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Formulation Development and Human In Vitro-In Vivo Correlation for a Novel, Monolithic Controlled-Release Matrix System of High Load and Highly Water-Soluble Drug Niacin

S. Turner,[1] C. Federici,[1] M. Hite,[1] and R. Fassihi[2,*]

[1]Product Development, SCOLR Pharma, Inc., Bellevue, Washington, USA
[2]School of Pharmacy, Temple University, Philadelphia, Pennsylvania, USA

ABSTRACT

Novel, controlled-release formulations for high drug load, highly water soluble compound niacin based on polyethylene oxide (PEO) and hydroxypropylmethyl cellulose (HPMC) matrices were developed and investigated. The effect of sodium bicarbonate as a modulator of swelling, erosion, and drug release and its impact on changes in the kinetics of axial swelling and gel strength were evaluated by textural analysis during dissolution study. The drug release rate from PEO-based matrices was faster and correlated with lower gel strength, greater water uptake, and greater matrix erosion. Slower release rate and greater release duration correlated significantly with greater matrix swelling with negligible matrix erosion for the HPMC-based matrix system. Inclusion of sodium bicarbonate in the polymeric matrix salted out the macromolecules and increased gel strength and gel viscosity, especially in the vicinity of the swelling fronts. An in vivo study in human subjects after administration of the formulations and a commercial product exhibited similar plasma concentrations. For the formulation of interest, the mean drug fraction absorbed by the body was calculated by the Wagner-Nelson technique, and a level A ''in vitro-in vivo correlation'' was observed between the percent released in vitro and percent absorbed in vivo. The developed formulations appear to be robust and easy to manufacture with maximum flexibility with respect to drug dose, polymeric carriers, duration, and kinetics of drug release.

Key Words: Matrix system; Niacin delivery system; IVIVC; Swelling dynamics; Controlled release; Polymeric carriers.

*Correspondence: R. Fassihi, School of Pharmacy, Temple University, 3307 North Broad St., Philadelphia, PA 19140, USA; Fax: (215) 707-3678; E-mail: reza.fassihi@temple.edu.

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INTRODUCTION

The human gastrointestinal (GI) tract is a multi-compartment, complex organ, influencing both the drug delivery system and drug absorption process in a time-site-pH-metabolism-dependent manner. Such complexity is further compounded by the physico-chemical properties of a drug, including solubility, ionization potential, stability, lipophilicity, and permeability across various segments of the GI tract. In the context of controlled-release delivery systems, in addition to the required pharmacokinetic parameters, ideally it is expected that drug has high permeability in the entire GI tract (Class I and II drugs according to the Biopharmaceutical Classification System (BCS).[1] Therefore, the rate-limiting factor controlling drug absorption is exclusively associated with the rate of drug release from the dosage form. Release rate optimization under well-defined hydrodynamics and fluid environment is thus likely to result in a predictable in vivo drug release with possibility for the development of in vitro-in vivo correlations (IVIVCs). In effect, the adjustment of the in vitro release data through formulation changes to match the in vivo data for BCS Class I drugs would provide for the successful establishment of IVIVC as long as the drug release rate is slower than the absorption rate (i.e., the drug must be readily absorbed). It is generally assumed that if the in vivo release-controlling mechanism also controls the in vitro drug release, then it would be possible to establish a Level A ''IVIVC.''[2,3]

Currently, the vast majority of therapeutic agents are administered as oral dosage forms, and this route of administration continues to maintain a dominant position as we move forward into the 21st century. While a large number of preparations deliver drugs in immediate release form that are absorbed in the upper regions of the small intestine, an increasingly important group of products frequently referred to as modified, controlled, or extended-release delivery systems are designed to deliver drug in the entire GI tract but always in a controlled manner. Controlled drug delivery systems are an extremely diverse group in terms of mechanisms used to control drug delivery, complexity of technology, and manufacturability, and includes systems such as film-coated tablets and pellets, Oros®, Ringcap™, Pulsincap™, dry film coating Phoqus™; various matrix technologies utilizing hydrophilic or lipophilic materials with geometric shapes Geomatrix®, Smartrix™, Procise™, Asymatrix™ and wax-based matrix tablets. The common rationale underpinning all these systems is to modulate the magnitude and duration of drug action and to dissociate or modify these from the inherent limitations and properties of the drug molecules.

The number of therapeutic agents available in controlled-release form is expanding rapidly, and so is interest and research activity in oral controlled-release technologies as benefits that can be derived from oral controlled drug delivery are increasingly appreciated by practitioners, patients, and pharmaceutical companies.

