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Dissolution monitoring of diclofenac sodium and codeine phosphate tablets using fibre optic chemical sensor assisted by dual-wavelength isosbestic point spectrophotometry

Lu Zhang[1], Chunhui Lu[2], Xinxia Li[1] and Jianguang Li[1] *
[1]College of Pharmacy, Xinjiang Medical University, Urumqi, China
[2]The Fifth Affiliated Hospital of Xinjiang Medical University, Urumqi, China

Abstract: The purpose of this investigation was to establish a mathematical model for determining the dissolution of diclofenac sodium and codeine phosphate simultaneously. Based on the dual-wavelength isosbestic point spectrophotometry, the dissolution of diclofenac sodium and codeine phosphate tablets was determined using Fiber-Optic Dissolution Test (FODT) instrument capable of real-time measurement. Dissolution curves showed that the dissolution process of diclofenac sodium was similar to that of codeine phosphate. The dissolution profile of diclofenac sodium and codeine phosphate at 45 min was concordant with that stated in Chinese pharmacopoeia. There was no significant difference between results obtained from FODT and HPLC ($p>0.05$). A fibre-optic dissolution test system assisted by the mathematical separation model of linear equations was able to detect the dissolution of diclofenac sodium and codeine phosphate simultaneously. The dissolution profiles and overall data, which can directly reflect the dissolution speed at each time point, can provide the basis for establishing standards for the quality evaluation of drugs.

Keywords: Dissolution, fibre optic, dual-wavelength, real-time.

INTRODUCTION

Dissolution is one of the important indexes for evaluating the preparation quality of oral solid formulations. Dissolution refers to a simple experimental method for simulating the disintegration and dissolution of oral solid preparations in the stomach and intestine *in vitro*. Through this test, the inner technical quality of drugs manufactured can assess.

Traditionally, samples are withdrawn from the vessels in a drug dissolution test, either manually or automatically at selected times, filtered, diluted, and analyzed by UV or HPLC. Thus a dissolution release test could require a day to complete for a UV analytical method and even longer when analyzed by HPLC, making dissolution analysis a time-consuming and labor-intensive procedure.

From the 1990s, the traditional methods of drug dissolution testing have been changing due to the appearance of fiber-optic dissolution systems, in which a fiber-optic probe is inserted directly into each vessel to perform measurements in situ. Real-time drug dissolution release is determined in the vessels without sample removal, greatly simplifying the testing procedure. Josefson et al. published early research in this field in 1988. Our group monitored a multicomponent solid preparation by a fiber-optic sensor system in 2000. UV fiber-optic dissolution is gaining acceptance as a powerful technique in pharmaceutical industry.

**Corresponding author:* e-mail: L77117@163.com.

The Fiber-Optic Dissolution Test (FODT) instrument was developed by Chen et al. of Xinjiang Medical University and Xinjiang FOCS Biotech Development Co., Ltd. It was strictly validated for both the UV-vis spectro-photometry and dissolution test methods of the Ch. P. It consists of a deuterium (D2) lamp, six fiber-optic dipping probes, and a detector with a charge-coupled device (CCD) that can collect data at each wavelength point. Light from the deuterium lamp passes through incident optical fibers, which transfer the light from the source to the probes immersed in the vessels during testing. Light again reflects back from the mirror at the bottom of the probe tip to the CCD through the detection fiber. The probe path can be altered to 0.5, 1.0, 2.0, and 5.0 mm to adjust the sensitivity. The UV-vis spectra (220-600 nm) from six fiber channels with low noise can simultaneously be collected with the system.

The probe selection is based on the spectral characteristics of drugs. The change in concentration as the drug dissolves is recorded as a change in the absorbance and the background interference is corrected with the help of a mathematical model created by the software system. Finally we will obtain a real-time measurement curve featuring the drug dissolution process. Generally, the concentration of each ingredient in the compound drug mixture after dissolution is measured by HPLC and UV. At present, there are a very few relevant examples in the literature covering the use of the FODT method to measure the dissolution of compound drugs.

