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Effect of Common Excipients on the Oral Drug Absorption of Biopharmaceutics Classification System Class 3 Drugs Cimetidine and Acyclovir

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ABSTRACT

The objective was to assess the impact of larger than conventional amounts of 14 commonly used excipients on Biopharmaceutics Classification System (BCS) class 3 drug absorption in humans. Cimetidine and acyclovir were used as model class 3 drugs across three separate four-way crossover bioequivalence (BE) studies ($n = 24$ each) in healthy human volunteers, denoted as study 1A, 1B, and 2. In study 1A and 1B, three capsule formulations of each drug were manufactured, collectively involving 14 common excipients. Capsule formulations that incorporated hydroxypropyl methylcellulose (HPMC) or magnesium stearate exhibited lower absorption. The cimetidine commercial solution contained sorbitol and also resulted in lower absorption. Hence, in study 2, two capsule formulations with lower amounts of HPMC and magnesium stearate, the sorbitol-containing commercial solution, and a sorbitol-free solution were assessed for BE. Overall, 12 common excipients were found in large amounts to not impact BCS class 3 drug absorption in humans, such that these excipients need not be qualitatively the same nor quantitatively very similar to reference, but rather simply be not more than the quantities studied here. Meanwhile, for each HPMC and microcrystalline cellulose, BCS class 3 biowaivers require these two excipients to be qualitatively the same and quantitatively very similar to the reference.

Introduction

The Biopharmaceutics Classification System (BCS) is a scientific framework that characterizes drug substances according to their aqueous solubility and intestinal permeability.[1] Solubility, permeability, and drug product dissolution determine the rate and extent of drug absorption from immediate-release (IR) solid oral dosage forms (e.g., tablets and capsules). As BCS class 1 drugs have favorable oral biopharmaceutical properties, the United States Food and Drug Administration (US FDA) and the European Medicines Agency (EMA) have allowed waivers of *in vivo* bioequivalence (BE) studies for such rapidly dissolving IR solid oral dosage forms.[2,3] Rapid dissolution requires >85% of active ingredient be dissolved in 30 min. BCS-based biowaivers have allowed brand and generic products to receive regulatory relief based on *in vitro* data alone, which reduces unnecessary human testing and affords resource savings.[4-6]

The scientific community has suggested that biowaivers be extended to BCS class 3 drugs with a further requirement that dissolution be very rapid (>85% in 15 min).[7-9] IR products of BCS

Abbreviations used: ANDA, Abbreviated New Drug Application; BCS, biopharmaceutics classification system; BE, bioequivalence; HPMC, hydroxypropyl methylcellulose; IR, immediate-release; SLS, sodium lauryl sulfate.

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class 3 drugs can be expected to behave like oral solutions if dissolution is very rapid over a range of pH conditions. If dissolution is very rapid, the rate limiting step for oral absorption would be intestinal membrane permeation or gastric emptying, and not drug dissolution.[6,9,10] BCS class 3 drugs constitute almost 25% of drugs marketed in the United States.[4] Moreover, almost 40% of orally administered drugs on the WHO Model List of Essential Medicines are BCS class 3 drugs.[11] Extending biowaivers to class 3 drugs can reduce development costs and reduce human drug exposure.[4,5,11]

European Medicines Agency allows BCS-based biowaivers for class 3 drugs in very rapidly dissolving IR solid oral dosage forms, and US FDA has recently also proposed the same.[2,3] EMA and US FDA appear to indicate that, for excipients that are not known to affect bioavailability, BCS class 3 biowaivers require that excipients be qualitatively the same and quantitatively very similar. These limitations reflect concerns that excipients have potential to modulate class 3 drug absorption via impacting drug intestinal permeability, motility, or drug stability/metabolism.[6-8] By virtue of class 3 drug absorption being incomplete because of the lower drug intestinal permeability, excipient modulation of drug intestinal permeability and/or drug transit through the gastrointestinal tract are major concerns. Some excipients like sorbitol and mannitol can enhance *in vivo* transit time of low permeability drugs, causing bioinequivalence.[12,13] An additional potential concern is excipient modulation of protein expression with subsequent impact on drug disposition, although we have not seen such evidence in commonly used excipients.[14]

Previously, we employed Caco-2 monolayers to evaluate the effect of nine individual excipients on the Caco-2 permeability of seven low permeable compounds that differ in their physiochemical properties.[15] Generally, most excipients had no influence on drug permeability. Sodium lauryl sulfate (SLS) moderately increased the permeability of almost all the drugs. Hydroxypropyl methylcellulose (HPMC) appeared to increase cimetidine permeability. It was concluded that further work was needed to interpret the *in vivo* consequences of these observations from cell culture.

