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FLOATING INSITU GELLING SYSTEM: A REVIEW

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ABSTRACT

Floating insitu gelling system is the novel drug delivery system and affects abnormal physiology of stomach. This review paper discusses method materials, mechanism, how does act in stomach, preparation of formulation and floating insitu gelling system which can show significant result in the stomach and even with good mechanism. Approximately 50% of the drug delivery systems available in the market for oral route. The high level of patient compliance has been observed in taking oral dosage forms is due to the ease of administration and handling of these forms. Number of drug delivery system has been used administration of drug through oral rout and among them further research is going on floating drug delivery system.

KEYWORDS: insitu gelling system, NDDS.

1. INTRODUCTION

Oral route remains the prefer route for the administration of therapeutic agents because low cost of therapy and ease of administration leads to higher level of patient compliance. Approximately 50% of the drug delivery systems available in the market for oral route. The high level of patient compliance has been observed in taking oral dosage forms is due to the ease of administration and handling of these forms. Although a lot of advancements have been seen in oral controlled drug delivery system in the last few decades, this system has been of limited success in case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract). Modification of the GI transit time is one of the main challenge in the development of oral controlled drug delivery system. Gastric emptying of pharmaceuticals is highly variable and dependent on the dosage form and the fed/fasted state of the stomach. Normal gastric residence time usually ranges between 5 minutes to 2 hours.

In the fasted state the electrical activity in the stomach the "interdigestivemyoelectrical cycle" governs the activity and the transit of dosage forms.[1]

It is characterized by four phases:[2]

Phase I- Period of no contraction (30-60 minutes)

Phase II-Period of intermittent contractions (20-40 minutes)

Phase III-Period of regular contractions at the maximal frequency also known as housekeeper Wave (10-20 minutes)

Phase IV-Period of transition between Phase III and Phase I (0-5 minutes)

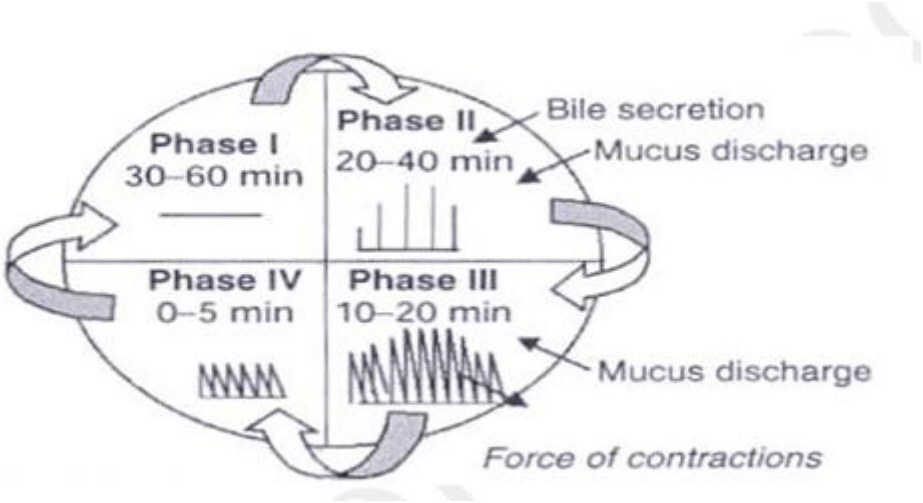


Fig. 1: Motility pattern in GIT.

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. One of such difficulties is the ability to confine the dosage form in the desired area of the gastrointestinal tract. To overcome this physiological problem, several drug delivery systems with prolonged gastric retention time have been investigated. Attempts are being made to develop a controlled drug delivery system that can provide therapeutically effective plasma drug concentration levels for longer durations, thereby reducing the dosing frequency and minimizing fluctuations in plasma drug concentration at steady state by delivering drug in a controlled and reproducible manner that are less soluble in high pH environment. The controlled gastric retention of solid dosage forms may be achieved by the mechanism of muco adhesion, floatation, sedimentation, expansion, modified shape systems or by the administration of pharmacological agents that

delaying gastric emptying. Based on these approaches, floating drug delivery systems seems to be the promising delivery systems for control release of drugs.[3]

