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Review Article

IN VIVO MONITORING STRATEGIES FOR EVALUATION OF FLOATING DRUG DELIVERY SYSTEMS

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ABSTRACT

In recent years, various advancements have been introduced in the development of controlled drug release devices for resolving different physiological problems for example, gastric retention inconsistency along with erratic gastric emptying time. Gastroretentive delivery formulations receive considerable attention to overcome these drawbacks and in optimizing the absorption of different medicaments. Gastroretentive technologies considerably extend the stomach retention time of dosage forms with increased bioavailability as well as therapeutic efficacy. Gastroretention can be successfully achieved utilizing gastric floating system. The rationale of the present manuscript focuses on current advancements of gastric floating systems so as to accomplish appropriate drug bioavailability and, subsequently drug targeting to the stomach. *In vivo* evaluation parameters, especially pivotal imaging techniques including roentgenography, gamma scintigraphy, gastroscopy, magnetic marker monitoring, magnetic resonance imaging, ultrasonography, ^{13}C octanoic acid breath test etc. have been emphasized in this manuscript for monitoring drug formulation behavior which extensively revolutionized thorough understanding in the avenue of improved bioavailability of gastroretentive systems.

Keywords: Gastroretentive technologies, Floating drug delivery systems, Gastric retention, *In vivo* imaging, Salient advantages

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INTRODUCTION

In order to accomplish and sustain optimum drug concentration in the body, the rationale for developing any delivery system is to target active molecule to the site of action. Among diverse routes, oral route is generally the popular, potential and efficient route intended for administration of therapeutic agents [1-3]. According to recent research, there is growing curiosity in innovative delivery formulations that can be retained in stomach for sustained as well as consistent time period. Gastroretentive drug delivery systems are one of the novel strategy in this avenue [4-6]. Gastroretentive systems are configured for delivering therapeutic agents to the GIT in manner that disadvantages associated with conventional dosage types can be resolved [7-11]. Gastroretentive drug delivery system significantly improved patient compliance due to attributes like enhanced gastric retention time coupled with precise drug release for extended time period and ultimately increased bioavailability and decreased drug waste. Targeting of drug to the stomach and upper small intestine is also achievable in an efficient manner [1, 8, 12-16]. Successful designing of floating formulations is one of the thriving strategies in enhancing dosage residence in the stomach.

Floating systems are recognized as low density systems for floating over the gastric content and thus remains buoyant in gastric region for an extended time without disrupting gastric emptying process, thereby increasing the retention of dosage type at the drug absorption site, especially in the stomach region. The aim of formulating buoyant systems is to render the dosage forms less dense as compared to gastric fluids so as to allow it for floating in a successful manner [17-20]. To ensure advantageous bioavailability and superior therapeutic effectiveness of drugs, prolonged stomach retention of the delivery system is a significant process. Floating drug delivery systems are appropriate for therapeutic molecules with less stability and poor solubility in intestinal fluids. Floating drug delivery systems are categorized according to the usage of formulation variables such as effervescent and non-effervescent. Further, effervescent systems are classified as gas generating systems and osmotically controlled drug delivery systems and non-effervescent systems are classified as hollow microspheres, alginate beads, microporous compartment systems and colloidal gel barrier systems etc [2, 13, 21-25]. The pertinent literature was collected from comprehensive search on various databases like PubMed, ScienceDirect, Google Scholar and others utilizing several keywords, including "floating systems", "*in vivo* imaging", "gastroretentive technology" and many others. Referred publications in the English language accessed till June 2022 were chosen for this manuscript. Floating drug delivery systems are efficiently described in fig. 1.

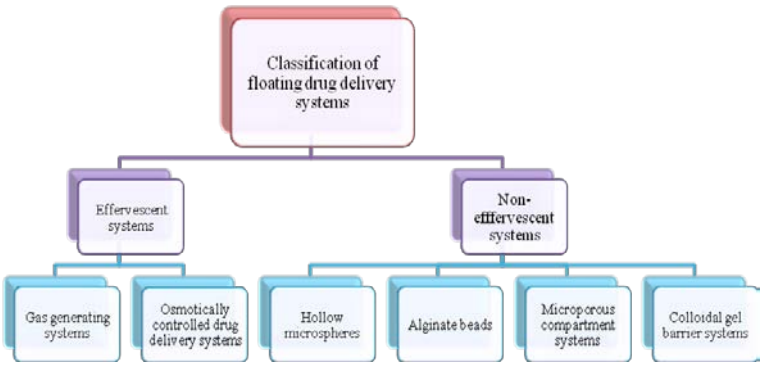

Fig. 1: Classification of floating drug delivery systems [25]

Significant advantages

Following useful advantages of floating drug delivery systems are represented pictorially in the fig. 2 [20, 26, 27].

