

Research Article

Mechanistic Approach to Understanding the Influence of USP Apparatus I and II on Dissolution Kinetics of Tablets with Different Operating Release Mechanisms

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Abstract. This article provides an analysis of dissolution kinetics associated with formulations subjected to different dissolution methods with the purpose of revealing credible direction on selection of apparatus type and hydrodynamics on *in vitro* drug release profiles using three different formulations. The dissolution kinetics of immediate release (IR) and controlled release (CR) ibuprofen tablets under different hydrodynamic conditions were determined, and potential existence of any correlation between USP apparatus I and II were analyzed using adequate kinetic models. Two types of CR tablets based on PEO (polyethylene oxide-N80) and HPMC (hydroxypropyl methylcellulose- K100M) polymers were prepared. Marketed ibuprofen 200-mg IR tablets were also used. Dissolution studies were carried out using USP 34 apparatuses I and II methods at stirring speed of 100 and 50 rpm in 900 mL phosphate buffer, pH 7.2 at 37°C. The drug release profiles for each formulation was determined and statistically analyzed using model-dependent, model-independent (f_2), and ANOVA methods. No significant dissolution differences existed between IR tablets, whereas CR tablets were significantly impacted by apparatus types and hydrodynamics. PEO matrices displayed higher sensitivity to hydrodynamics relative to HPMC matrices, and differences in dissolution profiles were confirmed by ANOVA and boxplot analysis. It is concluded that in the case of CR systems, selection of apparatus type and adherence to the monograph specifications and hydrodynamic conditions is critical, while for IR tablets, both apparatus types and agitation rates had no significant impact on drug release rate, suggesting the possibility of apparatus interchangeability if desired.

KEY WORDS: controlled release matrix tablet; hydrodynamics; immediate release tablet; release kinetic models; USP apparatus I and II.

INTRODUCTION

Drug absorption and drug dissolution are strongly intertwined with each other. The Noyes-Whitney and Nernst-Brunner equations [1–3] describe the variables that influence drug dissolution kinetics:

$$\frac{dm}{dt} = \frac{DS}{Vh}(C_s - C_t) \quad (1)$$

where dm/dt is the dissolution rate, expressed as the change in the amount of drug dissolved (m) per unit time (t) which is impacted by hydrodynamics and apparatus type; D is the diffusion coefficient in the stagnant film layer with

concentration C_s ; S is the surface area; V and h represent dissolution media volume and thickness of stagnant film layer around solid particles, respectively; C_t is the concentration of the dissolved drug in bulk solution. Upon integration, the above equation can be expressed as follows [4]:

$$m = \frac{C_s}{V}(1 - e^{-Kt}) \quad (2)$$

and

$$K = \frac{SD}{h} \quad (3)$$

The viscosity of the dissolution media or GI environment can affect the magnitude of D , the diffusion coefficient as shown below:

$$D = \frac{K_b T}{6\pi r \eta} \quad (4)$$

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where K_b is the Boltzmann constant, T is the temperature, r is the particle radius, and n is the viscosity. The main assumption in the Noyes-Whitney equation is that S remains constant over time which is not exact and equations cannot adequately model either S-shaped data or data with a steep initial slope. The more general approach is the application of Weibull function to describe dissolution profiles [5, 6]. The Weibull function can be described as follows:

$$M = 1 - \exp(-\alpha t^\beta) \quad (5)$$

where M is the accumulated fraction dissolved at time t , α is the scale parameter, defines the time scale of the process, and β is a shape parameter which characterizes the curve. When $\beta = 1$ curve shows an exponential relationship, $\beta > 1$ indicates an S-shaped with upward curvature followed by a turning point, and $\beta < 1$ indicates steeper initial slope than consistent with the exponential. Weibull function when properly applied may offer insight in the quantitative interpretation of dissolution rate data.

Likewise, the *in vitro* rate of drug release from pharmaceutical dosage forms is also influenced by the drug formulation and operating release mechanisms and by the conditions of the testing. For example, apparatus type(s) [7–9], hydrodynamics [10, 11], medium volume and composition [12, 13], temperature, perturbations [14], shape and design of stirrer [15], and gastrointestinal simulation conditions [16]. The increase in dissolution rate as a result of increase in agitation rate is also influenced by all or some of the factors described. For example, when the solid particles of a disintegrated tablet form an aggregated mound, the effective surface area with respect to dissolution is primarily the surface of the risen mound, depending to some extent upon the density or porosity of the aggregate and the viscosity and surface tension of the fluids in the accessible spaces, among other factors. Under these conditions, the effect of particle size (specific surface area) on dissolution rate is considerably less than that when the particles are dispersed throughout the medium by intensive agitation [17]. With higher agitation speed and type of the stirring, the effect of tablet components (i.e., formulation effects) could be masked. On the other hand, formulation effects and role of excipients can be considerable in the microenvironment of a solid aggregate or in matrix type modified release systems. For example, within the matrix system, viscosity will be higher due to hydrocolloids and gums, and interfacial tension would vary in the presence of surfactants, adsorption phenomena, changes in zeta potential associated with the presence of ionic species, chemical reactions because of high concentrations of potential reactants in the microenvironment, and particularly, changes in the pH of the microenvironment. These effects can directly or indirectly contribute and modify rate of dissolution.

Accordingly, this study analyzes the dissolution kinetics of both IR and CR ibuprofen tablets using various models (i.e., linear and non-linear regression analysis) to accurately describe the differences among dissolution profiles. In addition, dissolution data obtained under different hydrodynamic conditions (i.e., variations in rotation speed-rpm for both paddle and basket) will be compared to determine potential existence or lack of any correlation between dissolution rates achieved using USP apparatus I (basket) or II (paddle). It

further focuses on selection of appropriate dissolution method and conditions to obtain predictable dissolution data during formulation development.

