Solubilities of Flutamide, Dutasteride, and Finasteride as Antiandrogenic Agents, in Supercritical Carbon Dioxide: Measurement and Correlation

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The solubilities of flutamide, dutasteride, and finasteride in supercritical carbon dioxide were investigated at temperatures of (308.0, 318.0, 328.0, 338.0, and 348.0) K and various pressures in the range of (12.1 to 35.5) MPa. The measured results were then correlated using semiempirical equations presented by Chrastil and Bartle. With optimally fitted parameters, the average absolute relative deviations (AARD) ranged from 0.122 to 0.260 and from 0.024 to 0.137 for Chrastil and Bartle models, respectively. The heat of drug−CO_2 solvation and that of drug vaporization were approximated in the range of (−17.4 to −16.8) kJ·mol^{-1} and (73.7 to 90.1) kJ·mol^{-1}, respectively.

Introduction

Supercritical fluid technologies have received wide-ranging attention in the pharmaceutical industry where they have been applied in separation science and solute extraction.[1−5] Knowledge of solubility behavior of solutes of interest in supercritical carbon dioxide (SC−CO_2) is required for the design of any supercritical process.[6−10]

Androgens are important male sex steroid hormones that exert many physiological roles leading to the male characteristics and other phenotypes.[11−13] Antiandrogens are a class of drugs which compete with circulating androgens for binding sites on their receptors within the prostate cell, thus promoting apoptosis and inhibiting prostate cancer growth.[13]

Finasteride (*N*-(1,1-dimethylethyl)-3-oxo-4-aza-5-androst-1-ene-17-carboxamide) is a member of 4-azasteroids which are a newly developed family of compounds that block human 5-reductase, the intracellular enzyme that converts testosterone into 5a-dihydrotestosterone (DHT).[14]

Dutasteride (17b-*N*-(2,5-bis-(trifluoromethyl)phenylcarbamoyl)-4-aza-5-androst-1-en-3-one) is another synthetic 4-azasteroid compound that is a selective inhibitor of the 5-reductase enzyme.[15]

Flutamide, 4-nitro-3-trifluoromethyl-isobutilanilide, is a synthetic antiandrogenic agent devoid of hormonal agonist activity.[12,16]

In the present study, the solubilities of flutamide, dutasteride, and finasteride were measured in SC−CO_2 over a wide range of temperatures and pressures and were then correlated using two semiempirical equations (Chrastil and Bartle models).

Experimental Section

Materials. Flutamide (FLUT, CAS No.: 13311-84-7; IUPAC name: 2-methyl-*N*-[4-nitro-3-(trifluoromethyl)phenyl] propanamide), dutasteride (DUTA, CAS No.: 164656-23-9; IUPAC name: (1*S*,3a*S*,3b*S*,5a*R*,9a*R*,9b*S*,11a*S*)-*N*-[2,5-bis(trifluoromethyl) phenyl]-9a,11a-dimethyl-7-oxo-1,2,3,3a,3b,4,5,-5a,6,9b,10,11-dodecahydroindeno[5,4-f]quinoline-1-carboxamide)), and finasteride (FIN, CAS No.: 98319-26-7; IUPAC name: (1*S*,3a*S*,3b*S*,5a*R*,9a*R*,9b*S*,11a*S*)-*N*-*tert*-butyl-9a,11a-dimethyl-7-oxo-1,2,3,3a,3b,4,5,5a,6,9b,10,11-dodecahydroindeno [5,4-f]quinoline-1-carboxamide)) were purchased from Betapharma Company (Shanghai, China) with an assessed minimum purity of 0.98 (mass fraction). All of the drugs were used without any further purification. Extra pure ethanol from Daru Pakhsh (Tehran, Iran) was used as a collection solvent. Carbon dioxide with a minimum mass fraction purity of 0.9999 was purchased from Sabalan Co. (Tehran, Iran) and used for all of the extractions. The molecular structures and properties of the chemicals used are shown in Table 1.

Equipment and Procedure. A Suprex (Pittsburgh, PA) MPS/225 integrated SFE/SFC system equipped with a modified static system for the solubility determination in the SFE mode was used. The schematic diagram of the experimental apparatus and a detailed description of the apparatus and operating procedures have been given previously.[17]

The solubilities were calculated by absorbance measurements at λ_{max} of each compound (Table 1) using a model Cecil Aquarius CE 7200 Double Beam Spectrophotometer (London, UK).

