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Original article

Liquisolid pellets: A pharmaceutical technology strategy to improve the dissolution rate of ritonavir

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ABSTRACT

Liquisolid pellets (LPs) prepared by extrusion-spheronization are promising delivery systems to improve the dissolution rate of poorly water-soluble drugs. However, developing LPs for high dose drugs (e.g. antiretroviral ritonavir, RTV) is a major challenge due to technical and quality constraints. In this study, formulations LP1 and LP2 were obtained (RTV 100 mg/unit dose) using microcrystalline cellulose (carrier), Kollidon® CL-SF (coating and disintegrating material) and high load (30%, w/w) of Kolliphor® EL or PEG 400 (non-volatile solvent). LP1 and LP2 had narrow size distribution, good morphological properties, and excellent flowability. The partial conversion of RTV polymorph I to the less soluble form II occurred during the preparation of the liquid medications. LP1 (containing Kolliphor® EL) achieved 82.64 ± 2.17% of drug dissolved in 30 min (Q_{30min}), compared with 53.14 ± 0.6% and 42.42 ± 2.09% for LP2 (containing PEG 400) and Norvir® tablets, respectively. Also, LP1 promoted 1.9-fold/1.7-fold and 8.19-fold/8.29-fold increases in Q_{30min}/DE_{60min} (dissolution efficiency) as compared to neat RTV polymorphs I and II, respectively.
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1. Introduction

The physicochemical properties of drugs, such as water solubility and dissolution rate, directly influence the bioavailability and, hence, the efficacy of pharmaceutical products. Around 75% of the new drug candidates are poorly water-soluble (Di et al., 2012), therefore, there is great interest in developing techniques to improve the solubility and the dissolution rate of drugs (Kawabata et al., 2011).

Liquisolid technology is a very promising alternative to achieve fast and complete drug dissolution, with several advantages as compared to other techniques targeting at the same purpose (e.g., transformation into soluble polymorph or amorphization, solid dispersion, nanosuspension, complex formation). It is a simple, cost-effective method with great potential for industrial production (Nokhodchi et al., 2011; Spireas and Bolton, 1998).

The classic theory on liquisolid systems defines them as acceptably flowing and compressible powdered forms of liquid medications. The liquid medication is a drug solution or dispersion in a non-volatile solvent (e.g. liquid polyethylene glycols and polysorbates), which is incorporated into solid excipients, named carrier (e.g. microcrystalline cellulose) and coating material (e.g. amorphous silicon dioxide). The final dosage form is produced by converting the liquisolid formulation into capsules or tablets (liquisolid compacts), with the addition of extra excipients (e.g. disintegrant and lubricant) if necessary (Nokhodchi et al., 2011; Spireas et al., 1998; Spireas and Sadu, 1998).

Liquisolid pellets (LPs) have been proposed by our group as an improvement and expansion of the liquisolid technology, showing excellent drug dissolution performance due to the liquisolid microenvironment effect combined with good disintegrating properties and large surface area in contact with the dissolution medium (Pezzini et al., 2016). In addition, LPs have the inherent benefits of multiparticulate systems over single-unit dosage forms, such as the better distribution along the gastrointestinal tract (increasing drug bioavailability, lowering local drug concentration, and reducing side-effects and inter/intra individual variations on

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bioavailability), the easy adjustment in the dosage unit strength, and the possibility of simultaneous administration of incompatible drugs (Abdul et al., 2010).

Given the LPs innovative character, supplementary scientific studies are missing for the full development of the technology. The present study aimed at investigating two new aspects relevant for the successful adoption of LPs as new drug delivery systems: (a) the feasibility of incorporating high doses of poorly water-soluble drugs and (b) the use of high loads of non-volatile solvent; both while maintaining satisfactory technological and dissolution properties.

Ritonavir (RTV) is an antiretroviral drug approved by the Food and Drug Administration (FDA) in 1996 for the treatment of the human immunodeficiency virus (HIV) infection under the trade name Norvir®. It is a high dose and low solubility drug, categorized as either class II (Chowdary et al., 2012; Sinha et al., 2010; Tho et al., 2010) or IV of the Biopharmaceutics Classification System (Dengale et al., 2015). RTV shows polymorphism, which led to the temporary withdrawal of Norvir® from the market in 1998 due to dissolution problems and demanded the reformulation of the product (Chadha et al., 2013).

The great therapeutic relevance of RTV and the challenges posed by its physicochemical properties make it an interesting model to study the impact of manufacturing and composition on critical quality attributes of LPs. For obtaining the formulations, microcrystalline cellulose was used as a carrier; polyethylene glycol 400 (hydrophilic polymer), Tween 80 and Kolliphor® EL (surfactant agents) were tested as non-volatile solvents; and crospovidone was used as a new coating material recently introduced by our group (Anzilaggo et al., 2019; Pezzini et al., 2016).

2. Materials and methods

2.1. Materials

RTV polymorphs I and II were donated by Cristália (Brazil). Microcel® MC-101 (microcrystalline cellulose 101) was obtained from Blanver Farmoquímica (Brazil). Tween 80 (polysorbate 80) was purchased from Via Farma (Brazil). Kollidon® CL-SF (crospovidone) was donated by BASF (Germany). Kolliphor® EL (macrogolglycerol ricinoleate, viscosity of 650 to 800 mPa.s at 25 °C) was purchased from Sigma-Aldrich (Brazil). Polyethylene glycol (PEG 400, viscosity of ~100 mPa.s at 25 °C) was purchased from Vetec - Química Fina (Brazil). Norvir® (RTV 100 mg) tablets (batch number 1040149) were manufactured by AbbVie Deutschland GmbH & Co. KG (Germany) and imported by Abbott Laboratórios do Brasil Ltda. (Brazil). All reagents and solvents were of analytical or high-performance liquid chromatography (HPLC) grade.

2.2. Apparent solubility

The apparent solubility of RTV (polymorph I) was determined in Tween 80, Kolliphor® EL and PEG 400 (n = 3). Dispersions were prepared by adding an excessive amount of RTV in each solvent and agitating at 60 rpm for 72 h at 37 °C. Supernatants were centrifuged at 3000 rpm for 30 min and diluted volumetrically (4 mg mL^{-1}) with methanol:water (67:33 v/v). RTV was quantified by HPLC (Shimadzu, Japan), at room temperature, using a Phenomenex® Luna C18(2) reversed phase column (5 μm, 150 × 4.6 mm, 100 Å) with a Phenomenex® Universal C18 guard column. Mobile phase consisted of methanol:water (67:33, v/v). Flow-rate was 1 mL min^{-1} and the injection volume was 20 μL. RTV was detected by ultraviolet absorption at 210 nm and quantified using a regression curve ($r^2 = 1$). Data acquisition (n = 3) and calculations were performed using the CLASS-VP software (Shimadzu, Japan).

