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Solubility of Bicalutamide, Megestrol Acetate, Prednisolone, Beclomethasone Dipropionate, and Clarithromycin in Subcritical Water at Different Temperatures from 383.15 to 443.15 K

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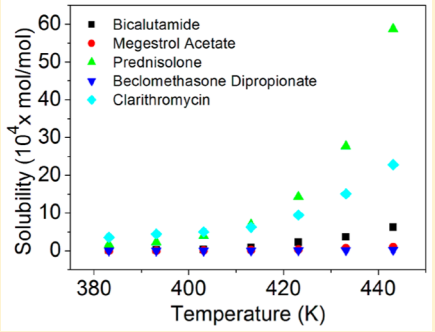
ABSTRACT: The solubility of bicalutamide, megestrol acetate, prednisolone, beclomethasone dipropionate, and clarithromycin in subcritical water (SBCW) at the temperature range from 383.15 to 443.15 K and constant pressure of 5.5 MPa were measured using a modified solvent−antisolvent method combined with SBCW technology. The chemical structures of these five kinds of solutes were stable after processed in SBCW at up to 443.15 K, which was demonstrated by Fourier transformed infrared analysis. The solubility of selected solutes increased exponentially as the temperature of the SBCW increased from 383.15 to 443.15 K. The obtained solubility data were correlated using a modified Apelblat model and the results of the predicted solubility show good agreement with the experimental value.



1. INTRODUCTION

Poor aqueous solubility of many drugs and drug candidates has been an industry wide problem for their development and clinical application.[1] Nanonization of poor water-soluble drugs has been demonstrated to be an efficient approach to overcome the limitations for low dissolution rate[2] and systemic side effects.[3] Consequently, a variety of nanonization strategies for drugs have emerged, including media milling,[4] high-pressure homogenization,[5] and solvent−antisolvent precipitation.[6] The issue of environmental safety, health improvement, and protection and also the advances in technology has lead researchers to develop interest in green environmental friendly processes which are less hazardous, more productive, efficient ,and economical in term of cost and space.[7−10] To overcome the bioavailability problem of active pharmaceutical ingredients (API) blocking pharmaceutical industries, researchers have recently developed more interest in the technology of subcritical fluids (SCF) as a green alternative.[10,11]

Subcritical water (SBCW), also known as near-critical water (NCW), pressurized hot water (PHW), hot compressed water (HCW), or superheated water (SHW) refer to liquid water at temperatures between the atmospheric boiling point of 373.15 K and the critical temperature of 647.15 K, which maintains its liquid state under pressurized condition up to 226 bar.[12] The subcritical fluid state of water occurs as a result of changes in its physical and chemical properties. This including the decrease in viscosity, surface tension, and permeability caused by the modification or disruption in the microstructural state of ion association, hydrogen-bonded lattice, and cluster-like structure when higher temperature and moderate pressure are been applied. Increasing the temperature of water above 373.15 K results in an increase in its ionic product and a decrease in its dielectric constant,[13] increasing the solvency properties of water. Above 473.15 K, water may be an acid or base catalyst because its H_3O^+ and OH^- ion concentrations are perhaps orders of magnitude higher than in ambient water.[14]

Several advantages exist in using SBCW including low cost, nontoxicity, and environmental friendliness to name a few.[10,12,15−18] The universal and unique solvency state and also the ease in process, disposal, and availability make water unique.[19] SBCW also displays low viscosity and higher diffusivity.[20] Consequently SBCW has a similar ability to that of organic solvents such as methanol and chloroform. Pressurized low polarity water under subcritical conditions can easily solubilize organic compounds from polar (at lower temperatures) to nonpolar (at higher temperatures) such as phytochemicals, which are normally insoluble in ambient water.

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Because of its higher solvency properties compared to water at ambient temperature, SBCW has intensively found application in extraction process including the extraction of agricultural, the extraction of substances from moderately polar to heavy molecular weight in medical plants, and also the recovery of highly polar compounds from natural products.[19] SBCW is an effective solvent for the decomposition and dissolution of a wide range of polar and nonpolar substances in the environmental matrices. It has also been used in high-performance liquid chromatography as chromatography mobile phase.[21] The ion product of the SBCW substantially increases with temperature, which can catalyze chemical reactions such as hydrolysis and degradation without any additional catalyst.[22] SBCW has been used extensively in environmental remediation processes including oxidation reaction for the destruction of hazardous product and toxic waste such as dioxins, phenanthrene, and fluorochemicals.[23] Others applications include the remediation of pesticides in soil and hydrocarbons from environmental solids.

