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## **“Solid As Solvent”- Novel Spectrophotometric Analytical Method to Estimate Indomethacin in Capsule Dosage Form Using Solids (Eutectic Liquid of Phenol and Metformin Hydrochloride) as Solubilizing Agents (Mixed Solvency Concept)**

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### **ABSTRACT**

The solubility of poorly water-soluble drugs is one of the major problems and has a challenging task to obtain the desired concentration of drug in systemic circulation for a better pharmacological response. To enhance the solubility of poorly soluble compounds, some common techniques are complexation, pH modification, hydrotropy, co-solvency, etc. A novel technique of solubility enhancement by a mixed solvency concept has been proposed by Maheshwari. The objective of our study is to show that solids can act as a solvent precluding the use of organic solvents. The present study describes the application of the solvent character of eutectic liquid consisting of phenol and metformin hydrochloride in a 4:1 ratio (PMHCL 41) for spectrophotometric estimation of indomethacin capsule dosage form. The solubility of indomethacin in a eutectic liquid of PMHCL 41 is more than 200 mg per ml. Absorbance was noted at 320 nm against reagent blank for the determination of drug content. The solubility of indomethacin in distilled water at room temperature was found to be 0.36 mg/ml. Analysis data of indomethacin capsule formulations with statistical evaluation reveals that the percent drug estimated in capsule formulation I and II were found to be  $100.34 \pm 1.449$  and  $99.49 \pm 1.921$  respectively. The range of percent recoveries varied from  $98.36 \pm 1.292$  to  $100.15 \pm 1.088$ . The proposed method can be successfully employed in the routine analysis of the indomethacin capsule. Eutectic liquid of PMHCL 41 can also be tried with other water-insoluble drugs which are estimated above 300 nm.

## INTRODUCTION

The solubility of poorly water-soluble drugs is one of the major problems and has a challenging task for researchers to obtain the desired concentration of drug in systemic circulation for a better pharmacological response. More than 40% of the new chemical entities are facing the problems for aqueous solubility and become a hurdle for the formulations. Maheshwari has stated that each liquid has the good solvent property for some solutes and non-solvent property for others solutes which means all substances existing on the earth whether they are liquid, gas or solids, they possess solubilizing power<sup>1-6</sup>. He has given a nice concept, known as mixed- solvency concept and provides us information about eco-friendly methods of solubility as well as the betterment of formulations while using a toxic organic solvent which causes pollution and toxicity. By application of this concept, innumerable solvent systems can be developed<sup>7-10</sup>.

The objective of our study is to show that solids can also be wisely used to act as a solvent precluding the use of organic solvents. To enhance the solubility of poorly soluble compounds some common techniques are micellar solubilization, complexation, salt formation, pH modification, hydrotrophy and co-solvency. A novel technique of solubility enhancement by the use of a mixed solvency concept has been proposed by Maheshwari<sup>11-22</sup>. By using a mixed solvency concept numerous solvent systems may be developed. By these concepts, toxicity issues can be solved which is provoked by a high concentration of solubilizing agents needed for solubility.

The present study describes the application of the solvent character of eutectic liquid consisting of phenol and metformin hydrochloride in a 4:1 ratio (PMHCL 41) on the weight basis for spectrophotometric estimation of indomethacin capsule dosage form. The solubility of indomethacin in a eutectic liquid of phenol and metformin hydrochloride (PMHCL 41) is more than 200 mg per ml.

In the present investigation, PMHCL41 was utilized to extract out (dissolve) the drug from the powder of the capsule. Distilled water was used for dilution purposes. Absorbance was noted at 320 nm against reagent blank for the determination of drug content. The proposed method is novel, economic, eco-friendly, rapid, free from the toxicity of organic solvent, accurate and reproducible. Recovery studies and statistical data proved the accuracy, reproducibility, and precision of the proposed method. The presence of excipients, phenol,

and metformin hydrochloride did not interfere in the spectrophotometric estimation of indomethacin at 320 nm. Phenol and metformin hydrochloride do not interfere above 300 nm in the spectrophotometric analysis.

## MATERIALS AND METHODS

Indomethacin bulk drug sample was a generous gift by M/S Alkem Laboratories Limited, Mumbai (India). All other chemicals used were of analytical grade. Commercial capsules of indomethacin were procured from the local market.

A Shimadzu-1700 UV visible spectrophotometer with 1 cm matched silica cells was used for spectrophotometric analysis.

### Calibration curve

For the preparation of a calibration curve of indomethacin, 50 mg of indomethacin standard drug was placed in a 500 ml volumetric flask. Then, 10 ml of PMHCL 41 were added and the flask was shaken properly to dissolve the drug to make a clear solution. Then about 400 ml of distilled water was added into this clear solution and shaken for 5 minutes to solubilize content. Then, volume was made up to 500 ml with distilled water to get the stock solution of 100 µg/ ml. From this stock solution (100 µg/ml), standard solutions containing 15, 30, 45 and 60 µg/ml were prepared by suitable dilution with distilled water. The absorbances of these solutions were noted at 320 nm against respective reagent blank.

