

W4122 *In vitro* Investigations of Alternative Controlling Polymer Formulations of a Novel, Self-Correcting Controlled Release Matrix Displaying BA/BE to a Reference-Listed Product

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Purpose. To investigate the *in vitro* robustness, ruggedness and formulation flexibility of a novel, self-correcting controlled release matrix containing nicotinic acid capable of displaying *in vivo* bioequivalence to a reference listed drug product, Niaspan®, through the selection of alternative controlling polymers and electrolytic salts. **Methods.** Multiple formulations were developed to represent the clinically relevant dosage strength of 500mg nicotinic acid, utilizing common pharmaceutical polymers such as guar gum and polyethylene oxide (PEO), and electrolytic salts such as sodium carbonate selected as alternatives to a hydroxypropylmethyl cellulose-sodium bicarbonate formulation, known to display a Level-A IVIVC. *In vitro* dissolution studies were conducted using a type II dissolution apparatus within physiologically relevant pH from 1.0 to 7.8. Dissolution of alternate controlling polymer and electrolytic salt formulations were compared with *in vitro* dissolution profiles of a formulation selected for its BA/BE with the reference listed drug. **Results.** First-order release over 18 hours was achieved with formulations containing PEO and guar gum. Several formulations showed slight deviations in the release of nicotinic acid when introduced to changes in pH and ionic strength, (0.1N HCl, pH 1.2 and 0.05M potassium phosphate buffer, pH 6.5). **Conclusions.** Results suggest that alternative polymer formulations displaying essentially similar *in vitro* dissolution performance to formulations known to be BA/BE with the reference listed drug are possible using a novel, self-correcting controlled release matrix.

Purpose: The purpose of this study was to explore the flexibility in formulation for novel, self-correcting controlled release matrixes containing nicotinic acid with the objective of achieving comparable bioavailability/bioequivalence (BA/BE) performance to a reference.

Introduction: "Self-Correcting" hydrophilic polymeric matrix systems, like SCOLR Inc.'s CDT™ Controlled Delivery Technology platforms offer benefits of low cost development and manufacturing and at the same

time offers superior performance over conventional first generation hydrophilic matrices. In addition, the robustness of the technology allows for the ability to substitute formulations with alternate, potentially lower cost excipients further exploiting cost savings, reducing tablet size and offering the manufacturer the ability to "tailor" the formulation to material availability.

Alternate solid oral dosage forms capable of matching the performance of the reference-listed product, Niaspan®, were developed. Described are 500mg nicotinic acid dose formulations. Alternate formulations containing different polymer components (such as PEO and guar gum) and different electrolyte components (sodium carbonate and sodium bicarbonate) were compared to the reference formulation containing HPMC and sodium bicarbonate. The reference formulation was shown to display a Level-A *in vivo-in vitro* correlation (IVIVC) and BA/BE with the reference-listed drug¹. *In vitro* dissolution studies were conducted over 18 to 24 hours in physiologically relevant media of pH ranges from 1.0 to 7.8. The dissolution profiles of the alternate CDT formulations were compared with the *in vitro* dissolution profiles of the reference formulation.

Materials & Methods:

Niacin was supplied by Zetapharm (New York, NY). Hydroxypropylmethylcellulose (HPMC) and polyethylene oxide (PEO) were both obtained from Dow Chemical (Midland, MI). Guar gum was purchased from Hercules/Aqualon (Wilmington, DE). Sodium bicarbonate was purchased from Natrium Products (Cortland, NY) and anhydrous sodium carbonate was purchased from Spectrum Chemical (Gardena, CA). Stearic acid was purchased from Ashland Chemical (Santa Ana, CA). Potassium phosphate, hydrochloric acid, and sodium hydroxide for dissolution media were obtained from Spectrum Chemical (Gardena, CA).

Preparation of tablets and *in vitro* dissolution studies:

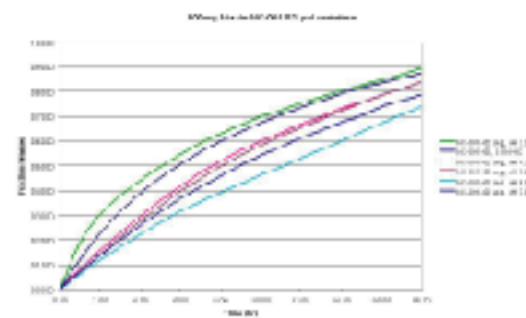
All materials were dry blended using a low-energy tumble blender or an 8-quart V-blender (Patterson-

Kelly, East Stroudsburg, PA) and were directly compressed using a hydraulic single station pellet press (Carver, Inc. Wabash, IN). Tablets were compressed to 4 tons. Dissolution studies were conducted in a USP 26 Type II apparatus (VanKel VK7000, Cary, NC and Hanson Research SR-8 Plus, Chatsworth, CA) with a paddle speed of 50 rpm and bath temperature of 37.0°C. Nicotinic acid release was monitored by UV detection at 275 or 262nm (Varian Cary 50, Cary, NC and Beckman Coulter DU-640, Fullerton, CA).

