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Research Article

Stabilization and Amorphization of Lovastatin Using Different Types of Silica

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ABSTRACT. Lovastatin (LOV), an antihyperlipidimic agent, is characterized by low solubility/poor dissolution and, thus, low bioavailability (<5%). A beneficial effect on its bioavailability could result from improving its dissolution. One of the most common methods used to enhance dissolution is the preparation of solid dispersions. Solid dispersions of LOV and silica with different surface areas were prepared. The effects of the type of silica, ratio of drug/silica, incubation period with silica, and the effect of surface area were all studied. Characterization of the prepared formulae for possible interaction between drug and polymer was carried out using differential scanning calorimetery, Fourier transform infrared spectroscopy, powder X-ray diffraction, surface area determination, and scanning electron microscopy. The dissolution profiles of all prepared formulae were constructed and evaluated. It was found that the formula made of LOV and Sylysia 350 FCP in a ratio of 1:5 after an incubation period of 48 h resulted in the best release, and it was stable after 3 months storage at 75% RH and 40°C.

KEY WORDS: Aerosil; amorphous; co-evaporates; Fujicalin; lovastatin; Neusilin; Sylysia.

INTRODUCTION

Oral administration of poorly water-soluble drugs is a challenge to dosage form formulators. This is due to the direct relationship between poor solubility/dissolution and bioavailability and therapeutic effectiveness. Thus, enhancing drug dissolution can solve this problem (1).

Enhancing drug dissolution was previously achieved using various methods including reduction in particle size (micro- or nano-sizing) (2), amorphization (3–5), cyclodextrin solubilization in the absence or presence of different polymers (6,7), salt formation (8), and dispersion of drug in polymeric matrices. The last method gained lots of interest due to its advantages which include simplicity and the presence of drug in the molecular level (9). However, these methods suffer from many disadvantages. For example, the production cost using the cyclodextrin solubilization method is high. Additionally, the stability is poor and the drug loading is low (10) in the other methods. Accordingly, there is a need to develop a method that is devoid of the above-mentioned disadvantages.

Adsorption of drugs onto high surface area carriers like silica is a well-known method for enhancing drug dissolution. It was first described in the early 1970s (11). During the last few years, new carriers were synthesized. These include pharmaceutically porous silicon dioxide (Sylysia 350 FCP®) (12–15), polypropylene foam powder (Accurel®), porous calcium silicate (Florite®) (13,16), magnesium aluminum silicate (Neusilin®) (17–20), and mesoporous silica nanoparticles (MCM-41 and SBA-15). The use of mesoporous silica nanoparticles was promising in the field of peptides, proteins, and gene drug delivery mainly because of their ordered structure, high surface area, large pore volume, tunable pore size, ease of surface functionalization, and their biocompatibility (10,21–25).

Lovastatin (LOV), belonging to the class statins, is widely used for the treatment of hypercholesterolemia (26,27). It is an inactive lactone that is hydrolyzed to the corresponding β-hydroxy acid form, which is the principal metabolite and the inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (9). According to the Biopharmaceutical Classification System, LOV belongs to class II drugs. It is a highly lipophilic and poorly water-soluble drug (26). Its water solubility is 0.3 μg/ml (28). The rate at which poorly water-soluble drugs dissolve is often the slowest step and therefore exerts a rate-limiting effect on drug bioavailability (29). Absorption of LOV, relative to an intravenous reference dose, is about 30% of the oral dose. This necessitates the administration of an unnecessarily large dose of drug. Also, LOV exhibits low and variable oral bioavailability (<5%) (30) because of the rapid metabolism in the gut and liver; the plasma half-life of oral LOV varies from 1.1 to 1.7 h in adults with normal renal function (30,31). These disadvantages necessitate frequent administration of drug. Thus, a formulation with enhanced dissolution is extremely desirable for LOV to increase the rate of drug

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absorption and improve the bioavailability and the therapeutic efficacy.

A variety of pharmaceutical formulation technologies were used to enhance the oral bioavailability of LOV, including inclusion in β-cyclodextrins (32), preparation of solid dispersions using different polymers (poloxamer, polyethylene glycol 4000, polyvinylpyrrolidone K30 (33), and modified locust bean gum (29)), superdisintegrants (crospovidone, croscarmellose sodium, and sodium starch glycolate) (34), microemulsions (35,36), microspheres (35,37), nanocrystals (38), solid lipid nanoparticles (39), microparticles prepared by coacervation (40,41), nanostructured lipid carriers (30,39,42), and mesoporous carbon spheres (43). However, these methods have many disadvantages, including recrystallization of the amorphous formed drug in solid dispersions, hygroscopicity or high viscosity of the used carriers, high production cost, poor wetting and poor flow of nanoparticles, limited drug loading, and expulsion of drug during storage. Accordingly, an easier, cost-effective method for enhancing the dissolution on a large scale is needed.

In this research, a relatively simple and well-known formulation technology (preparation of solid dispersions) will be used to enhance drug dissolution. Complexes of LOV with novel newly developed silica polymers (Sylysia 350 FCP, Neusilin US2, Fujicalin, and Aerosil 200) will be prepared and evaluated.