Fig. 2: Unique advantages of FDDS [18]

Numerous physiological and pharmaceutical factors affect the residence time of dosage form in the stomach. To ensure the effective release of drugs from gastroretentive systems, the dosage type needs comprehensive and meticulous assessment for optimum gastroretentive ability. This can be evaluated either explicitly by *in vivo* imaging technology or through measuring different crucial parameters. *In vivo* imaging assessment techniques are regarded as the most accurate and consistent methodologies. *In vivo* imaging evaluation result may also advances the prospect of obtaining a patent of any new gastroretentive drug delivery systems. Biorelevant approaches can also be implemented to reduce the probability of formulation failure in clinical trials [6, 28, 29].

***In vivo* evaluation techniques**

Numerous *in vivo* imaging approaches are available to assess the gastroretentive performance of dosage types. These are roentgenography, gamma-scintigraphy, gastroscopy, ^{13}C octanoic acid breath test, ultrasonography, magnetic resonance imaging, magnetic marker monitoring etc [28, 30-32]. Important *in vivo* imaging techniques are shown in fig. 3.

Fig. 3: *In vivo* imaging evaluation techniques [28]

Roentgenography

X-ray procedure is the most commonly employed tool for testing internal systems of human volunteers, beagle/mongrel dogs or albino rabbits. Compared with other approaches, it is one of the simplest and cheapest method. The study is conducted under fed and fasting conditions. Barium sulphate is a commonly employed radio-opaque marker inserted into the dosage form and X-ray imaging can be obtained at different intervals for illustrating positioning of *in vivo* environment of gastroretentive dosage type. Both floating time and gastro resident time of the systems are recorded. The chief disadvantage of this method is exposure to X-rays by volunteers which relies on the exposure period, frequency in addition to repetitions needed for verifying the effectiveness. High exposure condition to X-rays effect is considered as harmful risk to the human [4, 28].

Gamma-scintigraphy

Gamma-scintigraphy, a popular non-invasive technique utilizing gamma-emitting radioisotopes compounded into controlled release dosage forms has become a significant technique for gastrointestinal transit period evaluation. During preparation, a small amount of stable isotope i.e. ^{152}Sm is compounded into dosage forms. In a neutron source, dosage form is irradiated for converting the isotope into a gamma-emitting material such as ^{153}Sm [31, 33]. With images obtained from gamma camera, gastric emptying times can be revealed [34-36]**.** The gamma scintigraphic imaging is started just after dosing and then anterior images of the abdomen are performed after regular interval [30, 37]. High safety aspect owing to comparatively less radiation doses is the foremost and impressive benefit of this approach. However, some disadvantages of this approach include exposure to ionizing radiation, low sensitivity to several inserted markers, high cost etc. Also, drawbacks of gamma scintigraphy includes some ethical constraints that healthy subjects exposed to radiation without any personal benefit, low temporal and spatial resolution along with limited topographic information [32, 38, 39, 40-42].

Gastroscopy

Gastroscopy, a effective type of peroral endoscopy utilized for diagnosis and monitoring of gastroretentive systems. This approach comprises of optical fibre along with a video camera to assess dosage form position. This approach is appropriate and pivotal for different types of gastroretentive systems. For assessing the gastroretentive evaluation using peroral endoscopy, camera device should enter the volunteer body at regular time interval, concerning the gastroenterologist intervention for the whole assessment test. There are several challenging aspects of this process, such as invasiveness, the possibility of contamination and cross infection, expensive etc. which contributed to the restricted gastroscopy utilization [11, 29, 43].

Ultrasonography

Ultrasonic waves are utilized to provide images of some abdominal organs to determine the formulations intragastric position. Ultrasonic waves are reflected at significantly differing acoustic impedances across an interface in this approach, allowing imaging. An electronic equipment receives the reflected echoes and evaluates their intensity level. Findings can be viewed as either static photos or moving image of an interior body part. However, the disadvantage of this strategy is that some dosage forms may not reveal a satisfactory response. Also, this approach is less popular owing to lack of ultrasound traceability at the intestine and some dosage forms may not exhibit a sharp acoustic mismatch [6, 28, 31].

