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IN SITU GEL SYSTEM – A NOVEL APPROACH FOR CONTROLLED RELEASE

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ABSTRACT

Drugs that have a narrow absorption window in the gastrointestinal tract (GIT) when administered orally are often limited due to poor bioavailability due to incomplete release of drugs and short residence time at the absorption site. Novel drug delivery systems have been developed in the form of gasroretentive systems such as floating systems, mucoadhesive, high density, expandable, as they have an extended gastric residence period for controlled drug delivery. oral Liquid are more susceptible to low bioavailability as they are eliminated quickly from the stomach since they are subjected to faster transit from the stomach/ duodenum. Issues of immediate release and short gastrointestinal residence of liquids are avoided by formulating as oral in situ gels as they provide the best way to solve these problems The in situ gel dosage form is a liquid before administration and after it comes into contact with gastric contents due to one or more mechanisms being converted into gel that floats on gastric contents. It ensures both increased residency and sustained release. This method is useful both for the systemic and local effects of the prescribed medications. This analysis gives a brief idea of floating in-situ oral gel formation and work on a variety of drugs and polymers performed by various scientists.

INTRODUCTION

1.1 Gastro Retentive Drug Delivery System:

Different dosage forms have been developed recently which can be administered via different routes of administration. Among various routes, oral route is considered as the most competent way of drug delivery due to various reasons like ease of administration, more flexibility in designing, ease of production, low cost. Drugs given via oral route may subject to absorption throughout the gastrointestinal tract, and various processes may affect the absorption of drugs like degradation of drug by enzymatic, or microbial action, precipitation etc. Drugs that absorb from stomach should spend maximum time which may be difficult to occur due to gastric emptying. Various factors that affect gastric emptying includes volume and composition of the meal, temperature and viscosity of the meal, pH of stomach, body posture, emotional state of the individual, diseased state, gastric motility altering drugs etc. Due to the above mentioned factors that affect gastric emptying, new drug delivery systems were developed in order to stay a dosage form for a longer period of time in stomach. Among those systems gastro retentive drug delivery system (GRDDS) found to be the best.[1] GRDDS is a system which keeps the dosage form for longer period in gastric region and improves gastric retention time when compared to a conventional dosage form, in turn maintaining minimum effective concentration of drug in systemic circulation. Drugs which have a limitation of poor solubility in alkaline pH can overcome by GRDDS. Dosing intervals can be prolonged improving patient compliance. Controlled drug delivery can be achieved in gastric region with the help of GRDDS. Though,

novel dosage forms like nanoparticles, microspheres, liposome etc. can also be used for controlled release effect, GRDDS is considered as a better alternative for improved absorption through stomach.[2]

1.1.1 Advantages of GRDDS [3]

1. Absorption of drugs can be improved through gastric region
2. Drugs that irritate intestinal mucosal region can be minimized
3. Enhanced bioavailability
4. Proper design of GRDDS ensures controlled drug delivery
5. Perfect dosage form for local action to treat various diseases
6. Easy to manufacture, handle and administer
7. Improved patient compliance

1.1.2 Disadvantages of GRDDS [3, 4]

1. Floating systems has limitation, that they require high level of fluids in stomach for floating and working efficiently. Hence more water intake is prescribed with such dosage form.
2. In supine posture (like sleeping), floating dosage form may swept away (if not of larger size) by contractile waves. Therefore patient should not take floating dosage form just before going to bed.
3. Drugs having stability problem in high acidic environment, having very low solubility in acidic environment and drugs causing irritation to gastric mucosa cannot be incorporated into GRDDS.
4. Bioadhesive systems have problem of high turnover rate of mucus layer, thick mucus layer & soluble mucus related limitations.
5. Swellable dosage form must be capable to swell fast before its exit from stomach and achieve size larger than pylorus aperture. It must be capable to resist the housekeeper waves of Phase III of MMC.

1.1.3 Limitations of GRDDS [3]

1. Poor stability may be seen for the drugs that may degrade by gastric acid, gastric enzymes etc.
2. Drugs which show poor solubility at acidic pH are not suitable for GRDDS.
3. Drugs that absorb throughout the GIT are poor candidates for this system.
4. Gastro irritant drugs cannot be formulated as GRDDS.
5. First pass metabolism was found to be the major limitation.

1.2 Physiology of the stomach[5]

The gastrointestinal tract is essentially a tube about nine meters long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), oesophagus, stomach, small intestine (consisting of the duodenum, jejunum and ileum) and large intestine (consisting of the cecum, appendix, colon and rectum). The wall of the gastrointestinal tract has the same general structure throughout most of its length from the oesophagus to the anus, with some local variations for each region. The stomach is an organ with a capacity for storage and mixing. The antrum region is responsible for the mixing and grinding of gastric contents.