Among various technologies available, monolithic matrices continue to be popular because of simplicity, processing technologies required, reproducibility, and stability of the materials and dosage form as well as ease of scale-up operation. The main potential disadvantage of the matrix system is the lack of zero-order release kinetics due to time-dependant changes in drug depleted matrix surface area and diffusional path length.[4] In order to achieve linear (zero-order) release, various strategies that seek to manipulate tablet structure or geometry have been developed (Fassihi and Yang 1998; Colombo et al. 1989).[5–7]

The aim of this study was threefold: 1) develop a hydrophilic matrix-based, controlled-release formulation for high drug load (500 mg), highly soluble and highly permeable compound niacin, a Class I drug according to the Biopharmaceutic Classification System (BCS); 2) evaluate the textural property of the developed formulations during dissolution and determine time-dependent changes in the matrix structure and its relationship to potential GI contraction forces; and 3) establish a Level A ''in vitro-in vivo correlation'' in human subjects by controlling variables that influence the release rate and extent from the developed formulations.

Niacin (nicotinic acid) is a highly water-soluble vitamin, which has been used as a lipid-lowering agent and is rapidly absorbed from the human GI tract. Its peak plasma concentration after a single oral dose is attained within 45 minutes and ranges from 20 to 70 minutes. The plasma elimination half-life of nicotinic acid derived from the terminal (β) phase of the plasma level curves after administration of a readily bioavailable formulation was about 45 minutes. While delayed and slow-release formulations of nicotinic acid were originally developed to reduce or eliminate unwanted effects such as gastrointestinal disturbances, gastric irritation, and flushing of the skin, it was distinctly shown that slow absorption resulted in hypocholesterolemic effect in a well-controlled clinical trial.[8,9] Furthermore, it was shown that inhibition of very low-density lipoprotein (VLDL) and subsequent reduction in LDL levels in the plasma of patients with a variety of

hyperlipoproteinemias were related to prolonged exposure rather than high plasma levels of nicotinic acid.

For Niacin, the high load (500 mg) and high water solubility aspects (1.7% at 25°C; pKa = 4.8; MW = 123.11) are challenging in terms of formulation development, especially using simple matrix technology for once-a-day controlled-release delivery. In this work, a new formulation approach has been adopted

