



Research article

Preparation, characterization and dissolution study of spray dried solid dispersions of simvastatin with PVP k25 and Aerosil 200

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ABSTRACT

BCS class II is well-known for the drugs, having poor aqueous solubility and high permeability. Simvastatin is also categorized as BCS class II, suffering from poor aqueous solubility, affecting its bioavailability. In an attempt to resolve this problem, solid dispersions of simvastatin were prepared by spray-drying method. Solid dispersions of simvastatin with PVP K25 and aerosol in ratio (1:1:1 to 1:5:1) and without aerosil 200 (1:1 to 1:5) were prepared by spray drying method. The dissolution test showed the enhancement of dissolution as compared to the pure drug and nearly equal to marketed formulation "SIMVOTIN 20mg" in both types of formulation, but formulations with aerosil 200 showed faster drug release as compared to the simple formulations without aerosil. The formulation containing the 1:3:1 (simvastatin: PVP K25: Aerosil 200) showed the faster drug release as compared to other formulation that do not contain the Aerosil 200. Other characterization studies were also performed such as FTIR, differential scanning calorimetry and powdered X-ray crystallographic studies. These studies showed the increased amorphous nature of the drug in the formulation, which explain the enhanced dissolution rate of the drug for these formulations.

Keywords: Solid dispersions, Spray drying, Simvastatin, Dissolution studies.

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INTRODUCTION

Simvastatin is a semi synthetic anti-hyperlipidemic agent obtained from *Aspergillus terreus* and belongs to statin class. Simvastatin is a HMG-CoA reductase inhibitor, regulates the conversion of HMG-CoA to mevalonate as rate limiting step during the cholesterol synthesis. [1] Simvastatin comes under BCS Class 2 drug, well known for low solubility related issue. The absorption of this drug is affected by its solubility which is dissolution rate limited, finally affecting the pharmacological effect. [2].

Various methods have been employed to enhance the solubility of the simvastatin such as particle size reduction [3], Inclusion complexes,[4], solid dispersions,[5], co-crystals,[6], nanosuspension,[7], nano capsules,[8], dendrimers,[9], etc. However, out of these formulation approaches solid dispersion approach is easy and effective as compared to other sophisticated approaches. The literature shows numerous methods for preparation of solid dispersions like solvent evaporation, co-grinding, anti-solvent technique, spray drying etc.

During last decade spray drying technology has emerged as lucrative approach in the field of food, biotechnology and pharmaceuticals. [10-12] In the field of pharmaceuticals spray drying technique is widely used for fabrication of nano-crystals, solid

dispersions, encapsulation, co-crystals and other formulations. Spray drying technology is effective approach to enhance the dissolution in comparison to the conventional approaches. [13], Many solid dispersion formulations prepared through spray drying process have been reported by researchers. Spray drying is well known effective approach to prepare amorphous solid dispersions with homogeneous distributed drug within excipient matrix up to molecular level. [14].

Polyvinylpyrrolidone K 25 (PVP K25) is an excipient used for solid dispersion formulations to enhance the solubility of many poor water-soluble drugs. It is also known as povidone. [15]. another excipient used for stability is Aerosil 200, which acts as absorbent in the formulation. [16]. It is used to maintain the quality related parameters of drug formulation like stability and dissolution of the formulation.

In this research work solid dispersions of simvastatin and PVP K25 were prepared with or without Aerosil by spray drying method. Simvastatin and PVP K 25 solid dispersion were prepared in 1:1 to 1:5 ratios. In another segment of experiment solid dispersions of simvastatin and PVP K25 with aerosil were prepared in 1:1:1 to 1:5:1 ratio. All the formulations were subjected to dissolution, FTIR studies, Differential scanning calorimetry (DSC) and powdered X-ray

crystallographic study. These studies showed the enhancement in dissolution as well as the amorphous character of the solid dispersion formulation.

MATERIAL AND METHOD

Materials

Simvastatin pure drug and Aerosil 200 were gifted by Sun Pharmaceutical India limited, Gurugram (Haryana), India. Polyvinyl Pyrrolidone K25 (USP Grade), Sodium Lauryl sulphate (USP Grade), HCl and Methanol were purchased from LOBA CHEMIE PVT LTD. Mumbai, India. Sodium dihydrogen orthophosphate was purchased from, RFCL Limited (RENCHEM), New Delhi, India. The nylon syringe filters diameter 25mm and pore size 0.45 μm were purchased from AXIVA SicheM Pvt ltd. Sonipat, Haryana.

