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ORIGINAL ARTICLE

Preparation and characterization of solid dispersion of simvastatin

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Abstract

Context: Simvastatin (SIM), a widely used drug for the treatment of hypercholesterolemia, is a crystalline substance and practically insoluble in water. Its low dissolution rate leads to a poor absorption, distribution, and target organ delivery because the bioavailability of drugs with low aqueous solubility is limited by their dissolution rates. *Objective*: The aim of this study was to prepare solid dispersions (SD) of SIM with inert carriers in an attempt to improve the release profile. *Methods*: In this work, SIM SD with polyethylene glycol (PEG 6000) or polyvinylpyrrolidone (PVP K15) in 1:1, 1:2, 1: 3, 1:4, and 1:5 ratios were prepared and their stability and dissolution properties were investigated. SD were characterized by differential scanning calorimetry and X-ray powder diffraction. Tablets containing SD SIM : PEG 6000 were developed and their dissolution profile evaluated. *Results*: Drug release from all SD was significantly improved when compared to their corresponding physical mixture or SIM alone. SD SIM:PVP showed drug degradation. The tablets gradually released SIM with a final quantity greater than 80% in 60 minutes. *Conclusions*: The preparation of SIM SD with PEG or PVP is a promising strategy to improve the bioavailability of the drug. SIM SD with PEG are more advantageous over the dispersions prepared with PVP because they do not show drug degradation during preparation.

Key words: *Dissolution; PEG; PVP; simvastatin; solid dispersion; solubility; tablets*

Introduction

Simvastatin (SIM) (Figure 3) is a potent inhibitor of hydroxymethylglutaryl coenzyme A reductase, a rate-limiting enzyme for cholesterol biosynthesis through mevalonate pathway[1,2].

SIM is a low-solubility high-permeability drug by the classification of the biopharmaceutics system, class 2[3]. It is well known that drug release is a crucial and limiting step in the rate and extent absorption of a class 2 drug from a solid dosage form[4]. Therefore, strategies to increase dissolution rate are needed to improve oral bioavailability of poorly water-soluble drugs, consequently, to achieve therapeutic efficacy[5–8].

Several approaches have been developed to improve the bioavailability by increasing the drug's dissolution rate and solubility. They include micronization, preparation of solid dispersions (SD), complexation with cyclodextrins, conversion of drugs from crystalline to amorphous state, incorporation of surfactants, inclusion in liposomes, formation of soluble salts, and the use of excipients that help drug release[4,5,8–13].

SD are one of the most successful strategies to improve drug release of poorly soluble drugs. SD can be defined as molecular mixtures of poorly water-soluble drugs in hydrophilic carriers[7,9]. SD increase the dissolution rate by augmenting the drug surface area and enhancing wettability. Most commonly used carriers for preparing SD are polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), and cellulose derivatives[7,9,14–16].

Previous workers report the preparation of SIM SD using PVP K30[6] and PEG 4000[8] as carriers. However,

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high proportions of polymer to drug (10:1) as used may favor undesirable interactions. Moreover, formulation of high-dose tablets or capsules, for instance, in case of SIM 40 and 80 mg dosage forms may be troublesome. In these studies, the stability of SD was not evaluated. In this work, the aim was to prepare SIM SD using different polymers of different molecular weights (PVP K15 and PEG 6000) in lower ratios of polymer (up to 1:5 drug to carrier) and evaluate possible drug degradation.

Materials and methods

Materials

SIM (99.2%, batch 2113002/2007) raw material was generously donated by Laboratório Globo Ltda. (São José da Lapa, Minas Gerais, Brazil) and SIM (99.1%, batch 0080/00348) working standard was a gift from Medley S/A Indústria Farmacêutica (Campinas, São Paulo, Brazil). Excipients used in the preparation of SD or tablets were microcrystalline cellulose MC 102 Microcel® (Colorcon do Brasil Ltda., Cotia, São Paulo, Brazil), ascorbic acid and PVP K15 (Sigma, St. Louis, MO, USA), citric acid, sodium starch glycolate, and Aerosil® (Henrifarma, São Paulo, Brazil), butylhydroxytoluene (InduKern do Brasil Química Ltda., Osasco, São Paulo, Brazil), magnesium stearate and directly compressible lactose Tablettose® 100 (Ipiranga Química, Santo, São Paulo, Brazil), sodium lauryl sulfate (SLS) (Pharmacopeia—Attivos Magistrais, Barueri, São Paulo, Brazil), PEG 6000 (Labsynth, Diadema, São Paulo, Brazil), and talc (Proquímios, Rio de Janeiro, Brazil). High-performance liquid chromatography grade acetonitrile and methanol (Tedia Company, Fairfield, IA, USA) were used. All chemicals and reagents were used without ulterior purification. High-purity water was prepared by using a MilliQ water purification system (Millipore, Milford, MA, USA).

