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PREPARATION AND CHARACTERIZATION OF SIMVASTATIN SOLID DISPERSIONS BY SPRAY DRYING TECHNIQUE

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ABSTRACT

The objective of the present study was to formulate solid dispersions (SD) of simvastatin to improve the aqueous solubility and dissolution rate to facilitate faster onset of action. Simvastatin is a BCS Class II drug having low solubility (1.45 µg/mL) and therefore low oral bioavailability (5%). In the present study, SDs of simvastatin different drug–carrier ratios was prepared by a spray drying method. solid dispersions were characterized by differential scanning calorimetry (DSC), powder x-ray diffractometry (PXRD), scanning electron microscopy (SEM), and infrared spectroscopy (IR) and evaluated for drug content, saturation solubility, the PXRD study demonstrated that there was a significant decrease in crystallinity of pure drug present in solid dispersions, which resulted in an increased dissolution rate of simvastatin. Formulation is optimized on the basis of acceptable solid dispersion properties and in-vitro release.

KEYWORDS: Simvastatin, drug release, Solid dispersion.

INTRODUCTION

Simvastatin (SV) is a cholesterol-lowering agent that is derived synthetically from a fermentation product of Aspergills terreus[1] and widely used to treat hypercholesterolemia. SV, an inactive lactone, is converted to corresponding b,d-dihydroxy acid in liver by

cytochrome P450 (CYP) 3A after oral administration. SV is a potent inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMGCoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.[2,3] However, it is practically insoluble in water and poorly absorbed from the gastrointestinal (GI) tract.[4,5] Therefore, it is very important to introduce effective methods to enhance the solubility and dissolution rate of drug, substantially leading to its bioavailability.

In fact, most new chemical entities are poorly water soluble drugs, not well-absorbed after oral administration, which can detract from the drug's inherent efficacy 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. 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. Drug release is a crucial and limiting step for oral drug bioavailability. 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 by solvent evaporation method by spray drying technique was utilized to prepare solid dispersion of simvastatin with non ionic surfactant as poloxamer 407 by solvent evaporation spray drying method using adsorbent carrier. 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. 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**.** The rapid release of poorly soluble simvastatin from solid dispersions was influenced by the proportion of polymer and the method employed for its preparation. The solid dispersion in the form of spray dried powder where characterised initially in comparison with pure simvastatin, by drug content, saturation solubility, dissolution rate ,SEM, XRD and FTIR.

Keywords: spray drying, Simvastatin, release profile, solubility enhancement.

Experimental work

MATERIALS

Simvastatin was obtained as gift sample from Lupin Research Park, India. Poloxamer 407, and Arerosil200 were purchased from BASF Corporation. All other materials and solvents used in this study were either pharmaceutical or analytical grade.

METHODS

Preparation of simvastatin solid dispersions with poloxamer 407 and Aerosil200 by Spray drying Method: The microparticles are prepared by spray drying technique. The spray dried particle prepare by taking mixture of Simvastatin+poloxamer407+aerosil. The prepared solution sprayed using Lab-Ultima spray dryer having feed pump flow rate-20ml/min. inlet temp.-50-100 ^{0c} & outlet 65^{0c} (1:1:1, 1:2:1(w/w) ratio).were prepare by dissolving the drug poloxamer407 in mixture ratio ethanol/water(7:3) temp.-35±10^{0c}.,aspirater rate-40. The formed microparticles were separate using cyclone separator, collected &store in desiccators.

- Various solid dispersion batches with different ratios prepared by spray drying:-

Type of formulation	Simvastatin(gm)	Poloxamer407(gm)	Aerosil200(gm)
Batch-A	1	1	1
Batch-B	1	2	1

Evaluation of spray dried microparticles

Percentage Yield: The percentage yield of each formulation was determined according to the total recoverable final weight of microparticles (prepared by spray drying) & total original wt. of spray dried particle sample of each complex.

