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Application of mixed cosolvency concept in spectrophotometric estimation of acyclovir tablets

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ABSTRACT

The present study was aimed to develop a novel mixed cosolvency solubilization technique to increase the solubility of poorly water soluble drugs. This technique is used to estimate the amount of acyclovir in bulk drug and tablets by spectrophotometric method in the mixture of solvents 15% urea, 8% PEG 400 and 7% hydroxy propyl β-Cyclodextrin. Beer's law was obeyed in the concentration range of 2-20µg/ml and showed maximum absorbance at 251nm. The solubility of acyclovir in distilled water was found to be 0.525mg/ml, where as in this solvent mixture was found to be 6 mg/ml. Hence the solubility was increased by 12 folds as compared with distilled water. The analysis of tablets indicated good correlation between estimated and label claim. The results of recovery study revealed that any small change in the drug concentration in the solution could be accurately determined by the proposed method. The low values of LOD and LOQ of acyclovir in the solvent mixture indicated good sensitivity of proposed method. As urea, PEG 400 and HP-βCD were cheaper than most of the organic solvents, these can be used as a substitute for organic solvents. The study proved that mixed cosolvency phenomenon is an effective technique in enhancement of aqueous solubility of poorly water soluble drugs. The proposed method is new, simple, accurate, non-toxic and precise method that can be successfully employed for estimation of drugs in routine analysis of tablets.

Key Words: Mixed cosolvency, acyclovir, urea, solubilisation, spectrophotometry.

INTRODUCTION

Increasing the aqueous solubility of insoluble and slightly soluble drugs is major importance[1]. This is because most of the newly developed drugs are highly lipophilic in nature and its analysis was mainly carried out using organic solvents like methanol, chloroform, ethanol, benzene, acetone, toluene, carbon tetrachloride, diethyl ether and acetonitrile[2-4]. Most of these organic solvents are toxic, volatile and costlier. This may cause inaccuracy in analytical methods[5]. Various techniques have been employed by the researchers to improve the aqueous solubility of lipophilic drugs and hydrotropy is one among them. Hydrotropy can be considered to be potentially and industrially attractive technique since the observed increase in solubility is much

higher than that affected by other solubilization methods[6]. Several works have been reported on use of hydrotropic solvents in estimation of various poorly water soluble drugs using some of the hydrotropic agents like sodium benzoate, sodium salicylate, niacinamide, sodium ascorbate, and urea[7-12]. But it was observed that hydrotropy is another type of cosolvency, which is utilized to improve the aqueous solubility of poorly water soluble drugs. Based on this approach a novel mixed-co-solvency solubilisation phenomenon was developed to study the improvement in solubility of a lipophilic model drug acyclovir. Few works based on this mixed cosolvency technique was reported to study the improvement in solubility by titrimetric estimations[13,14]. This mixed cosolvency technique is based on the principle that instead of using one solubilizer in large concentration for a desired level of solubility, several solubilizers like hydrotropes (sodium ascorbate, urea, sodium benzoate), co-solvents (propylene glycol, PEG 200, 300, 400,) and water soluble solids (PEG 4000, 6000, cyclodextrins) in varying concentrations may be used that may show additive or synergistic enhancement in solubility. These solubilizers do not cause any toxicity and non-volatile in nature. Based on the literature it was observed that no spectrophotometric estimations of poorly water soluble drugs using the mixed cosolvency technique have been reported. In the present work the total concentration of solubilizers was kept constant (30% w/v) in all solubilizing systems. The selected solubilizers were urea (15%) as hydrotrope, PEG 400 (8%) as cosolvent and hydroxy propyl β-cyclodextrin (7%) as water-soluble solid. Acyclovir is an anti-viral drug, a synthetic nucleoside analogue which is active against herpes viruses. The molecular formula is $C_8H_{11}N_5O_3$. The chemical name is 9-[(2-Hydroxy) methyl] guanine; 2-Amino-1, 9-dihydro-9-(2-hydroxyetoxymethyl)-6H-purin-6-one. It is slightly soluble in water, whereas freely soluble in dimethylsulfoxide and dilute acids and alkali[15]. So an attempt was made in this investigation to demonstrate the application of mixed solvency concept for spectrophotometric estimation of acyclovir in the bulk drug sample and tablets.

MATERIALS AND METHODS

Acyclovir bulk drug was a gift sample from Remidex Pharmaceuticals, Bangalore. Urea PEG 400 and Hydroxy Propyl-β Cyclodextrin was purchased from S.D.Fine Chemicals, Mumbai. Tablets of acyclovir were purchased from local market. Shimadzu UV/Visible recording spectrophotometer (model-UV-1601) with 1cm matched silica cells was employed. All other chemicals and solvents used were of analytical grade.

