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Is it possible to enhance the dissolution rate of poorly-soluble active ingredients by supercritical fluid processes ?

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Scope:

As a growing number of new active compounds exhibit a very low solubility in biological media, the pharmaceutical industry is facing a major challenge to find routes to formulate such compounds in order to reach an "acceptable" bio-availability [1]: More than one third of the drugs listed in the US Pharmacopoeia are considered as poorly-soluble, and a recent study stated that 41% of failures in new drug development in seven UK-owned companies have been attributed to poor biopharmaceutical properties, including water insolubility [2].

In fact, it has been shown that, for most poorly-soluble compounds orally administered, the bio-absorption process is rate-limited by the dissolution in gastro-intestinal fluids; in the case of parenteral administration, the effective bio-availability of compounds is also limited by dissolution issues (risk of precipitation at the injection point, slow dissolution in serum,…). Many parameters related to solid morphology influences the dissolution rate of a compound, among which the particle size and the crystal habit and crystal pattern have a key-role.

On two posters, we review literature and present some of our own results on the ***dissolution rate enhancement*** of poorly-soluble active ingredients by using supercritical fluid (SCF) processes [3-5] in order to micronize these compounds into neat nano-/micro-particles (Part I), or to formulate them by micro-encapsulation, cyclodextrin (CD) inclusion and impregnation (Part II).

Supercritical Fluid particle design

For the purpose of dissolution enhancement, several SCF particle design processes can be used, classified according to several classes related to four main basic concepts (see details in [3]), with the possibility to micronize neat particles with the two first ones, and to prepare composite particles by the four ones:

- ✓ *Rapid Expansion of Supercritical Solutions (RESS):* A solution of the compound(s) in a supercritical fluid is rapidly depressurised through a nozzle, causing a rapid nucleation of fine particles (neat or composite);
- ✓ *Supercritical Anti-Solvent (SAS):* A solution of the compound(s) in an organic solvent is contacted with a supercritical solvent that causes solid precipitation by anti-solvent effect, the organic solvent being eventually entrained by the supercritical fluid; either neat particles of a unique compound, or micro-spheres of an ingredient embedded in an excipient, or CD-complex particles are generated;

- ✓ *Particles from Gas-Saturated Solutions (PGSS):* The compound(s) are melted in presence of a compressed gas that dissolves in the liquid phase which is pulverized towards a low-pressure vessel, leading to precipitation of solid particles of compound(s); when a suspension of fine particles of an ingredient dispersed in a liquid excipient is processed, composite micro-capsules are generated;
- ✓ *Impregnation:* The compound is dissolved in a supercritical fluid that is then depressurised into a vessel containing a porous excipient on which the compound gets adsorbed. In another concept called Concentrated Powder Formulation (CFP) applicable to liquid compounds, the liquid viscosity is decreased by saturation with a high-pressure CO_2, and the liquid penetrates the carrier pores where it is adsorbed during the co-pulverization of the solid and liquid phases.

Dissolution of SCF-micronized neat particles

We will not enter into the solubility theory and solubility prediction as the reader can find comprehensive syntheses in [1], but recall some fundamental aspects.
Applying the Fick's law, it is easy to demonstrate that the mass transfer rate of a particulate solid of mass $\boldsymbol{M}$ (composed of particles with an average volume $\boldsymbol{V_p}$) into a liquid of volume $\boldsymbol{V_L}$ is proportional to the solid surface $\boldsymbol{S}$:

$$\boldsymbol{\delta M/\delta t = - h.S.(C_S - C_b)} \qquad \boldsymbol{(1)}$$

where $\boldsymbol{h}$ is the mass transfer coefficient (generally estimated by $\boldsymbol{h = D/e}$ where $\boldsymbol{D}$ is the diffusion coefficient of the compound in the liquid and $\boldsymbol{e}$ the thickness of the diffusion layer), $\boldsymbol{C_S}$ the solid solubility and $\boldsymbol{C_b}$ the solute bulk concentration. This leads to the *Noyes-Whitney equation* giving the dissolution rate $\boldsymbol{R}$ (defined as the concentration change $\boldsymbol{R = \delta M/\delta t \,/\, V_L}$):

