"Solid as Solvent" - Novel Approach for Spectrophotometric Analytical Technique for Nalidixic Acid Tablets using Solids (Eutectic Liquid Of Phenol and Metformin Hydrochloride) as Solubilizing Agents (Mixed Solvency Concept)

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ABSTRACT

The present investigation is an attempt to show that solids can also be wisely used to act as solvent precluding the use of organic solvents. In the present study, a eutectic liquid (PMHCl 41) obtained by triturating phenol crystals and metformin hydrochloride in 4:1 ratio on weight basis was employed to extract (dissolve) the nalidixic acid from fine powder of tablets. Distilled water was used for dilution purpose to carry out spectrophotometric estimation at 330 nm without utilizing any organic solvent. The solubility of nalidixic acid in distilled water at room temperature was found to be 0.21 mg/ml while the solubility of nalidixic acid in PMHCl 41 was more than 180 mg per ml (of PMHCl 41). Proposed spectrophotometric analytical method is novel, free from organic solvent, accurate and reproducible. The accuracy, reproducibility and precision of the proposed method were confirmed by recovery studies and statistical data. The presence of tablet excipients, phenol and metformin hydrochloride did not interfere in the spectrophotometric estimation at 330 nm. Phenol and metformin hydrochloride do not interfere above 300 nm.

Keywords: *Mixed-solvency concept, nalidixic acid, phenol, metformin hydrochloride, spectrophotometric analysis, eutectic liquid.*

INTRODUCTION

Poor water solubility and slow dissolution rate are major issues for the majority of upcoming and existing biologically active pharmaceutical compounds. More than 40% of the new chemical entities being generated through drug discovery programmes are facing the problem for aqueous solubility and became a hurdle for the formulations. A large numbers of liquids are present on the earth and are known as solvents. Out of these, no liquid is solvent for each and every substance. In other words we can say that each liquid is solvent for some and non-solvent for others. Maheshwari[1-3] has stated that all substances (liquids, gases and solids) present on the earth possess solubilizing power. Each substance (in liquefied state or in solution form) shall show solubilizing power for some solutes and non-solubilizing power for others. The main drawbacks of organic solvents include high cost, toxicity and pollution. Organic solvents have innumerous adverse effects. They should be replaced by other eco-friendly alternative sources. The use of solids as solvent shall prove a boon in most of the pharmaceutical and non-pharmaceutical fields. Maheshwari[4-8] has nicely demonstrated the solvent action of solids.

Maheshwari[1-3] has given a nice concept, known as mixed-solvency concept. By application of this concept, innumerable solvent systems can be developed. The solubility of a large number of poorly soluble drugs has been enhanced by mixed solvency concept[1-27.] Mixed solvency concept[10,12,13,15,17,19,20,22,23,27] has shown improvement in the solubility of drugs and enhanced drug loading in pharmaceutical formulations.

The present investigation is an attempt to show that solids can also be wisely used to act as solvent precluding the use of organic solvents. The main objective of the present study is to demonstrate the solvent action of solids. In the present study, a eutectic liquid obtained by triturating two solids, phenol and metformin hydrochloride in 4:1 ratio on weight basis was employed to extract (dissolve) the drug (nalidixic acid) from fine powder of its tablets. Dilution was made with distilled water to carry out spectrophotometric estimation at 330 nm without the help of organic solvent. The presence of phenol, metformin hydrochloride

and the tablet excipients did not interfere in the spectrophotometric estimation at 330 nm. Phenol and metformin hydrochloride do not interfere above 300 nm.

MATERIALS AND METHODS

Nalidixic acid bulk drug sample was a generous gift by M/S Ranbaxy Laboratories Limited, Dewas (India). Metformin hydrochloride was generous gift from M/S IPCA Laboratories Limited, Ratlam (India). All other chemicals used were of analytical grade. Commercial tablets of nalidixic acid were procured from the local market.

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

Preparation of eutectic liquid: Phenol and metformin hydrochloride were triturated in 4:1 ratio on weight basis to obtain a eutectic liquid (PMHCl 41).

Calibration curve- Accurately weighed 40 mg of nalidixic acid standard drug was transferred to a 10 ml volumetric flask. Eight ml of PMHCl 41 was added and the flask was shaken to dissolve the drug. Then, the volume was made up to 10 ml with PMHCl 41 and the flask was shaken to homogenize the contents. Then, 1 ml of this solution was transferred to another 10 ml volumetric flask and sufficient PMHCl 41 was added to make the volume up to 10 ml producing a stock solution containing 400 µg/ml. This stock solution was suitably diluted with distilled water to obtain standard solutions of 10, 20, 30 and 40 µg/ml. The absorbances of these standard solutions were noted at 330 nm against respective reagent blank.