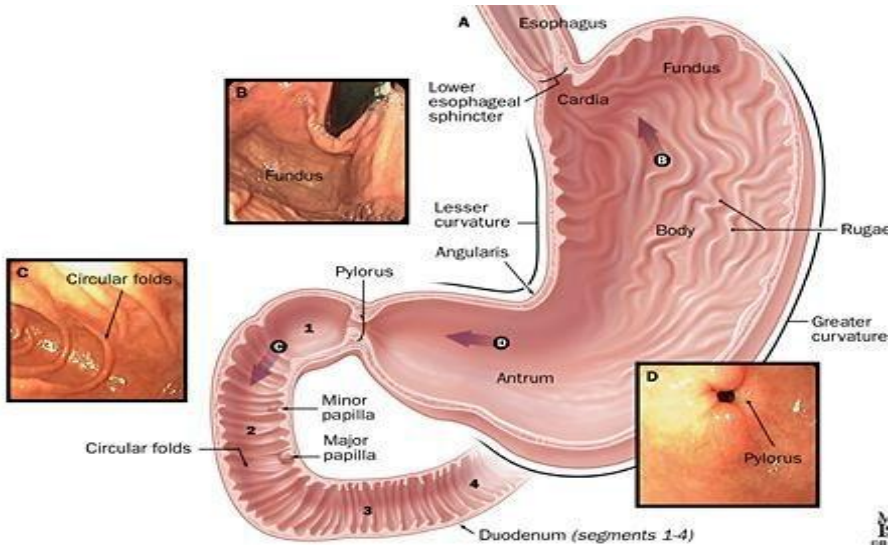


Fig. 2: Physiology of stomach.

Floating drug delivery systems (FDDS) are aimed to retain the drug in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids. The underlying principle is very simple i.e. to make the dosage form less dense than the gastric fluids so that it can float on them. The density of the system can be reduced by incorporating a number of low density fillers into the systems such as hydroxyl cellulose, lactates or microcrystalline cellulose. However, this system is not ideal because its performance is highly dependent on the presence of food and fluid in the stomach. The basic idea behind the development of such a system was to maintain a constant level of drug in the blood plasma inspire of the fact that the drug dose not undergoes disintegration. The drug usually keeps floating in the gastric fluid and slowly dissolves at a pre-determined rate to release the drug from the dosage form and maintain constant drug levels in the blood. Sometimes for generating a floating system we even need to add some effervescent or gas generating agent which will also ultimately reduce the density of the system and serve the goal of achieving a floating system. These systems have a particular advantage that they can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GIT. These systems continuously release the drug before it reaches the absorption window, thus ensuring optimal bioavailability.[2]

1.1 Need for gastroretension[4,5]

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous, controlled manner. Drugs delivered in this manner have a lower level of side effects and provide their therapeutic effects without the need for repeated dosage or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach dose not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, which is where absorption occurs and contact time is limited. In general, appropriate candidates for controlled release gastro retentive drug delivery systems have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT:

1. Drugs acting locally in the stomach
2. Drugs that are primarily absorbed in the stomach
3. Drugs that is poorly soluble at alkaline pH
4. Drugs with a narrow window of absorption
5. Drugs which are absorbed rapidly from the GI tract.
6. Drugs that degrade in the colon
7. Drugs that disturb normal colonic microbes

1.2 FACTORS AFFECTING THE GASTRIC EMPTYING AND HENCE THE GASTRIC RETENTION TIME OF AN ORAL DOSAGE FORM[6,7,8]

i. Size, shape and density of the dosage form.

ii. Concomitant ingestion of food, its nature, caloric content and frequency of intake. Interestingly, most studies related to effects of food on gastric residence time of floating systems share a common viewpoint that food intake is the main determinant of gastric emptying, while specific gravity has only a minor effect on the emptying process, or not have an effect at all.

iii. Drugs such as anticholinergic agents (e.g. atropine, propantheline); opiates (e.g. codeine) and prokinetic agents (e.g. metoclopramide, cisapride).

iv. Biological factors such as gender, posture, age, sleep, body mass index, physical activity and disease states e.g. diabetes and Crohn's disease**.** Many factors could lead to alterations in gastric emptying process, which may seriously affect the release of a drug from its delivery system; it is therefore, desirable to develop a drug delivery system that exhibits an extended GI residence and a drug release profile independent of patient related variables.

2. TYPES OF FLOATING DRUG DELIVERY SYSTEM[9,10,11,12,13,14,15]

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are:

Effervescent System

Non-Effervescent System

2.1 Effervescent System

Effervescent systems include use of gas generating agents, carbonates (e.g. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature.

These effervescent systems further classified into two types.

A. Gas generating systems

B. Volatile liquid/vacuum systems

2.1.1 Gas generating systems

2.1.1.1 Intra-gastric single layer floating tablets or Hydrodynamically Balanced System (HBS)

These are formulated by intimately mixing the CO_2 generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the greater and a better control over fluctuation in plasma drug concentration.

2.1.1.2 Intra gastric bilayered floating tablets

These are also compressed tablet as shown in Fig. 3 and containing two layer i.e.

(1) Immediate release layer.

(2) Sustained release layer containing CO_2 generating agent.

