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International Journal of Pharmaceutics 293 (2005) 35–42
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Release characterization of dimenhydrinate from an eroding and swelling matrix: selection of appropriate dissolution apparatus

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Received 6 August 2004; received in revised form 9 December 2004; accepted 10 December 2004

Abstract

The objective of this study was to evaluate the effect of various hydrodynamic conditions on drug release from an eroding and gel forming matrix. For this purpose, dimenhydrinate was formulated with hydroxypropyl methyl cellulose and polyethylene oxide into matrix tablets and the drug release in deionized water was evaluated spectrophotometrically, using multiple dissolution methods, namely, compendial USP 27-apparatus I–III, and a modified apparatus II (paddle over mesh). Various hydrodynamic conditions were examined at the agitation rates of 50 and 100 rpm for apparatus I and II, and 5 and 8 dpm for apparatus III. Similarity and difference factors were calculated using compendial apparatus II release data as reference. Among the methods, apparatus I showed the slowest initial release, while the release from apparatus III at 8 dpm was the highest among the methods. This was further compared via the dissolution half-times and calculation of the average release rate for each method. Based on the analysis of difference and similarity factors (f_1 and f_2), the study clearly demonstrates the significance of hydrodynamics and the choice of a dissolution method and their respective effect on overall release profiles when erodible and swellable matrix systems are involved. Full surface exposure with insertion of mesh device in apparatus II may provide more realistic conditions especially when release data are to be used in developing IVIVCs.

Keywords: Dimenhydrinate; Dissolution apparatus; Swelling and eroding matrix; Hydrodynamic effect; Similarity and difference factors; Modified release systems

1. Introduction

Drug release from the dosage form and its subsequent absorption depends upon the physicochemical properties of the drug, delivery system, and the physiologic environment within the gastrointestinal tract. Based on the Noyes–Whitney and Nernst–Brunner models, several factors may influence the drug dissolution kinetics, including, the effective surface area of the solid drug, diffusion coefficient of the drug, thickness of diffusion layer, the saturation solubility of the drug, volume of the dissolution medium, and the amount of drug in the solution. It is also known that the permeability of the gastrointestinal tract to the drug molecule

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doi:10.1016/j.ijpharm.2004.12.024

plays a role in maintaining the sink condition, hence influencing both dissolution rate and bioavailability of the drug (Dressman et al., 1988; Martin et al., 1993).

In vitro dissolution testing is a requirement in all USP monographs of oral solid dosage forms, where drug absorption is essential in order to achieve a therapeutic effect. Drug dissolution study is an integral part of quality control (QC), and it also plays an important role in pharmaceutical product development to assist in selection of a candidate formulation, and in research in order to detect the effect of different manufacturing variables such as granulation procedure, excipients type, coating parameters, for comparative studies of different formulations, in vitro–in vivo correlations (IVIVC), and possibly as a biowaiver under strictly defined conditions (Qureshi and McGilveray, 1995; Pillay and Fassihi, 1998; Dürig and Fassihi, 2000; FDA, 2000) (Fig. 1; Pillay, 2000).

In the case of swelling and eroding controlled release dosage forms, it is paramount to understand the interrelationship between physicochemical and hydrodynamic conditions in attaining sensitive and reproducible dissolution data. Several dissolution methods have been described in the USP; however, the selection of the appropriate method and data interpretation is not easily affordable due to the influence of technological differences and manufacturing process, involved in product design, on the dissolution outcome (Pillay and Fassihi, 1998; Dürig and Fassihi, 2000).

The importance of dissolution testing, its sensitivity to various factors, and consequently its impact on bioavailability is well recognized during the regulatory review. As a result, CDER (Center for Drug Evaluation and Research) at the FDA (Food and Drug Administration) has released guidelines such as BCS (Biopharmaceutical Classification Scheme) (FDA, 2000), and SUPAC (scale up and post approval changes) (FDA, 1997a) and their applications to dosage from design, potential post approval changes and establishment of IVIVC (FDA, 1997b). In addition, CDER has recently released a draft guidance document in regard with PAT (process analytical technology), as a framework for innovative pharmaceutical manufacturing, design and quality assurance (FDA, 2003).

