phasex

The Supercritical Fluids People

Processing of Medical Polymers with Supercritical Fluids

1. Supercritical Fluid Extraction–Current Status

Supercritical fluid extraction, especially with supercritical CO_2, has progressed from its position as solely a laboratory curiosity in the 1960s to today's very large scale commercial operation in the foods and beverages sectors. Coffee and tea are being decaffeinated at more than 150,000 Tons/yr in plants in the US and Europe, and hops (for flavoring beer) are being extracted at levels of more than 50,000 T/yr. On a smaller scale, spices, essential oils, and nutraceuticals are being extracted, concentrated, or purified by supercritical CO_2.

Other industries such as pharmaceuticals, specialty chemicals, lubricants, and polymers, are also applying the properties of supercritical fluids to develop products with increasing performance demands, processes under increasing scrutiny because of regulatory constraints, and entirely new products that offer advantages for unmet needs. A wide range of polymers can be a processed to unique technical and economic advantage with supercritical fluids, especially when wiped film evaporation (WFE), molecular distillation, and (liquid) solvent extraction cannot achieve the requisite properties for increasingly demanding in-body applications.

Processing of biomedical polymers such as PLA, PLGA, and EO-PO-EO, which are used in absorbable sutures, medical "fasteners", controlled-release drug delivery, implantable devices, and tissue engineering scaffolds are discussed in this paper. Additionally the efficacy of supercritical CO_2 in extracting non-crosslinked (and migratable) cyclic siloxanes from hydrocephalus shunts and other silicone medical tubing is presented.

2. Solubility In Supercritical Fluids

First discovered in 1879 in Scotland, a gas that is raised to pressure, temperature conditions above its critical point, becomes a solvent with a pressure-dependent dissolving power, the higher the pressure, the higher its dissolving power, and such solubility behavior was investigated by scores of academic researchers for the next 60 years, first in Europe, later in the US. In 1950 a seminal paper (by Princeton researchers) articulated process applications for this pressure dependent solvent behavior: A compound could be extracted from a mixture by a gas, the pressure lowered (elsewhere) to precipitate and recover the compound, and the gas repressurized and recycled to continue the extraction.

A graph of the pressure dependent solubility of naphthalene in CO_2 is shown in Figure 1. (Naphthalene has been studied by literally scores of researchers as a model compound for various hydrocarbons that were of interest to these groups.)

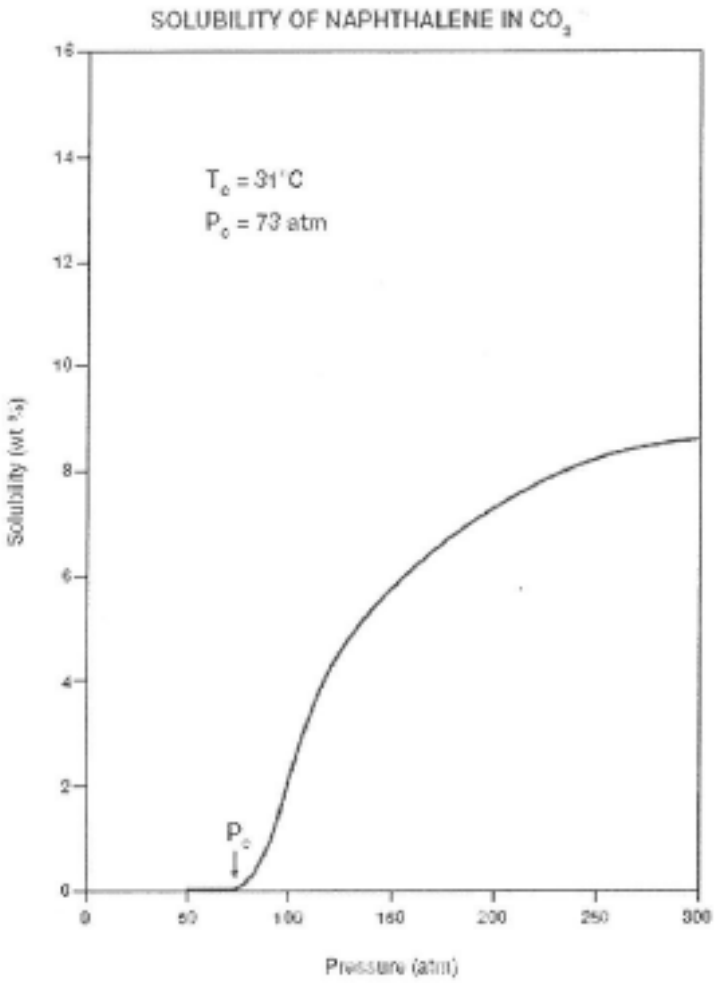


Figure 1. Solubility of Naphthalene in CO2 at 45°C

As the figure shows, the solubility curve starts to rise at about 70atm, the critical pressure of CO_2, and rises to quite high solubility levels, viz., ~ 8% at 300atm pressure. A relatively "simple" gas has become a quite good solvent for naphthalene (and by extension, for many other compounds) as its pressure is increased to above the critical pressure.

As related earlier in addition to its unique pressure dependent dissolving power, other industrial advantages attach to the use of supercritical CO_2 for extracting and purifying materials: No solvent residues remain in the extract or the substrate, CO_2 is non-toxic and environmentally conscious, and its low critical temperature (of 31°C) is ideally suited for processing heat sensitive biomaterials.

