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Co-precipitation with PVP and Agar to Improve Physicomechanical Properties of Ibuprofen

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ABSTRACT

Objective(s): Ibuprofen is a problematic drug in tableting due to its viscoelastic properties. Additionally its high cohesivity results in low flowability. In this study, co-precipitation of ibuprofen with varying concentration of agar and PVP to optimize properties of Ibuprofen was carried out.

Materials and Methods: Co-precipitates of ibuprofen- PVP or agar were prepared by solvent evaporation technique under vacuum condition. Differential scanning calorimetry (DSC), X -ray diffraction of powder (XRDP) and FT-IR spectroscopy were used to investigate the solid state characteristics of the co-precipitates. The dissolution behavior, flowability, particle size and compaction properties of various batches were also studied.

Results: Co-precipitation of drug with agar led to a change in habit from needle to plate shape crystals, while drug –PVP co-precipitates had agglomerated structure and consisted of numerous crystals which had been aggregated together. The co-precipitates showed improved flow properties compared with ibuprofen alone. Precipitation of ibuprofen with these additives led to modification in the dissolution of the drug. Agar in 1% w/w improved slightly the dissolution rate of drug while PVP had a negative impact and led to reduction in the dissolution rate of drug to less than that of pure drug. The all obtained co-precipitates exhibited significantly improved tableting behavior compared with drug crystals alone. This may be due to this fact that, the polymer covering the drug particles increases and changes the nature of the surface area available for interparticulate bonds between particles. DSC, XRDP and FT-IR experiments showed that drug particles, in co-precipitates samples, did not undergo polymorphic modifications.

Conclusion: The study highlights the influence of polymeric additives on crystallization process leading to modified performance.

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Introduction

Direct tableting has been renewed as a preferable process by simply mixing and compressing powder to save time and cost in comparison with granule tableting. The direct compression of a powder depends on its flowability and mechanical properties (1). Some drug crystals exhibit appropriately such properties, but many materials have very poor flowability and compactibility.

Direct tableting of latter materials has been successfully industrialized by coformulating higher amounts of additives (≥75%) (2).

However, it is desirable to reduce the amount of additive, thus decreasing the size of the dosage form, in order to improve patient compliance and save production costs. On the other hand, the use of direct compression in the production of high –dose formulations is limited, since large quantities of excipients are ordinarily re-

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Table 1. Results of solubility, contact angle, Carr index, particle size, melting point and enthalpy of fusion for the samples (mean±SD, n=3)

samples	Solubility (μg/ml)	Contact angle (°)	Carr index (%)	Mean Particle size (μm)	Melting point(°C)	Enthalpy (cal/g)
Ibuprofen	52.1±9	58.2±5.2	40±1.2	120/20 (length/breadth)	81.63±0.2	25.72±0.9
Agar 0.1%	60.5±8	30.3±4.8	33±1.1	100/15 (length/breadth)	80.98±0.3	22.29±0.8
Agar 0.5%	63.5±6	28.4±3.6	34±0.9	50/8 (length/breadth)	81.82±0.2	24.98±1.0
Agar 1%	64.3±5	38.3±4.3	31.3±1.1	10	80.92±0.4	23.48±0.8
PVP 0.1%	58.3±8	34.3±3.9	22±0.8	110	80.50±0.3	21.72±1.0
PVP 0.5%	59.6±7	25.3±4.2	18.5±0.9	150	80.88±0.3	21.83±0.9
PVP 1%	57.8±9	28.2±3.5	24±0.9	250	80.14±0.4	20.29±1.1

Table 2. The tensile strength of the compacts of the samples (mean±SD, n=5)

	Tensile strength(MPa)	
	Compression pressure	
Sample	25 (MPa)	50 (MPa)
Ibuprofen	0.51±0.20	0.60±0.22
Agar 0.1%	8.86±0.81	9.7±0.61
Agar 0.5%	8.05±0.75	10.09±0.54
Agar 1%	8.19±0.65	12.52±0.78
PVP 0.1%	8.55±0.58	10.75±0.81
PVP 0.5%	10.68±0.62	13.56±0.85
PVP 1%	11.10±0.72	14.40±0.63

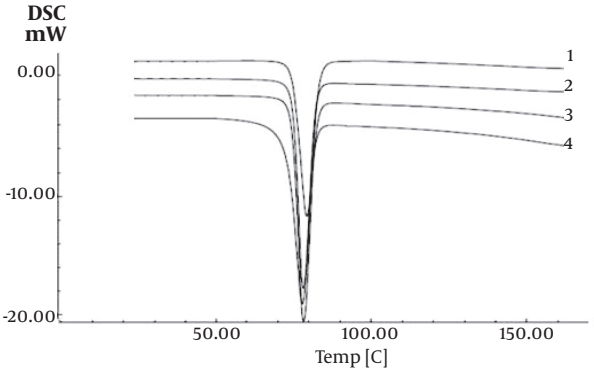

Figure 4. Thermograms of the samples; 1:drug -PVP (1%), 2:drug-agar (1%), 3: drug-agar (0.1%), 4: ibuprofen without additives

strength. The compact hardness of the drug significantly increased in the presence of the additives and with increasing concentration ($P<0.05$). The compression studies showed that the tensile strength of tablets made from the co-precipitates were sensitive to compression pressures. In other words, the tensile strengths of those tablets markedly increased as the compression pressure was increased from 25 to 50 MPa.

