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Research paper

Sustained-release of buspirone HCl by co spray-drying with aqueous polymeric dispersions

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Abstract

Sustained-release of buspirone HCl (BUH) was attempted by spray drying after dissolving in two commercially available aqueous polymeric dispersions (Eudragit® RS 30 D or Kollicoat® SR 30 D) at five different drug:polymer ratios (1:1, 1:2, 1:3, 1:6 and 1:9). The produced spray-dried agglomerates were evaluated in terms of their particle size and morphology, production yield, encapsulation efficiency and in-vitro release of BUH. Possible drug–polymer interactions were checked by Differential Scanning Calorimetry (DSC) and FT-IR spectroscopy. Scanning electron microscopy (SEM) was employed for the qualitative characterization of particle size and morphology. Encapsulation efficiency was generally high (around 100%) and independent of the polymeric dispersion type, while production yield was generally low (7.2–31.0%) and significantly lower for the case of Kollicoat SR 30 D (KSR) than for Eudragit RS 30 D (ERS). Scanning electron micrographs showed remarkable changes in size and shape of agglomerates due to the type of aqueous polymeric dispersion and drug:polymer ratio. In-vitro release of BUH from compacted co spray-dried agglomerates was remarkably slower and incomplete for the case of Kollicoat® at drug:polymer ratio below 1, presumably due to increased plastic deformation of the developed coating instead of fragmentation in the case of Eudragit® coating during compaction.
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1. Introduction

Aqueous dispersions of water-insoluble polymers are extensively used for coating of pharmaceutical tablets and pellets due to their advantages over traditional non aqueous solutions, e.g. the avoidance of costly, relatively toxic and environmentally hazardous organic solvents [1–3] and the convenience of handling due to their lower viscosity and availability for immediate application [4].

The major application of coating by aqueous polymeric dispersions is in membrane-controlled drug release modification of tablets and pellets. However, another suggested alternative for drug release modification, although not thoroughly investigated, was by co-agglomerating drugs and aqueous polymeric dispersions employing fluidized bed granulation [5,6] or spray drying [2,7,8] and then forming monolithic matrix systems.

Particularly, the spray-drying technique, which may result in products of good flow properties [9–11] can be applied with organic or aqueous, either solutions or dispersions containing drugs and polymers. In case of organic solutions or dispersions, the spray drying loses the above-mentioned advantages of aqueous environment and involves high risk of explosion. Moreover, some active

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pharmaceutical ingredients are poorly soluble in organic solvents but highly soluble in water. For these reasons, spray-drying of drugs after dissolution in commercially available aqueous dispersions of water-insoluble polymers seems to be a promising method for release modification compatible with subsequent compaction of the produced agglomerates and development of matrix-type dosage forms.

Buspirone hydrochloride (BUH), chemically *N*-[4-[4-(2-pyrimidinyl)-1-piperazinyl] butyl]-1,1-cyclopentanediacetamide monohydrochloride, is a crystalline water-soluble anti-anxiety drug existing in two enantiotropically related polymorphs [12,13]. Solubility of both forms is low in isopropanol but high in water. Form 1 (m.p. 188 °C) has lower solubility than Form 2 (m.p. 203 °C) in either solvent [14]. Form 1 converts to Form 2 at 95 °C [15]. Therefore, BUH is susceptible to polymorphic transformation during wet granulation or spray drying since they both involve heating. Also, extended release formulation of BUH showed greater bioavailability in comparison with immediate release formulation with lower intersubject variation and potential benefits of once daily dosing [16–18].

Since BUH is more soluble in water than in isopropanol and an extended release formulation is advantageous, in this work, two commercially available aqueous polymeric dispersions (Eudragit® RS 30 D and Kollicoat® SR 30 D) were utilized to prepare sustained-release buspirone HCl microparticles by the spray drying technique. For each type of polymeric dispersion, five different drug:polymer ratios were applied. The aim was to compare the two polymeric dispersions regarding their applicability in release sustaining by combining spray drying technique and compaction to monolithic matrixes.

2. Materials and methods

2.1. Materials

Buspirone HCl (Assay = 101.86%, water content = 0.14%) was kindly offered by JPM, Amman, Jordan. The aqueous polymeric dispersions were Eudragit® RS 30 D from Röhm Pharma, Darmstadt, Germany (containing 30% w/w copolymer of ethyl-acrylate, methyl-methacrylate and trimethyl-ammonioethyl-methacrylate chloride in the ratio of 1:2:0.1 and 0.25% sorbic acid) and Kollicoat® SR 30 D from BASF, Germany (containing polyvinyl acetate 27%, polyvinylpyrrolidone 2.7% and sodium lauryl sulphate 0.3% w/w). Spectroscopic-grade potassium bromide (Uvasol®, Merck, Darmstadt, Germany) was used for FT-IR spectroscopy. All other reagents and materials were of analytical grade and were used as supplied.

