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RESEARCH ARTICLE

FORMULATION & EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF SIMVASTATIN USING SYNTHETIC POLYMERS

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Abstract:

In the present research to formulate sustained release matrix tablet of simvastatin. This study examined the release of Simvastatin from polymer matrices PVP K-30 and PEG 4000 separately. Simvastatin is a anti-hyperlipidemic drug and short half life ($t^{1/2}$) and usually oral dose regimen (5 to 40 mg) taken to 4 times a day. Sistained release matrix tablet of simvastatin were prepared using PEG 4000, PVP K-30 and microcrystalline cellulose by using by direct compression technique. The tablets were evaluated for physical parameters like thickness, hardness, friability, weight variation, and in vitro release studies. The maximum drug release was found to be 98.59 % over a period of 24 hours in PEG 4000 based tablets as compare to PEG 4000 and PVP K-30. All the formulations were stored at $45^0 \pm 2^0$C, 75 ± 5%RH and subjected to stability studies up to 45 days. It showed that all the formulations are physically and chemically stable.

Key Words: Sustained release, Simvastatin, Direct compression Technique.

INTRODUCTION:

Historically, oral drug administration has been the predominant route for drug delivery. It is known to be the most popular route of drug administration due to the fact the gastrointestinal physiology offers more flexibility in dosage form design than most other routes.[1-3] Matrix tablets composed of drug and polymer as release retarding material offer the simplest approach in developing a sustained-release drug delivery system. Recent trend in development of sustained-release drug delivery systems was the use of gums of plant origin to fulfill the aim of retarding the drug release [4-7]. Sustained release and controlled release will represent separate delivery processes; sustained release constitutes any dosage from that provides medication over an extended period of time. Controlled release however, denotes that, system is able to provide same actual Therapeutic control, whether this be temporal nature, spatial nature, or both. In other words, the system attempts to control drug concentration in target tissue. This correctly suggests that there are sustained-release systems that cannot be considered as controlled release. Primary objectives of controlled drug delivery are to ensure safety and to improve efficiency of drugs as well as patient compliance. This 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 diseases of lipoprotein disorder and the single most important causes of premature death in the developed world. In the UK one in four men and one in 5 women die from this disease. It is necessary to formulate a new kind of formulation which is produced specific; affection sustained or prolonged action without producing side effects.[8, 9]

Simvastatin[10] is anti hyperlipidemic used to control elevated cholesterol, or hypercholesterolemia. Simvastatin is a member of the statin class of pharmaceuticals, is a synthetic derivate of a fermentation product of aspergillus terreus[11-13]. 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 tract to the active ß - hydroxy derivative. It decreases total cholesterol, LDL cholesterol, triglycerides, and apolipoprotein B, while increasing HDL.

The purpose of this research was to develop a sustained or controlled delivery system containing drug simvastatin with different ratio of synthetic hydrophilic polymers. Hydrophilic polymers are widely used in the formulation of modified release oral dosage forms. Their convenience and ease of manufacture may cut down the cost of the final product. Besides, hydrophilic polymer matrix system offers several additional advantages over other technologies for controlled release drug delivery.

METERIAL AND METHOD:

Simvastatin obtained as gift sample from Arihant Medicines Pvt. Ltd., Mumbai, Maharashtra. PEG 4000, PVP K-30 and Microcrystalline Cellulose were purchased from Himedia laboratory, Mumbai. Magnesium Stearate and other chemical was purchase from Loba Chemical Pvt. Ltd, Mumbai.

Method:

Preparation of Sustained release matrix tablet of Simvastatin:

The sustained release matrix tablet was prepared by direct compression technique. First Accurately weighed quantity of Simvastatin, PEG 4000, PVP K-30 and Microcrystalline cellulose were taken in mortar and mixed. Sufficient quantity of distilled water was mass was passed through a # 22 mesh sieve. Then granules were dried at 400C and dried. Granules were lubricated with talc (1 %) and magnesium Stearate (1 %) and compressed into tablets on a 8-station rotatory punching machine using 11mm concave punches. Each tablet contains 40 mg of Simvastatin. The drug matrix ratio was varied to obtain the matrix tablets of varying polymer concentration. The composition of sustained release matrix tablet was shown in Figure 1.

