



## SHORT COMMUNICATION

# Effects of temperature and wavelength choice on in-situ dissolution test of Cimetidine tablets

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**Abstract** The effects of temperature and wavelength choice on in-situ dissolution test instrument of Cimetidine were studied. Absorbance ( $A$ ) < 1.0 is required when using a fiber-optic dissolution test system. The detection wavelength of  $\lambda_{max}$  (218 nm) was replaced by 244 nm to carry out this test. The absorbance of Cimetidine solution at different temperature showed an obvious change. Calibration of Cimetidine solution should be tested at the same temperature (37° C) with the test solution. A suitable wavelength with smaller tangent slope could be chosen for in-situ dissolution test of Cimetidine tablets.

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## 1. Introduction

The traditional method of drug dissolution testing consists of the samples withdrawn from the vessels, filtered, diluted and analyzed by ultraviolet (UV) or high performance liquid chromatography (HPLC). It is a time-consuming process.

Since the 1990s, the testing has changed due to the appearance of fiber-optic drug dissolution test instrument (FODT). Compared with the traditional way, FODT is rapid and efficient [1–3], and it is a new way to test drug dissolution.

In-situ and process analysis for drug dissolution test has been accomplished with FODT in recent years [4,5]. However, new problems emerged along with the new method. In traditional method, samples dissolve at 37° C. The analysis of drug dissolution test has to be carried out at room temperature by UV, but dissolution and analysis are proceeded simultaneously at the dissolving temperature (37° C) by FODT. Therefore, when FODT is used to analyze drug dissolution, the effect of temperature should be considered.

Diluting a solution to a suitable concentration is commonly used according to the Lambert–Beer law [6,7]. It is a routine procedure for UV measurement, but it is impossible for

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diluting in the process of in-situ analysis when the absorbance ( $A$ ) exceeds 1.0. Therefore, the light path can be varied with different probes by FODT. However, for some drugs the labeled amount is large and the extinction coefficient is great at the detecting wavelength, so even the smallest probe is not suitable for measuring. Choosing another detection wavelength must be considered. In this paper, the effects of temperature and wavelength choice on absorbance of Cimetidine were studied.

## 2. Experimental

### 2.1. Materials and reagents

Cimetidine tablets (400 mg) were manufactured by China Tianjin SmithKline Pharmaceutical Company Limited. Cimetidine reference substance was provided by the National Institute for the Control of Pharmaceutical and Biological Products of China. Chemicals were all analytically pure. Purified water was produced in the laboratory and degassed before use.

FODT was developed by Professor Jian Chen's group of Xinjiang Medical University and Xinjiang FOCS Bio-Tech Development Co., Ltd. A UV-visible spectrophotometer (Cintra 40, GBC Scientific Equipment Pty. Ltd., Australia) was utilized to control UV determination.

### 2.2. Preparation of standard solution

Cimetidine reference substance was weighed accurately and dissolved in hydrochloride acid solutions (0.9→1000) to make a stock solution. A series of standard solutions were prepared with pH 1.2 media at concentrations of 89.48, 178.24, 266.96 and 356.68  $\mu\text{g/mL}$ , and the concentrations were equivalent to the dissolution rate of Cimetidine tablets (400 mg) 20.13%, 40.10%, 60.07% and 80.25%.

### 2.3. Choice of the wavelength for Cimetidine detection

Under the smallest probe of 1 mm light path, the absorbance of standard solutions was even far more than 1.0 at the maximum absorption wavelength of 218 nm. Therefore, the absorption of series standard solutions at different wavelengths has to be observed in order to find the suitable wavelength for Cimetidine by FODT. The absorbances of series standard solutions at 239, 240, 241, 242, 243 and 244 nm were tested with the probe of 2 mm light path.

