ORIGINAL ARTICLE

Application and Functional Characterization of Kollicoat Smartseal 30D as a Solid Dispersion Carrier for Improving Solubility

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Abstract

Introduction: Many new chemical entities that are getting developed are poorly aqueous soluble and have low bioavailability. Out of many methods available for improving solubility, the solid dispersion by melt extrusion (ME) and spray drying (SP) is scalable and industrially applicable methods. **Objective:** The main objective of the present study was to explore the application of Kollicoat Smartseal 30D polymer for the solubility enhancement of poorly water-soluble drugs using solid dispersion approach. **Materials and Methods:** The Biopharmaceutical Classification System Class II drug simvastatin (SIM) was used as a model drug in this study. Solid dispersions of SIM and Kollicoat® Smartseal 30D were prepared using two different processes, i.e., ME and spray-drying techniques. Both the techniques ME and SP are scalable and industry applicable. **Results:** The solid dispersion has been characterized using transmission using Fourier transforms infrared spectroscopy, scanning electron microscopy, differential scanning calorimetry, powder X-ray diffraction, saturation solubility, and *in vitro* drug release studies. **Discussion and Conclusion:** The improved dissolution profile portrayed the solubility enhancement of SIM in solid dispersions form compared to plain SIM. In nutshell, with the current research, a supportive argument was observed to suggest the suitability of Kollicoat® Smartseal 30D based solid dispersions for enhancing solubility of poorly soluble drugs.

Key words: Biopharmaceutical Classification System Class-II drugs, Kollicoat® Smartseal 30D, melt extrusion, solid dispersion, solubility enhancement, spray drying

INTRODUCTION

Many new chemical entities that are getting developed are poorly soluble and are classified as into the Biopharmaceutical Classification System (BCS) Class II or IV. The poor aqueous solubility, therefore, is limiting its development into a suitable oral dosage form. As the oral route is the most preferred route, formulation scientist is continuously working on strategies for solubility enhancement. Out of many methods available for improving solubility, preparation of solid dosage form is the most preferred method.[1-3] A solid dispersion is generally composed of a drug incorporated in a suitable matrix-like carrier. The drug is either present in amorphous or crystalline form. With solid dispersions, it has been reported by the researchers, there is an increase in dissolution rate/solubility of incorporated drugs, due to an increase in surface area/or change of crystalline to amorphous form.[4-6]

Simvastatin (SIM), a crystalline compound, is a lipid-lowering agent and practically insoluble in water. SIM is obtained as a product during the fermentation of *Aspergillus terreus*. SIM is itself an inactive moiety which on oral administration, hydrolyzes to the ß-hydroxyacid form. This ß-hydroxyacid form is the active metabolite that inhibits 3-hydroxy-3-methylglutaryl coenzyme-A reductase enzyme. This enzyme thereby controls the biosynthesis of cholesterol.

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SIM is a white to off-white BCS Class II molecule, which is non-hygroscopic, crystalline powder, insoluble in water, and 0.1 N HCl (30 µg/ml and 60 µg/ml, respectively).[7-10]

Kollicoat® Smartseal 30D is a methyl methacrylate and diethylaminoethyl methacrylate copolymer dispersion launched by BASF in 2009. The polymer is soluble in the acidic environment up to pH 5.5. Above pH 5.5, the polymer is insoluble but permeable. The main area of application of this polymer is into the area of taste masking and moisture protection.[11]

There is no literature reporting its application into the area of solubility enhancement by preparing solid dispersion. Thus, the present study was aimed to study the application of Kollicoat® Smartseal 30D into the preparation of solid dispersion by two distinct techniques, i.e., melt extrusion (ME) and SP in view to improve the solubility of SIM. The solid dispersed material was characterized for solubility, crystallinity, wettability, glass transition temperature (Tg), and accelerated stability performance. The optimized formulation was also subjected to fourier-transform infrared spectroscopy (FTIR), DSC, and X-ray diffraction (XRD) to confirm the amorphization of the drug in solid dispersion.[12-17]

MATERIALS AND METHODS

Materials

SIM was procured from Synodrug and Intermediates, Maharashtra, India. Kollicoat® Smartseal 30D was gifted by BASF India Ltd (Navi-Mumbai, India). Avicel® PH 101 was gifted from FMC Biopolymer (Mumbai, India). Sodium hydroxide, ethanol, and potassium dihydrogen phosphate were procured from Merck. All other ingredients used in the study were of analytical grade.