2.3. Preparation of liquisolid and conventional pellets

Conventional (CP1, CP2) and liquisolid (LP1, LP2) pellets of RTV (Table 1) were obtained by extrusion-spheronization (Fig. 1). The liquid medications were prepared by dispersing RTV (polymorph I) at 1:2 w/w ratio in the non-volatile solvent (Kolliphor® EL or PEG 400) using mortar and pestle for 5 min. Microcrystalline cellulose was added to the liquid medication as the carrier and to act as filler and binder for the extrusion-spheronization process. After complete incorporation of the liquid medication to the carrier, crospovidone (Kollidon® CL-SF) was added as both disintegrating agent and coating material, giving a dry aspect to the powder. The liquisolid mixture was slowly wetted with purified water until adequate plasticity for extrusion-spheronization was achieved. The wet mass was transferred to a screen extruder (Extruder 20, Caleva Ltd., England) and immediately extruded through a perforated screen of 1.0 mm diameter at a constant speed of 16 rpm. Extrudates were transferred to a spheronizer (Spheronizer 120, Caleva, England) equipped with a 3.0 mm square pitch cross-hatched friction plate and spheronized at 1000 rpm for enough time to obtain visually round pellets. CP1 and CP2 were obtained (for comparison purposes) using similar procedure but without dispersing the drug in a non-volatile solvent. After spheronization, pellets were dried in a fluid bed equipment (Mycrolab, Huttlin, Germany) for 15 min (batch size 50 g; air flow 15 m^3/h; inlet air temperature 60 °C).

2.4. Particle size distribution

The particle size distribution was evaluated by a sieving method, using sieves with screen sizes of 355, 500, 600, 850, 1180 and 1400 μm. The 850–1180 μm fraction of pellets (designated as usable fraction) was separated from each formulation and selected for further characterization to reduce the effect of distinct particle size profiles on the results obtained. The yield (%, w/w) of the usable fraction was calculated for all formulations.

2.5. Bulk (ρb) and tapped (ρt) densities, carr's index (CI), Hausner ratio (HR), and aspect ratio (AR)

The ρb, ρt, CI, HR, and AR data were obtained for the usable fraction of each formulation (n = 3). The ρb was

Table 1
Compositions of conventional (CP1 and CP2) and liquisolid (LP1 and LP2) pellets of RTV.

Components	Composition (g)			
	CP1	CP2	LP1	LP2
RTV (form I polymorph)	15	15	15	15
Kolliphor® EL	–	–	30	–
PEG 400	–	–	–	30
Microcrystalline cellulose	85	55	25	25
Crospovidone	–	30	30	30
Water*	62.50	65.97	63.47	36.78

* Water (g) required to achieve adequate plasticity for extrusion-spheronization.

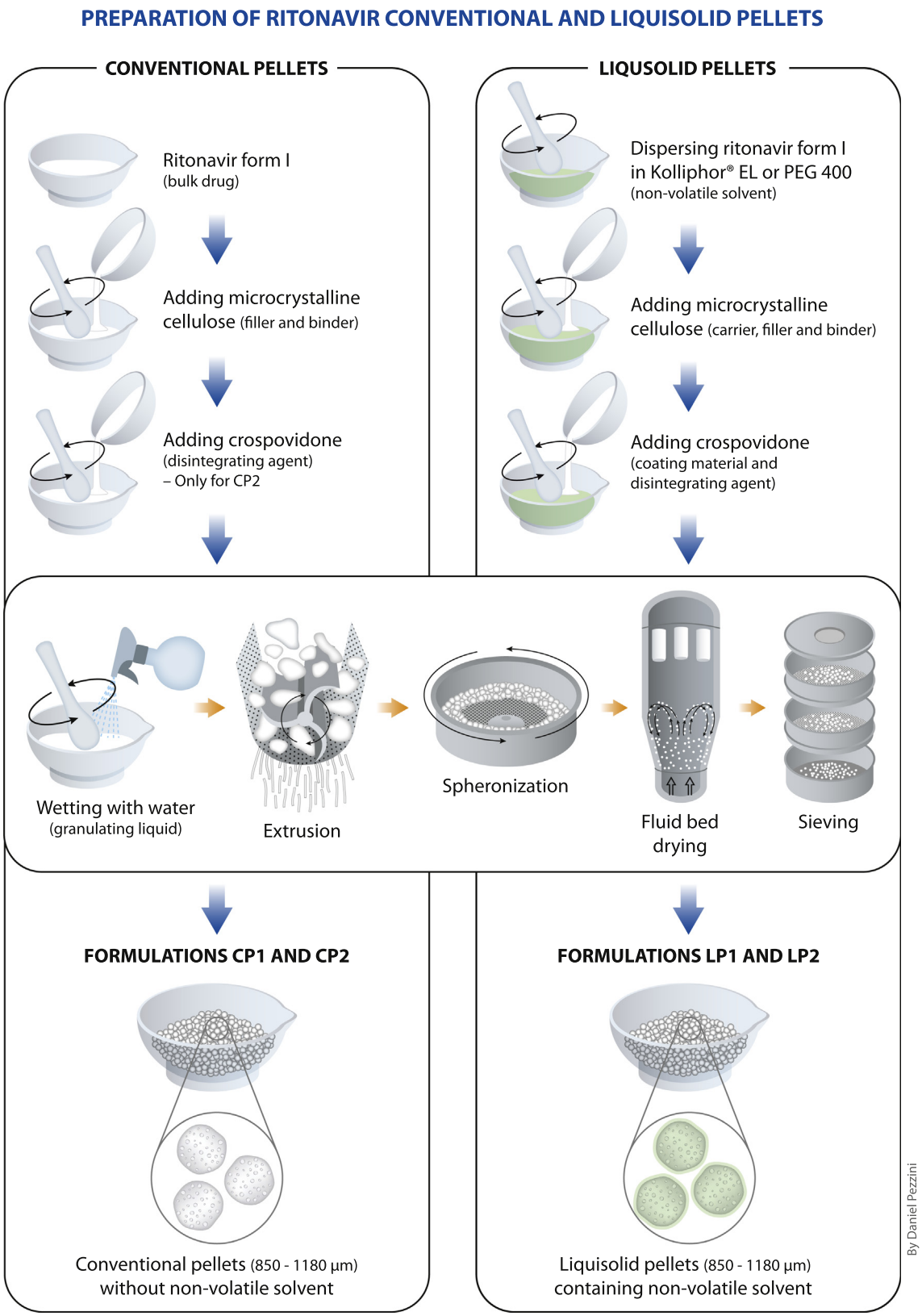

Fig. 1. Flow chart showing the preparation process of RTV conventional (CP1 and CP2) and liquisolid (LP1 and LP2) pellets.

obtained by filling a 10 mL cylinder with pellets and calculating the mass to volume ratio. The ρt was determined in a tapped density tester (Copley JV 1000, UK) by calculating the mass to volume ratio after 1250 taps or until the difference between successive measurements was less than or equal to 2 mL. HR and CI results were calculated from ρb and ρt according to the literature (Carr, 1965; Hausner, 1967; Qiu et al., 2009).

