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# SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE CELECOXIB FOR PARENTERAL FORMULATIONS

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## ABSTRACT

Celecoxib, a diaryl substituted pyrazole, is practically insoluble in water which precludes its use in parenteral and liquid dosage forms. This study explores the solubility enhancement of celecoxib using hydrotropy and cosolvency solubilization approaches. The equilibrium solubility studies were performed using hydrotropes piperazine, sodium citrate, and urea and cosolvents PEG 200, PEG 400, PEG 600, DMA, Ethanol and Propylene glycol at various temperatures. Parenteral formulations using hydrotrope and cosolvents were developed and studied for accelerated stability study. The solubility of celecoxib was found to increase upto 45 times in 3M piperazine solution and upto 10232 times in PEG 600 at 25±2$^0$C. The results of solubilization study showed that the increase in solubility of celecoxib is smaller in piperazine and urea when used alone as compared to the increase in solubility which was found when these hydrotropes were used in combination with cosolvents PEG 600, PEG 400, DMA and Eth. Stability studies indicated that all the formulations stored were found to be stable for drug content, pH and change in physical appearance i.e. color, precipitation.

**INTRODUCTION:** Non- steroidal anti- inflammatory drugs (NSAIDs) are among the most frequently prescribed medications. The mechanism of action of NSAIDs has been attributed to their ability to inhibit the cyclooxygenase enzyme (Cox).

Out of the 2 isoforms of cyclooxygenase, Cox-1 is responsible for mediating the production of prostaglandins while Cox-2 is primarily associated with inflammation, pain, and fever [1-3]. The traditional NSAIDs are nonselective Cox inhibitors. Concerns about the overuse of NSAID stems from the potential toxicity of these agents, particularly with respect to GI complications.

Attempts to reduce the GI effects of these drugs including enteric coating, non-acidic formulations and the use of prodrugs have not had a significant impact.

Many studies have shown that the newer NSAIDs are significantly better than traditional NSAIDs in terms of reduced micro-bleeding and endoscopically demonstrable GI lesions and ulcers. The Cox-2 selective NSAIDs are, therefore, ideal anti-inflammatory drugs with minimum drug-related side effects, since they spare Cox-1 activity. The very poor aqueous solubility and wettability of Cox-2 inhibitors, however, give rise to difficulties in the design of pharmaceutical formulations and lead to variable oral bioavailability.

Celecoxib is chemically designated as 4-[5-(4-methylphenyl)-3-7(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl substituted pyrazole [4, 5].

The mechanism of action of celecoxib is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of Cyclooxygenase-2 (Cox-2). It is supplied only in tablets and capsules for oral administration. Celecoxib is practically insoluble in water which precludes its use in parenteral and oral solutions dosage forms [6]. Formulation of lipophilic drugs is frequently hampered by their poor aqueous solubility which again can limit their therapeutic applications.

Poorly soluble drugs usually possess hydrophilic-hydrophobic balance favorable to their permeation through GI membranes so that dissolution becomes the decisive factor in the bioavailability of drugs. Solubilization of insoluble drugs has been extensively studied to overcome difficulties which may be encountered during pharmaceutical formulation.

Attempts have been reported in the literature for improving the aqueous solubility of various drugs for parenteral formulation, through various solubilization approaches. The major approaches for increasing the solubility of drugs are alteration of properties of solute or solvent.

According to Yalkowsky [7], buffers, hydrotropes, surfactants, cosolvents and complexing agents are the most commonly used excipients to improve the solubility of a non polar drug in aqueous media. These can be used either alone or in combination. Recently, the synergism of two or three techniques has drawn particular interest [8-11].

The present work explores the utility of hydrotropes and cosolvents as solubilizing agents for celecoxib. To enhance the solubility with an aim to formulate the aqueous injections, which will be definitely more effective, economical, safe and with the least side effects as compared to their oral dosage forms i.e. tablet, capsules.

Parenteral formulations may be useful in patients with rheumatic disorders, peptic ulcers etc. where the oral administration of these drugs is contraindicated.

## MATERIALS AND METHODS

**Materials:** The gift sample of celecoxib was provided by M/S Dr. Reddy's Labs, Hyderabad, India. Piperazine was procured from Fluka Chemicals, Germany; sodium citrate, sodium hydroxide, urea were from Loba Chemie, Mumbai, India. All other chemicals used were of analytical grade and used as is.

**Estimation of Celecoxib:** In the present study, UV spectrophotometric method [12] was used for the estimation of celecoxib. The calibration curve of celecoxib was prepared using 0.1N sodium hydroxide at 253 nm using double-beam spectrophotometer (UV-1601, Shimadzu, Japan).

### Solubility study

- **pH Solubilization:** The phosphate buffer [13] of pH 2.5 to 10 and citrophosphate buffers of pH 5.0 to 8.0 prepared in freshly boiled and cooled distilled water were used for solubilization study.
- **Hydrotropic Solubilization:** The solutions of hydrotropes of various molar concentrations were prepared i.e. piperzine (0.5-3.0 M), sodium citrate (0.2-1.2 M) and urea (0.8-4.8 M) by dissolving their required quantities in water for solubilization study.
- **Cosolvent Solubilization:** The cosolvents such as Polyethylene glycol (PEG) 200, PEG 400, PEG 600, Dimethyl acetamide (DMA), Ethanol (Eth) and Propylene glycol (PG) were selected in this study. The solubility of celecoxib was determined in different cosolvent: water blend of ratio i.e. 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1, respectively.
- **Solubilization Studies Using Combination of Cosolvents and Hydrotropes:** The combination of hydrotropes and cosolvent solubilization was also explored to improve the solubility of celecoxib [8-11]. The role of solvent in hydrotropic solubilization was observed by studying the effect of different hydrotropes like piperazine (3.0 M), urea (4.8 M) in combination with cosolvents PEG 600, PEG 400, PEG 200 and Eth as shown in **Table 4** [14-18]. Aqueous solutions of the above mentioned hydrotropes in different concentrations (10%-30% w/v) were prepared by dissolving their required quantities in

distilled water. The cosolvents were used in the 70-90% v/v concentration. The required amount of hydrotropic solution was added separately to each of the vials containing cosolvents to produce the effective combination of cosolvents and hydrotropic solution in the ratios 1:9, 3:7, 5:5, 7:3, 8:2 and 9:1.

