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ORIGINAL ARTICLE

# Development and Validation of a Spectrofluorimetric Method for the Quantification of Capecitabine in Bulk and Tablets

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## ABSTRACT

**Objectives:** A new, simple, and affordable spectrofluorimetric method was established for quantification of capecitabine in bulk and in marketed formulations.

**Materials and Methods:** Native fluorescence of capecitabine in 0.1% (*w/v*) cetrimide was measured at 386 nm after excitation at 313 nm.

**Results:** A linear relationship between fluorescence intensity and capecitabine concentration was noticed in 0.2-1.0 µg/mL range. The method was supported by checking several validation parameters as stated using International Conference on Harmonization (ICH) guidelines. The limit of detection (LOD) and quantification (LOQ) values (0.032 and 0.096 µg/mL, respectively) and results of validation parameters demonstrated that the method procedure were sensitive, accurate, precise, and reproducible (% relative standard deviation <2.0). The percentage assay in commercial formulation was found to be 99.2, which agrees with ICH guidelines.

**Conclusion:** Due to the above findings, developed method can be successfully adopted for routine analysis of capecitabine in pharmaceutical dosage forms.

**Key words:** Capecitabine, spectrofluorimetry, linearity, accuracy

## INTRODUCTION

Capecitabine is chemically known as pentyl *N*-[1-[(2*R*, 3*R*, 4*S*, 5*R*)-3,4-dihydroxy-5-methyloxolan-2-yl]-5-fluoro-2-oxopyrimidin-4-yl] carbamate (Figure 1). Being an antineoplastic drug, it is used for treating breast and colorectal cancers.[1,2] Extensive literature review of capecitabine disclosed several analytical methods for its quantification either alone or in combination with other drugs. Visible spectroscopic methods in methanol,[3] ultraviolet (UV) spectrophotometric methods in various solvents, such as methanol, ethanol, water, 0.1 N NaOH, 0.1 N HCl, water:acetonitrile (50:50),[4-12] electrochemical analysis,[13] atomic absorption spectroscopic method,[14] high performance liquid chromatography (HPLC) methods in combinations of

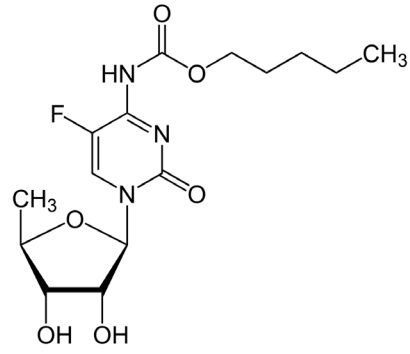


**Figure 1.** Chemical structure for capecitabine

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stationary and mobile phases,[15-27] high-performance thin-layer chromatographic (HPTLC) method,[11,28] ultra-high performance liquid chromatography (UPLC) method,[29,30] bioanalytical methods using HPLC,[31-35] HPTLC,[36] LC-MS/MS,[37] and UHPLC-MS/MS method[38] were reported in literature.

Although numerous instrumental techniques are available till date, no spectrofluorimetric method has been reported so far for capecitabine using cetrimide as solvent to the best of our knowledge. Chromatographic methods (HPLC, HPTLC, UPLC, *etc*.) require costly instrumentation, skilled technicians, and expensive solvents. Spectrofluorimetry attained exceptional status in drug analysis because of its appreciable specificity and sensitivity. Unlike spectrophotometry, the analysis can be achieved at both excitation and emission wavelengths in spectrofluorimetry.[39] Keeping these facts in view, a simple extraction free and sensitive spectrofluorimetric method was attempted for capecitabine using cetrimide as solvent. The method was validated as stated in International Conference on Harmonization (ICH) guidelines[40] and the same with success used for the quantification of capecitabine in marketed dosage form.