2.2. Methods

2.2.1. Spray drying

Spray drying was performed in a Pulvis mini-spray GA 32 (Yamato Scientific, Japan) equipped with a standard 406 μm spray nozzle. Buspirone HCl (BUH) was dissolved in distilled water and then polymeric dispersion [Kollicoat SR 30 D (KSR) or Eudragit RS 30 D (ERS)] was added to the solution, mixed well and completed to volume with distilled water so that the total solid concentration was kept constant (12.5% w/v) in all runs. Five different drug:polymer (D:P) ratios (1:1, 1:2, 1:3, 1:6 and 1:9) were applied for each type of aqueous polymeric dispersion (APD) by changing the amounts of BUH and ERS or KSR. The operation conditions were inlet air temperature 133–136 °C, outlet air temperature 70–80 °C, spray air pressure 1 kg/cm^2, and spray feed rate 6 ml/min. The co-agglomerated water-insoluble polymeric particles and BUH microcrystals which accumulated in the product vessel were collected, weighed and kept in screw-capped plastic containers until required for examination.

2.2.2. Scanning electron microscopy (SEM)

Size and morphology of the collected spray dried microparticles was evaluated by using samples mounted on aluminum stubs with double-sided sticky disks of conductive carbon and then gold-coated by sputtering method at 1200 V, 20 mA in a vacuum coater (Polaron E6100, UK) before the observation in the Scanning Electron Microscope (FEI Quanta 200, Netherlands).

2.2.3. Encapsulation efficiency

Weighed samples (about 10 mg) of each spray-dried batch were dissolved completely in 2 ml absolute ethanol and the volume was completed to 100 ml with distilled water. After filtration through 0.45 μm cellulose acetate syringe-filter and suitable dilution, the concentration of BUH was determined by UV spectroscopy (Spectronic 601, Milton Roy, USA) at wavelength corresponding to maximum absorbance (235 nm). The determination was performed in triplicate and the results were expressed as percentage of the corresponding BUH amount added initially.

2.2.4. Preparation of physical mixtures

Physical mixtures with the same composition of the spray-dried agglomerates were prepared in a small mortar by using 1 g of BUH and appropriate amount of dried and powdered APD (ERS or KSR) and mixing for 20 min with a spatula. For drying the APD, small portions (about 5 ml) of ERS or KSR was spread on glass petri dishes and allowed to dry at room temperature for 3 days. After drying, samples were triturated in a porcelain mortar and the size fraction below 300 μm was collected.

2.2.5. Differential scanning calorimetry (DSC)

Thermal behavior of BUH, dried and powdered APDs, agglomerates obtained by co spray-drying and of physical mixtures composed of BUH and dried-powdered APDs was examined by using differential scanning calorimeter (Mettler Toledo DSC 823, Mettler, Switzerland). Samples (4–5 mg) were weighed and sealed into aluminum pan with

a perforated lid to allow departure of water and other volatile substances. The samples were heated from 20 to 280 °C with a heating rate 10 °C/min in nitrogen atmosphere.

2.2.6. FT-IR spectroscopy

FT-IR spectra of the samples mentioned in DSC testing were obtained with a Shimadzu FT-IR 8400S (Shimadzu, Japan) spectrophotometer using the KBr disk method. Samples were scanned over the 500–4000 cm^{-1} spectral region at a resolution of 4 cm^{-1}. The ratio of sample in the KBr disk was 1%.

2.2.7. Dissolution testing

Dissolution study was carried out for uncompacted and compacted co-agglomerates as well. Distilled water (pH 6.5) was used as dissolution medium after preliminary comparison to phosphate buffer (pH 6.8), for simplicity and cost reduction.

For the uncompacted co-agglomerate the dialysis system described previously was used [19]. An amount of co-agglomerates equivalent to 5 mg BUH was suspended in 10 ml distilled water. The suspension was placed in a donor cell separated by a dialysis membrane (Mw cut-off 12000 Da and surface area 12.57 cm^2) from a receiving compartment containing 100 ml distilled water. The receiving medium was stirred using magnetic stirrer and thermostated at 37 °C. Distilled water was used as dissolution medium since preliminary testing showed no big difference between using phosphate buffer (pH 6.8) and distilled water (pH 6.5) although the dissolution behavior from pellets coated with Eudragit RS has been found to depend on the composition of dissolution medium rather than pH [20,21]. For the case of BUH-APD co-agglomerates no difference was observed, probably because BUH is highly soluble in water and the water permeability of the applied APDs (ERS and KSR) is pH independent. At certain time intervals, 5-ml samples were taken from the receiving medium and replaced by equal volume of distilled water. The concentration of BUH dissolved was determined by UV spectroscopy (Spectronic 601, Milton Roy, USA), at 235 nm, after suitable dilution. This dialysis system has the advantage of convenient sampling [22].

