Supercritical fluid applications in the pharmaceutical industry

Many promising new pharmaceutical applications are currently under development for supercritical fluid technology.

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During the last two decades, industrial applications of supercritical fluids have been mostly developed for natural product extraction/fractionation, both for food and pharmaceutical products (1-7). At the present time, these applications are still continuing to spread worldwide as requirements for high-quality products are growing, and concerns about health and the environment are being voiced more widely.

Extraction (supercritical fluid extraction, SFE) from solid materials is the most developed application of supercritical fluid technology. The number of industrial-scale SFE units now under operation is currently estimated to be one hundred, with a growth of around 10% per year. Some niche applications concern high-added value products, such as bone de-lipidation for allografts and specialty polymer stripping.

Preparative scale supercritical fluid chromatography (PSFC) is used for the ultimate fractionation of very similar compounds, especially for lipids such as polyunsaturated fatty acids. It is operated in a few large-scale units.

Reactions can be operated in supercritical media (supercritical fluid reactions, SFR) (4-6), and very promising processes are being developed for fine highly selective syntheses, especially hydrogenation.

New pharmaceutical applications of supercritical fluids

Particle design and drug formulation Particle formation processes using supercritical fluids (8) are now the subject of increasing interest, especially in the pharmaceutical industry. Here, the technology is being applied in various ways, including to increase the bio-availability of poorly-soluble molecules, to design formulations for sustained release and to develop less invasive alternatives to parenteral drug delivery (oral, pulmonary and transdermal systems). The most complex challenge relates to therapeutic proteins, as it is extremely difficult to deliver bio-molecules due to their instability and very short half-life in vivo.
**Rapid expansion of supercritical solutions (RESS)** involves atomising a solution of a product in a supercritical fluid into a low-pressure vessel. This process only has applications at a commercial scale when product solubility in the supercritical fluid (preferably CO₂) is not too low ($\geq 10^{-3}$ kg/kg), limiting the process to non-polar or low-polarity compounds. The example of micronisation of lovastatin, a cholesterol-lowering drug, by RESS is shown in Figure 1.

**Supercritical anti-solvent (SAS)** applies to most molecules that can be dissolved in a very wide range of “strong” organic solvents. Recent developments, especially for the preparation of very fine particle drugs for pulmonary administration, are opening up a bright future for the engineering of new types of materials. These include nanoparticles (50-500 nm) or micro-particles (500-5000 nm) or empty “balloons” (5-50 µm) made of nano-particles, permitting a very significant increase in the bio-availability of poorly water-soluble drugs (Figure 2), or micro-spheres of drug embedded in an excipient for sustained-release delivery.

**Micro-encapsulation** Supercritical fluids are very promising for micro-encapsulation, as shown in the examples in Figures 3 and 4. It is to be noticed that, according to a process developed and patented by Separex (9), micro-capsules of proteins can easily be prepared in “mild” conditions that do not lead to protein denaturation and loss of bio-activity - as demonstrated for lactase (Figure 4); this should, however, be confirmed for therapeutic proteins or other fragile bio-molecules.
Figure 3.  
*left* Ovalbumin micro-encapsulated in a lipid, and *below* release in a buffer solution at 37°C.

Figure 4. Lactase micro-encapsulated in a lipid.

Moreover, other processes using SCF permit micro-encapsulation using RESS, SAS and PGSS, while other variants can be used for liposome generation or carrier deposition by variation of pressure/temperature conditions.

- **Impregnation** The high diffusivity and controllable solvent power of SCF are the basis of supercritical impregnation; SCFs are excellent carriers, for example, through porous matrices or inside polymeric non-porous matrices swollen by fluid, such as pharmaceutical patches, sponges and catheters. We recently disclosed a new process for on-line impregnation after extraction, especially for natural product impregnation into an excipient (10).

**Pollution abatement** SCF - and especially carbon dioxide - leads to environmentally-friendly processes through the substitution of organic solvents. Water streams polluted with organic compounds can be treated with CO₂ for pollutant recovery. On the other hand, supercritical water appears to be a unique medium for the safe destruction of dangerous waste by total oxidation due to its special physicochemical properties - this is especially true in the case of highly hazardous waste. Moreover, pollutant destruction in subcritical water is also receiving a keen interest by pharmaceutical companies, even if the oxidation rate is lower than in supercritical water.

**Biological applications** As biotechnological syntheses of therapeutic products are in progress, cell lysis by SCF offers a number of benefits as it does not lead to very small membrane fragments compared with classical homogenisation, preserving fragile molecules and facilitating downstream-processing (11).

With regard to sterilisation, it has long been known that CO₂ has a biocidal effect on most bacteria. It has also been proven that viral inactivation can be achieved in plasma fractions (12, 13) with N₂O or CO₂ under “mild” conditions, thereby avoiding denaturation of the very fragile proteins, and during CO₂ de-lipidation of bone implants (14).

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Conclusion

Even if supercritical fluid technology is not yet widely used in the pharmaceutical industry - except for the extraction of active compounds from vegetable sources - many promising applications are now under development, especially for new drug formulations (15). Separex, a branch of Lavipharm Laboratories and its contract-processing subsidiary, Hitex, are in a position to offer extended services as they are now operating several flexible and dedicated plants - both at pilot and industrial scale. Moreover, we have already built three semi-industrial particle-design plants, under strict quality assurance and documentation according to GMP rules.

Dr Michel Perrut founded the companies Separex (1985), Separex-Equipements (1996) and Hitex (1997). He served as President and CEO of Separex from 1991 to 2000, and is presently Chief Technology Officer, Lavipharm Laboratories (East Windsor, New Jersey, USA). He graduated in Engineering from the Ecole Polytechnique (Paris, France, 1968) and obtained a PhD in Chemical Engineering (Nancy, France, 1972). He worked as a Research Group Leader at Elf-Aquitaine Research Centre on oil refining (Lyon, France) and was then appointed Professor of Chemical Engineering at the Institut National Polytechnique de Lorraine (ENSIC, Nancy), a position he held from 1979 to 1990. Dr Perrut is Founder and Vice-President of the International Society for the Advancement of Supercritical Fluids, has chaired several congresses on supercritical fluids and chromatography processes, and is the author of around 140 publications and communications, and 25 patents.

References


