eISSN:Awaiting
International Journal of Pharmacometrics and Integrated Biosciences
www.ijpib.com

Review Article *Open Access*

COMPREHENSIVE REVIEW ON GASTRORETENTIVE FLOATING *IN SITU* GEL

Srikrishna.T*, S.Sudheer, Sk.Mubashira, MD.Nayeem, P.V.Prasad

Department of Pharmaceutics, Narayana Pharmacy College, Chinthareddypalem, Nellore, Andhra Pradesh, India.

ARTICLE INFO

Article history:

Received: 19 December 2015
Revised: 24 December 2015
Accepted: 03 January 2016
Available online: 5 January 2016

Corresponding Author:

SriKrishna.T M.Pharm.,
Assistant Professor,
Department of Pharmaceutics,
Narayana Pharmacy College,
Chinthareddypalem,
Nellore-524002, AP, India.
Email:srikrishna.nlr@gmail.com

Keywords:

In-situ gel, Floating drug delivery system, Simulated gastric fluid, Polymers etc

ABSTRACT

Drugs with narrow absorption window in gastrointestinal tract (GIT) is limited to poor bioavailability with conventional dosage forms due to incomplete drug release and short residence time at the site of absorption. In-situ gel provides the best way to overcome the complications raised in immediate release dosage forms and for the dosage forms that have short gastrointestinal residence time. Floating in-situ gel is a liquid before administration and when it comes in contact with gastric contents, solution converts into gel and floats on gastric contents. The formation of gel depends on factors like temperature modulation, pH change, presence of ions and ultra violet irradiation from which the drug gets released in a sustained and controlled manner. Many natural, biodegradable, biocompatible and synthetic polymers like alginic acid, pluronic F127, xyloglucan, gellan gum, carbopol, pectin, chitosan, poly (DL lactic acid), poly (DL-lactide-coglycolide) and poly-caprolactone etc. are used in the preparation of in-situ gelling system. In-situ gels can be fabricated for both local and systemic therapy, where drug show therapeutic effect at the targeted site. This review gives a brief idea about advantages, limitations, mechanism of gelation, polymers used, method of preparation, evaluation and recent advancements of floating oral in-situ gels.

CONTENTS Page No

Citation: **Srikrishna.T*, S.Sudheer. Comprehensive review on gastro retentive floating *in situ* gel. International Journal of Pharmacometrics and Integrated Biosciences. 2016: Volume1 Issue 1: p 26-34.**

INTRODUCTION

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].

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

Limitations of GRDDS:

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.

Types of GRDDS: [4,5]

Gastric retention can be achieved by various approaches like

1. High-density drug delivery system
2. Floating drug delivery system
3. Hydrodynamically balanced drug delivery system
4. Gas-generating drug delivery system
5. Raft-forming drug delivery system
6. Low expandable drug delivery system
7. Super porous hydrogels
8. Mucoadhesive drug delivery system
9. Magnetic drug delivery system

Suitable Drug Candidates for Gastro Retention System: [6,7]

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, Amoxicilline trihydrate etc.

FLOATING DRUG DELIVERY SYSTEM

Owing to its less density, floating drug delivery system (FDDS) will float over the gastric fluid and releases the drug without affecting gastric retention time. FDDS can show maximum plasma concentration of drug with prolonged release. Longer residence time improves oral bioavailability of drug. FDDS mainly includes two types of systems:

1. Effervescent system
2. Non effervescent system

Effervescent System:

In this system carbon dioxide is liberated from the dosage form and floats on the surface of the gastric fluid. Agents that form effervescent system includes: Sodium bicarbonate, Citric acid, Tartaric acid, Calcium carbonate, Disodium glycine carbonate etc. Dosage forms related to effervescent system include-

Single Unit (monolithic unit)

a. Matrix tablet
b. Floating pills
c. Coated effervescent core
d. Programmable drug delivery

Multiple Unit

a. Porous alginate beads
b. Ion exchange resin beads

Non Effervescent System:

In this system, polymers with low density than gastric contents are preferred. Various polymers under this category include, more gel forming and highly swelleble, cellulosic hydro colloids (e.g. hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose) and matrix forming polymers (e.g. polycarbophile, poly acrylates, poly styrene). Due to hydrophilic nature of these polymers, they absorb gastric fluid and swell so that air trapped by swollen polymer leads to floating on gastric fluid. Various dosage forms related to non-effervescent system are-

Single unit (monolithic unit)

a. HBS^{TM} Capsule (Hydrodynamically balanced systems)
b. Matrix tablet - single layer
c. Non matrix bilayer system
d. Tablet with agar and mineral oil
e. Tablet with cylinder
f. Coated hallow globule shell

Multiple unit

a. Calcium alginate / pectinate beads
b. Alginate beads with air compartment
c. Floating powder
d. Oil entrapped gel beads

Advantages of Floating Drug Delivery System:[8]

1. Hydrodynamically balanced systems (HBS) are advantageous for drugs that absorb from stomach and the drugs that are absorbed from the intestine e.g. Chlorpheniramine maleate.
2. The principle of HBS has been found to be independent of the site of absorption for particular medicaments.
3. Better response of drugs can be seen even on vigorous intestinal movement and a short transit time which might occur during disease states like diarrhoea.

