Scanning of Cosolvents for Supercritical Fluids Solubilization of Organics

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The remarkable ability of supercritical fluids (SF) to dissolve solids, even nonvolatile ones, was first discovered by Hannay and Hogarth in 1879. In recent years, there has been increasing interest in using supercritical fluids extraction (SFE) as an alternative to conventional distillation and extraction processes. SFE involves first, a dissolution of the compound of interest in SF. Then the solution is rapidly depressurized, resulting in a dramatic decrease in the saturation concentration of the compound and subsequent precipitation (or liquefaction) of the extract. A number of investigators have found that addition of small amounts of a cosolvent to SF enhances solvent power by as much as a factor of 6 (Dobbs et al., 1986 and 1987; Wong and Johnston, 1986).

A new technology involving SF concerns the size reduction of solid products. Paulaitis et al. (1983) in their review of SF applications, mention redistribution of a solid's particle size via SF nucleation. They state that SF nucleation offers the potential to change size distribution without the limitations inherent in grinding and precipitation from solution, such as temperature effects and coprecipitation of impurities. Such a technique might have its greatest use in the pharmaceutical field, in which many compounds, which are thermally labile or are sensitive to contamination by organic solvents, may be precipitated with SF. Larson and King (1986) have studied the solubilities of pure component pharmaceutical products in supercritical CO_2 and have observed the effects of the addition of small amounts of polar cosolvents on solubility.

The selection of a proper cosolvent is the first step in using SFE technology. In this paper, we attempt to develop a systematic method for selecting cosolvents. It has been proposed that the affinity of a solvent vapor for a solute is directly related to its ability to dissolve the solute at supercritical conditions (Prausnitz, 1986). It is further proposed that this affinity can be measured by the following procedure. A gas chromatography column is packed with a mixture of the solid of interest and an inert filler. This constitutes the immobile phase. Small amounts of vaporized cosolvents are then introduced into the mobile phase (N_2) as a pulse and the retention time of this pulse measured. The same experiment is repeated using a column packed entirely with the inert filler, and the ratio of retention times is computed. This ratio is then divided by the retention time ratio of a reference compound (i.e., one giving a short residence time and a sharp peak, such as dichloromethane for griseofulvin). This value defines a ranking of cosolvent affinities for the solute of interest.

The validity of this procedure can be evaluated by measuring the solubilization of the solute in a solvent/cosolvent mixture at supercritical conditions. If the same cosolvent shows the highest affinity for the solute in both cases, then the proposed technique might be useful. The advantage of such a technique is clear: a large number of potential cosolvents can be screened using a simple gas chromatograph operated at 1 atm pressure. The GC is a ubiquitous instrument in most laboratories.

A similar study was performed by Tassios (1970) in which Gas-Liquid Chromatography (GLC) was used for screening extractive distillation solvents. It was shown that the ability of a liquid to successfully separate a liquid mixture in an extractive distillation process can be correlated with the interaction of a partitioning liquid with an injected gas mixture in a GLC column.

Experimental

In our experiments, a total of 16 potential cosolvents were screened for two pharmaceutical solutes, griseofulvin (an anti-

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Table 1. Screened SF Cosolvents for Griseofulvin and Digoxin

n-heptane	formaldehyde
carbon tetrachloride	ammonia
benzene	chloroform
dichloro-methane	*m*-xylene
toluene	methyl ethyl ketone
acetone	butyl acetate
ethanol	petroleum ether
methanol	cyclohexanone

