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In Vitro Evaluation of Dissolution Behavior for a Colon-Specific Drug Delivery System (CODES™) in Multi-pH Media Using United States Pharmacopeia Apparatus II and III

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ABSTRACT United States Pharmacopeia dissolution apparatus II (paddle) and III (reciprocating cylinder) coupled with automatic sampling devices and software were used to develop a testing procedure for acquiring release profiles of colon-specific drug delivery system (CODES™) drug formulations in multi-pH media using acetaminophen (APAP) as a model drug. System suitability was examined. Several important instrument parameters and formulation variables were evaluated. Release profiles in artificial gastric fluid (pH 1.2), intestinal fluid (pH 6.8), and pH 5.0 buffer were determined. As expected, the percent release of APAP from coated core tablets was highly pH dependent. A release profile exhibiting a negligible release in pH 1.2 and 6.8 buffers followed by a rapid release in pH 5.0 buffer was established. The drug release in pH 5.0 buffer increased significantly with the increase in the dip or paddle speed but was inversely related to the screen mesh observed at lower dip speeds. It was interesting to note that there was a close similarity (f_2 = 80.6) between the release profiles at dip speed 5 dpm and paddle speed 100 rpm. In addition, the release rate was reduced significantly with the increase in acid-soluble Eudragit E coating levels, but lactulose loading showed only a negligible effect. In conclusion, the established reciprocating cylinder method at lower agitation rates can give release profiles equivalent to those for the paddle procedure for CODES™ drug pH-gradient release testing. Apparatus III was demonstrated to be more convenient and efficient than apparatus II by providing various programmable options in sampling times, agitation rates, and medium changes, which suggested that the apparatus III approach has better potential for in vitro evaluation of colon-specific drug delivery systems.

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INTRODUCTION

Colon-specific drug delivery is considered beneficial in the treatment of colon-related diseases and the oral delivery of protein and peptide drugs.[1] Generally, each colon-specific drug delivery system has been designed based on one of the following mechanisms with varying degrees of success: (1) prodrugs, (2) pH-sensitive polymer coating, (3) time-controlled dissolution, and (4) microflora-activated drug release.[2,3] Recently, a unique colon-specific drug delivery system (CODES™) has been developed and evaluated.[4] Drug release from this system is triggered by colonic microflora coupled with pH-sensitive polymer coatings. The colon specificity of drug release has been confirmed in healthy human volunteers using γ-scintigraphy imaging.[5] In brief, a typical CODES™ configuration consists of a core tablet coated with 3 layers of polymer. The first coating (next to the core tablet) is an acid-soluble polymer (for the present study, Eudragit E), and the outer coating is enteric, with an HPMC (hydroxypropyl methylcellulose) barrier layer interposed to prevent any possible interactions between the oppositely charged polymers. The core tablet comprises the active ingredient, one or more polysaccharides (eg, lactulose), and other desirable excipients. During its transit through the gastrointestinal (GI) tract, the CODES™ remains intact in the stomach because of the enteric protection, but the enteric and barrier coatings dissolve in the small intestine, where the pH is above 6. Because of Eudragit E starting erosion at pH ≤5, the inner Eudragit E coating is only slightly permeable and swellable in the small intestine. Upon entry into the colon, the polysaccharide inside the core tablet dissolves and diffuses through the coating. The bacteria enzymatically degrades the polysaccharide into organic acids. This lowers the pH surrounding the system enough to effect the dissolution of the acid-soluble coating and subsequent drug release.

One challenge in the development of colon-specific drug delivery systems is to establish an appropriate dissolution testing method to evaluate the designed system in vitro.[6] This is because the rationale behind a colon-specific drug delivery system is quite diverse. Additional factors that complicate the development of such dissolution testing include the inadequate understanding of the colon's hydrodynamics and motility and how they are affected by disease.[1] A number of alternative or unconventional approaches have been reported for evaluating the performance of colon-targeted delivery systems in vitro, such as using a modular fermentor,[7] using a multichamber reactor or SHIME (simulated human intestinal microbial ecosystem),[8,9] and using rotating beads.[1] While noting that the conditions of alternative methods differed significantly from each other, the complexity of setup and operation may further prevent them from being routinely used in an industrial setting. In contrast, conventional United States Pharmacopeia (USP) dissolution testing in different buffers is relatively simple and convenient, although it provides essential information primarily on the functionality of a colon-specific delivery formulation rather than on the validity of the system design. Among several USP dissolution methods, the basket method has been extensively employed in recent years to evaluate the dissolution of colon-targeted drug delivery systems based on pH-sensitive polymer coating as well as time-controlled drug release.[10-12] However, relatively fewer studies have been performed using USP apparatus II (paddle) and III (reciprocating cylinder).[13,14] Apparatus III has had a quite short history.[15] Apparatus II is one of the most commonly used dissolution testing devices, but no automated paddle procedure in vitro was reported in the literature for the testing of colon-specific delivery systems.[6]

