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Drug Loaded Beads: Current Status

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ABSTRACT

The aim of writing this review is to put a light on the recent trends in development of Drug loaded Beads. Drug loaded beads are gastro retentive drug delivery systems based on multi Unit approach and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability, stability and target drug to specific sites. These are Spherical in shape and approximately 1.5 mm in diameter. These can be prepared by various methods like ionotropic gelation, hydrogel embedment, solvent evaporation and Melt Solidification by using different polymers. Promising enhancement in bioavailability and site specificity has been achieved by drug loaded beads.

Keywords: FDDS, Beads, Buoyancy, Polymers

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INTRODUCTION

In recent years researchers and academicians developed various approaches to design innovative controlled drug delivery system to achieve better patient compliance with minimal side effects. Various drug delivery systems have been reported in research literature. These drug delivery systems can release the drug at a predefined rate and time. Various attempts have been approached to develop oral controlled release delivery system, yet few limitations like variable drug absorption and uncontrolled gastric transit time need more advanced research or intelligent drug delivery systems[1]. The novel oral controlled delivery has advantages over oral conventional drug delivery system for reduction in blood level fluctuations and dose frequency of the drug. The GRDDS including Floating and High density system is one of the most common delivery system that emphasized on the ability of being retained in stomach by several techniques like swelling/ Expanding and Bioadhesion to provide the local action. The basic approach behind designing the GRDDS includes:

(1) Decrease the gastric emptying rate, (2) Polymer Bioadhesives (3) By altering the formulation density.[2-5]

There are several approaches that have been adopted by researchers for oral controlled delivery via gastric retention, among them one is FDDS. The Floating systems can remain in the gastric region for many hours which result in prolonged GRT (gastric residence time) of drugs. Prolonged gastric retention improves bioavailability and solubility for drugs that are less soluble in a high pH environment. This concept has been applied also for local drug delivery to the stomach and proximal small intestine.[6]

Floating Drug Delivery System

Floating drug delivery systems is one of the usual approaches in these days regarding industrial and academician's point of view to attain sufficient drug bioavailability by gastric retention. A lot of drugs are suitable for these systems which have an absorption window in the stomach or in the upper small intestine[7-8]. In 1968, Davis first described "Floating systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for longer time". The drug is released slowly at the predefined rate when system floats over gastric contents which results in increased GRT and also control fluctuation in plasma drug concentration.[9-10] various approaches that have been attempted to FDDS includes single unit and Multiple unit systems. Various multiple-unit floating system like air compartment multiple-unit system, hollow microspheres (microballoons), floating beads have been prepared by different techniques.

Classification of FDDS

Floating drug delivery systems are classified into two depending on the use of formulation variables: effervescent and noneffervescent systems.

Effervescent Systems

These systems are prepared along with excepients (swellable polymers) such as methylcellulose, Corboxy metyle cellulose(CMC), cross-linked polyvinyl pyrrolidone, chitosan, sodium starch and various effervescent compounds[11] e.g. sodium bicarbonate, tartaric acid, and citric acid(may be present in amounts about 10-30 % by weight of total weight of composition). When the system reaches to stomach and comes in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

Sriamornsak et al prepared calcium pectinate beads containing carbonate salt as a gas forming agent. The beads were prepared by dispersing carbonate salt in pectin solution and then extruding into neutral or acidified solution of calcium chloride. Incorporation of carbonate salt results in formation of porous beads which upon reaction with acid caused release of carbon dioxide providing buoyancy to beads[12].

Non-effervescent Systems

Generally, NES (Non-effervescent systems) are prepared through gel-forming agents or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. When system comes in contact with gastric fluid after oral administration they swell up and maintains a relative integrity of shape and a bulk density less than unity within the gastric environment. Excipients used most commonly in these systems include hydroxypropyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonate[13].

Wong et al developed a prolonged release dosage form adapted for gastric retention using swellable polymers. It consisted of a band of insoluble material that prevented the covered portion of the polymer matrix from swelling and provided a segment of a dosage form that was of sufficient rigidity to withstand the contractions of the stomach and delayed the expulsion of the dosage form from the stomach.