## MATERIALS AND METHODS

*Chemicals*

Capecitabine (active pharmaceutical ingredient) was procured from Gland Pharma (Hyderabad, India). The marketed formulation containing capecitabine (Xeloda tablets, Sunrise Remedies Pvt. Ltd., Gujarat, India) was acquired from nearby drug store.

*Instrumentation*

Various instruments including digital balance (Shimadzu, AUX 220D, Japan), pH Meter (Elico L120, Hyderabad, India), ultra sonicator (Sonica Ultrasonic Cleaner, Italy), melting point apparatus (DBK, Mumbai, India), UV-visible spectrophotometer (1800, Shimadzu, Japan), fourier transform infrared-spectrophotometer (IR affinity 1, DRS 8000, Shimadzu, Japan), and spectrofluorometer (Shimadzu, RF 5301 PC, Japan) were used in the present investigation. The standard statistical functions in MS-EXCEL were used to compute statistical parameters such as arithmetic mean, standard deviation (SD), and percent relative standard deviation (RSD%).

*Chemicals and reagents*

*Cetrimide (0.1% w/v)*

Cetrimide was accurately weighed (0.1 g) and dissolved in adequate distilled water (in a volumetric flask) and diluted to 100 mL.

*Capecitabine stock solution*

A stock containing 1000 µg/mL of capecitabine was produced by transferring 10 mg of analyte to 10 mL of 0.1% (*w/v*) cetrimide in a volumetric flask and the contents were mixed well. These aliquots were transferred into 10 mL volumetric flasks and were suitably diluted with 0.1% (*w/v*) cetrimide to obtain final concentration of 10 and 100 µg/mL of capecitabine.

*Analytical method development*

The spectrofluorimetric method development for capecitabine was attempted by dissolving the analyte in various solvents. Cetrimide 0.1% (*w/v*) was found to be suitable through optimization studies. The stock solution containing 10 µg/mL of capecitabine in cetrimide 0.1% (*w/v*) was used to identify the excitation and emission wavelengths. The excitation wavelength was fixed and solutions were scanned to get emission spectra. Capecitabine showed fluorescence at emission wavelength 386 nm following excitation at 313 nm, when 0.1% (*w/v*) cetrimide was used as a blank.

*Analytical method validation*

The emerged method was validated as stated in the ICH specifications to prove applicability of the analytical method in quality control of capecitabine.

*Linearity*

A set of 10 mL volumetric flasks holding aliquots of capecitabine in 0.2-1.0 µg/mL range in 0.1% (*w/v*) cetrimide was prepared. Intensities of above solutions were recorded for fluorescence at $\lambda_{em}$ 386 nm using an appropriate blank. The features of the calibration curve such as slope, intercept along with correlation coefficient were computed.

*Accuracy (recovery studies)*

Degree of closeness of the results was determined by computing recoveries of capecitabine using the standard addition method. Standard solutions of capecitabine at 80, 100, and 120% levels were spiked to a fixed concentration of capecitabine from the tablet powder (equivalent to 0.5 µg/mL) contained in volumetric flasks. The volume in each flask was made up to mark with 0.1% (*w/v*) cetrimide. Fluorescence intensities of the emerged solutions were resolved at the emission wavelength of 386 nm. The recovery was verified by analyzing analyte in triplicate preparations at each concentration level.

*Precision*

The repeatability/intra-day precision of the present method was set by assessing the corresponding response three times in a single day for three distinct concentrations of capecitabine (0.2, 0.6, and 1.0 µg/mL). The intermediate/inter-day precision was deliberated by estimating selected concentrations (0.2, 0.6, and 1.0 µg/mL) response in triplicate on three different days over a week period. The results of both studies were expressed as percentage relative standard deviation (% RSD).

*Sensitivity and robustness*

Sensitivity of the analytical method was represented by determining the lowest detectable amount (LOD) and the lowest quantifiable amount (LOQ) using samples containing very low concentrations of capecitabine as *per* ICH guidelines. LOD and LOQ were calculated using the formulae 3.3* (SD/slope) and 10* (SD/slope), respectively. Fluorescence intensity of the analyte solutions was also recorded by making small changes in emission wavelength to establish robustness in the analytical method.

