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Review

Gastro-retentive drug delivery systems and their *in vivo* success: A recent update

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ABSTRACT

Gastro-retentive drug delivery system (GRDDS) has gained immense popularity in the field of oral drug delivery recently. It is a widely employed approach to retain the dosage form in the stomach for an extended period of time and release the drug slowly that can address many challenges associated with conventional oral delivery, including poor bioavailability. Different innovative approaches like magnetic field assisted gastro-retention, plug type swelling system, muco-adhesion technique, floating system with or without effervescence are being applied to fabricate GRDDS. Apart from *in vitro* characterization, successful GRDDS development demands well designed *in vivo* study to establish enhanced gastro-retention and prolonged drug release. Gama scintigraphy and MRI are popular techniques to evaluate *in vivo* gastric residence time. However, checking of their overall *in-vivo* efficacy still remains a major challenge for this kind of dosage form, especially in small animals like mice or rat. Reported *in vivo* studies with beagle dogs, rabbits, and human subjects are only a handful in spite of a large number of encouraging *in vitro* results. In spite of the many advantages, high subject variations in gastrointestinal physiological condition, effect of food, and variable rate of gastric emptying time are the challenges that limit the number of available GRDDS in the market. This review article highlights the *in vivo* works of GRDDS carried out in the recent past, including their limitations and challenges that need to be overcome in the near future.

1. Introduction

Oral formulations have earned a significant place among the various dosage forms developed so far for human administration. In most of the cases, the conventional oral delivery systems show limited bioavailability because of fast gastric-emptying time among many other reasons involved [1,2]. However, the recent technological development has resulted to many novel pharmaceutical products, mainly the controlled release drug delivery systems to overcome this problem. Gastro-retentive drug delivery system (GRDDS) is one such

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example where the attribute like gastric retention time coupled with the drug release for extended time has significantly improved patient compliance. Some inherent limitations of the conventional oral drug delivery systems have ignited the interest to this new delivery system. Fast gastric emptying associated with conventional oral medications leads to a bioavailability issue for many drug molecules (e.g. pranlukast hydrate, metformin HCl, baclofen, etc.), of which the main principal site of absorption is the stomach or the proximal part of the small intestine, or have the absorption issue in the distal part of the intestine [3–5]. Solubility can also be improved by prolonging the gastric retention of drugs that are less soluble in an elevated pH environment of the intestine [2]. There are many drugs (e.g. captopril, metronidazole, ranitidine HCl, etc.) that are prone to degradation in the colonic area [2,6]. To attain required therapeutic activity, recurrent dosing is needed for the drugs with short half-lives as they have the tendency of getting eliminated quickly from the systemic circulation. However, an oral sustained-controlled release formulation with additional gastric retention property can avoid these limitations by releasing the drug slowly in the stomach along with maintaining an effective drug concentration in the systemic circulation for an extended period of time [7]. Apart from the systemic action, GRDDS has proved to be effective locally to treat gastric and duodenal ulcers, including esophagitis, by eradicating the deeply buried *Helicobacter pylori* from the submucosal tissue of the stomach [2,5,8–10]. The history of GRDDS formulations dates back to almost three decades [11]. The basic fabrication techniques, including their *in vitro* characterizations, are also well established. Even in recent times, quite a few reviews have been published on GRDDS [5,12–18]. These reviews are more focused on the formulation aspects or *in vitro* characterization studies done by various researchers or overall GRDDS. The industrial aspects covering physicochemical, biopharmaceutical and regulatory considerations of GRDDS have been reviewed by Pawar et al. [19]. Still, the number of marketed gastro-retentive formulations is not significant. So, it is very important to look through the *in vivo* studies done with GRDDS in order to find out the pharmacokinetic performances of the developed systems considering their significant roles in successful commercialization of any dosage form. As per our literature search, there is no review available to date focusing on *in vivo* performances of GRDDS, especially on recent works. In this context, the aim of this review is to summarize the *in vivo* studies of GRDDS in terms of pharmacokinetic parameters as well as gastro-retention times and the inherent challenges or constraints for *in vivo* evaluations recorded by various researchers.

2. Stomach physiology

Success of GRDDS relies on the understanding of stomach physiology and related gastric emptying process. Structurally the human stomach is composed of three anatomical regions: fundus, body and antrum (pylorus), as depicted in Fig. 1. After a meal, the average volume of a stomach is about 1.5 l, which varies from 250 to 500 ml during the inter-digestive phases [18]. The part made of the fundus and the body acts as a reservoir

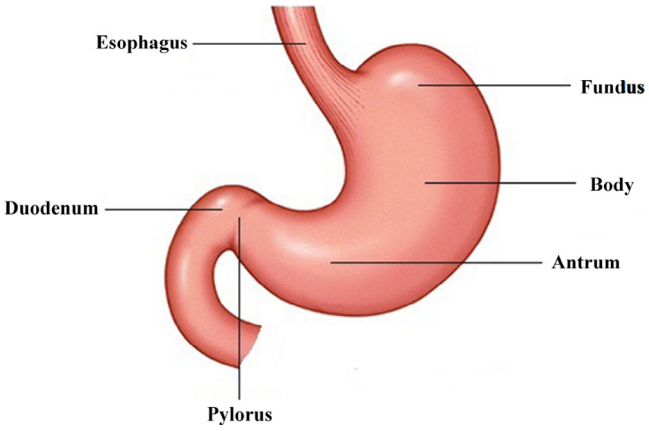

Fig. 1 – Diagram of human stomach.

Table 1 – Four phases of migrating motor complex (MMC).[a]

Phase	Description	Duration (min)
Phase I (basal phase)	Idle state without any contraction	30 to 60
Phase II (pre-burst phase)	Intermittent contraction	20 to 40
Phase III (burst phase)	The regular contraction at the maximal frequency causes the good material to migrate distally.	10 to 20
Phase IV	Transition period between phase III and phase I	0 to 5

[a] From Talukder and Fassihi [21].

of any undigested material, while the antrum performs as the principal site for the mixing action. Being the lower part, the antrum works as a pump for gastric emptying by a propelling action. Pylorus acts to separate the stomach from the duodenum and plays a major role in gastric residence time of the ingested materials. However, the pattern of the gastric motility is different for the fasting and fed state [20]. The gastric motility pattern is systematized in cycles of activity as well as quiescence. The duration of each cycle is 90–120 min and it contains four phases, as mentioned in Table 1 [21]. The motility pattern of the stomach is usually called migrating motor complex (MMC) [17].

3. Approaches to fabricate gastro-retentive systems

Different approaches have been adopted by researchers to enhance gastric residence time with the prolonged drug release. The concept of high density formulation is one such approach (Fig. 2). The developed dosage form was made heavy (density: 2.5 to 3.0 g/ml) to withstand *in vivo* peristaltic movement and remained intact in spite of the GIT disturbance. Accordingly, the GI transit time was expected to prolong for