SBCW process has emerged as a green and efficient approach for the preparation of nanoparticles of poor aqueous soluble drugs in recent years. The knowledge of solubility of drugs in SBCW is critical for formation of nanoparticles. To provide basic data for enlarging the applied range of SBCW, the solubility data of five kinds of active pharmaceutical ingredients, including bicalutamide (BC), megestrol acetate (MA), prednisolone (PDL), beclomethasone dipropionate (BDP), and clarithromycin (CLA) in SBCW, were measured at temperatures from 383.15 to 443.15 K at constant pressure of 5.5 MPa. The experimental solubility data were also correlated using the modified Apelblat equation.

2. EXPERIMENTAL SECTION

2.1. Materials. Bicalutamide (≥99.7%) was obtained from Shanghai Puyi Chemical Co. Ltd. Megestrol acetate (≥99%) and prednisolone (≥98%) were purchased from Shandong Taihua Bio & Tech Co. Ltd. The beclomethasone dipropionate (≥98%) was purchased from Shenzhen Shijingu Technology Co. Ltd. The clarithromycin (≥99.5%) was purchased from Guangzhou Puhe Medical Science and Technology Co. Ltd. The chemical structures of BC, MA, PDL, BDP, and CLA are shown in Figure 1 and the physical specifications of them are presented in Table 1. Ethanol (≥99.7%) was obtained from Shanghai Macklin Biochemical Technology Co., Ltd. Nitrogen gas (≥99.9%) was purchased from Beijing Ruyuanruquan Technology Co. Ltd. The specifications of the chemical samples are presented in Table 2. All the chemical samples were used as received without further

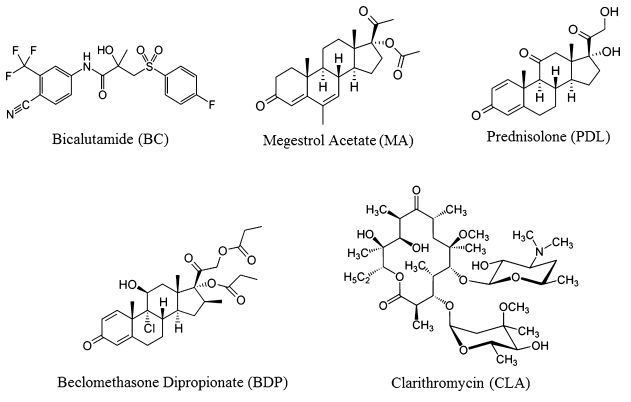

Figure 1. Chemical structures of BC, MA, PDL, BDP, and CLA.

Table 1. Physical Specifications of BC, MA, PDL, BDP, and CLA

	BC	MA	PDL	BDP	CLA
formula	$C_{18}H_{14}F_4N_2O_4S$	$C_{24}H_{32}O_4$	$C_{21}H_{26}O_5$	$C_{28}H_{37}ClO_7$	$C_{38}H_{69}NO_{13}$
melting point (K)	465.15[24]	490.15[25]	507.15[26]	485.15[27,28]	504.15[29]
molecular weight ($g \cdot mol^{-1}$)	430.37	384.51	360.40	521.04	747.95
function	antiandrogen for prostate cancer[30]	antineoplastic for breast and endometrial cancer[31]	antiinflammatory and immunosuppressant agent[32]	steroid medication for asthma, dermatitis, psoriasis and ulcerative colitis[18]	antibiotic for various bacterial infections[10]

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Table 2. Specification of Chemical Samples

chemical name	source	crystal phase	initial mole	purification
BC[a]	Shanghai Puyi Chemical Co. Ltd.	monoclinic	0.997	none
MA[a]	Shandong Taihua Bio & Tech Co. Ltd.	orthorhombic	0.99	none
PDL[a]	Shandong Taihua Bio & Tech Co. Ltd.	orthorhombic	0.98	none
BDP[a]	Shenzhen Shijingu Technology Co. Ltd.	orthorhombic	0.98	none
CLA[a]	Guangzhou Puhe Medical Science and Technology Co. Ltd.	orthorhombic	0.995	none
ethanol	Shanghai Macklin Biochemical Technology Co., Ltd.		0.997	none
nitrogen	Beijing Ruyuanruquan Technology Co. Ltd.		0.995	none

[a]BC = bicalutamide, MA = megestrol acetate, PDL = prednisolone, BDP = beclomethasone dipropionate, CLA = clarithromycin.

purification. The deionized water was prepared by an Eco-Q15 deionized water system (Shanghai Hitech Instruments Co., Ltd.) with resistivity of 16−18.2 MΩ·cm and was used in all experiments.

