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The Mini Paddle Apparatus–a Useful Tool in the Early Developmental Stage? Experiences with Immediate-Release Dosage Forms

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Introduction

In recent years, there has been a strong push to identify bioavailability problems of a drug formulation based on the results of appropriately designed dissolution experiments. Particularly for immediate release (IR) dosage forms, the paddle apparatus has evolved as the method of choice for this purpose (*1, 2*). However, standard paddle experiments require both large volumes of test media which, particularly when using biorelevant media, can be cost intensive and large sample sizes that are typically not available in the early stage development when the main objective is to characterize the physicochemical properties of the active ingredient and the final formulation has not been established. Therefore, it would be very helpful to use a test system that requires smaller sample sizes and smaller volumes of media but has the same reliability and predictivity as the standard test apparatus.

The objective of the present series of tests was to determine if standard paddle experiments could be scaled down without losing the reliability and the predictivity of the standard method. Of particular concern are the hydrodynamic conditions, since these are known to influence in vivo dissolution of drugs after their oral administration (*3, 4*). However, provided suitable in vitro test conditions are chosen, it is often possible to predict dissolution limitations to oral absorption of drugs and to reflect variations in hydrodynamic conditions in the upper gastrointestinal (GI) tract (*5*). For this purpose, drug release profiles of four IR dosage forms containing drugs that belong to the BCS classes I, II, and III (*6–8*) were compared in the paddle and the mini paddle under different hydrodynamic conditions.

Materials and Methods

Materials

Hydrochlorothiazide (lot # 122K1567), metoprolol tartrate salt (lot # 41K1098), theophylline (lot # 102K0547), and indomethacin standard substances were purchased from Sigma-Aldrich, Steinheim, Germany. The test formulations HCT (hydrochlorothiazide) Hexal™ 25 mg (lot # 34D570, Hexal AG, Holzkirchen, Germany), Meprolol ™ (metoprolol tartrate) 50 & 100 (100 mg: lot# 2000164, 50 mg: lot # 2010177, TAD Pharma, 27472 Cuxhaven, Germany), Aminophyllin™ 125 (lot # 330676, Altana Pharma, Oranienburg, Germany), and Indometacin AL 50 (lot # 53115, Aliud Pharma, Laichingen, Germany) were purchased commercially. All other chemicals were analytical-reagent (AR) grade or equivalent and purchased commercially.

Dissolution test conditions

Drug release experiments were performed with the USP paddle (DT 706 HH, Erweka, Heusenstamm, Germany) and the ERWEKA mini paddle (modified DT 600 HH, Erweka, Heusenstamm, Germany). The mini paddle is based on the USP paddle setup but scaled down exactly 1/3 with respect to the dimensions (see Figure 1). A 500-mL volume of test medium was used in the paddle and 250 mL in the mini paddle apparatus. The distance between the mini paddle and the vessel bottom was adjusted to 2/3 of the compendial height. Simulated gastric fluid without pepsin SGFsp USP 29 pH 1.2 was used as the test medium for HCT Hexal™, Meprolol™, and Aminophyllin™, whereas simulated intestinal fluid without pancreatin SIFsp USP 29 pH 6.8 was used for Indometacin AL. Mini paddle experiments were run with half of the dose of drug used for the paddle experiments. Experiments were run at 37 ± 0.5 °C applying stirring speeds of 50, 75, 100, and 150 rpm. Samples (5 mL in the paddle and 2.5 mL in the mini paddle) were removed at predetermined time points using a 5-mL or 3-mL glass syringe (Fortuna™ Optima™ Luer Lock, Wertheim, Germany), respectively. Experiments were run in triplicate and results expressed as mean % (± SD) dissolved at the given sampling time.

