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An Overview on Gastroretentive Drug Delivery System (GRDDS)

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Research Article

ABSTRACT

A Controlled release dosage forms have been extensively used to improve therapy with several important drugs. However, the development processes are faced with several physiological difficulties such as the inability to restrain and localize the system within the desired region of the gastrointestinal tract and the highly variable nature of the gastric emptying process. This variability may lead to unpredictable bioavailability and times to achieve peak plasma levels. The present review addresses briefly about the classification, formulation consideration for GRDDS, factors controlling gastric retention, merits, demerits and applications of gastroretentive drug delivery systems.

Key words: Gastroretentive drug delivery system; floating system; swelling; Review.

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Introduction

A drug that is released from a dosage form in a controlled manner in the stomach will empty together with fluids and will have the whole surface area of the small intestine available for absorption[1]**.** Oral drug delivery has been known for decades as the most widely used route of administration among all the routes that have been explored for the systemic delivery. Oral route is the most convenient and extensively used route of drug administration. All controlled release systems have limited applications if the systems cannot remain in the vicinity of the absorption site. The controlled release drug delivery system possessing the ability of being retained in the stomach is called gastro retentive drug delivery system. They can help in optimizing the oral controlled delivery of drugs having "absorption window" continually releasing the drug prior to absorption window for prolonged period of time, thus ensuring optimal bioavailability. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is, however, distinct in the two states. Gastric emptying studies revealed that orally administered controlled release dosage forms are subjected to basically two complications: that of short gastric residence time and unpredictable gastric emptying rate[2].

Table 1: Comparison between conventional and gastro retentive drug delivery system [3]

Parameters	**Gastroretentive Drug Delivery System**	**Conventional Drug Delivery System**
Risk of toxicity	Lower	Higher
Patient compliance	High compliance level	Less compliance level
Dose dumping	High risk	No risk
Drugs	**Beneficial for drugs:** That have rapid GI absorption Degrade in colon	**Not beneficial for drugs:** That have low GI absorption Degrade in colon

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Need for GRDDS

- Conventional oral delivery is widely used in pharmaceutical field to treat diseases. However, conventional delivery had many drawbacks and major draw-back is non-site specificity.
- Some drugs are absorbed at specific site only. They require release at specific site or a release such that maximum amount of drug reaches to the specific site.
- Pharmaceutical field is now focusing towards such drugs which require site specificity.
- Gastro-retentive delivery is one of the site specific delivery for the delivery of drugs either at stomach or at intestine. It is obtained by retaining dosage form into stomach and drug is being released at controlled manner to specific site either in stomach, duodenum and intestine [4].

Basic Gastrointestinal Tract Physiology [5-7]

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.13 Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours.14 This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington.

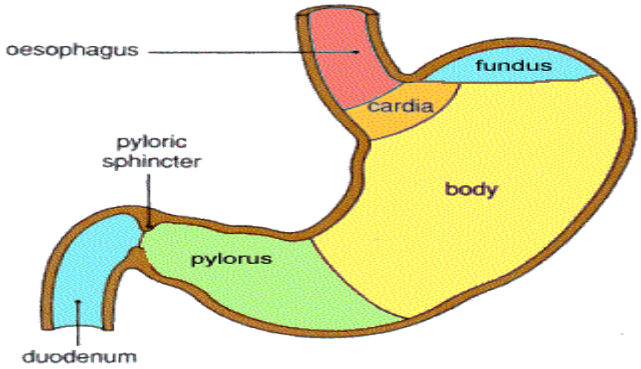

Fig.1: Anatomy of the gastrointestinal tract

1. **Phase I (basal phase)** lasts from 40 to 60 minutes with rare contractions.
2. **Phase II (preburst phase)** lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. **Phase III (burst phase)** lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4. **Phase IV** lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

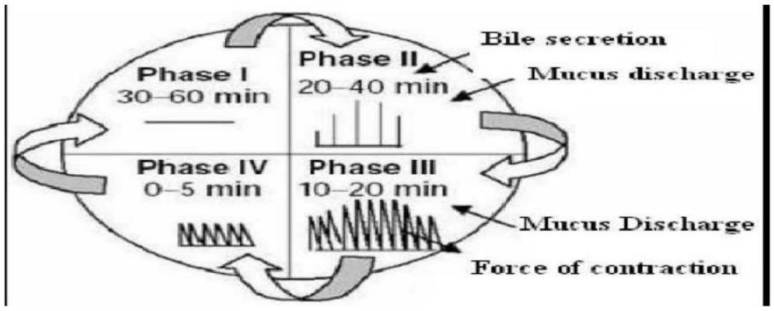

Fig.2 Schematic representation of inter digestive motility

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size

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of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.16 Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate 3.

