Evaluation methods and polymers used in gastroretentive dosage forms: A recent update.

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Abstract

Recently in the field of oral drug delivery, the Gastro retentive Drug Delivery system (GRDDS) has gained immense popularity. By this systems dosage form retain in the stomach for an extended period of time and release the drug slowly that can challenge may disadvantages associated with conventional oral delivery, including poor bioavailability. Such dosage forms aim to release drugs in the upper part of the gastro intestinal tract especially in the stomach in a controlled release manner that might provide sustained release characteristics without sacrificing much of total bioavailability. Apart from in vitro characterisation, 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 used to evaluate *in vivo* gastric residence time. The floating drug delivery systems are required to possess proper floating capability in gastric systems and use of natural polymers in such delivery system has been very beneficial. Natural gums are among the most popular hydrophilic polymers be because of cost-effectiveness and regulatory acceptance. Natural polymers have no of advantages like nontoxic, biocompatible, natural in origin. This review also gives a brief idea about advanced polymers including Eudragit, Carbopol, Hydroxyl Propyl Methyl Cellulose etc. and other excipients used for formulating GRDDS. This review also highlights the different *in vivo* evaluation parameters of GRDDS.

Keywords: Polymer swelling, *In vivo* methods, Applications, Gastro retention.

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Introduction

Oral formulations have a significant place among the various dosage forms developed so far for human administration. Conventional oral delivery shows limited bioavailability because of fast gastric emptying time. However, the recent technological development has resulted to many novel pharmaceutical products, mainly the controlled drug delivery systems to overcome this problem .The prolonged residence of dosage form in the stomach, called gastro retention, have various therapeutic and biopharmaceutical benefits. Some of the benefits are decreased fluctuations of drug concentration in the plasma, improved patient compliance due to reduced dosing frequency, improved local drug activity in the stomach and improved bioavailability of certain drugs with absorption window in the upper small intestine. In developing novel drug delivery systems, natural polymers and semi synthetic derivatives broaden admiration. Natural polymers have many advantages, their compatibility with other agents, readily available, chemical modification and degradability. Synthetic excipients causes' unwanted effect in humans and natural excipients are always given preference. Natural gums have variety of applications as binders, suspending agents, disintegrates and emulsifying agents; in drug delivery systems and are also useful in preparing sustained release and immediate release formulations [1]. Floating drug delivery system have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. This system will float on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. Single and multi-unit dosage forms are two types of approaches available to formulate floating dosage forms. Floating time of dosage form in the stomach can be improved by number of approaches such as gas generating systems, raft forming systems, low density systems etc. Basically this floating systems are classified two effervescent and non-effervescent systems. In effervescent systems, gas-generating agents are used for the effervescence in dosage form and swell able polymers and hydrocolloids are used in non-effervescent systems and it is given in Figure 1.

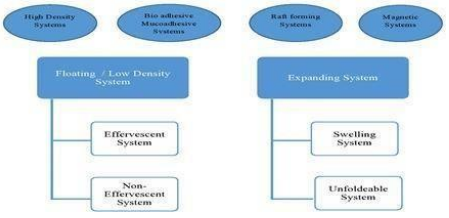

Figure 1. *Different approaches of GRDDS.*

Literature Review

Polymers used in gastric retention systems

Mainly two types of polymers are used in formulation, it may be naturally occurring or may be synthetic or may be semi-synthetic. Natural polymers has advantages over synthetic polymers and is given in Figure 2.

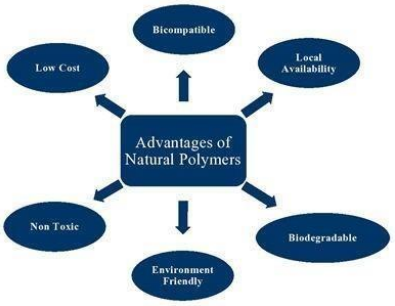

Figure 2. *Advanges of natural polymers.*

Natural Polymers have some disadvantages like:

- Microbial contamination
- Reduced viscosity on storage
- Extraction process very complicated and high cost
- High degree of variability
- Uncontrolled rate of hydration

Disadvantages of Synthetic Polymer

- Toxic
- Synthetic process is very complicated and high cost
- Poor biocompatible
- Acute and chronic adverse effect

Natural polymers

Chitosan: Natural swellable polymer is Chitosan and it is N–deacetylate derivative of Chitin. Chitin is a straight homopolymer composed of–(1,4)–linked N–acetyl glycosamine units, while Chitosan comprises of co polymers of glucosamine and N–acetyl glycosamine. Different grades of Chitosan are available on the basis of their degree of deacetylation and molecular weight.