Sylysia 350 FCP is an amorphous silicon dioxide with high specific surface area and porosity, making it a good candidate for efficient drug loading and rapid release. It contains many silanol groups on its surface and is considered safe by the Food and Drug Administration (11,44).

Neusilin US2 is an amorphous magnesium aluminosilicate. It is available as porous granules. It has a neutral pH and a wide range of compatibility. It is similar to Sylysia in having many silanol groups on its surface. The presence of silanol groups on its surface makes it a potential proton donor and acceptor. It is believed that the interaction with the drug and the presence of metal ions prevent recrystallization of the drug (stabilize its amorphous form) (45–47).

Fujicalin is a type of spherical particle containing microcrystals of anhydrous dicalcium phosphate, soluble in acidic media, with high porosity and large specific surface area (48,49).

Aerosil 200 differs from these polymers in that it is a non-porous material made of hydrophilic fumed silica (silicon dioxide) (50).

Accordingly, the aims of this study were: firstly, to prepare solid dispersions of LOV using various silica polymers in different ratios and different incubation periods; secondly, to identify the polymer and drug/polymer ratio that best enhance the dissolution of the drug; and, thirdly, to study the stability of the prepared formula after storage for 3 months at 75% relative humidity (RH) and 40°C.

MATERIALS AND METHODS

Materials

Lovastatin was purchased from Ningbo Tianhong Biotech, China. The three types of silica (Neusilin US2, Fujicalin, and Sylysia 350) were kindly donated by Fuji Chemical Ltd., Japan. Aerosil 200 was obtained from Evonik Industries, Germany. Ethanol (HPLC grade) and sodium hydroxide were supplied by Fisher Chemical, UK. Potassium dihydrogen phosphate (extra pure) was supplied by Scharlau Chemie, Spain. Water used in all experiments was distilled. All chemicals were used as supplied without further modification.

Preparation of Co-evaporates

Fifty milligrams of Neusilin US2 was added to 100 ml ethanolic solution of LOV, resulting in a drug/polymer weight ratio of 1:1. After ultrasonication for 5 min, the suspension was dried using Heidolph rotary evaporator (Laborota 4010 Digital, Germany), the rotation speed of the rotary evaporator was set at 15 rpm, and the solvent was slowly driven off by heating the flask in a hot water bath kept at 75°C and pulling vacuum with an aspirator. Samples were then collected by scraping them from the walls of the flask and drying in a vacuum oven at 40°C (the temperature was predetermined to ensure the stability of LOV) overnight. All the co-evaporates were subsequently passed between sieves of mesh numbers of 80 and 100, further dried, and stored in desiccators over silica gel until further use.

The preparation of the co-evaporate was repeated as mentioned above, but with changing the type of silica (Sylysia 350 FCP, Fujicalin, and Aerosil 200), the drug/polymer ratio (1:2, 1:3, and 1:5), and the time of soaking in ethanol (48 and 24 h).

Preparation of Physical Mixtures

Predetermined amounts of LOV and silica were weighed and mixed using a mortar and a pestle. The same ratios used in the co-evaporation method were used in the preparation of the physical mixtures. Then, the physical mixtures were passed between sieves with mesh numbers 80 and 100 and stored in desiccators for further use.

Characterization of Co-evaporates and the Physical Mixtures

Differential Scanning Calorimetry

Thermal analysis was carried out to assess the thermotropic properties of the drug and the silica polymers and the presence of any interaction between them. Samples of 3–4 mg were heated in aluminum pans at a rate of 5°C/min in the range of 10–400°C. Empty aluminum pans were used as references. Differential scanning calorimetry (DSC) thermograms were recorded using a Shimadzu differential scanning calorimeter (DSC-50, Japan).

Powder X-Ray Diffraction Patterns

Powder X-ray diffraction (PXRD) patterns of LOV, the raw materials, the co-evaporates, and the physical mixtures were obtained for the detection of crystallinity. These were recorded in the range 0–40° using an Ultima IV X-ray diffractometer (Rigaku, Japan) with cobalt radiation at a voltage of 40 kV and a current of 40 mA. The scan step was 0.02°.