Preparation of solid dispersions and physical mixtures

Physical mixtures (PM) were prepared by accurately weighing drug and carrier and mixing for 2 minutes for SIM:PEG or SIM:PVP of 1:1, 1:2, 1:3, 1:4, and 1:5 ratios. Corresponding SD ratios were prepared by means of melting (MET), solvent evaporation (SVE), or a blend of 'melting–solvent' method (MET/SVE)[7,9].

Melting method

After accurate weighing of drug and carrier, SD were prepared by heating proper amounts of PEG 6000 in a glass beaker in an oil bath at 58 ± 2°C. After total melting of PEG, SIM was slowly added with stirring. As the resultant dispersion was homogeneous, the mixture was cooled in ice water. After solidification, the solid was pulverized using a mortar and pestle. Subsequently, the SD was stored in a desiccator (over silica gel).

Solvent evaporation method

In a glass bottle SIM and PVP were dissolved in sufficient amount of ethanol and the solvent was removed by evaporation under reduced pressure at 58 ± 2°C. The film obtained in the glass bottle was stored in a desiccator (over silica gel) for 48 hours and then crushed and pulverized with a mortar and pestle.

Melting–solvent method

SD SIM:PEG in the 1:5 ratio was also prepared by PEG 6000 addition onto SIM ethanolic solution. The mixture was transferred to a rotavapor and heated at 58 ± 2°C to eliminate solvent and melt PEG at the same time, to yield a homogeneous mixture. After complete removal of the solvent, the mixture was cooled in ice water bath and the solid obtained was pulverized using a mortar and pestle. The SD was stored in a desiccator (over silica gel).

Characterization of solid dispersion

SD were characterized by differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD). PM were also evaluated for comparison.

DSC measurements were carried out in a TA-2910-modulated calorimeter (TA Instruments, New Castle, DE, USA). The specific heat measurement was standardized with sapphire. SIM, polymers, PM, and SD were grounded for 2 minutes using a mortar and pestle. The powders obtained were slightly compacted in an aluminum pan by a steel plunger. The samples (2–4 mg) were heated (25–250°C) at a constant scanning speed (5°C/min) using nitrogen as purging gas (50 mL/min).

XRPD patterns for PM and SD containing SIM and PVP or PEG 6000 were collected on a Geigerflex powder diffractometer (Rigaku, Tokyo, Japan) with a CuKα radiation at room temperature (298 K). Each sample was scanned between 4° and 40° in 2θ with 20 s/degree.

Solubility study

To evaluate the effect of SD on SIM solubility (0.03 mg/mL in water), phase solubility studies were performed. SIM only and their PM were also evaluated for solubility comparison. An amount of PM or SD containing the equivalent to 4 mg of SIM was added to 25 mL phosphate buffer solution (PBS, pH 7.40 ± 0.20). Samples were maintained under magnetic stirring in water bath at 37 ± 0.5°C. After 1 hour, the content of each flask was filtered through 0.45 mm membrane and the filtrate was suitably diluted and spectrophotometrically analyzed at

239 nm (HP8453 Agilent Technologies, Santa Clara, CA, USA). All solubility measurements were performed in triplicate. The SIM concentration was measured through the obtained absorbance values plotted by means of a calibration curve ($y = 0.0629x - 0.0018$; $r = 0.9999$) in a linear range of 2.0–17.0 μg/mL.

Stability evaluation of SD

To evaluate a possible degradation of the drug during preparation in different batches (duplicate) of PM and SD, samples were assessed in reverse-phase liquid chromatography (HP1100, Agilent Technologies, Santa Clara, CA, USA) coupled to a quaternary pump and an ultraviolet diode array detector (UV/DAD). Chromatographic conditions used were C_8 column (250 × 4 mm; 5 μm), acetonitrile:0.1% phosphoric acid (65:35), flow rate 1.5 mL/min, 30°C, and UV detection λ 238 nm. Sample concentration was 28 μg/mL in acetonitrile.

