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A Novel Application of Simultaneous Estimation and Validation of Nelfinavir Mesylate Formulations Using Paracetamol as Hydrotropic Solubilizing Agent in Tablet Dosage Form

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Abstract : Hydrotropic solubilization technique is one of them. In the present investigation hydrotropic solution of 1M Paracetamol has been employed as solubilizing agent to solubilization poorly water soluble drug Nelfinavir Mesylate, from fine powder of its tablet dosage form for spectrophotometric determination in ultraviolet region. Levofloxacin shows maximum absorbance at 283 nm. Beer's law was obeyed in the concentration range of 50-400 µg/ml. Results of analysis were validated statistically and by recovery studies. The proposed method is new, simple, environment friendly, accurate and cost-effective and can be successfully employed in routine analysis of Nelfinavir Mesylate in tablets.
Key words: - Nelfinavir Mesylate, Hydrotropic solubilization, Paracetamol.

Introduction

Nelfinavir Mesylate [1] is a novel HIV-1 protease inhibitor; with a chemical name (3S, 4aS,8aS)-N- (1,1-Dimethylethyl) decahydro-2- [(2R, 3R)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl) amino]–4-(phenylthio) butyl]-3-isoquinolinecarboxamide methanesulfonate .It is an antiretroviral drug that acts by binding reversibly to HIV protease thereby preventing cleavage of the viral precursor polyproteins. Literature survey reveals many Chromatographic methods [3-10] for the determination of Nelfinavir in biological fluids and in combination with other antiviral and few Spectrophotometric methods [11-14] The term "hydrotropy" has been used to designate the increase in aqueous solubility of various poorly water-soluble compounds due to the presence of a large amount of additives. Sodium benzoate, sodium salicylate, niacinamide, sodium hydroxide, and urea have been employed to enhance the aqueous solubility of poorly water-soluble drugs [15-17].Various organic solvents like methanol, chloroform, ethanol, dimethyl formamide, benzene, hexane, acetone, toluene, carbon tetrachloride, diethyl ether and acetonitrile are widely used in spectrophotometric estimations of poorly water-soluble drugs. Most of these organic solvents are toxic, costlier and sources of pollution. Inaccuracy in spectrophotometric estimations due to volatility of organic solvents is another drawback of these solvents. There was tremendous increase in aqueous solubility of dimethyl formamide, in 1M paracetamol solution. Paracetamol does not show absorbance above 296 nm. The Beer's law was obeyed in the range of 50 to 400 mcg/ml at 283.5 nm for Nelfinavir Mesylate in presence of paracetamol. In the present investigation Nelfinavir Mesylate tablets have been estimated by BP method (spectrophotometric) which involved use of an organic solvent, methanol and also by the hydrotropic solubilization technique which involved use of Sodium benzoate as hydrotropic solubilizing agent. The results of analysis obtained by the proposed method compared

very well with those obtained by the pharmacopoeial method. Recovery studies and low values of standard deviation, % coefficient of variation and standard error validated the proposed method.

Experimental

Instruments and chemicals

UV/Visible spectrophotometer (Shimadzu Model 1601) was employed with spectral bandwidth of 1 nm and wavelength accuracy of 0.3 nm (with automatic wavelength correction with a pair of 1 cm matched quartz cells). Acetonitrile HPLC grade, sodium hydroxide AR grade, potassium hydrogen orthophosphate AR grade of Rankem ltd. Water HPLC grade of Milli-Q were used. Commercial tablets of Nelfinavir Mesylate were purchased from the local market.

Method of preparation of 1 M Paracetamol solution

Paracetamol (13.65 g) was suspended in 100 ml distilled water in a 250 ml beaker. Sodium chloride 2 g was dissolved in 50 ml distilled water, separately. Sodium chloride solution was added in Paracetamol solution in successive portions and was stirred after each addition. When a clear solution was obtained due to conversion of ibuprofen in ibuprofen sodium, the pH of the solution was adjusted to 8.2 to 8.7 with sodium chloride solution and volume was made up to 250 ml with distilled water.

Calibration curve

Nelfinavir Mesylate (100 mg) was accurately weighed and transferred in a 25 ml volumetric flask and 20 ml of 1 M Paracetamol was added and the drug was solubilized by shaking the flask. The volume was made up to the mark with distilled water. The stock solution was further diluted with distilled water to obtain various dilutions. Standard solutions of 50, 150, 250, 300, 350 and 400 mcg/ml of drug were used to plot the calibration curve by taking the absorbance at 301 nm against corresponding reagent blanks.

Preliminary solubility studies of Nelfinavir Mesylate:

Solubility of Nelfinavir Mesylate were determined at 25±1°c in 1 M Paracetamol solution, distilled water and buffer of pH 8.5 Sufficient excess amount of drug was added to screw capped glass vials of 30 ml capacity, containing distilled water, buffer of pH8.5,1 M Paracetamol solution. The vials were shaken mechanically for 15 hours at 25±1°c in orbital flask shaker the solution were allowed to equilibrate for next 24 hours and then centrifuge for 5 min. at 2000 rpm. The supernatant of each vial was filtered through whatman filter paper #41. Filtrates were diluted suitably and analyzed spectrophotometrically against corresponding solvent blanks.

