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Design of Dissolution Apparatus for the Flow-through Cell Method Based on the Low Pulsation Peristaltic Pump

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ABSTRACT

The emergence of the flow-through cell (FTC) method has made up for the limitations of previous dissolution test methods, but the high cost of the FTC dissolution devices have seriously hindered the progression of research and application of the FTC. This new design uses a peristaltic pump to simulate the sinusoidal flow rate of a piston pump. The flow profile of each peristaltic pump was sinusoidal with a pulsation of 120 ± 1 pulses per minute, and the flow rate ranged from 1.0 - 36.0 mL/min. The flow control of each channel was adjusted independently so the flow errors of the seven channels were close to 2%. The structure of the system was simplified, and the cost was reduced through manual sampling and immersing the FTC in a water bath. The dissolution rate of the theophylline and aminophylline films was determined, and good experimental results were obtained.

Keywords : FTC(에프티씨), Peristaltic Pump(연동펌프), Flow-through Cell(플로우스루셀)

1. Introduction

Efficacy and safety are crucial to medicine, and bioavailability of medicine is closely related to those factors. Bioavailability depends on the types of drug, the environment in which the medicine is located, and the physicochemical properties of the medicine. A bioavailability test can only be performed if urine and blood are collected after the medicine is absorbed into the blood circulation system, It requires significant time and effort, and the process is extraordinarily complicated[1-2]. Dissolution rate of medicine correlates to the bioavailability. Dissolution rate under specified conditions can be used as an indicator of bioavailability for medicine such as pharmaceutical tablets and capsules[3]. This test determines the amount of active ingredient(s) released from a solid oral dosage form, such as a tablet or a capsule, under controlled conditions using a known volume of dissolution medium within a predetermined length

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of time. A dissolution test can be carried out in vitro, and the procedure is simple and reliable. At present, there are three main methods for determining dissolution rate: 1. Basket method 2. Paddle method 3. FTC method[4]. Although the basket method and the paddle method are classic methods for determining dissolution rate, these two methods still have limitations. The basket or filter is easily blocked by viscous substances in the medicine, and when using the paddle method or the basket method, it is difficult for the operator to change the pH value of the solution many times during the experiment. Therefore, it is almost impossible to completely simulate the physiological environment in vivo; Some high-density particles will also form a pile at the bottom of the experimental device, inhibiting the dissolution of the drug under the paddle. A similar situation may also occur when using the paddle method for a test[5]. For drugs with saturation problems, it is difficult to provide accurate data when using basket and paddle methods. The development of FTC makes up for the limitations of the current methods. The FTC method can be used to test various drugs such as tablets, coated tablets, suppositories, soft capsules, implants, pellets, and stent drugs. It is especially suitable for the dissolution analysis of powders, suspensions, sustained release preparations or drugs that require a change in pH during the test.

At present, the common dissolution apparatus on the market for the FTC method is the CE7 smart automatic dissolution apparatus of SOTAX of Switzerland. The apparatus is suitable for determining the dissolution rate of various kinds of drugs, but its structure is complicated and it is expensive, making it a less popular test. In addition, the Chinese Pharmacopoeia has not yet included FTC, and the research on it has just started. There is no domestic experimental device. In this research, we designed and developed a dissolution apparatus for FTC based on a low pulsation peristaltic pump. The instrument can work in open and closed working modes. It uses a low pulsation peristaltic pump to simulate the sinusoidal flow rate of a piston pump. Each peristaltic pump is independently controlled, and the operator can input calibration parameters to adjust the flow of each channel so that the flow error of each channel is less than 2%. The structure of this system is simplified, and the cost is reduced by manual sampling and immersing the FTC in a water bath.

An experiment was carried out on theophylline film and aminophylline film, which verified the reliability and practicality of this instrument.

2. Structure and Working Principle of Apparatus

2.1 Design of Instrument Structure

The apparatus consists of a main engine, a water bath, stainless steel tube heating rings, solvent bottles, circulating pipes, flow-through cells, and sample holders. Fig. 1 is a schematic diagram of the structure of the instrument. The main engine consists of 7 double-roller low-pulsation peristaltic pumps, pump control modules, a touch screen, and power supplies. The flow profile of each channel is sinusoidal with a pulsation rate of 120 ± 1 pulses

