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PROCESSING PHARMACEUTICALS WITH SUPERCRITICAL FLUIDS

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Carbon dioxide is non-toxic, non-flammable, odorless, tasteless, inert, and inexpensive. The critical temperature of carbon dioxide is 88°F, just above room temperatures. In the past five years research and process development activity has focused on utilizing supercritical carbon dioxide technology in processing fine chemicals, pharmaceutical intermediates, and nutraceuticals. In addition to being a solvent for extraction and fractionation (purification) of organic compounds, carbon dioxide is increasingly being utilized as a medium for reactions, as a micronizing agent in Rapid Expansion in a Supercritical Solution process (RESS), as an anti-solvent for crystallization in Gas Anti-Solvent process (GAS), and as a carrier solvent for coating and depositing materials onto or into a solid matrix. Carbon dioxide technology is one of the fastest growing new process technologies being adopted by the food, pharmaceutical and nutraceutical industries.

Supercritical fluid technology will allow pharmaceutical and nutraceutical companies to develop products of standardized concentration of active ingredients, and will simultaneously produce nutraceutical and pharmaceutical products of much higher concentration (higher yields and purity) and quality (with less creation of artifacts), than possible by conventional chemical engineering unit operations, such as liquid/liquid extraction, distillation, mechanical micronization, liquid and/or gas phase reactions, etc.

Advantages of Carbon Dioxide as an Extraction Solvent for Pharmaceuticals

Carbon dioxide as a solvent has many advantages. Probably the most important advantage is that it is a GRAS solvent that leaves no traces in the product. After extraction, the carbon dioxide is recycled and any trace carbon dioxide in the product dissipates to the atmosphere within a few hours. Also, unlike solvent extraction, the carbon dioxide is readily recycled by pressure and temperature adjustment, which is very mild and does not harm the product. Another advantage of supercritical fluid extraction is the capability of fractionating products to create co-products. Solvent extraction requires a distillation step, (in which top notes are lost and distillation notes are created), that many times alters the taste, aroma and chemical composition of the product. Also, trace quantities of residual organic solvent are usually present in the product.

Botanicals can be fractionated to produce a natural color fraction, an aroma fraction, an anti-oxidant fraction and/or a flavor fraction. This is important in producing nutraceuticals because unwanted strong flavors in certain botanicals such as garlic and rosemary can be separated from the nutraceutical components.

Finally, supercritical fluids can be adjusted to selectively extract certain compounds. For example, the supercritical fluid solvent can be adjusted to extract the pesticides from ginseng. The supercritical fluid process can be further adjusted to extract allergenic compounds from the gingko biloba. Supercritical carbon dioxide is finding broad acceptance in the food, flavor, fragrance, pharmaceutical and nutraceutical industries because it does not harm products and produces higher concentration (quality) extracts.

Supercritical Fluid Particle Sizing Technology

Particle formation by methods utilizing supercritical or sometimes subcritical carbon dioxide are subjects of great interest in the pharmaceutical and fine chemical industries. Several techniques are available (RESS, GAS, PCA, SEDS, PGSS, etc.) to form particles utilizing supercritical carbon dioxide. If a material is highly soluble in liquid or supercritical carbon dioxide, then the process known as Rapid Expansion from a Supercritical Solution (RESS) should be considered. This is a process in which a supercritical fluid mixture is

expanded into an expansion vessel through a specially designed orifice to achieve the desired mean particle size and particle size distribution. This process however is very limited in its application because very few compounds are highly soluble in supercritical carbon dioxide.

Gas Anti-Solvent (GAS) is a far more universal process because the compounds of interest do not have to be soluble in carbon dioxide for the process to work. The GAS process can be utilized for the separation of mixtures into individual, nearly pure component fractions. The degree of separation possible is a function of the volume expansion of the liquid solvent phase.

In the Particles from Gas Saturated Solutions (PGSS) process, the substance to be powdered is melted in an autoclave. Next, supercritical carbon dioxide is dissolved in the melt and forms a solution. At moderate pressures (typically between 70-200 bar), gas concentrations of 5-50 wt/% in the melt solution are obtained. This gas-saturated solution is expanded in a nozzle. The combination of cooling and volume increase of the released gas causes the substance to precipitate in a fine dispersed form. The powder is separated from the gas by sedimentation in a spray tower or centrifugal forces in a cyclone separator. PGSS offers a major advantage if large-scale production of particles is being considered: the amount of gas required is extremely low (<0.1 kg gas/1.0 kg powder) compared to RESS, GAS, PCA, and SEDS.