Disadvantages of Floating Drug Delivery System:

1. Extended release of NSAID'S with FDDS leads to gastric irritation and ulcers.
2. Drugs that may irritate the stomach lining or are unstable in acidic environment should not be formulated as FDDS.
3. Drugs that absorb well from gastric region doesn't show benefit in formulating as FDDS.

Floating *In-Situ* Gel: [9]

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. 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.

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
d. Method of preparation is easy when compared to other FDDS.

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.

Various approaches to produce *In Situ* gel: [10,11,12,13]

Floating In Situ gels can be produced by various approaches given below

a) By Physical Change:

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.

c) By Changing Temperature:

Change in temperature leads to change in the solubility of polymer, thereby polymer- polymer interaction takes place to form a macromolecule of hydrophobic nature.

d) By Changing pH:

Polymer with anionic groups leads to increase in swelling with increase in the pH, while polymer with cationic groups shows a decrease in the swelling.

e) 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

f) Electrical Signal Sensitive hydrogels:

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

g) 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.

h) 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.

MECHANISM OF *IN- SITU* GELATION

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 Ca^{2+} which leads to in-situ gelation. Complexation with cations and hydrogen bonding with water leads to in-situ gelation. [14]

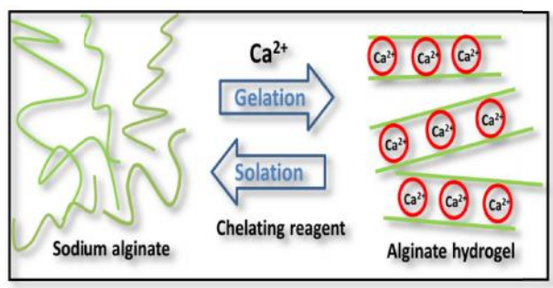

Fig 1: Gelation and Solation of alginate gel

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.[15]

$$F = F_{buoyancy} - F_{gravity} = (D_f - D_s)gv$$

Where,

F= total vertical force, D_f = fluid density, D_s= object density, v= volume, g= acceleration due to gravity.

POLYMERS

Polymers that undergo solution to gel transition in aqueous solution at body temperature were used in the preparation of floating in-situ gel. Some of them are

Pectin:
Pectin is originated from plant origin, it is an anionic polysaccharide isolated from the cell wall of most plants comprising mainly esterified D-galacturonic acid residues in a-(1–4) chain. The acid groups along the chain are largely esterified with methoxy groups in the natural product. The hydroxyl groups may also be acetylated. Pectin gelation characteristics can be divided into two types: high-methoxy and low-methoxy gelation. Gelation of high methoxypectin usually occurs at pH < 3.5. Low-methoxy pectin is gelled with calcium ions and is not dependent on the presence of acid or high solid content.

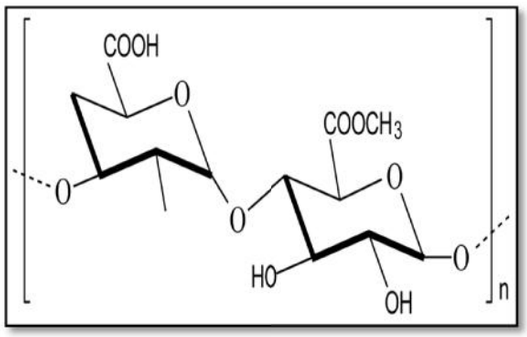

Fig 2: Chemical structure of pectin[16]

Gellan Gum:

a) Gellan gum secreted by *Sphingomonas elodea (Pseudomonaselodea)* is an anionic deacetylated polysaccharide with repeating tetrasaccharide units composed of -D-glucuronic acid (1 unit), -L-rhamnose (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+}).
b) Gellan gum secreted by Pseudomonas elodea is an anionic deacetylatedexocellular polysaccharide with a tetrasaccharide repeating unit of one α-L-rhamnose, one β-D-glucuronic acid and two β-D-glucuronic acid residues. It is a water soluble polysaccharide. It forms a gel via formation of double helices, followed by their ionic cross-linking.