Drug Content: Surface solid dispersions equivalent to 20 mg of SIM were weighed accurately and dissolved in 10 mL of ethanol. The stock solutions were diluted in distilled water and analyzed by UV-vis spectrophotometry (Jasco V-550, Japan) at 238 nm.

Saturation Solubility Studies: Saturation solubility was determined by the shake-flask method.[16] Plain SIM and SDs in excess quantity were placed in separate glass-stoppered flasks containing 10 mL of distilled water. The samples were placed in an orbital shaker (CIS-24 Remi, India) at 37 °C and 100 rpm until equilibrium was achieved (24 h). The aliquots were filtered through Whatmann No. 41 filter paper. The filtrates were diluted appropriately in distilled water and assayed spectrophotometrically at 238 nm.

pH- Dependent Solubility Studies: The pH-dependent solubility of SIM and SDs were determined in pH 1.2 and pH 7.0 buffers using similar procedure as for saturation solubility.

Powder X-Ray Diffractometry (PXRD): The PXRD spectra of samples were recorded using a high-power powder x-ray diffractometer (Ru-200B, India) with Cu as target filter having a voltage/current of 40 KV/40 mA at a scan speed of 4°/min. The samples were analyzed at a 2θ angle range of 2–45°. Step time was 0.5 sec, and acquisition time was 1 h.

Differential Scanning Calorimetry (DSC): The DSC thermograms were recorded using a differential scanning calorimeter (DSC 823E, Mettler Toledo, Japan). Approximately 2–5 mg of each sample was heated in a pierced aluminum pan from 30 to 300 °C at a heating rate of 10 °C/min under a stream of nitrogen at a flow rate of 50 mL/min. Thermal data analyses of the DSC thermograms were conducted using STARe software (version 5.21).

Fourier Transform Infrared Spectroscopy (FTIR): The IR spectra were recorded using an FTIR spectrophotometer (Jasco-450 Plus, Japan) with diffuse reflectance principle. The samples were scanned over the frequency range 4000–400 cm^{1}.

Scanning Electron Microscopy (SEM): The surface morphology of samples was determined using an analytical scanning electron microscope (JSM- 6360A, JEOL, Tokyo, Japan). The samples were lightly sprinkled on a double-sided adhesive tape stuck to an aluminum stub. The stubs were then coated with platinum to a thickness of about 10 Å under an argon atmosphere using a gold-sputter module in a high-vacuum evaporator. Afterwards, the stubs containing the coated samples were placed in the scanning electron microscope chamber.

In Vitro Dissolution Studies: The in vitro dissolution studies for plain SIM and SDs were carried out in triplicate in USP Apparatus 2. Samples equivalent to 20 mg of SIM were added to 900 mL of 0.01 M phosphate buffer pH 7.0 with 0.5% sodium lauryl sulfate at 37 ± 0.5° C and stirred at 50 rpm (*19*). Aliquots of 5 mL were withdrawn at specified time intervals and 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 analyzed spectrophotometrically at 238 nm.

RESULT AND DISCUSSION

Evaluation of solid dispersions of Simvastatin

Percentage drug content of various solid dispersions of Simvastatin

Drug Content: Drug content for all SDs were in the range of 98.54–100.87%, which is acceptable according to the *United States Pharmacopeia*. In this study, the results showed that the drug content of the solid dispersions of Simvastatin prepared were up to 96.65% for spray drying method . Which containing the mainly Poloxamer-407 due their highly hydrophilic in nature and using porous adsorbent carrier (Aerosil 200).

Saturation Solubility Studies, pH Solubility Profile

Figure 1 and 2 represents the saturation solubility of the SDs and plain SIM. SIM showed a solubility of 1.45 µg/mL in distilled water, 18.5 µg/mL in pH 1.2 buffer, and 27.7 µg/mL in pH 7.0 buffer. The saturation solubility increased with an increase in carrier proportion for both carriers. This might be due to better wetting ability associated with poloxamer and Aerosil 200 solid dispersions have very fine particle size and, hence, large surface area, so as the proportion of carrier increases, a larger surface is presented for adsorption of the drug crystals. Evaporation of solvent leads to an increase in interfacial area of contact between the drug particles and dissolution medium. The affinity between the hydrophilic inert carriers of the dissolution fluids facilitates rapid penetration into the particles, further enhancing the dissolution process.