The AR value (n = 500), i.e., the ratio between the longest caliper distance and the caliper distance perpendicular (Chopra et al., 2002), was determined using an optical microscope (SMZ-168, Motic, China) coupled to a photographic camera (Moticam 10 M, Motic, China) followed by image analysis (Size Meter 1.1, LCP, UFSC, Brazil).

2.6. Brunauer-Emmett-Teller (BET) measurements

Specific surface areas of the usable fraction of formulations were measured by the BET nitrogen adsorption method in a NOVA 2200e surface area analyzer (Quantachrome Corporation, USA). Samples were analyzed employing a multipoint nitrogen adsorption/desorption method. The Barrett-Joyner-Halenda (BJH) model was subsequently applied to determine the pore volume.

2.7. Scanning electron microscopy (SEM)

SEM was carried out on a Jeol JSM 6701F (Japan) scanning electron microscope using an accelerating voltage of 10.0 kV. Samples were coated with a fine gold layer (Denton Vaccum Desk V, Japan) prior to the analyzes.

2.8. Differential scanning calorimetry (DSC) and hot stage microscopy (HSM)

DSC curves were obtained in a Shimadzu DSC-60 (Japan) thermal analyzer using around 2 mg of each sample in partially opened aluminum pans. The temperature ramp was set from 25 to 250 °C at a heating rate of 10 °C min^{-1} under dynamic nitrogen atmosphere (100 mL min^{-1}).

HSM analyzes were carried out by polarizing optical microscopy (POM) using an Olympus BX50 microscope equipped with a Mettler Toledo FP-82 hot stage. Images (10x) were collected with an Olympus DP73 digital camera.

2.9. Fourier transform infrared spectroscopy (FTIR)

FTIR spectra were obtained in a FT-IR/NIR Frontier Spectrometer equipped with an Attenuated Total Reflectance accessory (PerkinElmer, USA) at a scan range of 4000 to 600 cm^{-1} and spectral resolution of 4 cm^{-1}. Spectrum software version 10.03.07 was used to determine the peak positions.

2.10. X-ray powder diffraction (XRPD)

XRPD analyzes were carried out using a 2θ X-ray powder diffractometer (D2 Phaser, Bruker, Germany), operating with Kα copper radiation (λ = 1.5418 Å) at 10 mA current and 30 kV voltage. Detection was performed through a scintillation counter one-dimensional LYNXEYE detector. Measurements were performed scanning 2θ from 5° to 50°, with 0.091° step size.

2.11. In vitro dissolution

In vitro dissolution study was performed using the paddle method at 50 rpm (Varian VK 7000, USA). The dissolution medium was 900 mL of sodium lauryl sulphate 0.7% (w/v) at 37 °C (Rossi et al., 2007). After adding the sample (amounts equivalent to 100 mg of RTV, n = 3) directly into the dissolution medium, aliquots were collected at 5, 15, 30, 60 and 120 min, volumetrically diluted (1:1, v/v) in methanol:water (67:33, v/v) and filtered through a 0.45 mm membrane (Millipore, USA). Aliquots were quantified by HPLC (as described in Section 2.2) to determine the RTV cumulative dissolution. The percentages of drug dissolved in 15 min (Q_{15min}) and in 30 min (Q_{30min}) and the dissolution efficiencies in 60 min (DE_{60min}) were taken to compare the drug dissolution profiles. The software DDSolver® was used to calculate DE_{60min} values (Zhang et al., 2010).

2.12. Statistical analyzes

Statistical analyzes were performed by one-way ANOVA and Tukey's Multiple Comparison test, using GraphPad Prism® v5.0 software. Differences were considered significant when $p < 0.05$ for a confidence level of 95%.

3. Results and discussion

3.1. Apparent solubility

The apparent solubility of RTV (polymorph I) was 22.10 ± 0.29 μg mg^{-1} in PEG 400, 17.42 ± 0.38 μg mg^{-1} in Kolliphor® EL, and 14.24 ± 1.27 μg mg^{-1} in Tween 80. Once PEG 400 and Kolliphor® EL showed higher solubilizing capacities for the drug, they were selected for producing the LPs.

3.2. Preparation of liquisolid and conventional pellets

Our previous work (Pezzini et al., 2016) described the preparation of LPs containing 5% of drug (felodipine), 5% of non-volatile solvent (PEG 400 or Cremophor® EL), microcrystalline cellulose as the carrier and crospovidone as the coating and disintegrating material. In the present study, we have satisfactorily obtained LPs containing 15% of drug (RTV) and 30% of non-volatile solvent (PEG 400 or Kolliphor® EL), which are 3-fold and 6-fold higher, respectively, compared with the previously used concentrations.

Concerning the classic liquisolid systems, it is very difficult to convert a high dose of a poorly water-soluble drug (more than 50 mg) into a liquisolid compact weighing less than 1 g (Singh et al., 2012). This is because a large amount of non-volatile solvent is required to promote the satisfactory dissolution of the high dose drug and high quantities of carrier and coating material are needed to adsorb the liquid vehicle. The resulting large dosage form is problematic – or even impractical – for oral administration (Hentzschel et al., 2011; Javadzadeh et al., 2007; Lu et al., 2017; Nokhodchi et al., 2011; Singh et al., 2012). In this scenario, the development of LPs in the present work allowing the allocation of a high drug load (100 mg of RTV in 667 mg of pellets) is an important advancement in the liquisolid technology, expanding its application to a wide variety of drugs that require higher doses to promote their therapeutic efficacy.

Regarding the excipient ratio (R) between the amounts of the carrier (Q) and the coating material (q), improved drug dissolution rates were obtained in our previous work for formulations with lower R value, i.e., higher crospovidone concentration. Also, increasing the crospovidone content, associated with the presence of a non-volatile solvent, had a synergistic effect leading to faster disintegration times and therefore higher drug dissolution rates (Pezzini et al., 2016). Considering those, in the present work a very high concentration of crospovidone (30%, w/w) was selected for LP1 and LP2, resulting in an R-value of 0.83. Although such low R-value is not typical for traditional liquisolid compacts, it seemed to be feasible considering the specificities of LPs. Interestingly, we observed that using high amounts of crospovidone favored the incorporation of high loads of non-volatile solvent, resulting in liquisolid formulations with suitable characteristics for extrusion/spheronization.