The objective of this study was to develop a convenient and efficient testing procedure for routinely acquiring release profiles of CODES™ drug formulations in multi-pH media. The procedure involved a paddle method and a reciprocating cylinder method coupled with automatic sampling devices and software. Several instrumental parameters and some formulation variables were investigated and compared in this study.

MATERIALS AND METHODS

Materials

The following materials were used in the formulation: acetaminophen (APAP, as a model drug, Mallinckrodt, St Louis, MO), lactulose crystals (Inalc Pharmaceuticals, San Luis Obispo, CA), lactose monohydrate (DMV International, Veghel, The Netherlands), HPMC2910 (ShinEtsu Chemical Co, Tokyo, Japan), and Eudragit E100 and L100 (Rohm America, Piscataway, NJ). All other ingredients, such as magnesium stearate, and chemicals for preparation of dissolution media (buffers) were obtained from Sigma Chemical Co (St Louis, MO) or Fisher Scientific (Fair Lawn, NJ) and used as received. An APAP reference standard was purchased from USP (Lot J-1, Rockville, MD).

Tablet Preparation

The CODES™ prototype core tablet was 250 mg in weight and 9 kp in hardness. Each tablet consisted of approximately 20% APAP, 78% lactulose, and 2% HPMC unless otherwise indicated.

Briefly, APAP was mixed and granulated with lactulose in a fluidized bed granulator (GPCG-1, Glatt Air Technologies, Ramsey, NJ). Then a suitable amount of 5% HPMC2910 solution was applied to the fluidized power mix via a peristaltic pump (Masterflex, Barrington, IL). The dried granulation was blended with an appropriate quantity of magnesium stearate in a PK V-blender (Patterson-Kelly Co, East Stroudsburg, PA) for 5 minutes. The core tablets were produced using a Korsch tableting press (Model PH101, South Easton, MA) with standard concave tooling of 7.0 mm.

Three layers of pH-sensitive polymer were applied to the prototype core tablets in this order: Eudragit E100 (acid-soluble coating), HPMC2910 (barrier coating), and Eudragit L100 (enteric coating). A Vector Laboratory Development coating system (LDC5, Marion, IA) was used. The coating weight gain was approximately 8%, 2%, and 6%, respectively.

Dissolution Testing

Dissolution testing was carried out on USP dissolution apparatus II and III in 3 pH buffers - artificial gastric fluid (pH 1.2), artificial intestinal fluid (pH 6.8), and pH 5.0 buffer - that were prepared by combining appropriate amounts of sodium chloride with hydrochloric acid, potassium phosphate monobasic with sodium hydroxide, and citric acid with sodium phosphate dibasic, respectively.[14,16] All the solutions were degassed for 20 minutes before use. **Table 1** summarizes the general conditions in this study. Prior to dissolution run, the system was examined for suitability in terms of carryover diagnostics, bracketing standard and standard check, sink conditions, volume correction evaluation, air bubbles and light-scattering effects.

For apparatus II, Distek Model 2100B (Distek Inc, North Brunswick, NJ) or Hanson Research Model SR8Plus (Hanson Research Corporation, Chatsworth, CA) was used and integrated with Agilent autosampling assembly, HP 8453 UV-VIS spectrophotometer (Wilmington, DE) with 8-position multicell transport and data processing software. To prepare a paddle dissolution test, the 50-mg potency CODES™ tablet was placed in a sinker to prevent it from floating or adhering. When the bath was equilibrated, we started the dissolution run by first dropping the tablet into each vessel, then following a

Table 1. Summary of General Dissolution Conditions for Paddle and Reciprocating Cylinder Methods in This Study*