The interdigestive motility pattern is commonly called the 'migrating motor complex' ('MMC') and is organized in cycles of activity and quiescence. Each cycle lasts 90–120 minutes and consists of four phases. The concentration of the hormone motilin in the blood controls the duration of the phases. In the inter digestive or fasted state, an MMC wave migrates from the stomach down the GI tract every 90–120 minutes. A full cycle consists of four phases, beginning in the lower oesophageal sphincter/gastric pacemaker, propagating over the whole stomach, the duodenum and jejunum, and finishing at the ileum. Phase III is termed the 'housekeeper wave' as the powerful contractions in this phase tend to empty the Stomach of its fasting contents and indigestible debris. The administration and subsequent ingestion of food rapidly interrupts the MMC cycle, and the digestive phase is allowed to take place. The upper part of the stomach stores the ingested food initially, where it is compressed gradually by the phasic contractions.

The digestive or fed state is observed in response to meal ingestion. It resembles the fasting Phase II and is not cyclical, but continuous, provided that the food remains in the stomach. Large objects are retained by the stomach during the fed pattern but are allowed to pass during Phase III of the interdigestive MMC. It is thought that the sieving efficiency (i.e. the ability of the stomach to grind the food into smaller size) of the stomach is enhanced by the fed pattern or by the presence of food. (Figure 1 & 2)

1.3 Factors controlling gastric retention of drugs: [5]

The factors which are to be considered during the development of gastro retentive drugs are;

1.3.1 Physiological factors:

a. Size of dosage form: Dosage forms having greater diameter than the diameter of pyloric sphincter remain in the gastric region as these cannot move away along with the gastric contents into intestine nor they can be affected by the gastric emptying.

b. Shape of dosage form: Round or spherical or ring shaped dosage forms are considered to be better in comparison to other shapes.

c. Density: 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 to the surface, while high density systems sink to bottom of the stomach. Dosage form with density lesser than 1.0 gm/ cm3 is required to exhibit floating property.

1.3.2 Biological factors:

a. Age: Gastric retention time is longer in geriatric patients, while it is lower in neonates and children when compared to normal adults.

b. Gender: Gastric retention time in male (3-4 hours) is less than the female (4-6 hours).

c. Fed or unfed state: Gastric retention time is less during fasting conditions as the gastric motility increases during fasting conditions.

d. Feed frequency: Higher the frequency of taking food, longer will be the gastro retention time.

e. Nature of meal: Higher the amount of fatty acids and other indigestible polymers lesser the gastric retention time due to alteration in gastric motility.

f. Concomitant drug administration: Administration of certain drugs along with gastric motility enhancers or depressants, greatly affect gastric retention time and hence absorption of stomach specific absorbing drugs.

g. Disease state: Gastric disease conditions like diabetes, Crohn's disease etc alters the Gastric retention time.

1.4Suitable Drug Candidates for Gastro Retention System: [2,6]

Prolonged/controlled drug release dosage forms exhibits less side effects decreasing the dosage frequency. Good candidates for GRDDS include molecules that have poor colonic absorption but shows better absorption properties at the upper part of GIT:

1. Narrow absorption window in GIT, Eg. Riboflavin in vitamin deficiency, Furosemide, P-amino benzoic acid levodopa etc.
2. Drugs which show low solubility at high pH values, Eg; Verapamil, Diazepam, Calcium supplements, Chlordizepoxide and Cinnarazine.
3. Drugs that locally acting on stomach, Example. Antacids and Misoprostol.
4. Drugs which are unstable in colon, Eg; Captopril, Ranitidine HCl and Metronidazole.
5. Drugs that disturbs normal colonic bacteria, Example. Tetracycline, Clarithromycin, Amoxicillin trihydrate etc.

1.7 Floating *In Situ* Gel: [3]

In situ gel forming systems have been widely studied, for their capability of producing the sustained and controlled drug delivery. In recent years, research has been carried out in formulating *In situ* gel via popular routes like oral, nasal, ophthalmic and other routes like vagina. This showed the promising result, for the use of system as a potential way of producing the controlled drug delivery. The tablet/capsule floating dosage forms are stable as compare to liquids but the problem with them is that they are needed to swallow as whole unit. In case of dosage adjustment these cannot be broken in halves as these are also designed for controlled release and floating ability also depends on dimensions of tablets. Elderly patients, children some adult persons and patient with certain conditions suffer from dysphasia, so it becomes difficult for them to swallow tablet/capsule dosage forms. Also in case of dosage adjustments these floating solid dosage forms are needed to be available in different strengths. Where an environment specific gel forming solution, on conversion to gel, floats on the surface of the gastric fluids (due to less density than gastric contents). In this technique, a solution of low viscosity is used which on coming in contact with the gastric fluids, undergo change in polymeric conformation and a viscous gel of density lower than the gastric fluids is produced. This low density gel formation called as raft not only provide the much desired gastro retention to prolong the contact time, but also produce the continuous and slow drug release. This system basically utilizes polymers which undergo transformation from solution to gel like consistency, due to change in their physicochemical properties. This system comprises of *In situ* gel forming polymers of synthetic or natural origin, e.g. gellan gum, alginic acid, xyloglucan, chitosan,

polycarolactone etc. Addition of bicarbonates or carbonates to this system improves floating ability by producing effervescence by releasing carbon dioxide (air generation) will make the gel much lighter and in turn helps to float. Ability of the gel for prolonged and controlled release may also be enhanced by raising its viscosity with the help of viscosity enhancers.

