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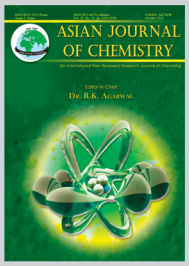

Formulation and Evaluation of Simvastatin Fast Dissolving Tablets with Croscarmellose Sodium as Super Disintegrant

G.V. RAMANA REDDY[1], S. VIDYADHARA[2,*] and CH. ANUSHA[2]

[1]Center for Biotechnology, Acharya Nagarjuna University, Nagarjuna Nagar, Guntur-522 510, India
[2]Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Chowdavaram, Guntur-522 019, India

*Corresponding author: E-mail: svidyadhara@gmail.com

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The objective of the present study is to formulate solid dispersions of simvastatin to improve the aqueous solubility and dissolution rate to facilitate faster onset of action. Solid dispersion of simvastatin with croscarmellose sodium (CCS), were prepared and compressed as tablets by using diluents such as spray dried lactose, dicalcium phosphate (DCP) and microcrystalline cellulose (MCC). The solid dispersion of simvastatin with croscarmellose sodium at different ratios were prepared by physical mixing, solvent evaporation and kneading methods. These were found to release drug faster than the pure drug in dissolution media. The rapid release of poorly soluble simvastatin from solid dispersions was influenced by the proportion of polymer and the method employed for its preparation. Among the three methods employed solvent evaporation and kneading methods were found to be suitable for improving the dissolution rate of simvastatin. The release was found to follow the first order kinetics. Some of the dispersions prepared by solvent evaporation and kneading method were further formulated in to a tablet with diluents such as spray dried lactose, dicalcium phosphate and microcrystalline cellulose. All the tablet preparations containing diluents were found to release drug in order of dicalcium phosphate > microcrystalline cellulose > spray dried lactose. The dissolution rate of such tablet formulations were found to release drug at a faster rate than that of tablets prepared with plain drug.

Key Words: Simvastatin, Croscarmellose sodium, Solid dispersions, Fast dissolving tablets.

INTRODUCTION

Oral drug delivery is the simplest and easiest way of administering drugs. Because of the greater stability, accurate dosage and easy production, solid oral dosage forms have many advantages over other types of oral dosage forms[1,2]. Therefore, most of the new chemical entities (NCE) under development these days are intended to be used as a solid dosage form that originate an effective and reproducible *in vivo* plasma concentration after oral administration[3]. In fact, most new chemical entities's are poorly water soluble drugs, not well-absorbed after oral administration[4], which can detract from the drug's inherent efficacy[5-7]. Moreover, most promising new chemical entities's, despite their high permeability, are generally only absorbed in the upper small intestine, absorption being reduced significantly after the ileum, showing, that there is a small absorption window[8,9]. Consequently, if these drugs are not completely released in this gastrointestinal area, they will have a low bioavailability. Therefore, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs[10,11]. Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability. By improving the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce side effects[12-14]. Solubility is an important physicochemical factor affecting the absorption of drugs and their therapeutic effectiveness. Poor aqueous solubility leads to formulation development failures. The poor solubility of drug substances in water and their low dissolution rate in aqueous G.I.T fluid often leads to insufficient bioavailability and an increase in dosage and variability in blood concentrations[15].

Solubility enhancement can be achieved by increasing the surface area of the drug which is accessible to the dissolution medium. The solid dispersion is the most commonly used technique for improving the dissolution and bioavailability of poorly soluble drugs. Molecular dispersion of drug in polymeric carriers may lead to particle size reduction and surface area enhancement, which result in improved dissolution rates. Furthermore, no energy is required to break up the crystal lattice of a drug during dissolution process[16].

Higher drug dissolution rates from a solid dispersion can be facilitated by optimizing the wetting characteristics of the compound's surface and also by increasing the interfacial area

available for drug dissolution[17]. A wide variety of water soluble carriers have been used for enhancing the aqueous solubility of drugs. Several insoluble drugs have been shown to improve their solubility, dissolution rate and oral absorption when incorporated into a solid dispersion[18].

