Effect of Sampling Procedures of Release Testing on Drug Release and Scale-up Production Feasibility of Multiple-Unit Dextromethorphan Resinate Tablets: A Technical Note

Thaned Pongjanyakul[1]

[1]Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen 40002, Thailand

INTRODUCTION

Oral sustained-release dosage forms can be divided into 2 types: single unit and multiple unit. Multiple-unit dosage forms have been found to provide advantages over single-unit dosage forms.[1] The multiple-unit dosage forms consist of many small particles, which are contained in a capsule or a tablet. The small particles are mixed with the contents in the gastrointestinal (GI) tract and are distributed over a large area. Thus high local concentration of the drug is avoided and the risk of local irritations is reduced. Moreover, multiple units are also less variable and less dependent on gastric transit time, resulting in reproducible bioavailability of the drug.

Ion exchange resins have been widely used as a drug carrier in pharmaceutical dosage forms for taste masking[2] and controlling release.[3-6] These resins are cross-linked water-insoluble polymers carrying ionizable functional groups. Drugs can be loaded onto the resins by an exchanging reaction, and hence a drug-resin complex (drug resinate) is formed.[7] Drug is released from the resinates, by exchanging with ions in the GI fluid, and followed by drug diffusion.[8] The sustained-release profiles of drug can be obtained by using a mix of uncoated and semipermeable coated resonates[9,10] and by selecting a degree of cross-linking and particle size of the resins without a coating process.[11,12] Moreover, the drug resinates can also be used as a drug reservoir, which has caused a change of the drug release in hydrophilic polymer tablets.[13] Recently, multiple-unit sustained-release dextromethorphan (DMP) resinate tablets consisting of DMP resinates and direct compression fillers were prepared by using direct compression method. The DMP resinate tablets using microcrystalline cellulose (MCC) provided a small change of drug release when compared with the DMP resinates. Moreover, these tablets could rapidly disintegrate to provide individual DMP resinates. Thus the release of DMP was mainly controlled by the resinates.[6]

Drug released from ion exchange resins is driven by the exchange of ions toward an equilibrium,[7,14,15] which is likely to occur with a substantial percentage of drug still bound to the resins, even under sink conditions. This is a problem that occurs with a fixed-volume dissolution apparatus because it does not obtain a complete drug-release profile. For example, DMP released from the resinates was ~60% and 65% of total drug loading in simulated gastric and intestinal fluids, respectively.[15] Thus, continuous release of the drug from the resinates may be achieved by changing almost all the release medium in order to maintain the ion exchange process. However, this method causes the process to become complicated. To solve this problem, sampling of release medium to analyze the concentration of drug released and replacing a fresh medium to the system should be done following the appropriate procedure. This method might drive the ion exchange process, which may lead to continuous drug release from the resinates.

The aims of the present study were to investigate the effect of sampling volume and frequency on drug release from the DMP resinate tablets using a factorial design study and to prepare the DMP resinate tablets in large-scale production. Physical properties and in vitro drug release in various media of the DMP resinate tablets were also performed.

MATERIALS AND METHODS

Materials

Dextromethorphan HBr was a gift from F. Hoffmann-La Roche, Basel, Switzerland. Cation exchange resin, Dowex 50W (100-200 dry mesh), 4% degree of cross-linking, was purchased from Aldrich Chemical Co (Milwaukee, WI) and used as received. Microcrystalline cellulose (Avicel PH102, Asahi Chemical Industry Co, Tokyo, Japan), sodium starch glycolate (Explotab, Rama Production Co, Bangkok, Thailand), colloidal silicon dioxide (Aerosil 200, Degussa Japan Co, Ltd, Tokyo, Japan), and magnesium stearate (Mallinckrodt Inc, Hazelwood, MO) were used as tablet excipients. All other reagents used in this study were analytical grade and were used as received.

Purification of Ion Exchange Resin

Dowex 50W was purified using the method that was previously reported.[12] Resin (30 g) was washed successively with

Corresponding Author: Thaned Pongjanyakul, Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen 40002, Thailand. Tel: 66-43-362092; Fax: 66-43-362092; E-mail: thaned@kku.ac.th

distilled water, methanol (300 mL), benzene (300 mL), and methanol (300 mL); and several times with distilled water to eliminate organic and color impurities. Then, the wet resins were activated by 0.1 N HCl 300 mL and washed several times with distilled water. The wet resins were dried overnight in hot air oven at 50°C and kept in an amber glass vial.

