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Jacques Fages, Élisabeth Rodier, Alain Chamayou, Michel Baron. Comparative Study of Two Processes to Improve the Bioavailability of an Active Pharmaceutical Ingredient: Kneading and Supercritical Technology. *kona powder and particle journal*, 2007, 25, p. 217-229. hal-01618298

HAL Id: hal-01618298

<https://hal.science/hal-01618298>

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Comparative Study of Two Processes to Improve the Bioavailability of an Active Pharmaceutical Ingredient: Kneading and Supercritical Technology[†]

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Abstract

Two processes have been developed for the enhancement of bioavailability of a poorly-soluble active substance, Eflucimibe by associating it with γ -CD (γ -cyclodextrin).

In the first process (process a), Eflucimibe was added to an aqueous slurry of CD, in a kneading device. The evolution of the transformation was followed by DSC, FTIR, Eflucimibe dissolution kinetics, as well as semi-solid state change of the mixture. An optimization of the process was performed and a prevision of the scaling-up was made using dimensionless numbers. This process is simple and robust. It can be compatible at the industrial scale with a good economy and appropriate control.

In the second process (process b), Eflucimibe and CD are co-crystallized using an anti-solvent process, dimethylsulfoxide being the solvent and supercritical carbon dioxide being the anti-solvent. Then, the co-crystallized powder is held in a static mode under supercritical conditions for several hours. A final stripping step, is used to extract the residual solvent. The coupling of the first two steps brings about a significant synergistic effect to improve the dissolution rate of the drug.

Both processes resulted in a strong acceleration of the in vitro dissolution rate of the drug. Finally, in an in vivo test, these two processes appeared to be very effective, process (a) and (b) giving respectively an 8-fold and 11-fold increase in bioavailability.

Keywords: Eflucimibe, Cyclodextrin, Kneading, Supercritical CO₂, Scale-up, Bioavailability

Introduction

An important parameter in pharmaceutical formulations is the bioavailability of the active substance. Many new Active Pharmaceutical Ingredients (API) are very poorly water soluble. Their absorption by the human organism is therefore extremely low and difficult to control. In case of very low solubility, one of the first rule of the formulation process is to increase this bioavailability by enhancement of the dissolution rate and apparent solubility. A way to reach this goal is to associate these low-solubility active molecules with cyclodextrins (CDs) by forming inclusion complexes.

Although many articles describe the interactions between active molecules and CD only few papers deal with the processes used for such complexes production. Four classes of processes can be distinguished: liquid (co-precipitation, co-evaporation, spray-drying, freeze-drying, neutralisation), using supercritical CO₂, semi-solid (kneading), and solid (sealed-heating, high energy co-grinding). Anyhow, the success of a drug delivery technology and of the process used to produce it, are highly dependent on whether it can be scaled-up, is reproducible and allows for cost-effective manufacturing. This paper is focused on the comparison of two of them: kneading (a) and supercritical fluid processing (b), in the case of the complexation of Eflucimibe with γ -cyclodextrins (γ -CDs).

A first description of the kneading process has been presented by Gil¹⁾ and Hutin²⁾. The use of supercritical carbon dioxide (SC-CO₂) for particle generation of pharmaceuticals and for improving their

[†] Accepted: September 12, 2007

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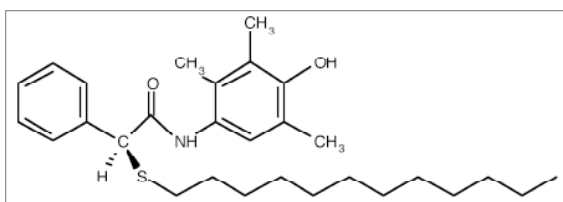


Fig. 1 Structure of Eflucimibe.

Table 1 Biopharmaceutics Classification System

	High Solubility	Low Solubility
High Permeability	Class I	Class II
Low Permeability	Class III	Class IV

bioavailability is well documented³⁾.

These processes (a) and (b) will be described in the case of Eflucimibe, a highly potent acyl-coenzyme A O-acyltransferase (ACAT) inhibitor with the molecular formula $C_{29}H_{43}NO_2S$ (**Fig. 1**), treating hypercholesterolemia. Its structure and extreme hydrophobicity confers to this molecule a very poor solubility in water.

In terms of solubility and permeability, according to the Biopharmaceutics Classification System BCS⁴⁾, it can be considered as a Class IV compound (**Table 1**), with low solubility in aqueous media and low permeability through the intestinal mucosa. The result is a high variability in blood level when formulated in lactose capsules¹⁾ and a poor bioavailability.

γ -CD is a cyclic octasaccharide (**Fig. 2**) obtained by enzymatic degradation of starch, consisting of 8 D-Glucose units, and presenting an hydrophilic external wall and an hydrophobic internal cavity that can receive organic molecules.

This configuration allows to perform the dissolu-

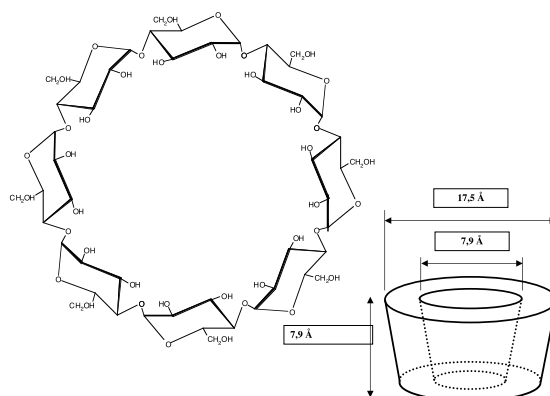


Fig. 2 Structure of γ cyclodextrin.

tion of the drug substance in aqueous solutions and to liberate it by dissociation of the complex, followed by the absorption of the drug in the circulatory system (**Fig. 3**)

Eflucimibe was provided by Pierre Fabre Laboratories (Castres, France). γ -CD was purchased from Wacker-Chemie GmbH (München, Germany).