For the compaction 100-mg of accurately weighed co-agglomerates were transferred in a 5-mm diameter set of biconvex punch and die and compressed without additional excipients in a hydraulic press (Karl Kolb, Germany) by applying 10 kN force for 30 s. Dissolution testing of the compacted co-agglomerates was carried out in a USP II paddle system (Pharma Test PTW 2, Hainburg, Germany), at 50 rpm with 500 ml of distilled water as a dissolution medium. At certain time intervals, samples were taken and filtered through 0.45 μm cellulose acetate syringe filter and the concentration of BUH dissolved was determined by UV spectroscopy at 235 nm. All tests were performed in triplicate.

2.2.8. Statistical analysis

The statistical significance of the effects of the main variables (APD type and drug:polymer ratio) on the production yield and the encapsulation efficiency was evaluated applying analysis of variance (ANOVA) by using the program SPSS 13.0 (Chicago, IL, USA).

3. Results and discussion

Scanning electron micrographs of co-agglomerates containing ERS or KSR at high (1:1), medium (1:3) and low (1:9) drug:polymer (D:P) ratios are given in Fig. 1. They show the presence of many small and some large agglomerates for samples prepared at low D:P ratio for both APDs (Fig. 1e or f) while for high D:P ratio (Fig. 1a or b) almost all the agglomerates obtained are large. The larger size of agglomerates obtained with high D:P ratio might be presumably explained by extensive coalescence of polymer particles caused by crystallization of BUH, taking place as the sprayed droplets are dried. Also, the shape of the spray dried BUH–KSR co-agglomerates is almost spherical at D:P ratio 1:1 (Fig. 1a) and some concave microparticles appear at low (1:9) and medium (1:3) ratios (Fig. 1c and e). The BUH–ERS co-agglomerates of high (1:1) D:P ratio (Fig. 1b) have rougher surfaces than those of BUH–KSR prepared with the same D:P ratio (Fig. 1a). However, as the proportion of BUH decreases relatively to polymer, the surface of the co-agglomerates becomes smoother and some toroid microparticles are seen at 1:3 and 1:9 D:P ratios (Fig. 1c–f).

The results of the production yield and the encapsulation efficiency are given in Table 1. The effects of the main variables (APD type and D:P ratio) on the production yield and the encapsulation efficiency are given in Table 2 as *F*-values and significance *p* evaluated by applying analysis of variance (ANOVA).

From Table 1 it can be seen that production yield, which is expressing the mass of the harvested microparticles as percentage of the initially used mass of drug and dry solid polymer, was generally low (7.2–31.0%). The low values of production yield are quite frequent in spray drying methods [23]. However, the production yield was significantly higher for all the co-agglomerates prepared with ERS than for those prepared with KSR ($F = 25.707$, $p = 0.007$, in Table 2). KSR contains 2.7% polyvinylpyrrolidone (PVP) which might be responsible for the lower production yield in general with KSR as well as for the increased reduction of yield as the D:P ratio decreases or the presence of polymer relatively to BUH increases, although the general effect of D:P ratio on yield was not significant ($F = 3.027$, $p = 0.154$, in Table 2). Particularly the increased binding ability of PVP (well-known very capable binder) may result in increased adherence of the sprayed droplets to the internal surfaces of the drying chamber and the cyclone before they dry and reach the collection vessel. Another possible explanation for the remarkably low production yield values at lowest D:P

