

TABLETS CONTAINING MICROSPHERES OF EUDRAGIT E 100, POLY(3-HYDROXYBUTYRATE) AND SIMVASTATIN WITH IMPROVED DRUG DISSOLUTION RATE

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Received: 31 Jul 2013, Revised and Accepted: 07 Jan 2014

ABSTRACT

Objective: The aim of this study was to obtain tablets from microspheres composed of Eudragit E 100, poly(3-hydroxybutyrate) [PHB] and simvastatin with improved drug dissolution rate.

Methods: Eudragit E 100/PHB/simvastatin microspheres were prepared by the emulsion-solvent evaporation method and characterized using loading efficiency determination, scanning electron microscopy and dissolution test (basket apparatus, 100 rpm, 500 mL, 0.1 N HCl, pH 1.2, 37 ± 0.5 °C). Tablets were obtained from the Eudragit E 100/PHB/simvastatin microspheres, microcrystalline cellulose, Kollidon CL-SF and magnesium stearate by direct compression in lab and pilot scale and subjected to a dissolution study under the same conditions used for the microspheres. Tablets prepared in pilot scale, packaged in polyvinyl chloride/aluminum blisters, were stored in a climatic chamber (40 °C, 75% of relative humidity, 60 days) for a preliminary stability study.

Results: Eudragit E 100/PHB/simvastatin microparticles were spherical, porous, with high drug encapsulation (107.7% ± 5.5%), and released the drug rapidly (>95% dissolved in 15 min) when compared to the unencapsulated simvastatin. The rapid drug dissolution rate observed for the microspheres was maintained for tablets prepared in laboratory and pilot scales. Tablets submitted to a preliminary stability test showed decreased dissolution of simvastatin after 60 days of storage, which could be related to the physical instability of the solid dispersion system.

Conclusion: This study shows that tablets containing microspheres of solid simvastatin dispersed in Eudragit E 100 and PHB are promising to enhance the oral bioavailability of this drug.

Keywords: Tablets, Microspheres, Simvastatin, Solid dispersion, Dissolution rate.

INTRODUCTION

The oral route is the most convenient for drug administration mainly because of its practicality and patient compliance. Tablets remain the most commonly used pharmaceutical dosage form administered by oral route because of its ease of manufacturing, convenience in administration, accurate dosing, better stability compared with oral liquids, and because it is more tamper proof than capsules [1]. However, problems are associated with the low oral bioavailability of some poorly water-soluble drugs, such as simvastatin.

Simvastatin is a lipid reducing agent broadly used worldwide for the treatment of hypercholesterolemia as well as for minimizing the severity of chronic heart disease.

Simvastatin is a class II (low soluble and high permeable) drug according to Biopharmaceutics Classification System (BCS) which is poorly absorbed in the gastrointestinal tract because of its low water solubility [2]. Thus, it is important to enhance its dissolution rate and bioavailability from oral solid dosage forms [3].

Several strategies have been employed to improve the solubility of simvastatin and increase its dissolution rate in aqueous media including complexes of the drug with hydroxypropyl-β-cyclodextrin [4-5], mesocellular foam nanoparticles [6] and simvastatin lipid nanoparticles [7].

In a previous study, our research group developed microspheres containing a solid dispersion of simvastatin in Eudragit E 100 and poly(3-hydroxybutyrate) - PHB [8].

The results were very promising, indicating an increased drug dissolution rate when compared to the unencapsulated simvastatin. We concluded that the enhancement of the dissolution rate occurred mainly due to amorphization of the drug. In this context, the aim of this study was to obtain a final pharmaceutical dosage form containing Eudragit E 100/PHB/simvastatin microspheres in the

tablet form in order to enhance the dissolution rate of the drug. A preliminary study of the tablets stability was also carried out.

