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Using a Laser Monitoring Technique for Dissolution and Thermodynamic Study of Celecoxib in 2-Propanol and Propylene Glycol Mixtures

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ABSTRACT

In the current work, a laser monitoring technique was used to study dissolution and solubility of celecoxib (CBX) in 2-propanol and propylene glycol mixtures at temperatures of 293.2–313.2 K. The solubility data were fitted to mathematical models, i.e., the van't Hoff model, the mixture surface model, the Jouyban-Acree and Jouyban-Acree-van't Hoff equations, and the modified Wilson model. Model accuracy was evaluated by mean relative deviation (MRD%) for back-calculated solubility values. The thermodynamic behavior of CBX dissolution was evaluated according to the van't Hoff and Gibbs equations. CBX exhibited maximum solubility in 2-propanol with a mass fraction of 0.8 at all temperatures. CBX dissolution was identified as an endothermic and enthalpy-driven process, which was more favorable in mixtures with high drug solubilizing capacity. The various models described solubility data from the laser monitoring technique adequately, and the studied cosolvent mixtures have the potential to be used in analytical pharmaceutical development or as intermediate bulk solutions for CBX products.

KEYWORDS: Solubility, celecoxib, mathematical models, thermodynamics, dissolution

INTRODUCTION

Celecoxib (CXB, Fig. 1) is a nonsteroidal anti-inflammatory drug (NSAID) that is prescribed to ease the symptoms of osteoarthritis and rheumatoid arthritis. In comparison to other NSAIDs, CXB shows better efficacy in these pathophysiological states (*1*). The anti-inflammatory, analgesic, and antipyretic activities of CXB are based on a selective banner for cyclooxygenase-2 (COX-2), which has a role in biosynthesis of prostaglandin (*2*). According to the Biopharmaceutics Classification System, CXB belongs to class 2, with high permeability and low solubility (*3*).

In different stages of drug discovery and development, equilibrium solubility is an important property and represents critical knowledge in pre-formulation, preparation of liquid pharmaceutical dosage forms, purification, and/or extraction (*4*). Different formulation techniques were used for the solubilization of CXB including solid dispersions, mesoporous formulations, cyclodextrin inclusion complex, microencapsulation, micellar formulation, nanoemulsion formulation, polymeric nanoparticles, co-crystal, hydrotropy, and cosolvency (*5–13*). Cosolvency is a feasible and reliable technique for solubilization of a drug compound exhibiting low aqueous solubility. Previously reported cosolvency systems for CXB include: NMP (N-methyl-2-pyrrolidone) and water; 2-propanol and water; ethanol and water; 1-propanol and water; choline chloride (ChCl)/ethylene glycol, ChCl/glucose, ChCl/maltose, or ChCl/urea and water; PEG (polyethylene glycol) 200, 400, or

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600 and water; PEG 200, 400, or 600 and ethanol; and PG (propylene glycol) and ethanol. However, solubility of CXB in 2-propanol and PG has not been reported. Both of these solvents are commonly used in the pharmaceutical industry.

The aims of the present study are (1) solubility determination of CXB in mixtures of 2-propanol and PG; (2) data fitting to selected cosolvency equations; and (3) investigation of the thermodynamic behavior for dissolution of CXB.

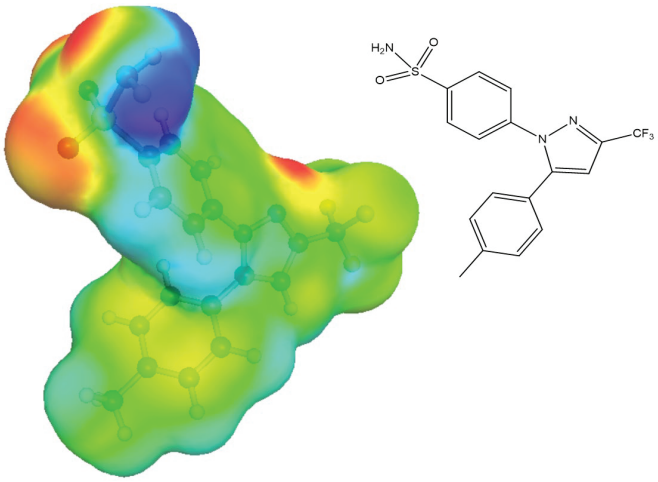

Figure 1. Molecular structure of CXB and sigma surface of most stable coformer as calculated from density functional theory (DFT) based on triple-zeta valence polarized basis set (TZVP) level of theory (BIOVIA COSMOquick database v.2020, Dassault Systèmes Germany GmbH). CXB: celecoxib; PG: propylene glycol.

