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Enhancement of solubility and dissolution rate of Simvastatin by Ternary Solid Dispersion Technique

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ABSTRACT

Simvastatin is a poorly soluble drug exhibiting poor dissolution pattern. Simvastatin, PEG 6000 & Poloxamer 407 solid dispersions were prepared with a view to study the influence of polymer on solubility and dissolution of this poorly soluble drug Simvastatin. Solid dispersions of Simvastatin were prepared using different ratios of PEG 6000 & Poloxamer 407 as carrier by, solvent evaporation method. They were evaluated for percentage yield, drug content, FTIR spectral studies, DSC, XRD, solubility, and in-vitro dissolution. The solubility profile indicated that there is increase in solubility of Simvastatin when polymer concentration is increased. The solid dispersion complex of drug (1:5:5 ratios) was giving better dissolution profile as compared to pure drug and other solid dispersions. This in turn can improve the bioavailability. FT-IR, DSC shows the compatibility of drug and carrier.

Keywords: Ebola haemorrhagic fever, EBOV, WHO, NHP, EVD

INTRODUCTION[1-8]

Solid dispersions can be defined as molecular or amorphous mixtures of poorly water soluble drugs in hydrophilic carriers in which the polymer properties play an important role in the drug dissolution profile. It has been estimated that 40% of new chemical entities being discovered
are poorly water-soluble. With recent advances in screening methods for identifying potential drug candidates, an increasing number of poorly water-soluble drugs have been identified as potential therapeutic agents. Unfortunately, these drugs have poor bioavailability due to their poor solubility. This has limited the commercial potential of these drugs. The solid dispersion technique is one of the most efficacious to improve the bioavailability of drugs with low water solubility. Among the important factors increasing the solubility of drugs in solid dispersions, particle size reduction, reduced agglomeration, improved wettability and solubility, or dispersion of the drug as micro-fine crystals, amorphous materials or in a molecular form must be mentioned. These formulations offer many advantages over others and the most relevant are the lower cost of the adjuvants and the feasible industrial application.

Solid dispersion in an inert carrier or matrix of solid state prepared mainly by the melting
(or fusion) and solvent evaporation methods. The melting method involves heating a physical mixture of an active agent and a carrier until melted, followed by rapidly solidifying under vigorous mixing, resulting in supersaturation of the drug by instantaneous solidification. On the other hand, the solvent evaporation method involves dissolving a physical mixture of two or more chemicals in a common solvent, followed by evaporation of the solvent. The proper selection of solvent and its removal rate are crucial in determining the quality of the final dispersion. The release mechanism of drug from a variety of solid dispersions depends on the

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physical properties of carriers as well as drug substances and preparation methods.

Simvastatin was used as a model drug, which is hypolipidemic agent with to systemic action that can be incorporated into several pharmaceutical forms. Lercanidipine HCl is a HMG CoA reductase of the statin class. Effective in the treatment of hypercholesterolemia, reduction in the risk of cardiac heart disease mortality and cardiovascular events. Oral bioavailability is approx less than 5% only due to extensive hepatic first pass metabolism into inactive metabolites. Indicated as 20-80 mg once a day. The main objective of this work was to investigate the possibility of improving the solubility and dissolution rate of Simvstatin by preparing Solid dispersion with various water soluble polymers such as PEG 6000, Poloxamer 407 and PVP K30. The prepared Solid dispersions were evaluated for % practical yield, drug content, in- vitro dissolution rate studies and interactions between the drug and polymer using IR spectral studies and differential scanning calorimetry.

MATERIALS AND METHODS

Materials

Simvastatin was recieved from Temis lab, Mumbai, India. PEG 6000, Poloxamer 407, KBr, Di Chloro Methane were supplied by Research–Lab Fine Chem Ind, Mumbai, India. All other materials used were of pharmaceutical or analytical grade.

Preparation of solid dispersion by solvent evaporation method: [10]

Required amount of Simvastatin was dissolved in 20 ml of Di Chloro Methane. Accurately weighed carrier corresponding to different drug: carrier ratio by weight was dispersed in drug solution. Then the solvent was allowed to evaporate completely. The resulting solid mass was then pulverized in a mortar to get dry free-flowing powder. The powder was passed through a #60 mesh sieve. The resulting mass was transferred to desiccators containing CaCl2 and stored until completely dry. Solid dispersion of Simvastatin with polymers in the ratio (1:1:1, 1:2:2, 1:3:3, 1:4:4 and 1:5:5 resp.) was prepared.