Simvastatin is an antihyperlipidemic drug mainly used in treatment of lowering the lipid profiles particularly in the diseased states such as congenital heart diseases, lipoidal edema and diabetes *etc*. Simvastatin is rapidly absorbed by the liver after oral administration. It undergoes extensive first pass metabolism in the liver. In humans, the main metabolite is the β- hydroxyl acid[19]. It is practically insoluble in water and other aqueous media. The very poor aqueous solubility and wettability of simvastatin give rise to difficulties in the design of pharmaceutical formulations and led to variable oral bioavailability. A few reports are available on the enhancement of solubility, dissolution rate of simvastatin[20]. Rate of absorption and/or extent of bioavailability for such insoluble drug is controlled by rate of dissolution in gastrointestinal fluids. The peak plasma concentration (C_{max}) and t_{max} depend upon extent and rate of dissolution of drug respectively. Hence the present investigation is aimed to increase rate of dissolution of simvastatin[21].

EXPERIMENTAL

Simvastatin was a gift sample from Matrix Pharma Ltd., Hyderabad and croscarmellose sodium was a gift sample obtained from M/s. Natco Pharma Ltd., Hyderabad, microcrystalline cellulose, dicalcium phosphate, spray dried lactose were gift samples obtained from Pellets Pharma Ltd, Hyderabad. Methanol, sodium hydroxide, hydrochloric acid, potassium hydrogen phosphate (S.D. Fine Chemicals, Mumbai) was procured from commercial sources. All other materials used were of pharamacopeial grade.

Saturated solubility studies: 100 mg of simvastatin was weighed and transferred in a conical flask containing 100 mL of different dissolution media. These flasks were hermetically sealed and incubated at 37 ºC in a incubator shaker, rotated at 50 rpm for 24 h. Then the samples were filtered and subsequently diluted with same media. The corresponding absorbance values were noted at 238 nm.

Preparation of solid dispersions: Simvastatin solid dispersions with croscarmellose sodium were prepared by employing three methods such as:1) Physical mixing; 2) Solvent evaporation; 3) Co-grinding (kneading method).

Physical mixing method: Known quantity of drug (20 mg) simvastatin and croscarmellose sodium were weighed separately and passed through sieve no. 80. The materials passed through sieve no. 80 were collected and transferred into a clean and dry glass mortar and were triturated together for 5 min. Then the blended mixture was passed again through sieve No. 80 and is collected and packed in a wide mouthed amber coloured glass containers and were hermetically sealed[22].

Solvent evaporation method: Simvastatin was taken in a china dish and was dissolved in few mL of methanol. To the methanolic solution, specified amount of croscarmellose sodium was added and the mixture was heated at 50 ºC on a heating mentle with continuous stirring until the solvent is evaporated. Then the mixture was collected and packed in an amber coloured glass containers and was hermetically sealed. Then the mixture was stored at ambient conditions[23].

Kneading method: Simvastatin and croscarmellose sodium were taken in a glass mortar and few mL of water was added and triturated vigorously until the damp granular mass was obtained. The mixture was then dried in a hot air oven to form dry granules. Then the mixture was taken and passed through sieve no. 80 and the granules were collected, which were packed in a wide mouthed amber coloured glass container and hermetically sealed for storage[24]. Various compositions of solid dispersion are shown in Table-1.

TABLE-1
COMPOSITION OF VARIOUS SOLID DISPERSIONS OF SIMVASTATIN

Composition	Ratio
Physical mixtures	*Drug : polymer
SIM + CCS (SIMP – 1)	1:0.5
SIM + CCS (SIMP – 2)	1:1
SIM + CCS (SIMP – 3)	1:1.5
SIM + CCS (SIMP – 4)	1:2
Solvent evaporation	
SIM + CCS (SIMS – 1)	1:1
SIM + CCS S(IMS – 2)	1:1.5
SIM + CCS (SIMS – 3)	1:2
Kneading method	
SIM + CCS (SIMK – 1)	1:1
SIM + CCS (SIMK – 2)	1:1.5
SIM + CCS (SIMK – 3)	1:2

*One part is equal to 20 mg
SIM = Simvastatin; CCS = Croscarmellose sodium.