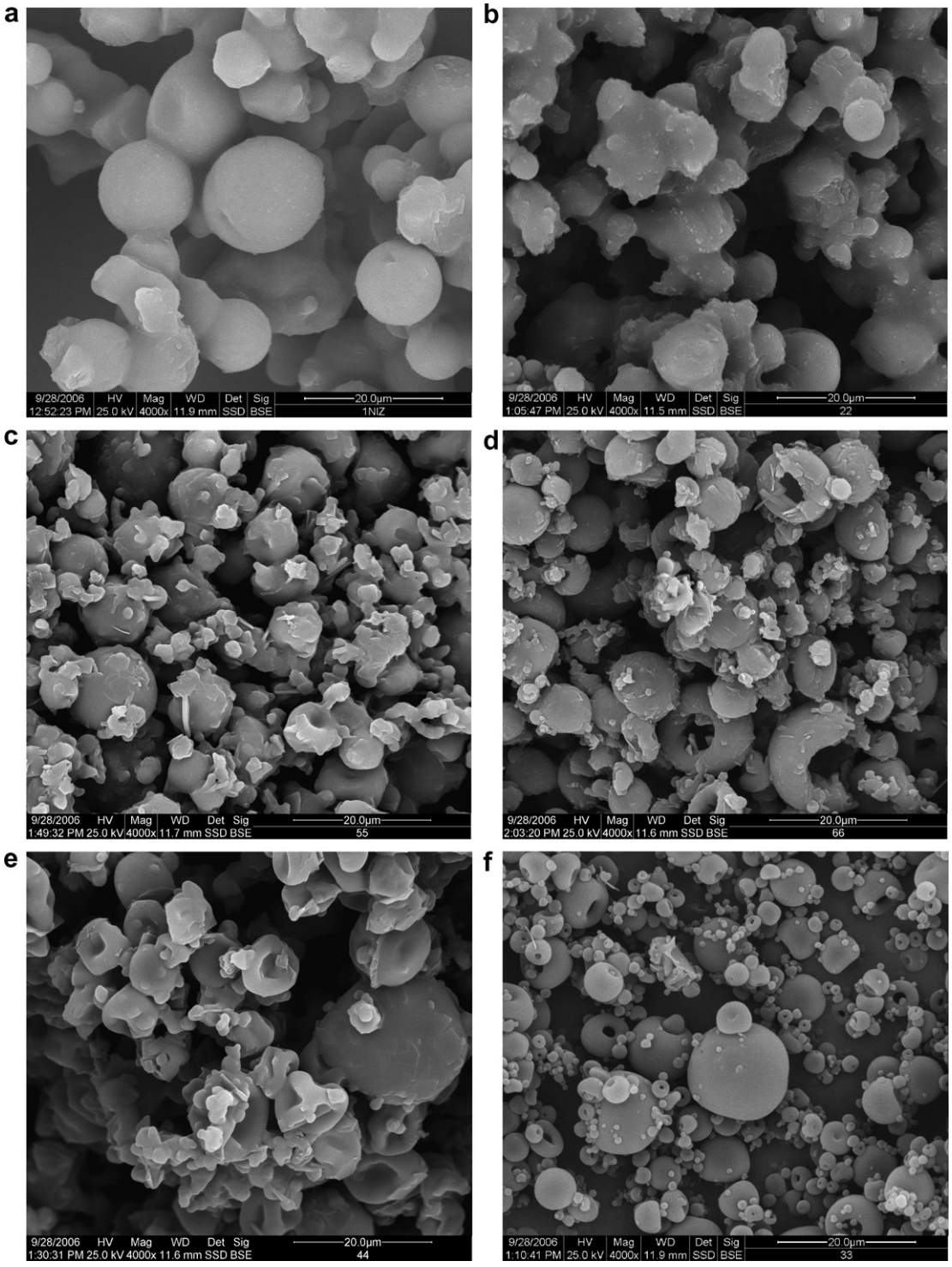

Fig. 1. Scanning electron micrographs of the co-agglomerates obtained by co-spray drying, at high (1:1), medium (1:3) and low (1:9) drug:polymer ratios, with KSR (a, c, and e) and ERS (b, d, and f, respectively).

level, for both ERS and KSR polymer (17.3% and 7.2%, respectively), may be the formation of very small co-agglomerates in higher polymer or low drug proportion and increased loss through the exhaust of the spray dryer. Experimental trials with both the APDs alone (ERS or KSR without BUH) resulted in practically impossible collection of co-agglomerates. Similar difficulty in obtaining spray-dried product was reported by Takeuchi et al. for the case of spray-drying Eudragit L100-55/ammonia solution without drug [2]. Therefore, specific study is necessary for selection of optimal processing conditions, equipment design and scaling up of the spray drying.

Table 1
Production yield and encapsulation efficiency (means ± SD, $n = 3$) for co-agglomerates obtained with different Aqueous Polymeric Dispersion (APD) and dug:polymer (D:P) ratio

APD	D:P ratio	Production yield (%)	Encapsulation efficiency (%) (means ± SD)
Eudragit RS 30 D	1:1	25.8	98.1 ± 0.7
	1:2	26.3	99.7 ± 0.6
	1:3	27.7	101.7 ± 1.5
	1:6	31.0	101.5 ± 0.6
	1:9	17.3	102.4 ± 0.7
Kollicoat SR 30 D	1:1	21.8	98.0 ± 1.4
	1:2	14.5	101.5 ± 1.1
	1:3	13.1	103.0 ± 0.8
	1:6	13.4	104.1 ± 0.6
	1:9	7.2	102.1 ± 0.5

Table 2
Effects of the main variables (type of APD and D:P ratio) on the production yield and the encapsulation efficiency (F-value and significance p) evaluated by applying analysis of variance (ANOVA)

Variable	Type of APD		D:P ratio	
	F	p	F	p
Production yield (%)	25.707	0.007	3.027	0.154
Encapsulation efficiency (%)	3.641	0.129	9.894	0.024

Encapsulation efficiency was generally high (around 100%, Table 1) and independent of the APD type ($F = 3.641$, $p = 0.129$, Table 2), but significantly affected by the D:P ratio ($F = 9.894$, $p = 0.024$, Table 2). Also, encapsulation efficiency was increasing, although slightly, with the D:P ratio decrease for both APDs, except the case of low D:P ratio (1:9) of KSR. In many cases the encapsulation efficiency is higher than 100% and it is attributed to different drug contents between small and large co-agglomerates. In particular the reason should be the extensive coalescence caused by crystallized BUH and the reduced drug content in very small particles composed mainly of polymer, which are produced in higher proportion as the drug:polymer ratio is reduced due to decreased coalescence and are easily lost through the exhaust of the spray dryer.

