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Research paper

Dissolution rate enhancement of the novel antitumoral β-lapachone by solvent change precipitation of microparticles

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Abstract

β-Lapachone [βLAP] is a novel antitumor drug, which was recently on clinical trials with promising preliminary results. Problems derived from its low water solubility, its instability in solution and its high therapeutic dose constitute some challenges for pharmaceutical researchers. The purpose of the present work is to enhance the limited dissolution rate of βLAP by the design of particles using a solvent change precipitation process. The procedure induces the spontaneous crystalline growth of the βLAP in the presence of a stabilizing polymer (Hydroxypropylmethylcellulose) that limits the size of the particles generated. Physicochemical characterization of microparticles and the βLAP dissolution rate was carried out. The utility of the βLAP microcrystals in the development of tablets with adequate dissolution properties was also stated. The procedure was optimized in order to obtain stable and homogeneous particles with a small mean particle size (~3 μm) and a narrow particle size distribution. There were no differences between the drying methods evaluated (in an oven and freeze-drying) with regard to particle morphology or dissolution behaviour, which is almost instantaneous. Tablets having suitable mechanical properties were produced by dry granulation prior to compression. The compression process did not compromise βLAP dissolution characteristics.

Keywords: β-Lapachone; Solvent change precipitation; Stabilizing agent; Dissolution rate; Tablets

1. Introduction

β-Lapachone [βLAP] is a novel drug with a promising biological activity against several diseases, outstanding its antineoplastic potential [1]. This molecule acts by an innovator mechanism based on a DNA checkpoint activation inducing apoptosis selectively in a broad range of cancer cells without causing the death of normal cells [2]. Currently, βLAP clinical trials are being carried out with encouraging preliminary results [3–5], especially those corresponding to the combinations with other antitumoral drugs such as taxol [6] or gemcitabine [7].

Despite the potential of βLAP as an anticancer drug, some problems have been derived from its poor water solubility, instability in solution and large therapeutic doses represent some challenges for pharmaceutical technology researchers [3,8]. Different approaches to the formation of inclusion complexes of βLAP with cyclodextrins have been tested in order to mitigate the problem associated to its low solubility ($0.03\ mg\ mL^{-1}$) [9,10] that would also have an effect on its bioavailability. However, the use of cyclodextrins means a high load excipient which is not the best approach when oral dosage forms including high doses are required (higher than 800 mg of βLAP were used for the clinical trials) [3,4]. Thus, research on βLAP particle design in order to improve drug dissolution rate is of a great interest.

Different authors have reported the techniques of obtaining microcrystals or submicro size particles or even amorphous particles with a controlled particle size

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distribution and polymorphic purity using solvent change precipitation [11–14]. The use of stabilizing agents improves the drug dissolution rates [15–18].

These approaches are advantageous against the traditional milling techniques. Jet-milling, milling in a pearl-ball mill or high-pressure homogenization frequently produce agglomerates due to the high energetic surfaces creating materials with poor wettability properties. Microcrystallization by precipitation permits homogeneous systems of small and non-cohesive particles of different poor water soluble drugs with enhanced dissolution properties to be obtained, such as carbamazepine [12], ibuprofen, ketoconazol or itraconazol [13,17,18].

On this basis, the aim of this study is to prepare and characterize enhanced dissolution βLAP particles by solvent change precipitation technique [SC]. An optimization of solvent change precipitation process with regard to solvent ratio and stabilizing agent concentration has been previously carried out. The utility of the βLAP microcrystals in the development of fast dissolving tablets will also be carried out.

2. Materials and methods

2.1. Materials

β-Lapachone [βLAP] (3,4-dihydro-2,2-dimethyl-2H-naphthol[1,2-*b*]pyran-5,6-dione; PM 242,3; batch L503) was supplied by Laboratorio Farmacêutico do Estado de Pernambuco/LAFEPE (Recife, Brazil). Purity estimated by DSC and HPLC is 99.9%.

