Dissolution Profiles of Lanoxin Tablets in Media Supplemented with Soluble and Insoluble Forms of Fiber

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Abstract: Lanoxin (digoxin) is available as 125 µg or 250 µg tablets for oral administration used to treat heart failure and arrhythmias. The objective of this study was to develop and investigate a comparative dissolution study performed on lanoxin tablets in presence of insoluble or soluble forms of fiber. This study was performed to understand possible influence of fiber (psyillium husk, wheat dextrin, or powdered cellulose) on dissolution of lanoxin in physiological relevant temperature and pH. Dissolution testing was performed using a USP dissolution testing apparatus II paddle rotating at 100 r/min, in 600 mL simulated gastric fluid (pH 1.2) which was maintained at (37 +/- 0.5 °C). A floating cellulose dialysis tube was used to collect sampling fractions. Quantification was performed using a developed and validated high performance liquid chromatographic (HPLC) method. Results indicate that the presence of psyillium husk in the dissolution medium hindered digoxin release. Statistical results reveal that the release profiles of digoxin in presence of wheat dextrin or powdered cellulose did not influence drug release.

Keywords: Digoxin, psyillium husk, dextrin, cellulose, dissolution hinderance.

INTRODUCTION

In order for any drug to be absorbed and generate a desired therapeutic effect, it must first dissolve into solution and be absorbed into systemic circulation, prior to being transported to the site of action. However, co-administration of a drug with food may alter the rate and extent of absorption depending on the formulation food composition co-mixture [1]. Therefore, in order to successfully illustrate this phenomenon, it is essential to duplicate conditions as closely as possible extant in the gastrointestinal tract post administration of any tablet formulation. In practice, the interaction between a drug product and food is quite difficult to model possible *in vitro* [2]. Dissolution testing is used as the standardized test providing quality control data [3], with respect to oral solid dosage forms, for pharmaceutical companies. Additionally, *in vitro* dissolution tests are also useful for research and development purposes, and in particular when investigating the manufacturing process [4]. Using universally accepted methodology, this study attempts to provide additional data to help identify possible dietary interactions between fiber and a model drug Lanoxin®. It has been reported by Reppas et al that the consumption of water soluble fibers can increase gastrointestinal viscosity in canine studies [5]. For example, Reppas et al reported that oral formulations prepared with 2 or 5% methycellulose solutions and that after oral administration, rate and extent of absorption of nitrofuranontoin decreased significantly [5]. However, the absorption of another model drug, riboflavin and thiamine was not influenced in the presence of a viscosity enhancing agent. However, the extent at which this is known has not been evaluated to date. Ultimately a better understanding of the effect of food on drugs may enable pharmaceutical companies and regulatory firms to better predict drug performance, this could enable physicians and pharmacists to better educate and pass along safer directions for prescription medications taken by patients. Specifically, the research presented in this paper investigates the possible effect of insoluble and soluble forms of fiber on the dissolution rate of Lanoxin® tablets *in vitro.*

MATERIALS & METHODS

Chemicals and Excipients, and Dietary Components

HPLC-rated acetonitrile, HPLC-rated water, HPLC-rated methanol, and digoxin (analytical) were purchased from Sigma-Aldrich (St. Louis, MO). Lanoxin tablets (Lot#A67953), manufactured for GlaxoSmithKline by DSM Pharmaceuticals, Inc. (Greenville, NC), containing 250 mcg if digoxin was purchased from the University of Texas at Austin pharmacy. Psyillium husk (Metamucil®) was manufactured by Procter & Gamble Co (Cincinnati, OH). Wheat dextrin (Benefiber®) was manufactured by Novartis Consumer Health, Inc. (Parsippany, NJ). Powdered cellulose (UniFiber®) was manufactured by Dr.Natura (Fort Mill, SC). Simulated gastric fluid (SGF, 0.1 M hydrochloride acid, pH 1.2) was prepared by adding 2 g sodium chloride (Fisher Scientific; Pittsburg,

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PA) and 7 mL of hydrochloride acid (HCl; Sigma-Aldrich; St. Louis, MO).All solvent were prepared using de-ionized (Millipore Milli-Q; Billerica, MA) and filtered (0.22 µm) water.

Equipment

In vitro dissolution testing of lanoxin tablets was performed using the standard USP dissolution apparatus II paddle method (Varian VK *7010*; Varian, Inc., Santa Clara, CA). Data analysis was performed using an Agilent high performance liquid chromatography (HPLC) with an Agilent ZORBAX Eclipse Plus C_{18} column (4.6 × 150 mm, 5 µm; Santa Clara, CA). The mobile phase was water-acetone (72:28, v/v). The flow rate was 1.1 mL/min, and 20 min for the retention time. To detect and quantify peak concentrations of digoxin, a wavelength 210 nm was used.