The results of DSC analysis are shown in Figs. 2 and 3. They show a sharp endothermic peak in the case of pure BUH (A) with melting onset close to 203 °C, corresponding to Form 2. Melting endothermic peak of BUH is also seen for the agglomerates obtained by co spray-drying indicating that the incorporated BUH exists in crystalline form, but there are remarkable differences in the melting onset either between the pure BUH and the BUH-ERS co-agglomerates and physical mixtures or between the co-agglomerates obtained with different APDs. These differences in melting onset may be attributed either to the effect of the polymer on the developed polymorphic form of BUH crystals or to the type of the APD present but not to transformation during mixing, since Form 2 was that of raw pure BUH and transformation of Form 1 to Form

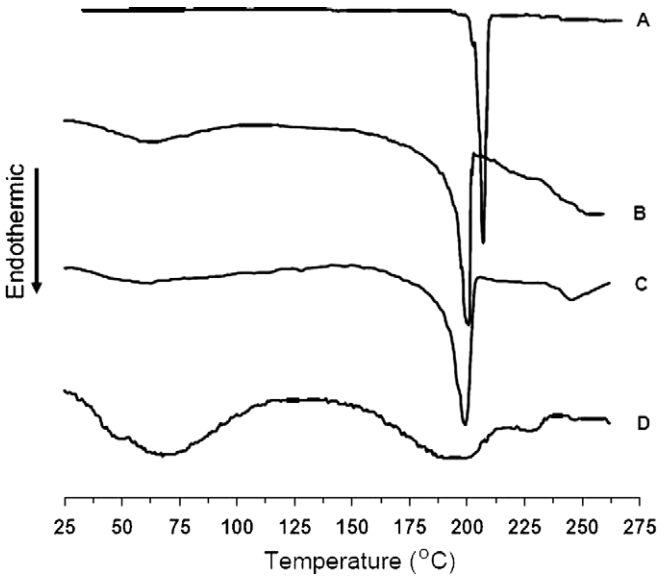

Fig. 2. DSC thermographs of: BUH (A), co spray-dried agglomerates of BUH and ERS in 1:1 D:P ratio (B), physical mixture of BUH and dried powdered ERS in 1:1 D:P ratio (C) and dried-powdered ERS (D).

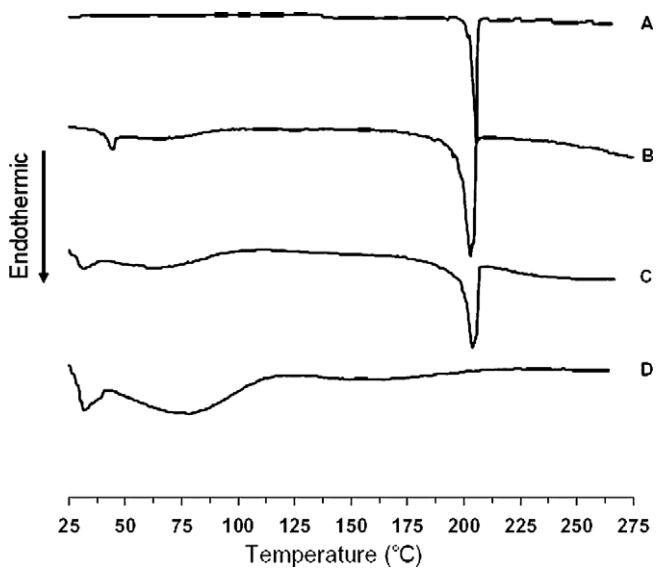

Fig. 3. DSC thermographs of: BUH (A), co spray-dried agglomerates of BUH and KSR in 1:1 D:P ratio (B), physical mixture of BUH and dried-powdered KSR in 1:1 D:P ratio (C) and dried-powdered KSR (D).

2 occurs at 95 °C according to Behme et al. [15]. Particularly for the co-agglomerates or physical mixtures containing ERS (Fig. 2B and C) the melting onset is much lower than that of pure BUH. However for the physical mixture the remarkably lower melting onset may be attributed to the broad endothermic peak of dried-powdered ERS polymer (Fig. 2D) around the melting of both BUH forms (188–203 °C) while for the BUH-ERS co-agglomerates the lower melting onset (very close to the m.p. of Form 1, 188 °C) might also be indicative of development of Form 1 during the co spray-drying. Between the co-agglomerates or physical mixtures containing KSR (Fig. 3B and C) and

