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Review

Exploring gastrointestinal variables affecting drug and formulation behavior: Methodologies, challenges and opportunities

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ABSTRACT

Various gastrointestinal (GI) factors affect drug and formulation behavior after oral administration, including GI transfer, motility, pH and GI fluid volume and composition. An in-depth understanding of these physiological and anatomical variables is critical for a continued progress in oral drug development. In this review, different methodologies (invasive versus non-invasive) to explore the impact of physiological variables on formulation behavior in the human GI tract are presented, revealing their strengths and limitations. The techniques mentioned allow for an improved understanding of the role of following GI variables: gastric emptying (magnetic resonance imaging (MRI), scintigraphy, acetaminophen absorption technique, ultrasonography, breath test, intraluminal sampling and telemetry), motility (MRI, small intestinal/colonic manometry and telemetry), GI volume changes (MRI and ultrasonography), temperature (telemetry) and intraluminal pH (intraluminal sampling and telemetry).

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1. Introduction

In 2015, the FDA's Center for Drug Evaluation and Research (CDER) approved 45 new drugs for clinical use (U.S. Food and Drug Administration, 2016). Of these new drugs, 55% were commercialized as oral formulations either as tablets (16), capsules (8) or granules (1), indicating that the oral route of administration is still of major interest. For the last couple of decades, efforts are underway to develop and validate biorelevant *in vitro* and *in silico* tools to predict the oral absorption of new drug products prior to the start of animal studies or clinical trials (Lennernäs et al., 2014). Reliable models are essential to reduce the occurrence of failures in a late phase, resulting in time- and cost-saving drug development.

After oral intake, a drug formulation is challenged by several gastrointestinal (GI) barriers. Complex variables such as pH, GI secretions and GI transit/motility along the GI tract can affect drug release and absorption in a positive or negative way depending on the physicochemical properties of the drug compound (e.g. pH/pKa interplay for ionizable drugs) and/or the formulation characteristics (e.g. pH-sensitive coating). In addition, inter-subject variability in characteristics of the GI environment may cause variable drug absorption and systemic drug availability (Riethorst et al., 2015). Determining the median and range for specific GI variables, and understanding how they influence oral drug behavior along the GI tract, will be helpful in the field of drug development.

The present review provides an overview of different methodologies that can be applied to study physiological variables of the human GI tract and their impact on oral drug absorption in healthy and patient populations. The methodologies have been subdivided into two groups: (i) noninvasive and (ii) invasive methodologies. Although some of the methodologies are more historical than operational, they have been of paramount importance for innovations in drug and formulation development; in addition, they have created the basis for several novel methodologies, leading to an in-depth comprehension of different GI variables: gastric emptying (magnetic resonance imaging (MRI), scintigraphy, acetaminophen absorption technique, ultrasonography, breath test, intraluminal sampling and telemetry), motility (MRI, small intestinal/colonic manometry and telemetry), GI volume changes (MRI and ultrasonography), temperature (telemetry) and GI pH (intraluminal sampling and telemetry).

2. Noninvasive methodologies

2.1. Scintigraphy

Disturbances in the normal movement of food along the GI tract can be associated with abdominal pain, early satiety and nausea. Measurement of GI transit, especially gastric emptying (GE), therefore has become a routine and important test in clinical physics and gastroenterology clinics for patients with dyspeptic symptoms. Techniques previously used by physiologists include gastric intubation to sample dye dilution, sampling of gastric meal volumes (recoverable after different periods; Hunt, 1963), or the movement of radio-opaque markers using X-rays. The principle of incorporating gamma-emitting radiopharmaceuticals into a food matrix or a formulation allowed the non-invasive visualization of the ligand with a much reduced dose compared to X-rays and less interference with normal function (Digenis et al., 1977).

Studies of GE using scintigraphic techniques with radiolabeled standard meals were introduced by Griffith and colleagues in 1966 (Griffith et al., 1966) and further refined in the seventies with the introduction of simultaneous measurement of GE of both solids and liquids in 1976 (Heading et al., 1976). This was facilitated by labeling the phases with radionuclides of different energies that could be distinguished by gating in separate channels. GE scintigraphy has been used for more than 50 years for clinical and investigative purposes, and is usually ordered to confirm or exclude whether gastroparesis (delayed GE) is a cause of patient's symptoms (Maurer, 2015). Scintigraphy employing a gamma camera has become the gold standard for the evaluation of GE of solids and liquids in all types of GI disorders and for assessing the efficacy of gastroprokinetic drugs and surgical procedures (Cuomo et al., 2001). Besides planar scintigraphy, single-photon emission computed tomography (SPECT) can be performed. The extra dimension of this technique is the ability to detect changes in gastric accommodation after intravenous injection of the radiopharmaceutical ^{99m}Tc-pertechnetate which shows uptake in the gastric mucosa (Bennink et al., 2004). It was demonstrated that dynamic gastric scintigraphy allows visualization and characterization of antral contractions and can also be used to evaluate the distribution of food inside the stomach and to quantify the emptying of a radiolabeled test meal from each compartment (Bennink et al., 1998). In the scintigraphic determination of GE, there are many parameters which can affect the final result. Factors such as meal size and composition, subject age and weight and measurement technique are known to influence GE. It is therefore of paramount importance that, as much as possible, standardized conditions are used in performing scintigraphic GE studies. Until recently, there were no accepted standards for performing GE scintigraphy. This problem raised concerns about the continued acceptance of GE scintigraphy without consistent methodology (Maurer, 2008). As a result, in 2007 a consensus recommendation was published jointly by the Gastrointestinal Council of the Society of Nuclear Medicine and Molecular Imaging and the American Neurogastroenterology and Motility Society (Abell et al., 2008). The consensus group recommended a solid-meal GE test "using readily available technology and normative data, which can provide clinicians with standardized results". This consensus recommendation was adopted by the Society of Nuclear Medicine and Molecular Imaging (Donohoe et al., 2009) and was included in a joint practice guideline from the American College of Radiology/Society for Pediatric Radiology and the Society of Nuclear Medicine and Molecular Imaging. In interpreting GE studies, one needs to understand the multiple factors that affect GE, particularly the separate roles of the fundus and antrum. Visual inspection of early distribution of a solid meal in the stomach has become increasingly recognized as important. Although liquids rapidly disperse throughout the stomach, solids will initially localize predominantly in the fundus until slow, sustained fundal contractions move them to the antrum (Bennink et al., 1998). The normal values for scintigraphic GE studies are usually based on male controls or a mixed control population. Historically it has been assumed that men and women have identical GE but gender differences were