*Assay of capecitabine in pharmaceutical dosage form*

Twenty tablets of marketed formulation (Xeloda®) containing 500 mg of capecitabine were taken, precisely weighed and powdered. A quantity of powder analogous to 10 mg of capecitabine was transferred into a 10 mL volumetric flask and the volume was made up to mark with 0.1% (*w/v*) cetrimide (1000 µg/mL). The resulting solution was screened *via* Whatman filter paper (no: 41). An aliquot of the clear filtrate was suitably diluted to obtain 0.5 µg/mL of capecitabine in 0.1% (*w/v*) cetrimide and the same was used for testing. The amount of capecitabine was determined by substituting responses into equations of the straight line representing the calibration curves with a correction for dilution.

## RESULTS AND DISCUSSION

*Analytical method optimization*

Capecitabine structure contains 5-fluoro-pyridimidin-2-one moiety in conjugation with amide group. The fluorescence potential of capecitabine may be attributed to the abovementioned chromophoric groups. This fluorometric method was optimized by studying type and concentration of the solvents. Stock solutions of capecitabine in solvents such as water, methanol, chloroform, dimethylsulfoxide, acetate buffer (pH 5.0), potassium dihydrogen orthophosphate (pH 3.0), tween 80 (0.25% *v/v*), sodium lauryl sulphate (0.1 N), urea (0.1 M), cetrimide, sodium hydroxide (0.1 N), and hydrochloric acid (0.1 N) were prepared separately from respective standard solutions (1000 µg/mL). Fluorescence intensity of capecitabine in cetrimide was found to be maximum among all. Hence, cetrimide was chosen as a suitable solvent for further analysis. Capecitabine in cetrimide exhibited maximum fluorescence at emission wavelength 386 nm, following excitation at 313 nm (Figure 2). Therefore, the same wavelengths were used in further method optimization. The effect of concentration of cetrimide on fluorescence intensity of the analyte was studied by testing different concentrations of cetrimide (0.1, 0.25, 0.5, 0.75, and 0.1% *w/v*). Sample solutions of capecitabine (10 µg/mL) prepared using the above cetrimide solutions were scanned and the results are provided in Table 1. Cetrimide, 0.1% (*w/v*) was found to be optimum as maximum fluorescence potential was noticed with the same. Capecitabine sample solutions prepared by dissolving in 0.1% (*w/v*) cetrimide were found to be stable up to 48 h at room temperature.

*Analytical method validation*

*Linearity*

The optimized method was further justified as *per* ICH guidelines. The relationship between capecitabine concentration and corresponding fluorescence intensity was found linear over 0.2-1.0 µg/mL concentration range with an $r^2$ of 0.9991. The regression equation obtained was y= 9.8571x + 0.1514. The method established a good correlation between concentration and fluorescence intensity of capecitabine over the studied concentration range. The results of linearity studies are given in Table 2 and Figure 3.

*Accuracy (recovery studies)*

Three distinct levels (80, 100, and 120%) of standards (in triplicate) were spiked to commercial tablet powder to determine the accuracy of the proposed method. The mean percentage

