Susan Jacob et al /J. Pharm. Sci. & Res. Vol. 12(8), 2020, 1056-1061

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

ORAL *IN-SITU* GELLING SYSTEM – A REVIEW

Susan Jacob*, Anu Mathew, Shyma M.S
Department Of Pharmaceutics, Mar Dioscorus College of Pharmacy
Alathara, Sreekaryam, Thiruvananthapuram, Kerala, India

Abstract

Oral drug delivery is the preferable drug delivery due to the ease of administration, patient compliance and flexibility in the formulations. Conventional oral dosage forms produce low bioavailability problems due to their rapid gastric transition from stomach. Gastro retentive drug delivery system is facing many challenges which can be overcome by *in- situ* gelling (Raft forming) system. The formation of *in-situ* gels depends on factors like temperature modulation, pH change, ionic crosslinking and solvent exchange from which the drug gets released in a sustained and controlled manner. Some of the polymers that are used in *in-situ* gelling system are guar gum, Xanthan gum, Sodium alginate, gellan gum, pectin, chitosan, Sodium Benzoate, Sodium Citrate, Polyethylene glycon and Hydroxy Propyl methyl cellulose.

Keywords: In situ gel, Approaches, Polymers, Evaluation.

INTRODUCTION

In-situ gelling (Raft forming) system is an intermediate state of liquid and solid components. Hydrogels is a three dimensional structures which has capacity to retain bulk amount of water and also biological fluids to swell. *In-situ* gels are type of hydrogels that are in the solution form and undergo gelation in contact with body fluids or change in pH or temperature. *In-situ* formulations are in sol form before administration in the body, but once administered to form a gel in contact with gastric fluid. *In-situ* gels can be administered by oral, ocular, rectal, vaginal, injectable and intraperitoneal routes and it has several advantages when compared to conventional drug delivery systems. Oral route of drug delivery is the most favoured and practiced drug delivery.

The novel drug deliveries of gastroretentive systems such as floating systems, mucoadhesive, high-density, expandable have been developed. They provide controlled delivery of drugs with prolonged gastric residence time. Gastroretentive floating drug delivery systems have bulk density lower than gastric fluid and then float on gastric fluid. Liquid orals are low bioavailability because they are eliminated quickly from the stomach. Oral *in-situ* gel can overcome the problems of immediate release and short gastrointestinal residence of liquids. The *in-situ* gel dosage form is a liquid at room temperature and after it comes in contact with gastric contents they show gelation. This approach increased residence as well as sustained release and effective for systemic as well as localization at the site of action.

PRINCIPLE OF *IN-SITU* GEL

Formulation of *in-situ* gel system involves the use of gelling agent form a stable suspension system, which contain the dispersed drug and other excipients. The gelling of this sol/suspension system is to be achieved in gastric environment due to change in pH. The formulation adopted is a gellan gum or sodium alginate solution containing calcium chloride and sodium citrate, which complexes the free Calcium ions and releases them only in the acidic environment of stomach. Gellan gum or sodium alginate acts as gelling agent and the free calcium ions gets entrapped in polymeric chains of gellan gum or sodium alginate thereby causing crosslinking of polymer chains to form matrix structure. This gelation involves the formation of double helical junction followed by re-aggregation of double helical segments to form a three dimensional network by complexation with cations and hydrogen bonding with water.

Fig.1: example of *in-situ* gel

ADVANTAGES

- Floating obtained faster than the other floating dosage form.
- Improve patient compliance.
- Improve therapeutic efficacy.
- Easy to administer to a patient.
- It increases the contact time of drug at the site of absorption (stomach).
- It provides advantages such as the delivery of drugs with narrow absorption in the small intestinal region.
- Reduction in plasma level fluctuation.
- Target stomach specific drug delivery system like H. pylori-induced gastric ulcer

DISADVANTAGES

- These systems are formulated in the form of solution which is more susceptible to stability problems like chemical degradation (oxidation, hydrolysis, etc.) or microbial degradation.
- The formulation must be stored properly because if the formulation is not stored properly it may cause stability problem due to change in the pH of the system on prolonged storage or on storing inappropriate temperature conditions.
- Exposure of certain polymer to radiations (e.g. UV, Visible, electromagnetic, etc.). so induces the formation of gel within the package.

