Original Article

New spectrophotometric estimation of indomethacin capsules with niacinamide as hydrotropic solubilizing agent

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Abstract

Background: Hydrotropic solubilization process involves cooperative intermolecular interaction with several balancing molecular forces, rather than either a specific complexation event or a process dominated by a medium effect, such as co-solvency or salting-in. **Materials and Methods:** In the present investigation, hydrotropic solution of 2 M niacinamide was employed as the solubilizing agent to solubilize the poorly water-soluble drug, indomethacin, from the capsule dosage form for spectrophotometric determination in ultraviolet region. **Results:** Hydrotropic agent used did not interfere in the spectrophotometric analysis. In preliminary solubility studies, it was found that there was more than fivefold enhancement in the aqueous solubility of indomethacin (poorly water-soluble drug) in 2 M niacinamide solution as compared to its aqueous solubility at 28 ± 1°C. **Conclusion:** The proposed method is new, simple, safe, environmentally friendly, economic, accurate and cost-effective and can be successfully employed in routine analysis.

Key words: Environmentally safe, hydrotropic solubilization, indomethacin, niacinamide, spectrophotometric

INTRODUCTION

Hydrotropy is the term originally put forward by Neuberg to describe the increase in the solubility of a solute by the addition of fairly high concentrations of alkali metal salts of various organic acids.[1] Hydrotropic solubilization process involves cooperative intermolecular interaction with several balancing molecular forces, rather than either a specific complexation event or a process dominated by a medium effect, such as co-solvency or salting-in. Hydrotropic agents have been observed to enhance the aqueous solubility of poorly water-soluble drugs.[2-15]

It is a phenomenon where addition of large amount of second solute results in increase in aqueous solubility of another solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium glycinate have been observed to enhance the aqueous solubilities of poorly water-soluble drugs. Hydrotropic solutions can be employed to replace organic solvents employed in analysis of poorly water-soluble drugs.[15-22]

Mixed hydrotropic solubilization technique is the phenomenon to increase the solubility of poorly water-soluble drugs, using blends of hydrotropic agents.[19-25] This technique can provide additive or synergistic effect on the solubility of poorly water-soluble drugs. Utilization of this method in the formulation of dosage forms made of water-insoluble drugs can also reduce the concentration of individual hydrotropic agents, in order to minimize the side effects (in place of using a large concentration of one hydrotrope, a blend of several hydrotropes can be employed in much smaller concentrations, reducing their individual toxicities).

The spectrophotometric analytical method available for indomethacin in literature is in United States Pharmacopeia, in which methanol and methylene chloride

were used to solubilize indomethacin. In this method, approximately 200 ml of methylene chloride was used, which is a toxic and costlier organic solvent.[26]

Therefore, the basic objective of the present investigation was to employ the use of hydrotropic solution to extract the drug from the dosage forms, excluding the use of costlier solvents. Costlier organic solvents are more often employed to solubilize the poorly water-soluble drugs for spectrophotometric analysis. Volatility, high cost, toxicity and pollution are the drawbacks of such solvents. In this investigation, a hydrotropic solution has been employed to solubilize the drug for its spectrophotometric analysis precluding the use of organic solvent.

MATERIALS AND METHODS

Materials

Indomethacin Capsules, Indocap® manufactured by Jagson Pharmaceuticals, Uttarakhand (B No JR09A009) as formulation I and Donica® manufactured by IPCA Pharmaceuticals, Uttarakhand (B No IP18D105) as formulation II were purchased from local market. Gift sample of bulk indomethacin drug was provided by Ranbaxy Laboratories Ltd., Dewas, India. Free gift sample of niacinamide was obtained from Alkem Laboratories Ltd., Mumbai, India.

Calibration curve

A Shimadzu® 1700, double-beam UV-visible spectrophotometer, with 10-mm matched silica cells was used for spectrophotometric analysis (software used UV Probe Ver 7.0). 2 M niacinamide was scanned against water and no interference was found in 300–350 nm range, in which indomethacin is being analyzed [Figure 1]. Twenty milligrams of indomethacin was dissolved in 50 ml of methanol and the volume was made up to 100 ml with methanol. Further dilutions were made with water and analyzed against the corresponding reagent blank [Figure 2]. From Figure 2, the characteristic peak of indomethacin was found at 320 nm, peak 1, which is far out of the range of niacinamide peak. So, we can conclude that no interference was there due to the use of hydrotropic agent.