3. Processing Of Biodegradeable Polymers

Biodegradable polymers for use in the body have been receiving wide attention during the past twenty years; absorbable sutures, drug delivery vehicles, implantable devices, tissue engineering scaffolds, and controlled phase change "valves" are examples of products that benefit from monomer-free or molecular weight-tailored polymers. These new applications are demanding higher performance from the polymers, and usually the requisite

performance cannot be achieved during their synthesis and workup. Hence, further treatment of the polymers is required to meet the specifications for these highly demanding applications. Phasex Corporation's supercritical fluid extraction processes can purify many different biodegradable polymers of their residual monomers. Further, by operating over a range of pressure levels supercritical CO_2 can fractionate the polymers to provide viscosity and phase change behavior of a degree not achievable by conventional technologies.

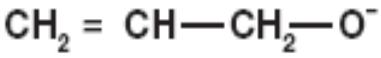
Several selected case studies of work carried out at Phasex are presented, all of which have progressed either to Toll Processing operation in the Tolling Plant or to production operation on smaller scale product-specific extraction equipment. Not at the 100s of MMs lb/yr level of coffee, tea, hops, or nutraceuticals, and instead at only 1000s of kg/yr, supercritical CO_2 extraction produces superior products for specialty applications such as drug delivery reservoirs, tissue scaffolds, and implantable devices, with product specifications that cannot be achieved as economically (or at all) by other processing operations.

A. Removal of Allyl-Terminated Moieties from EO-PO-EO Block Copolymers

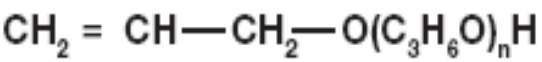
Block copolymers of ethylene oxide/propylene oxide have been used for 50 years as industrial surfactants in laundry detergents, metal cleaners, gel carriers, and lubricants. One (short-lived) biomaterial application of an EO-PO polymer involved its use as a surfactant for stabilizing a substitute blood formulation. The substitute blood did not gain acceptance because of its toxicity caused by impurities in the EO-PO polymer. EO-PO block copolymers do exhibit beneficial biological effects in humans and animals, e.g., they have been shown to inhibit growth of bacteria, yeasts, and viruses, but the commercially available products contain components that exhibit toxicity or are otherwise undesirable.

EO-PO polymers are synthesized in basic solution. During the reaction some of the propylene oxide is converted (by reaction with base) to an allyl anion via the two step reaction:

Some of the PO anion intramolecularly converts to the allyl anion



which subsequently reacts with PO blocks to form an allyl-terminated PO block, e.g.,



(and also allyl-terminated PO-EO blocks).

The allyl termination renders that end of molecule unreactive to EO, and thus in the EO-PO-EO product some PO and PO-EO moieties are present.

Figure 2 is a GPC of a commercially available EO-PO-EO block copolymer, Poloxamer 188. Poloxamer 188 is a block copolymer with molecular weight of 8400 daltons; the EO block is 3400 daltons, the PO, 1800 daltons. A large US producer, BASF, has trade named its Poloxamer 188, Pluronic® F68.

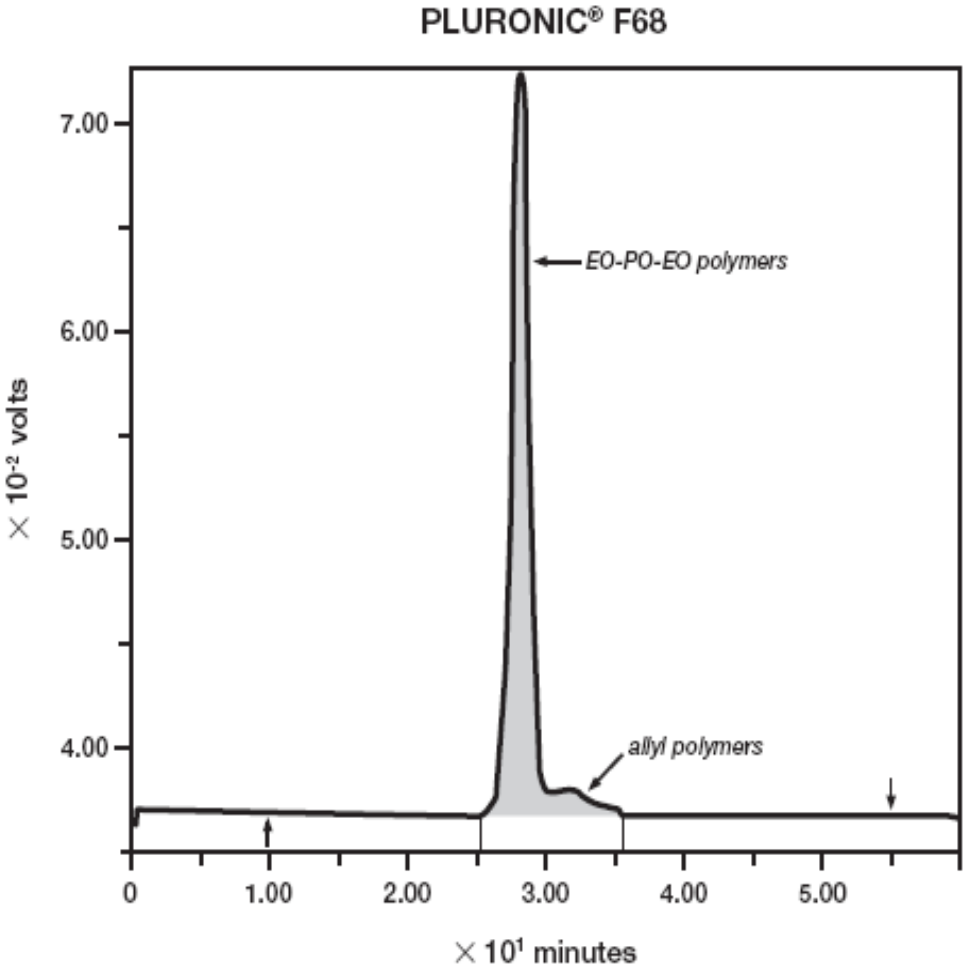


Figure 2. GPC of Pluronic® F68

The small peak at 32min retention is composed of the allyl-terminated moieties; the peak constitutes about 4% of the parent polymer (but it ranges from ~ 2 to 6% in the commercially available product). EO-PO-EO elutes at ~ 29min, the allys at 32min.