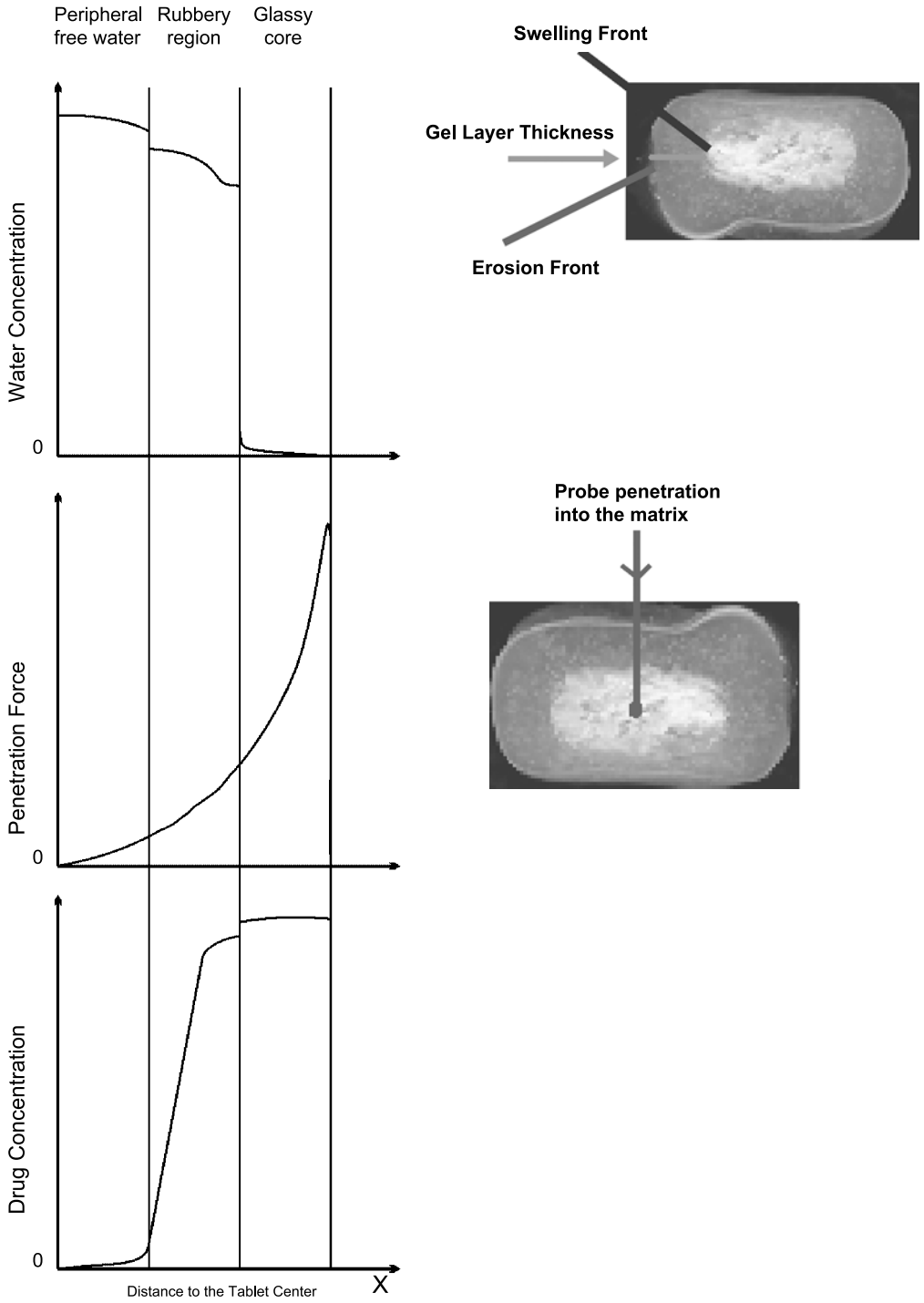

Figure 1. Interrelationship between water concentration gradients, matrix resistance to probe penetration, and changes in drug concentration at different interfaces as swelling progresses. Inset: actual swelling tablets with various fronts and gel layer thickness.

for the containment of the drug in the matrix for controlled delivery over a long time period.[6] From review of the literature it is apparent that the value of hydrophilic, polymer-based matrix systems as carriers for controlled-release delivery is well recognized and increasingly demonstrated by the numerous patents, research papers, and U.S. Food and Drug Administration (FDA)-approved matrix based products.[10–12] In particular, water soluble cellulose ethers [e.g., hydroxypropylmethylcellulose (HPMC) and hydroxypropylcellulose (HPC)], polyethylene oxide, polyvinyl alcohols, carbopol, and polysaccharides such as xanthan gum; chitosan, alginic acid, pectin, and guar gum have been extensively used. Once polymeric matrix tablets are manufactured and exposed to an aqueous environment, simultaneous polymer swelling, gel formation, drug dissolution, drug diffusion, and matrix erosion at both macromolecular and molecular levels will determine drug transport and various concentration gradients within the hydrated matrix as shown in Fig. 1. The interrelationship between overall swelling of the matrix from hydrated tablet surface to the tablet center (glassy core), and water and drug concentration gradients in different regions of the swelling tablet is illustrated along with the actual photographs of the tablet cross sections. The kinetics of swelling, polymer relaxation, drug dissolution, diffusion, transport, particle translocation, and erosion within the swelling and erosion fronts are the key factors in drug release kinetics and have been extensively investigated.[13–21]

MATERIALS AND METHODS

Materials

Granular niacin USP was obtained from Zetapharm (NY), Hydroxypropylmethyl cellulose (HPMC) ''K'' 100 M and polyethylene oxide (PEO) WSRN301 of various molecular weights and viscosity were obtained from Dow Chemicals (Midland, MI and Danbury, CT respectively). Sodium bicarbonate USP was purchased from Natrium products (Cortland, NY), and Stearic acid, NF from Ashland (Santa Ana, CA).

Preparation of Matrix Tablets

Two different formulations containing 500 mg of active niacin were developed for sustained release delivery. For convenience, these formulations will be referred to as formulations A and B. In formulation A, drug was blended with appropriate quantities of HPMC and sodium bicarbonate in a V-shaped blender for 60 minutes, after which stearic acid was added and the mixture blended for an additional 5 minutes. The final blend was fed into a hopper, and caplet-shaped tablets weighing 1263 mg were compressed using appropriate sized punches and die on a single-punch, Manesty type F2 tableting machine. For formulation B, PEO was used in place of HPMC, following the identical procedure. The quantities of polymer and excipients were adjusted in order to achieve a 24-hour extended release, with final tablet weight of 884 mg.

Dissolution Testing

Tablet dissolution was assessed using standard USP 24 Apparatus II equipment. A stirring speed of 50 rpm was used to agitate the dissolution medium, which was kept at 37°C throughout and consisted of deionized water and 0.1 N hydrochloric acid or 0.05 M USP phosphate buffer pH 6.8. The drug concentration was determined automatically every 30 minutes by UV spectrophotometer at 270 nm (Varian Cary 50), using VanKel VK 7000 bath (Cary, NC).

Textural Analysis of Swelling Behavior

The swelling behavior of the formulations was investigated in deionized water after placing individual tablets in the dissolution vessel apparatus 2, at 50 rpm, modified with an inserted mesh below the paddle for full tablet hydration. Individual swollen tablets were removed at different time intervals, weighed, and subjected to texture analysis in the manner described previously.[22] Briefly, the textural profiling was performed by measuring the force-displacement-time profiles associated with the penetration of a 2-mm round end steel probe into the swollen matrix. The data acquisition rate was at 200 points per second, and a trigger force of 0.005 N was selected for actual detection of gel periphery while the probe advanced into the entire sample thickness at a test speed of 0.1 mm per second until the maximum force of 40 N was detected. All measurements were carried out in triplicate.