Tablet formulation

The SD containing SIM:PEG 6000 1:5 prepared by MET/SVE method was selected for preparation of tablets. SIM tablets formulation was SD SIM:PEG 6000 (15%), ascorbic acid (0.05%), citric acid (0.8%), aerosil® (0.5%), butylhydroxytoluene (0.5%), microcrystalline cellulose (43%), magnesium stearate (0.5%), sodium starch glycolate (2.0%), lactose (36.15%), SLS (0.5%), and talc (1.0%).

The SD tablets (containing 10 mg SIM), average weight 400 mg, were prepared by direct compression on a 10-station rotary press (Piccola, Riva, Argentina) using a 9-mm standard concave plunger. The tablets were assessed for weight variation (BP210D analytical balance, Sartorius, Göttingen, Germany), tablet breaking force (TBH30 durometer, Erweka, Heusenstamm, Germany), friability (TA3R friabilometer, Erweka, Heusenstamm, Germany), disintegration time (ZT3 disintegrator, Erweka, Germany), assay, content uniformity, and drug dissolution profile (DT80, Erweka, Germany).

Weight variation, tablet breaking force, friability, and disintegration time were evaluated according to the methods described in the Brazilian Pharmacopeia[17].

Chromatographic quantitative analyses were carried out for assay and content uniformity in the same conditions as described for stability evaluation. Dissolution profile was assessed by derivative UV (second order, λ 248 nm, PBS, pH 7.40).

Dissolution profile of tablets

A fast and reliable ultraviolet spectrophotometric method by second derivative was developed for the determination of SIM release. Second-derivative absorption of samples was recorded at λ 200–400 nm against PBS with 0.5% SLS as blank solvent. Suitable settings were slit 1 nm width and slow scan speed. The measurements were automatically performed at λ 248 nm (HP8453 Agilent Technologies, Santa Clara, CA, USA), second-order derivative by the zero-crossing method.

Dissolution conditions were (DT80, Erweka, Germany) 900 mL of PBS (pH 7.40 ± 0.20) with 0.5% (w/v) SLS, paddle apparatus stirring speed 50 rpm. The medium was maintained at 37 ± 0.5°C. Sampling aliquots of 5 mL were withdrawn at 5, 10, 15, 30, 45, and 60 minutes after placing the tablets in the dissolution medium.

The drug release was evaluated by measurements in the second-derivative absorbance (A/nm^2) found for the aliquots and calculated by means of a calibration curve in the concentration range 2.0–17.0 μg/mL. The dissolution profiles were obtained plotting time versus average percentage of drug release.

Results and discussion

Solid dispersions

SIM SD prepared in different drug to carrier ratios (1:1, 1:2, 1:3, 1:4, and 1:5) with PVP or PEG was evaluated with regard to their effect in the drug dissolution performance. The dissolution studies were compared between their corresponding SIM PM ratios and SIM only.

SIM : PVP SD was prepared by SVE method at 58°C to avoid exposure of the drug to high temperatures. SIM : PEG SD was prepared by MET method and the polymer was melted at 58°C. SD SIM:PEG in the 1:5 ratio was also prepared by MET/SVE method because of the difficulty to obtain homogeneous dispersion of the drug into the molten polymer. By using this method, it was possible to obtain a more homogeneous drug : carrier mixture.

Characterization of solid dispersion

The DSC thermal behavior of SIM, PEG and PVP, SIM:polymer PM, and their corresponding SD ratios was studied. DSC curve of SIM showed a typical pure crystalline substance profile with a sharp endothermic peak at 142.5°C. PEG 6000 DSC curve showed an endothermic sharp peak near 60°C because of polymer melting (Figure 1). On the contrary, a broad peak because of water bonded to molecules was verified for PVP (Figure 2).