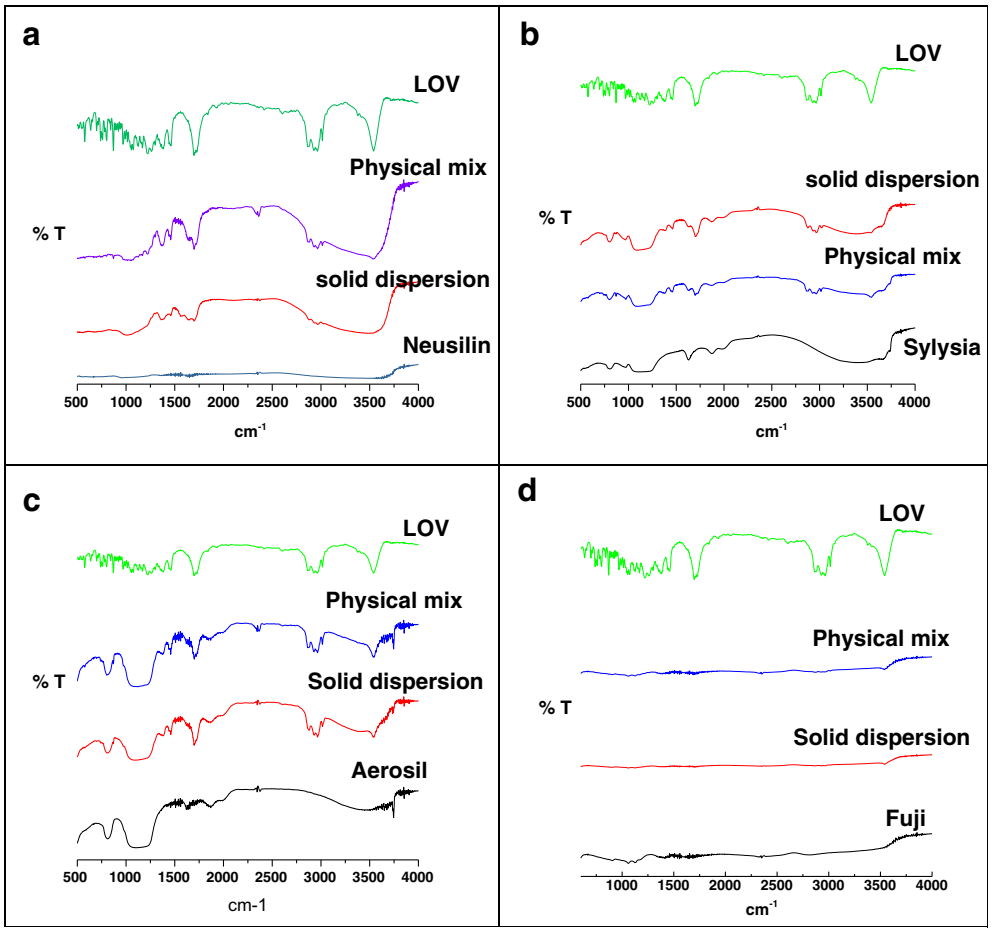

Fig. 1. FTIR spectra of lovastatin, different silica polymers (Neusilin (**a**), Sylysia (**b**), Aerosil (**c**), and Fujicalin (**d**)), solid dispersion, and physical mixtures prepared using these polymers in a drug/polymer ratio of 1:1 and an incubation period of 48 h

Fourier Transform Infrared Spectroscopy

Fourier transform infrared (FTIR) spectroscopy for pure drug, silica polymers, co-evaporates, and the physical mixtures was carried out for additional characterization of polymorphic changes and drug interactions using IRAffinity^{-1} (Shimadzu). Samples were blended with potassium bromide powder and the test was conducted over a frequency range of 4700–340 and 0.04 cm^{-1} resolution.

Scanning Electron Microscopy

Scanning electron microscopy (SEM) was used to examine the morphological characteristics and surface properties of the drug, silica polymers, the co-evaporates, and the physical mixtures. Samples were mounted on an aluminum stub by a double-sided sticky disc of conductive carbon, then coated with platinum by a sputter coater to render them electrically conductive. The electron beam was scanned over the specimen to produce a digital image using a Philips scanning electron microscope (model Quanta 200, Holland).

***In Vitro* Release Study**

The release rate of LOV from the co-evaporates and the physical mixtures was studied using a USP dissolution apparatus type II (paddle). Twenty milligrams of LOV powder or an equivalent amount of the co-evaporates or the physical mixtures was placed in 900 ml phosphate buffer (pH 7) containing 0.01% (*w*/*v*) SLS, at 37 ± 0.5°C and 50 rpm. Five-milliliter samples were withdrawn at predetermined intervals (5, 10, 15, 30, 45, 60, 90, 105, and 120 min), filtered using a 0.45 micro-syringe filter paper, diluted as needed, and assayed spectrophotometrically at λ_{max} (237 nm). The dissolution test was conducted in triplicate and the percentage of drug release was calculated.

Surface Area Determination

A Nov. 2200 multi-speed high gas sorption analyzer (version 6.11, Quantachrome Co., Syosset, NY, USA) was used to obtain nitrogen vapor adsorption isotherms at 77 K. Different silica polymers were degassed by heating in a vacuum oven at 100°C for 24 h prior to use.

Stability Study

The co-evaporates of different polymers were placed in glass vials and stored at 40 ± 2°C and 75 ± 5% relative humidity in a Schutzart-Memmert stability chamber (Germany) according to the ICH guidelines for 3 months. The FTIR spectra and the DSC and PXRD patterns of the stored samples were obtained and compared to those of the freshly prepared samples to detect any changes in crystallinity.