Water Uptake and Calculation of Percent Swelling

Water uptake and percent of axial swelling for each formulation were determined under conditions identical to those described under textural analysis conditions for the given time points. Water uptake and swelling were determined gravimetrically and by inspection of textural profiles (obtained by measuring

displacement value—distance traveled by probe in mm into the actual swollen matrix) according to the following equations:

$$\%\text{Water uptake(weight gain)} = 100(\text{wet weight} - \text{dry weight})/\text{dry weight}$$

$$\%\text{Axial swelling} = 100(\text{swollen thickness} - \text{original thickness})/\text{original thickness}$$

Two tablets were used per time point. At the predetermined times, individual swollen tablets were carefully lifted with a meshed scoop, drained for 10 seconds, weighed, and analyzed for thickness measurements with a texture analyzer.

In Vivo Study in Humans

Eighteen healthy male volunteer subjects who met all inclusion and exclusion criteria were enrolled and received niacin formulations (tablets). They ranged in age from 18–45 years. All subjects had normal clinical chemistry laboratory values. The study followed the tenets of the declaration of Helsinki promulgated in 1964 and its subsequent revisions. The Institutional Review Board approved the study. All subjects provided written informed consent.

The study consisted of two periods in which 18 subjects were assigned to treatments A, B, or C and received one dose from the corresponding dosage forms with 240 mL of room temperature water. Subjects were fasted overnight for approximately 10 hours prior to dosing and until 4 hours post dose during Period 1. Subjects were discharged after the completion of the 24-hour procedures and were instructed to return 36 hours post dose for a pharmacokinetic blood sample collection. During Period 2, subjects were dosed within 5 minutes after the completion of a standardized meal. Water was allowed ad libitum 2 hours post dose.

This was a single-center, single-blind, single-dose, randomized study to evaluate the pharmacokinetic profile of three formulations of niacin (formulations A and B and an extended-release marketed product) in healthy volunteers. All tablets tested contained 500 mg niacin in a hydrophilic matrix base.

Blood Analysis

Blood samples were collected for pharmacokinetic measurements at predose (0 hour) and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, and 36 hr post dose. Immediate release data were used to obtain the ''system function.'' All subjects successfully completed all phases of the study. Blood samples were analyzed by reversed-phase chromatography using a Synergi Polar RP column maintained at 45°C. Plasma samples containing niacin, nicotinic-d4-acid as internal standard (IS), and heparin as the anticoagulant were precipitated with acetonitrile, and an aliquot of each sample was diluted with 0.2% formic acid. The mobile phase was nebulized using heated nitrogen in a Z-spray source/interface, and the ionized compounds were detected using a tandem quadruple mass spectrometer. Peak height ratios of niacin/IS were calculated and calibration curves constructed. The equations of the calibration curves were then used to interpolate the concentrations of niacin in the samples using their peak height ratios.

Pharmacokinetic Analysis

The area under the plasma concentration-time curve to 36 hr (AUC 0—36) was determined by the trapezoidal rule, and the AUC (0—∞) was determined by the sum of the (AUC 0—36) and the last log-linear concentration divided by the terminal disposition rate constant (β) obtained from a least squares analysis of the terminal log-linear concentration-time data.[23]

The fraction-absorbed calculations employed the Wagner-Nelson Method[24] and were applied to the mean niacin plasma concentration-time data. The percentages absorbed vs. time were calculated with Eq. 1.

$$\%\text{Absorbed} = \{[C(t)/Ke + AUC(0 - t)]/AUC(0 - \infty)\} \times 100 \quad (1)$$

where C (t) = plasma concentration at time t, Ke = the elimination rate constant; AUC (0—t) and AUC (0—∞) = area under the curve from zero to time t and infinity, respectively. No statistical comparison was done on any of the pharmacokinetic parameters because this was a preliminary study to evaluate the performance of the prototype formulation of a controlled-release matrix system.

RESULTS AND DISCUSSION

As depicted in Fig. 1, during the swelling and drug release, water gradually penetrates into the exterior of