2.2. Apparatus and Procedure. In this study, a batch method was devised to determine the solubility of hydrophobic compounds in SBCW. The method have been validated by measurements for naproxen, budesonide, griseofulvin, and polycyclic aromatic hydrocarbons in our previous reports.[33−36] Figure 2 shows the schematic diagram of the experimental

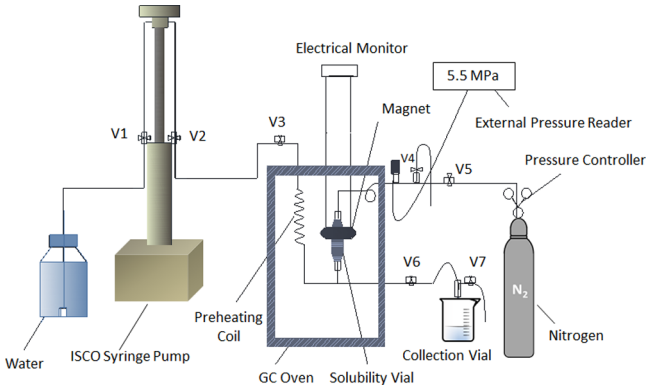

Figure 2. Schematic diagram of the SBCW apparatus.

apparatus in this study. An experimental system made from a combination of deionized water tank, syringe pump (Teledyne ISCO Model 260D-Series), heating oven (Binder FD series), automatic oscillating magnetic bar, external pressure controller, and nitrogen tank was used for solubility analysis. The system was connected with a series of stainless steel fittings and tubing lines controlled by different valves (V1−V7). The drug sample (100 mg) was weighed using an electronic balance Mettler-Toledo Model XS105 and loaded into a solubility vial (SV) together with a small magnet for each run. At each end of the SV was placed a threaded tube fitting with 0.5 μm filter stone pore, which was used to retain undissolved particles in the SV. The ISCO syringe pumps were refilled with deionized water at a constant flow rate by opening V1. The flow of deionized water from the syringe pump through the stainless steel to the SV (6.4 mL) was made by opening V2 and V3. The constant flow of water from lines and the dripping out from to the outer line end of the tubing without linkage shows that air was remove out of the system and that the fittings were well tighten. Air tightness was also controlled by opening the V2 and V3 valves and raising the pressure a little bit higher than the experimental pressure to ensure no linkage occurs from system. The selected temperature (from 383.15 to 443.15 K, gradually) was set from the heating oven Binder GC-8A chromatography controller which provides precise temperature control for solubility determination.The constant operating pressure was set from the ISCO syringe pump controller providing a constant supply of 5.5 ± 0.05 MPa. V4 was occasionally opened to reduce the excess pressure cause by thermal expansion. When the selected temperature and pressure have reached equilibrium, the solution in SV containing a magnetic bar was allowed to internally stir using a magnetic stirring bar driven by an external magnetic iron ring for 20 min. After the magnetic stirrer stopped, the higher-pressure nitrogen was pushed into the system by opening the V5 to keep constant the vessel pressure and prevent the SBCW from vaporizing. The solution was finally collected into the collection vial (CV) by opening the V6. After collection, the valves were closed and the oven was turned off to allow cooling; pressure was then released from the system through V7. The collected solution was transferred from the capped CV to a beaker. The collection line was also removed and washed with a Peristaltic pump subjecting a constant flow of reagent grade ethanol to collect the residuals of deposited drug sample. The solution of ethanol was gradually collected in a beaker and dried along with the solution of SBCW from the capped CV. After drying, both solutions were diluted with 100 mL of analytical grade ethanol and the absorbance was measured under a UV spectrophotometer (Varian model Cary 50 Conc) at 271, 285, 243, 239, and 290 nm for BC, MA, PDL, BDP, and CLA, respectively. For each temperature, the experiments were repeated at least four times to ensure accuracy in the results.

2.3. Characterization of Chemical Structures. Fourier transformed infrared (FTIR) analysis was performed to investigated the stability of BC, MA, PDL, BDP and CLA upon processing, using a FTIR Bruker IFS66 spectrometer. The spectra were recorded in the range 500−4000 cm^{-1} using a resolution of 2 cm^{-1} and 32 scans. Samples were diluted with KBr mixing powder at 1% and pressed to obtain self-supporting disks that were used for reading.

