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VISIBLE SPECTROPHOTOMETRIC DETERMINATION OF CAPECITABINE IN BULK DRUG AND PHARMACEUTICAL FORMULATIONS

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ABSTRACT

Two new simple, sensitive and cost effective visible spectrophotometric methods were developed for the estimation of capecitabine in both bulk drug samples and formulations. The two methods were based on the formation of ion pair complexes of the drug with two acidic dyes namely bromocresol green (BCG Method) and bromophenol blue (BPB Method) in acidic buffer solution followed by their extraction in organic solvent (chloroform). The absorbance of the organic layer for both the methods was measured at their respective absorption maxima i.e. at 426.5 nm for bromocresol green and 427.5 nm for bromophenol blue against the corresponding reagent blank. The methods obeyed Beer's law between 20-120 µg/mL for bromocresol green and 10-250 µg/mL for bromophenol blue.The interference studies also revealed the common excipients and other additives usually present in pharmaceutical dosage forms did not interfere in the proposed methods. The methods were statistically evaluated and the proposed methods were precise, accurate, sensitive, and cost effective and can be used in routine analysis in quality control laboratories.

Key words: Capecitabine, Spectrophotometry, Bulk drug, Formulation, Bromocresol green, Bromophenol blue.

INTRODUCTION

Capecitabine is a new, orally administered, enzyme-activated fluoropyrimidine carbamate designed to generate high levels of fluorouracil (5-FU) in tumor cells. Selective tumor activation of 5'-deoxy-5-fluorouridine, the last enzymatic step of a three-enzyme process, is catalyzed by thymidine phosphorylase, a tumor-associated angiogenic growth

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factor. Since levels of thymidine phosphorylase are often higher in tumors than in surrounding normal tissues, this stepwise process provides tumor selectivity and potentially decreases toxicity to normal tissues. Preclinical studies show that capecitabine has significant activity against a variety of tumor types when used as monotherapy and in combination with other chemotherapeutic agents. The drug is official in Martindale: The Extra Pharmacopoeia[1]. The chemical structure of capecitabine is shown in Fig. 1.

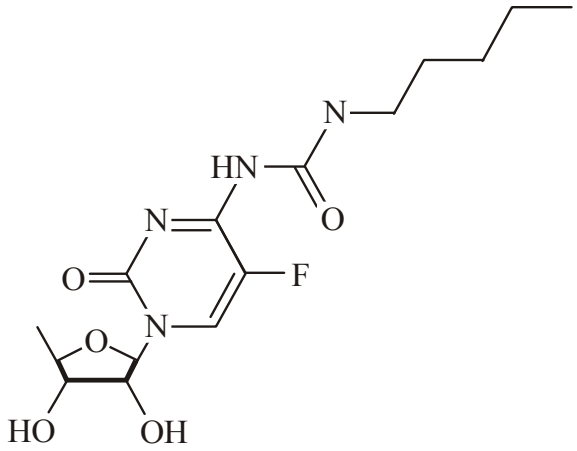

Fig. 1: Chemical structure of capecitabine

Few HPLC methods for quantitative determination of capecitabine were reported in the literature. Majority of these HPLC methods were applied in the determination of capecitabine and it's metabolites in biological fluids [3-9] and are mainly useful for therapeutic monitoring of the drug in biological fluids. No visible spectrophotometric method for quantitative determination of capecitabine in bulk drug samples and formulations was reported. The objective of this research was to develop and validate rapid, economical and sensitive visible spectrophotometric method for quantitative determination of capecitabine in bulk drug samples and formulations. Capecitabine contains secondary amino group in the molecular structure making it possible to form the ion-pair complexes with acidic dyes namely bromocresol green (BCG) and bromophenol blue (BPB).

EXPERIMENTAL

Instruments

Pharmaspec -1700 Ultraviolet-Visible spectrophotometer (double beam) was used for all spectral measurements. Digisun Model DI-707 pH meter was used for all the pH measurements.

Chemicals and reagents

All the chemicals used were of analytical grade.

BCG (0.1% w/v), BPB (0.1% w/v), phthalate buffer of pH 2.2, chloroform.

BCG: 100 mg of bromocresol green was dissolved in 0.72 mL of 0.1N NaOH and 20 mL of methanol. After solution was affected, sufficient distilled water was added to produce 100 ml**.**

BPB: 100 mg of bromophenol blue was approximately weighed and taken in a 100 ml volumetric flask. To this, 1.5 mL of 0.1N NaOH and 20 mL of methanol were added. The solution was then diluted with distilled water to make up the volume to 100 mL.

(This solution was treated with methanol to remove methanol soluble impurities.)

Phthalate buffer: of pH 2.2 was prepared as per Indian Pharmacopoeia.

Chloroform: AR grade chloroform was used directly.

Procedure

Preparation of standard drug solution

10 mg of capecitabine was dissolved in 10 mL of methanol (concentration-1 mg/mL). Aliquots of standard drug solution were diluted to 10 mL from the stock solution.

Preparation of sample solution

A quantity of the powder from tablets equivalent to 10 mg of the drug was dissolved in methanol, filtered and volume was made up to 10 mL with methanol.