1. The Kneading Process

The kneading process can be considered as a mechanochemical process carried out in the presence of a small amount of solvent (water or other) that acts as lubricant for the molecular diffusion. This catalyst behaviour of the solid state process, results in a smooth transformation of the reactants into the final products avoiding the contamination of the active ingredient by secondary transformation not suitable in the production of pharmaceutical products⁵⁾.

We applied this process to the complexation of Eflucimibe with γ -CD.

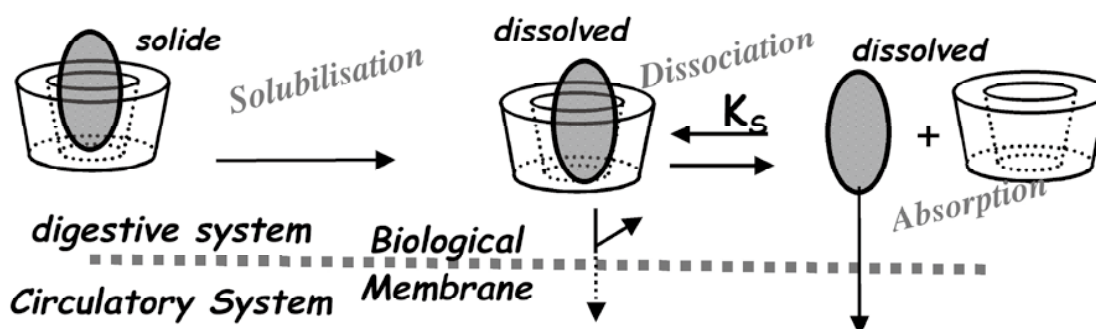


Fig. 3 Mechanism of the API (Active Pharmaceutical Ingredient) liberation from its complex with cyclodextrin.

Experimental set-up and process

Kneading equipment

The kneading equipment was a 316 L stainless steel Aoustin[®] kneader with dual Z blades (**Fig. 4**). Those dual blades take up an important relative volume and the space between the wall of the kneader and the side of the blades is very small, initiating large shearing effects. Two scales of this apparatus were used : MX1 with a nominal capacity of 1.5 L and MX2 with a nominal capacity of 3 L.

Kneading process

The blade speed of the kneader was fixed at 50 rpm. γ -CD was introduced in the kneader bowl kept at 305 K (optimized temperature²⁾); Purified water (1 ml.min⁻¹) is added to a mixture of Eflucimibe/CD at a (1:2) molar ratio and the blend is kneaded thoroughly while following simultaneously the tempera-

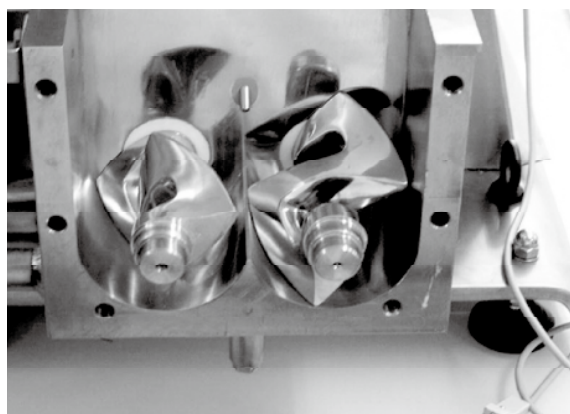


Fig. 4 Kneading equipment.

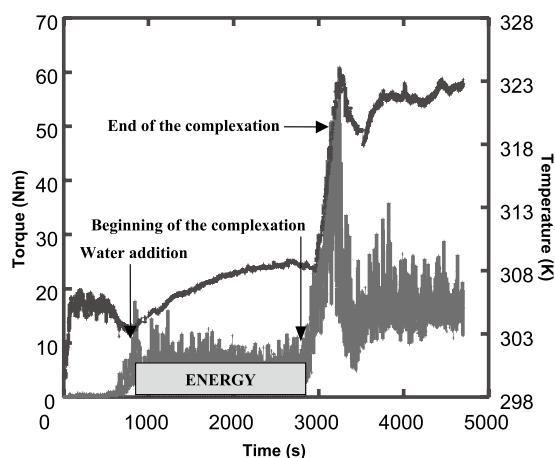


Fig. 5 Torque and temperature versus time during complexation of Eflucimibe and cyclodextrin.

ture and torque measurement until the increasing of the viscosity of the mixture which is a characteristic of the complexation (**Fig. 5**)¹⁾. The final mass quantity of purified water in the mixture was 27.5 %. The evolution of the transformation was followed by DSC (Differential Scanning Calorimetry), FTIR (Fourier Transform Infrared Spectroscopy), Eflucimibe dissolution kinetics, as well as semi-solid state change of the mixture (**Fig. 6**). For each sample taken, the paste obtained was dried at 313 K for 12h using a vacuum oven. The dried product was sieved below 50 μ m. The area called "ENERGY" under the curve is a characteristic of the process. The interaction between Eflucimibe and CD occurs if this area is sufficient.