Method for preparing Solid Dispersion

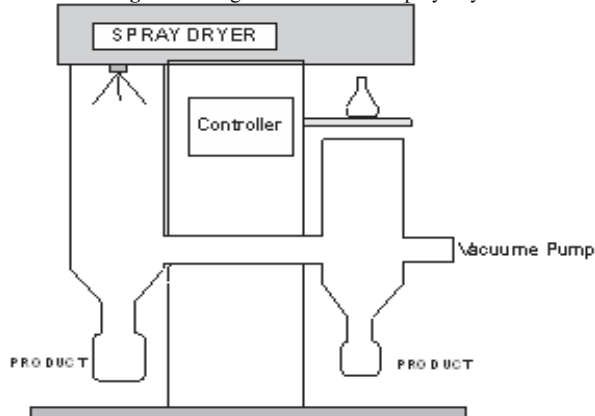
Solid Dispersion with PVP K25

Solid dispersions of simvastatin SD 1 to SD 5 were prepared with PVP K25 in 1:1 to 1:5 ratios. First of all, the ratios were mixed in methanol with the help of a magnetic stirrer till it transformed to a transparent solution. After that this solution is dried using lab scale spray dryer “Spray Mate Lab Spray Dryer” manufactured by “Jay Instruments & Systems Pvt. Ltd.” Mumbai, India. The process parameters such as input temperature 38 °C, output temperature 33 °C and a flow rate of 2 ml per minute were set to achieve good quality of product. The aspirator was maintained as 2500 rpm with vacuum 250 mbar. After spray drying the powdered solid dispersions were obtained from the glass assembly of the spray dryer. These dispersions were kept in desiccators for one week to remove the moisture present in the formulation if any [figure 1].

Solid Dispersions of PVP K25 and Aerosil 200

Solid dispersions of simvastatin and PVP K25 with aerosil (SD 6 to SD 10) were prepared in 1:1:1 to 1:5:1 ratio. In this process drug and polymer PVP K25 were first dissolved in methanol with the help of magnetic stirrer till it transformed in to a transparent solution. After the complete solubilization of drug and PVP K25 a transparent solution was formed. After that separately prepared slurry of Aerosil 200 prepared in methanol was added to this solution then this mixture was spray dried by using process parameters as described above.

Figure 1: Diagram of Lab Scale Spray Dryer



In Vitro dissolution studies of solid dispersions

The dissolution studies of all solid dispersions were performed in 0.1 N HCl with 20% methanol and phosphate buffer at pH 7.0 with 0.5 % Sodium Lauryl Sulphate (as per Indian Pharmacopoeia). The dissolution of pure drug, physical mixture and solid dispersions were performed with USP Dissolution apparatus II manufactured by “Lab India Instruments Pvt. Ltd. Thane, India”, and stirred at 37 $\pm$ 5 °C with 50 rpm. The aliquots of 5ml were withdrawn from a syringe and filtered with nylon syringe filter (0.45 μm). The results of dissolution study are shown in figure 2 and 3.

Similarity factor

Similarity factor application was proposed by Moore in 1996 later accepted by USFDA. The similarity factors contain two factor figure 2 and figure 3, which define the similarity as well as difference index of two immediate release pharmaceutical dosage form. Figure 2 factor is a measurement of relative error between two curve and it is equivalent to percentage difference between two corresponding curves at each time points, whereas figure 2 factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves. It is clear from the above statements that similarity factors are an important tool for assessment of a dissolution profile of any formulation with standard formulation. The main objective of the similarity factors calculation was to perform a comparison of the solid dispersions with pure drug, physical mixture and marketed formulation to find out best formulation.

Contact Angle Photography

The photography of the spray dried solid dispersion was performed with the help of magnifying lens “Apexel 12X Super Macro”. Photography of solid dispersion pure drug and optimized formulation prepared by spray drying was performed to ensure any visible change in the contact angle. The images of pure drug and solid dispersion formulation were captured. For the study samples of the pure drug and solid dispersion were taken separately and then compressed with the help of machine ‘Spectra Lab., India’ used for preparation of KBr pellets for spectroscopic studies. After the preparation of the pellets, these pellets were taken and a drop of water was dropped with the help of 60 μL syringe “Hamilton”. The photography was performed to observe any change in the contact angle of the pure drug and solid dispersion formulation.

Differential Scanning Colorimetric Studies (DSC Studies)

The differential scanning colorimetric studies were carried out by using DSC Q10 model manufactured by “TA instruments, USA”. The samples were hermetically sealed in standard aluminum pans and allowed to heat at a ramp of 10 °C /minute up to 250 °C. An inert environment of the furnace was created by purging the nitrogen gas with flow rate of 50ml/ minute. The data process and analysis

were carried out through Universal Analysis (version 4.4, TA Instruments, Leatherhead, U.K.).