Chitosan is non-toxic, biodegradable, biocompatible polymer and use of the Chitosan for the oral extended release tablet, it can be either by granulation or simply direct compression method. It is odour less, creamy or white flakes or powder and partially insoluble in 95% ethanol and soluble in water. It is used as viscosity enhancer, mucoadhesive, tablet binder, coating agent and disintegrant [2].

Chitosan plays an important role in stomach–specific drug delivery, intestinal delivery and colon-specific drug delivery. Chitosan achieves a sustained release behaviour at a concentration =50% of tablet weight.

Guar gum: Guar gum belongs to family Leguminosae and is a natural non-ionic polysaccharide derived from seeds of cymopsis tetragonolobus. It is used as binder, disintegrent, polymer in solid dosage forms. It contains linear chains of – (1-4) –b-D-mannopyranosyl units with a D-galactopyranosyl units attached by (1-6) Linkages. It is water soluble and not soluble in inorganic solvents. It is whitish yellow powder and has no taste or odour. It mainly consists of polysaccharides of high molecular weight (50000-8000000) composed of galactomannans, mannose. The viscosity of gum is influenced by temperature, PH and presence of solids.

Xanthan gum: It is a well-known biopolymer which is natural, biosynthetic, edible gum and consists of glucose, mannose and glucuronic acid. It is used as gelling agent, stabilizing agent, viscosity increasing agent, suspending agent, thickening agent and emulsifying agent. The drug release kinetics with Xanthan gum is zero order and this is an advantage over HPMC drug release has been shown to be faster at higher electrolyte concentrations (Sodium or Potassium Chloride). Xanthan gum is a suitable candidate for controlled release formulation especially with the incorporation into tablet. It is used as Pharmaceutical excipient since it is of natural origin, biocompatible and safe and is relatively cheap to produce.

Sodium alginate: Alginate is a polysaccharide, it is synthesised by brown sea weeds and soil bacteria. It is biocompatible, bioadhesive, PH sensitive and non-immunogenic. Sodium alginate has several biological activity of vascular endothelial growth factor, immunomodulatory, anti-tumour activity, anti-coagulant activity [3].

Carrageenan: It is commonly used as bulking agent and thickening agent. It is a gel-forming polysaccharides extracted from red sea weeds species as Euchema, Chondrus Crispus. It is used as tablet excipient agent during granulation and compression because of its viscoelastic nature and robustness.

Pectin: Pectin, basically a polymer of D-galacturonic acid with (1-4) linkages. Pectin is an inexpensive, nontoxic poly-saccharide extracted from citrus peel or apple pomaces. It is also used as thickening agent and gelling agent. Usually a concentration of 1-5% Calcium Pectinate is used for the preparation of beads. It is stable in low pH solution and used as carrier material for different controlled release systems. Numerous approaches are used to induce buoyancy in cross linked gel beads, some of which include freeze drying, gas forming agents, use of volatile oil or fixed oils.

Gum karaya: It is known as Sterculia gum obtained from Sterculiaurens Roxburgh and belongs to family sterculiaceae. Gum Karaya is sparingly soluble in water, poorly soluble in 0.1 NHCL and slightly insoluble in ethanol (95%). Other similar organic solvents and alkali solutions at PH above 6.5. This gum is used as release rate controlling polymer and gum karaya swells in water. With this gum zero order drug release is observed along with erosion of matrices.

Psyllium husks: Psyllium obtained from the husk and seed of plantagoovata. Psyllium is coming under the category of

mucilaginous fibre due to its powerful gel forming ability in water. This husk is biocompatible, inert, swell able, biocompatible, inexpensive and easily available and environment friendly. This husk serve as reliable means for gastro retentive drug delivery system as it shows release retardant properties [4].

Tamarind gum: Tamarind Gum is collected from seed of tamarind tree, Tamarindus Indica. This gum is a polysaccharide composed of Galactosyl: Xylosyl: Glucosyl in ratio 1:2:3. Plant primary cell walls has major structural polysaccharide called Xyloglucan, which is used as binder, gelling agent, stabilizer and thickener in pharmaceutical industries. Wet-granulation technique is used for formulating matrix tablet using tamarind gum and drug release study can be characterised. Different concentrations of polymer can be used for tablet preparation. Decrease in drug release is observed with increase in polymer content.

