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Supercritical processes for particle formation in the pharmaceutical industry

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I am going to talk about supercritical processes for particle formation in the pharmaceutical industry. First of all, I would like to thank my co-workers because they did a lot of the work I will be describing. My colleagues Elizabeth Rodier and Jean-Jacques Letourneau, two former PhD students, Martial Sauceau and Hubert Lochard, two present PhD students, Miss Abla Adamou and Miss Marilyn Calderone. You have already met her; she is passing the microphone during the question times conferences. The outline of my talk will be as follows: First of all, I would like to give a short resumé about supercritical fluids, definitions and properties. Afterwards, I will talk a bit about phase equilibria and solid solubilities and finally I would like to explain the three main families of particle generation processes.

Let's start with a definition and a description of the properties of supercritical fluids. A pure component is described exactly by two variable states. I mean that if you know, for instance, pressure and temperature, the molar volume V or the density are also fixed and on this 3-D diagram (**figure 33**) where you can see what is called the state surfaces. In other words, it's an equation of state, which links pressure, molar volume and temperature. On two-dimension projections of this diagram, for instance the PT diagram, you can see two remarkable points; the triple point at which the gaseous, solid and liquid states

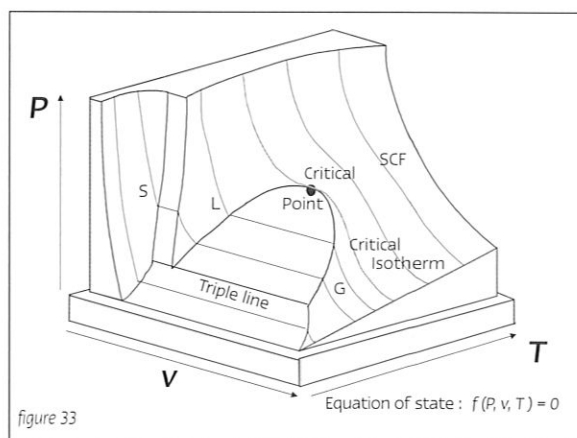


figure 33

A pure component can be characterised by two and only two of variables-of-state. If, for instance, P and T are fixed, then the density (or the molar volume V) can only take one value.

Another way to express this fact, is to say that these three variables are linked by an equation of state (EoS) : $f(P, V, T) = 0$

This is shown on figure 1 where the so-called state surfaces are represented on a three-dimensional diagram.

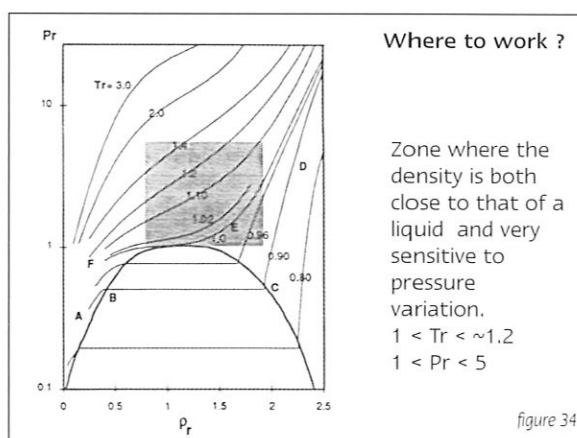


figure 34

Suivre ABCD. Comparer avec FE puis avec l'isotherme $T=2Tr$.
Le pouvoir solvant est lié à la capacité des molécules du solvant de venir entourer une molécule de soluté (« clustering »). Une augmentation de la densité va donc favoriser ce phénomène et augmenter le pouvoir solvant.

Another fundamental property of the SCF can be deduced from this curve: by varying the operating pressure, the concentration of a solute can dramatically change. Therefore SCF are tuneable solvents which explains the numerous industrial applications of extraction using these solvents.