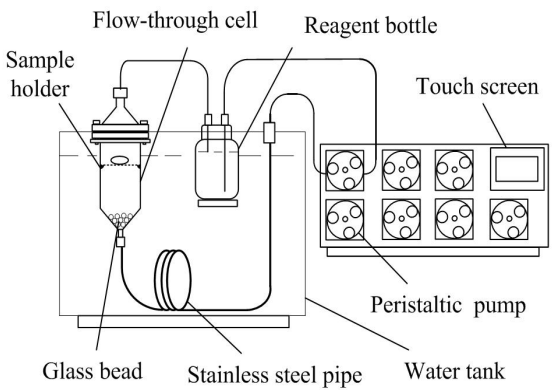

Fig. 1 Structure of apparatus

per minute, and the flow rate ranges from 1.0 to 36.0 ml/min. The volume of a FTC is 20 mL, and each FTC is equipped with a lid. The FTC and the lid are sealed with a silicone ring, and a filter can be placed inside the lid. The FTC, solvent bottle, and peristaltic pump are connected by Teflon tubes of 1/8 inch outer diameter (the inner diameter is 1.6 mm). The volume of the solvent bottle is 100 ml. The internal volume of the water bath is 15L, and the temperature can be set from 10 °C to 50 °C. It is generally set at 37 °C.

The FTC in the water bath is connected to the stainless steel pipe for heating the solvent from the solvent bottle, and the solution flows from the stainless steel tube into the FTC. Small glass beads with a diameter of 2 mm are placed at the bottom cone to control the flow type of the fluid. If glass beads are used, the fluid has a laminar flow. If no beads are used, it has turbulent flow. In general, the flow type of the fluid should be laminar flow when conducting the experiment on drugs such as powders, suspensions, and pellets[6]. A tablet holder is available, which can be used to fix drugs during the experiment.

Operators can choose open and closed working modes. In the closed working mode, the solvent in the solvent bottle circulates continuously. In the open working mode, the 37 °C solvent is either continuously added to the solvent bottle or the inlet of the pump is connected to a large-capacity solvent bottle, and the solvent passing through the FTC is directly discarded.

2.2 Design of FTC and Sample Holder

Each flow-through cell is equipped with a lid, and they are manually made of transparent glass. The outer diameter of the flow-through cell is 25 mm, the outer diameter of the annular flange is 30 mm, and the height is 57 mm. The length of the connecting glass tube is 10 mm, and its inner diameter is 2 mm.

Fig. 2 Structure of flow-through cell

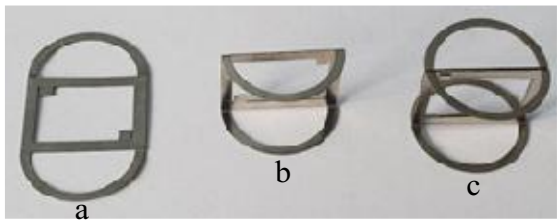

Fig. 3 Structure of stainless sample holder

Using a 0.2 mm thick 316 stainless steel plate, the sample holder is machined into the shape shown in the left part of Fig. 3 by wire cutting, and then it is processed into the shape shown in the middle part of Fig. 3 using a bending machine. Finally, after butting the steel sheets shown in the middle part of Fig. 3, the narrow strips of the protruding parts on both sides are folded to form the shape shown in the right part of Fig. 3. During the experiment, the stainless wire net of 80 meshes is placed on the sample holder, and a sample can be placed on the sample holder. Adhesive patches can be applied on both sides of the holder, and non-adhesive patches can be sandwiched between the holder. There are two kinds of holders, one is 16 mm and 20 mm in height and diameter, and the other is 35 mm × 20 mm.

2.3 Working Principle of Peristaltic Pumps

The USP requires that piston pumps are used in the apparatus for the FTC method. The flow profile should be sinusoidal with a pulsation of 120 ± 10 pulses per minute. In one cycle, the two working

processes of the piston pump are pushing and sucking. First, the inlet valve is opened to allow liquid to be drawn in. Then, the inlet valve is closed and the outlet valve is opened to allow the liquid to be pushed out. Piston pumps are characterized by high precision and high pressure, but they are expensive. In order to reduce the cost of the device, a double-roller low-pulsation peristaltic pump is used. The structure of the double roller reduces the amplitude of the pulsation by phase compensation. Under the normal flow rate, the pulsation of the pump is small, so it is assumed that it outputs a constant amount of solvent per time unit. In order to simulate the working mode of the piston pump, the peristaltic pump is controlled to make its speed change sinusoidally. The DMD5-2A low-pulsation pump head of Huiyu Weiye Company and PharMed NSF-51 No. 14 pump pipe (the inner diameter and thickness are both 1.6mm) are adopted. The pump can rotate one circle to push out about 0.5 ml of solvent. A two-phase stepping motor with a step angle of 1.8 degrees is used. The stepper motor requires 200 pulses per revolution, and when the microstep resolution is set to 1/4, the number of pulses is 800.The stepper motor runs sinusoidally in the first half cycle and stops in the second half cycle. Fig. 4 shows the working curve of the stepper motor. When the flow