bacterial agent) and digoxin (a cardiac glycoside). Conventional particle size reduction techniques are often not suitable for these compounds. The choice of 16 cosolvents covered a range of organic compounds having different functional groups. Table 1 lists these potential cosolvents. All gas chromatographic experiments were performed at 1 atm pressure and 50°C (column temperature). This temperature selected was low enough to ensure that no solute dissociation or polymorphic transformation of sulute would occur during the experiments. Small volumes of cosolvent vapor (from .001 mL to 1 mL, depending on the volatility of the cosolvent) were injected into the N_2 carrier gas as a pulse, and the retention times were measured. To ensure that the solid did not adsorb certain compounds irreversibly (therefore resulting in changes in surface properties), the experiment was repeated changing the order of the injected cosolvents. A Perkin-Elmer model Sigma 2B GC unit was used. Concentration pulses were measured with a flame ionization detector. Butyl acetate and cyclohexanone were found to be the most interacting cosolvents for griseofulvin, while for digoxin the most interacting cosolvents were cyclohexanone, ethanol, and methanol. Only these most active cosolvents and the reference cosolvent were tested at supercritical conditions. Results of the GC affinity tests are summarized in Table 2.

It is not our purpose to measure the solubilization of these solutes in all 16 possible CO_2/cosolvent fluids, but rather to screen this list for an effective SF mixture which might later be used in precipitation studies of the given organic solutes.

Figure 1 shows a diagram of the equipment used (Milton-Roy Supercritical Extraction System, Model X10) to measure solubilization in SF mixtures. The first vessel acts as premixer and preheater to mix cosolvent with CO_2, and to heat the solvents to the desired temperature. After the desired pressure was attained in the first vessel, the Tescom pressure regulator automatically opened to discharge fluid into the saturator. The saturator was closed by the expansion valve located downstream. The desired solvent flowrate to maintain the given pressure was set by the fine metering valve (Whitey 31RS4 with 0.157 cm orifice and 6.190 cm length of pass), which was wrapped with heating tape

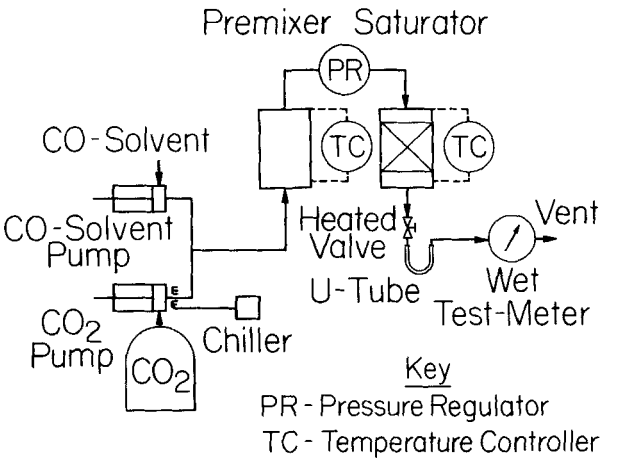

Figure 1. SF apparatus used for solubility measurements.

regulated by a rheostat. The valve was adjusted manually, and discharged solvent/dissolved solute through a glass U tube (0.635 cm OD, 30.5 cm long) and wet test meter (Precision Instrument Company). All solubility experiments were performed at 50°C and 238 atm. The apparatus resembles that of Kurnik et al. (1981, 1982).

A few grams of solute (griseofulvin or digoxin) were packed with alternate layers of glass wool into the 10.2 cm long by 2.54 cm ID (55 mL) 316SS saturator. Once saturator steady-state was achieved, approximately two residence times, a tared U tube was inserted after the expansion valve. After an experiment, the mass of precipitate solid was found by weight gain of the tube on a Mettler analytical balance (model B6), accurate to ±0.1 mg. With both this value and the total extractant flow from the wet test meter, the concentration of the organic compound in pure $SFCO_2$ (or $SFCO_2$ and cosolvent mixture) can readily be calculated.

To further investigate the validity of the cosolvent selection procedure, solute cosolvent affinity was measured by gas chromatography for certain compounds for which solubility in supercritical CO_2 data are available in the literature (Dobbs et al., 1987; Wong and Johnston, 1986). The additional solutes studied were cholesterol, stigmasterol, and 2-aminobenzoic acid. It was not intended to find "the best" cosolvent for these compounds, thus GC affinity tests were only performed on the cosolvents that were reported in the literature on these solutes. Solute concentrations in the SF phase for griseofulvin and digoxin as well as for the three compounds mentioned above, are presented in Table 3.