CRITERIA OF DRUGS SUITABLE FOR *IN-SITU* GEL DRUG DELIVERY SYSTEM

- Drugs that act primarily in the stomach like misoprostol.
- Drugs that are primarily absorbed from the stomach like amoxicillin trihydrate.
- Drugs those are poorly soluble at alkaline pH like verapamil HCl and diazepam.
- Drugs with a narrow absorption window like levodopa and cyclosporine.
- Drugs which are rapidly absorbed from the GIT like tetracycline.
- Drugs that degrade in the colon like ranitidine and metformin.
- Drugs that disturb normal colonic microbes like ampicillin.

CRITERIA OF DRUGS UNSUITABLE FOR *IN-SITU* GEL DRUG DELIVERY SYSTEM

- Drugs that have limited acid solubility e.g. (phenytoin).
- Drugs that suffer instability (erythromycin) or solubility (phenytoin) problem in GIT
- Drugs that intended for selective release in the colon e.g. (5- amino salicylic acid and corticosteroids).
- Drugs that are absorbed along entire GIT, which under go first-pass metabolism e.g. (nifedipine, propranolol).

PHYSIOLOGICAL FACTORS EFFECTING DRUG ABSORPTION

Gastric Motility

The motility of the stomach is mostly contractile, controlled by a complex set of neural and hormonal signals. There are two marked differences between gastric motility:

a) In the fasting state; the motoric activity termed interdigestive myoelectric motor complex (IMMC) or migrating myloelectric cycle (MMC) which is a series of electrical events happening every 2-3hr., also this cycle of peristaltic movements generated to clear the stomach and the small intestine of indigested debris, swallowed saliva and sloughed epithelial cells.

b) In the fed state; the digestive mode comprises continuous contractions. These contractions result in reducing the size of food particles (< 1 mm), which are propelled towards the pylorus in suspension form. During the fed state, MMC is delayed resulting in slowdown of gastric emptying rate.

Gastric Emptying Rate

Passage of drug from stomach to the small intestine is called gastric emptying and it occurs during fasting as well as fed states. MMC is further divided into following 4 phases:

Phase I (basal phase): It lasts from 30 - 60 minutes with rare contractions.

Phase II (preburst phase): It lasts for 20 - 40 minutes with intermittent action potential and contractions. The intensity and frequency also increases gradually.

Phase III (burst phase): It lasts for 10 - 20 minutes including intense and regular contractions for short period. It is due to this wave that all the undigested material is passing out of the stomach into the small intestine. It is also known as the housekeeper wave.

Phase IV: It is a period of transition from phase III and phase I and last for 0 - 5 minutes.

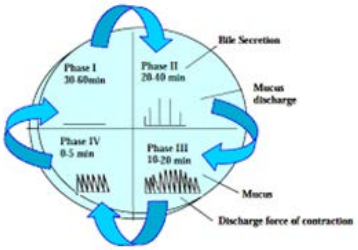

Fig.2: Gastrointestinal motility pattern

FACTORS AFFECTING GASTRIC RETENTION

Various attempts considered to retain the dosage form in the stomach as a way of increasing the retention time. These gastroretentive systems are floating dosage forms (gas generating systems and swelling or expanding system), high density systems, muco adhesive systems, modified shape systems and gastric-emptying delaying devices. Most of these approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastroretentive system. These factors are as follows.

Density: - Gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density. The density of the dosage form should be less than the gastric contents (1.004 gm/ml). It affects the gastric emptying rate and patient compliance.

Size: - Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.

Shape of dosage form: - Ring shaped devices and tetrahedron with a flexural modulus of 48 and 22.5 kilo pounds per square inch are reported to have a better GRT at 24 hours compared with other shapes.

Single or multiple unit formulation: - Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow coadministration of units with different release profiles compared with single unit dosage forms.

Fed or unfed state: - Under fasting conditions, gastro intestinal motility is characterized by periods of strong motor activity that occurs every 1.5 to 2 hours. The GRT of the unit can be expected to be very short if the timing of administration of the formulation coincides with that of the MMC. MMC is delayed and GRT is considerably longer in the fed state.

Nature of meal:- In the gastrointestinal tract, the presence of food and Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate.

Caloric content: - GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.

Frequency of feed: - The GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC. [1]

Gender: - Mean ambulatory GRT in males (3.4 ± 0.6 hours) is less compared with their age and race matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, height and body surface. [1]

Age: - Elderly people, especially those over 70 years, have a significantly longer GRT.