### 2.4. Effect of temperature on absorbance of Cimetidine

The absorbance of standard solutions was tested at the temperature of 19, 24, 30 and 37° C to study the effect of temperature on the absorption of Cimetidine by FODT. The standard curve equations of six channels at 24° C and 37° C were applied for dissolution test of Cimetidine tablets to compare the difference of accumulate dissolution percentage.

### 2.5. Dissolution test

Drug release testing was performed in 900 mL of hydrochloride acid solutions (0.9→1000) at 37° C. The detection

wavelength and reference wavelength were set at 244 nm and 300 nm, respectively. The dissolution test time was 15 min. On the other hand, according to the Chinese Pharmacopeia 2010 (Ch. P) [8], samples were measured at 15 min by UV, and the end accumulate dissolution percentage was calculated with the standard curve equation at 24° C to compare the difference.

## 3. Results

### 3.1. Choice of the wavelength for Cimetidine detection

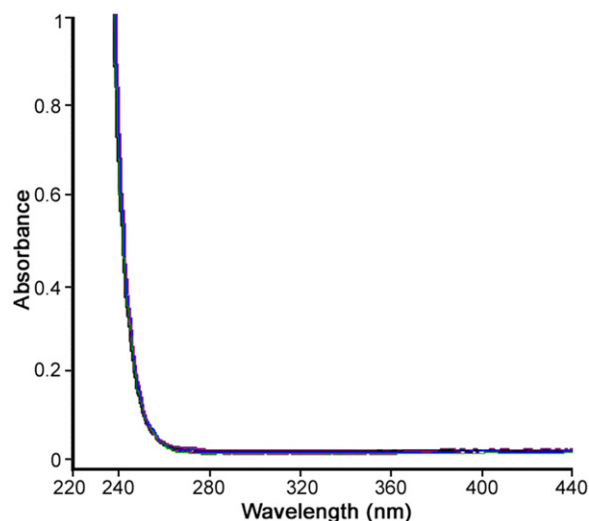
Detecting at the wavelength of 244 nm obtained a better linear correlation (Table 1). The suitable wavelength is the absorbance ( $A$ ) between 0 and 1, and the smaller slope of wavelength in the spectrum would not produce bigger error (Fig. 1). So the detection wavelength was set at 244 nm and the reference wavelength was set at 300nm.

### 3.2. Effect of temperature on absorbance of Cimetidine

Fig. 2 shows that the same concentration solution had a higher absorbance at high temperature. And the variance was obvious in the solution of higher concentration. Therefore, the standard curves were different at different temperatures

**Table 1** Linear equations at different detection wavelengths.

Detecting wavelength (nm)	Linear equation	Correlation coefficient of the standard solution
239	$y=93.50x - 8.1031$	0.9972
240	$y=106.95x - 5.8924$	0.9986
241	$y=118.63x - 4.8326$	0.9990
242	$y=141.22x - 3.7449$	0.9993
243	$y=170.45x - 2.7959$	0.9994
244	$y=195.20x - 2.4305$	0.9995



**Fig. 1** UV spectrum of Cimetidine.

(Table 2). The slope of the standard curves at 37° C was the highest (Fig. 2).

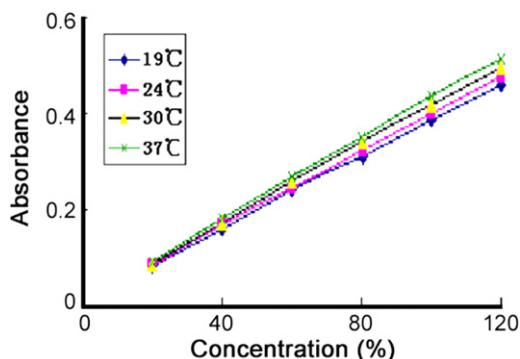


Fig. 2 Absorbance changes of series solution of Cimetidine at different temperatures.

Table 2 Linear equations at different temperatures.

