THERMODYNAMIC STUDY OF THE DICLOFENAC SODIUM SOLUBILITY IN VARIOUS OILS

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Abstract. Diclofenac sodium is sodium salt of [o-(2,6-dichloro aniline) phenyl] acetate and is a potent non-steroidal anti-inflammatory drug (NSAID). In the present communication, the thermodynamic study of diclofenac sodium solubilization in various oils like olive oil, castor oil, arachis oil, sunflower oil, soybean oil and liquid paraffin was investigated. Diclofenac sodium was found to have the increasing solubility and partition coefficient with the temperature rise in various oils used in this investigation. The maximum solubility and partition coefficient were found in case of castor oil, while these were minimum in case of liquid paraffin at various temperatures. Diclofenac sodium solubilization in all these oils, used in this investigation was found to be endothermic process. The valuable data obtained from this investigation can be utilized for designing and development of various oil based formulations of diclofenac sodium.

Keywords: diclofenac sodium, solubilization, partition coefficient, thermodynamics

Introduction

Diclofenac sodium is a potent non-steroidal anti-inflammatory drug (NSAID) and widely used clinically, because of its anti-inflammatory, analgesic and anti-pyretic effect [1-3]. It is mainly indicated in the treatment of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. However, diclofenac has a relatively high therapeutic

index in comparison to other NSAIDs [4]. Diclofenac sodium is sodium salt of [o-(2,6-dichloro aniline) phenyl] acetate and its molecular weight is 318.13 [5]. The structure of the diclofenac sodium is shown in Fig. 1.

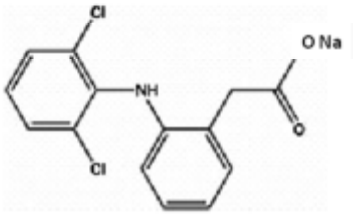

Fig. 1. Structure of diclofenac sodium

The presence of the heteroatoms like nitrogen, oxygen, chlorine and sodium in the molecular structure of diclofenac sodium causes high polarizability of the molecule and hence specific interactions with solvents that strongly affect the solubility of the drug in different solvents. Because of the presence of the -NH group that can act either as proton donor or proton acceptor toward the solvents and the presence of the carboxylic group, the drug possesses a Lewis acid-base character. The solubility characteristics of diclofenac sodium in aqueous media with various ionic strengths, ionic compositions and pH in the range of 1 to 10 were studied by Kincl et al. [6]. Ahuja et al. have investigated the solubility of diclofenac in various oils to study the *in vitro* corneal permeation of diclofenac from oil drops [7]. The thermodynamic behavior including the solubility of a drug in a vehicle, plays an important role in drug design as well as in the design and optimization of the production process. For a successful design of dosage form, a good vehicle has to be chosen. However, no such information is available on the thermodynamic behavior of diclofenac sodium solubility in various oils. In the present communication, the thermodynamic study of diclofenac sodium solubilization in various vegetable oils like olive oil, castor oil, arachis oil, sunflower oil, soybean oil and a mineral oil, liquid paraffin was investigated.

Experimental

Diclofenac sodium was gift sample from Techno Remedies, Kolkata, India. Liquid paraffin (Nice Chemicals Pvt Ltd, India), arachis oil (B D & Co, India), olive oil (RP Oomerbhoy Pvt Ltd, India), castor oil (BD Pharmaceutical Works, India), sunflower oil (Amrit Banaspati Co. Ltd, India) and soybean oil (Adani Wilmer Ltd, India) were purchased commercially. All other chemicals and reagents used were of analytical grade.

Excess amount of diclofenac sodium was added to the test oils. The mixture was then allowed to stand at various temperatures like 300 K, 305 K, 310 K and 315 K for 24 hours under agitation and filtered through membrane filter with a pore size 0.45 μ. The concentration of diclofenac sodium was measured by UV-Visible Spectrophotometer (Shimadzu UV-Visible Spectrophotometer, UV-1601) using methanol as solvent.

The partition studies were conducted by shake flask method. Accurately weighed amount about, 1000 mg of diclofenac sodium was added to each 20 mL of oil and water mixture (1:1 ratio). The solution was kept for 24 hours shaking at various temperatures like 300 K, 305 K, 310 K and 315 K in a reciprocating shaker bath. Two phases were separated and filtered through 0.45 μ membrane filter. The concentration of the drug in the aqueous phase was analyzed spectrophotometrically; concentration of the drug in vehicle was calculated from the difference between the initial amount and amount in aqueous phase. The partition coefficient (*K*) was calculated using following equation:

$$K = \frac{[drug]_{oil}}{[drug]_{aqueous}} \qquad (1)$$

Result and discussion

The solubility of diclofenac sodium in various oils (olive oil, castor oil, arachis oil, sunflower oil, soyabean oil and liquid paraffin) and partition coefficients of various oil/aqueous phases were determined at various temperatures like 300 K, 305 K, 310 K and 315 K (Tables 1 & 2). Diclofenac sodium was found to have the increasing solubility and partition coefficient with the increasing of temperature in various oils used in this investigation. The maximum solubility and partition coefficient were found in case of castor oil and these were minimal in case of liquid paraffin at various temperatures.

