ELABORATION OF IBUPROFEN MICROCOMPOSITES IN SUPERCRITICAL CO_2

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ABSTRACT

A multitude of pharmaceutical compounds are often insoluble or slightly soluble in aqueous media. Hence, the bioavailability of the drugs are low and their toxicity thresholds are close to the therapeutic dosage. A promising method to improve the bioavailability of such drugs is the reduction of the particle size by supercritical fluids. Their unique properties are used to produce pharmaceutical compounds as micron-sized particles with a narrow particle size distribution. The rapid expansion of supercritical solutions (RESS) process, without any organic solvents, was used to elaborate a non-steroidal anti-inflammatory drug : ibuprofen.

Prior to attempting ibuprofen micronization, it was necessary to understand and establish drug behaviour in SC CO_2 and optimum conditions for producing micronic particles of ibuprofen by the RESS process. At 35 °C and 120 bar, discrete particles of ibuprofen ranging from 1 to 2 µm were formed. However, the decrease of its particle size leads to low delivery and release kinetics because of its poor manipulability and their high surface tensions. This is why, the same process (RESS) was performed at similar conditions to produce ibuprofen microcomposites by impregnation with α-lactose and β-cyclodextrin as excipient.

I - INTRODUCTION

The solubility and manipulability behaviours of drugs remain two of the most challenging aspects on pharmaceutical developments. One solution to act on drug solubility consists in modifying its design with action on morphology and particle size to improve delivery, decrease side effects and reduce the required dosage.

The unique properties of SC-CO_2 are used, in this sense, to elaborate pharmaceutical compounds with particular properties (narrow size distribution, fine size particle, large specific area…) and microcomposites with optimised (accelerated or sustained) releases or enhanced manipulability. In fact the interest of the last technique is built on elaboration of microcomposites (drugs and excipients) which involves dissolution phenomena bounded to formulation and not to drug properties. With microparticulate systems, better tolerance (administration, secondary effects) is looked for.

In the present study, we focus to elaborate in SC-CO_2 microcomposites of a model drug : ibuprofen. Literature gives one example of its SC-CO_2 micronization. It concerns the using of RESS process to allow 1 µm particles production with narrow distribution [1]. This

investigation also concludes to enhance of ibuprofen solubility in release media with surfactant addition. In fact, this operation permits ibuprofen aggregates break-up and therefore gives best dissolution test.

As it seems difficult to take advantage of the precipitation of ibuprofen alone (due to aggregates formation), the main interest of our study consists of ibuprofen microcomposites elaboration in SC-CO_2 impregnation with excipient addition. New processes were investigated to elaborate a material presenting real improvement : fine particles with manipulability increasing. Ibuprofen will be precipitated according to RESS process and impregnated in a stirred lactose or β-cyclodextrin bed, guaranteeing no organic solvent all along the process. The same investigation has been conducted to produce microcomposites of ibuprofen with methyl-beta cyclodextrin [2].

II - MATERIALS AND METHODS

Chemicals and experimental set-up

Ibuprofen (ibuprofenum) was used as the model drug and supplied by INTSEL CHIMOS (France). Carbon dioxide (99.98 %) was supplied by Air Liquide (France). α-lactose monohydrate (Lactochem TG 206 average size of 100 μm) was supplied by Friesland. Roquette (France) supplies β-cyclodextrin (Kleptose 10 average size of 10 μm)

A schematic diagram of the RESS apparatus used for ibuprofen micronization and ibuprofen/lactose impregnation is shown in Figure 1.

