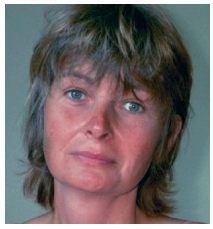
Compressed CO_2 antisolvent to produce drug-polymer formulations



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Introduction

Precipitation using supercritical fluids (SCF) was mostly developed as an alternative approach to conventional liquid crystallization, with aims of controlling particle sizes and reducing the residual solvent content in drugs, in addition to the environmental advantage of reducing liquid waste. Carbon dioxide (CO_2) is by far the fluid the most extensively used when processing pharmaceutical or food compounds, thanks to its mild critical conditions of temperature (T_c = 31.05 °C) and pressure (P_c = 7.28 MPa). Its non-polar nature that restricts its solvation capability, was turned into advantage years ago, with the introduction of the compressed anti-solvent concept. In these techniques, the compound is initially dissolved in an organic solvent and the subsequent addition of CO_2 causes the solute precipitation. The antisolvent CO_2 is also potential for coprecipitating a drug and a matrix in order to prepare suitable formulations, since, again, many biopolymers are not soluble in compressed CO_2. However, polymers –and specially the amorphous- might interact strongly with CO_2, which leads to a dramatic decrease of the glass-to-rubber transition temperature, that in turn, makes the recovery of a powder very difficult. When the drug/solute is moderately soluble in CO_2, formulations can be carried out by impregnation, in which the supercritical fluid acts as solvent and carrier for the drug to be transported into the matrix [Diankov 2007]. This technique has the unique advantage to be completely 'solvent free', since no organic solvent is added to the fluid. This paper presents various examples of coprocessing drug and matrix with the help of compressed CO_2, using mostly the fluid as antisolvent in precipitation; biodegradable PLA, PLGA, Eudragits or PEGs were considered as polymer matrix.

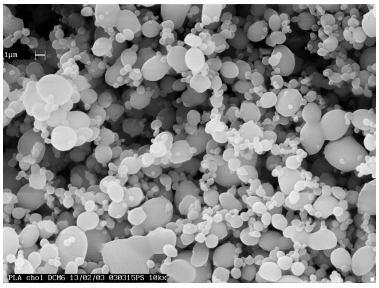
Methods

Antisolvent experiments are performed in a semi-continuous set-up, in which CO_2 flows continuously through a vessel of 0.5 L whose temperature and pressure are maintained by heating tapes and metering valve, respectively [Duarte 2007]. The solution that contains the species to precipitate is sprayed through a nozzle into the CO_2 flow; the precipitate is separated from the out flow by filters; drying of particles is realized in-situ by maintaining a CO_2 flow during 30 or 60 min depending of the solvent. After depressurization, particles are collected and further analyzed.

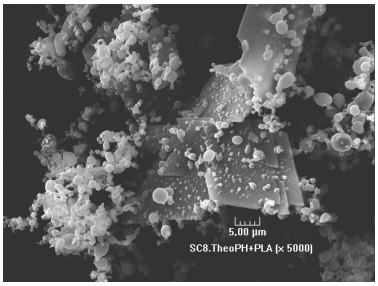
Results and Discussion

Poly lactic acid, specially l-PLA, semi-cristalline, is the most processed polymer by CO_2 antisolvent, and is easily produced as spherical particles, even when processed as single compound. When co-precipitated with a drug, the obtention of a suitable formulation is more dependent of the drug processability than of the polymer behaviour. The following pictures show the morphology of powders produced with l-PLA (Galastic, >100 kD) and two model compounds. Cholesterol is a steroid quite soluble in compressed CO_2; its precipitation gives particles of needle-like morphology, whose sizes can be controlled by acting on concentration and conditions of miscibility between the solvant and the antisolvent [Subra 2004]. Its coprecipitation with PLA was feasible, and the morphology of particles was mainly modified by the drug concentration. Best conditions used a

diluted solution of cholesterol, and yielded to spheroid particles (see figure 1) with no visible needles of cholesterol, although the RMN analysis estimated the cholesterol content at 16%.
In case of theophylline, PLA was a suitable polymer to sustain the release of the drug in biological fluids. Theophylline is moderatly soluble in CO_2, and its precipitation as pure drug was effective providing the use of a two-solvents mixture [Subra 2005]. Our investigations [Roy 2007] yield to formulations that enable to sustain the release of the drug (exemple of 50% of the drug released in 4 hours compared to 10 min when pure), but whatever the conditions, the products were made of two particle populations where plate-like drug, coated or not, existed besides the PLA spheroids.



