

In Vitro Dissolution Studies of Immediate-Release and Extended-Release Formulations Using Flow-Through Cell Apparatus 4

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ABSTRACT

The aims of this study were to evaluate the dissolution performance of solid dosage forms using the open and closed modes of the FTC Apparatus 4 under different flow rates and provide examples to demonstrate the advantages of the FTC method, in particular the possibility of changing the pH during experiments, in studying the release mechanisms of extended-release products. Immediate-release (IR) paracetamol and extended-release (ER) theophylline formulations were used in this study. Results from commercially available IR paracetamol tablets using FTC Apparatus 4 have shown similar dissolution behavior in the closed and open systems, reflecting well-maintained apparent sink conditions and controlled hydrodynamics in the test cells. The flow rate of FTC Apparatus 4 significantly affected the disintegration process of IR tablets. This information can be used as a discriminating tool to support formulation development and to set quality control standards and specifications. To mimic the continuous absorption of theophylline during the passage at different pH values through the whole gastrointestinal tract, dissolution tests were conducted using FTC Apparatus 4 with pH-dependent media for three different commercially available theophylline formulations. Two formulations of Uniphyllin 200-mg tablets and Nuelin SA 175-mg tablets provided a constant release rate during the course of medium pH changes, and their release behavior was predicted with accuracy by appropriate mathematical models. However, wide intervariability and biphasic release in the dissolution profiles were found for Slo-Phyllin 125-mg capsules.

KEYWORDS: Dissolution test; flow-through cell; Apparatus 4; paracetamol; theophylline; immediate release; extended release.

INTRODUCTION

Dissolution testing plays an important role in the pharmaceutical industry for drug formulation development, quality control testing for batch manufacturing consistency and specification setting, and establishment of in vitro–in vivo relationships between release of drug from the dosage form and drug absorption (1, 2). USP Apparatus 1 (baskets) and 2 (paddles), the most widely used methods for dissolution tests, provide a well-stirred, medium-rich environment in which dosage form disintegration and dissolution can be evaluated. However, there are obvious limitations with the rotating basket and paddle methods, for example, difficulty in maintaining sink conditions and poor reproducibility (3, 4). The flow-through cell (FTC) USP Apparatus 4 has become a popular dissolution device because it offers distinct advantages that can effectively solve the problem of non-sink conditions by supplying an unlimited quantity of fresh dissolution medium with an easy change of pH within a single run. This facilitates testing of formulation robustness with respect to variations in the gastrointestinal environment, which is particularly important to lead to data that are collected from in vivo results. Another advantage is that the FTC can offer controlled hydrodynamics in a well-defined

geometry of cells, not affected by medium change and sampling (5).

Drug dissolution rate from a tablet is the result of a combination of the physicochemical properties of the drug itself, the formulation including excipients, and the manufacturing conditions. When dissolution testing is employed to assist in choosing the best formulation, it is important that these tests are performed under appropriate conditions that are sensitive to variations that can affect in vivo performance. These conditions include the type of dissolution apparatus, paddle design, basket mesh size, agitation speed, fluid-flow velocity and pattern, media temperature, and so on (2). For immediate-release (IR) formulations, many studies have shown that compendial in vitro dissolution tests with Apparatus 2 make it difficult to show the differences among them. This is mainly related to the higher agitation level that causes the rapid disintegration of the tablet (6). Therefore, FTC Apparatus 4 is more suitable to assess excipient and process changes that could affect the release rate of drug from the dosage form during formulation development. FTC Apparatus 4 has been extensively used to facilitate development of in vitro–in vivo correlations for extended-release (ER) products because media with different pH values can be used with a single run, which provides a progressive dissolution that mimics the continuous absorption during the pas-

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sage of the drug at different pH values through the entire gastrointestinal tract (7–9).

A typical FTC Apparatus 4 system consists of a reservoir containing the dissolution medium, a pump that forces the medium upward through the vertically positioned flow cell, and a water bath to control the temperature of the cell. Studies have shown that many factors can affect the dissolution performance of the tested dosage forms using the FTC Apparatus including flow rate, medium, temperature, and cell preparation (10), among which the flow rate of the dissolution medium plays a key and profound role on drug release, in particular for disintegrating tablets (10, 11). Another important feature of the FTC apparatus is that it can operate in two different modes: (1) as an open system with fresh solvent from the reservoir continuously passing through the cell and (2) as a closed system in which a fixed volume of liquid is recycled (5). Compared with a closed dissolution system, a significant difference in an open dissolution system is that the data collected represents the amount dissolved/released at specific time intervals, and they produce estimates of release rate during the time intervals instead of the dissolution rates at specific time points.