Preparation of Dextromethorphan Resinates

DMP resinates were prepared using a batch process. Resin (10 g) was placed in an Erlenmeyer flask and then 500 mL of 2% wt/vol DMP HBr solution was added. The mixture was shaken in a water bath at 37°C for 2 hours. Then, the DMP resinates were separated from filtrate by filtration, and washed several times with distilled water to remove any unreacted drug and other ions. The DMP resinates were dried overnight at 50°C and kept in a desiccator. The amount of free drug in the filtrate as well as the washing water was determined spectrophotometrically at a wavelength of 278 nm (model UV-1201, Shimadzu, Kyoto, Japan). Determinations were performed in duplicate for each preparation. The difference in weights between the initial amount of drug added and the remaining amount of drug in the solution was the amount of drug loaded onto the resins.[16,17] The percentage of drug in the resinates was calculated in the form of DMP free base and related to the dry weight of the resinates.

Preparation of Dextromethorphan Resinate Tablets

The preparation method of the DMP resinate tablets was modified from the method that was previously reported.[6] The tablets consisted of DMP resinates equivalent to DMP HBr 30 mg, sodium starch glycolate (10% wt/wt), magnesium stearate (1% wt/wt), colloidal silicon dioxide (0.5% wt/wt), and appropriate amount of MCC used to adjust weight of each tablet to 300 mg. The DMP resinates, MCC, colloidal silicon dioxide, and sodium starch glycolate were mixed in a rotomixer for 20 minutes. Magnesium stearate sieved through a 180-μm sieve was blended with the mixture for 5 minutes before tableting. A 10-mm-diameter flat-faced punch and die were used. Tablets were compressed using a single-punch tableting machine (Yeo Heng Co, Ltd, Bangkok, Thailand), which controlled the tablet hardness in the range of 78 to 98 N. Each batch size of this study was 600 tablets.

Evaluation of DMP Resinate Tablets

Thickness and Hardness

The thickness of the tablets was determined using a digital caliper (model 500-136, Mitutoyo, Japan). The hardness of tablets prepared was determined using a tablet hardness tester (model 40-2100, Vankel, Cary, NC).

Disintegration and Wetting Times

The disintegration time of the DMP resinate tablets was determined using a basket-rack assembly disintegration test apparatus (model QC-21, Hansan Research, Northridge, CA). The disintegration medium was distilled water maintained at 37.0°C ± 0.5°C. Each tablet was placed into the basket and disintegration time was recorded at the point at which the tablet disintegrated and passed through the screen of the basket. The method for determining wetting time of the tablets was modified from that previously reported.[18] A 10-cm-diameter Petri dish containing 10 mL of distilled water was used. A tablet was put into the Petri dish, and the time for complete wetting of the tablet was measured.

Friability

Ten tablets were weighed, and then placed in a friabilator (model PTF-1, Pharma Test, Hainburg, Germany), which was rotated for 4 minutes at 25 rpm. The tablets were reweighed and the loss in weight (%) was calculated.

Scanning Electron Microscopy

Surface morphology and internal structure of the DMP resinate tablets were studied using scanning electron microscopy (SEM). Samples were mounted onto stubs, sputter-coated with gold in a vacuum evaporator, and viewed using an SEM (model JSM-5800LV, Jeol, Tokyo, Japan).

Drug Release Studies

A United States Pharmacopeia (USP) dissolution apparatus II (paddle method) (Hanson Research, Northridge, CA) was used to characterize the release of DMP from the tablets. The paddles were rotated at 50 rpm and 37.0°C ± 0.5°C. The release studies were performed in 500 mL of simulated gastric fluid without enzyme (SGF), 500 mL of pH 6.8 simulated intestinal fluid without enzyme (SIF), or 440 mL

