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Coprecipitation on slurry to prepare drug–silica-polymer formulations by compressed antisolvent

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ABSTRACT

This work proposes for the first time a coprecipitation-on-slurry method using CO_2 as antisolvent to prepare formulations of a poorly water-soluble drug (tolbutamide) with micrometric silica (60 and 5 μm) and biopolymers. Mixtures were processed from acetone using the batch gas antisolvent method. Polyethylene glycols and Eudragits were selected as polymers capable to modify the drug dissolution behavior. Morphology, size distribution, crystal lattice and dissolution kinetic were characterized. Products were recovered as powders providing a polymer/silica ratio of 50/50, with coarser grains in Eudragits powders compared to PEG's. The size distribution evidenced populations between 10 and 100 μm that were not obtained when TBM was single processed, together with larger agglomerates. In terms of precipitation mechanism, the drug has grown almost unaffected by the presence of silica and polymer in the liquor except for a smaller size, since neither the morphology nor the crystal lattice was significantly changed. The products exhibited substantially different rates of dissolution in accordance with the polymer function: the water-soluble PEGs improved the dissolution rate whereas the water-insoluble Eudragit sustained notably the drug release.

1. Introduction

Preparation of solid formulations is a difficult task in pharmaceutical industry since it has to merge both the therapeutic action and the process requirements. The particles agglomeration can affect the downstream processing operations that transform the active ingredient into a formulation (tabletting, granulation, mixing, blending, coating), and consequently prejudices the formulation homogeneity as well. Agglomeration is very difficult to avoid since it comes from interactions between particles that, being alike, exhibit the same surface characteristics. Size, surface roughness and irregular shape contribute to the cohesion of powders that conversely do not flow well [1]. Addition of glidants to powders, as for instance silica, is a common practice in pharmaceutical industry to aid the powder flowability [1–4] or to achieve high aerosolization efficiency of inhaled products [5]. For orodispersible tablets, the formulation comprises additional particles to silica such as lubricant or diluent in order to improve the product dispersal efficiency [6,7].

Employing silica particles as delivery vehicles of therapeutic, biological sensing or imaging agent has gained significant interests lately because of their biocompatibility, versatility and ease of functionalization [8]. Because of their large pore size and their high porous volume, mesoporous silicas (MCM-41, FSM-16, SBA-15) have attracted much attention to formulate hydrophobic drugs of poor solubility in biological fluids, ca class II-drugs of the Biopharmaceutic Classification System. The loading depends on matrix characteristics, on molecular interactions between the drug and the matrix, on the loading method as well [9–15] and loadings as high as 40–45 wt% were reported for ibuprofen [9,12]. Regarding the targeted property, the dispersion of the drug in an amorphous state rather than as crystals and the improved wettability of the system are responsible for the enhanced drug dissolution rate [15–18].

This work examines the feasibility of preparing complex formulations of a hydrophobic drug, tolbutamide, in presence of polymer and silica. The proposed formulation route uses compressed CO_2 as an antisolvent to induce both the drug and the polymer coprecipitation on a silica slurry. The starting solution is therefore an organic solvent that contains the drug and polymer as dissolved species and silica as dispersed particles. As outlined before, silica particles can act for the benefit of the preparation route, as passive spacers to deagglomerate API particles, as a wetting agent, or as an active carrier if API molecules are physically sorbed. But presence of particles can also impact the precipitation behavior of the drug and polymer. Indeed, since the proposed route proceeds as a crystallization operation, any substances other than the material to crystallize may act as impurities and therefore are susceptible to affect considerably nucleation and growth behaviors [19]. For polymers, their

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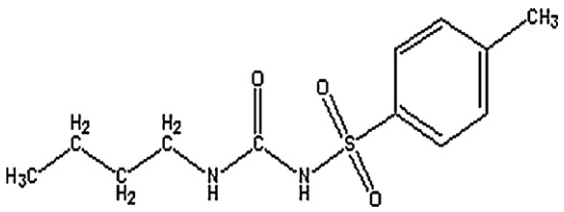

Fig. 1. Tolbutamide chemical structure.

precipitation by CO_2 as antisolvent remains challenging especially for amorphous or semi-crystalline polymers since a CO_2-induced plasticization effect [20,21] often leads to particles agglomeration or to the recovery of a film [22–24]. The addition of silica to a polymer solution can thus offer an extra surface for the polymer to film upon and consequently to help their recovery as particulate products. To summarize, we can expect that the presence of silica particles in preparations impact in several ways the processing route and the product characteristics as well.