The diversity of dosage form designs, the new technologies in development of modified release formulations, the existing problems associated with current dissolution testing procedures and the regulatory concerns mandate the dissolution studies to be performed with scrutiny and under specified conditions. For certain non-conventional dosage forms, it may also necessitate appropriate modification to the current methods or potentially the development of new procedures (Pillay and Fassihi, 1998; Dürig and Fassihi, 2000). For instance, Muzzio et al., using a computational model, have recently reported that a possible reason for high variations, observed in the dissolution profiles of certain delivery systems obtained with USP apparatus II, is the relative positioning of tablets in the dissolution vessels, hence, the difference in hydrodynamic effects and fluid shear forces in each test vessel (Haystead, 2003; Kukura et al., 2003). Similar results have been presented elsewhere as well (Khoury et al., 1988; Bocanegra et al., 1990; Kamba et al., 2003). Dosage form positioning within the dissolution vessels is especially of importance when dealing with low or high density delivery systems, where the position of the dosage form may vary due to floatation or sticking issues respectively. This further leads to inconsistent impact of hydrodynamics on the dosage form within the vessels (Pillay and Fassihi, 1998; Dürig and Fassihi, 2000).

Therefore, a more in depth understanding of the role of delivery systems, release mechanisms, composition, volume, hydrodynamics, and role of potential mechanical forces on the structure of delivery system within the moving dissolution media in some cases necessitates the development of alternative dissolution methods in order to obtain reliable dissolution data, to be able to discriminate among different dissolution methods, and to more closely mimic in vivo conditions (Dressman et al., 1988; Pillay and Fassihi, 1998).

The present study has been carried out on dimenhydrinate, an antihistaminic agent possessing antiemetic effect, which is commonly used to prevent or relieve motion sickness. Chemically, dimenhydrinate is composed of two active moieties, diphenhydramine and 8-chlorotheophylline (approximately 1:1; mass ratio slightly favors diphenhydramine) (Kraemer, 2001; USP, 2004), with the aqueous solubility of approximately 3 mg/ml (Budavari, 1996). Pharmacokinetic studies have shown that dimenhydrinate has a short duration of action of about 3–6 h (WholeHealthMD, 2000); therefore, it is considered as a potential candidate for development into a controlled release formulation with an initial burst. Considering the popularity and robustness of hydrophilic matrices as a means

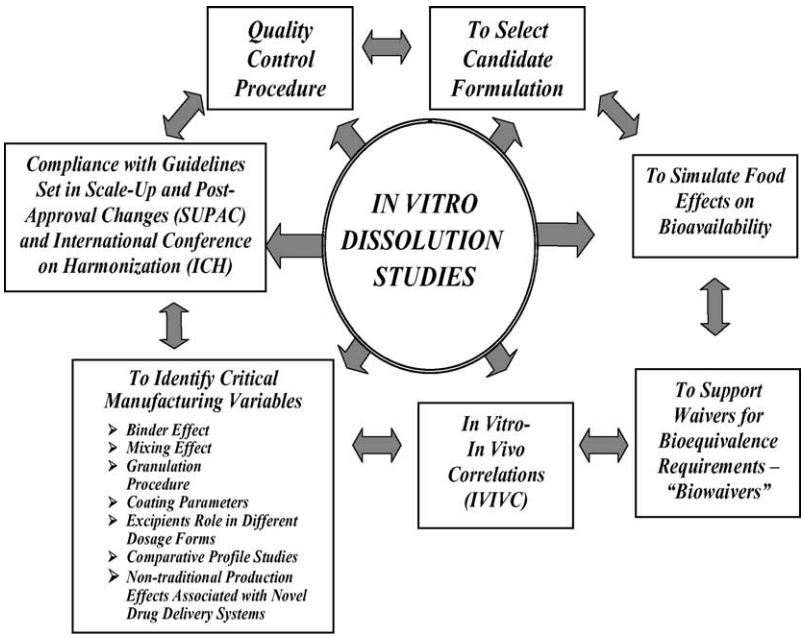

Fig. 1. Potential applications of dissolution studies in drug development process (Fassihi and Pillay, unpublished).

