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Formulation and Evaluation of Sustained Release Matrix Tablet of Simvastatin Using Synthetic Polymers

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Rupali*, Anupam Attri, Reena Thakur, Shivali Singla, Sachin Goyal

Himalayan Institute of Pharmacy,
Kala-Amb, Himachal Pradesh-173030, India

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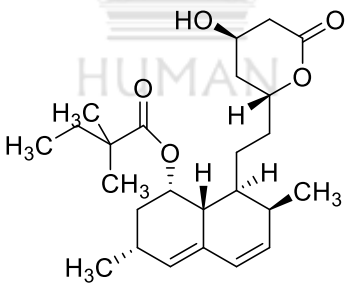
ABSTRACT

The aim of this work to formulate a sustained release matrix tablet of Simvastatin. In this study, the release of Simvastatin examined from polymer matrices Polyvinyl pyrrolidone K-30 and Polyethylene glycol 4000. Simvastatin is an antihyperlipidemic drug and short half-life and usually taken to 4 times a day. Sustained release matrix tablets 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 weights of the tablets were in the range of 250±5 and 254±5 mg. The thickness and hardness of the tablet were in the range of 3.09±0.13 to 3.33±0.35 mm and 4.3±0.24 to 4.8±0.28 kg/cm^2 respectively. The drug content uniformity study showed uniform dispersal of the drug throughout the formulation. Friability is less than 1 indicated the formulations were good. The maximum drug release was found to be 97.19±0.69% over 24 hours in pH 7.4 phosphate buffer. All the parameters were found satisfactory. It showed that all the formulations are physically and chemically stable.

INTRODUCTION

Oral administration is the most suitable, widely used route of administration for both conventional and novel drug delivery systems. This route preferred for the systemic action of drugs. Several drugs have shown limited oral bioavailability due to their unfavorable physicochemical characteristics or absorption in specific sites **[1].** In the case of chronic diseases, long term therapy, conventional formulations vital to be administered in numerous doses along these lines have a few burdens. Even. When administered orally, numerous therapeutic agents are subjected to wide pre-systemic elimination by first-pass hepatic metabolism and gastrointestinal degradation because of which low systemic bioavailability, the shorter extent of therapeutic effect and formation of inactive or harmful metabolites **[2-3].** Matrix tablets composed of drug and polymer as release delaying material offer the simplest approach in developing a sustained release drug delivery system **[4-6]** Sustained-release (SR) tablet formulations are mostly preferred because of their better patient compliance, maintain uniform drug levels, moderate dose and side effects, and increase the safety boundary for high-potency drugs **[7].** Simvastatin is an anti-hyperlipidaemic drug that widely used to control a high level of cholesterol in blood or hypercholesterolemia **[8]**.



[(1*S*,3*R*,7*S*,8*S*,8*aR*)-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxooxan-2-yl]ethyl]-3,7-dimethyl -1,2,3,7,8,8*a*-hexahydronapthalen -1-yl]2,2-dimethyl butanoate

It is on the World Health Organization's List of Essential Medicines, which lists the Simvastatin most effective and safe medicines needed in a health system**[9]**. Synthetically derived from a fermentation product of the fungus Aspergillus terreus. Simvastatin inhibits hepatic hydroxymethyl-glutaryl coenzyme A (HMG-CoA) reductase, the enzyme which catalyzes the conversion of HMG-CoA to mevalonate, the main step in cholesterol synthesis. This agent lowers plasma cholesterol and lipoprotein levels. Simvastatin modifies immune responses by suppressing MHC II (major histocompatibility complex II) on interferon gamma-stimulated, antigen-presenting cells such as human vascular endothelial cells.**[10-13]**.

2. MATERIALS AND METHODS

2.1 Materials

Simvastatin was obtained as a complimentary sample from Drug Centre, Delhi India. PEG 4000, PVP K-30, Microcrystalline cellulose, Talc, Magnesium stearate was received from Zee Laboratories Pvt. Ltd. Paonta Sahib Distt. Sirmour HP, India. All the reagents and solvents used were of analytical grade.