Note the infinite compressibility at the critical point.
This figure shows another aspect of this peculiar solvent power : that of staying in a zone where the density is at the same time close to that of a liquid ($rr > 1$) and very sensitive to pressure variation, it is necessary to work not too far from the critical point. In other words, the reduced temperature must be in the interval $1 < Tr < \sim 1.2$ and the reduced pressure must be less than 4 to 5.

co-exist and the critical point which ends the vaporization curve. In fact, you can see that on the PV diagram. The critical point is in fact the maximum of the vaporization curve in which liquid and gas co-exist. A supercritical fluid is simply a fluid with pressure and temperature over the critical coordinates and if you follow the arrow on the diagram, you can see that it's possible to go from the liquid to the gaseous state without at any moment being subject to any phase change.

What are the properties of supercritical fluids? They are, in fact, intermediate between those of liquids and gases. For instance, if you look at the column « density », you can see that the supercritical fluid density is close to that of a liquid, meaning that they display quite good solvent properties. On the other hand, viscosity is much closer to that of a gas, meaning that, for instance, they will have gas-like transport properties. Supercritical fluids can, for instance, impregnate micro-porous matrices like a gas but have the solvent power of a liquid, which is, of course, extremely interesting. There is an interesting zone where the fluid is at the same time, dense like a liquid and compressible like a gas. This is the grey zone on this diagram a (figure 34) and you can see that even at the critical point there is an infinite compressibility, meaning that a slight increase in pressure will be translated into a huge variation in density that is in solvating power. To sum up this introduction, a supercritical fluid is both dense and compressible and you can tune its solvating power very easily by varying the pressure, which is a very convenient operating parameter.

As I already said, low viscosity and surface tension imply gas-like transport properties and this explains why extraction and extract fractionation have been, and are still, the most used properties of these fluids. Several common chemicals have been tested as supercritical fluids. As you probably already know, it is carbon dioxide, which is the most commonly used. Supercritical water, you can see that its critical coordinates are rather difficult to attain. However, supercritical water is mainly used for hydrothermal oxidation of waste. Among the other chemicals, CO₂ is by far the most used because it displays several advantages: it has a solvent spectrum which is relatively close to that of several chlorinated solvents which as you may know are going to be, if they aren't already, banned. It is natural, non-toxic, non-flammable, abundant and cheap (figure 35). Cheap, that depends in fact on the purity. It can be expensive but let's say rather cheap. It is environmentally acceptable; the CO₂ used has already been produced, therefore it doesn't add to the greenhouse effect. Its critical coordinates are rather mild and easy to reach. However, it has a major drawback. It is a rather poor solvent for a lot of molecules, especially polar and big molecules, as is often the case in the pharmaceutical industry.

Here is a non-exhaustive list of the industrial application of supercritical fluids. I will not detail all of these applications; I will only concentrate on the last one, which is a rather new particle generation process which has been described in the

carbone dioxide : CO₂

- **SC-CO₂ is by the most used solvent in industry**
- It advantageously replaces several organic solvents (CHCl₃, CH₂Cl₂, CFC's, hexane,...).
- It is natural, non toxic, non flammable, abundant and cheap (depends on the purity).
- It is environmentally acceptable.
- Its critical temperature and pressure are : T_c = 31,1°C ; P_c = 7,38 MPa
- **Its solvating power is rather poor for a large number of (bio)molecules.**

figure 35

CO₂ is the far most widely used supercritical fluid. Its P_c and T_c are relatively easy to reach. In addition, its solvent power is relatively close to those of chlorinated solvents (CHCl₃, CH₂Cl₂, CFC's) and normal alkanes like hexane which are already or might soon be banned. Nevertheless, CO₂ is a poor solvent for polar molecules. However, CO₂ can also solubilise highly polar compounds provided adequate CO₂-soluble surfactants (like fluoro-ethers) are used.

literature for almost 20 years now but it's still rather recent and which leads to ultra-fine and mono-dispersed powders. Before detailing this particle generation process, I would like to stress a few points on phase equilibria and solid solubilities which are a prerequisite before studying these processes.

This is now the second part of my talk. An equation of state is very useful for understanding the behavior of a supercritical fluid. As I already said, it links pressure, temperature and density. It is also usable with mixtures. Mole fractions can be introduced into an equation of state. I'm sure that you all know the ideal gas law; the Boyle-Marriotte law which is valid only for ideal gases, meaning when there is no interaction between the molecules. This is obviously not the case with a supercritical fluid which is dense. Therefore, other equations of states have been introduced. The first one, a long time ago by Van der Waals. He introduced two parameters. A represents an interaction between the molecules while B is known as a co-volume. In fact the lower molar volume obtained when you get the most compact arrangement between molecules. Several authors have improved this equation and other analytical equations are now commonly used by researchers. When dealing with mixtures, the molar fraction of each compound is introduced in the calculation of A and B in what is called the mixing rules.