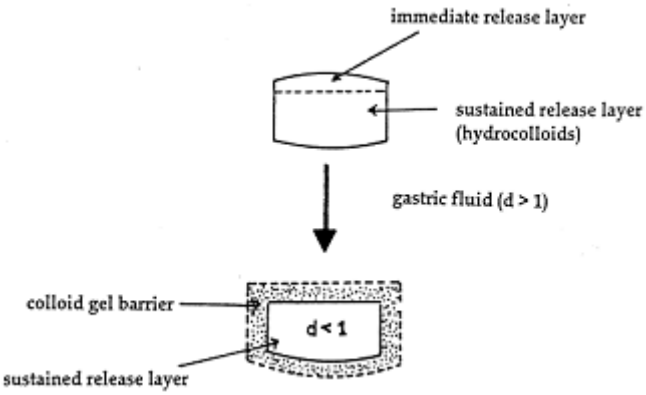


Fig. 3: Intragastric floating bilayer tablet.

2.1.1.3 Multiple unit type floating pills

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO_2 within the systems.

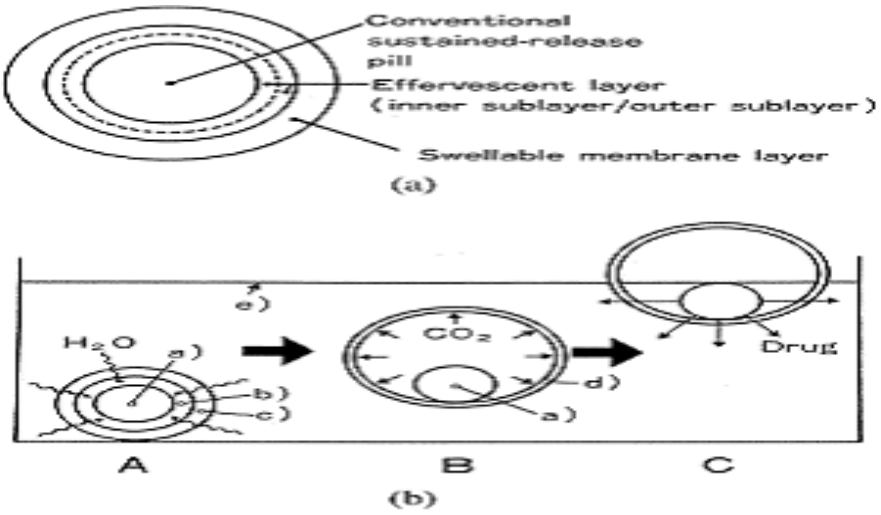


Fig. 4: (a) Multiple-unit oral floating dosage system.

(b) Stages of floating mechanism.

2.1.2 Volatile liquid / vacuum containing systems

2.1.2.1 Intragastric floating gastro-intestinal drug delivery system

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment.

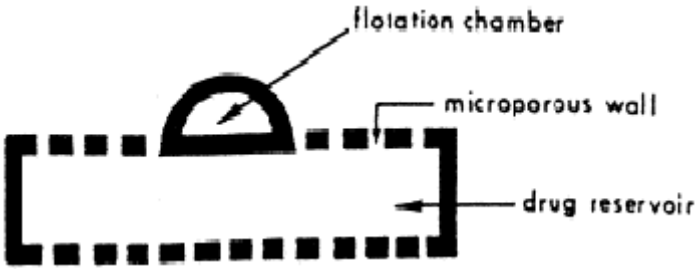


Fig. 5: Intragastric floating drug delivery device.

2.1.2.2 Inflatable gastro-intestinal delivery systems

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir into the gastric fluid.

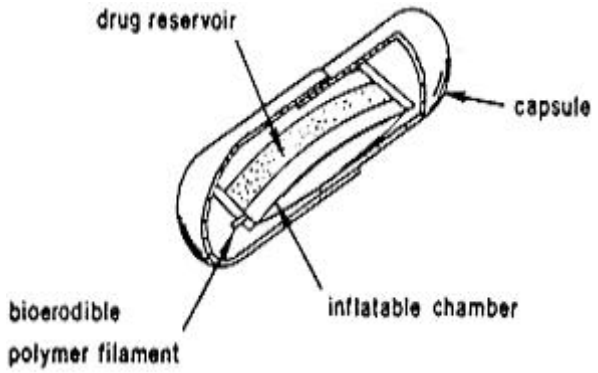


Fig. 6: Gastro-inflatable drug delivery device.

2.1.2.3 Intragastric osmotically controlled drug delivery system

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components: drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active

compartment contains an osmotically active salt and is enclosed within a semi-permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semi-permeable membrane into osmotically active compartment to dissolve the osmotically salt. An osmotic pressure is then created which acts on the collapsible bag and in turn forces the bag reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice. The floating support is also made to contain a bio-erodible plug that erodes after a predetermined time to deflat the support. The deflated drug delivery system is then emptied from the stomach.

