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# RP-HPLC METHOD FOR DISSOLUTION TESTING OF CAPECITABINE TABLETS

Chung Duong Dinh *, Trung Vo Hong, Thao Truong and Yen Nguyen Ngoc

Faculty of Pharmacy, Nguyen Tat Thanh University, 300A Nguyen Tat Thanh, Xom Chieu Ward, Ho Chi Minh City, Vietnam.
* Corresponding Author

ORCID Details
Chung Duong Dinh: https://orcid.org/0000-0002-2760-2031
Trung Vo Hong: https://orcid.org/0000-0002-6999-7334
Thao Truong: https://orcid.org/0009-0001-8386-460X
Yen Nguyen Ngoc: https://orcid.org/0000-0003-1807-6727

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## ABSTRACT

The United States Pharmacopeia (USP) monograph for capecitabine tablets uses a UV spectrophotometric method for dissolution testing, although UV detection lacks selectivity for capecitabine over co-absorbing excipients or degradation products. In the present study, an isocratic RP-HPLC technique was developed and validated for the measurement of capecitabine in dissolution samples under USP conditions. Separations were performed on a C18 column (100 × 4.6 mm, 3.5 µm) using methanol–0.1% phosphoric acid (50:50, v/v) at 1.5 mL/min; detection was at 240 nm. The approach was verified as per ICH Q2(R2). The linearity was established in the range of 5–100 µg/mL ($r^2$ = 0.999) with LOD and LOQ of 0.83 and 2.55 µg/mL, correspondingly. The recovery was 98.0%–100.1% (RSD < 2%). The stability-indicating nature of the approach was established by forced degradation studies in acid, alkali, oxidative, thermal, and photolytic environments. Capbize® 500 mg tablets released >84% of capecitabine within 30 min, which fulfilled the USP requirement (Q ≥ 80%). The approach is more selective than the compendial UV method and suited for regular quality control of capecitabine tablets.

**Keywords:** Capecitabine; RP-HPLC; Dissolution Testing; Quality Control; ICH Q2(R2); USP

## 1 INTRODUCTION

Colorectal cancer (CRC) is one of the most frequent malignant tumors in the world and is associated with a high mortality rate [1]. Epidemiological statistics indicate that CRC is quite common in Asian populations, with several countries experiencing considerable increases in incidence over the past decades [2, 3]. Capecitabine (CAP) is an oral fluoropyrimidine prodrug that is broadly used for the treatment of breast cancer, colorectal cancer and other gastrointestinal neoplasms [4]. Once absorbed by cells, CAP is enzymatically converted to 5-fluorouracil (5-FU), resulting in localized cytotoxicity [4, 5]. Figure 1 shows the structural formula.

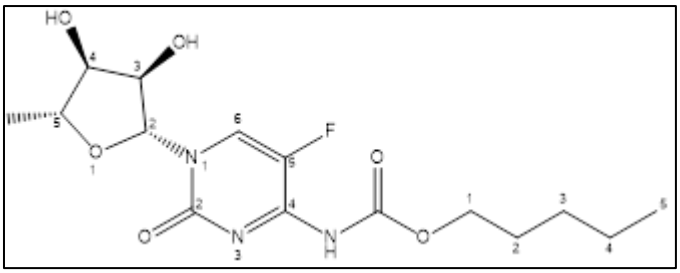

**Figure 1: Structural formula of capecitabine.**

The therapeutic effect of capecitabine is directly related to the drug-release properties of its oral film-coated tablet formulation [6]. Dissolution testing is a key quality control technique used to evaluate the in vitro release characteristics of solid oral dosage forms [7]. The current USP monograph describes a UV spectrophotometric method for the dissolution testing of capecitabine tablets. Although UV detection is effective and fast, it lacks selectivity, as it cannot distinguish the active ingredient from co-absorbing excipients or degradation products [8, 9].

Several analytical techniques have been reported for the determination of capecitabine in pharmaceutical formulations, including fluorescence spectroscopy [27], high-performance thin-layer chromatography [26], UV-Vis spectrophotometry [28], and high-performance liquid chromatography (HPLC) [6, 10, 11, 12]. However, most of this work has focused on method development and optimization rather than on rapid application to routine dissolution testing for quality control purposes. Moreover, many of these methods are not feasible in resource-limited facilities due to complex mobile phase formulations or extended run times.