For moderate pain relief, a 40-mg tablet containing 15 mg

of diclofenac sodium and 25 mg of codeine phosphate has been used. Additionally, this combination can be prescribed for cancer pain therapy. Diclofenac sodium is a derivative of phenyl acetic acid having intrinsic analgesic, anti-inflammatory and antipyretic properties, and it belongs to the class of peripheral analgesics. Codeine phosphate is the methyl derivative of morphine and can directly influence the cough centre of the medulla oblongata; it is a fast-acting pain reliever and can be classified as a weak opioid analgesic. A rapid and simultaneous release of the active ingredients from tablet formulations would produce a synergistic effect of this analgesic action. The presence of two or more active ingredients in the same drug will produce background interference during spectroscopic measurements at their maximum absorption wavelengths.

Chinese pharmacopoeia (2010) mentioned that the contents resulting from the dissolution of tablets containing a combination of diclofenac sodium and codeine phosphate should be measured by HPLC. This experiment revealed the absorption coefficient and UV spectrum characteristics of diclofenac sodium and codeine phosphate contents in each piece of diclofenac sodium and codeine phosphate tablets. Next, by keeping the same optical distance as determined by the mathematical model, the dissolution of two-component drug mixture containing diclofenac sodium and codeine phosphate can be analysed simultaneously.

Based on the dual-wavelength isosbestic point spectrophotometry, the dissolution of diclofenac sodium and codeine phosphate tablets was determined using Fiber-Optic Dissolution Test (FODT) instrument capable of real-time measurement.

MATERIALS AND METHODS

Materials and instruments

The following materials and instruments were used: FODT instrument (Developed by Xinjiang Medical University and Shanghai FOCS Biotech Firm), HPLC analyzer (Agilent 1100 Series), chromatographic column (Eclipse XDB-C8 5 μm, 4.6 mm × 150 mm, Agilent), analytical balance (AB135-S, Mettler Toledo) vacuum degassing instrument (ZKT-18), diclofenac sodium reference substance (NIFDC, 100334-200302), codeine phosphate reference substance (NIFDC, 171203-171203, purity approximately 97.5%), diclofenac sodium and codeine phosphate tablets (Taiyuan, Shanxi Province Jinyang Pharmaceuticals, 20130924), chromatographic grade acetonitrile and secondary distilled water (degassed before use). The rest of the reagents were all analytically pure.

Solution preparation

Stock solution of diclofenac sodium: Diclofenac sodium reference substance (27.83 mg) was weighed precisely and then added to a 100 mL volumetric flask. The volume was made up to 100 mL mark with distilled water; the final concentration of diclofenac sodium in the stock solution was 278.3μg/mL.

Stock solution of codeine phosphate

Codeine phosphate reference substance (16.34 mg) was weighed out and added to a 100-mL volumetric flask. The volume was made up to 100 mL mark by adding distilled water and the final concentration of codeine phosphate in the stock solution was 159.3μg/mL.

Serial dilutions of diclofenac sodium reference substance solution: From the stock solution of diclofenac sodium volumes of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5 and 6.0mL were precisely taken and added to 50mL volumetric flasks, respectively and the remaining volumes were made up with distilled water. The relative percent concentrations (%) were 10.02, 20.04, 30.06, 40.08, 50.10, 60.11, 70.13, 60.11, 90.17, 100.19, 110.21 and 120.23, respectively.

Serial dilutions of codeine phosphate reference substance solution: Exact volumes of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5 and 6.0mL were taken from stock solution of codeine phosphate and added to 50-mL volumetric flasks, respectively; the remaining volumes were made up with distilled water. The final relative percent concentrations (%) were 9.77, 19.53, 29.30, 39.06, 48.83, 58.60, 68.36, 78.13, 87.89, 97.66, 107.43 and 117.19, respectively.

Preparation of a series of hybrid reference substance solution at different concentrations: Precise volumes of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5 and 6.0 mL were taken from the stock solution of diclofenac sodium and codeine phosphate and were added to 50-mL volumetric flasks. Distilled water was added to make the final volume equal to 50mL.

