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Formulation and Evaluation Simvastatin Solid Dispersions by Using Different Polymers

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ABSTRACT

The aim of the present study is to enhance solubility of simvastatin by solid dispersion technique. Solid dispersions were prepared by fusion method by using various polymers. Formulation is optimized on the basis of acceptable solid dispersion properties and *in-vitro* release. In order to obtained best optimized product, 5 different formulations were developed. Different polymers like PEG 6000, HPMC 6000,HPC 1000 were taken as variables. Angle of repose, carr's index, particle size, drug content and dissolution study were studied as response variables. The different physical properties showed best comparable results with drug. But higher percentage of drug release was observed when the formulation contained PEG6000 in 1:1.5 ratio (f5) compared to other formulations. Form this study it concluded that formulation (f5) which contained PEG (1:1.5) as polymer showed best dissolution profile compared to the drug. The formulation contained PEG 6000 was selected as optimized product.

Keywords: Simvastatin, PEG 6000, HPME 6000, HPC 1000.

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INTRODUCTION

Solid dispersion technology is the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or the melting solvent method. Solid products consists of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix may be crystalline or amorphous. Solid dispersions reduce the particle size and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Simavastatin is a Hyperlipidimic which involves abnormally elevated levels of any or all lipids and/or lipoproteins in the blood. It is used to reduce LDL-cholesterol, apolipoprotein B, triglycerides and to increase HDL-cholesterol in the treatment of hyperlipidaemias, including hypercholesterolemias, combined hyperlipidaemia, hypertriglyceridaemia and primary dystalipoproteinaemia. Based on their physicochemical and biopharmaceutical properties of Simvastatin were selected as a drug candidates for developing solid dispersion formulations for improving its solubility and bioavailability by improving the dissolution rate. Formulation is optimised on the basis of acceptable solid dispersion properties and *in-vitro* release. The aim of the present study is to enhance solubility of simvastatin by solid dispersion technique.

MATERIALS AND METHOD

Drug and Exceipient Profile

Drugs: simvastatin.

Polymers: PEG 6000, Hydroxypropyl Cellulose, Hydroxy Propyl Methyl Cellulose.

Methodology

Preformulation Studies

Analytical Methods

Estimation of Simvastatin

A spectrophotometric method based on the measurement of absorbance at 239nm in 7.0 pH phosphate buffer was used in the present study for the estimation of simvastatin.

Saturated Solubility Studies of Simvastatin

Saturated solubility studies of simvastatin were performed in different dissolution media. 500mg of simvastatin was weighed and transferred into different conical flasks. 50ml of different dissolution media were transferred into individual conical flasks and were closed appropriately. All the conical flasks were placed in the REMI incubator shaker. The shaker was allowed to operate at 50 rpm at 37º C ± 1º C for 24 hrs. Then the conical flasks were removed from the incubator shaker and the

samples were filtered by using whatman filter paper. The clear solution obtained by filtration was suitably diluted with appropriate dissolution media and the absorbance values were noted at 239 nm by using corresponding dissolution media as blank solutions.

Formulation of Solid dispersions

The solid dispersions were prepared by fusion technique. Specified quantity of PEG-6000 was taken in a china dish and it was heated at on a mantle until molten mass was formed. To the molten mass specified quantity of drug was added and triturated vigorously at room temperature. The mixture obtained was triturated thoroughly in a glass mortar and screened through sieve no.100. Then the mixture was collected, packed in a wide mouthed amber coloured glass container and was hermetically sealed. Then the mixture was stored at ambient conditions.

Table 1: Formulation Plan

S.No	Formulation code	Composition	Drug+polymer ratio
1	F1	HPMC	1:1
2	F2	HPC	1:1
3	F3	PEG 6000	1:0.5
4	F4	PEG 6000	1:1
5	F5	PEG 6000	1:1.5

Characterization of Solid dispersions

Angle of Repose

The Angle of repose was known by passing the blend through a funnel fixed to a burette stand at a particular height (4 cm). A graph paper was placed below the funnel on the table (Neumann, 1953). The height and radius of the pile was measured[34]. Angle of repose of the blend was calculated using the formula:

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

Carr's Index

It is measured by tapped density apparatus for 500, 750 and 1250 taps for which the difference should be not more than 2%[35] (Dahlinder, 1982) Based on the apparent bulk density and tapped density the percentage compressibility of the blend was determined using the following formula.