UV analysis

Following appropriate dilution, samples were analyzed at 270 nm (Aminophyllin™), 273 nm (Meprolol™), 316 nm (HCT Hexal™), and 319 nm (Indometacin AL) using a UV

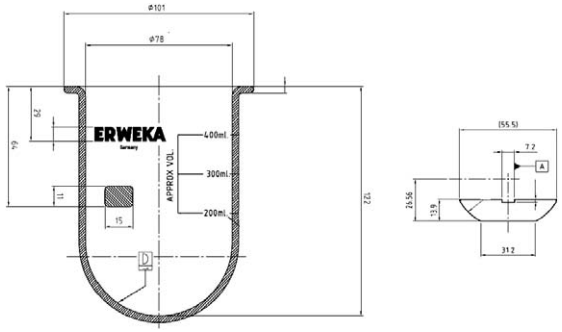

Figure 1. Dimensions of a mini paddle and a mini vessel (courtesy of ERWEKA GmbH, Heusenstamm, Germany).

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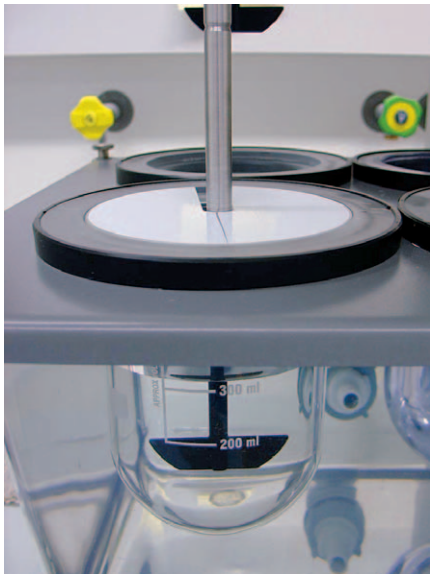

Figure 2. Picture of a mini vessel and mini paddle.

spectrophotometer (U 2000, Hitachi Ltd, Tokyo, Japan) equipped with a 10-mm cuvette.

In vitro dissolution profile comparison

The similarity factor f2 (*9, 10*) was calculated to indicate similarity of the two test methods by comparing the release profiles. In general, the comparison of dissolution profiles is intended to compare different batches of a product in order to ensure batch to batch conformity, product quality after scale up and/or post approval changes (SUPAC), or comparing release rates from different strengths of products for biowaiver purposes. However, the principle can be applied any time a profile comparison is needed (*11*). The similarity factor f2 is inversely proportional to the average squared difference between two dissolution profiles. During the last decade, f2 calculation has become a recommended method in several FDA Guidances for Industry (*12–14*). The f2 value is calculated as follows:

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

where LOG = logarithm base 10, n = number of sampling points, S = summation over all time points, Rt and Tt = the cumulative percentage dissolved at each of the selected time points of the reference and test product, respectively. When the two profiles are identical, f2 = 100. An average difference of 10% at all measured time points results in a f2 value of 50. FDA has set a public standard of 50 < f2 < 100 to indicate similarity between two dissolution profiles. In contrast to the requirements of the FDA guidances, 3 instead of 12 units of each product were used for similarity testing. However, in accordance with the guidances, dissolution measurements were performed under the same test conditions, and the sampling times used for f2 calculation were the same. Because f2 values are sensitive to the number of dissolution time points, only one measurement was considered after 85% dissolution of the product had been reached (*10*).

Results and Discussion

To check whether the drug release rate from the test formulations is influenced by different stirring speeds, dissolution profiles were first generated with the standard paddle apparatus at 50, 75, 100 rpm for all formulations and additionally at 150 rpm for Meprolol™ and Indometacin AL (see Figures 3–6).