The FTC approach has gained popularity in dissolution tests and has been employed for many years in testing different dosage forms such as tablets and capsules. However, very little research has evaluated its different operation modes or compared it with other techniques. Most recently, a collaborative study (12) involving six Scandinavian laboratories compared the FTC method with the paddle method to explore its applicability for enteric-coated dosage forms and found that the dissolution results from the FTC method were similar to those obtained with the official USP paddle method. However, the FTC method can generate data in a more convenient way. The aims of this study were to evaluate the dissolution performance of solid dosage forms using the open and closed modes of the FTC Apparatus 4 under different flow rates; to demonstrate the advantages of the FTC method, in particular the possibility of changing the pH during experiments; and to study the release mechanisms of extended-release products. The tasks were detailed as: (1) investigate the effect of different flow rates on the dissolution profiles using the open and closed FTC Apparatus 4 systems; (2) compare the dissolution profiles for the same IR tablets using FTC Apparatus

4 in an open system and USP Apparatus 2; and (3) study the pH influence on the release profile for an ER product using FTC Apparatus 4. Commercially available IR paracetamol tablets were used for studies in tasks 1 and 2, and three different theophylline ER tablet and capsule dosage forms were used in task 3. The similarity factor f_2 was used to compare paracetamol release profiles obtained by the open and closed FTC Apparatus 4 systems (13). To analyze the release mechanisms of different ER theophylline formulations, the drug release profiles were fitted to different release models including Higuchi, Hixson–Crowell, Korsmeyer–Peppas, Weibull, Logistic, and first-order (14).

MATERIALS AND METHODS

Materials

A marketed IR oral tablet formulation of paracetamol (Table 1) was studied to investigate the drug release with different flow rates in the open and closed FTC systems and standard USP Apparatus 2. Three marketed ER oral tablet and capsule formulations of theophylline summarized in Table 1 were used to study the drug release profiles under pH gradients.

Anhydrous theophylline and paracetamol purchased from Sigma–Aldrich UK were used as received. Hydrochloric acid, potassium phosphate monobasic, sodium acetate (ReagentPlus, 99%), and acetic acid (ACS reagent, ≥99.7%) were also obtained from Sigma–Aldrich UK and used as received. Distilled water generated from a Cyclon Ultrapure Water Still distiller (WSC044.MH3.7, Fistree International Limited, Loughborough, UK) was used through the study.

Buffer solutions including 0.1 N HCl, pH 4.5 acetate buffer, and pH 7.5 phosphate buffer were prepared according to the *British Pharmacopeia 2011*.

Methods

UV Spectrometer

A standard curve of absorbance versus concentration was studied using a Helios γ UV–vis spectrophotometer (Thermo Electron Corporation, Cambridge, UK). Pure anhydrous paracetamol powder was dissolved in distilled water to make a series of standard calibration solutions with different concentrations for development of a calibration model at a wavelength of 295 nm. A similar approach was used to develop three different calibration models of theophylline in three different buffers of pH 1.2

Table 1. IR Paracetamol and ER Theophylline Products Used in the Tests

	Brand	Lot	Dosage	Excipients
IR paracetamol	Boots	PAK22i11	500-mg tablets	pregelatinized maize starch, sodium metabisulphite, magnesium stearate
	Uniphyllin	164087	200-mg tablets	hydroxyethylcellulose, povidone, magnesium stearate, cetostearyl alcohol, macrogol, talc
ER theophylline	Nuelin SA	GMC136C	175-mg tablets	lactose, cellulose acetate phthalate, magnesium stearate
	Slo-Phyllin	71084	125-mg capsules	sucrose, maize starch, refined bleached shellac, talc, ethanol

HCl, pH 4.5 citrate buffer, and pH 7.5 phosphate buffer at a wavelength of 270 nm.

FTC Apparatus 4

The automated system of Sotax CE7 Smart with CY 7 piston pump (Sotax AG, Switzerland), fraction collector, and a medium splitter was used in the FTC dissolution tests.

The paracetamol tablet release tests were carried out by both the open and closed systems with 22.6-mm cells at 37.0 ± 0.5 °C. A ruby ball (5-mm diameter) and 1 g of glass beads (1-mm diameter) were placed at the bottom of the cone to damp the central pulse of the jet of fluid entering the cell. The paracetamol tablet was placed vertically on a tablet holder in the cell. Six tablets were tested for each experiment at the flow rates of 4, 8, and 16 mL/min. Distilled water was used as the dissolution medium. Glass microfiber filters (GF/D grade, pore size 2.7 μ m, thickness 0.67 mm, and diameter 25 mm) were used in the filter head in each experiment. For the open system tests, samples of 10 mL were collected automatically at predetermined sampling times of 5, 10, 15, 20, 30, 45, 60, and 90 min. For the closed system, 500 mL of medium was used in each test. Samples of 5 mL were withdrawn manually at 5, 10, 15, 20, 30, 45, 60, and 90 min and replaced with an equal volume of distilled water to maintain a constant dissolution volume. The drug concentration of each sample was determined by the calibration model. Each test lasted for 90 min, and dissolution rate and cumulative dissolution profile were the average of all the tablet results in each experiment. Extra sample points were taken for experiments at 4 mL/min to ensure the completion of drug release.

The theophylline formulation release profiles of different commercial products were determined using the FTC Apparatus 4 in an open system with 12-mm cells at 37.0 ± 0.5 °C. A ruby ball (5-mm diameter) and 0.5 g of glass beads (1-mm diameter) were placed at the bottom of the cone. For the tablet formulations of Uniphyllin and Nuelin SA, each tablet was placed vertically on a tablet holder in the cell. For the capsule formulation of Slo-Phyllin, each capsule was placed on the top of the glass beads in the cell. Six tablets or capsules were tested for each experiment at flow rates of 4, 8, and 12 mL/min with pH-dependent buffers for 12 h. The media used in the tests were pH 1.2 HCl buffer for the first 2 h, pH 4.5 acetate buffer for 2 h, and pH 7.5 phosphate buffer for the last 8 h. Samples of 10 mL were collected every 30 min using an automated sampler. The drug concentration of each sample was determined by the UV spectrometer with the developed calibration models.

