RESEARCH ARTICLE

Comparative Pharmacokinetics Studies of Immediate- and Modified-Release Formulations of Glipizide in Pigs and Dogs

RAJESH KULKARNI,[1] NATHAN YUMIBE,[1] ZHONGYI WANG,[1] XIN ZHANG,[1] CHENG CAI TANG,[1] KENNETH RUTERBORIES,[1] AMY COX,[1] ROBYN MCCAIN,[3] GREGORY T. KNIPP[2,3]

[1]Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285

[2]Department of Industrial and Physical Pharmacy, College of Pharmacy, Purdue University, West Lafayette, Indiana 47907

[3]Purdue Translational Pharmacology Facility, Bindley Biosciences Center, Purdue University, West Lafayette, Indiana 47907

Received 5 July 2012; revised DD MM YYYY; accepted 31 July 2012

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23292

ABSTRACT: The utility of pigs as preclinical animals for pharmaceutical development was assessed by evaluating the pharmacokinetics and pharmacodynamics of glipizide (Glucotrol®) following oral administration of immediate-release (IR) and modified-release (MR) formulations. Doses of 10 and 30 mg were administered to six male pigs in a crossover design. Blood samples were collected at selected time-points up to 48 h after dose. Relative to the IR formulation, the time to reach the maximum concentration (t_{max}) was delayed with the MR formulation from 1.3 to 8.7 h with the 10 mg dose and to 6.2 h with the 30 mg dose. The relative bioavailability (BA) was approximately 92% at 10 mg and 79% at 30 mg dose. The area under the curve of the plasma concentration versus time curve (AUC) increased nearly proportionally with the dose. Interanimal coefficient of variation (CV) in AUC ranged from approximately 40% to 60%. Blood glucose results suggest that pigs demonstrate formulation-dependent response to glipizide. Compared with the pigs, the 10 mg MR formulation in dogs showed a higher AUC CV of approximately 80%, a t_{max} of 5.5 h, and a lower relative BA of 18%. These data indicate that the MR formulation performed less consistently in dogs as compared with humans, whereas the porcine absorption kinetics and BA were consistent with published clinical data. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: absorption; bioavailability; controlled release; pharmacokinetics/pharmacodynamics model; physiological model; dissolution; *in vitro/in vivo* correlation (IVIVC)

INTRODUCTION

Modified- or controlled-release (MR) formulations offer significant advantages over immediate-release (IR) formulations by increasing patient compliance, reducing the frequency of dosing for drugs with a short terminal elimination half-life, and minimizing the degree of fluctuation in the drug's plasma concentration over the dosing intervals.[1] The development of MR formulations is a complex and iterative process that requires an integrated understanding of the effects of formulation design and manufacturing process on the drug product performance attributes.[2] However, the intricacies of formulation development get increasingly challenging if meaningful *in vitro–in vivo* correlations (IVIVC) cannot be developed. Consequently, even minor formulation changes may need to be substantiated with *in vivo* studies to ensure that the changes have not affected the desired pharmacokinetics (PK) profile and pharmacodynamics (PD) response. This lengthens the development timeline because multiple clinical studies are needed to optimize the formulation.

Abbreviations used: AUC, area under the curve of the plasma concentration versus time curve; BA, bioavailability; C_{max}, maximum concentration reached in the plasma concentration versus time curve; CV, coefficient of variation; EDTA, ethylenediaminetetraacetic acid; GI, gastrointestinal; IR, immediate-release formulation; IVIVC, *in vitro–in vivo* correlation; MR, modified-release formulation; PD, pharmacodynamics; PK, pharmacokinetics; rpm, revolutions per minute; t_{max}, time to reach the maximum concentration; USP, United States Pharmacopeia

Correspondence to: Rajesh Kulkarni (Telephone: + 317-433-8285; Fax: +317-277-2560; E-mail: kulkarni_rajesh@lilly.com), Nathan Yumibe (Telephone: +317-433-4088; Fax: +317-655-1185; E-mail: yumibe_nathan_p@lilly.com)