Parameter	USP Apparatus II	USP Apparatus III
Dissolution medium	Buffers (pH 1.2, 6.8, and 5.0)	Buffers (pH 1.2, 6.8, and 5.0)
Temperature	37.0 ± 0.5°C	37.0 ± 0.5°C
Initial volume	900 mL	250 mL
Paddle/dip speed†	100 rpm	15 dpm
Screen size†	NA	40 mesh (405 micron)
Filter size	10 micron	10 micron
Drawn volume	5.4 mL	6.0 mL
Running time	1 hr in pH 1.2, 4 hrs in pH 6.8, and 4 hrs in pH 5.0	1 hr in pH 1.2, 4 hrs in pH 6.8, and 4 hrs in pH 5.0
Medium replacement	Media refilling at 60 and 300 min	No media refilling

*NA indicates not applicable; USP, United States Pharmacopeia.
†Or otherwise indicated.

predeveloped automatic testing procedure in which the sampling parameters were specified (**Table 1**). The sample solutions were measured online in a 0.1-cm quartz flow-through cell at 243 nm. The percent APAP release for each pulling point and release profile was calculated against a calibration curve that was established using APAP standard solutions. To switch the medium pH from 1.2 to 6.8, the pH 1.2 buffer was replaced with a preheated pH 6.8 buffer at the end of reading for the last pH 1.2 sample. The same was true for the pH 5.0 buffer.

For apparatus III, VK Bio-Dis (VanKel Technology Group, Cary, NC) was used and integrated with VK 8000 dissolution sampling station, VK type bidirectional peristaltic pump, and VK 750D digitally controlled heater/circulator. During a reciprocating cylinder test, the dissolution run was guided by a preprogrammed procedure in which both Bio-Dis and VK 8000 parameters were specified (**Table 1**). The cylinders containing a tablet each moved between rows successively and switched the pH from one to another. All sample solutions were collected in the VK 8000, then filtered and tested offline using the HP 8453 UV-VIS spectrophotometer. The percent drug release data were calculated with volume correction in both paddle and reciprocating cylinder tests.[17]

RESULTS AND DISCUSSION

pH Dependence of Drug Release

Figure 1 shows the release profiles of APAP from core tablets with acid-soluble coating only (Eudragit E coating) using apparatus II. It can be seen that there was no significant APAP released (less than 3%) up to about 8 hours in pH 6.8 buffer. Under the same conditions, an extended dissolution run (data not shown here) indicated that no more than 15% APAP was released at the time point of 15 hours. In contrast, in pH 5.0 buffer, the percent release of APAP increased with time significantly within the first 2 hours and after that the release leveled out. **Figure 2** presents both paddle and reciprocating cylinder results for APAP release profiles from CODES™ tablets (ie, 3 layers of coating). The coated tablets remained intact in pH 1.2 buffer and no APAP release was observed. As the buffer pH was switched to 6.8, the outer enteric coating and barrier coating dissolved, but the inner cationic coating was still resistant to the pH and less than 1% of APAP was released at the time point of 5 hours. However, a rapid APAP release followed as the buffer was changed to pH 5.0. Similar release trends can be seen when using apparatus III, where the pH gradient was triggered automatically.

In the CODES™ technology, the functionality of the enteric coating is to maintain the integrity of the system in the stomach, while the cationic acid-soluble coating is intended to minimize the drug release in the small intestine. In this study, the dissolution media of pH 1.2 and 6.8 were used to simulate the pH conditions in the stomach and intestine, while the pH 5.0 buffer was used to