Table 1: Formulation plan of Simvastatin solid dispersions

Drug	Simvastatin	Simvastatin	Simvastatin
Carrier	PEG 6000:Polo 407 (A)	PEG 6000:PVP (B)	Polo407:PVP (C)
SSD-S 1	1:1:1	1:1:1	1:1:1
SSD-S 2	1:2:2	1:2:2	1:2:2
SSD-S 3	1:3:3	1:3:3	1:3:3
SSD-S 4	1:4:4	1:4:4	1:4:4
SSD-S 5	1:5:5	1:5:5	1:5:5

% Practical Yield: [10,15]

Percentage practical yield is calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation.

$$PY(\%) = \frac{\text{Practical Mass (Solid dispersion)}}{\text{Theoretical Mass (Drug + carrier)}} \times 100$$

Drug content: [11,15]

10 mg of solid dispersions were weighed accurately and dissolved in 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 238 nm by UV spectrophotometer. Each sample analyzed in triplicate. Actual drug content was calculated for all batches using the equation as follows:

$$\text{Drug content \%} = \frac{Tact}{Tss} \times 100$$

$$= \frac{\text{Actual Simvastatin content in weight quantity of solid dispersion}}{\text{Theoretical amount of Simvastatin in solid dispersion}} \times 100$$

In Vitro dissolution study: [12,15]

Dissolution studies were performed assuring sink condition according to the paddle method (USP)

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using USP XXIII apparatus type-II (electrolab TDT-O9T). The dissolution medium was 900 ml 0.1N HCl kept at 37°C ± 0.5°C. The solid dispersions containing 100 mg of Simvastatin was taken in a muslin cloth and tied to the rotating paddle kept in the basket of dissolution apparatus, the paddle was rotated at 50 rpm. Samples of 5 ml were withdrawn at specified time intervals and analyzed spectrophotometrically at 238 nm using Shimadzu-1800 UV-visible spectrophotometer. The samples withdrawn were replaced by fresh buffer solution. Each preparation was tested in triplicate and then mean values were calculated.

Differential scanning calorimetry (DSC): [13,15]

Thermal analysis of Simvastatin, PVP K30 and the solid dispersion were carried out using differential scanning calorimetry method. Samples were examined using a Shimadzu TGA- 50 DSC instrument. Samples equivalent to approximately 8 mg Simvastatin were placed in aluminum pans and heated from 40 to 250°C with a heating rate of 10°C/min.

X-ray Powder Diffraction (XRD): [14, 15, 16, 17]

Simvastatin was assessed by carrying out physical state analysis. The cavity of the metal sample holder of X ray diffractometer was filled with ground Sample powder & then smoothed out with a spatula. X-ray Diffraction pattern of Simvastatin was obtained using the X-ray Diffractometer (Siemens", Germany D-5000).

RESULTS AND DISCUSSION

Solid dispersions of Simvastatin were prepared by different methods using carriers like PEG 6000 and Poloxamer 407. In the present work, total 15 formulations were prepared and their complete composition is shown in Table-2. All the Solid dispersions prepared were found to be fine and free flowing powders.

Table 2: Result of percentage yield, & Drug content of solid dispersion of Simvastatin

Sr. No	Formul-ation code	Percentage Yield (%)	Drug content (%)	% Drug release in 60 min
1	SSD-A1	63.57	58.69	59.31
2	SSD-A2	72.12	63.92	67.12
3	SSD-A3	85.45	85.48	78.65
4	SSD-A4	92.67	93.62	87.26
5	SSD-A5	96.34	97.89	92.25
6	SSD-B1	41.95	44.21	51.19
7	SSD-B2	52.59	61.35	58.63
8	SSD-B3	65.12	78.41	63.47
9	SSD-B4	74.58	82.71	77.51
10	SSD-B5	86.37	89.92	85.21
11	SSD-C1	58.70	51.63	49.93
12	SSD-C2	69.48	63.25	53.82
13	SSD-C3	76.93	77.18	64.59
14	SSD-C4	83.84	87.54	73.58
15	SSD-C5	88.27	90.79	88.16

Percent practical yield:

The results of percent practical yield studies are shown in Table No. 2. The % Practical yield of the prepared solid dispersions was found to be in the range of 41.95 - 96.34% The maximum yield was found 96.34 % in SSD- A5 formulation.