METHODS

Materials

Raw CXB powder (0.990, Arastoo Pharmaceutical Company, Iran), PG (Scharlau Chemie, Spain), and 2-propanol (Merck, Germany) were used materials for the preparation of the mixed solvents.

Solubility Determination

We used a custom automated smart system equipped with a laser monitoring technique for the determination of CXB solubility in 2-proppanol and PG mixtures. The system adds powder to the solubility vessel using a mechanical arm, and a laser probe is used for particle monitoring. The solubility of CXB in a binary system has been investigated and reported using this method (*14*).

For the current study, 120 g solvent or mixed solvents were prepared and transferred into the dissolution vessel. The temperature was set at the desired value (293.2–313.2 K) and the setup was turned on. After an initial scope of the solution to check its purity, CXB powder was dispersed into the vessel using a robotic arm. A magnetic stirrer was used for the solution while monitoring with the laser probe. The addition of CXB powder continued until the mixture became saturated, at which point a green light on the instrument indicated the end of the experiment. Solubility was computed using the weight of powder added to the dissolution vessel.

Data Analysis

The solubility data measured for CXB were correlated to mathematical models and equations including: van't Hoff; mixture response surface (MRS); Jouyban-Acree; Jouyban-Acree-van't Hoff; and modified Wilson's. The details of these models and equations are mentioned in our previous publications (*15*, *16*).

After data fitting, the mean relative deviation (MRD%) of the back-calculated value was computed using the following equation to investigate the model's accuracy.

$$\mathrm{MRD\%} = \frac{100}{N}\sum\left(\frac{|\text{Calculated Value} - \text{Observed Value}|}{\text{Observed Value}}\right) \quad \text{Eq. (1)}$$

where N is the number of data points. MRD% facilitates the comparison between datasets or models with different scales due to normalizing the data by dividing the variance to the observed values. Prior work suggests that MRD may be the best error criterion (*17*).

Thermodynamic Studies

The enthalpy, entropy, and Gibbs free energy change as the apparent thermodynamic parameters were computed according to the van't Hoff and Gibbs equations. T_{hm} is temperature of the mean harmonic, which is computed from the following equation:

$$T_{hm} = n / \sum_{i=1}^{n}(1/T) \quad \text{Eq. (2)}$$

where n is the number of temperatures (*18*). The intercept and slope of the curve of ln x against $(1/T - 1/T_{hm})$ were used for computing $\Delta G°$ and $\Delta H°$ of procedure, and Gibbs equation was employed to calculate $\Delta S°$. In addition to thermodynamic parameters, the portion of entropy (ζ_{TS}) and enthalpy (ζ_{H}) to $\Delta G°$ were also computed (*19*).

RESULTS AND DISCUSSION

Solubility

Experimental data generated for CXB in 2-propanol and PG mixtures at different temperatures along with standard deviation are given in Table 1. CXB shows maximum solubility in 2-propanol with a mass fraction of 0.8 at all temperatures. Furthermore, in any given solvent composition, solubility was positively related to temperature. A comparison between CXB solubility values obtained in the current study for neat 2-propanol

Table 1. Experimental Mole Fraction Solubility Data Obtained for CXB in 2-propanol + PG Mixtures at Different Temperatures