Establishment of mathematical model

We recorded the ultraviolet absorption spectrum of the solutions prepared by serial dilutions in order to obtain a series of concentrations for diclofenac sodium, codeine phosphate and hybrid reference substance solution.

Fig. 1. Ultraviolet absorption spectrum (1: hybrid control, 2: diclofenac sodium, 3: codeine phosphate) From (fig. 1), the absorbance of codeine phosphate reference substance solution at wavelength (226 nm), diclofenac sodium reference substance solution (302 nm) and hybrid reference substance solution at wavelength 302 nm were equal; the absorbance of codeine phosphate reference substance solution at wavelength 302 nm is zero. Because the absorbance of hybrid reference substance solution and diclofenac sodium reference substance solution at 302 nm

are equal, therefore according to the principle of absorbance addition, the absorbance of the hybrid reference substance is equal to the sum of diclofenac sodium absorbance and codeine phosphate absorbance at 226 nm and can be expressed with the following formula (H: hybrid, D: diclofenac sodium, C: codeine phosphate):

$$A_{226}^{H} = A_{226}^{D} + A_{226}^{C} = E_{226}^{D} \cdot L \cdot CD + E_{226}^{C} \cdot L \cdot CC$$

$$= E_{226}^{D} \cdot CD + E_{226}^{C} \cdot CC \quad (L=1cm)$$

From the measured absorbance of serial concentrations of codeine phosphate reference substance solution at 226 nm we can obtain the following:

$$A_{226}^{C} = A_{302}^{D} = A_{302}^{H} = E_{226}^{C} \cdot CC$$

$$CC = \frac{A_{302}^{H}}{E_{226}^{C}} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(1)$$

From the measured absorbance of serial concentrations of diclofenac sodium reference substance solution at 226 nm and 302 nm, respectively, we can obtain the following:

$$A_{226}^{D} = E_{226}^{D} \cdot L \cdot CD = E_{226}^{D} \cdot CD = A_{226}^{H} - A_{226}^{C} = A_{226}^{H} - A_{302}^{H}$$

$$CD = (A_{226}^{H} - A_{302}^{H}) / E_{226}^{D} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(2)$$

By measuring the absorbance of series concentration of diclofenac sodium, codeine phosphate and the hybrid reference substance, it also proved that the relationship between them in accordance with the above equations. Because differences existed in each channel, measured absorbance of different concentrations of diclofenac sodium reference substance solution, codeine phosphate reference substance solution at 226 nm wavelength on six channels in turns, respectively, then we can obtain the percentage absorption coefficient of reference substance solution of diclofenac sodium and codeine phosphate at 226 nm on six channels (table 1).

The data were incorporated into the software and according to absorbance of test solution at wavelengths 226 nm and 302 nm we could calculate the amount of the two substances in the test samples with the help of equations (1) and (2).

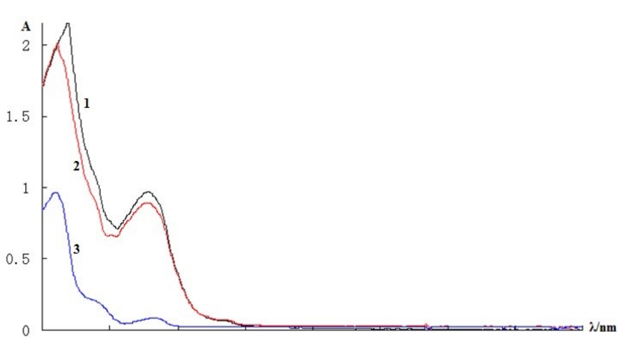

Fig. 1: Ultraviolet absorption spectrum (1: hybrid control, 2: diclofenac sodium, 3: codeine phosphate)

Linearity

After calculation, the regression equations of diclofenac sodium and codeine phosphate were performed, absorbance linear within the range 0 to 2 was good.