2.2. Drug Excipients Compatibility Study

Compatibility studies were done to recognize the possible interactions between drug Simvastatin and excipients utilized in the formulation. Physical mixtures of drugs and excipients in the proportion 1:1 were set up to study the compatibility. Drug polymer compatibility studies were completed utilizing FTIR spectroscopy. The IR spectra were recorded in the middle of 500–4000 cm^{-1}.

2.3 Preparation of Sustained Release Matrix Tablets of Simvastatin: The direct compression method was used for the preparation of sustained release matrix tablets. The composition of different sustained release formulation prepared using a varying amount of polymers (PEG 4000, PVP K-30) and MCC as the diluents, along with talc, magnesium stearate as the lubricant. All the ingredients were accurately weighed and mixed in a mortar pestle. The sufficient quantity of distilled water added and mass is passed through sieve 22. The granules were dried. Add the lubricant to the prepared granules and compressed into tablets. **[14]**

The drug matrix ratio was varied to obtain the matrix tablets of varying polymer concentration were shown in table no. 1.

Table No. 1: Composition of SR 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**

2.4. Evaluation of Tablet Properties

2.4.1.1 Determination of Pre-compression Parameters

The granules prepared for compression of Matrix tablets of Simvastatin were evaluated for their flow properties. The angle of repose, Bulk density, tapped density, Compressibility Index or Carr‟s Index (%) and Hausner ratio calculated for granules of different formulations. **[15]**

2.4.1.2 Organoleptic evaluation of pure drug

Organoleptic characters like color, odor, and taste of drugs were observed and recorded using descriptive terminology.

2.4.2. Determination of Post compression Parameters. [16- 20]

2.4.2.1. Thickness

Ten tablets were taken and their thickness was recorded by using calibrated vernier caliper. It was measured in mm. The individual crown-to crown thickness of 10 tablets was determined using slide caliper for each batch.

2.4.2.2. Hardness Test

Monsanto hardness tester was used for the determination of hardness or tablet crushing strength of tablets.

2.4.2.3. Friability

Friability of the tablets was determined using Roche's Friabilator. The pre-weighed sample of tablets was placed in the friability and operated for 100 revolutions. Tablets were dedusted using soft muslin cloth and reweighed**.** The tablets that lose less than1%weight were considered to be compliant.

The % friability was calculated by using this formula:

$$\% \text{ Friability} = (1-W_0/W) \times 100$$

Where W_0 is the weight of the tablets before the test and W is the weight of the tablet after the test.

2.4.2.4. Weight Variation

Twenty tablets were selected randomly from the lot and the average weight was determined**.** Then individual tablets were weighed and were compared with average weight.

2.4.2.5. Drug Content

The 20 tablets were randomly selected, powdered and weighed accurately equivalent to 100mg of Simvastatin. The powder was transferred to a 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 the solution was filtered (0.22 µ, Millipore) after 24 hours. Form the above 10ml of aliquot was pipette into a 10ml volumetric flask to make the 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. 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.

2.4.2.6. *In vitro* drug release studies:

In vitro dissolution of Simvastatin, sustained-release formulations were carried out in USP type-II dissolution apparatus using a paddle stirrer at 50 rpm using 900 ml of pH 1.2 HCl buffer, pH6.8 and 7.4 Phosphate buffer solution as dissolution medium maintain at temp. of37ºC±0.5. One tablet was used in each test. Sink condition was maintained the equivalent

amount of fresh medium was replaced to maintain a constant volume. After each sampling suitably diluted up to 10ml with a suitable buffer solution. Then 1 ml of the resulting solution was diluted up to 10ml with a suitable buffer solution medium and the resolution was filtered. The amount of drug dissolved was determined by UV-visible spectrophotometer by measuring the absorbance at239 nm. The average percent drug release with standard deviation was calculated and recorded.

3 RESULTS AND DISCUSSION

3.1 Evaluation of Pre-compression Parameters:

The granules prepared for compression of tablets were evaluated for their flow properties. The bulk density was within the range of 1.210±0.08 to1.678±0.09 gm/cm3. Tapped density ranged between 1.561±0.16to 1.930±0.04gm/cm3. The angle of repose was within the range of 23±1.76 to29±1.35. Compressibility index was found to be 13.13±1.12 -19.26±1.32 and Hausner's ratio ranged from 1.127±0.03- 1.595±0.04 for granules of different formulations as shown in table no. 2. These values show that the prepared granules exhibited good flow properties.