Figure 2: Solid Dispersions Simvastatin: PVPK25 (1:1 to 1:5)

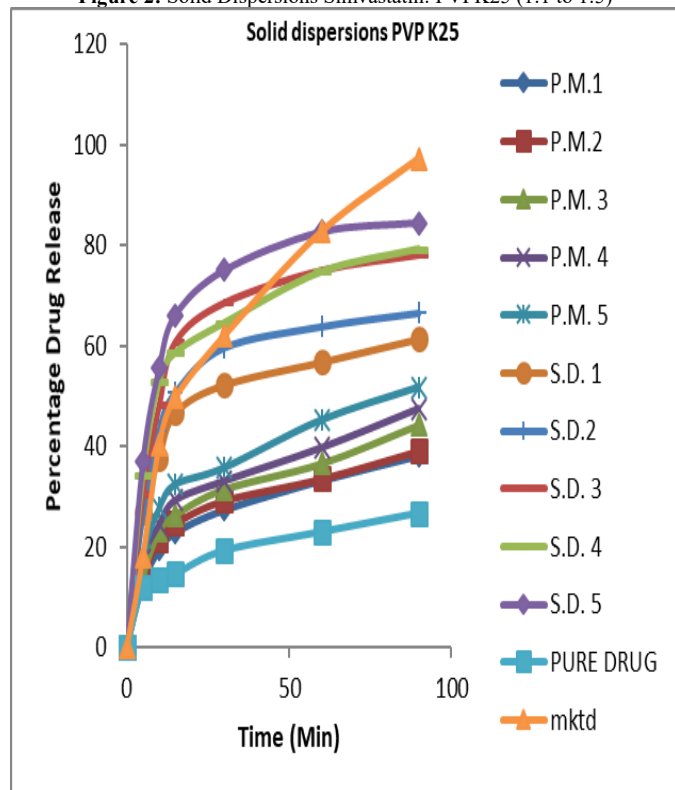


Figure 3: Simvastatin: PVP K25: Aerosil (200 1:1:1 to 1:5:1) Drug Release in 0.1NHCL with 20% Methanol

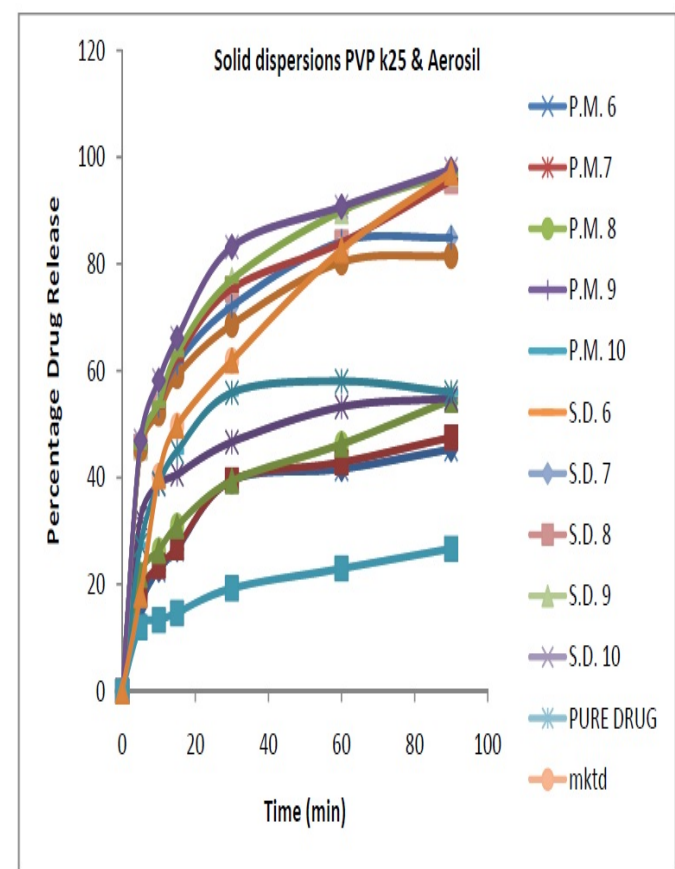


Figure 4: Solid Dispersions Simvastatin: PVPK25 (1:1 to 1:5)