Preparation solid of powder of Kollicoat® Smartseal 30D from an aqueous dispersion

Kollicoat® Smartseal 30D is available as aqueous dispersion; therefore, to achieve a powder form for preparation of solid dispersions, SP was carried out in Labultima (LU 222) spray dryer with the feed flow rate of 4.0 ml/min using compressed air. The air aspirator and inlet drying temperature were set to 50 m^3/h and 90°C, respectively. The obtained powder was sealed in a high-density polyethylene container until further processing. This process is well established at the industrial level for the preparation of solid powder of Kollicoat® Smartseal 30D.

Preparation of solid dispersions by SP

The SIM and Kollicoat® Smartseal 30D powder (1:3 ratio) was dissolved in acetone and isopropyl alcohol mixture (1: 1 ratio) to get a 10% w/v solution. The SP was carried out in a spray dryer (Make: Labultima; Model: LU 222) operated in a nitrogen inert loop. The SP conditions were maintained at a feed flow rate of 6.0 ml/min with an inlet drying temperature at 90°C and an air aspirator setting at 45 m^3/h. The spray-dried solid dispersion was stored, with a desiccant, in a double polybag.[18-20]

Preparation of solid dispersions by ME

The SIM and Kollicoat® Smartseal 30D (1:3 ratio) was sifted separately through a 425-micron sieve aperture to get uniform particle size. The sieved SIM and Kollicoat® Smartseal 30D were blended for 5 min at 25 rpm in cone blender and again sifted through a 425-micron sieve. The twin-screw Pharma Lab 11 mm (Thermo Scientific, Germany) was used to melt extrude the drug and polymer blend. It has eight zones with an aperture opening of 2 mm. The ME process was carried out at 100 rpm of corotating twin-screw with a feed rate of 8 g/min. The temperature recipe set for the process was Zone 2: 40°C, Zone 3: 60°C, Zone 4: 90°C, Zone 5: 135°C, Zone 6: 135°C, Zone 7: 130°C, Zone 8: 125°C, and die at 120°C. The extrudes were collected at 25 ± 2°C and 50 ± 5% RH. The collected extrudes were further milled and sifted through 425-micron sieve. The resulting solid dispersion was stored, with a desiccant, in a double polybag.[21-23]

Characterization

Thermal stability study of Kollicoat Smartseal 30D powder

Thermogravimetric analysis (TGA) was carried out for Kollicoat Smartseal 30D powder to understand the thermal stability of the polymer. A Thermogravimetric Analyzer-STAR^e SW 9.10 (Mettler, Greifensee, Switzerland) was used for carrying out the TGA measurements. The system calibration was performed using indium as a reference standard. The samples were accurately weighed over aluminum pans and were crimped using a crimper. The system was tuned to scan the sample from 40°C to 400°C with an increase in temperature in a step of 10°C/min. An inert gas, nitrogen, was used to flush the system to maintain the inert environment within the furnace at an average flow rate of 50 ml/min.[24,25]

Differential scanning calorimetry (DSC)

DSC (Mettler Toledo, DSC 821e, Schwerzenbach, Switzerland) was performed for SIM and optimized batch solid dispersion prepared by SP and ME. The system was previously calibrated using indium as a standard reference. Samples were weighed accurately over aluminum pans and were crimped. The crimped pans were heated at a rate of 10°C/min from 50°C to 300°C. An inert environment in the furnace was maintained by nitrogen gas purged at a flow rate of 50 ml/min.[25,26]

Scanning electron microscopy (SEM)

To visualize any changes occurring over the surface, the topography of solid dispersion prepared by ME and SP was observed with the aid of SEM (Cemeca, Tokyo, Japan). Solid dispersion was mounted as a thin film on a metal holder and is adhered to using silicon adhesive. Then, the samples were sputter-coated with gold. The sample was inspected under the SEM operating at an accelerating voltage of 20 kV.[27]

Fourier transform-infrared (FT-IR)

A Jasco 6100 FTIR spectrometer (Tokyo, Japan) was employed for obtaining the FTIR spectra. The system is equipped with a deuterated triglycine sulfate detector. Before sample analysis, a background scan was performed to eliminate background noise. The system was set to operate over the 4000–400/cm frequency with an average of 16 scans and a resolution of 2/cm. Solid dispersions of SIM prepared by ME and SP, Kollicoat® Smartseal 30D, and physical mixtures of SIM and Kollicoat® Smartseal 30D were triturated with KBr in 1:100 in mortal pastel and fill the mixture in the sample holder. The samples for infrared analysis and the KBr were dried for at least an hour before analysis in a drying oven at 100°C ± 0.5°C. The IR spectra obtained were analyzed with Spectra Manager software (Ver. 2.0).[28,29]