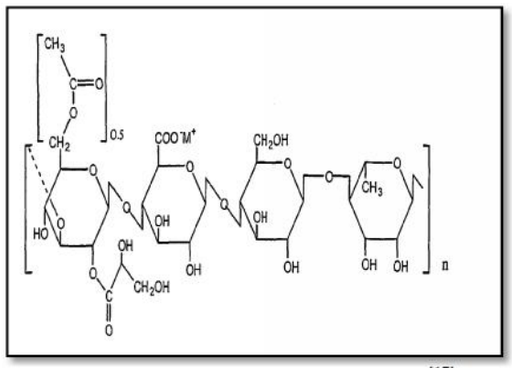

Fig 3: Chemical structure of pectin[17]

Sodium Alginate: (Alginic Acid)
Alginic acid is a polysaccharide consisting of β-D-mannuronic acid (M) and L-guluronic acid (G) residues joined by 1,4-glycosidic linkage. Alginate is a well known polysaccharide widely used due to its gelling properties in aqueous solutions related to the interactions between the carboxylic acid moieties and bivalent counter ions, such as calcium, lead, and copper; it is also possible to obtain an alginic acid gel by lowering the environmental pH value. Sodium alginate has been employed in the preparation of gels for the delivery of biomolecules such as drugs, peptides and proteins.

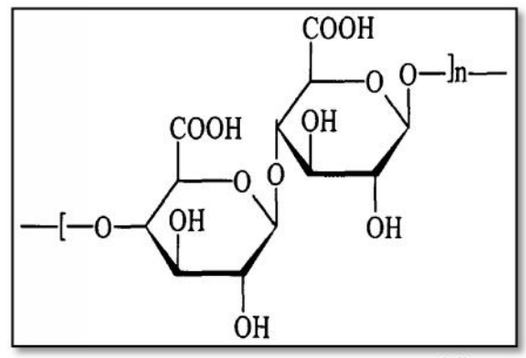

Fig 4: Chemical structure of pectin[18]

Pluronic Acid F127:
The Poloxamers or pluronic consist of more than 30 different nonionic surface active agents. Poloxamers, commercially available as PluronicR, are the most commonly used thermal setting polymers. They are formed by central hydrophobic part (polyoxypropylene) surrounded by hydrophilic part (ethylene oxide). Pluronic F-127 gives colorless transparent gels which is most commonly used polymer in pharmaceutical technology. Pluronic F-127 was used as an in situ gel forming polymer together with mucoadhesive polymers such as Carbopol 934 and hydroxyl propyl methyl cellulose to ensure long residence time at the application site.

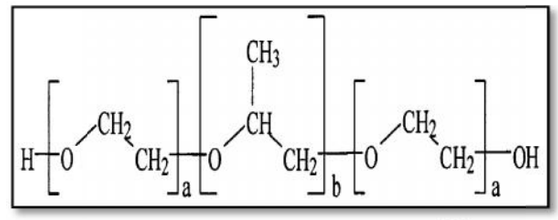

Fig 5: Chemical structure of pectin[19]

Xanthum Gum:
Xanthan gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram negative bacterium Xanthomonas campestris. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (β-D-glucose residues) and a trisaccharide side chain of β-D-mannose-β-D-glucuronic acid-α-D-mannose attached with alternate glucose residues of the main chain. The anionic character of this polymer is due to the presence of both glucuronic acid and pyruvicacid groups in the side chain.

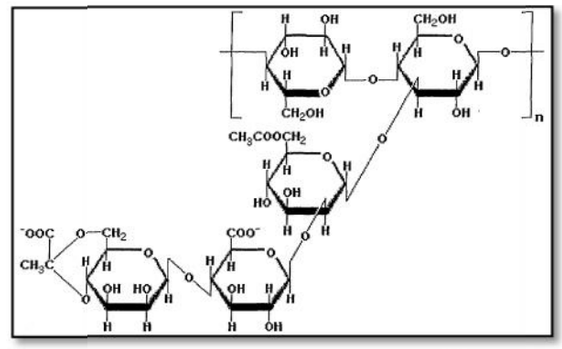

Fig 6: Chemical structure of pectin[20]

Xyloglucan:
Xyloglucan is a polysaccharide derived from tamarind seeds and is composed of a (1-4)-β-D-glucan backbone chain, which has (1-6)-α-D xylose branches that are partially substituted by (1-2)-β-D-galactoxylose. Xyloglucan is composed of heptasaccharide, octasaccharide and nonasaccharideoligamers, which differ in the number of galactose side chains. Although

xyloglucan itself does not gel, dilute solutions of xyloglucan which has been partially degraded by galactosidase exhibit a thermally reversible sol–gel transition on heating.

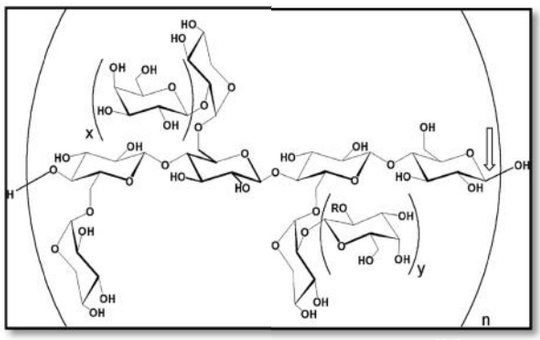

Fig 7: Chemical structure of pectin[21]

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. A 25-40% aqueous solution of this material will become gel at body temperature, and drug release from such a gel occurs over a period of up to one week.