Factors Controlling Gastric Retention Time

Retention of Dosage Forms

The stomach anatomy and physiology contain parameters to be considered in the development of gastroretentive dosage forms. To pass through the pyloric valve in to the small intestine the particle size should be in the range of 1 to 2 mm .

Density of dosage forms

The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float tothe surface, while high density systems sink to bottom of the stomach [16]. Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/ cm3 is required to exhibit floating property.

Shape and size of the dosage form

Shape and size of the dosage forms are important in designing indigestible single unit solid dosage forms. The mean gastric residence times of nonfloating dosage forms are highly variable and greatly dependent on their size, which may be large,medium and small units. In most cases, the larger the dosage form the greater will be the gastric retention time (GRT) due to the larger size of the dosage form would not allow this to quickly pass through the pyloric antrum into the intestine . Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm . Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared with other shapes .

Food intake and its nature

Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract (GIT) influences the gastric retention time (GRT) of the dosage form. Usually the presence of food in the gastrointestinal tract (GIT) improves the gastric retention time (GRT) of the dosage form and thus, the drugs absorption increases by allowing its stay at the absorption site for a longer period. Again, increase in acidity and caloric value shows down gastric emptying time (GET), which can improve the gastric retention of dosage forms.

Effect of gender, posture and age

Generally females have slower gastric emptying rates than male. The effect of posture does not have any significant difference in the mean gastric retention time (GRT) for individuals in upright, ambulatory and supine state. In case of elderly persons, gastric emptying is slowed down[6] .

Advantages of Gastroretentive Drug Delivery Systems

1) The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by this gastroretentive drug delivery approach in comparison to the administration of nongastroretentive drug delivery. There are several different factors related to absorption and transit of the drug in the gastrointestinal tract (GIT) that act concomitantly to influence the magnitude of drug absorption.
2) For drugs with relatively short half life, sustained release may result in a flip- flop pharmacokinetics and also enable reduced frequency of dosing with improved patient compliance.
3) They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because their bulk density is lower than that of the gastric fluids.
4) Gastroretentive drug delivery can produce prolong and sustain release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.
5) The controlled, slow delivery of drug form gastroretentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable effects of side effects.

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6) Gastroretentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index[7] .
7) **Disadvantages of Gastro-Retentive Drug Delivery Systems**

1. Unsuitable for drugs with limited acidsolubility. E.g. Phenytoin.
2. Unsuitable for drugs those are unstable inacidic environment. E.g.Erythromycin.
3. Drugs that irritates or causes gastric lesions on slow release. E.g. Aspirin &NSAID's.
4. Drugs that absorb selectively in colon E.g. Corticosteroid.

Approaches for GRDDS [8-10]

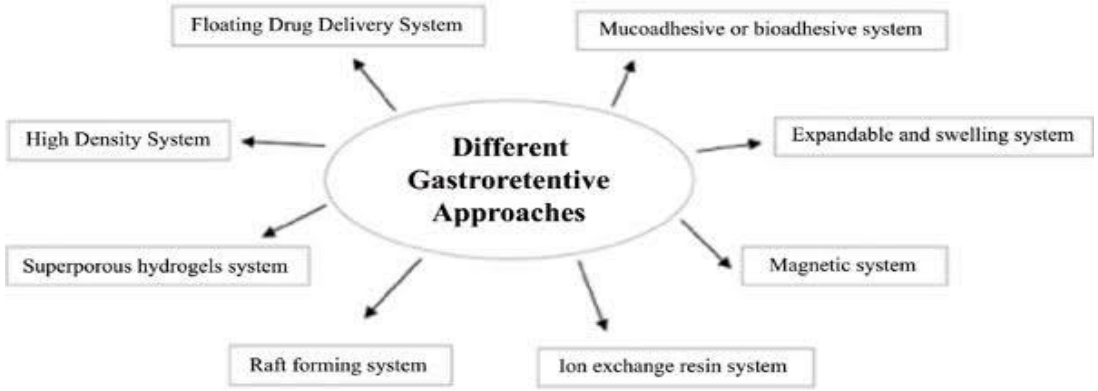

Fig.3 Different Gastroretentive approaches

Effervescent system
Gas generating system
Volatile liquid containing system
Effervescent systems include use of gas generating agents, carbonates (ex.Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature.

Effervescent (gas generating) systems
Floatability can be achieved by generation of gas bubbles. These buoyant systems utilize matrices prepared with swellable polymers such as polysaccharides (e.g. chitosan), effervescent components (e.g. sodium bicarbonate, citric acid or tartaric acid) . The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1 . In this system carbon dioxide is released and causes the formulation to float in the stomach .Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating dosage forms that generate gas (carbon dioxide) when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone (PVP) coated with hydroxypropyl methylcellulose (HPMC), and floating system based on ion exchange resin technology etc .