The dissolving power of supercritical CO_2 can be tailored by pressure to confer to CO_2 the ability to selectively extract narrow groups of molecules, in this instance the allyl-terminated ones. Figure 3 shows a GPC of the extract obtained from the parent Pluronic® F68.

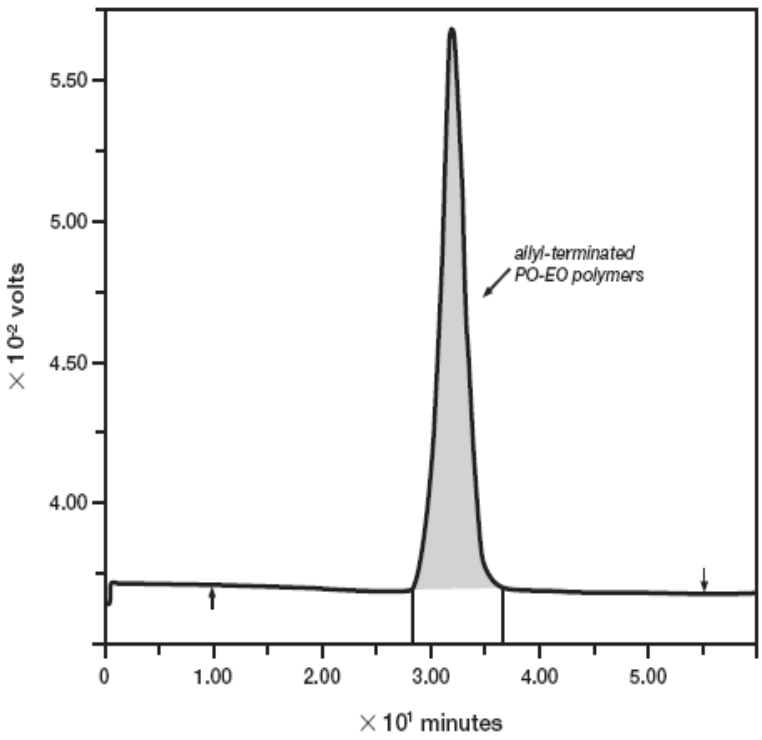


Figure 3. GPC of Allyl-terminated Moieties Extracted with Supercritical CO2

Supercritical CO_2 has selectively extracted the allyl-terminated moieties that comprise the 32min peak of Figure 2; the extract fraction contains virtually no EO-PO-EO blocks.

The GPC of the purified polymer is shown in Figure 4.

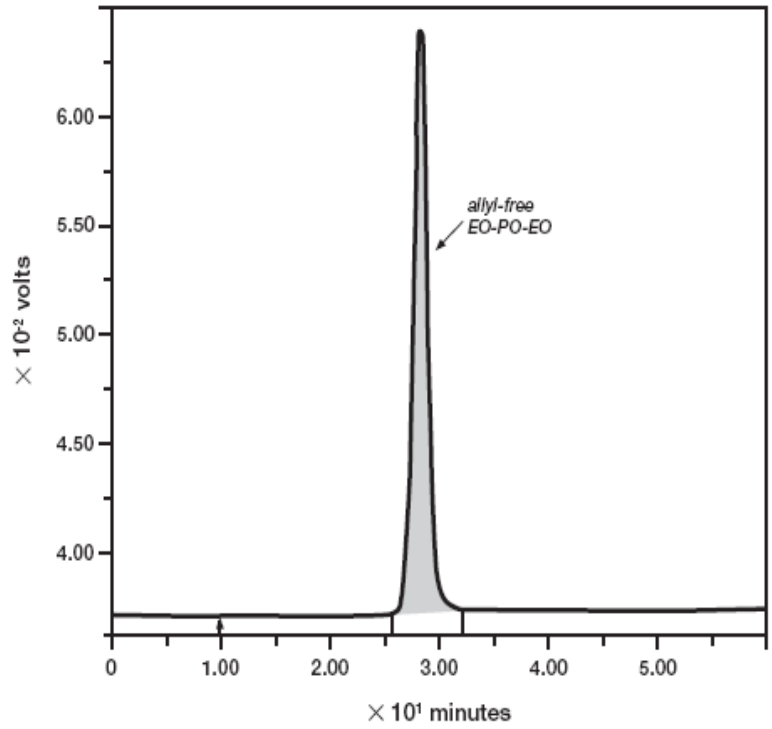


Figure 4. GPC of Allyl-Free EO-PO-EO block copolymer

The polymer is virtually allyl free.

The allyl-free Pluronic® polymers are being investigated for many applications; e.g., as antimicrobials for many bacteria and viruses (HIV among them). Some innovative uses for temporarily blocking various lumens in the body are taking advantage of the polymers' property to solidify when the temperature is raised. EO-PO-EO fractions of narrow molecular weight (and concomitant narrow temperature/phase transition behavior) can be obtained from a parent EO-PO-EO polymer.