Rotating Paddle Apparatus 2

Paracetamol tablet dissolution tests were carried out using USP rotating paddle Apparatus 2 (PHARMA Test model PT-DT7, Germany) at rotation speeds of 0, 25, 50, 75, and 100 rpm in 500 mL of distilled water as the dissolution medium at 37 ± 0.5 °C. Samples of 5 mL were taken manually at 5, 10, 15, 20, 30, 45, 60, and 90 min and replaced with

an equal volume of fresh medium to maintain a constant dissolution volume. The samples were filtered through a 0.45- μ m cellulose nitrate membrane filter, and the drug concentration was determined by the UV spectrometer with the developed calibration models. Each profile was the average of six individual tablet results. Extra sample points were taken for the experiment at a zero rotation speed to ensure the completion of drug release.

Similarity Factor f_2

The similarity factor f_2 is a logarithmic reciprocal square-root transformation of the sum of squared error of differences between the test and product dissolution profiles over all time points and is a measurement of the similarity between the curves, which is given by (13)

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{i=1}^n (R_i - T_i)^2 \right]^{-0.5} \times 100 \right\}$$

where R_i and T_i are the percentage drug dissolved of the reference and test products respectively at each sample point i , and n is the total number of samples.

The values of f_2 are between 0 and 100, and the test and reference formulations are considered to be similar when a value is greater than 50. This threshold was empirically derived assuming that at any sample point, the average difference of percentage release of active drug cannot be more than 10%; however, this assumption may not be true in some cases. The similarity factor f_2 is gaining popularity due to its recommendation by several regulatory authorities, such as FDA, as a criterion for the assessment of similarity between dissolution profiles.

Mathematical Models

The mathematical models of a dissolution profile can be deduced by a theoretical analysis of the process, such as the first-order kinetics model, Higuchi model, and Hixson-Crowell model. In most cases, because of the complexity of dosage forms (e.g., tablets, capsules, coated, or prolonged release), a theoretical foundation does not exist. As a result, semi-empirical and empirical models, such as the Korsmeyer–Peppas, Weibull, and logistic models, have to be used to fit dissolution data. The mathematical models used in this study to determine the mechanism of theophylline drug release are summarized in Table 2 (14). The mathematical models were fitted to the average dissolution data at the flow rate of 8 mL/min for each theophylline formulation using the Statistics Toolbox module of Matlab version 6.5. The model parameters were determined by the Gauss–Newton algorithm with Levenberg–Marquardt modifications for global convergence.

RESULTS AND DISCUSSION

Drug Release from IR Paracetamol Tablets

Figure 1 shows the paracetamol release from tablets both in the closed and open loops using the FTC Appara-

Table 2. Mathematical Models for Drug Dissolution Profile Analysis^a

Model	Mathematical equation	Release mechanism
First order	$100(1 - \exp(-c_1 t))$	Fick's first law diffusion mechanism
Higuchi	$c_1 t^{0.5}$	Diffusion medium based mechanism in Fick's first law
Hixson-Crowell	$100(1 - (1 - c_1 t)^3)$	Erosion release mechanism
Korsmeyer-Peppas	$c_2 t^{c_1}$	Semi-empirical model, diffusion medium based mechanism
Weibull	$100 \left(1 - \exp \left(- \left(\frac{t}{c_1} \right)^{c_2} \right) \right)$	Empirical model, life-time distribution function
Logistic	$100 \frac{\exp(c_1 + c_2 \log t)}{1 + \exp(c_1 + c_2 \log t)}$	Empirical model, S-shaped model

^a c_1 and c_2 are the model parameters.

tus 4 at three different flow rates of 4, 8, and 16 mL/min. The flow rate variations resulted in substantial differences in the dissolution profiles of the paracetamol tablets for both the closed and open loops. As expected, the amount of drug released at a given time has a direct relationship with the flow rate. Within 45 min, the percentage of paracetamol released reached 84.8% for the closed loop and 94.7% for the open loop at the flow rate of 16 mL/min, whereas the percentage of the paracetamol released only reached 48.2% for the closed loop and 35.8% for the open loop at the flow rate of 4 mL/min. These large differences in the release rates at different flow rates were caused by changes in the tablet disintegration time caused by hydrodynamics in the cells. At a higher flow rate, the tablet can disintegrate rapidly, and the surface area of the drug can increase dramatically. Therefore, an acceleration of drug release is expected as shown in Figure 1.

Interestingly, the drug release profiles are very similar at each flow rate in both open and closed loops as shown in Figure 1. All of the similarity factors f_2 at different flow rates are greater than 50 as shown in Table 3, indicating their similarity. This could be due to the high solubility of paracetamol, which is 19.3 mg/mL in water at 37 °C (15). In the closed-loop tests, the use of a dissolution volume of 500 mL (the maximum concentration of paracetamol was 1 mg/mL in the dissolution medium) allows sink conditions to be maintained throughout the experiment; therefore, similar dissolution profiles were obtained in the closed and open systems.