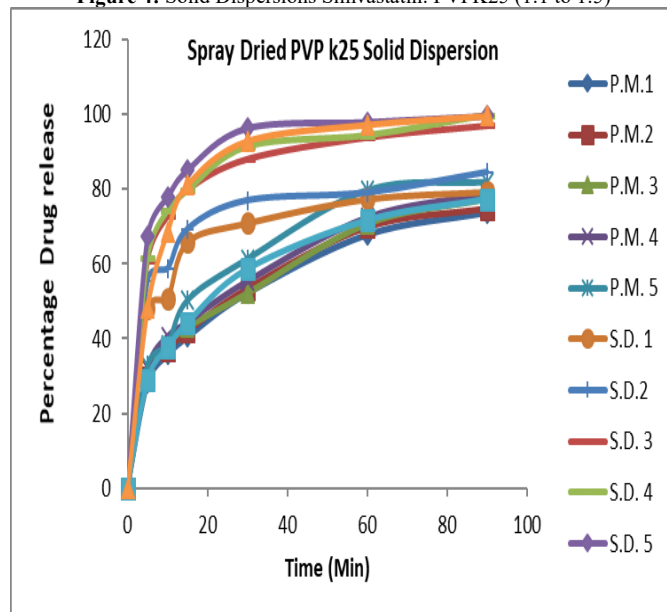
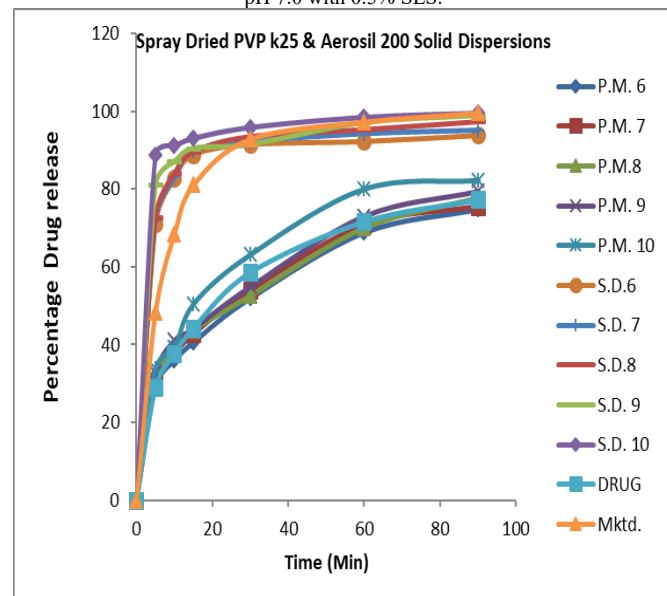


Figure 5: Simvastatin: PVP K25: Aerosil (200 1:1:1 to 1:5:1) Drug Release in pH 7.0 with 0.5% SLS.

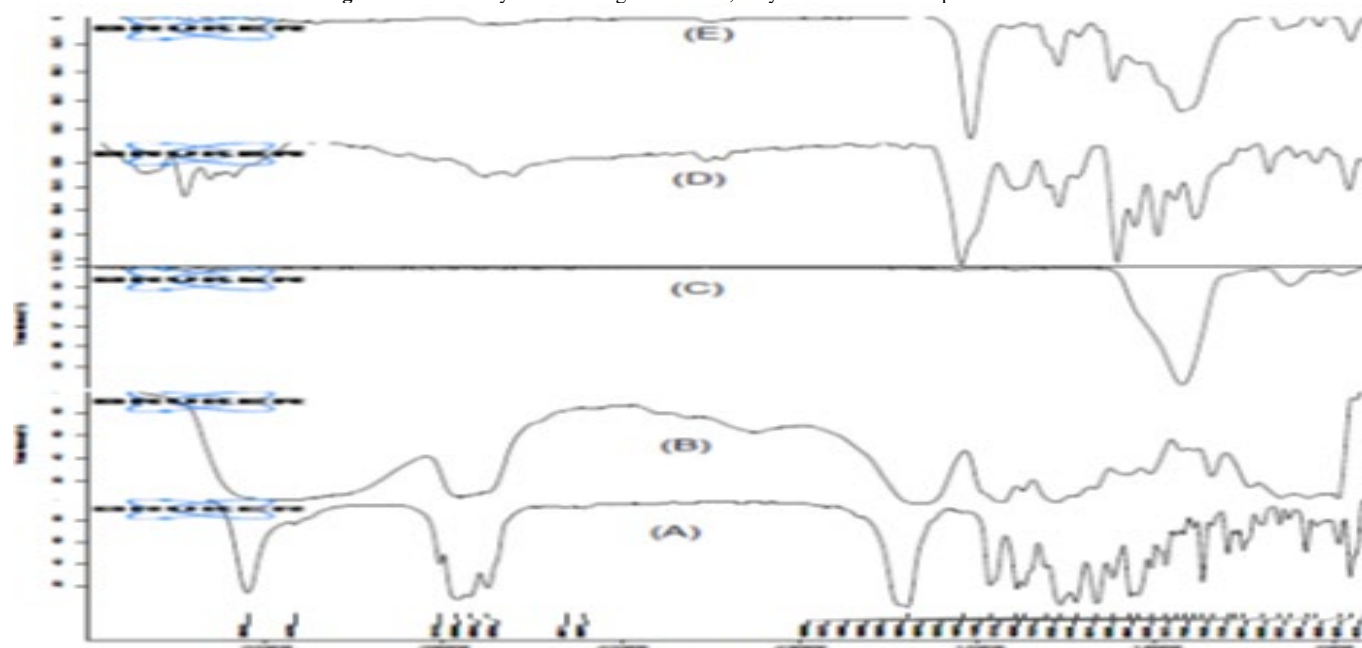


X-Ray Powder Diffraction (XRPD)