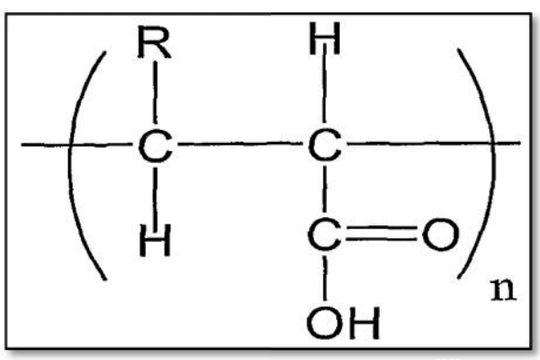

Fig 8: Chemical structure of pectin[22]

METHOD OF PREPARATION OF FLOATING IN-SITU GEL

1. Preparation of polymeric solution with the help of deionized water.
2. Polymeric solution is heated to 60^0c with stirring.
3. Cool the solution to 40^0c.
4. To the above solution calcium carbonate is added as a crosslinking agent.
5. The prepared solution is stored and preserved.

EVALUATION OF *IN SITU* GEL[23]

Determination of drug content:
Formulation equivalent to an amount of drug has to be dissolved in a suitable medium, stirred for required time, filtered and analysed for drug content.

pH determination:
The pH of solution can be determined using digital pH meter and the favourable conditions that facilitate in situ gelling can be identified.

In-vitro gelling capacity:
In-Situ gel forming systems are observed visually to calculate invitro gelling capacity. By adding the in-situ gelling formulation to a medium (simulating gastric fluid), various parameters like the time taken for *in situ* gel formation, its stiffness and the duration of gel that remains intact, can be estimated.

In-vitro buoyancy studies:
After adding a fixed volume of *in situ* gelling formulation to a medium (simulating gastric fluid), the parameters like the time taken for the system to float over the surface of medium (floating lag time) and the time the formed gel constantly float over the surface of the dissolution medium (floating time) can be estimated.

In-vitro drug release studies:
The release rate of drug from in situ gel can be determined using USP dissolution apparatus I (basket covered with muslin cloth) at 50 rpm. 900 ml of 0.1 N Hcl can be used as dissolution medium and temperature of 37+0.5^{o}C can be maintained. 5 ml samples can be withdrawn at various time points for estimating the drug release using spectrophotometry. Same volume of fresh medium has to be replaced every time the sample is withdrawn. The drug release studies from in-situ gel can also be done using plastic dialysis cell.

Measurement of rheological property of sol and gel:
Viscosity of the solution prepared using various concentrations of gelling agents can be determined by Brookfield viscometer, Cone & plate viscometer etc.

Water uptake study:
Once the sol is converted to gel, it is collected from the medium and the excess medium was blotted using a tissue paper. The initial weight of thus formed gel has to be noted. Again the gel has to be exposed to the medium/distilled water and the same process is repeated for every 30 min to note down the weights of the gel at each interval after removing the excess amount of medium/distilled water, using filter paper. The weight gain due to water uptake has to be noted from time to time.

Gel strength:
Gel strength is evaluated by using rheometer. After the formation of gel the beaker is raised pushing the probe of rheometer through the gel. The change in the load on the probe is measured as a function of depth of merge of the probe below the gel surface.

Spreadability
Spreadability was determined by adding the sample between the two plates. Increasingly weights are added to the pan till the upper plate moves, and the weights in the pan is caluculated which is a measure of spreadability.
Spread ability (g.cm/s) (S)=M×L/T
Where M = weight tide to upper plate, L = length moved on the glass slide, T = time taken.

Sol-gel transition temperature and gelling time:
Phase transition of solution temperature is noted first, during which the sample is kept at a specific temperature and heated at a specified rate in a glass tube/test tube. Gel formation is indicated by a lack of movement of meniscus on tilting the tube. Gelling time is the required for first detection of gel formation of sol formulation.

RECENT ADVANCEMENTS IN STOMACH SPECIFIC FLOATING IN-SITU GEL

Patel R.P et al formulated in situ gel of clarithromycin and metronidazole benzoate. Sodium alginate is used as a polymer and $CaCO_3$ was used as a cross-linking agent. The In situ formulation exhibited well, viscosity, drug content and sustained drug release; this study reports that oral administration of aqueous solutions containing sodium alginate results in formation of in situ gel, such formulations are homogenous liquids when administered orally and become gel at the contact site. Evaluation revealed that the concentration of sodium alginate and concentration of $CaCO_3$ significantly affected the drug release from in situ gel[24].