Suitability of Drug for Floating System[14-16]

Those drugs which show following properties are suitable for FDDS:

- Drugs that have Half-Life in the range of 2 -8 hr.

- Drugs that have narrow absorption window in GIT (e.g. L-DOPA, p-amino benzoic acid, Furosemide, Riboflavin).
- Drugs that exhibit low solubility at high pH values (e.g. Diazepam, Chlordiazepoxide, Verapamil).
- Drugs those are locally active in the stomach (e.g. Misoprostol, Antacids).
- Drugs those are unstable in the intestinal or colonic environment (e.g. captopril, ranitidine HCl, metronidazole).
- Certain antibiotic Drugs such as tetracycline, clarithromycin, amoxicillin used for the eradication of Helicobacter pylori that disturb normal colonic microbes. In this case floating system can protect the colonic microflora.
- Drugs those have aqueous Solubility.
- Drug Stability to Wide pH Range, GI Enzymes and Flora.

Development of Floating Beads

Floating beads are gastro retentive drug delivery systems based on multi Unit approach and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability, stability and target drug to specific sites. Due to several disadvantages of single unit dosage forms the reliable multiunit floatable dosage forms have been designed. Beads can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing the dosing frequency and improving patient compliance. They are Spherical in shape and approximately 1.5 mm in diameter can be prepared by various methods by using different polymers. In recent years, alginate gel beads have frequently been employed as a unique vehicle for FDDS.

Yao et al [17] Prepared a novel kind of inner-porous floating beads with foam solution using poloxamer 188 as foaming agents, alginate as foaming stabilizer. Poloxamer 188 is an effective amphiphilic surfactant and can lower the water surface tension significantly. Foam solution can be formed by stirring in the presence of poloxamer 188, the alginate can winding in microbubbles and stabilised the foam solution. Then the foam solution was dripped into CaCl2 solution through a syringe, the porous beads were formed. The water insoluble Ca–Alg was rapidly formed by gelation of alginic acid in the presence of calcium ions. Poloxamer 188 has also already used in nimodipine sustained-release tablet capable of floating on gastric fluid with prolonged gastric resident time.

Tripathi et al [18]. Prepared Oil entrapped calcium pectinate gel beads of amoxicillin by ionic gelation method. A 0.65 % w/v of drug was dispersed in varying concentrations (1.50 -2.10 % w/v) of aqueous solution of pectin with continuous stirring until a uniform dispersion was

obtained. The mixture was emulsified with either mineral oil or castor oil using Silverson emulsifier (Hicon, India) stirred at 500 rpm for 5 min.

The resultant drug loaded emulsions was dropped through a 21 gauge syringe needle separately into 100 ml of 0.275- 0.45 mol ml -1 of calcium chloride solution, maintained under gentle agitation to improve the mechanical strength of the beads and also to prevent aggregation of the formed beads.

Ray et al [19] developed a multiunit sustained release dosage form of diltiazem using a natural polymer from a completely aqueous environment. Diltiazem was complexed with resin and the resinate-loaded carboxymethyl xanthan (RCMX) beads were prepared by interacting sodium carboxymethyl xanthan (SCMX), a derivatized xanthan gum, with Al+3 ions. The beads were evaluated for drug entrapment efficiency (DEE) and release characteristics in enzyme free simulated gastric fluid (SGF, HCl solution, pH 1.2) and simulated intestinal fluid (SIF, USP phosphate buffer solution, pH 6.8). Increase in gelation time from 5 to 20 min and AlCl3 concentration from 1 to 3% decreased the DEE respectively from 95 to 79% and 88.5 to 84.6%. However, increase in gum concentration from 1.5 to 2.5% increased the DEE from 86.5 to 90.7%.

S.K. Jain et al[20]. Prepared and characterize beads of Gelucire 43/01 for floating delivery of metformin hydrochloride (MH). The beads were evaluated for particle size, surface morphology, percent drug entrapment, percent yield, differential scanning calorimetry (DSC), in vitro floating ability, and in vitro drug release. Aging effect on storage was evaluated using hot stage microscopy (HSM), DSC, scanning electron microscopy, and in vitro floating ability. The formed beads were sufficiently hard and spherical in shape. Photomicrographs show that the surface was porous in nature. The average particle diameter of beads was found to be in the size range of 3.85 to 3.95 mm, and percent entrapment was 83.07% to 86.13%. The beads demonstrated favorable in vitro floating ability.