DSC curves of PM and SD containing SIM and PEG were very similar. In PM and SD SIM:PEG 1:1 curves, the endothermic peak because of SIM melting was shifted to lower temperatures, accompanied by a significant decrease in the enthalpy. Otherwise, DSC curves of PM and SD at higher proportions of PEG exhibited no

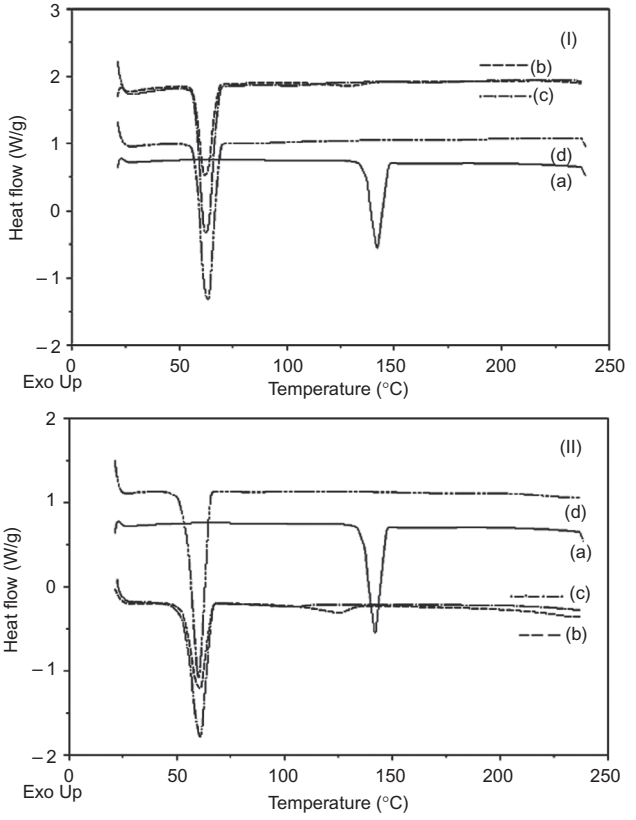

Figure 1. DSC curves for the drug (a) SIM to polymer (PEG 6000) ratios (b) 1:1, (c) 1:3, and (d) 1:5 in their (I) PM and (II) SD prepared by melting method.

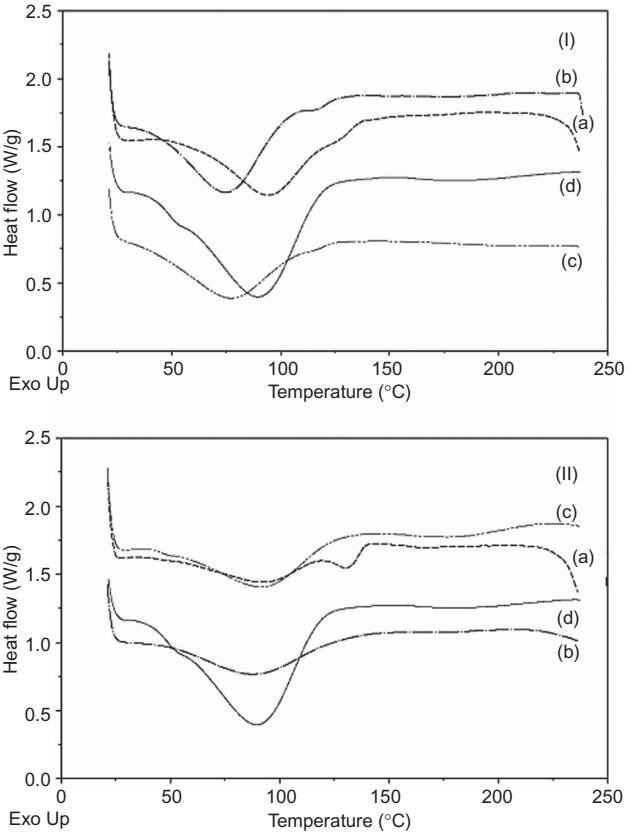

Figure 2. DSC curves for the drug (SIM) to polymer [(d) PVP K15] ratios (a) 1:1, (b) 1:3, and (c) 1:5 in their (I) PM and (II) SD prepared by solvent evaporation method.

drug endothermic peak. The absence of SIM melting endothermic in these samples may be due to either the solubility of the drug in PEG, during analysis in the pan, or to the presence of amorphous drug.

DSC curve obtained for SIM:PEG 1:5 SD prepared by MET/SVE method presented the same thermal profile as that of SIM:PEG 1:5 SD prepared by MET method. However, a very low enthalpy peak that shifts to lower temperature corresponding to drug melting was observed in the DSC curve of PM containing SIM and PVP in 1:1 and 1:3 ratios. No endothermic event corresponding to melted SIM was observed in the DSC curve of PM containing SIM and PVP 1:5 ratio (Figure 2I). Probably, the amount of SIM in PM containing SIM and PVP 1:5 is too small to observe a melting peak.

