Asian Journal of Chemistry; Vol. 23, No. 12 (2011), 5481-5485

ASIAN JOURNAL OF CHEMISTRY

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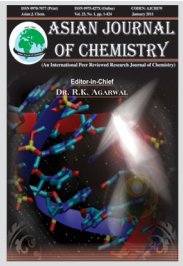

Solubility Enhancement of Simvastatin by Co-compression with Hydrophilic Polymers (PEG & PVP) and surfactant (SLS)

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(*Received*: 10 March 2011; *Accepted*: 24 August 2011) AJC-10310

The aim of the present investigation is to enhance the dissolution of simvastatin (SIM) by co-compression with hydrophilic polymers [poly(ethylene glycol) and poly(vinyl pyrolidone)] and surfactant (sodium lauryl sulfate). Phase solubility studies are conducted by using poly(ethylene glycol) (PEG), poly(vinyl pyrolidone) (PVP) and sodium lauryl sulfate (SLS). The apparent stability constant (Ka), thermodynamic parameters like Gibb's free energy change (ΔG), Enthalpy change (ΔH) and Entropy change (ΔS) are calculated from the phase solubility data. All the values indicated that the used carriers were favouring the dissolution of drug in water and this is increased with increase in the carrier concentration. After confirming the positive effect on the dissolution of drug, the carriers were co-compressed with drug and other ingredients in to tablets. FTIR studies revealed no interaction between drug and ingredients. The prepared tablets were evaluated for tablet properties like hardness, weight variation, thickness, content uniformity, friability and disintegration time according to USP. It was found that the tablets passed all the above tests as the values were within the prescribed limits according to USP. From the dissolution studies, it was known that there is tremendous enhancement in the dissolution rate of pure drug with the co-compression of carriers. The cumulative % drug releases of pure simvastatin was 14.3 % and of the tablets containing carriers were 89.9 (sodium lauryl sulfate), 74.6 [poly(ethylene glycol)] and 81.1 [poly(vinyl pyrolidone)] after 3 h.

Key Words: Simvastatin, Dissolution enhancement, Co-compression, Hydrophilic carriers and Surfactants.

INTRODUCTION

The discovery of biologically active molecules is taking place at a pace never seen before because of the advent of high- throughput screening techniques. Most of the chemical entities that are being discovered are lipophilic and have poor aqueous solubility, so that they pose difficulties for formulation to the biopharmaceutical scientist[1]. The enhancement of the oral bioavailability is the greatest challenges in the formulation of poorly water soluble drugs[2]. In general, drug dissolution can be defined as the extent and the rate of dissolution involves 2 steps, drug release from the dosage form and drug transport within the dissolution medium[3].

The rate and extent of dissolution of the drug from any solid dosage form determines the rate and extent of absorption of the drug[4]. Dissolution is the rate limiting step in the process of drug absorption for the poorly soluble drugs. Poor soluble compounds show low and eratic bioavailability and poor dose proportionality because they tend to be eliminated from the gastro-intestinal tract before they fully dissolve and be absorbed into the circulation. These drawbacks have limited the development of poorly soluble molecules.

Simvastatin (SIM) is a lipid lowering agent derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, an inactive lactone is hydrolyzed to corresponding β-hydroxy acid form which is a principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, the enzyme that catalyzes an early and rate-limiting step in the biosynthesis of cholesterol[5]. However, it is practically insoluble in water (*ca.* 30 mg/mL) and poorly absorbed from the gastro-intestinal tract[6-8]. The compounds with very low aqueous solubility will show dissolution rate limited absorption and hence poor absorption and distribution. Improvement of aqueous solubility in such a case is a valuable goal to improve therapeutic efficacy. A simple co-compression of hydrophilic polymers[9,10] and surfactant[11] with poor water soluble drugs will enhance the dissolution rate. The present investigation aims at enhancing the dissolution rate of simvastatin by using excipients like poly(ethylene glycol) (PEG), poly (vinyl pyrolidone) (PVP) and sodium lauryl sulphate (SLS).