Correlation of Experimental Solubility Data. Semiempirical and empirical correlations, based on the density of the pure SC−CO_2, were widely used for the correlation of solid−supercritical fluid equilibrium mainly due to their simplicity and easy application. In the present study, the experimental data were correlated using two frequently employed density-based models: the Chrastil[18] and the Bartle et al. models.[19]

Chrastil Model. The Chrastil model[18] is based on the hypothesis that one molecule of a solute A associates with k molecules of a solvent, B, to form a salvation complex AB_k in equilibrium with the system. The definition of the equilibrium constant in terms of thermodynamic considerations leads to the following expression for the solubility

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$$S/\mathrm{kg \cdot m^{-3}} = (\rho/\mathrm{kg \cdot m^{-3}})^{a_1} \cdot \exp\left(a_0 + \frac{a_2}{T/\mathrm{K}}\right) \quad (1)$$

where S is the solubility of the solid in the supercritical phase; ρ is the density of the pure supercritical fluid; a_1 is the association number; a_2 is a constant, defined as $\Delta H/R$ (where ΔH is the sum of the enthalpies of vaporization and solvation of the solute and R is the gas constant); and a_0 is another constant somehow related to the molecular weight of the solute and solvent. The parameters a_0, a_1, and a_2 are obtained by performing a multiple linear regression on the experimental solubility data.

Bartle et al. Model. Bartle and co-workers[19] proposed a simple density-based semiempirical model to correlate the solubility of solids in SC−CO_2

$$\ln \frac{y_2 P}{P_{\mathrm{ref}}} = A + b_1(\rho - \rho_{\mathrm{ref}}) \quad (2)$$

where

$$A = b_0 + \frac{b_2}{T} \quad (3)$$

and

$$\ln \frac{y_2 P}{P_{\mathrm{ref}}} = b_0 + b_1(\rho - \rho_{\mathrm{ref}}) + \frac{b_2}{T} \quad (4)$$

where y_2 is the equilibrium mole fraction of the solute in SC−CO_2; P_{ref} is assumed as a standard pressure of 0.1 MPa; ρ_{ref} is a reference density assumed as 700 kg·m^{-3}; and b_0, b_2, A, and b_1 are empirical constants. From the experimental solubility data, each isotherm is fitted using eq 2, to obtain the values of A and b_1. The b_1 values are averaged, and these values are then used to recalculate the A values for the various isotherms. The A constants are then plotted against $1/T$ and correlated with eq 3, to determine constants b_0 and b_2. Finally, the values b_0, b_1, and b_2 are used to predict the solubility, applying eq 4. In this model, the parameter b_2 is related to the enthalpy of sublimation of the solid solute, $\Delta_{\mathrm{sub}}H$, by the expression $\Delta_{\mathrm{sub}}H = -Ra_2$.

Table 1. Compound, Formula, and Structure of the Drugs with Molar Mass Melting Temperature T_m Obtained at the Absorbance Wavelength λ_{max}

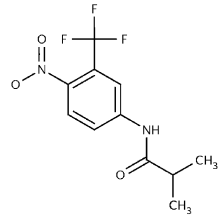
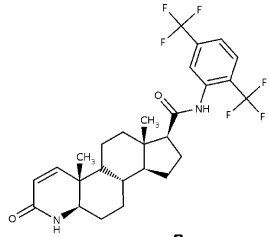
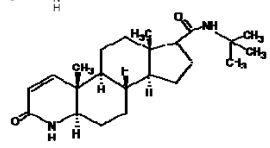
Compound	Formula	Structure	M/g.mol^{-1}	T_m/K	λ_{max}/nm
Flutamide	$C_{11}H_{11}N_2F_3O_3$		276.1	384	292
Dutasteride	$C_{27}H_{30}N_2F_6O_2$		528.5	515	243
Finasteride	$C_{23}H_{36}N_2O_2$		372.5	525	206

