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NOVEL SPECTROPHOTOMETRIC ESTIMATION OF IZETEMIB, LOSORTON AND SIMVASTATIN USING HYDROTROPIC SOLUBILIZING AGENTS

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ABSTRACT: Ultraviolet absorption spectrophotometric method for the estimation of poorly water soluble drugs like Izetemib, Losorton and Simvastatin in pharmaceutical formulations has been developed. Aqueous solubilities of this selected model drugs was to a great extent (6 to 96 fold) in 1 M sodium acetate, 1M sodium chloride, 1 M sodium gluconate and 1 M urea solutions. The primary objective of the present investigation was to employ these hydrotropic solutions to extract the drug from dosage forms, precluding the use of costlier organic solvents. The selected ëmax for Izetemib, Losorton and Simvastatin were 258.5 nm, 231.5 nm and 232 nm respectively. The hydrotropic solutions used did not show any absorbance above 226 nm, and therefore, no interference in the estimation was seen. The results of analysis have been validated statistically, and by recovery studies. The proposed methods are new, simple, economic, accurate, safe and precise.
KEYWORDS: IZETEMIB, LOSORTON, SIMVASTATIN, HYDROTROPIC SOLUBILIZING AGENTS,SPECTROPHOTOMETRIC ESTIMATION.

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. The term hydrotropy has been used to designate the increase in solubility of various substances in water due to the presence of large amounts of additives. Sodium benzoate, sodium acetate, sodium bicarbonate, sodium chloride, sodium gluconate, thiourea, trisodium citrate and urea have been employed to enhance the aqueous solubility of many poorly water soluble drugs.[1-16]

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. The primary objective of this study was to employ hydrotropic solubilizing agents for Izetemib, Losorton and Simvastatin to preclude the use of organic solvents. In the preliminary it was found that there was considerable enhancement in the aqueous solubility of Izetemib, Losorton and Simvastatin in 1 M sodium acetate, 1M sodium chloride, 1 M sodium gluconate and 1 M urea solutions. Since these solutions do not absorb above 226 nm, it was thought to use these agents' hydrotropic agents, to extract out the drugs having ëmax above 226 nm, from their corresponding solid dosage forms. Recovery studies and statistical analysis were used to validate the methods.

MATERIALS AND METHODS Apparatus and solutions

A Jasco UV-530 Visible double beam Spectrophotometer with 1 cm matched silica cells, were employed. Sodium acetate, sodium chloride, sodium gluconate and urea was used is analytical grade obtained from research laboratory, Pune.

Procedures

I) Preparation of standard solution and calibration curve:

The standard solutions (200 µg/ml) of the model drugs were prepared in distilled water. It was necessary to warm on a water bath to accelerate the dissolution process. The standard solutions were diluted with distilled water to obtain various dilutions (5, 10, 15, 20, 25, 30, 35, and 40 µg/ml) The ëmax for Izetemib, Losorton and Simvastatin were found at 258.5 nm, 231.5 nm and 232 nm respectively. A linear relationship was observed over the range of 5-30 µg/ml for Izetemib, 5-30 µg/ml for Losorton, and 5-25 µg/ml for Simvastatin.

II) Preliminary solubility study of drug:

Solubility of Izetemib, Losorton and Simvastatin was determined at 28±1^{0}C. An excess amount of drug was added to screw capped 30 ml glass vials containing different aqueous systems viz. distilled water, buffer of pH 7.5 to 9.5 and hydrotropic solutions. The vials were shaken mechanically for 12 h at 28±1^{0}C in mechanical shaker. These solutions were allowed to equilibrate for the next 24 hours, and then centrifuged for 5 min 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.

III) Analysis of the tablet formulations of the drug by proposed method:

Twenty tablets of Izetemib formulation–I were weighed, and ground to a fine powder. An accurately weighed powder sample equivalent to 40 mg of Izetemib, was transferred to a 25 ml volumetric flask. 20 ml of 1.0 M sodium acetate solution was added, and the flask was shaken for about 10 min to dissolve the drug, and the volume was made up to the mark with distilled water. The solution was filtered through Whatman filter paper No. 41. The filtrate was divided into two parts A, and B. Part A was kept at room temperature for 48 h to check its chemical stability and precipitation, if any. Part B was diluted appropriately with distilled water, and was analyzed on a UV Spectrophotometer against reagent blank. The drug content of the tablet formulation was then calculated. There was no precipitation in Part A solution after 48 h. After 48 h (at room temperature), Part A solution was analyzed in the same way as Part B solution.

