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DEVELOPMENT OF AN ANALYTICAL METHOD FOR SPECTROPHOTOMETRIC ESTIMATION OF KETOPROFEN USING MIXED CO SOLVENCY APPROACH

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ABSTRACT

Keywords:

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The present study demonstrates the use of mixed co solvency in the enhancement of solubility and estimation of ketoprofen, practically water insoluble drug and thus precludes the use of organic solvents. The selected solubilizers were sodium citrate (15%), PEG 400 (8%) and polyvinyl pyrrolidone (7%). Beer's law was obeyed in the concentration range of 2-20 μ g/ml at wavelength of 256nm. The solubility of ketoprofen was increased by 30 folds in the mixed co-solvents as compared to distilled water. The recovery study revealed that any small change in the drug concentration in the solution could be accurately determined by the proposed method. The low values of LOD and LOQ indicated good sensitivity of proposed method. The study proved that mixed co-solvency phenomenon is an effective technique in enhancement of aqueous solubility of poorly water soluble drugs and can be successfully employed for estimation of drugs in routine analysis of tablets.

INTRODUCTION: In the pharmaceutical formulation development most of the newly developed drug molecules are lipophilic in nature and poor aqueous solubility is one of the most difficult problems of these drugs¹. The analysis of these poorly water soluble drugs and insoluble drugs were carried out by spectrophotometric estimation using organic solvents like methanol, chloroform, ethanol, benzene, acetone, toluene, carbon tetrachloride, diethyl ether and acetonitrile²⁻⁴. But the disadvantage of these organic solvents mentioned include costly, toxic and volatile in nature which would provide inaccuracy with the results⁵.

Several approaches have been proposed in literature to improve the aqueous solubility and hydrotropic solubilization is one of them⁶. Various works have been reported on use of hydrotropic solvents in estimation of various lipophilic drugs⁷⁻¹². Hydrotrophy is another type of co solvency and this gave a new concept a mixed-solvency concept that may be tried to

observe the effect on solubility of poorly water soluble drugs. Few works based on this mixed co-solvency technique was reported to study the improvement in solubility by titrimetric estimation^{13, 14}. This mixed co-solvency technique is based on the principle that instead of using one solubilizer in large concentration for a desired level of solubility, several solubilizers like hydrotropes (sodium ascorbate, urea, sodium benzoate), co-solvents (propylene glycol, PEG 200, 300, 400) and water soluble solids (PEG 4000, 6000, cyclodextrins) in varying concentrations may be used that may show additive or synergistic enhancement in solubility.

These solubilizers do not cause any toxicity and are non-volatile. Ketoprofen a propionic acid derivative that possesses anti-inflammatory activity and hence used in the treatment of inflammation and pain associated with arthritis. Its molecular formula is C₁₆H₁₄O₃. It is chemically (RS) 2-(3-benzoylphenyl)-propionic acid. It is practically insoluble in water, freely soluble in alcohol,

in acetone, and in dichloromethane¹⁵. The primary goal of this study is to employ the concept of mixed co-solvency using for the spectrophotometric estimation of ketoprofen in the bulk drug sample and tablets thereby eliminating the use of organic solvents. The total concentration of solubilizers was kept constant (30 % w/v) in the solubilizing system. The selected solubilizers were sodium citrate (15%) as hydrotrope, PEG 400 (8%) as co-solvent and poly vinyl pyrrolidine (7%) as water soluble solid.

MATERIALS AND METHODS: Ketoprofen bulk drug was purchased from Yarrow chem products, Mumbai. Sodium citrate, poly vinyl pyrrolidine and PEG 6000 was purchased from S.D.Fine Chemicals, Mumbai. Tablets of ketoprofen were formulated in laboratory using formula obtained from literature. Shimadzu UV/Visible recording spectrophotometer (model-UV-1601) with 1cm matched silica cells was employed. All other chemicals and solvents used were of analytical grade.

Experimental Method:

Preliminary Solubility Studies of the Drug: Solubility of ketoprofen was determined by saturation aqueous solubility method¹⁶ in mixed co-solvents containing 15% sodium citrate, 8% PEG 400 and 7% PVP (SCPP) in distilled water. An excess amount of drug was added to 50ml beakers containing SCPP and distilled water. The beakers were shaken for 12 hours at $28 \pm 1^\circ\text{C}$. The solutions were filtered through Whatman filter paper #41, and the resulting filtrates were suitably diluted and analyzed spectrophotometrically at 256nm against solvent blank.