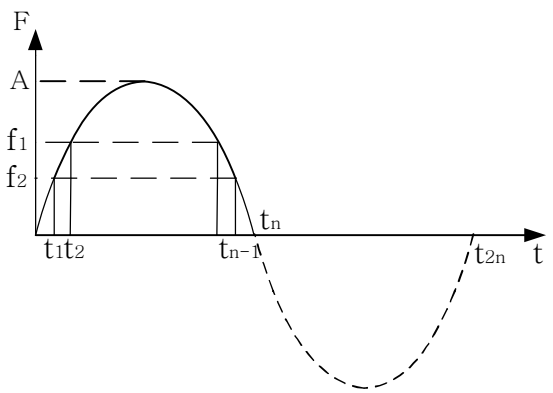

Fig. 4 Working curve of peristaltic pump

rate of the peristaltic pump is Q=1.0~36.0 ml/min, the number of pulses in the first half of the cycle can be calculated as $N=Q/120*0.5\times800\times K_Q$. K_Q is the flow calibration coefficient.

$$f(t)=Asin(\pi/t_n t)(0<t<t_n) \quad (1)$$

The expression of the working curve of the motor in the running state is Equation (1). The motor takes N steps in t_n seconds (t_n=0.25s), and the start time of each step is 0, t_1, t_2,..., t_{n-1},t_n. In each time period (t_1-0, t_2-t_1,...,t_n - t_{n-1}), a pulse will be sent out by the microcontroller. It is assumed that the maximum operating frequency of the motor is A, the starting frequency and ending frequency are 0, the area enclosed by the function and the upper part of the x-axis is N, and the area enclosed by the function and t_1-0, t_2-t_1,...,t_n - t_{n-1} is 1[7-8].

$$\int_0^{tn} Asin(\frac{\pi}{tn}t)dt=N \quad (2)$$

$$\int_{t-1}^{ti} Asin(\frac{\pi}{t_n}t)dt=1(1\le i\le N,t_{0=0)} \quad (3)$$

$$t_i=\frac{t_n}{\pi}\arccos[\cos(\frac{\pi}{t_n}t_{i-1})-\frac{\pi}{A}t_n](i=1,2\cdots n-1) \quad (4)$$

From Equation (2), $A = \pi N/2t_n$ can be obtained, and from Equation (3), Equation (4) can be obtained. When the system is initialized, the period of each pulse can be calculated according to Equation (4), and then it is stored in RAM. Each pulse is a square wave with a different period.

When the flow rate is set to 16 ml/min, N=213, t_0=0, t_1=0.010714, t_2=0.015163, t_3=0.018585,……, and t_{n-1}=0.239286.

3. Design of Hardware and Software

3.1 Hardware Components

The control system consists of the circulating pump control system and the water bath control module. Fig. 5 is a block diagram of the circulation pump control system. The circulating pump control system consists of 7 peristaltic pump control modules, the STC8F2K16S2 microcontroller, the MAX485 driver circuit, the 3.5-inch touch screen, and the power supply.

The STCF2K16S2 microcontroller mainly includes the 8-bit CPU, the 16K program memory, the 2KB RAM, the 2KB EEPROM, 2 UARTs, and 18 I/O ports[9]. The serial port 1 of the MCU is connected to the touch screen through a bus driver, and the serial port 2 is connected to 7 peristaltic pump control modules. Each peristaltic pump control module controls a low pulsation peristaltic pump.

As shown in Fig. 6, each peristaltic pump control module consists of the STC8F2K16S2 microcontroller, the two-phase DC stepper motor drive module called ZD-M42, the 3-digit DIP switch and the 24V power supply. The 3-digit DIP switch is connected to the P3.3~P3.5 ports of the MCU.P3.6 and P3.7 are connected to the pulse input port (CP) and the steering control port (DIR) of the stepper motor drive module. The four pins (A+, A-, B+, B-) are connected to the stepper motor. The microstep resolution is set to ¼, and the current is set to 1.5 A.