Drug content:

The actual drug content of all the 15 formulations are shown in Table No. 2. The drug content of the prepared Solid dispersions were in the range of 44.21 - 97.89% indicating the application of the present methods for the preparation of Solid dispersions with high content uniformity. The maximum % drug content was found 97.89% in SSD-A5 formulation.

In vitro dissolution study

Solid dispersion prepared by solvent evaporation method shows improved dissolution at the end of 60 min which is 92.25%. The ratio Drug: PEG 6000: Poloxamer 407 (1:5:5) showed better in vitro release when compared with that of pure drug which is 28.78 % at the end of 60min. The solid dispersion prepared by solvent evaporation method and

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showed 1.5 fold increase in dissolution. This is due to increased wet ability and dispersibility of drug by the carrier. Hydrophilic carrier will help to improve wetting property and reduce the interfacial tension between hydrophobic drug and dissolution medium. The increase in dissolution rate was in the order of PEG 6000: Poloxamer 407 > Poloxamer 407: PVP K30 > PEG 6000: PVP K30.

Infrared spectroscopy (IR)

IR spectroscopic studies were conducted to determine possible drug: carrier interactions. IR spectra of pure drug Simvastatin, and optimized Solid dispersion of Simvastatin were obtained which shows all the characteristic peaks of Simvastatin and carrier was present in the Solid dispersion, thus indicating no significant evidence of chemical interaction between drug and carrier, which confirms the stability of drug with its solid dispersion. The result of IR study shown in Figure No: 1.

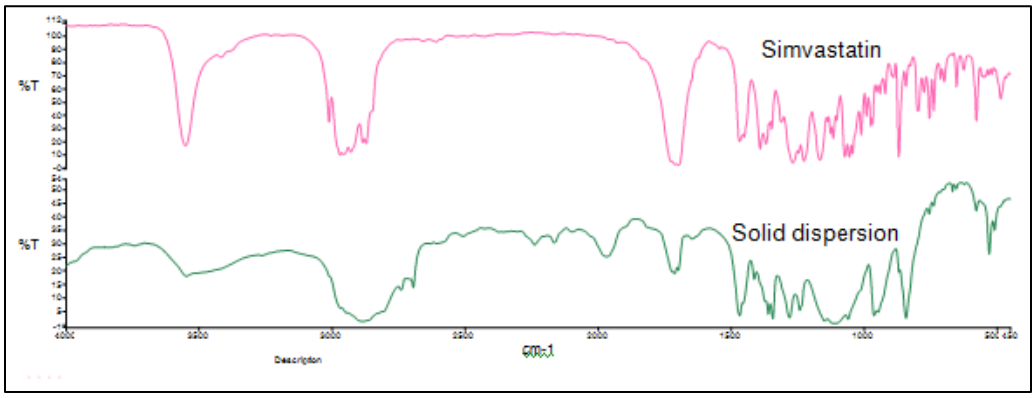

Fig. 1: IR Specta of Pure Simvastatin and Solid dispersion

Differential scanning calorimetry

Differential Scanning Calorimetry (DSC) study was carried out for Surface solid dispersion of Simvastatin. The obtained result is shown in Figure No: 2. DSC studies indicate that there was no any major change in the position of peak in comparison with pure drug (Simvastatin). The decrease in the sharpness of the peak in the surface solid dispersion was the indication of drug convert from crystalline to disorder crystalline or amorphous form. There was no change in melting point is indication of the drug is in the stable form in the surface solid dispersion.

