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Der Pharma Chemica, 2015, 7(5):112-115
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

"Solid as solvent"- Novel spectrophotometric analysis of indomethacin capsules using melted phenol as solvent

R. K. Maheshwari[1] and R. Dahima[2]

[1]Department of Pharmacy, Shri G S Inst. of Tech. and Science, Indore, Madhya Pradesh, India
[2]School of Pharmacy, Devi Ahilya University, Khandwa Road, Indore, Madhya Pradesh, India

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ABSTRACT

Each and every substance present on the earth possesses solubilizing power (mixed-solvency concept proposed by Maheshwari). All substances i. e. gases, liquids and solids have solubilizing power. All substances which are liquids at room temperature are known as solvents and this is very well known to us. Supercritical fluid technology is a good proof that gases have solubilizing power. In this technology, liquefied carbon dioxide gas acts as solvent to perform various functions like extraction of active constituents from herbal drugs, purification, production of nanoparticles etc. Similarly, solids also possess solubilizing power. The solubility of nalidixic acid in ethanol is 0.198 % w/v while its solubility in a solution containing 20 % w/v ibuprofen in ethanol was found to be 2.689 % w/v. This 13 fold enhancement in solubility is due to solubilizing power of ibuprofen (a solid). Also, the solubility of nalidixic acid in a solution containing 20 % w/v ibuprofen and 20 % w/v benzoic acid combinedly, in ethanol was found to be 5.753 % w/v. Again, this further enhancement in solubility of nalidixic acid is due to the solubilizing power of benzoic acid (a solid). These all proofs show that solids also have solubilizing power (or solvent character). 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 a separate study, author has attempted soxhelation using phenol as solvent. The vapours of boiling phenol got condensed in extraction chamber to effect the extraction of active constituents from powder of crude drugs. The main objective of the present study is to demonstrate the solvent action of solid. Solid excipients can nicely be employed as solubilizers in the development of pharmaceutical dosage forms in solution form of poorly soluble drugs (mixed solvency concept). Present study describes the application of solvent character of melted phenol (at 50-60°C) for spectrophotometric estimation of indomethacin capsules. Solubility of indomethacin in distilled water was found to be 0.36 mg/ml at room temperature. More than 380 mg of indomethacin dissolves in one gram of melted phenol (at 50-60°C). In the present investigation, melted phenol (at 50-60°C) was utilized to extract out (dissolve) the drug from the fine powder of indomethacin capsules. Distilled water was used for dilution purpose. Absorbances of standard solutions containing 15, 30, 45 and 60 µg/ml were noted at 320 nm against reagent blanks to obtain calibration curve. Proposed method is novel, economic, eco-friendly, 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 tablet excipients and phenol did not interfere in the spectrophotometric estimation of indomethacin at 320 nm. Phenol does not interfere above 300 nm in spectrophotometric analysis.

Keywords: Mixed-solvency concept, indomethacin, phenol, spectrophotometric analysis.

INTRODUCTION

In one study, Maheshwari [1] has explained about the mixed solvency concept. If a concentrated aqueous solution is made by dissolving small concentrations of different additives (solubilizers), this solution may show additive or synergistic solvent action for a poorly water-soluble drug. If, the solubility of the same drug is enhanced by large

concentration of a single solvent/solubilizer or so, then, this may result in toxicity due to employed solvent/solubilizer. However, by application of mixed solvency concept, this problem of toxicity can be solved. The small concentrations of solubilizers may solve the problem of toxicity of large concentration of a single solubilizer.
Majority of drugs show the problem of poor solubility, whether in the case of their analytical estimations or in the field of liquid dosage forms in the form of solutions. Commonly used organic solvents for spectrophotometric analysis of water insoluble drugs include methanol, ethanol, chloroform, benzene, dichloromethane, dimethyl formamide, actonitrile, ethyl acetate, toluene, carbon tetrachloride, acetone, hexane etc. The main drawbacks of organic solvents include high cost, toxicity and pollution. Organic solvents have innumerous adverse effects caused by single exposure like dermatitis, headache, drowsiness, nausea, eye irritation and long term exposure causes serious effects such as neurological disorders, chronic renal failure, liver damage, necrosis, mutagenesis disorder. They should be replaced by other eco-friendly alternative sources. The pollution and toxicity caused by most of the organic solvents is a big challenge. The researchers are doing much work to give eco-friendly solutions for this challenge. Maheshwari [1-3] has given a nice concept, known as mixed-solvency concept. By application of this concept, innumerable solvent systems can be developed. Maheshwari is of the opinion that each substance possesses solubilizing power. He has given several eco-friendly methods in the area of drug estimations and formulations precluding the use of toxic organic solvents. The present research work also provides an eco-friendly method to estimate spectrophotometrically, the indomethacin drug in capsule formulations without the help of organic solvent.
There are very few safe liquids e g propylene glycol, glycerin, tweens, ethanol, liquid polyethylene glycols (like PEG 300, 400 etc) which are employed by pharmaceutical industries in various dosage forms for making solution type dosage forms of poorly soluble drugs. Mixed solvency concept, proposed by Maheshwari [1-3] provides a means to develop innumerable solvent systems employing combination of the pharmaceutical excipients in small concentrations. Each substance present on the earth has got solubilizing power. By combining the excipients, additive solvent actions and synergistic solvent actions can be obtained. The problem of toxicity issue due to high concentration of a solvent can be solved in this manner. The solubility of a large number of poorly soluble drugs has been enhanced by mixed solvency concept [1-27].

