A Desk-top Literature for Research on Gas Engendering and Low-density Floating Drug Delivery Systems

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ABSTRACT

These studies aimed at providing information on floating drug delivery systems. By studying various international, and national journals, and reviewing articles on floating drug delivery systems as well as gastro retentive drug delivery systems, the authors congregated the information on floating drug delivery systems. In developing various drug delivery systems, gastro retentive drug delivery systems (GRDDS) has got an important place, as the conventional oral dosage forms have numerous problems such as gastric emptying time, enzymatic activity, and gastric pH changes. To overcome these problems, control drug delivery systems have been developed in the recent drug development approaches. Both effervescent and non-effervescent systems are the two main gastro retentive systems. Effervescent forms were developed using two systems, such as raft formation and gas generating systems. For gas generating systems, the most extensively used agent is sodium bicarbonate and, in some cases, ratios of sodium bicarbonate and citric acid. Developing an efficient gastro-retentive formulation is a real challenge, and the drug delivery system should remain for a sufficient time in the stomach. Various techniques and approaches have been employed to develop gastro-retentive dosage forms, and floating drug delivery systems (FDDS) has emerged as promising gastro-retentive drug delivery system. The currently available polymer-mediated non-effervescent and effervescent FDDS systems, which are designed based on the delayed gastric emptying and buoyancy principle, appear to be an effective and rational approach to modifying the controlled oral drug delivery.

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1. Introduction

The oral formulations have earned significant attention out of various dosage forms for human administration. The limited bioavailability is the most common problem in conventional oral formulations due to gastric-emptying time, enzymatic activity, and many other reasons. Due to such reasons, conventional oral dosage forms need to administer frequently, which may cause undesired effects [1, 2]. Recent technological development gave rise to many novel pharmaceutical products to overcome these issues, primarily the sustained release dosage forms. One of such dosage forms was gastro retentive systems which can attribute gastric-retention time and an extended period of drug release, which improves the patient compliance. The interest in this new drug delivery system was ignited due to the characteristic limitations of the conventional oral drug delivery systems [3, 4]. The fast gastric emptying time of conventional oral medications leads to a bioavailability issue for many drug molecules (e.g., pranlukast hydrate, metformin HCl, and baclofen) for which the leading principal site of absorption is the stomach / the proximal part of the small intestine. Solubility can be improved by prolonging the gastric retention time of drugs that are less soluble in intestinal pH and many drugs (e.g., captopril, metronidazole, and ranitidine HCl) which undergo degradation in the colon. To achieve the required therapeutic activity, frequent dosing is required for drugs with a short half-life [5]. However, oral sustained-controlled release formulations improving both gastric retention time and drug release for an extended period in a systemic circulation were developed to evade these problems. Apart from the systemic action, the gastro-retentive drug delivery systems (GRDDS) have proved to be locally effective in treating gastric and duodenal ulcers. GRDDS is also effective in treating esophagitis and eradicating Helicobacter pylori from the submucosal tissue of the stomach. GRDDS formulations' history has been reverted to almost three decades and they have established perfectly in-vitro characterization as well as development techniques [6]. Recently the development of various GRDDS, such as magnetic field-assisted gastro-retention, plug type swelling system, mucoadhesion technique, and floating system (i.e. the effervescence and non-effervescence) were employed. Factors impacting the Gastro retention were classified based on pharmaceutical technology factors such as size, density, and physiological factors like extrinsic and biological factors [7, 8].

2. Advantages of gastro retentive drug delivery systems

The merits of GRDDS are as presented as follows [9, 10].

- The floating dosage form retains for an extended period in the stomach.

- The floating dosage form is advantageous for producing local action in the stomach.
- Controlled delivery of the drug is possible.
- Reduction in mucosal irritation is possible by substantial drug release.
- Ease of administration.
- Improved patient compliance can be achieved.
- Targeted drug delivery is possible.
- GRDDS is advantageous for the drug absorbed through the stomach.
- The bioavailability of therapeutic agents is significantly enhanced.
- For the drug with a short half-life, the sustained release can be achieved and reduce the dosing frequency, as well.
- Gastro-retentive dosage form minimizes the fluctuation of drug concentration.

GRDDS minimizes the counter activity of the body, and the drug's efficacy is increased.

3. Disadvantages of gastro retentive drug delivery systems

The demerits of GRDDS are illustrated as follows [11, 12].

- Drugs which may produce gastric irritation are not suitable.
- The stomach contains mucus in a continuous renewal state, so unpredictable adherence may occur.
- The retention time in the stomach depends on the digestive state. Hence, the floating system should be administered after a meal.
- The ability to float depends upon the hydration state of the dosage forms.
- This system is unsuitable for drugs that have limited acid solubility.
- It is not proper for the drugs which have selective absorption in the stomach.

The floating system is not appropriate for those drugs having stability problems in the stomach.