Accurately weighed 50 mg of indomethacin was transferred to 50 ml volumetric flask and 40 ml of 2 M niacinamide was added, the drug was solubilized by shaking and the volume made up to the mark with distilled water. The standard stock solution was diluted with distilled water to obtain various dilutions. The dilutions of 10, 20, 30, 40 and 50 μg/ml were used to plot the calibration curve by noting the absorbance at λ_{max} 320 nm against the corresponding reagent blank. Beer's law was obeyed in the concentration range of 10–50 μg/ml ($R^2 = 0.999$).

Table 1: Analytical data of indomethacin capsules with statistical evaluation (n = 3)

Capsule formulation	Label claim per capsule (mg)	Percent label claim estimated* (Mean ± SD)	Percent coefficient of variation	Standard error
I	25	98.39 ± 2.113	2.147	1.220
II	25	98.04 ± 1.387	1.415	0.801

*Average of three determinations

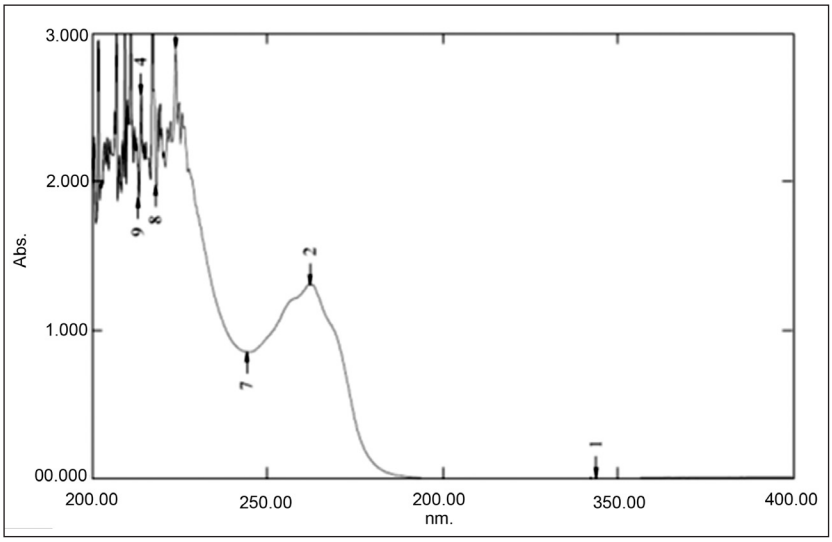

Figure 1: 2 M niacinamide scanned against water from 200 to 400 nm

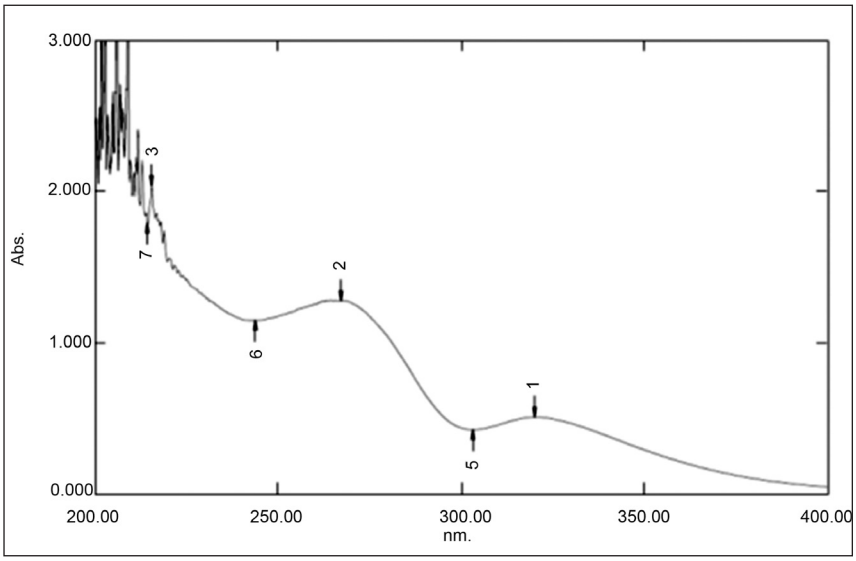

Figure 2: Indomethacin scanned against water from 200 to 400 nm

Table 2: Reproducibility and precision data (intraday and interday study)

Validation parameter	Capsule formulation	Label claim per capsule (mg)	Percent label claim estimated* (Mean ± SD)	Percent coefficient of variation	Standard error
Repeatability	I	25	99.74 ± 1.071	1.710	0.347
	II	25	99.40 ± 1.294	1.301	0.981
Interday	I	25	99.54 ± 1.231	1.777	0.780
	II	25	99.70 ± 0.735	1.711	1.351
Intraday	I	25	99.55 ± 1.828	1.638	1.109
	II	25	99.15 ± 1.989	1.414	0.910

*Average of six determinations

Table 3: Results of LOD and LOQ study

Capsule formulation	LOD (µg/ml)	LOQ (µg/ml)
I	0.023	0.700
II	0.610	0.850

Preliminary solubilities study of indomethacin

In the solubility studies, it was found that there was more than fivefold enhancement in the solubility of indomethacin in 2 M niacinamide solution at 28 ± 1°C (in comparison to its solubility in distilled water).