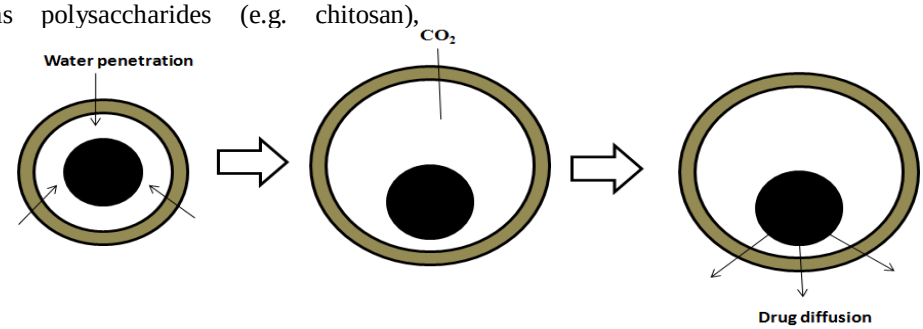

Fig.4: **Drug release from effervescent (Gas generating) systems**

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Bilayer or multilayer system has also been designed. Drugs and excipients can be formulated independently and the gas generating material can be incorporated in to any of the layers. Further modifications involve coating of the matrix with a polymer which is permeable to water, but not to carbon dioxide. The main difficulty of these formulations is finding a good compromise between elasticity, plasticity and permeability of the polymers

Non- effervescent system

- Colloidal gel barrier system
- Micro porous compartment system
- Floating microspheres
- Alginate floating beads
- Raft forming systems

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excepient in non effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as Chitosan and carbopol.

Microballoons/ Hollow microspheres

Microballoons / hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion / evaporation methods to prolong the gastric retention time (GRT) of the dosage form. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer polymer ratio and the solvent used for formulation. The microballoons floated continuously over the surface of an acidic dissolution media containing surfactant for >12 hours . At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating.

Alginate beads

Recently developed a multiple-unit floating system based on cross-linked beads. They were made by using Ca^{2+} and low methoxylated pectin (anionic polysaccharide) or Ca^{2+} low methoxylated pectin and sodium alginate. In this approach, generally sodium alginate solution is dropped into aqueous solution of calcium chloride and causes the precipitation of calcium alginate. These beads are then separated and dried by air convection and freeze drying, leading to the formulation of a porous system, which can maintain a floating force for over 12 hrs. These beads improve gastric retention time (GRT) more than 5.5 hrs.

Microporous compartment system

This approach is based on the principle of the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls . The peripheral walls of the device were completely sealed to present any direct contact of the gastric surface with the undissolved drug. In the stomach the floatation chamber containing entrapped air causes the delivery system to float in the gastric fluid . Gastric fluid enters through the aperture, dissolves the drug and causes the dissolved drug for continuous transport across the intestine for drug absorption.

Applications of GRDDS [11]

Sustained drug delivery

Floating system remains in the stomach for longer period and release the drug over a prolong period of time. This system has bulk density less than 1 so it may float on the gastric content.

Site specific drug

This system is particularly advantageous for the drugs which are absorbed from the stomach or proximal part of the small intestine.

Absorption enhancement

Drugs having a poor bioavailability are potential candidate for formulating as a floating system to enhance its absorption.

Maintenance of constant blood flow

This system provides an easy way for maintaining constant blood flow with relatively ease of administration.

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Table 2: Drug used in the gastro-retentive formulation [12,13]

Types	Examples
Floating Granules	Diclofenac sodium, Indomethacin and Prednisolone, Ranitidine Hydrochloride-Gelucire.
	Aspirin, Griseofulvin, ciprofloxacin hydrochloride, P-nitro aniline, Indomethasone, Ibuprofen, Ketoprofen, Piroxicam, Verapamil, orlistat, Cholestyramine, Theophylline, Nifedipine, Nicardipine, captorlil, cimetidine, Dipyridamol , Tranilast and Terfinadine
Films	Cinnarizine, Albendazole

Table 3: Other Excepient (Excepient used in GRDDS) [14]

Types	**Examples**
Polymers hydroc	Pectin, Chitosan, Agar, Casein, Bentonite, Veegum, Hydroxy Propyl MethylCellulose (HPMC) (K4M, K100M and K15M), Gellan gum(Gelrite, Sodium Carboxy Methyl Cellulose (CMC), Methyl Cellulose (MC), Hydroxy Propyl Cellulose (HPC).
Inert fatty Material	Bees wax, Fatty acids, Long chain fatty alcohols, Gelucires® 39/01 and 43/01.
Effervescent Agents	Sodium bicarbonate, Citric acid, Tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate), CG (Citroglycine).
Release rate Accelerators	Lactose, Mannitol
Increasing agents-	Ethyl cellulose.
Low density Material	Polypropylene foam powder (Accurel MP 1000®).