Considering the DSC curves of SIM : PVP SD (Figure 2II), the drug melting peak appeared in the SD 1:1 ratio only. The absence of drug peak in SIM:PVP SD 1:3 and 1:5 ratios indicates a possible drug phase transition into the amorphous state during SD preparation. This result was checked by XRPD studies.

XRPD analysis was performed to evaluate the crystallinity of the samples as well as a possible size reduction of the crystal particles.

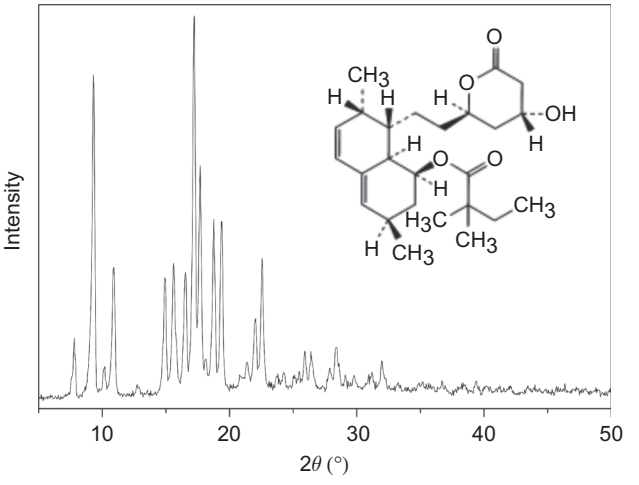

Figure 3. XRPD pattern of SIM (insert), a lactone.

The XRPD pattern of SIM (Figure 3) and PEG (Figure 4, bottom) exhibited well-defined diffraction peaks, characteristic of crystalline structures. In contrast, the XRPD pattern of PVP alone contained no peaks, which is consistent with an amorphous material (Figure 5, bottom).

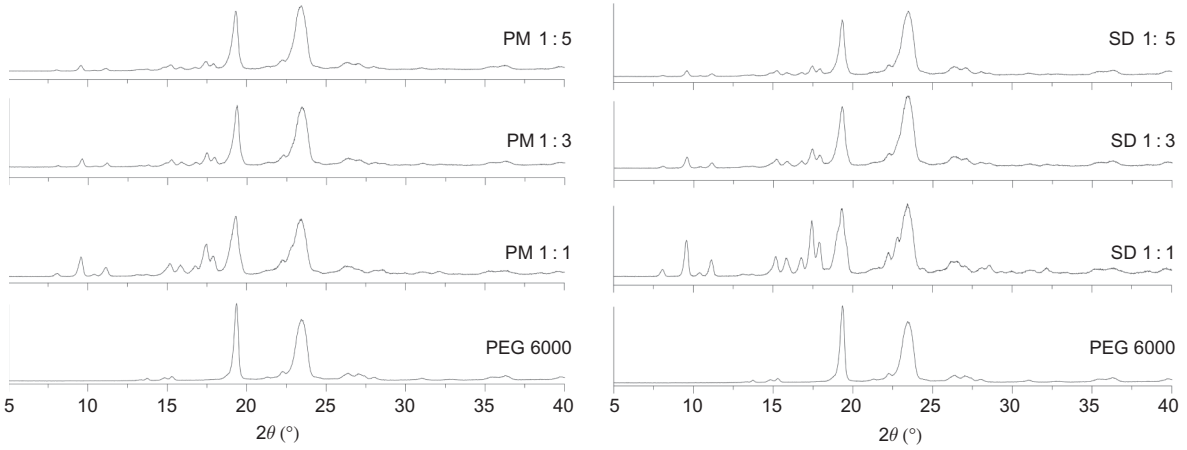

Figure 4. XRPD pattern for the drug to polymer (PEG 6000, bottom) ratios 1:1, 1:3, 1:5 in their (left) PM and (right) SD prepared by melting method.