The X-Ray Powder Diffraction graphs were recorded by using the instrument "Xpert Pro" diffractometer (PANalytical, Almelo, Netherlands) at angle 2θ with scale 10 to 50. The processing and analysis of data was done with the help of X'pert Data Viewer (PANalytical, Almelo, Netherlands). The changes in height of the Bragg's peaks were noted to characterize the pure drug, physical mixture and optimized solid dispersion.

FTIR Studies of Drug, Polymers and Solid Dispersion formulation

The Fourier Transform Infra-Red (FTIR) Spectroscopic studies were done with Spectrophotometer 'Bruker Optics Inc. USA'. The pellets of pure drug, physical mixture and solid dispersion were prepared and finally analyzed by FTIR. The samples were scanned over range of 4000 to 400 cm^{-1} . [Figure 6].

Figure 6: FTIR study of Pure Drug simvastatin, Polymers and Solid Dispersion formulation

RESULT AND DISCUSSION

Dissolution Studies

The dissolution study were performed in 0.1 N HCl with 20% methanol and phosphate buffer at 7.0 pH with 0.5% SLS. The dissolution studies were performed on pure drug, physical mixture and solid dispersions formulations in both mediums. The dissolution studies in 0.1N HCl (figure 2) showed that only 26% of the pure drug was released in 90 minutes whereas the solid dispersions with aerosil showed about 97% drug release in 90 minutes. However in phosphate buffer pH 7.0 solid dispersions containing aerosil released the drug only in 10 minutes.

The solid dispersions formulation (SD6 - SD 10) gave the burst release with (71.1-88.87%) as compared to formulations (SD1-SD5) without aerosil (48.15-67.38%) at time point 5 minutes. The formulations with aerosil gave the release about 93.86-99.58% and formulation without aerosil gave about 79.36-99.69% drug release in phosphate buffer pH7 with 0.5% SLS. The marketed formulation “SIMVOTIN 20mg” also showed good release with 97.17% and 99.56% at 90minutes time point within 0.1%HCl with 20% methanol and pH7.0 phosphate buffer media.

Table 1: Similarity Factor Comparison of Solid Dispersion with Pure Drug, Physical Mixture and Marketed Formulation

Sample	SIM		SD1		SD2		SD3		SD4		SD5		SD6		SD7		SD8		SD9		SD10	
	f1	f2	f1	f2	f1	f2	f1	f2	f1	f2	f1	f2	f1	f2	f1	f2	f1	f2	f1	f2	f1	f2
SIM			62	25	66	21	71	16	71	16	74	12	72	15	73	14	74	13	75	02	76	11
PM 1	31	52	44	32	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
PM2	35	49	---	---	48	28	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
PM3	40	44	---	---	---	---	51	23	---	---	---	---	---	---	---	---	---	---	---	---	---	---
PM4	69	18	---	---	---	---	---	---	47	25	---	---	---	---	---	---	---	---	---	---	---	---
PM5	50	35	---	---	---	---	---	---	---	---	49	21	---	---	---	---	---	---	---	---	---	---
PM6	45	39	---	---	---	---	---	---	---	---	---	---	49	24	---	---	---	---	---	---	---	---
PM7	46	38	---	---	---	---	---	---	---	---	---	---	---	---	49	23	---	---	---	---	---	---
PM8	51	34	---	---	---	---	---	---	---	---	---	---	---	---	---	---	88	23	---	---	---	---
PM9	59	28	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	39	25	---	---
PM10	62	25	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	36	26
SD6	---	---	26	37	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
SD7	---	---	---	---	20	41	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
SD8	---	---	---	---	---	---	11	51	---	---	---	---	---	---	---	---	---	---	---	---	---	---
SD9	---	---	---	---	---	---	---	---	13	46	---	---	---	---	---	---	---	---	---	---	---	---
SD10	---	---	---	---	---	---	---	---	---	---	4	73	---	---	---	---	---	---	---	---	---	---
Mktd.	---	---	30	35	20	40	16	47	15	47	15	44	13	49	13	49	11	50	13	47	16	41