Powder XRD (PXRD)

The XRD patterns of SIM and the developed solid dispersions were determined using an X-ray diffractometer (FR 590, Netherlands). The diffractometer is equipped with Ni-filtered Cu-target operating at 30 kV, voltage, and 15 mA, current. A graphite monochromator detector collects the diffracted beam. The scanning was performed in step scan mode with a step size of 0.5 and 2θ in the range of 10–70˚.[28]

Drug content in solid dispersions

The content of SIM in the milled extrudes, or spray-dried particles were analyzed by accurately weighing and dissolved the samples, equivalent to 20 mg of SIM, in 50 ml ethanol: water (3:2) and sonicated for 15 min in a sonicator (Sharp UT-204). The mixture was filtered through a 0.45 µ filter before analysis. Further, the sample was diluted to 30 times, and the absorbance was measured using a ultraviolet (UV) spectrophotometer (Perkin Elmer, Lambda 35) at λ_{max} of 238 nm. The equation of the calibration curve was used to calculate the amount of drug present.

Solubility studies

The saturation solubility study was performed in different solvents such as water, 0.1 N HCl, pH 4.5 acetate buffer, and phosphate buffer pH 6.8. The shake-flask method was used to carry out for the saturation solubility study.[30,31] The excess amount of plain active (SIM), melt-extruded, and spray-dried solid dispersion of SIM and Kollicoat® Smartseal 30D was added into 10 ml separate violin an above solvent. These vials were shaken at 25 ± 2°C at 100 rpm for 48 h using an orbital shaker. Before analysis, the aliquots were filtered through 0.45 microns filter. To assay the solubilized SIM, the filtrates were diluted, if required, using appropriate medium and then spectrophotometrically analyze at λ_{max} 238 nm using a UV spectrophotometer (Perkin Elmer, Lambda 35).[19,28]

In vitro drug release studies

The drug release of SIM from the prepared solid dispersions was evaluated using a dissolution apparatus. The dissolution of solid dispersion was carried out using the paddle apparatus (USP method II). The dissolution rate of SP and ME formulations was compared with the dissolution rate of plain SIM. In detail, the dissolution studies were performed using unit dose (equivalent to 40 mg) in the automated dissolution tester (Jasco, DT-610) operated at a rotational speed of 50 rpm. The dissolution media consisting of 900 ml of phosphate buffer pH 7.0 maintained at temperature 37 ± 0.5°C were used to understand the release of SIM from the developed formulations. The aliquots of 5 ml were withdrawn at a time interval of 5, 10, 15, 30, 45, 60, 90, and 120 min. The aliquots were analyzed spectrophotometrically measured using UV detection (Perkin-Elmer, Lambda 35, India) to quantitate the amount of SIM released from the solid dispersions. All the analysis was performed in triplicates. The procedure for the dissolution study was adopted from USP NF29, 2014.

RESULTS AND DISCUSSION

Solid dispersion

Kollicoat® Smartseal 30D is a colloidal aqueous dispersion of methyl methacrylate and diethylaminoethyl methacrylate copolymer with approx. 0.6% macrogol cetostearyl ether and 0.8% sodium lauryl sulphate to stabilize the dispersion. Hence, it could be easily spray dried and resulting from the Kollicoat® Smartseal 30D powder.

Thermal Stability study of Kollicoat Smartseal 30D powder

The important part in the preparation of solid dispersion by hot methods such as ME and SP is to know the degradation temperature of the polymer, so as to avoid the formation of monomers or other entities, which may have toxic effects on humans. Thus, TGA was used as an analytical tool to understand the degradation behavior of Kollicoat Smartseal 30D. The result of the TGA analysis of Kollicoat Smartseal 30D is represented in the form of a graph in Figure 1. The graph depicts that the Kollicoat Smartseal 30D is stable up to 220°C. No decomposition is observed before 220°C, indicating its stability up to 200°C. Furthermore, the absence of peaks signifies that the polymer was structurally and chemically stable. On further application of heat up to 340°C, only a 26% loss in mass was seen, thus, revealing the absence of complete