Teerawat Sahasathian, Nalena Praphairaksit et al developed a mucoadhesive and floating chitosan-coated alginate beads as a gastro retensive delivery vehicle for amoxicillin, towards the effective eradication of *Helicobacter pylori*, a major causative agent of peptic ulcers. Alginate was used as the core bead core polymer and chitosan as the mucoadhesive polymer coating. Amoxicillin-loaded alginate beads coated with 0.5% (w/v) chitosan (ALG/0.5%CHI) exhibited excellent floating ability, high encapsulation efficiency, high drug loading capacity, and a strong *in vitro* mucoadhesion to the gastric mucosal layer. *In vitro*, amoxicillin was released faster in simulated gastric fluid (pH 1.2, HCl) than in simulated intestinal fluid (phosphate buffer, pH 7.4). ALG/0.5%CHI could be prepared with a > 90% drug encapsulation efficiency and exhibited more than 90% muco-adhesiveness, 100% floating ability, and achieved sustained release of amoxicillin for over six hours in SGF. [25]

T.Sivannarayana et al developed moxifloxacin hydrochloride floating in situ gel to release the drug for an extended period of time and buoyant, thus prolong the residence time of formulation in the stomach. Sodium alginate and pectin are used as polymers. Tri sodium citrate and calcium carbonate are the main ingredients for the formation of gelling solution. In the present study calcium ions released from calcium carbonate complexes with citrate ions. The conversion of complexed calcium into free calcium causes gelation of alginate. In order to release the drug from the formulation, the gelled material floats upwards with a potential in the stomach. Based on the concentration of polymer the drug release was varied. [26]

Mitesh kumar J. Patel developed a new intra-gastric floating in situ gelling system for controlled delivery of levetiracetam for the treatment of partial onset seizures. High dose of levetiracetam (750 to 1000 mg) is difficult to incorporate in floating tablets but can easily be given in liquid dosage form released. Sodium alginate-based in-situ gelling systems were prepared by dissolving various concentrations of sodium alginate in deionized water, to which drug and calcium carbonate were added. [27]

Lena Murad Thomas developed gastro-retentive*in situ* gelling system of metronidazole. Sodium alginate based metronidazole floating *in situ* gelling systems were prepared by dissolving sodium alginate in distilled water, to which varying concentrations of viscosity enhancing polymer (methylcellulose, hydroxypropyl methylcellulose, or sodium carboxymethylcellulose), drug, and gas-forming agent (s) as calcium carbonate/and sodium bicarbonate were added and dissolved by stirring. Prepared formulae were evaluated for viscosity, floating behavior, drug content and *in vitro* drug release behavior. The prepared *in situ* gelling formulations of metronidazole could float in the gastric conditions and release the drug in controlled manner. [28]

RECENT ADVANCEMENTS OF IN- SITU GEL

Ocular Delivery

For *in situ* gels based ocular delivery, natural polymers such as gellan gum, alginic acid and xyloglucan are most commonly used polymers. Local ophthalmic drug delivery has been used for various compounds such as antimicrobial agents, anti-inflammatory agents and autonomic drugs used to relieve intraocular tension in glaucoma. Advancements in understanding the principles and processes governing ocular drug absorption and disposition have brought some improvements in the efficacy of ophthalmic drug delivery. A successful controlled release product focuses on increasing patient compliance with the help of in-situ gels. Use of biodegradable and water soluble polymers for the preparation of ophthalmic in-situ gel can make them more acceptable and excellent drug delivery systems. [29,30,31]

Parenteral Delivery

The Parenteral administration route is the most effective and common form of delivery for active drug substances with poor bio-availability and the drugs with a narrow therapeutic index. Delivery systems consisting of microparticles can be injected into the body using conventional needles and syringes and have been the most widely accepted biodegradable polymer system for parenteral use. Delivery system that combines the simplicity and reliability of solid implant devices along with convenience and ease of administration of microparticles is desired where in situ gel forming systems represent a desired alternate.
Eg; ATRIGEL Technology [32]

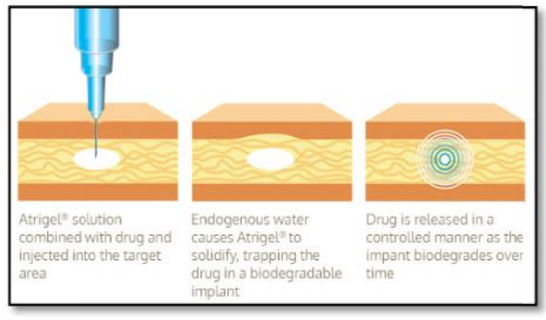

Fig 9: Atrigel technology

Rectal Delivery

Poloxamer 407 has excellent thermo-sensitive gelling properties. Nevertheless, these gels possess inadequate poor bioadhesiveness and high permeability to water, which limited its' application as a thermoresponsive matrix. A thermosensitive and mucoadhesive rectal in situ gel of nimesulide (NM) was prepared using mucoadhesive polymers such as sodium alginate (Alg-Na) and HPMC. These gels were prepared by addition of mucoadhesive polymers (0.5%) to the formulations of thermosensitive gelling solution containing poloxamer 407 (18%) and nimesulide (2.0%). Polyethylene glycol (PEG) was used to modify gelation temperature and drug release properties. Among the formulations examined, the poloxamer 407/nimesulide/sodium alginate/PEG 4000 (18/2.0/0.5/1.2%) exhibited the appropriate gelation temperature, acceptable drug release rate and rectal retention at the administration site. [33]