w_i[a]	293.2 K	298.2 K	303.2 K	308.2 K	313.2 K
0.00	2.19 × (± 0.33) 10^{-3}	3.86 × (± 0.54) 10^{-3}	6.36 × (± 0.56) 10^{-3}	8.19 × (± 0.81) 10^{-3}	1.15 × (± 0.02) 10^{-2}
0.10	3.47 × (± 0.56) 10^{-3}	5.53 × (± 0.09) 10^{-3}	8.34 × (± 0.84) 10^{-3}	9.74 × (± 0.13) 10^{-3}	1.30 × (± 0.08) 10^{-2}
0.30	4.24 × (± 0.26) 10^{-3}	6.20 × (± 0.76) 10^{-3}	8.97 × (± 0.76) 10^{-3}	1.16 × (± 0.23) 10^{-2}	1.45 × (± 0.25) 10^{-2}
0.50	5.04 × (± 0.16) 10^{-3}	8.47 × (± 0.79) 10^{-3}	1.07 × (± 0.15) 10^{-3}	1.31 × (± 0.26) 10^{-2}	1.59 × (± 0.27) 10^{-2}
0.70	7.47× (± 0.77) 10^{-3}	1.09 × (± 0.09) 10^{-3}	1.37 × (± 0.10) 10^{-3}	1.56 × (± 0.17) 10^{-2}	1.75 × (± 0.22) 10^{-2}
0.80	7.55 × (± 0.88) 10^{-3}	1.14 × (± 0.09) 10^{-3}	1.40 × (± 0.04) 10^{-3}	1.69 × (± 0.08) 10^{-2}	1.86 × (± 0.32) 10^{-2}
0.90	7.08 × (± 0.42) 10^{-3}	9.26 × (± 0.70) 10^{-3}	1.13 × (± 0.14) 10^{-3}	1.36 × (± 0.16) 10^{-2}	1.66 × (± 0.17) 10^{-2}
1.00	5.95 × (± 0.53) 10^{-3}	8.23 × (± 0.28) 10^{-3}	1.06 × (± 0.17) 10^{-3}	1.28 × (± 0.20) 10^{-2}	1.51 × (± 0.09) 10^{-2}

[a]w_i is mass fraction of 2-propanol in 2-propanol + PG mixtures in the absence of CXB.
CXB: celecoxib; PG: propylene glycol.

(x = 8.23 × 10^{-3}) with a reported value (x = 9.02 × 10^{-3}) in the literature showed very good agreement considering typical experimental variation by the purity of the compound and analytical methodology used (*20*). Solubility of CXB in other solutions was not reported for comparison.

Solubility of CXB has been investigated in various mixtures of cosolvent + water including: NMP + water; 2-propanol + water; ethanol + water; 1-propanol + water; ChCl/ethylene glycol, ChCl /glucose, ChCl/maltose, ChCl/urea + water; PEGs + water; PEGs + ethanol; PG + ethanol; and the present system (2-propanol + PG). The solubility profiles are given in Figure 2, which shows that most systems possess the same trend for CXB solubility, with a maximum amount in neat solvent (*1*). However, the solubility profile of CXB in PEG 200 + ethanol and in 2-propanol + PG displayed a maximum mass fraction (w_i) of 0.8–0.9. A comparison between the studied systems for CXB solubility demonstrated that both PEG 600 + ethanol and 2-propanol + PG had an excellent solubilization effect on CXB, which is a poorly soluble drug.