Several approaches are available for controlling

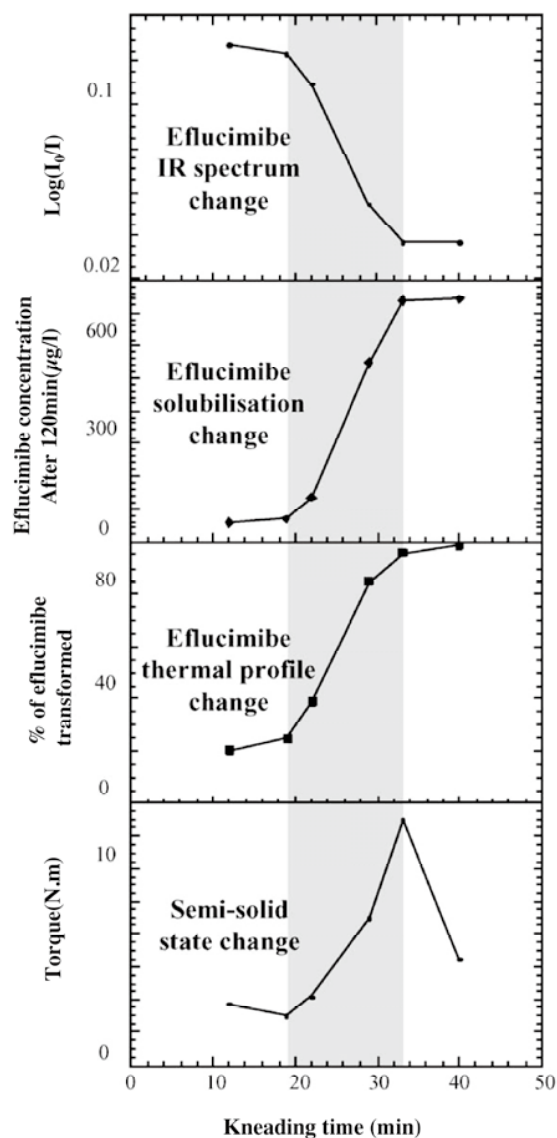


Fig. 6 Characterisation of kneading process evolution.

the process at one scale and for scaling-up to another scale. The experimental design approach can be a powerful tool to model processes. Three input variables that are water extent, blade speed and temperature have already been selected. Two output variables are also selected : dissolution rate of the product and the extent of inclusion determined by DSC. The principle is to determine for each output variables a model involving each input variables and their interactions. By comparison of the models it is possible to optimise the different input variables to obtain a compromise between them and achieve the desired results of the output variables. The effect of the following process parameters on the extent of inclusion and solubility enhancement (Fig. 7) has been investigated by means of an experimental design analysed at MX1 scale which allows the definition of an optimised experiment with those operating conditions.

DSC and thermoanalytical procedure for the determination of the percentage of transformed Eflucimibe (Y)

Thermal analysis by DSC was carried out using a Perkin Elmer DSC 7 apparatus. Samples of 3 mg were introduced into sealed aluminium pans.

DSC scans were performed in triplicate under nitrogen, at a heating rate of 5 K.min⁻¹ in the temperature range of 303 K to 378 K. Heats of fusion were automatically determined by the software following calibration with Indium (28.4 J.g⁻¹), using integration of the areas under the DSC endothermic peaks of melting. A thermoanalytical procedure can be applied to quantify the interaction yield⁶. F is the fraction by weight of Eflucimibe in the starting mixture and N,

the fraction by weight of Eflucimibe in the initial state after the kneading step. The percentage of transformed Eflucimibe after interaction, Y, is calculated according to equation (1)

$$Y = 100 - 100 \left(\frac{N}{F} \right) \quad (1)$$

where N is calculated according to DSC results and equation (2)

$$N = \frac{\Delta H_{\text{eflucimibe melting after kneading step}}}{\Delta H_{\text{pure eflucimibe melting}}} \quad (2)$$

FTIR spectroscopy and spectroscopic procedure to follow Eflucimibe interaction

The infrared spectra were recorded on a Nicolet FTIR spectrometer. The analysed component was dispersed in KBr medium in solid state before acquisition.

The Eflucimibe interaction with CD led to a decrease of Eflucimibe band intensity. In order to quantify this modification, the Beer-Lambert law was applied by the determination of Log I₀/I with I₀ corresponding to the absorbance at 1572 cm⁻¹ (spectral region where Eflucimibe and CD do not present spectral band) and I corresponding to absorbance at 1537 cm⁻¹ (spectral region where only Eflucimibe presents spectral band).

Determination of Eflucimibe solubilisation kinetics

The Eflucimibe solubilisation kinetics were determined with samples corresponding to 50 mg of Eflucimibe. These samples were added to 100 ml of the solubilisation medium corresponding to an aqueous solution containing 5 % (w/V) of sodium lauryl sulfate. The samples were continuously stirred while remaining in a water bath at 310 K (normalized temperature for pharmaceutical test). At various time intervals, samples were withdrawn and filtered through 0.45 μm membrane. The amount of Eflucimibe dissolved was determined by HPLC using UV detection at 220 nm. Acetonitrile and purified water at 82 : 18 V/V was run at 1ml.min⁻¹ flow rate through a reverse phase C8 column.

Use of dimensionless numbers to study the scaling-up

The principle of the methodology is to solve the relationship on one scale and then to use it to calculate the power required on another scale to obtain a same finished product quality.

