Preparation and characterization of lovastatin polymeric microparticles by coacervation-phase separation method for dissolution enhancement

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ABSTRACT: Dissolution rate of lovastatin is slow, only 30% of the oral dose is absorbed, and it undergoes extensive first-pass extraction resulting in low and variable bioavailability. The objective of this research was to enhance the dissolution rate through preparing polymeric microparticles. Coacervation-phase separation method through the addition of a non-solvent was used to prepare polymeric microparticles. The method was optimized through studying effects of the type of solvent, the type of polymer, drug : polymer ratio and concentration of surfactant on particle size, particle size distribution, and *in-vitro* drug release. Optimized polymeric microparticles and unprocessed drug were characterized using different techniques (SEM, FTIR, DSC, and PXRD) and their flow properties were evaluated. The optimum microparticles were prepared using ethanol as a solvent, Eudragit® L 100 as a polymer in a drug:polymer ratio of 1:2 and SDS in a concentration of 0.25%. Characterization techniques indicated a change from the crystalline form to an amorphous form that was molecularly dispersed into the polymer. Flow properties of these microparticles were improved as compared to unprocessed drug. Drug release was enhanced 4- to 5-folds probably due to precipitation of the drug in an amorphous form; wetting enhancement; size reduction and stabilization by polymers and surfactants. In conclusion the selection of proper process parameters enhanced drug release 5 folds. The use of DMSO as a solvent and the preparation of physical mixtures in this research provided a means for controlled or prolonged release. © 2015 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2016**, *133*, 43277.

INTRODUCTION

Lovastatin belongs to the class statins and it is widely used for the treatment of hypercholesterolemia. It is an inactive lactone that is hydrolyzed mainly to the corresponding β-hydroxy acid form. It has a strong affinity to the enzyme and competes effectively to inhibit 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) reductase which is the rate limiting step in cholesterol synthesis. Thus it depletes the intracellular supply of cholesterol.[1]

Lovastatin is a highly lipophilic and a poorly water soluble drug.[2] The partition coefficient ($K_{o/w}$) in octanol/water system is $\sim 1.2 \times 10^4$.[3] Its water solubility is 0.3 μg/mL.[4] According to the Biopharmaceutical Classification System (BCS), it belongs to Class II drugs (high permeability, low solubility).[5] The rate at which poorly water soluble drugs dissolve is often the slowest step and therefore exerts rate-limiting effect on drug bioavailability.[6] Absorption of lovastatin after oral administration compared to an intravenous reference dose is about 30% of the dose. Also lovastatin undergoes extensive first-pass extraction in the liver resulting in low and variable bioavailability. In a single

dose study in four hypercholesterolemic patients, it was estimated that less than 5% of an oral dose of lovastatin reached the general circulation as active inhibitors. Following administration of lovastatin tablets the coefficient of variation, based on between-subject variability, was $\sim 40\%$ for the area under the curve (AUC) of total inhibitory activity in the general circulation.[7] Thus, the main problem with lovastatin is the slow rate of dissolution and the extensive first-pass extraction which resulted in low and variable bioavailability. Therefore enhancing the rate of dissolution is expected partly to solve this problem.

Several approaches were investigated to enhance the rate of dissolution of lovastatin and/or improve bioavailability. These include: preparation of amorphous lovastatin using freeze drying;[8] inclusion complexes with β-cyclodextrin (β-CD) in the absence and the presence of a dissolved polymer or its monomeric compound;[4,9,10] solid dispersions using different polymers and superdisintegrants;[6,11–13] a sustained release gastroretentive drug delivery system based on floating microspheres using various polymers and their blends;[14] a bilayer regioselective floating tablets of atenolol and lovastatin to give immediate release of

lovastatin and sustained release of atenolol;[15,16] A microemulsion formulation;[17,18] Nanocrystals prepared using simple precipitation method without using stabilizers or surfactants;[2] Nanostructured lipid carriers (NLCs);[19] and solid lipid nanoparticles (SLNs) prepared by hot homogenization followed by ultrasonication.[20–22]

Another approach for delivering drugs with limited water solubility is the use of polymeric microparticles (microspheres). This approach offers many advantages including producing amorphous drugs with desirable physical properties, improving bioavailability, reducing dosage frequency and toxicity, and reducing local side effects like GIT disturbances. Additionally, this approach can be used for immediate drug delivery, sustained drug delivery, and targeted drug delivery to specific organs.[23,24]

Polymeric microparticles were previously investigated for lovastatin. They were prepared using different polymers and different techniques but they were mainly intended for oral sustained or controlled release rather than immediate release with enhanced dissolution.[25–28] Only one article described the preparation of microspheres with the aim of enhancing the dissolution using starch. It resulted in the formation of a porous bed that limited the crystallinity of the drug due to the spatial confinement of the drug within the pores.[29] The aim of this research was to prepare polymeric microparticles using coacervation-phase separation method combined with freeze drying to obtain an amorphous rather than crystalline form of the drug to enhance the dissolution rate.

