M1168

Investigation of the Robustness of USP and Modified-USP Methods of Weighting Floatable Dosage Forms during Dissolution

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Introduction

The USP describes "several turns of wire" as a useful tool to sink floatable tablets. Hydrophilic matrix tablets may display swelling characteristics sufficient to induce buoyancy or adhesion to the vessel bottom during dissolution. Floating at on the surface of dissolution media or adhesion either the vessel bottom, paddle shaft or sampling cannula (for buoyant tablets) may inhibit dissolution media contact with tablet surface and-or prevent equal three-dimensional swelling. For extended release formulations which rely upon swelling and erosion forces to control drug release, such hydrodynamic and swelling changes are compounded over the duration of dissolution. In this study, we present data from studies using helical wire sinkers and screen mesh against free-to-float tablets of conventional hydrophilic polymer formulations and novel hydrophilic polymer-electrolyte formulations (CDT®). Matrix constituents and tablet geometry are also known to determine the swelling characteristics of a formulation: formulations that control release through erosional forces are more susceptible than those who rely primarily upon diffusional forces. In this study, we also present data from novel polymer-electrolyte formulations which control release primarily by diffusion, and formulations which control release through a combination of diffusion and erosion.

Objective

To compare methods of weighting extended release hydrophilic matrix tablets in a USP type II dissolution apparatus using helical wire sinkers, wire mesh screens and simple twists of wire against floating dosage forms.

To evaluate the effects of weighting methods on drug release from novel extended-release polymer-electrolyte formulations (CDT®) of ibuprofen and pseudoephedrine HCl.

Methodology

Materials:

Ibuprofen (BASF Corporation. Bishop, TX), Pseudoephedrine HCl (Novus Fine Chemicals. Carlstadt, NJ), Hydroxypropylmethyl cellulose (Dow Chemical Company, Midland, MI), Polyethylene Oxide (Dow Chemical Company, Midland, MI), Microcrystalline cellulose PH102 (FMC Corp. Newark, DE), Dicalcium Phosphate (Rhodia. Cranbury, NJ), Sodium Carbonate, anhydrous (Natrium, Inc. Cortland, NY), Sodium Bicarbonate (Natrium, Inc. Cortland, NY), and flow agents and other excipients. Dissolution media (Chata Biosystems. Fort Collins, CO).

Tablet Manufacture:

The self-correcting matrix formulations were prepared through dry-blend and direct-compression. The formulations were blended in a V-blender (Patterson-Kelly/Harsco Corporation. East Stroudsburg, PA) in either a 1-stage or 2-stage process depending on matrix constituents, and prior to compression, the blend was lubricated with one or more flow agents at 1.5-2.5%. Conventional tablet formulations were manufactured on a Carver single-station press (Carver, Inc. Wabash, IN) and novel formulations were manufactured on a Piccola (Riva) 10-station rotary press (Specialty Measurements Inc. Lebanon, NJ).

In Vitro Dissolution Testing:

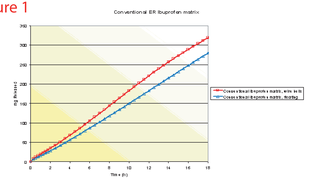
The in vitro release profiles of tablets manufactured in this study was evaluated by a USP Type II dissolution apparatus (Varian, Inc. Cary, NC; Hansen Research. Raleigh, NC) and UV-Vis spectrophotometer (Varian, Inc. Cary, NC; Beckman Coulter. Fullterton, CA). The dissolution apparatus was modified through the use of helical wire-sinkers and wire mesh screens. Dissolution studies were conducted according to USP guidelines at 37 degrees C in 900mL of 0.05M phosphate buffer media pH 7.2 for ibuprofen and de-ionized water (dH2O) for pseudoephedrine HCl formulations, respectively. Ibuprofen samples were analyzed in real-time at 264 nm and pseudoephedrine HCl samples were analyzed at 254.5 nm.