Table 1. The solubility of diclofenac sodium in different oils at various temperatures

Oils	Solubility of diclofenac sodium at various temperatures (% w/v)			
	300 K	305 K	310 K	315 K
Olive oil	0.292 ± 0.040	0.300 ± 0.057	0.308 ± 0.042	0.331 ± 0.037
Castor oil	1.608 ± 0.075	1.632 ± 0.082	1.650 ± 0.087	1.712 ± 0.093
Arachis oil	0.709 ± 0.043	0.723 ± 0.062	0.733 ± 0.068	0.760 ± 0.087
Sunflower oil	0.520 ± 0.042	0.538 ± 0.060	0.560 ± 0.062	0.608 ± 0.053
Soybean oil	0.309 ± 0.040	0.312 ± 0.042	0.330 ± 0.060	0.363 ± 0.052
Liquid paraffin	0.207 ± 0.019	0.220 ± 0.026	0.228 ± 0.023	0.252 ± 0.025

Table 2. The partition coefficient of diclofenac sodium in different oils at various temperatures

Oils	Partition coefficient of diclofenac sodium at various temperatures			
	300 K	305 K	310 K	315 K
Olive oil	1.571 ± 0.109	1.628 ± 0.123	1.723 ± 0.206	1.980 ± 0.313
Castor oil	11.844 ± 0.936	12.003 ± 1.062	12.246 ± 1.002	12.563 ± 1.070
Arachis oil	6.438 ± 0.345	6.528 ± 0.386	6.660 ± 0.442	6.893 ± 0.486
Sunflower oil	3.178 ± 0.239	3.257 ± 0.258	3.535 ± 0.307	3.863 ± 0.429
Soybean oil	3.436 ± 0.304	3.608 ± 0.327	3.788 ± 0.388	3.979 ± 0.412
Liquid paraffin	1.129 ± 0.098	1.222 ± 0.106	1.328 ± 0.221	1.412 ± 0.106

Table 3. The calculated values of standard free energy change $\Delta G°$ of diclofenac sodium solubolization in various oils at various temperatures

Oils	Standard free energy change (ΔG°) of diclofenac sodium solubilization in various oils at various temperatures (cal.mole^{-1})			
	300 K	305 K	310 K	315 K
Olive oil	- 269.437	- 295.139	- 335.088	- 427.493
Castor oil	- 1480.116	- 1505.997	- 1543.005	-1584.166
Arachis oil	- 1109.938	- 1136.922	- 1163.567	-1208.623
Sunflower oil	- 689.092	- 715.727	- 777.070	- 845.589
Soybean oil	- 735.587	- 777.543	- 820.472	- 864.375
Liquid paraffin	- 72.128	- 121.207	- 174.935	- 232.837

Solubilization may be considered as a partitioning of the drug between the oil phase and aqueous phase. Thus, a mathematical relationship exists between the free energy change and the partition coefficient. The standard free energy change of solubilization, ΔG°, can be computed from partition coefficient, *K* of oil/aqueous medium:

$$\Delta G^0 = -RT \ln K \qquad (2)$$

where, R is the gas constant and T is the temperature in Kelvin [8]. The calculated values of standard free energy change (ΔG°) of diclofenac sodium solubilization in various oils at various temperatures are presented in Table 3.

The standard free enthalpy of solubilization can be computed from van't Hoff equation:

$$\ln K = \Delta H^0 / RT + \Delta S^0 / R \qquad (3)$$

where, ΔH° and ΔS° are standard free enthalpy and entropy of solubilization, respectively [8].

