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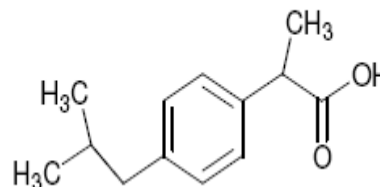
**Solubility enhancement of ibuprofen using hydrotropic agents**Shravan Kumar Patel<sup>1\*</sup>, Dinesh Kumar<sup>1</sup>, Amol P. Waghmode<sup>2</sup> and Avinash S. Dhabale<sup>2</sup><sup>1</sup>, Dept. of Pharm. Analysis, Vinayaka Mission's College of Pharmacy, Salem, (T.N.)-India<sup>2</sup>, Dept. of Pharmaceutics, Vinayaka Mission's College of Pharmacy, Salem, (T.N.)-India<sup>3</sup>, Dept. of Pharmaceutics, P. Wadhwani College of Pharmacy, Yavatmal, (M.H.)-India**Abstract**

Ibuprofen, a weakly acidic, non-steroidal anti inflammatory drug having high permeability through stomach but due to its solubility limitation it can't enter in to systemic circulation and gastric emptying time ranging from 30 min to 2 hr, after this time ibuprofen goes in to small intestine where it is solubilise but can't permeate through its membrane. The same problem arises in quantitative analysis; because of poor solubility of ibuprofen it involves organic solvents which are costly and toxic. To improve dissolution of such drug is challenging and rational. The purpose of the present study was to examine the enhancement of solubility of the Ibuprofen on addition of hydrotropic substances. Solubility of ibuprofen was determined with various surfactants and of various concentrations using phase solubility analysis. Since solubilization of non-polar drugs constitutes one of the most important tasks in formulation design, quantitative analysis and dissolution study.

**Key-Words:** Ibuprofen, solubility enhancement, hydrotropic agents.**Introduction**

Aqueous solubility of a therapeutically active substance is a key property as it governs dissolution, absorption and thus the efficacy *in vivo*. Solubilization may be defined as the preparation of a thermodynamically stable solution of a substance that is normally insoluble or very slightly soluble in a given solvent by the introduction of one or more amphiphilic compound<sup>1</sup>. Recently more than 40% NCEs (new chemical entities) developed in Pharmaceutical Industry are practically insoluble in water. Formulation of poorly soluble compounds for oral delivery now presents one of the interesting challenges to formulation scientists in the pharmaceutical industry. In the case of poorly water-soluble drugs, dissolution is the rate-limiting step in the process of drug absorption. Potential bioavailability problems are prevalent with extremely hydrophobic drugs (aqueous solubility less than 0.1 mg/ml at 37°C), due to erratic or incomplete absorption from GIT<sup>2</sup>.

Ibuprofen [(+/-) 2-(*p*-isobutylphenyl) propanoic acid (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>-CH<sub>2</sub>CHCO<sub>2</sub>H] is well known as a non-steroidal anti-inflammatory (NSAID), analgesic and antipyretic agent (figure- 1)<sup>3</sup>. It is a weakly acidic drug having high permeability through stomach because it remain 99.9 % unionize in stomach (pKa of Ibuprofen - 4.43, pH of gastric fluid - 1.2). Ibuprofen mostly permeable through stomach but due to its solubility limitation it can't enter in to systemic circulation and gastric emptying time is 30 min to 2 hr. After this time ibuprofen goes in to small intestine where it is solubilised but can't permeate through its membrane (Ibuprofen having pH depended solubility and permeability). To improve dissolution of such drug is challenging and rational<sup>4</sup>.

**Fig. 1. Structure of ibuprofen.****\* Corresponding Author:**E-mail: shrvanpharma01@gmail.com  
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In the context of drug delivery, solubility issues are one of the major factors that are concern for the