Table 1. Factorial Study Design of Sampling Procedures

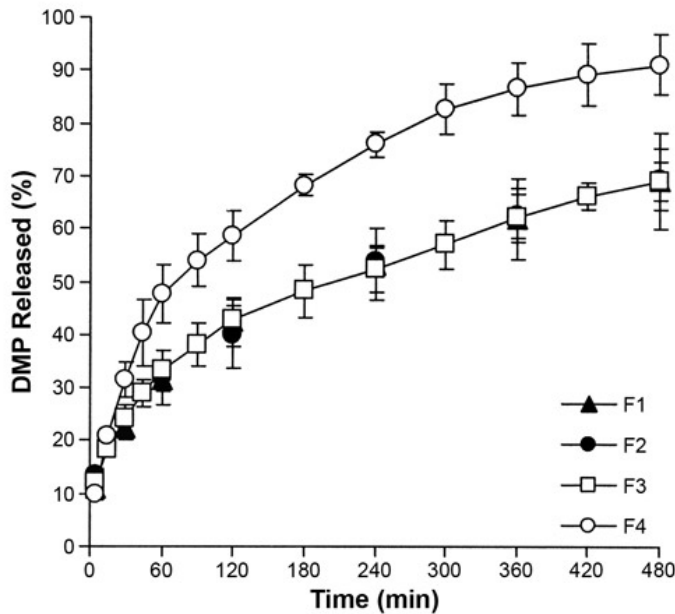| Factors	Low Level	High Level
Factorial design		
Sampling volume (mL)	5	20
Sampling frequency for 8 hours testing (time)	7	13
Study	**Sampling Volume**	**Sampling Frequency**
Treatment conditions used in the factorial study		
F1	5	7
F2	5	13
F3	20	7
F4	20	13

Figure 1. Dextromethorphan (DMP) release profiles of DMP resinate tablets in simulated gastric fluid using various sampling procedures. Each point is mean ± standard deviation, n = 3.

of 0.1 N HCl for 2 hours; and then 160 mL of 0.2 M tri-sodium phosphate was added for adjusting pH of this medium (the final pH of this system was over the range of 6.7 to 6.9). Samples were collected and replaced with a fresh medium at various intervals. The amount of DMP released was analyzed spectrophotometrically at a wavelength of 278 nm.

In this study, the effects of sampling procedure, such as sampling volume and frequency, on DMP released from the resinate tablets were investigated using a factorial design as shown in Table 1. Four experiments for a 2^2 factorial design were conducted on lot 1 of DMP resinate tablets and SGF was used as a medium. Total DMP released at 8 hours and

DMP release rate were calculated and used as release parameters for statistical analysis.

DMP release kinetics of the resinates can be described using a matrix diffusion-controlled model.[15] The release of drug from the resinates could be expressed by the following equation:

$$Q = kt^{0.5} \tag{1}$$

where Q is the percentage of drug released at a given time (*t*), and *k* is the release rate. An approximation of the equation could be shown by plotting Q and $t^{0.5}$, and the slope (*k*) of this relationship could be calculated using linear regression analysis.

Statistical Analysis

Univariate analysis of variance (ANOVA) was performed to determine the significant effect of sampling volume and frequency on drug release parameters, and ANOVA with the least significant difference (LSD) test for multiple comparisons was used to test the significant difference of drug release rate of the DMP resinate tablets in scale-up production studies. Differences were considered to be significant at a level of $P < .05$. All statistical tests were run on SPSS program for MS Windows, release 11.5 (SPSS Inc, Chicago, IL).