Characterization and evaluation of solid dispersions: The solid dispersions prepared by various methods were characterized by particle size determination and flow properties such as angle of repose and Carr's index[25].

Estimation of simvastatin in solid dispersions: 20 mg of solid dispersions was dissolved in methanol by vigorous shaking in the solvent. The solutions were filtered and the filtrate was diluted suitably with 6.4 pH buffer containing 0.5 % sodium laurly sulphate (SLS). Drug content of samples were determined by measuring absorbance at 238 nm.

Dissolution rate studies on simvastatin solid dispersions: Dissolution rate studies of pure simvastatin and solid dispersions were performed in 8 stage Toshiba dissolution test apparatus with rotating paddle method at 50 rpm using 900 mL of 6.4 pH buffer containing 0.5 % sodium laurly sulphate. The temperature of the bath was maintained at 37 ± 0.5 ºC throughout the experiment. 5 mL of the sample were withdrawn at various time intervals and were further diluted with 6.4 pH buffer containing 0.5 % sodium laurly sulphate medium. The absorbance of the sample was measured at 238 nm for determining the amount of drug released at various time intervals. Each time the same volume of buffer was added to the dissolution media for maintaining the sink conditions. The dissolution studies were carried out in triplicate. Based upon the data obtained from the dissolution studies various parameters such as T_{50}, T_{90}, DE_{30} %, zero order and first order release rate constants were estimated.

The dissolution parameters such as T_{50} and T_{90} were measured directly from the dissolution profile curves and DE_{30} % was estimated by employing trapezoidal rule to the dissolution profiles. The zero order constant (K value) was obtained by calculating the slope value from the percent drug released versus time profile curve. The first order constant was calculated by multiplying the slope value obtained from log percent drug undissolved versus time plot with 2.303.

Preparation of simvastatin tablets with solid dispersions: Among the solid dispersions prepared and based upon the dissolution studies performed, two optimized dispersions were selected for preparation of tables. The selected solid dispersions were blended with diluents like spray dried lactose, dicalcium phosphate, microcrystalline cellulose and 0.5 % of lubricant and then directly compressed by using 16 station rotary punching machine with 3 mm flat surfaced punches with a compression force of 3-5 kg/cm^2. The compositions of various tablet formulations were given in Table-2.

TABLE-2
COMPOSITION OF SIMVASTATIN SOLID DISPERSIONS CONTAINING TABLETS

Ingredients (mg/tablet)	Formulations with SIMS 3			Formulations with SIMK 3		
	FS_1	FS_2	FS_3	FK_4	FK_5	FK_6
Solid dispersions mixture	30	30	30	30	30	30
DCP	169.5	-	-	169.5	-	-
MCC	-	169.5	-	-	169.5	-
Spray dried lactose	-	-	169.5	-	-	169.5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5
Total wt. of the tablet (mg)	200	200	200	200	200	200

Evaluation of physical parameters of simvastatin tablets: The physical parameters such as weight uniformity, hardness, friability, drug content and disintegration time were evaluated for the prepared tablets as per the I.P standards[26].

Dissolution rate studies on simvastatin tablets: Dissolution rate studies of simvastatin tablets were performed in 8 stage Toshiba dissolution test apparatus as per the procedure described earlier.