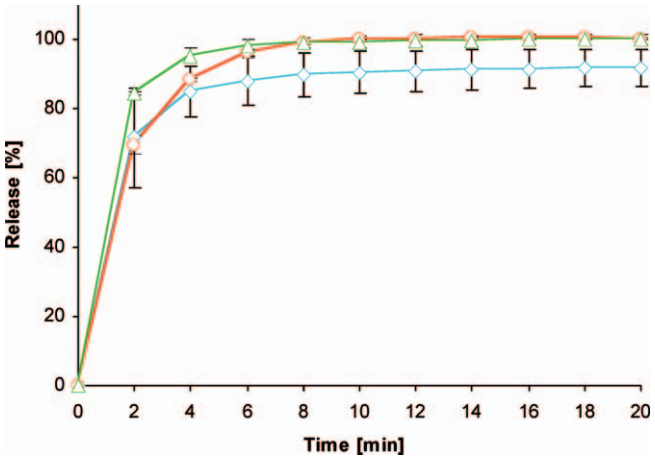

Figure 3. Drug release profiles of HCT Hexal™ 25-mg tablets in the standard paddle apparatus at 100 (△), 75 (○), and 50 (◇) rpm.

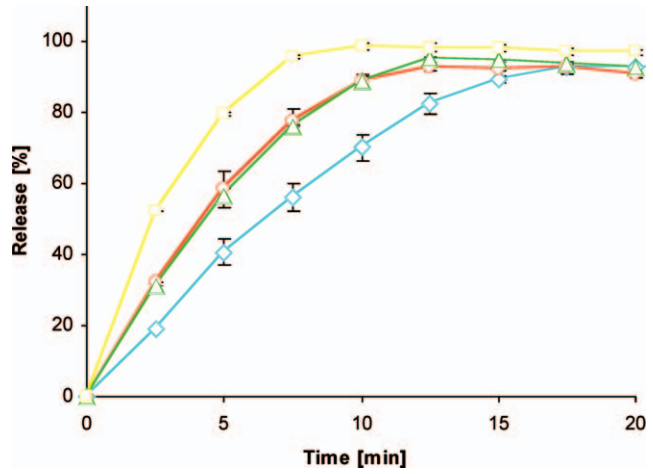

Figure 4. Drug release profiles of Meprolol™ 100-mg tablets in the standard paddle apparatus at 150 (□), 100 (△), 75 (○), and 50 (◇) rpm.

The dissolution profiles shown in Figures 3–6 clearly indicate that the paddle speed has some impact on drug release rate. Coning was observed during release experiments with Meprolol and Indometacin AL at a paddle speed of 50 rpm (see Figure 7 for Indometacin AL), resulting in a large decrease in the dissolution rate of these products (see blue lines in Figures 4 and 6). Such a coning effect is mainly confined to those types of IR dosage forms that are formulated with high amounts of insoluble excipients that form a disintegrated mass at the bottom of the vessel. Recently it has been shown that the coning effect is more pronounced for such formulations that contain poorly soluble drugs (*15*). Based on these observations, it is reasonable that the coning effect observed at low stirring speeds had the highest impact on drug release from Indometacin AL™, the formulation that contained a BCS class II drug with a low solubility.

Increasing the paddle speed to 75 rpm or higher helped to overcome the coning. The higher paddle speeds resulted in a better dispersion of the disintegrated particles and, therefore, in more significant dissolution profiles (see Figure 8 and the corresponding dissolution profiles in Figures 4 and 6).

With the objective of generating a drug release profile similar to that at 75 rpm in the paddle apparatus, corresponding experiments were performed with the mini paddle apparatus (see Figures 9–12).

As observed in the paddle apparatus, drug release rate in the mini paddle apparatus was influenced by the hydrodynamic conditions. The coning observed in the paddle experi-

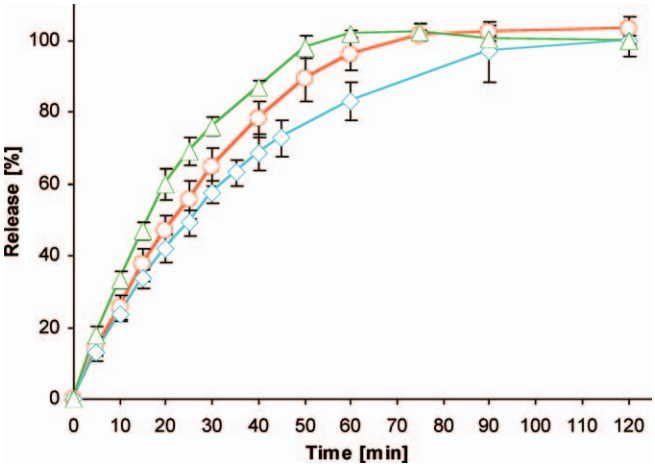

Figure 5. Drug release profiles of Aminophyllin™ 125 tablets in the standard paddle apparatus at 100 (△), 75 (○), and 50 (△) rpm.