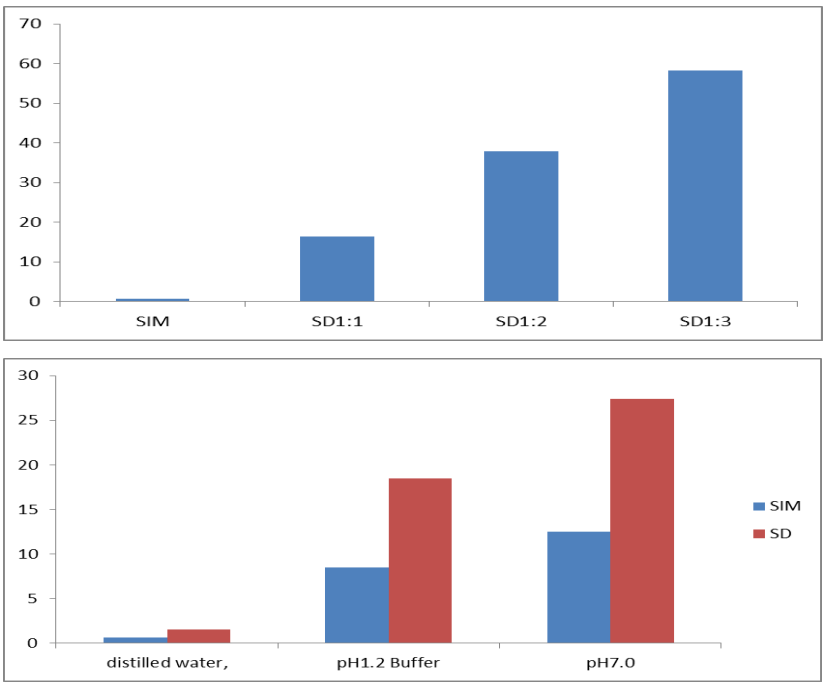


Figure No. 1: Saturation solubility of solid dispersion batches.

Powder X-Ray Diffractometry (PXRD): The PXRD patterns of pure drug and solid dispersions are depicted in Figure 3. The diffraction patterns of the SIM and SD indicate changes in the crystalline nature of the drug. The diffraction pattern of the pure drug simvastatin shows a highly crystalline nature, indicated by numerous distinctive peaks at a diffraction angle of 2θ.

On the other hand, the PXRD of SD processed SIM and poloxamer complex was characterized by the complete absence of any diffraction peak corresponding to SIM. These results indicate that the drug is no longer present as a crystalline form when complexed with using adsorbent carrier during spray drying process, but exists in the amorphous state. These results may be attributed to a possible complexation of SIM inside the poloxamer during SD process, suggesting the possible interaction such as hydrogen bonding between SIM and poloxamer.

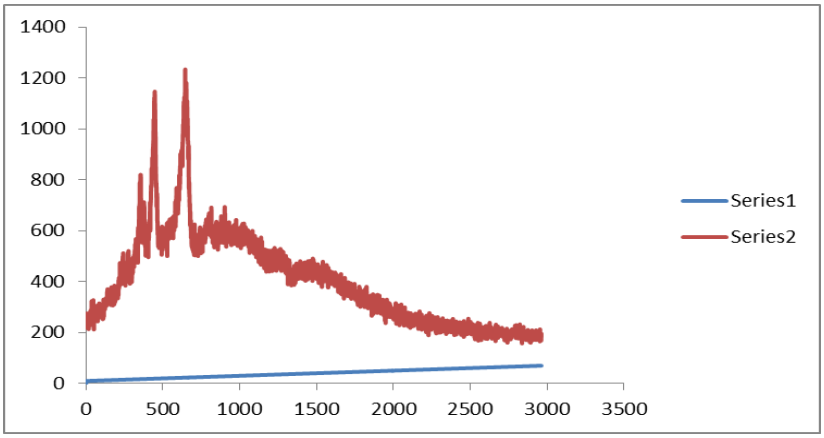


Figure No. 2: XRD of optimized batch.