of controlled release drug delivery (Genc et al., 1999; Dürig and Fassihi, 2000; Yang and Fassihi, 2003), this approach has been adopted in formulating dimenhydrinate tablets (Missaghi and Fassihi, 2002, 2003).

This study focuses on: (1) evaluation of in vitro release characteristics of a controlled release dimenhydrinate tablet formulation with burst components under defined hydrodynamic conditions, employing compendial methods; USP apparatus I (basket), II (paddle), III (reciprocating cylinder), and a non-compendial dissolution method, namely, modified apparatus II (paddle over mesh), (2) selection of appropriate dissolution method by comparison of the dissolution profiles obtained from each method using similarity and difference factors as a tool for interpretation of dissolution data.

2. Materials and methods

2.1. Materials

Dimenhydrinate (Sigma Chemical Company, St. Louis, MO), hydroxypropyl methyl cellulose (HPMC) (Methocel® K4M, Dow Chemical Company, Midland, MI), polyethylene oxide (PEO) (Sentry™ Polyox™ WSR N60K-NF, Union Carbide Corp., Danbury, CT), maltodextrin (Maltrin® M510, Grain Processing Corp., Muscatine, IA), microcrystalline cellulose (MCC) (Avicel® PH 101, FMC Corp., Philadelphia, PA), and magnesium stearate NF (Mallinckrodt, St. Louis, MO).

Table 1
The formulation used in preparation of dimenhydrinate matrix tablets

Ingredients	Amount per tablet (mg)
Dimenhydrinate	100
HPMC	35
Maltodextrin	25
PEO	37
MCC	100
Magnesium stearate	3
Total weight	300

2.2. Methods

2.2.1. Preparation of hydrophilic matrix tablets

Table 1 displays the formulation used in preparation of dimenhydrinate tablets. For this purpose, half of the drug was ground and mixed with maltodextrin and

HPMC applying wet granulation method. The granules were vacuum-dried at 40 °C for 15 min. The dried granules were then passed through a 40-mesh sieve. The other half of dimenhydrinate was dry blended with PEO and MCC; the two separate portions were then homogeneously mixed together. Prior to compression, the formulation blend was lubricated with magnesium stearate at 1% level. Tablets were then manufactured on a single station Stokes press (Bristol, PA), using a set of 11 mm diameter concave punch and die to achieve a target tablet weight of 300 mg.

2.2.2. Physical evaluation of tablets

The compressed tablets were evaluated for weight variation, using an analytical balance (A&D Company Ltd., Tokyo, Japan), for crushing strength, using a Schleuniger hardness tester (Schleuniger and Co., Zurich, Switzerland), and for thickness and diameter, using a texture analyzer, TA.XT2i (Texture Technologies Corp., Scarsdale, NY), equipped with a 5 kg load cell and Texture Expert Exceed software (Version 2.56) along with a suitable probe. These tests were carried out on 20 tablets.

Dimenhydrinate tablets were also evaluated for in vitro drug release by means of a dissolution tester (VK 7000, Varian Inc., Cary, NC), using USP 27-apparatus I, II, a modification of apparatus II, and USP 27-apparatus III (BIO-DIS II system, Vankel Industries, Edison, NJ). Apparatus II was modified with the insertion of a stainless steel mesh device in each vessel as described previously (Dürig and Fassihi, 2000).

