

W4203 *In Vivo - In Vitro* correlation (IVIVC) of a novel monolithic controlled release dosage form: Niacin CR Delivery System

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Introduction

- Nicotinic acid (Niacin) 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 minutes to 70 minutes. The plasma elimination half-life of nicotinic acid derived from terminal (b) phase of the plasma level curves after administration of a readily bioavailable formulations 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 slowly absorbed pattern resulted in hypocholesterolemic effect in a well controlled clinical trial (Weiner 1979; Gugler 1978). Furthermore it was shown that inhibition of VLDL and subsequent reduction in LDL levels in the plasma of patients with a variety of hyperlipoproteinaemias were related to prolonged exposure rather than high plasma levels of nicotinic acid.

Purpose

- To design, develop and manufacture a controlled release delivery system of Niacin for prolonged release period (18-24 hours) using a patented technology (US patent # 6090411).
- To examine *in-vivo - in-vitro* relationships among the two formulations developed as well as to determine bioavailability of the formulations relative to the reference formulation Niaspan[®] 500mg.
- To perform a randomized, two period crossover study to evaluate the effects of fasted and fed on the pharmacokinetic profile of single dose of two different controlled release niacin formulations in comparison with 500mg Niaspan[®] extended release tablet in healthy male volunteers

Study design and clinical protocol

This is a single center, single blind, single dose, randomized study to evaluate the Pharmacokinetic profile of 3 formulations of Niacin in Healthy Volunteers.

- The study consists of two period in which 18 subjects were assigned to treatment A, B or C and received one dose from the corresponding treatment group with 240 ml of room temperature water. Subjects were fasted overnight for approximately 10 hours prior to dosing and until four 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 at libitum 2 hours post- dose.

Study Design

Treatment Assignment	Period 1 Fasted	Period 2 Test Meal
A (reference)	500 mg NIASPAN [®] , extended release formulation	500 mg NIASPAN [®] , extended release formulation
B (test)	500 mg niacin 18 hour controlled release formulation	500 mg niacin 18 hour CR formulation
C (test)	500 mg niacin 24 hour controlled release formulation	500 mg niacin 24 hour CR formulation

Subjects:

- 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 study was approved by the Institutional Review Board. All subjects provided written informed consent.
- Blood sampling:
 - Blood samples were collected for Pharmacokinetic measurements at pre-dose (0 hour) and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24 and 36 hrs post dose. Immediate release data were used to obtain the "system function".

Tablet formulations, dissolution testing and *In Vivo-In Vitro* relationship:

- The method of manufacturing and formulation composition for pilot batch and scale up manufacturing is described in detail elsewhere (Hite, M., Federici, C., Turner, S., Fassihi, R. "Development of a high drug load monolithic controlled release oral delivery system for niacin: A novel approach." AAPSPHarmSci Vol. 3, No. 3, pages (2001))
- The *in vitro* dissolution testing employed the USP paddle method at 50 rpm with 900 ml of either HCl buffer pH 2.0 or phosphate buffer pH 6.8. Six tablets of each product were tested, and samples of the dissolution media were removed via an automated sampling system (Vankel VK7000, peristaltic pump & Varian Cary 50 spectrophotometer).

Data Analysis

- The area under the plasma concentration-time curve to 36 hr (AUC₀₋₃₆) was determined by the trapezoidal rule, and the AUC (0 - ∞) was determined by the sum of the (AUC₀₋₃₆) and the last log-linear concentration divided by the terminal disposition rate constant (λ) obtained from a least squares analysis of the terminal log-linear concentration-time data (Gibaldi and Perrier 1975).
- The fraction absorbed calculations employed the

Wagner-Nelson Method (Wagner 1975), applied to the mean Niacin plasma concentration-time data, and the percentages absorbed versus time were calculated with equation 1.

- $\% \text{ Absorbed} = \left\{ \frac{C(t)}{K_e} + \frac{AUC(0-t)}{AUC(0-\infty)} \right\} \times 100$
- Ct is plasma concentration at time t, Ke is the elimination rate constant for an IR tablet; AUC (0—t) and AUC (0 - ∞) represent area under the curve from zero to time t and infinity respectively.

Results and Discussion

- All subjects successfully completed all phases of the study.
- Mean dissolution profiles for Niaspan 500mg and Niacin-24hCR formulation and their corresponding mean plasma concentrations are shown in Figures 1 and 2.
- Mean and individual Niacin plasma concentrations through 36 hr for reference product and a 24 hour release formulation were essentially identical among the two products with similar plasma levels over entire sampling times. Mean ratio of AUC for test (Niacin formulation) versus reference(Niaspan) is given in the Figure and indicates that developed formulation has similar bioavailability (F_{relative} = 0.89) to the marketed product.
- Mean plasma profiles for fed versus fasted in a two period study for Niaspan and two formulations of Niacin (Niacin 18h-CR and 24h-CR) are shown in Figure 3. Inspection of the profiles reveal similarity of the over all plasma concentration-times. Note that under fed conditions as expected the plasma concentration levels are significantly lower for all the formulations.

Development of Niacin CR 500mg tablets

The *in vitro* dissolution testing for Niaspan 500mg and developed Niacin formulation 500mg The *in vitro* dissolution testing employed the USP paddle method at 75 rpm with 900 ml of either HCl buffer pH 2.0 or phosphate buffer pH 6.8. Six tablets of each product were tested, and samples of the dissolution media were removed via an automated sampling system (N= 6).