Table 1: Composition of Sustained Release Matrix Tablet of Simvastatin

Ingredients(mg)	F_1	F_2	F_3	F_4	F_5	F_6
Simvastatin	40	40	40	40	40	40
PEG 4000	40	80	120	--	--	--
PVP K-30	--	--	--	40	80	120
MCC	165	125	85	165	125	85
Talc	2.5	2.5	2.5	2.5	2.5	2.5
Mg. Stearate	2.5	2.5	2.5	2.5	2.5	2.5
Total wt.	**250**	**250**	**250**	**250**	**250**	**250**

Evaluation of Matrix Tablet:

Precompression Parameter:

Angle of Repose:

Angle of repose was determined using funnel method. The height of the funnel was adjusted in such a way that 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. The height and diameter of the powder cone was measured and angle of repose was calculated using the following equation.

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

Where,

h= Height of pile

r= Radius of pile

Θ= Angle of Repose

Different ranges of flow ability in terms of angle of repose are given below.

Table 2: Relationship between Angle of repose (Θ) and Powder Flow

Angle of Repose (Θ) (degrees)	Degree of flow
<25*	Excellent
*25-30	Good
30-40	Passable
>40	Very poor

*****Adding glidant, e.g. 0.2% Aerosol and Talc may improve flow.

Bulk density:

The sample under test was screened through sieve no. 20, the sample equivalent to 2 gm ($50cm^3$) was weighed accurately and filled in a 10 ml of graduated cylinder, the power was leveled and the unsettled volume V_o was noted. The bulk density was calculated in g/cm^3 by the formula.

Bulk density= M/V_o

Where, M= mass of power taken, and V_o= apparent unstirred volume

Tapped density:

The sample under test was screened through sieve no.20 and the weight of sample equivalent to 2gm was filled in 10ml graduated cylinder. The mechanical tapping of the cylinder was carried out using tapped density tester at a nominal rate of 300 drops per minute for 500 times initially and the tapped volume V_o was noted. Tapping was proceeding further for an additional tapping of 750 times and tapping volume V_b was noted. The difference between two tapping volume was less than 2%, so V_b was considered as a tapping volume V_f . The tapped density was calculated in g/cm^3 by the formula.

Tapped density= M/V_f

Where, M= weight of sample taken,

V_f = tapped volume

Hausner's Ratio:

Hausner's ratio is an indication of the flowability of powder and the ratio is greater than 1.25 is considered to be an indication of poor flowability. Hausner's ratio was determined by the following equation. The test was done in triplicate.

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

If the value of Hausner's ratio <1.24 than it shows good flow properties.

Carr's Index:

Flowability of untreated and agglomerated samples was also assessed from Carr's Index (CI) The compressibility of sample blend was determined from their apparent bulk density and the tapped densities by using the following formula. The test was carried out in triplicate.

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100.$$

Table 3: Grading of powders 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

*Adding the glident, e.g. 0.2 % Aerosil should improve the flow.

Evaluation of Matrix Tablet:

Evaluation of tablet: [14, 15]

General Appearance:

The general appearance of the tablet, visual identity and over all "elegance" is essential for consumer acceptance. This may include tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Size and Shape:

The size and shape of the tablet can be dimensionally described, monitored and controlled. The size and shape of the tablet can also influence the choice of tablet machine to use, the best particle size for granulation, production lot size that can be made, the best type of tablet processing.

Tablet thickness:

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded by using calibrated vernier caliper. It was measured in mm.

Tablet Hardness:

Hardness of the tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Pfizer hardness tester. It was measured in kg/cm^2.

Friability:

Twenty (20) tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions, the tablets were dedusted and weighed again. The percentage friability was measured using formula:-

$\% F = \{1-(W_t/W)\}*100$

Where, % F= Friability in percentage,

W= Initial weight of tablets,

W_t= weight of tablets after revolution,

Weight variation:

Initially twenty (20) tablets were taken and their weight was determined individually and collectively on a digital weighing balance having sensitivity to the four places after decimal. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determined the drug content uniformity. Hence the weight variation test is under the limits for all the tablets, the limits for the tablet as specified in the USP is 7.5%.