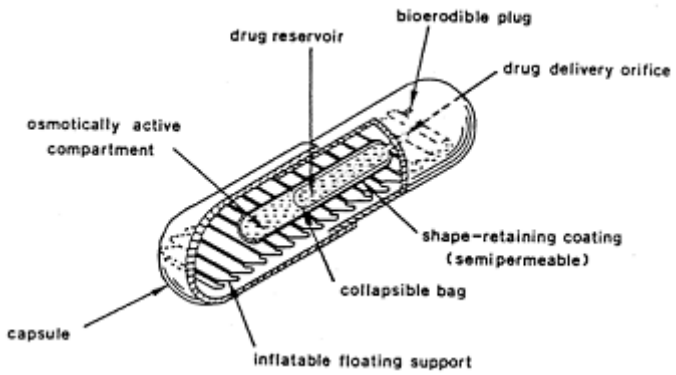


Fig. 7: Intragastric osmotic controlled drug delivery system.

2.2 Non Effervescent Systems

The non effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GIT. The most commonly used excipients in non effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrics forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bio-adhesive polymer such as chitosan and carbopol. The various types of this system are as follows:

2.2.1 Single layer floating tablets

They are formulated by intimate mixing of drug with gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

2.2.2 Bilayer floating tablets

A bilayer tablet contain two layer immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

2.2.3 Alginate beads

Multi unit floating dosage forms are developed from freeze dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence, time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours.

2.2.4 Hollow microspheres

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells were prepared by a novel emulsion solvent diffusion method. The ethanol: dichloromethane solution of drug and enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40° C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug. The microballoons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro.*

The successful development of oral controlled drug delivery systems requires an understanding of the three aspects of the system, namely:

1. The physiochemical characteristics of the drug.
2. Anatomy and physiology of GIT. And
3. Characteristics of Dosage forms.

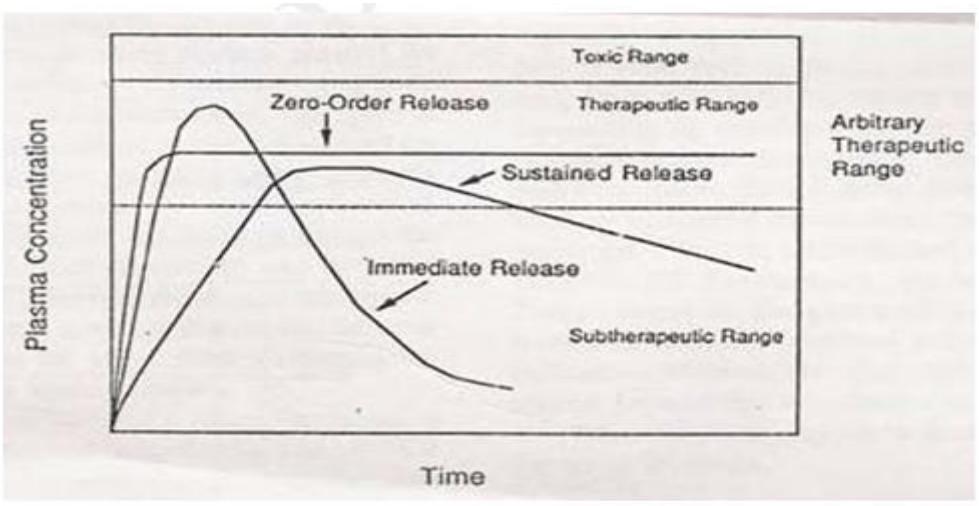


Fig. 8: Drug level versus time profile showing differences between zero order, controlled releases, slow first order sustained release and release from conventional tablet.

Good fundamental understanding of the anatomic and physiological characteristics of the human GIT is required to modulate the gastrointestinal transit time of a drug through FDDS for maximal gastrointestinal absorption of drugs and site-specific delivery.[16,03]

2.3 ADVANTAGES OF FDDS[17,18]

Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine.

FDDS are advantageous for drugs meant for local action in the stomach eg: Antacids

FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhoea to keep the drug in floating condition in stomach to get a relatively better response.

Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence; HBS/FDDS formulations may be useful for the administration of aspirin and other similar drugs.

The FDDS are advantageous for drugs absorbed through the stomach eg: Ferrous salts, Antacids.

Drugs with considerably short half life can be administered in this manner to get an appreciable therapeutic activity.

Enhancement of the bioavailability for drugs which can metabolized in the upper GIT.

2.4 DISADVANTAGES OF FDDS[19,20,21]

Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.

Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo significant first-pass metabolism, may not be suitable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.

One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach, so that the drug dosages form float therein and work efficiently.

These systems also require the presence of food to delay their gastric emptying.

Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.

3. FLOATING *INSITU* GELLING SYSTEM

3.1 Principle of *insitu* gel[22,23,24]

Formulation of *insitu* gel system involves the use of gelling agent (e.g. gellan gum, sodium alginate etc.) which can form a stable sol/suspension system to contain the dispersed drug and other excipients. The gelling of this sol/suspension system is to be achieved in gastric environment, triggered by ionic complexation due to change in pH. Ion-sensitive polymer can produce textures in the final product that vary from hard, non elastic, brittle gels to fluid gels. Inclusion of calcium carbonate in formulation produces carbon dioxide when come in contact with gastric fluid. The released carbon dioxide can entrapped in the gel network producing buoyant formulation and then calcium ion reacted with ion sensitive polymer can produce a crosslinked three dimensional gel network that might restrict the further diffusion of carbon dioxide and drug molecules and may result in extended period of floating and drug release, respectively.