A few words about the solubility of the solid in a supercritical fluid. Plotting solubility versus the pressure, at low pressure you can see the ideal gas behavior. In fact, the solubility is a sublimation pressure divided by the total pressure of the system. But very rapidly, there is the

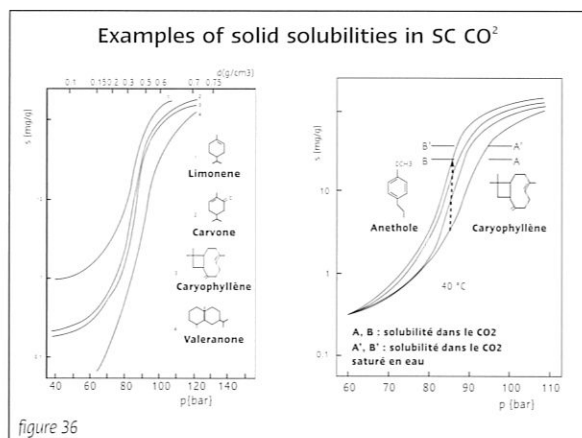


figure 36
Solubility depends on the size and the polarity of the molecule : compare 1-3 and 1-2
Cosolvency effect depends on the molecular interactions. On the right hand-side figure, water enhances the solubility of anethole while it reduces that of caryophyllene

fugacity coefficient which is in an equation explaining the quite steep increasing solubility at intermediate pressure with the pressure. And at higher pressure, the solubility is almost independent of pressure and you can see that there is what is called a retrograde region in the middle of the steep slope. Thus by increasing the temperature from T1 to T2 and T3, there is a decrease in solubility. The next slide will explain a little more the phenomena involved. When increasing the temperature, two antagonistic phenomena occur; first of all, increasing the temperature means decreasing the density and therefore the solubility decreases. This is the predominant phenomenon while working at lower pressures. On the other hand, increasing the temperature increases the sublimation pressure of the compound and this leads to an increase in the solubility. This phenomenon is prominent at higher pressure. This is the reason why there is a crossing point, and if you have to deal with two compounds, you can have what is called a crossover region in which increasing the temperature will increase the solubility of compound A, for instance and decrease the solubility of compound B.

Solid solubility in supercritical fluids can be represented by the help of what is called an enhancement factor which is in fact the ratio of the actual solubility to the solubility of an ideal gas. In other words the non-idealities of the supercritical fluids are represented by this enhancement factor, which can be extremely high; 104 to 108 times. Another way to increase the solubility in a supercritical fluid is to add what is called a co-solvent. A co-solvent is generally a small molecule, like ethanol or acetone, which is added in only a few mole percent which may enhance solubility by several factors up to 103 and even 103 times. It acts by two different phenomena. First of all, it modifies

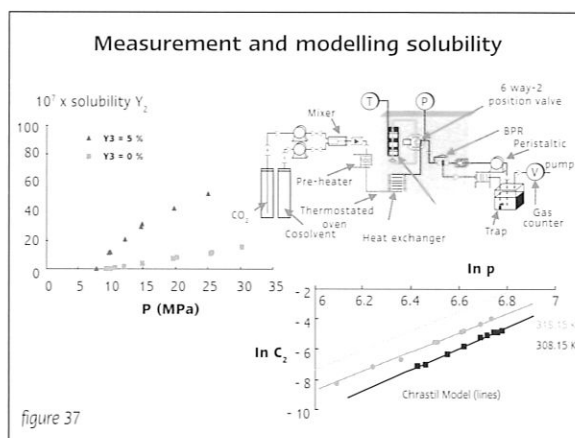


figure 37
A dynamic open-flow method where the fluid passes through a bed of the solid. The fluid flow (which determines the contact time), the geometry of the equilibrium cell, determine whether or not the residence time is long enough to reach the equilibrium. The solubility of the solid in supercritical fluid is calculated from the total volume of gaseous solvent (extraction solvent) used and the concentration of solid in the recovery solute liquid phase. From these two measurements and knowing the total volume of the recovery solute liquid solvent, the solubility of the solid in the supercritical fluid can be calculated. A model which links the logarithm of the concentration and the logarithm of the density, allows prediction of new isotherms. Example of the cosolvent effect with ethanol. 5% addition of ethanol gives a 5 fold increase at 300 bars.