Microspheres are prepared by three basic techniques: solvent extraction/evaporation, phase separation (Coacervation), and spray drying. Spray drying is simple and the throughput is high but it is not suitable for compounds that are sensitive to high temperatures. Coacervation is frequently impaired by residual solvents and coacervating agents found in the microspheres. Furthermore, it is not well suited for producing microspheres in the low micrometer size range. Even though these drawbacks are avoided when using solvent extraction/evaporation technique, careful selection of encapsulation conditions and materials is needed to yield high encapsulation efficiencies and low residual solvent content, and using simple beaker/stirrer setup is not suitable for large production of microspheres in an economic, robust and well controlled manner.[30] As can be seen each technique has its own advantages and drawbacks and the choice of the most suitable technique depends on the type of polymer to be used, the chemical properties of the drug and the desired particles size.[24]

The coacervation phase separation method involves the following steps with continuous agitation: dissolving or dispersing the drug in a polymer solution; deposition of the coating polymer on the drug; and finally rigidising of coating by thermal, cross linking or desolvation techniques to form microparticles. Coacervation-phase separation can be obtained by temperature change, nonsolvent or salt addition, incompatible polymer addition, and polymer–polymer interaction.[23]

In this research, addition of a nonsolvent (Liquid Antisolvent (LAS) precipitation) with continuous stirring at a 500 rpm was used for deposition of the coating polymer on the drug. The formulation was optimized by investigating the effects of: type of polymer; drug:polymer ratio; type of organic solvent; and concentration of surfactant on the particle size, Particle Size Distribution (PSD), physical properties and on the *in-vitro* release of the drug from the microparticles.

EXPERIMENTALS

Materials

Lovastatin was bought from Ningbo Tianhong Biotech (China), CAS No. 75330-75-5.

Eudragit® L 100 was kindly donated by Evonik Rohm GmbH, Pharma Polymers (Germany), PEG4000, CAS: 25322-68-3, and PVP K 30, CAS: 9003-39-8, were bought from Acros Organics (Belgium). Sodium Dodecyl Sulfate (SDS), CAS: 151-21-3, was bought from AZ chem For Chemicals (Germany).

Concerning solvents: Ethanol absolute (Minimum 99.5% by volume), CAS: 64-17-5, was bought from Uni-Chem (USA). Methanol (HPLC Grade), CAS: 67-56-1, was bought from Fisher Scientific (UK). Dimethyl sulfoxide (DMSO) (991%), CAS: 67-68-5, was bought from Janssen Chimica (Belgium).

METHODS

Preparation of Polymeric Particles and Drug Loading

The microparticles were prepared as follows: Lovastatin was mixed with a Eudragit® L 100 polymer in a ratio of 1:1 and dissolved in an organic solvent (ethanol). The organic solution was filtered using 0.45 μm pore size membrane to remove any undissolved material. A volume of 10 mL of the organic solution was poured into 500 mL distilled water containing SDS surfactant at a concentration of 0.125% under mechanical stirring using overhead stirrer IKA EUROSTAR (Germany) at 500 rpm. The ratio of organic solution to the aqueous solution was 1:50. Polymeric microparticles formed (precipitated) immediately upon mixing, resulting in the formation of a microsuspension. The microsuspension was then freeze dried using Telstar LyoQuest freeze drier (Spain).

To determine drug loading, a weighed amount of the polymeric microparticles was dissolved in 0.1N NaOH. The sample was filtered through 0.45 μm pore size membrane, diluted as needed and assayed spectrophotometrically at $\lambda_{\max}$ (238 nm) using Shimadzu UV-spectrophotometer, Model UV-1800 (Japan). The concentration of lovastatin in the sample was calculated from a predetermined calibration curve. The drug loading was calculated using the following equation

$$\text{Drug loading } \% = \frac{W_{\text{LVT}}}{W_{\text{microparticles}}} \times 100\% \qquad (1)$$

where W_{LVT} represents the amount of lovastatin loaded in the microparticles; $W_{\text{microparticles}}$ represents the weight of the lovastatin microparticles.[26]

Optimization of Process Parameters

The process was optimized through studying the effect of the following parameters on the particle size, PSD, and *in vitro* drug release from the polymeric microparticles:

Table I. Experimental Design Followed during the Optimization Process

Experiment number	Polymer type	Drug:polymer ratio	Solvent	SDS Conc.
Experiment 1	Eudragit® L 100	1:1	Ethanol	0.125
Experiment 2	PVP K30	1:1	Ethanol	0.125
Experiment 3	PEG 4000	1:1	Ethanol	0.125
Experiment 4	Eudragit® L 100	1:1/2	Ethanol	0.125
Experiment 5	Eudragit® L 100	1:1	Ethanol	0.125
Experiment 6	Eudragit® L 100	1:2	Ethanol	0.125
Experiment 7	Eudragit® L 100	1:1	Ethanol	0.125
Experiment 8	Eudragit® L 100	1:1	Methanol	0.125
Experiment 9	Eudragit® L 100	1:1	DMSO	0.125
Experiment 10	Eudragit® L 100	1:1	Ethanol	0.0625
Experiment 11	Eudragit® L 100	1:1	Ethanol	0.125
Experiment 12	Eudragit® L 100	1:1	Ethanol	0.25

1. Type of polymer: Eudragit® L 100, PEG 4000, and PVP K30.
2. Drug:polymer ratio: 1:1/2, 1:1, and 1:2.
3. Type of organic solvent: ethanol, methanol, and DMSO.
4. Concentration of SDS surfactant: 0.0625, 0.125, and 0.25%.

During the optimization process, polymeric microparticles were prepared as mentioned above and the effect of a given parameter was studied by varying this parameter while keeping all the other parameters constant. The experimental design followed is shown in Table I.

Physical mixtures of drug, polymer, and SDS were prepared by accurately weighing the materials and mixing them in a mortar and pestle for a specified time interval (2 min). The same parameters studied in the optimization process were studied using the physical mixtures except for the type of solvent.

CHARACTERIZATION OF POLYMERIC MICROPARTICLES

Particle Size and Particle Size Distribution
Particle size and PSD of the microsuspension were analyzed using particle size analyzer (Microtrac 3500S). It measures volume-weighted particle size distribution over the size range 0.02550 to 2000 μm particle-size distribution which typically includes $d(10)$, $d(50)$, and $d(90)$ representing the percentage of particles below a given size (micron).