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 a separate study, author has attempted soxhelation using phenol as solvent. The vapours of boiling phenol got condensed in extraction chamber to effect the extraction of active constituents from powder of crude drugs. The main objective of the present study is to demonstrate the solvent action of solids. Solid excipients can nicely be employed as solubilizers in the development of pharmaceutical dosage forms in solution form of poorly soluble drugs (mixed solvency concept). Present study describes the application of solvent character of melted phenol (at 50-60°C) for spectrophotometric estimation of indomethacin capsules. Solubility of indomethacin in distilled water is 0.36 mg/ml at room temperature. More than 380 mg of indomethacin dissolves in one gram of melted phenol (at 50-60°C). In the present investigation, melted phenol (at 50-60°C) was utilized to extract out (dissolve) the drug from powder of indomethacin capsules.

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

In order to prepare a calibration curve of indomethacin, 50 mg of indomethacin standard drug was placed in a 500 ml volumetric flask. Then, 10 gram of phenol crystals were added and the flask was heated on a water bath (at 50-60°C) to melt the phenol. Then, the flask was shaken to dissolve the drug in the melted phenol. About 400 ml of distilled water (at 50-60°C) was poured in the volumetric flask and the contents were shaken for about 5 min to give a clear solution. The flask was allowed to cool to room temperature and sufficient distilled water was added to make up the volume (500 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 for indomethacin were carried out to observe its solubility behavior. To determine the solubility of the drug 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, the filtration was done through Whatmann filter paper # 41.The filtrate was appropriately diluted with distilled water to measure the absorbance at 320 nm.

In order to determine the approximate solubility of drug in melted phenol, 1 g phenol was transferred to a 10 ml volumetric flask. The weight of the stopered volumetric flask (initial weight) was noted. Then, the flask was heated on the water bath to melt the phenol (at 50-60°C). 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 melted phenol (at 50-60°C) 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 gram of melted phenol (at 50-60°C).

Proposed method of analysis

The weight of contents of emptied 20 hard gelatin capsules of indomethacin (capsule formulation I) was determined to know the average weight. Capsule powder equivalent to 50 mg indomethacin was transferred to a 500 ml volumetric flask and 10 g phenol was added. The flask was heated on a water bath (at 50-60°C) to melt the phenol. Then, the flask was shaken vigorously for 10 min by hand shaking to extract (solubilize) the drug from the tablet powder. Then, 400 ml distilled water (at 50-60°C) was added and the flask was again shaken for 5 min by hand to solubilize phenol and drug in water. The flask was allowed to cool to room temperature and sufficient distilled water was added to make up the volume (500 ml). Filtration was carried out through Whatmann filter paper # 41 to remove the capsule excipients. Ten ml filtrate was diluted to 50 ml with distilled water and the absorbance was noted at 320 nm against the reagent blank. The drug content was calculated using the calibration curve. Same procedure was repeated for capsule formulation II. Table 1 shows the results of analysis of indomethacin capsules with statistical evaluation.

Recovery studies

In order to validate the proposed analytical method, recovery studies were performed for which standard indomethacin drug sample was added (15 mg and 30 mg , separately) to the pre-analyzed capsule powder equivalent to 50 mg indomethacin and the drug content was determined by the proposed method. Results of analysis with statistical evaluation are reported in table 2.

Table 1: Analysis data of indomethacin capsule formulations with statistical evaluation (n=3)

Tablet formulation	Label claim (mg/capsule)	Percent drug estimated (mean ± SD)	Percent coefficient of variation	Standard error
I	25	98.34±1.241	1.262	0.717
II	25	100.31±1.743	1.738	1.006

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

Tablet formulation	Drug in pre-analyzed capsule powder (mg)	Amount of standard drug added (mg)	% Recovery estimated (mean ± SD)	Percent coefficient of variation	Standard error
I	50	15	101.46±1.087	1.071	0.628
I	50	30	100.92±1.173	1.162	0.677
II	50	15	100.43±1.740	1.732	1.005
II	50	30	99.58±1.666	1.673	0.962

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 melted phenol (at 50-60°C) was more than 380 mg/gm of phenol.

It is evident from table 1 that the percent drug estimated in capsule formulation I and II were 98.34±1.241 and 100.31±1.743, 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 further validated the method. Further, table 2 shows that the range of percent recoveries varied from 99.58±1.666 to 101.46±1.087 which are again very close to 100.0, indicating the accuracy of the proposed method which 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 indomethacin capsules. Melted phenol can also be tried with other water insoluble drugs which are estimated above 300 nm. Phenol does not interfere above 300 nm.

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