GASTROINTESTINAL INTUBATION USING A MULTI-PORT ASPIRATION CATHETER TO STUDY DRUG RELEASE OF EXTENDED-RELEASE GLIPIZIDE DRUG PRODUCTS IN THE GASTROINTESTINAL TRACT OF HEALTHY HUMANS

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Introduction

- Understanding the luminal behavior of oral drugs in the gastrointestinal (GI) tract can assist generic drug development of extended release (ER) formulations.
- Limited data are available on the performance of ER drugs within the GI lumen.

Objective

This study investigated the in vivo drug release and pharmacokinetics of **two orally administered ER formulations of glipizide**, with the same therapeutic equivalence rating, in healthy subjects.

Methods

- This study includes two phases: with GI intubation (phase 1) and without GI intubation (phase 2). Two phases were separately by 5-14 days washout period (figure 1a).
- Phase 1:
  (1) Total of **7 subjects** were randomized to receive either one of the two **glipizide ER tablet 5 mg**. The **stable-isotope glipizide solution 1 mg** was co-administered to characterize individual clearance. In addition, **240 mL of 20% or 25 % glucose solution** was administered to mitigate hypoglycemia. Blood samples were collected over 78 hours for glipizide assay by liquid chromatography and mass spectrometry (LC-MS).
  (2) Intubation catheter with four aspiration ports was orally inserted (figure 1b). GI fluid samples were collected over 7 hours. Drug content and GI fluid pH were analyzed.
- Phase 2:
  The subject received the same glipizide ER tablet with stable-isotope glipizide solution and glucose solution as phase 1. No GI intubation in this phase.

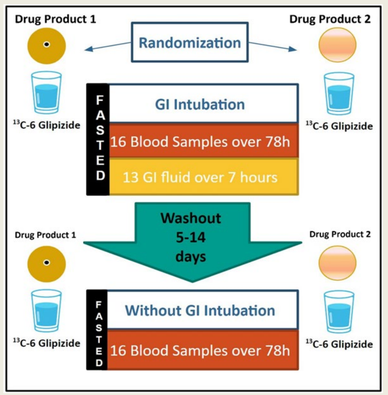

Figure 1a. Study scheme

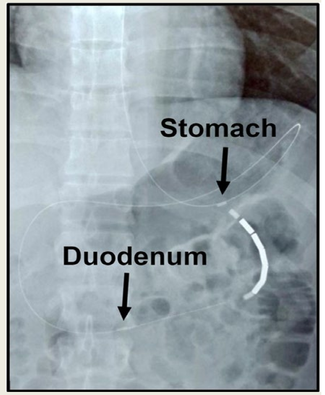

Figure 1b. Fluoroscopic photo of GI tube with aspiration ports

Figure 2. Plasma concentration-time profiles of stable-isotope glipizide solution with and without intubation (2a) and isotope glipizide concentration in stomach (2b), duodenum (2c) and mid jejunum (2d).

Isotope solution

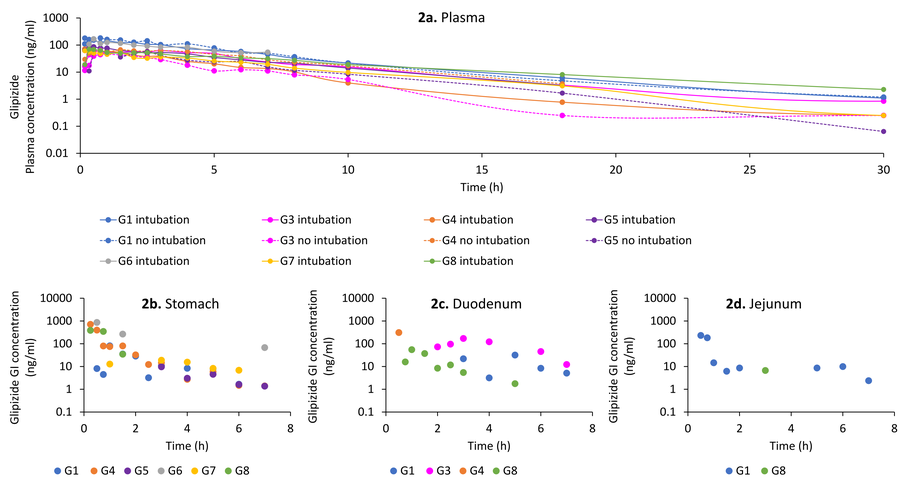

Figure 3. Plasma concentration-time profiles of glipizide ER tablet with and without intubation [Drug Product 1 (3a) and Drug Product 2 (3b)], and glipizide concentration in stomach (3c),duodenum (3d) and jejunum (3e).

Modified-release products

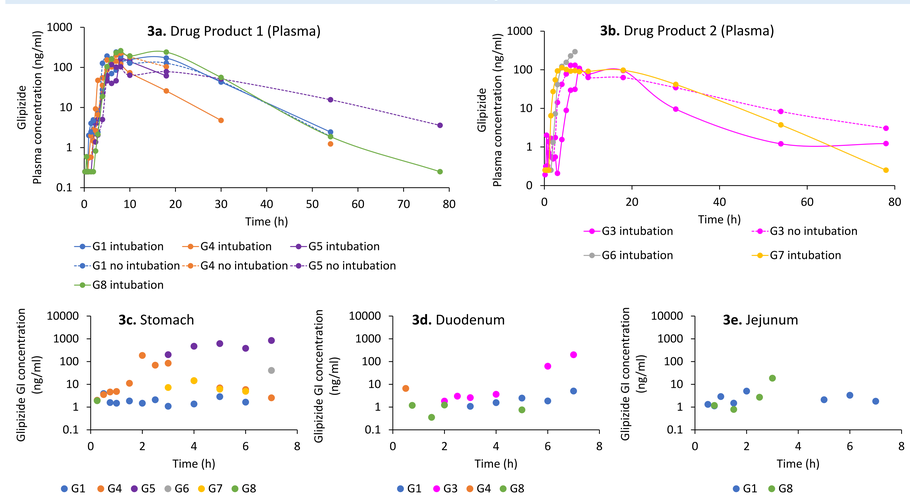

Table 1. Demographic Profile of Study Subjects

	Drug Product 1	Drug Product 2
Gender	**4** females	**2** males, **1** female
Age*	**22 – 29**	**29 – 50**
Mean Body Mass Index (BMI)^	**23.95 ± 4.78**	**24.31 ± 6.93**

* Range
^ Mean ± standard deviation

Table 2. In Vivo Results of Stable-Isotope Glipizide and Glipizide ER tablets (Drug Product 1 and Drug Product 2)

	Stable-Isotope Glipizide	
Individual clearance	**1.0 – 4.1** L/h	
	Drug Product 1	**Drug Product 2**
C_{max}*	**117 – 260** ng/mL	**73 – 292** ng/mL
T_{max}*	**7 – 8** hours	**7 – 8** hours
GI Fluid Concentrations*	**5.1 – 844.5** ng/mL at 7h	**40.9 – 200** ng/mL at 7h
pH in Stomach*	**1.14 – 2.24**	**1.17 – 2.91**
pH in Duodenum*	**4.54 – 6.92**	**6.3 – 6.94**
pH in Jejunum*	**5.88 – 7.45**	**----**

* Range

Conclusion

- **C_{max}** and **T_{max}** for both glipizide drug products were within a **similar range.**
- **Glipizide concentrations and pH were measurable in different regions of the GI tracts.**
- Serial fluid sampling from the GI tract using intubation is **feasible and may help inform in vivo drug release performance.**

Acknowledgment

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