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Relevance of ionotropic gelation technique in the development of floating multiparticulate drug delivery systems

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Abstract
Various attempts have been made in the development and evaluation of novel dosage forms which can be retained in the stomach for an extended period of time in a predetermined manner. Gastroretentive dosage forms enable prolonged and continuous input of the drug to the upper part of the gastrointestinal tract and overcome physiological adversities. In pursuit of this endeavour, different novel strategies have been undertaken for the design of several gastroretentive drug delivery systems including floating systems. Ionotropic gelation technique is a feasible approach for achieving a prolonged and predictable drug release to control the gastric residence time using the floating dosage form that can provide newer therapeutic benefits. In this review, we have focused on exploring the design considerations, various advantages and methodology of ionotropic gelation technique along with various significant research findings in the vistas of floating multiparticulate systems.

Keywords: Ionotropic gelation technique, gastroretentive dosage forms, floating systems

1. Introduction

During the past two decades, there has been an increasing interest in optimizing the efficiency of existing drugs through the use of better-designed drug delivery systems. Various technological and scientific attempts have been devoted to the design and evaluation of oral drug delivery systems [1]. Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation, etc. [2]. Conventional oral dosage forms provide a specific drug concentration in the systemic circulation without offering any control over drug delivery [3]. Design of oral controlled drug delivery system should primarily be aimed to achieving more predictable and increased bioavailability of drugs [4, 5]. However, the development process is precluded by several physiological adversities such as inability to restrain and localize the drug delivery system within desired regions of the GIT and highly variable nature of the gastric emptying process [6].

It can be anticipated that, depending upon the physiological state of subject and design of pharmaceutical formulation, the emptying process can last from a few minutes to 12 h. This variability, in turn, may lead to unpredictable bioavailability and times to achieve peak plasma levels [7]. Furthermore, the relatively brief gastric emptying time in humans normally averages 2-3 h through the major absorption zone (stomach or upper part of the intestine) can result in incomplete drug release from the dosage form leading to diminished efficacy of the administered dose. Drugs having a short half-life are eliminated quickly from the blood circulation. Various oral controlled drug delivery systems have been designed which can overcome these problems and release the drug to maintain its plasma concentration for a prolonged period of time [8]. Thus, control over placement of drug delivery system in a specific region of the GI tract offers numerous advantages, especially for drugs exhibiting an absorption window in the GI tract or drugs with a stability problem. Overall, the intimate contact of drug delivery system with an absorbing membrane has potential to maximize drug absorption and may also influence the rate of drug absorption. These considerations have led to the development of oral controlled release dosage forms possessing gastric retention capabilities [9, 10].

Gastroretentive drug delivery system (GRDDS)

Dosage forms that can be retained in the stomach are known as a gastroretentive drug delivery system. GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time. After oral administration, these dosage forms would be retained in the stomach and release the drug in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption site in the upper GIT as represented in (figure 1) [11]. Gastroretentive dosage forms have application for local drug delivery in case of peptic ulcer disease which embraces both gastric and duodenal ulcer [12]. GRDDS can remain in the gastric region for several hours and hence considerably prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility of drugs that are less soluble in a high pH environment [13].

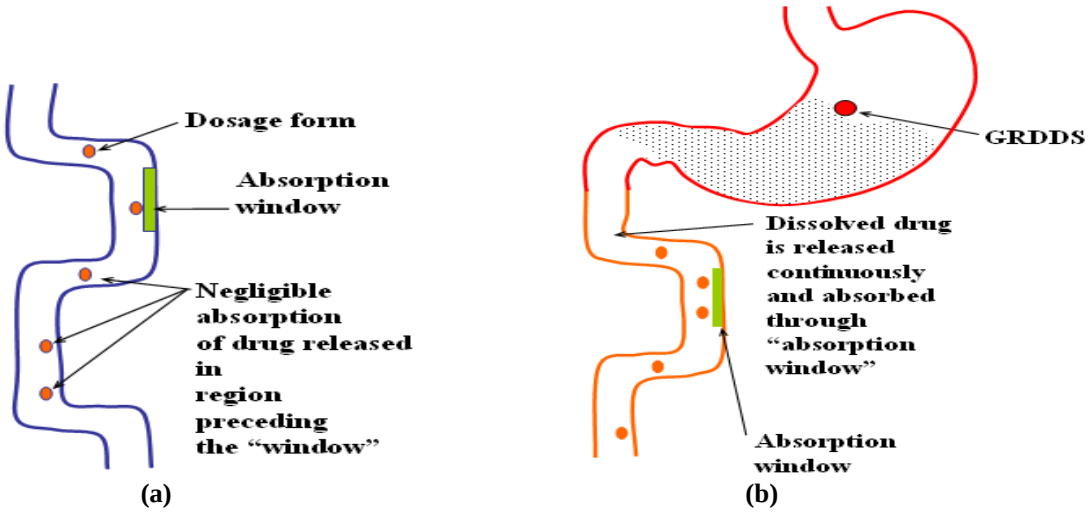

Fig 1: Drug absorption in the case of (a) Conventional dosage forms (b) Gastroretentive drug delivery systems.