Magnetic marker monitoring

Formulation is magnetically labelled along with the addition of iron powder within dosage type and subsequently, images may be obtained using an extremely responsive bio-magnetic instrument of measurement. Method does not involve radiation and is thus not much hazardous than other reported methods. However, formulative improvements are still needed in this technique, such as iron powder incorporation which impact the performance and efficacy of gastroretentive drug delivery systems [28].

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is an imaging technology and is also non-invasive. In this technique, investigations can be carried out

with a commercial 1.5 Tesla whole body imager. In order to generate accurate images of bone, soft tissues, organs, and nearly every inner body components, magnetic resonance imaging utilizes strong magnetic field, radio frequency signals along with computers. Images may be examined on a computer display during the investigational study [11, 40]. In gastrointestinal research, magnetic resonance imaging has been the most useful and attractive method of investigation of stomach emptying, motility as well as intragastric delivery of macronutrients along with active molecules. This particular magnetic resonance imaging technique consists of various useful advantageous features such as lack of ionizing irradiation, high temporal and spatial resolution, high soft tissue contrast, supra-magnetic and harmless paramagnetic, magnetic resonance imaging contrast agents etc. which may be used exclusively for improving or restraining the fluids and tissues signal and therefore allowing improved description and investigation of organs. However, temporal resolution of traditional magnetic resonance imaging measurements is reasonably low [6, 44-46].

^{13}C Octanoic acid breath test

Octanoic acid, a medium-chain fatty acid which is absorbed by the upper portion of small intestine, transported rapidly to the liver and oxidised instantaneously to form CO_2 and is exhaled out. ^{13}C octanoic acid can be incorporated into gastro retentive systems. Octanoic acid produces CO_2 owing to reaction in the stomach and emerges into the air. The "carbon atom" in octanoic acid, which essentially forms CO_2 can be substituted with ^{13}C isotope. Therefore, time until $^{13}CO_2$ gas is detected in breath can be regarded as dosage form stomach retention period. No response will be obtained and without release of CO_2 as dosage form transit to intestine. Major drawbacks of this test include lack of accuracy in comparison to scintigraphy, challenging mathematics for calculations, the requirement of multiple sampling, and extended sampling times etc. [47, 48].

Miscellaneous research efforts concerning with *in vivo* imaging characterization of floating dosage types have been reported. Some important results are meticulously depicted in table 1.

Table 1: *In vivo* characterization of floating dosage types

S. No.	Drug	Floating dosage form	Method of preparation	*In vivo* technique	Authors	Year	Ref.(s)
1	Vildagliptin	Floating microspheres	-	X-ray imaging	Kumari *et al.*	2021	[49]
2	Moxifloxacin	Floating matrix tablets	-	X-ray imaging	Sheikh *et al.*	2020	[50]
3	Valsartan	Floating matrix tablets	Direct compression	X-ray imaging	Rahamathulla *et al.*	2019	[51]
4	Itraconazole	Floating microspheres/beads	Ionotropic gelation	Gamma scintigraphy	Gokbulut *et al.*	2018	[52]
5	Calcium ion	Floating tablets	Direct compression	Gamma scintigraphy	Sharma *et al.*	2017	[53]
6	Metformin hydrochloride	Hydrodynamically balanced matrix tablets	Wet granulation	Gamma scintigraphy	Razavi *et al.*	2015	[54]
7	Metformin hydrochloride	Floating tablets	Wet granulation	Gamma scintigraphy	Razavi *et al.*	2015	[55]
8	Ascaridole	Floating tablets	Direct compression	Gamma scintigraphy	Zhao *et al.*	2015	[56]
9	Bergenin and cetirizine dihydrochloride	Floating tablets	-	Gamma scintigraphy	He *et al.*	2012	[57]
10	Riboflavin	Floating beads	-	Gamma scintigraphy	Yao *et al.*	2012	[58]
11	Ciprofloxacin hydrochloride	Floating matrix tablets	Direct compression	X-ray imaging	Tadros *et al.*	2010	[59]
12	Atenolol and lovastatin	Floating tablets	Direct compression	Roentgenography	Kulkarni *et al.*	2009	[60]
13	Levodopa and carbidopa	Floating minitablets	Direct compression	Gamma scintigraphy	Goole *et al.*	2008	[61]
14	Diltiazem hydrochloride	Floating microspheres	Ionotropic gelation	Gamma scintigraphy	Ma *et al.*	2008	[62]
15	Propranolol hydrochloride	Floating tablets	Direct compression	Magnetic resonance imaging	Strubing *et al.*	2008	[63]
16	Clarithromycin	Floating tablets	Wet granulation	Radiographic studies	Nama *et al.*	2008	[64]
17	Metformin	Floating capsules	-	Gamma scintigraphy	Ali *et al.*	2007	[65]
18	Celecoxib	Floating capsules	Physical blending	Gamma scintigraphy	Ali *et al.*	2007	[66]
19	Verapamil hydrochloride	Floating pulsatile capsule	-	Gamma scintigraphy	Zou *et al.*	2007	[67]
20	Repaglinide	Floating microspheres	Solvent diffusion technique	Gamma scintigraphy	Jain *et al.*	2006	[68]
21	Orlistat	Floating microspheres	Solvent evaporation	Gamma scintigraphy	Jain *et al.*	2006	[69]
22	-	Floating beads	-	Gamma scintigraphy	Stops *et al.*	2006	[70]
23	Riboflavin	Floating beads	-	Gamma scintigraphy	Stops *et al.*	2006	[71]
24	Riboflavin	Floating microballons	Solvent diffusion	Gamma scintigraphy	Sato *et al.*	2004	[72]
25	Amoxicillin	Polyionic complex gastroretentive hydrogels	-	^{13}C octanoic acid breath test	Torrado *et al.*	2004	[73]
26	Riboflavin	Floating hollow microballons	Emulsion Solvent diffusion	-	Sato *et al.*	2003	[74]
27	-	Floating tablets	-	Magnetic resonance imaging	Steingotter *et al.*	2003	[42]
28	-	Floating beads	Freeze-drying	Gamma scintigraphy	Whitehead *et al.*	1998	[75]
29	-	Floating resin beads	Ion exchange resin	Gamma scintigraphy	Atyabi *et al.*	1996	[76]
30	Theophylline	Floating tablets	-	Gamma scintigraphy	Desai *et al.*	1993	[77]
31	Propranolol hydrochloride	Hydrodynamically balanced capsules	-	Gastroscopy	Khattar *et al.*	1990	[78]
32	-	Floating tablets, capsules and pellets	-	Gamma scintigraphy	Davis *et al.*	1986	[79]