Posture: - GRT can vary between supine and upright ambulatory states of the patients.

Concomitant drug administration: - Anticholinergics like atropine and propentheline increase the GRT. Metoclopramide and cisapride decrease GRT.

Disease state: - Gastric ulcer, diabetes and hypothyroidism increase the GRT. Hyperthyroidism and duodenal ulcers decrease the GRT.

APPROACHES OF DESIGNING *IN-SITU* GEL SYSTEM

1) physically induced *in-situ* gel systems

a) **Swelling:** *In-situ* formation occurs when material absorbs water from surrounding environment and expands to give the desired space. Example of substance is myverol 18-99 (glycerol mono-oleate), which is polar lipid that swells in water to form liquid crystalline phase structures.

b) **Diffusion:** This method involves the diffusion of solvent from solution of polymer into surrounding tissue and results in solidification or precipitation of polymer matrix. N-methyl pyrrolidone (NMP) has been shown to be useful solvent for diffusion.

2) Chemically induced *in-situ* gel systems

a) **Ionic crosslinking:** Certain ion sensitive polysaccharides such as iota carrageenan, pectin, gellan gum, sodium alginate undergo phase transition in presence of various ions such as k+ , Ca2+, Mg2+, Na+. *In-situ* gel formation involves administration of aqueous liquid solutions, once administered they form gel under certain conditions involve the use of gelling agent which can form a system that contain the dispersed drug and other excipients. The gelling of this system is achieved by using polymer solutions such as gellan gum & sodium alginate triggered by ionic complexation that contains divalent-ions complexed with Na-citrate which breakdown in acidic environment of stomach to release free divalent ions (Ca2+) due to change in pH. The free Ca2+ ions get entrapped in polymeric chains thereby causing cross linking of polymer chains to form matrix structure causes the in situ gelation of orally administered solution as shown in equation:

Sodium citrate + NaHCO3 + CaCl2 →Ca. citrate

Complex Acidic Environment Ca2+ + COO-

In-situ gel involves formation of double helical junction zones by aggregation of double helical segments to form dimensional network by complexation with cations & hydrogen bonding with water. While the system is floating in the stomach the drug is released slowly at the desired rate from the system.

b) **Enzymatic crosslinking:** *In-situ* gel formation catalyzed by natural enzymes. For example, cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin. Thus adjusting the amount of enzyme controls the rate of gel formation, which allows the mixtures to be injected before gel formation.

c) **Photo-polymerization:** A solution of monomers such as acrylate or other polymerizable functional groups and initiator can be injected into tissue site and the application of electromagnetic radiation used to form gel designed to be readily 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, while short wavelength ultraviolet is not used because it has limited penetration of tissue and biologically harmful.

3) *In-situ* gel formation based on physiological stimuli

a) **Temperature dependent *in-situ* gelling:** These hydrogels are liquid at room temperature (20ºC-25ºC) and undergo gelation when contact 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) and formation of negative temperature sensitive hydrogel in which hydrogen bonding between the polymer and water becomes unfavorable, compared to polymer–polymer and water–water interactions. Also an abrupt transition occurs as the solvated macromolecule quickly dehydrates and changes to a more hydrophobic structure. Alternatively, some amphiphilic polymers increase LCST, where self-assembles in solution show more micelle packing and gel formation because of polymer– polymer interactions when temperature is increased for e.g. crosslinked N-isopropylacrylamide-co-butylmethacrylate {P(NIPAAmco-BMA)} polymer. A positive temperature-sensitive hydrogel has an upper critical solution temperature (UCST), such hydrogel contracts upon cooling below the UCST and swell at high temperature for e.g. poly acrylic acid (PAA) and polyacrylamide (PAAm) have positive temperature dependence of swelling.

b) **pH dependent *in-situ* gelling:** Polymers containing acidic or alkaline functional groups that respond to changes in pH are called pH sensitive polymers. Gelling of the solution is triggered by a change in pH. The polymers with a large number of ionizable groups are also known as polyelectrolytes. Swelling of hydrogel increases with external pH increases in the case of weakly acidic (anionic) groups of polymer, but decreases in case of polymer contains weakly

basic (cationic) groups. For example: carbomer and its derivatives as anionic polymer.