Sriamornsak et al[21] prepared Drug (Theophylline anhydrous) loaded calcium pectinate gel (CaPG) beads by either mixing, absorption or swelling method. The effects of drug loading method as well as the drug loading factors (i.e., drug concentration, soaking time in drug solution, type of solvent) on drug content and drug release were investigated. The amount of drug uptake (i.e., drug content) into CaPG beads increased as the initial drug concentration increased and varied depending on the loading method.

Elmowafy et al[22], developed and evaluated polysaccharides beads of Famotidine by ionotropically emulsion gelled. They used different polysaccharides (sodium alginate and

pectin), oil concentrations (10%, 20% and 30% w/w) and drug: polymer (D:P) ratios (1:1, 2:1 and 3:1) to study the influence on beads uniformity, drug entrapment efficiency (DEE) and *in vitro* drug release. They concluded that retardation of drug release for 4 h was achieved by the oil hydrophobic diffusional barrier, especially in the presence of the compact network of alginate beads.

Park et al[23], developed and evaluated floating beads from sodium alginate solution containing calcium carbonate or sodium bicarbonate as gas-forming agents with riboflavin as a model drug. *In vitro release* studies revealed that calcium carbonate is superior to sodium bicarbonate as gas forming agent in alginate bead preparations, with enhanced buoyancy and sustained release properties making them excellent for floating drug delivery system.

Shishu et al[24], developed a multi unit type oral floating form of 5-fluorouracil to prolong the gastric residence time. They employed Sodium Alginate and HPMC K15M to formulate floating alginate beads by dropping drug polymer mixture containing calcium carbonate as gas generating agent into a cross linking solution comprising of calcium chloride and acetic acid. They observed that formulations containing higher amount of calcium carbonate demonstrated instantaneous and excellent buoyancy.

Badve et al[25], developed hollow calcium pectinate beads for floating-pulsatile release of diclofenac sodium intended for chronopharmacotherapy. Floating pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. They prepared hollow/porous beads by simple process of acid-base reaction during ionotropic crosslinking. The result suggested the use of hollow calcium pectinate microparticles as promising floating-pulsatile drug delivery system for site- and time-specific release of drugs acting as per chronotherapy of diseases.

Jaiswal et al[26], developed a multi-unit gastroretentive sustained release dosage form of a water soluble drug, ranitidine hydrochloride, from a completely aqueous environment avoiding the use of any organic solvent, which could cure peptic ulcer more efficiently by releasing the drug especially in stomach and also for a prolonged duration of time. The effects of factors like concentration of oil, curing time, drug: polymer ratio, alginate: pectin ratio and curing agent on drug entrapment efficiency, floating lag time, morphology and drug release were studied. They found that the beads in combinations of sodium alginate and pectin provide the sustain release of drug.

Halder et al[27], prepared propranolol HCl loaded calcium alginate beads by ionotropic gelation method. They found that the drug release from the beads was slow because of the less

swelling of the beads. They investigated the effect of amount of calcium chloride solution and the duration of cross linking on drug entrapment efficiency of the beads. They found that with increasing both the drug entrapment was decreased.

Fassihi et al[28], prepared Cross-linked beads by using calcium and low methoxylated pectin (LMP), which is an anionic polysaccharide, and calcium, LMP, and sodium alginate. Beads were dried separately in an air convection type oven at 40 ^{0}C for 6 hours and in a freeze dryer to evaluate the changes in bead characteristics due to process variability. Riboflavin (B-2), tetracycline (TCN), and Methotrexate (MTX) were used as model drugs for encapsulation. Ionic and nonionic excipients were added to study their effects on the release profiles of the beads.