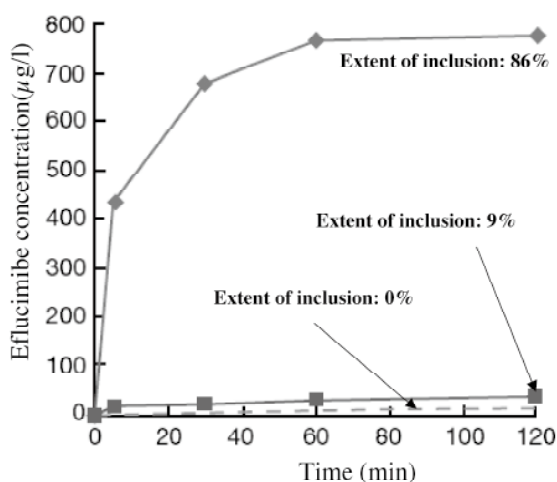


Fig. 7 Eflucimibe dissolution kinetics.

We applied the Buckingham theorem⁷; the main physical variables are found to be:

The power number :
$$Np = \frac{\Delta P}{\rho \cdot N^3 R^5}$$

The Reynolds number :
$$Re = \frac{\rho \cdot N R^2}{\eta}$$

The Froude number :
$$Fr = \frac{R N^2}{g}$$

The fill ratio of the kneader : H/R

The blade size : $(R)/L$

Where g is the gravitational constant, R , L respectively the blade, length and radius, N the blade rotational speed, h the height of powder, ρ the bulk density of the powder, η the viscosity and ΔP the net blade power consumption that is to say total power less power required to stir the dry powder.

Hence, the physical phenomena before complexation can be described by a relationship as follows (equation 3) :

$$Np = f(Re, Fr, H/R, (R)/L). \quad (3)$$

Results and discussion

The process is fast and evolves as shown on **Fig. 6**

The complexation induced a dramatic increase of Eflucimibe dissolution rate (**Fig. 7**)

An optimization of the process was performed and a prevision of the scaling-up was made using dimensionless numbers.

As the viscosity is unknown, it was replaced by the mean torque before complexation and the dimensionless Re becomes a pseudo-Reynolds ψRe ⁸.

The relationship between the power number and the other dimensionless group is established by **Fig. 8** and equation 4:

$$Np = k (\psi Re \cdot Fr \cdot (H/R) \cdot (R/L))^{-n} \quad (4)$$

$$k = 338.4 \text{ (m}^3 \cdot \text{s)}^{-n} \text{ and } n = 0.84$$

Where the correlation coefficient is 0.99 for 17 experiments.

One experiments has been repeated three times under the same conditions to test the reproducibility of the process. The resulting points on the scale-up relationship (**Fig. 8** and **9**) were very close to another.

Three experiments carried out under the optimised conditions give good results in agreement with the dimensionless relationship.

Those equations are applicable for a series of geometrically similar kneader of different sizes. It was possible to check those predictions at a twice scale, with an MX2 kneader. Plot of Np versus the combination of the four remaining dimensionless numbers

are presented in **Fig. 9** with those last experiments. The relationship between the power number and the other dimensionless group stay the same as equation 4 where the correlation coefficient is 0.99 for 17 experiments at MX1 scale and 6 experiments at MX2 scale.

The results show that the process is fast, simple and robust. Using dimensionless numbers it can be conducted at the industrial scale with a good economy and appropriately monitored using technologies recommended by FDA's Process Analytical Technology (PAT).

2. The Supercritical Process

SC-CO₂ has recently emerged as a new medium for complexation with CD due to its properties of improved

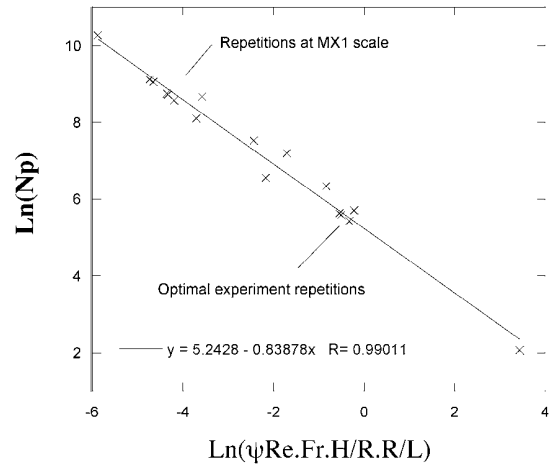


Fig. 8 $\ln(Np)$ versus $\ln(\psi Re \cdot Fr \cdot H/R \cdot R/L)$ at MX1 scale.

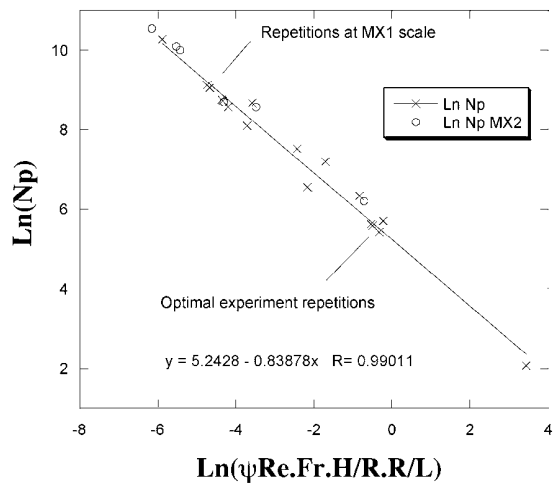


Fig. 9 $\ln(Np)$ versus $\ln(\psi Re \cdot Fr \cdot H/R \cdot R/L)$ experimental results at the MX2 scale.