4. Floating Drug Delivery System (Low-Density System)

The floating drug delivery system (FDDS) possesses a bulk density lower than the gastric fluid. For this, it remains buoyant in the stomach without affecting the extended period of gastric emptying time. The drug releases slowly at the desired rate when the dosage form floats on the gastric fluid contents, through which gastric retention time and plasma drug concentration can be increased and maintained. The residual system is void of the stomach after the drug release [2, 13]. Floating drug delivery systems were developed under two different systems.

4.1. Non-Effervescent System

It is also known as Hydrodynamically Balanced System (HBS). This system stays buoyant through the air entrapment in the swelled polymer. When this system contacts the gastric fluid, the hydration of hydrocolloids occurs by forming a gel on the surface and ultimately controls the drug release. As the outer surface goes into the solution, a barrier layer of gel is maintained immediately by an adjacent hydrocolloid layer [14].

4.2. Effervescent System

This system is made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum or inert gas. Swellable polymer and effervescent components were used in this system. The matrices are formulated so that they liberate carbon dioxide in the stomach due to the acidic environment. The hydrocolloids entrap the liberated carbon dioxide, leading to the floating of the dosage form and maintaining their buoyancy. These systems were divided into a volatile liquid-containing system and a gas-generating system [15, 16].

4.3. Advantages of floating drug delivery systems

The merits of floating delivery systems are as demonstrated as follows [17].

- Enhanced bioavailability.
- Sustained drug delivery/reduced frequency of dosing.
- Targeted therapy for local aliments in the upper GIT.
- Reduced fluctuations of the drug concentration.
- Improved selectivity in receptor activation.
- Reduced counter activity of the body.
- Extended effective concentration.

Minimized adverse activity in the colon.

4.4. Limitations of floating drug delivery systems

The demerits of floating delivery systems are as mentioned in the following [18].

- These systems require a high level of fluid in the stomach for drugs to float.
- Not suitable for drugs that have solubility or stability problems in GIT.
- Drugs such as Nifedipine which is well absorbed along with the entire GIT and undergoes first-pass metabolism, may not be desirable.
- Drugs which are irritant to the gastric mucosa are no longer desirable or proper.
- The unstable drugs in the acidic stomach environment are not the appropriate candidates to be incorporated into the systems.
- The dosage form should be administered with a full glass of water (200-250 mL).

These systems do not offer significant advantages over the conventional dosage forms for drugs absorbed throughout the gastrointestinal tract.

4.5. Mechanism of floating drug delivery systems

The gas-generating engine (mainly citric acid and sodium bicarbonate combination) releases CO_2 gas upon reacting with water or gastric juices. This gas makes the tablet float. The polymer incorporated into the tablet swells and forms a permeable film surrounding the tablet to release the drug from it. **Figure 1** displays how a floating tablet buyout in gastric fluid.

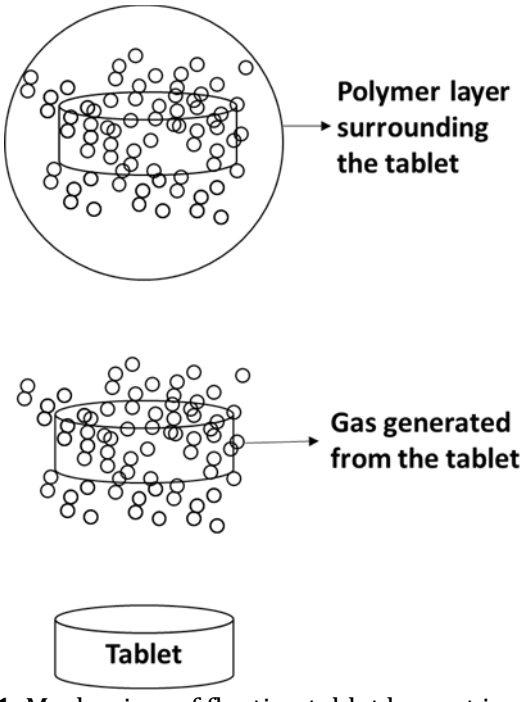

Figure 1. Mechanism of floating tablet buyout in gastric fluid

The past work done on gas generating floating drug delivery systems is elucidated in **Table 1**.