2. Approaches to increase gastric retention time

Controlled gastric retention from the dosage form may be achieved by formulating low density dosage form that remains buoyant above gastric fluid (floating system), high density system that is retained at the bottom of the stomach. Gastric retention can also be increased by imparting bio- or muco-adhesion to the stomach mucosa, reducing the motility of the GI tract by concomitant administration of drugs or pharmaceutical excipients. Expansion of the dosage form by swelling or unfolding to a large size which limits gastric emptying of the dosage form through the pyloric sphincter, utilizing ion - exchange resin, superporous hydrogels, and magnetic systems using modified shape system can also improve gastric retention. Among the various approaches employed to increase the gastric retention of an oral dosage form, floating drug delivery system is considerably easy and logical approach in the development of GRDDS [14-19].

Floating drug delivery systems

Floating systems are intended to float in and over the gastric contents resulting in prolonged gastric residence time [20-22]. These systems have a bulk density less than the gastric content and so remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug [23]. While the system is floating over the gastric contents, the drug is released slowly at the desired rate, which reduces fluctuations in plasma drug concentration. The following approaches have been used in the design of various floating dosage forms such as single and multiple-unit dosage forms.

Single unit dosage form

Single unit floating dosage forms such as floating tablets utilizes matrices prepared with swellable polymers such as methocel, natural polysaccharides etc. and various effervescent components, e.g., sodium bicarbonate, citric acid and tartaric acid. These systems are fabricated so that upon contact with gastric fluid, carbon dioxide is liberated that is entrapped in the gellified hydrocolloid which produces an upward motion of the dosage form and maintains its buoyancy. These dosage forms are variable in prolonging the GRT in the stomach when administered orally and are associated with problems such as sticking together or being obstructed in the GIT, which may have a potential danger of producing irritation [24].

Multiple unit dosage forms

Multiparticulate drug delivery technology represents a frontier and promising avenue of pharmaceutical sciences which involves interdisciplinary scientific advancements in better health care along with improved therapeutic interventions [25]. Considerable research efforts have been undertaken in oral sustained or controlled release multiparticulate drug delivery system due to its advantages over single unit dosage forms [26]. After oral administration, multiple unit system retains their structure in GIT and each unit acts as an individual entity [27]. Multiparticles can be developed in various forms such as granules, pellets, beads, mini-tablets, microspheres etc. [28]. With floating multiple unit dosage forms, it is considered that majority of particles will remain above the stomach contents for an extended period of time. This approach reduces the inter subject variability in absorption, lower the probability of dose dumping and bursting associated with the single-unit systems [29-32]. It has also been described that multiple unit floating dosage forms, distribute more uniformly within the gastric content, resulting in long lasting effects.

3. Development of floating multiparticulate systems

Wide ranges of developmental techniques are available for the preparation of floating drug delivery systems. However, ionotropic gelation technique has been extensively employed by a large number of scientific investigators worldwide for the preparation of multiple units floating drug delivery system. Ionotropic gelation is earlier known as "ion induced gelation" and; is widely utilized for the encapsulation of the large number of drugs. In this method, cross linking of the polyelectrolyte takes place in the presence of counter ions (generally divalent cations) to form gel matrix. For this purpose, different cross- linking agents, including: Ca^{2+}, Ba^{2+}, Mn^{2+}, Co^{2+}, Sn^{2+} and Pb^{2+}, also used for preparation of the floating multiple unit. But most widely Ca^{2+} ions are used as a cross linking agent.

Polyelectrolyte such as sodium alginate having a property of a coating on drug core and acts as a release retardant material and contains certain anion in their chemical structure. These anions forms mesh-work structure by combining with polyvalent cations and induced gelation. Floating microparticles are prepared by dropping the drug loaded polymeric solution through the needle of the required particle

size into the solution of polyvalent cation as represented in (figure 2). The cations diffuse into the drug loaded polymeric drops, forming a three dimensional lattice of ionically cross linked moiety. Microparticle formed left in the original solution of cross linking agent for sufficient time period for internal gelification and they are separated by filtration. Natural polysaccharides such as sodium alginate can be used to improve drug entrapment and are widely employed for the preparation of floating microparticles [33-36].