Spheronization was successfully achieved in 2 min for CP1 and CP2, and 1.5 min for LP2, resulting in round pellets (Fig. 2).

However, LP2 showed a trend towards agglomeration and formation of fragile spheres and dust particles during the process.

LP1 was spheronized for 10 min and it still showed some pellets with halter-like shape (Fig. 2), suggesting that Kolliphor® EL reduced the plasticity of the formulation. Considering the most accepted mechanism for pellets formation, the wet extrudates must have enough plasticity to change into halter-like structures, break and further round up (Koester and Thommes, 2010), which was not entirely observed for LP1. Moreover, changes in process parameters, such as rotational speed of the spheronizer equipment, can be carried out to increase the linear peripheral velocity of the friction plate, possibly resulting in spherical pellets in lesser spheronization time (Podczeck and Newton, 2014).

CP1 (containing only RTV and microcrystalline cellulose) showed pellets with a narrow particle size distribution, with 93% of the pellet batch within the 600–1180 μm range, and 65% within the 850–1180 μm range (Fig. 3). The last range was defined as the usable fraction for all formulations and used for further tests.

CP2 had broader size distribution and lower yield of the usable fraction (26%, w/w) than CP1 (65%, w/w) indicating that adding crospovidone led to a shift in the size distribution of the conventional pellets (Fig. 3). On the other hand, the use of a non-volatile solvent in the LPs increased the yield of the usable fraction in comparison to CP2 by 2-fold for PEG 400 (LP2; 52%, w/w) and 3.4-fold for Kolliphor® EL (LP1; 89%, w/w). The much better performance regarding particle size distribution and yield of the usable fraction is a very relevant technological advantage of LPs over CP2 in terms of the feasibility of large-scale manufacturing.

3.3. Carr's index (CI), Hausner ratio (HR), and aspect ratio (AR)

The values of HR (1.02–1.04) and CI (2.37–3.39) for CP1, CP2, LP1 and LP2 were similar ($p > 0.05$) and indicated excellent flowability according to the literature (Carr, 1965; Hausner, 1967; Qiu et al., 2009). This is of upmost importance considering that pellets are used as intermediate products targeting at the preparation of capsules in gravity-fed machinery (Sarraguça et al., 2010).

CP1, CP2, LP1 and LP2 were satisfactorily spherical with AR values between 1.08 and 1.15, within the acceptable target range of 1.0 to 1.2 (Chopra et al., 2002), which is important for the filling ability of pellets into capsules (Beringhs et al., 2013; Podczeck et al., 2008). LP1 had the AR mean and SD values (1.15 ± 0.14) slightly higher than the other formulations due the presence of some halter shape-particles (Fig. 2), but it still displayed acceptable morphology.

3.4. Brunauer-Emmett-Teller (BET) measurements

The BET results (Table 2) showed similar specific surface area and pore volume for CP1, LP1 and LP2. The values of both parameters were higher for CP2.

3.5. Scanning electron microscopy (SEM)

At 50× and 150× magnifications, CP1 and CP2 showed smooth surface, while LP1 and LP2 had roughened surface (Fig. 4). Under higher magnification, CP1 and CP2 showed the characteristic lath crystals of RTV form I polymorph (data not shown), suggesting that the preparation process did not alter the original drug crystalline form of these formulations. On the other hand, both LP1 and LP2 showed the presence of needle crystals, consistent with RTV polymorph II (Fig. 4, 1000×).

3.6. Differential scanning calorimetry (DSC) and hot stage microscopy (HSM) measurements

DSC curves for both RTV polymorphs I (used to prepare the formulations) and II (analyzed for comparison purposes) showed a melting point around 122 °C, and form II had higher enthalpy of fusion (ΔH) than form I (Fig. 5), as stated in the literature (Bauer et al., 2001; Chemburkar et al., 2000). An endothermic peak at the same temperature range of that observed for RTV form I (neat drug) appeared in the DSC curves of binary mixtures (1:1, w/w) of RTV form I with excipients (crospovidone and microcrystalline

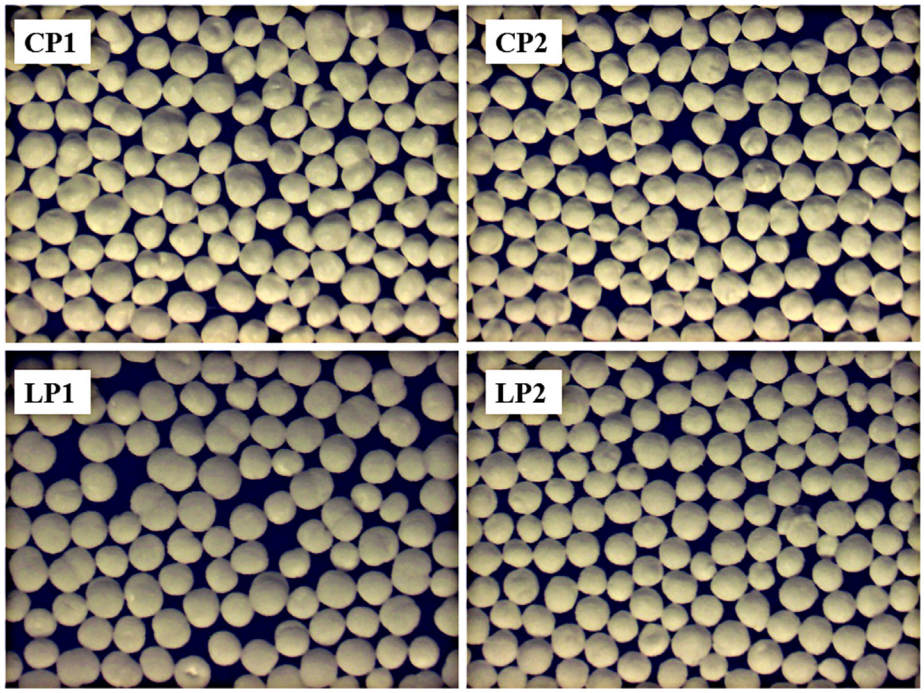

Fig. 2. Microscopic images (7.5x) of the usable fraction (850–1180 μm) of RTV conventional (CP1 and CP2) and liquisolid (LP1 and LP2) pellets.