- **Solubility Determination:** Solubilization studies were performed according to the method of Higuchi and Conners [19]. An excess quantity of celecoxib was added to screw capped 20 ml glass vials containing the different aqueous systems viz. distilled water, phosphate buffers of pH 2.5–10; hydrotropic solutions; cosolvent-water blends and combination of cosolvents with hydrotropes. These vials were shaken mechanically for 12 h at 25±2°C, 37±2°C and 45±2°C in a mechanical shaker (Elico Pvt. Ltd, Mumbai, India). These solutions were allowed to equilibrate for next 24 h and then centrifuged for 5 min at 2000 rpm. The supernatant of each vial was filtered through Whatman filter paper no. 1, filtrate diluted with suitable quantity of 0.1N NaOH and analyzed spectrophotometrically at 253 nm. The solubility was determined in triplicate.

**Formulation of Aqueous Injection:** On the basis of solubility data obtained, four formulations of aqueous injection of celecoxib were prepared using piperazine and urea as hydrotrope[20-26] and PEG 400 and PEG 600 as cosolvents. The quantity of different ingredients for the prepared aqueous injections was taken as given in the **Table 1**.

**TABLE 1: FORMULAE DESIGNED FOR AQUEOUS INJECTIONS OF CELECOXIB**

| Ingredients | Formulation code | | | |
|---|---|---|---|---|
| | CPEG6W | CPEG4W | CPEG6U | CPEG6P |
| Celecoxib | 0.83 g | 0.83 g | 0.83 g | 0.83 g |
| Urea | - | - | 6.0 g | - |
| Piperazine | - | - | - | 6.0 g |
| PEG 600 | 35 ml | - | 30 ml | 30 ml |
| PEG 400 | - | 35 ml | - | - |
| Sodium bisulfate | 50 mg | 50 mg | 50 mg | 50 mg |
| Water for injection (ml) q.s. | 50 | 50 | 50 | 50 |
| Final strength of formulation | 50 mg/3 ml | 50 mg/3 ml | 50 mg/3 ml | 50 mg/3 ml |

In all the formulations, 0.1% w/v sodium bisulfite was added as an antioxidant. Other additives like chelating agent and buffering agent were not included in these formulations as they might lead to change in the solubility behavior and upset the basic solubility enhancement ratio.

- **Selection, Washing and Sterilization of Packaging Materials and Preparation of Aseptic Area [13]:** Glass vials of 3 ml and 5 ml capacity were used for preparation and dispensing of final formulations. Glass vials were evaluated as per I.P. 1996. Test for alkalinity was carried out using powdered glass test. The vials were first washed several times with distilled water, dipped in 5% v/v nitric acid for a period of 10 h to neutralize surface alkalinity. The vials were then rinsed with distilled water and immersed in 0.5% Teepol® solution for a period of 2 h. The vials were then scrubbed with a soft brush and rinsed with distilled water. The vials were then soaked in 5% v/v nitric acid for 30 min to remove the excess soap and then rinsed with distilled water. Finally vials were rinsed under a laminar air flow bench with filtered double distilled water.

The vials were placed inverted in an enameled tray, covered with an aluminium foil and sterilized by dry heating in hot air oven at 160°C for 3 h. Rubber stoppers used for plugging the vials were first washed several times with distilled water and then boiled in distilled water for 20 min and finally dried in vacuum oven.

The walls and floor of aseptic room were thoroughly washed with water and then disinfected with 5% w/v phenol solution. The laminar airflow bench was cleaned with 70% v/v ethanol and the UV light was switched on for 30 min prior to filling of injections into vials.

- **Preparation of Aqueous Injection:** The weighed quantity of drug was taken in each of the glass vials and dissolved in the required amount of respective cosolvent. Then the weighed amount of hydrotropes were separately dissolved in measured quantity of water for injection and mixed with the above solution. In case of formulations without hydrotrope and only in cosolvents, the drug solution in cosolvent was mixed with the sufficient water for injection (WFI). In each of the vials 0.1% w/v sodium bisulfite was added. The pH of these preparations was recorded using digital pH meter. The solutions were filtered through 0.22 μ disposable membrane filter (Sartorius, Germany), under vacuum and transferred aseptically to the clean and sterile glass vials of 3 and 5 ml capacity stoppered with rubber stoppers. The solutions were analyzed spectrophotometrically at 253 nm for drug content after appropriate dilutions with 0.1N NaOH.

**Stability Study:** The protocol of the stability studies was in conformity with the recommendations given in WHO document pertaining to stability testing of products intended for global market [27] and ICH guidelines [28-29]. To assess the accelerated stability, the sealed vials of the formulations were stored in ICH certified stability chambers (Forma Scientific Ltd., Mumbai, India)at 40±2°C and 75%±5% relative humidity (RH) for six months. The samples were withdrawn periodically and evaluated for change in physical appearance (color, precipitation) and percent drug content, if any [31-32]. The change in pH of each formulation was recorded using digital pH meter after 1, 3 and 6 months. The observations are reported in **Table 6**.

## RESULTS AND DISCUSSION:

**pH Solubilization:** The results of solubility studies at different pH indicated that celecoxib was more soluble at alkaline pH than acidic pH. This may be due to the acidic nature of celecoxib by virtue of its sulphonamide group. The aqueous solubility of celecoxib was increased upto 49 times at pH 10.0 One of the major factors responsible for dissolution of an organic compound is its ability to dissociate into ionic species, which depends on the pH of the media[18].The percentage ionized and hence solubility may increase of celecoxib was more with an increase in pH value of the buffers used for solubilization.

**TABLE 2: pH DEPENDENT SOLUBILITY OF CELECOXIB IN PHOSPHATE BUFFERS OF pH 2.5 TO 10 AT DIFFERENT TEMPERATURES**

| Temp (°C) | Solubility* (mg/ml) of drugs in water and phosphate buffer of pH | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Water | 2.5 | 4.0 | 5.5 | 7.0 | 7.5 | 8.0 | 9.0 | 10.0 |
| 25±1 | 0.0069 | 0.0885 | 0.1059 | 0.1192 | 0.1412 | 0.1433 | 0.1589 | 0.2588 | 0.3413 |
| 37±1 | 0.0071 | 0.0891 | 0.1068 | 0.1192 | 0.1412 | 0.1465 | 0.1592 | 0.2595 | 0.3912 |
| 45±1 | 0.0072 | 0.0905 | 0.1125 | 0.1223 | 0.1503 | 0.1499 | 0.1622 | 0.2623 | 0.4011 |

*Average of three determinations

**Hydrotropic Solubilization:** The solubility of celecoxib was found to increase upto 45 times at 25±2°C in 3M piperazine solution. The elevation of the temperature from 25±1°C to 45±1°C was accompanied by a minor but detectable increase in the solubility of drug, which indicates that the solubilization process in endothermic.