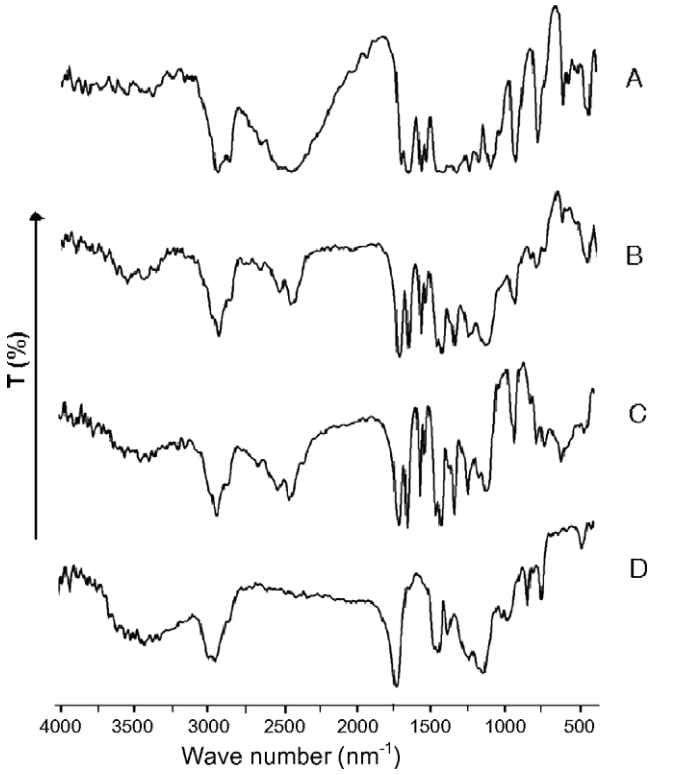

Fig. 4. FT-IR spectra of: BUH (A), co spray-dried agglomerates of BUH and ERS in 1:1 D:P ratio (B), physical mixture of BUH and dried-powdered ERS in 1:1 D:P ratio (C) and dried-powdered ERS (D).

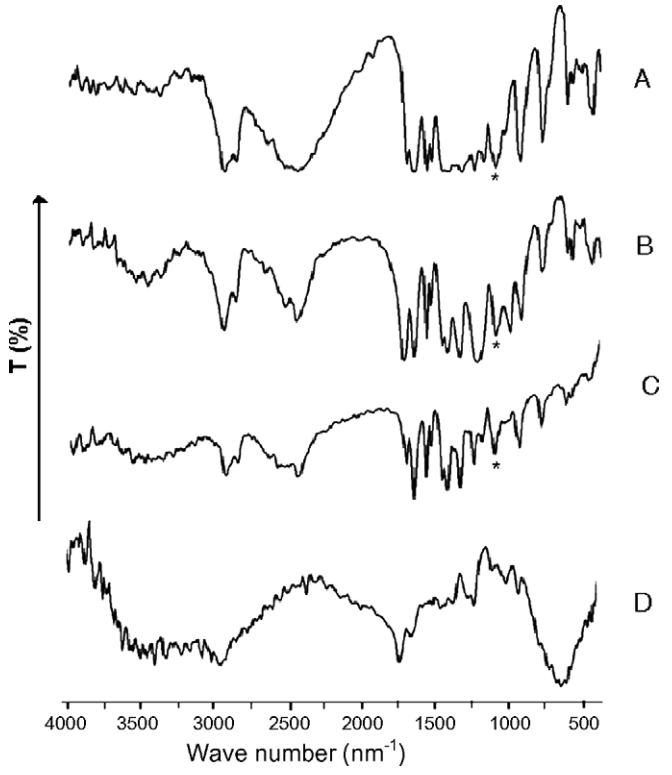

Fig. 5. FT-IR spectra of: BUH (A), co spray-dried agglomerates of BUH and KSR in 1:1 D:P ratio (B), physical mixture of BUH and dried-powdered KSR in 1:1 D:P ratio (C) and dried-powdered KSR (D).

the pure BUH (Fig. 3A) very small differences are observed in melting onset. The dried-powdered KSR (Fig. 3D) does not show endothermic peak around the BUH melting point and the melting onset of the co-agglomerates and physical mixtures is very slightly lower than that of pure BUH (203 °C) indicating development of Form 2 BUH crystals during the co spray-drying.

The results of FT-IR spectroscopy are shown in Figs. 4 and 5. The FT-IR spectra of both physical mixtures and co-agglomerates of the same D:P ratio (1:1) show the presence of characteristic bands of BUH found in both crystal forms including those due to C═O stretching vibrations in the region 1650–1700 cm^{-1}, C═C stretching vibrations in the region 1500–1600 cm^{-1} and C─H in aromatic ring in the region 3000–3100 cm^{-1} [12] confirming that no remarkable drug-polymer interaction occurred upon spray drying. According to Sheikhzadeh et al. the most distinct difference between the two BUH polymorphs is the presence of a unique absorption band at 1153 cm^{-1} in Form 2 that is useful for qualitative and quantitative determination [12]. In Figs. 4 and 5 the FTIR spectrum of BUH raw material (A) show this peak confirming the results obtained by DSC that it is Form 2. In the case of BUH-ERS co-agglomerates and the corresponding physical mixture the confirmation of polymorphic Form 2 is not feasible either due to growth of BUH Form 1 or due to the presence of a wide large absorption band in the region 1050–1200 cm^{-1} of the dried-powdered polymer (Fig. 4D) that masks the 1153 cm^{-1} distinct band and does not allow the detection of Form 2 in Fig. 4B and C. Therefore, more capable identification methodology is needed for clarification of the existing crystal form of BUH in the BUH-ERS co-agglomerates. In the case of KSR the peak at 1153 cm^{-1} is present in both spray-dried co-agglomerates and corresponding physical mixture confirming the existence of BUH in Form 2 (Fig. 5B and C).