Drug content uniformity

The 20 tablets were randomly selected, powdered and weighed accurately equivalent to 100mg of Simvastatin. The powder was transferred to 100ml volumetric flask. To this 70ml of HCl acid buffer of pH 1.2 was added, and stirred for 15 min. The volume was made up to 100ml with HCl acid buffer of pH 1.2 and allowed to equilibrate for overnight and solution was filtered (0.22 µ,Millipore) after 24 hours. Form the above 10ml of aliquot was pipette into 10ml volumetric flask to make final volume up to 100ml with HCl acid buffer of pH 1.2. Further suitable dilutions made with HCl acid buffer of pH 1.2 to get the in Beer's range. The absorbance of the solution was analyzed spectrophotometrically at 239 nm against suitable blank using UV-visible spectrophotometer (1800,Shimadzu, Japan) and drug content per tablet was calculated.

***In vitro* drug release studies:**

In vitro dissolution of Simvastatin sustained release formulations were studied in USP XXIII type-2 dissolution apparatus employing a paddle stirrer at 50 rpm using 900 ml of Phosphate buffer solution at pH 1.2, 7.4, 6.8 as dissolution medium maintain at temp. of 37±0.5°. One tablet was used in each test. Aliquots of dissolution medium (1 ml) were withdrawn at regular intervals of time (1 hour) and equivalent amount of fresh medium was replaced to maintain a constant volume. After each sampling suitably diluted up to 10ml 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 239 nm. Average percent drug release with standard deviation were calculated and recorded. Cumulative percentage of Simvastatin released was plotted against time.

Preparation of Buffer Solutions:[16]

A. Hydrochloric Acid Buffer (1.2 pH) solution:

50 ml of 0.2 M Potassium Chloride solution was taken in a 200 ml volumetric flask, to which 85 ml of 0.2 M Hydrochloric acid solution was added. Then volume was made up to the mark with distilled water and pH was adjusted to 1.2 with diluted Hydrochloric acid solution.

B. Phosphate buffer (6.8pH) solution:

50 ml of 0.2 M Potassium Chloride solution was taken in a 200 ml volumetric flask, to which 22.4 ml of 0.2 M Sodium Hydroxide solution was added. Then volume was made up to the mark with distilled water and pH was adjusted to 6.8 with diluted Sodium Hydroxide solution.

C. Phosphate buffer (7.4 pH) solution:

50 ml of 0.2 M Potassium Chloride solution was taken in a 200 ml volumetric flask, to which 22.4 ml of 0.2 M Sodium Hydroxide solution was added. Then volume was made up to the mark with distilled water and pH was adjusted to 7.4 with diluted Sodium Hydroxide solution.

Kinetic Analysis:

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

1. Log cumulative percent drug remaining versus time (first order kinetic model).[17]
2. Cumulative percent drug release versus square root of time (Higuchi model).[18]
3. Log cumulative percent drug released versus time (zero order kinetic model).[19]
4. Log cumulative percent drug released versus log time (korsmeyers model).[20]

Stability Studies:

Stability studies were carried out to assess the stability of all formulated controlled release simvastatin tablets.[21] The prepared tablets were kept at 45^0 C $\pm 2^0$C, 75±5% RH for 45 days. At 15 days intervals the tablets were evaluated for all physical parameters. The percentage of simvastatin content and invitro drug release studies were also determined.

Results and Discussion:

Evaluation of Simvastatin Granules and Tablets:

The granules prepared for compression of matrix tablets were evaluated for their flow properties. The bulk density was within the range of 1.201±0.03 to 1.652±0.05 gm/cm^3. Tapped density ranged between 1.430±0.04 - 1.843±0.12 gm/cm^3. Angle of repose was within the range of 23 ±1.75 to 29±1.85. Compressibility index was found to be 14.25±1.64 - 18.37±1.45 and Hausner's ratio ranged from 1.125±0.04 - 1.214±0.01 for granules of different formulations (Table-2). These values indicate that the prepared granules exhibited good flow properties.

Table-2: Various evaluating Per-compression parameters of Direct compressed sustained release matrix tablet of Simvastatin

Batch	Angle of Repose (Θ^0)	Bulk Density	Tapped Density	Compressibility Index (%)	Hausner's Ratio
F_1	23±1.75	1.201±0.03	1.430±0.04	18.37±1.45	1.166±0.03
F_2	25±1.5	1.621±0.02	1.821±0.16	14.25±1.64	1.125±0.04
F_3	25±1.73	1.503±0.05	1.752±0.06	15.46±1.34	1.133±0.01
F_4	29±1.85	1.425±0.01	1.644±0.14	14.38±1.62	1.142±0.04
F_5	26±1.73	1.652±0.05	1.843±0.12	17.15±1.43	1.125±0.02
F_6	24±1.23	1.421±0.02	1.712±0.09	14.38±1.52	1.214±0.01