the matrix, drastically lowering the glass transition temperature (Tg) of the polymer and resulting in peripheral polymer swelling and formation of a rubbery region next to the glassy region with sharp fronts between the interfaces. Various fronts and gel boundary during matrix swelling are shown in Fig. 1 (see insets). While the drug concentration gradient rapidly decreases between the swelling and erosion fronts, it remains relatively constant in the glassy region. The overall textural behavior of the swelling matrix and demonstration of resistance to probe penetration into the matrix are also consistent with water concentration profiles.[16,25] To control the release rate of a highly water-soluble and high drug load tablet a large amount of polymer would be required for the matrix formation, and often, size of the dosage form can become unacceptably large. A further problem with highly water-soluble drugs is that of significant and variable ''burst'' often observed in the initial portion of release profiles. In this study, such limitations in the design of the formulations were taken into consideration. In order to reduce the overall size of the tablet and polymer content inclusion of specific electrolytes, namely sodium bicarbonate, into the polymeric matrix, composition was considered. We have shown that by increasing the ionic strength of the matrix composition it is possible to cause shrinkage of the polymeric chains and thus control the textural characteristics, chain expansion, swelling rate, and erosion kinetics.[6,22,26,27] Through such manipulations the rate of drug release and various fronts within the hydrating matrix may be synchronized in order to achieve a desirable release rate and duration. The original tablet sizes as well as the photographs and cross sections of both formulations A and B at two different time intervals are shown in Fig. 2. Figure 3 demonstrates axial force-displacement profiles determined at different time intervals for matrix formulations A and B, respectively. These profiles indicate that depending on the composition and polymers used, the swelling dynamics would change and associated release mechanisms would be impacted. As shown in Fig. 3, in the case of the PEO matrix, swelling is relatively rapid up to 4 hours; however, as time progresses, significant erosion is taking place as the displacement (distance traveled by the probe into the gel) values are consistently reduced (see profiles for 6, 14, and 16 hr in Fig. 3). In the HPMC-based matrix, swelling of the matrix continuously increases as time progresses, with some resistance to probe penetration during the first 6 hours, indicating greater gel strength and stiffer textural characteristics with minimal erosion. The overall swelling and textural behaviors of the profiles shown in Fig. 3 also indicate that in the late time period gel

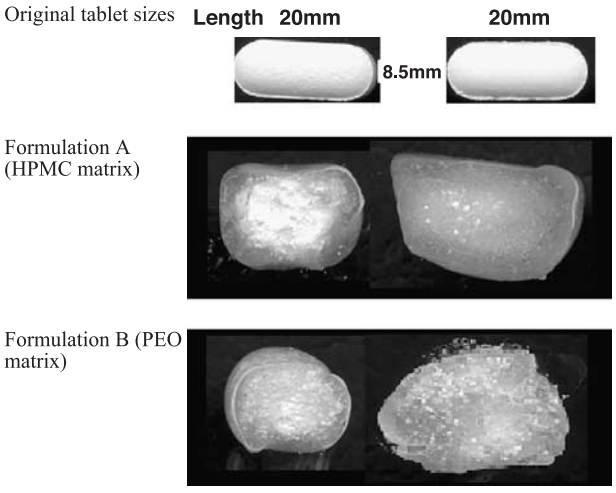

Figure 2. Cross sections of swollen tablets after 3 hours (Left panel) and 18 hours (right panel) in deionized water, apparatus 2, 50 rpm, 37°C.

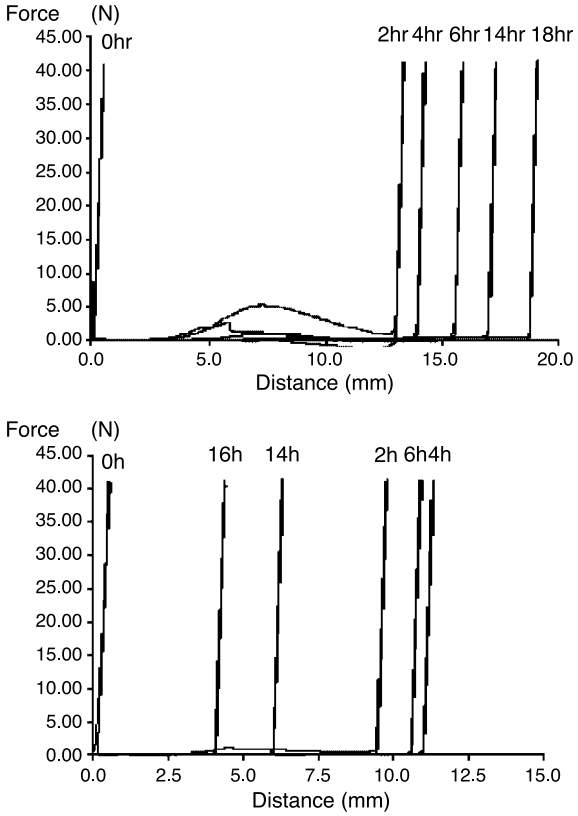

Figure 3. Force-displacement profiles for formulation A (upper panel) and formulation B (lower panel) at different time points.