Environmental Scanning Electron Microscopy
An Environmental Scanning Electron Microscope (ESEM) Quanta 450 FEG-USA/EEU was used to observe the surface morphology of the precipitated polymeric microparticles without any further treatment (without coating).

Fourier- Transform Infrared Spectroscopy
Fourier-Transform Infrared (FTIR) spectra of unprocessed drug, Eudragit® L 100, surfactant and polymeric microparticles were obtained on Shimadzu (Japan). The spectra were scanned over the wave range of 4000 cm^{-1} to 500 cm^{-1}.

Differential Scanning Calorimetry
Differential Scanning Calorimetry (DSC) thermograms of unprocessed drug, Eudragit® L 100, surfactant, and polymeric microparticles, were obtained using DSC 204F1 Phoenix instrument (Germany). Samples (powder) were hermetically sealed in aluminum pans and heated at a constant rate of 20°C/min, over a temperature range of $20 - 240$°C. Inert atmosphere was maintained by purging nitrogen at the flow rate of 20 mL/min.

Powder X-ray Diffraction
Powder X-ray Diffraction (PXRD) patterns of unprocessed drug, Eudragit® L 100, surfactant, and polymeric microparticles were obtained at room temperature using Ultima IV (185mm) X-ray diffractometer (Rigaku, Japan) with Cu as anode material and graphite monochromatic, operated at a voltage of 40 kV, current 40 mA. The samples were analyzed in the 2θ angle range of 0°–50° and the process parameters were set as: scan step size of 0.02° (2θ), scan step time of 0.5 s.

Flow Properties
The flow properties of unprocessed drug and of the polymeric microparticles were evaluated by calculating Compressibility Index (CI) and Hausner Ratio (HR). A carefully weighed amount of powder was poured into a 50 ± 0.5 mL cylinder, the surface was leveled carefully, and the bulk volume (V_{bulk}) was read. The cylinder was tapped using a Jolting volumeter (Stav 2003, UK) for 10, 500, and 1250 taps and the V_{10}, V_{500}, and V_{1250} were recorded, respectively. If the V_{1250} was not different from V_{500} it was considered as the tapped volume (V_{tapped}), otherwise the tapping was continued until the change in the volume was less than 2%. The bulk density (ρ_b), tapped density (ρ_t), CI, and the HR were calculated using the following equations:

$$\rho_b = \frac{Wt}{V_{bulk}} \qquad (2)$$

$$\rho_t = \frac{Wt}{V_{tapped}} \qquad (3)$$

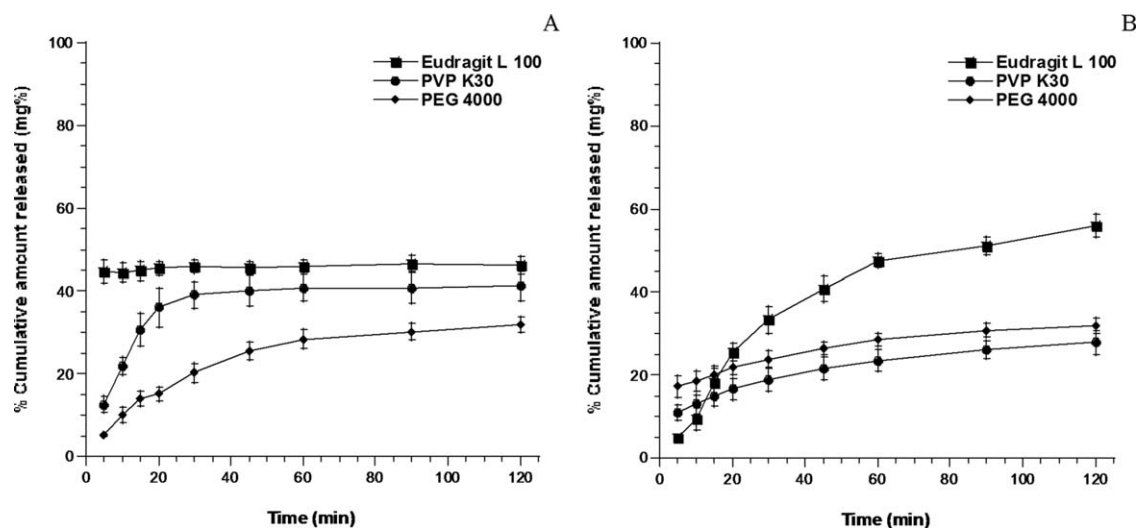$$CI = 100 \times \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \qquad (4)$$

Figure 1. Effect of type of polymer on drug release into 900 mL 0.1N HCl at 37°C and 50 rpm ($n = 3$) from (A) polymeric microparticles prepared using drug:polymer ratio of 1:1 precipitated from an ethanolic solution upon addition to water containing 0.125% SDS; and (B) Physical mix prepared using drug:polymer ratio of 1 : 1 and 0.125% SDS.

$$HR = \frac{\rho_{tapped}}{\rho_{bulk}} \qquad (5)$$

where V_{tap} is the tap volume and V_{bulk} is the bulk volume, ρ_{tap} is the tap density, and ρ_{bulk} is the bulk density.[31]

In Vitro Release Studies

Release rate of lovastatin from polymeric microparticles was determined using USP dissolution testing apparatus II (paddle) in 900 ml of 0.1N HCl containing 0.01% w/v of SDS, at 37 ± 0.5°C and 50 rpm. A weighed amount of polymeric microparticles equivalent to 20 mg lovastatin was added to the dissolution media. Samples (5 mL) of dissolution medium were withdrawn at 5, 10, 15, 20, 30, 45, 60, 90, and 120 min. Samples were filtered through 0.45 μm pore size membrane, diluted as

needed, and assayed spectrophotometrically at λ_{max} (238 nm). The UV-visible spectrophotometric method was shown satisfactory for measuring the drug release *in vitro* by many investigators.[1,2,4,7,11,13,14,32] The dissolution test was conducted in triplicates ($n = 3$) and the percentage drug release was calculated.