the phase diagram – we are going to see an example in a few minutes – and there are also specific molecular interactions between the co-solvent and the solute, which may explain this enhancement.

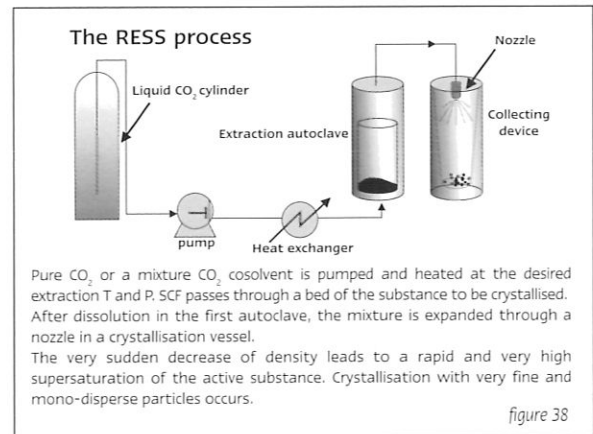
A few examples from the literature. For instance, here you can see that solubility decreases when the size of the molecule increases (figure 36). If you compare for instance, molecule one, (limonene) and molecule three (cariophelene). And if you add say a ketone group, by comparing molecule one and molecule two, or molecule three with molecule four, you can see that because carbon dioxide is a non-polar solvent the solubility has decreased. The other diagram explains why it is necessary to be cautious when using a co-solvent. In this case, by adding a few percent of water, which is a co-solvent, you can increase the solubility of one molecule, in this case anetol and you can decrease the solubility of another one. Therefore it is extremely important to be able to accurately measure solid solubilities and model these solubilities. This is a diagram of an apparatus that we have developed in our laboratory here in Albi in collaboration with a team at the Ecole des Mines de Paris (figure 37). With this apparatus, we can measure very low solubilities, as low as 10⁻⁷ in mole fraction. As an example, here is the solubility plotted against the density. The dots are the experimental results and you can see that we can fit and even predict solubilities at temperatures not tested, by using several models from the literature and also by

developing new models of our own. The last diagram is just to show you the importance of a co-solvent. By adding 5 % ethanol in you can see that at 300 bars for instance, (30 megapascals) the solubility has been multiplied by a factor of about five.

Now moving to the third part of this lecture. The particle generation process. As you know, about two-thirds, maybe more, of the products used in the pharmaceutical industry are in the form of powders and the classical way to produce particulate solids is still of course : starting from the solid state and using size reduction processes like crushing, grinding. Or starting from the liquid state using crystallisation processes, by evaporation, cooling etc. Supercritical fluid technology is a third route which avoids a lot of the drawbacks of the classical routes and which displays several advantages. By using this technology, it is possible to manufacture drug-release systems; coated and encapsulated core particles, liposomes, etc. It is also possible to tailor the particle-size distribution in order to have the particles in the correct range for say pulmonary delivery. Another advantage is that by mastering the operating condition it is often possible to control crystal polymorphism. The problem of bioavailability of poorly soluble molecules can be addressed with this technology too, since it is possible to improve the dissolution rate, which is often linked with bioavailability or to make, for instance, inclusion complexes. Finally, it's what is called green technology since there are no solvent residues which is an additional advantage of this kind of technology.

We can roughly divide the processes into three families depending on the way the supercritical fluid is used. If it is used as a solvent, it is what has been called the Rapid Expansion of Supercritical Solution (RESS process). If it is used as an anti-solvent, it is a Supercritical Anti-Solvent (SAS process), and finally, when it is used as a solute, it is a process called Particle from Gas Saturated Solution (PGSS process). I will now go into more detail about these three main families of processes.