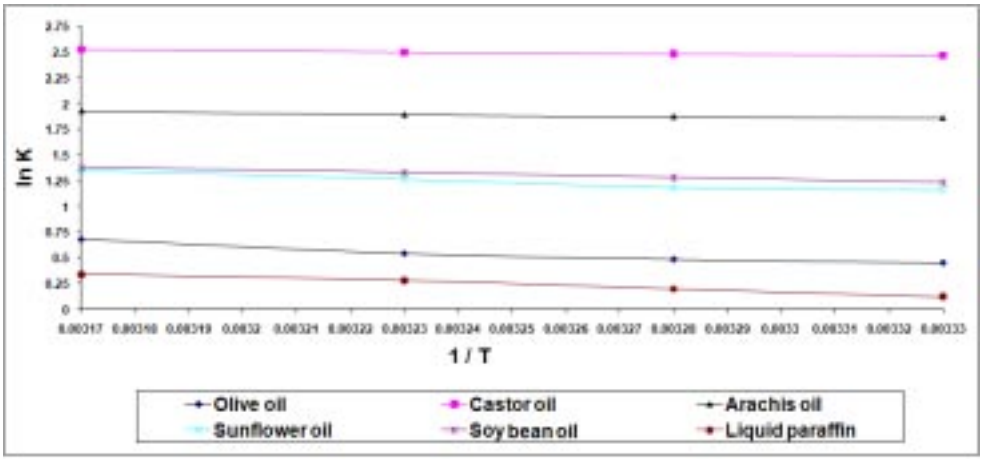

Fig. 2. The plot of ln K against corresponding 1/T values for various oils

From Eq. (3), a regression of ln *P* against 1/T gives the value of $\Delta H°$ from the slope. The plot of ln *P* against corresponding 1/*T* values for various oils are presented in Fig. 2. Various equations for various oils were obtained from regression analysis (Table 4). The standard free enthalpy of diclofenac sodium solubilization ($\Delta H°$) at various temperatures were determined (Table 5) from slopes. The R^2 values for various regression lines were within the range of 0.9317 to 0.9979.

Table 4. Various equations obtained from regression analysis
(ln *K* against 1/*T* for various oils)

Oils	Various equations obtained from regression analysis	R^2
Olive oil	Y = - 1432.700 X + 5.201	0.9317
Castor oil	Y = - 373.180 X + 3.712	0.9886
Arachis oil	Y = - 431.440 X + 3.295	0.9737
Sunflower oil	Y = - 1265.200 X + 5.353	0.9642
Soybean oil	Y = - 922.560 X + 4.308	0.9979
Liquid paraffin	Y = - 1419.200 X + 4.853	0.9878

Table 5. The calculated values of standard free enthalpy ($\Delta H°$) of diclofenac sodium solubilization in various oils

Oils	Standard free enthalpy (ΔH°) of diclofenac sodium solubilization in various oils (cal. mole^{-1})
Olive oil	2846.775
Castor oil	741.509
Arachis oil	857.271
Sunflower oil	2513.952
Soybean oil	1833.127
Liquid paraffin	2819.950

The sign magnitude of the thermodynamic functions $\Delta G°$ and $\Delta H°$ may be related to the location of the solubilized drug in the oil phase. The determined values of $\Delta G°$ were negative, while $\Delta H°$ values were positive. The positive values of $\Delta H°$ for various oils, included in this investigation indicates that the partition coefficient was increased with temperature rise. The increasing values of partition coefficient in the Table 2 show this to be a fact. So, the diclofenac solubilization in all these oils, used in this investigation was endothermic.

$\Delta S°$ values of diclofenac sodium solubilization for various oils at various temperatures can be calculated from Gibbs-Helmholtz equation [8]:

$$\Delta G^0 = \Delta H^0 - T\Delta S^0 \qquad (4)$$

Table 6. The calculated values of standard free entropy $\Delta S°$ of diclofenac sodium solubilization in various oils at various temperatures

Oils	Standard free entropy (ΔS°) of diclofenac sodium solubilization in various oils at various temperatures (cal. mole^{-1} deg^{-1})				
	300 K	305 K	310 K	315 K	From regression line
Olive oil	10.387	10.301	10.264	10.395	10.335
Castor oil	7.405	7.369	7.369	7.383	7.374
Arachis oil	6.554	6.538	6.519	6.552	6.546
Sunflower oil	10.336	10.589	10.619	10.665	10.636
Soybean oil	8.562	8.560	8.560	8.563	8.560
Liquid paraffin	9.640	9.643	9.661	9.691	9.645

Also from the intercept of the regression lines (ln K vs $1/T$), $\Delta S°$ values of diclofenac sodium solubilization for various oils can be calculated. These all values of $\Delta S°$ are presented in Table 6.

The $\Delta S°$ values of diclofenac sodium solubilization for various oils were positive at various temperatures. These $\Delta S°$ values, obtained from the regression line (ln K vs $1/T$) were very similar to the $\Delta S°$ values obtained by the use of Eq. (4). This indicates that these thermodynamic models of diclofenac sodium solubilization in various oils were well fitted.

Conclusion

The thermodynamic study of diclofenac sodium solubilization in various vegetable oils like olive oil, castor oil, arachis oil, sunflower oil, soybean oil and a mineral oil, liquid paraffin was investigated. Diclofenac sodium was found to have the increasing solubility and partition coefficient with the increasing of temperature in various oils used in this investigation. The maximum solubility and partition coefficient were found in case of castor oil, while these were minimum in case of liquid paraffin at various temperatures. The determined values of $\Delta G°$ were negative, while $\Delta H°$ and $\Delta S°$ values were positive. From this investigation, this is revealed that the diclofenac sodium solubilization in various oils was endothermic. The valuable data obtained from this investigation can be utilized for designing and development of various oil based formulations of diclofenac sodium.

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