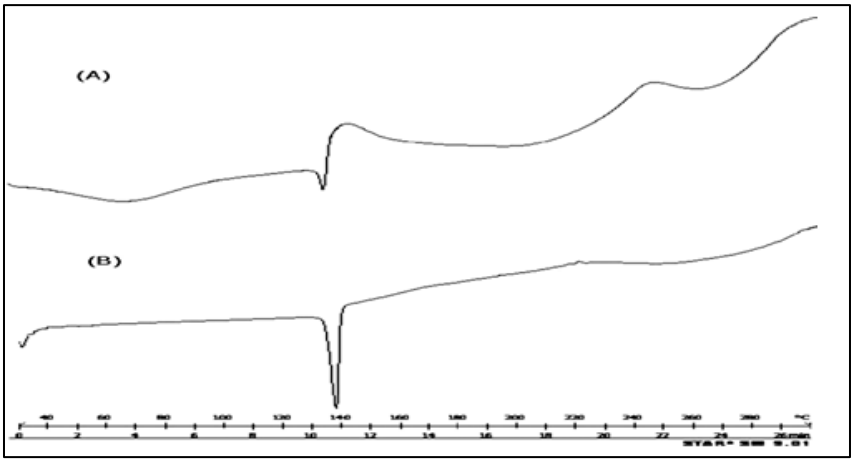

Fig. 2: DSC thermogram of Simvastatin & slid dispersion
A: Solid dispersion of Simvastatin
B: Simvastatin

X-ray Powder Diffraction (XRD):

Powder X ray diffraction analysis was carried out for Solid dispersion of Simvastatin. Powder X ray diffraction study indicates the number of peaks and peak height was reduced in surface solid dispersion which was the indication of change in crystal habits. There was also change in Diffraction angle (2θ) value indicate change in crystal lattice of Simvastatin. These findings suggest that the Simvastatin crystals get converted to disorder crystalline form or amorphous form in surface solid dispersion. XRD graph of surface solid dispersion of Nifedipine is shown in fig. No: 4.

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Fig. No. 3: XRD Pattern of Pure Drug (Simvastatin)

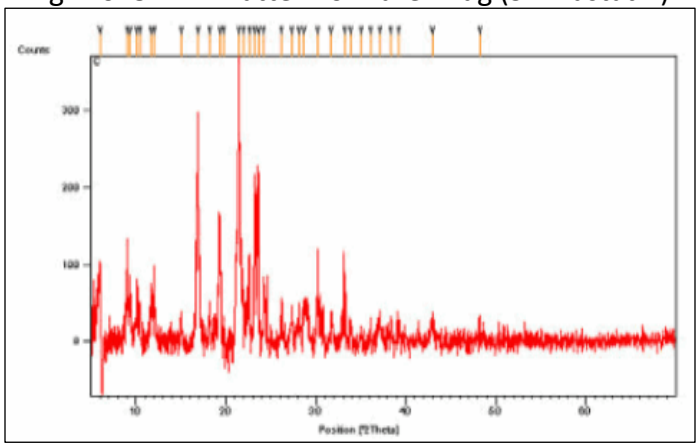
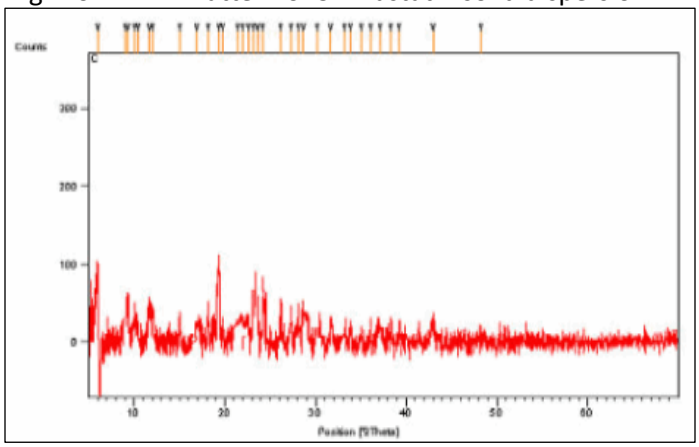


Fig. No. 4: XRD Pattern of Simvastatin solid dispersion



CONCLUSION

The objective of the present study was to improve the solubility and dissolution behaviour of the poorly soluble drug, Simvastatin by solid dispersion technique using PEG 6000 and Poloxamer 407 as carrier. Solid dispersion of Simvastatin prepared by a Solvent evaporation method showed significantly higher drug solubility in comparison with pure drug. FTIR and DSC studies showed no evidence of interaction between the drug and carrier. XRD study shows amorphization of drug.

Out of the 15 prepared formulation SSD- A5 showed marked increase in the solubility as well as the dissolution when compared to pure drug. Thus it can be concluded that the solubility of the poorly soluble drug, Simvastatin can be improved markedly by using solid dispersion technique and the carrier PEG 6000 & Poloxamer 407 has increased the dissolution of the drug without any interaction.

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