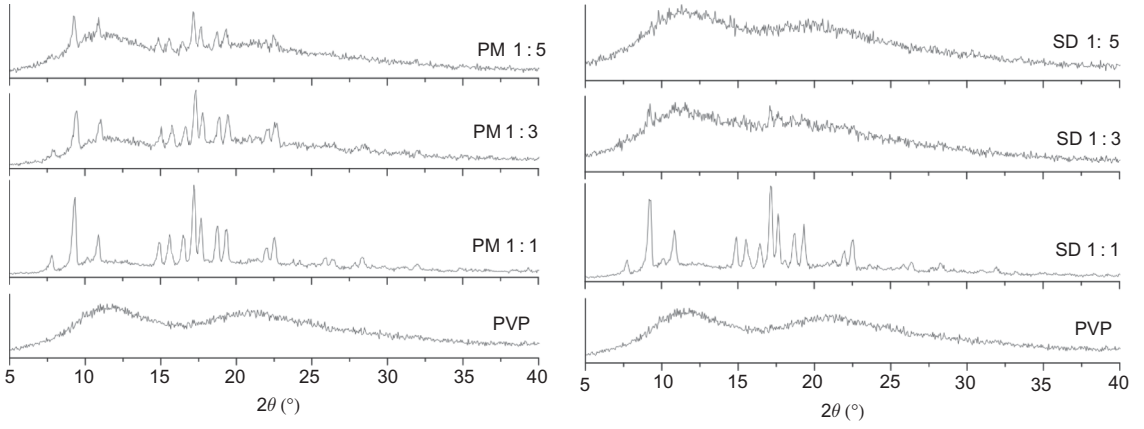

Figure 5. XRPD pattern for the drug to polymer (PVP K15, bottom) ratios 1:1, 1:3, and 1:5 in their (left) PM and (right) SD prepared by solvent evaporation method.

Comparison of XRPD pattern between PM and their corresponding SD containing SIM : PEG revealed that the drug remains crystalline in both systems and in all ratios (Figure 4). XRPD pattern obtained for SIM:PEG 1:5 SD prepared by the MET/SVE method is quite similar to that of SIM:PEG 1:5 SD prepared by the MET method. These results confirm that the absence of SIM melting peak in the DSC curves is due to its dissolution in the melted carrier. Diffraction peaks were investigated for drug particle size reduction; however, no peak width change was observed (results not shown).

XRPD pattern of PM containing SIM and PVP, in all ratios, presented characteristic peaks of drug indicating that SIM was present as a crystalline material in these samples (Figure 5). On the contrary, crystalline characteristic peaks were observed only in SIM:PVP SD 1:1 ratio. Peaks of very low intensity were observed in the diffractograms of SIM:PVP SD 1:3 ratio. No diffraction peaks were observed in the diffractograms of SIM:PVP SD 1:5 ratio. Such low-intensity drug peaks or the lack of crystalline peaks suggests that either a partial drug transformation into amorphous state, with drug entrapment in the polymeric matrix, may have occurred or SIM was present in the amorphous state. These results are consistent with those obtained by thermal analysis experiments.

Solubility study

The partial solubility of SIM alone determined by UV spectrophotometry, $\lambda = 239$ nm [$n = 6$, relative standard deviation (RSD) 2.76%], yielded a value of 3.03 μg/mL (in 1 hour, sextuplicate). The percentage increase in SIM release (triplicate) from PM or SD was determined in comparison to the drug.

Table 1. Percentage increase in SIM concentration release in phosphate buffer solution pH 7.40, after 1-hour solubility study.

	Increase of SIM (±SD) (%)			
	PEG 6000		PVP	
Statin : polymer ratio	PM	SD	PM	SD[a]
1 : 1	[b]	21.67[c] (0.06)	11.32 (0.03)	39.94 (0.003)
1 : 2	5.89 (0.01)	50.58[c] (0.02)	30.85 (0.01)	146.35 (0.05)
1 : 3	17.82 (0.03)	46.63[c] (0.04)	60.38 (0.03)	305.04 (0.03)
1 : 4	31.47 (0.06)	51.89[c] (0.05)	108.42 (0.08)	251.56 (0.11)
1 : 5	42.54 (0.06)	88.66[c] (0.07)[a] 147.51[d] (0.01)	52.13 (0.02)	273.31 (0.20)

[a]Solvent evaporation method, [b]not observed, [c]SD prepared by melting, [d]melting–solvent.

As shown in Table 1, the drug release from all SD was remarkably improved when compared to their corresponding PM or SIM itself. A direct relationship between PEG proportion and drug percentage dissolved from SD was observed. A significantly higher release was obtained for SIM:PEG 1:5 SD prepared by MET/SVE than for that prepared by the MET method. This is an evidence that a more homogeneous drug:carrier mixture was obtained by MET/SVE method.