Table 2. Solubilities S and y of Flutamide, Dutasteride, and Finasteride in SF−CO_2 at Temperatures T and Pressures P at Density ρ

			flutamide		dutasteride		finasteride	
T	P	ρ	$10S$		$10S^a$		$10S$	
K	MPa	kg·m^{-3}	g·L^{-1}	10^5y_2	g·L^{-1}	10^5y_2	g·L^{-1}	10^5y_2
308	12.2	771	3.14	6.48	0.61	0.57	2.51	3.85
	15.2	818	2.59	5.04	1.04	1.02	2.33	3.36
	18.2	850	2.59	4.85	1.44	1.48	2.74	3.81
	21.3	876	3.07	5.59	1.88	1.97	3.11	4.19
	24.3	897	3.71	6.59	2.30	2.47	3.41	4.49
	27.4	916	4.62	8.04	2.76	3.04	3.71	4.78
	30.4	931	5.29	9.06	3.46	3.87	3.92	4.97
	33.4	946	5.48	9.22	3.65	4.15	4.18	5.22
	35.5	955	6.18	10.30	3.98	4.56	4.34	5.37
318	12.2	661	1.65	3.96	0.32	0.26	2.39	4.28
	15.2	745	1.62	3.45	0.99	0.89	2.60	4.12
	18.2	792	3.62	7.28	1.75	1.67	3.62	5.39
	21.3	826	3.96	7.63	2.58	2.56	4.48	6.41
	24.3	852	3.99	7.45	3.42	3.50	5.19	7.20
	27.4	875	6.30	11.46	4.00	4.20	5.91	7.98
	30.4	893	7.94	14.16	5.27	5.66	6.45	8.53
	33.4	910	8.12	14.22	6.29	6.88	7.04	9.13
	35.5	919	8.88	15.39	6.85	7.56	7.31	9.39
328	12.2	516	0.88	2.73	0.08	0.05	2.31	5.29
	15.2	657	1.61	3.91	0.63	0.49	2.30	4.14
	18.2	726	3.80	8.35	1.57	1.37	4.11	6.69
	21.3	771	4.26	8.80	2.77	2.56	3.21	4.92
	24.3	804	5.72	11.33	4.11	3.96	4.72	6.93
	27.4	831	7.57	14.52	5.62	5.61	6.10	8.66
	30.4	853	8.64	16.13	7.19	7.36	9.82	13.59
	33.4	872	10.46	19.11	7.86	8.23	12.45	16.86
	35.5	884	13.32	24.00	9.04	9.60	14.24	19.02
338	12.2	396	0.31	1.24	0.03	0.01	2.30	6.87
	15.2	561	0.73	2.08	0.33	0.22	1.74	3.66
	18.2	654	3.89	9.49	1.22	0.96	4.13	7.46
	21.3	712	4.53	10.14	2.65	2.26	6.72	11.15
	24.3	754	6.17	13.05	4.53	4.10	9.32	14.61
	27.4	786	8.70	17.63	6.72	6.34	11.75	17.65
	30.4	812	12.22	23.98	9.16	8.93	14.02	20.39
	33.4	834	15.60	29.79	11.40	11.42	16.17	22.90
	35.5	848	19.24	36.15	13.96	14.21	17.73	24.70
348	12.2	327	0.09	0.46	0.02	0.01	2.30	8.32
	15.2	477	0.35	1.16	0.19	0.11	1.40	3.48
	18.2	585	3.44	9.36	0.87	0.61	4.05	8.17
	21.3	652	4.23	10.33	2.17	1.70	7.35	13.32
	24.3	702	7.06	16.01	4.21	3.55	10.28	17.30
	27.4	740	10.76	23.17	6.87	6.11	12.50	19.95
	30.4	772	16.20	33.44	10.93	10.14	15.56	23.81
	33.4	796	21.37	42.77	13.76	13.16	19.13	28.39
	35.5	811	25.93	50.93	16.50	16.07	22.83	33.25

[a] S is the solubility of the solid in the supercritical phase.

The percent average absolute relative deviations (AARDs) were determined for each compound from each isotherm using the models from the following equation

$$\mathrm{AARD} = \frac{1}{N}\sum \frac{|y_i^{\mathrm{cal}} - y_i^{\mathrm{obs}}|}{y_i^{\mathrm{obs}}} \quad (5)$$

where N is the number of data points; y_i^{obs} is the experimental solubility of the solid for experimental point i; and y_i^{cal} is the calculated solubility corresponding to point i.

Result and Discussion

Solubility Data. The solubilities of the drugs in SC−CO_2 were determined at (308.0, 318.0, 328.0, 338.0, and 348.0) K, in the pressure range from (12.1 to 35.5) MPa. Results are summarized in Table 2. Each data point is an average of, at least, three experimental measurements, with reproducibility within ± 7.6 %.