Table No. 2: Various Pre-compression parameters of sustained release matrix tablet of Simvastatin

Batch	The angle of Repose (Θ^0)	Bulk Density	Tapped Density	Compressibility Index (%)	Hausner's Ratio
F_1	24±1.50	1.210±0.08	1.930±0.04	19.26±1.32	1.595±0.04
F_2	23±1.76	1.261±0.01	1.561±0.16	13.13±1.12	1.237±0.15
F_3	26±1.98	1.678±0.09	1.892±0.06	16.56±1.43	1.127±0.03
F_4	28±1.69	1.543±0.06	1.764±0.14	16.86±1.65	1.143±0.08
F_5	25±1.67	1.643±0.03	1.899±0.12	18.25±1.47	1.155±0.09
F_6	29±1.35	1.432±0.05	1.751±0.09	15.23±1.89	1.227±0.04

3.2 Evaluation of Post compression Parameters

The prepared matrix 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 250±5and 254±5mg. The thickness and hardness of the tablet were in the range of 3.09±0.13to 3.33±0.35mm and 4.3±0.24-4.8±0.28 kg/cm^2 respectively. Drug content

uniformity study showed uniform dispersal of the drug throughout the formulation in the range of 94.31±0.45to 99.57±0.31%. Friability is less than 1 indicated the formulation was good. All the post-compression parameters were tabulated in table no.3.

Table No. 3: Evaluation parameters of sustained release matrix tablet of Simvastatin

Batch code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content uniformity (%)
F_1	3.13±0.11	4.4±0.15	0.151±0.06	251±5	97.67±0.38
F_2	3.09±0.13	4.3±0.24	0.159±0.10	250±5	99.57±0.31
F_3	3.17±0.11	4.8±0.28	0.174±0.17	252±5	96.67±0.89
F_4	3.33±0.35	4.7±0.14	0.169±0.19	251±5	94.31±0.45
F_5	3.26±0.31	4.5±0.12	0.166±0.18	253±5	95.85±0.38
F_6	3.15±0.22	4.6±0.16	0.170±0.17	254±5	95.73±0.56

*(n=3, ±S.D. All the above evaluation parameters are found to be within normal limits as per the USP standards.

3.2.1 *In Vitro* release:

The percent drug release of the drug was studied in different pH buffer solution like 1.2, 6.8 and 7.4. A maximum drug release was found in 7.4 pH Phosphate buffer solution. F2 formulation showed the maximum drug release. All the release was shown in table no. 4, 5 and 6.

Table No. 4: *In-vitro* drug release studies of Simvastatin in pH 1.2 HCl buffer

Time in hours	Formulation code (% Drug release)					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	8.76±0.22	9.31±0.21	7.11±0.56	9.11±0.11	7.05±0.31	6.28±0.11
4	12.58±0.26	15.15±0.35	11.66±0.32	14.16±0.32	11.12±0.91	10.26±0.22
6	19.56±0.30	23.59±0.33	20.56±0.69	21.24±0.53	21.51±0.15	19.15±0.25
8	26.67±0.14	30.31±0.15	25.23±0.25	29.73±0.79	25.15±0.11	26.75±0.41
10	33.484±0.17	37.41±0.15	31.50±0.73	35.21±0.61	32.21±0.26	30.39±0.29
12	41.67±0.32	45.98±0.11	37.88±0.88	42.67±0.51	36.69±0.18	36.15±0.24
14	49.56±0.28	54.31±0.14	45.49±0.35	52.65±0.39	44.45±0.23	43.85±0.74
16	55.67±0.29	62.66±0.17	54.56±0.64	61.43±0.26	53.25±0.81	54.03±0.11
18	62.59±0.79	71.30±0.24	61.25±0.35	69.41±0.34	61.10±0.16	61.05±0.21
20	73.95±0.38	78.17±0.15	71.13±0.22	74.90±0.27	70.30±0.41	69.15±0.29
22	81.48±0.89	85.87±0.55	79.75±0.61	81.41±0.56	78.55±0.71	77.29±0.51
24	89.65±0.71	92.80±0.13	87.36±0.78	90.86±0.38	86.36±0.43	84.11±0.54