The drug exhibits sufficient stability in the dissolution media for the required period (T_{90} is 272 ± 8 h in 0.1 N HCl and 3.8 ± 0.2 h in phosphate buffer with SDS pH 7.0) and the hydrolysis products still contain the chromophore and could be determined using UV-Visible spectroscopy.[33]

The dissolution profile of unprocessed drug and the *in-vitro* release from physical mixtures were studied in a similar manner and the results were compared.
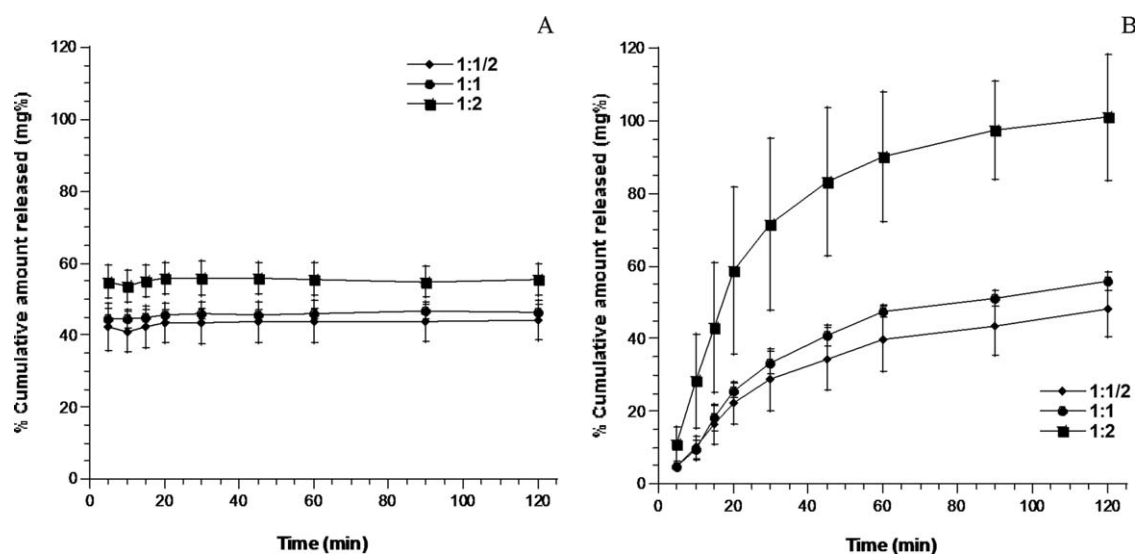

Figure 2. Effect of drug:polymer ratio on drug release into 900 mL 0.1N HCl at 37°C and 50 rpm ($n = 3$) from: (A) polymeric microparticles prepared using Eudragit® L 100 precipitated from ethanolic solution upon addition to water containing 0.125% SDS; and (B) Physical mix prepared using Eudragit® L 100 and 0.125% SDS.
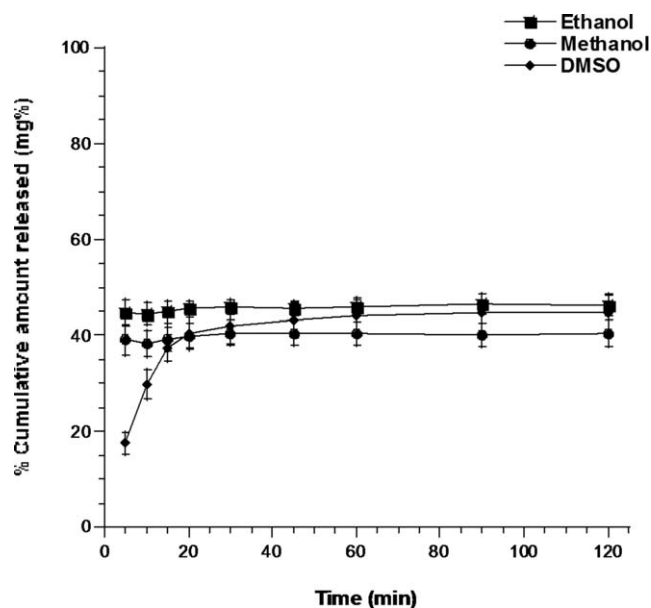
Figure 3. Effect of type of organic solvent on drug release into 900 mL 0.1N HCl at 37°C and 50 rpm ($n = 3$) from polymeric microparticles prepared using Eudragit® L 100 in a drug:polymer ratio of 1 : 1 precipitated from organic solution upon addition to water containing 0.125% SDS.

Stability Study

The stability of the optimized polymeric microparticles stored at room temperature and humidity for almost 2 years (23 months) was studied by obtaining PXRD pattern and comparing it to that of the freshly prepared polymeric microparticles.

RESULTS AND DISCUSSION

Preparation of Polymeric Particles and Drug Loading

Coacervation-phase separation method was applied successfully to prepare the polymeric microparticles. A nonsolvent (water) was added with continuous stirring at a 500 rpm to result in the deposition of the coating polymer on the drug (LAS precipitation). Drug loading of the optimized polymeric microparticles (nine batches) was determined and it was 6.76 ± 0.40 w/w %. Many factors probably resulted in low loading of the microparticles in addition to the fact that the polymer constituted 2/3 of the microparticles while the drug constituted only one third (Drug : polymer ratio of 1:2). These include the high solubility of the polymer in the organic phase, thus, the polymer required greater amount of water to precipitate and took longer time to solidify. This resulted in increased diffusion of the drug into the continuous phase through the nonsolidified (semi-solid) polymer. The second factor was the relatively low ratio of the organic dispersed phase to the aqueous continuous phase (1:50) which resulted in slow solidification of the polymer. Large volume of continuous phase provides a high concentration gradient of the organic solvent across the phase boundary by diluting the solvent, leading to fast solidification of the microparticles. The third factor was probably the slow solvent removal during the freeze drying.[34,35] Even though the loading was low, it was consistent with small variability between different batches indicating the suitability and/or reproducibility of this method.