Semi-synthetic / synthetic polymers

HPMC: HPMC act as binder, emulsifying agent and thickening agent, they are widely used in the oral, ophthalmic, nasal and topical formulation. They also used as tablet binder and coating solution for extended release. HPMC are available in different molecular weight 10000-1500000 Dalton. HPMC is a semisynthetic polymer and it is odourless and tasteless, white to slightly off-white colour. Fibrous or granular, free-flowing powder. which is used for the preparation of floating tablets and microspheres. HPMC belongs to the family of hydrophilic polymer, which in contact with liquid swell and make a gel layer around dry core of polymer matrix.

Ethyl cellulose: It is a long-chain polymer of b-anhydro glucose units joined together by acetal linkages. Ethyl cellulose is ethyl ether of cellulose and is used as tablet binder, coating agent, tablet filler and viscosity increasing agents. It is white in colour, odourless and tasteless with melting point 2400-2550^{2}C. It is non-biodegradable in nature, non-toxic, non-irritant, they are available in different grades as K, N and T type.

Acrylic acid derivatives: It is a derivative of acrylic and methacrylic acid. It is mainly used for the preparation of floating microspheres and available in different grades like Eudragit RL, E, and RS. RL100 and RS 100 are granular form and widely used and have mucoadhesive and PH independent swelling polymer [5]. It is non-biodegradable, non-absorbent and non-toxic in nature. RS and RL grades contains quaternary amino groups and used for sustained release formulations.

Excepients used in floating systems

Hydrocolloids: The agents that have the capacity to form gel are called hydrocolloids. Hydrocolloids which swells in contact with gastric fluid and maintains a relative integrity of shape and bulk density less than the gastric content.

Eg: Pectin, Agar, HPMC, Sodium Alginates etc.

Inert fatty materials: Pharmaceutically Inert Fatty Materials having a specific gravity <1, can be added to the formulation to increase the buoyancy.

Eg: Beeswax, Long chain alcohols, mineral oils and long chain alcohols.

Release rate retardants

These are agents that retards the release action of drug by decreasing the stability by using substances such as calcium phosphate, magnesium stearate, talc etc.

Release rate accelerants

These are agents that increases the rate of drug release eg: Lactose, mannitol. These may be present from about 5% to 60% of weight.

Buoyancy increasing agents

These agents are used to enhance the buoyancy of formulation eg. Ethyl cellulose polypropylene foam powder can be used to increase the buoyancy. It may be adapted up to 80% by weight.

Application of gastro retentive drug delivery systems

This system offers several applications for drugs having poor bioavailability, especially in the case of drugs having narrow absorption window with in upper part of the gastro intestinal tract. These are summarized as follows.

Sustained drug delivery

These systems can release the drug over a prolonged period of time and can remain in the stomach for a long period. Main problem of conventional drug forms is their short residence time in stomach, this can overcome with these systems [6]. In case of Hydro Dynamically Balanced Systems (HDBS) which have bulk density of <1 and as a result of this they can float on the gastric contents. These systems are relatively large in size and which prohibits its passage from the pyloric region. In general drug which display narrow absorption window, difficult to be formulated as immediate release DDS or oral controlled release drug delivery system because of the preparation of these drugs in the form of immediate release forms require frequent use of a dosage form which did not improve patient compliance in addition, these are some side effects related to rapid release of those drugs, while sustain drug release would prolong these release time, in such cases shows no benefits because the drug absorbed in the definite segment of GIT and in this case if the drugs are formulated as GRDDS they will retain in the stomach and improve the bioavailability.

Absorption enhancement

Drugs having poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates for the floating drug delivery systems. Prolonging in the gastric residence time might improve the bioavailability due to the enhancement of the solubility of drugs which are more soluble at low PH .

Site-specific drug delivery

Prolonged gastric retention time in the stomach leads to effective local action in the upper part of the small intestine especially in the treatment of peptic ulcer. Hydro dynamically balanced gastric retentive drug delivery is an innovative approach play important role in prolonging gastric residence time by targeting site specific drug release in the upper intestine for local as well as systemic effect [7].

Evaluation parameters of GRDDS

In vivo* Evaluation Parameters: In vivo* evaluation parameters can be used to predict the *in vivo* performance. The common methods of evaluation methods of gastro retentive strength, weight variation, friability, drug content, contact uniformity and in vitro drug release studies. Floating lag time and total floating duration is also used for evaluation studies of low density systems floating mechanism and the in vitro evaluation parameters are given in Table 1.

