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EVALUATION METHODS AND POLYMERS USED IN GASTRORETENTIVE DOSAGE FORMS

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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 and release the drug slowly that can challenge may disadvantage associated with conventional oral delivery, including poor bioavailability. Such dosage forms aim to release drugs in the upper part of the gastrointestinal 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. Gamma scintigraphy and MRI are popular techniques used to evaluate *in vivo* gastric residence time. The floating drug delivery systems are required to possess the proper floating capability in gastric systems and the use of natural polymers in such a 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: **Applications, Gastro Retention, I*nvivo* and *Invitro* Methods, Polymer Swelling**

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, recent technological development has resulted in many novel pharmaceutical products, mainly the controlled drug delivery systems to overcome this problem. The prolonged residence of a 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 a 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 has a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period, 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 the 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 several approaches such as gas generating systems, raft forming systems, low-density systems etc. Basically, these floating systems are classified as effervescent and non-effervescent systems. In effervescent systems, gas-generating agents are used for the effervescence in dosage form and swellable polymers and hydrocolloids are used in non-effervescent systems and it is given in **Figure 1 [1, 2]**. The current review deals with the different types of natural and semisynthetic polymers that has recently

become the leading methodology in this field. This review also focussed on various in vitro and in vivo evaluation techniques used for GRDDS and also about various applications of GRDDS.