In vitro Simulation of *In vivo* Conditions

To evaluate the effects of supplemental fiber on the rate and extent of digoxin release, pre-determined servings of psyillium husk, wheat dextrin, or powdered cellulose were added to dissolution medium. The standard USP paddle method (USP 24) was used to perform dissolution tests of lanoxin tablets at 100 rpm. To simulate *in vivo* conditions, the dissolution apparatus was maintained at 37 °C, with 600 mL of supplemented fiber media. Aliquots of dissolution media (3 mL) were collected from the dissolution vessel at intervals of 0, 5, 15, 25, 35, 45, and 60 minutes. In effort to minimize sampling interference with the supplemented fibers, cellulose ester dialysis tubes (MWC 50,000, Spectrum Chemicals & Laboratory; New Brunswick, NJ) were modified with floating membranes, and mounted to the dissolution vessel top cover. Here, 1 mL aliquots were taken from the cellulose ester dialysis tube and replaced with fresh dissolution media.

2.4. Evaluation of Bulk Viscosity and pH in Dissolution Release Media

Prior to the dissolution experiment, the bulk viscosity and pH of the dissolution medium was evaluated. All measurements were performed in triplicate, and expressed as an average +/- standard deviation.

It is well known that inherent or induced gastrointestinal viscosity may influence drug release or absorption, as seen *in vitro* and *in vivo* [5, 6].

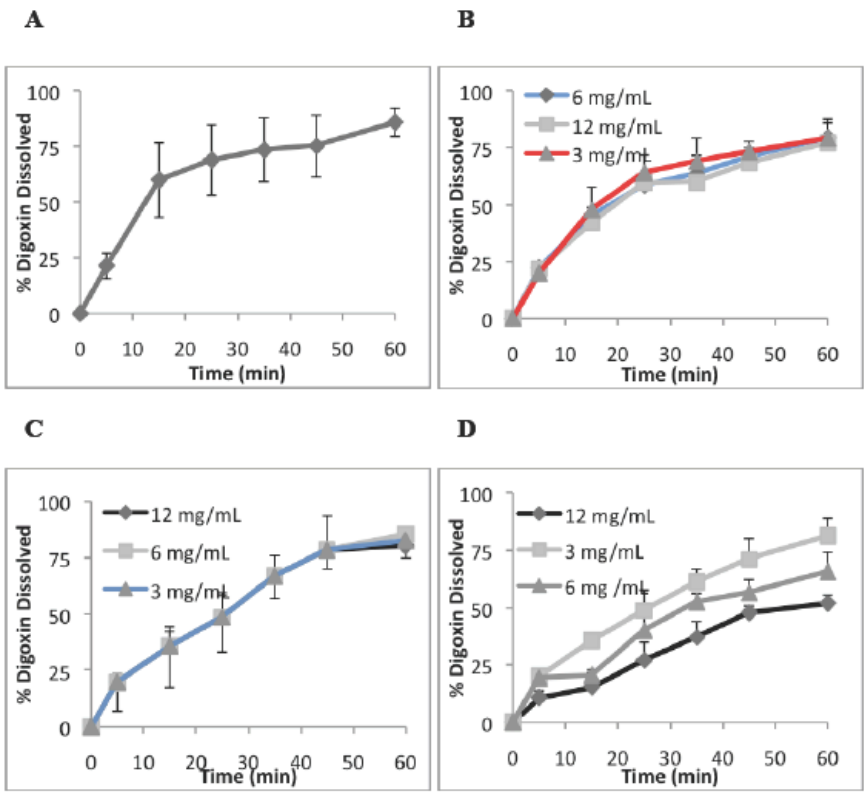

Figure 1: In vitro dissolution of lanoxin tablets in simulated gastric fluid (pH 1.2) supplemeneted with various amounts of fiber. (A) no fiber, (B) Wheat dextrin, (C) Powdered cellulose, and (D) Psyillium husk. Data shown are mean ± S.D. (n = 3).

Therefore, assessing inherent viscosities of each dissolution medium containing supplemented fibers during the dissolution test is of value to reveal probable (if any) rate limiting release characteristics. Pre-determined amounts of soluble or insoluble fiber (12.0, 6.0, 3.0, and 1.5 mg/mL) were dissolved in 600 mL of dissolution medium (pH 1.2) at 37 °C. The viscosity of each was determined using a Brookfield Viscometer (DV-II+ Pro; Brookfield Engineering Laboratories, Inc., Middleboro, MA). Sampling intervals were 0, 5, 15, 30, 45, 60, 75, and 90 minutes. All determinations were performed in triplicates, and expressed as an average +/- standard deviation.