The purpose of this study was to develop and validate a simple, isocratic reversed-phase HPLC (RP-HPLC) method for the dissolution testing of capecitabine tablets under pharmacopoeial conditions. The aim was to provide a method applicable for routine quality control operations with improved selectivity and analytical reliability.

## 2 MATERIALS AND METHODS

### 2.1 Chemicals and Reagents

Capecitabine reference standard (> 98.0% purity) was purchased from Sigma-Aldrich (St. Louis, MO, USA). The commercial product used in this study was Capbize® 500 mg film-coated tablets (Minh Hai Pharmaceutical Joint Stock Company, Vietnam). Methanol (HPLC grade) and phosphoric acid (85%, analytical grade) were purchased from Merck KGaA (Darmstadt, Germany). Ultrapure water (resistivity > 18.2 MΩ·cm) was obtained using a Pall Cascada III.I purification system.

### 2.2 Instrumentation

All chromatographic analyses were performed using an Agilent 1260 Infinity HPLC system (Agilent Technologies, Santa Clara, CA, USA) equipped with a G1311C quaternary pump, G1329B autosampler, G1316A thermostatted column compartment, and G4212B photodiode array (PDA) detector. Data were collected and processed with ChemStation software (Rev. B.04.02). Sample preparation was performed using an Elma Elmasonic S180H ultrasonic bath (37 kHz, 800 W; Elma, Germany). Dissolution studies were conducted using a PTWS 820D eight-vessel dissolution testing apparatus (Pharma Test, Hainburg, Germany). All mass measurements were carried out on a Mettler Toledo MS105DU analytical balance (readability 0.01 mg), and Class A or AS volumetric glassware was used throughout.

### 2.3 Preparation of Solutions

A reference solution of capecitabine (1000 µg/mL) was produced in 50% methanol, and working solutions were made by serial dilution with mobile phase. All solutions were filtered using 0.45 µm nylon membrane filters (Sartorius, Germany) before to injection. Twenty Capbize pills were weighed and ground finely. A quantity equivalent to 50 mg of capecitabine was placed into a 100 mL volumetric flask, mixed with 70 mL of mobile phase and sonicated for 15 min. The solution was allowed to cool to room temperature and then made up to volume with mobile phase. A tenfold dilution was then carried out to get a final concentration of around 50 µg/mL. The solution was filtered using a 0.45 µm nylon membrane filter before to injection.

### 2.4 Chromatographic Conditions

Separation was carried out on a Zorbax Eclipse Plus C18 column (100 × 4.6 mm, 3.5 µm). The mobile phase consisted of methanol and 0.1% phosphoric acid (50:50, v/v) delivered at a flow rate of 1.5 mL/min. The injection volume was 10

µL and the column temperature was maintained at 45 °C. Detection was performed at 240 nm, with a total run time of 5 min.

### 2.5 Dissolution Testing

Dissolution tests were performed on capecitabine tablets according to the USP monograph using Apparatus II (paddle method). The dissolution medium was 900 mL of filtered water maintained at 37 ± 0.5 °C with a paddle speed of 50 rpm [13, 14]. Aliquots of 5 mL were withdrawn at 5, 10, 15, 30, 45 and 60 min and promptly replaced with an equal volume of pre-heated fresh medium. Each sample was diluted tenfold, filtered through a 0.45 µm nylon membrane filter, and analyzed using the developed RP-HPLC method. Drug release was expressed as the percentage of labeled content. The acceptance criterion was not less than 80% dissolved within 30 min (Q ≥ 80%).

### 2.6 Method Validation

The RP-HPLC method was validated in accordance with ICH Q2(R2) guidelines [15] for system suitability, specificity, linearity, limit of detection (LOD), limit of quantification (LOQ), accuracy, precision, and robustness.

## 3 RESULTS

### 3.1 System Suitability

The suitability of the system was evaluated by six replicate injections of a standard capecitabine solution. The results are presented in Table 1. The relative standard deviation (RSD) for retention time and peak area were 0.13% and 0.16%, respectively, both well below the 1.0% criterion, thereby confirming satisfactory system stability and repeatability.