The dissolution performance of an IR formulation is the combined effect of tablet disintegration and drug diffusion properties. To investigate individual factors on the dissolution performance, paracetamol tablets were ground into fine powders and then tested using USP Apparatus 4 in the open loop at flow rates of 4, 8, and 16 mL/min (Figure 2). The flow rate represents the hydrodynamic

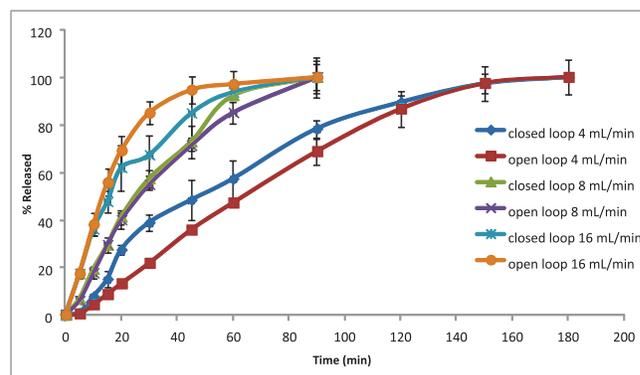


Figure 1. Effect of flow rates on paracetamol tablet release in the open and closed systems using FTC Apparatus 4.

Table 3. Similarity Factors f_2 Between Tablet Dissolution Profiles in Closed and Open Systems at Different Flow Rates

Flow Rate (mL/min)	f_2
4	51.0
8	74.4
16	52.5

agitation of the dissolution medium on the powder and modifies the status of the solid-liquid interface. From the classical diffusion theory of the Noyes-Whitney equation, the static dissolution layer thickness is reduced by a higher force of agitation at the surface of the dissolving particles. The results show that increasing the flow rate increases the dissolution rate of powder. However, the difference of the dissolution profiles was not significant, and all drug contents were dissolved within 15 min at different flow rates. When whole tablets were tested, the difference

of the dissolution profiles was significant at different flow rates, indicating that disintegration was the key factor affecting the release profiles of IR tablets.

The in vitro dissolution of IR paracetamol tablets was also studied using USP rotating paddle Apparatus 2 at rotation speeds of 0, 25, 50, 75, and 100 rpm as shown in Figure 3. The dissolution profiles using the FTC Apparatus 4 in the closed loop are also reported for comparison. The volume of dissolution medium was 500 mL for the Apparatus 2 tests, which was the same as that of closed-loop FTC dissolution tests. The results show that the drug release percentage curves are nearly identical using Apparatus 2 at rotation speeds of 50, 75, and 100 rpm. In these experiments, the paracetamol tablets disintegrated immediately once in contact with the medium. As discussed above, the key factor affecting the release profiles of IR tablets is disintegration time. It was not surprising that the release profiles are similar. When the rotation speed was low (0 or 25 rpm), paracetamol tablets disintegrated slowly, resulting in different release profiles.

The two dissolution profiles are nearly identical for Apparatus 4 at the flow rate of 16 mL/min and Apparatus 2 at the rotation speed of 25 rpm, which is consistent with those of the theoretical analysis using computational fluid dynamics (CFD) (16). An estimate of average flow velocity over time at 4 mL/min through the 22.6-mm diameter cell results in a small average fluid velocity of 1.66×10^{-4} m/s. Therefore, the release profile of Apparatus 2 at zero rotation speed was similar to that of Apparatus 4 at the flow rate of 4 mL/min, as shown in Figure 3.

Drug Release from ER Theophylline Tablets and Capsules

The dissolution tests of three formulations of ER theophylline were performed in the open system with the pH gradient changes defined above. Figures 4–6 show the dissolution profiles and dissolution rates of the three different ER formulations at flow rates of 4, 8, and 12 mL/min. Interestingly, the flow rate does not significantly affect drug release for all three formulations.

According to the ingredients of the Uniphyllin tablets shown in Table 1, hydroxyethylcellulose is used as the controlled drug delivery matrix, which can be described as a swellable erodible system. When the polymer hydroxyethylcellulose is in contact with water, it becomes hydrated and swells to form a hydrated matrix layer, which then controls further diffusion of water into the matrix. The outer hydrated matrix erodes as it becomes more dilute. The amount of drug released depends not only on the two diffusion processes of water penetration through the hydrated matrix into the nonhydrated core and diffusion of the dissolved drug through the hydrated matrix, but also on the erosion rate of the hydrated layer. For erodible tablets, drug release is determined by the erosion rate of the device (17). Because the erosion rate of the tablets was slow and not significantly affected by

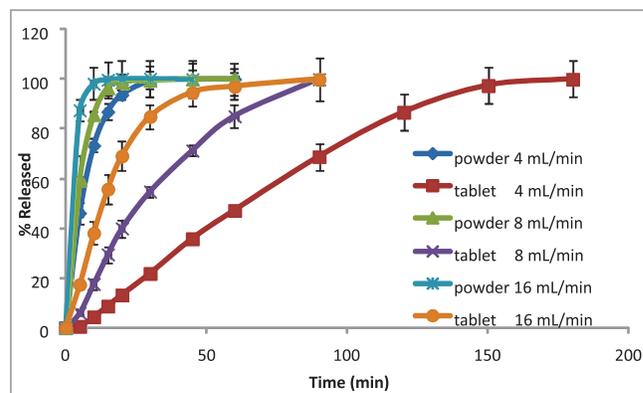


Figure 2. Comparison of dissolution profiles of paracetamol tablets and powders from the ground tablet at different flow rates in the open system.