The results of drug release from uncompacted co-agglomerates are shown in Fig. 6A and B. They show that the release of BUH from the co-agglomerates increases with increasing D:P ratio for both APDs. This can be explained by an increased amount of drug being close to the surface and by the fact that the likelihood of a part of the drug being uncoated increases with higher drug loading [24]. However, Fig. 6A and B shows negligible difference due to the type of APD.

For the compacted co-agglomerates the dissolution results are shown in Fig. 7A and B. They show that the release of BUH increases with increasing D:P ratio for both APDs, as in the case of uncompacted co-agglomerates. Also, Fig. 7A and B shows that the release rate decreases with time for both APDs. By comparing the dissolution profiles between compacted BUH-ERS and BUH-KSR co-agglomerates (Fig. 7A and B), it can be seen that ERS retards the dissolution of BUH from matrix tablets much less than KSR. In the case of BUH-ERS compacts 80% of BUH was released at 4 h for lowest (1:9) D:P ratio cor-

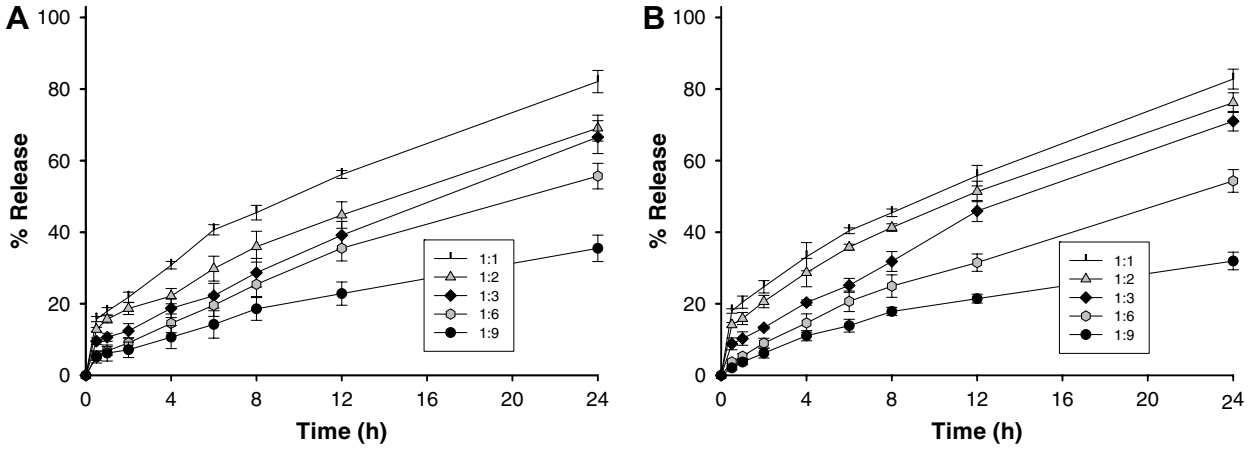

Fig. 6. Release profiles of uncompacted BUH-ERS (A) and BUH-KSR (B) co-agglomerates differing in drug:polymer ratio. Points represent the mean of three replicates and error bars represent the standard deviation.