EXPERIMENTAL

Simvastatin was procured as a gift sample from Aurobindo's laboratories, Hyderabad. Poly(ethylene glycol) 4000 (PEG), poly(vinyl pyrollidone) K 30 (PVP) and sodium lauryl sulphate (SLS) were obtained from the S.D. Fine Chemicals Limited, Mumbai. All other chemicals and solvents used in this study were of analytical reagent grade.

Phase solubility studies: Phase-solubility studies were performed according to the method reported by Higuchi and Connors[12]. Simvastatin in amounts more than saturation, were transferred to screw capped vials containing 25 mL aqueous solution of different PEG 4000, PVP K 30 and SLS concentrations (0, 1, 2, 3, 4 and 5 %). The contents were stirred on gyrator shaker at room temperature and 40 ºC for 72 h. After reaching equilibrium, samples were filtered through a 0.45 µm membrane by vaccum filtration and suitably diluted and analyzed spectrophotometrically for drug content at the wavelength of 238 nm using UV spectrophotometer (Elico SL159). All readings were taken in triplicate. Phase solubility curve was plotted by taking concentration on X-axis and solubility of simvastatin (g/L) on Y-axis. The apparent stability constants (Ka) and thermodynamic parameters were derived from phase solubility curve by following equation given below[13-15].

$$K_a = \frac{\text{Slope}}{\text{Intercept}(1-\text{slope})}$$

An indication of the process of transfer of simvastatin from pure water to aqueous solution of PEG, PVP and SLS was obtained from the values of Gibbs free energy change. The Gibbs free energy of transfer (ΔG) of simvastatin from pure water to aqueous solutions of carriers was calculated using eqn.

$$\Delta G = - RT \ln (S_s S_w^{-1})$$

The enthalpy of transfer (ΔH in J/mol) can be calculated from a modification of the van't Hoff equation.

$$\ln S_s = -\Delta H (RT)^{-1} + C$$

The entropic change for the dissolution process is obtained from the respective enthalpies and Gibbs energies.

$$\Delta S = \frac{(\Delta H - \Delta G)}{T}$$

where S_s/S_w = the ratio of molar solubility of simvastatin in aqueous solution of PEG, PVP or SLS to that of the pure water, R the gas constant (8.3143 J/K mol), T the absolute temperature (K), C is a constant.

Fourier-transform infrared (FTIR) spectra of moisture free samples of SIM and its physical mixture (PM) with solubilizing agents were obtained by using potassium bromide pellet method.

Preparation of tablets by direct compression method: SIM along with SLS, PEG and PVP were formulated into tablets by direct compression method after preformulation studies like angle of repose and carr's index. Tablets with 100 mg of simvastatin were prepared as per the formula given in Table-1.

Characterization of tablets

Tablet properties: The prepared tablets were evaluated for the properties like hardness (by Pfizer tester), weight variation (by Citizen electronic balance), thickness (by screw guage), content of uniformity (by Elico spectrophotometer), friability (by Roche friability tester) and disintegration time (Electro Lab disintegration apparatus) according to USP.

TABLE-1
FORMULATION OF SIMVASTATIN TABLETS

Ingredients (mg/ tablet)	F_1	F_2	F_3	F_4
Drug	10	10	10	10
Magnesium sterate	0.25	0.25	0.25	0.25
Talc	0.25	0.25	0.25	0.25
Mannitol	50	50	50	50
Aerosil	1	1	1	1
Lactose	38.5	28.5	28.5	28.5
Sodium lauryl sulfate	-	10	-	-
Poly(ethylene glycol)	-	-	10	-
Poly(vinyl pyrollidone)	-	-	-	10

Water absorption ratio: Twice folded tissue paper was placed in a petri dish having an internal diameter of 5 cm containing 6 mL of water. A tablet was carefully placed on the surface of the tissue paper in the petri dish. The time required for water to reach the upper surface of the tablet and to completely wet it was noted as the wetting time. Water absorption ratio (R) was then determined according to the following equation[16].

$$R = \frac{(W_a - W_b)}{(W_a)}$$

where, W_a and W_b were tablet weights before and after water absorption respectively.