The solubility enhancement power of different hydrotropes for celecoxib could be ranked in decreasing order- as piperazine>sodium citrate>urea as shown in Fig 2-4 and the solubility enhancement ratio as 45.0, 44.4 and 44.1, respectively (**Table 2**). The enhancement in solubility is not a linear function of hydrotrope concentration. The solubility of drugs increased slowly with increase in hydrotrope concentration.

To explain the mechanism of solubilization of celecoxib, in presence of structurally different hydrotropes, it is necessary to have the basic understanding of chemical structures of drugs and hydrotropes.

The structures of drugs and hydrotropes with different centers of different electro negativity (denoted by 'a' in the structure) where the intermolecular hydrogen bonding and electrostatic attraction may be possible, have been shown in **Fig. 1**.

**TABLE 3: SOLUBILITY ENHANCEMENT RATIO OF HYDROTROPES FOR CELECOXIB**

| Hydrotrope | Temp (°C) | Solubility factor* for celecoxib in different concentrations of hydrotrope (%w/v) | | | | | |
|---|---|---|---|---|---|---|---|
| | | 5 | 10 | 15 | 20 | 25 | 30 |
| Piperazine | 25±1 | 8.27 | 16.02 | 20.62 | 28.27 | 44.23 | 45.14 |
| | 37±1 | 8.41 | 17.15 | 21.40 | 28.72 | 44.31 | 45.41 |
| | 45±1 | 8.50 | 17.98 | 21.00 | 29.13 | 44.09 | 44.69 |
| Sodium citrate | 25±1 | 13.79 | 25.52 | 26.50 | 30.76 | 37.42 | 44.86 |
| | 37±1 | 13.72 | 25.81 | 26.94 | 31.21 | 37.55 | 45.08 |
| | 45±1 | 13.73 | 25.87 | 26.56 | 30.68 | 37.36 | 44.55 |
| Urea | 25±1 | 8.86 | 16.91 | 18.39 | 24.20 | 27.02 | 44.07 |
| | 37±1 | 8.80 | 17.52 | 18.78 | 24.59 | 27.71 | 44.10 |
| | 45±1 | 8.65 | 17.88 | 19.41 | 24.75 | 27.58 | 43.83 |

*Solubility factor = solubility in hydrotropic solution (mg/ml)/solubility in water (mg/ml)

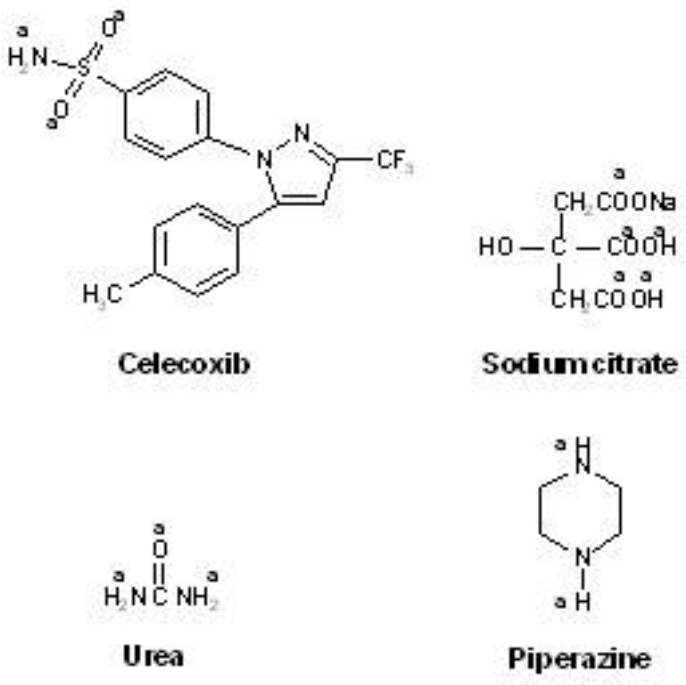


**FIGURE 1: STRUCTURES OF DRUG AND HYDROTROPES**

The piperazine has solubilized celecoxib to the maximum level possibly due to the semipolarity of the molecule and strong intermolecular hydrogen bonding between hydrogen of –NH group of piperazine. In case of sodium citrate simply electronegative carboxylate ion is attracted towards the hydrogen of sulphonamide group of celecoxib and sulphonyl group of celecoxib to the hydroxyl group of sodium citrate.

This includes formation of hydrogen bond and electrostatic attractive forces therefore the solubilization is more than in urea. The interaction of urea with celecoxib can be explained on the basis that the enhancement in solubility of drug may be attributed to the intermolecular hydrogen bonding between oxygen of C=O group of urea and hydrogen of $–NH_2$ group of celecoxib and electrostatic attraction between electron rich nitrogen (because of lone pair of electrons) of urea and electron deficient oxygen of sulphonamide group of celecoxib.

The phase solubility diagrams (**Fig. 2-4**) indicated that initially the solubility was increased linearly with the increase in hydrotrope concentration, and then a nonlinear increase in solubility was found on increasing the hydrotrope concentration. The positive deviation in the phase solubility diagrams, which is characteristic of hydrotropic solubilization, could be the result of aggregation of hydrotrope molecules at higher concentration.

The tendency of aggregation lies in the fact that in aqueous media essentially all molecules containing the exposed organic groups are not protected by polar groups on more than one side and show some degree of hydrophobicity.