MATERIALS AND METHODS

Materials

Ibuprofen USP (No. ZG0097, Spectrum Chemical Mfg. Corp., New Brunswick, NJ) was chosen as model drug for the experimental study. Marketed Ibuprofen 200 mg immediate release product was obtained from Pharmacy. Polyethylene oxide (Polyox WSRN-80, NF) having molecular weight of approximately 200,000 (apparent viscosity between 55–90 mPa s for 5% w/v solution) was obtained from Dow Chemical (Danbury, CT). Hydroxypropyl methylcellulose (Methocel K100M Premium CR, apparent viscosity between 75,000 and 140,000 mPa s for 2% w/v solution) was a gift from Colorcon Inc. (West Point, PA). Microcrystalline cellulose (Emcocel USP/NF, Lot E5B5J91X, JRS Pharma, Patterson NY) of particle size around 50 μm was used as filler. Lactose Monohydrate NF (#316 Fast Flo, modified-spray dried) was obtained from Foremost (Baraboo WI). Magnesium Stearate (Hyqual®, Mallinckrodt Chemicals) was used as lubricant.

Preparation of Matrix Tablets

Matrix tablets were prepared by dry blending of Ibuprofen and other excipients with the help of mortar and pestle. A constant amount of mixture (800 mg) was then compressed on a hydraulic press (Fred S. Carver, Wabash, IN) at a force of about 500 lbs, using a 13-mm flat-end round punch and die set, pre-lubricated with magnesium stearate dissolved in acetone. The compositions of studied formulations are summarized in Table I. Two types of controlled released matrix tablets based on different polymers and release mechanisms were prepared.

Dissolution Study

Dissolution testing was carried out on 6 tablets of each batch, using standard USP 34 Apparatus 1 (basket) and 2 (paddle) equipment (VK 7000, Varian Inc.) with the stirring rate (rotation per minute-rpm) of 100 and 50 rpm in 900 mL phosphate buffer at pH 7.2 and 37°C. The percentage dissolved was determined at each sampling point by UV

Table I. Composition of Experimental Formulations (Quantities in mg)

	PEO-base	HPMC-base
Ibuprofen ^a	400	400
PEO WSRN-80	200	
HPMC K100M		40
MCC	200	120
Lactose		240
Total	800	800

^a Biopharmaceutical Classification System (BCS) Class II drug, weak acid, pKa = 4.91, solubility at pH 1.2 = 0.058 mg/mL, solubility at pH 7.0 = 3.89 mg/mL [18], LogP = 3.97

Table II. Applied Mathematical Models to the Dissolution Data of Ibuprofen CR and IR Tablets

Models	Equation		Reference
Exponential (Power Law)	$\% Diss = kt^n$	(6)	[20]
Higuchi	$\% Diss = k\sqrt{t}$	(7)	[21]
Zero-order	$\% Diss = kt$	(8)	[22]
First-order	$\% Diss = 100(1 - e^{-kt})$	(9)	[23]
Baker-Lonsdale	$\frac{3}{2} \left[1 - \left(1 - \frac{\% Diss}{100} \right)^{\frac{2}{3}} \right] - \frac{\% Diss}{100} = kt$	(10)	[24]
Hixson-Crowell	$\% Diss = 100 \left[1 - (1 - kt)^3 \right]^{\frac{1}{3}}$	(11)	[25]
Weibull	$\% Diss = 100 \left(1 - e^{-\left(\frac{t-T_0}{T_d} \right)^p} \right)$	(12)	[5, 6, 26]

spectrophotometer at 221 nm (Cary 50 UV-Visible spectrophotometer, Varian Inc.).

Data Analysis

The drug release under different dissolution conditions for each formulation was analyzed and compared using model-dependent methods, model-independent method (i.e., similarity factor, f_2), and ANOVA-based method as described in the literature [19]. Various models describing drug release were fit to the dissolution data using linear and non-linear regression analysis (Table II).

Drug release data obtained under different stirring rates (100 and 50 rpm) and with different dissolution apparatuses (USP apparatus 1 and 2) for each of the formulations were compared to determine if they were similar or “roughly equivalent” as stated in the literature [27]. Data analysis is based on pairs comparison of time required to achieve different percent amount of drug released (i.e., 20, 50, and 80% drug release represented by $t_{20\%}$, $t_{50\%}$, and $t_{80\%}$) between different formulations for the given apparatus and dissolution conditions. The differences for these dissolution parameters were examined statistically by one-way analysis of variance (ANOVA) and Tukey’s test.

Release profiles obtained for CR tablets with different stirring rates and with different dissolution apparatus were also compared by calculating a statistically derived mathematical parameter, “similarity factor” (f_2) [28]. Percentage dissolved data up to $\leq 85\%$ drug released was used in this comparison, and data were normalized for drug content (i.e., the percent drug released values for the amount of ibuprofen present in each delivery system). The similarity factor was calculated using:

$$f_2 = 50 \cdot \log_{10} \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n w_t (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (13)$$

where R_t and T_t are the percent drug dissolved at each time point for one hydrodynamic condition (paddle at 50 rpm as reference) versus another hydrodynamic condition (basket at 100 rpm as test) using the same dosage form, n the number of dissolution sample times, t the time sample index and W_t is an optional weight factor (in the current work $W_t = 1$). If the two profiles are identical, f_2 is 100. Values of $f_2 \geq 50$ indicate overall similarity of two dissolution profiles. The f_2 value ≥ 90

is an indication of equivalent release performance with little variation and potential correlation between different dissolution apparatus and rotation speeds.