RESULTS AND DISCUSSION

Effect of Sampling Volume and Frequency on Drug Release

DMP release profiles of lot 1 DMP resinate tablets of F1 to F4 study are shown in Figure 1. The drug release profile using F4 study showed a higher DMP release than those using other studies, and total DMP released at 8 hours was
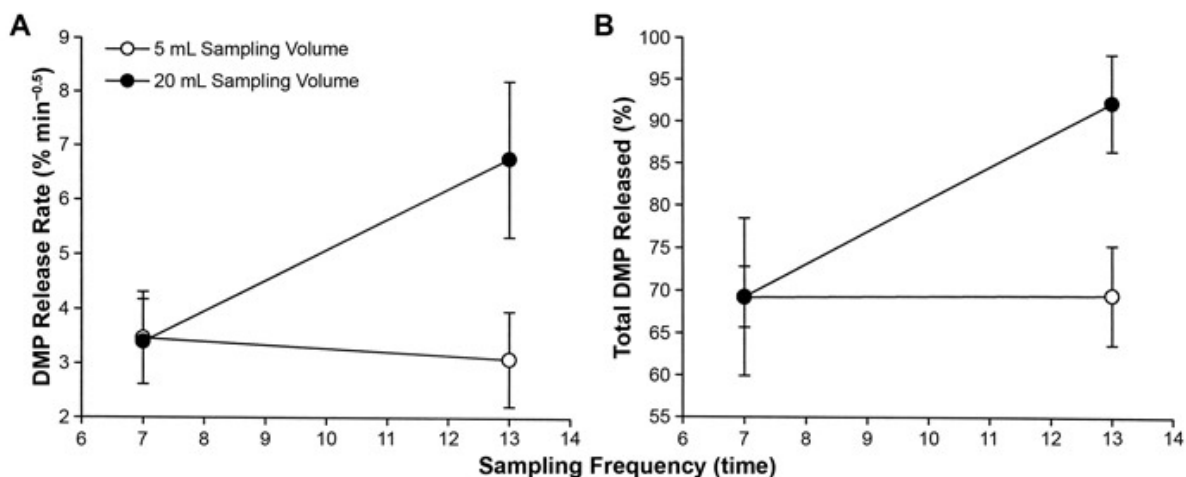

Figure 2. Interaction between sampling frequency and sampling volume on (A) DMP release rate and (B) total DMP released of DMP resinate tablets. Each point is mean ± standard deviation, n = 3. DMP indicates dextromethorphan.
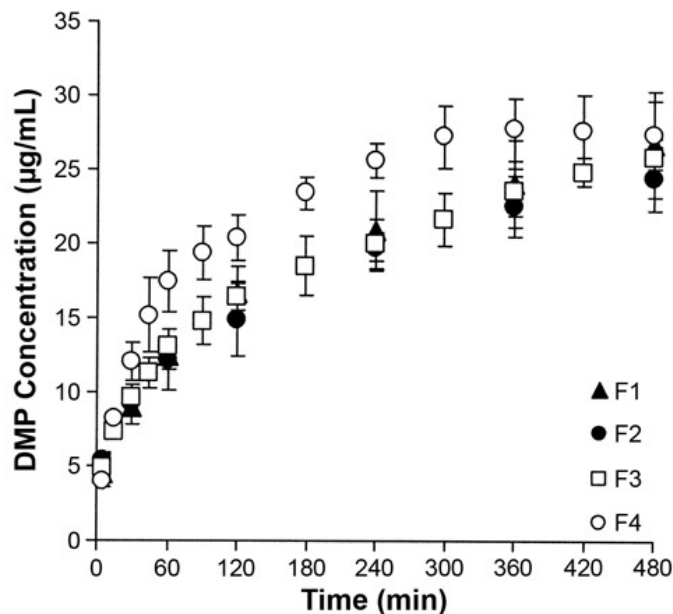
Figure 3. Dextromethorphan (DMP) concentration profiles of DMP resinate tablets using various sampling procedures. Each point is mean ± standard deviation, n = 3.

more than 85%. The DMP release profiles of F1 to F3 studies were comparable. However, the DMP gradually released from the resinates throughout the test can be observed in all studies. Using statistical analysis, sampling volume, and frequency significantly affected ($P < .05$) total DMP release and DMP release rate. The interactions of sampling frequency with sampling volume on both release parameters were significant ($P < .05$), as well, and are presented in Figure 2. It can be seen that the highest total DMP release and DMP release rate were found when using high level of both factors. The increase in either sampling volume or sampling frequency was not statistically affected ($P > .05$) by both release parameters.