Table 2. Solute/Cosolvent Affinity Measured by GC Retention Times

Normalized Pulse Retention Ratio	Griseofulvin	Digoxin	Cholesterol	Stigmasterol	2-Amino *Benzoic Acid*
dichloromethane	1.00	1.00	—	—	—
butyl acetate	1.40	1.20	—	—	—
cyclohexanone	1.43	1.42	—	—	—
methanol	1.03	1.15	1.27	2.23	1.21
ethanol	1.02	1.29	1.20	1.47	—
acetone	0.98	1.03	1.00	1.00	1.00

Reference no-affinity compounds used for normalization: dichloromethane for griseofulvin and digoxin; acetone for cholesterol, stigmasterol, and 2-amino benzoic acid.

Table 3. Solid Solubilities in Supercritical CO_2 and CO_2/Cosolvent Solution

Solute	Cosolvent mol %	Solubility × 10^5 mol Fraction	Solubility Enhanced by Cosolvent	Reaction/Complex Formation
Griseofulvin	a —	1.50 ± 0.25	1.0	no
	b 3.5	1.37 ± 0.99	0.9	no
	c 3.4	6.36 ± 1.50	4.2	no
	d 3.5	5.45 ± 2.69	3.6	yes
Digoxin	a —	0.18 ± 0.07	1.0	no
	b 3.2	0.19 ± 0.05	1.1	yes
	d 3.0	1.76	9.8	yes
	e 3.5	0.39 ± 0.24	2.2	yes
	f 7.2	0.17 ± 0.03	1.0	no
Cholesterol*	a —	0.81	1.0	no
	f 3.5	19.30	7.2	no
	e 3.5	6.54	2.4	yes
	g 3.5	10.10	3.8	no
Stigmasterol*	a —	0.81	1.0	no
	f 3.5	0.98	1.2	yes
	e 3.5	3.25	3.9	yes
	g 3.5	1.41	1.6	no
2-Amino* Benzoic Acid	a —	12.70	1.0	no
	f 3.5	91.00	7.2	no
	g 3.5	39.00	3.1	no

a = pure CO_2
b = CO_2/dichloromethane
c = CO_2/butyl acetate
d = CO_2/cyclohexanone
e = CO_2/ethanol
f = CO_2/methanol
g = CO_2/acetone
*From Wong, J. M., and K. P. Johnston, *Biotech. Prog.*, 2(1), 20 (1986).

Conclusions

Tables 2 and 3 show that there is correspondence between solvent/solute affinity (as measured by the GC pulse retention time ratio) and the CO_2/cosolvent solubility in the SF phase. This one-to-one correspondence breaks down, however, when solid complexes are formed or chemical reactions occur. For example, the highest affinity index for griseofulvin was obtained in conjunction with cyclohexanone. At supercritical conditions, use of cyclohexanone as a cosolvent resulted in the decomposition of griseofulvin. When butyl acetate was used as co-solvent, only pure griseofulvin was detected in the product solid, Figure 2a. As a result, butyl acetate is considered to be the best cosolvent for griseofulvin.

The problem was more pronounced for solid digoxin, which formed complexes or compounds with several of the selected cosolvents. At first glance, cyclohexanone would appear to be a good cosolvent for digoxin (solubility enhancement of 9.8 based on weight gain measurements in the U-tube trap). Further analysis of the solid product by thin layer chromatography, however, showed that there was no digoxin present, Figure 2b.