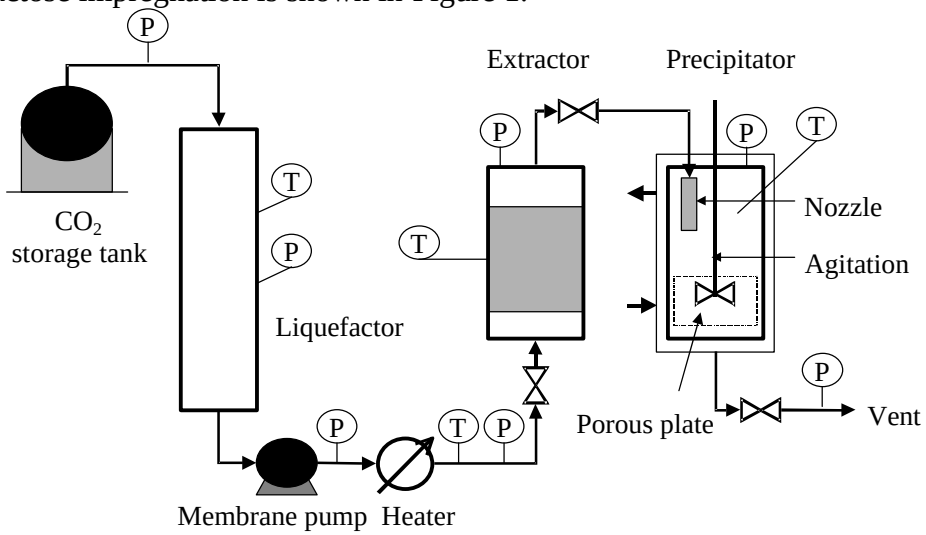


Figure 1 : Schematic diagram of RESS apparatus

Equipment consists of three sections : the CO_2 supply unit, the 1 L extraction unit and the 2.5 L precipitator vessel. The maximum pressure in this plant is set at 300 bar, the extraction temperature ranging from 35 to 300 °C. Carbon dioxide, at desired pressure and temperature is loaded with ibuprofen in the extractor. This mixture is then sent in the precipitator which is set at the atmospheric pressure. The supercritical solution is expanded through a nozzle with a 340 μm diameter and a 54° spray angle (Spraying Systems Emani, 1/4 SK), where a known amount of excipient is previously introduced in case of impregnation experiment. Due to the sudden pressure decrease, inducing a lost of the CO_2 solvating power,

ibuprofen precipitates. The particles produced are thus collected on a 5 µm porous plate, put at the bottom of the precipitator. Since no organic solvents are added, there is no need to perform a rather long stripping of a submicronic powder. It must be quoted that the precipitator is equipped with a magnetic stirrer, the excipient bed can thus be continuously stirred.

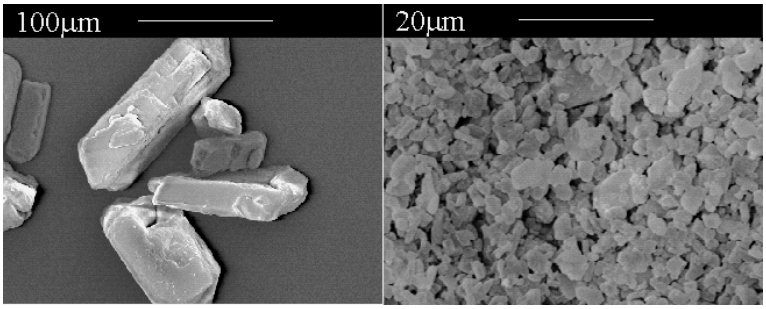
Particle characterization

Precipitation impact on chemical nature and structure of ibuprofen treated with SC CO_2 were evaluated with X-ray diffraction (XRD) and differential scanning calorimetric (DSC) (Perkin Elmer DSC-4 apparatus, coupled with 3600 computer). The morphology of particles precipitated was analysed by scanning electron microscopy (SEM-Cambridge Stereoscan 240). The determination of PSD profile and the size is performed with a Malvern 2600. Lastly, release kinetics (Erweka DT 6R) were conducted to observe ibuprofen dissolution rates. Powder dissolution studies were performed in phosphate buffer solution (pH 7.2) kept at a constant temperature of 37 °C and stirred at 50 rpm. Accurately weighed samples were introduced into dissolution medium. All samples of the solution were withdrawn at regular intervals with a peristaltic pump to ensure dissolution media circulation between the balloon and spectrophotometer (Perkin Elmer Lambda 15). The ibuprofen concentration in the samples was determined with an UV spectroscopy at 223 nm.

III - RESULTS AND DISCUSSION

Micronization experiments

For micronization of ibuprofen by the RESS process, it is determinant to define the extraction conditions domain, in terms of pressure and temperature. Indeed, the work of Charoenchaitrakool reveals a specific behaviour of ibuprofen in SC-CO_2. Due to its melting point decrease from 76 °C at atmospheric pressure to 45 °C at 180 bar, we observe that ibuprofen becomes liquid and leads to plugs in our installation. This is why, temperature extraction will be ranging from 35 to 45 °C and pressure from 90 to 190 bar. Several attempts were performed within the extraction domain. For all pressure investigated, RESS process produces the same fine particles size (1 to 3 µm) with narrow distribution (Figure 2) from unprocessed drug with irregular particles ranging in size from 100 to 200 µm. This phenomenon can be explain with the small variation of ibuprofen solubility at constant temperature in this pressure range.



(a) (b)

Figure 2 : (a) ibuprofen before treatment, (b) ibuprofen after RESS treatment operating at 35 °C and 110 bar

An in vitro investigation of ibuprofen availability was also carried out in reference media, i.e., distilled water kept at a constant temperature of 37 °C to compare raw and micronized ibuprofen. The dissolution rate profiles of the original and processed material are shown in Figure 3.

