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Mixed Hydrotropy in Spectrophotometric Analysis of Nitazoxanide

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Abstract: The present investigation illustrates the application of mixed hydrotropy. There was significant synergistic effect on enhancement in solubility of a poorly water soluble drug by mixing two hydrotropic agents. The enhancement in solubility of nitazoxanide was more than 10 and 12 folds in 1M sodium benzoate solution (SB) and 1M sodium salicylate (SS) solution, respectively as compared to its solubility in distilled water. The enhancement in the solubility of nitazoxanide in a mixed hydrotropic solutions (SB-SS) containing 1M sodium benzoate and 1M sodium salicylate was more than 17 folds. Thus, a mixed hydrotropic solution of sodium benzoate and sodium salicylate was employed to carry out spectrophotometric analysis precluding use of organic solvents. The tablets containing nitazoxanide were analyzed successfully. Recovery studies and statistical data proved accuracy, reproducibility and the precision of the proposed method. The presence of hydrotropic agents did not interfere in the analysis.
Key Words: Sodium benzoate, sodium salicylate, nitazoxanide, mixed hydrotropy.

Introduction:

Increasing the aqueous solubility of insoluble and slightly soluble drugs is of major importance. Various techniques have been employed to enhance the aqueous solubility of poorly water-soluble drugs. Hydrotropic solubilization is one of them. Sodium benzoate, niacinamide, sodium salicylate, sodium acetate, sodium citrate, and urea, have been employed to enhance the aqueous solubility of many poorly water soluble drugs. Various organic solvents like methanol, chloroform, alcohol, dimethyl formamide, and benzene have been employed for the solubilization of poorly water soluble drugs for spectrophotometric estimations. Drawbacks of organic solvents include higher cost, toxicity, pollution, and error, in analysis due to volatility (1).

The primary objective of this study was to employ hydrotropic solubilizing agents, sodium benzoate and sodium salicylate for the selected model drugs to preclude the use of organic solvents. The study also includes development of simple, reproducible and economical spectrophotometric method for the determination of nitazoxanide in bulk drug and its tablet formulation.

Nitazoxanide, is a synthetic nitrothiazolyl-salicylamide derivative and a poorly water soluble drug. Chemically it is [2-[(5-nitro-1,3-thiazol-2-yl) carbamoyl]phenyl] acetate. It is used as an anti-protozoal agent and is approved for treatment of infectious diarrhea. Extensive literature survey revealed HPLC, HPTLC and spectrophotometric methods for estimation of nitazoxanide alone or in combination with other drugs which require use of costlier and toxic organic solvents (2-10).

Experimental:

A Jasco double beam UV-Visible spectrophotometer (Model- V-630) with 1cm matched quartz cells was used for the spectral measurements. Nitazoxanide was

obtained from M/s. Ind-Swift Laboratories Ltd., India. All reagents and chemicals were of analytical grade.

I) Preparation of standard solution and calibration curve:

The standard solution (100µg/ml) of the nitazoxanide was prepared in distilled water. It was necessary to warm on water bath to accelerate the dissolution process. The standard solutions were diluted with distilled water to obtain concentration ranging from 2µg/ml to10 µg/ml. The wavelength of maximum absorption (λmax) of nitazoxanide was found at 418nm.The linear relationship was observed over the range of 2-10 µg/ml.

II) Preliminary solubility study of drug:

Solubility study of nitazoxanide was determined at 28 ± 1°C. An excess amount of drug was added to screw capped 30ml glass vial containing different aqueous systems viz.distilled water, 0.1M hydrochloride, 0.1M sodium hydroxide and hydrotropic solutions alone and in combinations. The vials were shaken mechanically for 12hrs at 28 ± 1°C in mechanical shaker. These solutions were allowed to equilibrate for the next 24hrs, and then centrifuged for 5min at 2000 rpm. The supernatant of each vial was filtered through Whatman filter paper No.41. The filtrates were diluted suitably and analyzed spectrophotometrically against corresponding solvent blank.

Analysis of nitazoxanide by proposed method:

Powder equivalent to 100mg of nitazoxanide was taken in a 250ml volumetric flask and dissolved in 150ml of mixture of sodium benzoate (1M) and sodium salicylate (1M). The flask was shaken properly for 10 min to solubilize the drug; and the volume was made up to the mark with mixed hydrotropic solution. After filtration through a Whatman filter paper no. 41, the filtrate was divided into two parts A and B. Part A was kept at Room Temperature for 48 hrs to check its chemical stability and precipitation, if any. Part B was diluted with water. The resulting solution was scanned in the range of 300-500 nm. From the UV-Visible spectrum of nitazoxanide, 418nm (λmax) was selected as the wavelength of determination. The standard stock solution of nitazoxanide was diluted to obtain a concentration range of 2-10µg/ml and absorbances were measured at selected wavelengths. The concentrations of drugs against absorbance was plotted to obtain a calibration curve. It obeys Beer's law within the concentration range of 2-10 µg/ml. The calibration curve of nitazoxanide is shown in fig 1. The absorptivity values (A 1%, 1 cm) of drug at selected wavelengths was determined. The concentration of drug in laboratory mixture was determined by substituting the absorbance and absorptivity values in Beer- Lambert Law equation A=abc where, A= absorbance, a= Absorptivity (g/100ml), b= path length and c= concentration (g/100ml) of drug. Part A solution was analyzed in the same way as part B solution.