Table 3. Parameters for (Flutamide + CO_2), (Dutasteride + CO_2), and (Finasteride + CO_2) for Equation 1 (Chrastil Model, a_0, a_1, and a_2) and Equation 2 (Bartle Model, b_0, b_1, and b_2) along with the Total Enthalpy of Reaction ΔH_{total}, Solvation Enthalpy ΔH_s, and Enthalpy of Vaporization ΔH_v

model	drugs	a_0	a_1	a_2 K	[a]AARD	[b]ΔH_{total} kJ·mol^{-1}	[c]ΔH_v kJ·mol^{-1}	[d]ΔH_{sl} kJ·mol^{-1}
Chrastil	flutamide	−56.7	7.15	−7338	0.122	61.0	−	−
	dutasteride	−74.7	9.30	−8787	0.174	73.0	−	−
	finasteride	−31.3	4.34	−6771	0.260	56.3	−	−
		b_0	b_1 L·g^{-1}	b_2 K				
Bartle	flutamide	23.7	0.013	−9353	0.137	−	77.8	−16.8
	dutasteride	26.9	0.015	−10840	0.240	−	90.1	−17.1
	finasteride	22.4	0.009	−8861	0.640	−	73.7	−17.4

[a] AARD was obtained from eq 5. [b] Obtained from the Chratil model. [c] Obtained from the Bartle model. [d] Obtained from the difference between the [c]$\Delta_v H$ and [b]ΔH_{total}.

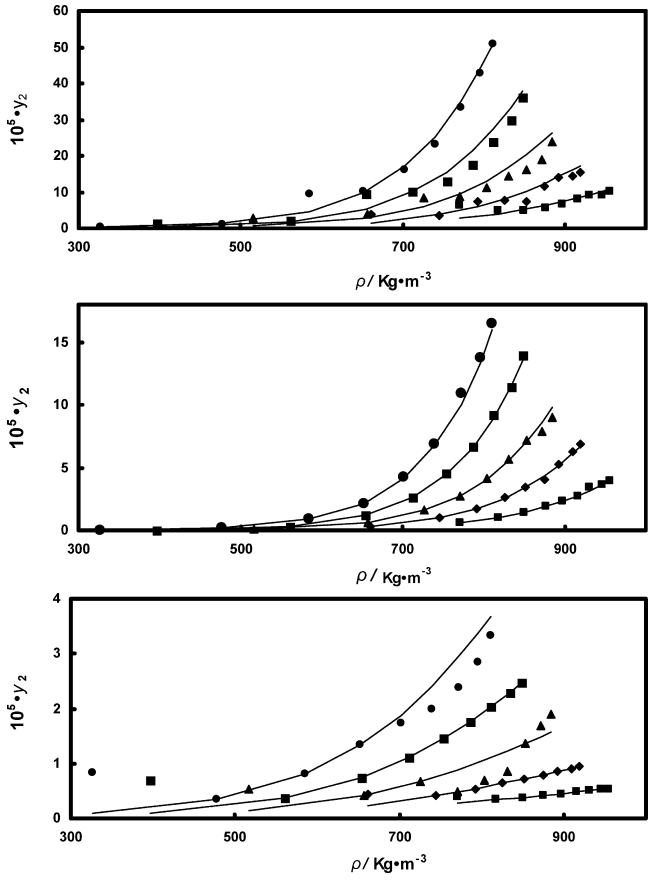


Figure 1. Solubility S of flutamide (TOP), dutasteride (MIDDLE), and finasteride (BOTTOM) in CO_2 as a function of the density ρ of CO_2. ■, T = 308 K; ◆, T = 318 K; ▲, T = 328 K; ■, T = 338 K; ●, T = 348 K; and −, eq 4, Bartle's model.

Data Correlation. The fitted parameters for the drugs/SC−CO_2 system and also the corresponding AARD values, obtained with the two investigated density-based correlations, are presented in Table 3. The graphic representation of these results can be observed in Figure 1, where the experimental data and the fitted curves for the two models are shown. As can be seen, the obtained AARD values range form 0.122 to 0.26 (for the Chrastil model) and from 0.024 to 0.137 (for the Bartle et al. model). Using the correlation results, the heat of drug−CO_2 solvation and that of drug vaporization were separately approximated in the range of (−17.4 to −16.8 and 73.7 to 90.1) kJ·mol^{-1} listed in Table 3.

