31^0 and carr's index values were less than 25 for the pre compression blend of all the batches indicating good to fair flowability and compressibility. Haunser's ratio was less than 1.25 for all the batches indicating good flow properties.

Evaluation of Simvastatin Matrix Tablets

Table No. 5: Evaluation of matrix tablets of simvastatin

Formulation code	Weight variation(mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Content uniformity(%)
F_1	98.9±1.49	3.12±0.43	1.76±0.17	0.23	99.65±1.35
F_2	100.3±0.53	3.32±0.32	1.86±0.27	0.54	99.34±2.45
F_3	99.2±0.83	3.14±0.37	1.76±0.71	0.61	98.34±1.87

F_4	98.8±1.64	3.0±0.76	1.63±0.88	0.27	99.21±1.56
F_5	98.7±1.64	2.9±0.67	1.68±0.36	0.12	100.34±2.18
F_6	100±1.14	3.0 ±0.67	1.55±0.89	0.51	99.96±1.22
F_7	99.6±0.43	3.26±0.69	1.62±0.25	0.29	98.45±1.98
F_8	96.5±0.80	3.31±0.70	1.56±0.58	0.21	99.35±1.98
F_9	99±0.43	3.0±0.56	1.48±0.86	0.11	99.78±2.15
F_{10}	101.6±0.83	3.0±0.80	1.67±0.45	0.24	100.2±1.58
F_{11}	103.3±0.94	3.24±0.18	1.48±0.18	0.34	98.84±1.24
F_{12}	98.3±0.67	2.82±0.57	1.75±0.14	0.46	99.45±1.17

The results of the weight variation, hardness, thickness, friability, and drug content of the tablets are given in table 5. All the tablets of different batches complied with the official requirements of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 2.8 to 3.3kg/cm^2 and the friability values were less than 0.6% indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged from 1.48 to 1.86 mm. All the formulations satisfied the content of the drug as they contained 90 to 100% of simvastatin and good uniformity in drug content was observed. Thus all the quality control parameters of the prepared tablets were found to be practically within limits.

In-Vitro Drug Release Studies

Table No. 6: *In-vitro* Release Data of simvastatin matrix tablet containing Eudragit RLPO

Time (hrs)	F_1	F_2	F_3	F_4	F_5	F_6
1	41.19±1.036	37.16±1.036	32.25±1.656	24.22±0.552	19.23±0.439	14.44±0.335
2	63.27±1.114	52.33±1.015	47.25±1.224	46.18±0.557	27.18±0.662	23.44±0.130
4	77.21±1.047	64.17±1.218	58.17±1.137	58.17±0.385	42.26±0.586	34.34±0.219
6	84.23±1.295	83.18±1.137	64.19±1.257	62.32±0.555	57.13±0.585	46.54±0.333
8	93.28±0.803	87.37±1.000	87.46±0.564	73.24±1.131	63.18±0.586	57.6±0.579
10	98.39±1.255	94.22±1.090	92.26±1.896	88.22±1.107	72.18±0.585	63.1±0.774
12		98.28±1.106	98.22±1.552	91.15±1.136	85.22±1.374	71.15±1.255
14				98.29±1.137	87.49±1.017	76.11±1.259
16					91.22±1.218	82.14±1.108
18					95.34±1.001	88.49±1.438
20					98.89±1.656	93.14±2.479
22						96.7±1.756
24						99.41±1.279