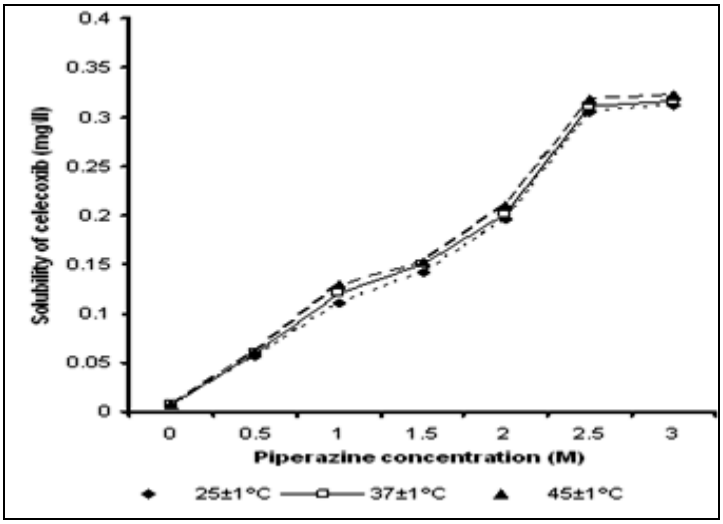


**FIGURE 2: PHASE SOLUBILITY CURVES OF CELECOXIB IN PIPERAZINE**

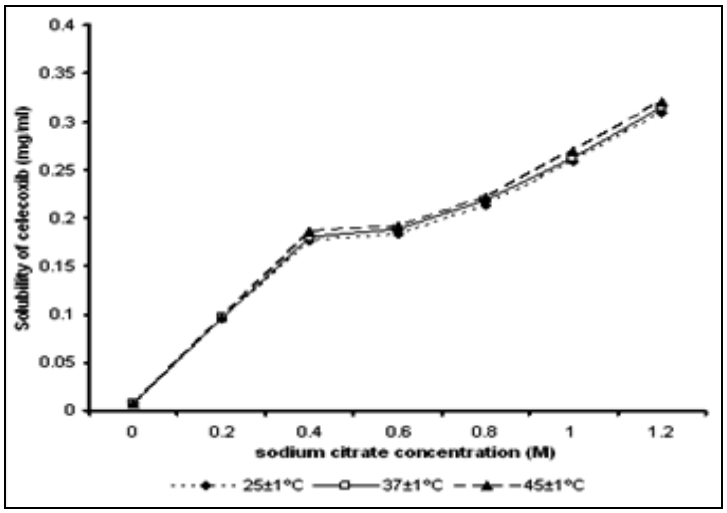


**FIGURE 3: PHASE SOLUBILITY CURVES OF CELECOXIB IN SODIUM CITRATE**

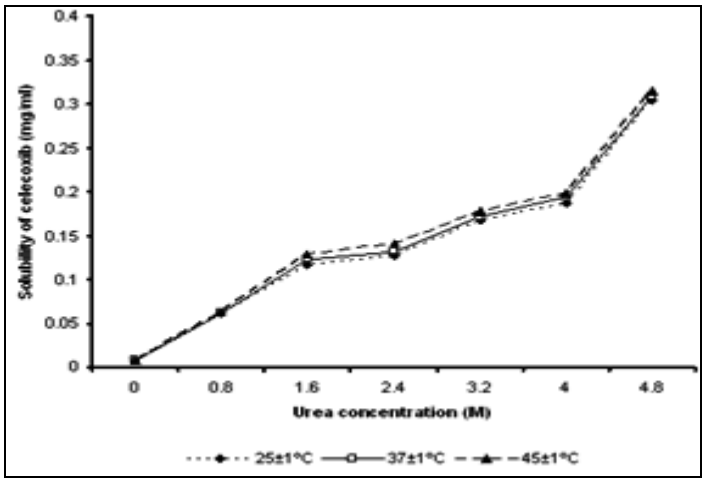


**FIGURE 4: PHASE SOLUBILITY CURVES OF CELECOXIB IN UREA**

Water is a solvent in which the molecules of water join to form cluster together. For solubilization the ionized hydrotropes break this association and use the ion dipoles of water for solvation. The increasing hydrotrope concentrations result in unassociated form to make cluster around the hydrophobic sites by inter and/or intramolecular association such as hydrogen bonding and non-bonding interactions at the various centers of drug molecule.

Therefore, the planar structure of hydrotrope molecules allows a stacking type of association in which one hydrotrope molecule can lie flat on the top of another one. Drug planar molecules may be solubilized by inclusion within the hydrotrope aggregates and interaction of drug with these aggregates may have significant contribution to the increase in solubility by hydrotropes.

The increase in temperature of hydrotropic salt solution was accompanied by a detectable increase in drug solubility. The increased solubility by temperature could probably due to the expansion of hydrotrope aggregates leading to accommodation of a much higher number of drug molecules. Thus a higher concentration of drug gets entrapped in the stacks of the hydrotrope molecules to bring about greater solubilization.

Moreover, the thermodynamics of drug solubility in the hydrotropic solution were calculated and the results are shown in **Table 4**. The free energy change (ΔG) associated with the solubility process indicating the type of reaction occurring between the drug and hydrotropes were calculated by using eq:

$$\Delta G = -2.303RT \log K \quad \text{.....(I)}$$

Where ΔG is free energy change during solubilization process; K is ratio of the molar solubilities of the drug in water and hydrotropic solutions and R gas constant (8.314 $JmoleK^{-1}$) and T is absolute temperature respectively. The results showed that in case of celecoxib the negative values of ΔG can be arranged in the following order: sodium citrate>urea> piperazine. These finding are in accordance with the order of solubilizing power of different hydrotropes used for celecoxib. The free energy values showed that the increase in hydrotrope concentration provided a more thermodynamically suitable environment for the solubility of drug in all the cases (ΔG decreases).

The negative free energy of solubilization process is indicative of spontaneity of the process; more negative the free energy of the complexation, the more will be the solubility. This possibility is determined by three factors, the change in heat ΔH (bonding strength), temperature (T) and entropy change (ΔS) (disordering or bond breaking). At a constant temperature, the free energy will be determined by the change in the heat content and the entropy change of the system.

$$\Delta S = \frac{\Delta H - \Delta G}{T} \quad \text{.....(II)}$$

Regression analysis of log K vs. 1/T (a Van't Hoff plot) yield ΔH (slope value). The enthalpy change ΔH is related to ΔS and ΔH.