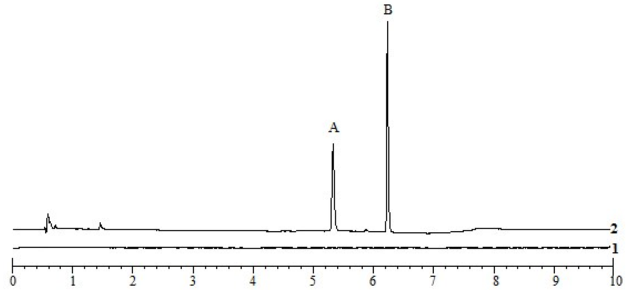

Fig. 2: High performance liquid chromatograms of diclofenac sodium and codeine phosphate

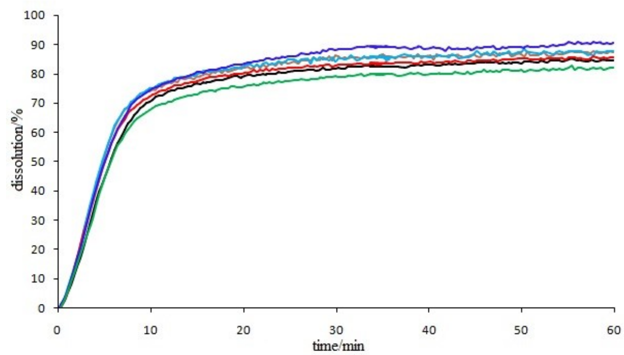

Fig. 3: The real-time dissolution curve of diclofenac sodium tablets obtained using FODT

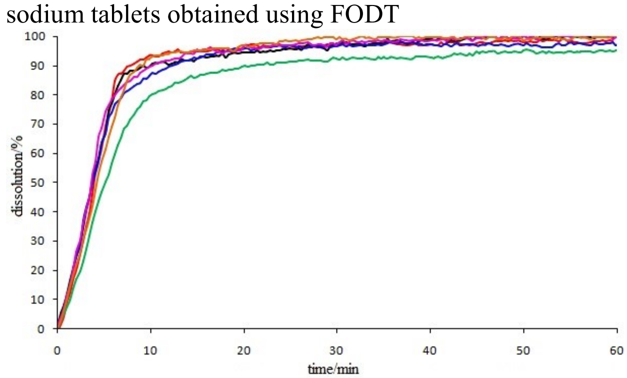

Fig. 4: The real-time dissolution curve of codeine phosphate tablets obtained using FODT

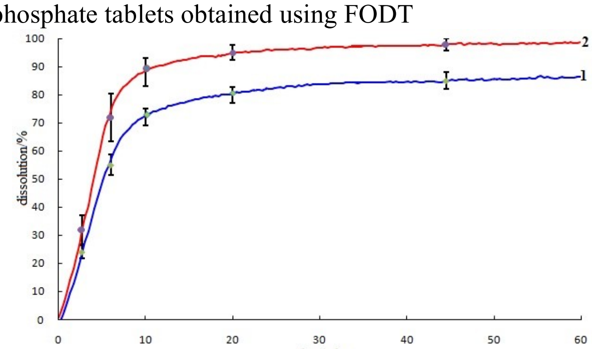

Fig. 5: The average dissolution curve of diclofenac sodium (1) and codeine phosphate (2) tablets obtained using FODT

Table 1: Percentage Absorption Coefficient

Channel	E^{D}_{226}	E^{C}_{226}
CH 1	79.05 3	363.9 7
CH 2	77.71 1	358.0 3
CH 3	80.58 3	345.7 4
CH 4	77.29 2	346.1 1
CH 5	78.39 1	347.9 2
CH 6	76.28 8	400.4 0

Precision

The diclofenac sodium and codeine phosphate concentrations of 5.57 and 3.19, 16.70 and 9.56 and 27.83 and 15.93µg/mL (equivalent to percent dissolution of about 20.04 and 19.53, 60.11 and 58.60, 100.1 9 and 97.66%, respectively), could be categorised into low, medium and high concentration groups, respectively. Parallel measurements for the above samples were repeated six times on FODT during daytime and for precision, measurements were done once a day for six days.