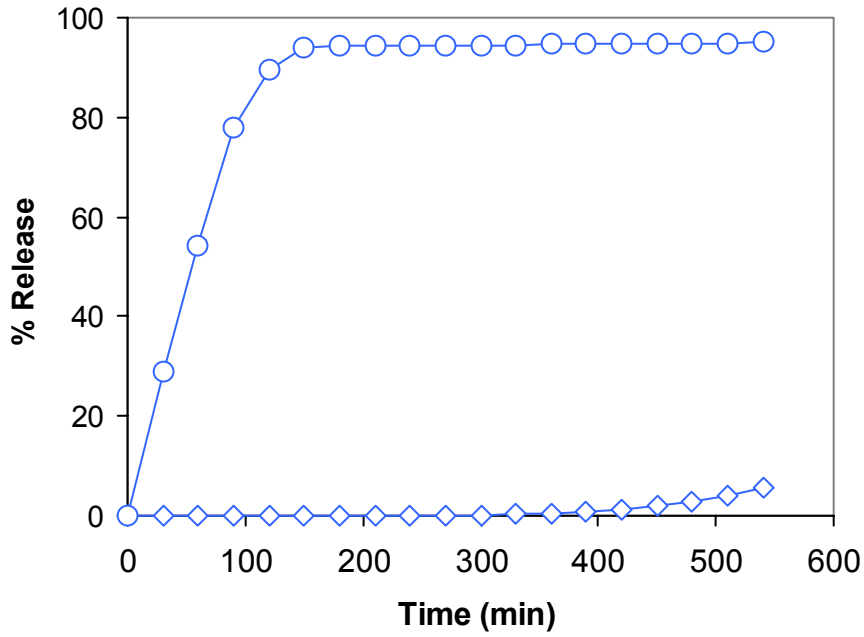

Figure 1. Release profiles of APAP from core tablets with Eudragit E coating only. Conditions: paddle at 100 rpm; buffer pH 6.8 (◊) and 5.0 (O); n = 3.

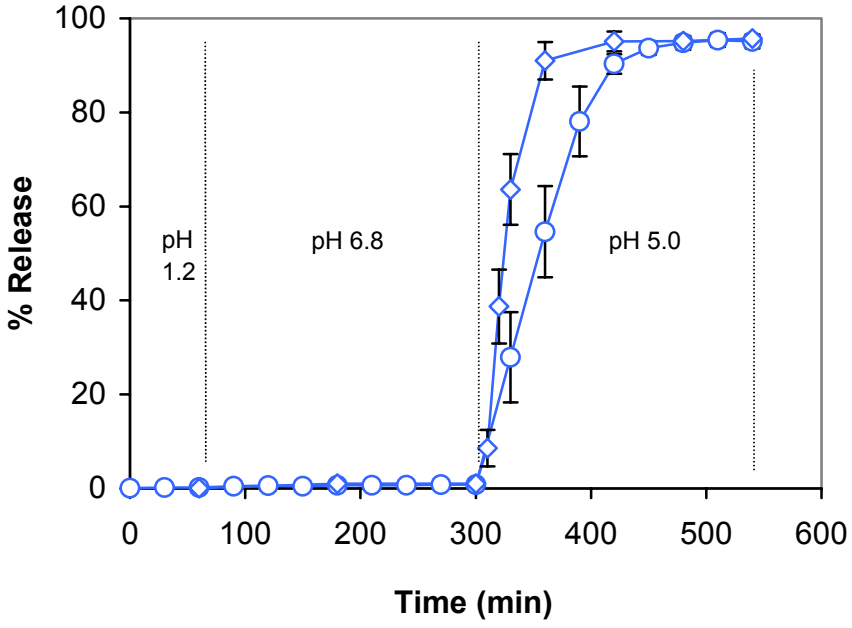

Figure 2. Release profiles of APAP from CODES™ tablets. Conditions: paddle at 100 rpm (O), reciprocating cylinder at 15 dpm (◊); buffer pH 1.2 (0-60 min), 6.8 (60-300 min), and 5.0 (300-540 min); n = 6.

represent the environment after the system entered the ascending colon, where lactulose was degraded into organic acids by colon bacteria. During a dissolution run, the duration of 4 hours in pH 6.8 buffer was chosen for simulating the average transit time of a solid dosage form in the small intestine.[11] It was evident from the above results that the release of APAP in pH 1.2 and 6.8 buffers was negligible. This indicated that the enteric and cationic coatings applied appeared sufficient to prevent premature drug release in the stomach and small intestine. Once the medium of pH 5.0 was switched to, the drug was completely released within approximately 2 hours. As has been commonly recognized, to a greater extent, the conventional USP dissolution testing in different buffers can be routinely used to evaluate the functionality of a system design during formulation development. The selection of the buffer pH in this study was considered to suitably investigate the colon-targeted drug delivery concept.[7, 11, 14, 18] The above test results substantiated the design rationale that APAP release from the tablets was triggered by the decrease in pH surrounding the system and, therefore, clarified that the CODES™ formulation had achieved its objective drug release pattern.