RESULTS AND DISCUSSION

Saturated solubility studies revealed that simvastatin exhibit maximum solubility in the 6.4 pH phosphate buffer containing 0.5 % sodium lauryl sulphate as medium among the different media used. Hence 6.4 pH phosphate buffer containing 0.5 % sodium lauryl sulphate was used as dissolution medium for further studies. The drug concentration was measured at 238 nm using UV spectrophotometer for all the dissolution media. The solid dispersions were prepared with a novel super disintegrant such as croscarmellose sodium by physical mixing, solvent evaporation and kneading methods as per the composition shown in Table-1. All dispersions were prepared under similar conditions to avoid batch to batch variations. The dispersions were found to be uniform in their characteristics. All the solid dispersions were in the size range of 178 ± 10 µm. The angle of repose and Carr's index values of all the dispersions prepared indicated the good and free flowing characteristics (Table-3). The drug content estimated in all the solid dispersions were highly uniform and in the range of 98 ± 2 %, indicated the uniformity (Table-3). The dissolution studies of simvastatin as pure drug and its solid dispersions was performed in 6.4 pH phosphate buffer containing 0.5 % sodium lauryl sulphate medium by using paddle method. The dissolution rate of all the solid dispersions were found to be rapid than compared to its pure drug simvastatin. The T_{50}, T_{90} and DE_{30} %, values of the dispersions indicated their rapid drug dissolution than their respective counterpart simvastatin pure drug. The kinetics of drug release from all the dispersions followed first order. The R^2 values obtained for all the dispersions were linear for the first order plots (Table-4). Among the solid dispersions prepared, solvent evaporation and kneading methods were found to be suitable in increasing the dissolution rates of poorly soluble simvastatin. It was also observed that as the concentration of croscarmellose sodium increases the rate of dissolution of the drug was also increased. Solid dispersions prepared by solvent evaporation and kneading methods at a drug to superdisintegrant ratio of 1:2 were found to undergo rapid dissolution rates.

TABLE-3
FLOW PROPERTIES AND DRUG CONTENT OF SIMVASTATIN SOLID DISPERSIONS

Solid dispersion	Angle of repose (°)	Carr's index (%)	Particle size (µ)	Drug content (%)
SIMP–1	26	19	179 ± 4	99.2 ± 0.4
SIMP–2	25	16	176 ± 5	98.5 ± 0.8
SIMP–3	24	18	170 ± 6	99.1 ± 0.4
SIMP–4	28	19	167 ± 5	99.5 ± 0.5
SIMK–1	31	17	170 ± 4	99.2 ± 0.4
SIMK–2	28	20	175 ± 6	98.8 ± 0.7
SIMK–3	29	19	178 ± 5	99.5 ± 0.3
SIMS–1	26	21	172 ± 4	99.3 ± 0.4
SIMS–2	29	26	179 ± 6	99.4 ±0.7
SIMS–3	23	20	170 ± 5	98.8 ±0.8

Hence solid dispersions, SIMS 3 and SIMK 3 were further directly compressed as tablets by using spray dried lactose, microcrystalline cellulose and dicalcium phosphate as diluents. All the tablets were compressed under identical conditions to avoid processing variables. The physical parameters such as weight uniformity, friability and drug content and disintegration time were evaluated for all the tablets prepared. The physical parameters evaluated were highly uniform (Table-5) and all the tablets were found to be within the I.P. specified limits[26]. The dissolution studies on the simvastatin marketed tablet and all the tablet formulations were performed in 6.4 pH phosphate buffer containing 0.5 % sodium lauryl sulphate medium using paddle method. The rate of dissolution of tablet formulations was rapid when compared to the marketed tablet of simvastatin. The rate of drug release from all the tablets followed first order kinetics (Table-6). Among the tablets prepared with the spray dried lactose, microcrystalline cellulose and dicalcium phosphate as diluents, tablets with dicalcium phosphate tend to exhibit rapid dissolution. The rate of rapid drug release is in the order of dicalcium phosphate > microcrystalline cellulose > spray dried lactose in tablet formulations.

The disintegration time for the dicalcium phosphate containing tablets were found to be much faster than its respective