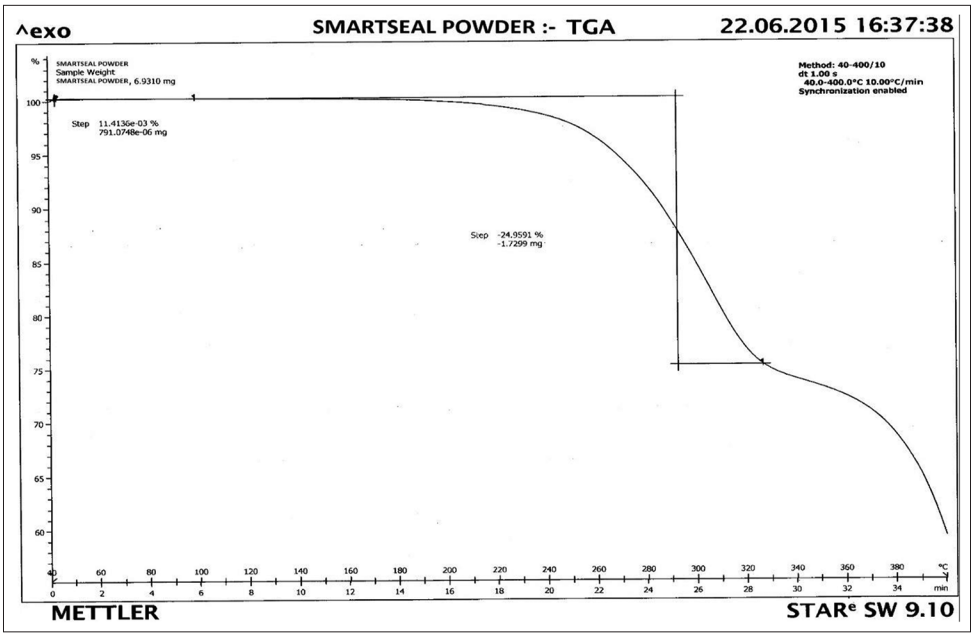

Figure 1: TGA of Kollicoat® Smartseal 30D

degradation of the polymer before this temperature. Thus, a good range of processing temperatures from 70 to 220°C could be employed for the formulation of solid dispersion.

DSC

The DSC plots corresponding to the qualitative composition of solid dispersion formed by both the process are depicted in Figure 2. Plain SIM showed a melting endothermic peak at 141.4°C, while the same was observed at 137.3°C in the physical mixture of Kollicoat® Smartseal 30D and SIM. Similarly, the glass transition temperature (Tg) of Kollicoat® Smartseal 30D was observed at 69.7°C in the physical mixture.[32] Post 220°C degradation of Kollicoat® Smartseal 30D began (similar results were observed in TGA analysis of Kollicoat® Smartseal 30D) and therefore different peaks appeared in thermograms of the physical mixture and solid dispersion prepared by SP and ME. Endothermic peaks of SIM were no longer observed at 137.3°C or near any value for solid dispersions prepared by SP and ME technique. These reveal the possibility of alterations in the physical state of SIM from a crystalline to amorphous state and formation of a single-phase solid dispersion system.[33] The sharp peak of plain SIM 141.4°C was disappeared; it means the formation of amorphous solid dispersion that represents the crystallized drug converted into the amorphous form after the solid dispersion processing. The form amorphous solid dispersion shows the faster the drug release as compared to the plain crystalline API.

SEM

SEM images of SIM loaded solid dispersions prepared with ME and SP technique are depicted in Figure 3. Solid dispersion prepared by SP was more spherical in shape with an internal diameter of 20–90 mm [Figure 3a]. It could be conferred from the results that small particles gave the higher surface areas to spray-dried products, and thereby making is easily dispersible in the dissolution media and thus, lead to an increase in the dissolution rate. The particles of melt-extruded SIM loaded solid dispersion product after milling through 425 µm aperture sieve were observed to be irregular in shape [Figure 3b]. This would have probably caused a slower dissolution rate in comparison to the SP product.