**Table 1: System suitability parameters (n = 6)**

| No. | Retention time (min) | Area (mAU·s) | N | Tf | k′ |
|---|---|---|---|---|---|
| 1 | 2.792 | 1144.4 | 5659 | 1.133 | 3.202 |
| 2 | 2.783 | 1142.7 | 5616 | 1.073 | 3.186 |
| 3 | 2.783 | 1143.7 | 5610 | 1.131 | 3.191 |
| 4 | 2.789 | 1145.3 | 5629 | 1.133 | 3.196 |
| 5 | 2.786 | 1146.3 | 5650 | 1.145 | 3.191 |
| 6 | 2.788 | 1147.9 | 5663 | 1.090 | 3.194 |
| Mean | 2.787 | 1145.05 | | | |
| RSD (%) | 0.13 | 0.16 | | | |

N = number of theoretical plates; Tf = tailing factor; k′ = capacity factor

### 3.2 Specificity

Figure 2 shows exemplary chromatograms of blank, placebo, standard solution, test solution and spiked sample. No interfering peaks were seen during the retention time of capecitabine (about 2.78 min) in the placebo chromatogram. The test sample demonstrated a well-defined peak at the same retention time as the reference solution. An increase in peak area was seen in the spiked sample matching to the enhanced quantity of capecitabine. No influence from matrix components was found, verifying the specificity of the suggested approach.

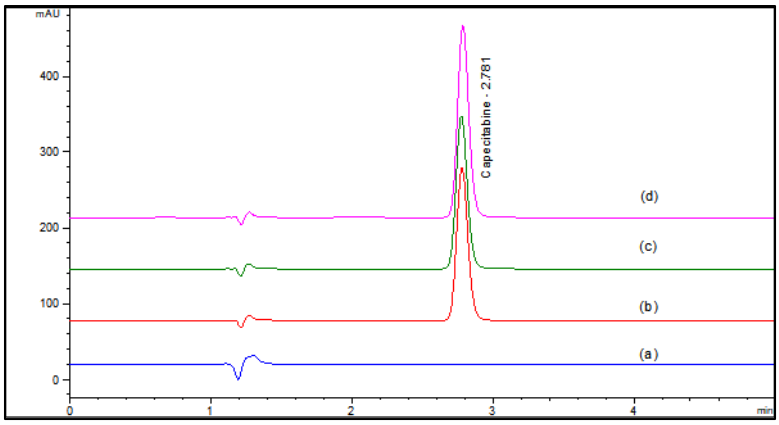


**Figure 2: Chromatograms of (a) placebo, (b) standard solution (50 µg/mL), (c) sample solution, and (d) spiked sample.**

### 3.3 Linearity, LOD, and LOQ

A linear relationship between peak area and capecitabine concentration was observed over the range of 5–100 µg/mL (Figure 3), with a correlation coefficient ($r^2$) of 0.999. The LOD and LOQ values, calculated from the standard deviation of the response and the slope of the calibration curve according to ICH Q2(R2) [15], were 0.83 µg/mL and 2.55 µg/mL, respectively.

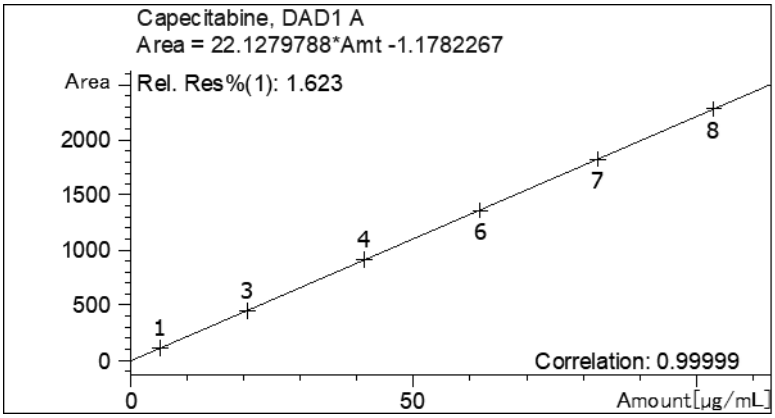


**Figure 3: Calibration curve of capecitabine (5–100 µg/mL).**

### 3.4 Accuracy

Accuracy was evaluated at three concentration levels (80%, 100% and 120% of the nominal test concentration of 50 µg/mL) with three replicates at each level (Table 2). Mean recoveries ranged from 98.0% to 100.1% with RSD values of 0.99% to 1.56%, demonstrating good accuracy across the tested range.