Journal of Pharmaceutical Sciences

Modified-release formulation development generally involves the following systematic approaches including: development of formulation prototypes possessing different release rates, characterization of release rates utilizing *in vitro* dissolution tests [potentially United States Pharmacopeia (USP) based], and the evaluation of *in vivo* performance of the prototype formulations in clinical studies.[3–5] It should be noted that human physiology is complex and clinical drug absorption from a dosage form is influenced by various factors such as gastric residence time, composition and volume of gastrointestinal (GI) fluids, mechanical destructive forces during peristalsis, and differences in absorption along the GI tract.[6–9] It is well established that the presence of food can dramatically alter the oral bioavailability (BA) of drugs from MR formulations.[10–13] For example, the composition of meal and dosing time relative to meal intake was found to affect the PK of controlled release theophylline formulation.[13]

in vitro dissolution tests are developed and modified with intent to serve as a biological fluid surrogate to mimic *in vivo* release and increase the potential to establish an IVIVC.[3,5,14] However, for reasons mentioned above, it is practically impossible for *in vitro* dissolution to simulate the complex processes involved with drug release and absorption that occur within the *in vivo* GI environment. The multiple physiological confounding variables with general and USP-based *in vitro* dissolution methods often lead to lack of an observed *in vitro–in vivo relationship* or IVIVC. Several references describe limitations of the dissolution method in predicting *in vivo* performance.[3,4,14–16]

We hypothesize that the out-bred, domesticated farm pig is an appropriate preclinical model to assess the *in vivo* performance of MR formulations during development. The porcine model has several physiological characteristics that are more similar to humans than other nonprimate species.[17–19] In particular, among the factors that govern drug absorption—pH, surface area, and transit time in the GI tract—it should be noted that pigs are the closest to humans in these measures when compared with the other preclinical species.[18–32] Literature references suggest that the porcine model may be the most appropriate human surrogate for drug metabolism and PK studies.[26–32] This animal can also be dosed with the intact monolithic dosage form to protect its integrity and prevent burst release, which is a critical requirement for many MR formulations.[33,34] There is a high likelihood that the MR dosage form will remain intact during administration to the pig. The use of this animal model in this manner could streamline MR formulation development by enabling the drug development scientists to screen and compare the PK/PD of prototype MR formulations in a preclinical animal model that is more relevant to human anatomy and physiology. Such information can empower scientists and increase their confidence in selecting the most appropriate MR formulation for clinical testing.[35,36]

Glipizide, available commercially under the brand name Glucotrol®, is a second generation oral hypoglycemic agent used in the treatment of diabetes mellitus. Glipizide is a weak acid and exhibits pH-dependent solubility. It is absorbed rapidly (in the small intestine) and has a rapid onset of action.[37,38] The absorption mechanism in the intestine is primarily passive diffusion and the driving force is the concentration gradient of the unionized species in accordance with the pH-partition hypothesis.[39] Furthermore, the PK of glipizide in humans is characterized with high peak blood concentrations within 1–3 h after administration, and short elimination half-lives ranging from 2 to 4 h. Therefore, it is routinely administered two to three times daily. Careful adjustment of the dose is necessary to avoid hypoglycemic symptoms. Glipizide is also available in a MR, GI therapeutic system, tablet dosage form under the brand name Glucotrol XL®. The MR formulation allows once-daily administration and minimizes peak-to-trough fluctuation in plasma glipizide concentration.[40,41]

To test the hypothesis that the pig is a better preclinical, nonprimate animal model for nonclinical evaluation of MR formulations than the dog, this study compared the PK/PD of IR and MR glipizide tablet formulations in pigs with the PK collected in dogs dosed with the same formulations. The tablets were administered orally at two different doses, 10 and 30 mg in pigs. The PK parameters for the same two formulations were evaluated in beagle dogs at a 10 mg dose. The relationship between *in vitro* dissolution and *in vivo* absorption was also explored for the MR formulation. Moreover, the comparative PK parameters in the pig and dog models were contrasted with published human PK data to assess the relative preclinical prediction of potential clinical outcomes.

MATERIALS AND METHODS

Materials

Glucotrol® and Glucotrol XL® were purchased from Purdue University Pharmacy in West Lafayette, Indiana. The glipizide reference standard was purchased from the USP (Rockville, Maryland). Trifluoroacetic acid (0.1%) was purchased from EMD Chemicals Inc. (Gibbstown, New Jersey). Monobasic potassium phosphate was purchased from Fisher Scientific (Fair Lawn, New Jersey). The 5 N NaOH was purchased from Red Bird Service (Batesville, Indiana). Catheters, tubing, and other supplies for the PigTurn-Culex-L® where purchased from Bioanalytical Systems, Inc. (West Lafayette, Indiana), as previously