



Application of the Stationary Basket in the USP Type II Dissolution Apparatus to the Study of Hydrophilic Matrix Tablets

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Introduction

Large differences in tablet-to-tablet release profiles are frequently encountered when using USP Type II dissolution apparatus. These differences can be exacerbated with extended-release dosage forms. In 1990, A.B. Hässle reported on an alternative tablet placement believed to be one of the first uses of a stationary hanging basket for dissolution measurement (1). Hässle used felodipine extended-release tablets in an effort to "achieve reproducible hydrodynamic conditions." Additional work by Astra reported in 1998 (2) used nifedipine extended-release tablets with a stationary basket to avoid "random sticking of the tablets to the beaker wall."

The current USP 28 method incorporates a stationary hanging basket in a monograph for felodipine extended-release tablets. Varian offers a commercial version of a stationary basket.

The purpose of this study was to compare drug and polymer release from hydrophilic matrix tablets when placed in a stationary basket suspended within a Type II dissolution apparatus versus conventional placement at the bottom of the vessel.

Materials

Materials included acetaminophen (Spectrum Chemical, Gardena, CA); theophylline (BASF, Ludwigshafen, Germany); commercial 200-mg sustained-release theophylline caplet (550 mg tablet weight) (Inwood Laboratories, Commack, NY); impalpable lactose monohydrate (Sheffield Products, Norwich, NY); magnesium stearate (Mallinckrodt, St. Louis, MO); METHOCEL* K15M Premium CR and METHOCEL K4M Premium hypromellose (HPMC) (The Dow Chemical Company, Midland, MI).

Methods

Formulations

Table 1 lists the formulations used in these experiments. Both experimental formulations included 19% impalpable lactose monohydrate and 1% magnesium stearate. The control was a commercial 200-mg

sustained-release theophylline caplet, 550 mg tablet weight.

Table 1. Formulations for dissolution apparatus experiments.

Drug	HPMC	Drug (%)	HPMC (%)
Acetaminophen	METHOCEL K15M Premium CR	50	30
Theophylline	METHOCEL K4M Premium	50	50

Tableting Conditions

Acetaminophen tablets were prepared using a Manesty Beta 12-station press at 1214 rpm with 10.3-mm-diameter (0.406 inch) flat-face, beveled edge tooling. Compression force was 22.2 kN (5000 lb), dwell time was 0.04 s, and tablet weight was 300 mg.

Theophylline tablets were prepared using an automated Carver press with 9.5-mm-diameter (0.375 inch) round flat-face tooling. Compression force was 13.3 kN (3000 lb), dwell time was 6 s, and tablet weight was 400–500 mg.

In Vitro Drug Release Measurements

Dissolution testing was done with the USP 27 Type II (paddle) apparatus (Distek Dissolution System 2100C, Crescent Scientific Pvt. Ltd., Goregaon-East, Mumbai, India). Modifications regarding the stationary basket were made as shown in Figure 1.

For experimental acetaminophen tablets, dissolution medium ($V = 900$ mL, $T = 37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$) was 0.05 M phosphate buffer, pH 5.8. Paddle speed was 100 rpm. The drug was detected using a diode array spectrophotometer (Hewlett-Packard, Model 8452A, Palo Alto, CA), 1-mm flow cells, and 242–244 nm wavelength.

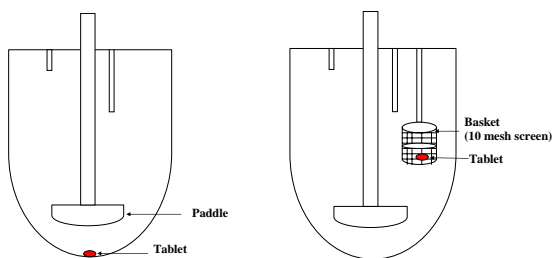
For experimental theophylline tablets, dissolution medium ($V = 900$ mL, $T = 37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$) was microfiltered deionized water. Paddle speed was 50 rpm. The drug was detected using an Applied Biosystems 757 UV absorbance detector for theophylline (Applied Biosystems, Foster City, CA), Waters 2410 RI detector for hypromellose

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(Waters, Milford, MA), 100- μ l injections, and 290 nm wavelength.