RESULTS AND DISCUSSION

Analysis of Dissolution Data for Controlled-release (CR) Matrix Tablets

Figures 1 and 2 show the dissolution profiles of PEO-based and HPMC-based tablet formulations obtained under different stirring rates and dissolution apparatuses ($n=6$). In this study, two different types of hydrophilic polymers were used to prepare the controlled release matrix tablets, PEO WSRN-80 and HPMC K100M. The molecular weight and viscosity of these two types of polymers are distinctly different from each other. For PEO WSRN-80, the viscosity of its 5% w/v solution is only about 55–90 mPa·s, while the 2% w/v solution of HPMC K100M has an apparent viscosity between 75,000 and 140,000 mPa·s. Since drug solubility is limited, it was decided to use low end and upper end of required polymers to meet the percolation threshold [29], together with other matrix components based on their contributory effect to drug release in line with the principle of percolation theory. Upon hydration, HPMC K100M could form a more viscous and thicker gel layer on the surface of swollen tablets compare to PEO WSRN-80. This could affect the mechanism of drug release from these two types of formulation. In order to have a better understanding of the physical changes in these two types of matrices, we have carefully observed their swelling and erosional changes during dissolution as shown in Fig. 3a. There were no significant changes in aspect ratios associated with the PEO-based tablets. As dissolution progressed, hydrated matrix gradually eroded while the aspect ratios of the tablets tended to remain relatively unchanged with time as shown in Fig. 3b. However, for HPMC-based tablets, they swelled extensively and became extremely soft to the extent that it was not possible to remove them for further measurements. They gradually swelled, eroded, and transformed into a more spherical shape.

Table III shows the fitting results for different kinetics model. The fitting result of Peppas equation for HPMC-based tablet at paddle speed of 100 rpm is not available due to fast release of ibuprofen under this condition and too few data points obtained before $<60\%$

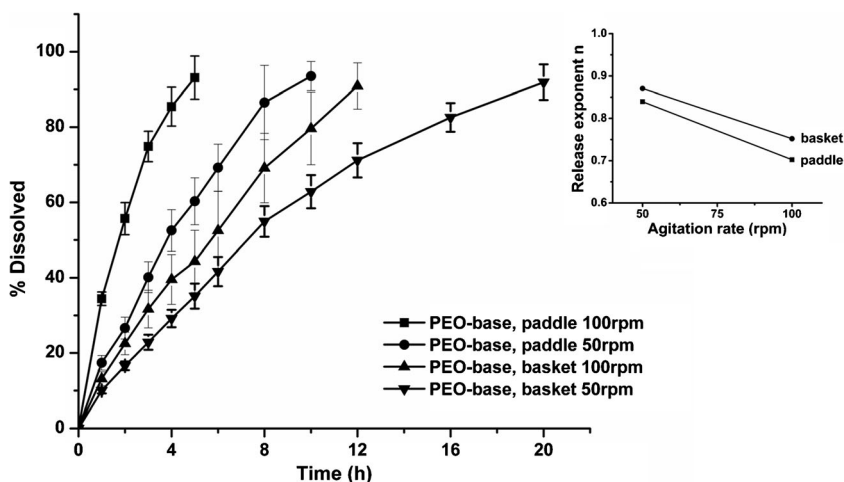


Fig. 1. Comparison of dissolution profiles of PEO-based tablets obtained under different stirring rates (50 and 100 rpm) using USP 34 dissolution apparatuses I (*basket*) and II (*paddle*). Insert: relationship between release exponent n (Equation 6) and agitation rate

drug release. For each of the matrix systems where different hydrophilic polymers were the main release controlling excipient, the release mechanism of drug substance from the matrix tablet is generally based on two competing mechanisms, Fickian diffusion and polymer relaxation followed by erosion [30–33]. The contributions of these two mechanisms are considered additive. To describe the mechanism of drug release, the amount of drug released from the system was analyzed using the commonly used exponential Equation 6. In the equation, k is the kinetic constant with units of t^{-n} , t is the release time, and n is the release exponent for drug release. For cylindrical devices like tablets, n values of about 0.45 and about 0.89 indicate purely Fickian diffusional release and case-2 transport (relaxation/erosion), respectively. The value in between 0.45 and 0.89 indicates an anomalous transport mecha-

nism (mixing mechanism of Fickian diffusion and relaxation/erosion). As shown in Table III, the fitting n values for PEO WSRN-80 based matrix tablets are between 0.70 and 0.87 with different stirring rates and different dissolution apparatus, which indicate an anomalous release with relaxation/erosion as dominant mechanism. However, for tablets made of HPMC K100M, the n values are between 0.44 and 0.50 under different described dissolution conditions and apparatuses. Tablets made of HPMC K100M follow an anomalous mechanism as well; however, the contribution of diffusional release is the main and a more dominant feature related to the overall drug release from these matrices. This further confirmed that these two dosage forms could be used to evaluate the effect of stirring rate and different dissolution apparatuses on the release rate of matrix tablets with different release mechanisms.