Hydroxypropylmethylcellulose 100 LV Methocel Premium [HPMC] (batch NE04012N22), was furnished by Colorcon (Kent, UK), Microcrystalline cellulose PH 101 [MCC] (batch 9120562001) was supplied by Guinama (Valencia, Spain), and sodium stearyl fumarate [PRUV] (batch 142-01) was purchased from Juliá- Parrera S.A. (Barcelona, Spain). All solvents were of analytical grade.

2.2. Optimization of solvent change precipitation procedure [SC]

The solvent change precipitation was conducted by instantaneously mixing two liquids in the presence of a stabilizing agent as described by Gassmann and coworkers [11]. The organic phase was a βLAP ethanolic solution at 20 mg mL^{-1}, close to the saturation concentration. For the aqueous phase, a low viscosity HPMC was selected as a stabilizing agent based on Rasenack and Muller previous results [15].

The non-solvent (water) was poured rapidly from a beaker into the drug solution under stirring conditions using a magnetic stirrer. The process was carried out at room temperature. The effect of experimental variables on the yield of the precipitation techniques is extremely important as pointed out by Douroumis and Fahr [19]. Four different solvent ratios (organic: water) were tested, 1:2, 1:4, 1:9 and 1:19 in order to select the most appropriate to simultaneously achieve the smallest particles and the maximum yield of the process. For this experiment, a high concentration of HPMC (0.5%) was selected in order to avoid the stabilizing agent, concentration being a limiting factor. A second experiment was carried out using the selected solvent ratio and five different HPMC concentrations (0%, 0.01%, 0.05%, 0.1% and 0.5%) in order to estimate the minimum concentration of HPMC necessary to obtain the smallest stable drug particle size.

2.3. Crystallization procedure

βLAP crystals were obtained by pouring an aqueous solution of HPMC (0.05%) into a βLAP ethanolic solution (20 mg mL^{-1}) under stirring conditions at room temperature for approximately 2 min.

The aqueous microsuspension of βLAP was dried using two different methods; Freeze-drying in an apparatus Labconco (Labconco Corp., Kansas City, USA) by previous frozen microsuspension in liquid nitrogen and freeze dried for 48 h [SCL] and drying in an oven at 40 ± 2 °C for 2 h previous filtration through a nylon membrane (0.22 μm) [SCE].

2.4. Product characterization

2.4.1. Drug content

A UV spectrophotometric method was developed for quantitative βLAP determination using an UV–visible spectrophotometer Agilent 8453 (Agilent Corp., Santa Clara, USA) with photodiode array detector at 257 nm. Calibration curve in water/ethanol (1:1 v/v) was made using standard solutions in the range of 2–10 μg mL^{-1}. No effect of HPMC addition on the UV spectrum of βLAP solution was verified.

The chemical stability of βLAP was performed on a high performance liquid chromatograph, Waters M600, equipped with a C18 cartridge column (125 mm × 45 mm × 5 μm) (Waters, Milford, USA) using in the mobile phase a mixture of methanol/water 65% (v/v). The isocratic flow rate was 1 mL min^{-1} at room temperature. The injection volume was 20 μL. Chromatographic detection was set at 253 nm with a photodiode array detector. The mobile phase and samples were filtered using a 0.45 μm nylon membrane (Waters, Milford, USA) [20].

2.4.2. Particle morphology

Optical morphological characteristics of samples were analysed using an Olympus SZ60 (Opelco, Tokyo, Japan) microscope connected to a videocamera Olympus DP12 (Opelco, Tokyo, Japan). Particle surface morphologies were also examined using Scanning Electron Microscopy [SEM] LEO-435VP (Leica Microsystems, Cambridge, UK) fixed on a brass stub using double-sided tape and were gold coated in vacuum.

2.4.3. Particle size

Particle size distribution of microsuspensions was analysed using equipment Coulter Counter Multisizer II (Beckman Coulter, High Wycombe, UK) using Isoton II® and fitted with tube analysis of aperture size of 30 μm. The mean equivalent diameter and standard deviation of the reference particle size distributions were estimated by probit transformation.