Table 3: Evaluation parameters of sustained release matrix tablet of Simvastatin

Batch code	Thickness (mm) N=5	Hardness (kg/cm^2) N=10	Friability (%)	Weight variation (mg) N=10	Drug content uniformity (%)
F_1	3.23±0.13	4.5±0.17	0.123±0.09	253±5	99.62±0.34
F_2	3.15±0.03	4.7±0.24	0.126±0.18	250±5	96.45±0.26
F_3	3.17±0.10	4.6±0.18	0.134±0.43	251±5	95.35±0.54
F_4	3.03±0.35	4.8±0.15	0.151±0.34	251±5	98.53±0.53
F_5	3.20±0.5	4.3±0.22	0.146±0.56	254±5	95.55±0.43
F_6	3.05±0.12	4.4±0.19	0.146±0.45	254±5	95.43±0.62

*(n=3±S.D. All the above evaluating parameters are found to be within normal limits as per the USP standards. For simultaneous estimation of Ranitidine hydrochloride in a tablet formulation, estimation techniques named as absorbance ratio or Q- analysis method was employed.

The prepared tablets were evaluated for physical parameters like thickness, hardness, friability, weight variation, and in vitro release studies. The weights of the tablets were in the range of 253 ± 5 and 254 ± 5 mg. The thickness of the tablet was in the range of 3.03 ± 0.35 to 3.23 ± 0.13 mm. Drug content uniformity study showed uniform dispersion of the drug throughout the formulation in the range of 95.35 ± 0.54 to 99.62 ±0.34 % (Table 3).The percent drug release of the drug was studied in different pH buffer solution like 1.2, 6.8 and 7.4. Maximum drug release was found in 7.4 pH Phosphate buffer solution.

Table 4: In-vitro drug release studies of Simvastatin in 1.2 pH HCl buffer

Time in hours	Formulation code (% Drug release)					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	9.91±0.21	7.96±0.12	7.13±0.51	9.31±0.31	7.31±0.33	6.30±0.12
4	16.41±0.15	13.59±0.16	12.69±0.31	15.66±0.12	14.42±0.51	13.26±0.62
6	21.69±0.03	20.87±0.31	20.36±0.59	22.94±0.23	21.31±0.25	20.45±0.35
8	29.21±0.16	28.95±0.54	24.02±0.25	28.78±0.29	29.35±0.31	28.75±0.61
10	36.49±0.25	34.44±0.51	32.50±0.63	37.42±0.41	34.21±0.26	33.39±0.39
12	44.78±0.31	40.78±0.57	39.88±0.78	43.35±0.61	42.19±0.14	41.15±0.24
14	52.31±0.24	48.22±0.16	46.45±0.15	54.41±0.32	50.15±0.43	49.95±0.84
16	63.66±0.57	56.09±0.24	54.55±0.62	62.50±0.25	57.05±0.84	54.43±0.51
18	70.40±0.24	64.45±0.36	62.95±0.15	71.62±0.64	66.20±0.26	63.35±0.61
20	79.57±0.12	76.97±0.12	72.16±0.32	78.81±0.21	72.40±0.51	70.15±0.29
22	86.78±0.65	82.44±0.41	81.15±0.21	85.71±0.31	80.85±0.61	76.20±0.31
24	93.80±0.23	90.35±0.31	87.76±0.61	93.43±0.51	86.96±0.38	83.71±0.84

Table 4: In-vitro drug release studies of Simvastatin in 6.8 pH Phosphate buffer

Time in hours	Formulation code(% Drug release)					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	10.59±0.51	8.43±0.35	7.60±0.31	10.58±0.26	7.59±0.31	7.18±0.32
4	18.39±0.25	16.46±0.61	15.81±0.26	17.78±0.15	14.95±0.21	12.66±0.26
6	26.81±0.31	23.93±0.29	21.69±0.28	31.7±0.17	22.87±0.15	24.90±0.35
8	35.76±0.25	33.23±0.35	29.03±0.27	39.49±0.59	31.45±0.26	30.70±0.28
10	42.43±0.24	40.15±0.14	36.21±0.54	48.35±0.97	36.78±0.14	43.40±0.45
12	48.51±0.61	46.41±0.51	41.05±0.36	56.45±0.32	42.44±0.25	51.57±0.42
14	55.68±0.29	57.66±0.27	48.49±0.26	67.88±0.15	55.97±0.29	63.47±0.61
16	62.31±0.38	61.73±0.39	56.96±0.94	73.20±0.26	61.45±0.51	66.80±0.25
18	71.81±0.84	69.21±0.34	64.78±0.24	78.85±0.98	68.22±0.61	71.79±0.84
20	82.43±0.31	76.98±0.15	73.31±0.15	83.85±0.71	73.45±0.26	76.80±0.15
22	88.49±0.61	84.31±0.26	80.45±0.16	87.48±0.25	79.09±0.31	80.76±0.26
24	94.91±0.64	91.67±0.39	89.44±0.94	92.82±0.14	87.37±0.25	84.48±0.34