MECHANISMS OF DRUG RELEASE FROM IN-SITU GEL SYSTEM

1) **Diffusion- controlled mechanism:**
   a) **Matrix system:** The active agent is homogenously dispersed as a solid into a hydrogel inert bio-degradable polymers matrix as in Figure.

   The release of drug depends on:

   - Diffusion of water into the matrix followed by the dissolution of the drug and finally the diffusion of the dissolved drug from the matrix.
   - Polymers interact with drugs leading to modulate the release of the drug.
   - The Thickness of the hydrated matrix is considered as the diffusional path length of the drug. If we consider the polymer matrix to be inert and the drug release is diffusion-controlled, then the release rate of the drug could be described by Higuchi equation.

   b) **Reservoir devices:** The drug is contained in a core (often termed as reservoir) which is surrounded by a rate-controlling polymeric membrane of hydrogel which allows the diffusion of drug as shown in Figure. As the system comes in contact with water, water diffuses into the system and dissolves the drug, and then drug transport (from the core through the external polymer membrane) occurs by dissolution at one interface of the membrane and diffusion driven by a gradient in thermodynamic activity. Drug transport can be described by Fick's first law, if the activity of the drug in the reservoir remains constant and infinite sink conditions are maintained, then the drug release rate may be continued to be constant since it depends on the membrane permeability and it will be independent of time, thus zero-order kinetics can be achieved. Once drug is exhausted, the release becomes concentration dependent following first order kinetics. These kinds of drug delivery systems are mainly used to deliver the active agent by oral routes.

2) **Swelling-controlled mechanism**
   a) **Solvent activated system**: It occurs when diffusion of drug is faster than hydrogel swelling. When a hydrogel is placed in an aqueous solution, water molecules will penetrate into the polymer network that occupy some space, and as a result some meshes of the network will start expanding, allowing other water molecules to enter within the network. But, swelling is not a continual process; the elasticity of the covalently or physically cross-linked network will counter-balance the infinite stretching of the network to prevent its destruction. For example the release of drugs from (HPMC) hydrogel is commonly modeled using this mechanism.

   b) **Osmotic swelling**: For hydrogels, the total swelling pressure of gel could be related to volume fraction, relaxed volume of network, and cross-link density while it is independent on gel pH and swelling time.

3) **Chemically-controlled mechanism :**It can be categorized according to the type of chemical reaction occurring during drug release within a delivery matrix into:
   a) Pendant chain system is the most common reaction where the drug is covalently attached to a polymer backbone. The bond between the drug and the polymer is labile and can be broken by hydrolysis or enzymatic degradation and then the drug release.
   b) Erodible drug delivery system where the release of the drug is controlled by the dissolution during surface-erosion or bulk-degradation of the polymer backbone then the drug diffuses from erodible systems.

Depending on whether diffusion or polymer degradation controls the release rate, the drug is released following different mechanisms; if erosion of polymer is much slower than diffusion of the drug through the polymer, then drug release can be treated as diffusion controlled process. While if diffusion of the drug from the polymer matrix is very slow, then polymer degradation or erosion is the predominate mechanism, for example hydrophobic erodible polymers.

POLYMERS USED IN THIS STUDY

Sodium alginate:

Sodium alginate is a polymer of natural origin. Chemically, sodium alginate is alginic acid salt, consisting of β–D-mannuronic acid and α-L-glucuronic acid residues linked by 1,4-glycosidic linkages. The alginates solution in water form firm gels in the presence of di-or trivalent ions (e.g., magnesium and calcium ions). Sodium alginate is mostly used for the preparation of the gel-forming solution, for delivery of the drugs, peptides and proteins. Alginate salts are considered most favorable because of biodegradable and nontoxic nature, with additional bioadhesive property. This indicated that the alginates form compact structures when the ionic radical of the cation are lower. Sodium alginate applied pharmaceutically as a water-soluble polymer so useful in sustained release liquid preparations for oral administration, act as a stabilizing agent; viscosity-increasing agent.

Pectin:

These are plant origin anionic characteristics can be divided into two polysaccharides isolated from the cell wall of most plants and consist of -(1-4) -D-galacturonic acid residues. Pectin undergoes gel formation in the presence of the medium; a stiff gel is produced. Pectin is a complex polysaccharide comprising mainly esterified D-galacturonic acid residues in an a-(1-4) chain. On the basis of methyl esterification of galacturonic acid, there are two different types of pectin-high methoxy and low methoxy gelation. Gelation of high methoxy pectin 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 solids content.