**TABLE 4: THERMODYNAMIC PARAMETERS FOR DRUG-HYDROTROPE INTERACTION OF CELECOXIB IN AQUEOUS SOLUTION**

| Hydrotrope | Temp (°C) | ΔG ($JM^{-1}$) | ΔH ($JM^{-1}$) | ΔS ($JM^{-1}$) |
|---|---|---|---|---|
| Piperazine | 25±1 | -6511.39 | 0.5456 | 21.85 |
| | 37±1 | -6947.95 | | 22.41 |
| | 45±1 | -7296.65 | | 22.93 |
| | 25±1 | -7058.35 | 7.4463 | 23.71 |
| | 37±1 | -7389.94 | | 23.86 |
| | 45±1 | -7624.41 | | 23.99 |
| Sod. Citrate | 25±1 | -10452.01 | 0.7467 | 35.07 |
| | 37±1 | -10887.27 | | 35.12 |
| | 45±1 | -11213.24 | | 35.26 |
| | 25±1 | -11173.60 | 1.6890 | 37.49 |
| | 37±1 | -11613.56 | | 37.46 |
| | 45±1 | -11921.49 | | 37.49 |
| Urea | 25±1 | -5682.60 | 0.306 | 19.07 |
| | 37±1 | -5919.48 | | 19.09 |
| | 45±1 | -6082.70 | | 19.12 |
| | 25±1 | -9311.14 | 1.1359 | 31.25 |
| | 37±1 | -9692.23 | | 31.26 |
| | 45±1 | -9972.69 | | 31.36 |

The breaking up of water clusters surrounding the non polar portion requires heat (ΔH). The variation in the enthalpy of the systems may be due to the formation of intermolecular interaction between the hydrotropes and drug molecules. Moreover the solubilization process is endothermic one as ΔH is positive in this case. Therefore an increase in temperature from 25±1°C to 45±1°C caused an increase in solubility of celecoxib. The hydrotropic solubilization was found primarily to be entropy driven process at high hydrotrope concentration that was accompanied by small free energy change, and large entropy change.

The positive values of entropy change ΔS as shown in Table 4 suggest the involvement of weak hydrophobic interaction in solubilization process. Stripping the water molecules from the hydrotrope, results in randomization of water molecules and drug molecules in the aqueous medium during the solubilization process. These cause a disordering and increase in the entropy associated with the system. The more positive the entropy change, the greater will be the randomness or disorder degree of the system and the environment is thermodynamically more favorable for solubilization ΔS [32, 25].

On the basis of these data obtained, the overall solubility enhancement can be differentiated in two categories: solubility at lower hydrotrope concentration and solubility at higher hydrotrope concentration. The solubility enhancement of drug in hydrotropic solution may be due to weak ionic interaction and hydrogen bonding. These interactions are small in magnitude and contributed solubility enhancement at lower hydrotrope concentration. The solubility at higher hydrotrope concentrations may be the result of hydrophobic effect and charge transfer phenomenon.

Further, the probability of some kind of molecular interaction taking place between drug and hydrotrope was monitored by UV spectral studies. Celecoxib in water, 0.1 N NaOH, methanol gives peaks at 217 and 253 nm. In case of celecoxib-piperazine-water system there is slight bathochromic shift of 2-3 nm for celecoxib, which suggest some sort of complexation but the degree of complexation is very low. Similarly in case of celecoxib-sodium citrate-water system, there is negligible shift in $\lambda_{max}$ values of celecoxib.

In case of celecoxib-urea-water system, the values of $\lambda_{max}$ remain almost same. It can be concluded that the minor shift in $\lambda_{max}$ may be because of electronic changes in the structure of drug molecules. There is very weak possibility to assume any complex formation, as the complex formation can be evidenced by the formation of new chromophore, which is indicated by the appearance of a new peak or merging of two peaks to the hydrotrope self-association significantly plays a role in solubilization mechanism.

In addition to this, high concentration of hydrotrope in conjunction with self-association changes the solvent behavior of water.

**Cosolvent solubilization:** The solubility of celecoxib was increased upto 10232 times in PEG 600 at 25±2°C (**Fig. 5**). The cosolvent solubilizing power of different cosolvents i.e. ratio of solubility of drug in cosolvent-water blends to solubility of drug in water may be ranked in the order: PEG 600>PEG 400>PEG 200> Eth>DMA>PG and cosolvent efficiency ratio as- 10232, 9171, 6139, 5548, 2592 and 806, respectively (**Table 5**).

The solubility figures (**Fig 5-10**) showed the exponential increase in the solubility of drugs with increasing concentration of cosolvents [14-18].

**TABLE 5: SOLUBILITY ENHANCEMENT RATIO OF COSOLVENT-WATER SYSTEM FOR CELECOXIB**

| Cosolvent used | Temp (˚C) | Solubility enhancement ratio* for celecoxib of cosolvent-water blends of different ratios | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 |
| PG | 25±1 | 3.50 | 4.52 | 5.34 | 22.57 | 33.79 | 103.14 | 251.65 | 439.10 | 806.91 |
| | 37±1 | 4.27 | 5.50 | 6.07 | 23.63 | 34.27 | 103.04 | 106.74 | 434.27 | 796.81 |
| | 45±1 | 4.51 | 6.76 | 7.25 | 24.36 | 34.58 | 101.74 | 105.35 | 423.88 | 775.13 |
| DMA | 25±1 | 5.69 | 10.31 | 14.82 | 28.86 | 37.43 | 54.86 | 224.36 | 1479.88 | 2592.31 |
| | 37±1 | 6.50 | 11.45 | 16.97 | 29.21 | 38.10 | 55.50 | 221.42 | 1460.07 | 2469.31 |
| | 45±1 | 7.11 | 12.48 | 17.61 | 31.58 | 38.75 | 55.12 | 218.05 | 1422.05 | 2404.44 |
| Ethanol | 25±1 | 3.89 | 5.18 | 7.08 | 50.72 | 114.44 | 1738.82 | 1758.53 | 3989.13 | 5548.63 |
| | 37±1 | 4.26 | 5.54 | 7.17 | 50.86 | 114.18 | 1732.31 | 1855.05 | 4040.13 | 5569.98 |
| | 45±1 | 4.24 | 5.71 | 7.58 | 52.08 | 112.64 | 1740.76 | 1806.31 | 3890.59 | 5419.79 |
| PEG 200 | 25±1 | 8.39 | 14.27 | 20.55 | 111.04 | 194.07 | 606.39 | 1026.30 | 4138.69 | 6139.71 |
| | 37±1 | 8.74 | 16.07 | 21.77 | 116.21 | 202.87 | 600.00 | 1014.64 | 4080.47 | 6055.36 |
| | 45±1 | 7.44 | 17.84 | 22.61 | 114.64 | 198.76 | 584.72 | 988.74 | 3969.79 | 5866.94 |
| PEG 400 | 25±1 | 18.49 | 35.94 | 59.53 | 138.55 | 197.07 | 817.42 | 3911.21 | 6598.11 | 9171.66 |
| | 37±1 | 18.55 | 36.23 | 58.68 | 137.55 | 194.60 | 807.66 | 3874.57 | 6568.14 | 9106.86 |
| | 45±1 | 18.68 | 40.26 | 59.54 | 135.70 | 190.42 | 786.55 | 3849.10 | 6400.69 | 8863.08 |
| PEG 600 | 25±1 | 19.23 | 43.21 | 64.86 | 168.08 | 200.10 | 943.55 | 8292.52 | 9008.11 | 10232.85 |
| | 37±1 | 19.51 | 42.10 | 64.46 | 166.06 | 200.00 | 931.26 | 8270.94 | 8964.88 | 10142.71 |
| | 45±1 | 19.62 | 43.95 | 63.92 | 162.79 | 196.59 | 905.97 | 8056.33 | 8763.94 | 9875.77 |