Dissolution studies were conducted in deionized water, maintained at 37 ± 0.5 °C with the volume of 250 ml for apparatus III and 900 ml for the other dissolution methods. Various hydrodynamic conditions were examined using the agitation rates of 50 and 100 rpm (revolution per minute) for apparatus I, II and modified II, and 5 and 8 dpm (dip per minute) for apparatus III. Samples were collected periodically from each vessel, and the amount of drug released, was quantitatively determined at the wavelength of 277 nm using a UV-spectrophotometer (Agilent 8453, Agilent Technologies Inc., Wayne, PA) over 24 h. All dissolution tests were performed in triplicates.

2.2.3. Comparison of dissolution profiles

To compare the dissolution profiles of dimenhydrinate tablets under different hydrodynamic conditions, two indices or fit factors were determined, as described by Moore and Flanner (1996). This approach is model independent, and it uses mathematical indices to define difference and similarity factors (f_1 and f_2, respectively) for comparison of dissolution profiles:

- Difference factor, f_1:

$$f_1\,(\%) = \left(\frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right) \times 100$$

- Similarity factor, f_2:

$$f_2 = 50 \log \left[\left(1 + \frac{1}{n} \sum_{t=1}^{n} W_t (R_t - T_t)^2 \right)^{-0.5} \times 100 \right]$$

n represents the number of time points, W_t is the optional weight factor, R_t the dissolution value of the reference method at time t, while T_t the dissolution value of the test method at time t.

f_1 value indicates the percent difference between two profiles at each time point and is a measurement of the relative error between them. f_2 value, however, is a measurement of the similarity between the dissolution profiles. In general, to ensure sameness between the profiles, f_1 should be in the range of 0–10, and f_2 in the range of 50–100. To calculate the fit factors, the mean dissolution values from both profiles at each time interval were used, including only one pull point at greater than 85% level of drug release in order to avoid bias in the similarity assessment (FDA, 1997c; Shah et al., 1998).

3. Results and discussion

The rationale for designing the dimenhydrinate controlled release formulation as described earlier, was to achieve a rapid onset of therapeutic activity of the drug for the early time period (2.0 ± 0.5 h), followed by a prolonged release pattern to maintain steady plasma concentration level of dimenhydrinate up to 12 ± 2 h.

Results of the physical testing of the tablets ($n = 20$) demonstrated that the weight variation falls within ±2.7% of the target weight which is in compliance with

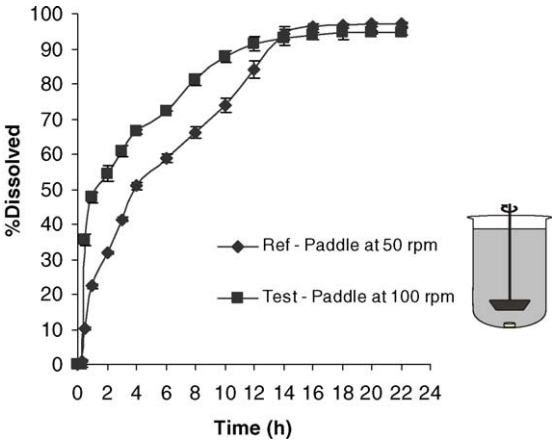

Fig. 2. Comparison of the dissolution profile of standard USP apparatus II (paddle) at 100 rpm against the reference profile (reference: compendial USP-apparatus II, paddle, at 50 rpm). Data points are the mean of three tablets ($n = 3$), and the error bars indicate the standard deviation.

the USP 27 (2004). The mean values for tablet thickness and diameter were 4.1 and 10.89 mm, respectively. The average value obtained for crushing strength of the tablets was 7.5 kp. After placing the tablets within the dissolution media, slight visible surface bursting on the periphery of tablets was evident which was then followed by matrix swelling and gradual erosion of the swollen mass during the 12 ± 2 h of dissolution. Accordingly, the drug release profiles exhibited an initial burst followed by a prolonged release in a near zero order manner which was considered desirable in the context of this study. The early burst effect was due to the presence of drug particles on the matrix surface and the hydrophilic property of MCC and high aqueous solubility of maltodextrin which tends to rapidly leach out and create channels within the hydrating matrix. This would further lead to the more gradual diffusion and release of the drug molecules from the matrix.