Results and Discussion:

Three alternate formulations were tested for *in vitro* dissolution and compared to the previously developed reference formulation NC-001-02 for performance. The goal was to match release kinetics seen for the standard, with no burst and a first order profile over 18 hours with complete release at 24 hr. The formulations utilized PEO and guar gum as the hydrophilic polymers. **Figure 1** shows the *in vitro* dissolution profile of the reference formulation NC-001-02 across a physiologically relevant pH range of 1.2 to 7.8.

Figure 1. *In vitro* release profile of reference formulation NC-001-02 across pH range 1.2-7.8.



Two alternates that most closely match the controlled delivery performance characteristics of the reference formulation contain PEO, with sodium carbonate or sodium bicarbonate electrolytes. Guar gum and combinations of guar gum and HPMC were evaluated but proved to be a poor substitution which yielded significantly different release kinetics from the reference formulation. The PEO/sodium bicarbonate formulation produced a finished tablet that was

significantly smaller than the reference formulation; the PEO/sodium carbonate formulation was similar in tablet weight as the reference formulation. The guar and guar/HPMC formulations, while not achieving the desired release, were up to 300mg additional tablet weight above the reference. **Figure 2** compares the release of both PEO/sodium carbonate and PEO/sodium carbonate formulations with the HPMC/sodium bicarbonate reference formulation. **Figure 3** compares guar/sodium carbonate and guar/HPMC/sodium carbonate release with the reference formulation.

Figure 2. *In vitro* release performance of alternate PEO formulations in 0.1N HCl.

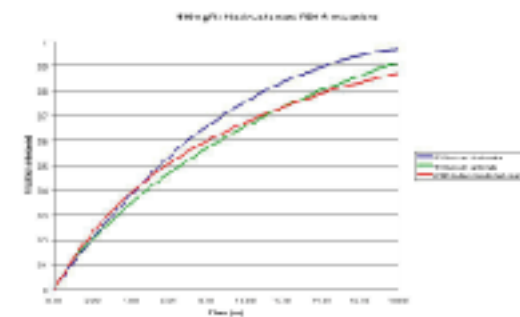
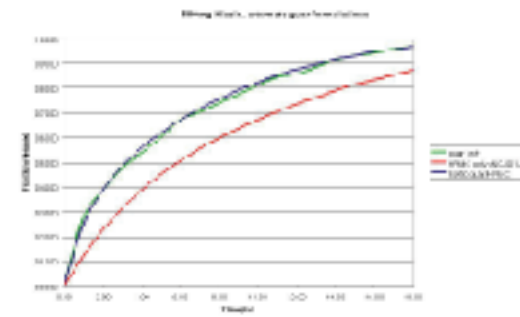


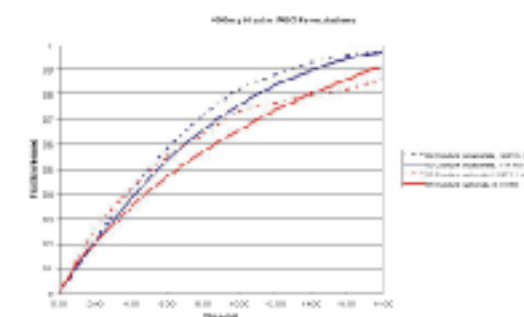
Figure 3. *In vitro* release performance of alternate guar formulations in 0.1N HCl.



Initial robustness studies of both PEO formulations showed good reproducibility in alternate media when compared with the performance in 0.1N HCl. **Figure 4** shows the *in vitro* release of both PEO formulations in 0.1N HCl, pH 1.2, and 0.05M KH₂PO₄ buffer, pH 6.5.

These formulations are expected to yield appropriate first-order release profiles in a variety of media conditions, as does the reference formulation.

Figure 4. Comparison of release profiles of PEO formulations in various media.



Conclusions:

Results suggest that alternative polymer formulations displaying essentially similar *in vitro* dissolution performance to a formulation known to be BA/BE with the reference listed drug are possible using a novel, self-correcting controlled release matrix. The formulations provide support to the capabilities of this self-correcting hydrophilic matrix and its ability to provide flexibility in manufacturing. Final tableting can be optimized by region and excipient availability such that equivalent formulations can be produced as efficiently as possible.

References:

1. Turner, Hite, Federici and Fassihi, *In Vivo-In Vitro* Correlation of a Novel Monolithic Controlled Release dosage Form: Niacin CR Delivery System, presented at AAPS 2002.

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Title	View Full Text
Authors	Michael Patrick Hite ¹ , Stephen Turner ¹ , Catherine Federici ¹ , Reza Fassihi ²
Journal	SCOLR, Inc. AAPS PharmSci
ISSN	Vol. 5, No. 4, Abstract W4122 (2003) 1522-1529
Publisher	American Association of Pharmaceutical Scientists