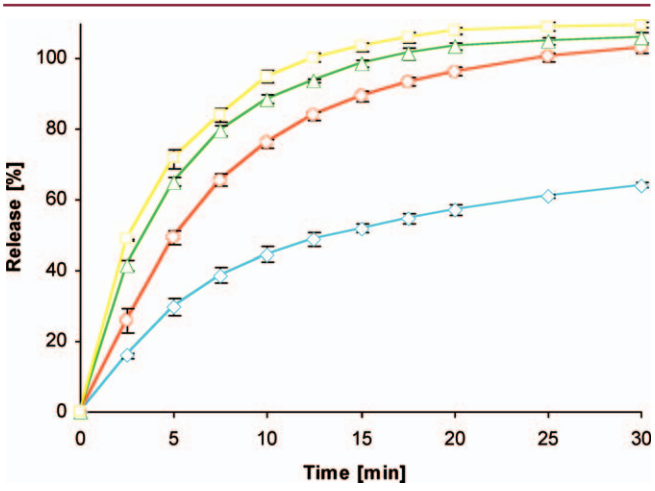

Figure 6. Drug release profiles of Indometacin AL 50 tablets in the standard paddle apparatus at 150 (□), 100 (△), 75 (○), and 50 (◇) rpm.

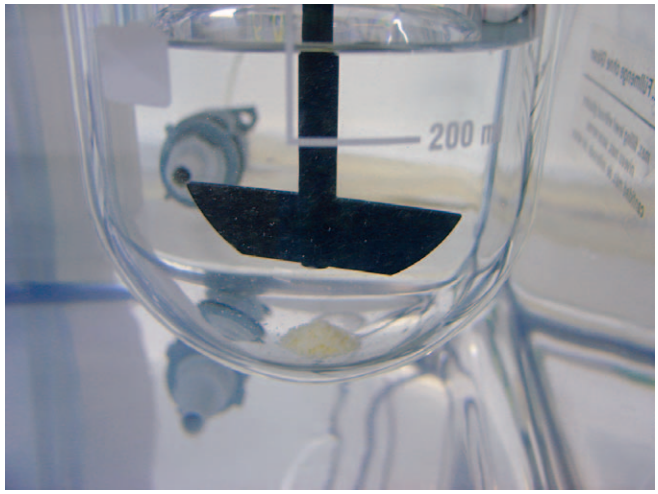

Figure 7. Indometacin AL: cone formation of particles at a paddle speed of 50 rpm.

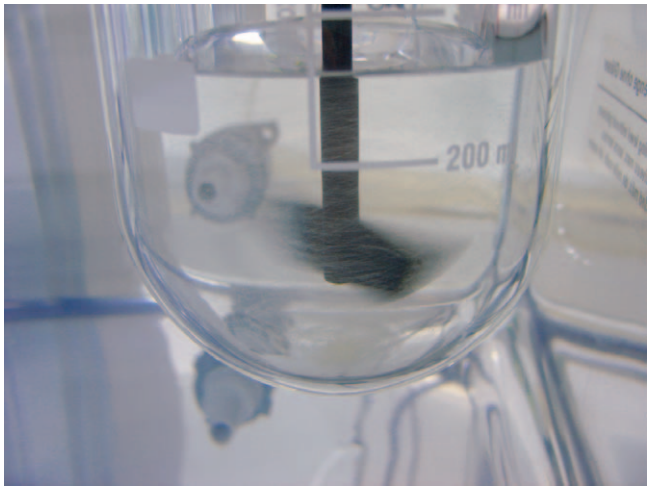

Figure 8. Indometacin AL: dispersion of particles at a paddle speed of 100 rpm.