Vaginal Delivery

For efficient vaginal delivery of drugs, the delivery system should reside at the site of infection for a prolonged period of time. *In situ* gel formulation which combines advantages of both gels and solution so that an accurate dose can be administered with ease. These formulations remain in solution state before administration and transforms to gel after administration in to vaginal cavity. Clindamycin loaded hydroxypropyl methycellulose (0.1%) (bioadhesive) and gellan gum (ion activated gelling polymer) based *in situ* gel system for vaginal application were developed using NaCl (0.9%) as an isotonic agent. The developed formulation was found to be nonirritant, bioadhesive with good retention properties. [34]

Peroral Delivery

Pectin, xyloglucan and gellan gum are the natural polymers used for *in situ* forming oral drug delivery systems. In-situ gel of voriconazole were developed and found capable of exhibiting controlled release with the stability and the optimized formulation containing carbopol 934 and HPMC E-50 has fulfilled the objectives like reduction in the frequency of administration and improved patient compliance. [35]

Dermal and Transdermal Delivery

The in situ hydrogels (ISGs) of Curcumin and its inclusion complexes were prepared using poloxamers 407 and 188 as the matrix. The extent of drug's in vitro release from the ISGs depended on the dissolution of drugs. Both of the ISGs had transdermal effect and cytotoxicity on B16-F10 cells. The ISGs of Curcumin inclusion complexes are a promising formulation for melanoma treatment. [36]

Nasal Delivery

In order to improve the bioavailability of the antidepressant drug, venlafaxine hydrochloride, *in situ* mucoadhesive thermoreversible gel, was formulated using Lutrol F127 (18%) as a thermo gelling polymer. Mucoadhesion was modulated by trying carbopol 934, PVP K30, HPMC K4M, sodium alginate, tamarind seed gum, and carrageenan as mucoadhesive polymers. Results revealed that as the concentration of mucoadhesive polymer increased the mucoadhesive strength increased but gelation temperature decreased. From the results of pharmacodynamic study, mainly forced swim test (FST), it was concluded that venlafaxine hydrochloride was more effective as an antidepressant by nasal route as *in situ* gel nasal drops in comparison to oral administration of equivalent dose. [37]

PROPRIETARY FORMULATIONS OF IN-SITU GEL

Regel depot technology:

Regel is one of the Macromed's proprietary drug delivery system and based on triblock copolymer, composed of poly (lactide-co-glycolide)-poly (ethylene glycol)-poly(lactide-co-glycolide). It is a family of thermally reversible gelling polymers developed for parenteral delivery that offers a range of gelation temperature, degradation rates and release characteristics as a function of molecular weight, degree of hydrophobicity and polymer concentration. Following injection, the physical properties of polymer undergo a reversible phase change resulting in formation of a water insoluble, biodegradable gel depot.[38]

Cytoryn:

This is one of the Macromed's products, which is a novel, 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 by conventional IL-2 therapy. Cytoryn also activates the systemic antitumor immunity. Regel system stabilizes and releases IL-2 in its bioactive form. The release of drugs is controlled by the rate of diffusion from and degradation of the depot. [39,40]

Oncogel:

OncoGel, a novel injectable formulation of paclitaxel in a biocompatible biodegradable gel (ReGel), provides controlled release of paclitaxel at the injection site, resulting in high intralesional paclitaxel concentrations and continuous radio sensitization without attendant systemic toxicities. This dose-escalation study evaluated the toxicity, pharmacokinetics, and preliminary antitumor activity of OncoGel injected intralesionally in patients with inoperable esophageal cancer who were candidates for palliative external-beam radiotherapy (RT). [41]

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 is260-330 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 preservativeused 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. [42]

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 in still 1 drop in the affected eye (s) once daily for the next five days. [43]

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. [44,45]

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. [46]

Virgan:

Vigran is an ophthalmic antiviral that is indicated for the treatment of acute herpes simplex keratitis. The recommended dosing regimen for Virgan is 1 drop in the affected eye 5 times perday (approximately every 3 hours while awake) unti the corneal ulcer heals, and then 1 drop 3times 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. [47]

CONCLUSION

Formulating an efficient GRDDS is a challenge and for desired gastro retention, various approaches have been developed in GRDDS. Among various GRDDS oral floating in-situ gels was found to be a promising one. These systems provide the advantage of better absorption of drugs which are absorbed from the upper part of stomach. As the system remains in the stomach for longer duration, prolonged local action of drug in gastric mucosa is increased, and this leads to decrease in frequency of administration and improved efficiency of treatment. In situ gels are not only helpful for sustained drug delivery but increase the pediatric and geriatric patient compliance. In situ gel have good stability and biocompatibility characteristics and better drug release which make it more reliable dosage form over the conventional one.