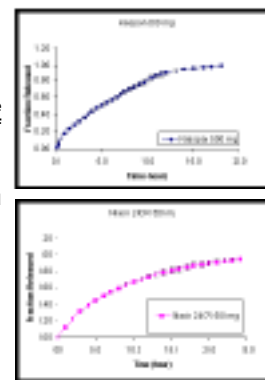


Figure 1.

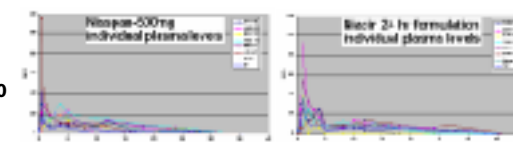


Figure 2. Single blind, single dose, randomized study to evaluate the Pharmacokinetic profile of 2 formulations of Niacin in 12 Healthy Volunteers under fasted conditions

Figure 3.

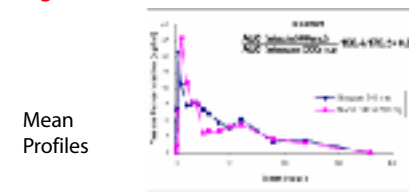


Figure 3.

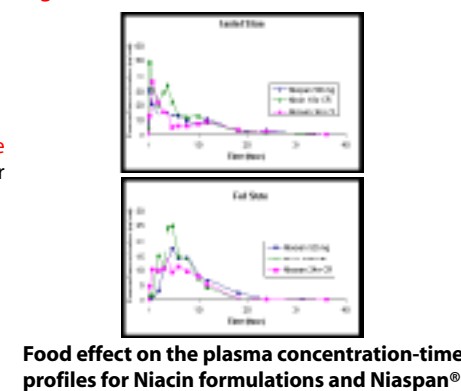


Figure 5. Food effect on the plasma concentration-time profiles for Niacin formulations and Niaspan[®].

In Vitro-In Vivo relationships

- 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 constitute change in regulatory perspective of dissolution and a considerable widening of 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*.
- Using mean data for Niacin 24hCR formulation in Figure 2 and applying Wagner-Nelson equation, plasma data were de-convoluted. The percent *in vivo* absorbed values against time after de-convolution are

presented in Figure 4.

Percent absorbed versus time profile for Niacin 24hCR tablet

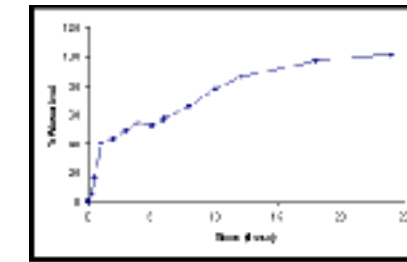


Figure 4.

Results and discussion

Figure 5 illustrates an attempt at a level A, 1:1, *in vivo - in vitro* correlation, for Niacin 24h-CR formulation. The IVIVC is thought to be the most useful relationship for predicting *in vivo* performance from dissolution data. It is also noteworthy to recognize the existence of an excellent association between percent drug absorbed *in vivo* and percent drug dissolved *in vitro* in this study. This observation further adds credibility to the use of dissolution profiles and release kinetics as a means to predict absorption kinetics as well as overall plasma concentration profiles. This aspect is clearly demonstrated in both Figures 5 and 6 showing the release patterns for *in vitro* and corresponding *in vivo* absorption. From the data it is evident that formulations developed (Niacin 18hCR and 24hCR) have demonstrated robustness and insensitivity to the hydrodynamics that prevails within GI tract thus resulting in a predictable *in vivo* plasma concentrations.

Level A, 1:1, in vivo-in vitro correlation for Niacin delivery system

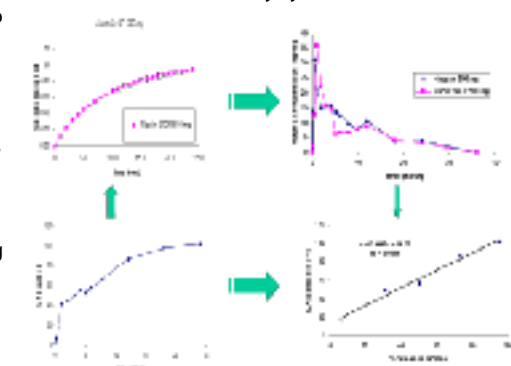


Figure 5.

Relationship between *in-vitro* dissolution profiles for the developed formulations (Niacin 18hCR and 24hCR) and their corresponding plasma profiles under fasted conditions.

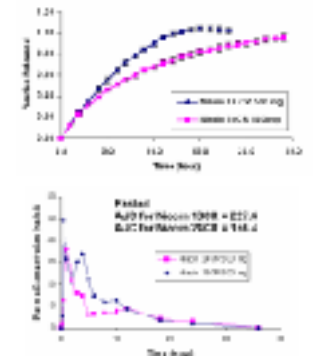


Figure 6.

Conclusion

- 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, 3, 6, 12 and 24 hours versus percent absorbed *in vivo* data derived from Figure 4 at equivalent time intervals. Level "A" IVIVC with high correlation coefficient was obtained.
- The designed Niacin formulations appear to provide a dosage form with maximum flexibility in terms of release duration, *in vivo* predictability, robustness and ease of production.
- Developed formulations demonstrated comparable bioavailability to that of a marketed product under both fasted and fed conditions.
- The patented formulation has unique property and is competitively superior to other technologies in drug delivery domain.
- Formulation approach and technology employed has favorable technical and regulatory position with excellent commercialization potential.

References

- Gugler R., Clinical Pharmacok. 3:425-439 (1978)
- Weiner M., Drug Metabolism Reviews, 9(1), 99-106 (1979).
- US Patent # 6,090,411

Citation:

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