Effects of Screen Sizes

The screen size effect was investigated with apparatus III, in which each glass cylinder (containing the formulation) is enclosed by 2 Teflon caps and the bottom cap is covered with a polypropylene screen. The percent release of APAP was observed to depend on the screen size (mesh). Three levels of screen size (20, 40, and 78 mesh) were tested for APAP release under different dip speeds (10 and 30 dpm) in 3 pH buffers. **Table 2** shows only the most discriminating data (in pH 5.0 buffer and at 10 dpm). It can be seen that the percent release rate became lower substantially over the first hour when screen sizes varied from 20 to 40 and 78 mesh (equivalent to 840, 405, and 177 micron, respectively). However, there were no discrepancies demonstrated over the same time period at the higher dip speed (30 dpm).

It has been well established that the hydrodynamic conditions or mechanical forces of a dissolution medium are crucial in affecting the drug release rate.[19-21] It is reasoned that drug release from an erosion-controlled device would be more influenced by changes in the hydrodynamic flow than would drug release from a diffusion-controlled device.[22] The CODES™ was basically formulated as a disintegrating, erodible dosage form coated with pH-sensitive polymers. Since the top Teflon cap of a glass cylinder has larger holes (3.9 mm in diameter), the fluid flow in the cylinder is controlled primarily by the bottom screen. The larger screen mesh sizes (ie, smaller screen pores) could dominate the hydrodynamic effect at the lower dip speeds and constitute a relatively more stagnant region that decreased the so-called mechanical shear on the polymer coating (Eudragit E coating) and, therefore, suppressed the drug release. In contrast, the higher dip speeds could offset the effect of different screen sizes on the hydrodynamics, showing no significant or observable changes in the percent drug release. Nevertheless, the screen mesh effect was relatively small and lasted over a shorter period of time (less than 2 hours), as seen in **Table 2**. The drug release eventually matched the maximum release level in pH 5.0 buffer, no matter what screen size was tested.

Effects of Agitation Rates

There is no direct correlation between the setting of rpm (rotations per minute) or dpm (dips per minute) and the GI tract. The variance over a wide range can be accounted for by such factors as the portion of the GI tract, the state (fed or fasted), and formulation characteristics.[13, 22, 23] In this study, the agitation rates were held constant at 15 dpm for the reciprocating cylinder[19] and 100 rpm for the paddle, or as otherwise specified.

As can be seen, the percent release of APAP was greatly influenced by the paddle and dip speeds. **Figure 3A** shows the release profiles of APAP from core tablets with Eudragit E coating only in pH 5.0 buffer under different paddle speeds (50, 75, and 100 rpm), and **Figure 3B** shows the release profiles from CODES™ tablets in 3 buffers under different reciprocation rates (5, 10, 20, and 30 dpm). Apparently, the reciprocating action played a dominant role in affecting the drug release. Although the APAP release still remained near zero levels in pH 1.2 and 6.8 buffers over the first 5 hours, the release rate in pH 5.0 buffer was strongly affected by the dip speed and increased considerably with the dip speed increasing from 5, to 10, 20, and 30 dpm. As a comparison, the estimated T(50%) values (the time to 50% release) were approximately 52, 28, 17, and 14 minutes, respectively, for the tested dip speeds.[22] Similarly, the percent release of APAP increased significantly when the paddle speed changed from 50 to 75 and 100 rpm. The T(50%) values were about 71, 65, and 45 minutes, respectively, for the tested paddle speeds.

The increased drug release was presumably attributed to the greater turbulence or agitation in the dissolution medium caused by the higher reciprocation (cylinder) or rotation (paddle) speeds.[19-22] As described above, the cylinder system at 30 dpm was faster than at 5 dpm by a factor of about 4 (14 vs 52 minutes to achieve a 50% APAP release). However, the changes in paddle speeds apparently resulted in relatively less discriminating profiles. As can be seen from **Figure 3A**, for the same percent APAP release the paddle system at 100 rpm was faster than at 50 rpm by only a factor of less than 2 (45 vs 71 minutes). Similar observation with apparatus II was reported by Khougaz et al, in which the percent drug release for short time intervals increased with stirring speeds from 50 to 75 and 100 rpm.[24]

Table 2. Percent Release of APAP from CODES™ Tablets as a Function of Different Screen Sizes*