REFERENCES

1. Patel J.K, J.R. Chavda. M.K. Modasiya. Floating *in situ* gel based on alginate as carrier for stomach-specific drug delivery of famotidine. IJPSN.2010;volume3issue3;p 1092-1104.
2. Garg, S.and S. Sharma. Gastro retentive drug delivery systems. Business Briefing Pharmatech NIPER.2003; p160-166.
3. Sharma N, D. Agarwal, M.K. Gupta and M.P. Khinchi. A comprehensive review on floating drug delivery system. IJRPBS.2011;Volume 2 issue 2; p 428-441.
4. Mojaverian P, P.H Vlasses, P.K. Kellner and M.L. Rocci Jr,. Effects of gender, posture and age on gastric residence time of an indigestible solid: pharmaceutical considerations, Pharmaceutical Research, 10; p 639-644.
5. Shah Shreeraj, Upadhyay Pratik, Parikh Darsh, Shah Jinal. In Situ Gel: A Novel Approach of Gastro retentive Drug Delivery. Asian journal of biomedical and pharmaceutical sciences.2012 volume 2(8); p1-8.
6. Lovenish Bhardwaj, Pramod Kumar Sharma and Rishabha Malviya. A Short Review on Gastro Retentive Formulations for Stomach Specific Drug Delivery. African Journal of Basic & Applied Sciences. 2011; vol 3 (6); p 300-312.
7. Kadam Shashikant M, Kadam S.R, Patil U.S, Ratan G.N, Jamkandi V.G. Review on floating drug delivery systems: An approach to oral controlled drug delivery via gastric retension. International Journal of Research in Ayurveda & pharmacy.2011; volume 2(6); p 1752-1755.
8. Patel Miteshkumar J, Patel Kanu R, Patel Mukesh R, Patel Natubhai M. Strategy for development of pH triggered floating *in-situ* gel of levetiracetam. International Journal of pharmtech Research. 2012 volume 2(3); p 828-841.
9. Nirmal H.B, Bakliwal S.R, Pawar S.P. *In-Situ* gel: New trends in controlled and sustained drug delivery system. International Journal of Pharm Tech Research. 2012; Vol-2, No-2; p 1398-1408.
10. Kishor K. Bhalerao et al. A short Review on Stomach Specific Floating in-situ gel. Journal of Biomedical and Pharmaceutical Research. 2012; Volume 1 (3); p 01-04.
11. G mamaheswara Rao, Murari P. Buoyant sustained release drug delivery systems current potentials advancements and role of polymers: a review. Pharmacie Globale (IJCP). 2012; Volume 2 (01): p 1-7.
12. Shah SH, Patel JK, Patel NV. Stomach specific floating drug delivery system: a review. International Journal of PharmTech Research.2009; Volume 1(3); p 623-633.
13. Parekh HB, Rishad J, Jivani NP, Patel LD, Ami M, Krunal S. Novel insitu polymeric drug delivery system: a review. Journal of Drug Delivery & Therapeutics. 2012;Volume 2(5); p 136-145.
14. Patel RP, Baria AH, Pandya NB, Tank HM. Formulation Evaluation and optimization Of stomach specific in situ gel of Ranitidine hydrochloride. International journal of Pharmaceutical sciences and Nanotechnology 2010; volume 3(1); p 834-843.
15. 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; volume 2(3); p 828-841.
16. Joasis H. Hamman. Chitosan based polyelectrolyte complexes as potential carrier materials in drug delivery systems. Mar Drugs. 2010;8(4); p1305-1322.
17. Neil A. Morrison, Raymond C. Valli. Methods of making sterilized milk compositions comprising native gellan gum. EP1355535 B1. Nov 23, 2005.
18. Louis Danoux, Thomas Market et al. Method for treating skin by administering an agent that decreases GMCSF release from keratinocytes **.** WO2008034535 A1. Mar27, 2008.
19. John J Eisch, John F Kay. End-capped polyalkylene glycols and compositions containing such compounds. WO 2003055933 A1. Jul 10, 2003.
20. Jack Curr, Brain Hallett. Potassium formate gel designed for the prevention of water ingress and dewatering of pipelines or flowlines. WO 2010001105 A1. Jan 7, 2010.
21. Lavinia Cicortas Gunnarsson et al. Engineered xyloglucan specificity in a carbohydrate-binding module. Glycobiology. 2006; vol. 16 no. 12; p 1171–1180.
22. Farooq Amjad et al. Fragrance-containing gel for delivering fragrance from structured liquid detergentcompositions.WO 2002077150 A1. Oct 3, 2002.
23. K. B. Wataru, M. Shozo, D. Masatake, and T. Mitsuo, “Oral sustained delivery of ambroxol from insitu- gelling pectin formulations,” International Journal of Pharmaceutics. 2004;vol. 271, no. 1-2; p 233–240.
24. Patel R.P, Dadhani B et al. Formulation, evaluation and optimization of stomach specific in situ gel of clarithromycin and metronidazole benzoate. International Journal of Drug Delivery 2 2010; p 141-153.
25. Teerawat Sahasathian, Nalena Praphairaksit et al. Mucoadhesive and floating chitosan-coated alginate beads for the controlled gastric release of amoxicillin. Pharmacal Research. June 2010; Volume 33; p 889-899.
26. T.Sivannarayana,Varanasi.S.N.Murthy et al. Formulation and evaluation of oral floating in situ gel of moxifloxacin hcl. Indo American