Srinatha et al.[29] Ciprofloxacin loaded alginate beads were prepared by simultaneous external and internal gelation. The effect of blending of alginate with gellan, hydroxypropyl methylcellulose, starch, and chitosan on the bead properties were evaluated. Beads were spherical with incorporation efficiency in the range of 52.81 ± 2.64 to 78.95 ± 1.92%. Beads exhibited buoyancy over a period of 7–24 hr based on the formulation variables. *In vitro* release of ciprofloxacin from the alginate beads in simulated gastric fluid (SGF) (0.1 N HCl, pH 1.2), was influenced significantly ($p < 0.001$) by the properties and concentration of additives. Among the polymers incorporated into alginate beads. Hydroxy propyl methylcellulose (HPMC) provided an extended release over 7 hr. The drug release predominately followed Higuchi's square root model.

Drugs and Polymers used in Beads

Table 1: Drugs & Polymers used in Beads

S. No.	Drug	Polymers used	Ref.
1	Amoxicillin	Low methoxy pectin & Ethyl cellulose	30
2	Riboflavin	Poloxamer 188 , Alginate	31
3	Diltiazem	Sodium Carboxymethyl xanthan (SCMX)	32
4	Metformin HCl	Gelucire 43/01	33
5	Theophylline anhydrous	Low methoxy pectin(LM104 AS-FS)	34
6	Ranitidine HCl	Sodium alginate,HPMC	35
7	Famotidine	Sodium alginate & Pectin	36
8	Riboflavin	Sodium alginate	37
9	5 Fluorouracil	Calcium carbonate , sodium alginate and hydroxypropyl methylcellulose	38
10	Diclofenac sodium	Calcium pectinate	39
11	Propranolol HCl	Resin complex (resinate)-loaded calcium alginate (RALG)	40
12	Ketoprofen	co-polymer of polyacrylamide (PAAm) and Sodium alginate	41
13	Aceclofenac	Low-methoxy pectin	42
14	Tetracycline	Low methoxylated pectin (LMP)	43
15	Methotrexate	Low methoxylated pectin (LMP)	43

16	Loratidine	Pectin & Sodium alginate	44
17	Rifabutin	Gellan gum (Kelcogel)	45
18	Glipizide	Sodium alginate, carbapol 974P and SCMC	46
19	Clarithromycin	hydroxypropylmethylcellulose (K100M) and sunflower oil	47
20	Verapamil HCl	Sodium alginate, Pectin	48
21	Acetohydroxamic acid	Gellan	49
22	Prednisolone	Calcium alginate	50
23	Domperidone	Sodium alginate	51
24	Ibuprofen	Sodiumcarboxymethylcellulose, (NaCMC), Alginate	52
25	Rifampicin	Sodium alginate	53
26	Cloxacillin	Sodium alginate	54
27	Doxorubicin	Polyvinyl alcohol	55
28	Metronidazole	Sodium alginate	56
29	Furosemide	Methocel K- 15M (Hydroxy propyl methyl cellulose), Surelease (Ethyl Cellulose) and Acrycoat E30D	57
30	Valsartan	Sodium alginate	58
31	Meloxicam	Porous calcium silicate (Florite RE) and sodium alginate	59
32	Ciprofloxacin	Alginate with gellan, hydroxypropyl methylcellulose, starch, and chitosan	60
33	Atenolol	Alginate & Ethyl cellulose	61

Methods

The investigators use various methods to development of beads using natural, semi synthetic and synthetic polymers in different concentrations. Some most recently explored methods are discussed below.

Inotropic Gelation Method[62]

Narra et al Prepared alginate beads by this method, they prepared 3 % w/v of Sodium alginate solution in 25 mL of deionized water under gentle mixing while heating and added 250 mg of rifampicin to this sodium alginate solution and stirred using an over head stirrer for 5-10 min at 1000 rpm to obtain a homogenous mixture. The mixture was kept aside until the air bubbles disappeared completely and then it was extruded dropwise into 50 mL of 1% calcium chloride solution through the 26 gauge needle. Similarly the different formulation was developed by using different polymer drug ratio. The gel beads were cured in gelation solution for 1 h, then filtered, and rinsed several times with distilled water and dried at 45°C for 12-16 h in hot air oven.