1.7.1 Advantages of Floating *In Situ* Gel over other GRDDS

a. Improved floating property when compared to floating tablets.

b. Increase in bioavailability with reduction in dosage frequency

c. Production cost is low and Method of preparation is easy when compared to other FDDS.

1.7.2 Limitations of Floating *In Situ* Gel Forming Gastro Retentive Drug Delivery System:

a. *In situ* gel forming systems are more susceptible to stability problems due to chemical degradation or microbial degradation.

b. Change in pH may lead to degradation.

1.7.3 Various Approach for in Situ Gel Formation[9]

There are various mechanism for the in Situ gel formulation: physical changes in biomaterials (e.g.,diffusion of solvent and swelling), Chemical reactions (e.g.,ionic cross linking, enzymatic crosslinking), physiologically stimuli (e.g.,temperature and pH))

a) By Physical Change (Swelling and Diffusion):

By this approach physical change like swelling or diffusion may takes place. In swelling, polymer in the system absorbs water from the surrounding environment and swells to form a viscous gel. In diffusion, solvent in which the drug and polymer is dissolved or dispersed, diffuse into the surrounding tissues causing the precipitation of the polymer to form gel.

b) By Chemical Change:

Change in chemical environment leads to polymeric cross linking thereby formation of gel. Ion sensitive polymer (sodium alginate, calcium alginate, gellan gum, pectin) undergo phase transition in present of various monovalent and divalent cation (ca+2, mg+2, Na+, k+) for the formation of gel. For e.g: gelation of low methoxypectin in present of divalent cation (ca+2). Alginate contain molecule (sodium alginate) undergo gelation in presence of di/polyvalent cation e.g.ca+2 interact with guluronic acid block in alginate side chain.

c) By Physiologically Changes:

(i) pH dependent gelling- Another formation of in situ gel based on pH dependent. For these perpose various pH sensitive polymers are use such as PAA (carbomer) or its derivatives, polyvinyl acetyl dimethylamino acetate(AEA),mixture of poly (methylacrylic acid)(PMA), and poly(ethylene glycol)(PEG) shows change from sol to gel when changes in pH.at higher pH range wickly acidic group shows gel formation and vice-versa. Triggered floating in situ gel of levetiracetam.

(ii) Temperature Dependent Gelling - Dosage form are solution at room temperature (20 – 25 ˚c) but when in contact with body temperature (35 – 37◦c) they convert into gel. Some of the polymer have drastic changes in solubility in response to increase in environmental temperature (lower critical solution temperature) LCST. At the LCST the interaction between polymer and water is unfavorable as compared to polymer-polymer and water-water. so molecule becomes dehydrated and produce hydrophobic structure polymer such as pluronic (poly (ethyleneoxide)-poly (propyleneoxide poly (ethyleneoxide)(PEO-PPO PEO) triblock) , polymer network of poly(acrylic acid)(PAA) and poly acrylamine (PAAM) or poly (acrylamide-co-butyl methoacrylate). Below the upper critical solution temperature (UCST) hydrogel contracts upon cooling they form hydrogel this called positive temperature sensitive hydrogel. Polymer used such as poly acryclic acid, poly acryl amide and co-butyl methacrylate. Eg: In situ gelling formulation based on the methylcellulose / pectin systems for oral sustain drug release to dysphagic patient.

d) Dilution-Sensitive: In this approach, a polymer that undergoes phase transition in presence of higher amount of water may lead to formation of gel. eg; Lutrol F68

e) Electrical Signal Sensitive hydrogels:

Hydrogels sensitive to electric current undergo shrinking or swelling in the presence of an applied electric field.

f) Light-Sensitive hydrogels:

Light-sensitive hydrogels can be used in the development of in situ forming gels for cartilage tissue engineering. eg; Quinone can be injected into a tissue and applied electromagnetic radiation is used to form a gel by enzymatic processes. For that long ultraviolet wavelengths are used.

g) Glucose-Sensitive hydrogels:

Delivery systems which are responsive to stimuli using hydrogels that can release insulin have been investigated. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin in a pulsatile fashion. Another approach is based on competitive binding of insulin or insulin and glucose to a fixed number of binding sites in concanavalin A, where insulin is displaced in response to glucose stimuli, thus functioning as a self-regulating insulin delivery system.

1.7.4 Mechanism Of *In Situ* Gelation: [10]

These are liquids before administration and gel under physiological conditions. *In situ* gel formation is possible by various mechanisms like ionic cross linkage, pH change & temperature modulation. Polymers that contain divalent ions eg; sodium alginate can form a complex with sodium citrate, thereby breakdown of complex takes place in acidic environment to release Ca2+ which leads to *In situ* gelation. Complexation with cations and hydrogen bonding with water leads to *In situ* gelation.