For commercial theophylline caplets, the dissolution medium ($V = 900$ mL, $T = 37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$) was 0.05 M phosphate buffer, pH 7.4. Paddle speed was 50 rpm. The drug was detected using a diode array spectrophotometer, 1-mm flow cells, and 266–270 nm wavelength.

Figure 1. Modifications to standard USP drug dissolution apparatus (left) to accommodate the stationary basket (right).

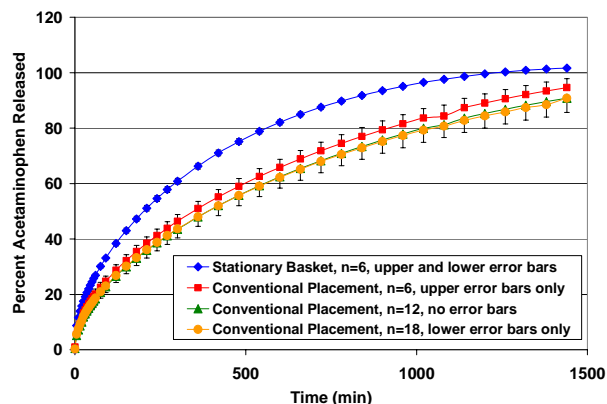


Results and Discussion

Acetaminophen Formulation

For the acetaminophen formulation, placement of tablets within the stationary basket gave faster overall dissolution compared to that obtained when tablets were placed in the bottom of the vessel (Figure 2). Dissolution curves were not equivalent between the hanging basket and conventional tablet placement (f_2 metric < 50 for all $t \geq 10$ h).

Figure 2. Comparison of acetaminophen release using stationary basket vs. conventional tablet placement.



The mean percent acetaminophen released when an additional 6 and 12 tablets were tested at the bottom of the conventional vessel decreased slightly (Figure 2). The precision (tablet-to-tablet standard deviation) was not improved (Table 2, Table 3). However, precision in tests involving the stationary basket was considerably improved compared to tests involving conventional placement (Table 2, Table 3).

Table 2. Comparison of acetaminophen release using stationary basket vs. conventional tablet placement, $t = 6$ h.

Method	Mean Amount Released (%)	Std Dev (%)	Range (%)
Stationary basket, n=6	66.3	1.1	2.7
Conventional placement, n=6	51.0	2.6	6.0
Conventional placement, n=12	47.9	4.2	13.0
Conventional placement, n=18	48.0	3.4	13.0

Table 3. Comparison of acetaminophen release using stationary basket vs. conventional tablet placement, $t = 12$ h.

Method	Mean Amount Released (%)	Std Dev (%)	Range (%)
Stationary basket, n=6	87.5	0.8	1.8
Conventional placement, n=6	71.8	3.1	7.2
Conventional placement, n=12	68.3	5.0	14.9
Conventional placement, n=18	67.9	4.1	14.9

Theophylline Formulation

As with the previous acetaminophen formulation, theophylline release was faster when the stationary basket was used (Figure 3). Hypromellose release also followed the same trend. Drug release “led” polymer release by approximately 20%, indicating a significant diffusion contribution to overall theophylline release from the matrix.

At earlier dissolution times (e.g., ≤ 6 h, see Table 4), the tablet-to-tablet standard deviation and range of the conventional method were about twice that of the stationary basket method.

At later times (Table 5), the precision and range of tablet-to-tablet variation of the stationary basket method were much superior to the conventional method as indicated by both drug and polymer release.

Commercial Theophylline Caplets

Contrary to the two experimental formulations, drug release was slightly slower for commercial theophylline caplets using the stationary basket compared with conventional tablet placement in the bottom of the vessel (Figure 4). The use of clips (employed to prevent tablets from floating) had very little effect on drug release. Curves were

equivalent as indicated by f_2 metric (greater than approximately 70 throughout).

Figure 3. Comparison of theophylline and hypromellose release using stationary basket vs. conventional placement.