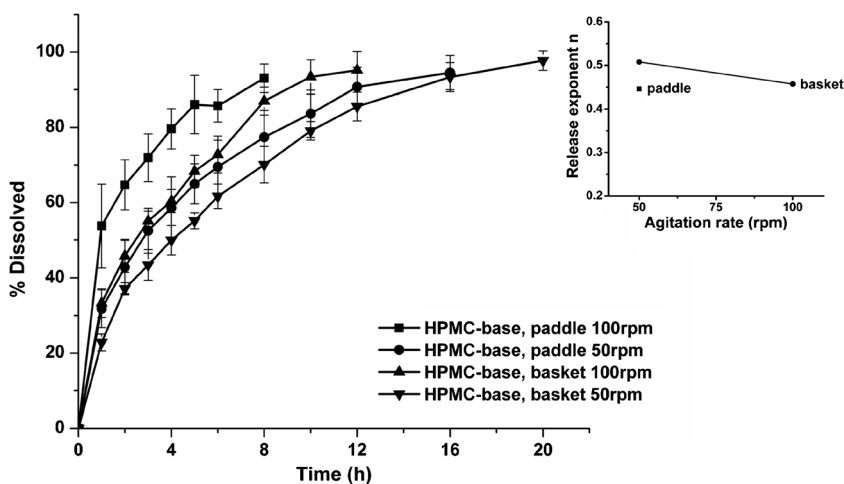


Fig. 2. Comparison of dissolution profiles of HPMC-based tablets obtained under different stirring rates (50 and 100 rpm) using USP 34 dissolution apparatuses I (*basket*) and II (*paddle*). Insert: relationship between release exponent n (Equation 6) and agitation rate

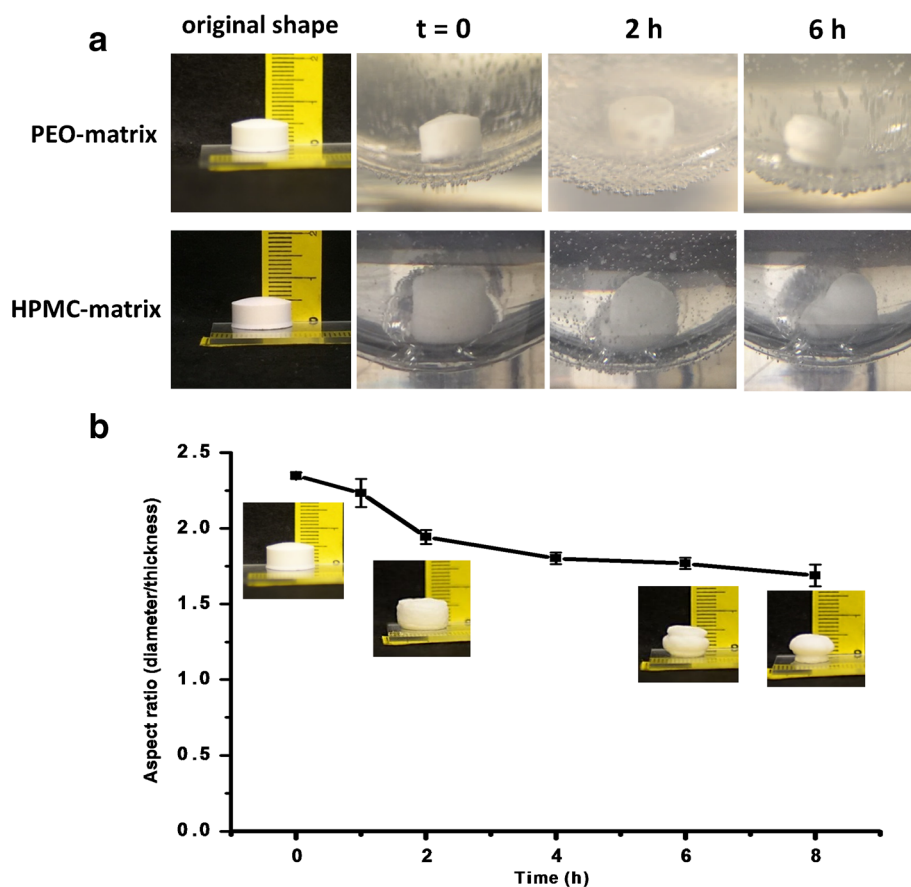


Fig. 3. Dimensional changes associated with hydration of PEO-based and HPMC-based tablet matrices (a) as well as by removing the hydrated PEO tablets periodically to measure aspect ratios (b)

As shown in the Table III when increasing the stirring rate from 50 to 100 rpm, regardless of type of apparatus used (paddle or basket), the value of n changes, indicating increased contribution of diffusional release in some case (i.e., smaller “ n ” value) and decrease in other cases (i.e., larger “ n ” value indicates potential erodibility) depending on the type of formulation used. The driving force for drug diffusion depends on extent of polymer swelling, free volume, and erosion associated with each matrix and also the difference between the saturation solubility in the stagnant layer created around the matrix “ C_s ,” and the concentration in the bulk solution, “ C_b ” as discussed by the Noyes-Whitney (Equation 1). As the stirring rate increases, the thickness of stagnant layer (h) decreases, and more drugs diffuse out of the delivery system into the bulk solution. Among the kinetic models mentioned in Table II, the Hixson-Crowell equation generally gave a more favorable adjusted R^2 ($R^2 > 0.99$) for PEO-based tablets under all dissolution conditions. For a dosage form to follow Hixson-Crowell kinetics, the

dissolution usually occur in planes that are parallel to the drug surface while the tablet dimensions diminish proportionally, i.e., the initial geometrical form (aspect ratio) tends to remain constant during dissolution period. This is consistent with the observed morphological change as mentioned above. However, for the HPMC-based tablets, the dissolution profile using all different stirring rates and apparatus tends to follow Baker-Lonsdale kinetics. This model was developed from the Higuchi model and used to describe the drug controlled release from a spherical matrix. As mentioned before, the HPMC-based tablet swells significantly and transforms into a spherical shape during the prolonged dissolution process.