Time	Average APAP Release (%)		
(min)	20 mesh	40 mesh	78 mesh
310	5.1 ± 1.3	1.8 ± 0.3	1.9 ± 0.6
320	35.0 ± 2.1	27.0 ± 2.7	22.8 ± 7.0
330	56.8 ± 5.8	47.7 ± 4.2	42.9 ± 6.3
360	93.0 ± 3.4	90.4 ± 2.3	86.8 ± 4.9
420	95.8 ± 2.3	95.4 ± 1.5	93.3 ± 2.0
480	95.7 ± 2.0	95.3 ± 0.8	94.5 ± 1.9
540	95.8 ± 1.8	95.6 ± 0.5	95.1 ± 1.3

*Conditions: reciprocating cylinder in pH 5.0 buffer and at 10 dpm (n = 3). APAP indicates acetaminophen; CODES™, colon-specific drug delivery system.

Comparison of Release Profiles

Obviously, the drug release rate was more influenced by the dip speed than by the paddle speed, as has been seen earlier. **Figure 4** presents a comparison of APAP release profiles between the paddle and the reciprocating cylinder. It was interesting to note that the release profile at 5 dpm was demonstrated to be similar to the release profile at 100 rpm. In contrast, the reciprocating cylinder at higher dip speeds (eg, 30 dpm) produced a much faster drug release rate as compared to the paddle at 100 rpm. This was further assessed by conducting a statistical similarity test.[25,26] The release profile at 100 rpm was used as the reference. Two profiles would be considered similar if the similarity factor, f_2, was close to 100 (usually ≥50). The resultant f_2 was 80.6 for the comparison of 5 dpm versus 100 rpm, but only 23.4 for the comparison of 30 dpm versus 100 rpm. This clearly indicated a very close drug release pattern between 5 dpm and 100 rpm, which was a result of similar or equivalent hydrodynamic conditions.

In general, the paddle method can provide an automatic approach suitable for CODES™ extended drug release testing. The reciprocating cylinder method was capable of providing various convenient and programmable options in sampling times, agitation rates, and medium changes, which was necessary during the dissolution testing of a pH-gradient release product like CODES™. Importantly, this method offered a sound hydrodynamic system that was superior to the paddle method. Therefore, the more aggressive behavior observed with apparatus III was a consequence of its favorable operation mechanism. During up and down strokes, the reciprocating action generated a steady fluid flow across the bottom screen and allowed the glass cylinder to carry the tablet being tested through a medium that was constantly in motion. This was obviously different from apparatus II, for which the "coning" phenomenon – a poorly stirred zone – has been commonly recognized.[20] The cone formation was reported to significantly reduce the dissolution rate and produce a wide variation in result.[19] Therefore, it was not surprising to see the equivalence of the release profiles between the reciprocating cylinder at 5 dpm and the paddle at 100 rpm. The result was consistent with the observation of Rohrs et al if considering the difference of formulation or manufacturing, in which, for the 100 rpm paddle and 100 rpm basket, the estimated apparatus III equivalent agitation rates were about 10 dpm or less.[22] In addition, Borst et al reported similar dissolution rates between USP apparatus III at 15 dpm and USP apparatus II with "peak" vessels at 100 rpm.[19] This can be understood if it is noted that the peak bottom could avoid the drawbacks inherent in ordinary vessels and thereby improve the system hydrodynamics to some degree.[20] Schauble's study indicated that even a sample probe present in the medium could create a turbulence in the cone, leading to a rise in the dissolution rates, especially for the paddle at 100 rpm.[21] A recent article by Yu et al reported that USP apparatus III at the extreme low end of the possible agitation range, such as 5 dpm, gave hydrodynamic conditions equivalent to USP apparatus II at 50 rpm for immediate release products.[27] It was reasoned that the polymer-coated CODES™ formulations required more aggressive mechanical forces (higher paddle speeds) in order to achieve dissolution profiles similar to those of the cylinder method.