### Preliminary solubility studies:

Preliminary solubility studies were done to study the solubility behavior of indomethacin. For the determination of the solubility of the drug (indomethacin) in distilled water at room temperature, a sufficient quantity of the drug was added to 25 ml capacity vial containing distilled water. Then the vial was capped and sealed with aluminium seal, the vial was shaken mechanically in an orbital flask shaker (Khera Instrument Pvt. Ltd., India) for 12 hours at room temperature ( $27 \pm 1$ ). Thereafter, the solution was allowed to stand for 24 hours undisturbed and then by using Whitman filter paper # 41, filtration was done. The filtrate was adequately diluted with distilled water and measured the absorbance at 320 nm.

To determine the approximate solubility of the drug in PMHCL 41, one ml of PMHCL 41 was transferred to a 10 ml volumetric flask. The weight of the stoppered volumetric flask

(initial weight) was noted. About 5 mg of drug was added and the flask was shaken to solubilize the drug. As soon as a clear solution was obtained, again about 5 mg of drug was added and the flask was shaken to solubilize the drug to get a clear solution. The same process was repeated until the eutectic liquid of PMHCL 41 was saturated with the drug. Again the weight of the volumetric flask was noted (final weight). The difference in these two weights (initial and final) gave the approximate amount of drug which saturates (nearly) one ml of eutectic liquid of PMHCL 41.

### **The proposed method of analysis**

For spectrophotometric analysis of the formulation I of indomethacin, the contents of 20 capsules were weighed and powder equivalent to 50 mg of the drug was transferred to a 500 ml volumetric flask containing 10 ml of eutectic liquid of PMHCL 41. The flask was shaken for 10 minutes to solubilize the drug and the volume made up to the mark by adding 400 ml of distilled water and the flask was again shaken for 5 min by hand. Then, the volume was made up to the mark with distilled water. Then, filtration was done through Whatman filter paper no. 41. Ten ml of filtrate was diluted to 50 ml with distilled water and absorbance was noted at 320 nm against reagent blank. The drug content was calculated using the calibration curve. The same procedure was repeated for capsule formulation II. The results of the analysis are reported in table 1.

### **Recovery study**

To study the accuracy, reproducibility, and precision of the proposed method, recovery studies were conducted for which pure indomethacin drug was added (15 mg and 30 mg separately) to the pre-analysed capsule powder equivalent to 50 mg of indomethacin and the drug content was determined by the proposed method. Results of analysis with statistical evaluation are reported in table 2.

**Table no 1: Analysis data of indomethacin capsule formulations with statistical evaluation (n=3)**

Drug	Batch	Label claim (mg/capsule)	% Label claim estimated (mean $\pm$ SD)	Percent coefficient of variation	Standard error
Indomethacin	I	25	100.34 $\pm$ 1.449	1.444	0.837
Indomethacin	II	25	99.49 $\pm$ 1.921	1.931	1.109

**Table 2 Results of recovery studies with statistical evaluation (n=3)**

Capsule formulation n	The drug in pre-analysed capsule powder (mg)	Amount of standard drug added (mg)	% Recovery estimated (mean $\pm$ SD)	Percent coefficient of variation	Standard error
I	50	15	98.36 $\pm$ 1.292	1.314	0.746
I	50	30	98.71 $\pm$ 1.494	1.522	0.863
II	50	15	99.44 $\pm$ 1.767	1.777	1.020
II	50	30	100.15 $\pm$ 1.088	1.086	0.628

## RESULTS AND DISCUSSION

The solubility of indomethacin in distilled water at room temperature was found to be 0.36 mg/ml. The solubility of indomethacin in a eutectic liquid of phenol and metformin hydrochloride (PMHCL 41) was more than 200mg.

It is evident from analysis data of indomethacin capsule formulations with statistical evaluation reveals (table 1), that the percent drug estimated in capsule formulation I and II were found to be 100.34 $\pm$ 1.449 and 99.49 $\pm$ 1.921 respectively. These values are very close to 100.0, which manifests the reliability of the proposed analytical method. Small values of statistical parameters viz. standard deviation, percent coefficient of variation and standard error (table 1) further validated the method. Further, table 2 shows that the range of percent recoveries varied from 98.36 $\pm$ 1.292 to 100.15 $\pm$ 1.088. Which are again very close to 100.0 which again manifests the reliability of the proposed analytical method. The proposed analytical technique is further supported by significantly small values of statistical

parameters viz. standard deviation, percent coefficient of variation and standard error (table 2).

## CONCLUSION

The proposed method is new, simple, environment-friendly, accurate and reproducible. The proposed method can be successfully employed in the routine analysis of the indomethacin capsule. Eutectic liquid of phenol and metformin hydrochloride (PMHCL 41) can also be tried with other water-insoluble drugs which are estimated above 300 nm. Phenol and metformin hydrochloride do not interfere above 300 nm in the spectrophotometric analysis.

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