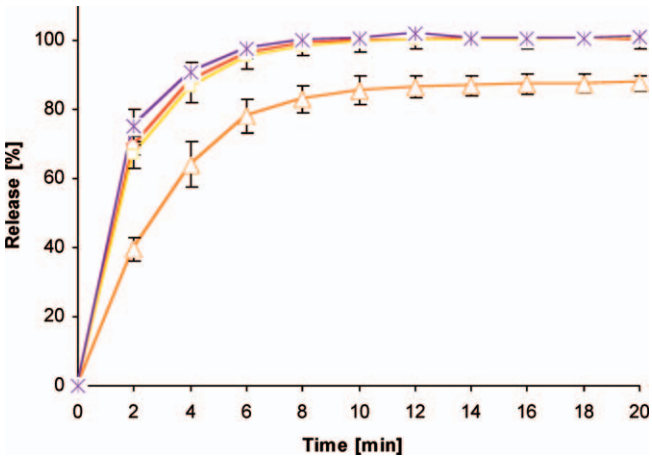

Figure 9. Drug release profiles of HCT Hexal™ 25-mg tablets in the paddle apparatus at 75 rpm (○) and half of a HCT Hexal™ 25-mg tablet in the mini paddle apparatus at paddle speeds of 50 (△), 75 (□), and 100 (x) rpm.

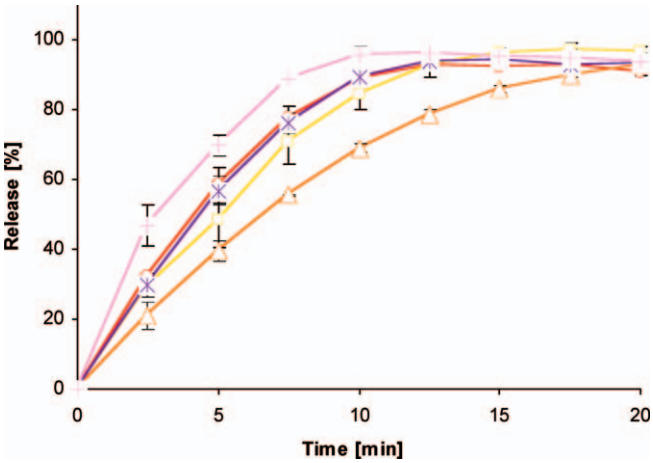

Figure 10. Drug release profiles of Meprolol™ 100-mg tablets in the paddle apparatus at 75 rpm (○) and Meprolol™ 50-mg tablets in the mini paddle apparatus at paddle speeds of 50 (△), 75 (□), 100 (x), and 150 (+) rpm.

ments run at 50 rpm also occurred in the mini paddle setup at the same stirring speed. These results indicate that higher paddle speeds are necessary in both paddle and mini paddle to achieve meaningful dissolution profiles. As the main objective of the present series of experiments was to identify the mini paddle settings that fit best a paddle agitation of 75 rpm, f2 values were calculated for all formulation / paddle speed combinations (see Table 1) except HCT Hexal™.

The hydrochlorothiazide formulation showed a very rapid release behavior (> 85% within 4 min) that made it impossible to calculate the f2 value. Nevertheless, a visual inspection of the resulting profiles indicates that mini paddle profiles generated at both 75 and 100 rpm fit well to those obtained with a paddle speed of 75 rpm.