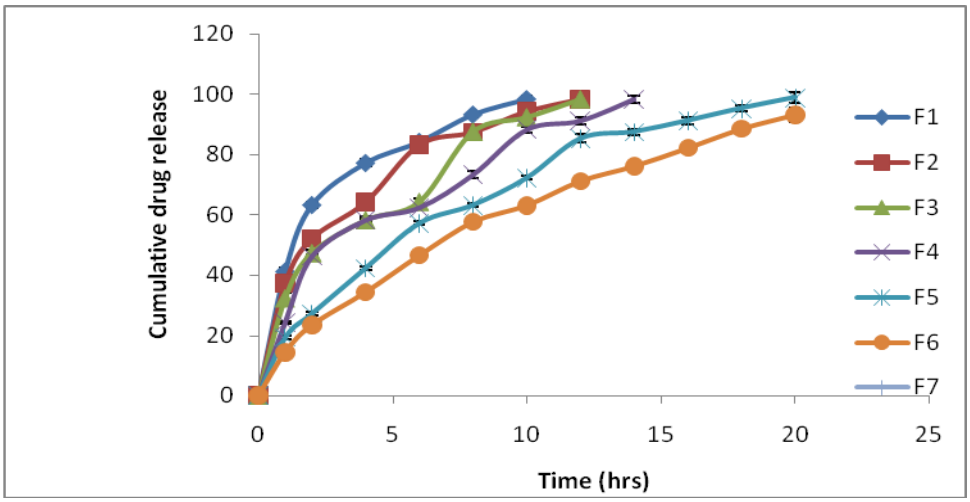

Fig.No.7: *In- vitro* Release profile of simvastatin from matrix tablets containing Eudragit RLPO

The cumulative percent drug release for formulation, F1 with drug :Eudragit RLPO in 1:0.25 ratio was 98.39% after 10th hour and formulation F2 with drug:Eudragit RLPO in 1:0.5 was 98.28%after 12th hour.

The cumulative percent drug release for formulation F3 with drug:Eudragit RLPO in 1:0.75 ratio was 98.22% after 12th hr, and F4 with drug: Eudragit RLPO with was 91.15% after 12th hr. The F4 formulation could sustain the drug release up to 14th hour with 98.29% release.

The cumulative percent drug release for formulation F5 with drug :Eudragit RLPO was 98.89% after 20th hour (drug: polymer ratio1:1.25)and formulation F6 with drug:Eudragit RLPO was 99.41 after 24hrs,(drug :polymer in1:1.5 ratio).

Table No. 7: *In-vitro* Release Data of simvastatin matrix tablet containing Eudragit RSPO

Time (hrs)	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
1	43.18±1.036	39.44±1.036	35.3±1.656	27.19±0.552	18.19±0.439	16.36±0.335
2	62.29±1.114	57.46±1.015	53.57±1.224	42.15±0.557	30.3±0.662	26.55±0.130
4	74.39±1.047	72.39±1.218	72.25±1.137	57.22±0.385	43.84±0.586	37.16±0.219
6	85.31±1.295	83.5±1.137	82.35±1.257	69.86±0.555	57.14±0.585	49.14±0.333
8	92.48±0.803	89.54±1.000	89.53±0.564	83.14±1.131	65.11±0.586	56.21±0.579
10	98.48±1.255	94.38±1.090	92.41±1.896	88.42±1.107	76.23±0.585	62.37±0.774
12		98.31±1.106	96.67±1.552	93.26±1.136	83.26±1.374	69.17±1.255
14			98.31±1.412	95.54±1.137	88.32±1.017	75.2±1.259
16				98.63±1.041	92.42±1.218	81.36±1.108

18					95.38±1.001	87.15±1.438
20					98.34±1.656	92.11±2.479
22						98.13±1.721