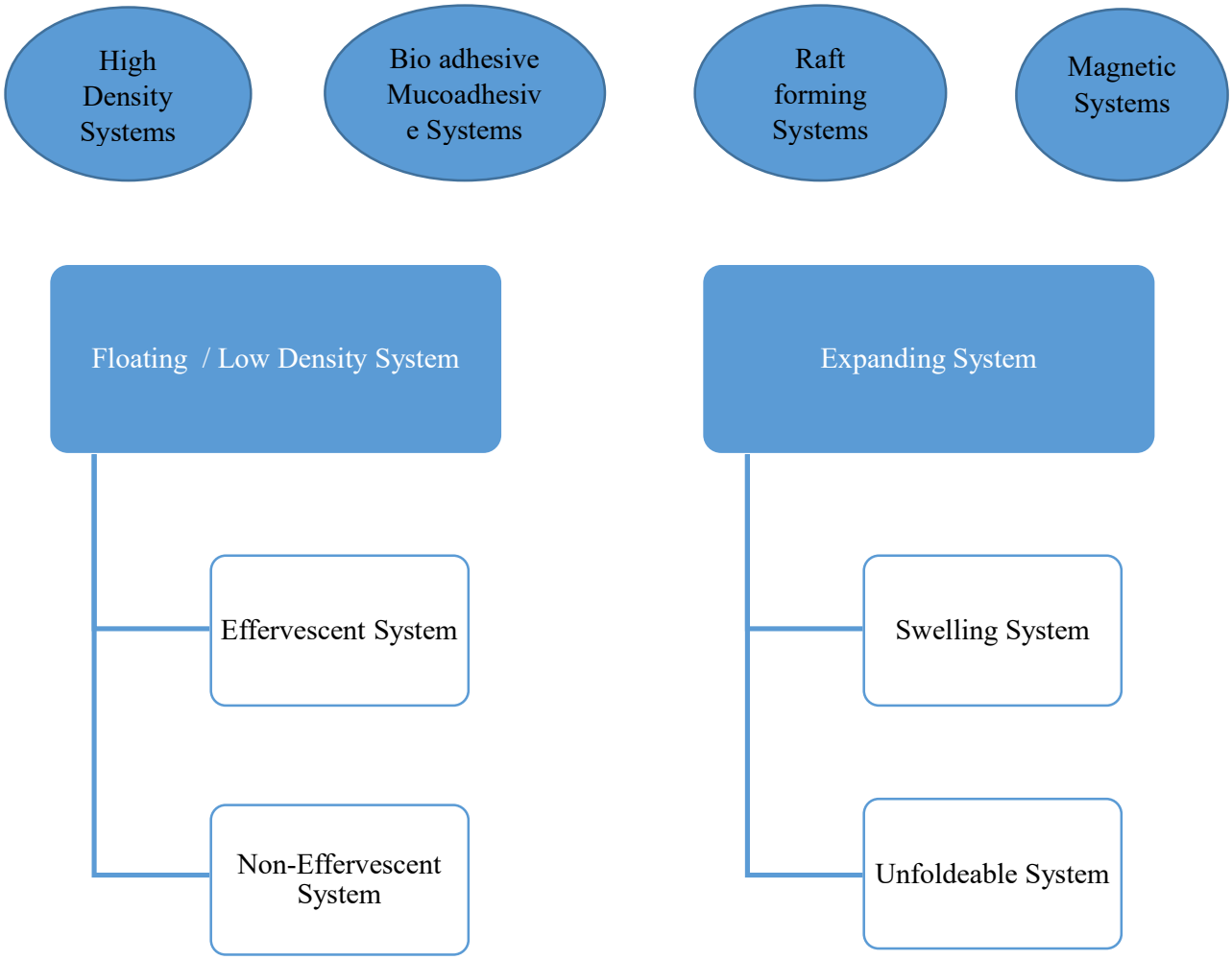

Figure 1: Different Approaches to GRDDS [3]

POLYMERS USED IN GASTRIC RETENTION SYSTEMS [3]

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

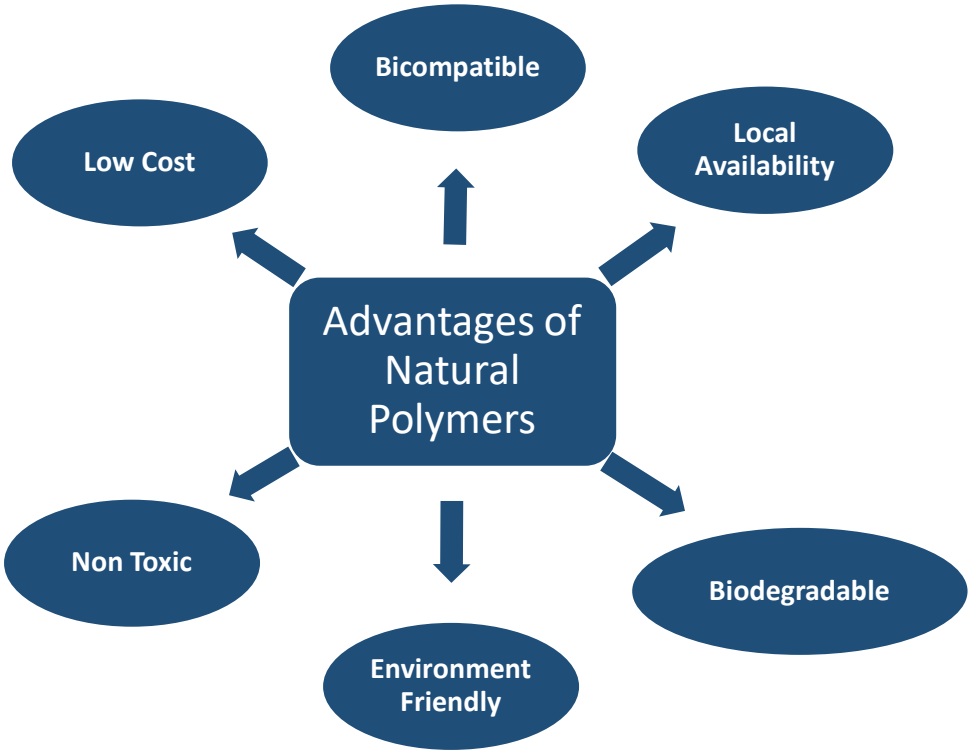

Figure 2: Advantages of Natural Polymers

Natural Polymers have some disadvantages like:

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

Disadvantages of Synthetic Polymer

- Toxic
- Synthetic process is a very complicated and high cost
- Poor biocompatible
- The acute and chronic adverse effect

