UNIFORM SHAPE AND SIZE DRUG PARTICLES PREPARED BY A NEW PRESSURE INDUCED WATER ANTI-SOLVENT PRECIPITATION (PIWASP) METHODOLOGY

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The poor water solubility of many drugs is a challenge in pharmaceutical research. Because of their low bioavailability, several potential drugs have to be abandoned in pharmacological screenings because of their lipophilicity. Their dissolution rate is the limiting factor since drugs with a high lipophilicity can permeate biomembranes quickly. Thus, the research on strategies for drug dissolution enhancement is of high interest. The administration of a drug in a reduced particle size is a very promising way to improve drug bioavailability of poorly soluble substances [1]. For instance, in the case of nanosuspensions, the drug is delivered suspended in an aqueous media, and has a particle size small enough for pharmaceutical acceptability. In addition to overcoming issues of solubility, nanosuspensions enable a higher mass per volume loading in comparison to solutions, allowing reduced administration volumes, which is crucial for low-volume intramuscular and ophthalmic applications. On the other hand, the particulate nature of the dosage form might offer alternative pharmacokinetic profiles; both in intravenous delivery, where one might expect lower toxicity and more efficacious regimens, and in oral delivery, where we might find potential for first-pass hepatic metabolism [2].

In principle there are two strategies for producing fine particulate therapeutically active materials, with particle size in the range of 50nm-1μm: 1) mechanical milling of the raw material by wet or drying processes; 2) the conversion of the molecular products or educts dissolved in suitable solvents into micro- or nanoparticulate materials by precipitation, condensation, or by specific synthesis procedures. Milling techniques have several disadvantages resulting from the mechanical disruption process. The micronization process using mills is extremely inefficient because of the high-energy input that can alter the surface properties as a thermodynamically activated surface is created [3]. Thus milling affects several physical properties of the drug, such as powder flow, agglomeration behavior, or electrostatic behavior. Besides these effects, the chemical reactivity, crystallinity and physico-chemical stability can also be affected by milling [4,5]. Because of the disadvantages of milling processes, there is a strong concern on the development of new bottom-up strategies that produce directly the particulate drug [6]. In any «bottom-up» process involving precipitation from solution particle characteristics depend on the evolution, during the precipitation process, of the supersaturation rate (β), which drives nucleation rate and crystal growth, at each point in the solution [7]. Therefore, in the design of a precipitation technology, the control over β profile, by process parameters, is a crucial issue with a strong relevance in the scale-up. Compressed fluids (CF) have shown to be promising solvent media for the straightforward preparation of micro- and nanoparticulate molecular materials. The solvent power of CF, in contrast with liquid solvents, can be tuned by pressure changes, which propagate much more quickly than temperature and composition solvent changes [8,9].

Here, we present a new procedure, called Pressure Induced Water Anti-Solvent Precipitation (PIWASP), which enables the straightforward production of micro- and nanosized crystalline powders [10]. The driving force of this new methodology is the anti-solvent character of

water coming-out, by a pressure change, in a pressurized solution of the drug, dissolved in a "water/organic solvent/compressed fluid" mixture. Because ibuprofen is a widely used non-steroidal anti-inflammatory drug with a poor solubility in water, it has been used as a model drug to show the goodness of this new methodology. In fact, as it can be observed in the SEM images represented in the Figure, ibuprofen could be straightforward prepared as uniform spherical nanosized particles, using acetone as organic solvent and CO_2 as compressed fluid. Surprisingly, by powder X-ray diffraction and differential scanning calorimetry, it was observed that these particles have a high crystallinity degree. In contrast with conventional antisolvent precipitation techniques by liquid mixing [6], in the PIWASP process, the quality and characteristics of the final particles do not depend on the mixing efficiency. Indeed, in this new technology the antisolvent character of water emerges homogeneously over all the solution, and homogeneous supersaturation is achieved at molecular level.

P-PIWAS can be regarded as a "green" technology because the process wastes can be easily recycled, and the comminution and homogenization downstream process steps, which are required after conventional crystallization procedures, can be avoided.

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[7] β is the ratio between the actual concentration, C, and the saturation concentration, or solubility, Cs, of the solute to crystallize.

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Figures:

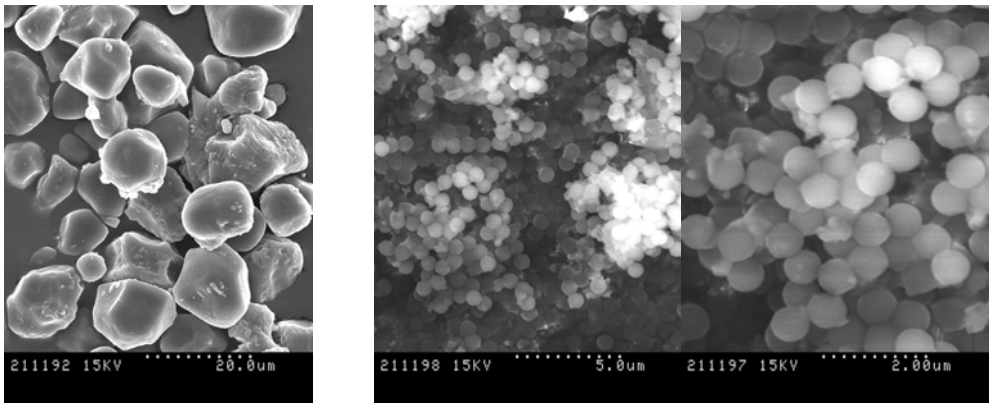

Figure. Unprocessed ibuprofen (left); processed ibuprofen by PIWASP (right)