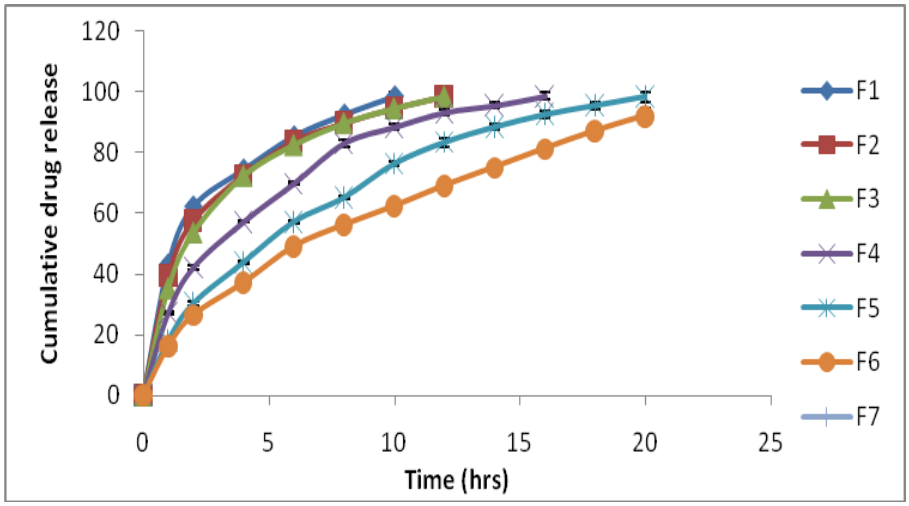

Fig.No.8: *In- vitro* Release profiles of simvastatin from matrix tablets containing Eudragit RSPO.

The cumulative percent drug release for formulation, F7 with drug : Eudragit RSPO in 1:0.25 ratio was 98.48% after 10th hour and formulation F8 with drug: Eudragit RSPO in 1:0.5 was 98.31%after 12th hour.

The cumulative percent drug release for formulation F9 with drug : Eudragit RSPO in 1:0.75 ratio was 98.31 % after 14th hr, and F10 with drug: Eudragit RSPO with was 95.54% after 12th hr. The F10formulation could sustain the drug release up to 14th hour with 98.63% release.

The cumulative percent drug release for formulation F11 with drug : Eudragit RSPO was 98.34% after 20th hour (drug: polymer ratio1:1.25)and formulation F12 with drug:Eudragit RSPO was 98.13 after 24hrs,(drug :polymer in1:1.5 ratio).

Out of total 12 batches, the drug release in the initial burst release was found to be low for the formulation F_6.

Kinetic analysis of dissolution data

Table No.8: Drug release kinetics of simvastatin from matrix tablet formulations F_1- F_{12}

Formulation code	R^2 value				n value
	Zero order	First order	Higuchi	Krosmeyer Peppas	
F_1	0.766	0.99	0.961	0.948	0.415
F_2	0.831	0.967	0.977	0.987	0.393
F_3	0.893	0.922	0.984	0.976	0.441
F_4	0.891	0.902	0.985	0.959	0.487
F_5	0.92	0.921	0.992	0.993	0.566
F_6	0.943	0.858	0.995	0.996	0.61
F_7	0.783	0.951	0.961	0.98	0.344
F_8	0.783	0.975	0.959	0.978	0.358
F_9	0.771	0.991	0.95	0.961	0.379
F_{10}	0.855	0.975	0.982	0.984	0.466
F_{11}	0.91	0.958	0.992	0.991	0.562
F_{12}	0.938	0.844	0.993	0.994	0.564

R^2 = Correlation coefficient

To analyze the drug release mechanism the *in-vitro* release data was fitted into various Release equations and kinetic models first order, zero order, Higuchi, and Krosmeyer Peppas. The release kinetics of formulation F6 is shown in table. Drug release data was best explained by Higuchi equation and Krosmeyer Peppas so it was chosen as the optimized formulation because it showed more linearity among all the formulations. As indicated by the value of R^2 the n value of optimized formualtion was found to be 0.610. The release was found to be non fickian diffusion.

CONCLUSION

The FT-IR study indicates that there is no interaction of the drug with polymer used for the study. Precompression parameter indicated that granules prepared with binders were free flowing. Post compression parameters (hardness, friability, and weight variation) were within the acceptable limit. Formulation containing Eudragit RLPO in 1:0.25 ratio could retard drug release for 24 hours with drug release of 98.39%. Formulation containing Eudragit RSPO in 1:0.25 ratio could retard drug release for 24 hours with drug release of 98.48%. Matrix tablet of Simvastatin that contained a blend of Eudragit RLPO in 1:1.5 showed 99.41% of drug release in a period of 24 hours. The drug release mechanisms for formulations were best described by Higuchi's and Krosmeyer Peppas. The drug release of optimised formula followed non fickian type of diffusion.

Optimized Formulation F-6 containing Eudragit RLPO showed drug release for 24hours, emerging as best formulation. Mechanism of drug release of optimized formulation F-6 found to be Higuchi model and non-Fickian diffusion.

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