1.7.5 Mechanism of Floating *In Situ* Gel:

When this system floats in the gastric region, drug releases slowly at a desired rate. Floating force (F) is required to keep the dosage form reliably buoyant on the surface of the meal. In order to measure the floating force, a novel apparatus is used for the determination of resultant weight. This apparatus operates by measuring continuously the force equivalent to 'F' (as a function of time) that is required to main submerged object. The dosage form floats better if 'F' is high. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.

F = F buoyancy - F gravity = (Df - Ds)gv

Where, F= total vertical force, Df = fluid density, Ds= object density, v= volume,
g= acceleration due to gravity.

1.8 Polymers Frequently Used for *In situ* Gelling for Gastro Retentive Reasons:

a) Sodium alginate:

Sodium alginate is a widely used polymer of natural origin. Chemically, it is alginic acid salt, consisting of ά – L-glucuronic acid and ά -D-mannuronic acid residues connected by 1,4-glycosidic linkages. Solution of alginates in water form firm gels in presence of di-or trivalent ions (e.g. calcium and magnesium ions). Alginate salts, specifically, sodium alginate is mostly used for preparation of gel forming solution, for delivery of the drugs and proteins. Alginate salts are considered most favorable because of biodegradable and non toxic nature, with additional bio-adhesive property.

b) Pectin:

These are plant origin anionic polysaccharides isolated from the cell wall of most plants and basically consist of ά-(1-4)-D-galacturonic acid residues. Pectin undergoes gel formation in presence of medium, a stiff gel is produced. The gelling capacity divalent ions (e.g. Ca) which causes cross linking of the is determined on the basis of stiffness and time galacturonic acid units (ionic cross linking) and also in the period for which gel remains, as such presence of the H^+ ions (pH dependent gelling).

c) Gellan Gum:

Gellan gum (FDA approved) is gastric fluid (0.1 N HCl, pH 1.2) at 37 C using USP secreted by the *Sphingomonas elodea (Pseudomonaselodea)* and chemically is anionic deacetylated polysaccharide with repeating tetrasaccharide units composed of ά-D-glucuronic acid (1 unit), ά-L-rhamnose (1 unit) and ά-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}).

d) Xyloglucan:

It is a plant based polysaccharide obtained from seeds of tamarind. Chemically, this polysaccharide composed of a chain of (1-4)-ά -D-glucan having (1-6)- ά-D xylose units as branches which have partial (1-2)- ά-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). Besides the use in oral drug delivery, it is also being used for ocular and rectal drug delivery. Xyloglucan has shown a very low gelation time of up to few minutes.

1.9. Applicability of *In situ* polymeric drug delivery system[7]

A) Oral drug delivery system:

The pH-sensitive hydrogels have a potential use in site specific delivery of drugs to specific regions of the GI tract. Hydrogels made of varying proportions of PAA derivatives and cross linked PEG allowed preparing silicone microspheres.

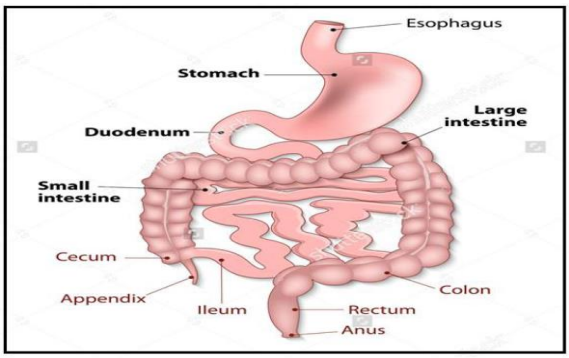

Fig. 1. Anatomy of The Gastrointestinal Tract

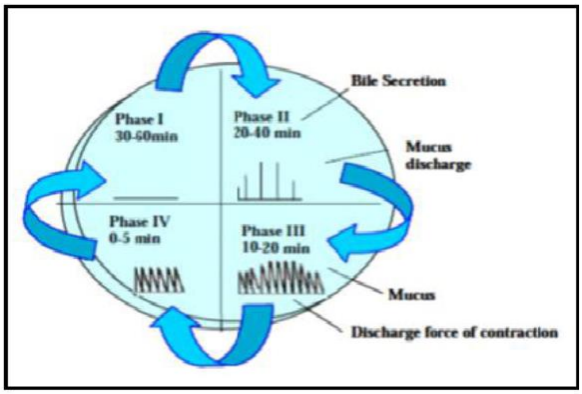

Fig. 2. Phases of Gastric Cycle

Table No. 2: Polymers used in *in-situ* formulation

Natural		Synthetic	
Sodium alginate	Pluronic F-27	HPMC K4M	HPC
Pectin	Carbopol	HPMC K15M	HEC
Tragacanth	Xanthan gum	HPMC K100M	Poly amides
Gelatin	Malgum	Polyvinyl alcohol	Sodium CMC
Carrageenan	Taragum	Carbopol 934p	Ethyl cellulose
Tamarind gum	Isapgulla	Poly carbonates	Methyl cellulose
Guar gum	Locust gum	Poly vinyl ether	Polymethacrylic acid