Another researcher (*Narkar et al*) prepared beads by the cation-induced ionotropic gelation method using acidic and alkaline cross-linking medium. Gellan solution (1.5%, 1.75%, and 2.0% w/v) was prepared by dissolving the gellan in double-distilled water by heating at 90°C. Different quantities of amoxicillin were dispersed uniformly in 10 ml of gellan solution with constant stirring (300 rpm) at 40°C until a homogeneous solution was formed. The homogeneous

bubble-free solution was extruded dropwise through 18 G syringe needle into the 100 ml crosslinking solution containing 5% calcium chloride of pH 5 or pH 9 with constant stirring (100 rpm) and curing time 5 min to provide sufficient mechanical strength. The beads were separated by filtration, washed with double-distilled water, and dried at 25–30°C for 24 h.

Hydrogel Beads[63]:

Gattani et al. Preparated of Alginate Gel Bead using HPMC K4M and Liquid Paraffin (LP). Sodium alginate (3% w/w) was dissolved in 50 ml of distilled water with agitation and HPMC K4M was added with slow stirring. Simultaneously Clarithromycin (250 mg) and LP (5/10/15/20% w/w) were added to the above solution. Solution containing CL and LP was added drop-wise into 100 ml calcium chloride (2% w/v) and left at room temperature for 2 h. The resultant hydrogel beads were washed twice with 50 ml of distilled water and dried at room temperature for 24 h As CL is insoluble in LP, both exist in gel beads.

Solvent Evaporation Technique[64-65]

It is the most extensively used method of microencapsulation, first described by Ogawa *et al.* A buffered or plain aqueous solution of the drug (may contain a viscosity building or stabilizing agent) is added to an organic phase consisting of the polymer solution in solvents like dichloromethane (or ethyl acetate or chloroform) with vigorous stirring to form the primary water in oil emulsion.

Sher *et al.* prepared porous Ibuprofen loaded beads by solvent evaporation. In this method Accurel MP 1000 was closely sieved in the range of 250–350 μm. In a typical study, they dissolved various amounts of drug in the multiple volumes of solvent (Methanol, dichloromethane) followed by the constant addition of 100 mg Accurel MP 1000 ®, kept to evaporate solvent under ambient conditions.

Melt Solidification Technique[66]:

Dixit *et al* Prepared Ketoprofen beads **:**A mixture of Ketoprofen and cetyl alcohol at different ratios were melted and stirred on a water bath maintained at 95°C to form a uniform molten mass. The Ketoprofen-cetyl alcohol melt was poured in 100ml water maintained at room temperature and was stirred continuously using propeller blade (2500rpm).The Ketoprofen beads obtained after solidification of dispersed droplets were separated by filtration and dried at room temperature.

Evaluation and Characterization of Beads

The multiple unit dosage forms are evaluated for various parameters. They are discussed below:

Particle Size and Surface Morphology:

The average particle size of beads is determined with a micrometer and calculates as the average value of size of beads. The surface morphology of beads have been visualized by scanning electron microscopy by several researchers .The sample for SEM is prepare by sticking the beads on a double adhesive tape, which stuck to an aluminum stub. The stub is then coated with gold to a thickness of about 300 Å using a sputter coater. These samples are then randomly scanned[67].

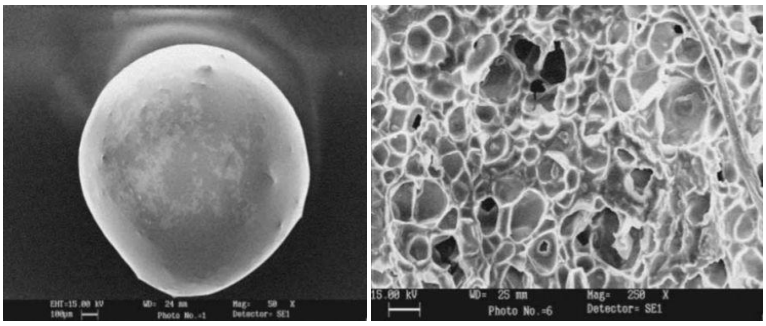

Figure 1: SEM of the Floating beads of Verapamil hydrochloride (Khan *et al*[68])

In vitro floating study:

The floating study performed using a USP/IP dissolution apparatus containing 500 ml of phthalate buffer solution (pH 3.4). The medium temperature should be kept at 37±0.5 °C. The floating beads (1.0 g beads) place in the dissolution medium and the medium was agitated with a paddle at 50 rpm. After agitation, the beads that floated on the surface of the medium and those that settled down at bottom of the flask were recovered separately. The percentage of floating was measured by visual observation[69].