Supercritical CO_2 extraction has been found effective in purifying and fractionating other EO-PO-EO polymers: Poloxamer 338 and 407, BASF trade names, Pluronic F108 and F127, respectively.

B. Purification, Fractionation of Poly (lactide co-glycolide)

Polylactide co-glycolide (PLGA), polylactide (PLA), and polyglycolide (PGA) polymers are currently used for many in-body applications, especially for temporary-service applications such as sutures, fasteners, and phase change "valves", where their biodegradability obviates surgical removal. Drug delivery reservoirs are also uniquely fashioned from these polymers; the release characteristics of the reservoirs can be tailored by judicious selection of composition (lactide/glycolide ratio), molecular weight, and melting point of the polymer.

As-produced lactide-glycolide polymers suffer from the presence of residual lactide and/or glycolide monomers which are deleterious to the performance of the device or deleterious to the body. Residual monomers can influence or adversely affect drug release kinetics, for example.

As for the case of the allyls from EO-PO-EO block copolymers, PLGA, PLA, and PGA are easily extracted of their residual monomers via supercritical CO_2 processing.

Figure 5 is a GPC of a commercial PLGA polymer. (The specific polymer is a 50/50 lactide/glycolide and was produced by Medisorb, now Alkermes.)

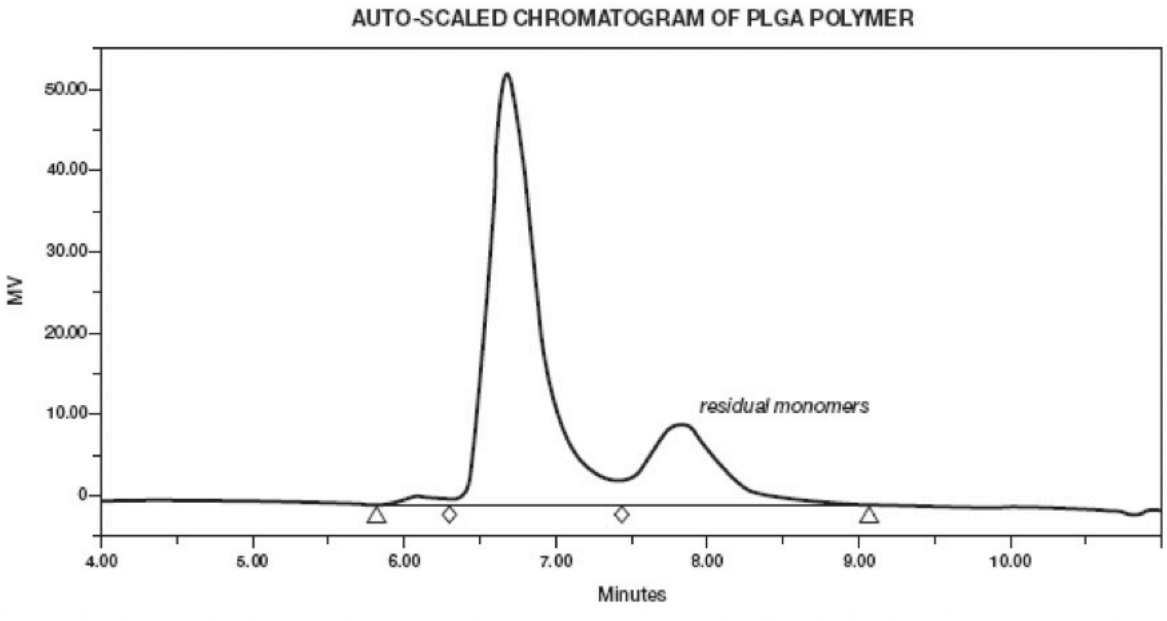


Figure 5. GPC of PLGA

The parent polymer contains 0.86% lactide, 0.42% glycolide monomers, the peak at ~ 7.8min.

The monomers were extracted with supercritical CO_2, and they were essentially completely removed from the parent. Figure 6 is a GPC of the extract. (Some of the very low MW PLGA molecules were co-extracted.)