Saturation solubility studies of the drug

Solubility of acyclovir was determined by saturation aqueous solubility method in 30% mixed cosolvents containing 15%urea, 8% PEG 400 and 7% HP-βCD in distilled water. An excess amount of drug was added to beakers containing 50ml of mixed cosolvents and distilled water. The beakers were shaken for 12 hours at 28 ± 1^0C. The solutions were filtered through Whatman filter paper #41, and the resulting filtrates were suitably diluted and analyzed spectrophotometrically against solvent blank.

Preparation of standard stock and calibration curve

Standard stock solution of acyclovir was prepared by dissolving 50mg of drug in 50 ml of mixed cosolvents. From this solution 5ml of solution was taken and diluted to 100ml with distilled water to get a solution containing 50µg/ml and scanned in the entire UV range of 400-200 nm to determine the absorption maxima of the drug. The absorption maxima of acyclovir were found to be 251 nm (Fig.1). Seven working standard solutions for the drug having concentration 2, 4, 6, 8 and 10µg/ml was prepared with distilled water from the stock solution. The absorbances of

resulting solutions were measured at wavelength of 251nm against solvent blank and a calibration curve was plotted to get the linearity and regression equation.

Analysis of acyclovir in tablets using mixed cosolvents

Twenty tablets were weighed and powdered. Powder equivalent to 200mg acyclovir was transferred to 50ml volumetric flasks containing 40ml of mixed cosolvents. The flasks were shaken for about 10min to solubilize the drug. Then volume was made up to the mark with distilled water. From this 5ml of solution was pipetted into 50ml volumetric flask and the volume was made up with distilled water. From this 5ml was pipetted into 100ml volumetric flask and the volume was made up to the mark with distilled water. The absorbance of the resulting solution was measured at 251nm against solvent blank and drug content was calculated.

Validation of the proposed method

The proposed method was validated for the following parameters[16].

Recovery studies

In order to check the accuracy and reproducibility of the proposed method, recovery studies were conducted. Tablet powder equivalent to 200 mg of acyclovir was transferred to a 100ml volumetric flask containing mixed cosolvents. Pure acyclovir (10 mg) was added to the same volumetric flask. The flask was shaken for 10 min to solubilize the drug. Then solution was filtered through Whatman filter paper #41. The filtrate was diluted with distilled water appropriately and absorbance was measured at 251nm against corresponding solvent blank. Drug content and percent recovery was calculated. Similar procedure was adopted using 20 mg and 30 mg of pure acyclovir as spiked concentration. The drug contents were determined and percent recoveries were estimated.

Precision

Precision was determined by studying the repeatability and intermediate precision. The standard deviation, coefficient of variance and standard error were calculated for the drug.

Inter- day and Intra- day precision

The intra-day concentration of the drug was calculated on the same day at an interval of one hour. Whereas the inter day concentration of drug was calculated on three different days within the laboratory conditions.

Linearity

The absorbances of appropriate dilutions of standard stock solutions were measured as per the developed method to confirm the linearity.

Limit of detection (LOD) and Limit of Quantitation (LOQ)

The LOD and LOQ of acyclovir by the proposed method were determined using calibration standards. LOD and LOQ were calculated as 3.3σ /S and 10σ/S, respectively, where S is the slope of the calibration curve and σ is the standard deviation of response.

RESULTS AND DISCUSSION

The solubility studies showed that aqueous solubility of acyclovir was increased in mixed co-solvents containing 15%urea, 8%PEG 400 and 7% HP-βCD. The solubility of pure acyclovir in distilled water was found to be 0.525mg/ml, whereas in mixed co-solvents it was found to be 6 mg/ml. The increase in solubility was more than 12 folds. The Beer- Lambert's concentration

range for acyclovir in mixed co-solvents was between 2-20µg/ml. To check drug stability and precipitation of drug in solvent, a part of solution were kept in room temperature for 48 hours. The results revealed that estimation of acyclovir can be done without substantial effect on drug stability as no precipitation was observed. From this study it is obvious that there was no interference of urea or PEG 400 or HP-βCD in estimation of acyclovir at the wavelength of 251nm. Urea, HP-βCD and PEG 400 are cheaper than most of the organic solvents and can thus may be better substitutes for expensive organic solvents that are used in routine analysis of pharmaceuticals.