development of the pharmacologically effective dosage form. The precise value of the solubility parameter of a drug is of significance, in terms of bioavailability. Lower solubility of a therapeutically active substance is often associated with the bioavailability problems, lack of in-vivo and in-vitro correlation, lack of patient compliance, and inter subject variations. These variations assume a practical significance for drugs with a low safety margin, for example, digoxin. A large fraction of new drugs which confine their possible application in formulation development, because of poor aqueous solubility and hydrophobicity. In order to acquire the desired bioavailability and subsequent therapeutic response, the drug must be soluble in aqueous solutions, which leads to its absorption at an optimum rate and extent and also facilitates the systemic delivery of the drug to the body. Solubility is an extrinsic physicochemical property of bioactive, which can be used to explain the drug action<sup>5</sup>, structure activity relationship<sup>6</sup>, drug transport kinetics<sup>7</sup> and in-situ drug release profile<sup>8</sup>. The therapeutic efficacy of any drug is often diminished by its incapability to gain access to the site of action and it is often in close proximity with poor solubility of the drug in the body's aqueous compartment. Various techniques have been proposed to overcome the solubility problems of therapeutic moieties. In this aspect a surfactant based system and cyclodextrins have been used to enhance the solubility and bioavailability<sup>9</sup>.

### Material and Methods

Ibuprofen was obtained as a gift sample by Cipla limited, Sikkim, India. Sodium acetate, sodium benzoate, sodium salicylate and were purchased from Muby Chemicals, Mumbai, India. All other chemical and solvents were of analytical grade and freshly prepared distilled water was used throughout study.

#### Phase solubility studies (UV method for analysis)

Ibuprofen is freely soluble in methanol. Hence methanol was used as a solvent to develop the calibration curve of Ibuprofen using the UV method. A stock solution of Ibuprofen (1mg/ml) was prepared by accurately weighing 100 mg of ibuprofen and was transferred to 100-mL volumetric flasks, and 75 ml of methanol was added. The mixture was shaken for 30 minutes on a laboratory planetary shaker. The mixture was then completed to volume with methanol, and the contents of the flask were mixed manually to ensure complete mixing. Then 1ml, 2ml, 3ml, 4ml, 5ml of this solution was taken in 10ml of volumetric flask and make up the volume up to the mark, and UV absorbance of each concentration was measured at 259 nm with UV-VIS Spectrophotometer (Shimadzu UV 160A). The graph of absorbance was plotted against the concentrations to give the standard curve. The

calibration curve for the ibuprofen method was linear over the range of 0.10 to 0.70 mg/ml ( $r^2 = 0.999$ ). The UV-Vis spectrophotometer was previously calibrated according to the method mentioned in Indian Pharmacopoeia (I.P.) 1996, i.e. control on absorbance test, in which absorbance of potassium dichromate solution was checked at the wavelengths indicated in I.P. 1996. The A (1%, 1 cm) for each wavelength was measured and found in the permitted limits according to I.P. 1996.

#### Comparative solubility analysis with different hydrotropic agents

Solubility studies were performed according to Higuchi and Connors<sup>10</sup>. It was determined with various hydrotropic agents (Sodium acetate, Sodium benzoate, Sodium toluene sulfonate, Sodium salicylate and Sodium toluate). of concentration 1M. Excess of Ibuprofen was added to different 50 ml volumetric flask containing 25 ml aqueous solution of different hydrotropic substance of concentration of 1M. Flasks were sonicated for 4 hrs and kept at 25°C for 24hrs and passed through a 0.45  $\mu$ m filter. Then clear solutions were analyzed spectrophotometrically at 259 nm using UV-Vis Spectrophotometer. Absorbance was extrapolated on the calibration curve to determine the unknown concentration and the solubility of each sample was calculated. Each Experiment was performed in triplicate.

#### Solubility analysis with variation in concentration of Sodium benzoate

Solubility was determined with hydrotropic substance of different concentration (0.5, 1.0, 1.5 and 2.0 aqueous solution of Sodium benzoate). Excess of Ibuprofen was weighed into glass vials containing 50 ml solvents of different concentration. The samples were sonicated for 4 hrs and kept at 25°C for 24 hrs and passed through a 0.45  $\mu$ m filter. Then clear solutions were analyzed spectrophotometrically at 259 nm using UV-Vis Spectrophotometer (UV-1601 A, Shimadzu). Absorbance was extrapolated on the calibration curve to determine the unknown concentration and the solubility of each sample was calculated. Each Experiment was performed in triplicate.