Optimization of Process Parameters

The process was optimized and the effects of type of polymer, drug:polymer ratio, type of organic solvent and concentration of SDS surfactant on particle size and PSD were studied and are presented in Table II. The effects of these parameters on *in-vitro* drug release were also studied and are presented in Figures 1–4, respectively.

It is clear from Tables I and II, that the use of polymers and SDS decreased the particle size and narrowed the PSD as compared to the unprocessed drug. Polymers and surface active agents are usually used as stabilizers (deflocculating agents) in suspensions. The main mechanism by which they work is by
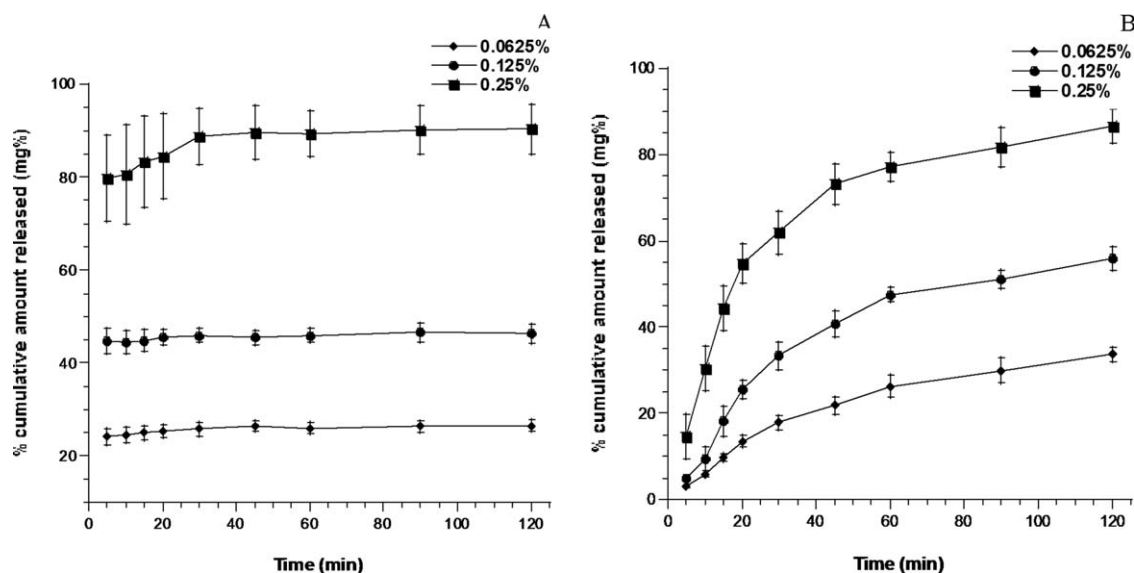

Figure 4. Effect of SAA concentration on drug release into 900 mL 0.1N HCl at 37°C and 50 rpm ($n = 3$) from: (A) polymeric microparticles prepared using Eudragit® L 100 in a drug:polymer ratio of 1:1 precipitated from an ethanolic solution upon addition to water containing SDS; and (B) Physical mix prepared using Eudragit® L 100 and 0.125% SDS.

Table II. Effect of the Different Parameters on Particle Size and Particle Size Distribution of the Microparticles during the Optimization Process ($n = 3$)

Experiment number[a]	Particle size MV ± SD (micron)	Particle size distribution $D_{10}/D_{50}/D_{90}$
Experiment 1	9.8 ± 1.53	2.30/7.12/21.92
Experiment 2	7.97 ± 2.79	1.78/5.61/18.69
Experiment 3	7.89 ± 0.81	2.11/6.11/17.12
Experiment 4	10.70 ± 0.94	2.25/7.50/23.64
Experiment 5	9.8 ± 1.53	2.30/7.12/21.92
Experiment 6	15.00 ± 1.82	2.82/11.63/33.70
Experiment 7	9.8 ± 1.53	2.30/7.12/21.92
Experiment 8	12.51 ± 3.64	2.32/8.73/28.09
Experiment 9	47.86 ± 9.74	7.72/34.21/118.69
Experiment 10	10.94 ± 0.88	2.32/8.42/24.72
Experiment 11	9.8 ± 1.53	2.30/7.12/21.92
Experiment 12	6.48 ± 1.76	1.98/5.63/12.15

[a] The experimental conditions (polymer type, drug : polymer ratio, solvent type, SDS concentration) are explained in Table I.