2.4. Calculation of the Solubility. A calibration equation in the form of eq 1 obtained from UV spectrophotometer reading by Beer's lambert law was used to calculate the solubility of the drug for all temperature ranges.[37] A stock solution for each drug was prepared in ethanol solution. With appropriate dilution, a set of standard solutions were obtained and a solubility curve relating absorbance against concentration was plotted with ≥0.999 regression coefficient for all three samples. The peak wavelength of BC, MA, PDL, BDP, and CLA solubility through absorbance reading was 271, 285, 243, 239, and 290, respectively.

$$\text{Abs} = A \times \text{Con} + B \quad (1)$$

where A and B are standard values obtained from the calibration plot representing the slope and intercept, respectively. Con is the concentration of the drugs (mg/mL) and Abs represents the absorbance, which is a variable.

The concentration of each fraction of the experiments was calculated by reading the absorbance of the solution in UV spectrophotometer. The samples were read at least three times using 10 mm thick cuvette and ethanol solution as the solvent.

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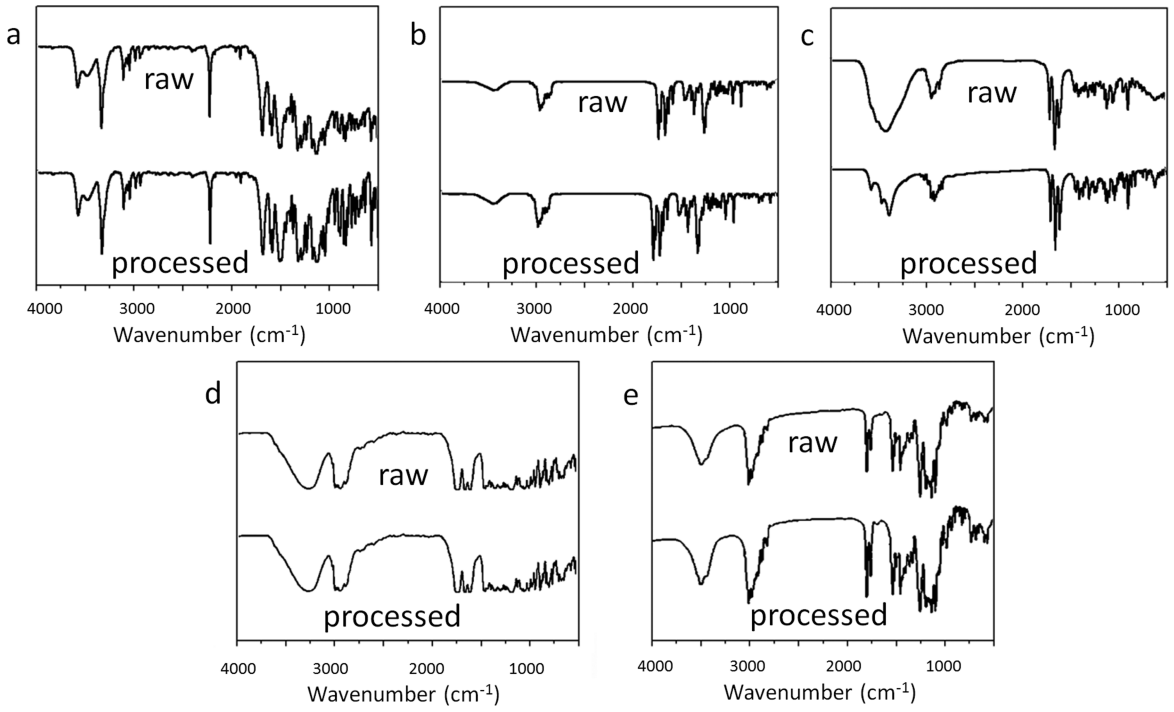

Figure 3. FTIR spectra of raw and SBCW-processed BC (a), MA (b), PDL (c), BDP (d) and CLA (d), respectively.