FTIR spectra of solid dispersion and Simvastatin

The FT-IR spectra of SIM showed the presence of the following peaks: 3553 cm_1 (Free O–H stretching vibration), 3011, 2959, and 2872 cm_1 (C–H stretching vibrations), 1714 cm_1 (stretching vibration of ester and lactone carbonyl functional group) and the FT-IR spectra of HP-b-CD showed prominent absorption bands at 3414 cm_1 (for O–H stretching vibrations), 2933 cm_1 (for C–H stretching vibrations) and 1164 cm_1, 1083 cm_1 (C–H, C–O stretching vibration). In addition, the FT-IR spectra of the SD processed

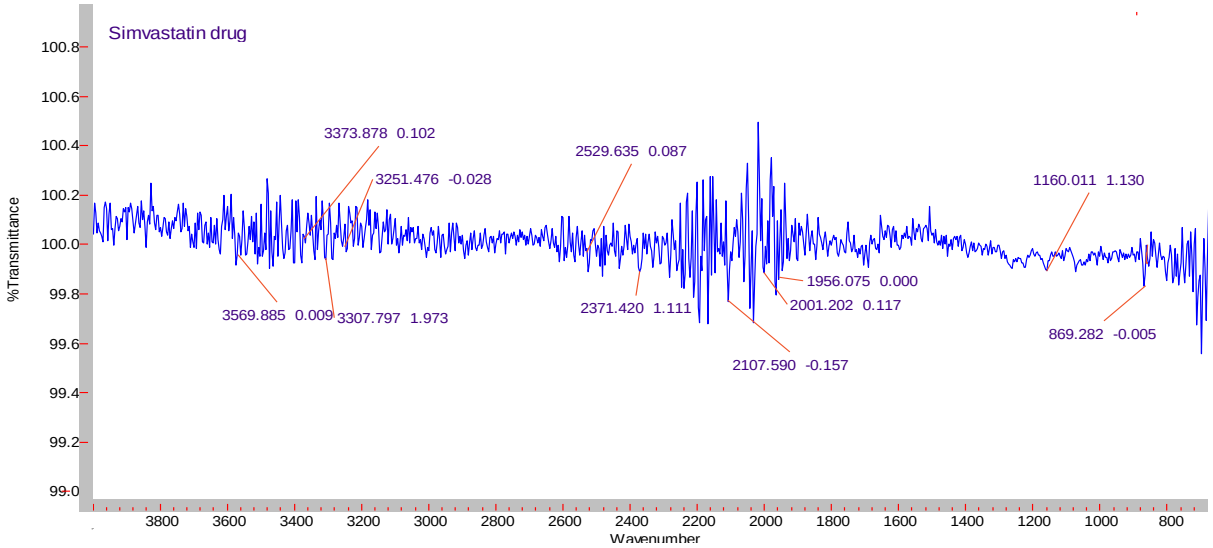


Figure No. 3: pure drug.