Evaluation of floating drug delivery system

- Evaluation of powder blend fora)
- Angle of Repose
- Bulk Density
- Percentage porosity

Evaluation of tablets fora)

- Buoyancy capabilities
- In vitro floating and dissolution behavior
- Weight variation
- Hardness & friability
- Particle size analysis, surface characterization (for floating microspheres and beads)
- X-Ray/Gamma Scintigraphy

Pre compression parameters

Bulk density

A quantity of drug powder was weighed initially and was introduced in to 10 ml measuring cylinder. The bulk volume was determined and the apparent bulk density in g/ml was calculated using the formula Bulk density=weight of powder/bulk volume[15].

Tapped density

A quantity of drug powder blend from each batch, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to tap under its own weight on to a hard surface from the height of 2.5cm at second intervals. Tapping was continued until no further change in volume was noted[16].

Tapped density=weight of powder/tapped volume

Angle of repose

Angle of repose is defined as “the maximum angle possible between the surface of the pile of powder and the horizontal plane.” Lower the angle of repose, better the flow properties. The angle of repose may be calculated by

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measuring the height (h) of the pile and the radius of the base(r) with ruler[17].

$$\text{Tan } \_ = h/r$$

Percentage porosity

Whether the powder is porous or nonporous, the total porosity expression for the calculation remains the same. Porosity provides information about hardness, disintegration, total porosity etc[18].

% porosity, € = void volume × 100 / Bulk volume

% porosity, € = (bulk volume – true volume) × 100 / True density

Particle size analysis, surface characterization (for floating microspheres and beads)

the particle size andthe size distribution of beads or microspheres are determined in the dry state using the optical microscopy method. The external and cross-sectional morphology (surface characterization) is done by scanning electron microscope (SEM)[19].

Drug release study

The drug release study for the Floating tablets were carried out in USP XXIII type-II dissolution test apparatus (Paddle type) using 900 ml of 0.1 N HCl as dissolution medium at 50 rpm and temperature 37±0.5°C. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed for the presence of the drug release by measuring the absorbance at λmax of API (nm) using UV Visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate (n=3)[20].

Table 4: List of Drugs Formulated as Single and Multiple Unit Forms of Floating Drug Delivery Systems [21,22]

Dosage Forms	Drugs
Floating tablets and Pills	Cinnarizine, p-Aminobenzoic acid, Prednisolone and Piretanide
Floating Films	Acetaminophen, Isosorbide mononitrate, Ampicillin, Atenolol, Theophylline, p-aminobenzoic acid, Aspirin, Verapamil hydrochloride, Sotalol
Floating microspheres	Aspirin, p-nitroaniline, Griseofulvin, Ketoprofen, Ibuprofen, Verapamil and Terfinadine
Floating Capsules	Diazepam, Furosemide, Misoprostol, L-Dopa and Benserazide, Pepstatin, Verapamil HCl and Nicardipine
Floating powders	Riboflavin, Phosphate, Sotalol and Theophylline
Floating granules	Diclofenac sodium, Indomethacin, Prednisolone, Cinnarizine, Diltiazem, Fluorouracil and Isosorbide mononitrate

Conclusion

Gastro retentive drug delivery technologies have been extensively explored in recent years. GRDDS has the potential to enable many drugs to provide less frequent dosing and remains undoubtedly beneficial for the drugs having NAW in the stomach and/or upper part of the intestine. All these gastroretentive drug delivery systems (high density, floating, expandable or unfoldable or swelling, superporous, Bioadhesive, magnetic systems etc.) are interesting and present their own advantages and disadvantages. Now, a lot of work is running to develop different types of gastro retentive delivery systems of various drugs. In the future, it is expected that they will become of increasing importance, ultimately leading to improved efficiencies of various types of pharmacotherapy.

