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SOLUBILITY ENHANCEMENT OF POORLY SOLUBLE DRUG SIMVASTATIN BY SOLID DISPERSION TECHNIQUE

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ABSTRACT:

The objective of the present study was to formulate solid dispersions (SDs) of Simvastatin (SIM) to improve the aqueous solubility, dissolution rate & to facilitate faster onset of action. Simvastatin is a BCS class II drug having low solubility & therefore low oral bioavailability. In the present study, SDs of Simvastatin different drug-carrier ratios was prepared by kneading method. The results showed that Simvastatin solubility & dissolution rate was enhanced with polymer SSG in the ratio 1:7 due to increase in wetting property (or) may be due to change in crystallinity of the drug.

KEYWORDS: Simvastatin, kneading, solid dispersions, SSG, carrier

INTRODUCTION:

Almost more than 90% drugs are orally administered. Drug absorption, bioavailability, pharmacokinetic profile of orally administered drug substances is highly dependent on solubility of that compound in aqueous medium. The formulation of poorly soluble drugs for oral delivery presents a challenge to the formulation scientists.

Simvastatin is hypolipidemic drug available as tablet dosage form. Simvastatin is a crystalline compound which is practically insoluble in water & hence poorly absorbed from GI tract. It is a potent and specific inhibitor of 3-hydroxy-3-methyl-glutaryl coenzymeA (HMG COA) reductase. Among various approaches the solid dispersion technique has often proved to be the most successful in improving the dissolution & bioavailability of poorly soluble, active pharmaceutical ingredients because it is simple, economical & advantageous.

Solid dispersion can be defined as “the dispersion of one or more active ingredients in an inert carrier matrix in solid-state prepared by a melting (fusion), solvent or melting-solvent method.”

Deposition of drug on the surface of an inert carriers (acids: citric acid, tartaric acid etc., & for sugars : dextrose sucrose, sorbitol etc.,) leads to a reduction in particle size of the drug, thereby providing a faster dissolution rate. Different methods of preparation of solid dispersions are: 1) Melt (or) cool method 2) Solvent evaporation 3) Co-precipitation 4) Dropping method 5) Kneading method. In this study kneading method is used for preparation of SIM solid dispersions since this method is easy, economical & advantageous. Being a BCS class II drug, Simvastatin shows dissolution rate-limited oral absorption, so its improvement in solubility & dissolution rate may lead to enhancement in bioavailability by preparing it as solid dispersions[1,2].

MATERIALS AND METHODS:

Simvastatin was obtained as gift sample from Reddy laboratories, Hyderabad, India. SSG, methanol, potassium hydrogen phosphate & sodium hydroxide were purchased from Qualikems fine chemicals pvt ltd. All these materials & solvents used in this study were of analytical grade.

Methodology:

Preparation of Simvastatin solid dispersions with SSG by kneading method:

The solid dispersions were prepared by weighing Simvastatin & SSG according to their ratios (1:1 to 1:7). They were triturated using small volume of solvent (Methanol-water) to obtain a thick paste, it was kneaded for 30 min & then dried in an oven. The dried mass then pulverized, passed through #30 & stored in vacuum desiccators (48 hrs) & then passed through #60 before packing in an air tight container[(3)].

Table No:1 preparation of solid dispersions

S.No	Carrier	Product Name	Drug (mg)	Carrier (mg)	Ratio Of drug:Carrier	Preparation method
1	SSG	D	250	0	1:0	kneading
2	SSG	S1	250	250	1:1	Kneading
3	SSG	S2	250	500	1:2	Kneading
4	SSG	S3	250	750	1:3	Kneading
5	SSG	S4	250	1000	1:4	Kneading
6	SSG	S5	250	1250	1:5	Kneading
7	SSG	S6	250	1500	1:6	Kneading
8	SSG	S7	250	1750	1:7	kneading