Dissolution studies: Dissolution studies of simvastatin in powder form and its tablets with solubilizing agents were performed to evaluate *in vitro* drug release profile. Dissolution studies were performed using USP apparatus type 2 with 900 mL dissolution medium (distilled water with 0.25 % SLS) at 37 ± 0.5 ºC at 100 rpm for 3 h. Samples of pure simvastatin and its tablets equivalent to 10 mg of drug were added to the dissolution medium. At fixed time intervals, 5 mL aliquots were withdrawn, filtered, suitably diluted and assayed for simvastatin content by measuring the absorbance at 238 nm using UV spectrophotometer (Elico SL159 Mumbai, India). Equal volume of fresh medium at the same temperature was replaced into dissolution medium after each sampling to maintain its constant volume through out the test. Each test was performed in triplicates (n = 3) and calculated mean values of cumulative drug release were used while plotting the release curves.

DP_{30min} values (per cent drug dissolved within 0.5 min), $t_{50\%}$ (time to dissolve 50 % drug) and mean dissolution time (MDT) values were calculated from dissolution data.

$$MDT_{invitro} = \frac{\sum_{i=1}^{n} t_{mid} \Delta M}{\sum_{i=1}^{n} \Delta M}$$

Here, i is dissolution sample number, n is number of dissolution times, t_{mid} is time at the midpoint between times t_i and t_{i-1} and ΔM is the amount of simvastatin dissolved (mg) between time t_i and t_{i-1}. In order to understand extent of improvement in dissolution rate of simvastatin, the obtained dissolution data of all samples were fitted into equation.

TABLE-2
THERMODYNAMIC PARAMETERS FOR SOLUBILIZATION PROCESS OF SIMVASTATIN IN AQUEOUS SOLUTIONS OF CARRIERS AT 25 ºC AND 40 ºC

Concentration of solubility aiding agent (%w/v)	ΔG (JM^{-1})		ΔS (JKM^{-1})		ΔH (KJM^{-1})
	25 ºC	40 ºC	25 ºC	40 ºC	
Sodium lauryl sulfate (SLS)					
1	-3639	-2577	-0.97	-0.31	-39
2	-3974	-4179	-1.01	-0.32	-42
3	-4139	-4356	-1.28	-0.55	-45
4	-4356	-4622	-4.00	-3.11	-55
5	-4911	-5307	-11.23	-9.90	-82
Ka (M^{-1})	298.5	141.2			
Poly(ethylene glycol) (PEG)					
1	-884	-1822	-63	-60	-19
2	-1294	-2368	-71	-67	-22
3	-1609	-2815	-79	-75	-25
4	-2199	-3470	-82	-77	-26
5	-2722	-4044	-83	-79	-27
Ka (M^{-1})	333.1	260.5			
Poly(vinyl pyrolidone) (PVP)					
1	-1252	-1921	-42.69	-37.90	-13
2	-1682	-2474	-49.83	-44.21	-16
3	-2551	-3671	-69.85	-61.94	-23
4	-3174	-4498	-82.05	-72.73	-27
5	-3639	-4988	-82.25	-72.83	-28
Ka (M^{-1})	297.9	291.6			

Per cent dissolution efficiency (% DE) was also computed to compare the relative performance of various carriers in solid dispersion formulations. The magnitude of % DE at 10 min (% DE_{10} min) and 0.5 h (% DE_{30} min) for each formulation was computed as the per cent ratio of area under the dissolution curve up to the time t, to that of the area of the rectangle described by 100 % dissolution at the same time.

$$\%DE = \frac{\int_0^t Y.dt}{Y_{100}t} \times 100$$

Statistical analysis: Model independent mathematical approach proposed by Moore and Flanner[17] for calculating a similarity factor f_2 was used for comparison between dissolution profiles of different samples. The similarity factor f_2 is a measure of similarity in the percentage dissolution between two dissolution curves and is defined by following equation.

$$f_2 = 50 \text{ X } \log \{[1+ (1/n) \sum_{t=1}^{n} W_t (R_t - T_t)^2]^{-0.5} \text{X } 100\}$$

where, n is the number of withdrawal points, R_t is the percentage dissolution of reference at the time point t and T_t is the percentage dissolution of test at the time point t. A value of 100 % for the similarity factor (f_2) suggests that the test and reference profiles are identical. Values between 50 and 100 indicate that the dissolution profiles are similar whilst smaller values imply an increase in dissimilarity between release profiles.