Dissolution

Results of the dissolution study are illustrated in Fig.5. The percentage of drug dissolved within the first 20 min was used to compare dissolution profiles of the various samples. According to this Fig, co-precipitation with agar (0.5% and 1%) produced crystals with slightly higher dissolution rate than crystals obtained without any additive. However, co-precipitation with PVP (0.5% and 1%) led to decreasing dissolution rate of drug even lower than pure ibuprofen.

The aqueous solubilities of drug crystals alone and also in presence of additives are listed in Table 1. There were

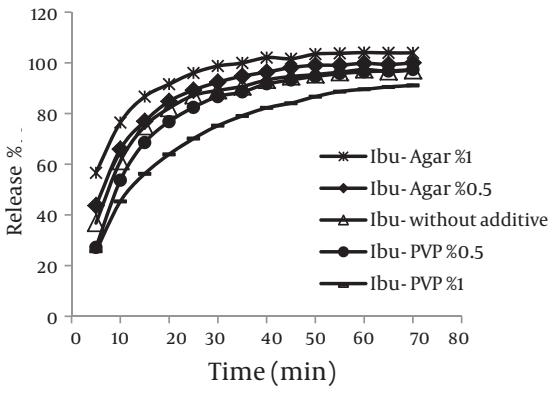

Figure 5. Dissolution profiles of the co-precipitated samples and ibuprofen powders (Mean±SD, n=3)

no significant differences between the solubility of these samples (P>0.05). Table 1 also gives the mean contact angle values of water droplets on the sample surfaces. The results for co-precipitated samples indicate better wettability (lower contact angle) by water compared to pure ibuprofen (θ= 58.2).

Discussion

Micromeritic properties

It has been reported that effective additives influence the crystallization process and produce crystals of a different shape to those formed from a pure solution (15). Ibuprofen recrystallized without polymer occurs as fine micronized needles, while the recrystallized product using agar and PVP had different external appearances. Crystallization in the presence of agar led to a change in habit from needle to plates. Also an increase in the concentration of agar led to reduction in crystal size. The crystals generated in the presence of agar (1%) were very fine and in the range of 10 μm. This may be because polymers prolong supersaturation and increase the viscosity of the medium for controlling crystallization (16). Reported studies have suggested that adsorption of polymer on the surface of nuclei leads to the formation of a diffusional boundary layer, which inhibits nucleation and growth, resulting in finer crystals yield (16, 17).

Figs. 1d and f show that the majority of the crystals obtained in presence of PVP are aggregated.

PVP has been shown to be a strong crystallization inhibitor for numerous drugs including captopril and levonorgestrel (18), zolmitriptan (19), and sulfamerazine (20). When PVP was added to supersaturated solutions of sulfathiazole, the growth of the seeded crystals initially slowed down and then completely stopped. A similar effect is likely for the ibuprofen-PVP systems studied. PVP because of its strong inhibitory effect on crystal growth, doesn't allow for construction of initial big crystals and therefore fine microcrystals were formed. Aggregation of these very small crystals of ibuprofen could be expected by their flat shape and high hydrophobicity as it has been reported by other research (21). Obviously, by increasing concentration of PVP, the inhibitory effect of PVP on crystal growth has been promoted and finer crystals with higher trend to aggregation have been produced which interpreted forming larger particles.

In order to achieve uniformity in tablet weight, the feed crystals must flow and pack smoothly into the die cavity of the tablet machine. Therefore, in design of particles for direct compression it is essential to improve the flow and packing properties. The low values of Carr's index for co-precipitates in comparison to drug alone indicated their better flowability and packability (10, 11). The flowability correlates with the observations by microscope, the crystals that are mainly aggregated (drug-PVP) have the best flowing properties; while ibuprofen crystallized without additives shows the worst flow properties. Drug-agar powder takes an intermediate position. These results can be attributed to particle size of samples. The drug –PVP co-precipitates had superior flow due to larger particle size and near spherical shape (Figures. 1d and e). The area of contacts in the powder bed for spherical shapes was smaller than that for others and this might lead to better flowability. Results of this study confirmed previous works which have shown that differences in crystal habit may strongly influence the particle orientation and modify the flowability and packing characteristics of a drug powder (22).

FT-IR, X-ray and DSC

FT-IR spectra of all samples showed characteristic peaks of ibuprofen at 1720 cm-1(C stretching) and 2955 cm-1 (bonded –OH stretching) indicating that there was no any interactions between the drug and the additives. Change in the relative intensities of XRPD peaks of co-precipitate samples compared with pure drug can be interpreted as follows. Garekani *et al* (23) have attributed decrease in the intensity of XRPD peaks to the changes in crystal habit of drug crystals. As a result of changing crystal habit, the relative abundance of the planes exposed to the X-ray source would have been altered, producing the variations in the relative intensities of the peaks. On the other hand, it has been shown the crystal size can have influence on the intensities of XRPD peaks (24). Change in size and habit of crystals of the co-precipitates in comparison with crystals of pure drug can be seen in Fig. 1. Moreover, decrease in the intensity of XRPD peaks may be due to presence of amorphous regions in the crystals, or due to weakening and disruption of crystal lattice and order.