forming a protective film around the particles providing steric and/or electrostatic hindrance. Also, they reduce the interfacial tension by being adsorbed onto the surface of drug particles and increase the rate of nucleation, resulting in a reduction of the particle size. The reduction in interfacial tension is more significant in the case of surface active agents. Additionally, polymers increase the viscosity of the suspension and hence decrease the rate of collision between the particles and hence the growth in size.[36]
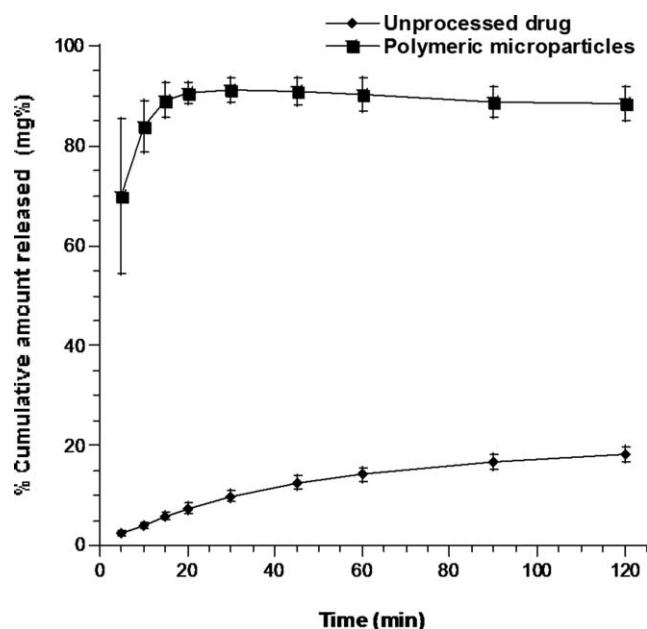
Figure 5. Drug release from unprocessed drug and optimized polymeric microparticles into 900 mL 0.1N HCl at 37°C and 50 rpm ($n = 3$).

Table III. Particle Size and Particle Size Distribution of Unprocessed Drug ($n = 3$) and Optimized Polymeric Microparticles ($n = 9$)

Sample	Particle size MV ± SD (micron)	Particle size distribution $D_{10}/D_{50}/D_{90}$
Unprocessed drug	28.28 ± 0.88	7.93/22.22/55.45
Optimized polymeric microparticles	17.21 ± 5.46	3.25/12.03/38.65

Among the three polymers used, Eudragit® L 100 was the most effective in enhancing the drug release of the drug from polymeric microparticles even though the particle size was the highest and the PSD was the widest. The difference between the effects of the polymers can be attributed to the following factors: firstly, to the aqueous solubility of the polymer and, consequently, to the quantity of the polymer adsorbed, which is inversely proportional to the solubility in the liquid phase (according to Lundelius' rule). Eudragit® L 100 is practically insoluble in water[37] while PEG 4000 and PVP K30 are readily or freely soluble in water.[38,39] Hence, a higher amount of Eudragit® L 100 polymer was adsorbed onto the surface of the drug resulting in better stabilization and release as compared to the other two polymers. Secondly, in addition to steric hindrance, Eudragit® L 100 provided electrostatic hindrance. It is anionic copolymer based on methacrylic acid and methyl methacrylate. The ratio of the free carboxyl groups to the ester groups is approximately 1:1 in Eudragit® L 100.[40] Lovastatin is a neutral lactone prodrug and is classified as a nonelectrolyte.[41] The anionic copolymer was adsorbed onto hydrophobic drug particles and provided them with a negative charge. The repulsion between like charges prevents coagulation. There was no clear difference in the particle size, and PSD, when PEG 4000 and PVP K30 were used but the release of the drug from the polymeric microparticles was higher in the case of PVP K30. This is probably because they both have good solubility in water and since they are neutral polymers they contributed only to the steric hindrance. The difference in the release of the drug from polymeric microparticles in the case of PVP K30 could be attributed to better wetting.

Increasing the concentration of the polymer (Drug : polymer ratio of 1:1/2 and 1:1 to 1:2) and increasing the concentration of SDS resulted in better release of the drug probably due to more stabilization by the above mentioned mechanisms. SDS is negatively charged and provided electrostatic hindrance in addition to the static hindrance. The increase in the particle size and widening in the size distribution in the case of increasing the polymer concentration is probably due to more polymer being adsorbed onto the surface of the precipitated drug particles and not the increase in the size of the particles themselves. There was no clear difference in the particle size, PSD, and in the release of the drug from polymeric microparticles in the case of drug : polymer ratios of 1:1/2 and 1:1 probably due to insufficient polymer being adsorbed onto the surface.
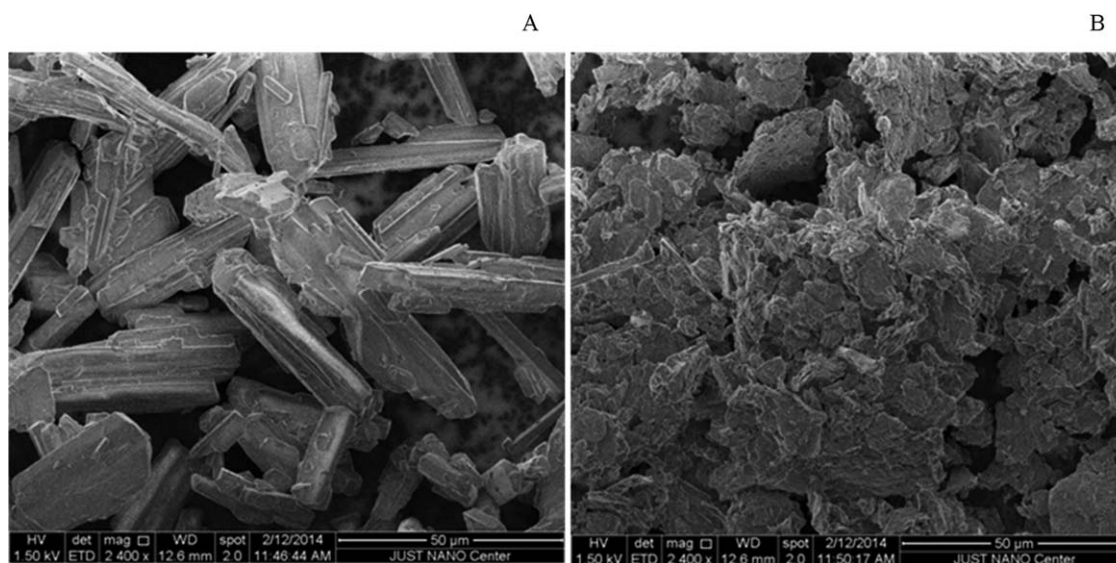
Figure 6. ESEM images of (A) unprocessed drug; and (B) optimized polymeric microparticles.