The RESS process first (**figure 38**). It's a rather simple process in its principle. Pure carbon dioxide or a mixture of carbon dioxide and a co-solvent is pumped and heated to extract the compound to be micronised. Therefore it is important to know the solubility of the solid in the supercritical fluid. The supercritical mixture is expanded through an orifice, a capillary leading to a very sudden nucleation and particle formation. Very often, very fine and mono-dispersed particles are obtained with this simple process. One may wonder what happens during

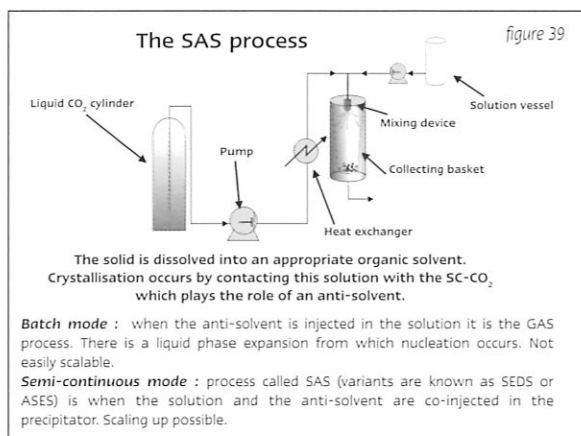


A solid dissolved in a SCF can be crystallised from the homogeneous supercritical solution -P and T are chosen to give a monophasic mixture- provided the density has dropped enough. The easiest way to provoke a drop in density is to force the fluid to pass through a hole or a capillary or a nozzle in which an adiabatic expansion can be achieved. Nozzle diameter must be small enough to allow a large depressurisation. Typically it is of a few decades of micrometers. Downstream the nozzle, the fluid is generally in the gaseous state with a very poor solvating power. Figure gives a schematic view of a device aimed for RESS particle production.

It is important either to collect data in the literature when they exist, or to perform experiments or modelling, about the solute solubility in the SCF. The key parameters of this extraction step are obviously the operating T and P. The flow rate of the fluid may also play an important role since a thermodynamic equilibrium may or may not be reached in the extraction autoclave. In fact, the kinetics of the dissolution must not be neglected and diffusional limitations can occur. An additional problem may be encountered when the solid to be extracted is not a pure component. Fractionation of the load can lead to a variation in the composition of the particles upon depressurisation.

this sudden depressurisation. Here on the screen you have on the left a pressure-temperature diagram. The depressurisation is the dashed arrow you can see with its starting point here. Here are the conditions in terms of temperature, pressure and density at the starting point, and at the arrival point. Much lower temperature, much lower pressure and much lower density. At the end we are generally at atmospheric pressure in a gaseous environment. The pressure enthalpy diagram is very useful because we can assume that the depressurisation is enthalpic. Therefore it is a vertical line in this diagram, and it's very useful to work on the single phase of this diagram in order to avoid a liquid phase which could redissolve particles, for instance. Or involve the formation of carbice for instance, which may cause problems, too.

As I have already said, there is at another level a mechanical perturbation at the speed of sound which leads to very uniform conditions. This explains why there is a very narrow particle size distribution of the particles obtained with this process. The key parameters in this case being the difference in pressure upstream and downstream of the nozzle, and of course, the solute concentration. Again, it is important to know about solubility. Several morphologies of particles could be obtained. If you read the literature you can find absolutely



When both the organic solution and the anti-solvent are contacted, the anti-solvent dissolves in the organic phase decreasing the density, the solvent power and therefore the solubility of the solute. Inversely the solvent evaporates in the supercritical phase increasing the solute concentration. It is this mass transfer in both directions which accounts for the quick supersaturation of the solute and therefore the nucleation of crystals.