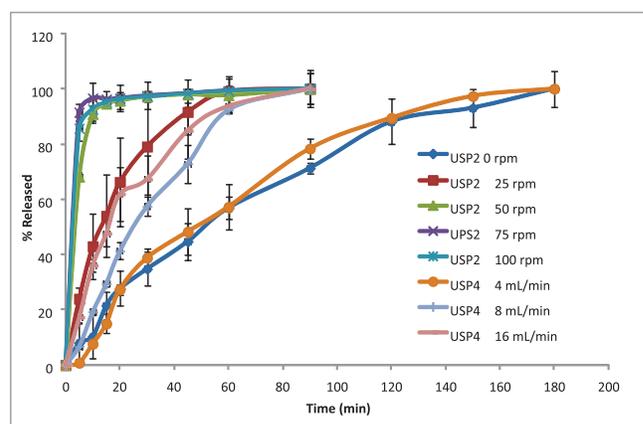


Figure 3. Comparison of paracetamol tablet dissolution profiles using USP Apparatus 2 and 4 in a closed system at different agitation rates.

the given range of the flow rate in this study, the drug release of Uniphyllin tablets was mainly controlled by the rate of water permeation and drug diffusion out of the gel matrix. Within an hour of the start of the test, the dissolution rate of the dissolved drug increased slightly with an increase in the flow rate of the dissolution medium due to a quicker hydration process affected by a higher velocity of the dissolution medium as shown in Figure 4B. After 2 h, the hydration process was controlled mainly by the matrix diffusion mechanism, which was not affected by the medium flow rate, so that the dissolution rate was independent of the flow rate. The effect of dissolution medium pH gradients is also revealed in Figure 4B, in which there was no significant change of the dissolution rate when the pH rose to pH 4.5 at 2 hr and to pH 7.5 at 4 h. The dissolution rate of the drug decreased slightly due to the increasing distance that drug molecules traveled by diffusion in the matrix and also the decreasing surface area in contact with the solubilized zone as hydration and dissolution proceeded.

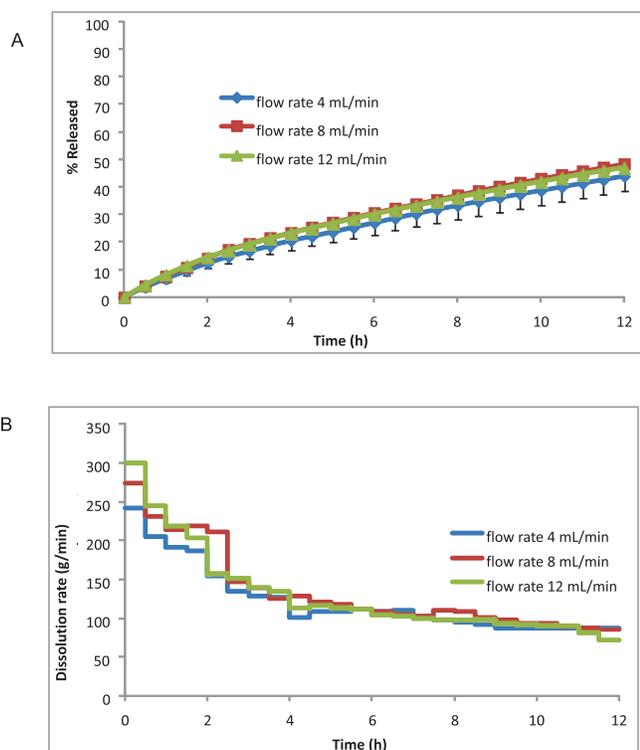


Figure 4. Effect of flow rate on drug release for Uniphyllin 200-mg tablets: (A) dissolution profiles; (B) dissolution rates.

Therefore, theophylline was released from Uniphyllin 200-mg tablets in a pH-independent manner. After 12 h, the release of theophylline was around 48%; therefore, Uniphyllin 200-mg tablets were designed for 24-h release.

For Nuelin SA 175-mg tablet formulation, cellulose acetate phthalate (CAP) polymer is used as the controlled drug delivery matrix and porous enteric coating. CAP exhibits a pH-dependent solubility profile. In aqueous media at a low pH value, CAP is almost insoluble, and it readily dissolves at pH 5.2. For the dissolution media of pH 1.2 and pH 4.5 used in this study, Nuelin SA 175-mg tablets were essentially nonerodible matrices. Therefore, theophylline release was controlled mainly by the matrix diffusion mechanism, in which the drug has to travel through the depletion zone in the matrix to the surface to be released. The diffusion layer of a nonerodible matrix is composed of both an aqueous diffusion layer at the tablet surface and a depletion zone in the matrix. The latter was the key factor for the drug dissolution and was not affected by different flow rates. Therefore, the dissolution profiles were independent of the flow rates within 4 h as shown in Figure 5A. The effect of dissolution medium pH change on the drug dissolution profile was not significant either, as shown in Figure 5B. When the medium was changed to pH 7.5 phosphate buffer at 4 h, the matrix of CAP started to dissolve. The rate of drug release was therefore controlled by both erosion and diffusion mechanisms.