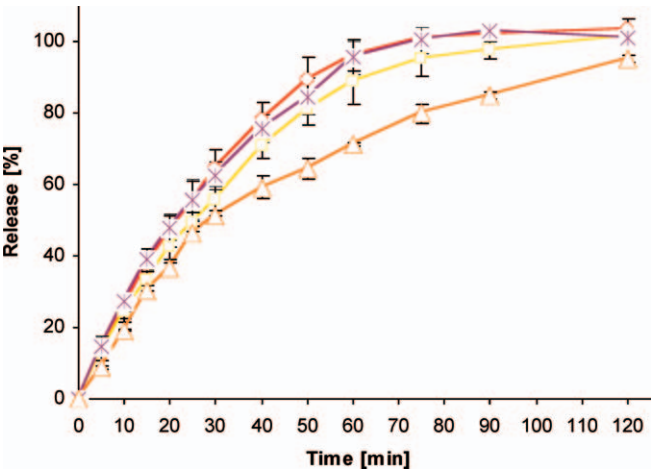

Figure 11. Drug release profiles of Aminophyllin 125™ tablets in the paddle apparatus at 75 rpm (○) and half of an Aminophyllin 125™ tablet in the mini paddle apparatus at paddle speeds of 50 (△), 75 (□), and 100 (x) rpm.

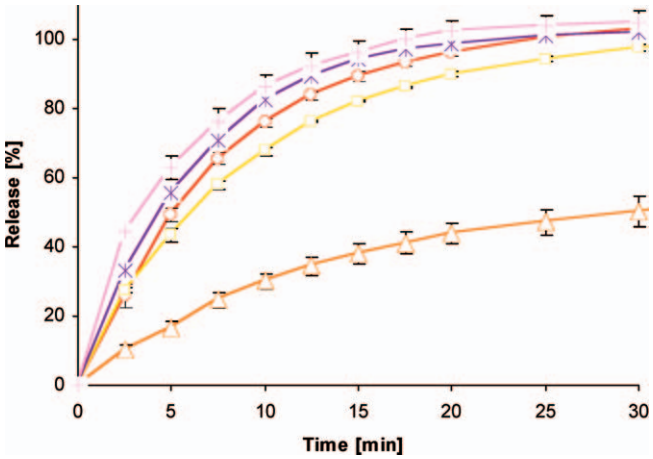

Figure 12. Drug release profiles of Indometacin AL 50 tablets in the standard paddle apparatus at 75 rpm (○) and half of an Indometacin AL 50 tablet in the mini paddle apparatus at paddle speeds of 50 (△), 75 (□), 100 (x), and 150 (+) rpm.

Results from the f2 calculation are in good agreement with this observation. Similar drug release profiles (f2 > 50) were obtained at both stirring rates, whereby higher f2 values were obtained at 100 rpm. However, this is not remarkable since it has already been demonstrated that hydrodynamic conditions may differ depending on the size of the container (5). Thus, a stirring rate of 100 rpm in the mini paddle apparatus appears to be the most favorable agitation speed for a scale-down of paddle experiments at 75 rpm, but it is most likely that performing the mini paddle experiments at 75 rpm will not result in significantly different release profiles.

Table 1. f2 values from comparison of dissolution profiles generated with the standard paddle apparatus at 75 rpm and the mini paddle at different stirring speeds.

		Mini Paddle			
		50 rpm	75 rpm	100 rpm	150 rpm
Meprolol ™	Paddle 75 rpm	36.70	58.82	85.54	45.01
Aminophyllin ™	Paddle 75 rpm	46.57	61.67	81.18	X
Indometacin AL ™	Paddle 75 rpm	19.27	58.61	59.72	42.88

Summary

Results from the present series of tests indicate that the mini paddle apparatus might be a useful tool in characterizing drug release profiles under "standard test conditions." Due to the possibility of using smaller sample sizes and smaller volumes of media, it offers various advantages in terms of substance, analytical, and material cost savings when evaluating release properties of drug candidates. The mini paddle set-up is also a promising alternative if the analytics are not very sensitive or in the case of highly potent drugs. Because the size and shape of dosage forms can also impact drug release, the mini paddle should preferably be used for powders, multiparticulate dosage forms, and small tablets or capsules (i.e., where the paddle apparatus would be the usual method of choice).

Acknowledgement

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