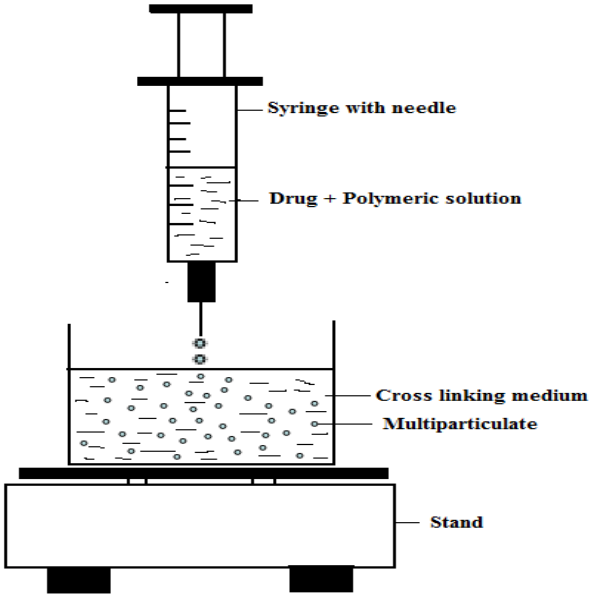

Fig 2: Schematic representation of preparation of floating multiparticulate by ionotropic gelation technique.

4. Advantages of ionotropic gelation technique

The encapsulation techniques (e.g., solvent evaporation or coacervation–phase separation) normally involve water insoluble polymers as carriers which require large quantity of organic solvents for their solubilisation. As a result the processes become vulnerable to safety hazards, toxicity and increases the cost of production, making the techniques non reproducible, economically and ecologically at an industrial scale. These concerns demand a technique free from any organic solvent. Thus, the aqueous polymeric dispersions have played a great role in replacing organic solvents in the coating of solid dosage forms with water soluble polymers. Ionotropic gelation method has numerous advantages which are given in the following text [37-40].

- Ionotropic gelation is a versatile method and can be adopted for encapsulation of soluble and insoluble solid materials.
- Optimization of drug concentration in plasma and reduction of side effects, particularly for drugs with low therapeutic indexes.
- This technique can be used to produce particles of micro and nano sizes.
- It offers a simple and mild preparation method in the aqueous environment, easy and feasible at an industrial scale.
- Floating dosage forms formulated from this provide controlled, sustained or site specific drug release of active ingredients.
- Ionotropic gelation is a low cost, economical process which is used for encapsulation of large variety of therapeutic agents.
- This technology is rapid, simple and provides high production efficiencies.
- Ionotropic gelation process is suitable for the preparation of drug loaded floating multiple unit systems based on biodegradable and biocompatible polymers.
- This technique demand or free from any organic solvent and becomes vulnerable to safety hazards, toxicity.
- The hygroscopic properties of many therapeutic agents may be reduced by the floating system prepared by ionotropic gelation method.
- Floating multiple unit system prepared by this technique provides content uniformity.
- In the fabrication of multiple unit system, it gives high encapsulation efficiencies.

5. Significant research findings

Concerted research efforts have been carried out worldwide to explore the different vistas of floating multiparticulate system formulated by ionotropic gelation technique. Significant numbers of innovations and advancements have been done with floating dosage forms and are presented in the (table 1).

Table 1: Various research findings in the arena of floating multiparticulate system

Author	Drug	Floating Dosage Form	Polymer(s)	References
Bobade *et al.,* (2016)	Diltiazem	Microspheres	Sodium alginate, Chitosan and HPMC K4M	[41]
Saxena *et al.,* (2016)	Diltiazem Hydrochloride	Beads	Sunflower oil	[42]
Kala and Nair, (2016)	Budesonide	Microspheres	Chitosan	[43]
Khan *et al.,* (2015)	Tinidazole	Beads	Sodium alginate and pectin	[44]
Nagasree *et al.,* (2015)	Gemifloxacin Mesylate	Microspheres	HPMC	[45]
Singh *et al.,* (2013)	Famotidine	Beads	Sodium alginate alone or together with pectin and HPMC K4M	[46]
Malakar *et al.,* (2012)	Cloxacillin	Beads	Sodium alginate	[47]
Madhvi *et al.,* (2012)	Piperine	Beads	HPMC K4M, Sodium alginate	[48]
Yao *et al.,* (2012)	Riboflavin	Beads	Sodium alginate, Poloxamer 188	[49]
Mosareddy *et al.,* (2011)	Metformin HCl	Microspheres	HPMC E50, Methyl cellulose, Ethyl cellulose	[50]
Raja *et al.,* (2011)	Acyclovir	Beads	Gellan gum, HPMC, Chitosan	[51]
Verma *et al.,* (2011)	Rifabutin	Beads	Gellan gum	[52]
Mishra *et al.,* (2010)	Torsemide	Microspheres	HPMC	[53]
Somani *et al.,* (2010)	Aceclofenac	Beads	Pectin	[54]
Gaikwad *et al.,* (2010)	Aceclofenac	Beads	Pectin, Sodium alginate	[55]