4. APPROACHES OF *IN SITU* DRUG DELIVERY[25,26]

There are four broadly defined mechanisms used for triggering the *in situ* gel formation of biomaterials:

Physiological stimuli (e.g., temperature and pH),

Physical changes in biomaterials (e.g., Diffusion of solvent and swelling), and chemical reactions (e.g., enzymatic, ionic and photo-initiated polymerization).

4.1 *In situ* formation based on physical mechanism Swelling and Diffusion

Swelling of polymer by absorption of water causes formation of gel certain biodegradable lipid substance such as myverol 99 (glycerol mono-oleate) forms in situ gel under such phenomenon. Solution of polymer such as N – methyl pyrrolidone (NMP) involves diffusion of solvent from Polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix.

4.2 *In situ* gelling based on chemical stimuli

4.2.1 Ionic crosslinking

Certain ion sensitive polysaccharides such as carrageenan, Gellan gum (Gelrite®), Pectin, Sodium Alginate undergo phase transition In presence of various ions such as k^+, Ca^+, Mg^+, Na^+**.** e.g., alginic acid undergoes gelation in presence of divalent/polyvalent cations. eg. Ca^{2+} due to the interaction with glucoronic acid blocks in alginate chains.

4.2.2 Enzymatic crosslinking

Certain natural enzymes which operate efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators provides a convenient mechanism for controlling the rate of gel formation, which allows the mixtures to be injected before gel formation *in situ*.

4.2.3 Photo-polymerization

A solution of monomers such as acrylate or other polymerizable functional groups and initiator such as 2, 2- dimethoxy-2-phenyl acetophenone, camphorquinone and ethyl erosin can be injected into a tissues site and the application of electromagnetic radiation used to form gel designed readily to be degraded by chemical or enzymatic processes or can be designed for long term persistence *in vivo*. Typically long wavelength ultraviolet and visible wavelengths are used. A photopolymerizable, biodegradable hydrogels as a tissue contacting material.

4.3 *In situ* gel formation based on physiological stimuli

4.3.1 Temperature dependant *in situ* gelling

These are liquid aqueous solutions before administration, but gel at body temperature. These hydrogels are liquid at room temperature (20ºC - 25ºC) and undergo gelation when in contact with body fluids (35ºC - 37ºC), due to an increase in temperature This approach exploits temperature-induced phase transition. Some polymers undergo abrupt changes in solubility in response to increase in environmental temperature (lower critical solution temperature, LCST). At the LCST, hydrogen bonding between the polymer and water becomes unfavorable, compared to polymer–polymer and water–water interactions, and an abrupt transition occurs as the solvated macromolecule quickly dehydrates and changes to a more hydrophobic structure. Alternatively, some amphiphilic polymers, that self-assembles in solution, show micelle packing and gel formation because of polymer–polymer interactions when temperature is increased. Temperature-sensitive hydrogels are probably the most commonly studied class of environment-sensitive polymer systems in drug delivery research. Polymers such as Pluronics (poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide), Polymer networks of poly (acrylic acid) (PAA) and polyacrylamide (PAAm) or poly (acrylamide-co-butyl methacrylate). Polymer solution is a free flowing liquid at ambient temperature and gels at body temperature. A positive temperature- sensitive hydrogel has an upper critical solution temperature (UCST), such hydrogel contracts upon cooling below the

UCST. Polymer networks of poly (acrylic acid) (PAA) and polyacrylamide (PAAm) or poly (acryl amide-co-butyl methacrylate) have positive temperature dependence of swelling.