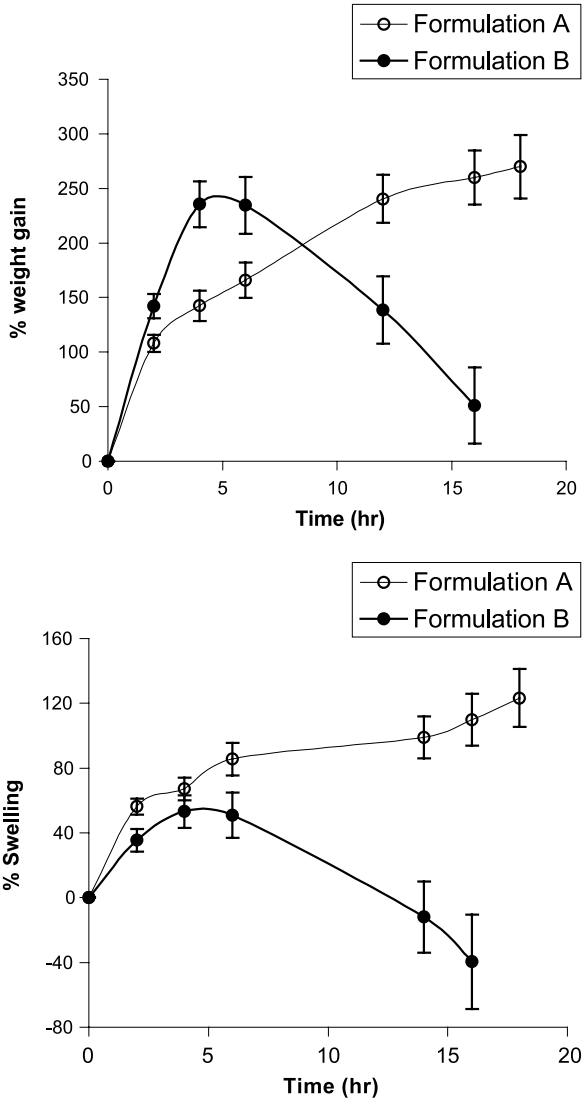

Figure 4. Percent swelling vs. time for formulations A and B.

resistance to probe penetration is well below 1 Newton. It has been reported that the destructive contraction forces of the human stomach and small intestine on a tablet as it passes through the GI tract is $\leq$2 N and $\leq$1.2 N, respectively.[28] Therefore, it is noteworthy that the textural characteristics of the developed formulations are well suited for the realistic peristaltic forces generated by the GI tract wall. This provides assurances that these matrix systems are texturally strong and will resist rapid breakdown and possible drug burst within the normal physiological motility of the GI tract. In fact, these systems may provide greater distal delivery of the drug as the matrix structure is considerably weaker after many hours of swelling in the lower GI segments. This may result in complete delivery of the drug with potential for greater predictability between in vitro and in vivo drug release. This aspect is currently under investigation. Figure 4 illustrates the corresponding profiles for percent swelling and weight gain for formulations A and B at different time points during dissolution. The loss of percent weight gain and loss of percent swelling vs. time is significant for formulation B (PEO-based matrix) in Fig. 4, and this is consistent with measured displacement values and textural properties (see Fig. 3). The PEO tends to swell and erode at a much faster rate relative to HPMC used in these formulations.

In vitro dissolution studies are routinely performed to ensure process and manufacturing quality and product standard. However, considerable effort has gone into setting dissolution specifications that are more meaningful and could directly impact the relationship between in vivo and in vitro characteristics known as IVIVC. This has constituted a change in the regulatory perspective of dissolution and a considerable widening of the earlier role of dissolution testing. Thus, IVIVC can be regarded as an ideal approach for relating drug release/dissolution in vitro to the performance of the drug in vivo.[1,2]

Figure 5 shows mean dissolution profiles of the developed formulations A and B as well as the marketed product. Release profiles of the developed formulations show that a PEO-based matrix releases its content completely within 16 to 18 hours while an HPMC matrix releases its content at a slower rate during a 24-hour period. The marketed product demonstrated a slower release rate relative to formulation A while it showed faster release rate relative to formulation B.

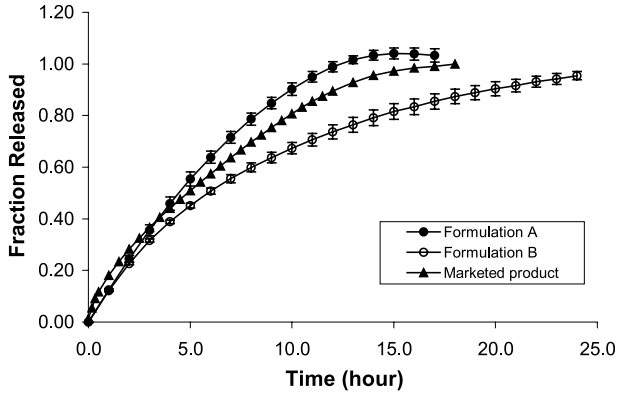

Figure 5. Dissolution profiles for different formulations in phosphate buffer pH 6.8 using apparatus 2, USP 24 at 50 rpm (N = 6).