Proposed method

For spectrophotometric analysis of formulation I and II containing indomethacin, the contents of 20 capsules were weighed and powder equivalent to 50 mg of the drug was transferred to a 50-ml volumetric flask containing 40 ml of 2 M niacinamide hydrotropic solution. The flask was shaken for 10 minutes to solubilize the drug and the volume made up to the mark with distilled water. After filtration through Whatmann filter paper no. 41, the filtrate was appropriately diluted with distilled water and absorbance was noted at 320 nm against reagent blank [Figure 3]. To study accuracy, reproducibility and precision of the proposed method, recovery studies were conducted by spiking the preanalyzed capsule content with pure indomethacin at two levels and following the same proposed analysis method. Each type of analysis was performed three times. [Table 1].

Validation of method

1) Linearity and range: Drug solutions were prepared in the concentration range of 10–50 µg/ml. The solutions were analyzed against reagent blank at λmax 320 nm.
2) Precision and reproducibility: Six solutions of same concentration were prepared and analyzed on the same day and the values of relative standard deviation were calculated to determine intraday precision. These studies were also repeated on different days to determine interday precision [Tables 2 and 3].

RESULTS AND DISCUSSION

The mean percentage label claims estimated for formulation I was 98.39 and for formulation II was 98.04. These values are close to 100, indicating

Table 4: Recovery studies for spiked concentration of indomethacin added to preanalyzed capsule powder with statistical evaluation (n = 3)

Capsule formulation	Drug present in preanalyzed capsule powder (mg)	Pure drug added (spiked) (mg)	Percentage recovery estimated* (Mean ± SD)	Percent coefficient of variation	Standard error
I	50	15	100.48 ± 0.803	0.799	0.464
I	50	30	99.33 ± 1.467	1.477	0.847
II	50	15	101.04 ± 0.771	0.763	0.445
II	50	30	99.89 ± 1.130	1.131	0.652

*Average of three determinations

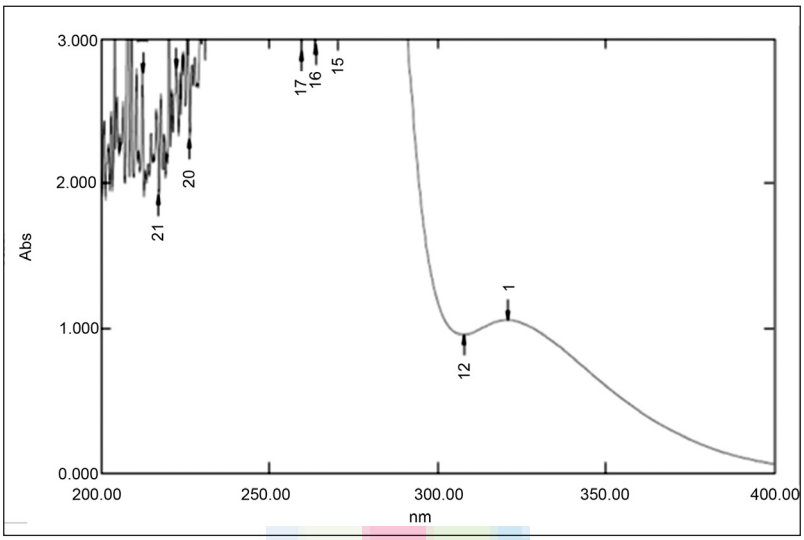

Figure 3: Indomethacin capsule content dissolved in 2 M niacinamide against reagent blank

the accuracy of the proposed method. The mean percentage recoveries ranged from 99.33 to 101.04 [Table 4]. These values are very close to 100, indicating the accuracy of the proposed method. Low values of standard deviation, percentage coefficient of variation and standard error further validated the method.

Thus, it may be concluded that the proposed method of analysis is new, simple, cost-effective, environment friendly, safe, accurate and reproducible. This method can be successfully applied in the routine analysis of indomethacin capsule formulation.

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