RESULTS AND DISCUSSION

Fourier Transform Infrared Spectroscopy

The FTIR spectra of pure LOV, silica polymers, co-evaporates, and physical mixtures are presented in Fig. 1. Pure LOV showed sharp characteristic peaks at 3532.73, 1706.74, and 1220.66 cm^{-1}. The FTIR spectra of the co-evaporates showed the same peaks of the drug without any changes in their positions, indicating the absence of interaction between the drug and the polymers. The same trend was seen when comparing the FTIR spectra of pure LOV and the physical mixtures prepared using Fujicalin (Fig. 1d). The spectra of the co-evaporates and of the physical mixtures showed both the peaks of the drug and the peaks of the silica polymers, indicating the absence of chemical interaction between drug and polymer.

Differential Scanning Calorimetry

The DSC thermograms of LOV, silica polymers, co-evaporates, and physical mixtures are presented in Fig. 2. The thermogram of pure LOV showed a single sharp endothermic peak corresponding to the melting point of the drug (175°C) and indicating its crystalline nature. Figure 2a showed the effect of Neusilin US2 on the melting point of LOV. The sharp endothermic peak disappeared in the co-evaporate, which might indicate the loss of crystallinity and conversion of the drug to the amorphous form. The same trend was seen in all co-evaporates prepared using Sylysia 350 FCP, Aerosil, and Fujicalin.

By comparing the DSC thermograms of the physical mixtures prepared using Neusilin, Sylysia 350 FCP, Fujicalin, and Aerosil with that of pure LOV, it is clear that the endothermic peak of LOV decreased or almost vanished, indicating a decrease in the crystallinity of the drug. This was expected since, firstly, in the physical mixtures, half the amount of the drug was present compared with pure LOV (drug/polymer ratio, 1:1); secondly, it is proven in the literature that milling using a mortar and a pestle reduces the size of the particles and increases the surface area and

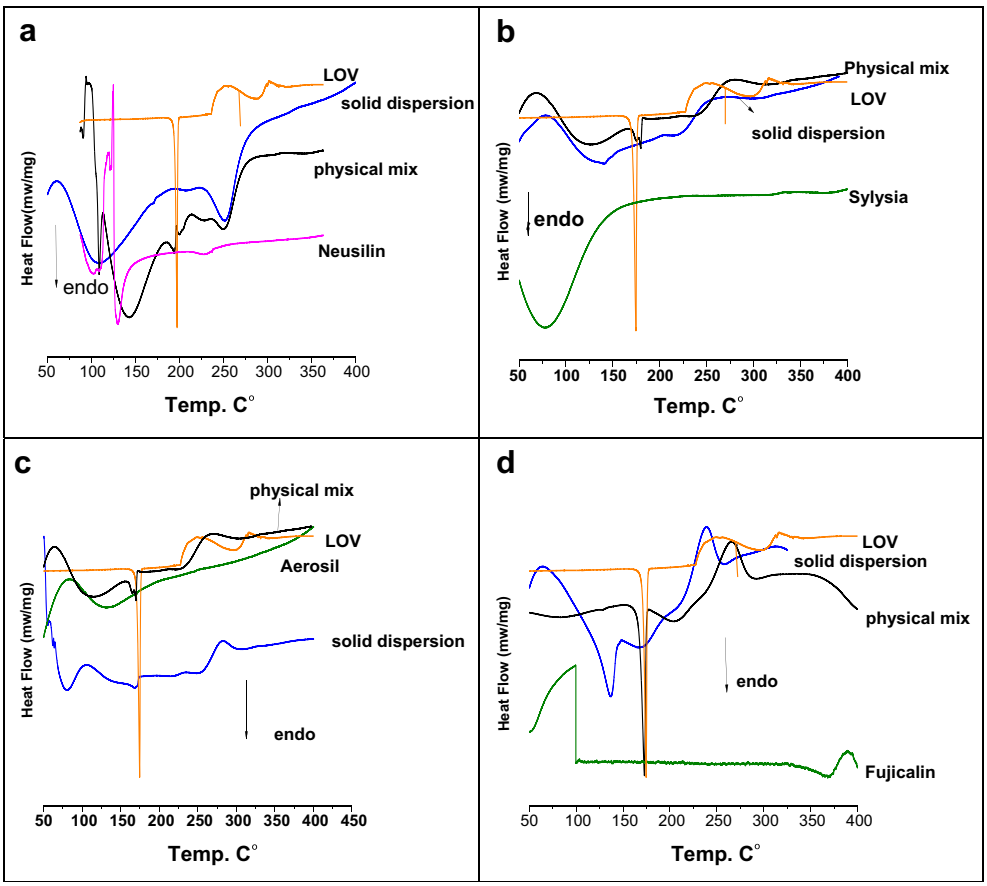

Fig. 2. DSC spectra of lovastatin, different silica polymers (Neusilin (**a**), Sylysia (**b**), Aerosil (**c**), and Fujicalin (**d**)), solid dispersion, and physical mixtures prepared using these polymers in a drug/polymer ratio of 1:1 and an incubation period of 48 h

surface free energy, converting the drug to the amorphous form. It is worth noting that the decrease in the endothermic peak of the drug in the physical mixture prepared using Fujicalin (Fig. 2d) was less than that in the case of the other silica polymers. This could be due to the difference in the chemical structure between Fujicalin and the other silica polymers. The milling effect on the drug (conversion to the amorphous form) was higher in the case of the physical mixtures prepared using the other silica polymers than in the case of Fujicalin. Fujicalin is composed of microcrystals of dicalcium phosphate and has a lower surface area than the other silica polymers used. Thus, only a small amount of drug was adsorbed onto its surface and the remainder was free (crystalline), resulting in a small decrease in the endothermic peak.