In this work, Tolbutamide (TBM, Fig. 1) was selected as a model hydrophobic drug whose formulation with hydrophilic carriers is one method to improve the dissolution rate. This aryl sulfonylurea compound is an oral hypoglycemic agent used clinically in the treatment of insulin-dependent diabetic patients [25]. Tolbutamide exists as four polymorphs whose crystal pattern, bioavailability and stability are already documented [26]. As for formulations at atmospheric conditions, solid dispersions and inclusion complex of TBM have been obtained with silica [26] and cyclodextrins [27,28], respectively. Takeuchi's work [26] highlighted the influence of the silica type on the TBM dissolution property, with an increased rate obtained with hydrophilic silica and a sustained release obtained with hydrophobic silica. For TBM – processing by CO_2 as antisolvent, the only work reported in literature is author's own investigations [29]: the neat drug was recovered as polyedric particles with a crystal lattice of form III providing that acetone or ethylacetate were used as liquor solvent. The micronization of Tolbutamide was also realized by rapid expansion of supercritical CO_2 solutions [30], a method that produced three of the four polymorphs depending on the dissolution conditions (forms I, II and IV). The use of menthol as a co solvent to enhance the TBM solubility was investigated by Lin et al. [31] who evidenced in addition the polymorph conversion of form I to form II after the RESS processing. Regarding the polymeric carriers, polyethylene glycols were selected as water-soluble polymers due to their well-known ability to increase bioavailability of hydrophobic drugs [32–36]. However, it was complained that drugs prepared with water-soluble polymer carrier tend to be difficult to handle since often sticky or tacky [26]. Furthermore, the target release of a drug is an area that attracts much attention nowadays. Supercritical formulation of tolbutamide with carriers for sustained release was thus attempted as an additional application of the methodology. Eudragit® polymers fulfill requirements of controlled and localized release of the active drug to a very high extend enabling the development of tailor-made solutions [37]. Eudragit® are copolymers of acrylic and methacrylic acid esters branched with various functional groups. The Eudragit RL- and RS-types have a quaternary ammonium as functional group, and contrary to PEGs they are water-insoluble. Nevertheless they are both swellable, so they represent interesting materials for the dispersion of drugs [38–42].

Preparation of oxide-based formulations of pharmaceutics by supercritical CO_2 has been marginally reported in literature, contrary to the coating of oxide particles with polymers [43–49] or to the co-precipitation of polymer and API [24,50–52]. For the preparations of silica–API systems, CO_2 can act as a solvent that conveys the drug within a porous material [53,54] according to the same approach developed for polymer loading [55,56]. When reported [53], characterizations of formulations revealed that the drug existed mainly in an amorphous state, which contributed to the observed increase of the dissolution rate.

Closer to the procedure hereby proposed is the use of CO_2 as antisolvent for the drug [57]. The addition of CO_2 to a liquor that contains the dissolved griseofulvin and the silica in suspension provokes the precipitation of the API and leads further to the recovery of an oxide–API solid mixture. The technique was shown to produce a powder of enhanced flowability and of lower size compared to the neat drug, but the presence of silica did not improve the dissolution rate of this poorly water-soluble compound. Finally, a third route uses CO_2 as a suspension medium [58]: nanoflakes of itraconazole and nanoparticles of silica were pressurized with supercritical CO_2 before being rapidly depressurized through a nozzle. The concept is different from the two previous methods since there are no steps of initial dissolution and recrystallization. Aiming at deagglomerating and mixing the two powders without any solvent, the technique produced a powder of improved flow properties and of better quality upon storage. Dissolution studies evidenced a substantially higher dissolution rate of the preparation compared to the raw API.

The previous cited literature is dealing with binary systems, i.e. API–oxide or polymer–oxide, but to author's best knowledge, the processing of the ternary API–polymer–oxide mixture has not been reported yet. The objective of the work is therefore to propose a coprecipitation-on-slurry method using CO_2 as antisolvent to prepare ternary products made of a hydrophobic drug, a silica excipient and a polymer. Polyethylene glycols and Eudragit polymers were selected as polymers capable to modify the dissolution behavior of the drug, whereas two silica of different particle size were selected for processing purpose. The prepared products were characterized for morphology, size distribution and crystalline state and the dissolution kinetic of selected samples was investigated as well.

2. Materials and methods

2.1. Materials

Tolbutamide (TBM, chemical structure in Fig. 1) and polyethylene glycols (PEG) of 3400, 4600 and 8000 MW were purchased from Sigma–Aldrich. Acetone (ACE, 99.8% purity) and CO_2 (99.5% industrial grade) came from VWR and Air Liquide (France), respectively. Eudragits (RL100, RS 100, L 100) from Evonik Rohm Pharma Polymer (Degussa) were kindly supplied by IMCD (France). In the preparations, Eud RL and RS were used as a mixture, with a RL:RS ratio of 1:2. Silica UP120 (SiO_2-UP120, Interchim, France) is made of porous spherical particles of 5 μm mean size and 120 Å of pore diameter. Lichroprep Si60 (Merck) is made of coarse particles in the range of 30–150 μm in size. All components were used as received.

2.2. Experimental set-up and procedure

Experiments were carried out in a batch GAS apparatus already described (see [29,59] for details). Briefly, the precipitation unit is a 0.490 l vessel equipped with a stirrer ended by a Rushton-type turbine that plunges into the solution. The CO_2, introduced by a Lewa pump, is dispersed into the solution through the eight turbine holes. The vessel temperature is controlled by heating jackets. A stainless steel filter (porosity 5 μm) overtopped by a membrane disk of 0.22 μm in porosity collects the produced particles at the vessel bottom. In a typical experiment, 65 ml of a drug/polymer/silica suspension was processed. The polymer and the drug were first dissolved in acetone – at variable concentration for the polymer, at the fixed value of 58 mg/ml for the drug – before adding a variable