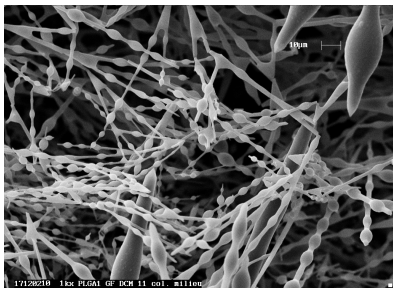
35°C 10 MPa, from DCM
Particle size : 0.5 – 5 µm ;



40°C, 10 MPa,
from EtOH :DCM

Figure 1 : precipitation of Cholesterol (left) or Theophylline (right) and l-PLA by CO2 antisolvent technique

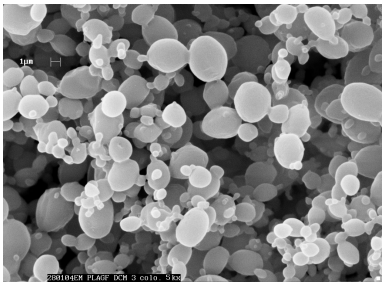
PLGA, a copolymer of lactic and glycolic acids offers the opportunity to modify the biodegradability of the product by varying the lactic and glycolic content. We used d,l-PLGA 50:50 (50-75 kD), which is amorphous. Contrary to l-PLA, the copolymer can be plasticized when contacted with compressed CO2; this behaviour precludes its precipitation as powder when processed alone, but enable however a coating of a coprecipitated drug. In Figure 2, several examples of products are reported.



40°C 8.5 MPa C_{gri} = 8 mg/ml

Details of coated needles

40°C 8.5 MPa C_{gri} = 100 mg/ml



With PLA, 36°C 10.0 MPa

Figure 2 : precipitation of Griseofulvine and d,l-PLGA or l-PLA by CO2 antisolvent technique from DCM solutions

The film forming ability of the PLGA in CO_2 medium is emphasized on the upper pictures, where the crystal of the Griseofulvine drug is coated by a a continuous layer of polymer, which however shows regularly expansions as balloons. When concentrated solutions are used, the product exhibits a different morphology, as long fibers embedded in droplets-like structures. The high concentration deeply influences the viscosity of the solution, which in turn, modifies the break-up mechanism of the jet sprayed by the nozzle, and thus can generate different structures than those issued from diluted regime of visosity. Finally, attemps were made to precipitate the drug with PLA, and again, provided very diluted concentration of drug, spherical particles were produced

Mesalazine (5-ASA) is another compound that we are actually dealing with. Carriers are selected according to the administration problem, that is a release of the active ingredient only in the colon. Eudragit® polymers (copolymers derived from esters of acrylic and methacrylic acid) offer ideal solutions for sustained release formulations, whereas Ethylcellulose has already been used for ASA delivery. Thus we explore the use of several polymer blends, as mixtures of Eudragit® (ERL 100 / ERS 100), Eudragit® ERL 100 and ethylcellulose or Eudragit® ERS100 as well. The products were usually recovered as a combination of big and small particles, as shown in Figure3. The dissolution profiles in acidic media (pH 1.2) showed a delay of the drug dissolution compared to pure 5-ASA, but the CO_2-produced formulations have to be improved in order to cut down completely the dissolution at this pH.

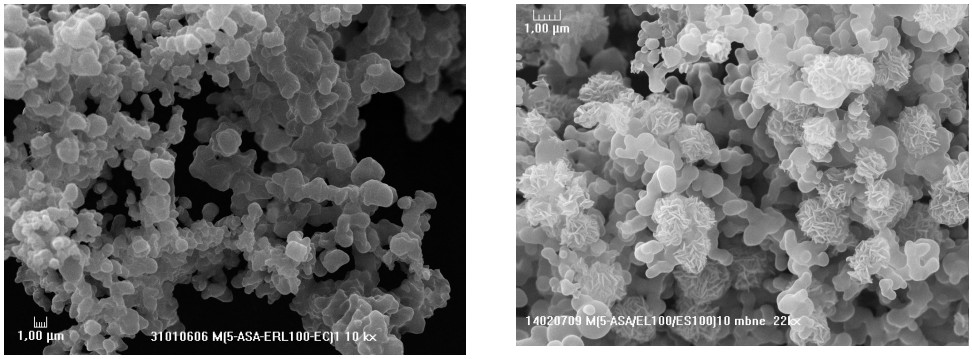


Figure 3 : Formulations of 5-ASA by CO_2 anti-solvent; left : with a blend of ethyl cellulose and ERL100; right : with a blend of EL100/ES100