Dissolution profiles demonstrate a similar pattern of drug release under all dissolution conditions, showing two distinct phases of drug release, the initial burst phase followed by a controlled release pattern which is associated with the swelling phase. The former indicates the drug release up to 50%, while the latter signifies the release from 50% up to the point where 100% release is reached (Figs. 2–4). The differences among the methods lay in the duration of each phase and its respective average release rate, obtained from

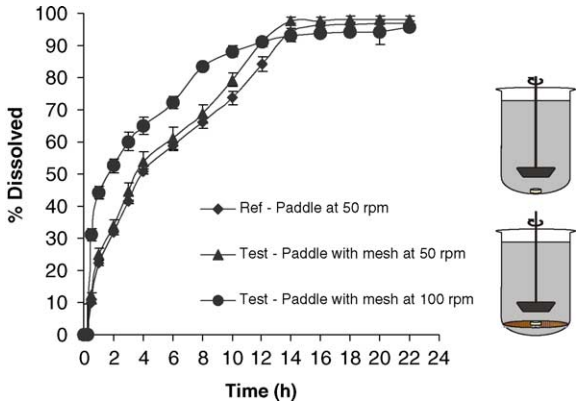

Fig. 3. Comparison of the dissolution profile of the modified apparatus II (paddle with mesh) at 50 and 100 rpm with the reference profile (reference: compendial USP-apparatus II, paddle, at 50 rpm).

the regression analysis of that segment (Table 2). Given the design of the matrix formulation and the graphical presentation of the dissolution results, duration of the initial phase indicates $t_{50\%}$ or dissolution half-time. When comparing the release rates, it is apparent that the rate for the initial burst is directly related to the intensity of hydrodynamics, fluid flow, and apparatus type. Higher intensity of the agitation rate in the dissolution medium increased the extent of burst effect and consequently decreased the duration of the initial phase. On the contrary, the average release rates calculated for the controlled release phase of the profiles show that an increase in the agitation rate is not leading to a drastic change in the release rate of this phase.

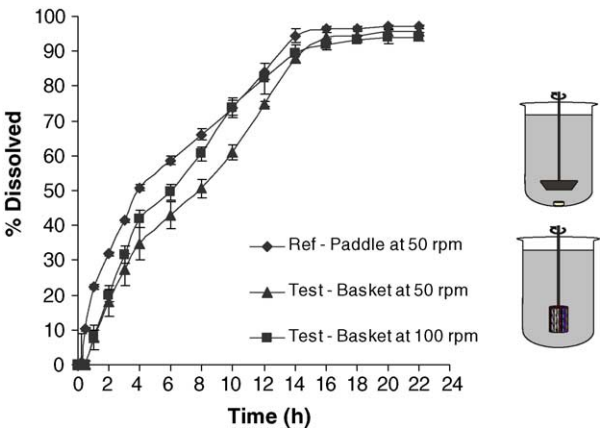

Fig. 4. Comparison of the dissolution profile of standard USP apparatus I (basket) at 50 and 100 rpm with the reference profile.

Table 2
Average release rate of the drug at each phase of the dissolution profile obtained for all methods

Dissolution method	Agitation rate	Initial burst phase		Swelling phase	
		Duration ($t_{50\%}$)[a] (h)	Release rate (%/h)	Duration (time to steady state− $t_{50\%}$) (h)	Release rate (%/h)
Paddle	50 rpm	4	12.85	10	4.32
	100 rpm	1.5	35.71	8.5	4.03
Paddle over mesh	50 rpm	3.5	14.08	10.5	4.75
	100 rpm	1.7	31.80	8.3	4.43
Basket	50 rpm	7	7.97	7	5.70
	100 rpm	6	9.33	8	5.05
Oscillating cylinder	5 dpm	2	20.91	2	5.03
	8 dpm	0.3	174.80	9.7	3.95

[a] $t_{50\%}$ indicates time for 50% of the drug to dissolve (dissolution half-time).