Table 1. *in vitro evaluation parameters of various grdds.*

GRDDS	Evaluation Methods	Description of Evaluation Method
Low Density	Floating Strength, Floating lag time, Total floating time	Test carried out at 37^{o}C in simulated gastric fluid and FLT and TFT were measured i.e., the time between introduction of dosage form and its buoyancy and time during which the dosage form remain buoyant is measured. Floating strength is measured using specifically designed basket holder connected with analytical balance
Systems	*In vitro* unfolding study	Place the folded dosage form into dissolution medium and examine the unfolding behaviour
Expandable Systems		Brookfield/Ostwald's viscometer at different interval is used to measure the viscosity of polymer
Raft forming Systems	Viscosity and Rheology	Place the weighed amount of dosage form into swelling medium (0.01 NHCL) and predetermined time point, the weight, diameter and length of swollen samples are measured
Super porous Hydrogel Systems	Swelling studies	Sieve Shaker and Coulter counter analyser is used for particle size analysis. Moisture content measured with Karl Fischer. The capacity of ion exchange depends upon the functional group available for cross linking
Ion Exchange Resin Systems	Particle size, moisture content, ion exchange capacity	Using USP type II apparatus at 50 rpm at 37 (Generally 0-12 hr.).
		High gel strength indicates better mechanical integrity
	In vitro drug release	FI-IR spectroscopy, HPLC, Differential scanning calorimetry
Applicable for all GRDDS	Gel Strength	
	Drug Excipient interaction study	

In vivo evaluation parameters

Radiology: X Rays are widely used method for examining internal body systems. X-Ray is used in floating dosage form as one of the assessment parameter. One of the most widely used Radio Opaque marker is Barium Sulphate, so widely used in dosage forms and GR imaging is done by X-Rays at intervals. X ray imaging is done at different time intervals (0, 1, 6, 12 and 24 hr). By this technique we can correlate the route of dosage form and gastric emptying time in the GIT. By using X-ray images we conclude whether the dosage form available in stomach or not.

Gamma scintigraphy: In Gamma Scintigraphy, the X-rays emitted by nucleotide are directed on a camera, which aids to focus and view to locate the location of dosage form in the GIT. ϒ Camera or scinti Scanner is used for the in direct observation of a formulation bythe involvement of a ϒ emitting radio nucleotide. But one major drawback regarding scintigraphy is the fact that anatomical information is missing. It may be unclear whether a formulation is located within the stomach or within an intestinal segment. In recent years, this technique has not often been used due to the decreased availability of radio nucleotide and regulatory issues in connection with the radiation exposure of the subjects [8].

Gastroscopy: Another invasive way to confirm the intra gastric localization of a dosage form is the visual examination via andendoscope. The gastro scope usually does not remain with in the stomach for extended time periods and thus it has to be reinsertedafter certain intervals during the evaluation of gastro retentive systems. Per oral endoscopy is also known as gastroscopy [9].

Magnetic marker monitoring*:* It is more beneficial method, because no radiations are used and making this method safer. Structures are elegantly checked by the help of iron powder and pictures are taken in accurate and in attractive way. By this method, magnetic dipole signal and appropriate sensors are used to track dosage forms in three dimensions way. In this method extremely sensitive sensors are applied, which also require measurement inside a magnetically shielded room to reduce the noise of the Earth's magnetic field. One of the major drawback is the need of sufficient dipole moment and the restriction that only one signal is detectable at a time.

Ultrasonography: This method is occasionally used as it does not shows results inintestine. This method is not used on regular bases for conclusion of FDDS [10].

Conclusion

GRDDS is a novel approach and drug delivery through this system has opened a new horizon for effective way of increasing patient compliance and bioavailability of various drugs can be improved by this method. Many approaches with use of different polymers i.e. Natural and synthetic polymers can produce different range of gastro retentive systems. GRDDS have great potential to improve the therapeutic efficiency of drugs with narrow absorption window, high solubility at acidic pH, and instability at alkaline PH. With the help of novel developments in the field of diagnostics and in vitro testing, completely new possibilities are already available today. These should be applied in a smart and sophisticated way in order to reach the goal of reproducible gastro retention. Polymer selection remains a critical factor for the formulation that combine high doses. This selection of polymer is essential for the compressibility needed to exploit the high doses of APIS. The criteria of ideal polymer, based on the minimum quantity that provides required gastric retention should be most preferred. Commercially it is emerging as a novel drug delivery due to the potential benefits offered by this delivery systems. The efficacy of GRDDS can be obtained by properly designing *in vivo* studies because of the complex Pharmacokinetic and Pharmacodynamics for a separate drug.

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