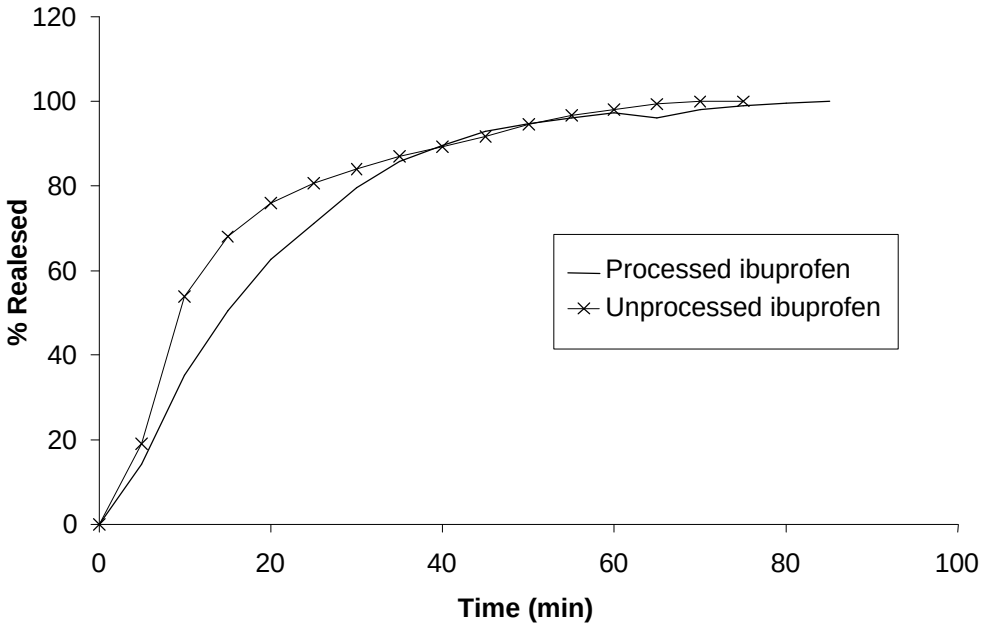


Figure 3 : Dissolution profiles of ibuprofen before and after RESS processing

Release kinetics of raw ibuprofen is better than the one micronized. In fact, the time after which 80 % of the initial amount of drug had dissolved was around 10 min. The processed drug reaches the same dissolution rate after only 40 min. So the release kinetics of micronized ibuprofen (average diameter of 1 μm) are 4 times lower than those of original material (average diameters between 100 and 200 μm). This low dissolution rate is attributed to the reduction in particle size and especially to the increasing of surface tensions.

So, micronization technique raises a new problem bound to particle size reduction : the enhancement of surface tensions. These latter give electrostatic powder appearance which can not permit observation of ibuprofen solubility improving. This is why we propose the addition of news components, lactose and beta-cyclodextrin-as excipients- to enhance ibuprofen manipulability and dissolution rate.

Impregnation experiments

Development of the RESS technique to impregnate excipient bed by ibuprofen is therefore investigated. An innovative impregnation method is evaluated with a supercritical solution of ibuprofen injected in 2.5 L stirred vessel, at atmospheric pressure, where a known amount of lactose is previously introduced. The jet power and agitation permit homogenous mixture of two components.

This study was conducted to take advantage of the optimum operating conditions defined previously by ibuprofen micronization. So, several experiments were performed with three mass ratio of ibuprofen/lactose (1/1, 1/2 and 1/4) and one for ibuprofen/β-cyclodextrin (1/1). Temperature and pressure extraction were kept constant : 35 °C and 120 bar. In this way,

impregnation process was well controlled and product yield ranged form 80 to 90 %. The most significant experiments performed are gathered in Table 1.

Runs	*T (°C)*	*P (bar)*	*Experiment time, (min)*	*CO_2 flow rate (kg/h)*	*Mass of ibuprofen (g)*	*Mass of excipient (g)*	*Ibuprofen solubility (g/kg of CO_2)*	*Mass precipitated (g)*
1	35	120	60	27.9	10	10	0.45	16.1
2	33	120	60	27.1	10	10	0.46	19.36
3	34	120	60	27.3	10	10	0.43	18.33
4	35	120	40	25.7	5	5	0.38	7.82
5	36	120	40	29	5	10	0.32	11.89
6	36	120	40	25.7	5	20	0.42	22.71
7	35	120	60	27.3	10	10	0.49	19.11
8	35	120	60	30.3	10	10	0.47	19.44

Table 1 : Experimental conditions (lactose for runs 1 to 6 and β-cyclodextrin for runs 7 to 8)

The composition powder produced is analysed by UV spectroscopy (λ = 264 nm) to determine ibuprofen ratio using a buffer solution (phosphate pH 6.8) analytical medium [3, 4]. These analyses also permit repartition estimation of ibuprofen in the precipitator. During impregnation experiment, the powder was recovered on the bottom (porous plate) and on the walls of the precipitator.