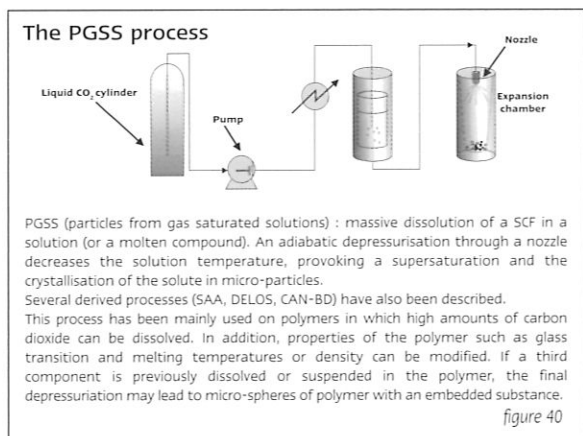
Several ways of achieving a SAS process can be encountered. The figure gives a schematic view of a SAS device in which both streams are contacted at the nozzle level. This operating way has been referred as the SEDS process, for Solution Enhanced Dispersion by Supercritical Fluids. It is a continuous process except for the particle collection which has to be done sequentially. The solvent can be collected in separators while the antisolvent can be recycled by compression, heating and re-injection. A washing of the expansion vessel with pure SCF is recommended before particle collection. Ruchatz et al. (1997) have evidenced the importance of process parameters on the solvent residues concentration. Several other possibilities exist : batch mode with injection of the antisolvent in the solution (GAS) or the reverse (ASES)

all kinds of particle morphologies, from spheres to fibres. Very often, agglomerated particles are obtained because there is crystal growth and coagulation within this vessel. And obviously, nozzle geometry plays an important role, which is not always as is expected. Recently, a German team published a very beautiful paper in which they showed that large orifices may lead to smaller particles. And very often, the particles obtained are crystalline, which is surprising since very quick nucleation would give mainly amorphous material. There are several explanations about, for example, the effect of the temperature in the expansion vessel which may explain why crystalline material is obtained and not amorphous material. So, to sum for this process. It can be said that RESS is very simple in its principle. It leads to fine mono-dispersed powders and it is, I would say, the first process to be considered. Its main advantages can be summed up as follows: nanosized particles with high specific surface area; no organic solvent used, so it is the perfect « green » process. It can be used for encapsulation in a biodegradable polymer, for instance, polylactic acid, providing of course that the polymer is soluble in the supercritical fluid. And another advantage is that the crystallisation by depressurisation has been known for a long time. So it's probably simpler in terms of industrial properties compared with the other processes.

However, there is one main drawback, as I already said, most organic molecules, are poorly soluble in supercritical carbon dioxide. This might be partially overcome by the use of co-solvents; however, it is still a drawback. There are a lot of examples of molecules processed by RESS, so this is a non-exhaustive list and there are very good reviews in the literature if you want to know which kind of molecules can be processed by RESS.

Let's go now to the SAS process (figure 39). The anti-solvent process, which is, used mainly when the compound is not soluble in CO₂. In this case, the solid is dissolved in an appropriate organic solvent which must be miscible with supercritical CO₂ which then acts as an anti-solvent. In fact, it is by contacting the two flows of organic solution and supercritical fluid that the reciprocal dissolution of solvent and anti-solvent will provoke nucleation and crystal growth. In batch mode, which is not on this scheme, the anti-solvent is injected into the organic solution leading to an expansion of the liquid phase. This process is not easily scaleable and most of the researchers have concentrated, in recent years, on the semi-continuous mode which is represented on this scheme. Semi-continuous because obviously, the collecting of the particle is still in batch mode. Here again, the pressure enthalpy diagram is very useful. This is the diagram of a mixture of 95 % carbon dioxide and 5 % ethanol. You can see that the biphasic envelope has been considerably enlarged by the presence of ethanol and the red dot is one possible set of operating conditions which could be used. It is advantageous here again to work in the single-phase zone of the diagram because a much higher mass transfer and super-saturation ratio can be obtained in this zone. This is because there is no interface between the droplet and the gas and therefore crystals will appear in a cloud of the anti-solvent.