*Average of three determinations

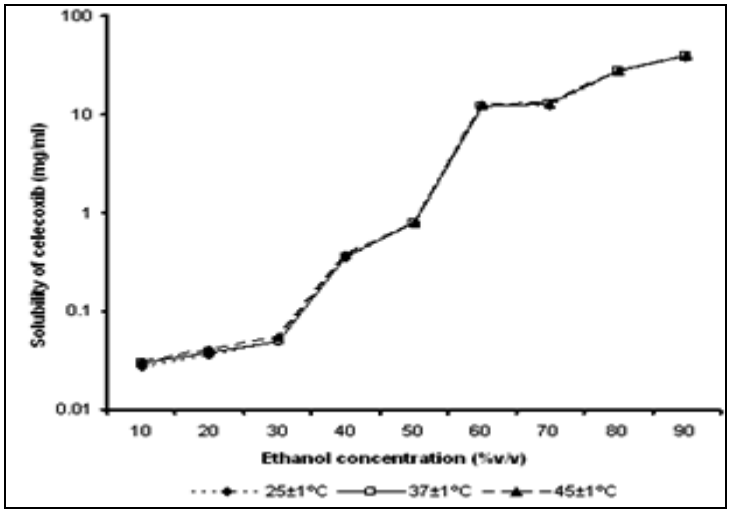


**FIGURE 5: EFFECT OF ETHANOL ON SOLUBILITY OF CELECOXIB AT DIFFERENT TEMPERATURES**

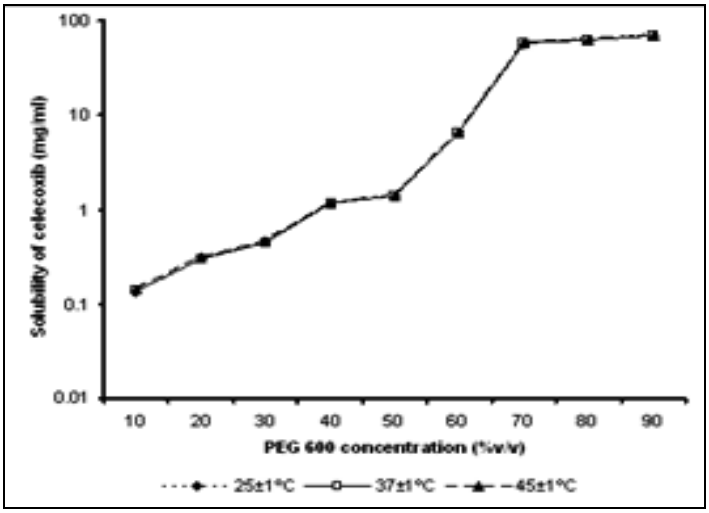


**FIGURE 6: EFFECT OF PEG 600 ON SOLUBILITY OF CELECOXIB AT DIFFERENT TEMPERATURES**

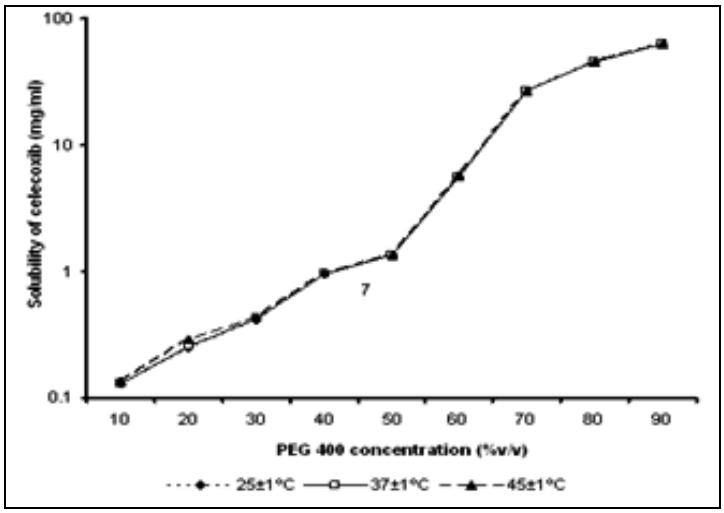


**FIGURE 7: EFFECT OF PEG 400 ON SOLUBILITY OF CELECOXIB AT DIFFERENT TEMPERATURES**

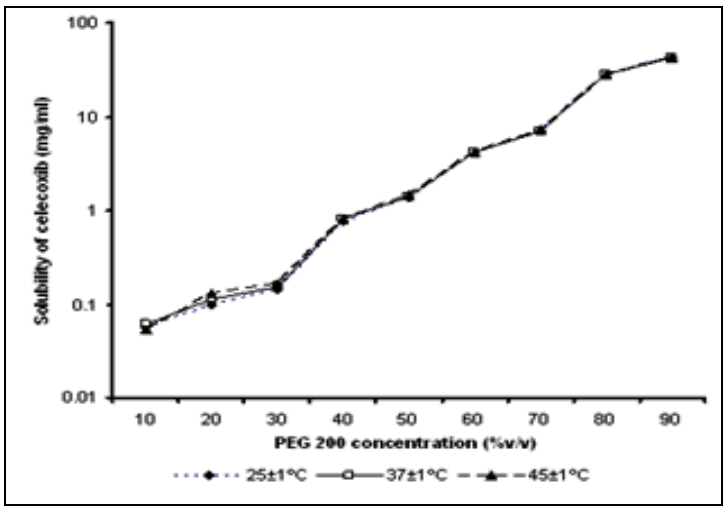


**FIGURE 8: EFFECT OF PEG 200 ON SOLUBILITY OF CELECOXIB AT DIFFERENT TEMPERATURES**

Most cosolvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen bonding groups ensure water miscibility while their hydrophobic hydrocarbon regions interfere with water's hydrogen bonding network, reducing the overall intermolecular attraction of water.