References

1. Durga Jaiswal, Arundhati bhattacharya1, Indranil kumar yadav , Hari pratap singh, Dinesh chandra and d.a. jain, Formulation and evaluation of oil entrapped floating alginate beads of ranitidine hydrochloride. International journal of pharmacy and pharmaceutics science 2009;1(1):1.
2. Swati C. Jagdale, Amit J. Agavekar, Sudhir V. Pandya, Bhanudas S. Kuchekar, and Aniruddha R. Chabukswar Formulation and Evaluation of Gastroretentive Drug Delivery System of Propranolol Hydrochloride AAPS PharmSci Tech, 2009;10(3):1-5.

e-ISSN: 2590-3357; p-ISSN:2590-3365
DOI: https://doi.org/10.30750/ IJHBS.2.2.1

3. Harries D, Sharma HL; GI transit of potential bioadhesive formulations in man: A scintigraphic study; Journal of Controlled Release; 1990; 12(1); 45-53.
4. Shailaja pant, Ashutosh badola, Preeti kothiyal , A Review On Gastroretentive Drug Delivery System, Indian J. Pharm. Biol. Res.2016; 4(2):1-10.
5. Shweta Arora, Javed Ali, Alka Ahuja, Roop K. Khar, and Sanjula Baboota ,Floating Drug Delivery Systems: A Review, AAPS PharmSci Tech 2005; 6 (3) Article 47.
6. Amit Kumar Nayak , Ruma Maji, Biswarup Das, Gastroretentive drug delivery systems: a review, Asian Journal of Pharmaceutical and Clinical Research 2010
7. Meenakshi Jassal, Ujjwal Nautiyal, Jyotsana Kundlas, Devendra singh, A review: Gastroretentive drug delivery system (GRDDS). Indian Journal of Pharmaceutical and Biological Research 2015;3(1):82-92.
8. Meenu Bhatt, Satinder Kakar, Ramandeep Singh. A Review On Floating Drug Delivery System.IJRAPR.2015;5(2):57-67
9. Satinder Kakar, Ramandeep Singh, Alok Semwal. Drug release characteristics of dosage forms: a review. Journal of Coastal Life Medicine.2014;2(4):332-336
10. Singh Bandana, Kanoujia Jovita, Pandey Manisha, Saraf Shubhini A. Formulation and Evaluation of Floating Microspheres International Journal of PharmTech Research CODEN (USA): IJPRIF ISSN : 0974-4304 Vol.2, No.2, pp 1415-1420, 2010.
11. Hemali Soni, V. A. Patel, review article Gastro Retentive Drug Delivery System , Int. J. Pharm. Sci. Rev. Res., 31 , 2015.
12. Nayak K Amit, Maji Ruma, Das Biswarup. Gastroretentive drug delivery systems: A review. Asian J.Pharma Clinical Research [ISSN 0974-2441]. 2010; 3(1),1-10.
13. Mayavanshi AV, Gajjar SS. Floating drug delivery systems to increase gastric retention of drugs: A Review.Res J. Pharma. Tech [ISSN 0974-3618]. 2008; 1(4), 345-348.
14. Satinder Kakar, Ramandeep singh, Shallu sandhan. Gastroretentive drug delivery system: A Review, African Journal of Pharmacy and Pharmacology, 2015;9(12):405-417.
15. Jain NK. Progress in Controlled and Novel Drug Delivery Systems.1st ed., New Delhi, India, CBS publishers and Distributors Pvt. Ltd, 2010; 76-95.
16. Goyal M, Prajapati R, Purohit KK and Mehta SC. Floating drug delivery system. Journal of current pharmaceutical research, 2011; 5(1): 7-18.
17. Umamaheshwari RB, Jain S, Bhadra D, Jain N.K. Floating microspheres bearing acetohydroxamic acid for the treatment of Helicobacter pylori. J Pharm Pharmacol, 2003; 55(12): 1607-1613.
18. Soppimath KS, Kulkarni AR, Rudzinski W E, Aminabhavi TM. Microspheres as floating drug delivery system to increase the gastric residence of drugs. Drug metabolism Review. 2001; 33, 149-160.
19. Atyabi, F; Sharma, HL; Mohammad, HAH and Fell, JT; Controlled Drug Release from Coated Floating Ion Exchange Resin Beads; J. Control. Release, 1996; 42: 25- 28.
20. Raghavendra Kumar Gunda, J. N. Suresh Kumar, Chandan Kumar Brahma, V. Satyanarayana, K. Naga Prashant. Design, Formulation and Evaluation of Atenolol Gastro Retentive Floating Tablets. Asian Journal of Pharmaceutics, 2015; 9(4): (Suppl)
21. Gupta G, Singh A; A Short Review on Stomach Specific Drug Delivery System; International Journal of PharmTech Research; 2012; 4(4); 1527-1545.
22. Devkant Sharma , Anjali Sharma. Gastroretentive drug delivery system - a mini review. Asian Pac. J. Health Sci., 2014; 1(2): 80-89

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