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SPECTROSCOPIC ESTIMATION OF IBUPROFEN BULK DRUG SAMPLE USING HYDROTROPIC SOLUBILIZATION TECHNIQUE

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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 empting 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 1M N,N-dimethylurea (DMU) as a hydrotropic substance using a novel, safe, and sensitive method of spectroscopic estimation in ultraviolet region. beer's low obeyed in the concentration range of 5-30µg/ml. Solubility of ibuprofen was determined with various concentrations using Spectroscopic estimation analysis. Since solubilization of non-polar drugs constitutes one of the most important tasks in formulation design, quantitative analysis and dissolution study.

Keywords: Ibuprofen, solubility enhancement, hydrotropic agents.

INTRODUCTION

Increasing the aqueous solubility of insoluble and slightly soluble drug is of major importance. Several techniques have been used to solubilize the poorly water-soluble drugs. Hydrotropic solubilization technique is one of them [1-5]. Sodium benzoate, sodium salicylate, sodium acetate, sodium ascorbate, niacinamide, sodium citrate, urea are the most popular examples of hydrotropic agents which have been used to solubilize a large number of poorly water-soluble compounds [6-12].The primary objective of the present investigation was to

employ a hydrotropic solution to increase the solubility of fine powder of ibuprofen, precluding the use of costlier organic solvents for spectrophotometer analysis. Costly organic solvents are more often employed to solubilize the poorly water soluble drug .hydrotropic solubilisation is one of them. Hydrotropy refers to the ability of a concentrated solution of a chemical compound to increase the aqueous solubility of another compound (usually a sparingly soluble organic compound). Compounds that have this property are called 'hydrotropes' [13-18].

Ibuprofen [(+/-) (2-(*p*-isobutylphenil propanoic acid) [(CH3)2CHCH2-C6H4CH3CHCO2H] is well known as a non-steroidal anti-inflammatory (NSAID), analgesic and antipyretic agent (figure- 1) [19] .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 circulat ion and gastric empting time is 30 min to 2 hr. After this time ibuprofen goes in to small intestine where it is solubilized but can't permeate through its membrane (Ibuprofen having pH dependent solubility and permeability).To improve dissolution of such drug is challenging and rational [20].

There was tremendous increase in solubility of Ibuprofen in 1 M DMU. Therefore, it was thought worthwhile to solubilize the drug with the help of DMU solution to carry out the estimation.

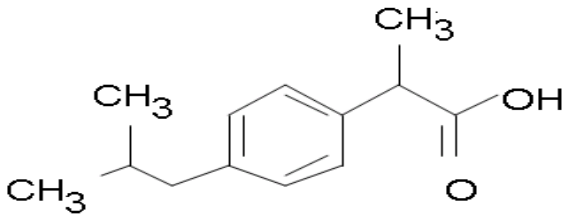

Figure1: Structure of Ibuprofen

MATERIAL AND METHODS

Ibuprofen was obtained as a gift sample by IPCA Pharmaceutical private limited, Ratlam (M.P), India. Sodium acetate, sodium benzoate, sodium salicylate, and Urea 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.

Determination of interference of hydrotropic agent in the spectroscopic estimation of Drugs

A Shimadzu UV-Visible spectrophotometer (Model-UV 1800) with 1 cm matched silica cells was used for spectrophotometric analysis. For determination of interference of hydrotropic agents in the spectrophotometric estimation of Ibuprofen, the absorbances of the standard solutions of drugs were determined in DW alone and in the presence of the maximum concentration of the hydrotropic agent employed for spectrophotometric analysis purpose in the present investigation. The absorbances were recorded against respective reagent blanks at appropriate wavelenth.

Preparation of stock solution of Ibuprofen in distill water (DW)

Ibuprofen was accurately weighed (50 mg) and transferred to a 500 mL volumetric flask. DW (450 mL) was added and flask was shaken vigorously to dissolve the drug. After complete dissolution of drug, the volume was made up to the mark with DW to get 1mg/mL stock solution.

Comparative solubility analysis with different hydrotropic agents

Solubility studies were performed according to Higuchi and Connors10. It was determined with various hydrotropic agents (Sodium acetate, Sodium benzoate, urea, 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^{o}C for 24hrs and passed through a 0.45 µm 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.

Table 1: Solubility study with different hydrotropic agent

Hydrotopic agent used	Conc. of hydrotopic agent	Solubility of Drug (mg/ml)
Sodium acetate	1M	0.409
Sodium benzoate	1M	0.663
Sodium salicylate	1M	0.657
Sodium toluate	1M	0.499
Urea	1M	8.443

Solubility analysis with variation in concentration of Urea

Solubility was determined with hydrotropic substance of different concentration (0.5, 1.0, 1.5 and 2.0 aqueous solution of Urea). 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 25oC for 24 hrs and passed through a 0.45 µm 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.