Though XRPD results have not shown the presence of amorphous SIM but only of low-intensity peaks, drug release was significantly increased in the SIM:PEG SD 1:5 ratio prepared by the MET/SVE method. A better wettability and dispersibility of the drug by the carrier may be the main reason for the observed improvements.

SD prepared with PVP showed the highest improvement in the dissolution rate of SIM compared to the other dispersions. An increase of 305% in the dissolved statin concentration was observed (Table 1). Such increment can be explained by the presence of amorphous SIM, as indicated by XRPD and DSC experiments. SIM:PVP 1:3 SD showed the best results of all. Unlike SD containing PEG, the increase in PVP proportion (1:4 or 1:5) did not result in an increment of drug release.

Stability evaluation of SD

PM and SD containing SIM and PEG or PVP were analyzed by high-performance liquid chromatography to investigate the drug's chemical stability. No drug degradation products were detected in PM or SD containing PEG prepared by MET or MET/SVE methods (Figure 6a). This indicates that the drug remains stable at 58°C, during the time interval of preparation. In contrast, drug reduction and appearance of degradation products could be detected in the chromatograms obtained from samples of SIM:PVP SD (Figure 6b). The area ratio of the degradation products peaks to SIM, 6.81% and 10.46%, increased with the increase of PVP ratio, in 1 : 3 and 1:5 SD, respectively. However, degradation products peaks were not observed in the chromatograms of PM containing SIM and PVP.

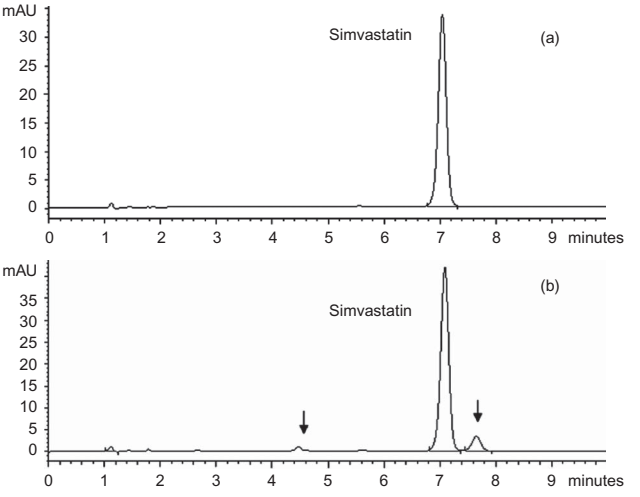

Figure 6. Chromatograms of (a) SIM:PEG 6000 1:5 SD prepared by melting–solvent method (SIM retention time t = 7.2 minutes; retention factor K = 6.9) and (b) SIM:PVP 1:5 SD (arrows show degradation products; t = 4.4 minutes, K = 3.8 and t = 7.6 minutes, K = 7.3). Conditions: SIM 28 μg/mL in acetonitrile, acetonitrile:phosphoric acid 65:35 mobile phase, 1.5 mL/min, λ 238 nm.

These results suggest that the combination of SIM with PVP in ethanol at 58°C favors drug degradation. Yang and Hwang[18] have reported the formation of less-polar degradation product for SIM and lovastatin, in stability studies of these statins. These studies were carried out at 45°C in alkaline medium with different amounts of methanol–water. According to the authors, the presence of degradation product is due to a methyl ester formed after the opening of the lactone ring. Based on these data, we assumed that the less polar product detected in our studies can be an ethyl ester of SIM. Therefore, the degradation reaction was favored by the presence of PVP. The formation of degradation products from SIM:PVP SD had not been previously reported[6,8]. This may have been due to the employment of UV spectrophotometric method used for SIM quantification in the formulations, a method not capable of distinguishing the drug from its degradation products.

Tablet formulation

Based on solubility study results and stability evaluation, SD SIM:PEG 1:5 prepared by MET/SVE method was selected for use in tablet formulation.

Physicochemical characteristics of the tablets were initially evaluated. The summary of weight determination, hardness test, friability, and disintegration time is presented in Table 2. The developed tablets met all test requirements according to the Brazilian Pharmacopeia[17].

SIM active ingredient was assayed and the uniformity of content in the tablet samples determined. The results of drug assay and uniformity of content are presented in Table 2. The tablets assay showed a drug content between 90.0% and 110.0% of the claimed value[19]. For the content uniformity, all samples met general specification for tablets (85.0–115.0%, RSD ≤ 6.0%)[20].