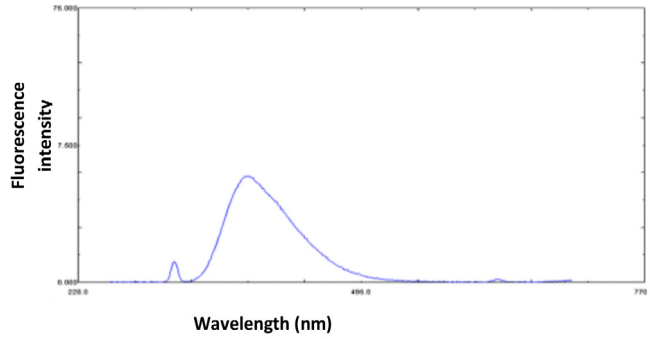


**Figure 2.** Excitation and emission spectra of capecitabine in 0.1% *w/v* cetrimide

**Table 1. Effect of concentrations of cetrimide on capecitabine at $\lambda_{em}$ 386 nm**

| Serial no | Concentration (% *w/v*) | Fluorescence intensity at 386 nm |
|---|---|---|
| 1 | 0.1 | 106.627 |
| 2 | 0.25 | 74.588 |
| 3 | 0.5 | 44.781 |
| 4 | 0.75 | 56.643 |
| 5 | 1.0 | 35.618 |

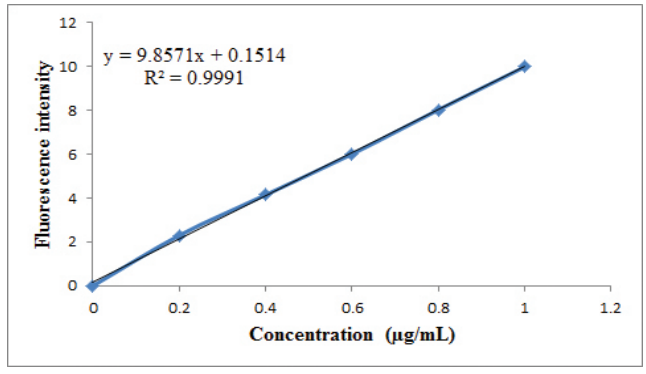


**Figure 3.** Calibration curve of capecitabine (0.2-1.0 µg/mL) in 0.1% (*w/v*) cetrimide

**Table 2. Calibration curve data of capecitabine at $\lambda_{em}$ 386 nm**

| Serial no | Concentration (µg/mL) | Fluorescence intensity at 386 nm (AM ± SD) (n=3) |
|---|---|---|
| 1 | 0.2 | 2.30 ± 0.095 |
| 2 | 0.4 | 4.15 ± 0.253 |
| 3 | 0.6 | 6.01 ± 0.303 |
| 4 | 0.8 | 8.03 ± 0.297 |
| 5 | 1.0 | 9.99 ± 0.143 |

AM: Arithmetic mean, SD: Standard deviation

**Table 3. Data for accuracy studies of capecitabine**

| Analyte | Recovery level (%) | Conc. of sample (µg/mL) | Conc. of standard spiked (µg/mL) | Total amount (µg/mL) | Amount recovery (AM ± SD) (µg/mL) (n=3) | %Recovery | %RSD[a] |
|---|---|---|---|---|---|---|---|
| Capecitabine | 80 | 0.5 | 0.4 | 0.9 | 0.866 ± 0.0035 | 96.22 | 0.40 |
| | 100 | 0.5 | 0.5 | 1.0 | 1.08 ± 0.006 | 108.00 | 0.56 |
| | 120 | 0.5 | 0.6 | 1.1 | 1.16 ± 0.020 | 105.45 | 1.72 |

[a]Acceptance criteria: % RSD should not be more than 2.0, AM: Arithmetic mean, SD: Standard deviation, RSD: Relative standard deviation

**Table 4. Data for precision of analytical method**

| Concentration (µg/mL) | Intra-day precision | | Inter-day precision | |
|---|---|---|---|---|
| | Concentration estimated (µg/mL) (AM ± SD) | % RSD[a] | Concentration estimated (µg/mL) (AM ± SD) | %RSD[a] |
| 0.2 | 0.23 ± 0.0018 | 0.78 | 0.224 ± 0.0026 | 1.16 |
| 0.6 | 0.727 ± 0.0047 | 0.65 | 0.658 ± 0.0053 | 0.81 |
| 1.0 | 0.946 ± 0.0034 | 0.36 | 0.927 ± 0.0071 | 0.77 |

[a]Acceptance criteria: %RSD should not be more than 2.0, AM: Arithmetic mean, SD: Standard deviation, RSD: Relative standard deviation