A similar procedure was used in case of tablet formulation II of Izetemib, tablet formulations III and IV of Losorton, and tablet formulations V and VI of Simvastatin. Like 1.0 M sodium acetate solution, 1.0 M hydrotropic solutions were also used to analyze all types of tablet formulations. Table 1 shows the results of all such analyses.

Recovery studies:

For recovery studies, tablet powder (formulation I to VI of drugs), equivalent to 40 mg drug was taken in a 25 ml volumetric flask. In this flask, 20 mg of pure drug (corresponding spiked drug) was transferred 20 ml of 1.0 M sodium acetate solution was added, and the flask was shaken for about 10 min. The volume was made up to the mark with distilled water, and filtered through Whatman filter paper No. 41. The solution was diluted appropriately with distilled water, and analyzed for drug content. A similar procedure was repeated using 1.0 M other hydrotropic solutions, in place of 1.0 M sodium benzoate solution, in all the cases. The results of analysis of recovery studies are presented in Table 2.

RESULTS AND DISCUSSION

Results of solubility studies indicated that, enhancements in aqueous solubilities in 1 M sodium acetate solution, as compared to solubility in distilled water, were more than 6, 15 and 20 fold in case of Izetemib, Losorton and Simvastatin respectively. Similarly, enhancement in aqueous solubility in 1 M sodium chloride solution as compared to solubility in distilled water, were more than 63, 78 and 90 fold in cases of Izetemib, Losorton and Simvastatin respectively. Similarly, enhancement in aqueous solubility in 1 M sodium gluconate solution as compared to solubility in distilled water, were more than 25, 32 and 52 fold in cases of Izetemib, Losorton and Simvastatin respectively. Similarly, enhancement in aqueous solubility in 1 M urea solution as compared to solubility in distilled water, were more than 75, 88 and 96 fold in cases of Izetemib, Losorton and Simvastatin respectively.

The pH of hydrotropic solutions was ranges from 7.5 to 9.5. Therefore, in order to study the influence of pH on solubilities, buffer solutions of pH 7.5 to 9.5 were made, and the solubilities of all the drugs were determined. This study proves that increase in solubilities of these three drugs in hydrotropic solutions are not due to alteration in pH, but are due to hydrotropic phenomenon. This indicates that the enhancement in the aqueous solubility of model drugs in 1.0 M hydrotropic solutions was largely due to hydrotropy.

Part A solution of drug was kept at room temperature for 48 h. There was no precipitation of drug in Part A solutions within 48 h. In addition, drug contents of Part A solutions (after 48 h) were same as those of Part B solutions (fresh solutions).

This study reveals that the estimations can be done within 48 h at least, without having any detrimental effect on drug stability.

From Table 1, it is evident that there is good agreement between the amounts estimated, and those claimed by the manufacturers. Percent label claims are very close to 100, with low values of standard deviation, % coefficient of variation, and standard error.

Accuracy, reproducibility, and precision of the proposed methods, were further confirmed by percent recovery values, which were close to 100 with low values of standard deviation, % coefficient of variation, and standard error (Table 2).

Table 1 Results of analysis of commercial tablet formulations.