A more general function developed by Weibull [5, 6] as described earlier may be applied among the models to better understand the shape of dissolution curve. As shown in Table III, the shape parameters β of PEO-based tablets were greater than 1 under all dissolution conditions, indicating a sigmoid, S-shaped dissolution curve, with upward curvature followed by a turning point ($\beta > 1$) in

Table III. Fitting Results of the Mathematical Models for PEO and HPMC Controlled-Release Tablets for Different Hydrodynamics

Models	PEO-base paddle 50 rpm	PEO-base paddle 100 rpm	PEO-base basket 50 rpm	PEO-base basket 100 rpm	HPMC-base paddle 50 rpm	HPMC-base paddle 100 rpm	HPMC-base basket 50 rpm	HPMC-base basket 100 rpm
Exponential	Constraint % released ≤ 60							
k	15.7909	34.12	8.8498	13.5843	31.7578	-	24.6924	33.3412
n	0.8395	0.7024	0.8704	0.7521	0.4459	-	0.5078	0.4572
adj R^2	0.9956	0.9998	0.9982	0.998	0.9995	-	0.995	0.9999
Higuchi								
k	28.1108	41.2475	19.1407	22.9198	26.7465	37.7502	23.9102	29.7382
adj R^2	0.954	0.9802	0.9524	0.9271	0.9592	0.8908	0.9843	0.9854
Zero order								
k	9.7945	21.8285	4.9303	8.2411	8.1046	15.5262	6.54	10.2321
adj R^2	0.9091	0.8801	0.8684	0.9671	0.3347	0.2564	0.4992	0.5609
First order								
k	0.203	0.4441	0.0994	0.1388	0.2203	0.4779	0.1703	0.256
adj R^2	0.9718	0.9934	0.99	0.9755	0.9618	0.9315	0.9819	0.9729
Baker-Lonsdale								
k	0.021	0.0448	0.0089	0.012	0.0211	0.047	0.0162	0.0255
adj R^2	0.8805	0.9341	0.8932	0.8697	0.9982	0.9854	0.9834	0.9875
Hixson-Crowell								
k	0.055	0.1206	0.028	0.0398	0.0597	0.1256	0.0466	0.0688
adj R^2	0.9944	0.9973	0.9991	0.9918	0.9139	0.8656	0.956	0.945
Weibull								
β	1.2934	1.1017	1.1654	1.2167	0.7299	0.5706	0.84	0.8094
Td	5.0725	2.2705	9.833	6.9804	4.4472	1.7385	5.8704	3.8126
adj R^2	0.9911	0.9958	0.9973	0.9865	0.9948	0.9956	0.9916	0.985