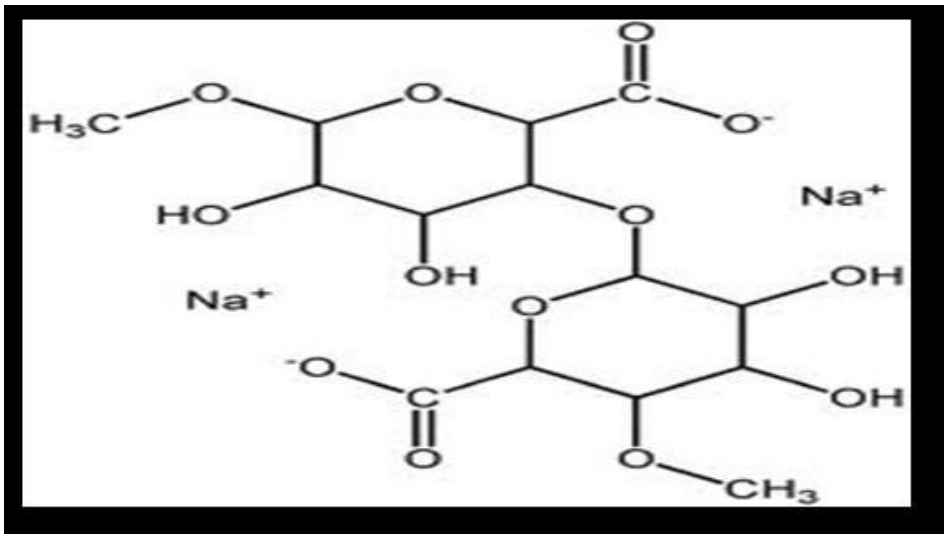
4.3.2 pH dependant gelling

Another formation of *in situ* gel is based on change in pH. Certain polymers such as PAA (Carbopol®, carbomer) or its derivatives, polyvinylacetal diethylaminoacetate (AEA), mixtures of poly (methacrylic acid) (PMA) and poly (ethylene glycol) (PEG) shows change from sol to gel with change of pH. The polymers with a large number of ionizable groups are known as polyelectrolytes. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups.

5. POLYMERS FREQUENTLY USED FOR *IN SITU* GELLING FOR GASTRO RETENTIVE REASONS

5.1 Sodium alginate[27,28,29]

Sodium alginate is a widely used polymer of natural origin. Chemically, it is an alginic acid salt, consisting of L-glucuronic acid and -D-mannuronic acid residues connected by 1, 4-glycosidic linkages.



5.2 Pluronic F-127

Poloxamers or pluronic (marketed by BASF Corporation) are the series of commercially available difunctional triblock copolymers of non-ionic nature. They comprise of a central block of relatively hydrophobic polypropylene oxide surrounded on both sides by the blocks

of relatively hydrophilic poly ethylene oxide. Pluronics or Poloxamers also undergo in situ gelation by temperature change.[29]

5.3 Xanthum gum

Xanthan gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram negative bacterium Xanthomonas campestris. The anionic character of this polymer is due to the presence of both glucuronic acid and pyruvic acid groups in the side chain.[29]

Table: Natural polymer use in preparation of *in situ* gel.[30]

Natural polymer	Basic chain	Solubility	Source
Psyllium husk	ß-(1-4)-linked D-xylopyranosyl.	Swells in water.	Seed coats of Plantago ovate.
Pectin	α-(1,4)-linked Dgalacturonic acid.	Soluble in water, insoluble in ethanol (95%) & organic solvents.	Citrus peel, apple pomace, sugar beet pulp etc.
Xanthum gum	α-(1,4)-linked D-glucose.	Soluble in hot/cold water and acid/alkane conditions.	Fermentation of glucose by Xanthomonascampestris.
Chitosan	Deacetylated P-1, 4-Nacetyl-1-D glucosamine.	Insoluble in neutral and alkaline pH.	Shell of marine invertebrates.
Gellan gum	D-glucose, D-glucuronic acid and rhamnose in ß-1, 4 linkage.	Soluble in hot water.	Pseudomonas elodeae.
Karaya gum	Mixture of d-galactose & Lrhamnose.	Insoluble but swells in water.	Plant (Sterculiaurens)

5.4 Pectin

These are plant origin anionic polysaccharides isolated from the cell wall of most plants and basically consist of (1-4)-D-galacturonic acid residues. Pectin undergoes gel formation in presence of medium, a stiff gel is produced.[31]

5.5 Xyloglucan

It is a plant based polysaccharide obtained from seeds of tamarind. Chemically, this polysaccharide composed of a chain of (1-4) -D-glucan having (1-6) -D xylose units as branches which have partial (1-2) -D-galactoxylose substitution. Xyloglucan, itself does not

undergo gel formation but dilute solutions partly degraded by galactosidase exhibit gelling properties on heating (temperature dependent gel formation).[31]

5.6 Gellan gum

Gellan gum secreted by the *Sphingomonas elodeae (Pseudomonaselodeae)* and chemically is anionic deacetylated polysaccharide with (1 unit) and -D-glucuronic acid (2 units) residues. Gellan gum undergoes gel formation due to change in temperature or due to presence of cations (e.g. Na^+, K^+, Ca^{2+}).[32]

5.7 Chitosan

Chitosan is a biodegradable, thermosensitive, polycationic polymer obtained by alkaline deacetylation of chitin, a natural component of shrimp and crab shell.[33]

5.8 Carbopol

Carbopol is a well known pH dependent polymer, which stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH. HPMC is used in combination with carbopol to impart the viscosity to carbopol solution, while reducing the acidity of the solution.[34]

6. EVALUATION OF STOMACH SPECIFIC FLOATING *IN SITU* GEL SYSTEM

Stomach specific floating *In situ* gel forming system should be evaluated for following parameters:

6.1 Physical appearance: *In situ* solutions should be clear and free of any particulate matter. Measure time required for time required for solution to convert in to gel in buffer pH 1.2 and check consistency of the gel formed visually.[35]

6.2 pH of system: Measure pH of gel forming solution using calibrated pH meter at 27°C. [35.]