Journal of Pharm Research.2013; 3(10); p 8211-8221.
27. Patel MJ et al. Strategy for Development of pH Triggered Floating Insitu Gel of Levetiracetam. American Journal of PharmTech Research. 2012; 2(3); p 828-841.
28. Lena Murad Thomas. Formulation and evaluation of floating oral in-situ gel of metronidazole. International journal of pharmacy and pharmaceutical sciences. 2014; vol 6, issue 10; p 265-269.
29. Rathore KS, Nema RK. Management of Glaucoma: a review. Int. J. Pharm Tech Res 2009; 1(3); p 863-869.
30. Rathore KS, Nema RK, Sisodia SS, Formulation and Evaluation of Brimonidine Tartrate Ocular Films. The Pharma Review 2010; 2: p133-139.
31. Michael H, Mostafa H, Mehdi J, Taravat G. Draiz e Rabbit eye test compatibility with eye irritation threshold in humans: A quantitative structural-activity relationship analysis. Toxicol Sci 2003; 76; p 384–391.
32. Karan Malik , Inderbir Singh et al. Atrigel: A potential parenteral controlled drug delivery system. Der Pharmacia Sinica. 2010; 1 (1); p 74-81.
33. Yuan Y, Cui Y, Zhang L et al. Thermosensitive and mucoadhesive in situ gel based on poloxamer as new carrier for rectal administration of nimesulide. Int J Pharm. 2012. Jul 1; 430(1-2); p 114-9.
34. Priya Patel and Paresh Patel. Formulation and evaluation of clindamycin HCL *in situ* gel for vaginal application. Int J Pharm Investig. 2015 Jan-Mar; 5(1); p 50–56.
35. E.Hima bindu, et al. Design, optimisation and evaluation of mucoadhesive peroral in situ gel containing anti fungal drug for candidiasis. Indo American Journal of Pharm Research.2014; 4(01); p 884-895.
36. Sun Y, Du L et al. Transdermal delivery of the in situ hydrogels of curcumin and its inclusion complexes of hydroxypropyl-β-cyclodextrin for melanoma treatment. Int J Pharm. 2014 Jul 20; 469(1); p 31-9.
37. Mandar J. Bhandwalkar and Amelia M. Avachat. Thermoreversible Nasal *In situ* Gel of Venlafaxine Hydrochloride: Formulation, Characterization, and Pharmacodynamic Evaluation. AAPS PharmSciTech. 2013 Mar; 14(1); p 101–110.
38. Ramesh CR, Zentner GM, Jeong B. Macro med, Inc. Biodegradable low molecular weight triblock poly (lactide-co- glycolide) polyethylene glycol copolymers having reverse thermal gelation properties. US patent.2001. 6201072.
39. Rathi R, Zentner C, Gaylen M, Jeong B. Macro med, Inc. Biodegradable low molecular weight triblock poly (lactide-co-glycolide) polyethylene glycol copolymers having reverse thermal gelation properties. US patent. 2000. 6117949.
40. Rathi R, Zentner C, Gaylen M. Macro med, Inc. Biodegradable low molecular weight triblock poly (lactide-co-glycolide) polyethylene glycol copolymers having reverse thermal gelation properties. US patent.1999. 6004573.
41. DuVall GA, Tarabar D et al. Phase 2: a dose-escalation study of OncoGel (ReGel/paclitaxel), a controlled-release formulation of paclitaxel, as adjunctive local therapy to external-beam radiation in patients with inoperable esophageal cancer. Anticancer Drugs. 2009 Feb; 20(2); p 89-95.
42. Sterile ophthalmic gel forming solution, Timoptic-XE®, 0.25% and 0.5%, (Timolol maleate ophthalmic gel forming solution) Whitehouse Station, USA: Merck and Company Inc.; NJ 08889.
43. Lyle M. Bowman, James F. Pfeiffer. Sustained release ophthalmic compositions containing water soluble medicaments. US 6159458 A. 12 Dec 2000.
44. AHFS Drug Information 2003. McEvoy GK, ed. Pilocarpine. Bethesda, MD: American Society of Health-System Pharmacists; 2003; p 2679-82.
45. AHFS Drug Information, McEvoy GK, ed. Miotics General Statement. Bethesda, MD: American Society of Health-System Pharmacists; 2003; p 2674-77.
46. Abu Alam, Elias Reichel, Brandon Busbee. Aqueous gel formulation and method for inducing topical anesthesia. US 8759401 B2. 24 Jun 2014.
47. Colin J, Hoh HB, Easty DL, Ganciclovir ophthalmic gel (Virgan; 0.15%) in the treatment of herpes simplex keratitis. Cornea. 1997 Jul; 16(4); p 393-9.