Wire mesh screens were made by cutting a disk from a sheet of stainless steel mesh with 0.016 inch spacing (Cambridge wire cloth). The disks were approximately 183mm in diameter, allowing them to lie several mm below the bottom of the paddles. The circumference of the disk was coated with an epoxy resin to seal the sharp ends, preventing damage to vessels and preventing disk movement during dissolution. Wire helical sinkers were made from stainless steel wire, consisting of 7-9 turns roughly 40mm long and 20mm in diameter at the center. The sinkers narrow toward the ends and are constructed so as to prevent escape of the tablets.

Results

Extended release (ER) hydrophilic matrix tablets of conventional formulations using polyethylene oxide (PEO) to control release of the sparingly soluble drug ibuprofen were evaluated using helical wire sinkers and un-weighted tablets. The conventional matrix tablets did not gain buoyancy, instead remaining in a single position after introduction into the dissolution media and swelling in-place. During hydration, the un-weighted tablets adhered to the vessel bottom, while the helical wire sinkers allowed the tablets to remain above the vessel bottom and permitted dissolution media more efficient access to the tablet surface. This is reflected in the suppressed dissolution rate of the tablets adhered to the vessel. (Figure 1)

Figure 1



The dissolution profile of a novel polymer-electrolyte ER formulation (CDT®) of ibuprofen was evaluated using both helical wire sinkers and wire mesh screens. Such a tablet-under-screen was previously described and evaluated using floating ER hydrophilic matrix tablets containing theophylline or diltiazem.1 The ER ibuprofen tablets in this study displayed suppressed release when allowed to freely float at the media surface, improved release when placed within wire helices, and yet further improvement in release when placed beneath a wire mesh screen. (Figures 2a and 2b) This behavior is consistent with observations that floating tablets may have reduced erosional forces acting upon them and wire mesh screens may provide maximal tablet surface area for media interaction. The initial 2h were shown to be critical in determining remainder of release profile, which may be due to differing rates of initial hydration and tablet disintegration. (Figure 2c)

Figure 2a

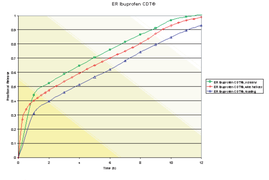
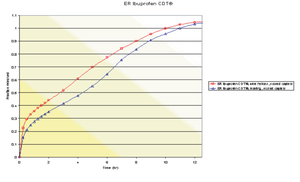


Figure 2b



Novel ER Ibuprofen tablets were also evaluated at higher paddle speed to evaluate the effects of increased hydrodynamic stress upon the weighting methods. (Figure 3a) At 150 rpm, the floating dosage forms displayed the most-rapid release, likely due to the increased sheer forces present at the media surface which cause increased matrix erosion. Similarly, the wire helices and wire mesh screens displayed equivalent release once the tablets were hydrated, due to the increased hydrodynamic stresses on the tablets overwhelming the differences in diffusional and erosional forces seen at 50 rpm. Tablets contained within a single coil of wire showed extreme suppression of release, likely due to a combination of tablets adhering to the vessel bottom within the much less agitated "dead volume" directly beneath the paddle blade and restriction of tablet swelling by the wire coil. It is notable that during the initial 2h of tablet hydration, the wire helices allowed slightly more rapid release to occur than the mesh screens, likely due to the tablets under the wire mesh screen initially resting against the vessel bottom prior to achieving buoyancy, whereas the wire helices allow the dissolution medium immediate access to all surfaces of the tablet. (Figure 3b) The variability in release (as measured by standard deviation from the mean fractional release) during the first 2h differed substantially between weighting methods, before reaching equilibrium once tablets were well-hydrated. (Table 1) Such variability is indicative of the relative hydrodynamic stress imparted upon the tablets immediately after introduction into the dissolution medium. Floating tablets displaying the greatest variability at initial timepoints, wire mesh screens displaying less variability and wire helices being the most consistent.