MATERIALS AND METHODS

Materials

The raw materials and their suppliers were: simvastatin (Henrifarma, São Paulo, Brazil), poly(vinyl alcohol)- PVA (Vetec, Rio de Janeiro, Brazil), Eudragit® E 100 (Röhm GmbH-Degussa-Hüls Gruppe, Darmstadt, Germany), poly(3-hydroxybutyrate)- PHB (PHB Industrial, Serrana, Brazil), microcrystalline cellulose PH-102 (Pharma Nostra, Rio de Janeiro, Brazil), Kollidon® CL-SF (BASF, São Paulo, Brazil) and magnesium stearate (Henrifarma, São Paulo, Brazil). U. S. Pharmacopeia primary standards of simvastatin and lovastatin were purchased from LAS Brazil (Aparecida de Goiânia, Brazil). All of the other chemicals were of analytical grade.

Preparation and characterization of microspheres

A new batch of Eudragit E 100/PHB/simvastatin microspheres were prepared by the emulsion-solvent evaporation method as previously described [8]. The drug (0.4 g) and the polymers (1.5 g of Eudragit E 100 and 0.25 g of PHB) were dissolved in 10 mL of dichloromethane and then slowly added to the aqueous phase (200 mL of 0.15% w/v PVA) under stirring at around 1000 rpm. The emulsion was kept under magnetic stirring at room temperature for 24 h until the complete evaporation of dichloromethane. The microspheres were washed three times with distilled water and dried in a lyophilizer (Terroni, Fauvel LT 1000, São Carlos, Brazil).

For the loading efficiency determination, an amount of microspheres equivalent to 5 mg of simvastatin was accurately weighed and then dissolved and diluted in dichloromethane to achieve a drug concentration of 10 mg L⁻¹. The solution was analyzed with a UV-Visible spectrophotometer (Shimadzu 1601 PC, Kyoto, Japan) at 240.5 nm and the drug content present in the microspheres was obtained from a calibration curve. Experiments were carried out in triplicate. The morphology of the microparticles was visualized by

scanning electron microscopy (SEM). Microparticles were mounted onto stubs using double-sided adhesive tape and coated with gold. Samples were analyzed under a Zeiss DSM 940 A scanning electron microscope (Oberkochen, Germany).

An *in vitro* dissolution study of simvastatin (5 mg) and the microspheres (equivalent to 5 mg of the drug), both encapsulated in hard gelatin capsules, was performed using the basket apparatus at 100 rpm and 500 mL of 0.1 N HCl, pH 1.2, at 37 ± 0.5 °C. At predetermined time intervals (5, 10, 15, 20 and 40 minutes) samples of the medium were taken, centrifuged and the drug concentration in the solution was determined using a UV-Visible spectrophotometer (Shimadzu 1601 PC, Kyoto, Japan) at 238.5 nm. Experiments were carried out in triplicate.

Tablet preparation and characterization

Tablets were obtained in laboratory scale by mixing simvastatin microspheres (22.4%), microcrystalline cellulose (71.6%), Kollidon CL-SF (5.0%) and magnesium stearate (1.0%). All the ingredients were mixed in the required amount to make tablets with a weight of 100 mg followed by direct compression in a hydraulic press (Protécni, Araraquara, Brazil) equipped with 9 mm punches. Tablets were obtained employing maximum compression forces of 2.5, 5, 10, 15 and 20 kN.

Tablets were also prepared in pilot scale by mixing simvastatin microspheres (22.4%), microcrystalline cellulose (71.6%), Kollidon CL-SF (5.0%) and magnesium stearate (1.0%) followed by direct compression in a rotary tablet press (Lawes 2000/14 PSC, São Paulo, Brazil) equipped with 7 mm concave punches. The tablet hardness was determined, in triplicate, in a hardness tester (Nova Ética, São Paulo, Brazil) and the tensile strength (TS) was calculated using equation 1.

$$TS = \frac{2F}{\pi dh} \quad (1)$$

Where F is the hardness, d is the tablet diameter and h is the tablet thickness.

The *in vitro* dissolution study of tablets was performed as described above for the microparticles.

Preliminary stability study

Tablets prepared in pilot scale, packaged in polyvinyl chloride (PVC)/aluminum blisters, were stored in a climatic chamber (Nova Ética, São Paulo, Brazil) at 40 °C with 75% of relative humidity for 60 days. Samples were collected after 0, 15, 30 and 60 days and subjected to an *in vitro* dissolution study (under the above-described conditions), using gas chromatography/mass spectrometry (GC/MS) for the quantification of the drug dissolution.