The drug released from the ion exchange resin was achieved by an ion exchange process that was likely due to a chemical reaction. This process can be illustrated as following equation:

$$\text{Re} - SO_3^- DMP^+ + X^+ \leftrightarrow \text{Re} - SO_3^- X^+ + DMP^+ \quad (2)$$

where $\text{Re} - SO_3^-$ is structure portion containing sulfonate groups ($-SO_3^-$), which are fixed ions. X^+ is cation in SGF

such as Na^+ and H^+. At the first state of the drug release, this reaction occurred when DMP^+ in the resinates was exchanged with cations in SGF and released from the resinates by using diffusion process. This process was driven until the ion exchange equilibrium occurred, resulting in a constant concentration of DMP^+ in medium. This problem occurs when using fixed-volume dissolution systems for testing drug release from drug resinates that do not simulate GI tract. In contrast, complete release of the drug resinates usually occurred because the drug released could absorb into the blood circulation, and this led to the continuous ion exchange process. This study showed that sampling volume and frequency of the release testing could involve the ion exchange process of DMP resinates in tablets, particularly the high levels of sampling volume and frequency (F4). The total replacement medium of sampling in F1 to F4 studies was 35, 65, 140, and 260 mL, respectively. It can be seen that the increase of the total replacement medium of F1 to F3 studies could not enhance the amount of drug release because this is not the crucial reason to describe the change of drug release. Apart from this, the DMP concentration in SGF was increased when using the high levels of sampling volume and frequency as shown in Figure 3. It can be found that the DMP concentration of the F4 study was remarkably higher than those of other studies at 30 to 360 minutes of the test. This finding led to more than 85% of DMP released from the tablets. This sampling procedure could be used for investigating the release of the drug resinate tablets in scale-up production studies.

This study suggests that the conventional dissolution apparatus, such as paddle method, can also be used for characterizing the drug release from the resinates in terms of the cumulative amount and the kinetics of drug release. The high level of sampling volume and frequency should be performed for obtaining the complete release of drug from the resinates. This method may lead to the drug release pattern that mimicked the release of drug from the resinates in the GI tract. However, the same sampling procedure should be used for characterizing drug release of the resinates.

Scale-up Production Studies

The 3 lots of DMP resinates using Dowex 50W were prepared using a batch procedure. This is an easy and high

Table 2. Characteristics of the DMP Resinate Tablets in Scale-up Production*

Lot No.	Weight (mg) n = 20	Thickness (mm) n = 6	Hardness (N) n = 6	Friability (%) n = 3	Disintegration Time (sec) n = 6	Wetting time (sec) n = 3	DMP Content (%) n = 3	DMP Release Rate (% min$^{-0.5}$) n = 3 SGF	SIF
1	296.1 ± 3.4	3.12 ± 0.06	87.5 ± 2.5	0.28 ± 0.06	26.0 ± 3.0	37.7 ± 3.5	91.1 ± 2.1	6.77 ± 1.44	5.95 ± 0.31
2	297.6 ± 8.2	3.23 ± 0.02	88.5 ± 8.3	0.03 ± 0.01	24.3 ± 2.4	28.3 ± 2.5	99.7 ± 7.9	6.86 ± 0.58	6.49 ± 0.29
3	295.9 ± 8.5	3.00 ± 0.02	87.5 ± 10.1	0.07 ± 0.04	33.9 ± 3.8	42.1 ± 3.4	103.4 ± 2.4	6.32 ± 0.95	6.96 ± 0.66

*DMP indicates dextromethorphan; SGF, simulated gastric fluid; SIF, simulated intestinal fluid.
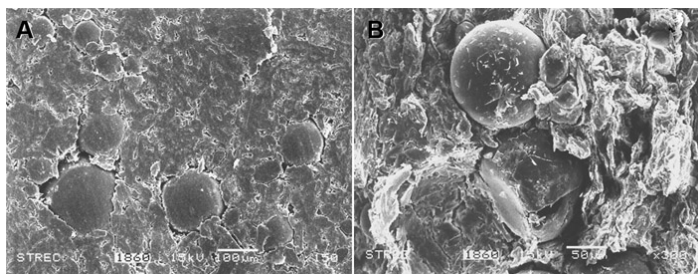
Figure 4. Surface morphology (A) and internal structure (B) of dextromethorphan resinate tablets from lot 3 production.

efficiency drug-loading method that has been previously reported.[6] The DMP loading of the resinates in lots 1, 2, and 3 preparations was 43.3% ± 0.3%, 40.6% ± 1.2%, and 40.5% ± 1.0% wt/wt (n = 3), respectively. It was suggested that the DMP loading obtained had reproducibility and could be accepted.