NATURAL POLYMERS [4, 5]

a. **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 copolymers of glucosamine and N – acetyl glycosamine. Different grades of Chitosan are available based on 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 odourless, creamy or white flakes or powder and partially insoluble in 95% ethanol and soluble in water. It is used as a viscosity enhancer, mucoadhesive, tablet binder, coating agent and disintegrant. 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.

b. **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 a binder, disintegrant, 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 a 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, P^H and presence of solids.

c. **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 a 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 is faster at higher electrolyte concentrations (Sodium or Potassium Chloride). Xanthan gum is a suitable candidate for controlled release formulation especially with the incorporation into a tablet. It is used as Pharmaceutical excipient since it is of natural origin, biocompatible and safe and is relatively cheap to produce.

d. **Sodium Alginate:** Alginate is a polysaccharide, it is synthesised by brown seaweeds and soil bacteria. It is biocompatible, bioadhesive, P^H sensitive and non-immunogenic. Sodium alginate has several biological activities of vascular

endothelial growth factor, immunomodulatory, anti-tumour activity, anti-coagulant activity.

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

f. **Pectin:** Pectin, basically a polymer of D-galacturonic acid with (1-4) linkages. Pectin is an inexpensive, nontoxic polysaccharide extracted from the citrus peel or apple pomaces. It is also used as a 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.

g. **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 P^H above 6.5. This gum is used as a release rate controlling polymer and gum karaya swells in water. With this gum, zero-order drug release is observed along with the erosion of matrices.

h. **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 the water. This husk is biocompatible, inert, swellable, biocompatible, inexpensive and easily available and environment friendly. This husk serves as a reliable means for gastro retentive drug delivery system as it shows release retardant properties.

i. **Tamarind Gum:** Tamarind Gum is collected from the 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 have major structural polysaccharide called Xyloglucan, which is used as a 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 the polymer can be used for tablet preparation. A decrease in drug release is observed with increase in polymer content.

SEMI-SYNTHETIC / SYNTHETIC POLYMERS [6, 7]

a. **HPMC:** HPMC act as a 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 is 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. Several grades of HPMC like k4m, k100m, k15m etc. which is used for the preparation of floating tablets and microspheres. HPMC belongs to the family of the hydrophilic polymer, which in contact with the liquid swell and make a gel layer around the dry core of polymer matrix.

b. **Ethyl Cellulose:** It is a long-chain polymer of β-anhydro glucose units joined together by acetal linkages. Ethylcellulose is ethyl ether of cellulose and is used as a tablet binder, coating agent, tablet filler and viscosity increasing agents. It is white, odourless and tasteless with melting point 240^0-255^0C. It is non-biodegradable, non-toxic, non-irritant, they are available in different grades as K, N and T type.

c. **Acrylic Acid Derivatives:**

   i. **Eudragit:** 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 P^H independent swelling polymer. It is non-biodegradable, non-absorbent and non-toxic. RS and RL grades contain quaternary amino groups and used for sustained-release formulations.

   ii. **Carbopol:** Carbopol is an acrylic acid derivative and used in floating drug delivery due to

mucoadhesive and swelling property. Carbopol along with other polymers decrease the floating lag time, which gives better result with Eudragit. Different grades of carbopol are available like Carbopol 934, Carbopol 940 etc.

EXCIPIENTS USED IN FLOATING SYSTEMS [7]

1. **Hydrocolloids**

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

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

2. **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

3. **Release Rate Retardants**

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

4. **Release rate Accelerants**

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

5. **Buoyancy Increasing Agents**

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

6. **Effervescent Agents**

   Agents that produce carbon dioxide by contact with the acidic medium.