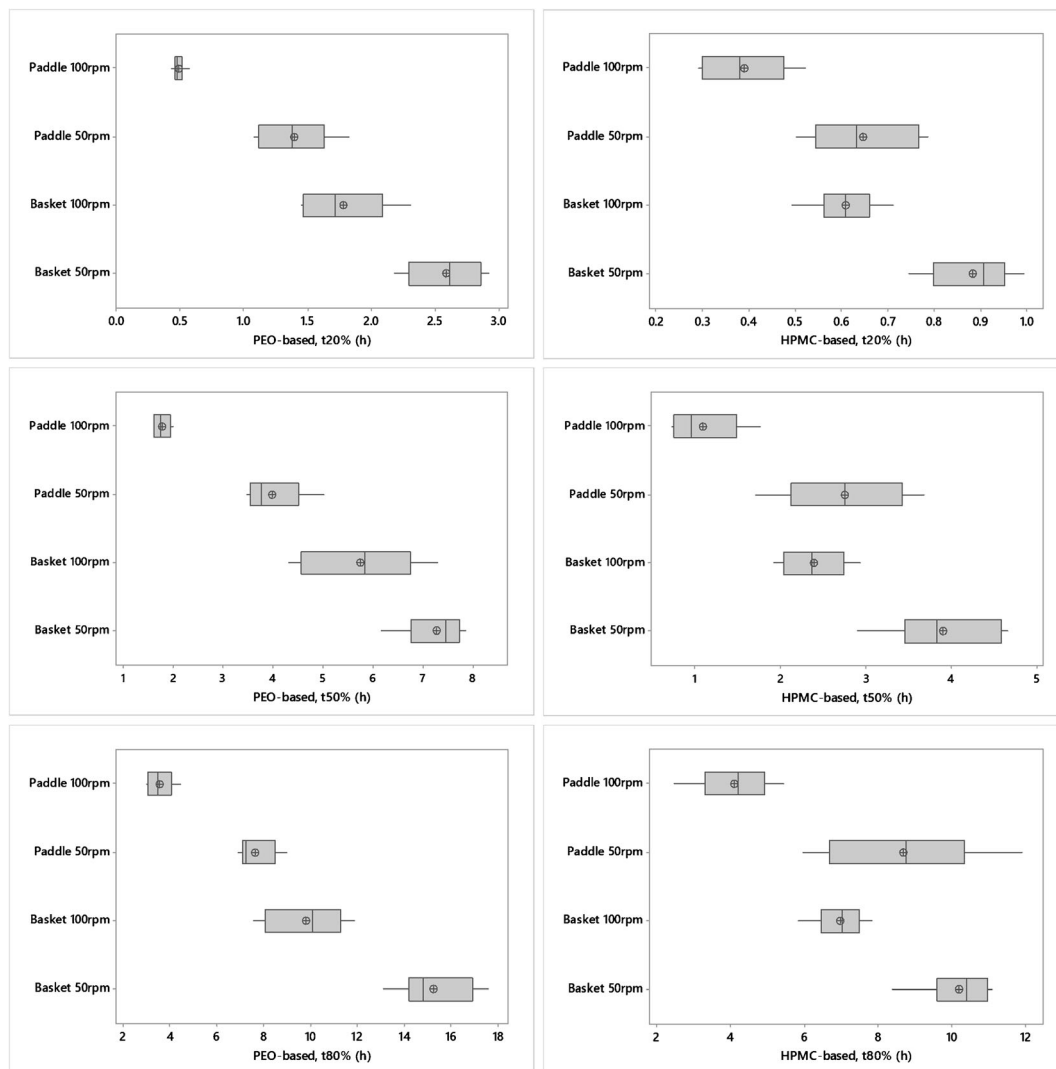


Fig. 4. Boxplots of dissolution parameters ($t_{20\%}$, $t_{50\%}$, and $t_{80\%}$) for controlled-release PEO and HPMC based tablets under different hydrodynamic conditions using USP apparatuses I and II

those conditions. However, for HPMC-based tablets, β were smaller than 1, indicating a parabolic curve with a higher initial slope, followed by some linearity and tailing towards the upper end of the release, consistent with the

Table IV. Comparison of Dissolution Parameters of PEO-Based Tablets by Tukey's Test

Parameter	Dissolution condition	Mean (h)	StdDev	95% CI for mean	Tukey grouping
$t_{20\%}$	paddle 100 rpm	0.485	0.0492	(0.2603, 0.7097)	A
	paddle 50 rpm	1.39	0.278	(1.166, 1.615)	B
	basket 100 rpm	1.779	0.343	(1.554, 2.004)	B
	basket 50 rpm	2.585	0.284	(2.360, 2.809)	C
$t_{50\%}$	paddle 100 rpm	1.765	0.159	(1.1564, 2.3736)	A
	paddle 50 rpm	3.982	0.59	(3.373, 4.591)	B
	basket 100 rpm	5.743	1.131	(5.134, 6.351)	C
	basket 50 rpm	7.269	0.625	(6.661, 7.878)	D
$t_{80\%}$	paddle 100 rpm	3.544	0.549	(2.457, 4.630)	A
	paddle 50 rpm	7.631	0.833	(6.545, 8.717)	B
	basket 100 rpm	9.817	1.711	(8.731, 10.904)	C
	basket 50 rpm	15.267	1.609	(14.181, 16.354)	D

Table V. Comparison of Dissolution Parameters of HPMC-Based Tablets by Tukey's Test

Parameter	Dissolution condition	Mean (h)	StdDev	95% CI for mean	Tukey grouping
t20%	Paddle 100 rpm	0.3886	0.0898	(0.3102, 0.4669)	A
	Paddle 50 rpm	0.645	0.111	(0.5666, 0.7234)	B
	Basket 100 rpm	0.6079	0.0727	(0.5295, 0.6863)	B
	Basket 50 rpm	0.8838	0.0907	(0.8054, 0.9622)	C
t50%	Paddle 100 rpm	1.087	0.405	(0.607, 1.567)	A
	Paddle 50 rpm	2.749	0.735	(2.269, 3.229)	B
	Basket 100 rpm	2.389	0.377	(1.909, 2.869)	B
	Basket 50 rpm	3.905	0.651	(3.425, 4.384)	C
t80%	Paddle 100 rpm	4.103	1.018	(2.968, 5.238)	A
	Paddle 50 rpm	8.683	2.152	(7.548, 9.818)	B C
	Basket 100 rpm	6.959	0.681	(5.824, 8.094)	B
	Basket 50 rpm	10.189	0.989	(9.053, 11.324)	C

exponential phenomena ($\beta < 1$). It should be noted that Weibull function is an empiric model, which is not derived from any kinetic fundament. Thus, it does not adequately characterize the dissolution kinetics of the drug [34].

Figure 4 shows the boxplot of dissolution parameters (t20%, t50%, and t80%) for PEO-based and HPMC-based formulation, respectively. In general the t20%, t50%, and t80% values decreased as the stirring speed increase. Using one-way ANOVA ($\alpha = 0.05$), statistically significant difference were found for t20%, t50%, and t80% between different stirring rates and different apparatuses ($P < 0.05$). In order to determine which mean is different from others, the Tukey test was applied. Means that do not share the same letter in the Tukey test are considered significantly different. As summarized in Table IV, for PEO-based matrix tablets, t20%, t50%, and t80% are significantly different with different stirring rate and apparatus except the t20% of paddle at 50 rpm and basket at 100 rpm. However, for HPMC-based tablets, there were significant differences between paddle at 50 rpm and paddle at 100 rpm as well as basket at 50 rpm and basket at 100 rpm at all time points (i.e., t20%, t50%, and t80%). It should also be noted that there was no significant differences in drug release at paddle 50 rpm and basket 100 rpm based on Tukey test (Table V) as well as box-plot shown in Fig. 4 with regard to HPMC-based matrix.

The value of f_2 (similarity factor) for paddle at 50 rpm versus basket at 100 rpm was calculated from the means of percent dissolved at each time points for each formulation. The f_2 value between paddle at 50 rpm versus basket at 100 rpm for PEO-based tablet was 44, while under the same conditions for HPMC-based tablets it was 63. According to FDA's guidelines, a minimum value of 50 ($50 < f_2 < 100$) for similarity factor is required to ensure sameness or equivalence of two dissolution curves. Therefore, the results revealed lack of correlation between paddle at 50 rpm and basket at 100 rpm for

PEO-based tablet (i.e., tablet with erosion dominant release mechanism). In the case of HPMC-based tablets, the result of f_2 analysis is consistent with the ANOVA-based methods where the dissolution parameters (t20%, t50%, and t80%) were not significantly different between paddle at 50 rpm and basket at 100 rpm. For PEO-based tablets, the t20% was not significantly different between paddle at 50 rpm and basket at 100 rpm at the beginning of the test; however, the difference between the dissolution curves increased with prolongation of dissolution time, and significant differences in all values were apparent (i.e., the t50%, t80%, and f_2 value of 44). These results indicate that system with erosional mechanism as its main dominating release mechanism is highly susceptible to changes in hydrodynamics and apparatus types.