$$\boldsymbol{R = D.S.\ (C_S - C_b)/(e.\ V_L)} \qquad \boldsymbol{(2)}$$

Supposing that $\boldsymbol{C_b}$ remains very small in comparison with the saturation solubility $\boldsymbol{C_S}$, and as the solid surface area $\boldsymbol{S_p}$ is proportional to $\boldsymbol{V_p^{2/3}}$, equation (1), into:

$$\boldsymbol{M^{1/3}(0) - M^{1/3}(t) = K.t} \qquad \boldsymbol{(3)}$$

known as the *Hixson-Crowell cube root law*.

On the contrary, when the initial amount of solid approaches the amount needed for reaching a saturated solution, the following equation is obtained, known as the *Negative two-thirds law*:

$$\boldsymbol{M^{-2/3}(t) - M^{-2/3}(0) = K'.t} \qquad \boldsymbol{(4)}$$

Equations (3) and (4) can be expressed in the case of spherical mono-dispersed particles, showing the dependence of the dissolution rate with the particle diameter. But, as powders are never mono-disperse and rarely spherical, this is of poor help. The knowledge of the particle size distribution may also mislead: A powder sample with a small mean diameter and large size distribution may have a deceptively low dissolution rate due to the presence of big particles at the end of the distribution. It is always better to consider the specific area $\boldsymbol{a}$ rather than the particle size, the more because the particle size information may hide particle re-agglomeration that considerably reduces the specific area.

Moreover, it is to be noticed that the ***solubility*** C_S of solid particles also depends on the particle size, increasing for colloidal suspensions: Particles with diameter below 1 µm possess significantly greater solubility than larger ones; this difference may be attributed to a greater specific surface area and higher surface free energy for fine particles in comparison with their larger counterparts. It was widely observed that the very fine particles have a tendency to dissolve and recrystallize onto the larger ones, producing a shift in particle size distribution until an equilibrium solubility is reached ("Ostwald ripening").

1. Experimental issues:

First of all, it must be emphasized that solid dissolution is a complex operation influenced by a great number of factors, not ***only*** the particle size! This can be illustrated on figure 1[6] showing the dissolution curves of a poorly soluble compound as bulk or micronized, compared with the theoretical curve of the micronized form, according to the Hixson-Crowell cube-root equation (3); further observations using a light microscope showed a high degree of re-agglomeration of the micronized particles.