In a preliminary study, the tablets, prepared by using a single-punch tableting machine, had a high variation of tablet weights. This resulted from a poor flowability of MCC.[19] To solve this problem, MCC was mixed with colloidal silicon dioxide before mixing with other ingredients to enhance the flowability of MCC. This process led to less weight variation of the resinate tablets. Characteristics of the resinate tablets in scale-up production are shown in Table 2. Good physical properties of the resinate tablets from the 3 lot productions were obtained, indicating a good reproducibility of the preparation process. Using SEM, the DMP resinates were distributed and embedded into MCC matrix, which provided a dense structure of the tablets (Figure 4A). This result was similar to the tablets compressed using a hydrostatic press.[6] Furthermore, the deformation and the

fracture of DMP resinates in the tablets was found as shown in Figure 4B. In a previous study, the DMP resinate tablets prepared using MCC as a filler showed a higher DMP release rate after compression, suggesting that the change of DMP release rate occurred from the fracture of the resinates[6] but the evidence was not shown. Thus, the fracture of some resinates can be confirmed in the present study.

The interesting characteristics of the resinate tablets were disintegration and wetting times. The disintegration and wetting times of the resinate tablets from the 3 lot productions decreased with increasing thickness of the tablets (Figure 5A). This finding can be explained by the disintegration and wetting process of the tablets, which are closely related to the inner structure of the tablets; especially pore size, which affects water penetration into the tablets.[20] An increase in the thickness of the tablets indicated a larger pore size in the tablet matrix structure, resulting in faster water penetration into the tablets. For these reasons, shorter disintegration and wetting times were found. Moreover, a good linear relationship between disintegration time and wetting time was obtained with correlation coefficient found to be 0.84 (Figure 5B), suggesting that wetting is a crucial step for the disintegration process. This result was similar with the study by Sunada and Bi.[20] The slope of this relationship was 1.28, indicating that the disintegration times were shorter than the wetting time as the whole tablets were immersed in distilled water for the disintegration test.

The DMP released from the 3 lot resinate tablets provided sustained release patterns over 8 hours when using both SGF and SIF; all drug release profiles were similar to those of the resinate tablets performed by F4 study (Figure 1). The release of DMP in both media can be described using matrix
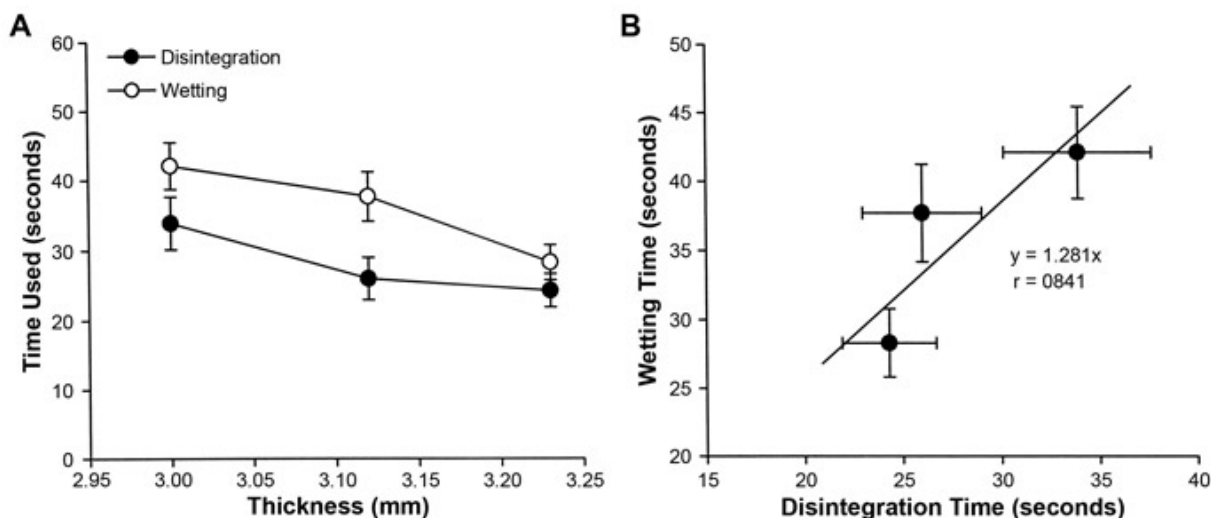