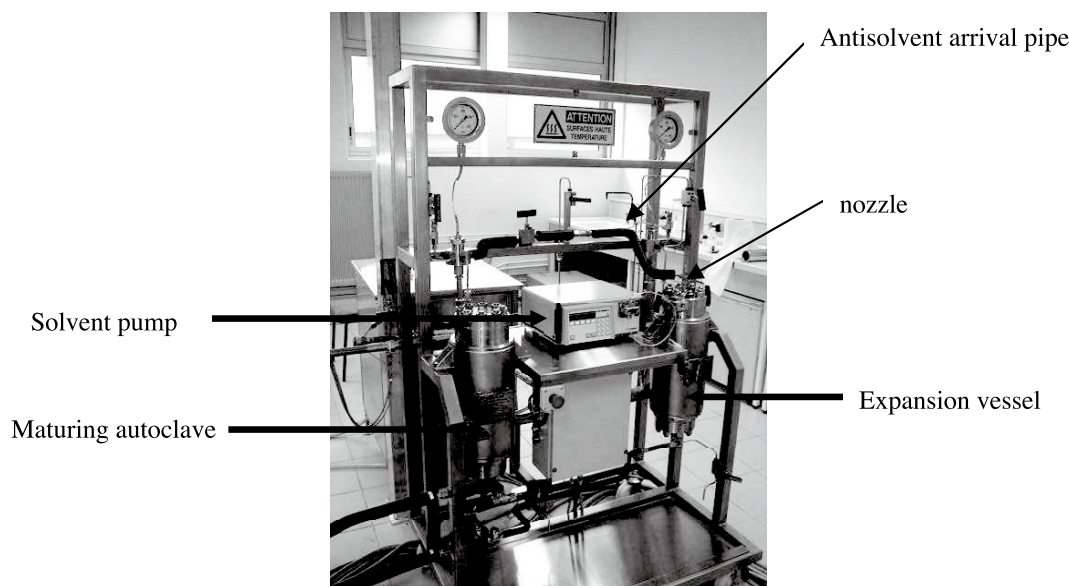


Fig. 10 Supercritical equipment.

mass transfer and increased solvating power^{9), 10)}. We have implemented a new process by combining a co-crystallisation anti-solvent process SAS¹¹⁾ with a maturing step⁹⁾ and adding finally a stripping step to extract residual solvent.

Experimental set-up and procedures

All experiments were performed in a flexible supercritical machine (Separex, France) shown on **Fig. 10**.

Dimethylsulfoxide (DMSO) as the solvent and SC-CO₂ as the antisolvent were used in the SAS experiments. CD and Eflucimibe were both dissolved in DMSO. This solution was injected into the CO₂ stream in the mixing chamber of a nozzle (Spraying System, France), and sprayed into an expansion vessel. The powder formed was collected in a porous bag placed in the expansion vessel after depressurisation.

For the maturing step, 7 g of Eflucimibe/CD powder (with a molar ratio of 1/2) were wetted by 2.33 g of water (corresponding to 25 mass% of total powder) and placed in a 2 l autoclave. This vessel was filled with SC-CO₂ at the desired pressure and temperature and left for several hours without any agitation. The powder was recovered after gentle depressurisation.

In the final stripping step, the powder was submitted to a continuous flow of SC-CO₂ for two hours in a stainless steel basket.

Powder characterisations

After each step, composition of the powder obtained was determined. Eflucimibe content was measured by HPLC, residual DMSO content by GPC and water content with a Karl Fisher titrator. γ -CD content was then calculated from all these results. Eflucimibe, DMSO and water contents are given in mass percentage of the total powder mixture.

The DSC thermograms were performed on a Perkin-Elmer, DSC-7 calorimeter equipped with a thermal flux cell device. The DSC patterns of the samples (2-3 mg) were obtained between 313 K and 413 K at a heating rate of 5K/min under a N₂ gas stream. They are shown in **Fig. 11**, for the initial powder mixture (**Fig. 11a**) and after each processing step (**Fig. 11b, c and d**). By integrating the melting peak of drug in DSC thermograms, which is generated by the crystalline form of the powder, and knowing independently the total drug content, it is possible to calculate the amount of non-crystalline Eflucimibe. This last one corresponds to the drug not visible on DSC thermogram, hence drug molecule likely implied in interactions with CD and microcrystalline aggregates dispersed among CD matrix. It acts as an indicator of the level of drug/CD complexation.

To estimate the dissolution rate improvement, *in vitro* dissolution studies were performed at 310 K as described elsewhere¹²⁾. The dissolution rate is defined as the Eflucimibe content dissolved in the medium after a fixed time, expressed in μ g of Eflucimibe per ml of solution. The dissolution curves are

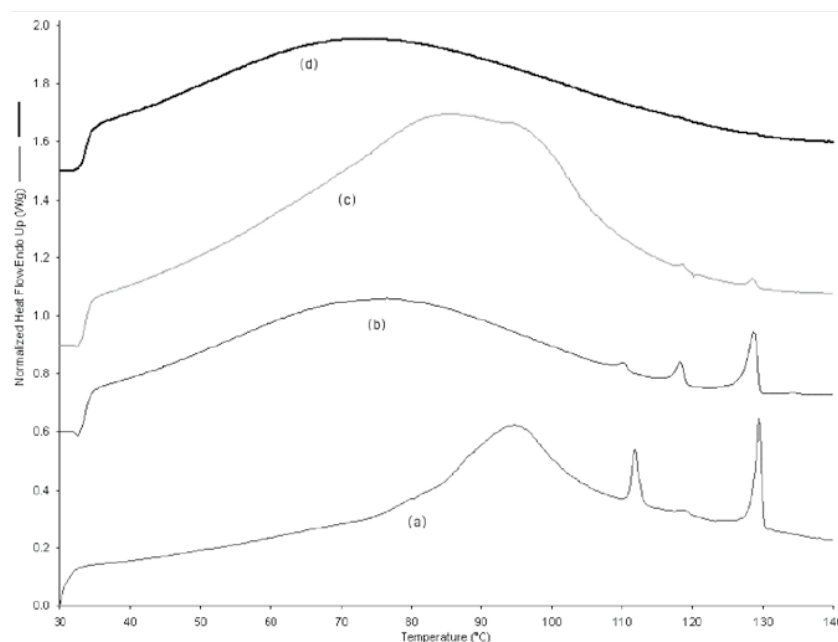


Fig. 11 DSC curve of physical mixture (a); co-crystallised powder (b); powder after co-crystallisation and maturing (c); powder after co-crystallisation, maturing and stripping (d).

presented on **Fig. 12** for the physical mixture (a), and after each processing step (b, c and d).