2.4.4. X-ray powder diffractometry [XRPD]

The X-ray powder diffraction patterns were collected using Copper radiation (40 kv, 30 mA), on a Philips PW 1729 diffractometer (Philips Corp., Netherlands) with Bragg–Brentano geometry, in the $2 < 2\theta < 60$ range with a step size of $0.02°2\theta$ and counting time of 2 s per step. Indexation was carried out using LeBail fit [21] by the program Riatica® (IUCR Powder Diffraction 22,21/1997) which permits the calculation of the crystal data; cell parameters (a, b and c), cell angles (α, β and γ) and cell volume, and the theoretical density.

2.4.5. Differential scanning calorimetry [DSC]

Samples weighing 2–3 mg were placed in open aluminium pans and heated from 30 to 250 °C at a rate of 10 °C min^{-1} using a temperature modulated DSC Q100 calorimeter (TA Instruments, New Castle, USA). Nitrogen was used as a purge gas at a flux rate of 50 mL min^{-1}. The calibration of temperature and heat flow was performed with standard indium samples. All measurements were carried out in duplicate.

2.5. Tablets preparation

The mixtures of 52% of SCE (approx. 50 mg βLAP), 47% of MCC and 1% of PRUV were blended in a Turbula T2 C mixer (WA Bachfen AG, Basel, Switzerland) for 15 min at 30 rpm. Tablets of 100 mg were produced by dry granulation prior to compression. The slugs (300 mg) were elaborated using an instrumentalized Bonals modelo B tipo MT (Barcelona, Spain) eccentric press fitted with 12 mm diameter flat Teflon® punches at a compaction force of 700 N. The slugs were broken in a mortar, sieved through 450 μm and compressed in the tablet machine fitted with 6 mm flat punches at a compression force of 1500 N.

2.6. Characterization of tablets

Formulation samples were subjected to the following tests:

Dimensions: The thickness and the diameter of six tablets were determined with a digital calibrator (Mitutoyo Corp., Tokyo, Japan) with 0–25 mm range and 0.001 mm sensibility.

Weight: The weights of 20 tablets were determined individually, and the mean weight and coefficient of weight variation were calculated.

Tensile strength (TS): The crushing strengths of six tablets were obtained using an Erweka TB2A apparatus (Heusenstamm, Germany), and the tensile strength was determined from the equation [22]:

$$TS = 2CS/\pi \cdot D \cdot E, \quad (1)$$

where CS is the crushing strength, D denotes the diameter and E is its thickness.

Friability: Weight loss through friability was determined for 10 tablets after 100 rev in an Erweka TAP (Erweka, Heusenstamm, Germany) apparatus at 25 rpm.

Disintegration time: The disintegration times of six tablets were measured individually in water in an apparatus Turu Grau DT-1 (Barcelona, Spain) fulfilling the USP specifications.

2.7. Powder and tablets dissolution testing

Dissolution studies were carried out following FDA specifications for poor soluble drugs using a USP dissolution apparatus 2 (paddle) (Turu Grau DT-6, Barcelona, Spain) at 75 rpm and 37 °C (±0.5 °C). In order to ensure sink conditions and increase the ability of the dissolution test to distinguish between formulations, the solubility of βLAP in water containing surfactants was tested. An aqueous solution volume of 900 mL containing sodium lauryl sulphate at a concentration of 0.5% was selected as a dissolution medium.

βLAP samples of 50 mg or equivalent amounts of each system (powder microparticles or tablets) were tested in triplicate. Microparticles samples were submerged rapidly in the medium. At required time intervals the samples were collected, filtered through cellulose filters and the concentration of the dissolved drug was determined spectrophotometrically. The dissolution profiles were evaluated and compared using the dissolution efficiency at 15 and 30 min parameter, which was calculated from the area under the dissolution curve at time using the trapezoidal rule and expressed as a percentage of the area of the rectangle described by 100% dissolution at the same time [23].

3. Results and discussion

Table 1 shows mean particle diameters of approximately 3 μm and below when precipitated in the presence of HPMC stabilizing agent. A normal and narrow drug particle size distribution was obtained for the different ethanol/water ratios tested with all particles lower than 6 μm. This means that there is a dramatic reduction in the particle size when compared with the mean geometric particle diameters of βLAP as supplied which presents 122.1 μm and geometric standard deviation of 2.16. There are no significant differences between the 0 and 24 h after precipitation, meaning that HPMC is able to protect βLAP microparticles from growth.