Gellan gum:

Gellan gum is a water soluble anionic polysaccharide, commercially known as Phytagel or Gelrite. Gellan gum (FDA approved) secreted by the Sphingomonas elodea (Pseudomonas elodea) and chemically is anionic deacetylated polysaccharide with repeating tetrasaccharide units composed of β-D-glucuronic acid (1 unit), α-L-rhamnose (1 unit) and β-D-glucose (2 units) residues. Gellan gum undergoes gel formation due to change in temperature or due to the presence of cations (e.g., Na+ K+, Ca2+ and Mg2+). Gellan gum can be applied pharmaceutically as a water-soluble polymer acts as a potential carrier for different oral floating sustained delivery dosage forms.

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 is composed of heptasaccharide, octasaccharide, and nonasaccharide oligamers, 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 sol to gel at a transition temperature. It is used for rectal, oral and ocular delivery of pilocarpine and timolol.

Xanthan gum:

Xanthan gum is a high molecular weight extracellular polysaccharide produced by xanthomonas campestris. It is a long chain polysaccharide with large number of trisaccharide side chains. The main chain consists of two glucose units. The side chains are composed of two mannose units and one glucuronic acid unit. Xanthan gum can form strong gel when mixed with positively charged polymers. This gum develops a weak structure in water, which creates high viscosity solutions at low concentration.

Pluronic F-127:

Poloxamers or pluronic (marketed by BASF Corporation) is the series of commercially available difunctional triblock copolymers of non-ionic nature. They comprise of a central block of hydrophobic polypropylene oxide surrounded on both sides by the blocks of hydrophilic polyethylene oxide. Due to the PEO/PPO ration of 2:1, when these molecules are immersed into the aqueous solvents, they form micellar structures above critical micellar concentration. They are regarded as PEO-PPO-PEO copolymers. The pluronic triblock copolymers are available in various grades differing in physical forms and molecular weight. Depending upon the physical designation for the grades are assigned, like F for flakes, P for paste, L for liquid. Pluronics or Poloxamers also undergo in situ gelations by temperature change.

Chitosan:

Chitosan is a natural and versatile polycationic polymer obtained by alkaline deacetylation of chitin. It is a biodegradable, thermosensitive and non-toxicity. Chitosan is a biocompatible pH dependent cationic polymer, which remains dissolved in aqueous solutions up to a pH of 6.2. Neutralization of chitosan aqueous solution to a pH exceeding 6.2 leads to the formation of a hydrated gel-like precipitate. The pH gelling cationic polysaccharides solution are transformed into thermally sensitive pH dependent gel-forming aqueous solutions by addition of polyol salts, without any chemical modification or cross linking.

Carbopol:

Carbopol is a pH dependent polymer, which forms a low viscosity gel at alkaline pH but stays in solution form at acidic pH. HPMC is used in combination with carbapol to impart the viscosity to carbopol solution while reducing the acidity of the solution. Various Water triblock copolymers change in solubility with the change in environmental temperature.

EVALUATION OF *IN-SITU* GELLING SYSTEM

CLARITY

The clarity of formulated solutions can be examined by visual inspection under black and white background.

VISCOSITY

Brook field Viscometer was used to determine the viscosities of the prepared formulations. A volume of 50 ml of the sample was measured and taken into Nessler's cylinder and sheared at a rate of 50 and 60 rpm using spindle number 63 at room temperature. Each sample's viscosity measurement was done in triplicate.

SOL TO GEL TIME

In vitro gelation time was determined by using USP (Type II) dissolution apparatus containing 500 mL of 0.1N HCl (pH 1.2) at 37±0.5^{0}C. It converted from sol to gel, when the formulation was coming in contact with 0.1N HCl and time was measured. Gelling time is the time required for the first gelation of *in-situ* gelling system. It was observed within seconds, the gel floated on buffer solution.

FLOATING LAG TIME (BUOYANT TIME)

Time taken by the gel to reach the top from the bottom of the dissolution flask is defined as the floating lag time(buoyant time).The floating lag time of gel determination was performed by visual inspection in a USP type II dissolution test apparatus containing 500 ml of 0.1 N HCl (pH 1.2) at 37±0.5^{0}C.

