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Gastroretentive Accordion Pill: Enhancement of riboflavin bioavailability in humans

Leonid Kagan [a], Noa Lapidot [b], Michel Afargan [b], David Kirmayer [b], Eytan Moor [a,b], Yael Mardor [c], Michael Friedman [a], Amnon Hoffman [a,*]

[a] Department of Pharmaceutics, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, POB 12065, Jerusalem 91120, Israel
[b] Intec Pharma Ltd., POB 45219, Jerusalem 91450, Israel
[c] Sheba Medical Center, Tel Hashomer 52621 , Israel

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Abstract

The purpose of this study was to evaluate the ability of the Accordion Pill™ (AP), a novel controlled release gastroretentive unfolding dosage form (DF), to increase the bioavailability of riboflavin (RF) in humans. Three formulations containing 75 mg of RF and differing in release rate (immediate release (IR) capsule, AP#1, and AP#2) were administered with a low-calorie meal. Gastric residence time (GRT) of the AP was assessed by magnetic resonance imaging. Serial blood and urine samples were taken and assayed for RF. The AP demonstrated prolonged (up to 10.5 h) GRT in humans. Significant elevation in RF bioavailability (209±37%, mean±S.E.) was achieved by the AP#1 in comparison to the IR capsule. A correlation was established between the in-vitro release rates from DF and bioavailability of RF in humans, and it was modeled taking into account the saturable nature of RF absorption transport and its narrow absorption window (NAW) in the upper gastro-intestinal tract. It is anticipated that the AP will provide a valuable pharmaceutical solution to enhance therapy with NAW drugs.

Keywords: Pharmacokinetics; Controlled release; Saturable absorption; Narrow absorption window; Gastric residence time

1. Introduction

Despite considerable efforts invested by the pharmaceutical industry and academic researchers, an effective controlled release gastroretentive dosage form (CR-GRDF) is still an unmet need. This dosage form (DF) is intended to be retained in the stomach for a prolonged time period while releasing its content in a continuous and controlled manner. A CR-GRDF can be especially advantageous for optimizing systemic treatment with drugs characterized by a "narrow absorption window" (i.e., negligible colonic absorption) [1–6] and for drugs applied for local treatment of upper gastro-intestinal (GI) tract ailments. The principal challenge in a GRDF development is to overcome the normal physiology of the stomach to clear its content (either by continuous propulsive forces in the fed state or by the "housekeeper waves" occurring every 1–2 h in the fasted state [7]).

Several approaches have been tried to provide gastric retentivity, including bioadhesion to gastric mucosa, buoyancy over gastric content, high-density units, co-administration with pharmacological agents that slow gastric motility, and expansion to large dimension following oral administration [4,5,8,9]. A number of these techniques were reported to be successful in various in-vitro tests [10–13] or in preclinical investigations, particularly demonstrating prolonged retention in a dog model [1,14,15]. However, accumulative experience in this field confirmed that the dog model might lead to a significant overestimation of the gastric retentive properties of a GRDF. Therefore, only human trials can give a reliable estimate of gastroretentivity [14,16,17].

There are several reports on GRDFs tested in humans; however, in most cases, a control group of non-GRDF taken under the same conditions is lacking. Thus, it is difficult to distinguish between prolonged gastric residence time (GRT) provided by physiologic conditions, such as a calorie content of the food, and the GRT prolongation produced by the GRDF per se. Some GRDF systems were shown to be effective only when administered in the fed state,

* Corresponding author. Tel.: +972 2 675 7014; fax: +972 2 675 7246.
E-mail address: ahoffman@cc.huji.ac.il (A. Hoffman).

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and especially with high fat content [18], which is known to prolong GRT [7]. Attaining gastroretentivity with low-calorie meals (e.g., standard breakfast) continues to be an imperative goal.

During the past few years, we have been working on the development of an unfolding expandable CR-GRDF [2,19–24]. It consists of planar polymeric sheets folded like an "accordion" into a standard gelatin capsule and therefore is termed "accordion pill" (AP). The two principal components of the accordion pill are the firm frame that together with dimensions of the DF contributes gastroretentivity; and the inner layer that consist of a polymeric matrix, loaded with the active compound, and controls the rate of drug release. Previously, we demonstrated both in preclinical studies [22] and in humans [20] that the combination of elasticity and geometric properties of the frame is the key for ensuring proper gastric retention of the AP. The compositions of the inner matrix and the frame polymers can be modified separately to provide independently desired gastric retentivity and control of drug release rate.

Until now, we have utilized the X-ray radiography to assess the location of the DF in the GI tract [20,21]. Although this approach enables a proper assessment of the unfolding process of the GRDF, it is unsafe for repetitive evaluation in human volunteers. Thus, in order to minimize health risks for participants in the present study, magnetic resonance imaging (MRI) technology was employed for visualization of the GRDF in the GI tract of volunteers.