Analysis of Nelfinavir Mesylate tablets using 1 M Paracetamol solution

Twenty tablets of formulation I was weighed and powdered. Powder equivalent to 100 mg Nelfinavir Mesylate was transferred to a 50ml volumetric flask containing 50 ml of 1 M Paracetamol solution. The flask was shaken for about 5 minutes to solubilise the drug. Then volume was made up to the mark with distilled water solution was filtered through whatman filter paper no 41. Filtrate was divided in 2 parts, A & B part A was kept at room temperature for 34 hours to check the effect on stability of drug in presence of Paracetamol and also to not precipitation, if any during this period. Part B filtrate was appropriately diluted with distilled water and absorbance was noted at 283 nm (λ max) against solvent blank and drug content was calculated (table 1).After 36 hour , filtrate of part A was appropriately diluted with distilled water and analyzed for drug content. There was no precipitation in the filtrate in 48 hours. Similar procedure was adopted in cases of formulation II and formulation III.

Recovery studies:

In order to check the accuracy, reproducibility and precision of the proposed method,

recovery studies were conducted. Preanalyzed tablet powder (formulation I) equivalent to 100 mg Nelfinavir Mesylate was transferred with 50 ml volumetric flask. Pure Nelfinavir Mesylate drug sample (625mcg) was added in the same volumetric flask. Now 50 ml of 1 M Paracetamol solution the flask was shaken about 5 min to solubilise the drug then the volume was made up to the mark with distill water then solution was filtered in whatman filter paper no. 41 the filtrate was diluted with distill water appropriately and absorbance was noted at 283 nm against corresponding reagent blank .Drug content was calculated and % recovery was estimated (table 2).

Table 1: Analysis Data of Tablet Formulations with Statistical Evaluation

Tablet Formulation	Label Claim (mg/Tablet)	%Label Claim Estimated* (Mean±S.D.)	% Coeff. of Variation	Standard Error
I	625	99.96±0.11	0.23	0.46
II	625	101.02±0.21	0.66	0,19
III	625	99.21±1.12	1.12	0.03

* Mean (n = 6)

Table 2. Recovery study for spiked concentration of drug added to the preanalyzed tablet powder with statistical evaluation

Tablet formulation	Tablet powder taken (mg)	Amount of standard drug added (mg)	% Recovery	% RSD	S.D.
	625	5	99.97	0.22	0.02
I	625	10	98.96	0.35	0.12
	625	15	100.06	0.65	0.34
	625	5	101.23	0.43	0.73
II	625	10	99.92	0.76	0.17
	625	15	101.01	0.88	0.97
	625	5	99.84	1.05	0.83
III	625	10	100.43	1.21	0.91
	625	15	99.95	0.86	0.28

*Average of six determinations

Result and Discussion:

The result of recovery studies (presented in table 2) indicates that % recovery estimated ranged from 100.12+0.12 to 101.23 + 1.05 by use of proposed method. Since the percent recovery values are close to 100, this indicates the accuracy of the proposed method. Values of standard deviation, % coefficient of variation and Standard errors are satisfactorily low and confirm further the accuracy, reproducibility, precision of the proposed method. Methanol, ethanol, chloroform, hexane, acetonitrile, acetone, diethyl ether, toluene and carbon tetra chloride are widely used in spectrophotometric estimation of poorly water soluble drug. Most of these organic solvents are toxic, costlier and source of pollution. Inaccuracy of spectrophotometric estimations due to volatility is another drawback of these solvents. Urea doest not interfere above 311 nm just like Nelfinavir Mesylate as model drug (poorly water soluble) other poorly water soluble drugs may be studied for the enhancement effect in solubility in 1M Paracetamol solution. If the λ max of such drug is above 311 nm and there is significant enhancement in solubility in hydrotropic solution the drug can be easily estimated like the proposed method avoiding the use of organic solvents. The solubility of Nelfinavir Mesylate in 1 M paracetamol solution was found to be more than 112 fold as compare to its solubility in distilled water. Part A solution of drug was kept at room temperature for 36 h. There was no precipitation of drug in Part A solutions within 36 h. In addition, drug contents of Part A solutions (after 36 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. 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

Conclusion

Thus, it may be concluded that the proposed method of analysis, using urea as the hydrotropic solubilizing agent is new, simple, cost-effective, environmentally friendly, safe, accurate and reproducible. Paracetamol and the commonly used tablet excipients did not interfere in spectrophotometric. Decided advantage is that organic solvent (methanol) is precluded but not at the expense of accuracy. The proposed method is worth adopting in pharmacopoeia. By proper choice of hydrotropic agents, the use of organic solvents in analysis may be discouraged to a large extent.

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