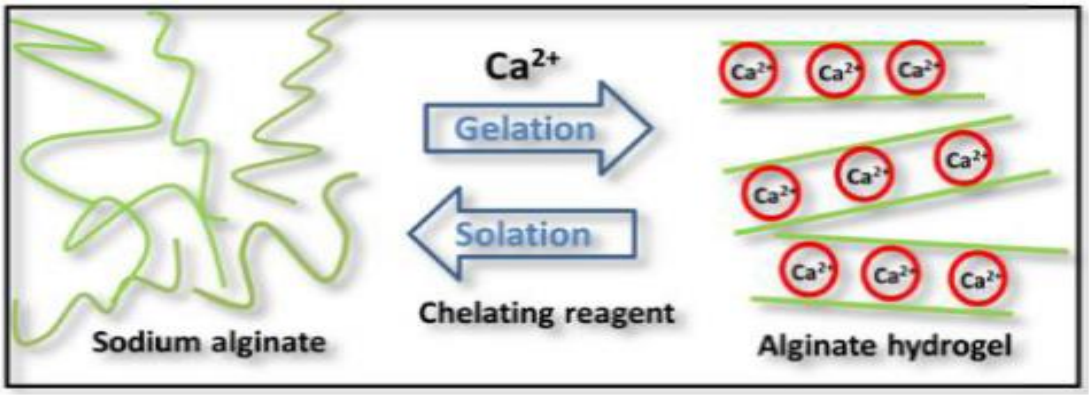

Fig.3.Gelation and Solation of Alginate Gel

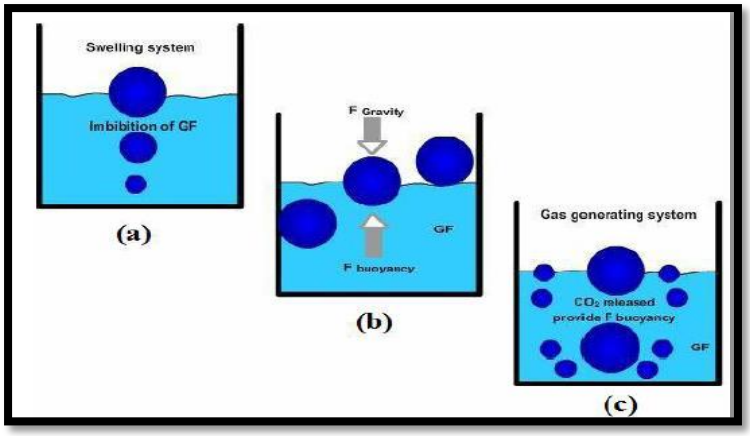

Fig. 4. Mechanism of Floating System

This released prednisolone in the gastric medium or showed gastroprotective property. Cross-linked dextran hydrogels with a faster swelling under high pH conditions, likewise other polysaccharides such as amide pectins, guar gum and insulin were investigated in order to develop a potential colon specific drug delivery system. Developed the formulations of gellan and sodium alginate both containing complexed calcium ions that undergo gelation by releasing of these ions in the acidic environment of the stomach. Oral delivery of paracetamol was also studied. For the oral in situ gel delivery system pectin, xyloglucan & gellan gum natural polymers were used. Pectin formulation for sustained delivery of paracetamol has been reported. Advantages of pectin is water soluble so, no need to add organic solvent.

B) Ocular drug delivery system

In ocular delivery system natural polymers like gellan gum, alginic acid & xyloglucan are most commonly used. For local ophthalmic delivery system various compounds like antimicrobial agent, anti-inflammatory agent & autonomic drugs are used to relieve intra ocular tension in glaucoma. Conventional delivery system often result in poor availability & therapeutic response because high tear fluid turn over & dynamics which cause rapid elimination of the drug from the eye so, the overcome the bioavailability problem ophthalmic in-situ gel was developed. To improve the bioavailability viscosity enhancers such as Hydroxy Propyl Methyl Cellulose, Carboxy Methyl Cellulose, Carbomers, Poly Vinyl alcohol used to increase the viscosity of formulation in order to prolong the precorneal residence time & improve the bioavailability, ease to manufacture

C) Nasal drug delivery system

In nasal *In situ* gel system gellan gum & xanthan gum are used as *In situ* gel forming polymers was evaluated for its efficacy for the treatment of allergic rhinitis. Animal study were conducted using allergic rhinitis model & effect of *In situ* gel on antigen induced nasal symptoms in sensitizes rats was observed. *In situ* gel was found to inhibit the increase in nasal symptoms are compared to marketed preparation nosonex (Momethasonefuroate suspension 0.05%).