Microencapsulation

The rapid expansion of supercritical solutions (RESS) process was used to produce polymeric microparticles or microspheres loaded with pharmaceuticals for drug delivery applications. Poly(L-lactic acid) (L-PLA), naproxen, and a mixture of naproxen/L-PLA were dissolved in supercritical CO_2 and precipitated by the RESS Process. Composite particles appear as a naproxen core encapsulated in a polymer coating.

Microspheres containing low molecular weight pharmaceuticals dispersed in poly (L-lactic acid) were also prepared using the PCA process. Supercritical carbon dioxide was used as the antisolvent and methylene chloride as the carrier. The drug polymer particles were

spherical in shape and between 0.2 and 1.0 microns in diameter as determined by scanning electron microscopy.

Supercritical Fluids as a Reaction Medium

An example of using supercritical fluids as a reaction medium is the hydrogenation of pharmaceuticals to promote enantioselective hydrogenation to favor a cis or trans version of a molecule during hydrogenation. By performing the reaction in two, instead of three phases, the rate of hydrogenation reactions can be increased over 1,000 times. As a results, the size of the reactor and the associated equipment is less than $1/10^{th}$ that of conventional autoclave systems. Oils and fatty acid esters, as well as H_2 are soluble in supercritical fluids such as carbon dioxide or propane. The reaction rate is increased because excess H_2 is always available for reaction, and the catalyst pores are not filled with stagnant liquid.

Production Scale SFC

Production scale SFC has been successfully used for the separation of enantiomers and fatty acid esters. Large quantities of DHA and EPA ethyl esters from fish oils are routinely separated to >95% purity on a commercial production scale SFC unit.

Extraction of Fermentation Broths

Supercritical carbon dioxide countercurrent column extraction is currently being investigated as a new process for the extraction of pharmaceutically active compounds from fermentation broths. This process offers an inexpensive method to extract and simultaneously fractionate compounds of interest without leaving organic solvent residues in the product.

Partial List of Pharmaceutical Products that can be Processed by Supercritical $C0_2$

- Extracts of chamomile flowers for anti-inflammatory and anti-spasmodic pharmaceutically active compounds (e.g. sesquiterpene, lactone, matricin, etc.)
- Extract of calamus root as an appetite stimulant—higher yield with SFE (8.3%) when compared to steam distillation (6.4%)

- Extracts of turmeric for bile preparations—no artifacts such as tolylmethylcarbinol created in steam distillation
- Valarian as a sedative preparation—valepotriates obtained undecompossed and at high yield (>90%)
- Wormwood extract as a carminative, cholagogue and stomachic—removal of toxic β-thujone by fractional extraction from thermally unstable pharmacology active components
- RESS (micronization) of mevinolin (Lovastatin), Efrotomycin, Imipenem, Digoxin, Griseofulvin, Salicylic Acid, Stigmasterol, Testosterone, Progesterone, Cholesterol, Ketoprofen, Piroxicam, Nimesulide, and Theophyline.
- SAS, PCA, or GAS (recrystallization) of insulin, poly (l-lactic acid), chlorpheniramine maleate, indomethacin, piroxicam, thymopentine, hydrocortisone, methylprednisolone acetate, salmeterol xinafoate, lysozyme and trypsin.
- Controlled release microspheres for low molecular weight pharmaceuticals produced by Precipitation with a Compressed Antisolvent (PCA).
- Hydrogenation reactions in supercritical carbon dioxide that are a factor of 1,000 faster than conventional hydrogenation reactions with greater control over *trans* isomer formation.
- Extraction of fermentation broths producing vitamins with pharmaceutically active compounds
- Enzymatic reactions in supercritical fluids such as conversion of lipids to methyl or ethyl esters; enrichment of ibuprofen and epi-Methyljasmonate from racemic mixtures

References

Kim, J-Hl, Paxton, E. R., Tomasko, D. L. Microencapsulation of Naproxen Using Rapid Expansion of Supercritical Solutions. *Biotechnology Progress*, Vol.12, No. 5; 1996.

Subramaniam, B., Rajewski, R. A., and Snavely, K. Pharmaceutical Processing with Supercritical Carbon Dioxide. *J. Pharmaceutical Sciences* 86, No. 8. 1997

Poudrier, J. K. SFC Boosts D rug Discovery and Other Processes. *Today's Chemist at Work*. January 1998.