For the GC/MS analysis each sample was extracted with dichloromethane and 0.2 µL of the extract was injected into an Agilent 7890A GC instrument with an HP5 column (length 30 m, internal diameter 0.25 mm, film 0.25 µm) and helium as the carrier gas (1 mL min⁻¹). The GC/MS temperatures were as follows: injector 280 °C and column 40 °C to 310 °C. Finally, the mass spectrometer (Agilent 5975C) was programmed from m/z 30–450.

RESULTS

The micrographs of the Eudragit E 100/PHB/simvastatin microspheres are shown in Figure 1, revealing spherical microparticles, without aggregation, with pores on the external surface and an average size of 81 ± 29 µm (estimated from the micrographs considering 50 particles).

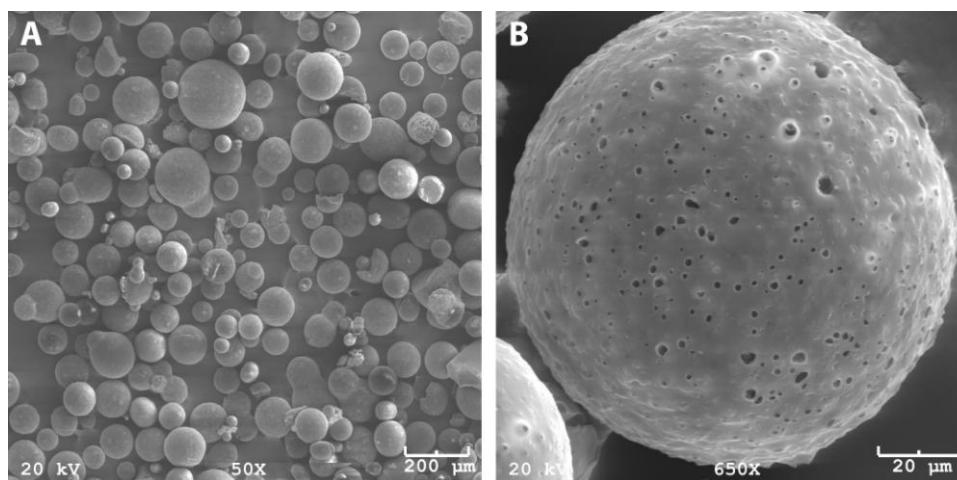


Fig. 1: Scanning electron micrographs of Eudragit E 100/PHB/simvastatin microspheres at 50 (A) and 650 (B) magnifications.

The value obtained for the loading efficiency ($107.7\% \pm 5.5\%$) indicated that the microencapsulation process led to efficient drug incorporation into the microspheres. In the dissolution profiles presented in Figure 2 it can be observed that over 95% of the simvastatin in the Eudragit E 100/PHB/simvastatin microspheres was dissolved within 15 min, this value being much higher than that of the unencapsulated drug (14.2% in the same time).

A minimum hardness of 30 N was obtained for the tablets prepared in laboratory scale applying only 2.5 kN of compression force, indicating suitable compactibility. The tensile strength of the tablets increased due to the increase in the maximum compression pressure applied, in the range of 2.5 to 15 kN. However, there was a decrease in the tensile strength of the tablets prepared at a maximum compaction pressure of 20 kN, as can be seen in Figure 3. The

dissolution profiles of the tablets prepared in laboratory and pilot scales (Figure 2) show over 95% of simvastatin dissolved after 15 min, as observed for the microspheres.

Figure 4 shows the dissolution profiles for the tablets prepared in pilot scale after 0, 15, 30 and 60 days during the preliminary stability study, indicating a significant decrease in the amount of drug dissolved after 60 days of storage.

In the GC/MS chromatograms (Figure 5) it can be observed that the primary standards of simvastatin and lovastatin have retention times of 20.9 and 20.5 min, respectively.

The simvastatin peak at 20.9 min is not observed in the chromatograms of the tablets stored for 0, 15 and 30 days, but it reappears after 60 days of storage.