D) Rectal drug delivery system

The rectal route may be used to deliver many types of drugs that are formulated as liquid, semisolid (ointments, creams and foams) and solid dosage forms (suppositories). Conventional suppositories often cause discomfort during insertion. In addition, suppositories are unable to be sufficiently retained at a specific position in the rectum, sometimes they can migrate up-wards to the colon that makes them possible for drug to undergo the first-pass effect. Choi et al. developed novel *In situ* gelling liquid suppositories with gelation temperature at 30–36°C. Poloxamer 407 and/ or poloxamer 188 were used to confer the temperature-sensitive gelation property. *In situ* gel possesses a potential application for rectal & vaginal route.investigated the use of xyloglucan based thermo reversible gel for rectal drug delivery of Indomethacin.

E) Vaginal drug delivery system

The vagina, in addition to being an important organ of reproductive tract, serves as a potential route for drug administration. Formulations based on a thermo-plastic graft copolymer that undergo *In situ* gelation have been developed to provide

the prolonged release of active ingredients such as nonoxynol-9, progestins, estrogens, peptides and protein Chang et al have recently reported a mucoadhesive thermo-sensitive gel (combination of poloxamers and polycarbophil), which exhibited, increased and prolonged antifungal activity of clotrimazole in comparison with conventional PEG-based formulation.

F) Transdermal drug delivery system

Thermally reversible gel of Pluronic F127 was evaluated as vehicle for the percutaneous administration of Indomethacin. *In-vivo* studies suggest that 20% w/w aqueous gel may be of practical use as a base for topical administration of the drug. Poloxamer 407 gel was found suitable for transdermal delivery of insulin.The combination of chemical enhancers and iontophoresis resulted in synergistic enhancement of insulin permeation.

EVALUATION OF GEL

1. Appearance: All formulations were evaluated for clarity by visual observation against a black and white background [39].

2. pH: The pH values of different formulations were measured using a calibrated digital pH meter at room temperature in triplicate [40].

3. *In Vitro* Gelation Studies: Gelation of in situ gelling solution was carried out by taking 500 mL of 0.1 N hydrochloric acid (HCL; pH 1.2) in a beaker. 10 mL of solution was added to HCL with mild agitation to avoid breaking of formed gel. Gelling was observed visually by qualitative measurement [39].

4. Measurement of Viscosity: The viscosities of the prepared gel formulations (F-9 to F-13) were determined by digital brook field viscometer. The samples (100 mL) were sheared at a rate of 100 rpm using suitable spindle at room temperature. Viscosity measurement for each sample was done in triplicate, while each measurement was taken approximately for 30 seconds [39].

5. Drug Content: The drug content in each unit dosage form was determined by UV spectroscopy. The UV absorbance of the sample was determined at a wavelength BioMed Research International 3 of 231 nm. The drug content for batches was measured in triplicate and the average values were recorded [41].

6. *In Vitro* Floating Studies: Floating studies of in situ gelling solution were carried out in 500 mL of 0.1 N HCL (pH 1.2) in a beaker. Sufficient quantity of solution was added to HCL with mild agitation. Time required for floating on the surface after adding solution (floating lag time) and total floating time were measured [39].

7. *In Vitro* Drug Release Studies: The in vitro release rate of drug from sustained release in situ gel was performed in USP apparatus fitted with paddle (50 rpm) at 37 ± 0.5∘ C. 0.1 N HCL (500 mL) was used as a dissolution medium. This speed was kept slow enough to avoid the breaking of gelled formulation under mild agitation conditions similar to physiological salt conditions. 10 mL sample was withdrawn and filtered through a 0.45 μm membrane filter. At the predetermined time intervals the samples were assayed by using a Shimadzu UV-1800 double-beam spectrophotometer. Percentage cumulative drug release (% CDR) was calculated using an equation obtained from a calibration curve [39].

6. Transmission Electron Microscopy: Morphology of drug loaded in situ gel was observed under transmission electron microscopy (TEM). One drop of diluted in situ suspension containing drug was put on a film-coated copper grid and stained with one drop of 2% (w/v) aqueous solution of phosphotungstic acid. The sample was permitted to dry for improving contrast. The sample was then examined by transmission electron microscopy.

7. Stability Studies: Prepared solutions were first packed in glass bottles and kept for three months. The stability of the in situ gels was monitored for 3 months at accelerated stability. Periodically (initially for 1.0, 2.0, and 3.0 months intervals) samples were removed and characterized by physical appearance, pH, and drug content.

CONCLUSION:

The literature searched revealed that gastroretentive drug delivery has numerous prospective benefits for drugs with low bioavailability due to rapid transition and limited absorption window at the upper gastrointestinal tract (GIT). The stomach pharmacotherapy itself is significantly enhanced by local drug release leading to high drug concentrations. So far as *in-situ* gel drug delivery system is a concern, it can be the potential tools towards the treatment of

diseases like chronic gastritis and peptic ulcers caused by *H. pylori*. It is not only helpful for sustained drug delivery of oral liquid dosage form but also become convenient for pediatric and geriatric patients having a swallowing problem. The exploitation of polymeric *in-situ* gels for controlled release of various drugs may provide several advantages over conventional dosage forms. Good stability and biocompatibility characteristics also make the *in-situ* gel dosage forms very reliable.