Table 3. Experimental Mole Fraction Solubility x of BC, MA, PDL, BDP, and CLA in Subcritical Water at Temperature T, Pressure p = 5.5 MPa, and Equilibrium Time t = 20 min[a]

solute	T (K)	10^4x	solute	T (K)	10^4x	solute	T (K)	10^4x
BC	383.15	0.079	MA	383.15	0.027	PDL	383.15	1.631
	393.15	0.204		393.15	0.037		393.15	2.294
	403.15	0.317		403.15	0.112		403.15	3.960
	413.15	0.765		413.15	0.194		413.15	6.887
	423.15	2.221		423.15	0.354		423.15	14.301
	433.15	3.675		433.15	0.631		433.15	27.710
	443.15	6.235		443.15	0.990		443.15	58.700
BDP	383.15	0.020	CLA	383.15	3.564			
	393.15	0.023		393.15	4.448			
	403.15	0.032		403.15	5.018			
	413.15	0.045		413.15	6.269			
	423.15	0.084		423.15	9.457			
	433.15	0.139		433.15	15.048			
	443.15	0.213		443.15	22.807			

[a]Standard uncertainty for temperature, pressure and equilibrium time are $u(T)$ = 0.05 K, $u(p)$ = 0.05 MPa, and $u(t)$ = 0.5 min, respectively. Relative standard uncertainties for solubility is $u_r(s)$ = 0.02.

The calibration equation obtained as $Abs_{(BC)} = 55.4 \times Con + 0.013$, $Abs_{(MA)} = 62.4 \times Con + 0.020$, $Abs_{(PDL)} = 40.4 \times Con + 0.007$, $Abs_{(BDP)} = 29.7 \times Con + 0.001$ and $Abs_{(CLA)} = 45.2 \times Con + 0.004$ were respectively for BC, MA, PDL, BDP, and CLA with concentration units in mg/mL and $R^2 \geq 0.999$ for all samples.

The solubility of investigated solutes was calculated using eq 2

$$x_{sol} = \frac{\frac{m_d}{M_d}}{\frac{m_d}{M_d} + \frac{m_w}{M_w}} \quad (2)$$

where x_{sol} represents the solubility (mol/mol) of the solute, m_d and m_w are the respective mass (g) of the solute (solid) and water. M_d and M_w represent the molar mass ($g \cdot mol^{-1}$) of the solid and water, respectively.

3. RESULTS AND DISCUSSION

The solubility studies of five solutes including BC, MA, PDL, BDP, and CLA in SBCW at different temperatures from 383.15 to 443.15 K were performed. The stabilities of the solutes during the SBCW process were first investigated by FTIR spectra analysis. Figure 3 shows the FTIR spectra of raw solutes and the solutes processed in SBCW at 443.15 K for 20 min. For all the selected samples, no significant differences between the raw and processed solutes were observed. The FTIR fingerprint patterns of each solute remained the same before and after the subcritical process, demonstrating that these solutes were stable in SBCW at up to 443.15 K.

The experimental solubility data of BC, MA PDL, BDP, and CLA in SBCW of various temperatures are listed in Table 3. The standard deviation was calculate based on four fraction

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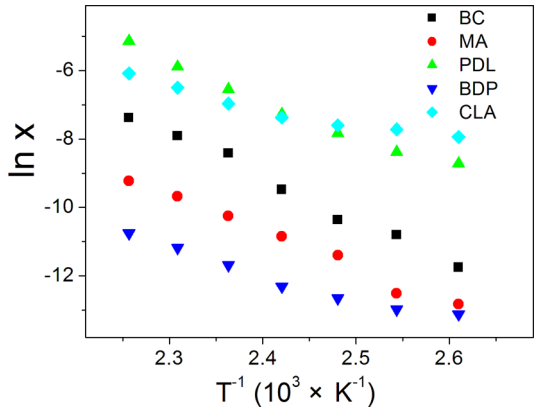

Figure 4. Plots of ln x versus the inverse of temperature (K^{-1}). x represents the mole fraction solubility of BC, MA, PDL, BDP, and CLA, respectively.

Table 4. Solubility Parameters of BC, MA, PDL, BDP, and CLA From Modified Apelblat Equation

solute	A	B	C	RMSE
BC	−32.54	−9493.72	7.66	0.19
MA	158.04	−19095.72	−20.37	0.18
PDL	−1190.29	60560.21	172.06	0.04
BDP	−1071.83	56106.38	153.36	0.09
CLA	−1042.97	56275.04	149.31	0.06

collections for each condition and was less than 3% for all data. Standard uncertainty for temperature and pressure are $u(T)$ = 0.05 K and $u(p)$ = 0.05 MPa, respectively. The plots of ln Y versus T^{-1} are presented in Figure 4, where Y is solubility expressed as mole fraction and T is the temperature of the SBCW. According to these experimental results, all the solutes exhibited strong dependence of solubility on the temperature of SBCW with a gradual increase in solubility as the temperature increased from 383.15 to 413.15 K with a large solubility increase between 413.15 and 443.14 K. The correlation of the solubility and temperature of the SBCW observed in our work was in agreement with previous reports on other kinds of active pharmaceutical ingredients.[38−41] The increasing of the solubility of the selected solutes was attributed to the decreasing of water dielectric constant in the range of 383.15 to 443.15 K.