Effects of Eudragit E Coating and Lactulose Loading

The effect of formulation variables, such as lactulose loading and acid-soluble coating levels, on the release

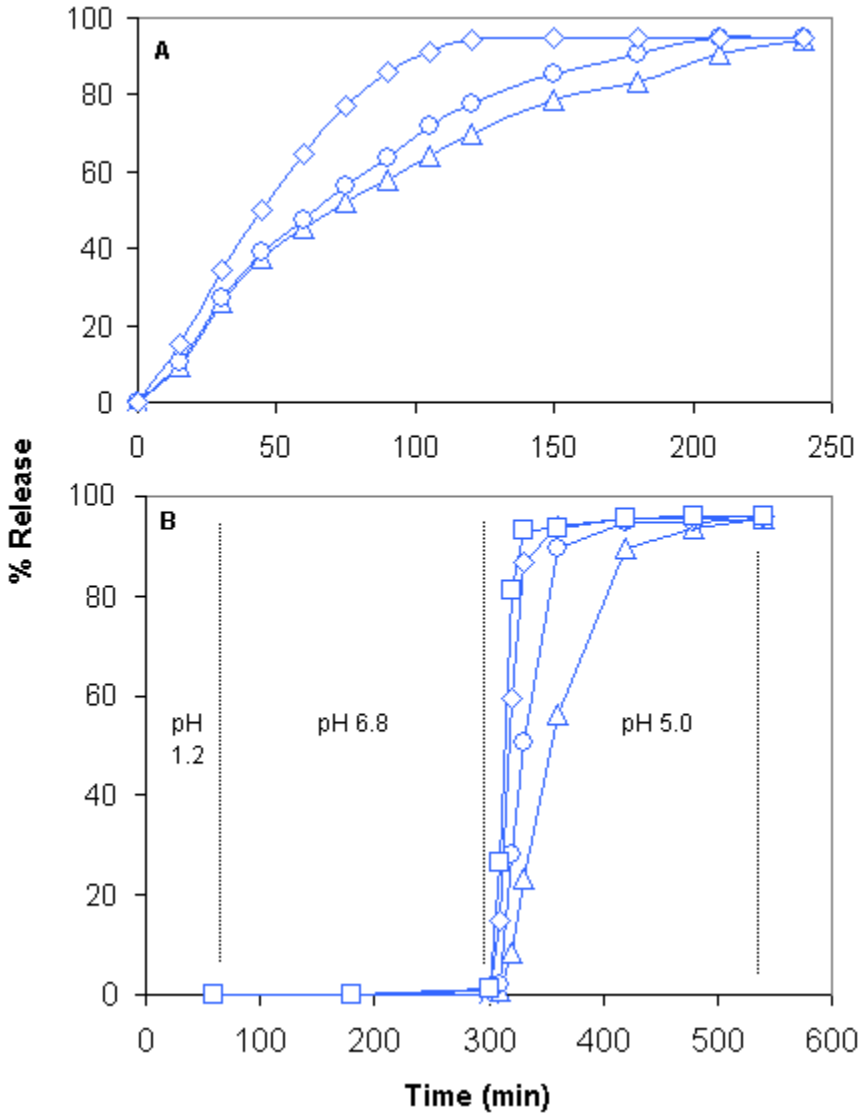

Figure 3. Release profiles of APAP as a function of paddle speeds (A) or dip speeds (B). Conditions: (A) core tablets with Eudragit E coating only; paddle at 50 rpm (Δ), 75 rpm (O), and 100 rpm (◊); buffer pH 5.0 (only 0-240 min data shown); n = 3. (B) CODES™ tablets; reciprocating cylinder at 5 dpm (Δ), 10 dpm (O), 20 dpm (◊), and 30 dpm (□); buffer pH 1.2 (0-60 min), 6.8 (60-300 min), and 5.0 (300-540 min); n = 3 (for 10 and 20 dpm) and 12 (for 5 and 30 dpm).

behavior of CODES™ drug products was investigated using the paddle method.

Three prototypes of APAP core tablets were prepared with lactulose levels of 78%, 58%, and 38%, respectively. These core tablets were coated sequentially with Eudragit E, HPMC, and Eudragit L polymers and then tested in 3 pH buffers. It was demonstrated that the release profiles were nearly overlapping regardless of the lactulose loading levels, indicating an identical APAP release pattern. Lactulose is a synthetic disaccharide that can be hydrolyzed into short chain fatty acids, such as lactic acid and acetic acid, by anaerobic bacteria in the colon.[28] Apparently, the above result was inconsistent with the observation of in vivo study, in which as the lactulose level decreased the average first appearance of APAP in the systemic circulation of dogs was further delayed.[29] This was attributed to the slow generation of organic acids in the colon due to the decreased availability of lactulose at lower loading levels. The discrepancy incurred here was expected because of the lack of lactulose enzymatic degradation under the in vitro dissolution conditions. Therefore, the resultant profiles were solely contributed by the active ingredient (APAP) that was released with the dissolution of the inner coating at the threshold pH value (≤5.0). The medium pH in vitro was irrelevant to the lactulose loading levels.