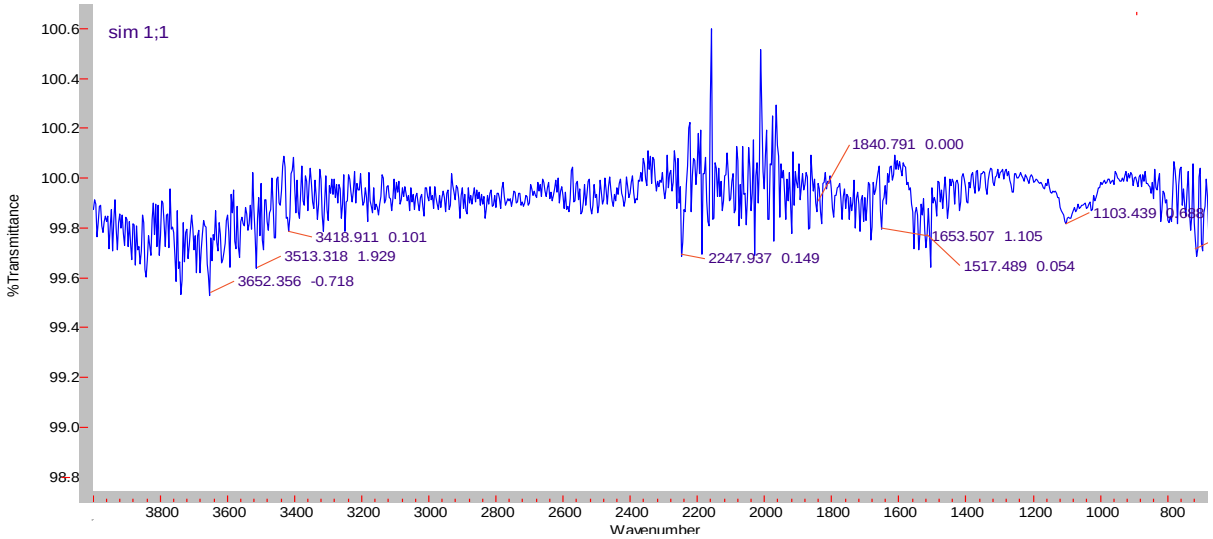


Figure No. 4: Simvastatin 1:1.

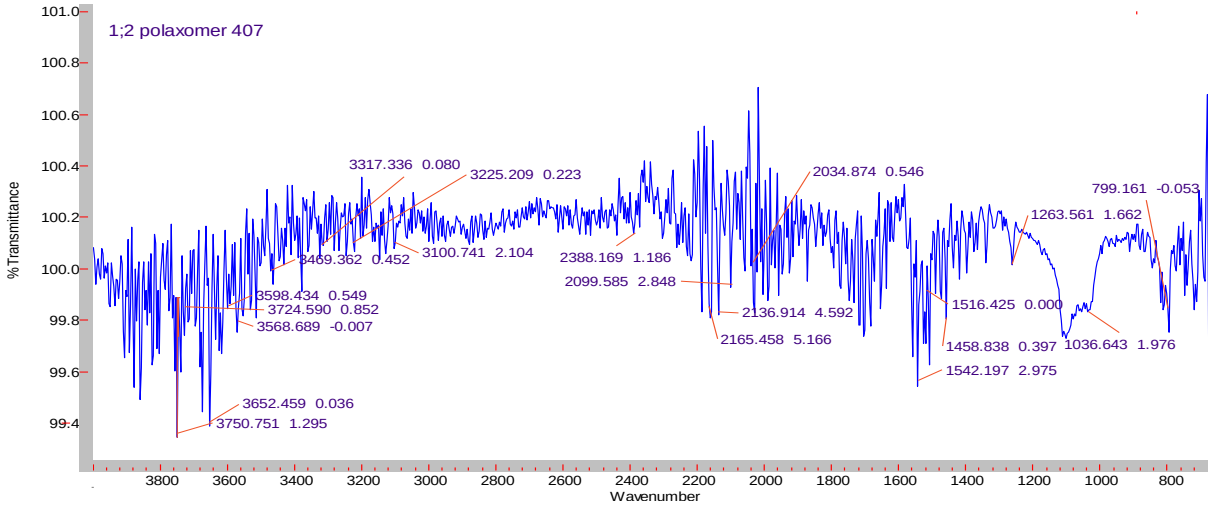


Figure No. 5: Simvastatin 1:2.

The characteristic peaks at 2858 cm−1 and 1080 cm−1 are assigned to stretching vibrations of the O- H and C-O groups of poloxamers. The spectra of SDs and physical mixtures are largely similar to the addition spectra of individual components, but there are also very subtle differences, which could indicate the existence of intermolecular interactions between SIM poloxamers. Increasing poloxamer ratio in SDs causes shifting of the N H stretching vibrations from 3048 cm−1 to 2951 cm−1 and at the same time disappearance of N H bending vibrations. These subtle changes in FTIR spectra are most probably the result of formation of hydrogen bonds between SIM and poloxamers.