This becomes more apparent when the coefficients of variation (CV%) are compared for both phases of the dissolution profiles at equivalent agitation rates as outlined in Table 3. Overall, the average release rates obtained for the initial phase at 50 rpm exhibit less variation among the methods as compared to the values achieved at 100 rpm (CV% of 27.78% versus 55.58%, respectively). On the other hand, CV% values for the swelling phase seem more comparable at both agitation rates (14.34% at 50 rpm versus 11.41% at 100 rpm). It may, therefore, be concluded that the average rate of the drug release from the matrix at the swelling phase is not affected by the hydrodynamics of the system. This also indicates that release mechanism during this phase is dominated by the diffusion rather than erosion process. It should further be noted that the biphasic nature of drug release was more pronounced when tested at lower agitation rates.

As seen in Table 2, the modified USP method demonstrated a slightly faster release compared to the standard compendial apparatus II, when tested at 50 rpm (14.08%/h versus 12.85%/h); however, an opposite effect was observed when tested at 100 rpm (31.80%/h versus 35.71%/h for modified apparatus II and standard apparatus II, respectively). This indicates the sensitivity of the swelling and eroding tablets to the extent of hydrodynamics intensity within the dissolution media as well as the non-discriminatory power of these dissolution methods at different rates of agitation.

As for apparatus III, the overall drug release was more rapid among the methods, with complete release at about 10 h. Due to the oscillating movement of the inner cylinder within the vessel, containing the dissolution media in apparatus III, all surfaces of the tablet are intensely exposed to the medium with a potentially greater degree of erosion. The higher rate of oscillation causes a more vigorous hydrodynamics within the dissolution media, which further intensifies the mechanical disruption of the tablet periphery and leads to a higher release rate of the drug (Fig. 5 and Table 2). Only if the agitation intensity was well defined, this type of hydrodynamics might resemble the actual environment

Table 3
Comparison of average release rates among the dissolution methods at equivalent hydrodynamic conditions

Agitation rate	Dissolution phase	Release rate (%/h) for dissolution methods					
		Paddle	Paddle over mesh	Basket	Mean	Standard deviation	CV (%)
50	Initial burst phase	12.85	14.08	7.97	11.27	3.85	27.78
	Swelling phase	4.32	4.75	5.70	5.12	1.04	14.34
100	Initial burst phase	35.71	31.80	9.33	25.61	14.24	55.58
	Swelling phase	4.03	4.43	5.05	4.50	0.514	11.41

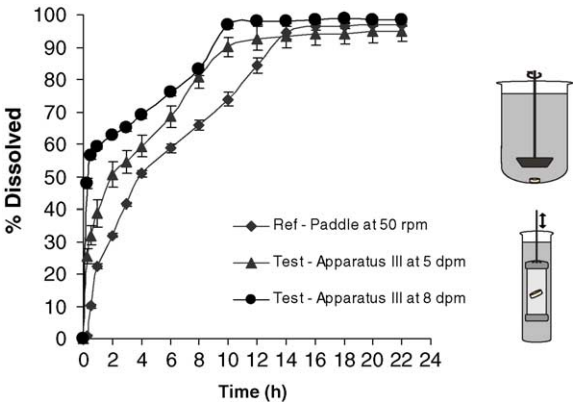

Fig. 5. Comparison of the dissolution profile of standard USP apparatus III (reciprocating cylinder) at 5 and 8 dpm against the reference profile.

of the gastrointestinal tract, within which the dosage form is exposed to a forceful contraction and peristaltic movement as opposed to having a constant position often associated with USP apparatus I and II. In this study, when comparing the average release rates for dissolution profiles from apparatus III at 5 and 8 dpm, with data obtained from other methods, it becomes apparent that performance of the former at 5 dpm is more in tune with apparatus I and II at their given conditions (Table 2). At 8 dpm, the average release rate for the initial phase was calculated as 174.80%/h. Due to the relatively high intensity of agitation, these results do not seem to provide a realistic situation comparable to that of the physiologic environment and further fail to be distinctive among the methods.