BCG Method

Aliquots of standard drug solution (0.2-1.2 mL) were added to 5 mL of phthalate buffer of pH 2.2 contained in a separating funnel followed by 0.5 mL of 0.1% w/v BCG solution**.**

The solution was extracted with chloroform and chloroform layer collected, was dried over anhydrous sodium sulfate. Volume was made up to 10 mL. A linear graph was obtained at 426.5 nm against reagent blank prepared simultaneously.

BPB Method

Aliquots of standard drug solution (0.1-2.5 mL) were added to 3 mL of phthalate buffer of pH 2.2 contained in a separating funnel followed by 1.0 mL of 0.1% w/v BPB solution.

The solution was extracted with chloroform and chloroform layer collected, was dried over anhydrous sodium sulfate. Volume was made up to 10 mL. A linear graph was obtained at 427.5 nm against reagent blank prepared simultaneously.

RESULTS AND DISCUSSION

Analytical data and method validation

The optimum conditions were established by varying one parameter at a time and keeping the others fixed and observing the effect on absorbance of chromogen.

The optimum pH required for complexation, effect of dye concentration and efficiency of the solvent to extract the ion pair were studied with respect to maximum sensitivity, colour stability, adherence to Beer's law and other optimum conditions are incorporated in the procedure.

The optical characteristics such as absorption maxima, Beer's law limits, molar absorptivity and Sandell's sensitivity are presented in Table 1.

Table 1: Optical characteristics and precision of the method

S. No.	Parameter	BCG Method	BPB Method
1	λ_{max} (nm)	426.5	427.5
2	Beer's law range (µg/mL)	20-120	10-250
3	Molar extinction coefficient (L. mole^{-1} cm^{-1})	2.28 x 10^4	0.99 x 10^4
4	Sandell's sensitivity (µg/cm^2/0.001)	0.0013	0.2816
	Regression equation (y = mx + b)*		
5	Slope (m)	0.0081	0.0036
	Intercept (b)	-0.0114	0.0035

Cont…

S. No.	Parameter	BCG Method	BPB Method
6	Correlation coefficient (r)	0.9986	0.9999
7	Precision (% Relative standard deviation)	0.6639	0.2763

*y = mx + b, where y is the absorbance unit and x is the concentration in µg/mL.

The regression analysis, using the method of least squares, was made to evaluate the slope (m), intercept (b) and correlation coefficient (r) obtained from different concentrations and the results are presented in Table 1**.** The graph showed negligible intercept as described by the regression equation y = mx + b, where y is the absorbance and x is the concentration in µg/mL.

Commercially available tablets of capecitabine were analyzed by the proposed method and as additional check on the accuracy of the method, recovery experiments were also conducted by spiking known amounts of pure drug in preanalysed formulation and the recovery was calculated in each of the case using the regression line equation developed under the linearity experiment. The results of recovery experiments are given in the Table 2 for Method A and B**.** The interference studies revealed the common excipients and other additives usually present in pharmaceutical dosage forms did not interfere in the proposed methods.

Table 2: Determination of capecitabine in formulations

Sample (Tablets)	Reagent	Label claim (mg)	Amount *(mg) found by proposed method	% Recovery**
1	BCG	150	149.25	99.95%
	BPB	150	149.85	99.90%
2	BCG	150	150.75	100.50%
	BPB	150	150.66	100.44%

*Average of three determinations **After spiking the sample

The proposed visible spectrophotometric methods enable quantitative determination of capecitabine in bulk drug samples and tablets. Efficient visible spectrophotometric detection at the respective absorption maxima was found to be suitable without any

interference from tablet excipients. The calibration curves were linear over a concentration range from 20-120 µg/mL for BCG and 10-250 µg/mL for BPB. The relative standard deviations (R.S.D.) were less than 1% and average recovery was around 100.20%. Analytical results of samples were in accordance with those of standard solution in the same concentrations. The proposed method is fast, precise, accurate, sensitive and efficient and can be used in routine analysis in quality control laboratories.

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REFERENCES

1. Martindale, The Extra Pharmacopoeia, 34th Edition, p. 533.
2. S. Budavari (Ed.), Merck Index, 14th Edition, Monograph No. 1754, Edited by Maryadele, J. O. Neil, Merck Research Lab, Division of Merck & Co., N J (2001).
3. M. R. Dhananjeyan, J. Liu, C. Bykowski, J. A. Trendel et al., J. Chromatogr A., **1138**, 101 (2007).
4. S. M. Guichard, I. Mayer and D. I. Jodrell, J. Chromatogr. B. Analyt. Technol. Biomed. Life Sci., **826**, 232 (2005).
5. K. M. Li, L. P. Rivory and S. J. Clarke, J. Chromatogr B. Analyt. Technol. Biomed. Life Sci., **820,** 121 (2005).
6. C. Siethoff, M. Orth, A. Ortling, E. Brendel and W. Wagner-Redeker, J. Mass Spectrom., **39**, 884 (2004).
7. L. Zufía, A. Aldaz and J. Giráldez, J. Chromatogr B. Analyt. Technol. Biomed. Life Sci., **809,** 51 (2004).
8. Y. Xu and J. L. Grem, J. Chromatogr B. Analyt. Technol. Biomed. Life Sci., **783**, 273 (2003).
9. K. Vanitha Prakash, J. Venkateswara Rao and N. Appala Raju, Oriental J. Chem., **24,** 335 (2008).

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