RESULTS AND DISCUSSION

FTIR has been used to assess the interaction between carrier and guest molecules. The spectrum of pure simvastatin presented characteristic peaks at 3553 cm^{-1} (alcohol O-H stretching vibration), 3011 cm^{-1} (olefinic C-H stretching vibration), 2957 and 2878 cm^{-1} (methyl and methylene C-H asymmetric and symmetric stretching vibration), 1719 and 1701 cm_{-1} (lactone C=O and ester C=O stretch), 1453, 1406 and 1383 cm^{-1} (methyl and methylene bending vibration), 1267, 1222, 1178 and 1080 cm^{-1} (lactone and ester C-O-C bending vibration), 1060 cm^{-1} (secondary alcohol C-O stretching vibration) and 879 cm^{-1} (tri substituted olefinic C-H wag), respectively.

The obtained values of ΔG, ΔH and apparent stability constants (Ka) were shown in Table-2. The Gibbs free energy values provide the information whether the reaction condition is favourable or unfavourable for drug solubilization in the aqueous carrier solution. Negative Gibbs free energy values indicate favourable conditions. ΔG and ΔH values were all negative for both polymers at various concentrations, indicating the spontaneous nature of simvastatin dissolution and it decreased with an increase in PEG, PVP and SLS concentration, demonstrating that the reaction became more favourable as the concentration of PEG, PVP and SLS were increased.

The formulations were studied for the physical properties to judge in tableting ability and the values are given in Table-3. In general, compressibility index values upto 15 % and angle of repose between 25º and 30º indicate good to excellent flow properties[10]. Percentage compressibility and angle of repose of physical mixtures with PVP, PEG and SLS were 8.16, 8.94, 9.12 and 27.27º, 28.12º, 28.74º, respectively. These values indicate good compressibility and flow properties, making it suitable for tabletting.

The prepared tablets were evaluated for weight variation, hardness, friability, disintegration and dissolution the values were given in Table-4. From the results it is clear that the tablets have passed the test for weight variation, disintegration and friability according to USP. The hardness of the tablets was around 5-7 kg/cm^2 indicating good mechanical strength. There was reduction in the disintegration time without any effect on the hardness with the incorporation of SLS, PEG and PVP.

TABLE-3
EVALUATION PARAMETERS OF THE PREPARED FORMULATIONS

Evaluation parameters	F_1	F_2	F_3	F_4
Angle of repose (^{0})	15.14 ± 0.2	23.17 ± 0.5	25.34 ± 0.4	26.11 ± 0.5
Carr's index (%)	18.31 ± 1.2	10.57 ± 1.3	12.64 ± 1.2	11.01 ± 1.2
Hardness (kg/cm^2)	4.6 ± 0.4	4.8 ± 0.2	4.8 ± 0.2	4.4 ± 0.4
Weight variation(mg)	101 ± 0.24	100 ± 0.61	101 ± 0.6	99 ± 0.52
Thickness (mm)	3.10 ± 0.20	3.28 ± 0.02	3.49 ± 0.03	3.65 ± 0.01
Content of uniformity (%)	98.40 ± 1.5	96.47 ± 1.6	94.71 ± 1.5	93.43 ± 1.4
Friability (%)	0.72 ± 0.5	0.63 ± 0.5	0.47 ± 0.5	0.32 ± 0.5
Disintegration time (min)	17 ± 1.5	8 ± 1.5	11 ± 1.5	12 ± 1.5
Water absorption ratio	66.84 ± 1.35	73.12 ± 1.56	70.34 ± 1.42	68.51 ± 1.63
DP_{30min} (% dissolved in 30minutes)	2.1	43.65	37.6	36.83
$t_{50\%\ (hrs)}$ (Time taken to release half amount)	>3	0.7	0.9	1.4
MDT (at 60 minutes)	26.7	23.2	24	24
$DP_{180\ min}$ (% dissolved in 180 min)	10.3	85.4	83.1	78.5
f_2 (Similarity factor)	90.8	72.5	82.4	71.9

F_1- pure SIM F_2- with SLS, F_3- with PEG, F_4- with PVP

This indicates that the incorporation had not resulted in softening of the tablet but by quick uptake of water the disintegration time was decreased. This is also evident from the water absorption values. The water absorption value was more for the tablets containing sodium lauryl sulfate.