The results obtained through comparing the average dissolution rates indicate that the overall release rate and pattern of release in this study followed the order of: apparatus III at 8 dpm > compendial apparatus II at 100 rpm > modified apparatus II at 100 rpm > apparatus III at 5 dpm > modified apparatus II at 50 rpm > compendial apparatus II at 50 rpm > apparatus I at 100 rpm > apparatus I at 50 rpm. Comparison of dissolution half-times yields the same rank order (Table 2).

The order of release described above illustrates large differences and complexity of release prediction especially when eroding systems are the subject of evaluation. To further assess the dissolution behavior and compare the test results, fit factors were calculated for the release profiles obtained for each dissolution method at different hydrodynamic conditions. For this purpose, the release data for compendial apparatus II at 50 rpm was considered as reference, in accordance with dimenhydrinate official monograph cited in the USP 27. Based on the obtained values of f_1 and f_2, the dissolution profile of the modified apparatus II at 50 rpm was considered the "same" as the reference profile. However, the profiles obtained from the other dissolution methods, were considered "different" compared to the reference (Table 4).

Table 4
Fit factor values, obtained for each dissolution method at different hydrodynamic conditions against the reference method (i.e. dissolution data from standard USP-apparatus II at 50 rpm)

Dissolution method	f_1 (%)	f_2
Paddle at 100 rpm	42.61	37.95
Paddle with mesh at 50 rpm	8.63	72.56
Paddle with mesh at 100 rpm	40.12	39.57
Basket at 50 rpm	36.20	45.94
Basket at 100 rpm	21.75	54.75
Apparatus III at 5 dpm	40.58	39.86
Apparatus III at 8 dpm	73.40	26.46

In all figures, data points represent the mean values of three tablets ($n = 3$), and the error bars indicate the standard deviation.

4. Conclusions

Although ideally, it is desirable to design delivery systems whose performance is independent of the influence of external factors, a vast variety of dosage forms exhibit sensitivity to such factors. Thus, the present study demonstrates the paramount importance of apparatus selection, shape and size of the apparatus make-up, variation of fluid dynamics from one dissolution apparatus to another due to the magnitude of the agitation intensity, and the extent of sensitivity of the eroding dosage forms to the hydrodynamics within the system. Therefore, the choice of the dissolution method and its respective agitation rate significantly influence the overall drug release profiles in the case of swelling and eroding systems.

In order to support the significance of in vitro data obtained for the dosage forms in this study, In vivo experiments have to be carried out for establishing and identifying the level of IVIVC. Accordingly, the

appropriate dissolution method and conditions can be selected for achieving predictable release data.

Examination of dissolution data discussed in this work may be useful to research scientists who are involved in formulation development of the swelling and eroding matrices and can be used as a "finger-print" in apparatus selection and may aid in scientifically sound data collection and interpretation.

References

Bocanegra, L.M., Morris, G.J., Jurewicz, J.T., Mauger, J.W., 1990. Fluid and particle laser Doppler velocity measurements and mass transfer predictions for the USP paddle method dissolution apparatus. Drug Develop. Ind. Pharm. 16, 1441–1464.

Budavari, S., 1996. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals, 12th ed. Merck & Co. Inc., Whitehouse Station, p. 3250.