No important disparity was achieved in particle size values among the different methods. The selection of optimum

Table 1
Mean particle size of micronized βLAP prepared using different ethanol/water ratios and the percentage of drug lost in the process

EtOH/ water ratio v/v	Mean particle diameter (μm)		Drug loss %
	$T = 0$ h	$T = 24$ h	
1:2	2.34 (1.24)	2.48 (1.86)	6.87 (1.21)
1:4	**2.55 (1.76)**	**2.99 (1.60)**	**3.55 (0.20)**
1:9	2.70 (1.80)	2.75 (2.02)	3.84 (0.17)
1:19	2.87 (2.03)	2.47 (2.18)	6.01 (0.23)

Standard deviations in parentheses. Process with maximum yield in bold type.

ethanol/water ratio was based on the differences in the percentage of the precipitated drug, the maximum process yield being at a solvent ratio 1:4 (Table 1). An ethanol/water ratio of 1:2 entails a little efficient polarity change whereas a 1:9 ratio means the use of a high aqueous phase volume that solubilizes a βLAP fraction.

The importance of using HPMC as a stabilizer can be derived from Table 2 that presents the mean diameter of βLAP particles precipitated using different concentrations of stabilizing agent after 24 h storage. The minimum necessary HPMC concentration to obtain small and stable size particles of βLAP was 0.05%, below this concentration the particle growth occurs.

βLAP particles produced by micronization without HPMC have a bigger size and broader particle size distribution which increases in size during the first 24 h after precipitation (Fig. 1), whereas the system with the stabilizer HPMC stops the molecular association and the crystal growth instantaneously at the moment of solvent change, which is in agreement with other authors' reports [17,18].

HPMC is a cellulose ether which is water soluble. It has been shown that cellulose ethers show surface activity, especially derivatives with methoxyl and hydroxypropyl groups making it suitable to be adsorbed onto hydrophobic solid surfaces as the newly created βLAP ones [24]. The interaction in the solid–liquid interface produces stable βLAP particles with narrow particle size distributions. The concentration of the stabilizing agent has a great effect on the resulting particle size, probably as a consequence of the variations in the viscosity of the precipitating liquid as it has been pointed out previously [17].

Crystallization was carried out employing the solvent change method using HPMC at 0.05% as the stabilizing agent and a solvent ethanol/water ratio 1:4. Fluffy powders

Table 2
Mean particle size of micronized βLAP prepared using different HPMC concentrations

HPMC %	Mean diameter μm after 24 h
0	8.77 (12.1)
0.01	**4.53 (3.6)**
0.05	**2.22 (2.6)**
0.01	2.90 (1.6)
0.5	2.20 (2.1)

Standard deviations in parentheses.

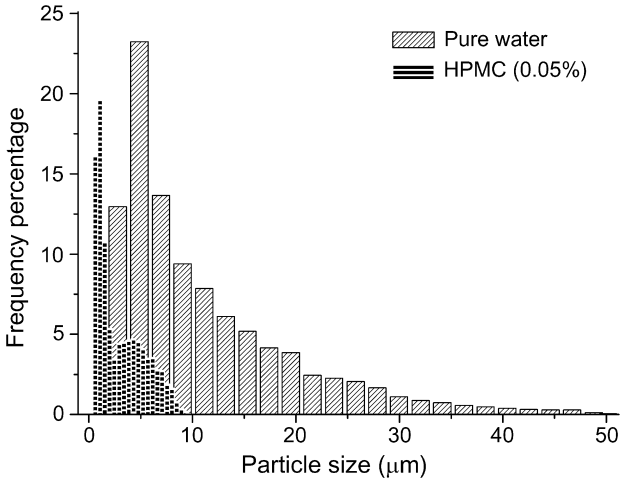

Fig. 1. Particle size distribution of βLAP 24 h after precipitation with and without 0.05% HPMC.

were obtained by the two drying methods used, drying in an oven (SCE) and freeze-drying the microsuspension system (SCL). SEM photographs (Fig. 2) show homogeneous acicular crystals similar to the original βLAP particles in shape but smaller in size and thickness for both the SC samples. No important differences in the SC crystals were observed between the drying methods.