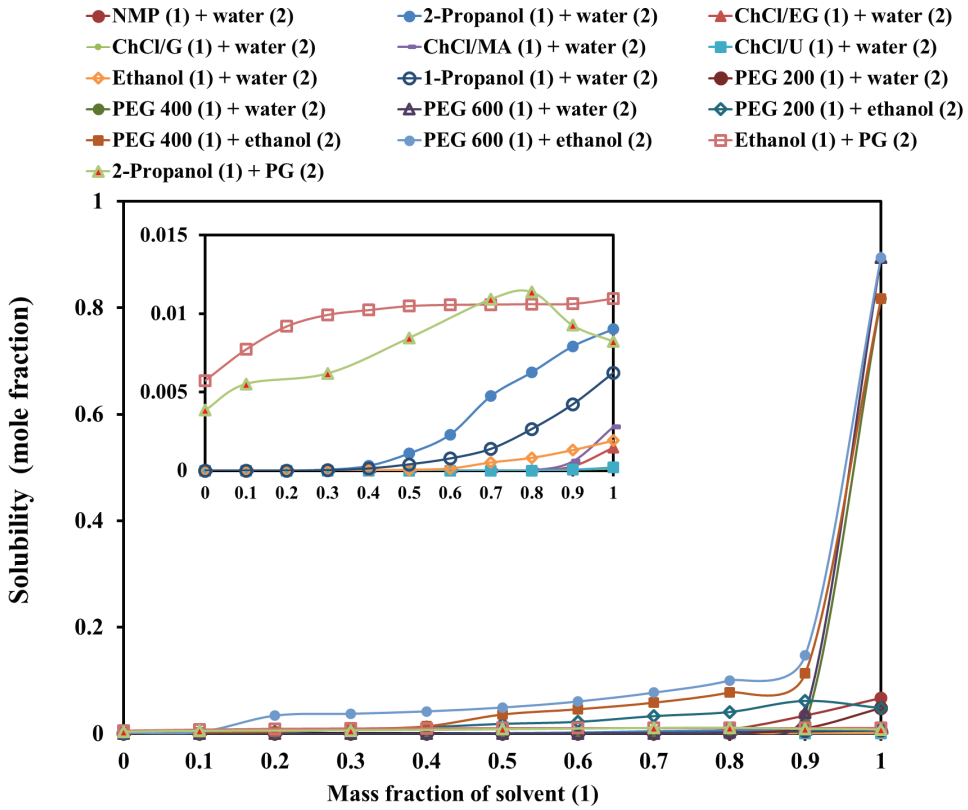

Figure 2. Comparison of CXB mole fraction solubility profiles in different reported systems at 298.2 K.
indicates data from the current study (2-propanol + PG mixture); (1) indicates first solvent that mass fraction is reported based on this solution; (2) indicates second solvent.
CXB: celecoxib; NMP: N-methyl-2-pyrrolidone; ChCl: choline chloride; EG DES: ethylene glycol deep eutectic solvent; PEG: polyethylene glycol; PG: propylene glycol

The solubilization efficacy of each system was computed using σ and ω parameters, which were computed using the equations reported in Ref. (*21*). The ω and σ values are equal when maximum solubility is in the neat cosolvent. These parameters were calculated for CXB in the above-mentioned mixtures, and the results are summarized in Table 2. The high solubilization power based on the solubilization factor of ω was for PEG 400 + water, demonstrating the high capability of this cosolvent for solubilization of CXB.

Table 2. Comparison of Solubilization Powers of Various Cosolvents Studied for CXB

Solvent Mixtures	Solubilization efficacy (σ)	Updated version of solubilization efficacy (ω)
NMP + water	5.92	5.92
2-Propanol + water	5.05	5.05
ChCl/EG DES + water	4.26	4.26
ChCl/glucose DES + water	3.15	3.15
ChCl/maltose DES + water	4.54	4.54
ChCl/urea DES + water	3.41	3.41
Ethanol + water	4.72	4.72
1-Propanol + water	4.97	4.97
PEG 200 + water	6.13	6.13
PEG 400 + water	7.36	7.36
PEG 600 + water	7.39	7.39
PEG 200 + Ethanol	1.40	1.68
PEG 400 + Ethanol	2.63	2.63
PEG 600 + Ethanol	2.67	2.67
Ethanol + PG	0.28	0.28
2-Propanol + PG	0.33	0.33

CXB: celecoxib; NMP: N-methyl-2-pyrrolidone; ChCl: choline chloride; EG DES: ethylene glycol deep eutectic solvent; PEG: polyethylene glycol; PG: propylene glycol

Mathematical Modeling

Solubility is dependent on both temperature and solvent composition. Thus, the models used for cosolvency systems are a function of temperature or solvent composition or both.

The van't Hoff is a simple model for the representation of solubility data as a function of temperature. Therefore, it needs an individual equation for each solvent composition. The model coefficients for each equation along with MRD% are given in Table 3. The overall MRD% is low (5.5%), which confirms the model accuracy for solubility prediction.

The MRS is a linear model that relates the solubility data to solvent composition. Therefore, it needs an individual equation for each investigated temperature. The model coefficients for each equation along with MRD% are given in Table 4. The overall MRD% for this model is 2.7%.

Table 3. van't Hoff Model Parameters and Corresponding MRD% for Back-Calculated CXB Solubility Data in 2-Propanol + PG Mixtures

w_i[a]	A	B	MRD%
0.00	-4242.727	9.396	3.7
0.10	-3839.795	8.169	1.5
0.30	-4053.756	9.038	7.2
0.50	-3803.638	8.169	6.6
0.70	-5040.844	12.019	7.4
0.80	-5678.728	13.949	3.8
0.90	-5908.488	14.573	6.7
1.0	-7493.098	19.525	7.0
		Overall MRD%	**5.5**

[a]w_i *is mass fraction of 2-propanol in 2-propanol + PG mixtures in the absence of CXB.*
CXB: celecoxib; MRD: mean relative deviation; PG: propylene glycol.