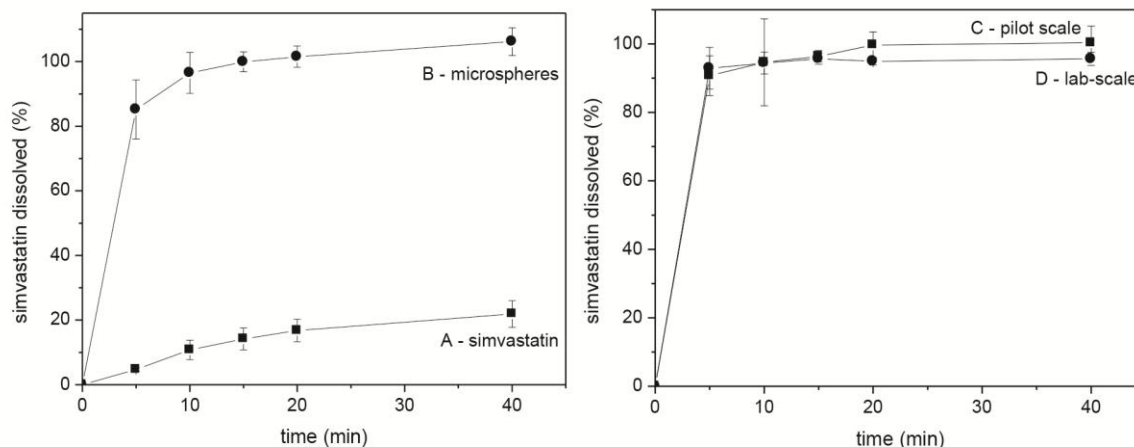


Fig. 2: Dissolution profiles for unencapsulated simvastatin (A), Eudragit E 100/PHB/simvastatin microspheres (B) and tablets containing Eudragit E 100/PHB/simvastatin microspheres prepared in pilot scale (C) and laboratory scale (D).

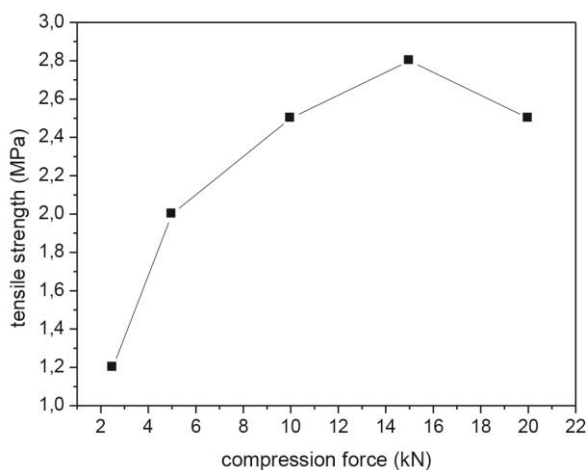


Fig. 3: Relation between tensile strength and maximum compression force for tablets containing Eudragit E 100/PHB/simvastatin microspheres prepared in laboratory scale.

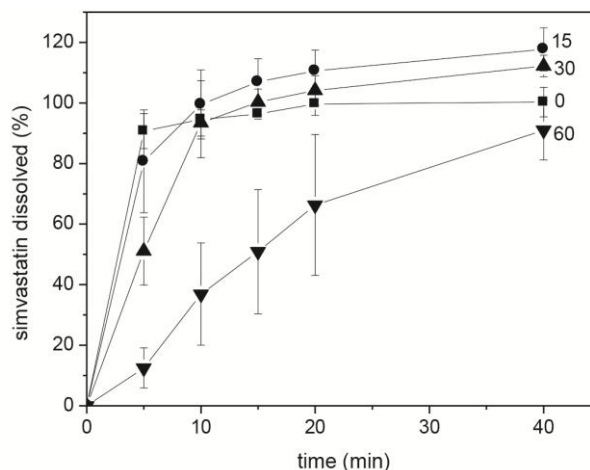


Fig. 4: Dissolution profiles for tablets containing Eudragit E 100/PHB/simvastatin microspheres prepared in pilot scale after 0, 15, 30 and 60 days of storage during the preliminary stability test.