Preparation of Standard Stock and Calibration Curve: The standard stock solution of Ketoprofen was prepared by dissolving 50mg of drug in 50 ml of SCPP (15% sodium citrate, 8% PEG 400 and 7% polyvinyl pyrrolidine). From this solution, 5ml of solution was taken and diluted to 100ml with distilled water to get a solution containing 50 $\mu\text{g}/\text{ml}$ and scanned in the entire UV range of 400-200 nm to determine the λ_{max} of the drug. The λ_{max} of Ketoprofen was found to be 256nm. Five working standard solutions for the drug having concentration 4, 8, 12, 16 and 20 $\mu\text{g}/\text{ml}$ was prepared with distilled water from the stock solution. The absorbance's of resulting solutions for the drug were measured at λ_{max} of 256nm and a calibration curve

was plotted to get the linearity and regression equation.

Analysis of Ketoprofen in Tablets using SCPP:

Prototype tablets of ketoprofen were prepared in the laboratory using the formula mentioned in US Patent No: 5776505¹⁷. Twenty tablets were weighed and powdered. Powder equivalent to 25mg ketoprofen was transferred to 100ml volumetric flasks containing 90ml of SCPP. The flasks were shaken for about 10min to solubilize the drug. Then volume was made up to the mark with distilled water. From this 1ml of solution was pipetted into 50ml volumetric flask containing distilled water to obtain a concentration of 50 $\mu\text{g}/\text{ml}$. From this, 5ml was pipetted into 25ml volumetric flask containing distilled water to obtain 10 $\mu\text{g}/\text{ml}$ and absorbance was measured at 256nm against solvent blank and drug content was calculated.

Validation of the Proposed Method: The proposed method was validated for the following parameters.

Linearity: The absorbances of appropriate dilutions of standard stock solutions were measured as per the developed method to confirm the linearity.

Recovery Studies: In order to check the accuracy and reproducibility of the proposed method, recovery studies were conducted. Tablet powder equivalent to 25 mg of ketoprofen was transferred to a 100ml volumetric flask containing SCPP. Pure ketoprofen drug sample containing 20mg was added to the same volumetric flask. The flask was shaken for 10 mins to solubilize the drug. Then solution was filtered through Whatman filter paper #41. The filtrate was diluted with distilled water appropriately and absorbance was measured at 256nm against corresponding solvent blank. Drug content was calculated and percentage recovery was calculated. Similar procedure was repeated using 40mg and 60mg of pure ketoprofen as spiked concentration. The drug contents were determined and percentage recoveries were estimated.

Precision: Precision was determined by studying the repeatability and intermediate precision. The standard deviation, coefficient of variance and standard error were calculated for the drug.

Inter- day and Intra- day precision: The intra-day concentration of the drug was calculated on the same day at an interval of one hour, whereas the inter day concentration of drug was calculated on three different days within the laboratory conditions.

Limit of Detection (LOD) and Limit of Quantitation (LOQ): The LOD and LOQ of ketoprofen by the proposed method were determined using calibration standards. LOD and LOQ were calculated as $3.3\sigma/S$ and $10\sigma/S$, respectively, where S is the slope of the calibration curve and σ is the standard deviation of response.

RESULTS AND DISCUSSION: Solubility of ketoprofen in mixed co-solvents containing 15% sodium citrate, 8% PEG 400 and 7% polyvinyl pyrrolidone was found to be 12mg/ml whereas the solubility in distilled water was found to be 0.36mg/ml. These results indicated that aqueous solubility of ketoprofen was increased to 30 folds in mixed co-solvents as compared to distilled water. So it was optimized to employ this mixture solution in the analysis of the tablet formulation. The spectrum of ketoprofen in SCPP is shown in **figure 1**.