Analysis of Dissolution Data for Immediate-release (IR) Tablets

Figure 5 shows the dissolution profiles of marketed ibuprofen immediate-release (IR) tablets under different hydrodynamic conditions within 60 min. Once the dissolution study was initiated, tablets stayed either at the bottom of the dissolution vessel below the paddle or at the bottom of the basket in apparatus 1. Upon hydration, the brown coating of the IR tablets dissolved quickly and tablets disintegrated fairly rapidly with complete dissolution within about 30 min as shown in Fig. 5. Table VI shows the fitting results of various kinetics models for IR tablets. Among various models, it appears that Hixson-Crowell model generally gave the highest adjusted R^2 value under most hydrodynamic conditions. The shape parameters, β , of Weibull model were > 1 , under all conditions, indicating a sigmoid, S-shaped dissolution curve with upward curvature followed by a rapid tailing of the profiles. Figure 6 boxplot and Table VII show the dissolution parameters (t20%, t50%, and t80%) of IR

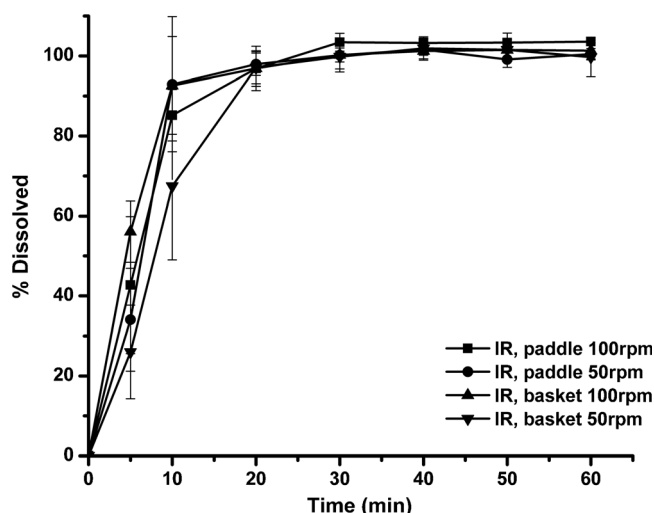


Fig. 5. Dissolution profiles of immediate-release tablet under different hydrodynamic conditions using USP basket and paddle methods

tablet under different hydrodynamic conditions. The P value of one-way ANOVA tests was found to be smaller than 0.05, indicating significant differences in $t_{20\%}$, $t_{50\%}$, and $t_{80\%}$ values between different stirring rates and different apparatuses. In order to determine which mean value was significantly different among the dissolution profiles, the Tukey test was applied. As summarized in Table VII, there is no significant difference between paddle at 100 rpm, paddle at 50 rpm, and basket at 100 rpm with respect to $t_{20\%}$, $t_{50\%}$, and $t_{80\%}$ based on the Tukey result. The mean value of basket at 50 rpm was significantly different from basket at 100 rpm at all time points. Overall, the drug release rate for ibuprofen IR tablet under basket 50 rpm was slower than all other conditions (see Fig. 5). The similarity factor (f_2) was not calculated for IR tablets due to the limited number of sampling points prior to about 85% drug release.

According to USP 34, the accepted tolerance for ibuprofen immediate-release tablets is that not less than 80% (Q) of the labeled amount of ibuprofen is dissolved in 60 min when using apparatus 2 (paddle) at 50 rpm. Therefore, despite the fact that significant statistical difference was found for some dissolution parameters, the $t_{80\%}$ of IR tablets was within 15 min under all dissolution conditions. From the practical point of view, it appears that in the case of ibuprofen IR tablets, both apparatuses I and II under all hydrodynamic conditions may result in comparable dissolution profiles as long as disintegration occurs rapidly enough not to delay the drug dissolution process.

CONCLUSION

The USP General Chapters <711, 724, 1088, and 1225> [35–38] provide monographs using standard

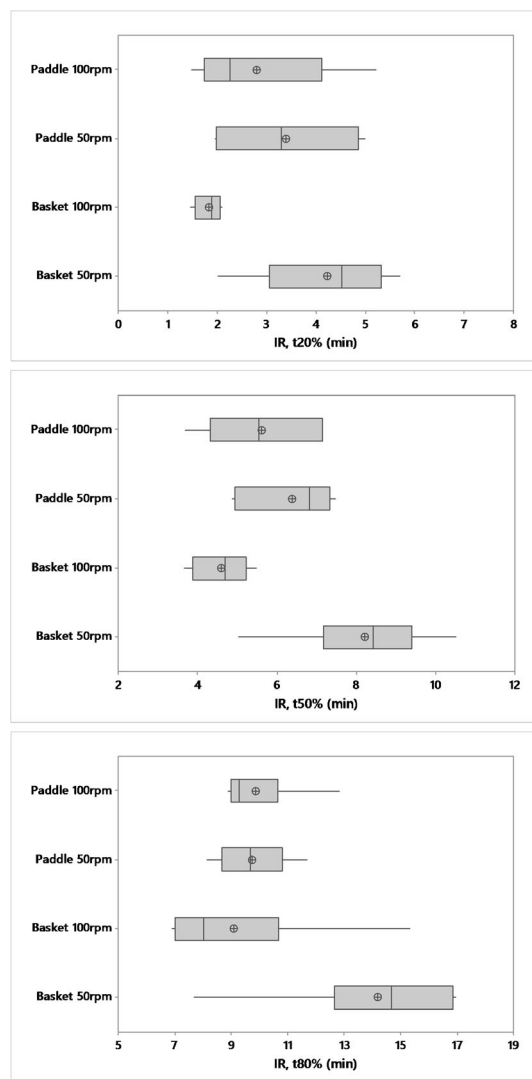


Fig. 6. Boxplot of dissolution parameters ($t_{20\%}$, $t_{50\%}$, and $t_{80\%}$) of immediate-release tablets under different hydrodynamic conditions