DISCUSSION

The formulation and the process used to obtain the Eudragit E 100/PHB/simvastatin microspheres were optimized in a previous study conducted by our research group [8], except for the drying step, which was previously performed by evaporation at room temperature and in this study by lyophilization. The microspheres obtained in this study were spherical and showed no aggregation, with an average particle size approximately four times smaller than that of the original formulation. Another change observed in the micrographs was the presence of pores on the surface of the microspheres (Figure 1). This result was attributed to the use of a different drying process. As reported previously [8], we observed a conversion of simvastatin from the crystalline form to the amorphous form (results obtained by X-ray diffraction analysis and not shown herein), which occurred during the microencapsulation process due to the formation of a solid dispersion of the drug in the Eudragit E 100/PHB polymers. The amorphization of a drug during the microencapsulation procedure has also been observed in other studies [9-10].

The Eudragit E 100/PHB/simvastatin microspheres showed a rapid release of simvastatin in the first minutes of testing, far greater than that of the unencapsulated simvastatin (Figure 2), this result being very promising and consistent with the data previously obtained for the original formulation [8]. The

presence of an amorphous form of a drug in polymeric carriers may lead to improved solubility and dissolution rates when compared with the crystalline material [11]. Thus, this appears to be the main factor contributing to the increase in the simvastatin dissolution rate in the proposed system.

After successfully incorporating simvastatin into Eudragit E 100/PHB microspheres, this study aimed to obtain tablets as a final oral dosage form of simvastatin with improved dissolution, which may result in improved bioavailability.

Tablets containing the simvastatin microspheres were prepared in laboratory and pilot scales. In the former case they were prepared in a hydraulic press using different compression forces in order to evaluate the tensile strength, which is a measure of the bond strength between particles in the tablet and is related to the compactibility [12-13]. The tensile strength of the tablets increased with an increase in the maximum compression force, in the range of 2.5 to 15 kN.

However there was a decrease in the tensile strength of the tablets prepared at a maximum compression pressure of 20 kN (Figure 3). The increase in tensile strength initially observed was due to an increase in the contact points between the surfaces of the particles, generated during compression [13]. However, defects such as cracks and laminations can occur when the formulation is subjected to very high pressures, leading to reduced tensile strength [14].