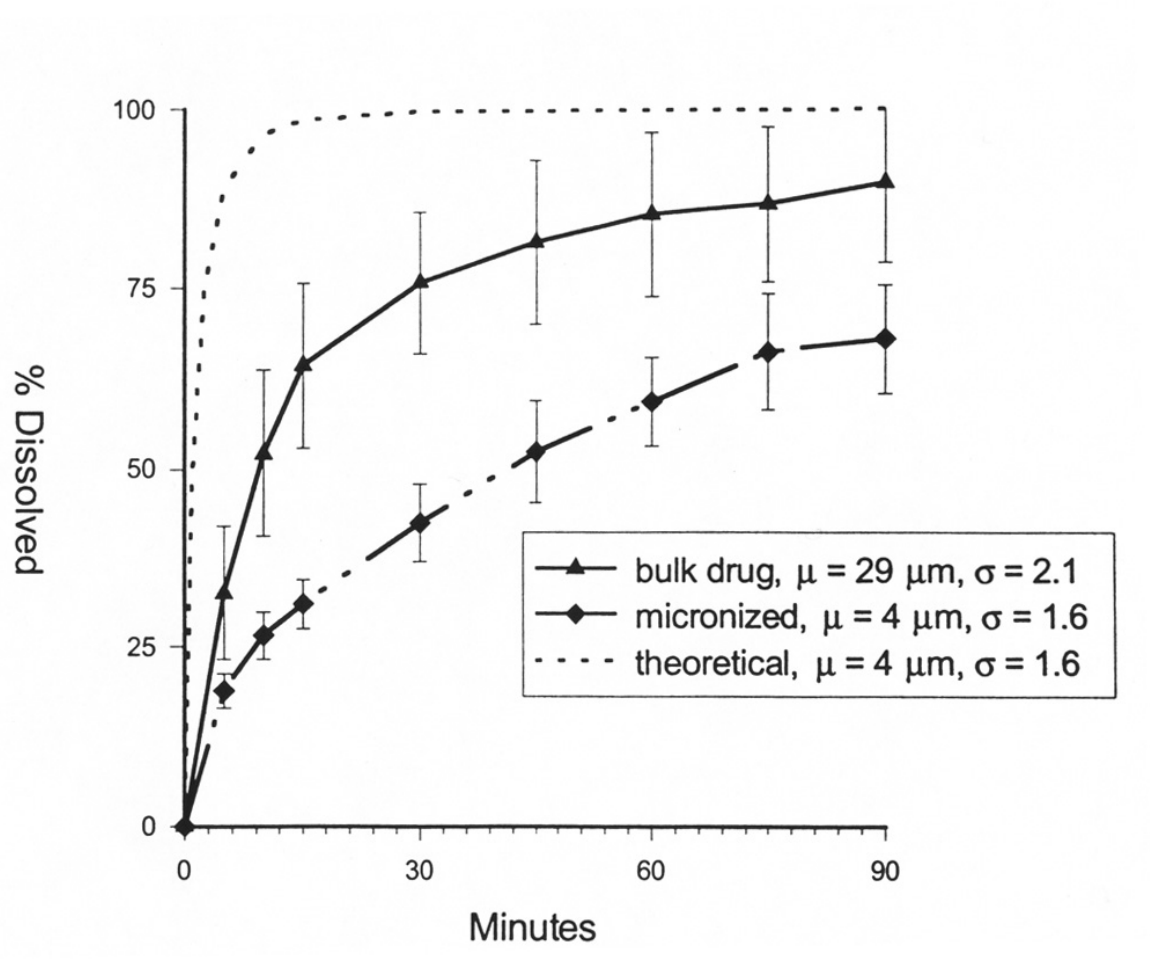

Figure 1: Dissolution curves of a poorly-soluble compound [6].
(By permission of …)

As a matter of fact, micronization – whatever is the process – alters the solid morphology more or less. This is of major importance when the solid presents polymorphism and when amorphous phase is formed, creating unexpected behavior and/or unstable properties. On the other hand, the particle or particle aggregate tends to adsorb air and becomes extremely

difficult to disperse into an aqueous media: the micronized powder is not wetted by the liquid, floating on the surface instead of dispersing in the liquid bulk, except when a surface-active agent is present in the medium.
So, experimental dissolution curves are often altered by artefacts or lead to unreliable results, when a robust method of particle processing and dissolution evaluation is not utilized. Of course, subsequent formulation may also dramatically affect the dissolution rate that becomes very different from what is observed with the non-formulated particles.

Among the hundreds of articles dealing with SCF particle design [3-5], it is rather surprising that very few ones disclosed interesting results on dissolution-rate comparison between the unprocessed material and the SCF micronized solid, as detailed below ; moreover, in most publications, data are not complete and physical properties of the solid material are lacking. Perhaps this is to be related to the difficulty to reach reliable results as mentioned before !
We would honestly confess that our team did experience such difficulty and prefer not to disclose some uncertain results, while other ones were covered by trade secrets; however, in spite of these reservations, our results on active ingredients micronization are presented in the poster (Part I).

2. Discussion:

From the results cited in this poster regarding 13 active compounds (***phenacetin, nifedipine, felodipine, griseofulvin, carbamazepine, lidocaine, ibuprofen, mefenamic acid, copper-indomethacin, phytosterol, lovastatin, celecoxib, rofecoxib***), we would drive the following main lines:

- Many works trying to demonstrate the enhancement of poorly-soluble compound dissolution rate in aqueous media by SCF-micronization did not lead to reliable conclusions as the final drug formulation plays a major role, meaning that dissolution curves of the neat compound particles are not significant;
- Although the accepted theory tends to predict a rate quasi proportional to the specific surface area ***a***, the sole micronization cannot guarantee a significant enhancement of the dissolution rate and, consequently, of the bio-availability of hydrophobic active compounds;
- Many other factors play a major role on the dissolution phenomenon among which the most important one is ***wettability***; addition of a surfactant in the excipient mixture is of prime importance.