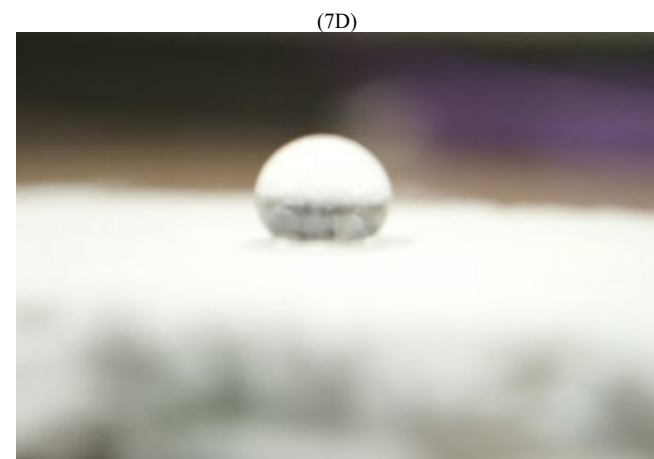
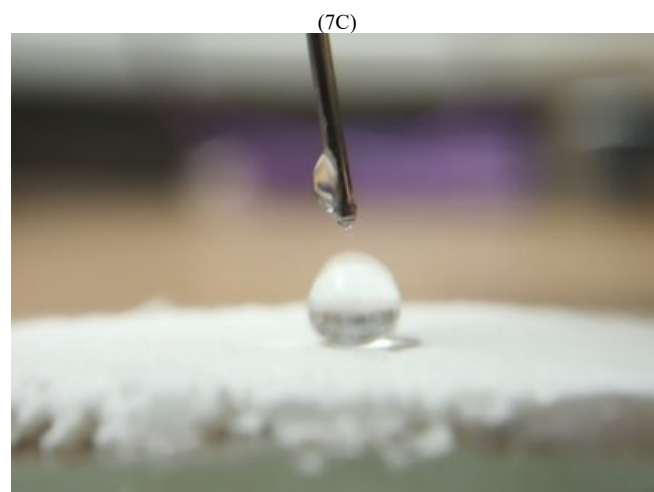
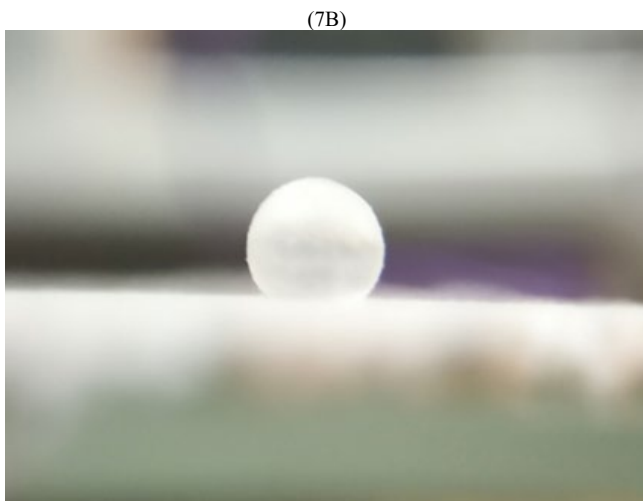
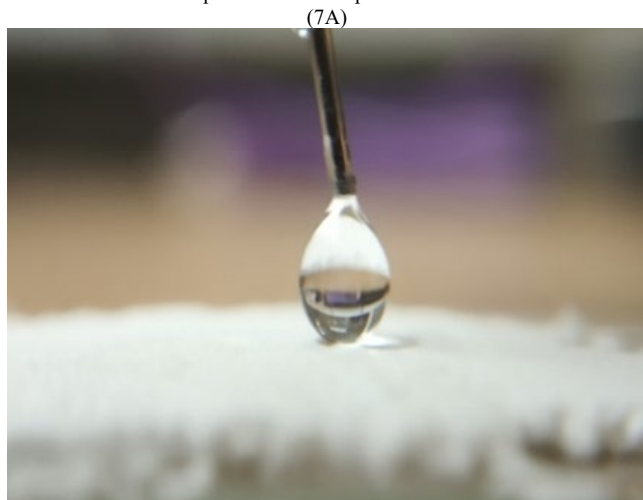
Similarity factors

The similarity factors f_1 and f_2 for pure drug simvastatin, physical mixture and solid dispersion were compared. The similarity factors show a remarkable difference between the solid dispersions and pure drug. The pure drug and physical mixture (1:1 to 1:5 and 1:1:1 to 1:5:1) showed a remarkable difference in dissolution. The difference in dissolution profiles of the solid dispersion and the physical mixture was also seen during the similarity factor study.