TABLE-4
DISSOLUTION PARAMETERS OF SIMVASTATIN SOLID DISPERSIONS

Solid dispersion	Drug release at 1.5 h (%)	T_{50} (min)	T_{90} (min)	DE_{30} (%)	Zero order K	Zero order R^2	First order K (min^1)	First order R^2
SIM Drug	67.52	45	> 90	22.00	0.8032	0.5134	0.0095	0.979
SIMP 1	80.64	12	> 90	28.72	0.4736	0.6627	0.0144	0.9793
SIMP 2	83.15	10	> 90	33.84	0.4889	0.6534	0.0149	0.9528
SIMP 3	86.76	8	> 90	37.36	0.4923	0.6526	0.0173	0.9419
SIMP 4	88.3	6	> 90	38.14	0.5232	0.6323	0.0192	0.9308
SIMS 1	91.82	10	86	44.24	0.5812	0.7137	0.0212	0.9860
SIMS 2	96.2	8	67	47.89	0.6324	0.7423	0.0238	0.9824
SIMS 3	99.68	6	48	48.25	0.6428	0.7284	0.0247	0.9890
SIMK 1	90.2	10	90	38.72	0.6576	0.7168	0.0225	0.9872
SIMK 2	94.45	9	60	42.32	0.6242	0.7380	0.0238	0.9826
SIMK 3	99.7	7	52	48.26	0.6158	0.7126	0.0245	0.9732

TABLE-5
PHYSICAL PARAMETERS OF SIMVASTATIN TABLET FORMULATIONS

Tablet	Weight uniformity	Friability loss (%)	Hardness (kg/cm^2)	Disintegration time (min)	Drug content (%)
MF	196 ± 4	0.26	3.5	14.3	99.3 ± 3
FS_1	195 ± 3	0.23	3.3	3.2	99.5 ± 4
FS_2	198 ± 5	0.24	3.2	3.5	99.2 ± 5
FS_3	196 ± 4	0.25	3.0	4.0	99.4 ± 2
FK_4	198 ± 5	0.24	3.3	3.8	99.3 ± 4
FK_5	197 ± 4	0.28	3.9	4.2	98.5 ± 3
FK_6	196 ± 5	0.26	3.6	4.5	97.5 ± 5

MF: Marketed tablet – (SIMSTAT – 20 mg)

TABLE-6
DISSOLUTION PARAMETERS OF SIMVASTATIN TABLET FORMULATIONS

Tablets	Drug release at 1.5 h (%)	T_{50} (min)	T_{90} (min)	DE_{30} (%)	Zero order K	Zero order R^2	First order K (min^{-1})	First order R^2
MF	80.56	15	> 90.00	28.00	0.6084	0.7458	0.0168	0.9764
FS_1	98.21	9	60.00	45.38	0.7231	0.8019	0.0281	0.9658
FS_2	95.00	11	66.30	42.14	0.7506	0.8102	0.0264	0.9812
FS_3	92.00	12	68.50	40.17	0.7483	0.8025	0.0252	0.9835
FK_4	99.13	7	54.32	45.36	0.7221	0.7964	0.0273	0.9730
FK_5	97.00	9	58.16	43.21	0.7054	0.7024	0.0261	0.9812
FK_6	93.32	12	62.00	40.76	0.7217	0.7934	0.0254	0.9845

counter parts. The rapid disintegration may be due to increased uptake of water by both diluent and superdisintegrant which lead to faster dissolution of the tablets gave improved dissolution profiles of poorly soluble simvastatin.

The dissolution profiles of simvastatin solid dispersions by physical mixing method, solvent evaporation method and by kneading method are given in Figs. 1-3, while the dissolution profiles of simvastatin marketed formulations and tablet formulations prepared by solvent evaporation method and by kneading method are given in Figs. 4 and 5, respectively.

Conclusion

The present study has shown that it is possible to increase the dissolution rate of poorly water soluble drug simvastatin by preparing solid dispersions with super disintegrant like croscarmellose sodium. The solid dispersions exhibit faster dissolution characteristics as compared to plain drug. This was due to solubilizing effect of the carrier or crystallization of drug entrapped in molecular state by the carrier. A higher dissolution rate was obtained with solid dispersions prepared by solvent evaporation method and kneading method in the ratio of 1:2 for the drug and polymer. Based on the study it may be concluded that simvastatin tablets prepared by solid dispersions with dicalcium phosphate as a diluent was found to be ideal for rapid disintegration and for improving the dissolution rate and bioavailability.