**Table 2: Accuracy results**

| Level (%) | Spiked conc. (µg/mL) | Recovery (%) ± SD | RSD (%) |
|---|---|---|---|
| 80 | 40 | 98.2 ± 1.53 | 1.56 |
| 100 | 50 | 100.1 ± 1.03 | 1.03 |
| 120 | 60 | 98.0 ± 0.97 | 0.99 |

### 3.5 Precision

Repeatability and intermediate precision were assessed by assaying six independently prepared Capbize samples on two consecutive days under identical chromatographic conditions (Table 3). The mean capecitabine content was 98.7 ± 0.52% and 97.8 ± 0.36% on Day 1 and Day 2, respectively. One-way ANOVA yielded an F value of 1.87 ($p = 0.20$), indicating no statistically significant difference between the two days at the 95% confidence level. The overall mean

content of all 12 determinations was 98.25 ± 1.11% with an RSD of 1.13%. These results were within the USP acceptable range for capecitabine tablets (93.0–105.0% of labeled content), demonstrating satisfactory method precision.

**Table 3: Precision of the RP-HPLC method**

| Parameter | Day 1 | Day 2 | Statistical analysis |
|---|---|---|---|
| Mean ± SD (%) | 98.7 ± 0.52 | 97.8 ± 0.36 | Overall: 98.25 ± 1.11%; $F$ = 1.87; $p$ = 0.20 |
| RSD (%) | 0.53 | 0.37 | |

### 3.6 Forced Degradation Study

The stability-indicating capability of the method was assessed by forced degradation studies under acidic (2 M HCl), alkaline (2 M NaOH), oxidative (3% $H_2O_2$), thermal (75 ± 2 °C) and photolytic (UV 254 nm) conditions (Figure 4). Capecitabine was particularly vulnerable to acid hydrolysis with around 50% of the medication remaining after 1 h and less than 10% surviving after 5 h. Alkaline degradation was less significant, as 67% or more of capecitabine remained after 5 h. More than 72% was preserved under oxidative stress, showing comparatively moderate degradation in comparison to acid hydrolysis [16, 17]. Thermal deterioration at 75 °C showed around 20% remaining after 5 h whereas photolytic degradation under UV light indicated about 32% remaining. In all instances the degradation products were well resolved from the capecitabine peak, suggesting that the approach was appropriate as a stability indicating test.

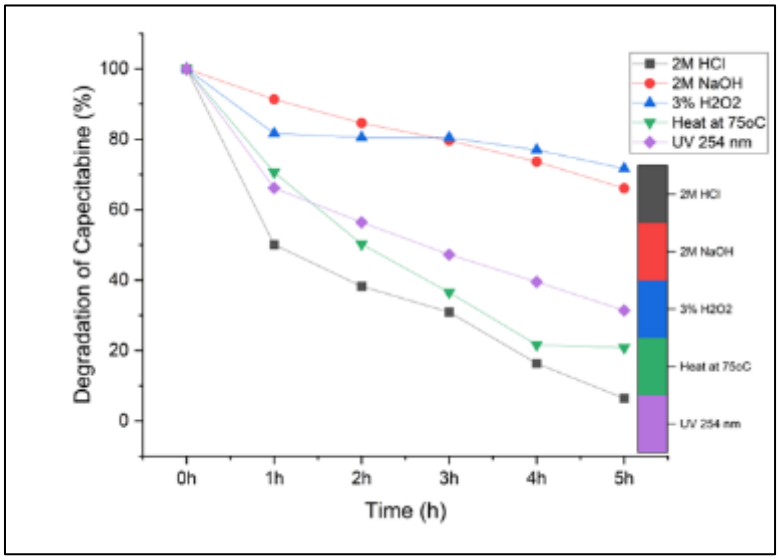


**Figure 4: Forced degradation profiles of capecitabine under acidic (2 M HCl), alkaline (2 M NaOH), oxidative (3% $H_2O_2$), thermal, and photolytic stress conditions.**