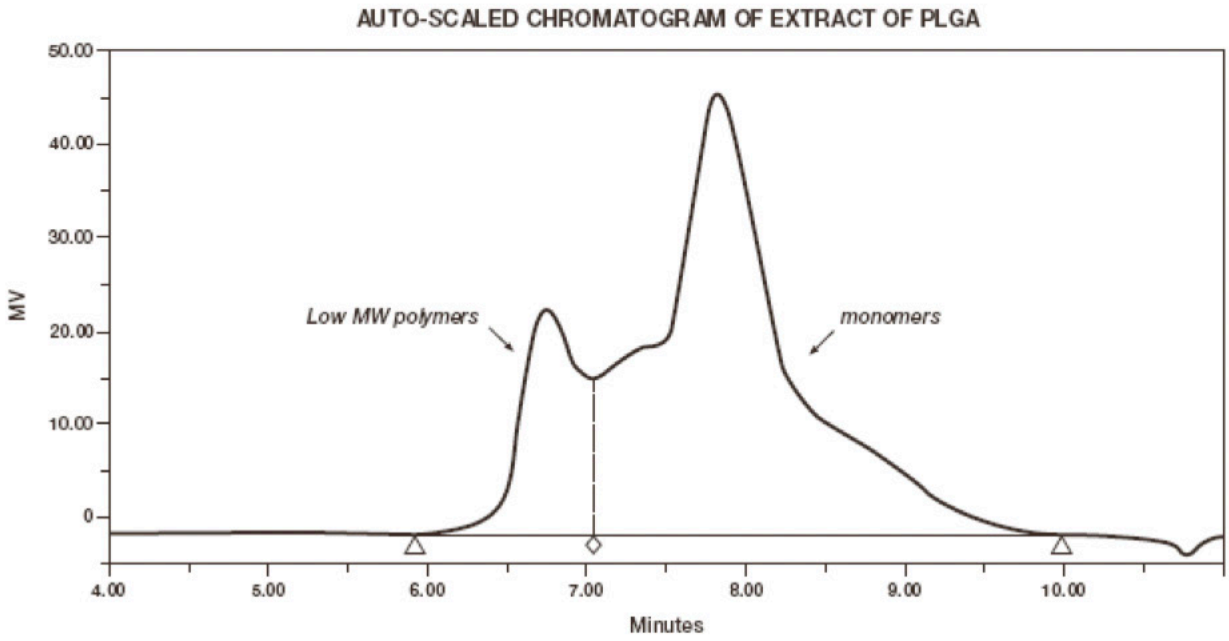
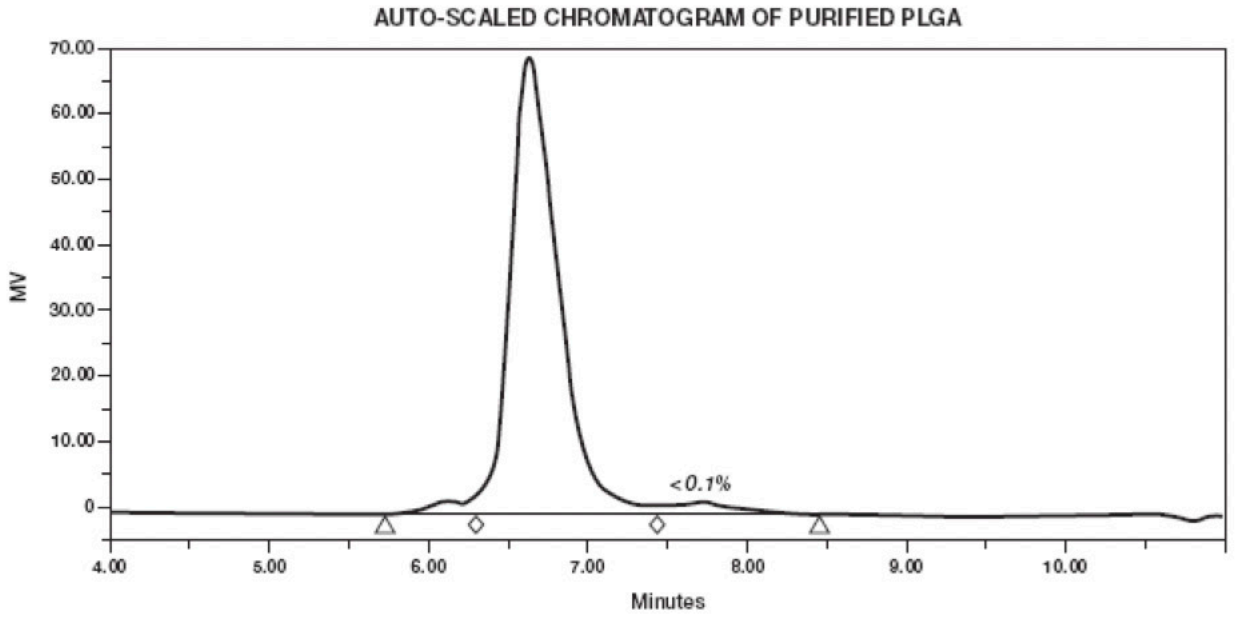


Figure 6. Supercritical CO2 Extract from PLGA

The monomer portion (at ~ 7.8min) comprises about 90% of the extract. (The low MW polymer chains elute at ~ 6.7min.) The overall yield of monomers-free PLGA, i.e., g polymer from the Parent, was 96%. Figure 7 is a GPC of the essentially monomers-free PLGA product.



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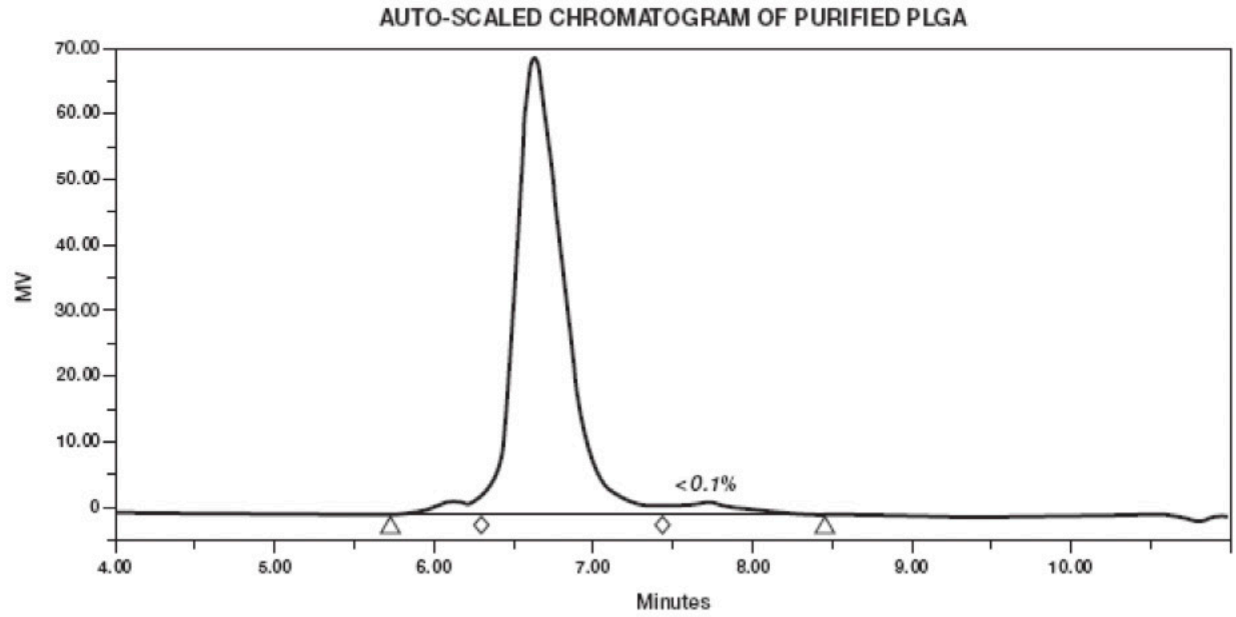