Table 4. MRS Model Constants at Investigated Temperatures and MRD% for Back-Calculated CXB Solubility Data in 2-Propanol + PG Mixtures

Temperature (K)	β_1	β_2	β_3	β_4	β_5	MRD%
293.2	-6.155	-5.153	0[a]	0[a]	2.871	3.6
298.2	-5.628	-4.851	0[a]	0[a]	2.808	3.0
303.2	-5.113	-4.593	0[a]	0[a]	2.106	3.5
308.2	-4.872	-4.398	0[a]	0[a]	1.921	2.1
313.2	-4.509	-4.199	0[a]	0[a]	1.303	1.2
					Overall MRD%	**2.7**

[a]*Not statistically significant ($p > 0.05$).*
MRS: mixture response surface; CXB: celecoxib; MRD: mean relative deviation; PG: propylene glycol.

The modified Wilson model may be employed as a non-linear model for data correlation at various temperatures. Again, individual equations are needed for each investigated temperature. The model coefficients for each equation along with MRD% are given in Table 5. The overall MRD% for this model was 2.3%.

Using several models can be a problematic for solubility prediction. In the current study, for example, one must use eight equations for solubility prediction with the van't Hoff model, and five equations using MRS and the modified Wilson models. The Jouyban-Acree and Jouyban-Acree-van't Hoff equations relate the solubility to both temperature and solvent composition. Thus, they need just one regression step and obtain one equation for all data. The model coefficients for each equation along with MRD% are given in Table 6. The overall MRD% was 6.7% for Jouyban-Acree and 8.9% for the Jouyban-Acree-van't Hoff.

Table 5. Modified Wilson Model Parameters at Investigated Temperatures and MRD% for Back-Calculated CXB Solubility Data In 2-Propanol + PG Mixtures

Temperature (K)	λ_{12}	λ_{21}	MRD%
293.2	1.437	1.252	3.2
298.2	1.323	1.406	3.0
303.2	1.211	1.374	3.2
308.2	1.152	1.416	1.6
313.2	0.999	1.470	0.6
		Overall MRD%	**2.3**

CXB: celecoxib; MRD: mean relative deviation; PG: propylene glycol.

Table 6. Parameters Calculated for the Jouyban-Acree and Jouyban-Acree-van't Hoff Models and MRD% for Back-Calculated CXB Solubility Data in 2-Propanol + PG Mixtures

Jouyban-Acree Model Parameters	
J_0	617.798
J_1	0[a]
J_2	0[a]
MRD	6.7%
Jouyban-Acree-van't Hoff Model Parameters	
A_1	19.525
B_1	-7493.098
A_2	9.396
B_2	-4242.727
J_0	618.032
J_1	0[a]
J_2	0[a]
MRD	8.9%

[a]*Not statistically significant ($p > 0.05$).*
CXB: celecoxib; MRD: mean relative deviation, PG: propylene glycol.

Using one equation for correlation or prediction is the main advantage for a cosolvency model, which can be helpful in the pharmaceutical industry. Another advantage of these models is using a minimum number of data points for model training. These data points are solubility data in mono-solvents at the minimum and maximum investigated temperatures and solutions with mass fractions (wi) of 0.7, 0.5, and 0.3 at 298.2 K. After training, the MRD% for predicted values are 5.9%, 5.2%, 10.3%, 16.1%, and 26.8% for 293.2, 298.2, 303.2, 308.2, and 313.2 K, respectively (overall MRD is 12.8%).

Thermodynamic Studies

The apparent thermodynamic parameters including $\Delta H°$, $\Delta G°$, and $\Delta S°$ of CXB dissolution are given in Table 7. All parameters are positive, with the maximum (62.17 kJ.mol^{-1}) and minimum (31.66 kJ.mol^{-1}) for w_1 = 0.0 and w_1 = 0.7 for $\Delta H°$, respectively, the maximum (161.89 J.mol^{-1}) and minimum (68.06 J.mol^{-1}) for w_1 = 0.0 and w_1 = 0.7 for $\Delta S°$, respectively, and a minimum value of 10.94 kJ.mol^{-1} for w_1 = 0.8 for $\Delta G°$. CXB dissolution in 2-propanol and PG is an endothermic process and more favorable in a mixture with high capability for CXB solubilization. $\zeta_H > \zeta_{TS}$ was seen in all mixtures, demonstrating enthalpy is the main contributor of $\Delta G°$ in the dissolution process.