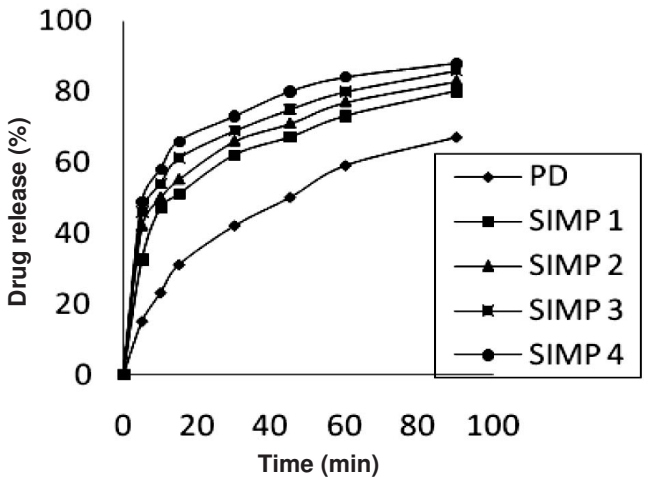

Fig. 1. Dissolution profiles of simvastatin solid dispersions by physical mixing method

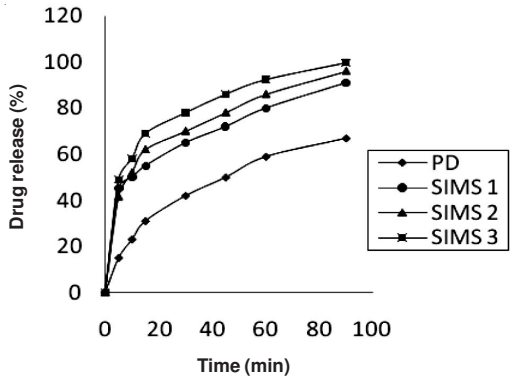

Fig. 2. Dissolution profiles of simvastatin solid dispersions by solvent evaporation method

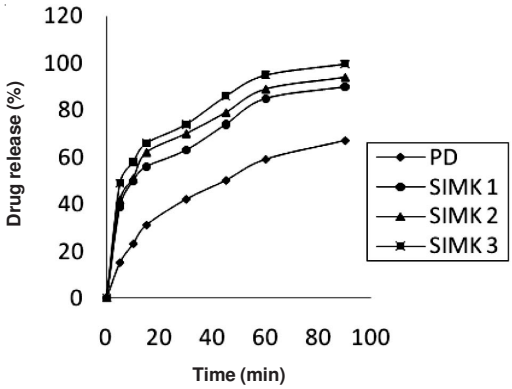

Fig. 3. Dissolution profiles of simvastatin solid dispersions by kneading method

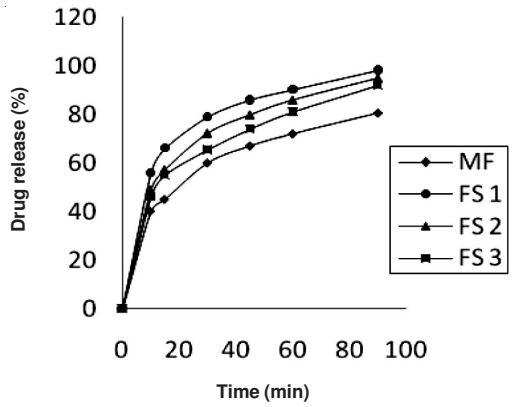

Fig. 4. Dissolution profiles of simvastatin marketed formulations and tablet formulations prepared by solvent evaporation method

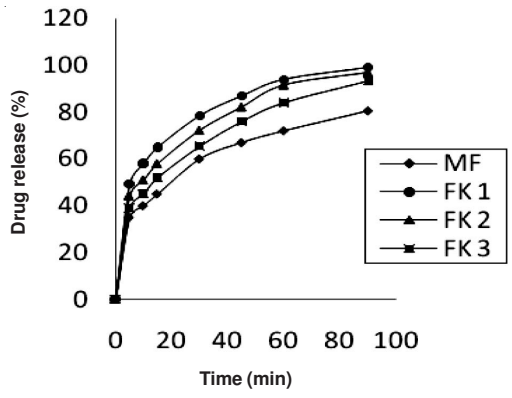

Fig. 5. Dissolution profiles of simvastatin marketed formulations and tablet formulations prepared by kneading method

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