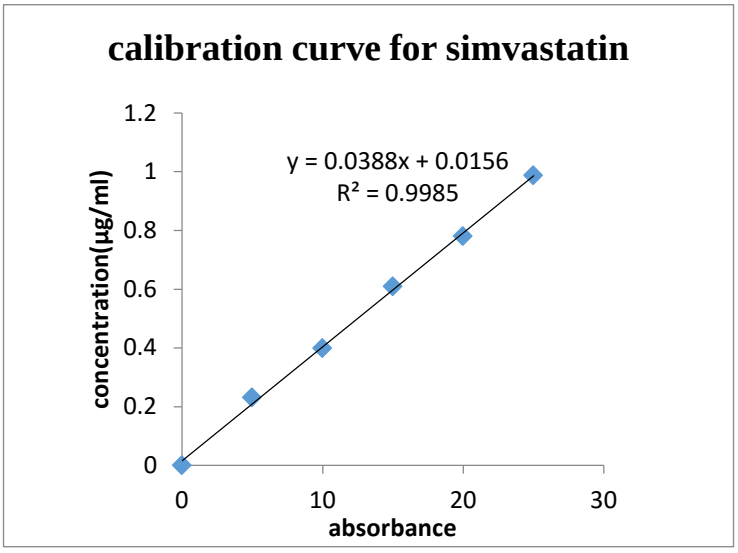
EVALUATION STUDIES:

Calibration curve: Simvastatin drug equivalent to 10mg was accurately weighed & dissolved in few ml of methanol. Simvastatin solid dispersions of weight 20mg (1:1 i. e equivalent to 10mg) were taken and dissolved in few ml of methanol. The stock solutions were diluted with methanol to prepare aliquots of standard solution containing 2ml, 4ml, 6ml, 8ml & 10ml (20, 40, 60, 80 & 100 µg/ml). They were analyzed by UV-Visible Spectrophotometer (sisco pvt ltd) at 238nm using methanol as blank. A calibration curve was plotted against concentration & absorbance [(4)].

Table No:2 Calibration curve for simvastatin:

Concentration(µg/ml)	absorbance
0	0
5	0.231
10	0.398
15	0.609
20	0.78
25	0.987

Fig:1 calibration curve for Simvastatin



***In-vitro* dissolution studies:** In-vitro dissolution studies for pure Simvastatin & SIM solid dispersions were carried out by using USP dissolution apparatus II. Samples equivalent to 10mg of SIM were added to 900ml of 0. 01M Phosphate buffer of P^H 7.4 at 37 $\pm$0.5°C using speed of 50 rpm. Sample volume of 5ml were withdrawn at specified time intervals (for every 5min) & filtered through whatmann no. 41 filter paper. An equal volume of fresh dissolution medium was replaced to maintain the volume of dissolution medium. The

filtered samples were estimated for their absorbance by using UV-Visible spectrophotometer at 238nm using buffer as reference.

DISCUSSION:

***In-vitro* dissolution studies:** The dissolution profiles of solid dispersions were shown in fig 1. Solid dispersions of Simvastatin: SSG (1:7) in pH 7. 4 Phosphate buffer showed maximum drug release: the solid dispersions with SSG carrier showed almost 100.8% drug release within 45 min, where as pure SIM showed a poor dissolution profile (43. 25% of drug released at 90 min). The improved dissolution can be attributed to a reduction in particle size of the drug, its deposition on the surface of the carrier & improved wettability. SSG have very fine particle size & hence larger surface area. As the proportion of carrier increases, more surfaces are available for adsorption of drug crystals leading to an increase in interfacial area of contact between the drug particles & dissolution medium. The affinity between the hydrophilic inert carriers of dissolution fluids facilitates rapid penetration into the particles, which further enhances the dissolution process

Table No:3 Dissolution profiles of simvastatin:SSG of (S1,S2,S3) in pH7.4 ph phosphate buffer

S.No	Time(MIN)	% Drug dissolved(S1)	% Drug dissolved(S2)	% Drug dissolved(S3)
1	0	0	0	0
2	5	20.4±0.22	21±0.26	22±0.35
3	10	22±0.21	23±0.24	24±0.35
4	15	22.5±0.23	23.4±0.23	25.2±0.32
5	30	25±0.25	26±0.23	28±0.33
6	45	27±0.21	30±0.22	35±0.34

Table No:4 Dissolution profiles of simvastatin: SSG (S4,S5,S6,S7) in pH7.4 pH phosphate buffer