Analysis of nitazoxanide in tablet by proposed method:

Twenty tablet of nitazoxanide were weighed and finely powdered. Powder equivalent to 100mg of nitazoxanide was taken in a 250ml volumetric flask and dissolved in 150ml of mixture of sodium benzoate (1M) and sodium salicylate (1M). The flask was shaken properly for 10 min to solubilize the drug; and the volume was made up to the mark with mixed hydrotropic solution. After filtration through a Whatman filter paper no. 41, the filtrate was divided into two parts A and B. The content of nitazoxanide in the tablet was determined was determined in the same way as pure drug.

Recovery studies:

The recovery studies were carried out at different level of concentration by spiking a known concentration of standard drug to the preanalyzed sample and contents were reanalyzed by proposed methods

Validation:

The methods were validated statistically as per ICH/USP guidelines for parameter like accuracy, precision, ruggedness, linearity and range. Accuracy was ascertained on the basic of recovery studies. Precision was studied by analyzing five replicates of sample solution and concentrations were calculated. Ruggedness was established by carrying out experiment at different time within a day (intraday), different day (interday) and by different analyst. Linearity and range were determined by analyzing 80-120% of test concentrations of each drug.

TABLE 1:Results of recovery studies of tablet formulation with statistical evaluation

Tablet formulation	Drug present in preanalysed tablet powder (mg)	Spiked drug added (mg)	% recovery (Mean ± SD)
Brand A	100	10	98.65 ± 0.6521
	100	20	99.85 ± 0.9746
Brand B	100	10	98.12 ± 1.0547
	100	20	98.73 ± 0.5762

- The values indicate the mean % estimation values of five replicate measurement (n=5) ± standard deviation.

TABLE 2:Analysis of Nitazoxanide tablet formulation

Sr. No.	Tablet formulation	Label claim	% Estimation (Mean± S.D.)*
1	Brand A	500	101.52 ± 0.8467
2	Brand B	500	98.76 ± 0.7643

* The values indicate the mean % estimation values of five replicate measurement (n=5) ± standard deviation.

Result and Discussion:

Results of solubility studies indicate that, the enhancement in the solubility of nitazoxanide was more than 10 folds and 12 folds in 1M sodium benzoate and 1M sodium salicylate solution, respectively, as compared to its solubility in distilled water and other hydrotropic agents. Therefore, these two hydrotropic solutions were selected to see the synergistic effect on enhancement in solubility of nitazoxanide.

In order to study the influence of pH on solubilities, solutions of 0.1 M HCl and 0.1 M NaOH were made, and the solubility of drug was determined. It was observed that there was negligible effect on solubilities in acidic solutions and slight increased in solubility in basic solution. This study proves that increase in solubility of nitazoxanide in hydrotropic solution, 1M sodium benzoate and 1M sodium salicylate (alone or in combination) are not due to alteration in pH, but are due to hydrotropic phenomenon.

Part A solution of drug in hydrotropic solution was kept at room temperature for 48 hrs. There was no precipitation of drug in Part A solution within 48 hrs. In addition, drug contents of Part A solutions (after 48 hrs) were same as those of Part B solutions (fresh solutions). This study reveals that the estimations can be done within 48 hrs at least, without having any detrimental effect on drug stability.

From Table1, it is evident that there is good agreement between the amounts estimated, and those claimed by the manufacturers. Percent label claims were very closed to 100%, with low values of standard deviation. The recovery study shows accuracy of the method. On observing the validation parameters the method was found to be accurate and precise (Table 2).

From this study, it is obvious that there was no interference of mixed sodium benzoate and sodium salicylate (1M) in the estimation of nitazoxanide (λmax-418 nm). Sodium benzoate and sodium salicylate do not absorb above 300 nm. Because of these reasons, it can be concluded, that a large number of poorly water soluble drugs having λmax above 300 nm, may be tried for estimation by the proposed method, provided that their preliminary solubility studies are conducted to observe the enhancement effect on solubility. Sodium benzoate and sodium salicylate is cheaper than most of the organic solvents and can thus substitute expensive methanol, dimethyl formamide, chloroform and carbon tetrachloride. Drawbacks of organic solvents include toxicity, error due to volatallity, pollution, and cost. The tablets containing nitazoxanide were analyzed successfully using mixed hydrotropic solution of Sodium benzoate (1M) and sodium salicylate (1M).

Further, it is thus concluded that the proposed method is new, simple, cost effective, accurate, safe, free from pollution and precise and can be successfully employed in the routine analysis of these drugs in pharmaceutical dosage forms.

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