FTIR

The FTIR analysis gives a proper idea of the formation of any complex between Kollicoat® Smartseal 30D and SIM. The characteristic peaks of SIM were observed at 3012 cm^{-1} (C=CH), 1698.9 cm^{-1} (aromatic C=O), and 1466.7 cm^{-1} (benzene ring). The peaks between 3400–3590 cm^{-1}, which was seen in the FTIR spectra of SIM, but not in spray-dried solid dispersion, indicate the presence of hydroxyl (–OH) group (seen in point c of Figure 4). These peaks were not seen in the spectra of spray-dried solid dispersion as it does not contain any hydroxyl group. Similarly, there was a very low-intensity peak in SP at 2250–2400 cm^{-1} indicating the presence of an amine, which was not seen in the SIM spectra. After ME and SP, the intensity of peak at 2250–2400 cm^{-1} increased many folds (seen in point signifies of Figure 4). This indicated the formation of a quaternary amine compound between drug and Kollicoat® Smartseal 30D. Similarly, there is a formation of a new broad peak at around wavenumber 3000 cm^{-1} (seen in point b of Figure 4). These indicated the formation of ammonium compounds in the product. Similarly, the peak of the –OH group, which was seen for SIM and physical mixture, was completely invisible after SP and ME thus indicating the formation of hydrogen bonds.

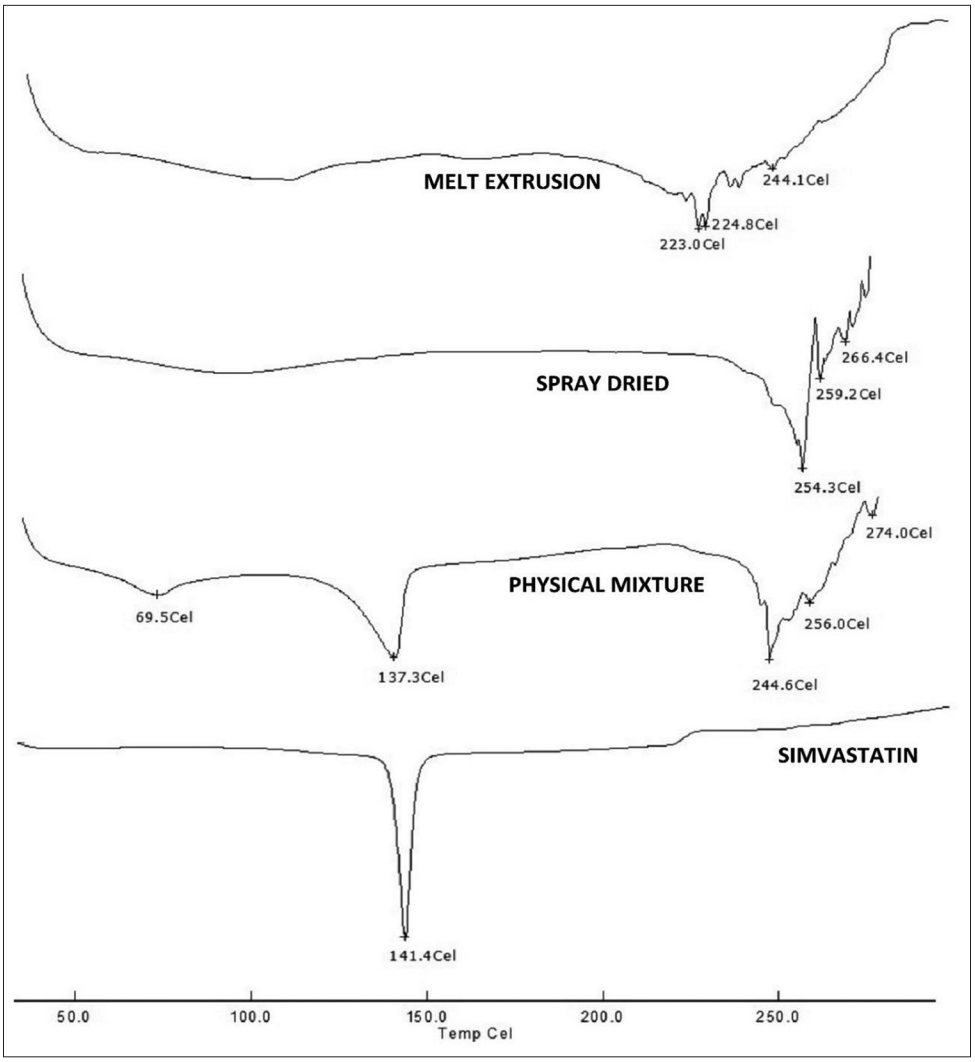

Figure 2: DSC thermograms of SIM, physical mixture, spray-dried product, and met extruded product

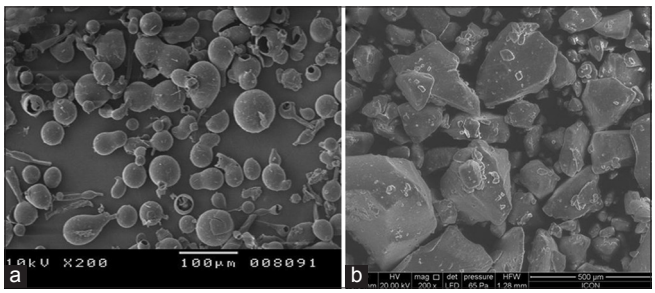

Figure 3: SEM images of (a) spray-dried solid dispersion and (b) melt-extruded solid dispersion

A depiction of hydrogen bond formation is shown in Figure 4, explaining the probable mechanism of hydrogen bond formation. The possible interaction between the SIM and Kollicoat Smartseal 30D has been described diagrammatically in Figure 5.