**Table 5. Assay of capecitabine in the marketed formulation**

| Formulation | Label claim (mg) | Amount found (mg) (AM ± SD) (n=3) | % Assay | % RSD* |
|---|---|---|---|---|
| Xeloda® | 500 | 496 ± 2.83 | 99.2 | 0.55 |

*Acceptance criteria: %RSD should not be more than 2.0, AM: Arithmetic mean, SD: Standard deviation, RSD: Relative standard deviation

recoveries and percentage RSD of the same were calculated and reported in Table 3. Percentage recoveries were found to be 96.22, 108.00, and 105.45, respectively, for the three levels. The results were found to be satisfactory, which was indicated by %RSD <2.0.

*Precision*

Triplicate samples of three dissimilar concentrations containing 0.2, 0.6, and 1.0 µg/mL of capecitabine were used for ascertaining the intra- and inter-day variability. Results of these studies are provided in Table 4. %RSD values were found to be <2.0, indicating the satisfactory exactness of the method.

*Sensitivity and robustness*

Sensitivity of analytical method was evidenced with LOD and LOQ values, which were found to be 0.032 and 0.096 µg/mL, respectively. Furthermore, robustness of the proposed method was established by evaluating the influence of small variations in the emission wavelength at 386 ± 2 nm. The results indicated that these changes did not greatly affect the fluorescence intensity.

*Analysis of capecitabine in marketed formulation*

The contemplated method was applied with success in commercial tablets. The amount of capecitabine in the formulation was found to be 496 ± 2.83 mg and assay% was 99.2 (Table 5), which is in the acceptance range of 98.0-101.0% for capecitabine as *per* ICH guidelines. Percentage RSD less than 2.0 indicated the reliability of this method. The details of optimized conditions for the spectrofluorimetric method of capecitabine are given in Table 6.

**Table 6. System suitability parameters**

| Parameters | Capecitabine |
|---|---|
| Excitation wavelength (nm) | 313 |
| Emission wavelength (nm) | 386 |
| Linearity range (µg/mL) | 0.2-1.0 |
| Slope (m) | 9.8571 |
| Intercept (c) | 0.1514 |
| Regression equation | Y= 9.8571x + 0.1514 |
| Correlation coefficient ($r^2$) | 0.9991 |
| Accuracy (%RSD) | Less than 2.0 |
| Precision (%RSD) | Less than 2.0 |
| LOD (µg/mL) | 0.032 |
| LOQ (µg/mL) | 0.096 |
| Assay (%) | 99.2 |

LOD: Lowest detectable amount, LOQ: Lowest quantifiable amount

## CONCLUSION

This spectrofluorimetric method developed for quantification of capecitabine in 0.1% (*w/v*) cetrimide was found to be simple, sensitive, and rapid. High scope of the method was evidenced through analysis of validation parameters. This method is more suitable, while working with low levels of capecitabine as the linearity range established over 0.2-1.0 µg/mL concentrations

confirms the same. Adoptability of the method in quality control analysis of capecitabine was ascertained in the marketed tablets. Non-interference of the formulation excipients in the actual determination of capecitabine was noticed. Assay values (%) and %RSD values obtained during accuracy and precision studies were within the ICH stated limits. With the said features, the contemplated spectrofluorimetric method can be employed for routine quality control analysis of capecitabine in tablet dosage forms.

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*Ethics*

**Ethics Committee Approval:** Not applicable.

**Informed Consent:** Not applicable.

**Peer-review:** Externally peer-reviewed.

*Authorship Contributions*

Concept: S.N., A.M., D.P.A., S.C., Design: S.N., A.M., D.P.A., S.C., Data Collection or Processing: S.N., A.M., D.P.A., S.C., Analysis or Interpretation: S.N., A.M., D.P.A., S.C., Literature Search: S.N., A.M., D.P.A., S.C., Writing: S.N., A.M., D.P.A., S.C.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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