Table 1: Analysis of tablet formulations of acyclovir

Tablet Formulation	Label Claim (mg)	Percent label claim estimated* (mean±S.D.)	Standard error
Commercial Tablet + 30% of mixed co-solvents (15% urea, 8% PEG 400 and 7% HP-βCD)	200mg	99.56±0.8188	0.3343

** Average of six determinations*

Table 2: Result of recovery studies

Formulation	Amount of acyclovir tablet powder(mg)	Amount of standard drug added (mg)	Percent recovery estimated* (mean ±S.D.)	Standard error
Commercial Tablet + 30% of mixed co-solvents (15% urea, 8% PEG 400 and 7% HP-βCD)	200	10	99.72±1.072	0.4378
	200	20	100.58±1.449	0.5915
	200	30	101.05±1.619	0.6610

****** *Average of six determinations*

Table 3: Optical characteristics data and validation parameters

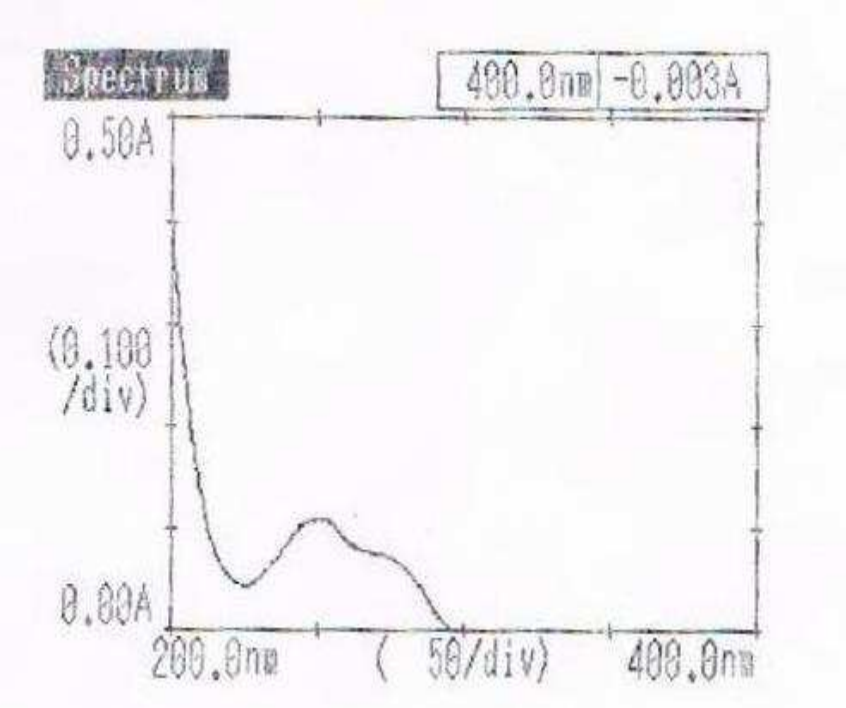
Parameters	Values of acyclovir in 30% of mixed co-solvents (15%urea, 8% PEG 400and 7% HP-βCD)
Working λmax (nm)	251nm
Beer's law limit (µg/ml)	2-20
Molar Absorptivity	15.6×10^3
Correlation coefficient*	0.990
Intercept*	0.0034
Slope*	0.058
LOD* (µg/ml)	0.1934
LOQ* (µg/ml)	0.5862
Intra-day* (precision) (Co-eff. of variation)	0.2624
Inter-day*(precision) (Co-eff. of variation)	0.2610
Robustness	Robust

****** *Average of 6 determinations*

The estimated label claim in the 30% mixed co-solvents was found to be 99.56 ± 0.8188 indicating good correlation between estimated and those claimed by the manufacturers. The results of percent label claim were shown in Table 1. The recovery studies showed proposed method is accurate and reproducible. The results of recovery study revealed that any small change in the drug concentration in the solution could be accurately determined by the proposed method. 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 and standard error as shown in Table 2. Repeatability results indicated the precision under the same operating conditions over a short interval time and inter-assay precision.

Intermediate precision study expresses within laboratory variation in different days. In both intra and inter-day precision study for the method co-efficient of variation were not more than 1.0% indicates good intermediate precision. The low values of LOD and LOQ, 0.1934 and 0.5862 for acyclovir in the mixed co-solvents indicated good sensitivity of proposed method. (Table 3).

Fig.1: UV-spectra of acyclovir in 30% of mixed co-solvents



CONCLUSION

It was thus confirmed that mixed solvency solubilisation phenomenon is an effective technique for enhancement of solubility of a poorly water soluble drug. Hence the proposed method is new, simple, accurate, non-toxic and precise method. This method can be successfully employed for estimation of drugs in routine analysis of tablets.

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