PXRD

The DSC studies revealed the possibility of alterations in the physical state of the drug in solid dispersion. The same was further confirmed using PXRD. The PXRD of SIM and solid dispersions prepared by ME and SP are depicted in Figure 6. The characteristics crystalline peak of SIM was not observed for solid dispersions prepared by ME and SP techniques. The data indicate a strong confirmation of the formation of amorphous solid dispersion of SIM and Kollicoat Smartseal 30D by ME and SP techniques. Thus, the results of DSC are well confirmed from the PXRD data. This also explains the possible reason for solubility enhancement of SIM when formulated into a solid dispersion by either of the techniques. The dissolution of SIM was improved because of it converts crystalline to amorphous during the solid dispersion processing. The rate of dissolution of amorphous dispersion was faster than that of the plain crystalline SIM. Hence, we can confirm that the solubility and dissolution were enhanced by converting the API form crystalline to the amorphous form.

Drug content in solid dispersions

The drug content of SIM and Kollicoat Smartseal 30D solid dispersion prepared by SP and ME techniques is shown in

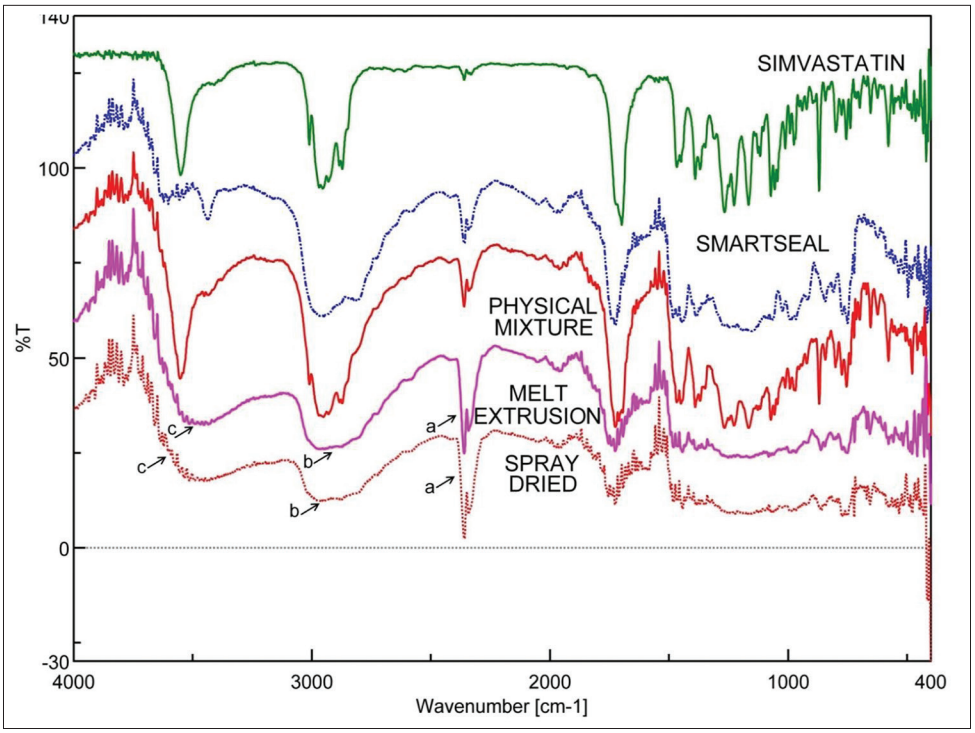

Figure 4: Fourier-transform infrared spectroscopy spectra of SIM, Kollicoat Smartseal 30D, physical mixture of SIM and Kollicoat Smartseal 30D, solid dispersion through ME and solid dispersion through SP