This technique allowed micronized βLAP particles with a minimum amount of excipient to be produced. The resulting drug load in the dried powder was 95% and 85% for the SCE and SCL, respectively, which is specially advantageous in order to produce solid dosage forms containing βLAP, that require a large therapeutic dose.

Fig. 3 shows XRPD patterns of βLAP, that exhibit a main sharp peak at 9.5 °2θ and other secondary peaks at 13.05, 19.05, 19.59, 24.67 and 39.31 °2θ, HPMC with an amorphous pattern, and SC samples. Apparently, some marked changes can be appreciated in SC samples compared with their individual components. New peaks and changes in the relative intensity of some peaks are observed. This fact, together with a slight shift in the drug melting peak observed by DSC thermograms from 157.4 to 156.5 °C (Fig. 4), suggests a change in the crystalline phase of the drug.

A deeper analysis of SC samples crystallinity was carried out by indexation XRPD dates compared with βLAP single crystal data [25]. These results (Table 3) allow us to state that both SCE and SCL crystals are not new crystalline entities or polymorphs, but keep the same orthorhombic crystallinity phase of original βLAP. The chemical stability of βLAP was also evaluated by HPLC. No evidence of decomposition was observed after the SC process.

The SC micronized βLAP powders show a dramatic enhancement in dissolution rate as illustrated in Fig. 5, the dissolution process being completed within the first 5 min, compared to the drug as supplied and the granulometric fraction selected (50–100 μm). This effect can be explained by the dramatic reduction in the particle size

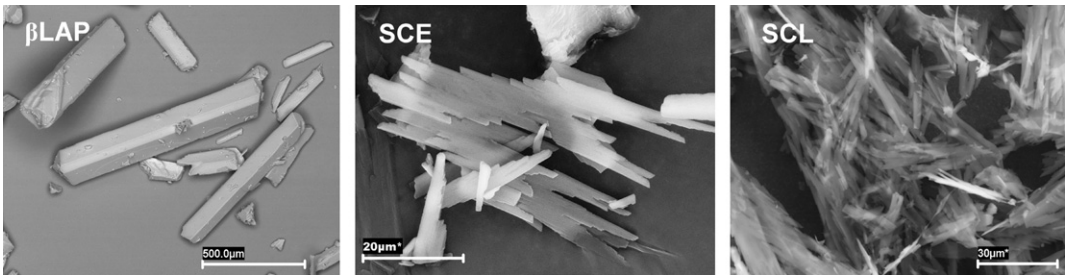

Fig. 2. SEM photographs of βLAP as supplied and SC samples.

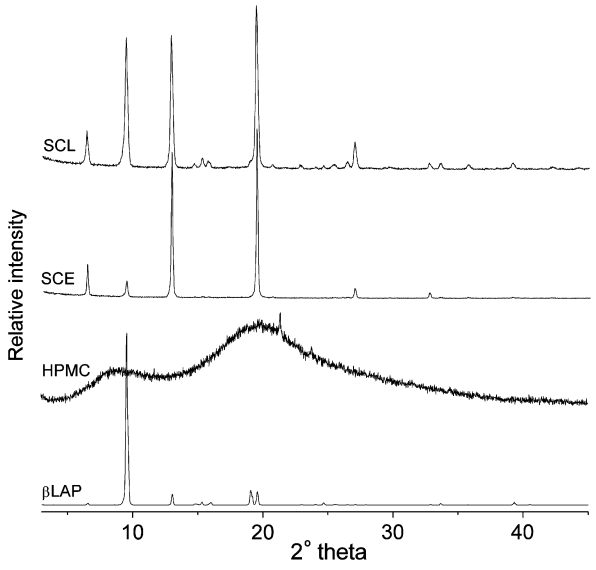

Fig. 3. XRPD of βLAP, HPMC and SC samples.