A modified Apelblat equation[42] from eq 3 was used to correlate the temperature dependency of the aqueous solubility of the five solutes in SBCW[43]

$$\ln(x_{sol}) = A + \frac{B}{T} + C \times \ln(T) \tag{3}$$

where x_{sol} is the mole fraction solubility of the investigated solute; T is the absolute temperature; and A, B, and C are the empirical parameters.

The root-mean-square error (RMSE) between the experimental and calculated value was calculated using eq 4.

$$\mathrm{RMSE} = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(x^{c} - x^{e})^{2}} \tag{4}$$

where N represents the number of all values; x^c and x^e represent the calculated and the experimental solubility in mole fraction.

Table 4 shows the empirical parameters of A, B, and C for each solute and the respective RMSE. The experimental solubility data along with the predicted solubility data from eq 3 are presented in Figure 5. It can be seen that the solubility prediction using the modified Apelblat equation provides good agreement with the experimental data for the solubility of the selected solutes in SBCW at the temperature range of 383.15 to 443.15 K.

4. CONCLUSION

The use of SBCW as the solvent has been demonstrated to be capable of preparing micrometer-sized particles or nanoparticles of pharmaceuticals by solvent−antisolvent precipitation. The solubility data of the pharmaceuticals in SBCW are instructive to the process particle formation. In this work, we investigated the solubility of five kinds of active pharmaceutical ingredients in SBCW at the temperature range from 383.15 to 443.15 K and constant pressure of 5.5 MPa. The selected solutes were bicalutamide, megestrol acetate, prednisolone, beclomethasone

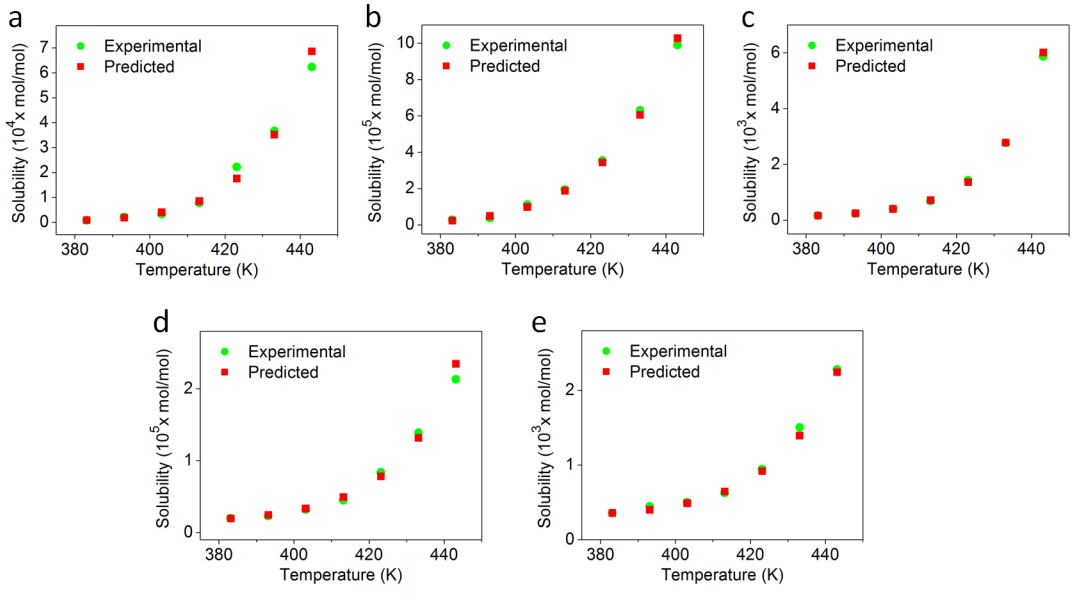

Figure 5. Experimental and predicted mole fraction solubility of BC (a), MA (b), PDL (c), BDP (d) and CLA (e) as a function of temperature.

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dipropionate, and clarithromycin. By using FTIR analysis, these solutes were demonstrated to be stable after processed in SBCW of up to 443.15 K. The solubility of selected solutes increased exponentially as the temperature of the SBCW increasing from 383.15 to 443.15 K and the experimental solubility data fitted well with the modified Apelblat equation.

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Notes

The authors declare no competing financial interest.

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