Contact Angle Photography

The images of pure drug and solid dispersion formulation shows clearly change in contact angle of the formulation given in the image below. The figure 7 image (7A) and (7B) contains the droplet of water on the pure drug with (crystalline nature) and figure 7 images (7C) and (7D) showed the image of optimized spray dried solid dispersion formulation (amorphous nature). These four images showed difference of the contact angle of the drug and solid dispersion separately. This study suggests that amorphous nature of the formulation offers enhanced contact angle as compare to pure drug which may be a reason for dissolution enhancement of simvastatin.

Figure 7: (A,B,C,D). Contact angle photography results of pure drug and optimized solid dispersion SD8



FTIR Study

The FTIR study of simvastatin showed characteristics peaks at 3551.29 cm^{-1} peak of OH group, methyl group at 2965.99 cm^{-1} (-CH asymmetric stretch) peak, peak of carboxylic group C=O stretch at 1698.95 cm^{-1} and -C-O-C (Lactone) stretch at 1267.82 cm^{-1} .

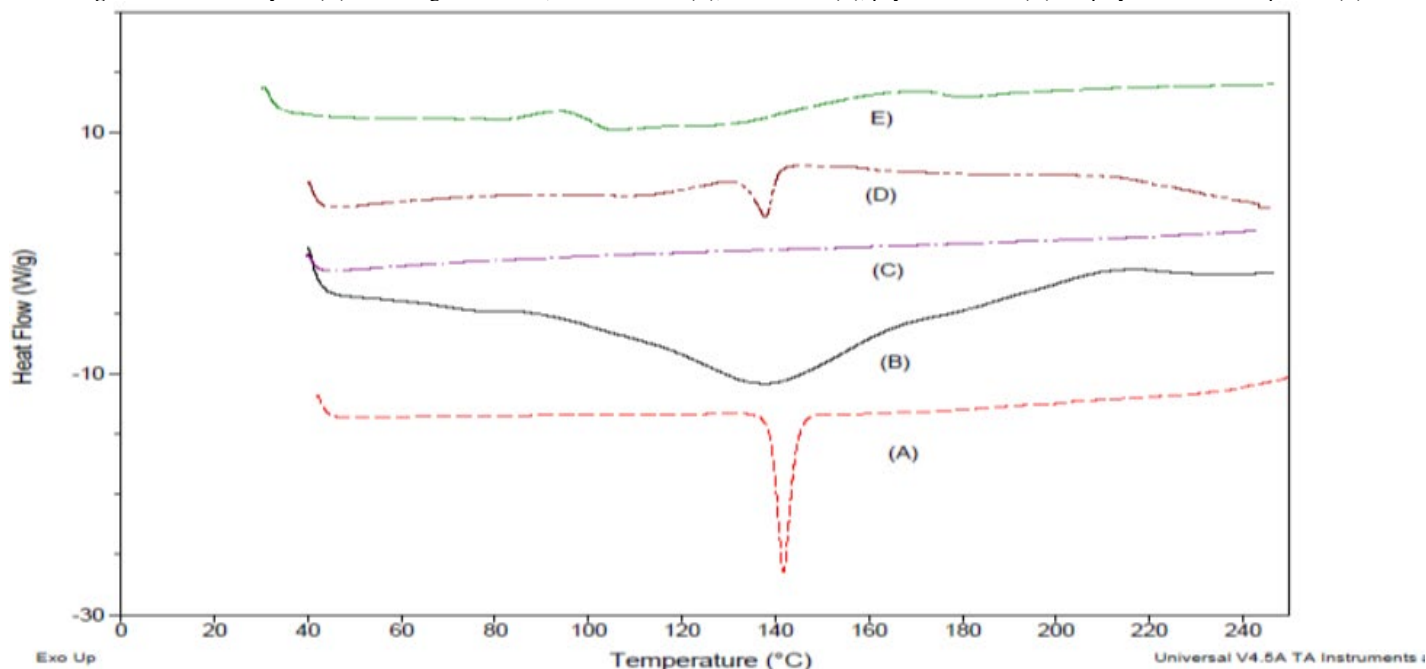
The FTIR study of PVP K25 showed characteristics peak at 3450 cm^{-1} (OH group), 1657 cm^{-1} (C=O stretch), Methylene Asymm. / sym. Stretch at 2953 cm^{-1} (-CH Stretching) and 1280.37 cm^{-1} (C-N stretching vibrations) and 1373.78 cm^{-1} (C-H bending). The FTIR study of aerosol 200 showed characteristics peak at 1098.15 cm^{-1} showing the presence of Si-O bond. The physical mixture and solid dispersion (1:3:1) do not show any major difference in the peaks of the simvastatin, PVP K25 and Aerosil 200. All the relevant peaks are present in the both spectra physical mixture as well as solid dispersion.