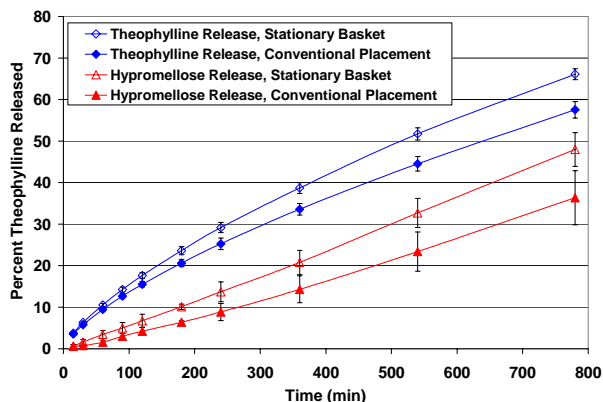


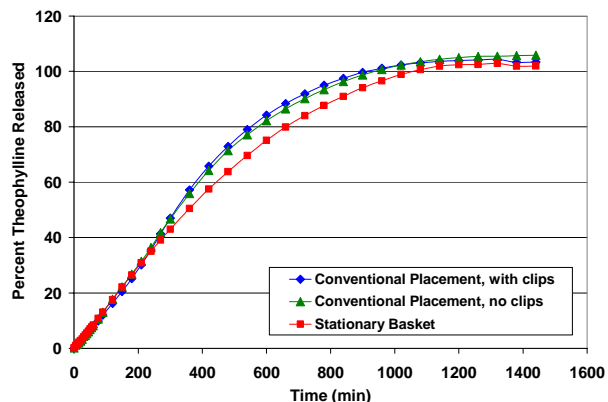
Table 4. Comparison of theophylline and hypromellose release using stationary basket vs. conventional tablet placement, $t = 6$ h.

Method	Mean Amount Released (%)	Std Dev (%)	Range (%)
Theophylline, stationary basket	38.7	1.3	3.6
Theophylline, conventional placement	33.6	2.9	7.9
Hypromellose, stationary basket	20.8	1.4	3.5
Hypromellose, conventional placement	14.3	3.2	9.8

Table 5. Comparison of theophylline and hypromellose release using stationary basket vs. conventional tablet placement, $t = 13$ h.

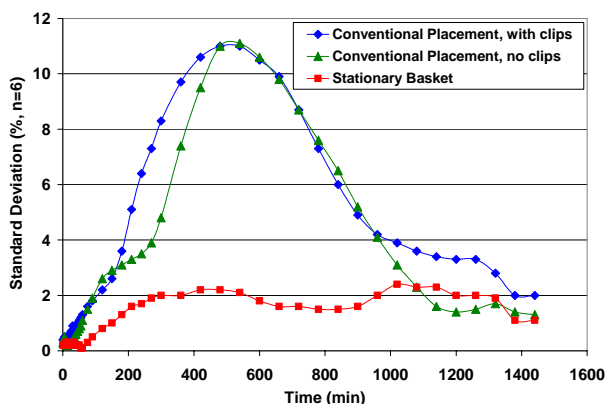
Method	Mean Amount Released (%)	Std Dev (%)	Range (%)
Theophylline, stationary basket	66.1	1.3	3.7
Theophylline, conventional placement	57.5	4.1	10.7
Hypromellose, stationary basket	48.0	2.0	5.0
Hypromellose, conventional placement	36.4	6.5	19.3

Figure 4. Comparison of theophylline release from commercial caplets using stationary basket vs. conventional placement.



Despite similar mean release profiles, the stationary basket method gave dramatically improved precision (Figure 5). The use of clips had negligible impact on precision.

Figure 5. Standard deviation of theophylline release from commercial caplets using stationary basket vs. conventional placement.



Variation in tablet-to-tablet drug release in USP Type II apparatus is well known; several modifications have been proposed to reduce the variability (1–3). The cause for this variation is now generally accepted to be variation in hydrodynamics (4). The effects are usually studied with infrared analysis or calibrator tablets.

The effects on sustained-release tablets can be even more significant because of the long time scale involved. Drug release from hydrophilic matrix tablets is normally the result of drug diffusion and polymer erosion, both of which are affected by the boundary layer that exists near the surface of the tablet determined by the local hydrodynamic conditions. Recent studies (4–7) show that the fluid velocity changes significantly over a relatively small distance in the region directly beneath

the paddle in a Type II apparatus. Use of the stationary basket increases surface area exposed for diffusion/erosion, placing the tablet in a region of the dissolution vessel where fluid velocity does not vary with small changes in position.

Conclusions

The use of a stationary basket positioned within a Type II dissolution apparatus leads to reduced variability in release data, is useful in collecting data for validation of models of drug release, and may have utility in studying the effects of hydrodynamics.

The stationary hanging basket has an advantage over the USP Type I apparatus since there is no centrifugal force to cause tablet deformation due to the flow of the viscoelastic gel structure.

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