Percent Drug Entrapment Efficiency:

Accurately weighed amount (apprx.20mg) of beads shaken for 24 h in 250ml USP phosphate buffer solution (pH 6.8) and then filtered. The filtrate is then collected following suitable dilution and assay spectrophotometrically[70]. DEE is determined from the following equation:

% Drug entrapment = [Calculated drug content/Theoretical drug content] x 100

Swelling study:

In this test, beads are kept in petri-dishes containing pH 6.8 phosphate buffers. At the end of 1 hour, the beads are withdrawn, soak with tissue paper and weigh. Then for every 1 hour, weights of the beads would be note, and the process is continuing till the end of 8 hours[71]. Percent weight gained by the beads would be calculated by the following formula:

$$\mathbf{S.I = \{(Mt-Mo) / Mo\} X 100}$$

Where, S.I = swelling index,
Mt = weight of beads at time‘t’ and
Mo = weight of beads at time, t = 0.

In Vitro Release studies:

Drug release studies performed according to the published literature (USP, BP.IP) by using the Dissolution apparatus at 100 rpm and 37 °C in 500 ml of simulated gastric fluid. Approximately 50 beads were used for each experiment. Samples were taken at appropriate time intervals and assayed spectrophotometrically at wavelength regarding to the drug. Fresh media should be added to replace the sample taken[72].

Gamma Scintigraphy:

Gamma scintigraphy is a technique whereby the transit of a dosage form through its intended site of delivery can be non-invasively imaged *in vivo* via the judicious introduction of an appropriate short lived gamma emitting radioisotope. The inclusion of a γ-emitting radionucleide in a formulation allows indirect external observation using a γ-camera or scintiscanner. But the main drawback of γ- scintigraphy are the associated ionizing radiation for the patient, the limited topographic information, low resolution inherent to the technique and the complicated and expensive preparation of radiopharmaceutical[73].

Advantages [74-75]

- Those drugs are suitable for these systems which act locally in the GIT. (e.g. Antacids)
- Floating system (Bead) is very useful in case of disease like diarrhoea when poor absorption is possible due to vigorous GIT movement.
- The stomach specific drugs (like ferrous salts and antacids) are easily absorbed.
- Hydrodyanamically Balanced System formulation may be useful for the acidic drug like aspirin and other similar drugs which cause irritation on the stomach wall.
- FDDS (Bead) is also helpful in reducing fluctuations of plasma drug concentration and dosing frequency.
- FDDS (Bead) seem to reduce counter-activity of the body, Minimize adverse activity at the colon and improve receptor activation selectivity.

Disadvantages [76-77]

- FDDS(Bead) is not suitable for those drugs that have solubility or stability problem in gastric juice.
- The systems require large amount of fluids in the stomach to float for proper delivery of drug.
- Limited suitability of drugs that undergoes significant first pass metabolism and absorbed through out GIT.
- FDDS (beads) cannot be dosed to patients just before going to Bed.

- Some drugs that have multiple absorption sites in the gastrointestinal tract can causes irritation to gastric mucosa.

Applications[78-82]

Drug loaded beads are applicable for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. Beads are applicable in following approaches:

- Sustained Drug Delivery
- Site-Specific Drug Delivery
- Absorption Enhancement

CONCLUSION

There is a lot of literature including books, research papers, patents and academician concepts concluded that the Drug loaded beads are most promising oral controlled delivery system. These systems not only increase the retention time but also helpful in enhancing the bioavailability and site-specificity of the drug. In the different studies various drugs have been entrapped in this formulation and shown positive results and established all quality control parameters. By the time, increasing sophistication of delivery technology will ensure the development of quality product of gastroretentive drug delivery. In the future perspectives, it is a need of time to adopt these types of technique on commercial scale to formulate efficient dosage forms.

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