Co-crystallisation step

This step has been conducted according to previously published procedure by Rodier et al.¹³⁾. On ESEM microphotographs (not shown) an intimate mixture of both components can be seen: large CD particles with drug fibres deposited on them.

The Eflucimibe melting temperature (**Fig. 11a**) of the physical mixture with γ -CD was found to be 402 K. For the co-crystallised powder, we observed a melting temperature of 399.1 ± 0.6 K (mean of 29 experiments). In addition, a part of Eflucimibe contained in the mixture after co-crystallisation is not visible by DSC.

After this step, the dissolution rate was higher than that of the physical mixture with the same profile (**Fig. 12b**). It was no longer correlated to the specific surface of the powder, which can be tuned by the operating conditions with Eflucimibe alone¹⁴⁾ but not in the presence of CD. For instance, the mass ratio CO₂ /DMSO, had no effect on the composition and dissolution rate of the resulting powder. On the contrary, decreasing the mole ratio of Eflucimibe to CD in the initial mixture from 1/1 to 1/3 increased the drug crystallisation yield from 40 % to 70 % (w/w). This yield is defined as the ratio between the mass of powder formed and the mass of powder initially dis-

solved in DMSO.

Maturing step

This process, first described by Van Hees et al.⁹⁾ is very effective for complexation. Several drugs have been processed successfully with this method^{15, 16)}. After this step, drug fibres are not so clearly distinguishable from CD particles on microphotographs (not shown). Furthermore, only a very small Eflucimibe melting peak can be seen on DSC thermogram (**Fig. 11c**). A strong increase in the drug dissolution profile is noticed with a peak at 500mg/ml

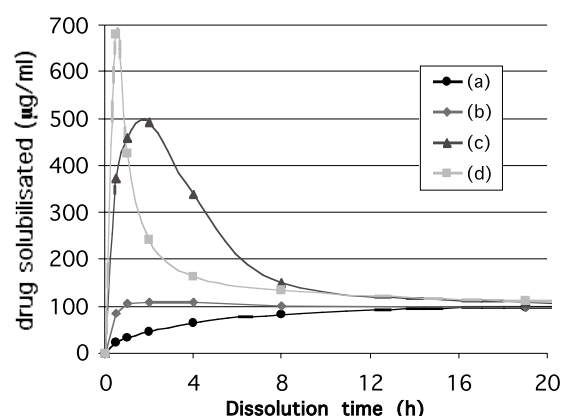


Fig. 12 Dissolution curve of co-crystallised powder (b); powder after co-crystallisation and maturing step (c); powder after co-crystallisation, maturing step and stripping (d); physical mixture (a).

Table 2 Effect of the maturing step on Eflucimibe-crystalline content and dissolution rate as a function of CO₂ density and viscosity

T, K	P, MPa	ρ , kg/m ³	μ , Pa.s	S _{Eflucimibe/CO₂} , × 10 ⁷ , mole fraction	Non-crystalline Eflucimibe, mass%	Dissolution rate at 2h, μ g/ml
373	10	278	2.40 10 ⁻⁵	54	98.8	678.4
313	10	564	3.78 10 ⁻⁵	1	88.5	522.9
373	30	644	4.70 10 ⁻⁵	571	88.6	503
353	30	734	5.41 10 ⁻⁵	169	84.1	596.5
313	20	830	6.16 10 ⁻⁵	5	82.3	487.9
333	30	831	6.26 10 ⁻⁵	46	83.2	499
313	30	928	7.20 10 ⁻⁵	11	73.8	336.9

Table 3 Maturing step, dissolution rates and specific surface areas as a function of the initial mixture

Eflucimibe	<i>Initial powder</i>	<i>SAS treated</i>	<i>Co-crystallised</i>
Cyclodextrin	<i>Initial Cavamax</i>	<i>SAS treated</i>	<i>Co-crystallised</i>
BET specific surface of the mixture, m ² /g	2.3	17.1	8.6
BET specific surface of the Eflucimibe alone, m ² /g	7.5	54	—
Dissolution rate at 2 hours of the mixture, just after mixing the powders, μ g/ml	19	69	100
Dissolution rate at 2 hours of the mixture, after adding maturing water, μ g/ml	33	58	88
Dissolution rate at 2 hours of the mixture, after the maturing step, μ g/ml	141.6	150.3	670

(Fig. 12c).

The influence of CO₂ density and viscosity was evaluated on the dissolution rate. Both the non-crystalline drug content and the dissolution rate increase when CO₂ density and viscosity decrease as shown on **Table 2**. Besides, the non-crystalline drug content is not linked to the solubility of the active substance in CO₂. This suggests that mass transfer would limit the maturing step and that CO₂ solvent power is not a crucial point.

In addition, the influence of the operating time of this static step has been studied. A classical saturation-shape evolution was noticed: up to 6 hours, the powder composition is modified and dissolution kinetics increases, while both remain constant beyond 6 hours.