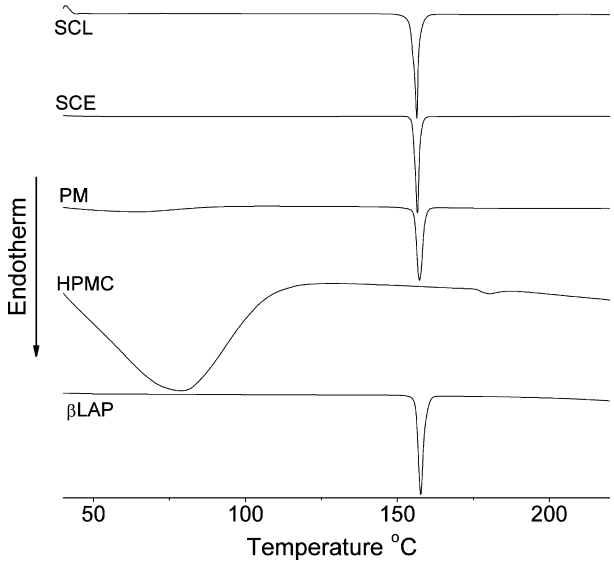

Fig. 4. DSC of βLAP, HPMC, 1:1 physical mixture (PM) and SC samples.

and as a consequence the increment in the surface area, which is additionally hydrophilized by the adsorbed hydrophilic polymer. Moreover, the natural crystalline growth creates particles with no electrostatic charge and with better wettability properties [13].

No differences among drying methods were found with regard to the dissolution profiles (Table 4); therefore, the

Table 3
Indexation data from XRPD results

Crystal data	Orthorombic		
	βLAP as supplied	PCE	PCL
Cell parameters (Å)			
a	12.80	12.77	12.76
b	7.04	7.06	7.04
c	27.27	27.32	27.29
Cell angles (°)			
α	90	90	90
β	90	90	90
γ	90	90	90
Z	8	8	8
Cell volume ($Å^3$)	2458.1	2462.3	2449.3
Density ($g\ mL^{-1}$)	1.31	1.31	1.31

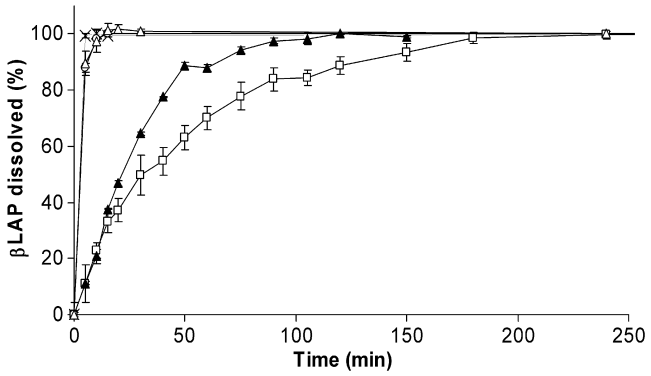

Fig. 5. Dissolution profiles of βLAP (□) as supplied and (▲) mechanically micronized (50–100 μm); (○) SCL powder and SCE (x) powder and (Δ) tablet containing SCE, in sink conditions.

Table 4
Mean values of the dissolution efficiency at 15 and 30 min

Samples	Dissolution efficiency (%)	
	15 min	30 min
$\beta lap_{as\ supplied}$	16.7 (0.2)	28.5 (0.9)
$\beta lap_{micronized}$	16.9 (0.1)	34.1 (0.2)
SCE	84.0 (0.6)	92.0 (0.4)
SCL	78.0 (1.9)	89.6 (1.0)
SCE_{tablet}	79.2 (1.5)	90.8 (0.9)

Standard deviations in parentheses.