By disrupting water's self-association, cosolvents reduce water's ability to squeeze out non-polar, hydrophobic compounds, thus increasing solubility. A different perspective is that by simply making the polar water environment more non-polar like the solute, cosolvents facilitate solubilization. A simple and accurate one suitable for preformulation that requires little or no experimental data is the well-known log-linear model proposed by Yalkowsky and coworkers [7, 33].

The log linear model [34] is commonly used to quantify the total solubility of drug in cosolvent system. The correlation between cosolvency and properties of drug, cosolvent and water can be established by applying log-linear model to the solubility data of drugs.

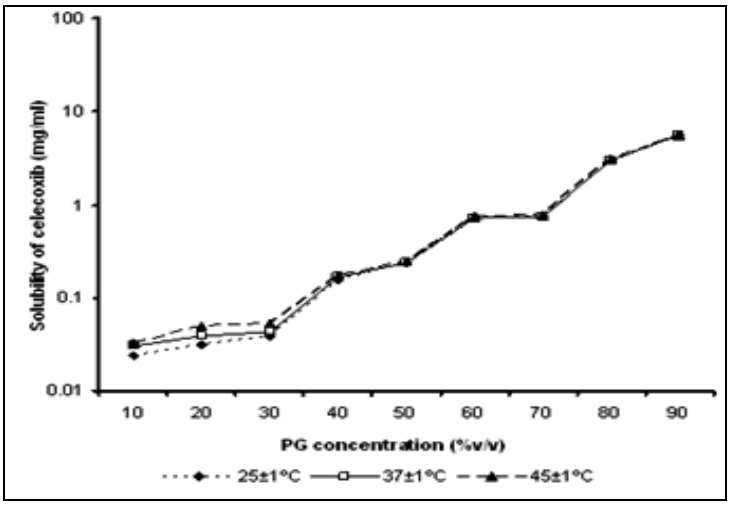


**FIGURE 9: EFFECT OF PROPYLENE GLYCOL ON SOLUBILITY OF CELECOXIB AT DIFFERENT TEMPERATURES**

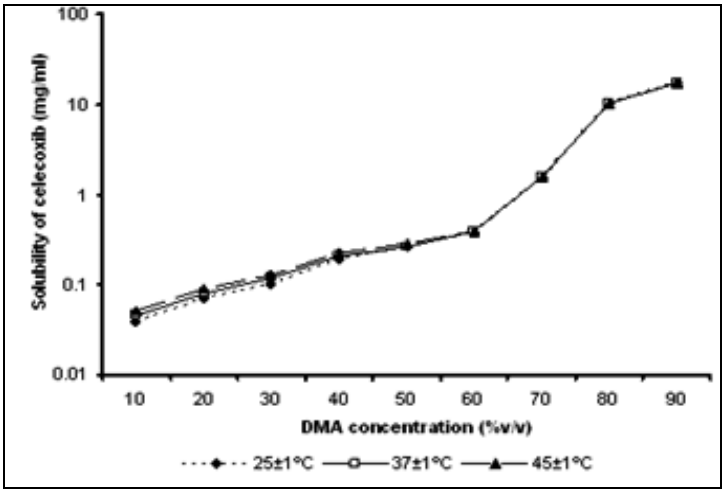


**FIGURE 10: EFFECT OF DMA ON SOLUBILITY OF CELECOXIB AT DIFFERENT TEMPERATURES**

The semi-logarithmic relationship between total drug solubility ($S_m$) in a mixture and cosolvent fraction f can be described by the equation:

$$\log S_m = \log S_w + \sigma f \quad \text{..... (III)}$$

Where $S_m$ is the solubility of drug in water-cosolvent mixture, volume fraction of the cosolvent is f; $S_w$ is the solubility of drug in water and σ is cosolvent solubilization power. Values of solubility can be either in moles or mg/ml.

The solubility diagrams of drugs in water-cosolvent mixture as shown in Fig. 5-10 showed slight deviation from the ideal line which indicates non-ideality of solvent mixture or less interaction between hydrate cosolvent molecules. It was apparent that solubility of celecoxib in water-cosolvent mixture confirms the semi-logarithmic relationship between total drug solubility ($S_m$) in cosolvent-water mixture and cosolvent concentration. The solubilizing power σ of cosolvent for each drug was determined from slope of the curves plotted log $S_m$ vs. cosolvent concentration (% v/v fraction in water). The value of σ depends inversely on polarities of both the solute and the cosolvent. For a single nonpolar solute, the value of σ depends only on cosolvent polarity.

The values of solubilizing power of different cosolvents 'σ' were found in the order PEG 600 (9.78)>PEG 400 (7.44)>PEG 200 (4.53)> Eth (4.52)>DMA (1.71)>PG (0.55). The slope value suggests that PEG 600 has high solubilization power for celecoxib. The semi-logarithmic relationship between total solubility of drug and cosolvent concentration in case of each drug suggest that the solubility of drug in mixed solvent to water (log $S_m$) is proportional to volume fraction of solvent (f). As the cosolvent concentration increases the solubility of drugs also increases.

The increase in solubility of celecoxib in presence of PEGs may be attributed to the sulphonamido hydrogen of celecoxib, that form hydrogen bonds with the numerous oxygens present in PEGs. As the molecular weight increases the number of oxygen also increases hence resulted in more enhancements in solubility in case of PEG 600, which is followed by PEG 400 and then PEG 200. The less increase in solubility of celecoxib in presence of DMA as compared to PEGs may be attributed to the fact that the oxygen of O=C-N group of DMA has low electron density as compared to PEG and the further solubilization of drug was not possible as hydrogen at amide group of DMA is knocked off by methyl group.