Sr. No.	Drug	T F	LC	Sodium acetate			Sodium chloride			Sodium gluconate			Urea		
				% LC estimated* (mean+S.D.)	cv	SE	% LC estimated* (mean+S.D.)	CV	SE	% LC estimated* (mean+S.D.)	CV	SE	% LC estimated* (mean+S.D.)	CV	SE
1	Izetemib	I	10	99.8+0.88	0.89	0.56	100.6+0.60	0.61	0.49	99.6+0.35	0.34	0.34	100.9+0.06	0.06	0.40
2		II	10	100.5+0.90	0.90	0.96	100.7+0.96	0.95	0.31	100.7+0.29	0.30	0.78	99.7+0.98	0.99	0.39
3	Losorton	III	50	101.4+0.83	0.84	0.26	101.2+0.78	0.77	0.56	100.1+1.02	1.01	0.16	99.8+0.49	0.49	0.75
4		IV	50	101.5+0.97	0.97	0.45	100.8+0.76	0.78	0.17	100.5+0.35	0.35	0.70	100.5+0.56	0.55	0.18
5	Simvastatin	V	20	100.8+0.75	0.76	0.99	99.7+0.89	0.90	1.02	100.8+0.77	0.77	0.90	100.4+0.89	0.89	0.77
6		VI	10	100.9+0.22	0.21	0.78	100.9+0.20	0.21	0.18	101.1+1.01	1.00	0.98	99.9+0.78	0.79	0.45

TF- Tablet formulation, AD- Amount of drug, LC- Label claim, SE- Standard error, *Mean of three determinations, I- Izetib tablets (Unichem Limited), II- Izedoc tablets (Lupin Limited, India), III- Angizar tablets (Micro carsyon Limited), IV- Alsartan tablets (Aristo Limited), V-Statin tablets (Unichem Limited, India), VI- Sim tablets (Orchird Limited).

Table 2: Recovery study for spiked concentration of drugs added to the preanalyzed dosage form.

Sr. No.	Drug	TF	AD	DA	Sodium acetate			Sodium chloride			Sodium gluconate			Urea		
					% LC estimated* (mean+S.D.)	cv	SE	% LC estimated* (mean+S.D.)	CV	SE	% LC estimated* (mean+S.D.)	CV	SE	% LC estimated* (mean+S.D.)	CV	SE
1	Atorva statin	I	40	20	100.5+0.88	0.87	0.57	101.6+0.67	0.67	0.97	98.9+0.88	0.87	1.02	101.2+0.78	0.78	0.34
2		II	40	20	99.9+0.78	0.77	0.77	100.8+0.78	0.78	0.42	101.5+0.65	0.65	0.89	100.4+0.78	0.78	0.55
3	Didano sine	III	40	20	99.8+0.58	0.57	0.83	100.4+0.64	0.65	0.77	100.8+0.95	0.95	0.74	100.9+0.76	0.76	0.28
4		IV	40	20	100.9+0.98	0.99	0.86	99.8+0.46	0.46	0.61	100.7+0.99	1.00	0.61	99.7+0.58	0.59	0.86
5	Parace tamol	V	40	20	101.4+0.56	0.56	0.90	99.7+0.47	0.48	0.58	100.1+0.19	0.20	0.89	99.9+0.48	0.48	0.46
6		VI	40	20	100.1+1.01	1.01	0.33	101.3+0.45	0.45	0.34	99.8+0.66	0.65	0.45	101.0+0.45	0.44	0.90

TF- Tablet formulation, AD- Amount of drug, DA- Drug Added (Spiked) mg, SE- Standard error, *Mean of three determinations, , I- Izetib tablets (Unichem Limited), II- Izedoc tablets (Lupin Limited, India), III- Angizar tablets (Micro carsyon Limited), IV- Alsartan tablets (Aristo Limited), V-Statin tablets (Unichem Limited, India), VI- Sim tablets (Orchird Limited).

From this study, it is obvious that there was no interference of hydrotropic solutions in the estimation of Izetemib (ëmax–258.5 nm), Losorton (ëmax–231.5 nm), Simvastatin (ëmax–232 nm) Hydrotropic solutions do not absorb above 226 nm. Because of these reasons, it can be concluded, that a large number of poorly water soluble drugs having ëmax above 226 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. Hydrotropic solutions are 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 volatility, pollution, and cost. Thus 1.0 M Hydrotropic solutions may be better substitutes for organic solvents.

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. The
proposed method shall prove equally effective to analyze Izetemib, Losorton and Simvastatin in the corresponding drug samples (basic drugs), and may prove to be of great importance in pharmaceutical analysis.

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