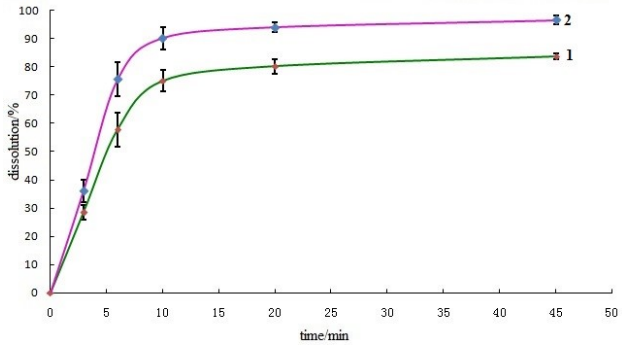

Fig. 6: The average dissolution curve of diclofenac sodium (1) and codeine phosphate (2) tablets obtained using HPLC

Analysing sample recovery

Ten pieces of diclofenac sodium and codeine phosphate tablets were weighed out. The calculated average weight per piece was 83.23 mg. The tablets were grinded into fine powder, and 9.81 mg of this fine powder was transferred into a 200mL volumetric flask (relative percentage 53.02%). The configured reference substance solution of diclofenac sodium and codeine phosphate were then prepared and the percent concentrations (%) of reference substance were 10.02 and 9.77, 30.06 and 29.30, 50.10 and 48.83, respectively. Measurements were done using FODT.

Measurement of Dissolution

Measurement conditions using FODT: According to the method described in Chinese pharmacopoeia (2010, second part, appendix XC), we used water (90mL) as the dissolution medium and maintained a dissolution speed of 75 rpm/min. We then opened the operational interface of software in-built in FODT and set up the following parameters: probe length 5 mm, λ1=226 nm, λ2=302nm, reference wavelength=550 nm; equations entered=(1) and (2), respectively, interval measurement=5s. Next, real-time monitoring on FODT was started by clicking the start button and tablets were put to each cup simultaneously; absorbance was recorded continuously for 60 min (fig. 3, 4).

Compared test: After 6 min and 45 min, 5mL of sample solution was taken from each of the six cups, respectively, while at the same time, 5mL of water was added to make up for the devoid volume. The sample solution was filtered using a disposable 0.22-µm membrane filter, and the filtrate was used for further analysis using HPLC. Moreover we have used the configured mixed reference substance solution containing diclofenac sodium and

Table 2: Calibration Curve Equations of diclofenac sodium.

Channel	0%-60.11%	r	70.13%-120.23%	r
CH 1	A=75.93C-0.121	0.9991	A=82.96C-5.608	0.9992
CH 2	A=74.69C-0.267	0.9994	A=81.33C-5.786	0.9991
CH 3	A=77.42C-0.160	0.9993	A=82.60C-3.462	0.9993
CH 4	A=73.93C-0.298	0.9993	A=80.47C-5.326	0.9991
CH 5	A=75.48C-0.124	0.9991	A=76.95C+1.168	0.9991
CH 6	A=73.28C-0.973	0.9992	A=79.77C-6.470	0.9992

Table 3: Calibration Curve Equations of diclofenac sodium codeine phosphate.

Channel	0%-117.19%	r
CH 1	A=363.9C-0.397	0.9994
CH 2	A=358.0C+2.465	0.9992
CH 3	A=345.7C+0.426	0.9995
CH 4	A=346.1C-1.070	0.9993
CH 5	A=347.9C-0.847	0.9992
CH 6	A=400.4C-0.142	0.9991