As shown in Fig. 7, the water bath control module consists of the STC15W408S -

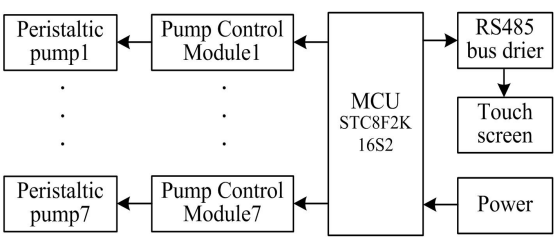

Fig. 5 Block diagram of circulating pump control system

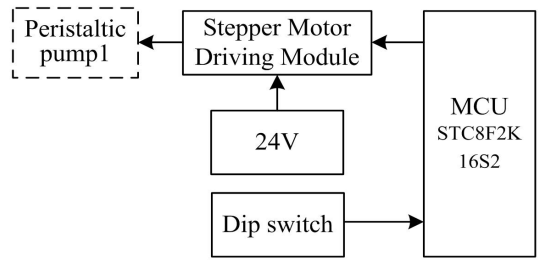

Fig. 6 Block diagram of peristaltic pump control module

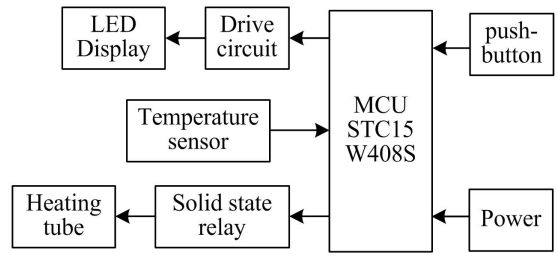

Fig. 7 Block diagram of heating system

microcontroller, the 8-segment LED display, the display driver circuit, the DS18B20, the solid state relay, the heating tube, the button, and the power supply. The power of the heating tube is 1500 W, and its working voltage is 220 V.

3.2 Design of Software

The program of the circulating pump control system includes a main program, a touch screen control subroutine, a serial communication subroutine, a sine time calculation subroutine, and so on. After the power is turned on, the main program calls the sine time calculation subroutine, and the calculation results are stored in RAM. Through the serial port, the calculation results are transmitted to each pump's control module, and the communication baud rate is 9600 bit/s. The touch screen control subroutine is used to set the flow rate and sampling time, input flow calibration parameters, and control the start and stop commands.

The control program of the peristaltic pump control module includes a main program, a communication subroutine, and a pump control subroutine. After the power is turned on, the module waits to receive the command sent by the main control board. After receiving the instruction, the data packet is analyzed, and it is confirmed whether the number of the pump is consistent with its own ID. After receiving the parameters such as the flow rate and time, the module will save and calculate each parameter. When receiving other commands such as start/stop or, pipeline cleaning, the module will send a pulse signal to the pump according to the received command. The first byte of the control command is to control the action of the pump, the second byte represents the number of the pump, the third byte and the fourth byte are 0x00, and the fifth byte represents the end of the instruction.

The control program of the water bath mainly includes a temperature collection subroutine, a temperature display subroutine, and a heating control subroutine. The algorithm for controlling the heating tube is an incremental PID control algorithm, and the heating tube is controlled by controlling PWM sent by MCU[9-11].

4. Analysis of Experimental Results

4.1 Instrument Operation

4.1.1 Pipe connection and installation

The peristaltic pumps in the first row are numbered No. 1, No. 3, No. 5, and No. 7. The pumps in the second row are numbered No. 2, No.4, and No.6. The numbers here correspond to the numbers of the pumps in the calibration interface. The numbers of the FTC and the solvent bottles increase from left to right, and the FTC and the solvent bottle on the left are No. 1. The inlet hose of each peristaltic pump is inserted into the bottom of the corresponding solvent bottle. The outlet hose of the pump is connected to the joint on the lid of the water bath. As shown in Fig. 8, the outlet of the heating pipe made of stainless steel is connected to the inlet of the FTC, and the hose connected to the outlet of the FTC is inserted into the hole in the lid of the solvent bottle.

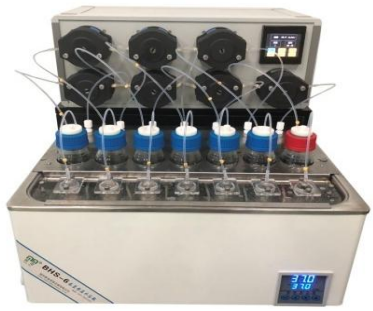

Fig. 8 Pipe connection diagram

4.1.2 Installation of FTC

The structure of the FTC is shown in Fig. 9. When it is necessary to filter the solvent, a filter is installed in the lid of the FTC. A glass cube is placed at the bottom of the FTC to prevent the glass beads from entering the pipe. The bottom of the FTC is filled with glass beads of 2 mm diameter to ensure that the flow type of the fluid is laminar. After connecting the hose at the inlet of the FTC, the FTC is placed in the acrylic bracket. Then, the sealing gasket made of silica gel and the lid of the FTC need to be placed on the FTC. The FTC is secured with an acrylic fixer and two nuts.