6.3 Viscosity of *in situ* gelling system: Determine viscosity of solution before and after gelling by using Brookfield viscometer or cone and plate viscometer at suitable temperature (25±1°C), using 1 or 2ml of sample aliquots.[27, 35]

6.4 *In vitro* gelation study: To evaluate *in vitro* gelling capacity of gel forming solution, prepare colored solution of the formulation and prepare 15 ml gelation medium (0.1N HCl, pH 1.2) in a test tube. After that, add 1ml of colored formulation. As, the solution comes in contact with gelation medium, a stiff gel produced. Determine the gelling capacity on the basis of stiffness and time period for which gel remains, as such.[29]

6.5 *In vitro* floating ability: Determine *In vitro* floating ability of the gel in 500ml simulated gastric fluid (0.1 N HCl, pH 1.2) using 37°C using USP dissolution apparatus (type II). After that, determine 10ml of prepared formulation in the dissolution vessel. Note time taken by formulation to float (floating lag time) and duration for which the formulation floats constantly on the surface (floating time).[27,29,35]

6.6 Water uptake by gel: Measure water uptake by gel by using thermo gravimetric analyzer. Use *in situ* gel formed in 40ml 0.1N HCl, pH 1.2. Collect gel portion formed in the buffer in a Petridish and excess buffer is removed using tissue paper. Take initial weight of the gel and add 10 ml distill water. After every 30 minutes, decant water and measure weight of the gel. The difference in the weight shows the water uptake by gel.[35]

6.7 Uniformity of content: Determine drug content by a suitable quantitative technique as specified in particular monograph or as per the established standard testing procedure.

6.8 *In vitro* drug release: Determine *In vitro* drug release using USP dissolution apparatus (type II) at 50 rpm in 900 ml, 0.1N HCl, pH 1.2 at 37°C. Take 10ml formulation in a Petridish and kept in dissolution vessel. Then take dissolution medium in the dissolution vessel without any disturbance. Draw Suitable sample at each predefined interval and replenished with fresh medium. Dissolution study should be carried out for at least 8 hours.[27,29]

7. APPLICATION OF FLOATING *IN SITU* DRUG DELIVERY SYSTEMS[36]

Floating *insitu* drug delivery offers several applications 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. These are summarized as follows.

7.1 Sustained Drug Delivery: The generally problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.

Eg. Itoh K. et al. prepared *in situ* gelling system by using pectin/ xyloglucan for oral sustained drug delivery. They found that dilute solution of xyloglucan will form gel by *in situ* gellation, when administered orally the study had shown that the gel strength and sustained release properties may be improved by inclusion of pectin in the formulation.

7.2 Site-Specific Drug Delivery: These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine. Eg. Debnath S. et al. developed floatable in- situ gel as carrier for stomach- specific drug delivery of metoclopramide Hcl. The objective of this study was to develop a novel in-situ gel system for sustained drug delivery using natural biodegradable polymers. In-situ gel was formed at biological pH.

7.3 Absorption Enhancement: Drugs that have poor bioavailability because of site specific absorption from the upper part of the Gastro-intestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby improving their absorption. Eg. A significantly increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available dosage form.

8. COMMERCIAL FORMULATIONS OF *IN-SITU* GEL[37,38]

8.1 Timoptic-XE

It is a timolol maleate ophthalmic gel formulation of Merck and Co. Inc., This formulation is available in two dosage strengths 0.25% and 0.5% in market. The pH of the solution is approximately 7.0, and the osmolarity is 260-330 mOsm. Each ml of Timoptic-XE 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate). Inactive ingredients include gellan gum, tromethamine, mannitol, and water for injection and the preservative used is benzododecinium bromide 0.012%. Timoptic-XE, when applied topically on the eye, reduces theelevated, as well as normal intraocular pressure, whether or not accompanied by glaucoma.

8.2 AzaSite

AzaSite is a marketed product of InSite Vision. AzaSite is a topical ophthalmic solution of azithromycin formulated in DuraSite (polycarbophil, edetate disodium, sodium chloride). AzaSite is supplied as a sterile aqueous ophthalmic formulation designed for topical administration. The recommended initial dose of the drug is in still 1 drop in the affected

eye(s) twice daily, eight to twelve hours apart for the first two days and then still 1 drop in the affected eye (s) once daily for the next five days.

8.3 Pilopine HS

Pilopine HS is a marketed product of Alcon Laboratories Inc. Pilopine HS (pilocarpine hydrochloride ophthalmic gel) 4% is a sterile topical ophthalmic aqueous gel which contains more than 90% water and employs Carbopol-940, a synthetic high molecular weight cross-linked polymer of acrylic acid, to impart a high viscosity.