Yellanki *et al.,* (2010)	Riboflavin	Beads	Sodium alginate, HPMC	[56]
Tripathi *et al.,* (2010)	Amoxicillin	Beads	HPMC K4M, Carbopol 934	[57]
Javadzadeh *et al.,* (2010)	Metronidazole	Beads	Sodium alginate	[58]
Salunke *et al.,* (2010)	Metformin HCl	Microcarriers	HPMC K4M, Sodium alginate	[59]
Kumaran *et al.,* (2010)	Mosapride	Beads	Sodium alginate	[60]
Gattani *et al.,* (2010)	Clarithromycin	Beads	Sodium alginate, HPMC K4M	[61]
Zhang *et al.,* (2009)	Riboflavin	Microballoons	Calcium alginate	[62]
Jaiswal *et al.,* (2009)	Ranitidine HCl	Beads	Sodium alginate	[63]
Bajapi *et al.,* (2008)	Calcium chloride	Beads	Sodium alginate	[64]
Ma *et al.,* (2008)	Dilitiazem HCl	Microspheres	Sodium alginate, Chitosan, Eudragit	[65]
Fursule *et al.,* (2008)	Propranolol	Beads	Sodium alginate	[66]
Srinatha *et al.,* (2008)	Ciprofloxacin	Beads	Sodium alginate, Gellan gum, chitosan	[67]
Hajare *et al.,* (2008)	Diltiazem HCl	Microspheres	HPMC K100M, Eudragit RS100	[68]
Rajinikanth *et al.,* (2007)	Acetohydroxamic acid	Beads	Gellan gum	[69]
Tang *et al.,* (2007)	Niacinamide, Ibuprofen	Beads	Calcium alginate	[70]
Badve *et al.,* (2007)	Diclofenac sodium	Beads	Pectin	[71]
Sahoo *et al.,* (2007)	Ciprofloxacin HCl	Microspheres	Sodium alginate, HPMC	[72]
Ishak *et al.,* (2007)	Metronidazole	Beads	Methyl cellulose, Carbopol 934P	[73]
Shishu *et al.,* (2007)	5-Fluorouracil	Beads	Sodium alginate, HPMC K15M	[74]
Stops *et al.,* (2006)	Riboflavin	Beads	Sodium alginate	[75]
Sharma *et al.,* (2006)	Meloxicam	Beads	Sodium alginate	[76]
Sriamornsak *et al.,* (2005)	Metronidazole	Beads	Pectin, Eudragit RL 100	[77]
Sriamornsak *et al.,* (2004)	Edible oil	Beads	Methoxy pectin	[78]
El-Kamel *et al.,* (2003)	Diltiazem HCl	Beads	Pectin, Methyl cellulose	[79]
Choi *et al.,* (2002)	Riboflavin	Beads	Sodium alginate, HPMC	[80]
El-Gibaly *et al.,* (2002)	Melatonin	Microcapsules	Chitosan	[81]
Whitehead *et al.,* (2000)	Amoxicillin trihydrate	Beads	Sodium alginate	[82]

6. Conclusion

Gastroretentive floating drug delivery technology has emerged as an efficient approach for enhancing the bioavailability and controlled delivery of various therapeutic agents. Floating multiparticulate prepared by ionotroipc gelation technique holds enormous applications as a vehicle for administration of therapeutic agents. It has also been used potentially in pharmaceutical preparation and drug formulation as a feasible approach for a wide variety of biologically active agents. Thus, proper designing of floating drug delivery system will enhance the patient compliance; optimise drug delivery to target site and minimizing the undesired side effects. By selection of the appropriate type of cross linking agent, added excipients, dosage forms of various morphologies and characteristics can be fabricated. As research and development continues with delivery system using the ionotropic gelation technique, we expect to see many innovative and exciting applications in the future for delivery of drug molecules in a more efficient manner. Furthermore, recent innovations in pharmaceutical investigation will surely provide real prospects for the establishment of novel and effective means in the development of these promising drug delivery systems.

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