DSC Studies

The DSC study of the pure drug simvastatin, PVP K25, Aerosil, physical mixture and solid dispersions were performed (shown in figure 5), Pure simvastatin shows melting endotherm at 139.96 °C. The PVP K25 shows characteristic broad endotherm. Aerosil 200 does not show the characteristic peak due to high melting point. Physical mixture does show any new peak indicating that there is no interaction between the drug and polymers.

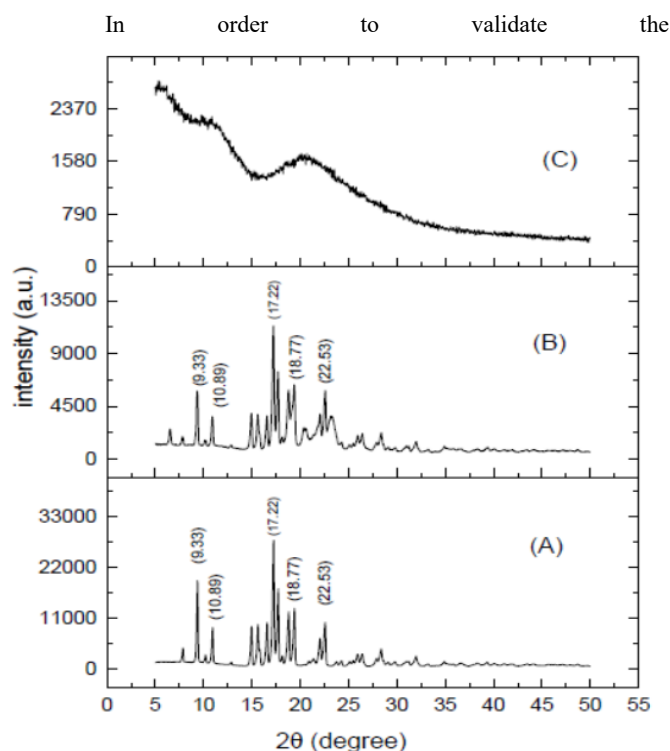
The optimized solid dispersion formulation prepared by spray drying method does not show any endotherm peak. It suggests that amorphous nature of the formulation supported by the powdered x-ray crystallographic studies. The similarity between the DSC curve and PXRD curve indicates that drug is uniformly present in the matrix of PVP K25 and aerosil matrix system in an amorphous form.

Figure 8: DSC Overlays of (A) Pure Drug Simvastatin, Pure PVP K25 (B), Aerosil 200 (C), physical Mixture (D) & Spray Dried Solid Dispersion (E).



Powdered X-Ray Diffraction Study

Figure 6: PXRD Studies Results of Pure Drug (A), Physical Mixture (B), and Optimized Solid Dispersion (C) SD 8.



results of the DSC study the powdered x-ray diffraction was performed shown in figure 6. All these studies were carried out by “Sophisticated Analytical Instrumentation Facility, Panjab University, Chandigarh”. The simvastatin and physical mixture show peaks at 9.33, 10.89, 17.22°, 18.77°, and 22.53° revealed that the drug is crystalline in nature. [17]. The PXRD study of Physical mixture of simvastatin with excipients shows that characteristics peaks of drug at 9.33, 10.89, 17.22°, 18.77°, and 22.53°. The optimized formulation SD 8 (simvastatin: PVP K25: Aerosil 200 1:3:1 ratio) shows that all the characteristics peaks of the drug absent in the PXRD, suggesting crystalline drug is changed in to amorphous form in the formulation.

CONCLUSION

The solid dispersions prepared by spray drying were evaluated for their potential use in the preparation of rapidly dissolving dosage form of simvastatin with PVP K25 and aerosil 200. Solid dispersions of simvastatin were prepared and characterized by DSC, Fourier transform infrared spectroscopy and powdered x-ray diffraction dissolution. During dissolution study solid dispersion with aerosil 200 showed fast drug release as compared to the solid dispersion without aerosil. The optimized solid dispersion 1:3:1 (simvastatin: PVP K25: Aerosil 200) showed

the change in rate and extent of drug release. The optimized solid dispersions formulation showed comparatively change in contact angle as compared to the pure drug. FTIR data suggested no interaction of the selected excipients with the drug, while DSC data output with PXRD studies, suggested that crystalline drug is changed into amorphous form in the solid dispersions, explaining the increased dissolution rate of the solid dispersions. These studies suggest that solid dispersion can be a viable approach to overcome the poor aqueous solubility of simvastatin.

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