S.No	Time(min)	% Drug dissolved(S4)	% Drug dissolved(S5)	% Drug dissolved(S6)	% Drug dissolved(S7)
1	0	0	0	0	0
2	5	22.6±0.31	26.8±0.22	29±0.01	34±0.02
3	10	23±0.32	27.6±0.23	30.3±0.21	44.1±0.32

4	15	25.5±0.32	30.3±0.19	31.6±0.25	50.1±0.45
5	30	30.3±0.31	47.8±0.18	63.9±0.26	73.7±0.52
6	45	44±0.3	66.2±0.19	98±0.24	100.8±0.58

Fig:2 Dissolution profiles for S1,S2,S3 in pH 7.4 phosphate buffer

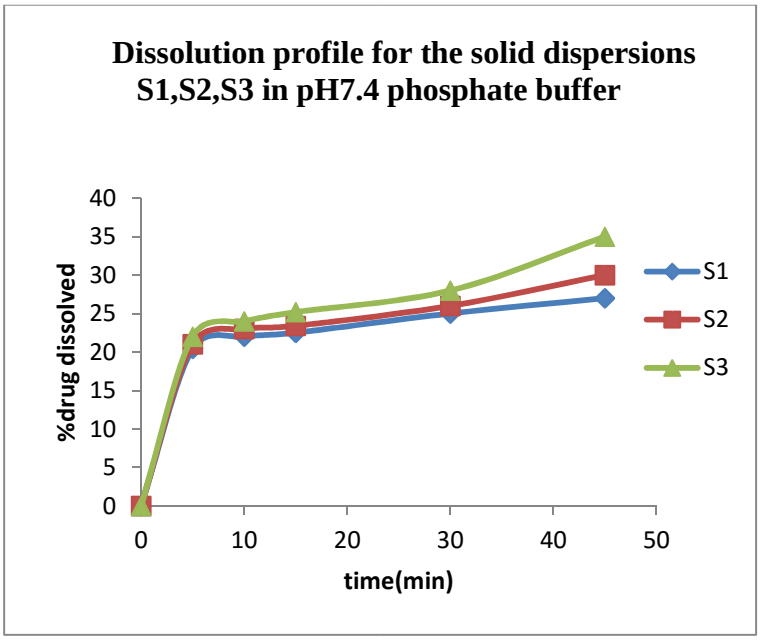
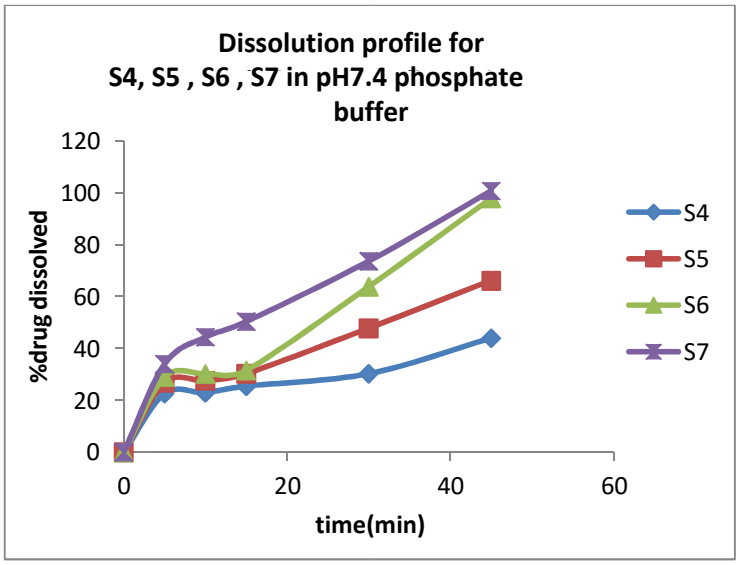


Fig:3 Dissolution profiles for S4,S5,S6,S7 in pH 7.4 phosphate buffer



CONCLUSION:

Dissolution rate of Simvastatin can be enhanced to great extent by solid dispersion technique using an industrially feasible method. Solid dispersions of Simvastatin were prepared in various ratios from 1:1 to 1:7.The maximum solubility was observed in the ratio 1:7 and it was considered as the optimum ratio of the polymer to be used. Hence Simvastatin SSG system could be considered for formulation of immediate release conventional tablets.

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