Powder X-Ray Diffraction Patterns

The PXRD pattern of LOV showed sharp characteristic diffraction peaks at angles (2θ) of 9.38, 10.86, 15.66, 16.68, and 18.9, indicating its crystallinity (Fig. 3). These diffraction peaks were still observed in the PXRD patterns of the physical mixtures prepared using different silica polymers, indicating that the drug still retained its crystallinity. On the contrary, no diffraction peaks were observed in the PXRD patterns of the co-evaporates. During processing, LOV was first solubilized in ethanol and then adsorbed and/or entrapped in the pores of the carriers. It was transformed into the amorphous state and was not capable of recrystallization. These results were consistent with those obtained from the thermal analysis experiments.

Scanning Electron Microscopy

The images of pure LOV, the silica polymers, the co-evaporates, and the physical mixtures are shown in Fig. 4. The image of pure LOV showed crystallinity, in contrast to the co-evaporates which showed loss of crystallinity. The images of the physical mixtures showed that some crystallinity was still found. These results were consistent with data obtained by the DSC and PXRD results.

Neusilin US2 and Fujicalin have a spherical characteristic shape, while LOV has a rod-like shape. The SEM images showed

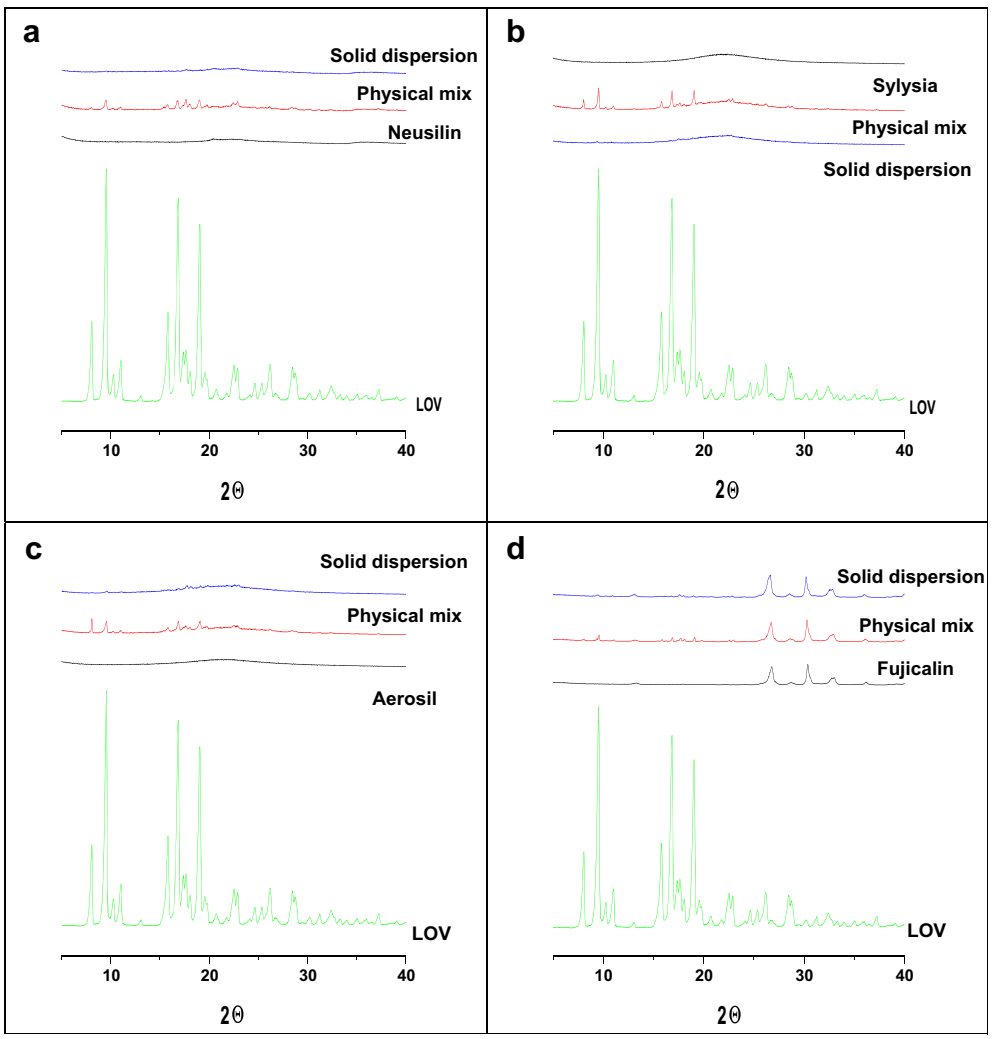

Fig. 3. PXRD patterns of lovastatin, different silica polymers (Neusilin (**a**), Sylysia (**b**), Aerosil (**c**), and Fujicalin (**d**)), solid dispersion, and physical mixtures prepared using these polymers in a drug/polymer ratio of 1:1 and an incubation period of 48 h

that the drug and the polymers retained their shapes in the physical mixtures prepared using Neusilin US2 or Fujicalin, indicating only mixing. The images also showed loss of crystallinity of the drug in the co-evaporates prepared using Neusilin, Aerosil, and Sylysia and a decrease in crystallinity in the co-evaporates prepared using Fujicalin. This indicated the transformation of the drug from the crystalline form to the amorphous form. This was again consistent with the results of the DSC and PXRD experiments.