conditions for dissolution testing of a particular dosage form. Each apparatus (i.e., USP-apparatus 1 to 4) has its own specific conditions for dissolution testing. As such dissolution data obtained on the same dosage form using two different apparatuses for example apparatus I and II may not correlate and any nonconformity or changes from the monograph conditions to correlate them requires proper justification. In the present study, the effect of hydrodynamic conditions on the dissolution rate was systematically evaluated using both IR tablet formulations undergoing disintegration and CR matrix type formulations where drug release followed slow diffusion-erosion type release mechanisms. The results showed that the type of operating release mechanisms associated with each of these tablet formulations and matrices significantly impacts

Table VI. Fitting Results of the Mathematical Models for Immediate-Release Tablet

Models	IR-paddle 50 rpm	IR-paddle 100 rpm	IR-basket 50 rpm	IR-basket 100 rpm
Higuchi				
k	20.8721	20.9947	19.2635	21.5479
adj R^2	0.8665	0.9325	0.9373	0.8649
Zero order				
k	4.2551	4.2847	4.0279	4.3169
adj R^2	0.5629	0.6058	0.8081	0.3643
First order				
k	0.1452	0.1473	0.1029	0.1912
adj R^2	0.9289	0.9763	0.9576	0.9881
Baker-Lonsdale				
k	0.0158	0.0158	0.0109	0.0201
adj R^2	0.8910	0.9531	0.9000	0.9751
Hixson-Crowell				
k	0.0404	0.0409	0.0284	0.0464
adj R^2	0.9481	0.9877	0.9792	0.9849
Weibull				
β	2.6703	1.7629	1.8567	1.6577
Td	6.9415	6.9550	9.4623	5.6234
adj R^2	0.9993	0.9964	0.9997	0.9982

the differences observed in release kinetics. PEO-based matrix tablets (swelling and erosion mechanism) were highly sensitive to dissolution conditions (i.e., rotation speeds of 50 and 100 rpm for both apparatuses I and II) and showed significant differences in release profiles while such differences were also apparent in the case of HPMC-based matrices (dominantly swelling and diffusion mechanism), however to a lesser extent. For IR ibuprofen tablets at an ideal pH of 7.2, there were no significant differences between roles of hydrodynamics or apparatus type and 80% drug release occurred within 15 min. Thus, in the case of CR tablets, it is conclusively shown that there is no correlation in the dissolution profiles obtained among various matrices when USP apparatus I or II are used either under different or identical rotational speeds. Therefore, when evaluating drug dissolution rate and extent for controlled release systems selection of apparatus type and dissolution conditions in the monograph or developed dissolution specifications must be adhered to

accordingly. Conversely, for IR tablets both apparatus types and agitation rates had no significant impact on drug release rate, suggesting the possibility of apparatus interchangeability if desired. Additionally, the current biowaiver criteria [39, 40] state that, in addition to similarity of dissolution profiles, the test and the comparator drug product should both be “rapidly dissolving” which is defined as: not less than 85% of API releases within 30 min, employing the dissolution conditions described therein. IR ibuprofen tablets studied in this work exhibited rapidly dissolving characteristics using apparatus I and II under two different hydrodynamic conditions. Indicating that in general for ibuprofen IR tablets where API has shown to have high permeability, dissolution results would be valuable to scientist for biowaiver consideration. Within the Biopharmaceutics Classification System (BCS) limit and biowaivers, ibuprofen tablets in an ideal pH of 7.2 showed similar dissolution profiles under both dissolution conditions, and

Table VII. Comparison of Mean Dissolution Parameters for Immediate-Release Tablets by Tukey Test

Parameter	Dissolution condition	Mean (h)	StdDev	95% CI for mean	Tukey grouping
t20%	Paddle 100 rpm	2.789	1.424	(1.771, 3.806)	AB
	Paddle 50 rpm	3.385	1.34	(2.368, 4.403)	AB
	Basket 100 rpm	1.815	0.257	(0.798, 2.833)	A
	Basket 50 rpm	4.22	1.349	(3.203, 5.237)	B
t50%	Paddle 100 rpm	5.597	1.409	(4.458, 6.735)	A
	Paddle 50 rpm	6.367	1.16	(5.229, 7.505)	AB
	Basket 100 rpm	4.586	0.704	(3.447, 5.724)	A
	Basket 50 rpm	8.209	1.822	(7.071, 9.347)	B
t80%	Paddle 100 rpm	9.849	1.502	(7.647, 12.051)	A
	Paddle 50 rpm	9.715	1.293	(7.303, 12.128)	A
	Basket 100 rpm	9.06	3.19	(6.86, 11.26)	A
	Basket 50 rpm	14.18	3.39	(11.98, 16.38)	B

results of this study may be of some value in deliberation within the regulatory authorities in the context of biowaivers.

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