The main goal of the study was to examine the ability of the AP to improve the bioavailability of narrow absorption window drugs, when administered with a low-calorie meal to humans using riboflavin as a model drug. A secondary goal was to reveal a relationship between the release rate of the drug from the GRDF in-vitro and the corresponding pharmacokinetic profile. The novelty of this work is that it is focused on bioavailability while previous reports on human studies with the accordion pill reported only on pharmacodynamic advantages with furosemide [21] or extension of the absorption phase of levodopa [20].

The model drug, riboflavin (vitamin B_2), is a water-soluble vitamin. It is a safe model drug with a recognized narrow absorption window in the upper part of the intestine and a saturable absorption mechanism [25]. It had been shown previously that administration of riboflavin with food (which delays gastric emptying) increases riboflavin bioavailability due to prolonged gastric residence time [26]. We have previously shown in dogs that the accordion pill significantly prolonged absorption time and increased the total amount of riboflavin absorbed over fourfold in comparison to a non-gastroretentive controlled release formulation [22].

In the present work the riboflavin-5′-phosphate sodium salt (RF5P) was used because of its better solubility. RF5P was shown to have the same absorption and excretion characteristics as riboflavin [25].

2. Materials and methods

2.1. Materials

All materials used for the Accordion Pill™ manufacturing were of pharmacopoeial grade unless specified otherwise. The following materials were used: methacrylic acid copolymer type A and B (Eudragit L®, Eudragit S®, Degussa); hydroxypropyl cellulose, ethylcellulose (Hercules); hydrolyzed gelatin (Byco E®, Croda); triethylcitrate, glycerintriacetate, polysorbate (Tween 80), riboflavin 5′-phosphate (RF5P) sodium salt dihydrate, (Merck), glutardialdehyde (microscopy grade, Merck), potassium hydrogen phosphate dibasic, glycerin (JT Baker); microcrystalline cellulose (Avicel, FMC Biopolymers); PEG 20,000 (Fluka); gelatin capsules 00EL white and 00CS white (Capsugel); iron oxide (Sigma Aldrich or BASF).

2.2. Accordion Pill production

The description of the structure and composition of the AP is detailed elsewhere [2,22]. Briefly, the AP is composed of three layers: two envelope membranes that "sandwich" between them the third layer composed from the frame that affords the physical properties to the device and the drug reservoir in the center. AP capsules for the trial were produced in a semi-industrial batch size at Intec Pharma's GMP pilot plant (Jerusalem, Israel). The semi-automated machines used for production were calibrated to ensure high repeatability and reproducibility.

The size of the AP used in the study was $45 \times 24 \times 0.8$ mm. For assessment of GRT of the AP in human volunteers by MRI, the inner part was loaded with fine powder of iron oxide (magnetite). Magnetite is a superparamagnetic MRI contrast agent that was reported to be a proper marker to allocate the DF in the stomach of human volunteers [27]. The inner layer was designed not to release the magnetite in the stomach, as was verified by in vitro examination. Preliminary in-vitro experiments had shown that the optimal amount of magnetite for labeling of the AP is 4.3% w/w of the inner layer (data not shown). Specifically the inner layer was composed of Eudragit L (57.4%), polyethylene glycol 20000 (38.3%) and magnetite dispersed as fine powder (4.3%).

In order to produce riboflavin AP, the RF5P films were prepared by solution casting and incorporated in the AP in the semi-automatic plant. Two types of AP with different riboflavin release rates were prepared (AP#1 and AP#2). The inner layer of the AP#1 was composed of Eudragit L100 (13.0%), Klucel EF (20.7%), triethyl citrate (13.1%), and RF5P (53.2%). The inner layer of the AP#2 was composed of Klucel EF (30.0%), glycerine (9.2%), polysorbate 80 (5.6%), and RF5P (55.2%). Both types of the AP and the control immediate release capsule contained 102.5 mg of riboflavin-5-phosphate sodium dihydrate (equivalent to 75 mg of riboflavin base).

2.3. In-vitro riboflavin release kinetic assessment

Riboflavin release rate from the AP was conducted in a standard USP dissolution apparatus type 2 (Erweka DT700) revolving at 50 rpm, in 900 ± 5 mL of 0.05M USP KCl buffer (pH 2.2, 37 °C). At pH 2.2, RF5P is at sink conditions, and the release rate is controlled by the reservoir polymers. This pH was selected since the dissolution of the active substance RF5P at pH 1.2 is slow and becomes the rate-limiting process in the release profile, and therefore, there were no differences in the release profiles between AP#1 and AP#2. In order to evaluate the release