In Vitro Release Study

The cumulative percentages of LOV released from different silica polymers (different ratios with different soaking times in ethanol) in comparison with pure LOV are shown in Fig. 5. The release of LOV from all polymers was much higher than that from pure LOV. The release from the different polymers was in the following order: Sylysia 350 FCP > Neusilin US2 > Aerosil > Fujicalin.

As the ratio of Sylysia 350 FCP polymer/drug increased, the release of the drug increased (1:5 > 1:3 > 1:2 > 1:1; Fig. 5a). This was expected since more carrier was available for trapping the drug. This was consistent with the data obtained from the PXRD, FTIR, DSC, and SEM results.

The same trend was seen with Neusilin US2 (Fig. 5b). It was observed that as the ratio of Neusilin US2 polymer/drug increased, the release of the drug also increased. The increase in the release of the drug could be due to the presence of the drug in the amorphous form and the increase of wetting (51,52).

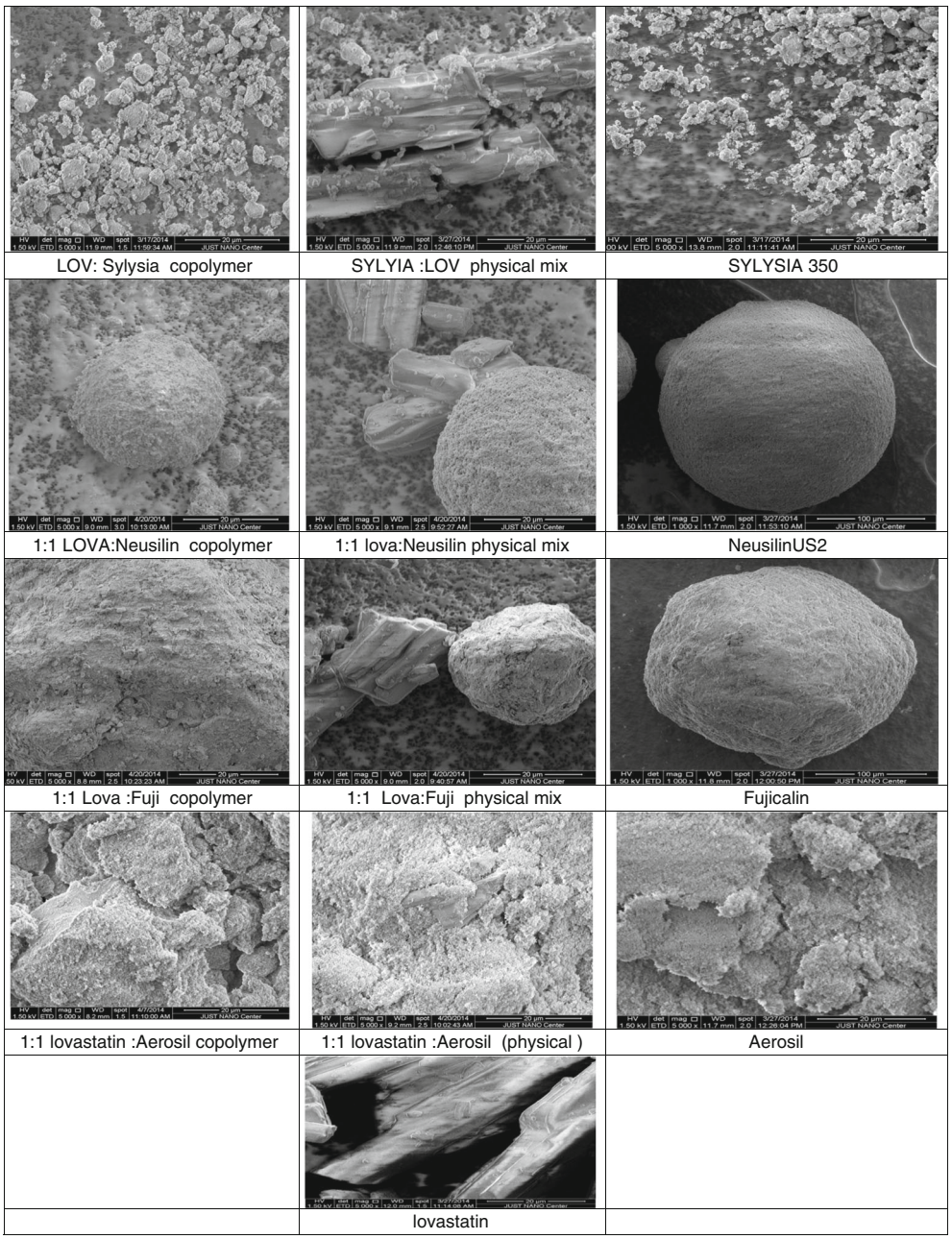

Fig. 4. SEM images of lovastatin, different silica polymers, solid dispersion, and physical mixtures prepared using these polymers in a drug/polymer ratio of 1:1 and an incubation period of 48 h at ×5000