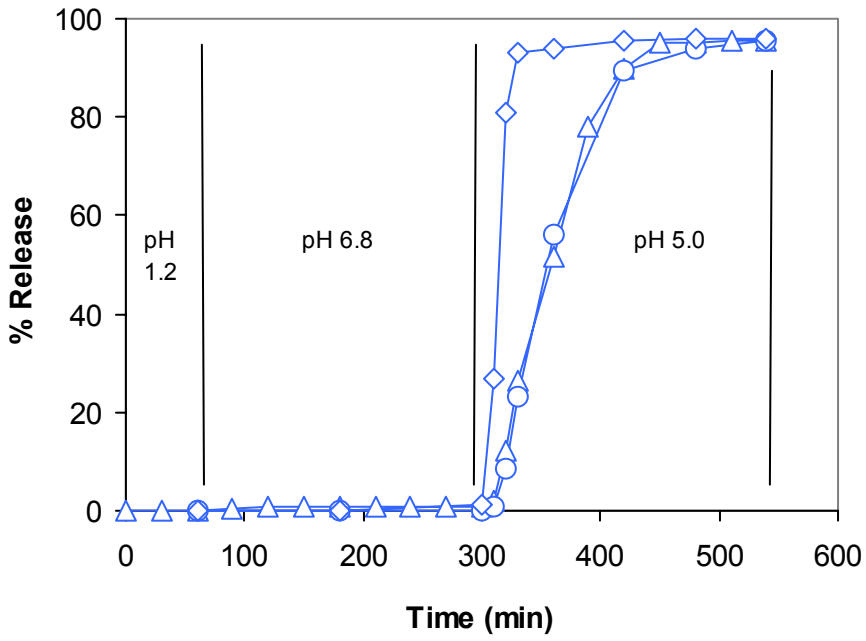

Figure 4. Comparison of release profiles of APAP from CODES™ tablets. Conditions: paddle at 100 rpm (Δ); reciprocating cylinder at 5 dpm (O) and 30 dpm (◊); buffer pH 1.2 (0-60 min), 6.8 (60-300 min), and 5.0 (300-540 min); n = 12.

In addition, the core tablets from a prototype of 78% lactulose loading were coated with Eudragit E at different levels: 4%, 8%, and 12%, respectively (HPMC and Eudragit L coatings remained the same). Drug release profiles were acquired in pH 6.8 buffer. It was shown that the drug release rate was reduced significantly when the coating level increased from 4% to 8% and 12%. For example, at the time point of 9 hours, the average APAP percent release was only about 11% or less with the Eudragit E levels of 8% and 12%, but it was almost complete at the lower coating level of 4%. Since acid-soluble Eudragit E coating was only slightly permeable at pH 6.8, it can be anticipated that higher coating levels will reduce the permeability as a result of the increase in coating layer thickness, leading to prolonged release of the drug and lactulose. This was in agreement with the in vivo result.[29] APAP did not appear in the systemic circulation until approximately 6 hours at the 12% weight gain – much longer than the lag time of 4 hours at lower Eudragit E coatings. This indicated that the transport of lactulose through the thicker coating was retarded in the colon, leading to a decrease in lactulose degradation and acid formation, which in turn increased the lag time for Eudragit E coating dissolution.

CONCLUSION

Automated flow-through or programmed dissolution procedure with USP apparatus II and III was developed and proven to be suitable for in vitro CODES™ evaluation. Relatively speaking, the reciprocating cylinder method was demonstrated to be preferable. This study has addressed the effects of both instrument parameters and formulation variables on drug release profiles from APAP CODES™ products. Briefly, under a certain level of Eudragit E coating (eg, 8%), the reciprocation speed was a major factor in affecting the drug release rate in contrast to the paddle speed; the bottom screen mesh played a lesser role. By comparison, the reciprocating cylinder at appropriately lower dip speeds (eg, 5 dpm) can give a release profile close or equivalent to that of the paddle at 100 rpm. This may help define a starting point in future dissolution method development for assessing the performance of controlled or extended release drug products. Detailed research results with APAP CODES™ formulation development and in vitro/in vivo correlation will be addressed in a separate paper.[29]

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