The solubility of lovastatin is in the following order: ethanol > methanol > DMSO.[42,43] When a solvent with higher solubilizing power for lovastatin was used, the particle size was the smallest, the PSD was the narrowest, and the drug release from the polymeric microparticles was somewhat higher. A similar result was observed by Nanjwade *et al.*[2] The higher solubilizing power of the solvent probably resulted in the formation of a less saturated solution. The rate of particle growth in this solution was smaller due to a lower number of collisions between the particles. The amount of polymer was enough to stabilize the small particles and the release was the highest. The use of DMSO resulted in the formation of a more saturated solution in which the rate of particle growth was higher probably due to a higher number of collisions between the particles. This large particle size and wide PSD resulted in slower release with almost the same cumulative amount of drug released after 120 min.

Drug release from the polymeric microparticles was rapid and almost complete within a short time as compared to that from the physical mixtures which was prolonged.

Accordingly, the optimum conditions were:

Type of polymer: Eudragit® L 100.
Drug : polymer ratio: 1:2.
Organic solvent: ethanol.
SDS concentration: 0.25%

Particle size and PSD of optimized polymeric microparticles (prepared using the optimum conditions mentioned above) and of unprocessed drug arerepresented in Table III while the release of drug is presented in Figure 5.

Characterization of Polymeric Microparticles
The ESEM images of unprocessed drug and of the optimized polymeric microparticles are shown in Figure 6. They showed that the unprocessed drug was crystalline with needle-shaped
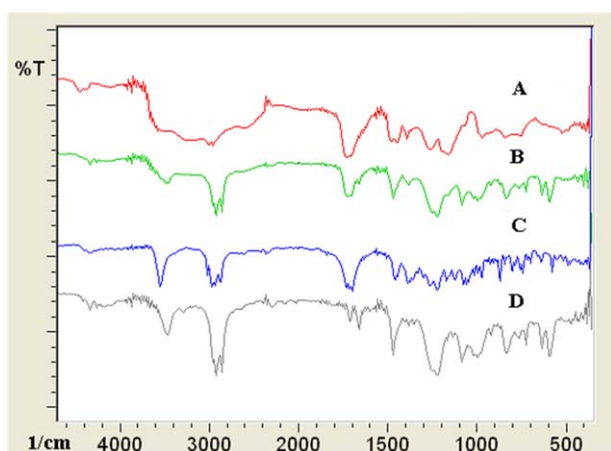

Figure 7. FTIR spectra for (A) Eudragit® L 100; (B) optimized polymeric microparticles; (C) unprocessed drug; and (D) SDS. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
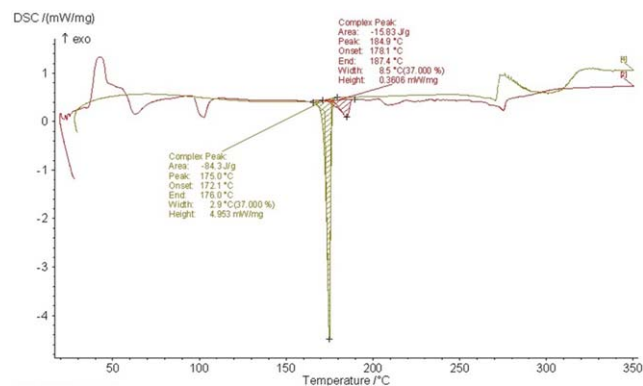

Figure 8. DSC thermograms of unprocessed drug and optimized polymeric microparticles. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
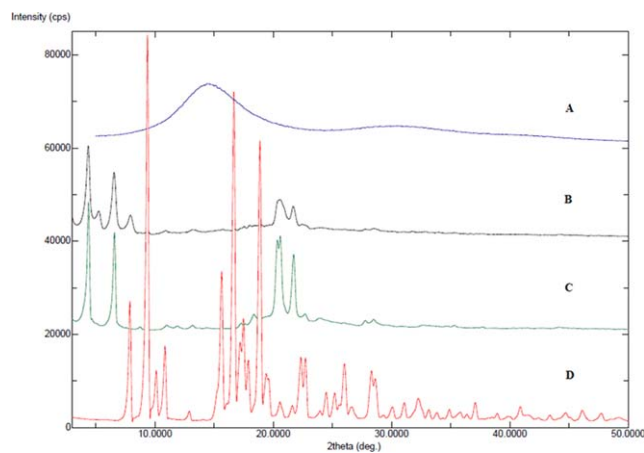
Figure 9. PXRD patterns of (A) Eudragit® L 100; (B) optimized polymeric microparticles; (C) SDS; and (D) unprocessed drug. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
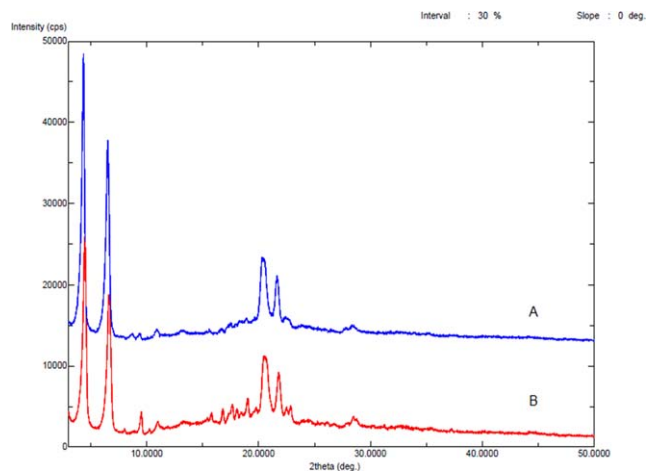

Figure 10. PXRD patterns of (A) optimized polymeric microparticles stored at room temperature and humidity for almost 2 years (23 months); and (B) freshly prepared optimized polymeric microparticles. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

crystals while the drug in the polymeric microparticles was amorphous. This could partially explain the enhancement in the release from polymeric microparticles since amorphous form is more energetic than the crystalline form and tends to interact better with the solvent.