FTIR spectroscopy was used to study the possible interactions between SIM and polymer carrier in the SD. For poloxamer and drug ratio. There is no significant difference in the FTIR spectra of pure drug, and SD (Figure 4). All major peaks of SIM observed at wavenumbers 3553 cm-1 (free O–H stretching vibrations); 3011, 2959, and 2872 cm-1 (C–H stretching vibrations); and 1714 cm-1 (stretching vibration of ester and lactone carbonyl functional groups) were retained in SD, which clearly indicate that no interaction exists between pure drug and SD.

Scanning electron microscopy(SEM): SEM photomicrographs that reveal the surface morphology of the samples are shown in fig. no. 6 Characteristic needle-shaped crystals of simvastatin were observed in the photomicrograph of pure drug SIM (A). SEM of the solid dispersion of batch ratio1:2 (B) reveals irregular particles with several microscopic cracks and crevices, which provide additional surface for deposition of the drug particle and. On the contrary, the solid dispersions appeared in the form of spherical particles and the original morphology of components disappeared, which supported DSC and XRD data. These results demonstrated that simvastatin in solid dispersion was homogeneously dispersed into poloxamer at the molecular level. SIM consisted of a mixture of large crystals, a drastic change in the morphology and shape of drug was observed in the SD processed of drug complex, revealing an apparent interaction in the solid state. The magnification power figures in C and D respectively.

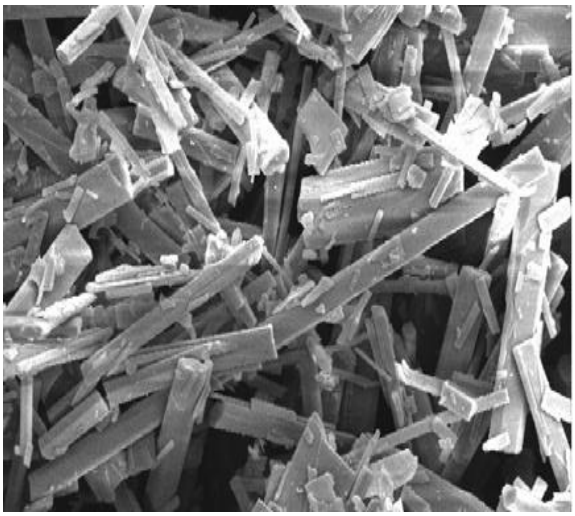


Fig. No. 6 Sem-Pure Drug (A).

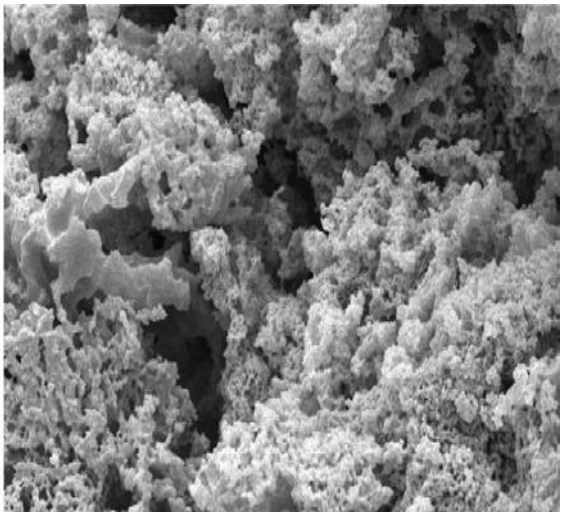


Fig. No. 6 Sem of SD (B).