FLOATING DURATION

The time taken for the formed gel floating on the surface of the dissolution medium is known as floating duration. The duration of the floating of gels was determined by visual inspection in a dissolution test apparatus USP (Type II) containing 500 mL of 0.1N HCl (pH 1.2) at 37±0.5^{0}C.

GEL-STRENGTH

The gel is prepared in a beaker from the sol form. This gel containing beaker is raised at a certain rate, so pushing a probe of rheometer slowly through the gel. It can be measured by the changes in the load on the probe can be

measured as a function of depth of immersion of the probe below the gel surface.

FOURIER TRANSFORM INFRA-RED SPECTROSCOPY AND THERMAL ANALYSIS

Fourier transform infra-red spectroscopy is performed to study compatibility between drug and excipients. Differential scanning calorimetry is used to observe if there are any changes in optimized formulation as compared with the pure ingredients used thus indicating the interactions.

IN-VITRO DRUG RELEASE STUDIES

An in-vitro release study was carried out using dissolution test apparatus of USP Type II Paddle Method. The release of drug from the formulations was determined using dissolution test apparatus USP Type II with a paddle stirrer at 50 rpm. The dissolution medium was 900 ml of (0.1N HCL, pH 1.2) solution and temperature was maintained at 37 ± 0.2°C. From this dissolution medium,1 ml of the sample solution was withdrawn at different time intervals and replenished with fresh medium. Drug concentration in the aliquot was determined spectrophotometrically.

CONCLUSION

The gastroretentive floating drug delivery is a challenging task for prolonging the gastric retention and physiological compatibility with the stomach. The in-situ gel preparation were developed for improve patient compliance and reduce dosing frequency. This approach increased residence as well as sustained release and effective for systemic as well as localization at the site of action. The formation of gel depends on various physiological environments like pH, temperature and ionic condition.

ACKNOWLEDGEMENT

I am highly thankful to my collegues Ms. Anu Mathew and Shyma M.S for encouragement and support for completing the article.

REFERENCE

1. Nilesh P. Salunkhe et.al., Oral in-situ floating gelling system: Review on.*World. J. Pharm.Pharma. Sci*. 2019,8*[4]*,478-496.
2. Sarada K, Firoz S, Padmin K., In-situ gelling system: A review. Int. *J.Curr.Pharm.Rev.Res.*2015,5*[4]*,76-90.
3. M.Madan et.al., In situ forming polymeric drug delivery systems. *Indian J. Pharm. Sci*. 2009.
4. Ashutosh Padhan, B.K. Nanda and B. C. Behera., Floating oral in-situ gel, A comprehensive approach of gastro-retentive drug delivery system: A review. *Int.J.Pharma.Sci*.2019,10*[9]*,4026-4039.
5. T.Sivannarayana et.al., Formulation and evaluation of oral floating in situ gel of moxifloxacin HCl. *Indo.Am.J.pharm.res.*2013,3*[10]*,8211-8221.
6. Rabiah Bashir et.al., Floating oral in-situ gel: A review.*J.drug deliv.ther*.2019,6*[2]*442-448.
7. Nirmal H.B, Bakliwal S.R, Pawar S.P., In-situ gel: New trends in controlled and sustained drug delivery system. *Int.J.pharmtech Res.*.2010,2*[2]*,1398-1408.
8. S.S Raut and H.A.Shinde., In-situ raft forming system : A review. *Int.J.pharmacogn*..2018,5*[6]*,337-349.
9. Avinash Sharma, Jyoti Sharma, Rupinder Kaur, Vinay Saini., Development and characterization of in situ oral gel of spiramycin.*Biomed Res.Int*.2014[1-7].
10. Pawar ashish yaswantrao, Jadhav khanderao R and Nikam manasi N., A raft forming system: An novel approach for gastroretention. *Int.J.Pure App.Biosci*.2015,3*[4]*,178-192.
11. Neha jameel, CVS.Raghu Kiran and Vijaya Kuchana., Formulation and evaluation of floating oral in-situ gel of ranitidine hydrochloride. Int. j.res.pharm.chem.2016,6[1],75-81.
12. Shreeraj Shah, Pratik Upadhyay, Darsh Pratik, Jinal Shah., In situ gel: A novel approach of gastroretentive drug delivery. *Asian j. biomed. Pharm.* 2012,2*[8]*,01-08.
13. Fariba Ganji, E. V Farahani.,Hydrogels in controlled drug delivery systems. *Iran. Polym. J.* 2009,18*[1]*,63-88.