Dissolution profile of tablets

The dissolution investigation is to provide an estimate of the drug release from the dosage form. The second-derivative UV spectrophotometry, λ 248 nm, was used to quantify drug release in dissolution medium, because it eliminates the interference from UV-absorbing excipients. Dissolution studies were performed under sink conditions in a PBS pH 7.4 with 0.5% (w/v) SLS as similarly described in USP 32[19].

The drug release amounts obtained for dissolution profile study (Figure 7) of SIM:PEG 6000 1:5 SD tablets were 13.34% in 5 minutes, 23.51% in 10 minutes, 33.47% in 15 minutes, 49.73% in 30 minutes, 64.56% in 45 minutes, and 83.56% in 60 minutes.

It can be observed that the drug release rate from tablets is constant throughout the study period. The gradual release of SIM from developed tablets can be explained by the formation of a viscous solution because of the presence of a high molecular weight polymer (PEG 6000), as reported by Anguiano-Igea and collaborators[14]. The compaction process of powders to form tablets may have promoted effective interaction between the drug and carrier, which resulted in modulation of its release from the polymer matrix. According to FDA[21], for poorly water-soluble drugs (class 2, BCS), a two-point dissolution specification is recommended to characterize a dissolution range, which means one point at 15 minutes and another at a later point (30, 45, or 60 minutes) to ensure 85% dissolution and attest the quality of low-solubility solid dosage form. Typical compendial acceptance criteria (Q 75%) for the amount of drug dissolved should be added of 5%, as for its interpretation[19]. Therefore, a total of 80% drug release should be attested from the dosage form in 30 minutes. SIM:PEG 1:5 SD tablets release profile presented 49.73% SIM dissolved in 30 minutes and 83.56% in 60 minutes. Despite the slow dissolution rate of SIM:PEG 1:5 SD tablets, the amount released was greater than the minimum final quantity required (80%) according to USP 32[19] in 60 minutes. Hence, there is a great chance to meet the recommendations by FDA[21]. By few formulation adjustments or a larger sampling, it is possible to meet the requirements for drugs of class 2. In addition, gradual release can result in maintenance of the drug plasma level and guarantee larger administration interval therapy with a lower dose exposition and less side effects for the patients.

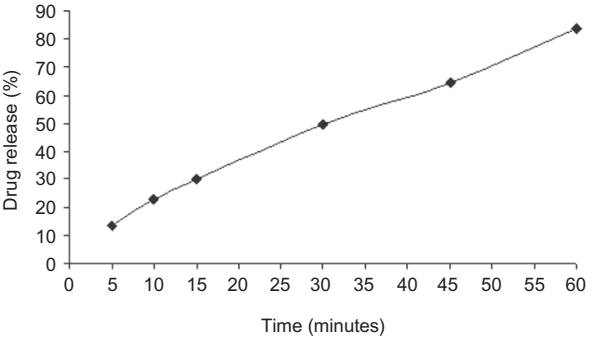

Figure 7. Dissolution profile of SIM:PEG 6000 1:5 SD tablets in phosphate buffer solution pH 7.4 with 0.5% (w/v) SLS.

Conclusions

SD are advantageous to increase dissolution of drugs of low solubility. However, appropriate ratios of drug to polymer, as well as their method of preparation, must

Table 2. Results for quality parameters of SIM : PEG 6000 1 : 5 SD tablets.

Tests	Specification[a]	Results
Weight determination	400 mg[b] ± 5.0% (n = 20)	411.2 mg (–2.69% to 4.46%)
Tablet breaking force	Min. 30 N (n = 10)	47–60 N
Disintegration time	Max. 30 minutes, water (n = 6)	Max. 5 minutes
Friability	Max. 1.5% (n = 20)	0.16%
Assay	90.0–110.0% (n = 6)	102.96%
Uniformity of content	85.0–115.0%; RSD[c] max. 6.0% (n = 10)	86.78–104.22%; 5.43%

[a]According to Brazilian Pharmacopeia[17,20], except the assay specification which was adapted from SIM tablets monograph[19], [b]theoretical mean weight, [c]relative standard deviation.

be investigated to yield significant drug solubility increase with no drug degradation. An SD blend method, MET/SVE, was proven to be more adequate than individual methods (MET or SVE) for SIM SD preparations.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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