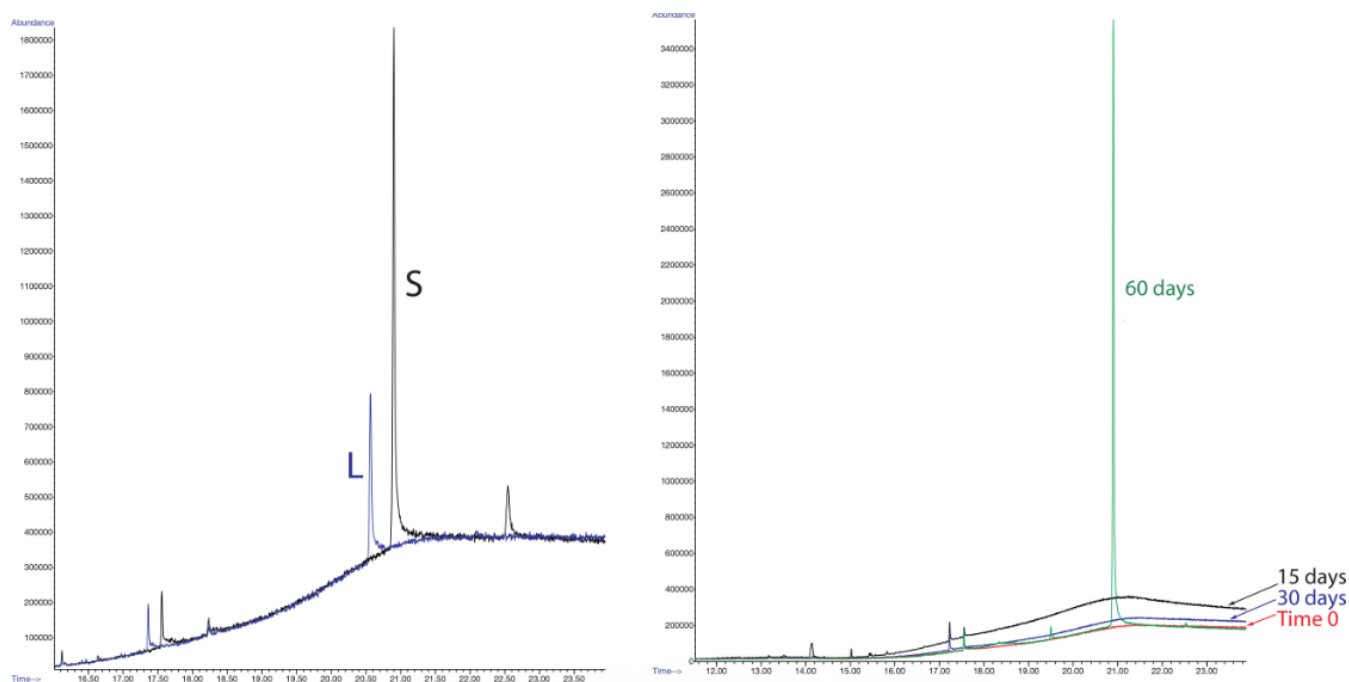


Fig. 5: GC/MS chromatograms for primary standards of simvastatin (S) and lovastatin (L) and tablets containing Eudragit E 100/PHB/simvastatin microspheres prepared in pilot scale after 0 (red), 15 (black), 30 (blue) and 60 (green) days of storage during the preliminary stability test.

The release profiles in Figure 2 show that the rapid release of simvastatin was maintained for the tablets, with more than 95% of the drug dissolved within 15 min. Furthermore, no difference was observed between the dissolution profiles of tablets prepared in laboratory and pilot scales. This result is better than those achieved with other systems described in the literature. Jun and co-workers [5] obtained tablets prepared with simvastatin- hydroxypropyl- β -cyclodextrin complexes, and 73.6% of the drug was dissolved after 10 min using phosphate buffer (pH 6.8) as the dissolution medium. Margulis-Goshen & Magdassi [15] obtained tablets prepared with simvastatin nanoparticles, with approximately 90% of drug dissolved in 20 min, using HCl (pH 1.2).

In order to evaluate the stability of the tablets during controlled storage conditions, a preliminary stability study was conducted. In the dissolution profiles for the tablets submitted to the stability test (Figure 4) a decrease in the dissolution rate of simvastatin can be observed after 60 days of storage, which could be related to the physical instability of the system. Recrystallization of the drug after a certain storage period is commonly observed for solid dispersions [16].

Therefore, the conversion of the amorphous form of simvastatin to the crystalline form, which is less soluble, may contribute to the decrease in the dissolution rate.

Furthermore, in the GC/MS chromatograms (Figure 5) the simvastatin peak was not observed for the tablets stored for 0, 15 and 30 days, suggesting the formation of a complex of the drug with the polymers employed in the preparation of the microparticles, which promotes the amorphization of the drug and the enhancement of the drug solubility. On the other hand, after 60 days this peak reappeared, suggesting that the simvastatin was no longer in the complexed form after this period. This may also be related to the decrease in the dissolution rate after this period which will be the subject of further investigation.

CONCLUSIONS

Tablets prepared with microspheres containing a solid dispersion of simvastatin in Eudragit E 100 and PHB represent a very promising system to enhance the bioavailability of this drug from an oral dosage form. A considerable enhancement in the simvastatin

dissolution rate was observed for the microspheres, compared to the unencapsulated drug, and this enhancement was maintained for the tablets. Stability and bioavailability studies are currently being conducted to complement these results.

ACKNOWLEDGEMENTS

The authors wish to thank Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação de Amparo à Pesquisa e Inovação do Estado de Santa Catarina (FAPESC) for the financial support and Prof. Theodoro Marcel Wagner for the GC/MS analysis.

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