Based on thermodynamic parameters, the enthalpy-entropy compensation curve was plotted for investigation of the involved mechanism in the dissolution process (Fig. 3). CXB shows a trend mainly with a positive slope, indicating an enthalpy-driven mechanism for the cosolvent action that could be attributed to better drug solvation.

The enthalpy of solution reflects the nature of the intermolecular interactions and its variation results from the contribution of several kinds of interactions, endoergic cavity formation and exoergic solute-solvent interactions (*22*). The enthalpy of cavity formation is endothermic because work must be done against the cohesive forces of the solvent to accommodate the solute. This unfavorable contribution should decrease as the solubility parameter of the medium becomes more like that of the solute. Solute-solvent interactions are

Table 7. Apparent Thermodynamic Parameters for Dissolution Behavior of CXB in 2-Propanol + PG Mixtures at T_{hm} = 303.0 K

w_i[a]	$\Delta G°$ (kJ.mol^{-1})	$\Delta H°$ (kJ.mol–1)	$\Delta S°$ (J.mol–1.K–1)	$T\Delta S°$ (kJ.mol–1)	ζ_H	ζ_{TS}
0.00	13.11	62.17	161.89	49.05	0.559	0.441
0.10	12.41	49.07	120.96	36.65	0.572	0.428
0.30	12.07	47.32	116.32	35.24	0.573	0.427
0.50	11.63	41.93	100.01	30.30	0.581	0.419
0.70	11.04	31.66	68.06	20.62	0.606	0.394
0.20	10.94	33.72	75.18	22.78	0.597	0.403
0.90	11.34	31.97	68.07	20.62	0.608	0.392
1.00	11.60	35.17	77.79	23.57	0.599	0.401

[a]*w_i is mass fraction of 2-propanol in 2-propanol + PG mixtures in the absence of CXB.*
CXB: celecoxib, PG: propylene glycol.

exothermic and result mainly from van der Waals and Lewis acid-base interactions. The exothermic heat of mixing values suggests that solute-solvent interactions overcome the energetically unfavorable cavity term and are responsible for favorable free energy changes.

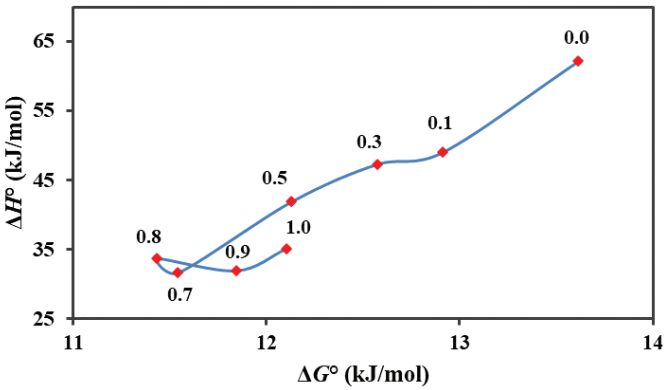

Figure 3. Enthalpy-entropy compensation plot for CXB in 2-propanol + PG mixtures at T_{hm} = 303.0 K. Red data points represent mass fraction of 2-propanol in the 2-propanol + PG mixtures in the absence of CXB. CXB: celecoxib; PG: propylene glycol.

CONCLUSIONS

A laser monitoring technique was used to study dissolution and solubility of CBX in 2-propanol and propylene glycol mixtures at temperatures of 293.2–313.2 K. CBX exhibited maximum solubility in 2-propanol and PG mixtures with a 2-propanol mass fraction of 0.8. CBX dissolution was identified as an endothermic and enthalpy-driven process. The various models described solubility data from the laser monitoring technique adequately, and the studied cosolvent mixtures have the potential to be used in analytical pharmaceutical development or as intermediate bulk solutions for CBX products.

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CONFLICT OF INTEREST

The authors declare no conflict of interest related to this article.

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