FTIR spectra of unprocessed drug, Eudragit® L 100, surfactant and the optimized polymeric microparticles are presented in Figure 7. FTIR spectrum of the polymeric microparticles as compared to that of the unprocessed drug, indicated that some of the characteristic absorption bands of lovastatin (for example the band at 3539.90 cm^{-1} corresponding to OH stretching vibration) disappeared and were replaced by broad peaks. Changes in the position or disappearance of any characteristic stretching vibration of lovastatin usually indicate an interaction between the drug and the excipients. This might be attributed to change in crystalline form into molecularly dispersed lovastatin into Eudragit® L 100. A similar interaction with the used polymer was reported previously by Patel et al.[44]

DSC thermograms of unprocessed drug and the optimized polymeric microparticles are presented in Figure 8. Unprocessed drug showed a sharp endothermic peak at 175.0°C while in the optimized polymeric microparticles the peak was shifted almost 10 degrees (at 184.9°C) and the peak area was much reduced. This might confirm the interaction between the drug and the excipients depicted in the FTIR patterns.

PXRD patterns of unprocessed drug, Eudragit® L 100, surfactant, and the optimized polymeric microparticles are presented in Figure 9. PXRD pattern of unprocessed drug and SDS exhibited sharp peaks indicating the crystalline nature of the drug and the surfactant. The PXRD pattern of the polymer did not exhibit sharp peaks. Eudragit® L 100 polymer is amorphous in nature due to the absence of complete stereo regularity and presence of bulky side groups. PXRD pattern of the optimized polymeric microparticles showed that most of the peaks of the unprocessed drug disappeared and the only peaks that were present are those of SDS. This indicated that the drug was converted from the crystalline form to the amorphous form. This result was also confirmed by ESEM images of the polymeric microparticles.

The flow properties of unprocessed drug and of the optimized polymeric microparticles were evaluated and the results are presented in Table IV. According to the CI and HR, the flow properties ofthe optimized polymeric microparticles were better than those of unprocessed drug and could be further enhanced by the addition of glidants. This probably resulted from the change in the shape (Figure 6) and the decrease in the particle size of the optimized polymeric microparticles as compared to the unprocessed drug. This is expected to improve the manufacturing process of the final dosage form selected whether it is a powder, capsule or tablet dosage form.

It is clear from the above discussion that many reasons resulted in the enhancement of drug dissolution from the prepared polymeric microparticles and not only the formation of an amorphous drug. Otherwise, the different parameters studied would not have an effect on the particle size, PSD, and drug release from the polymeric microparticles since every time the particles were prepared they were subjected to freeze drying and the drug was converted to the amorphous form. Additionally, similar polymeric microparticles containing a different drug (gliclazide) were prepared and the dissolution was enhanced 2.55-folds even though the drug was still in the crystalline form.[45]

Table IV. Flow Properties of Unprocessed Drug and Optimized Polymeric Microparticles ($n = 3$)

Flow properties	Unprocessed drug	Polymeric microparticles
Bulk density (g/mL)	0.30 ± 0.01	0.22 ± 0.01
Tapped density (g/mL)	0.49 ± 0.01	0.28 ± 0.02
Compressibility index (%)	40.00 ± 0.00	24.00 ± 0.00
Hausner ratio	1.67 ± 0.00	1.32 ± 0.00

Stability Study

The PXRD patterns of the optimized polymeric microparticles stored at room temperature and humidity for almost 2 years (23 months) and of the freshly prepared optimized polymeric microparticles are shown in Figure 10. The patterns were identical, indicated that the drug was still in the amorphous form, and did not recrystallize. Thus, the microparticles exhibited sufficient stability against recrystallization for an appreciable period of time.

CONCLUSIONS

Coacervation-phase separation by the addition of a non-solvent method was applied successfully to prepare polymeric particles with enhanced dissolution rate.

The concentration of the polymer and the concentration of the surfactant are important parameters that affected drug release. Increasing the concentration, in the ranges studied, enhanced drug release from the polymeric microparticles.

The selection of the solvent and polymer is important in achieving the desired release profile. A good solvent resulted in a small particle size and narrow size distribution. The charge on Eudragit® L 100 provided an additional mechanism for size stabilization due to electrostatic hindrance and resulted in higher enhancement in the release as compared to PVP K-30 and PEG 4000.

The selection of the drying method (freeze drying in this research as compared to air drying in Al-Nimry et al.)[45] is important in determining the form of the drug precipitated (amorphous or crystalline) and thus the release profile.

Several mechanisms were involved in enhancing the dissolution almost 4-5 folds including the drug being precipitated in an amorphous form; the wetting being enhanced; the size of the microparticles being reduced (optimized) and stabilized by the use of polymers and surfactants.

The flow properties of the optimized polymeric microparticles were enhanced.

Physical mixtures or the use of a solvent with a low solubilizing power like DMSO provided a means for prolonged release.

The microparticles exhibited sufficient stability against recrystallization when stored at room temperature and humidity for an appreciable period of time (almost 2 years).

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