The little changes in DSC data of co-precipitate samples compared with pure drug, may be attributed to the presence of amorphous regions in the crystals, or due to weakening and disruption of crystal lattice and order, or may be an effect of crystal size (25). Results from X-ray diffraction analysis and DSC ruled out polymorphic modification.

Tabletability

Tabletability is the capacity of a powdered material to be transformed into a tablet of specified strength under the effect of compaction pressure and is represented by a plot of tablet tensile strength against compaction pressure (26). Poor tabletability of ibuprofen crystals can be attributed to the presence of crystal faces that give poor adhesion to other crystals and the absence of the faces that are required for optimal adhesion (27). The presence of polymers (agar and PVP) with ibuprofen crystals in co-precipitated samples affected the properties of their

compacts. The increase in tablet strength is influenced by the properties associated with both the polymer and the drug crystals. When drug is co-precipitated with a polymer, the particles will be covered by the polymer which could act as binder. Addition of a binder to a compound generally resulted in an increase in tablet strength. According to previous researches, the addition of binder is normally expected to increase the tensile strength of a pharmaceutical compact compared with compacts of the pure material (28-30). Normally, the binder covering the drug particles increases and changes the nature of the surface area available for interparticulate bonds (28) and the available polymers can act as contact point between the ibuprofen particles. Therefore, both increased total contact points and effective bonding area increase the tablet tensile strength. It has been suggested that the tensile strength of the mixture may best be increased by ensuring a high degree of coverage of the particles by the binder (28) which could be expected to achieve by co-precipitation technique. On the other hand, compaction of the powders into tablets showed that for the materials which fragmented to a limited degree during compression, the particle size and shape affected the compact strength (31-33). However, for materials which fragment markedly during compression, the size and shape of the particles before compaction did not affect compact strength. It has been previously shown that various ibuprofen crystals undergo plastic deformation (low fragmentation) during compression (34, 35). Therefore, according to these facts, improved in tensile strength of the co-precipitated samples may also be attributed to change in crystal shape and size of the ibuprofen crystals. Two –way analysis of variance showed that there were significant differences ($P<0.05$) between the tensile strengths of tablets made from different co-precipitated samples at compression pressures of 25 and 50 MPa. The samples obtained with PVP exhibited the best compression properties, and at each compression force, the tablets had higher tensile strength than tablets made from drug –agar co-precipitates.

Dissolution

According to solubility results, modifying dissolution rate of drug with additive by affecting on solubility of drug was ruled out. The presence of hydrophilic polymers decreased the contact angle of these particles (Table 1). Therefore, the enhancement of the dissolution rate of drug in drug-agar co-precipitates can be attributed to the presence of this hydrophilic polymer, which increases wettability of sample. On the other hand, these data can also be attributed to the smaller particle size of ibuprofen crystals obtained with agar compared with the drug crystals obtained without additives.

However, the amount of drug released is markedly reduced by the presence of PVP (0.5% and 1%) and value even lower than those of ibuprofen alone obtained even though the powder had higher wettability (lower contact angle). Thus, a better wettability caused by PVP in the final product does not cause the effect. Aggregation of drug crystals and consequently larger particle size in drug-PVP co-precipitates may be the main factor that reduces dissolution rate of drug in comparison with other samples.

Moreover, lower dissolution rate of drug –PVP co-precipitates may be attributed to the increase in the thickness of the diffusion layer due to the high viscosity of the polymer (36). PVP does not show saturation solubility as such, but rather swell and absorb water to produce a continuum of concentration between the solid surface and the bulk medium (37). Once in solution in the diffusion layer, the viscosity is sufficiently high to render diffusion through the concentrated layer slow, thereby impeding dissolution. These finding are similar to results of the previous study, where in PVP was found to retard dissolution of mebendazol recrystallized in presence of the polymer (38).

No significant difference ($P>0.05$) could be observed in the percent of drug release from the co-precipitates obtained in presence of 0.1% additives (PVP or agar) compared to the drug crystals obtained without additives. To prevent confusion in dissolution profiles, these results were not reported.

Conclusion

The presence of small amount of additive in the co-precipitated samples modified significantly the drug crystal properties. The crystal shape changed from acicular without additive to platy form with agar. While the spherical particles obtained in the presence of PVP seem to be aggregates of numerous fine microcrystals which had stuck together.

Crystals generated using co-precipitation approach in presence of additives were isomorphic with untreated ibuprofen, although they exhibited variable crystal habit and size. While faster drug release was obtained from drug-agar system, those of the drug-PVP system gave slower drug release than crystals grown in the absence of additive. The presence of additives in co-precipitated samples affected the properties of their compacts. The compact tensile strength increased in presence of additives and these were concentration dependent. The co-precipitation technique used is simple and minimizes the use of additives. These co-precipitates may be useful for the preparation of ibuprofen tablets by direct compression method.

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