Hydrophilic polymers as PolyEthyleneGlycols family (PEGs) are also currently investigated, due to their ability at improving the dissolution rate of poorly water-soluble drugs. PEGs are compounds that interact with $SCCO_2$, leading to a large decrease of their glassy temperature [Weismet, 1997], that in turns, render their recovery as powders very challenging!. Processing PEGs from 1450 to 8000 with Tolbutamide, we found that an increase of the molecular weight favored the obtaining of a powder, whilst a free-flowing powder was more easily recovered with the water-swellable Eudragit® L100. A detailed view of co-precipitated TBM and PEG 8000 (left) or Eudragit® L100 (right) is given in Figure 4. Whilst crystals of the drug seem to be coated by PEG, the morphology of the powder with Eudragit more suggests an independent precipitation than a coating. Tolbutamide has the particularity to exhibit four polymorphs; we observed that depending on the liquor solvent and supercritical conditions, Form I and III could be produced. When TBM is coprocessed with PEGs, some powders exhibit a form IV that was not obtained when tolbutamide was processed alone, but this needs to be deeply confirmed and further correlated to the experimental conditions.

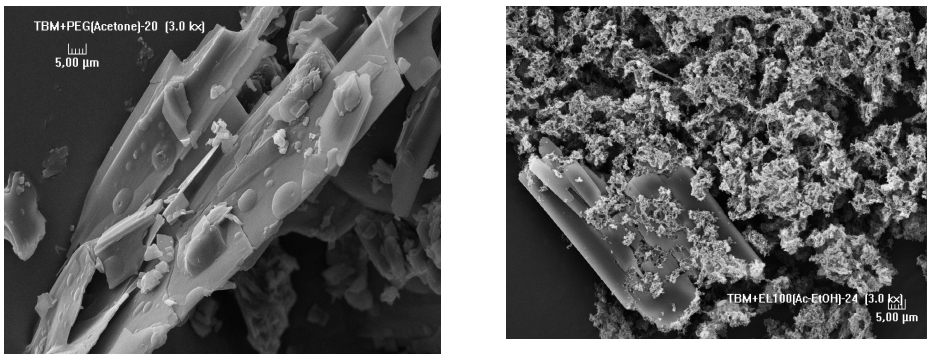


Figure 4 : Formulations of Tolbutamide by CO_2 as anti-solvent; left : with PEG 8000 from acetone ; right : with Eudragit L100 from acetone:ethanol

Conclusions

The successful coprecipitation of a drug and a carrier as a powder in which ideally, the drug is dispersed or entrapped in the excipient is a challenging task. Ideally, dealing with antisolvent precipitation (i.e. both species are dissolved in the solvent and an exterior agent makes the solids precipitated), the drug has to precipitate first to offer a surface available for polymer to coat. The precipitation conditions are under thermodynamic (solubility, miscibility, glassy depression) and kinetic (mixing rate of CO_2 and solvent, nucleation and growth rates) behaviours of the two species, so successful formulations are quite difficult to optimize. Although not discussed here, impregnation, in which only the drug is dissolved in compressed CO_2, is potentially a more favourable technique to achieve the fine dispersion of the drug in the carriers. When the drug is soluble enough in CO_2 to prevent the use of an organic cosolvent, the process is completely 'solvent free', which from health and environnemental concern is a major interest. However, polymers are susceptible to expand or to foam upon contact with CO_2, that in turn, might completely change the size and the release pattern of the final products. To conclude, supercritical route applied to the formulations is not yet mature, specially with the numerous CO_2 variants that are potential (emulsion, expansion of 'melted' phases..); close collaboration with chemists or pharmacists to specially adress therapeutic problems and challenges and to compare supercritical- and classical-products would largely contribute to the progress of CO_2 -based techniques.

References

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