   Eg: Sodium bicarbonate, Citric acid, Tartaric acid, Disodium Glycine Carbonate

APPLICATION OF GASTRO RETENTIVE DRUG DELIVERY SYSTEMS [8]

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

1. **Sustained Drug Delivery**

   These systems can release the drug over a prolonged time and can remain in the stomach for a long period. The main problem of conventional drug forms is their

short residence time in the stomach, this can overcome with these systems. In the case of hydrodynamically balanced systems (HBS) which have a bulk density of <1 and as a result of this they can float on the gastric contents. These systems are relatively large and which prohibits its passage from the pyloric region. In general, the drug which displays 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 also, these are some side effects related to a rapid release of those drugs, while sustaining 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.

2. **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 P^H.

3. **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 an important role in prolonging gastric residence time by targeting site-specific drug release in the upper intestine for local as well as systemic effect.

EVALUATION PARAMETERS OF GRDDS [8, 9]

In vitro Evaluation Parameters

In vitro evaluation parameters can be used to predict the *in vivo* performance. The common methods of evaluation methods of gastro retentive tablet include tablet tensile 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. Also, swelling rate, water uptake capacity and gel strength of the polymeric

dosage form can be evaluated using dissolution medium and can be tested for at least 8hrs to ensure the mechanism of drug release, 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 37oC in simulated gastric fluid and FLT and TFT were measured i.e., the time between the introduction of dosage form and its buoyancy and time during which the dosage form remain buoyant is measured. Floating strength is measured using a specifically designed basket holder connected with analytical balance [9, 10].**
Systems Expandable Systems	***In vitro* unfolding study**	**Place the folded dosage form into a dissolution medium and examine the unfolding behaviour [9, 11, 12,].**
Raft forming Systems	**Viscosity and Rheology**	**Brookfield/Ostwald's viscometer at different interval is used to measure the viscosity of polymer [12, 13].**
Super porous Hydrogel Systems	**Swelling studies**	**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 [9, 14].**
Ion Exchange Resin Systems	**Particle size, moisture content, ion exchange capacity**	**Sieve Shaker and Coulter counter analyser are 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 [14, 15].**
Applicable for all GRDDS	**a. *In vitro* drug release.** **b. Gel Strength** **c. Drug Excipient interaction study**	**a. Using USP type II apparatus at 50 rpm at 37°C (Generally 0-12 hr.).** **b. High gel strength indicates better mechanical integrity.** **c. FI-IR spectroscopy, HPLC, Differential scanning calorimetry [16, 17].**

IN VIVO EVALUATION PARAMETERS [9, 11, 12]

1. Radiology

X Rays are a widely used method for examining internal body systems. X-Ray is used in a floating dosage form as one of the assessment parameters. One of the most widely used Radio Opaque markers 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 the stomach or not.

2. **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 the dosage form in the GIT. Υ Camera or scinti Scanner is used for the indirect observation of a formulation by the 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 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.

3. **Gastroscopy**

   Another invasive way to confirm the intragastric localization of a dosage form is the visual examination via an endoscope. The gastro scope usually does not remain within the stomach for extended periods and thus it has to be reinserted after certain intervals during the evaluation of gastro retentive systems. Perioral endoscopy is also known as a gastroscopy.

4. **Magnetic Marker Monitoring**

   It is a 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 inaccurate and in an 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 drawbacks is the need for sufficient dipole moment and the restriction that only one signal is detectable at a time.

5. **Ultrasonography**

   This method is occasionally used as it does not shows results in the intestine. This method is not used on regular bases for the conclusion of FDDS.

CONCLUSION

GRDDS is a novel approach and drug delivery through this system has opened a new horizon for an effective way of increasing patient compliance and bioavailability of various drugs can be improved by this method. Many approaches with the use of different polymers i.e. Natural and synthetic polymers can

produce a different range of gastro retentive systems. GRDDS have great potential to improve the therapeutic efficiency of drugs with a narrow absorption window, high solubility at acidic pH, and instability at alkaline P^H. 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 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 these 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.

REFERENCES

[1] A review on applications of natural polymers in gastroretentive drug delivery system, R. Ananthakumar, K. Chitra, S. Satheshkumar, A review on applications of natural polymers in gastroretentive drug delivery system, Drug Invention Today. 10 (3)2018, 285-289.