Statistical Analysis

Statistical analyses were completed by performing analysis of variance (ANOVA) followed by Fisher's protected least significant procedure. A p-value of ≤ 0.05 was considered significant

RESULTS AND DISCUSSION

It is well acknowledged that the oral administration of drugs in combination with food may influence both the rate and extent of dissolution [1]. Current *in vitro* dissolution methodologies are designed for quality control purposes, and do not reflect the complexity of gastrointestinal physiology a formulation may experience *in vivo* [7]. Herein, we investigated the possible effects of dissolution media supplemented with different forms of soluble or insoluble fibers, and the resultant effect it may have on lanoxin dissolution in simulated gastric fluid. It was observed (Figure **1**) when dissolution media prepared with psyillium husk (1.5-12 mg/mL), experimental differences between *in vitro* dissolution profiles of lanoxin in comparison to wheat dextrin (1.5-12 mg/mL) and powdered cellulose (1.5-12 mg/mL) were seen (Figure **2**). For example, after 15 min there was a statistical difference seen between the initial rates of dissolution than that of the control (simulated gastric fluid), wheat dextrin, and powdered cellulose (p = 0. 0.014, 0.005, and 0.019, respectively). In fact, during the first 35 minutes, roughly 28% release of digoxin was detected. At 35 minutes after starting the dissolution, the percent of digoxin observed in media containing wheat dextrin or powdered cellulose reached as high as 66% (p = 0.011 and 0.012, respectively).

The dissolution rate and extent of digoxin was not seen to be dependent upon the concentration in medium supplemented with either wheat dextrin or powdered cellulose (Figure **1**). On the contrary, digoxin rate of dissolution in medium containing psyillium husk clearly illustrates concentration dependence. This can

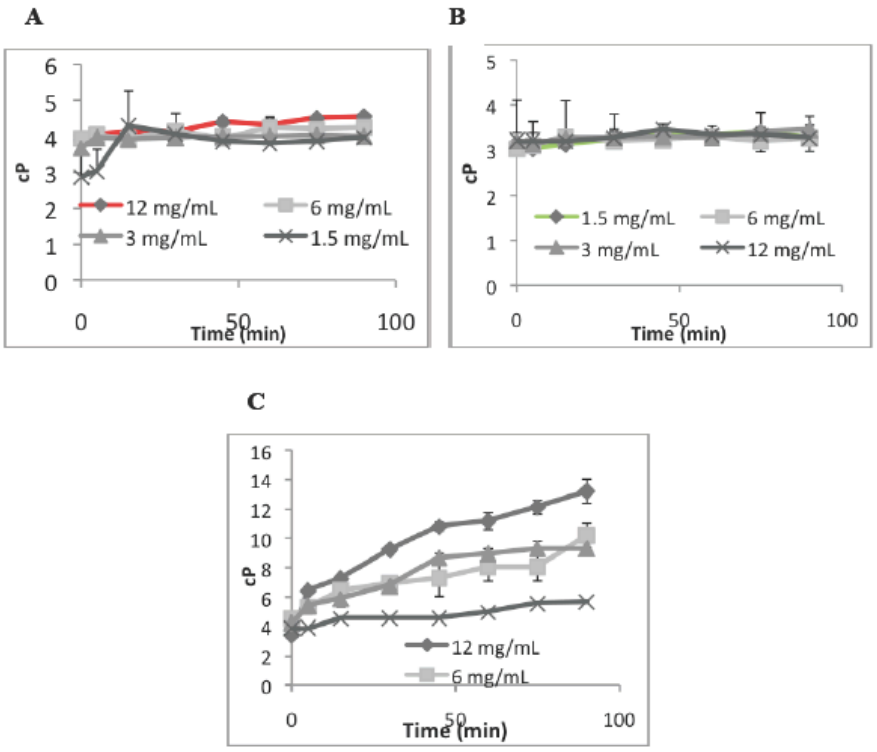

Figure 2: Rhealogical profiles of in vitro dissolution medias supplemented with various amounts and types of fiber. (A) Wheat dextrin, (B) Powdered cellulose, and (C) Psyillium husk. Data shown are mean ± S.D. (n = 3).

be further interpreted by the observed trend in viscosity shown in Figure **2C**, where bulk viscosity of the medium is positively correlated with concentration and time. Dissolution of digoxin in media containing wheat dextrin or powdered cellulose was not influenced by the inherent viscosity as well as concentration (Figure **2A**, **B**). Even at the highest concentration of wheat dextrin or powdered cellulose investigated, the percent of drug dissolved was recorded at as high values as 70-80 % (Figure **1B** & **C**). In addition to viscosity inducing effects of food, a meal may induce a change in pH (buffering capacity), which could hypothetically alter drug solubility and dissolution characteristics. Therefore, it's noteworthy to mention no oscillation in pH was observed by the addition of wheat dextrin, powdered cellulose, or psyillium husk into the 37 °C dissolution media at 30 minutes (p = 0.8, 0.10, and 0.7, as shown in Table **1**, respectively.

Table 1: Initial and Post pH of Dissolution Media

Time (Min)	Psyillium Husk	Wheat Dextrin	Powdered Cellulose
0	1.23 ± 0.015	1.21 ± 0.015	1.10 ± 0.019
30	1.24 ± 0.04	1.26 ± 0.037	1.15 ± 0.043

CONCLUSION

Herein, we demonstrate that the rate of dissolution or drug release in lanoxin tablets can be influenced by medium supplemented with psyillium husk. Psyillium husk may be acting as a viscosity enhancer, or drug release barrier due to the observed rate controlling nature in drug dissolution. Further studies are warranted in order to elucidate more complete and detailed release characteristics of lanoxin in mediums supplemented with insoluble and soluble fibers.

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