Figure 5. Effect of (A) tablet thickness on disintegration and wetting times and (B) relationship between disintegration time and wetting time of the dextromethorphan resinate tablets obtained from 3 lot productions. Each point is mean ± standard deviation of 3 experiments for wetting time and of 6 experiments for disintegration time.

diffusion-controlled model with R^2 more than 0.98; the release rates of the resinate tablets are listed in Table 2. The release rate of the resinate tablets from the 3 lot productions in SGF and SIF were not statistically different ($P > .05$), indicating less variation between lots. Moreover, a comparable DMP release rate in both media was found, although the cation concentration of SGF was higher than that of SIF.[15] This result was due to the influence of pH that affected the ionization of DMP. The higher pH of SIF caused a lower ionized form of DMP in the resinate. Therefore, the faster rate for DMP released in SIF may be obtained, leading to similar drug release rates in both media. This finding was in agreement with the previous report.[15] Moreover, the release of DMP from the resinate tablets was also investigated using 0.1 N HCl for 2 hours and followed with pH 6.8 phosphate buffer that was a simulated GI condition. The release profiles of DMP resinate tablets proceeded continuously when changing the dissolution medium from acid stage to pH 6.8 buffer stage (Figure 6), indicating that the release of DMP could take place continuously in GI conditions. An insignificant difference of release rate of the resinate tablets from the 3 lot productions in acid stage was found ($P > .05$). Furthermore, the DMP resinate tablets obtained did not have a dose dumping in all DMP release profiles, although some resinates were fractured and deformed under compression pressure. This result suggested that the DMP resinates could still control drug release by themselves.

This finding also suggested that the resinate tablets obtained gave a fast disintegration and might disintegrate in a person's oral cavity without the need for drinking water. The disintegrated mass could slide down smoothly along the esophagus with the help of saliva, thus making taking the drug easier for those who have swallowing or chewing problems. Moreover, the taste masking resulting from the drug being bound within the resinates and the sustained-release property of drugs were both advantages of this formulation. However, further investigation should be done regarding adding a flavoring agent to the tablets.

SUMMARY AND CONCLUSION

In conclusion, multiple-unit DMP resinate tablets showed a good feasibility for scale-up production for industrial manufacturing. Good physical properties and continuous drug release of the resinate tablets in simulated GI conditions were obtained. Moreover, the variation of drug release from the resinate tablets can be accepted. This study also suggests that a high level of sampling volume and frequency should be conducted in the sampling procedure when using a fixed-volume dissolution apparatus in order to obtain the complete drug release of the resinates.
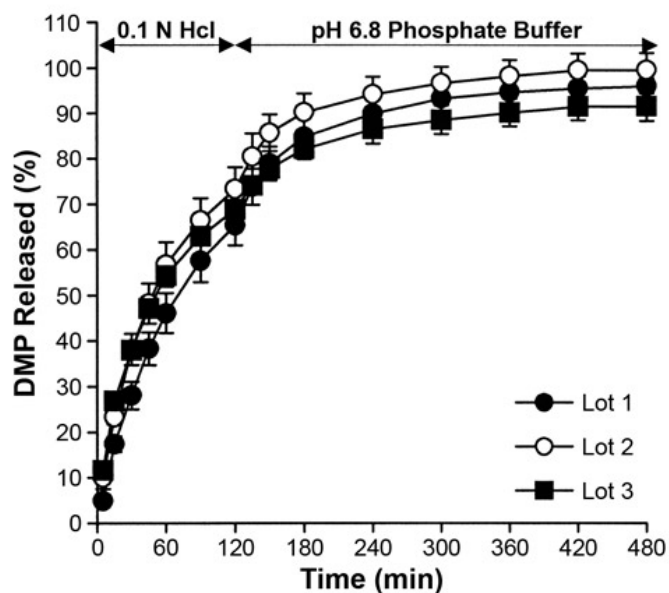
ACKNOWLEDGMENTS

Figure 6. Dextromethorphan (DMP) release profiles of DMP resinate tablets using 0.1 N HCl for 2 hours and followed with pH 6.8 phosphate buffer. Each point is mean ± standard deviation, n = 3.

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