Thus, the hydrogen bond formation would solubilize celecoxib but per carbon oxygen present in PEGs is one while in case of DMA the ratio of carbon to oxygen is 3:1, therefore better solubilization would be possible in case of PEGs.

**Combined effect of cosolvent and hydrotropic solubilization:** The study showed that the increase in solubility of celecoxib is smaller in piperazine and urea when used alone as compared to the increase in solubility which was found when these hydrotropes were used in combination with cosolvents PEG 600, PEG 400, DMA and Eth (**Fig. 11-12**).

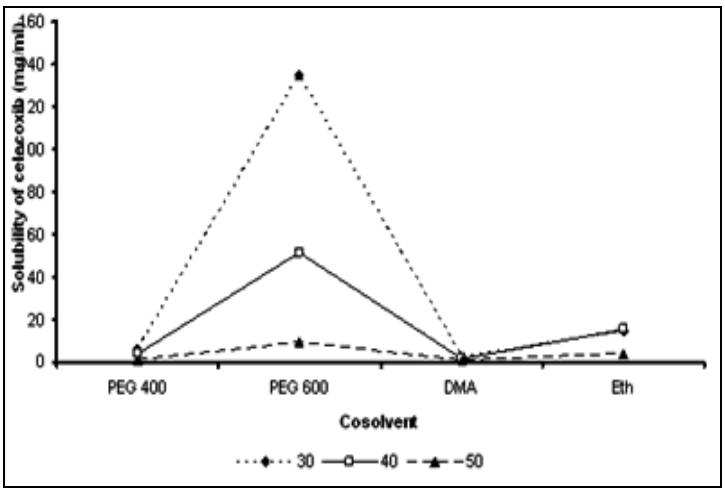


**FIGURE 11: PHASE SOLUBILITY DIAGRAM OF CELECOXIB IN DIFFERENT COSOLVENTS IN PIPERAZINE**

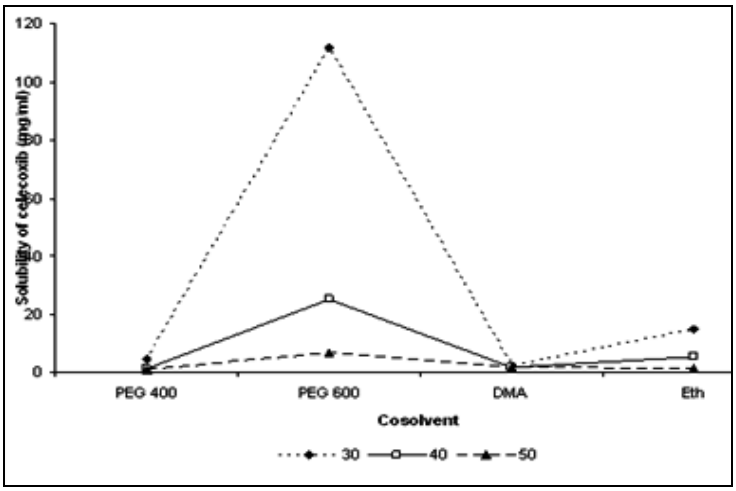


**FIGURE 12: PHASE SOLUBILITY DIAGRAM OF CELECOXIB IN DIFFERENT COSOLVENTS IN UREA**

The nonaqueous solvents used were of different nature and polarity. The more increase in solubility of celecoxib in combination of hydrotrope with cosolvent may be due to additive effect of both cosolvent and hydrotrope on solubility of drug. Solutropic behavior was observed in the case of all the solvents. The effect was found to be additive on solubilization of drugs. The solubility data suggest that there is no correlation between solvent polarity and solutropic solvent. However, some correlation with hydrogen bonding and electrostatic attraction may be possible.

All the solvents selected are capable of forming hydrogen bond. This suggested that the ability of a solvent to be hydrogen donor must be a key factor in solutropic solubilization phenomenon and there is no correlation between solvent polarity and hydrotropic solubilization (8-11).

**Stability Study:** During accelerated stability studies at 40°C/75% RH all the formulations stored were found to be stable against precipitate formation. The pH value was also stable (6.5) and no change in color (absorbance) was observed. The celecoxib content was also found to be within the pharmacopoeial limits (99.65 to 95.01) in all the formulations, indicated no degradation of drug in the formulations. The difference in drug content was statistically insignificant (P>0.05) as per ICH guidelines (**Table 6**). It may be concluded from the results of accelerated stability studies that the optimized formulations had a minimum shelf-life of two years.

**TABLE 6: DRUG CONTENT OF SELECTED FORMULATIONS OF CELECOXIB DURING 6 MONTHS OF STORAGE AT ACCELERATED STABILITY CONDITIONS (40°C AND 75% RH)**

| Time (days) | Percent residual celecoxib* in formulations | | | |
|---|---|---|---|---|
| | CPEG6U | CPEG6W | CPEG4W | CPEG6P |
| 7 | 98.26±2.15 | 99.65±2.10 | 99.12±1.99 | 99.52±1.90 |
| 15 | 97.52±2.76 | 99.05±1.34 | 98.99±2.45 | 98.83±2.32 |
| 30 | 96.89±3.20 | 98.55±2.33 | 98.12±3.42 | 97.88±3.16 |
| 45 | 96.14±3.33 | 97.87±1.87 | 97.35±2.67 | 96.70±2.09 |
| 60 | 96.05±2.98 | 97.25±3.10 | 96.84±2.12 | 95.82±2.90 |
| 75 | 96.00±2.56 | 96.85±2.46 | 96.71±2.98 | 95.59±3.10 |
| 90 | 95.95±2.55 | 96.14±2.55 | 95.22±3.16 | 95.26±3.21 |
| 105 | 95.55±3.02 | 96.01±3.03 | 95.15±2.44 | 95.11±3.22 |
| 120 | 95.00±2.22 | 95.24±3.11 | 95.00±3.35 | 95.01±4.23 |

* Average of three determinations

**CONCLUSION:** Results show that celecoxib can be conveniently prepared in aqueous solution in cosolvents or in combination of cosolvents and hydrotropes. These combinations eliminate the need for including any surfactant in the parenteral dosage formulation with the potential advantage of fewer toxic reactions.

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