Figures 6 and 7 demonstrate mean plasma profiles and relative bioavailability of the developed formulations and the commercial product under both fasted and fed conditions. Mean niacin plasma concentrations throughout 36 hr for test and reference (marketed product) formulations were essentially following a similar trend with comparable plasma levels over the entire time as shown in the figures. The mean ratio of AUCs for developed formulations A and B vs. the reference (marketed product; AUC = 175.2 ng hr/mL) formulation under fasted conditions was 1.29 and 0.89, respectively. Higher relative bioavailability of 1.29

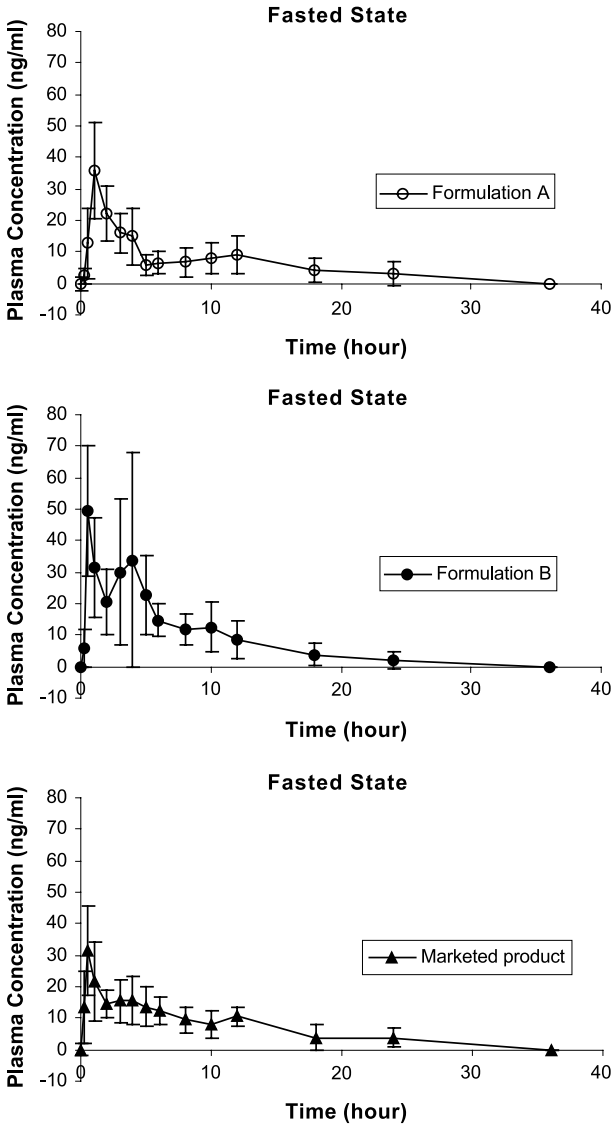

Figure 6. Mean plasma concentration time profiles for formulations A, B, and a marketed product containing 500 mg niacin under fasted conditions.

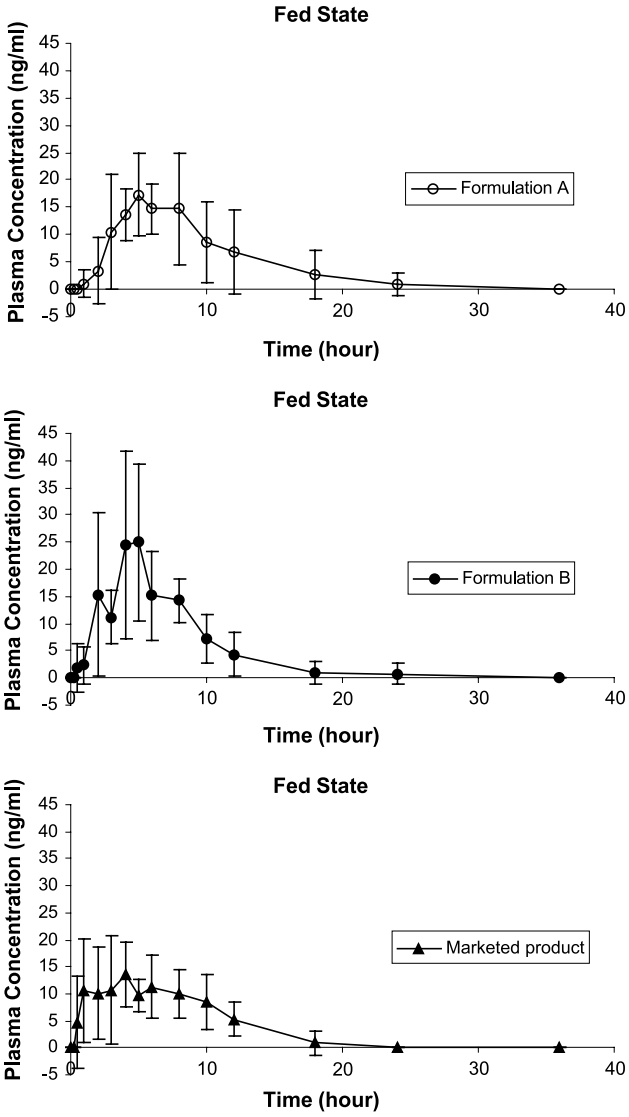

Figure 7. Mean plasma concentration time profiles for formulations A, B, and a marketed product containing 500 mg niacin under fed conditions.

for formulation A is related to faster drug release rate, while the opposite is true for formulation B, which demonstrated slower in vitro release rate. Due to the limited number of subjects, no attempt was made to do detailed statistical analysis at this point, the study was a feasibility evaluation only, intented to demonstrate the IVIVC potential for the hydrophilic-based matrix systems having different release durations and rates.