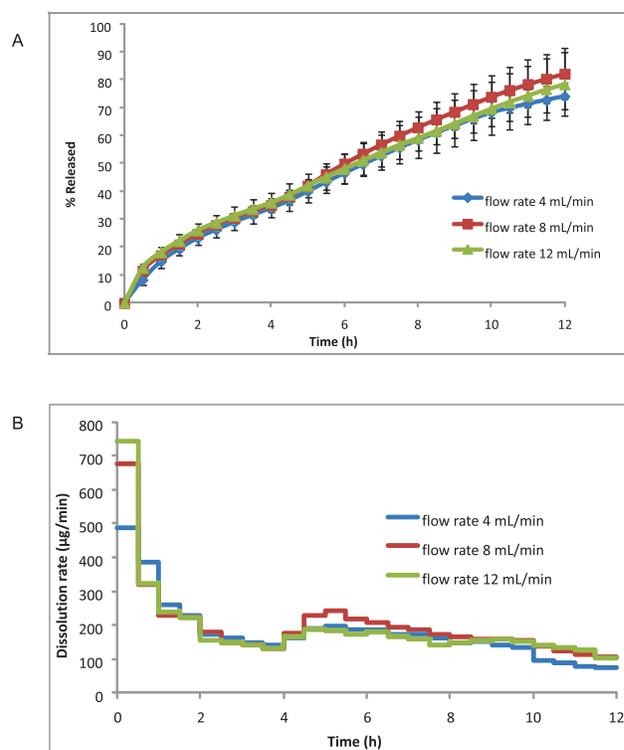


Figure 5. Effect of flow rate on drug release for Nuelin SA 175-mg tablets: (A) dissolution profiles; (B) dissolution rates.

In Figure 5B there was a notable increase in the drug dissolution rate when the pH was increased from 4.5 to 7.5. Similar to that of Uniphyllin 200-mg tablets, the hydrodynamics of the dissolution cells did not significantly affect the drug release for Nuelin SA 175-mg tablets, indicating a small change in dissolution rates with different flow rates in Figure 5B.

Slo-Phyllin 125-mg capsules are made of coated and uncoated drug pellets. The polymer of refined bleached shellac is used as an enteric coating to protect the pellets from the acid environment of the stomach, providing sustained release of the drug. Therefore biphasic release was observed in the dissolution profiles as shown in Figure 6A. Within the first 2 h in the medium at pH 1.2, around 60 % of drug was released. When the medium was changed to pH 4.5 acetate buffer, another 20% of drug was released within two hours. The trend of the drug dissolution rate, however, was not changed as shown in Figure 6B, indicating that the theophylline release was pH independent up to pH 4.5 dissolution medium. When the dissolution medium was switched to pH 7.5 phosphate buffer, a big increase in drug dissolution rate was observed as shown in Figure 6B, indicating that the coated drug pellets started to dissolve. The release of the remaining theophylline was completed well within one hour. Therefore, drug release from Slo-Phyllin 125-mg capsules was not affected by a low pH medium and was pH dependent at a higher pH medium. Because the size of the pellets was small (ap-

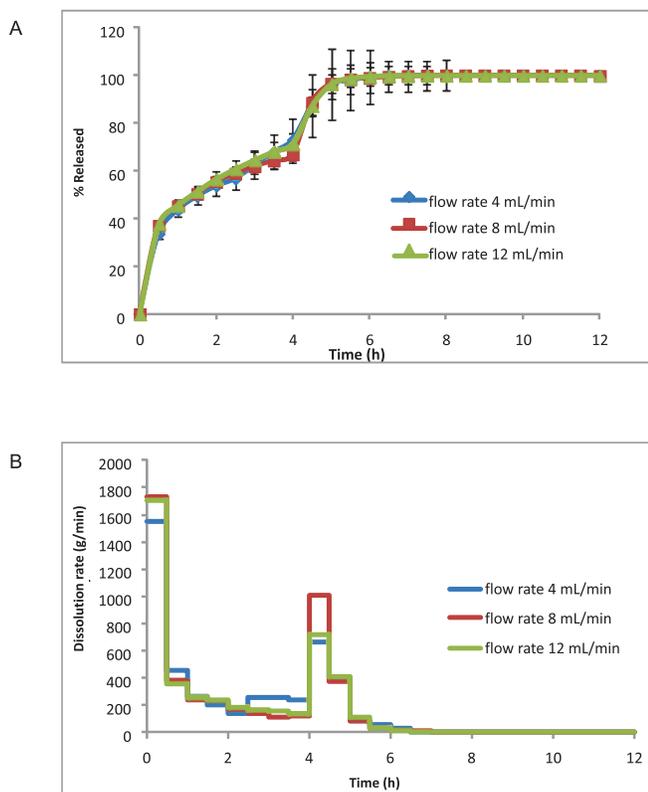


Figure 6. Effect of flow rate on drug release for Slo-Phylline 125-mg capsules: (A) dissolution profiles; (B) dissolution rates.