We have also studied the effect of the initial mixture composition. Three mixtures having the same mass composition were wetted, placed in the autoclave and submitted to the same conditions (30 MPa, 373 K, 16 hours). The first mixture was composed of the initial drug and CD, the second of drug and

CD crystallised separately by SAS process and the third of drug and CD co-crystallised by SAS. **Table 3** shows the dissolution rate after 2 hours for each mixture at different stages: just after mixing, just after adding water and after the static maturing step.

This table provides also the specific surface area of the mixtures. Comparison of the first and the second mixtures before the static step confirms that the amount of dissolved drug increases with the specific surface area. Comparing the second and the third mixtures, it appears that the amount of dissolved drug is no longer correlated to the specific surface area. Therefore, the static step may enhance the dispersion of the drug into the CD matrix and thus it may increase the dissolved drug concentration in all cases. However, the improvement of the compound dissolution is significantly higher for the before hand co-crystallised powder. In conclusion, a strong synergistic effect is obtained by coupling the co-crystallisation and the static steps.

Stripping step

After the stripping step, a homogeneous aspect of the powder was observed (not shown). This can be linked with the complete disappearance of the Eflucimibe melting peak (**Fig. 11d**) and in a sharper and higher dissolution peak (**Fig. 12d**). The aim of the stripping step was to decrease the solvent content below 5000 ppm, which is the pharmaceutical standard for a class III solvent. Decreasing the solvent below this threshold is possible, but some drug extraction will be unavoidable, which is the main drawback of this step. In addition, the stripping step has dehydrated the CD: roughly, water content drops from 13%_{mass} to 2-3%_{mass}. Some of the adsorbed water onto CD was dissolved into the SC-CO₂ flowing through the bed of powder, thus dehydrating it. This explains the fast initial dissolution rate due to its enhanced hygroscopicity.

Dissolution kinetics

The dissolution kinetics evolves in the following way. First, the dissolving medium diffuses into the CD matrix containing Eflucimibe. Then, Eflucimibe is dispersed into the dissolving medium and is temporarily stabilized into SDS micelles corresponding to the maximum dissolved drug concentration on **Fig. 12**. Then follows a recrystallization of Eflucimibe leading back, after a sufficient period of time (at least 20 h), to the solubility of pure Eflucimibe in this dissolving medium, (that is around 100 µg/ml). According to this scenario, the increase in dissolved drug concentration does not correspond to a true dissolution of the active substance, but to the generation of a metastable colloidal dispersion of SDS micelles including drug. Finally, the acceleration of the dissolution kinetics after the stripping step may be due to the acceleration and amplification of the first dissolution step, which is the diffusion of the aqueous medium through the dehydrated CD matrix.

Finally, this new process using supercritical CO₂ and γ -CD leads to a dramatic increase in the drug dissolution rate. This process includes three steps: (1) a semi-continuous co-crystallization by a supercritical anti-solvent process generating a solid dispersion, (2) a batch maturing step during which the powder mixture evolves towards a more intimate mixture, and (3) a final semicontinuous stripping step where residual solvent is extracted with some Eflucimibe and water.

The main novelty of this process lies in the coupling of these three steps, exhibiting a strong synergistic effect in the improvement of the dissolved drug

concentration of the drug.

Comments on both processes

A new innovative and promising supercritical process but not yet fully understood and controlled; a more classical, usual one but better controlled and more advanced in terms of scaling up.

Concerning the supercritical process, the main limiting point is the use of organic solvent in the SAS step. It has to be pointed out that the co-crystallization step leads to an intimate mixing of the API and CD; this can be an advantage when the API is a voluminous molecule that may present difficulties to be efficiently mixed. But this step is not needed in many others cases to improve the efficiency of the maturing step and therefore physical mixtures can be sufficient. This has been confirmed for instance for the binary Ketoprofen- β -CD¹⁰. In addition, the stripping step is needed only when SAS step is performed; it is a typical extraction process where enhanced transfer properties of the supercritical CO₂ are determining parameters. Besides, to be industrially conceivable, SAS and stripping steps imply that supercritical CO₂ is regenerated (a solvent/antisolvent separation is needed) to be recycled. The key-step that is the maturing step is a very simple one, easy to handle, and a “green” one, low energy-consuming (the main energy requirement is when pressurizing the CO₂). In addition, it delivers a ready-to-use product without any further processing: it has been observed with the Ketoprofen- β -CD mixture that no additional water remained in the produced association complex, not needing then a subsequent stripping or drying step¹⁰. On a scaling-up point of view, in the SAS step, the ratio Solvent/Antisolvent has to be kept constant together with the API concentration in the solvent: these are the predominant invariant parameters and the scaling up could be performed as “scaling out” by setting lab-scale autoclaves with their nozzles in parallel. As for the maturation step, the main invariant parameter that has to be kept constant when changing scale is the mixture (API/CD/Water) composition and duration, with mixing conditions unchanged. Yet, in spite of its already proved efficiency, this step has to be further investigated in order to fully understand the phenomena implied. On a process point of view, the handling of the produced powders could also be improved. The longest step is the maturing one, which is 6 hours. In any case, this newly set-up process has proved to be highly effective concerning the in vivo bioavailability of the Eflucimibe, which was multiplied by 11 (AUC, Area Under the time con-

centration Curve) in dog studies (unpublished data).