Fig. 9 Diagram of installation of flow-through cell

4.1.3 Device operation

First, add about 15 L of water to the water bath. After adding water, the water surface should be in contact with the underside of the acrylic holder. The water surface is about 1.5 cm from the upper end of the water bath. Second, add 50-100mL of degassed solvent at 37 °C into the solvent bottle, press the cleaning button to circulate the solvent for about 10 minutes to preheat the pipe, and then press the backflow button to empty the solvent in the FTC. Finally, open the lid of the FTC and place the sample holder and drug. After setting the flow rate, press the start button to start the circulation pump. When the sampling time is complete, remove the stopper made of tetrafluoroethylene in the lid of the solvent bottle and sample with a pipette. Add the same amount of solvent after sampling.

4.2 Flow Testing

When the flow error of one or more of the 7 channels is greater than 2%, or the dissolution apparatus is not used for a long time, it is necessary to calibrate the flow rate. First, take the hose connected at the outlet of the FTC out of the solvent bottle and insert it into the 100mL measuring cylinder with a precision of 1%. Finally, enter the calibration interface and start the circulation pump to collect the solvent. The flow rate is 32 ml/min, the running time is 3 min, and the total flow rate is 96 ml. The experimental results show that the maximum flow error of the seven channels before calibration is 5%, and both are less than 2% after two calibrations.

Table 1 Data table of flow calibration

Channel Number	1	2	3	4	5	6	7
Before (ml)	94.5	94.5	97	97.5	94	98	95.5
After (ml)	96.5	96	96	96	96	96	96

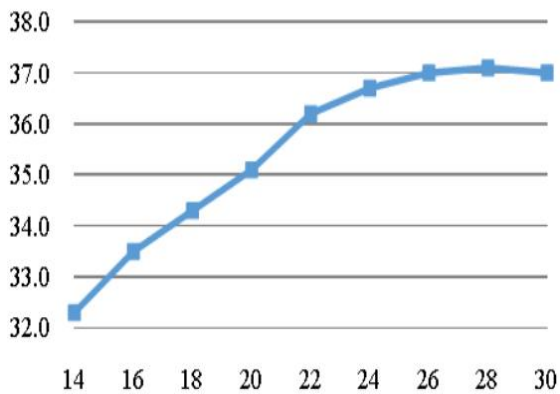

Fig. 10 Diagram of temperature variation curve

4.3 Heating Experiment

The temperature of the water bath is set to 37°C, and the temperature data is collected every 5 seconds. The temperature variation process between 14 minutes and 30 minutes is shown in Fig. 10. It can be seen from the figure that it takes about 18 minutes to heat up to 34 °C, and the temperature rises steadily after it reaches 36 °C. The temperature reaches 37 °C at about 26 minutes, and the temperature errors can be controlled within the range of 0.5 °C after that.

4.4 Dissolution Test

The dissolution test is performed on the theophylline film, the aminophylline film, and the solvent is ultrapure water. The apparatus works in the closed working mode, and the solvent circulation speed is set to 16 ml/min. Six sampling time points are set. The experimental results are shown in Fig. 11.

The results show that the aminophylline film has a faster dissolution rate than the theophylline film. The drug release of the aminophylline film can reach 60% within 60 minutes and can reach almost 100% in about 210 minutes. The drug release of the theophylline film at 60 minutes is about 40%, and the release at about 210 minutes is about 80%.

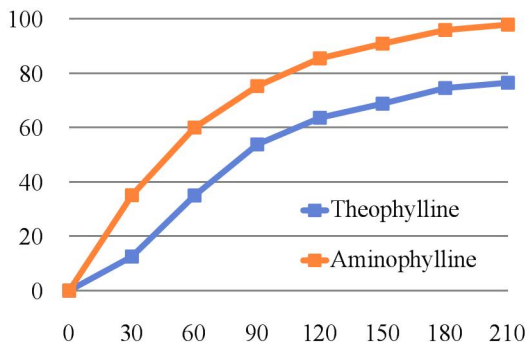

Fig. 11 Diagram of drug dissolution

5. Conclusion

This dissolution apparatus for the FTC method uses a low pulsation peristaltic pump to simulate the flow velocity curve of a piston pump. This apparatus has a low fabrication cost and a simple structure. When the flow rate of the 7 channels of the instrument is in the range of 1.0 - 36.0 ml/min, their flow error is less than 2%, and the temperature of the water in the water bath can be stably maintained at 37 °C. All the indexes of this instrument meet the requirements of USP. In experiments carried out on theophylline film and aminophylline film, good dissolution curves were obtained.

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