Preliminary solubility studies

To determine the solubility of the drug (nalidixic acid) in distilled water at room temperature, sufficient excess amount of the drug was added to a 25 ml capacity vial containing distilled water. After putting the vial cap and applying the aluminium seal, the vial was shaken mechanically for 12 hours at room temperature in an orbital flask shaker (Khera Instrument Pvt. Ltd., India). The solution was allowed to equilibrate for 24 hours undisturbed and then, filtration was done through Whatmann filter paper # 41. The filtrate was appropriately diluted with distilled water to measure the absorbance at 330 nm.

In order to determine the approximate solubility of drug in PMHCl 41, 1 ml of PMHCl 41 was transferred to a 10 ml volumetric flask. The weight of the stopered 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. Same process was repeated till the liquid was saturated with the drug. Again the weight of volumetric flask was noted (final weight). Difference in these two weights (initial and final) gave the approximate amount of drug which saturates (nearly) one ml of PMHCl 41.

Proposed method of analysis

In order to carry out the spectrophotometric analysis, twenty tablets of tablet formulation I were weighed and crushed to get a fine powder. Tablet powder equivalent to 40 mg nalidixic acid was transferred to a 10 ml volumetric flask. Then, 8 ml of PMHCl 41 was transferred to it and the flask was shaken vigorously for 10 min by hand shaking to extract (solubilize) the drug from the tablet powder. Then, volume was made up to 10 ml with PMHCl 41 and the flask was shaken for few min to homogenize the contents. Again, 1 ml of this liquid was diluted up to 10 ml with PMHCl 41. After this, 2.5 ml of this liquid of the flask was transferred to a 100 ml volumetric flask and 80 ml of distilled water, was added and the flask was again shaken for 5 min by hand to solubilize phenol, metformin hydrochloride and drug in the distilled water. Then, sufficient distilled water was added to make up the volume up to 100 ml. Filtration was carried out through Whatmann filter paper # 41 to remove the tablet excipients. Then, the absorbance of the filtrate was noted at 330 nm against the reagent blank. The drug content was calculated using the calibration curve. Same procedure was repeated for tablet formulation II. The results of analysis are reported in table 1.

Recovery studies

To perform the recovery studies, standard nalidixic acid drug was added (10 mg and 20 mg, separately) to the pre-analyzed tablet powder equivalent to 40 mg nalidixic acid

and the drug content was determined by the proposed method. Results of analysis are reported in table 2 with statistical evaluation.

Table I: Analysis data of nalidixic acid tablet formulations with statistical evaluation (n=3)

Tablet formulation	Label claim (mg/tablet)	Percent drug estimated (mean ± SD)	Percent coefficient of variation	Standard error
I	500	98.81 ± 1.314	1.330	0.759
II	500	100.55±1.448	1.440	0.836

Table II: Results of recovery studies with statistical evaluation (n=3)

Tablet formulation	Drug in pre-analyzed tablet powder (mg)	Amount of standard drug added (mg)	% Recovery estimated (mean ± SD)	Percent coefficient of variation	Standard error
I	50	15	99.08 ± 1.621	1.636	0.936
I	50	30	100.66 ±1.881	1.869	1.086
II	50	15	100.89 ±1.407	1.395	0.812
II	50	30	98.93±1.666	1.684	0.962

RESULTS AND DISCUSSION

The solubility of nalidixic acid in distilled water at room temperature was found to be 0.21 mg/ml. The solubility of nalidixic acid in PMHCl 41 was more than 180 mg per ml (of PMHCl 41). It is evident from table 1 that the percent drug estimated in tablet formulation I and II were 99.08±1.621 and 100.55±1.448, respectively. The values are very close to 100.0 indicating the accuracy 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 98.93±1.666 to 100.89±1.407 which are again very close to 100.0, indicating the accuracy of the proposed method. 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

In the present study, a eutectic liquid obtained by triturating phenol crystals and metformin hydrochloride in 4:1 ratio on weight basis was employed to extract (dissolve) nalidixic acid drug from fine powder of its tablets. Dilution was made with distilled water to carry out spectrophotometric estimation at 330 nm without the help of organic solvent. Proposed method is novel, rapid, free from 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 phenol, metformin hydrochloride and the tablet excipients did not interfere in the spectrophotometric estimation at 330 nm. Phenol and metformin hydrochloride do not interfere above 300 nm.

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