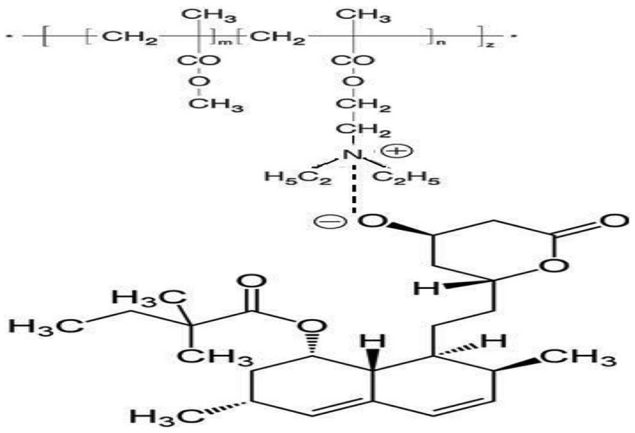

Figure 5: Probable mechanism of interaction between Simvastatin and Kollicoat Smartseal 30D

Table 1. As per the USP, the SIM formulation contains 90–110% of SEM. The drug content in both the formulations is within the limit, and no drug loss observed during processing.

Table 1: Drug content in solid dispersions formulations

Formulations	% Drug content
SIM and Kollicoat Smartseal 30D solid dispersion prepared by SP	99.32±1.47
SIM and Kollicoat Smartseal 30D solid dispersion prepared by ME	99.64±1.78

Solubility studies

The solubility of the drug is the main concern while developing an oral solid dosage form. The solubility of SIM in the gastrointestinal tract was determined using a different combination of buffer systems. The outcomes of the solubility study are reported in Figure 7. The solubility of SIM was increased in the results shown enhancement of aqueous solubility through solid dispersion in the 15 folds as compared to the plain SIM API. This reveals that there is nearly a similar solubility profile of solid dispersion by the SP and ME method. Thus, the process had no impact on solubilization efficiency. Solubility increment of around 100 times in acidic media. Similarly, these values were around 30 and 13 times in acetate and phosphate buffers, respectively. Thus, it can be clearly seen that even though the solubility of the solid dispersion was highest; thus, it can be said that Kollicoat® Smartseal 30D can be a good polymer for enhancement of solubility.

In vitro dissolution studies

The assay values for SIM were around 98–102% for both the processed solid dispersion formulations of SP and ME. Thus, ensuring that Kollicoat® Smartseal 30D can be used in either of the processes for the preparation of solid dispersion. The results of dissolution studies are depicted in Figure 8. The improved dissolution was found in solid dispersion. This could be attributed to the conversion of e crystalline SIM into the stable amorphous form in solid dispersion. This

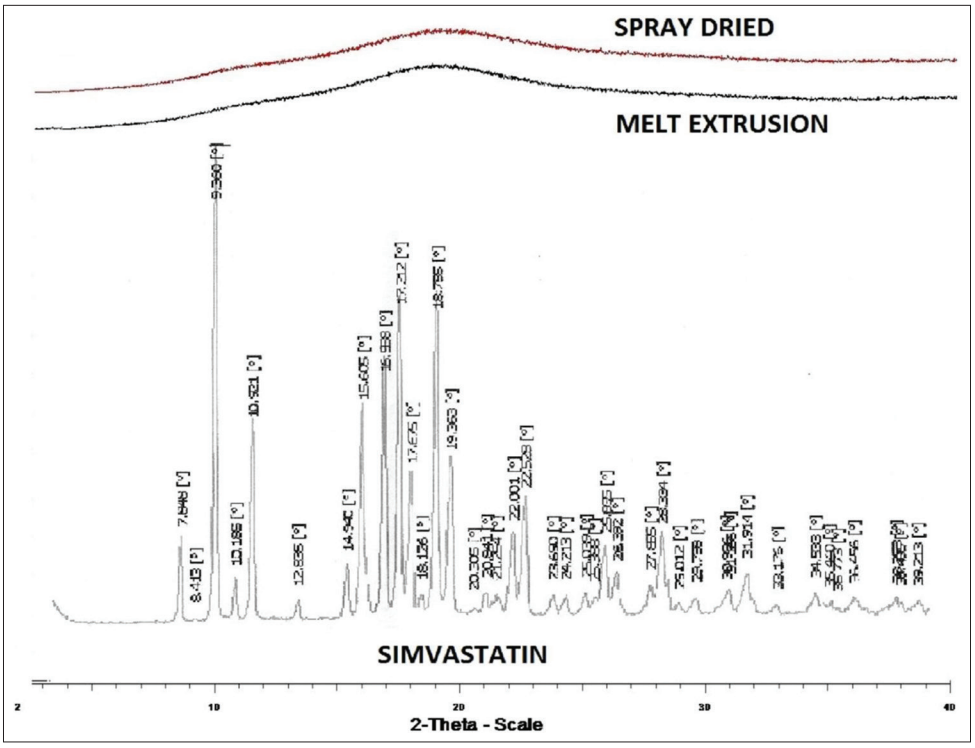

Figure 6: X-Ray diffractograms of spray-dried solid dispersion, melt-extruded solid dispersion and plain SIM drug