Table 2: Solubility study with increase in concentration of Urea

Concentration of Urea (M)	Solubility of drug (mg/ml)
0.5M	2.237
1.0M	8.443
1.5M	15.984
2.0M	29.047

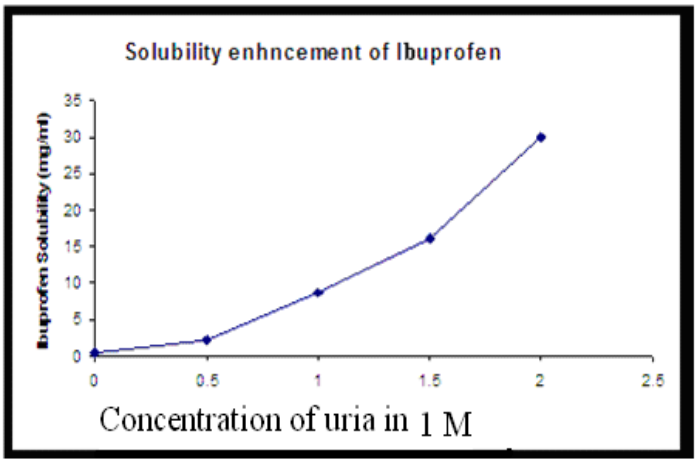

Figure 2:aqueous solubility of Ibuprofen as a function of the molar concentration of urea

Preparation of stock solution of Ibuprofen in DMU Solution

Ibuprofen was accurately weighed (50 mg) and transferred to a 500 mL volumetric flask and 100 mL of 1M DMU solution was added and drug was dissolved in this solution. After complete dissolution of drug, sufficient DW was used to make up the volume and to get the stock solution of 1mg/mL.

Equilibrium solubility determinations at room temperature

For equilibrium solubility determination at room temperature, the method used by Maheshwari *et al.* was employed.24-26 Sufficient excess amount of drugs were added to screw-capped 30 mL glass vials containing DW and the solution of hydrotropic agent separately. The vials were shaken mechanically for 12 h at room temperature (28±1ºC) in Orbital Flask Shaker (Khera Instruments Pvt. Limited, Delhi, India). The solutions were allowed to equilibrate for next 24 h and then centrifuged for 5 minutes at 2000 rpm using a centrifuge (Remi Instruments Limited, Mumbai, India). The supernatants liquid of each vial were filtered through Whatman's filter paper # 41. Filtrates of saturated solutions of drugs;

Ibuprofen was analyzed by spectrophotometric analysis, measuring the absorbances of appropriately diluted solutions with DW against respective blanks at their appropriate wavelengths. Equilibrium solubility of drug in DW alone and in presence of hyrdrotropic solubilizing agent was determined by intrapolation on the calibration curve. Solubilities so determined have been reported in Table 3. Enhancement ratio in solubility were also determined (Table 3), by following formula

$$\text{Enhancement ratio} = \frac{\text{Solubility of drug in hydrotropic solution}}{\text{Solubility of drug in distilled water}}$$

RESULTS AND CONCLUSION

Hydrotropes are amphiphilic in nature i.e. composed of hydrophilic as well as lipophilic portions. These molecules are genrally used as solubility enhancer (solublizers). This method is commonly known as micellar solublization 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. Hydrotropy 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 micro domains to solubilize hydrophobic solutes. However, the detailed mechanisms of hydrotropy 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 [21].

The aqueous solubility of ibuprofen is 0.068 mg/ml at 25°C. A number of hydrotropes were studied for solubility enhancement of ibuprofen and urea has been extensively studied. In the present investigation, solubility enhancement caused by Sodium acetate, Sodium benzoate, Sodium salicylate, urea, 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 toluate and urea, is given in table-1 and with different concentrations of urea is given in table 2.

Out of them urea shows significant enhancement in solubility, so urea was used for extensive study. Figure 2 shows increased aqueous solubility of ibuprofen by urea . The solubility's at 0.5M, 1M, 1.5M and 2.0M urea were 2.237 mg/ml, 8.443 mg/ml, 15.984 mg/ml, and 29.047 mg/ml, respectively. Solubility increases with further increase in concentration of urea. 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 urea. 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 urea. Increase in concentration of urea 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.

There is good enhancement in aqueous solubility of selected poorly water-soluble drugs in presence of large amounts of hydrotropic agents. Therefore, it was thought worthwhile to make use of hydrotropic solubilization techniques in development of new spectrophotometric methods for the analysis of poorly water-soluble drugs. The proposed method of solubility enhancement is new, simple, cost-effective and environment friendly. Thus hydrotropic solublization can be used for quantitative analysis, dissolution study and increase in bioavailabaility. Thus method provides the dynamics of the hydrotropes in solubilization of ibuprofen.

Table 3*:* Regression equation and equilibrium solubilities of selected drugs in DW alone and DMU solutions

Drug	Solvent used	Beer's range (µg/m)	Temperature (^oC)	Regression equation	R^2	F	Std. Error	Std. Deviation	Solubility(µg/mL)	SER
IBU	DW	5-30	28±2^oC	Y = 0.011x – 0.011	0.9881	331.7	0.09369	0.2479	68.045	--
	DW+DMU	5-30	28±2^oC	Y = 0.010x + 0.001	0.9975	1600	0.5289	1.399	356.859	5.244

SER: Solubility Enhancement Ratio, R^2: Regression coefficient # P value <0.0001 and significant

CONCLUSIONS

Like Ibuprofen other poorly water soluble drugs can also subjected to analysis by using hydrotropic solubilization method. The hydrotropic solubilization technique can also be used for titrimetric and spectrophotometric estimations of poorly water-soluble drugs from their bulk drug samples and solid dosage forms precluding the use of organic solvents providing simple, economic, eco-friendly, safe (free from toxicity) and accurate analytical methods. The proposed techniques would be economical, convenient and safe. The developed formulations would be definitely cheaper as compared to marketed formulations which employ costly additives/excipients. Further the proposed hydrotropic agents are known to be safe hence toxicities/safety related issues may not raise concern, suggesting the adoptability for large scale manufacturing i.e. industrial feasibility.

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