8.4 Akten™

Akten™ is an HPMC-based gel of lidocaine hydrochloride for ocular surface anesthesia. Akten™ contains 35 mg of lidocaine hydrochloride per mL as the active ingredient. Akten™ also contains Hypromellose, Sodium Chloride, and Purified Water as inactive ingredients. The pH may be adjusted to 5.5 to 7.5 with hydrochloric acid and/or sodium hydroxide. The recommended dose of Akten™ is 2 drops applied to the ocular surface in the area of the planned procedure. Akten™ may be reapplied to maintain anesthetic effect.

8.5 Virgan

Vigran is an ophthalmic antiviral that is indicated for the treatment of acute herpetickeratitis. The recommended dosing regimen for Virgan is 1 drop in the affected eye 5 times per day (approximately every 3 hours while awake) until the corneal ulcer heals, and then 1 drop 3 times per day for 7 days. Virgan (ganciclovir) contains carbomer 974. The carbomers are polyacrylic acid derivatives that impart high viscosity to their aqueous solutions at neutral pH (above their pKa values) due to ionization and hydration of the carboxyl groups.

8.6 Cytoryn

This is one of the Macromed's products, which is an ovel, peritumoral, injectable depot formulation of interleukin-2 (IL-2) for cancer immunotherapy using Regel drug delivery system. It is a free flowing liquid below room temperature that instantly forms a gel depot upon injection from which the drug is released in a controlled manner. Cytoryn enhances the immunological response by safely delivering four times the maximum tolerated dose allowed biconventional IL-2 therapy. Cytoryn also activates the systemic antitumor immunity. Regel system stabilizes and releases IL-2 in its bioactive form.

9. RECENT ADVANCEMENTS[39,40]

One of the challenges facing todays pharmaceutical industry centreson coming up with efficient treatment options that are readily acceptable to physicians and patients. Delivery systems must also contribute to a better therapeutic outcome if they are going to provide viable alternatives to pharmaceuticals currently delivered by other routes. *In situ* gel formulations are one of the challenging drug delivery systems. Various biodegradable polymers are used for formulation of *insitu* gels, but there are fabrication problems, difficult process ability, and use of organic solvents for their preparation (especially for synthetic polymer based systems), burst effect and irreproducible drug release kinetics. Natural polymers satisfy the characteristics of an ideal polymer but batch to batch reproducibility is difficult therefore synthetic polymers are used. The recent advancement of biotechnologies has lead to the development of liable macromolecular therapeutic agents that require complex formulations for their efficient administration N-stearoyl L-alanine(m) ethyl esters when mixed with a vegetable oil and biocompatible hydrophilic solvent led to the formation of injectable, *insitu* forming organ gel. Following subcutaneous injection, leuprolide-loaded organ gel degraded and gradually released leuprolide for 14 to 25d. The gastroretentive drug delivery system of famotidine was prepared, by employing two different grades of methocel K100 and K15 M by effervescent technique; these grades of methocel were evaluated for their gel forming properties. Sodium bicarbonate was incorporated as a gas generating agent. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, in-vitro buoyancy and dissolution studies.

The gastro-retentive controlled release drug delivery system of verapamil HCl was prepared in an effort to increase the gatric residence time of the dosage form and to control the drug release. Hydroxypropyl methyl cellulose, carbopol and xanthan gum were incorporated for gel forming properties. Buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. Invitro release studies were performed and drug release kinetics was evaluated by the linear regression method. Optimized intragastric floating tablet showed no significant change in physical appearance, drug content after storage at 75% relative humidity for 3 months. Formulation, evaluation and optimization of stomach specific *in situ* gel of clarithromycin and metronidazole benzoate was studied by using sodium alginate as polymer and calcium carbonate was used as a cross linking agent .This study reported that oral administration of aqueous solutions containing sodium alginate resulted in formation of *In situ gel*, such formulations are homogenous liquid when

administered orally and become gel at contact site. Stability study of check point batch after three month showed no change in in-vitro drug release profile, % assay and evaluation parameters. It was concluded that by adopting a systemic formulation approach, an optimum point could be reached in the shortest time with minimum effort.

Plasma levels of cimetidine after oral administration to rabbits were compared with commercially available cimetidine/alginate suspension and in-vivo release characteristics were found to be identical with commercial preparation.

CONCLUSION

Dosage form with prolonged gastric retention and its compatibility with stomach physiology is the real challenge. So in order to achieve gastric retention various approaches have been done from several years. Out of which floating in-situ drug delivery system is the most promising technique which undergo sol to gel transition in acidic medium of stomach and provide site specific release for longer duration of time by floating on the surface of gastric fluid, due to which its contact time with gastric mucosa is increased. This results in less frequent dosing and improves patient compliance. *In situ* gels are not only helpful for sustained drug delivery but also become convenient for pediatric and geriatric patients. Several biodegradable polymers are available with *in situ* gelling activity. By complete knowledge of floating behavior of biodegradable polymer we can look forward to improve gastric retention and hence bioavailability of pharmaceutical agents. *In situ* gel have good stability and biocompatibility characteristics and better drug release which make it more reliable dosage form over the conventional one.

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