TABLE-4
CUMULATIVE % DRUG RELEASE OF SIMVASTATIN TABLETS

Time (h)	Cumulative % drug release			
	F_1	F_2	F_3	F_4
0.0	0	0	0	0
0.5	2.1 ± 0.8	43.65 ± 1.1	37.60 ± 1.6	36.83 ± 1.7
1.0	3.5 ± 0.5	59.29 ± 1.3	52.25 ± 2.3	48.83 ± 2.0
1.5	5.26 ± 0.8	66.94 ± 2.9	63.60 ± 2.4	61.86 ± 1.6
2.0	6.6 ± 0.7	76.03 ± 3.5	71.62 ± 1.8	67.93 ± 2.7
2.5	8.6 ± 0.3	82.98 ± 2.9	78.97 ± 2.0	72.86 ± 2.8
3.0	10.3 ± 1.5	85.40 ± 2.2	83.14 ± 3.0	78.58 ± 1.1

F_1- pure SIM F_2- with SLS, F_3- with PEG, F_4- with PVP

From the data of cumulative % drug release presented in Fig. 1, it was evident that the cumulative % drug release of pure simvastatin was very low around 14.3 % and of the tablets containing carriers were 89.9 (SLS), 74.6 (PEG) and 81.1 (PVP) after 3 h. Tablets of simvastatin with PVP, PEG and SLS significantly enhanced dissolution rate of simvastatin within 3 h as compared to pure simvastatin. Mean dissolution time reflects the time for the drug to dissolve and was the first statistical moment for the cumulative dissolution process that provides an accurate drug release rate. A lower mean dissolution time value indicates greater drug dissolution. The mean dissolution time of pure simvastatin tablets was around 27 min and in case of tablets containing SLS, PEG and PVP the values were 23, 24 and 24 min respectively.

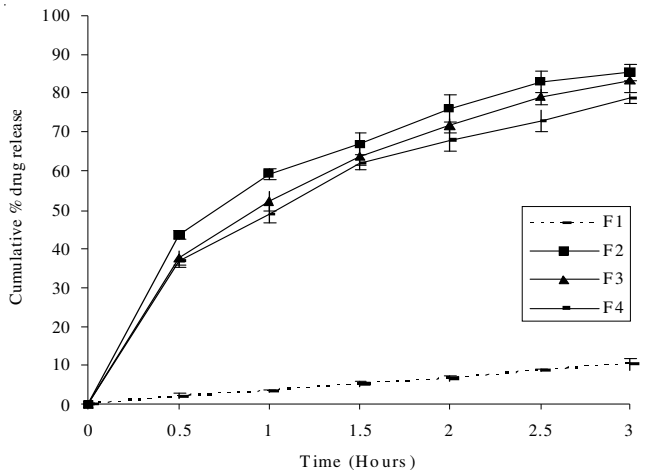

Fig. 1. Cumulative % drug release from the formulations with SD bars (n=3); F_1- pure simvastatin F_2- with SLS, F_3- with PEG, F_4- with PVP

There was an enhancement in the dissolution of simvastatin, when formulated along with SLS, PEG and PVP than in pure state. Both PEG and PVP have shown similar effect. The formation of hydrophilic matrix around the drug might be the reason for the dissolution enhancement. Among the used excipients SLS has shown more enhancements in dissolution. This may be because of the tendency of SLS to decrease the surface tension in the micro environment of dissolution along with quick uptake of water.

Conclusion

BCS class drugs were characterized by having low solubility apart from high permeability. The enhancement in dissolution may contribute to the improved bio availability. There are various methods to enhance dissolution. Among them, co-compression with dissolution enhancing ingredients is going to be the simple and effective method. In present investigation there was tremendous enhancement in dissolution almost 9 folds than the pure form with sodium lauryl sulfate. Further clinical studies are required to confirm the improved bio availability.

ACKNOWLEDGEMENTS

The authors express their deep gratitude to Central Analytical Department, Faculty of Technology, Osmania University, Hyderabad for providing FTIR facility. The authors thank the Management and the Department of Pharmaceutics, Nalanda College of Pharmacy, Nalgonda for providing facilities to carry out this research.

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