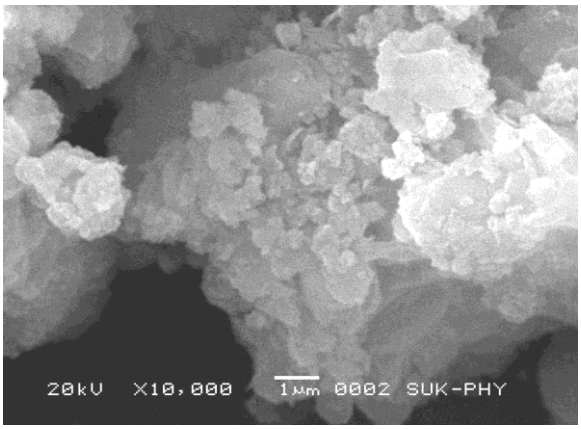


Fig 6.1 SEM C.

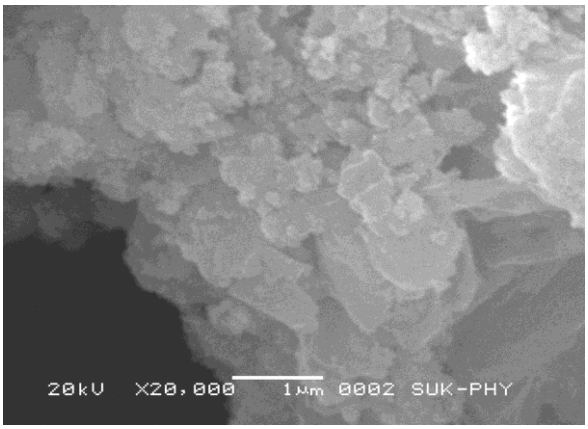
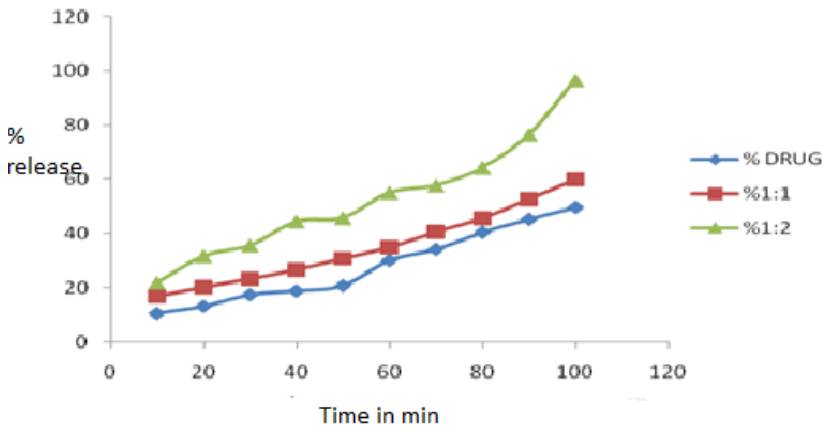


Fig 6.2 SEM D.

In-Vitro Dissolution Studies

The dissolution profiles of the solid dispersions are shown in Figure 7 Surface solid 1:2 dispersions with both carriers showed maximum drug release; the SD with carriers showed almost 96.68% drug release within 90 min, where as Plain SIM showed a poor dissolution profile (i.e., only 27 % of drug was released at the end of 120 min) The improved dissolution could be attributed to a reduction in particle size of the drug, its deposition on the surface of the carrier, and improved wettability. Poloxamer 407 and aerosil have very fine particle sizes and hence large surface areas. As the proportion of carrier increases, more surfaces is available for adsorption of drug crystals on evaporation of solvent, leading to an increase in interfacial area of contact between the drug particles and dissolution medium. The affinity between the hydrophilic inert carriers of the dissolution fluids facilitates rapid penetration into the particles, which further enhances the dissolution process.



CONCLUSION

In conclusion, SDs of SIM with hydrophilic carriers prepared by a spray drying method showed significantly higher drug dissolution in comparison with pure drug. FTIR and DSC studies showed no evidence of interaction between the drug and carrier. PXRD study confirmed amorphization of drug, which was further corroborated by SEM studies the study revealed that optimum levels of hydrophilic carriers and hydrophilic porous adsorbents ensure a prompt and complete dissolution of simvastatin from solid dispersions that are used in oral pharmaceutical formulations.

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