[2] A summarized review about natural polymers role in floating drug delivery system and in-vivo evaluation studies, Muhammad Umar Javaid, Qurat-ul-Ain, Umer Tahir and Safwan Shahid, Javaid , International Current Pharmaceutical Journal, March 2017, 6(4): 23-26.

[3] Current Approaches on Gastroretentive Drug Delivery systems, Aniket Uttam Pund, Raosaheb Sopanrao Shendge, Ajinkya Kailas Pote, Journal of Drug Delivery & Therapeutics. 2020; 10(1):139-146.

[4] Floating Tablets and Its Polymers, Shaika Saadia Zubedi, Shahid Mohammed, Journal of Drug Delivery & Therapeutics. 2018; 8(5):16-24.

[5] Gastro-retentive drug delivery systems and their in vivo success: A recent update, Uttam Kumar Mandal, Bappaditya Chatterjee, Faria Gias Senjoti, asian journal of pharmaceutical sciences 11 (2 0 1 6) 575–584.

[6] In Vitro and In Vivo Test Methods for the Evaluation of Gastroretentive Dosage Forms, Felix Schneider, Mirko Koziolek

and WernerWeitschies, Pharmaceutics 2019, 11, 416.

[7] Potential of natural polymer in the gastro retentive floating drug delivery system: A review, Amit K Nagariya, A. K. Meena, Dipika Jain, A. K. Yadav, B. K. Singh, P Panda, R Sannd, Bhavana Pal and Kiran Sharma, Journal of Pharmacy Research 2010, 3(5), 916-922.

[8] Role of excipients and polymeric advancements in preparation of floating drug delivery systems, Avinash Y Kaushik, Ajay K Tiwari, and Ajay Gaur, Int J Pharm Investig. 2015 Jan-Mar; 5(1): 1–12.

[9] Current State and Future Perspectives on Gastroretentive Drug Delivery Systems, Julu Tripathi, Prakash Thapa, Ravi Maharjan and Seong Hoon Jeong, Pharmaceutics 2019, 11, 193.

[10] Effects of Formulation and Process Variables on Gastroretentive Floating Tablets with a High-Dose Soluble Drug and Experimental Design Approach. Thapa P, Jeong S, Pharmaceutics 2018, 10, 161.

[11] Physiological relevant in vitro evaluation of polymer coats for gastroretentive floating tablets. Eisenächer F, Garbacz G, Mäder K, Eur. J. Pharm. Biopharm. 2014, 88, 778–786.

[12] New insights on poly (vinyl acetate)-based coated floating tablets: Characterisation of hydration and CO2 generation by benchtop MRI and its relation to drug release and floating strength. Strübing S, Abboud T, Contri R.V, Metz H, Mäder K, Eur. J. Pharm. Biopharm. 2008, 69, 708–717.

[13] Gastric retention properties of superporous hydrogel composites. Chen J, Blevins W.E, Park H, Park K, J. Control. Release 2000, 64, 39–51.

[14] Design and evaluation of biodegradable, biosensitive in situ gelling system for pulsatile delivery of insulin. Kashyap N, Viswanad B, Sharma G, Bhardwaj V, Ramarao P, Kumar M.R, Biomaterials 2007, 28, 2051–2060.

[15] Unfolding type gastroretentive film of Cinnarizine based on ethyl cellulose and hydroxypropylmethyl cellulose. Verma S, Nagpal K, Singh S, Mishra D, Int. J. Biol. Macromol. 2014, 64, 347–352.

[16] Rate of release of organic carboxylic acids from ion-exchange resins. Farag Y, Nairn

J.G, J. Pharm. Sci. 1988, 77, 872–875.

[17] Biodegradable Injectable Implant Systems for Long Term Drug Delivery Using Poly (Lactic-co-glycolic) Acid Copolymers. Chandrashekar G, Udupa N, J. Pharm. Pharmacol. 1996, 48, 669–674.