Table 1. Drugs that were tried as gas generating floating drug delivery systems

Drug	Polymers	References
Quetiapine Fumarate	Hydroxy ethyl cellulose (HEC)	Patel *et al.*, 2021 [19]
Apremilast	Carbopol 934P, HPMC K4M, tragacanth, and sodium alginate (SA)	Deshmukh *et al.*, 2021 [20]
Vildagliptin	HPMC K4M and Carbopol 934	Kothule *et al.*, 2021 [21]
Carvedilol	SA, carbopol 934P, and sodium CMC	Prasanta *et al.*, 2020 [22]
Nicardipine HCl	HPMC K15M and glyceryl behenate	Vijay *et al.*, 2018 [23]
Minocycline HCl	Methocel K100LV, Methocel K15M, and Carbopol 934	Ali *et al.*, 2017 [24]
Acyclovir	HPMC K4M, Carbopol 934, and Polyvinylpyrrolidone	Rahim *et al.*, 2017 [25]
Metoprolol succinate	Polyethylene oxide (PEO) and hydroxyethyl cellulose (HEC)	Kauser *et al.*, 2017 [26]
Cephalexin	HPMC K4M, Sodium CMC, and Cetyl alcohol	Kambham *et al.*, 2016 [27]
Cefuroxime Axetil	PEO 303 and HPMC K100 LV CR	Sanjay *et al.*, 2016 [28]
Cefpodoxime Proxetil	Plasdone S 630 and PEO	Hemali *et al.*, *2016* [29]
Labetalol HCl	Hydroxy propyl cellulose, HEC, and Xanthan gum	Subhash *et al.*, 2016 [30]
Febuxostat	HPMC (K4M, K15M, and K100M)	Mukesh *et al.*, 2015 [31]
Imatinib Mesylate	HPMC K4M, carbopol 934P, and SA	AliKadivar *et al.*, 2015 [32]
Pentoxifylline	Hydroxyethyl cellulose, and SA	Safwan *et al.*, 2015 [33]
Omeprazole	HPMC K4 M and HPMC K15 M	Patel *et al.*, 2015 [34]
Loratadine	HPMC K15 M and SA	Begum *et al.*, 2014 [35]
Metronidazole	HPMC K4M, carbopol 974P, SA, Locust Gum, and Guar Gum	Laila *et al.*, 2014 [36]
Levofloxacin	HPMC K100M and carbopol 940P	Sally *et al.*, 2014 [37]
Atenolol	HPMC K4M, and HPMC K100M	Kameswara *et al.*, 2014 [38]
Amlodipine Besylate	HPMC K100M and Carbopol 934P	Acharya *et al.*, 2014 [39]
Venlafaxine HCl	HPMC K15M and Cetyl alcohol	Harshal *et al.*, 2014 [40]
Metronidazole	HPMC K4M and Carbopol 934P	Amritha *et al.*, 2014 [41]
Lamivudine	Methocel, Polyox, and Carbopol	Suresh *et al.*, 2014 [42]
Atorvastatin calcium	HPMC and CMC	Hwisa *et al.*, 2013 [43]
Metronidazole	HPMC K15M and Sodium CMC	Rapolu *et al.*, 2013 [44]
Ofloxacin	HPMC K100M and Crospovidone	Rajani *et al.*, 2013 [45]
Pioglitazone	Guar gum, gellan gum, and gelatin	Seth *et al.*, 2013 [46]
Tramadol HCl	HPMC K4M, HPMC K15M, and HPMC K100M	Chandrashekhar *et al.*, 2012 [47]
Ranitidine HCl	HPMC and PEO	Gharti *et al.*, 2012 [48]
Amoxicillin Trihydrate	HPMC K100M, HPMC K15M, and HPMC K4M	Ranade *et al.*, 2012 [49]
Captopril	HPMC K100M, K15M, and K 4M	Singh *et al.*, 2011 [50]
Tizanidine HCl	HPMC K4M, K15M, and K100M	Someshwar *et al.*, 2011 [51]
Nifedipine	HPMC K4M, and carbopol 934P	Shaikh *et al.*, 2011 [52]
Dextromethorphan HCl	HPMC K4M, K15M, K100M, and ethyl cellulose (EC)	Liandong *et al.*, 2011 [53]
Furosemide	HPMC K100LV, HPMC K4M, HPMC K100M	Sungthongjeen *et al.*, 2010 [54]
Domperidone	HPMC K4M, Carbopol 934P, and SA	Prajapati *et al.*, 2009 [55]
Carbamazepine	HPMC K4 M and EC	Patel *et al.*, 2007 [56]
Ranitidine	HPMC K100 LV, K4M, and K15M	Yeole *et al.*, 2005 [57]

5. Conclusion

Due to its excellent swelling and direct compressibility, HPMC was used in more than 90% of GRDDS. The majority of the gas-generating excipients employed were sodium bicarbonate and citric acid combination. Based on the delayed gastric emptying and buoyancy principles, the currently available polymer-mediated non-effervescent and effervescent floating drug delivery systems appear to be an effective and rational approach to the modification of controlled oral drug delivery. From the above table, the authors concluded that various gas-forming polymers such as hydroxypropyl methylcellulose (K100M, K15M, and K4M), carbopol 974P, sodium alginate, ethyl-cellulose, PEO, and natural gums like guar gum, acacia, etc. can be used for the preparation of floating tablets to increase the gastric retention time. The gastro retention was elevated by incorporating gas-generating agents like sodium bicarbonate and citric acid.

Conflict of Interest

The authors declare no conflict of interest.

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