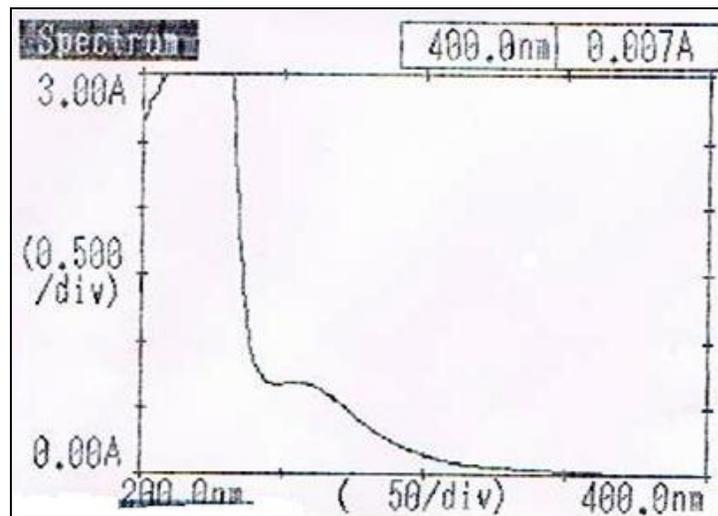


FIGURE 1: UV-SPECTRA OF KETOPROFEN IN SCPP

The Beer- Lambert's concentration range for ketoprofen in mixed co-solvents was between 2-20 μ g/ml. To check drug stability and precipitation of drug in mixed co-solvent, a part of solution were kept in room temperature for 48 hours. The results revealed that estimation of ketoprofen can be done without any substantial effect on drug stability as no precipitation was observed (**Table 1**).

TABLE 1: ANALYSIS OF TABLET FORMULATIONS OF KETOPROFEN

Tablet formulation	Label claim (mg)	Percentage label claim estimated* (mean \pm S.D.)	Standard error
Tablet + 15% sodium citrate, 8% PEG 400 and 7% Polyvinyl pyrrolidone (SCPP)	25mg	101.55 \pm 0.879	0.5076

* Average of six determinations

From this study, it is obvious that there was no interference of sodium citrate or PEG 400 or polyvinyl pyrrolidone in estimation of ketoprofen at the wavelength of 256nm. Based on this a large number of poorly water soluble drugs may be tried for estimation by the proposed method provided their preliminary solubility studies should enhance of solubility of drug in the mixed co-solvents. Also sodium citrate, polyvinyl pyrrolidone and PEG 400 are cheaper than most of the organic solvents and can thus, may be better substitutes for expensive organic solvents that are used in routine analysis of pharmaceuticals.

The tablets were prepared using the patented formula and were subjected to estimation using SCPP. The estimated label claim was 101.55% indicating good correlation between estimated and assay of formulated tablets. The recovery studies showed proposed method is accurate and reproducible. The results of recovery study revealed that any small change in the drug concentration in the solution could be accurately determined by the proposed method. Accuracy, reproducibility and precision of the proposed methods were further confirmed by percent recovery values, with low values of standard deviation and standard error as shown in **Table 2**.

TABLE 2: RESULT OF RECOVERY STUDIES

Formulation	Amount of ketoprofen tablet powder (mg)	Amount of standard drug added (mg)	Percentage recovery estimated* (mean \pm S.D.)	Standard error
Tablet+15% sodium citrate, 8% PEG 400 and 7% Polyvinyl pyrrolidone (SCPP)	25	20	100.71 \pm 0.1931	0.1115
	25	40	100.51 \pm 0.2219	0.1281
	25	60	100.62 \pm 0.2161	0.2161

* Average of six determinations

Repeatability results indicated the precision under the same operating conditions over a short interval of time. Intermediate precision study was reported to be within the laboratory variation in different days. In both intra and inter-day precision study, the coefficient of variation was not more than 1.0% indicating good intermediate precision. The low values of LOD and LOQ, 0.6211 and 0.1882 for ketoprofen in the mixed SSCP indicated good sensitivity of proposed method (**Table 3**).

TABLE 3: OPTICAL CHARACTERISTICS DATA AND VALIDATION PARAMETERS

Parameters	Values of ketoprofen in 15% sodium citrate, 8% PEG 400 & 7% PVP (SCPP)
Working λ_{\max} (nm)	256nm
Beer's law limit ($\mu\text{g/ml}$)	2-20
Molar Absorptivity	14.7×10^3
Correlation coefficient*	0.998
Intercept*	0.001071
Slope*	0.00569
LOD* ($\mu\text{g/ml}$)	0.6211
LOQ* ($\mu\text{g/ml}$)	0.1882
Intra-day* (precision) (Co-eff. of variation)	0.2040
Inter-day* (precision) (Co-eff. of variation)	0.2466
Robustness	Robust

* Average of 6 determinations

CONCLUSION: It was thus concluded that mixed solvency solubilization phenomenon is an effective technique in the enhancement of solubility of a poorly water soluble drug and this approach shall prove a boon in pharmaceutical field to develop various formulations of poorly water-soluble drugs by combining various water-soluble excipients in safe concentrations to give a strong solution to produce a desirable aqueous solubility of poorly water-soluble drugs. Hence, the proposed method is new, simple, accurate, non-toxic and precise method compared to the conventional use of organic solvent as they are costly, toxic and volatile. Therefore this method can be successfully employed as an alternative novel method for the estimation of drugs in routine analysis of tablets.

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