### Results and Conclusion

Hydrotropes are amphiphilic in nature i.e. composed of hydrophilic as well as lipophilic portions. These molecules are generally used as solubility enhancer (solubilisers). This method is commonly known as micellar solubilization since they forms micelles, which are association segregate of surfactants. Hydrotropic agents have been used to enhance aqueous solubility of hydrophobic drugs. In many instances, the aqueous solubility was increased by orders of magnitude simply by mixing with



hydrotropic agents in water. Hydrotrophy is a collective molecular phenomenon describing an increase in the aqueous solubility of a sparingly water-soluble drug by addition of a relatively large amount of a second solute. Hydrotropic agents self-associate into loose non-covalent assemblies of non-polar microdomains to solubilize hydrophobic solutes. However, the detailed mechanisms of hydrotrophy have not been fully understood.

Currently, the most widely used method for increasing the aqueous solubility is to add surfactants to the aqueous release media. However, this method is not applicable for polymeric micelle systems because even a small amount of surfactants could destroy their micellar structure and distort their release profiles. A hydrotropic agent could be a good alternative to increasing the aqueous solubility<sup>11</sup>.

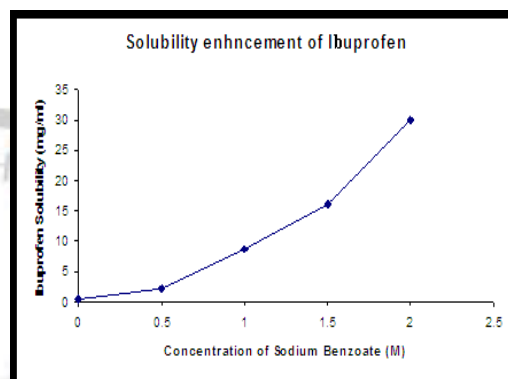
The aqueous solubility of ibuprofen is 0.37 mg/ml at 25°C. A number of hydrotropes were studied for solubility enhancement of ibuprofen and sodium benzoate has been extensively studied. In the present investigation, solubility enhancement caused by Sodium acetate, Sodium benzoate, Sodium salicylate, Sodium toluene sulfonate, Sodium toluate and Sodium benzoate were studied. The solubility of ibuprofen at 25°C in the presence of Sodium acetate, Sodium benzoate, Sodium salicylate, Sodium toluene sulfonate, and Sodium toluate is given in table-1 and with different concentrations of sodium benzoate is given in table 2.

**Table 1: Solubility study with different hydrotropic agent**

Hydrotropic agent used	Conc. of hydrotropic agent	Solubility of Drug (mg/ml)
Sodium acetate	1M	0.711
Sodium benzoate	1M	8.745
Sodium salicylate	1M	1.965
Sodium toluate	1M	1.027
Sodium toluene sulfonate	1M	0.869

**Table 2: Solubility study with increase in concentration of sodium benzoate**

Concentration of sodium benzoate solution (M)	Solubility of drug (mg/ml)
0.5M	2.273
1.0M	8.745
1.5M	16.084
2.0M	30.047



**Fig. 2: Aqueous solubility of ibuprofen as a function of the molar concentration of sodium benzoate.**

Out of them sodium benzoate shows significant enhancement in solubility, so sodium benzoate was used for extensive study. Fig. 3 shows increased aqueous solubility of ibuprofen by sodium benzoate. The solubilities at 0.5M, 1M, 1.5M and 2.0M sodium benzoate were 2.273 mg/ml, 8.745 mg/ml, 16.084 mg/ml, and 30.047 mg/ml, respectively. Solubility increases with further increase in concentration of sodium benzoate.

By performing solubility studies, it was found that enhancement in aqueous solubility by means of hydrotropes was more than 81 % as compared to solubility in distilled water. Maximum solubility increases with 2.0 M sodium benzoate.

This study indicates that the increase in ibuprofen solubility was due to addition of hydrotropes. Out of all hydrotropes significant enhancement in solubility was observed with sodium benzoate. Increase in concentration of sodium benzoate increased the solubility of the ibuprofen in distilled water. The present study describes the increase in solubility by hydrotropes as well as the increase in solubility with increase in concentrations of hydrotropic agents. This experimental method using a hydrotropic agent provides an alternative tool for increase in release of poorly soluble drugs in aqueous solution. The proposed method of solubility enhancement is new, simple, cost-effective and environment friendly. Thus hydrotropic solubilization can be used for quantitative analysis, dissolution study and increase in bioavailability. Thus method provides the dynamics of the hydrotropes in solubilization of ibuprofen.

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