We would conclude that this does not mean that SCF-micronization is not valuable; on the contrary, we would emphasize that an optimized formulation does permit to take profit of the resulting specific surface area increase.

Dissolution of composite particles

1. SCF formulation

Different SCF processes [3-5] are being developed to design ***composite*** particles with several purposes: Preparation of sustained-release drugs by incorporating the active in a slow-dissolving (bio-degradable or bio-erodable) matrix [6], stabilization of fragile molecules (mainly bio-molecules) in solid form, and bio-availability enhancement of poorly-soluble compounds by incorporating the active in a fast-dissolving hydrophilic excipient. For this latter purpose, many works are focused on the preparation of particles consisting in a complex of the active drug inserted in a cyclodextrin-type molecule : the cyclodextrin “cage” presents

a hydrophilic character on its outside, leading to a very fast dissolution in aqueous media, but a hydrophobic character on its inside, permitting a stable inclusion of poorly-soluble molecules of an adapted size. This explains that these inclusion compounds are widely considered for designing delivery systems adapted to poorly-soluble drugs [7], although these complexes are generally considered as new chemical entities with specific pharmacological properties different from the neat drug ones. Moreover, impregnation of hydrophilic porous carriers can be operated using a supercritical fluid as vector of the active ingredient.
The choice of the carrier and the choice of the process are correlated, as summarized on the table 1 [4]. One might be surprised as we do not list some other SCF processes applicable when the active compound is not soluble and the fluid and the carrier is soluble, like SCF deposition leading to micro-capsules; in fact, these processes seem not applicable when hydrophilic carriers are concerned for dissolution enhancement.

Table 1: Formation of composite micro-particles for dissolution enhancement (from [4])

Substrate solubility in SCF	**Matrix solubility in SCF**	**Available process**	**Type of particles produced**	**Remarks**
Yes	**Yes**	RESS	Micro-spheres	- Few substrates / coatings both soluble in SCF CO_2 - Possible use of polar SCFs
Yes	**No**	SCF Impregnation	Active adsorbed onto a porous carrier	- Carrier impregnation by extracted active - Easy scale-up - *Rarely used for dissolution enhancement*
No	**No**	Supercritical Anti-solvent	Micro-spheres/capsules CD complexes	- Difficult solvent/ fluid separation and scale-up
		Fluid-Assisted Micro-encapsulation	Micro-spheres/capsules	- Very low CO_2 consumption - Easy scale-up
		CPF impregnation	Liquid active adsorbed onto a porous carrier	- Continuous process - Easy scale-up - *Rarely used for dissolution enhancement*

2. Discussion:

Composite particle generation by SCF processes looks as a very promising solution to enhance the dissolution of poorly-soluble compounds, although results may deeply vary for one case to the other as shown by the brief review presented on the poster (Part II). At present time, most works were conducted with hydrophilic polymers and CDs leading to size-controlled particles that rapidly release the active compound in the aqueous media as shown for 10 active compounds (***carbamazepine, nifedipine, felodipine, cefuroxime axetil, lidocaine, sulfathiazole, ibuprofen, eflucimibe, naproxen , celecoxib***) on our poster (Part II).

We strongly believe that amphiphilic carriers could supply valuable alternatives as the hydrophobic moiety will permit a labile association of the excipient with the active compound by formation of a sort of cluster around each active molecule (or nano-aggregate of

molecules), meanwhile the hydrophilic moiety will induce a rapid dispersion at the molecular scale in the aqueous media, inducing a micellar-like solubilization that may lead to a high bio-availability of the active molecule associated with this amphiphilic excipient.

Notwithstanding these attractive results, it is certainly not wise to deduct that dissolution rate enhancement of these SCF-processed materials signifies a comparative enhancement of the *bio-availability* of the final drug, especially when dissolution tests were performed in pure water instead of "representative" artificial media. And finally, only animal or human tests could quantify the improvement, case-by-case.

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