With a drug/excipient ratio of 1/1, ibuprofen content is around 50 wt% on porous plate and reaches 80 wt% on the walls, for any stirring rate. As the quantity of powder on the walls represents only 5 % of total mass balance, the powder is considered as homogenous.

The solubility of ibuprofen/excipient was measured and compared with raw and processed drug. The dissolution medium is always phosphate buffer kept at a constant temperature : 37 °C. Dissolution profiles are shown in Figure 4.

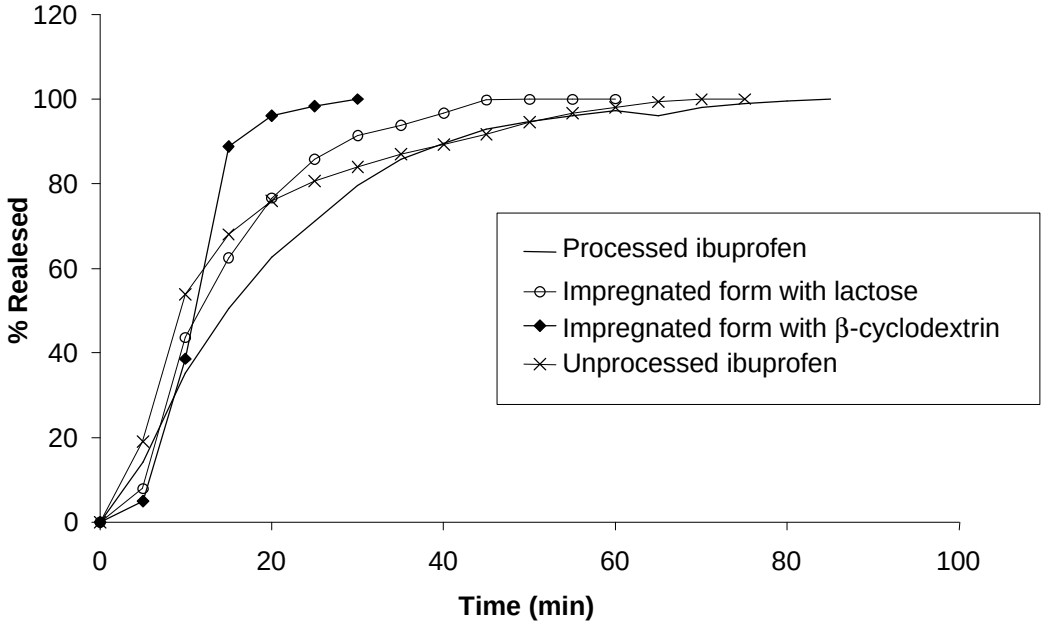


Figure 4 : Dissolution profiles of ibuprofen : processed, unprocessed and impregnated form with lactose and β-cyclodextrin

A significant enhancement in the dissolution rate of ibuprofen is observed for the impregnated one compared to the micronized ibuprofen for any excipient. This improvement was attributed to their capacity to reduce surface tensions effects.

However, dissolution profiles of lactose impregnated are still lower than those of original material. To explain this phenomenon, we must check whether interactions between ibuprofen and lactose exist. This is why, Differential Scanning Calorimetric (DSC) and XRD analyses were performed. Each analysis reveals ibuprofen and lactose compounds. DSC presents drug and excipient spectra corresponding at melting point of each component. Moreover, this analysis indicates also release of water molecule included in α-lactose monohydrate. These informations seem to prove that there are few interactions between the excipient and ibuprofen. In fact, once the impregnated lactose is quickly solubilized, the behaviour of micronized drug leads to low dissolution rates.

The behaviour of β-cyclodextrin impregnated material is different. Release kinetics are better than those of raw ibuprofen. Differential Scanning Calorimetric (DSC) were conducted to explain this solubility increasing but they cannot reveal interactions between our two products. The reason is their melting points are slightly similar, near 75 °C. This is why, XRD analyses will be carry out.

IV - CONCLUSION

This innovative impregnation method presents promising results. First, RESS process is well controlled and impregnation gives repeatable results. Secondly, no organic solvents are added and so there is no need to perform a rather complex stripping of a micronic powder. Thirdly, our technique can be used or taken into account as model for any drug with high solubility in SC-CO_2. This approach can therefore permit association of our two components and high product yields. Using two different excipients shows two specific behaviour of ibuprofen. With lactose, lower dissolution rate of impregnated material than those of raw form are obtained because the impregnated lactose seems to have not enough interactions with the processed ibuprofen to increase its dissolution rate. On the contrary, β-cyclodextrin gives promising results because leads to enhancement of release kinetics of impregnated form than those of ibuprofen/lactose and raw material. However, we should better check out whether interactions between ibuprofen and β-cyclodextrin could be taken into account.

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