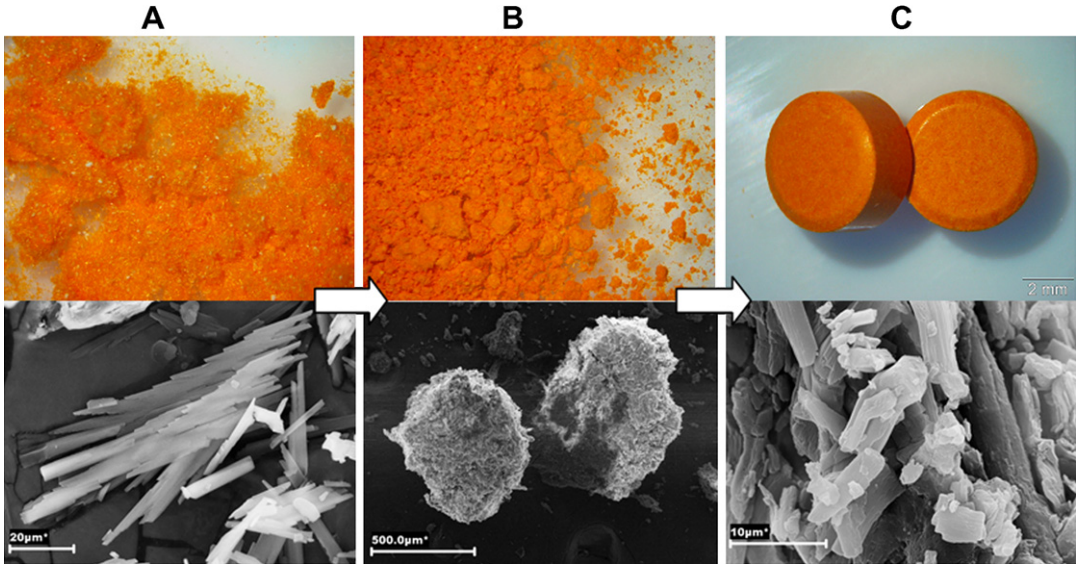

Fig. 6. SEM and optical micrographs of SCE βLAP microcrystals (A), granules by dry granulation (B) and tablets containing SCE (C).

SCE was selected to develop solid dosage forms. Filtering and drying in an oven at 40 °C is simpler and cheaper than the other proposed methods such as freeze-drying or spray drying [12,15].

The compression behaviour of this kind of microparticles was evaluated for the first time. The low densities of blends obtained by SC technique, together with their deficient flow properties, made the direct volumetric filling of the dies to obtain 100 mg tablets impossible. Dry granulation using low pressure to produce the slugs helps in increasing the particle size and the density of the mixture and improves flow properties [26] (Fig. 6). The tablets produced have a glossy surface (Fig. 6), no friability (0%), adequate tensile strength (1.96 MPa) and a disintegration time lower than 1 min. When MCC is used in a direct compression or a dry granulation prior to compression process, it acts as a diluent and also as a disintegrant having the tablets excellent mechanical properties and short disintegration times [27].

Regarding the drug dissolution profiles (Fig. 5 and Table 4), no statistically significant differences were found between the microcrystalline powders (SCE, SCL) and the tablets as these can be derived from their dissolution efficiency values at 15 and 30 min. The compression process does not deteriorate the excellent dissolution behaviour of βLAP particles obtained by the SC technique, demonstrated by the high values in dissolution efficiency for the tablet formulation at 30 min.

4. Conclusions

By the method used in this study, small βLAP particles have been prepared by controlled crystallization of the original molecularly dispersed drug, avoiding the critical effects resulting from milling processes, such as instability, agglomeration or electrostatic behaviour. As the production process can be carried out continuously, a scale-up process could be performed easily. From our experiments, the optimal conditions for producing βLAP particles by solvent change precipitation process include a solvent ratio (ethanol/water) 1:4 and a minimum concentration of HPMC equal to 0.05%. No differences between microcrystal characteristics have been found with regard to the drying methods studied, the use of the oven being cheaper and easier to the scale-up process.

SC βLAP microparticles are crystalline with a narrow particle size distribution, small mean particle size and an enhanced drug dissolution rate. Compared to other technological approaches to increase βLAP solubility as cyclodextrin inclusion complex, the amount of drug in the preparation is much higher (∼90%) and as a consequence the SC technique is more suitable in developing oral solid dosage forms.

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