Table 5: In-vitro drug release studies of Simvastatin in 7.4 pH Phosphate buffer

Time in hours	Formulation code (% Drug release)					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	11.69±0.25	8.59±0.25	7.10±0.54	10.29±0.54	8.08±0.61	8.45±0.74
4	21.36±0.32	16.95±0.54	15.81±0.21	18.66±0.35	15.18±0.14	13.59±0.54
6	30.02±0.15	23.78±0.54	21.72±0.65	27.73±0.91	22.88±0.34	21.95±0.24
8	41.50±0.35	31.45±0.25	30.85±0.48	35.42±0.41	30.95±0.51	29.87±0.31
10	48.45±0.26	40.87±0.36	42.61±0.51	44.59±0.32	93.45±0.31	36.45±0.28
12	56.55±0.65	48.50±0.21	51.35±0.61	52.62±0.17	47.69±0.64	42.78±0.61
14	63.16±0.58	57.42±0.65	59.20±0.24	60.76±0.54	54.46±0.34	50.44±0.34
16	71.76±0.41	66.35±0.25	68.41±0.31	67.48±0.12	61.83±0.57	58.97±0.74
18	79.39±0.26	73.44±0.15	76.91±0.47	75.62±0.34	72.45±0.94	66.45±0.24
20	86.88±0.36	80.63±0.24	84.23±0.37	84.51±0.61	81.69±0.93	74.22±0.21
22	93.02±0.54	88.72±0.31	90.58±0.18	91.39±0.62	89.35±0.29	84.09±0.68
24	98.59±0.29	96.35±0.21	94.38±0.69	97.41±0.25	95.680±.57	91.35±0.39

Table 6: Stability study for optimized formulations after 15, 30 and 45 days

S. No.	Evaluation parameters		Before stability study	After stability study		
				After 15 days	After 30 days	After 45 days
1.	Hardness (kg/cm^2)	F1	4.5±0.17	4.1±0.12	4.0±0.06	Not done
		F4	4.8±0.15	4.3±0.11	4.3±0.08	
2.	Drug Content uniformity (%)	F1	99.62±0.34	97.45±0.12	97.45±0.12	Not done
		F4	98.53±0.53	96.25±0.11	95.35±0.13	

As increasing the polymer concentration, the drug release was retarded due to presence of thick matrix of polymer. The maximum drug release was found to be 98.59 % over a period of 24 hours in PEG 4000 based tablets (F1). Similarly maximum drug release was found to be 97.41 % over a period of 24 hours in PVP K-30 based tablets (F4). The evaluating parameters indicates that the minimum quantity of PEG 4000 and PVP K-30 that is drug to polymer ratio of 1:1 is required to prepare the sustained release matrix tablets of Simvastatin. The in-vitro drug release result showed F1 matrix tablet containing PEG 4000 was best for the further study.

The in vitro drug release result indicates that formulation F1 and F4 released more drug and hence more drug is available at the absorption site from formulation F1 and F4 as compared to other formulations, hence the formulation F1 and F4 has better bioavailability than other formulation of Simvastatin tablet and also the sustained release matrix tablet was found to be beneficial in terms of reduction in frequency of administration.

Conclusion:

From the overall investigation, one can conclude that the optimized sustained release matrix tablet of simvastatin using both polymers can meet ideal requirements for matrix tablet. Once daily sustained release matrix tablet of Simvastatin having short half life was found to exert a satisfactory sustained release profile which may provide an improved bioavailability, increased therapeutic efficacy, patient compliance. less side effects and reduced dosage regimen with less toxicity for treatment for many acute and chronic diseases.

In future, the formulations can used as enteric coated or film coated SR matrix tablet for better bioavailability and improved patient compliance.

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