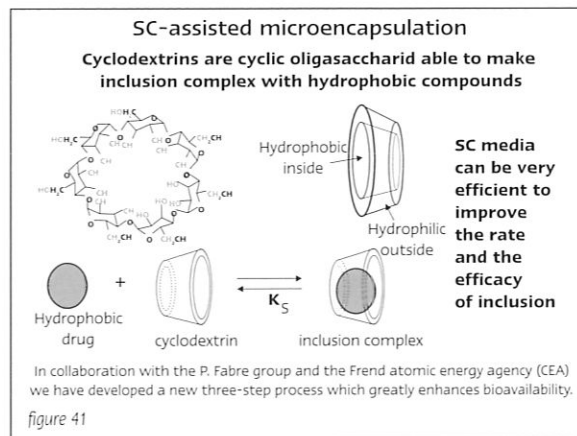
The phase behavior of the binary solvent-anti-solvent has obviously to be taken into account. The ratio of both flows is extremely important, as is the mixing device. The nozzle in this case is rather a mixing device than a depressurisation device as is the case in RESS. Particles of all types, sizes and morphologies have been obtained, and in terms of modeling, two Spanish colleagues, Martine and Cosero have recently published - in fact it is not yet published but it will be published before the end of the year- a paper where they have proposed a very nice comprehensive model. This is the first, to my knowledge, complete global approach, including thermodynamics, hydrodynamics, crystallisation and mass transfer. It's not perfect, since the prediction of particle size does not fit



exactly with the experiments. However, this is important progress which has recently been made in the modeling of this process. To conclude on the anti-solvent process. It is almost always possible to find the right couple of solute and solvent and therefore SAS is usable with all types of molecules. This is the reason why it has been the subject of a lot of research in the past five to ten years. You can, for instance, make an easy and efficient co-precipitation of two molecules with this process. You can improve dissolution rates. You can manufacture drug release systems. The main drawback however is the presence of an organic solvent which, of course, can be washed out at the end by pure CO₂ for instance, but we are not in the same case as in RESS, where no organic solvent at all was used. Here again, a lot of molecules have been processed ; proteins, antibiotics, carriers, etc.

The third category of processes uses another property of carbon dioxide. Carbon dioxide can dissolve in large quantities into organic solutions or into molten polymers. And it is this property which is used in the PGSS process (figure 40). By sending this gas-saturated solution through a nozzle to reducing the pressure and the temperature, to obtain particles. This process, and others, I have seen a poster on the Delos process in this conference. This process is very useful for manufacturing coated particles since the dissolution of carbon dioxide into polymers will lead to a shift in melting temperature. There are also two posters from our Portuguese colleagues here in this conference about that phenomenon. Microspheres can be manufactured by this process.

Another interesting way to improve bioavailability of a drug is to use cyclodextrines which are oligosaccharide molecules able to made inclusion complexes with hydrophobic drugs (figure 41). It is interesting to note that supercritical media can be very efficient in improving



Cyclodextrins are cyclic polymers of 6, 7 or 8 glucose residues. They exhibit a hollow cavity cone shape. The interior of the cavity is rather hydrophobic while the exterior is rather hydrophilic. Provided the size of the drug is compatible with that of the cyclodextrin, an encapsulation may occur which can greatly enhance the solubility.

the rate and the efficacy of the inclusion. Here in Albi we have worked a lot on this type of process in collaboration with the Pierre Fabre Group and the French Atomic Energy Agency. We have developed a new process for enhancing bioavailability and my colleague Bernard Freiss will talk about this in much more detail in a few minutes.

To conclude. There are several major advantages in using this technology. About the process; it is very often a single-step process. Dissolution, supersaturation, nucleation, growth, etc., can be very often done in only one step. It offers an easy and fine control of product properties through the pressure and is an environmentally acceptable technology. On the product side, now, small particles, narrow particle-size distribution, high purity and unique properties of the powders obtained. Possible control of crystal polymorphism and is usable with fragile molecules. Producing nanoparticles with this technology is already a reality and it is what my two colleagues Andreas Kordikowski and Bernard Freiss are going to explain to you now. Scaling up has also been addressed by several companies. However, there is still a lot of work to do for researchers, fortunately for us. There is still a lot of work to do to have a better understanding these processes. In spite of recent progress, a satisfactory global theoretical approach is still awaited. My final slide would be to invite you to have a look at our laboratory with several pieces of equipment from the French company Separex. Should you be interested, you can visit our lab, read our papers - I have brought with me, a few reprints of papers that have recently been published. Please don't hesitate to ask.

Thank you for your attention.