### 3.7 Dissolution Study

Figure 5 illustrates the dissolution profile of six Capbize tablets. Capecitabine release commenced from the start of the experiment, reaching 14.07 ± 4.17% at 5 min, 22.46 ± 6.48% at 10 min, and 39.69 ± 5.43% at 15 min. The cumulative percentage dissolved reached 84.75 ± 5.09% at 30 min, meeting the USP acceptance criterion for capecitabine tablets (Q ≥ 80%) [18, 19]. The dissolution profile showed a plateau after 30 min, with mean release values of 86.42 ± 5.44% and 87.77 ± 4.45% at 45 and 60 min, respectively.

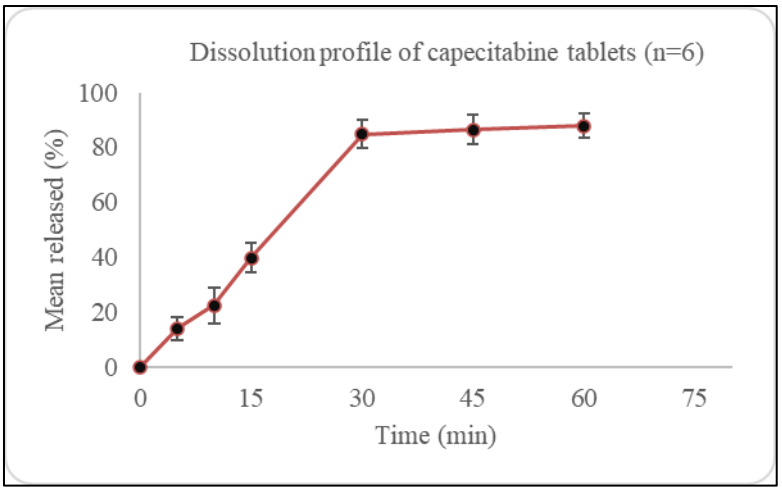


**Figure 5: Dissolution profile of capecitabine tablets (n = 6).**

## 4 DISCUSSION

Capecitabine is relatively hydrophilic (logP = 0.87) [22, 23], hence the quick initial drug release in aqueous medium is reasonable [13, 20]. The dissolution profile plateaued at 30 min which is consistent with the Noyes-Whitney model as seen with instant release formulations [21]. The little variability among the six tablets indicated satisfactory batch homogeneity [24].

With respect to sample analysis in dissolution testing, HPLC has a distinct selectivity advantage over UV spectrophotometry. Overestimation of drug concentration caused by co-absorbing excipients or breakdown products not distinguishable by UV detection might occur [8, 9]. The current approach chromatographically separated capecitabine from all the interfering components and the peak purity was validated by photodiode array detector [25]. This is particularly true for stability investigations where degradation products build over time during storage.

Most of the reported HPLC techniques for capecitabine have been related to analytical optimization rather than routine QC applicability [6, 10, 26]. Dissolution testing, where several samples must be examined in a limited time frame, does not permit gradient elution and sophisticated sample preparation [29]. The suggested approach employs isocratic elution with a binary mobile phase and a 6-min run time in compliance with ICH validation standards [15] and reduces organic solvent consumption according to green analytical chemistry principles [12].

## 5 CONCLUSION

A simple isocratic RP-HPLC technique was devised and validated for the analysis of dissolution testing of capecitabine tablets according to USP specifications. The method showed good specificity, linearity, accuracy, precision and stability suggesting capabilities More than 84.7% of capecitabine was released within 30 min, fulfilling the USP acceptance requirement for immediate-release tablets. This approach may be used in the regular quality control of capecitabine tablets in pharmaceutical labs due to its simple chromatographic settings and low analysis time.

## STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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### *Disclosure of conflict of interest*

The authors declare no conflict of interest.

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