Table No. 5: *In-vitro* drug release studies of Simvastatin in pH 6.8 Phosphate buffer

Time in hours	Formulation code(% Drug release)					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	7.43±0.15	9.59±0.31	7.10±0.91	9.18±0.36	7.59±0.81	7.08±0.32
4	15.12±0.41	17.39±0.15	14.81±0.06	16.18±0.55	13.15±0.21	12.16±0.12
6	22.93±0.29	25.11±0.21	21.29±0.18	24.7±0.17	22.27±0.15	23.90±0.35
8	32.22±0.15	34.76±0.15	29.43±0.67	33.49±0.59	31.15±0.26	30.10±0.28
10	39.15±0.11	41.43±0.23	35.21±0.54	40.35±0.97	36.18±0.14	37.01±0.45
12	45.41±0.51	47.11±0.31	41.15±0.56	46.45±0.12	42.44±0.25	44.57±0.42
14	56.66±0.27	58.18±0.29	53.49±0.26	57.88±0.15	52.97±0.29	51.47±0.61
16	62.76±0.29	64.31±0.18	62.96±0.34	63.20±0.26	61.05±0.51	60.80±0.15
18	69.21±0.34	71.81±0.64	65.78±0.64	70.85±0.18	68.22±0.31	66.79±0.64
20	79.98±0.14	82.43±0.31	74.31±0.15	81.85±0.61	75.45±0.56	74.80±0.15
22	83.31±0.46	87.49±0.41	83.45±0.16	86.28±0.23	80.06±0.81	79.76±0.16
24	90.17±0.19	94.71±0.64	88.44±0.94	91.12±0.13	86.87±0.39	83.28±0.14

Table No. 6: *In-vitro* drug release studies of Simvastatin in pH 7.4 Phosphate buffer

Time in hours	Formulation code (% Drug release)					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	8.49±0.15	10.39±0.15	7.19±0.54	10.09±0.14	8.12±0.81	8.03±0.72
4	15.55±0.44	21.56±0.67	15.71±0.91	18.66±0.15	15.23±0.34	13.79±0.94
6	22.18±0.54	31.05±0.35	21.32±0.85	28.77±0.61	21.18±0.34	21.15±0.24
8	32.15±0.25	40.50±0.35	30.88±0.48	36.52±0.31	30.85±0.61	29.97±0.91
10	40.17±0.16	47.75±0.38	43.71±0.71	45.19±0.92	43.15±0.11	39.45±0.18
12	47.80±0.71	55.09±0.15	51.15±0.91	53.22±0.13	47.69±0.64	42.78±0.61
14	56.42±0.65	62.16±0.58	58.20±0.24	60.32±0.23	54.16±0.14	50.24±0.54
16	65.55±0.15	70.56±0.56	62.41±0.21	67.18±0.02	61.83±0.17	57.37±0.64
18	72.14±0.25	78.39±0.26	74.91±0.47	75.12±0.14	71.15±0.64	67.35±0.34
20	81.13±0.34	85.18±0.16	83.23±0.17	84.11±0.61	81.09±0.13	79.22±0.11
22	86.72±0.31	91.01±0.54	89.58±0.18	90.19±0.12	87.05±0.19	85.01±0.18
24	95.15±0.31	97.19±0.69	93.18±0.39	96.46±0.35	94.60±.97	92.55±0.1

5. CONCLUSION

It could be concluded from the results, that the sustained release matrix tablet of simvastatin using synthetic polymers can meet ideal requirements for matrix tablets. Sustained release matrix tablet of Simvastatin having short half-life was found to exert a satisfactory sustained release profile which may provide 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. The success of the i*n-vitro* drug release

studies recommends the product for further *in-vivo* studies, which may improve patient compliance.

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