Figure 7. Monomer-free PLGA

Lactide and glycolide polymers normally exhibit a wide polydispersity index (PDI), but for some applications in the body a narrow molecular weight range is desired. A desired response of a PLGA (and PLA and PGA) for a particular application can be obtained by using fractions derived from the parent.

One PLGA with a composition of 85/15 lactide/glycolide was purified and fractionated using increasing pressure profiling fractionation, and the molecular weight results are shown in Table 1.

Table 1. SCF Fractionation of PLGA (85/15 lactide/glycolide)

Fraction	% Monomer (by NMR)	M_n	Mw	PDI
Parent	0.92	46,700	82,200	1.8
Fraction 1	3.97	19,900	51,800	2.6
Fraction 2	0.19	25,400	40,600	1.6
Fraction 3	0	57,500	74,800	1.3
Fraction 4	0	73,300	87,900	1.2
Fraction 5	0	78,900	96,500	1.2

The monomers content of this commercial material was 0.92% (0.71% lactide, 0.21 glycolide), and during the process of fractionation the monomers were concentrated in Fraction 1, co-mingled with a small amount of very low molecular weight polymer, Mn ~ 20,000 extracted from a Parent with Mn ~ 47,000. A PLGA with Mn of ~ 47,000 was fractionated to produce discrete fractions with Mn ranging from ~20,000 to ~79,000 daltons. (All soluble homologous series polymers exhibit this fractionation behavior.)

4. Extraction of Cyclic Siloxanes From Medical Tubing

All silicone tubing, whether medical or general purpose, contains cyclic siloxanes in amounts ranging from 2 to 5%. The polymerization of the siloxane monomer, octamethylcyclotetrasiloxane (D4), to polydimethylsiloxane is a base-catalyzed equilibration reaction which results in the formation of many cyclic species that appear in the polymer raw materials used to make the silicone tubing. (The raw materials for the tubing are "a bit" more complex than having been polymerized from just D4: One silicone component contains active Hs, the other vinyl groups, and the two parts are mixed together with a catalyst during extrusion to produce lightly cross-linked tubing; the cyclics are still present in the finished tubing, however.) The cyclics that are present in the raw materials and in the extracted tubing range from D3 to greater than D20 (twenty dimethylsiloxanes in a ring), and they are impossible to remove from the tubing by heating (whether ambient or in vacuo). Liquid solvent extraction, e.g., with hexane or dichloromethane, could be used to remove the cyclics, but the (liquid) solvent now presents its own removal difficulty.

The cyclics represent a potential leaching problem, e.g., leaching from the medical tubing used to transfer medicines or recirculate blood during operations can occur. Tubing that is surgically implanted (such as hydrocephalus shunts or defibrillator leads) suffer from leaching of cyclics in the body. In the former product the cyclics also interfere with lubricious surface coatings that are applied to aid in the procedure of implanting a shunt in hydrocephalus infants.

Congenital hydrocephalus is a buildup of excess cerebrospinal fluid (CSF) present in the brain at birth and is caused by an imbalance between the brain's production of CSF and the body's ability to distribute or absorb it properly. The excess fluid can increase pressure in the infant's brain, possibly resulting in brain damage and loss of mental and physical abilities. Treatment generally consists of surgically inserting a flexible tube (shunt) in the top of the brain to drain the CSF from the brain. The shunt remains permanently (being replaced as the infant grows).

Supercritical CO_2 is again advantageously applied to the cyclics removal opportunity. CO_2 can dissolve and extract all the cyclics at modest pressure, and when extraction is complete, no objectionable solvent residues remain in the tubing. Supercritical CO_2 extraction of hydrocephalus shunts was developed, optimized, and validated prior to scale-up and GMP processing at Phasex. During validation the ranges of parameters of extraction temperature, pressure, and the weight of CO_2 per weight of shunt, designated solvent-to-feed ratio, S/F, that produced specification product was determined by a quality control procedure used by the shunt manufacturing company: Soxhlet extraction (with dichloromethane for 4 hrs) of the shunts that had been extracted with supercritical CO_2.

During process validation S/F was found to be the single most important processing parameter. Many different lots of shunts were tested during the validation, extracted at various S/Fs, and residual cyclics measured by Soxhlet using dichloromethane, the solvent used in quality control.