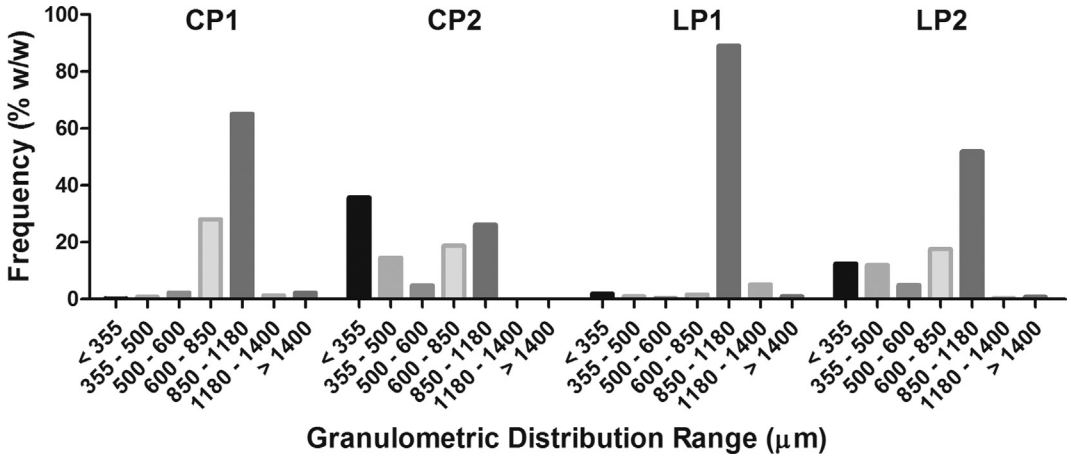

Fig. 3. Particle size distribution of RTV liquisolid (LP1 and LP2) and conventional (CP1 and CP2) pellets.

Table 2
Specific surface areas and pore volumes of RTV conventional (CP1 and CP2) and liquisolid (LP1 and LP2) pellets.

Formulation	Specific surface area ($m^2\ g^{-1}$)	Pore volume ($cm^3\ g^{-1}$)
CP1	2.31	7.38×10^{-4}
CP2	3.34	1.11×10^{-3}
LP1	2.29	7.51×10^{-4}
LP2	2.36	8.10×10^{-4}

cellulose) and CP1 and CP2, with ΔH values proportional to the drug concentration in these samples (Fig. 5). These results suggested, respectively, no interaction or incompatibility of the drug with crospovidone or microcrystalline cellulose, and no polymorphic transition during the pelletization process for CP1 and CP2 (ΔH values higher than expected, which was not observed, could suggest crystalline transition to form II). The DSC curves of

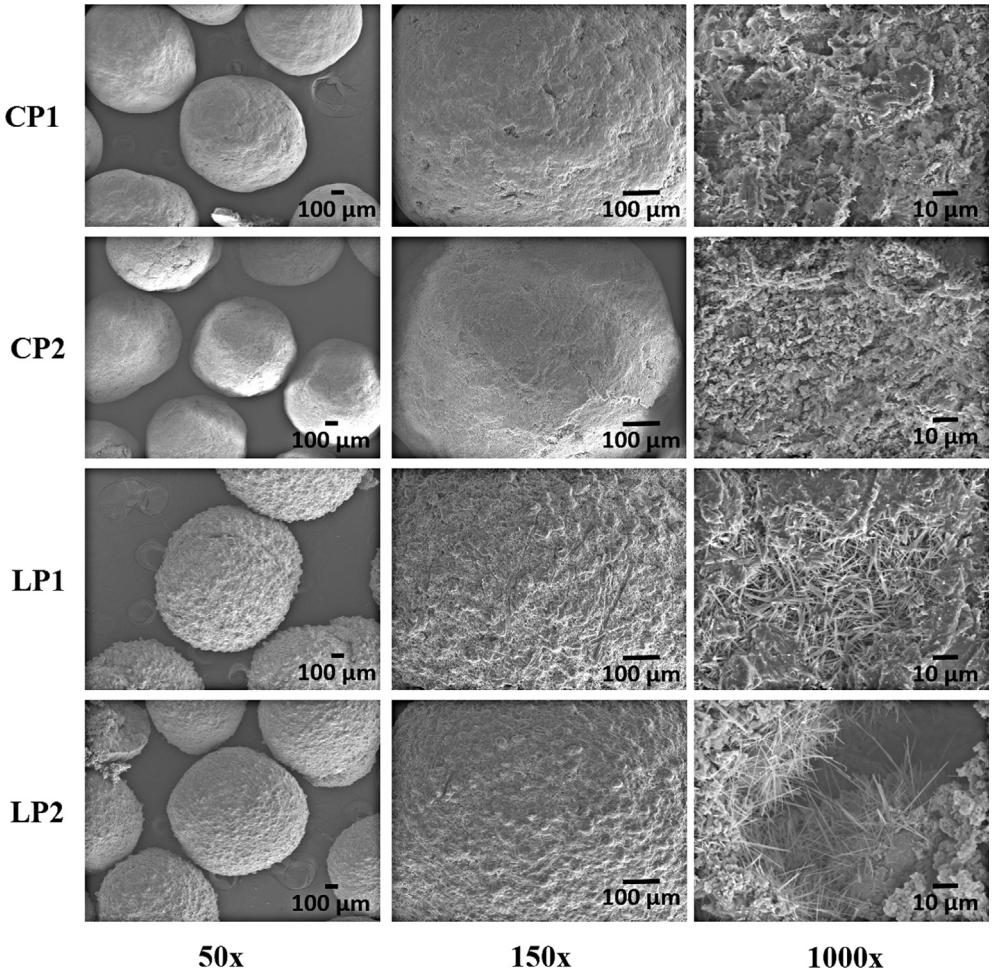

Fig. 4. SEM photomicrographs of RTV conventional (CP1 and CP2) and liquisolid (LP1 and LP2) pellets.

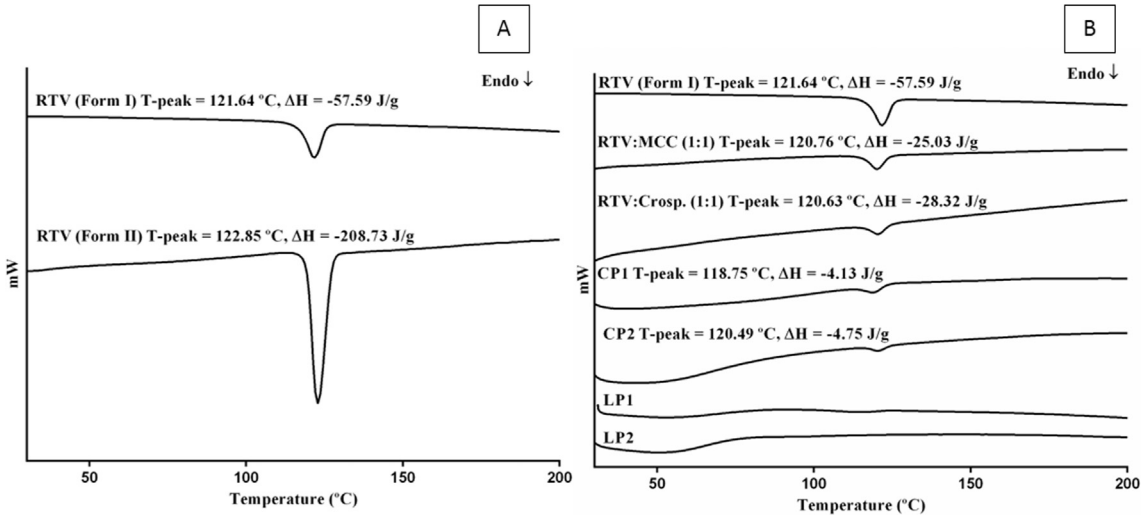

Fig. 5. DSC curves for RTV polymorphs I and II (neat drug), RTV form I binary mixtures (1:1, w/w) with crospovidone (Crosp.) and microcrystalline cellulose (MCC), and RTV conventional (CP1 and CP2) and liquisolid (LP1 and LP2) pellets.

crospovidone and microcrystalline cellulose were determined and did not exhibit any relevant thermal event (data not shown).