REFERENCES

1. Patel, J.K., J.R. Chavda and M.K. Modasiya, Floating *In situ* gel based on alginate as carrier for stomach-specific drug delivery of famotidine. International Journal of Pharmaceutical Sciences and Nanotechnology, 3(3): 1092-1104.
2. Lovenish Bhardwaj, Pramod Kumar Sharma and RishabhaMalviya, 2011. A Short Review on Gastro Retentive Formulations for Stomach Specific Drug Delivery: Special Emphasis on Floating *In situ* Gel Systems. African Journal of Basic & Applied Sciences 3 (6): 300-312.
3. Shrikrishna.T, S.sudheer, Sk.Mubashira, MD Nayeem, 201. Comprehensive Review on Gastro Retentive Floating *In situ* Gel. International journal of Pharmacometrics and integrated biosciences 1 (1): 26-34.
4. Joseph R. Robinson and Vincent H. L. Lee, Controlled Drug Delivery, Fundamentals and Applications, 2nd Edition, Revised and Expanded, Marcell. Dekker Inc., New York (2009).
5. Vipul D. Prajapati, Girish k. jani, Tohra A. Khutliwala, Bhumis.Zala, 2013 Elsevier. A Short Review on Raft forming system – An upcoming approach of gastroretentive drug delivery system. Journal of Controlled Release 1 (4): 151-165.
6. Swapnali R. Shinde, Preeti Sable, Babita B. Lodhi1, Sarfraz khan, 2014. A novel approach of gastroretentive drug delivery: *In situ* gel, Journal of Innovations in Pharmaceuticals and Biological Sciences,vol 1(1), 39-59.
7. Shah S, Upadhyay P, Parikh D, Jinal Shah. *In Situ* Gel: A Novel Approach of Gastroretentive Drug Delivery. Asian Journal of Biomedical and Pharmaceutical Sciences 2012; 2(8):01-08.
8. Gilbald, M,Perrier, D. in : Pharmacokinetics. 2nd ed.MarcelDekker ,New York; 1982:409-417.
9. Foster, TS, Human,SR Richards,VR et al, Nifedipine kinetics and bioavailability after single intravenous and oral doses in normal subjects.*JClin Pharmacol*.1983:23:161-170
10. Raymond Rowe, Paul J Shesky and Marian E Quinn et al., Handbook of Pharmaceutical Excipients, Published by Pharmaceutical press 2009;86-92.
11. Miteshkumar J. Patel, Kanu R. Patel1, Mukesh R. Patel. Strategy for Development of pH Triggered Floating *In situ* Gel of Levetiracetam. American journal of pharmaceutical research 2012; 2(3):828-841.
12. Kumawati Dinesh, Dr. Garg shiv,2014. In-situ gel: A novel path of gastroretentive drug delivery. Indo American journal of pharmaceutical research ; 4(8):3398-3410.
13. Patel RP, Baria AH, Pandya NB, Tank HM, 2010. Formulation Evaluation and optimization of stomach specific in situ gel of Ranitidine hydrochloride, International Journal of Pharmaceutical Sciences and Nanotechnology, 3(1): 834-843
14. Carelli V, Coltelli S, Di Colo G, Nannipieri E, Serafini MF, Silicone microspheres for PH controlled gastrointestinal drug Delivery, Int J Pharm, 1999, 17, 73-83.
15. Miyazaki S, Suzuki S, Kawasaki N, Endo K, Takahashi A, Attwood D. *In situ* gelling xyloglucan formulations for sustained release ocular delivery of pilocarpine hydrochloride. Int J Pharm 2001; 229: 29-36.
16. Pate J.K., J.R. Chavda and M.K. Modasiya, 2010. Floating *In situ* gel based on alginate as carrier for stomach-specific drug delivery of famotidine. International Journal of Pharmaceutical Sciences and Nanotechnology, 3(3): 1092-1104.
17. Garg, S. and S. Sharma, 2003. Gastro retentive drug delivery systems. Business Briefing Pharmatech NIPER, pp: 160-166.
18. JyotsanaMadan, kamalDua, Development and evaluation of *In situ* gel of pregabalin,

International Journal of pharmaceutical investigation, Vol (5) 226-233.