Figure 8 gives the relation between cyclics remaining in the shunt and the solvent-to-feed ratio that was used during supercritical CO_2 extraction. (The initial cyclics content of the shunts used in this series was 4.7%, wt of cyclics/wt of shunt; an S/F of only 2 lowered the cyclics content by 95%, from 4.7% to ~ 0.3%: Supercritical CO_2 has a very high capacity for cyclic siloxanes.)

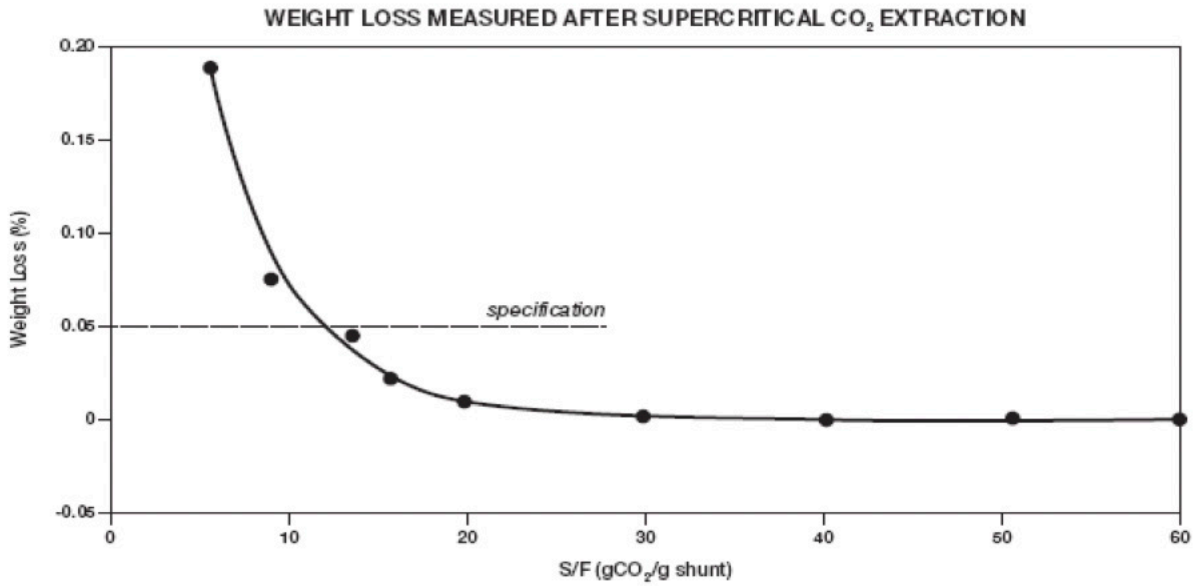

Figure 8. CO2 Required to Extract Cyclics

The residual cyclics specification of 0.05% weight loss was reached at an S/F of about 10. (A much higher S/F, 20, was used for GMP processing of the hydrocephalus shunts. In an aside, for a comparison, decaffeination of coffee to 97% requires an S/F of 200.)

Figure 9 shows a selection of medical products: upper left and right, polyester aorta graphs; lower left, silicone hydrocephalus shunt; middle, silicone urinary catheter; right, barium-filled hydrocephalus shunt. Extraction of cyclics from the silicone products has already been discussed. Many polyesters contain leachable species, and the specific polyester aorta grafts contain about 0.2% extractables, consisting primarily of cyclic ether reaction byproducts, and supercritical CO_2 extracts the reaction by products essentially quantitatively with no solvent residues remaining.

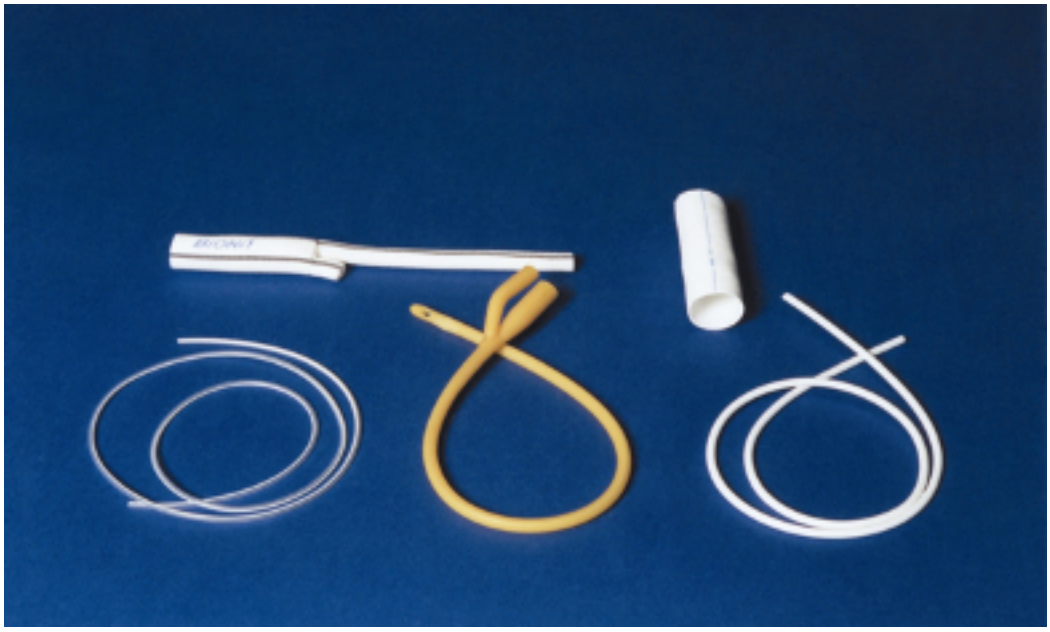

Figure 9. Selected Medical Devices

5. Non-Extractive Applications of Supercritical Fluids

Several processes besides extraction have been devised and developed using the pressure-dependent properties of supercritical fluids, and Phasex has pioneered their use for carrying out operations that are termed “non-extractive”.