The characteristic melting event of RTV was not evidenced in the DSC curves of LP1 and LP2 (Fig. 5), although crystalline drug was observed in the SEM photomicrographs (Fig. 4). The HSM images for liquid medications (Fig. 6) showed the solubilization of RTV particles in the non-volatile solvents as a function of temperature (~100–109 °C for Kolliphor® EL and ~ 83–93 °C for PEG 400). These phenomena explain the absence of RTV melting event for LP1 and LP2 in DSC curves (Fig. 5) due to drug solubilization during DSC analyzes.

3.7. Fourier transform infrared spectroscopy (FTIR)

RTV form I showed characteristic bands at (1) 3355 cm^{-1} (N—H stretching of secondary amide), (2) 1714 cm^{-1} (C=O stretching), (3) 1527 cm^{-1} (N—H bending of secondary amide) and (4) 1238 cm^{-1} (C—N stretching) (Dengale et al., 2014), as numbered in Fig. 7. RTV form II spectrum presented band shifts in the highlighted regions (compared to form I), allowing the differentiation between polymorphs. Numbered bands in the FTIR spectra (Fig. 7) reveal the presence of RTV form I in CP1 and CP2, and the form II in LP1 and LP2, suggesting a polymorphic transition (form I to II) for the liquisolid pellets. The regions (1) and (2) suggest some remaining amount of RTV form I in LP2. The spectra of pure excipients of pellets formulations are presented in Supplementary Material.

3.8. X-ray powder diffraction (XRPD)

RTV polymorphs I and II showed the characteristic diffraction peaks (Fig. 8) in accordance with XRPD patterns reported for the drug in the literature (Bauer et al., 2014) and catalogued by the Mercury CSD 3.7 (The Cambridge Crystallographic Data Centre). XRPD analyzes confirmed the partial polymorph transition of RTV (form I to II) during the preparation of liquid medications since RTV:Kolliphor® EL and RTV:PEG 400 mixtures exhibited characteristic reflections for both RTV forms I and II, as shown in Fig. 8. Identification of RTV polymorphs directly in the pellets formulations was not possible as most Bragg peaks of the drug were overlaid by the diffraction patterns of crospovidone and microcrystalline cellulose (Supplementary Material), which were in higher concentrations than the drug in those samples.

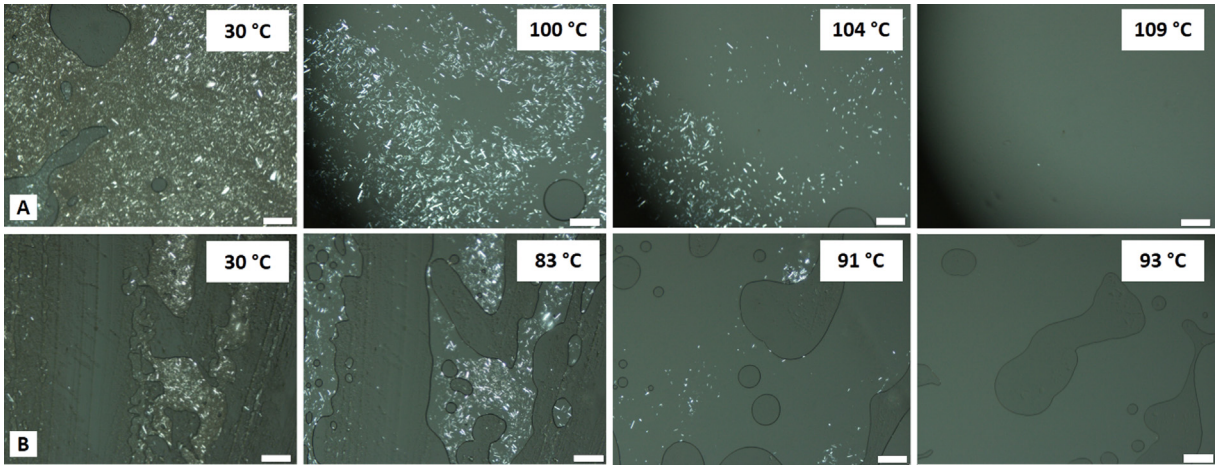

Fig. 6. HSM images of liquid medications (1:2, w/w) of RTV with Kolliphor® EL (Line A) and PEG 400 (Line B). The white bar in the inferior right of each image corresponds to 100 μm.