Detection temperature (°C)	Linear equation	Correlation coefficient of the standard solution
19	$y=0.3804x+0.0075$	0.9999
24	$y=0.3963x+0.0059$	0.9999
30	$y=0.4111x+0.0079$	0.9995
37	$y=0.4246x+0.0093$	0.9998

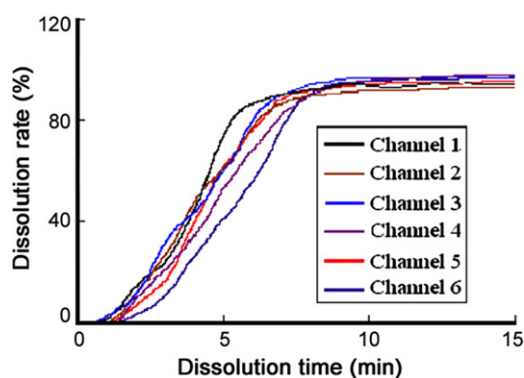


Fig. 3 In-situ dissolution profile of Cimetidine tablets.

### 3.3. Dissolution test

The in-situ dissolution profiles of six dissolution channels are displayed (Fig. 3). Sampling analysis at room temperature was carried out by UV as a control test. The data shows that the accumulate dissolution percentage calculated with the standard curve equations at 24° C was higher than that at 37° C by FODT; the standard curve test and dissolution test at the same temperature (37° C) by FODT did not differ significantly from the control test carried out by UV (Table 3).

## 4. Discussion

Absorption coefficient is a characteristic parameter of a compound at an assigned condition such as monochromatic light, solvent and temperature. Lambert–Beer law is an ideal state. Actually the absorption coefficient we got is an average measurement value ( $\epsilon_a$ ), which is a function of true absorption coefficient ( $\epsilon_t$ ) and refractive index ( $n$ ) of the solution:

$$\epsilon_a = \epsilon_t \frac{n}{(n^2 + 2)^2}$$

The refractive index of the solution will change with the concentration of the solution. The deviation will cause the change of absorbance. The absorbance of solution can be revised according to the following formula:

$$A = \epsilon Cl = \epsilon_t \frac{n}{(n^2 + 2)^2} Cl$$

FODT is an in-situ analysis of dissolution test. No diluting but different light path probe was utilized to meet the Lambert–Beer law. Therefore, the effect of concentration of the solution should be considered. Usually, the refractive index of the solution will change little when the concentration of a solution is  $\leq 0.01$  M.

UV spectrum is a molecular absorption generated by the transition of outer-shell electrons, simultaneously with the molecular vibration and rotation. Molecular movement (vibration and rotation) increases at a higher temperature; more energy is needed at a higher temperature, thus increasing the absorbance. In-situ analysis of dissolution test by FODT is usually performed at 37° C. The determination of reference substance solution should be performed at the same time.

The measurement wavelength of Cimetidine is 218 nm in Ch. P. But the absorbance of Cimetidine test solution is far beyond 1.0 at 218 nm even with the smallest probe. Another detection wavelength has to be chosen to accomplish the in-situ dissolution test. To minimize error, it is better to choose the wavelength with

Table 3 Comparison of FODT and UV methods for Cimetidine tablets release.

Method	Temperature (°C)	Accumulate dissolution percentage of six cups (%)						Mean $\pm$ SD
		1	2	3	4	5	6	
FODT	24	104.5	102.2	107.0	105.4	106.2	105.9	105.2 $\pm$ 1.5
	37	95.3	93.1	96.9	97.0	97.7	94.3	95.7 $\pm$ 1.8
UV	Room temperature	95.9	94.6	99.3	100.0	99.5	94.6	97.3 $\pm$ 2.6

the smaller tangent slope in the spectrum. So 244 nm was set to perform the FODT dissolution test with a probe of 1 mm light path. But can a bigger probe and a longer wavelength with a smaller slope (250–260 nm) in the test yield a better linear correlation? It deserves our further study.

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