Recrystallization of pharmaceuticals and sensitive biomaterials to nanosize using supercritical fluids is one such process, and it is an important current area of research and scale up, especially with the increasing product performance requirements of enhanced bioavailability of hydrophobic drugs. Conventional jet milling or grinding processes are usually not effective in producing material to below about 2-3μ size. Waxy, low melting point pharma compounds are especially good candidates for supercritical fluid recrystallization since they are not easily amenable to jet milling.

Recrystallization from supercritical fluids involves dissolving a compound in a gas at high pressure (and high solubility), then lowering the pressure to cause precipitation (recrystallization) of the compound. Because of the extremely rapid pressure decrease that can be achieved (across an orfice or expansion valve, for example), extremely high supersaturation ratios with concomitant high nucleation rates are reached forming

essentially monodisperse nano particles. (A variant process, GAS Recrystallization, exploits the miscibility characteristics of supercritical CO_2 and liquid solvents; the process entails admixing CO_2 with a solution of a pharma compound, lowering the solubility of the compound when CO_2 is absorbed, thus, resulting in recrystallization.)

Two other non-extractive processes take advantage of the transport and surface tension attributes of supercritical fluids: impregnation of substances into porous substrates and infusion of antimicrobial compounds into (non-porous) polymer devices (catheters, drug delivery reservoirs) "Gaseous" solutions can penetrate pores (of < 10A in size) and by pressure change materials can be deposited without radial gradients in the nanoporous structure. The ability of supercritical fluids, and again especially supercritical CO_2, to dissolve in many polymers and swell them (thereby increasing their free volume) suggests "gaseous" infusion of compounds into polymeric devices. Current work at Phasex involves infusing antimicrobial compounds into catheters.

6. About Phasex Corporation

Phasex Corporation, founded in 1981, is internationally recognized for its development of improved products and superior separations processes using supercritical fluid technology. The company is staffed with a team of problem-solving chemical engineers, chemists, and manufacturing specialists. Phasex offers laboratory feasibility testing and process optimization, product development, toll processing, and licensing for all sectors of industry.

Phasex directs the attributes of supercritical fluids to the solution of difficult processing problems for the pharmaceuticals, polymers, natural products, and fine chemicals industries, especially in those problems that cannot be carried out by industry's traditional processes. For example, supercritical fluids are currently used at Toll Processing scale for extracting residual raw materials and solvents from medical polymers, volatile materials from high vacuum adhesives, low molecular weight oligomers from synthetic lubricants, and non-functionalized species from very reactive macromonomers.

It is the unique combination of physical properties of supercritical fluids, viz., low viscosity, high diffusivity, liquid-like density, and the absence of surface tension limitations that afford these fluids unique capabilities compared to traditional liquid solvents. The complete absence of solvent residues in products is becoming an increasingly important attribute of supercritical fluids, especially for extraction of phytosterols, omega-3 oils, caroteniods, and other nutraceuticals from botanical and algal substrates; Supercritical CO_2 is a superior and environmentally conscious alternative to organic solvent processing.

Phasex has state-of-the-art facilities for developing supercritical fluid processes from laboratory scale to manufacturing. The company's equipment includes bench scale extraction systems for processing materials from the grams to kilograms level, and a Class 1, Division 2 production plant capable of processing liquid and solid feedstocks in multi-ton campaigns.

Several of these products (and a polymer used in a blood-contact application) are processed under GMP guidelines in the Toll Processing plant or in product-dedicated equipment in a Class 10,000 clean room.

7. Closing Remarks

It has been lamented by some that processing with supercritical fluids is not economical, and, unfortunately, the general impression still exists among chemists and chemical engineers that supercritical fluid processing is associated with high costs. However, supercritical fluid decaffeinated coffee is being sold competitive with organic solvent-decaffeinated coffee, and this fact certainly contradicts this high-cost impression. The misassociation of high cost with supercritical fluid processes undoubtedly derived from the fate of several widely publicized (but ill-advised) studies in the late 1970s, early 1980s, when their lack of industrial viability was attributed solely to a high processing cost when, in actuality, there were technical limitations (that were not described). Supercritical fluids are frequently excellent solvents with far ranging applications to many purification problems. But they may not be economically viable in each case, and applied industrial research should be sufficiently and justifiably motivated, especially in today's' economic climate with an evaluation of the potential for success in each case.

Supercritical fluids offer technical advantages for processing medical devices and medical and biopolymers. Interfering components are extracted with a gas, thus leaving no solvent residues in the parts. Additionally, supercritical CO_2 possesses attractive health, environmental, and work place characteristics. It is non-toxic, non-hazardous, Generally Recognized as Safe (GRAS), and Organic. Because of its ability to penetrate porous structures, supercritical CO_2 provides a superior means of cleaning machining oils from porous titanium components implanted in the body. Finally, because supercritical CO_2 can swell polymers, it can infuse and deposit antimicrobial compounds in polymeric components such as catheters.

Increasing performance demands and increasingly stringent regulatory constraints being placed on medical polymers and implantable devices are being satisfied with supercritical fluid based processes.

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