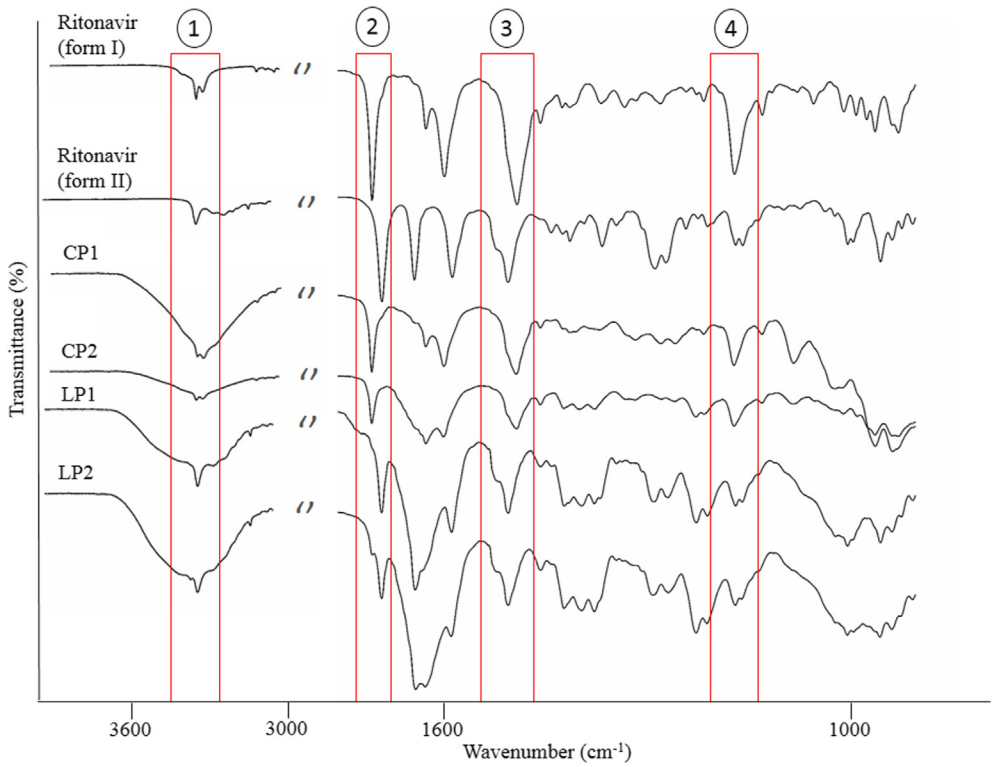

Fig. 7. FTIR spectra of RTV polymorphs I and II (neat drug), and RTV conventional (CP1 and CP2) and liquisolid (LP1 and LP2) pellets.

3.9. In vitro dissolution

LP1 and CP2 had higher drug dissolution rates when compared to neat RTV (polymorphs I and II), CP1, and LP2 (Fig. 9). The values of Q_{30min} and DE_{60min} were in the following order of magnitude: LP1 > CP2 > LP2 = RTV form I > CP1 = RTV form II ($p < 0.05$). Form II polymorph is the most thermodynamically-stable of the crystalline forms of RTV (Morissette et al., 2003), with a 6-fold lower apparent solubility in ethanol/water 75/25 at 5° C when compared to form I (Bauer et al., 2001). This justifies the much lower dissolution results (5.31-fold and 5.06-fold lower results for Q_{30min} and DE_{60min}, respectively, $p < 0.05$) for form II as compared to form I (Fig. 9).

CP1 showed very low drug dissolution results (Q_{30min} = 5.62 ± 0.18% and DE_{60min} = 5.32 ± 0.06%) due to poor disintegration (Fig. 10) caused by the absence of crospovidone (disintegrating agent) associated with the drug's inherent poor aqueous solubility. The improved drug release of CP2 over LP2 was likely related to the presence of RTV form II in LP2 (Sections 3.5–3.8), which displays very poor dissolution rate (Fig. 9). CP2 also had higher specific surface area and pore volume than all the other formulations (Section 3.4), which positively influenced the drug dissolution rate.

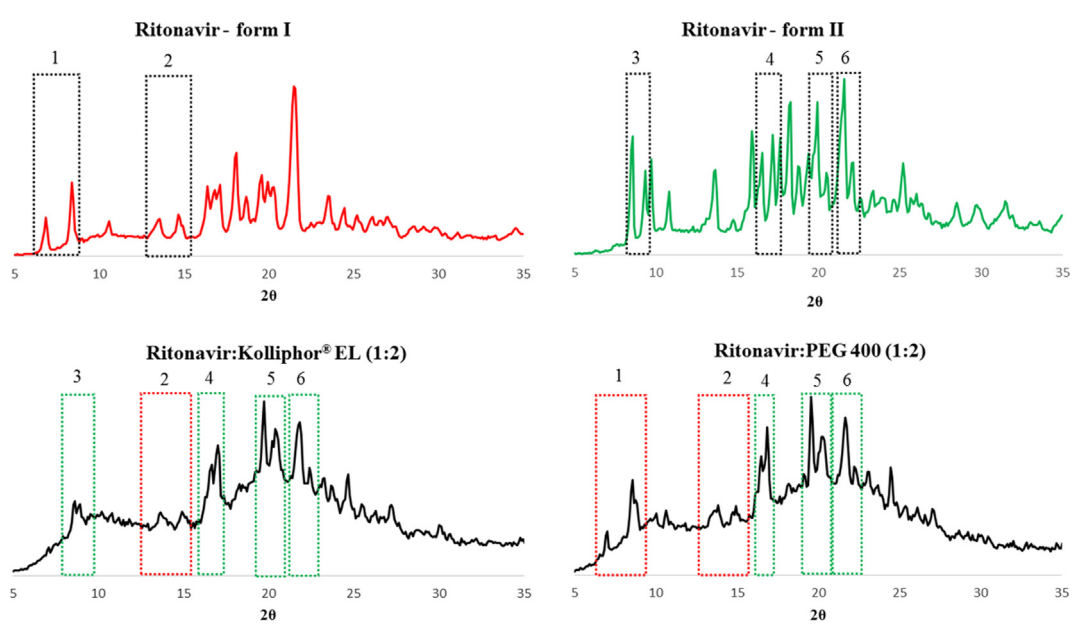

Fig. 8. X-ray powder diffractograms for RTV polymorphs I and II (neat drug), and RTV:non-volatile solvent (1:2, w/w) binary mixtures (liquid medications).

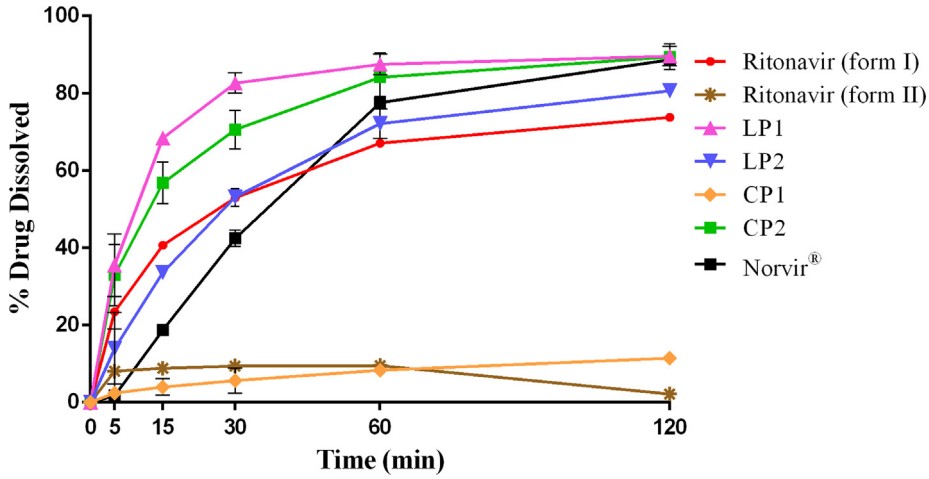

Fig. 9. Drug dissolution profiles of RTV polymorphs I and II (neat drug), RTV conventional (CP1 and CP2) and liquisolid (LP1 and LP2) pellets, and Norvir® tablets. Each point is expressed as mean ± standard deviation (n = 3).