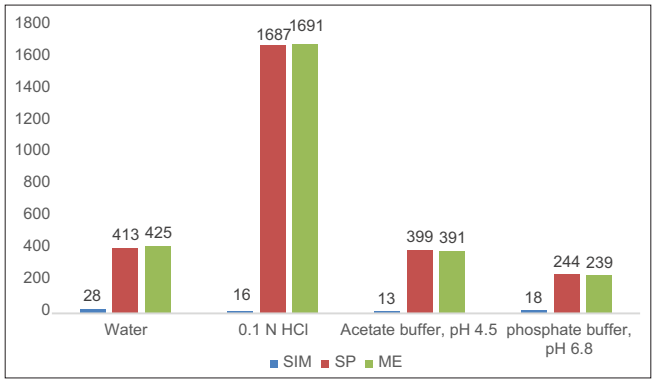

Figure 7: Solubility of plain SIM, solid dispersion through SP and ME formulations in different dissolution media

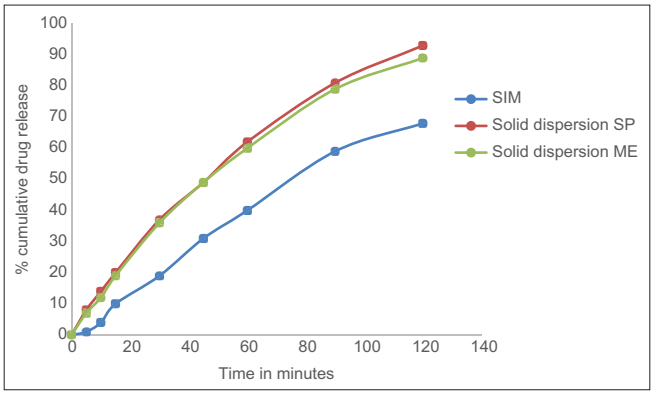

Figure 8: *In vitro* dissolution studies of SIM, solid dispersion by SP and ME in phosphate buffer

could also be due to the formation of water-soluble solid dispersion complex of SIM and Kollicoat Smartseal 30D Hence Kollicoat Smartseal 30D can be used as a carrier for improving the solubility of BCS class II drugs. The release of SIM was significant ($P > 0.05$) from SD prepared by SP and ME technique. Thus, SIM being the BCS Class II drug, the rate of solubilization will improve its bioavailability. This discussion is further elaborated in the SEM section of this paper. The bulk density of spray-dried powder was around 0.27 ± 0.06 g/ml as against 0.38 ± 0.04 g/ml of ME product. This difference in the release was, to a major extent, reduced due to the formation of solid dispersion with Kollicoat® Smartseal 30D. This can be attributed to the increased solubility of SIM.

The dissolution of particles in the acidic media (0.1 N HCl) at various time intervals was studied. The solid dispersion by SP particles tends to disperse rapidly than the solid dispersion by ME samples; this may be attributed to lower bulk density and finer nature of SP particles over ME products. At the same time, some particles were still not solubilized until the end of 5 min. All the particles finally solubilized within 10 min, which forms a clear solution.

CONCLUSION

The present study used novel carrier Kollicoat® Smartseal 30D for solubility enhancement of SIM. Kollicoat® Smartseal 30D shows very good stability up to 210°C as observed with TGA analysis. Thus, it was selected for formulating solid dispersions of SIM by SP and ME technique. The physicochemical properties of SIM did not interfere with Kollicoat® Smartseal 30D on the formation of solid dispersion

as was confirmed by FTIR, DSC, and PXRD analysis. The solid dispersion prepared by either technique showed enhanced solubility (15 folds) over plain SIM, which was all attributed to the conversion of crystalline SIM to amorphous form. This indicates that the new taste-masking polymer Kollicoat® Smartseal 30D can be explored as a carrier for or solubility enhancement of poorly soluble drugs like SIM.

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