Figure 2c

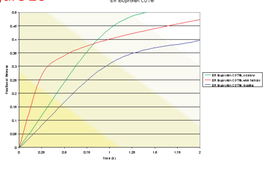


Figure 3a

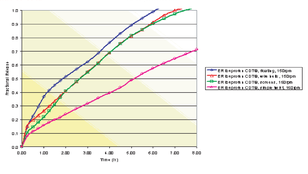
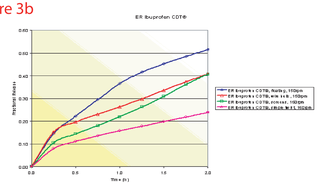


Figure 3b

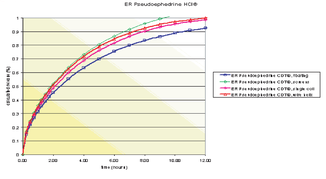


Novel hydrophilic polymer-electrolyte ER formulations of the pseudoephedrine were evaluated using the various weighting methods. (Figure 4) In contrast to ibuprofen, pseudoephedrine is freely soluble in water, permitting diffusion forces play a larger role in controlling drug release from these tablet formulations than in the case of ibuprofen. As was discussed in previous studies using floating diltiazem tablet formulations, the highly soluble nature of the drugs reduces the effect of hydrodynamics upon drug release. Moreover, the novel polymer-electrolyte delivery system employed in these tablet formulations allows for a much greater robustness irrespective of testing methods.

Table 1

Time (h)	Wire Mesh Screen	Wire Helix	Floating
0.25	14.48	6.64	15.50
0.50	11.44	7.58	20.76
0.75	10.03	7.09	18.69
1.00	9.70	6.61	15.39
1.25	9.60	6.39	14.32
1.50	8.25	7.46	12.82
1.75	7.74	8.50	11.79
2.00	8.92	9.05	10.81

Figure 4



Conclusions

USP and non-USP methods of weighting hydrophilic matrix tablets were examined using conventional and novel polymer-electrolyte ER formulations of ibuprofen and pseudoephedrine. Floating tablets were shown to suppress drug release in comparison to both wire mesh screens and wire helices for novel tablet matrices relying upon a combination of erosional and diffusional forces to control drug release. For these formulations, wire mesh screens were shown to increase drug release relative to helical wire sinkers. Helical wire sinkers were also shown to prevent tablets from adhering to the vessel bottom and showed a corresponding increase in drug release relative to those tablets.

Previous studies also showed single or double wire mesh2 screens were superior to wire helices that adhered to the vessel bottom. Our investigations used wire helices that were relatively large and did not allow for tablets to sit entirely in the "deal volume" in the vessel, which may have allowed for better flow of dissolution medium around tablet and prevented tablets from adhering to vessel bottoms. Our investigations also used tablet formulations containing much higher drug load of sparingly soluble drug than did previous studies, which may increase the impact of erosional forces on the tablets.

For the self-correcting extended-release hydrophilic matrix systems employed in this study, dosage forms remain intact for up to 20 hours after initial-hydration, during which time they may float or adhere to surfaces, thereby experiencing highly asymmetric hydrodynamic forces. While such buoyancy or adhesion may not reflect in vivo conditions, it is characteristic of in vitro evaluations and may bias any in vivo-in vitro correlation (IVIVC) resulting from the dissolution data. We feel that preventing tablet floatation while also preventing tablet adherence to any surface is critical to obtaining reliable dissolution results. Because of the potential artifacts caused by tablet sticking, we believe that this is important for all hydrophilic extended-release dosage forms, regardless of whether they float or sink.

References

1. V. Pillay and R. Fassihi. Journal of Controlled Release 55(1998)45-55

2. T. Durig and R. Fassihi. Journal of Controlled Release 67(2000)37-44