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

Particle Size Determination

The average particle size of the prepared solid dispersions was analyzed by simple sieve analysis method (Arambulo, 1953). The average particle size of different formulations was shown in tables.

Drug Content Uniformity

Solid dispersions of simvastatin from a batch were taken at random and was transferred into a 100ml volumetric flask and 70ml of methanol was added to it. It was shaken occasionally for about 30 minutes and the volume was made up to 100ml by adding methanol. About 10ml of the solution from the volumetric flask was taken and centrifuged. The supernatant solution from the centrifuge tube was collected and again filtered by using Whatmann filter. Then the filtrate was subsequently diluted with 7.0 pH phosphate buffer and the absorbance was measured at 239nm. This test was repeated six times (n=10) for each batch of tablets. The amount of simvastatin estimated from different batches were depicted in table.

Drug Release Studies From Solid Dispersions

Dissolution studies on solid dispersions were performed in a calibrated eight stage dissolution rate test apparatus equipped with paddles employing 900 ml of 7.0 pH phosphate buffer as a medium. The paddles were operated at 50 rpm and the temperature was maintained at 37±0.5^{0}C through out the experiment. Samples were withdrawn at 5, 10, 15, 20, 30, 45, 60 minutes and replaced with equal volume to maintain the constant volume of dissolution medium throughout the experiment. Drug content of the samples was determined by Elico double beam UV spectrophotometer at 239 nm after suitable dilutions of the samples

RESULTS AND DISCUSSIONS

Preformulation Studies

Analytical Method Development

Table 2: Calibration Curve For Estimation Of Simavastatin

Concentration(µg/ml)	absorbance at 239nm
2	0.326
4	0.645
6	0.956
8	1.288
10	1.624

Saturated Solubility Studies Of Simv Astatin In Different Dissolution Media

Table 3: Saturated Solubility Studies Of Simvastatin In Different Dissolution Media

S.No	Dissolution medium	Amount of Simvastatin dissolved in (µg/ml)
1	Distilled water	71.5
2	Distilled water + 10%	196.2
3	Methanol	262.6
4	1.2 pH Acidic buffer	250.5
5	4.5 pH Acetate buffer	351.4
6	6.4 pH Phosphate buffer	505.5

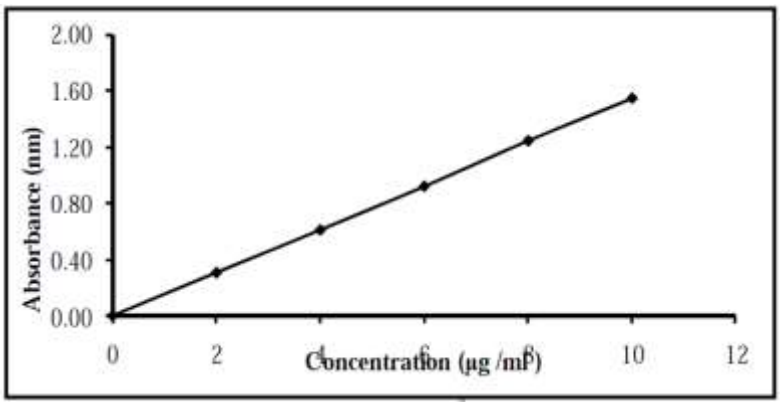

Figure 2: Standard Graph Of Simavastatin

Co-relation coefficient R^2=0.999

Regression equation Y=0.1546 ; x 0.00414

Physical Parameters Of Simvastatin

Table 4: Physical Parameters of Simvastatin

Formulation	Angle of repose	Carr's index(%)	Partical size (µg)	Drug content (mg)
F1	20.75	14.52	174±6	9.89±0.4
F2	20.62	14.43	173±6	10.15±0.3
F3	20.35	14.24	174±6	9.56±0.4
F4	20.45	14.42	174±6	10.06±0.4
F5	20.70	14.45	174±6	9.96±0.4