The objective of the present study was to assess the impact of very large amounts of 14 commonly used excipients on BCS class 3 drug absorption in humans. Study 1 involved two fasted, single-dose, four-way crossover BE studies in healthy human volunteers (i.e., study 1A and 1B). In study 1A, cimetidine was the model BCS class 3 drug.[16] In study 1B, acyclovir was the model BCS class 3 drug.[17] Each study involved 3 test drug capsule formulations, where each formulation contained very large quantities of three excipients. Excipient effect was intended to be assessed via BE of capsule against an oral liquid, although CimTest-2 and AcyTest-2 were the reference formulations employed. Results of study 1A and 1B lead to a subsequent study, denoted as study 2, focusing on HPMC, magnesium stearate, and sorbitol as excipients. Figure 1 illustrates a flowchart of excipient influences across studies 1A and 1B, including the rationale for subsequent study 2.

Materials and Methods

Materials

Cimetidine (study 1A), SLS, and acyclovir were obtained from Spectrum Chemical Manufacturing Corporation (New Brunswick, NJ). Cimetidine (study 2) and sodium hydroxide were obtained from Letco Medical (Decatur, AL). Microcrystalline cellulose (type PH-102) and croscarmellose sodium (type SD-711) were obtained from FMC BioPolymer (Newark, DE). HPMC was obtained from The Dow Chemical Company (Bay City, MI). Corn starch was obtained from Roquette America Inc. (Keokuk, IA). Sodium starch glycolate and lactose were obtained from DMV Fonterra Excipients (Foxhol, the Netherlands). Colloidal silicon dioxide was obtained from Evonik Industries (Aerosil 200 Pharma; Piscataway, NJ). Dibasic calcium phosphate was obtained from JRS Pharma (Patterson, NY). Crospovidone and povidone were obtained from BASF The Chemical Company (Jessup, MD). Stearic acid and magnesium stearate were obtained from Mallinckrodt (St. Louis, MO). Pregelatinized starch was obtained from Colorcon (West Point, PA). Empty hard gelatin capsules were obtained from Capsugel (Morristown, NJ). Propylparaben was obtained from Macron Fine Chemicals (Center Valley, PA). Methylparaben was obtained from Protameen Chemicals, Inc. (Totowa, NJ). Sodium 1-hexanesulfonate, sodium acetate trihydrate, potassium phosphate monobasic, sodium phosphate dibasic heptahydrate, hydrochloric acid, and sodium phosphate monobasic were purchased from Sigma-Aldrich (St. Louis, MO). Cimetidine hydrochloride oral solution 300 mg/5 mL (equivalent to cimetidine) and acyclovir oral suspension 200 mg/5 mL were purchased from Hi-Tech Pharmacal (Amityville, NY). Cimetidine and acyclovir reference standards were purchased from the United States Pharmacopeia (Rockville, MD). All solvents were HPLC grade and were purchased from Fisher Scientific Inc. (Pittsburg, PA).

Study 1: Formulations and In Vitro *Testing*

Cimetidine was used as a model BCS class 3 drug for study 1A. Acyclovir was used as model BCS class 3 drug for Study 1B. Three capsule formulations of each drug were manufactured, collectively involving 14 common excipients, which were: microcrystalline cellulose, HPMC, SLS, corn starch, sodium starch glycolate, colloidal silicon dioxide, dibasic calcium phosphate, crospovidone, lactose, povidone, stearic acid, pregelatinized starch, croscarmellose sodium, and magnesium stearate. These 14 excipients were selected from a list of the 20 most common excipients in oral solid Abbreviated New Drug Application (ANDA) formulations. Not selected from this list were: Opadry, talc, citric acid, sucrose, methyl cellulose, and titanium dioxide. Each capsule formulation contained 100 mg of either cimetidine or acyclovir in study 1A or study 1B, respectively, along with three excipients in quantities higher than those used in typical IR solid oral dosage forms. Capsule compositions are shown in Table 1. Capsules were not intended to exhibit dissolution-limited absorption, although formulation design was limited by the need to use only very large quantities of the 14 excipients. Regarding excipient composition, test capsules were not intended to be qualitatively or quantitatively the same as commercial cimetidine tablets or acyclovir capsules.

A Turbula mixer (Turbula, Type: T2F Nr 070759; Basel/Schweiz) was used to mix the drug and 3 excipients into powder blends, which were hand filled into capsules. Cimetidine and acyclovir capsules were manufactured under current good manufacturing practices (GMP) at the University of Maryland GMP Facility.

Capsules of cimetidine and acyclovir were subjected to a panel of 6 quality control (QC) tests: appearance, identification, assay, impurity, uniformity of dosage units, and dissolution, which were performed as specified in the USP monograph for cimetidine and acyclovir, respectively.[18,19] Uniformity of dosage units was performed by the weight variation approach. Furthermore, for each cimetidine and acyclovir whose tablet or capsule USP monograph employs pH 1.2 dissolution media, *in vitro* dissolution studies were also performed at the two additional pH values of 4.5 and 6.8.[20] All dissolution tests were performed on six units of each product using USP apparatus I at 100 rpm and at 37°C in 900 mL of pH 1.2, 4.5, and 6.8 media. pH 1.2 media was 0.1 N HCl. pH 4.5 media was 0.2 M sodium acetate trihydrate, adjusted with HCl to pH 4.5. pH 6.8 media was 0.2 M monobasic potassium phosphate, adjusted with sodium hydroxide to pH 6.8. The commercial oral liquid solution of