Dressman, J.B., Amidon, G.L., Reppas, C., Shah, V., 1988. Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms. Pharm. Res. 15, 11–22.

Dürig, T., Fassihi, R., 2000. Evaluation of floating and sticking extended release delivery systems: an unconventional dissolution test. J. Contr. Release 67, 37–44.

Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), 1997a. Guidance for Industry. SUPAC-MR: Modified Release Solid Oral Dosage Forms.

Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), 1997b. Guidance for Industry. Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations.

Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), 1997c. Guidance for Industry. Dissolution Testing of Immediate Release Solid Oral Dosage Forms.

Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), 2000. Guidance for Industry. Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-release Solid Oral Dosage Forms based on a Biopharmaceutics Classification System.

Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), 2003. Draft Guidance. Guidance for Industry, PAT: A Framework for Innovative Pharmaceutical Manufacturing And Quality Assurance.

Genc, L., Bilac, H., Guler, E., 1999. Studies on controlled release dimenhydrinate from matrix tablet formulations. Pharm. Acta Helv. 74, 43–49.

Haystead, J., 2003. Study highlights flawed dissolution testing procedure. Pharm. Technol. 27, 22.

Kamba, M., Seta, Y., Takeda, N., Hamaura, T., Kusai, A., Nakane, H., Nishimura, K., 2003. Measurement of agitation force in dissolution test and mechanical destructive force in disintegration test. Int. J. Pharm. 250, 99–109.

Khoury, N., Mauger, J.W., Stephen, H., 1988. Dissolution rate studies from a stationary disk/rotating fluid system. Pharm. Res. 5, 495–500.

Kraemer, J., 2001. In vitro dissolution testing of medicated gums. AAPSPharmScience 3, 3 (abstract).

Kukura, J., Arratia, P.E., Salía, E.S., Muzzio, F.J., 2003. Engineering tools for understanding the hydrodynamics of dissolution tests. Drug Develop. Ind. Pharm. 29, 231–239.

Martin, A., Bustamante, P., Chun, A.H.C., 1993. Physical Pharmacy, 4th ed. Lippincott, Williams & Wilkins, Baltimore.

Missaghi, S., Fassihi, R., 2002. Design and development of a controlled release formulation for dimenhydrinate via in-situ interactions of charged substances and polymers. In: Proceedings of the AAPS Annual Meeting and Exposition, Poster Presentation.

Missaghi, S., Fassihi, R., 2003. Evaluation and comparison of dissolution profiles for a swelling and eroding dimenhydrinate tablet using USP apparatus I, II, and III. In: Proceedings of the AAPS Annual Meeting and Exposition, Poster Presentation.

Moore, J.W., Flanner, H.H., 1996. Mathematical comparison of dissolution profiles. Pharm. Technol. 20, 64–69.

Pillay, V., Fassihi, R., 1998. Evaluation and comparison of dissolution data derived from different modified release dosage forms: an alternative method. J. Contr. Release 55, 45–55.

Pillay, V., 2000. Novel formulation approaches in the design strategy, development and evaluation of oral controlled release drug delivery systems. Ph.D. Thesis. Temple University School of Pharmacy, USA.

Qureshi, S.A., McGilveray, I.J., 1995. A critical assessment of the USP dissolution apparatus suitability test criteria. Drug Develop. Ind. Pharm. 21, 905–924.

Shah, V.P., Tsong, Y., Sathe, P., Lie, J., 1998. In vitro dissolution profile comparison—statistics and analysis of the similarity factor, f_2. Pharm. Res. 15, 889–896.

US Pharmacopeia XXVII, 2004. US Pharmacopeial Convention. Rockville, MD, pp. 628–631.

WholeHealthMD, 2000. WholeHealthMD.com, LLC. http://www.wholehealthmd.com.

Yang, L., Fassihi, R., 2003. Accessibility of solid core tablet for dissolution in an asymmetric triple-layer matrix system. J. Pharm. Pharmacol. 55, 1331–1337.