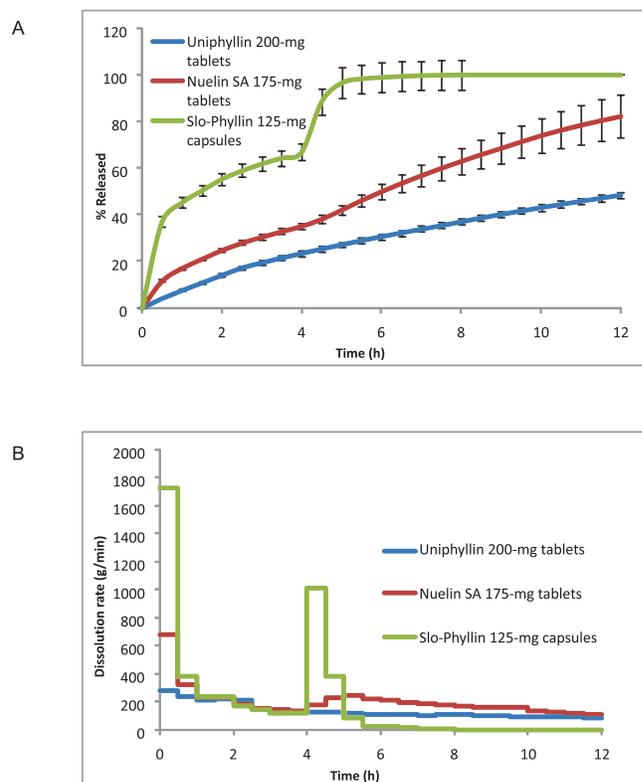


Figure 7. Comparison of three theophylline dosage forms at a flow rate of 8 mL/min: (A) dissolution profiles; (B) dissolution rates.

proximately 1-mm diameter) and they were moving with the inlet flow, the agitation force of flow rate did not play a significant role in affecting the drug diffusion rate, showing a consistent dissolution profile at different flow rates shown in Figure 6A,B.

A comparison of three commercial dosage forms of theophylline at the flow rate of 8 mL/min is shown in Figure 7A,B. The release profiles of three theophylline products are clearly different. Slo-Phyllin 125-mg capsules released drug significantly faster than Uniphyllin 200-mg and Nuelin SA 175-mg tablets; however, they show much wider interproduct variability than the other two products. Uniphyllin 200-mg tablets showed highly reproducible in vitro release profiles in this study. Based on the drug release rates shown in Figure 7B, the drug release profiles from Uniphyllin 200-mg and Nuelin SA 175-mg tablets were reasonably sustained over the course of the pH gradients. However, once the medium pH rose to pH 7.5, Slo-Phyllin 125-mg capsules had rapid drug release. Thus, Slo-Phyllin 125-mg capsules and Nuelin SA 175-mg tablets were designed for a 12-h sustained release in which drug release from a Slo-Phyllin 125-mg capsule was complete within 6 h and 82% of the drug was released from Nuelin SA 175-mg tablets within 12 h, while the Uniphyllin 200-mg tablets were designed for 24-h sustained release, in which 48% of the drug was released within 12 h.

To predict the drug release profiles for different formulations, different mathematical models in Table 2 were used to fit the dissolution curves shown in Figure 7A. The parameters of the mathematical models are shown in Table 4. The descriptive statistics of regression for the dissolution data in Table 4 were calculated including determination coefficient (r^2), maximum residual in absolute size between fitted and actual percentages of drug dissolved (R_{max}), and square root of mean of residuals square (SRRMS). For a well-fitting model, the calculated determination coefficient should be close to 1, and both the maximum residual and SRRMS should be small. Selection of the best-fitting model is based on the descriptive statistics of the regression in the following order: higher determination coefficient, smaller maximum residual, and smaller square root of mean of residuals square.

Overall, both the Weibull and Korsmeyer–Peppas models gave the best prediction for the dissolution profile of Uniphyllin 200-mg tablets with almost identical results. As the Weibull model is empirical, there is no direct connection with release mechanism. As discussed above, the Uniphyllin drug release system can be described as a swell–erodible system and is essentially dominated by the matrix diffusion mechanism. Therefore it is not surprising that the semiempirical matrix diffusion-based model, Korsmeyer–Peppas, can describe the dissolution data well.

Table 4. Model Parameters and Descriptive Statistics of Regression for Dissolution Profiles of Different Formulations at a Flow Rate of 8 mL/min

Model	Brand	C ₁	C ₂	r ²	R _{max}	SRRMS
First order	Uniphyllin	0.0587		0.977	3.60	1.92
	Nuelin SA	0.125		0.977	5.51	3.25
	Slo-Phyllin	0.428		0.885	17.7	7.30
Higuchi	Uniphyllin	13.0		0.951	5.37	2.80
	Nuelin SA	21.8		0.936	8.46	5.43
	Slo-Phyllin	34.5		0.737	19.5	11.0
Korsmeyer–Peppas	Uniphyllin	0.684	8.92	0.998	1.44	0.530
	Nuelin SA	0.716	14.1	0.994	3.11	1.6
	Slo-Phyllin	0.333	48.0	0.874	14.4	7.63
Hixson–Crowell	Uniphyllin	0.0179		0.960	4.38	2.53
	Nuelin SA	0.0357		0.983	6.73	2.79
	Slo-Phyllin	0.109		0.880	21.6	7.46
Weibull	Uniphyllin	20.1	0.824	0.999	0.825	0.359
	Nuelin SA	7.92	1.05	0.978	6.36	3.17
	Slo-Phyllin	2.25	0.914	0.888	14.7	7.19
Logistic	Uniphyllin	-2.53	2.25	0.998	1.13	0.580
	Nuelin SA	-2.39	3.28	0.955	8.72	4.58
	Slo-Phyllin	-0.486	3.41	0.817	19.0	9.21

For Nuelin SA 175-mg tablets, the drug delivery system was a nonerodible matrix in a lower pH medium and an erodible matrix in a higher pH medium. Therefore both the Korsmeyer–Peppas and Hixson–Crowell models gave the best fit rather than the first-order or Higuchi model. The Slo-Phyllin 125-mg capsules contained a mixture of uncoated and enteric coated pellets, which showed a biphasic release profile. Therefore, none of mathematical models shown in Table 2 can be used to fit the Slo-phyllin data well. Data of measured dissolution profiles and prediction by the best model for each of ER theophylline formulations are shown in Table 5.