Release of Simvastatin from Solid Dispersions Prepared By Fusion Method

Table 5: Dissolution Profile of Different Formulations of Simvastatin

Time	Cumulative percentage of simvastatin release				
	F1	F2	F3	F4	F5
5	12.24±0.95	18.21±1.12	24.12±0.98	31.24±1.12	35.63±1.02
10	16.71±1.21	21.24±1.24	30.24±1.02	38.48±1.02	44.27±1.14
15	19.58±0.96	27.52±0.98	5.54±1.12	45.65±0.98	52.24±1.16
20	24.21±1.24	34.25±1.02	44.47±1.24	52.47±1.24	57.18±1.12
25	28.45±1.14	39.87±1.24	49.78±1.26	60.24±1.22	65.61±1.42
30	33.37±1.20	43.21±1.20	57.24±1.54	68.73±1.43	75.84±1.16

The aim of the work is to enhance the solubility, dissolution rate and oral bioavailability of poorly soluble drugs simvastatin by formulating it as solid dispersions using various polymers like PEG-6000, HPME 6000,HPC 1000 by using fusion technique. The prepared solid dispersions were evaluated for pre compressional parameters such as angle of repose, carr's index, particle size and drug content. Solid dispersions of simvastatin were prepared by fusion method, and found to be stable, discrete particulate form with free flowing characteristics. The angle of repose values obtained for various solid dispersions were in the range of 19.56^0 to 24.28^o which indicated the good flow properties of dispersions [Table

4].The Carr's index values obtained for various solid dispersions were in the range of 14.17 to 15.52% which indicated the good flow properties of dispersions [Table 4]. The average particle size for all the solid dispersions were in the range of 173-178µm [Table 4]. The drug content for all the dispersions were in the range of 9.45 to 10.15 mg of Simvastatin respectively [Table 4]. Simvastatin solid dispersions prepared by fusion methods were found to release the drug by increasing the dissolution rate upto 1.20 to 2.97 folds than compared to pure drug dissolution [Table 5]. Based on the *in vitro* dissolution studies solid dispersions F4 and F5 prepared by Fusion method methods were found to exhibit high dissolution.

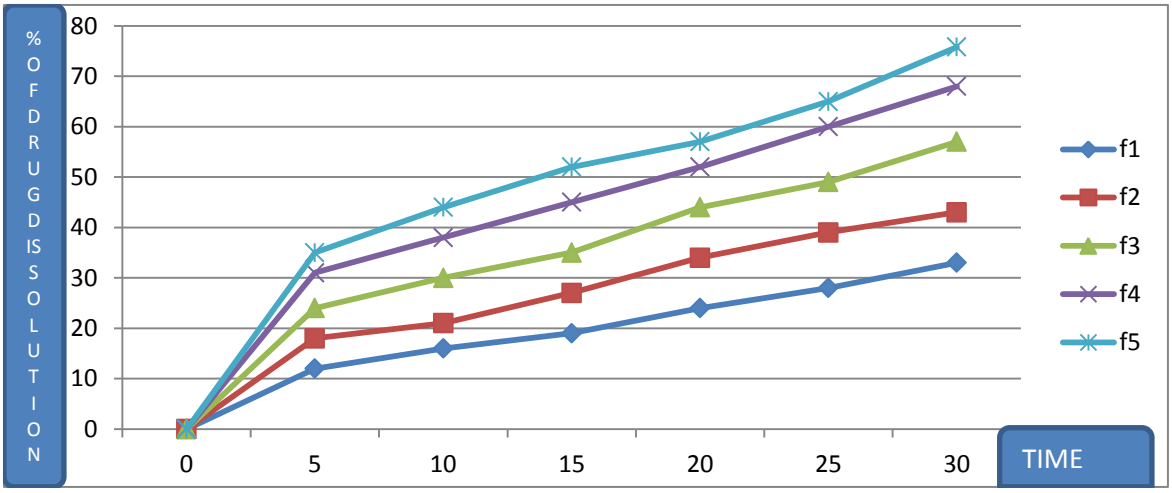

Figure 2: Dissolution Profile Of Simvastatin

CONCLUSION

The present study concluded that somvastatin solid dispersions have been formulated and developed by using fusion technique, in order to obtain best optimised product, 5 different formulations were developed. For 5 formulations the different physical properties showed best comparable with reference product. But higher percentage of drug release was observed when the formulation contained PEG 6000 (1:1.5) when compared with other formulations. The formulation F5 has shown drug release NLT 75% in 30min accordance with the USP dissolution criteria for solid dispersions. The results suggest that formulation F5 is best formulation.

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