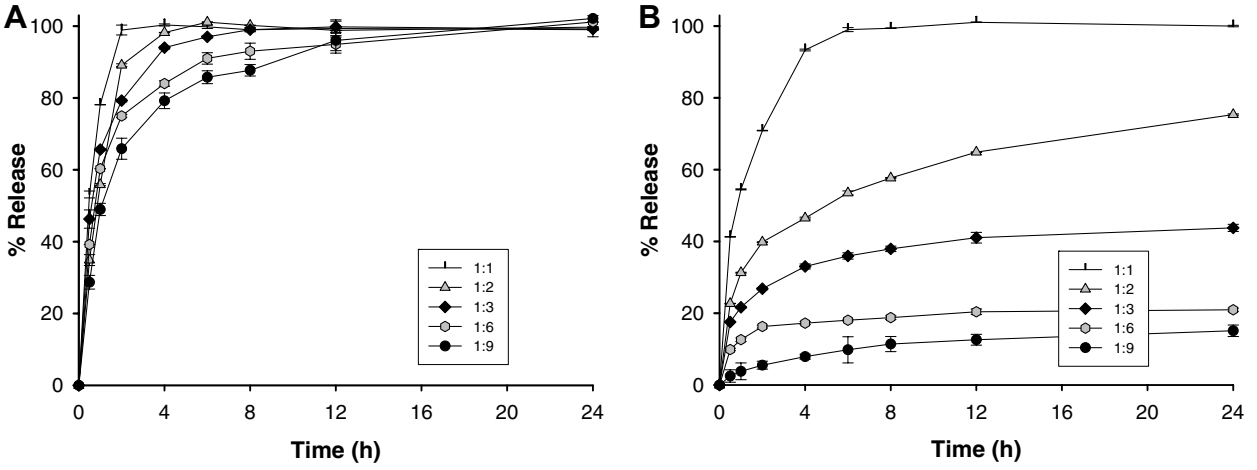

Fig. 7. Release profiles of compacted BUH-ERS (A) and BUH-KSR (B) co-agglomerates differing in drug:polymer ratio. Points represent the mean of three replicates and error bars represent the standard deviation.

responding to highest polymer content and complete dissolution (~100%, after 24 h) was observed for all D:P ratios, while in the case of BUH-KSR compacts only 13% of BUH was released at 24 h for lowest (1:9) D:P ratio and complete dissolution (~100%, after 24 h) was observed only for highest (1:1) D:P ratio. Therefore, the compacted BUH-KSR co-agglomerates of D:P ratio lower than 1:2 have the potential for application in extended release formulation of BUH. Similarly, less-than-expected release retardation by Eudragit RS was previously reported for the release of diltiazem HCl from microcapsules and microspheres prepared by spray drying of non aqueous systems [24].

Dissolution profiles of the uncompacted co-agglomerates cannot be compared to those of the compacted because of the difference in the employed methodology, but they are helpful in clarifying the differences between dissolution profiles of the compacted BUH-ERS and BUH-KSR co-agglomerates. The dissolution behavior of the compacted co-agglomerates was consistent with their disintegration. Tablets prepared from BUH-ERS co-agglomerates have shown remarkable erosion to almost complete disintegration, which should be responsible for inadequate release sustaining. Tablets prepared from BUH-KSR co-agglomerates did not disintegrate even at high D:P level. Since the release difference due to the type of APD is negligible for the uncompacted co-agglomerates, Fig. 6A and B, the longer retardation of drug release in the case of BUH-KSR tablets comparatively to BUH-ERS tablets might be attributed to increased adhesion and decreased erosion probably due to presence of PVP. Also PVP may increase the viscosity within the tablet channels and result in decreased drug diffusion and release. Higher dissolution rate in the case of BUH-ERS tablets might be explained also by the poor compactability of the BUH-ERS co-agglomerates since they showed increased tendency of lamination. Therefore, the slow and incomplete (less than 100%) release for the compacted BUH-KSR co-agglomerates may be presumably attributed to predominance of plastic deformation for the KSR coating, which may also be enhanced by the presence of PVP, instead of

fragmentation which may be predominant for the ERS coating during the tableting. This is in agreement with the lower glass transition temperature for KRS comparatively to ERS, Figs 2 and 3 (about 41 vs 55 °C). Improvement of release profile or programming regarding kinetics (zero order) and completeness in 24 h (which is considered the maximum suitable time for peroral administration), in case of KSR, needs further investigation by addition of suitable excipients (e.g. channeling agents, disintegrants) either to the dispersion before spray drying or to the co-agglomerates before tableting.

4. Conclusions

Larger co spray-dried agglomerates of slightly higher than 100% encapsulation efficiency are developed at high D:P ratio, presumably due to extensive coalescence caused by crystallized BUH. The surface of the co-agglomerates is rougher in the case of ERS and becomes smoother as the proportion of BUH is decreased relatively to that of the polymer for both APDs (ERS and KSR). Some toroid particles are formed at medium (1:3) and low (1:9) D:P ratios.

The BUH-ERS co-agglomerates show lower melting onset, possibly due to the incorporated ERS or due to development of Form 1 BUH during the co spray-drying while for the BUH-KSR co-agglomerates the melting onset is very close to that of pure BUH raw material (203 °C) indicating development of Form 2 BUH crystals during the co spray-drying. The FTIR spectra and particularly the presence of characteristic peak of form 2 (at 1153 cm^{-1}) in the case of BUH-KSR co-agglomerates confirms the development of Form 2 BUH crystals indicated by the DSC. For the clarification of BUH crystal form in the BUH-ERS co-agglomerates more capable identification methodology is needed.

The tablets of BUH-ERS co-agglomerates show remarkable erosion to almost complete disintegration and inadequate release sustaining, while those of BUH-KSR co-agglomerates with D:P ratio lower than 1:2 have the potential for application in sustained release formulation of BUH.

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