For cholesterol and stigmasterol, GC affinity testing (GCAT) predicts solubility enhancement in the SF phase by the introduction of selected cosolvents. However, it incorrectly rates these "potentially good cosolvents" when the introduction of these chemicals results in the formation of solid complexes in the SF phase (Wong and Johnston, 1986). This is evident in the case of stigmasterol in which GCAT predicts that both methanol and ethanol enhances stigmasterol solubility in SF CO_2, but predicts methanol to be a better cosolvent than ethanol. Both methanol and ethanol form complexes, which might be the reason for GCAT's incorrect ranking of the potential cosolvents. GCAT, a test performed at atmospheric pressure, cannot predict formation of solid complexes or reaction products at supercritical conditions. For 2-aminobenzoic acid, since no complex formation occurred, GC affinity results corresponded completely with the SF solubility data.

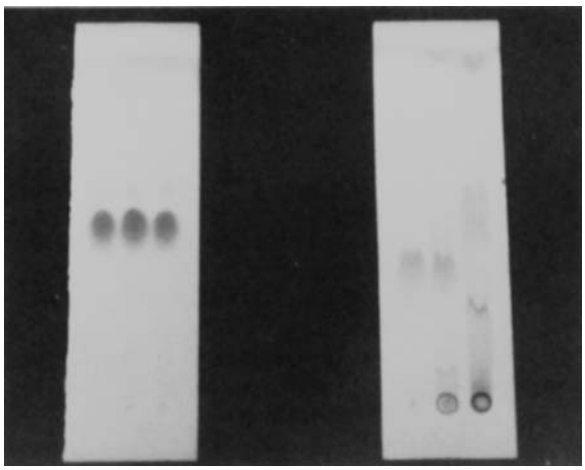

Figure 2. Thin-layer chromatography of (a) Griseofulvin and (b) Digoxin.
Spots 1, 2, and 3 represent the raw material, the mixture, and the solid from supercritical CO_2 with (a) butyl-acetate and (b) with cyclohexanone. Spectrum (a) does not show reaction compound formation and (b) does.

The rapid scanning technique presented here might be useful for selection of a cosolvent. Given a list of compounds, GC affinity testing (GCAT) can eliminate certain chemicals as not useful and predict others as potentially good cosolvents. As shown in Tables 2 and 3, all compounds having a GC normalized pulse retention time greater than 1.00, increased solute solubility when used as cosolvents in the SF phase. However, when the introduction of a cosolvent results in the formation of solid complexes/compounds at supercritical conditions, GCAT may give false positives (i.e., incorrectly predict a useful cosolvent), as in the case of cyclohexanone with griseofulvin, or may not be able to determine the best cosolvent among the potential candidates, as in the case of stigmasterol. Therefore, GCAT must be viewed more as a screening technique for elimination of certain chemicals as potential candidates, rather than as a technique for selection of "the best" cosolvent. Once a list of chemicals has been narrowed down through GCAT scanning, the remaining compounds must be tested at supercritical conditions; based on these latter tests, the best cosolvent can be determined.

Some observations can be made concerning the solubilities of the two pharmaceutical compounds in SF phase. They have much less solubility than aromatic hydrocarbons, partly due to their low volatility. For a solid solute, volatility is a good measure of its solubility in SF phase. For example, naphthalene is much more soluble in SF CO_2 than sterols (Wong and Johnston, 1986). Similarly, sterols are more soluble than either griseofulvin or digoxin since the two latter compounds are extremely nonvolatile, Table 3. The low solubilities of the two pharmaceutical compounds may be attributed to the large number of polar functional groups (OH, C = 0) that are present in these molecules. It has been observed that as the number of polar functional groups increase, solid solubility in the SF phase is reduced (Wong and Johnston, 1986; Larson and King, 1986).

Although remarkable progress has been made in relating SF solubilities to solvent/solute structure (Dobbs et al., 1987; Wong and Johnston, 1986; Schmitt and Reid, 1986), it appears that the simple GC test described in this paper might prove useful for scanning a list of potential cosolvents before making actual SF solubility measurements.

Acknowledgment

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