LP1 showed higher Q_{15min}, Q_{30min} and DE_{60min} results than CP2 ($p < 0.05$), despite the presence of RTV polymorph II in LP1 (Sections 3.5–3.8). This finding is a direct consequence of the liquisolid microenvironment and also an effect of the faster disintegration behavior (Fig. 10) of LP1 over CP2. LP1 promoted 1.9-fold/1.7-fold increases ($p < 0.05$) and 8.19-fold/8.29-fold increases ($p < 0.05$) in Q_{30min}/DE_{60min} as compared to RTV polymorphs I and II, respectively. Although the proportion between polymorphs I and II in LP1 is not known, the large amount of needle crystals in Fig. 4 indicates high form II content. So, the much better dissolution performance of LP1 over RTV form II (Fig. 9) is strong evidence that the LPs are a very efficient drug delivery system for low solubility drugs, even in high dose, as in the case of RTV.

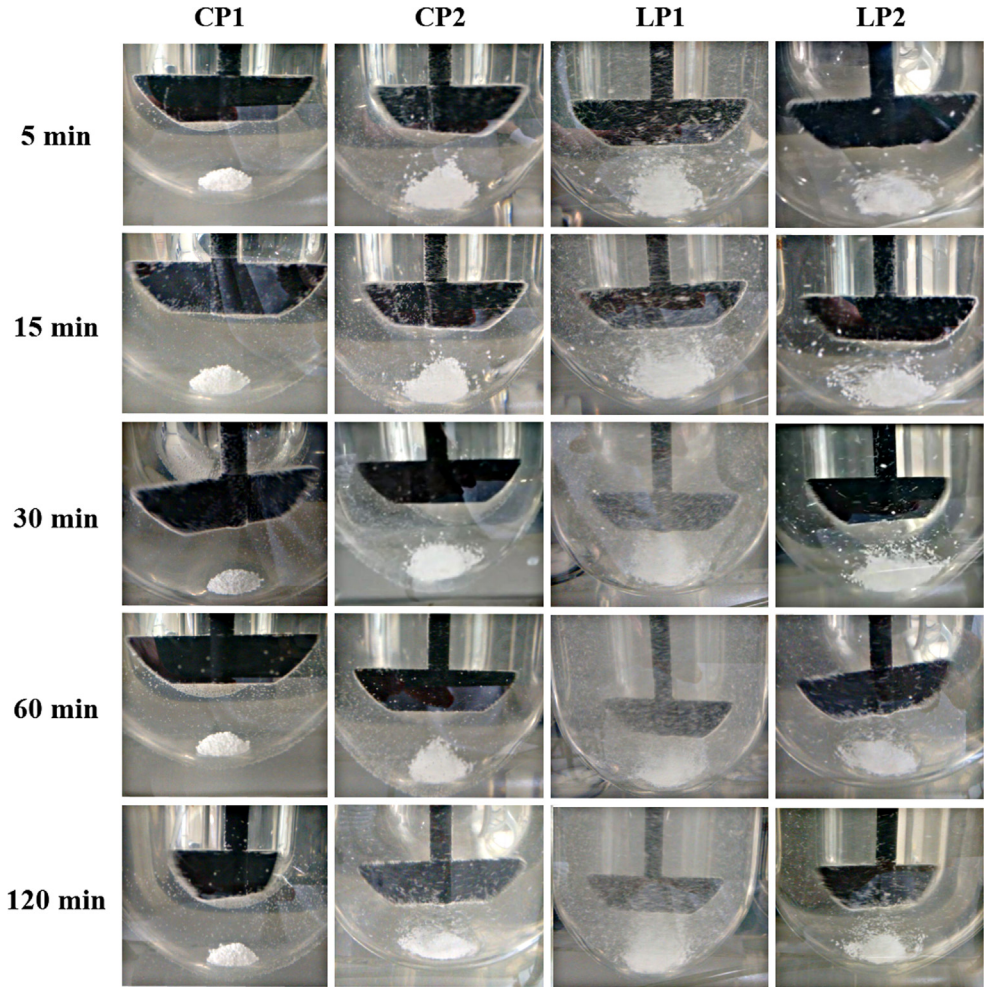

Fig. 10. Different disintegration behaviors of RTV conventional (CP1 and CP2) and liquisolid (LP1 and LP2) pellets during *in vitro* dissolution tests.

Other important evidence of the great potential of LPs as novel drug delivery systems for poorly water-soluble drugs is the outstanding dissolution performance of LP1 as compared with the reference listed drug (RLD) Norvir® (Fig. 9), comprised of tablets containing a melt-extruded solid dispersion of RTV in polyvinyl pyrrolidone–polyvinyl acetate (PVP-VA) copolymer (copovidone) (Newman, 2015). LP1 (Q_{30min} = 82.64 ± 2.17%, DE_{60min} = 71.54 ± 1.51) showed faster drug dissolution and higher dissolution efficiency compared with Norvir® tablets (Q_{30min} = 42.42 ± 2.09%, DE_{60min} = 39.41 ± 1.19) ($p < 0.05$).

The dissolution performance of RTV LPs (Fig. 9) also showed that Kolliphor® EL outperformed PEG 400 as a non-volatile solvent for RTV. In our previous work (Pezzini et al., 2016), we found that Cremophor® EL (former trade name of Kolliphor® EL) was more effective in improving felodipine dissolution rate compared with PEG 400, even though the drug solubility was slightly higher in the second non-volatile solvent. It was observed that Cremophor® EL formed LPs with faster disintegration time with respect to PEG 400, justifying the drug dissolution profiles obtained. Similar results were achieved in the present study, i.e., the apparent solubility of RTV was slightly higher in PEG 400 than Kolliphor® EL, but LP1 (Kolliphor® EL-based) had faster disintegration and higher dissolution rate than LP2 (PEG 400-based). The optimal performance observed for Kolliphor® EL in terms of pellets disintegration and drug dissolution resulted from its surfactant properties, while PEG 400 is a hydrophilic polymer. Besides, obtaining liquisolid systems using Kolliphor® EL can add extra advantage in terms of improving drug bioavailability by increasing drug permeability due to its known P-glycoprotein-inhibition effect, as this transporter reduces the intestinal absorption of many drugs by efflux transportation (Elkordy et al., 2013, 2012; Komala et al., 2015). These findings showed the great importance of Kolliphor® EL as a non-volatile solvent for liquisolid formulations.

4. Conclusion

This study shows that is possible to obtain LPs containing high loads of both poorly-water soluble drug and non-volatile solvent with narrow size distribution, good morphological properties, excellent flowability, and improved drug dissolution rate. This is important evidence that LPs can be successfully adopted by the pharmaceutical industry as new drug delivery systems for poorly-water soluble drugs.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2019.04.005.

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