As for the kneading process, the device used is more conventional and simple. Scaling-up is relatively easy to perform with the existing commercial devices using traditional approaches of chemical engineering like dimensional analysis and experimental design. This process performed with water avoids the use of organic solvent and works at low temperature level. The produced powder allows a significant enhancement of the API bioavailability. However, it has to be noticed that the operating parameters, in terms of formulation, have to be previously optimized in order to allow the scaling-up based on the capacities of commercial devices: a wrong formulation may induce a very high increase of the required torque, that is not acceptable on the mechanical point of view, by commercial devices.

Conclusion

Both processes resulted in a strong acceleration of the *in vitro* dissolution rate of the drug. Finally, in an *in vivo* test, different Eflucimibe processed formulations have been compared. In comparison with other technologies used (data not published) these two processes appeared to be the most effective, process (a) and (b) giving respectively a 8-fold and 11-fold increase in bioavailability.

Process (a) can be anticipated as a “green process”, as it does not use any organic solvent, but only a small amount of water, eliminated by final drying. It is fast, easily scalable and easy to monitor with Process Analytical Technology (PAT) tools; it can be continuously monitored, evaluated and adjusted using validated in-process measurements, tests, controls, and process end-point. In addition, it needs fewer investments, the material is easy to clean, and it allows the treatment of large quantities.

Process (b) appears to be the most efficient. It uses SC-CO₂ as antisolvent that can be recycled in the process and only a small amount of DMSO as solvent eliminated during the final stripping step. A drawback may lie in the fact that it requires high-pressure equipment.

Depending on the physical-chemical properties (solubility...) of the active ingredient and on the context of drug development and production (NDA-New Drug Application, generics) depending on economics, rationality and efficiency, and depending on how easy it is to obtain a good complexation percentage, energy needs, it can be better to use one or the other technique.

Acknowledgements

This article is dedicated by the authors to Professor John A. Dodds, head of EMAC-CNRS UMR 2392, who proposed this idea of paper to KONA's editorial committee. We wish him a happy new life after his retirement.

Pierre Fabre group is warmly acknowledged for providing the active molecule and for sponsoring this research.

A more detailed description of both processes have been published in two separate articles in the European Journal of Pharmaceutical Sciences.

Abbreviations

ACAT	Acyl-Coenzyme A O-acyltransferase
API	Active Pharmaceutical Ingredient
AUC	Area Under the time concentration Curve
BCS	Biopharmaceutics Classification System
CD	Cyclodextrin
β -CD	Beta-Cyclodextrin
γ -CD	Gamma-Cyclodextrin
CO ₂	Carbon dioxide
DMSO	DiMethylSulfOxide
DSC	Differential Scanning Calorimetry
ESEM	Environmental Scanning Electron Microscope
FDA	Food and Drug Administration
FTIR	Fourier Transform InfraRed spectroscopy
GPC	Gas Phase Chromatography
HPLC	High Performance Liquid Chromatography
NDA	New Drug Application
PAT	Process Analytical Technology
Ppm	Part per million
SAS	Supercritical AntiSolvent
SDS	Sodium Dodecyl Sulfate
SC-CO ₂	Supercritical Carbon Dioxide
UV	UltraViolet spectroscopy
W/V	Weight/Volume
W/w	Weight/weight

Nomenclature

ΔP	Net blade power consumption	[W]
ρ	Bulk density	[kg.m ⁻³]
N	Blade rotational speed	[rad.s ⁻¹]
R	Blade radius	[m]
D	Blade diameter	[m]
L	Blade length	[m]
H	Height of powder bed	[m]
g	Gravitational constant	[m.s ⁻²]
η	Viscosity	[Pa.s]

Np	Power number :	$Np = \frac{\Delta P}{\rho \cdot N^3 R^5}$
Re	Reynolds number :	$Re = \frac{\rho \cdot N R^2}{\eta}$
Fr	Froude number :	$Fr = \frac{R N^2}{g}$
I_0/I	FTIR absorbance ratio measured respectively at 1572 cm ⁻¹ (I ₀) and 1537 cm ⁻¹ (I)	

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Author's short biography



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Professor Jacques Fages is currently director of the RAPSODEE research centre at the Ecole des Mines d'Albi, ALBI, France. Under his leadership, RAPSODEE won the French innovation award in 2006.

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Born in 1962, Alain Chamayou is a Chemical Engineer from the “Ecole Nationale Supérieure de Génie Chimique” (Toulouse France), received his PhD in Process Engineering at the “Intsitut Nationa Polytechnique” of Toulouse in 1993. Actually he is an Assistant Professor in the RAPSODEE research centre of the Ecole des Mines d’Albi where he develops research in the fields of fine grinding,, mechanosynthesis and dry-coating.

Historically, he began working on fine grinding with air-jet mills (PhD thesis of L. Godet 2001) with a population balance modelling approach. Then a part of his works were oriented to organic mecanosynthesis (PhD thesis of A. Gil-2002) using this approach in order to improve the bioavailability of drug substances. More generally, mechanical actions are a way to combine (physically and/or chemically) particles in order to obtain new particles with desired user properties. He also extended the basic thematic of grinding (comminution) to co-grinding and then dry-coating (PhD Thesis of A.Vilela 2005) in order to design particles with specific properties. In parallel has developed collaborations with the university of Santiago of Chile to study the influence of ultrasound on grinding and co-grinding, and on products properties.

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He has served for 7 years as assistant professor at the University René Descartes in Paris, France.

He worked in industrial companies in France and Monaco for 7 years, in research and development of pharmaceutical active ingredients..

He then joined the Ecole des Mines d’Albi, France in 1993 where he developped original studies for engineers and pharmacist-engineers double-diploma .

He has served as visiting professor at Tohoku University, Institute for Advanced Materials Processing, Japan, and Keio University, Faculty of Science and Technology, Japan.

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