Therefore, significant and incessant research efforts have been done worldwide for *in vivo* imaging monitoring of innovative floating systems. Several *in vivo* strategies are available for the evaluation of gastro retentive floating dosage forms with site-specificity and unique drug release kinetics in the GIT region for achieving appropriate therapeutic needs.

FUTURE PERSPECTIVES

To assess *in vivo* gastric residence aspects, a variety of imaging methods frequently utilized involves gamma scintigraphy, roentgenography, ultrasonography, magnetic marker monitoring, magnetic resonance imaging etc. Different *in vivo* imaging monitoring approaches includes the use of radiation and exposure materials that need to be replaced with less hazardous materials in order to lessen the adverse impact of these substances. Improvements are also required so that more accurate *in vivo* imaging procedures should be risk-free, offer patient convenience and comfort, and get rid of various adverse effects. Additional sophisticated developments in dynamic scanning and imaging will improve the imaging technique more perfectly, particularly in the case of magnetic resonance imaging. New marker designs for magnetic resonance imaging should also be well exploited. Furthermore, ultrasound used in ultrasonosonography and gamma emitting radioisotopes in gamma scintigraphy need to be focused more precisely. Additionally, the utilization of advanced technologies which possesses all efficient characteristics for the successful imaging of gastroretentive delivery systems would be a suitable and promising futuristic endeavour in this vistas. It is also emphasized that further progress and technological advancements in the various *in vivo* imaging methodologies offers immense benefits to researchers in the avenue of gastroretentive floating systems.

CONCLUSION

Drugs having narrow absorption window in gastrointestinal tract is often restricted by reduced bioavailability, owing to inadequate drug release as well as less retention time at the absorption region. Gastroretentive systems revealed tremendous potential to enhance therapeutic efficacy and bioavailability of drugs to overcome constraints linked with conventional formulations. Among various promising approaches of gastroretentive technology, floating systems is one of the flourishing avenues for improving the drug residence into the stomach. This review provides insight into the significant characterization of floating drug delivery systems. Various *in vivo* imaging assessment techniques for comprehensive and effective analysis of gastroretentive drug delivery systems are summarized in this article along with their various salient advantages. Several research endeavours in the domain of *in vivo* imaging assessment methodologies for enhanced optimum efficacy of gastroretentive systems have also been distinctly presented.

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AUTHORS CONTRIBUTIONS

All authors have equally contributed.

CONFLICT OF INTERESTS

No conflict of interest.

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