19. ChienYie W., Concepts and System Design for Rate Controlled Drug Delivery in Novel Drug Delivery System, 2nd Edn., New york, Marcell Dekker Inc. (1992).
20. Lathori S.R, Syed Iftequar M, Dehghan M.H, Shoaib S, Mohiuddin S, An Overview of gastroretentive drug delivery system research. International Research Journal of Pharmacy, 2 (11), 2011.50-57.
21. Raosaheb S. Shendge , Ashwini A. Jamdhade, Vishal V. Pande, Novel Strategy In Controlled Gastroretentive Drug Delivery: In-Situ Floating Gel. International Journal of Drug Delivery 6 (2014) 230-243.
22. Shozo Miyazaki, Wataru Kubo , Oral sustain delivery of theophylline using *In situ* gelation of sodium alginate, *Journal of controlled release, (*2000), 275-280.
23. P.S.Rajinikanth, B.Mishra, Development and evaluation of novel floating *In situ* gelling system of amoxicillin for eradiction of helicobacter pylori, *International journal of pharmaceutics* (2007)114-122
24. Wataru Kubo, shozo Miyazaki, Oral sustained delivery of paracetamol from *In situ* gelling gellan and sodium alginate formulation, *Inrternational journal of pharmaceutics* (2003)55-64.
25. Shweta Arora., Javed Ali., Alka Ahuja., Roop K. Khar., SanjulaBaboota., Floating Drug Delivery Systems: A Review, AAPS Pharm SciTech, 2005; 6(3): 372-390.
26. Akash Singh Panwar, Manoj Sharma et al;Formulation and Evaluation of floating stomach specific *In situ* gel of nizatidine, International Journal of Pharmaceutical and Bioalogical Archives 2014;5(1): 115-123.
27. Kishor K. Bhalerao, Et al; A short Review on Stomach Specific Floating *In situ* gel. Journal of Biomedical and Pharmaceutical Research 1 (3) 2012, 01-04.
28. Mahak Shaikh, Aarti Mandloi, Vishnu Yadav, et al; Formulation and Evaluation of floatable *In situ* gel for stomach specific drug delivery of Vanalafaxin HCL. Research and Review: Journal of pharmacy and Pharmaceutical sciences,(2000) 235–259.
29. Rubinstein A., Friend D.R, Specific delivery to the gastrointestinal tract, in: Domb A.J (Ed.), Polymeric Site-Specific Pharmacotherapy, Wiley, Chichester, 1994, 282-283.
30. S. Parthiban, Shivaraju, G.P. Senthikumar et al; Formulation and Evaluation of gastroretentive drug delivery ornidazole*In situ* gelling system using gellan gum. International Journal of Research in Pharmaceutical and Nano sciences: Volume 5, Issue 2: 2015 (172-179).
31. Itoh K, Hatakeyama T, Shimoyama T, Miyazaki S, D'Emanuele A, Attwood D. *In situ* gelling formulation based on methylcellulose/pectin system for oral-sustained drug delivery to dysphagic patients.
32. Miyazaki S, Suzuki S, Kawasaki N, Endo K, Takahashi A, Attwood D. *In situ* gelling xyloglucan formulations for sustained release ocular delivery of pilocarpine hydrochloride. Int J Pharm 2001; 229: 29-36.
33. Balasaroj, Mahatma O.P, Azim Md. Sabir , Formulation and Evaluation of stomach specific *In situ* gel of Hydrochlorthiazide, International Research Journal of Pharmacy.2013,4 (9) 77-83.
34. Myung, K.C., Hongkee, S., Hoo-Kyun, C., 2005. Preparation of mucoadhesive microspherescontaining antimicrobial agents for eradication of *H. pylori. Int. J.Pharm*, 297: 172-179.
35. Monica Raghavendra Prasad Rao, SwapnilUttamraoShelar, Controlled Release Ion Sensitive Floating Oral *In situ* Gel of a Prokinetic Drug using Gellan Gum. Indian Journal of Pharmaceutical Education and Research. Vol 49(2) Apr-Jun, 2015.
36. R.Rajalakshmi, A.Sireesha*et al.*, Development and Evaluation of a Novel Floating *In situ* Gelling System of Levofloxacin Hemihydrate. International Journal of Pharmaceutical Research, 2011,2(1) 102-108.
37. VoraV., Basu B., Formulation and characterization of novel floating *Insitu* gelling system for controlled delivery of ramipril. International Journal of Drug Delivery 5 (2013) 43-55.
38. Paruvathanahalli R and Mishra B.Floating *In situ* gelling system of acetohydroxamic acid

for clearance of h. pylori. Drug Delivery and Industrial Pharmacy. 2008; 34: 577-587.

39. Patel A., Shah D., Modasiya M., and Ghasadiya R., "Development and evaluation of cefpodoxime Proxetil gellan gum based in situ gel," International Journal of Research in Pharmaceutical and Biomedical Sciences, vol. 1, no. 2, pp. 179–190, 2012.
40. Raghunadha Gupta. C, Purushothaman M, Dwrakanadha Reddy P, Vijaya Ratna J, Gastro retentive delivery systems : A Short Review, Journal of Pharmacy and chemistry, Vol 4, Issue 1, 2010.
41. Modasiya.M. K., Bhupendra G., and Prajapativisnu M., "Sodium alginate based in situ gelling system of Famotidine: preparation and in-vivo characterizations," European Journal of Lipid Science and Technology, vol. 5, no. 1, pp. 27–42, 2010.