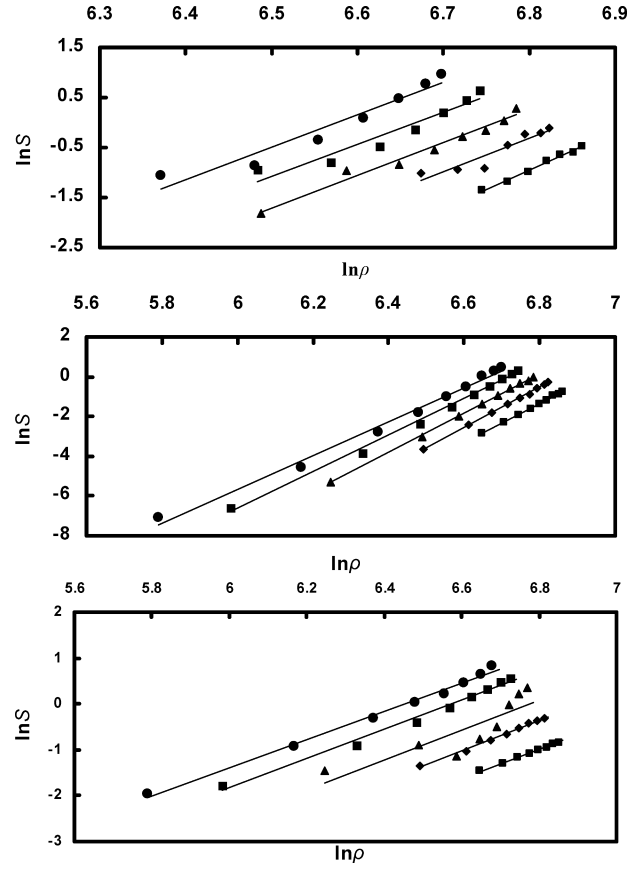


Figure 2. Logarithmic relationship between the solubility S of flutamide (TOP), dutasteride (MIDDLE), and finasteride (BOTTOM) in CO_2 and the density ρ of CO_2. ■, T = 308 K; ◆, T = 318 K; ▲, T = 328 K; ■, T = 338 K; ●, T = 348 K; and −, eq 1, Chrastil's model.

All the employed density-based correlation models fitted almost perfectly the obtained experimental data points, even for low pressure/low density points which normally present larger deviations from the experimental results.

Figure 2 represents the comparison of corrected results with the experimental values for FLUT, DUTA, and FIN in SC−CO_2. It is clear from Figure 2 that ln(S) varies linearly with ln(ρ) confirming the validity of the experimental data and Chrastil model.

As can be seen in Figure 2 and Table 3 and with obtained AARD values, all the two density-based models were able to successfully correlate the experimental solid drugs SC−CO_2 solubility data.

Conclusion

New solid solubility data for flutamide, dutasteride, and finasteride in supercritical CO_2 were presented at temperatures (308.0, 318.0, 328.0, 338.0, and 348.0) K over the pressures ranging from (12.1 to 35.5) MPa. Flutamide and finasteride had a similar solubility range of 10^{-5} to 10^{-4}. Dutasteride showed lower solid solubility ranged from $5.7 \cdot 10^{-6}$ to $1.6 \cdot 10^{-5}$. It is well-known that the solubility of solids in SCFs depends essentially on the specific interactions between the solid solutes and the SCFs, as well as on the polarity of the solids. Since the SC−CO_2 is a nonpolar solvent and dutasteride is a polar molecule, it has been less soluble compared with flutamide and finasteride.

Solubility data for pharmaceutical solids have been correlated by two density-based models (Chrastil and Bartle models). All fitted models were shown to be able to successfully correlate

experimental solubility data. However, best correlation results, in terms of AARD, were obtained with the Bartle model. The average absolute relative deviation in solid solubility (AARD) ranged form 0.122 to 0.26 (for the Chrastil model) and from 0.024 to 0.137 (for the Bartle et al. model).

Using the correlation results, the heat of drug−CO_2 solvation and that of drug vaporization were separately approximated in the range of (−17.4 to −16.8 and 73.7 to 90.1) kJ·mol^{-1}.

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