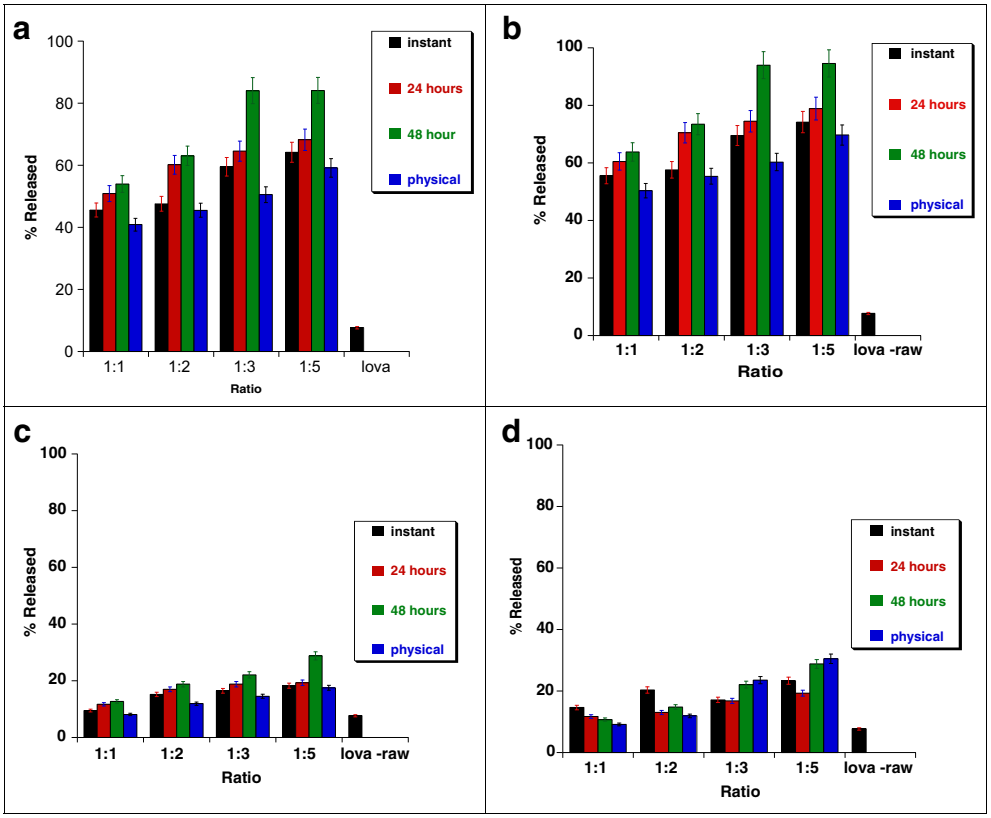

Fig. 5. Comparison of the percent cumulative amount of lovastatin released from solid dispersions prepared using different silica polymers (Neusilin (**a**), Sylysia (**b**), Aerosil (**c**), and Fujicalin (**d**)) in a drug/polymer ratio of 1:1 and an incubation period of 48 h and raw lovastatin in 900 ml phosphate buffer (pH 7) containing 0.01% (*w*/*v*) SLS at 37 ± 0.5°C and 50 rpm ($n = 3$)

The release from Aerosil, a non-porous silicon dioxide, was lower than that from both Neusilin US2 and Sylysia 350 FCP (Fig. 5c). This could be attributed to the differences in surface area between the different polymers (Table I). Neusilin US2 had the highest surface area, followed by Sylysia 350 FCP, then Aerosil, and finally Fujicalin.

The same trend concerning the polymer/drug ratio was observed in the case of Fujicalin (Fig. 5d). Increasing the polymer increased drug release (1:5 > 1:3 > 1:2 > 1:1), but the release was lower than that from the other polymers. This might be related to the lower surface area of Fujicalin. Additionally, Fujicalin is insoluble at pH 7 since it is a dibasic calcium phosphate compound (53).

As the soaking time increased, the cumulative amount of the drug released from all polymers for the same ration increased. Soaking for 48 h resulted in a higher release of the drug than soaking for 24 h or for 0 h (instant). This was probably due to more drug uptake by the polymers with longer soaking time. The location of the drug could be at the surface of the polymer or inside the pores. In Table I, it clear that the surface areas of all co-evaporates decreased as compared to those of the pure polymers. The polymers were processed in the same manner as the co-evaporates to rule out the effect of the processing technique. The decrease in the surface area could be due to two reasons. The first reason is the adsorption of the drug onto the surface of the polymer, resulting in increasing its size. The second reason is the entrapment of the drug inside the pores of the polymer, making it inaccessible to the nitrogen molecules during the measurement. This was supported by the SEM images of the co-evaporates which showed that the drug was adsorbed onto the surface of the polymer and entrapped inside the pores (Fig. 4). The second reason was more likely since as the soaking time increased, more drug was entrapped inside the pores of the polymers and the drug release increased.