CONCLUSION

Application of the flow-through cell USP Apparatus 4 tests in the closed and open systems for a commercially available IR paracetamol tablet formation has shown their similar dissolution behaviors, reflecting well-maintained, apparent sink conditions and controlled hydrodynamics in the test cells. This can significantly eliminate the variability of a dissolution test related to hydrodynamic artifacts and subsequently improve the reproducibility of the test. Drug release characteristics from the IR paracetamol formulation using FTC Apparatus 4 at different flow rates is significantly different due to the discriminating property of the hydrodynamics on the tablet disintegration. Therefore flow-through cell USP Apparatus 4 can be used as an important tool to support formulation development

and to set quality control standards and specifications. It would be difficult to distinguish the dissolution profiles performed by Apparatus 2 according to the compendial dissolution test due to a small difference caused by rapid disintegration of the tablets.

An extended-release formulation is usually designed to reduce dose frequency and maintain relatively constant or flat plasma drug concentration. The slow release of theophylline decreases side effects seen with rapid absorption and ensures therapeutic levels are maintained throughout the night, for instance. To mimic the continuous absorption of theophylline during passage through the various pH values of gastrointestinal tract, dissolution tests were performed for three different commercially available theophylline formulations using FTC Apparatus 4 with dissolution medium pH changes. Two formulations of Uniphyllin 200-mg tablets and Nuelin SA 175-mg tablets can provide a constant release rate with high reproducibility over the course of media pH changes, and their release behaviors can be predicted accurately by appropriate mathematical models. However, for Slo-Phyllin 125-mg capsules, there was wide intervariability and a biphasic release in the dissolution profiles.

Finally, we would like to emphasize that the experiments performed at 4 mL/min were outside the CY7 piston pump specification of 8–50 mL/min. Although the flow rate had been calibrated before each experiment, large variations in the results were inevitable. A higher

Table 5. Comparison of Measured Dissolution Profile with Prediction by the Best Model for ER Theophylline Formulations

Time (h)	Uniphyllin			Nuelin SA			Slo-Phyllin		
	Measurement (%)	Prediction (Korsmeyer–Peppas)	Error	Measurement (%)	Prediction (Korsmeyer–Peppas)	Error	Measurement (%)	Prediction (Weibull)	Error
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	4.11	5.55	-1.44	11.58	8.56	3.02	37.02	15.41	21.61
1	7.58	8.92	-1.34	17.08	14.05	3.02	45.23	29.15	16.08
1.5	10.79	11.77	-0.98	20.98	18.78	2.19	50.33	41.32	9.02
2	14.09	14.33	-0.24	24.81	23.08	1.73	55.31	52.00	3.30
2.5	17.25	16.69	0.55	27.92	27.07	0.84	58.86	61.31	-2.45
3	19.44	18.91	0.53	30.44	30.84	-0.40	61.89	69.32	-7.43
3.5	21.53	21.01	0.51	32.84	34.44	-1.60	64.33	76.15	-11.82
4	23.41	23.02	0.39	35.10	37.89	-2.80	66.85	81.88	-15.03
4.5	25.35	24.95	0.40	38.12	41.23	-3.11	88.48	86.60	1.88
5	27.17	26.82	0.35	42.05	44.46	-2.40	96.55	90.43	6.12
5.5	28.95	28.62	0.32	46.21	47.59	-1.39	98.35	93.45	4.90
6	30.62	30.38	0.24	49.96	50.65	-0.69	98.92	95.75	3.16
6.5	32.25	32.09	0.16	53.51	53.64	-0.12	99.41	97.44	1.96
7	33.82	33.76	0.06	56.84	56.56	0.28	99.73	98.61	1.11
7.5	35.35	35.39	-0.04	60.02	59.42	0.60	99.89	99.36	0.54
8	37.00	36.99	0.02	63.00	62.23	0.77	100.00	99.77	0.23
8.5	38.64	38.55	0.09	65.86	64.99	0.88	100.00	99.95	0.05
9	40.15	40.09	0.07	68.59	67.70	0.89	100.00	100.00	0.00
9.5	41.62	41.60	0.02	71.33	70.37	0.96	100.00	100.00	0.00
10	43.03	43.08	-0.05	74.00	73.00	0.99	100.00	100.06	-0.06
10.5	44.43	44.54	-0.12	76.35	75.60	0.76	100.00	100.27	-0.27
11	45.77	45.98	-0.22	78.50	78.15	0.34	100.00	100.73	-0.73
11.5	47.08	47.40	-0.32	80.44	80.68	-0.24	100.00	101.52	-1.52
12	48.37	48.80	-0.43	82.24	83.17	-0.93	100.00	102.76	-2.76

specification piston pump should be used for accurate delivery at low flow rates.

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