Table 4: The cumulative dissolution data of FODT and HPLC

Time/min	Channal	Diclofenac sodium%			Codeine phosphate%		
		FODT	HPLC	Error	FODT	HPLC	Error
	1	29.6	31.2	1.6	34.0	35.5	1.5
	2	30.4	32.5	2.1	37.5	39.7	2.2
3	3	24.4	27.6	3.2	27.4	29.5	2.1
	4	26.5	28.1	1.6	38.5	40.1	1.6
	5	24.0	26.3	2.3	36.0	39.3	3.3
	6	22.5	25.0	2.5	30.7	32.5	1.8
	Average	26.2	28.5	2.2	34.0	36.1	2.1
	1	64.3	59.9	4.4	74.8	78.2	3.4
	2	64.9	58.3	6.6	73.0	76.9	3.9
6	3	50.7	53.1	2.4	65.1	71.2	6.1
	4	58.8	56.2	2.6	76.8	79.7	2.9
	5	59.1	57.4	1.7	79.9	81.8	1.9
	6	53.0	56.7	3.7	72.3	75.2	2.9
	Average	58.5	56.9	1.5	73.7	77.2	3.5
	1	74.1	75.7	1.6	93.5	90.7	2.8
	2	75.2	76.9	1.7	89.7	88.5	1.2
10	3	70.4	73.3	2.9	79.6	81.1	1.5
	4	72.3	74.1	1.8	86.5	88.4	1.9
	5	74.4	72.5	1.9	89.6	90.9	1.3
	6	67.5	65.3	2.2	92.3	94.2	1.9
	Average	72.3	73.0	0.6	88.5	89.0	0.4
	1	82.0	81.6	0.4	96.9	95.1	1.8
	2	81.7	79.5	2.2	94.4	93.1	1.3
20	3	79.0	80.3	1.3	89.7	90.4	0.7
	4	80.1	81.5	1.4	95.8	93.7	2.1
	5	83.1	82.7	0.4	96.0	94.5	1.5
	6	75.4	74.8	0.6	96.7	95.7	1.0
	Average	80.2	80.1	0.2	94.9	93.8	1.2
	1	85.4	83.8	1.6	98.1	96.5	1.6
	2	86.5	84.2	2.3	99.6	97.3	2.3
45.0	3	84.1	82.9	1.2	94.0	94.2	0.2
	4	85.1	82.3	2.8	97.1	95.1	2.0
	5	86.4	85.3	1.1	99.2	98.9	0.3
	6	82.2	83.3	1.1	99.7	96.8	2.9
	Average	85.0	83.6	1.3	98.0	96.5	1.5

codeine phosphate as the known standard for comparison. The conditions employed for HPLC were the following: mobile phase: 0.4% acetonitrile and ammonium acetate-triethylamine (30:70:0.2); detection wavelength=250 nm; flow rate=1.0 mL/min; column temperature=37°C; sample volume injected=20 µL. After the HPLC run, we measured the peak areas of major peaks and used external standard to calculate the total dissolution of diclofenac sodium and codeine phosphate, respectively; when calculating the amount of codeine phosphate, results should be multiplied by 1.068.

According to above conditions of HPLC, took 20µL mixed reference substance solution of diclofenac sodium (100.19%) and codeine phosphate (107.43%) into the HPLC to record chromatogram and measure peak area, calculated sample dissolution based on the single point of reference.

STATISTICAL ANALYSIS

The data obtained were statistically analyzed using SPSS version 17.0 software. Statistical comparison was done

with paired t-test, $P<0.05$ was considered statistically significant.

RESULTS

The results of linearity were presented in the table 2 and 3. The coefficient of regression (R) value was greater than 0.999 for all the calibration curves, which is generally considered as evidence of acceptable fit of the data to the regression line.

Precision was evaluated by performing intra-day and inter-day precision. For diclofenac sodium, the RSD of intra-day precision was 0.59, 1.28 and 1.37%; the RSD of inter-day precision was 2.36, 2.36 and 2.70% (n=6). For codeine phosphate, the RSD of intra-day precision was 0.89, 1.34 and 1.05%; the RSD for inter-day precision was 2.57, 2.57 and 3.15% (n=6). That indicates the precision of proposed method with in laboratories.

The calculated recovery of diclofenac sodium were 102.5 3, 103.7 4 and 102.9 7%; RSD were 2.17, 3.05 and 2.58%, respectively (n=6); rate of recovery of codeine phosphate were 97.16, 100.59 and 99.82%; RSD were 3.14, 2.77 and 2.05%, respectively (n=6). The reliability of method was established from recovery studies by using standard addition method.