Figure 8 represents percent absorbed in vivo vs. time for formulation B after applying the Wagner-Nelson equation and deconvolution of mean plasma

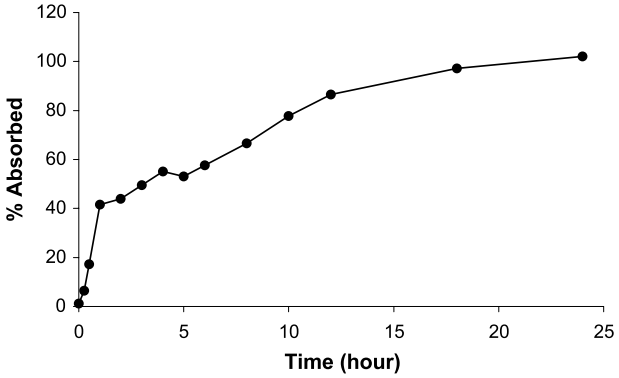

Figure 8. Percent in vivo absorbed vs. time for formulation A after deconvolution of plasma concentration time profiles according to the Wagner-Nelson method.

data. From the figure it is apparent that an initial burst commonly associated with monolithic matrix systems results in an initial rapid absorption followed by a prolonged and slow absorption consistent with actual in vitro release seen in the dissolution profiles.

An attempt was made to perform a ''level A'' IVIVC, which shows that the in vivo drug input rate of the dosage form matches 1:1 with the in vitro drug release rate for formulation B. The IVIVC is thought to be the most useful relationship for predicting in vivo performance from dissolution data, for establishing the ''bioequivalence'' of minor formulations and manufacturing site changes without having to do a full scale human bioequivalence study. The relation between the in vitro dissolution data and in vivo pharmacokinetic data was examined by plotting the percent drug dissolved in vitro after 0.5, 2, 3, 4, 5, 6, 8, 10, 12 and 18 hours vs. percent absorbed in vivo at equivalent time intervals. Level A ''IVIVC'' with relatively high correlation coefficient was obtained (see Fig. 9).

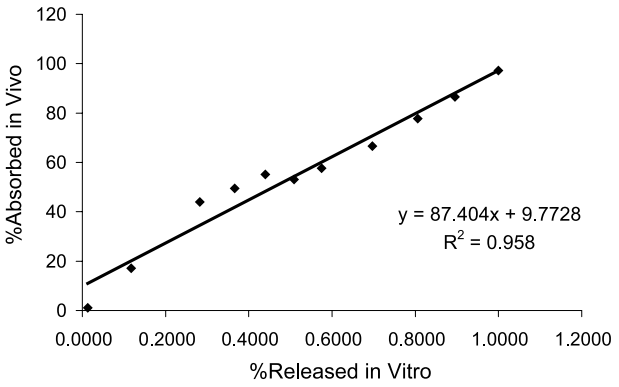

Figure 9. Level A, IVIVC for formulation A.

This observation further adds credibility to the use of dissolution profiles and release kinetics as a means of predicting absorption kinetics as well as overall plasma concentration-time profiles for the formulations. The development of successful IVIVCs have been reported for a number of formulations, including carbamazepine, diltiazem, metoprolol, acetaminophen, theophylline, and other drugs.[5,29–31] Drug release for niacin (BCS-Class I) HPMC-based matrix appears to be controlled by interactions of water with the polymer and drug diffusion through the swollen gel. Dosage form does not appear to be sensitive to erosion and changing pH conditions throughout the GI tract. This insensitivity to erosion is consistent with force-displacement profiles shown in Fig. 3 for formulation B.

CONCLUSION

From the data presented it is evident that experimental formulations A and B have demonstrated robustness and insensitivity to the hydrodynamics that prevails within the GI tract, resulting in predictable in vivo plasma concentrations consistent with dissolution profiles. The study further shows that in vitro dissolution data are a good predictor of in vivo fraction absorbed for niacin and supports the general use of in vitro dissolution data to predict in vivo disposition for highly soluble and highly permeable drugs (i.e., BCS Class I drugs) not only from immediate-release tablets but also from modified-release dosage forms. The designed niacin formulations appear to provide a dosage form with maximum flexibility in terms of release rate, release duration, in vivo predictability, robustness, ease of production, and scale up. Furthermore, developed formulation B demonstrated bioavailability comparable to that of a marketed product under fasted conditions. The designed direct compression monolithic formulations have unique properties and are competitively superior to other approaches where more complicated, expensive, multistep technologies are used. It is believed that simple, monolithic formulations based on hydrophilic polymers, inclusion of electrolytes, internal modification of gel strength, swelling and erosion kinetics, and conventional technology employed has favorable technical and regulatory position with excellent commercialization potential.

ACKNOWLEDGMENTS

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