Table I. Specific Surface Area of Different Silica Polymers and Solid Dispersions Prepared Using these Polymers in a Drug/Polymer Ratio of 1:1 with an Incubation Period of 48 h

Material name	Specific surface area (m^2/g)
Neusilin US2	317.5
Fujicalin	25
Sylysia 350 FCP	262.17
Aerosil	239.7
1:1 Lova/Aerosil	123.66
1:1 Lova/Neusilin	66.72
1:1 Lova/Fuji	6.347
1:1 Lova/Sylysia 350 FCP	93.14

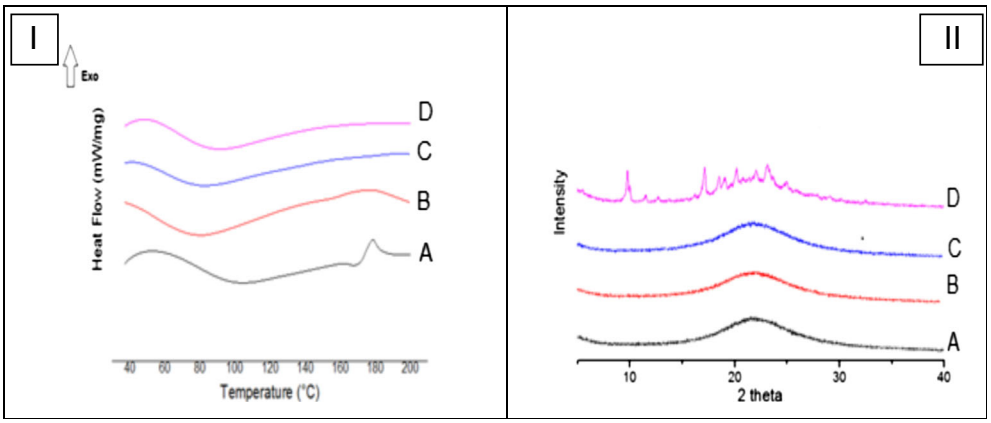

Fig. 6. DSC thermograms (*I*) and PXRD patterns (*II*) of solid dispersions prepared using different silica polymers (Neusilin (*A*), Sylysia (*B*), Aerosil (*C*), and Fujicalin (*D*)) in a drug/polymer ratio of 1:5 and an incubation period of 48 h after storage at 75% RH and 40°C for 3 months

The release rate from all co-evaporates was much higher than that from the physical mixtures prepared using different silica polymers in the same ratio. This could be due to many reasons. Firstly, the drug in the co-evaporates was dispersed at the molecular level, resulting in better wetting and dissolution. Secondly, as evidenced by the DSC and PXRD patterns, the drug was in the amorphous form inside the co-evaporates compared to the physical mixtures in which it was in the crystalline form. The amorphous form is generally more energetic and water-soluble than the crystalline form. Thirdly, more drug was available in the co-evaporates as compared to the physical mixtures due to differences in the method of preparation. In preparing the co-evaporates, the drug was soaked for different periods of time, resulting in entrapment inside the pores, while in preparing the physical mixtures the drug was added as a solid and mixed immediately with the polymers. Hence, it was only adsorbed onto the surface.

Stability Study

The amorphous form of LOV in the co-evaporates prepared using different polymers remained stable after 3 months of storage at 75% RH and 40°C, as was clear in the DSC and PXRD patterns. For example, LOV in the co-evaporates prepared using Sylysia 350 FCP remained in the amorphous form (Fig. 6) as compared to LOV without Sylysia 350 FCP, which was converted into the crystalline form. Similar results were obtained by other researchers for Tolbutamide (54), Carvedilol (44,55), K-832 (56), Spironolactone (12), and Meloxicam (13).

As suggested in the literature, the stabilization could be due to the porous structure of the silicates and the interaction with the silanol ring on the surface of Neusilin US2 (potential proton donor as well as proton acceptor) (45,57). Unfortunately, co-evaporates prepared using Fujicalin showed some crystallinity after 3 months. This could be due to the lower uptake of the drug in the polymer and lower adsorption onto the surface due to the lower surface area.

CONCLUSIONS

Silica polymers increased the dissolution of LOV possibly by two mechanisms: firstly, the high surface area of silica polymers increased the dispersibility and wetting of LOV, and, secondly, the crystallinity of LOV was decreased by hindering the transformation of the amorphous non-stable form into the crystalline form by physically protecting the drug. The type of polymer and mass transfer from the pores affected the dissolution of LOV entrapped inside the silica. The release of the drug from the different polymers was in the following order: Sylysia 350 FCP > Neusilin US2 > Aerosil > Fujicalin. The formula that resulted in the best release was LOV/Sylysia 350 FCP in a ratio of 1:5 after incubation period of 48 h; it remained stable and amorphous after 3 months storage in 75% RH and 40°C.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest The authors declare no conflict of interest.

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