The absolute error of cumulative dissolution of diclofenac sodium and codeine phosphate was larger at 3 and 6 minute and the reason for this is tablets were dissolving fast in the first 10 minute. FODT allows real-time measurements and converts absorbance into dissolution simultaneously based on mathematical equation. In contrast, manual sampling is required when using traditional HPLC and peak area has to be measured after filtering. Next, according to the peak area of reference substance, we calculated dissolution by the external standard method. The main cause of bigger absolute error stemming from HPLC was due to the inability of keeping same sampling time. The average absolute error associated with cumulative dissolution of diclofenac sodium and codeine phosphate were less at 10, 20 and 45 minute. In reality the results from FODT and HPLC were basically identical (Table 4).

Dissolution curves showed that the dissolution process of diclofenac sodium was similar to that of codeine phosphate. The dissolution profile of diclofenac sodium and codeine phosphate at 45 min was concordant with that stated in Chinese pharmacopoeia. There was no significant difference between results obtained from FODT and HPLC ($p>0.05$).

DISCUSSION

The absorbance measurement of compound drugs containing two or more active ingredients produces high background interference when absorbance is measured at the maximum absorption wavelength of the active constituents. At present there are more than 20 species of compound solid drugs mentioned in the Chinese pharmacopoeia for which it is necessary to perform dissolution experiments. It is a common practice to measure dissolution by using HPLC. However, by following the principle of absorbance addition in ultraviolet-visible spectrum, we can derive mathematical equations with the aid of which we can simply apply UV measurements to decipher the content of active components in the compound drug much more rapidly compared with HPLC. For instance, US pharmacopoeia have mentioned the use of UV for measuring absorption coefficient of two components for valsartan and hydrochlorothiazide tablets; by measuring absorbance at their maximum absorption wavelength and by formulating equations, the dissolution analysis of the two components was done. Using FODT for valsartan and hydrochlorothiazide tablets, the absorption coefficient and other spectral characteristics of ultraviolet absorption were determined. Next, a mathematical model based on dual-wavelength isosbestic point spectrophotometry was established for measuring real-time dissolution under the application of the same wavelength. Thus the real-time measurement of the dissolution process of two components can be done simultaneously.

FODT uses UV detector and an optical fibre sensing process with the help of which we could detect real-time dissolution of two components simultaneously. From the dissolution curve obtained for diclofenac sodium and codeine phosphate tablets, it is clear that the tablets belonged to the model of disintegration with two components dissolving rapidly in the first 10 min. Thus the dissolution process was rapid whereas, HPLC analysis needed manual sampling and the process is slow, inconvenient and time consuming. Additionally, HPLC is complex to operate, is expensive and we cannot obtain a complete dissolution curve directly. In contrast, FODT makes possible real-time monitoring of the dissolution process and gives a complete dissolution curve of two components of diclofenac sodium and codeine phosphate tablets. Clearly, it can be regarded as better technological option for quality evaluation of compound drugs.

Results obtained using FODT showed that the dissolution of diclofenac sodium and codeine phosphate was 75% in 10 minutes. Diclofenac sodium and codeine phosphate are analgesics with moderate pain-relieving capacity. Diclofenac sodium belongs to the category of peripheral analgesics while codeine phosphate belongs to the central type weak opioid analgesics. When combined together in tablet formulations, they are both quick releasing and can act synergistically to produce an additive analgesic effect. The dissolution curve reflected the specific process of

drug dissolution that cannot be reflected by single point.

This experiment has provided useful insights and better understanding of this new technology and method for dissolution of compound drugs.

CONCLUSION

A fibre-optic dissolution test system assisted by the mathematical separation model of linear equations was able to detect the dissolution of diclofenac sodium and codeine phosphate simultaneously. The dissolution profiles and overall data, which can directly reflect the dissolution speed at each time point, can provide the basis for establishing standards for the quality evaluation of drugs.

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