FLOATING IN SITU GEL: A EMERGING STRATEGY TO DESIGN AND DEVELOP GASTRO RETENTIVE DRUG DELIVERY

Shubham Vadak[a], Rohit Gorde[b], Vishal Pande*[c]

[a] Department of Pharmaceutics (PG), Sanjivani College of Pharmaceutical Education and Research, Kopargaon, Maharashtra-423603, India.
[b] Department of Pharmaceutics (PG), Sanjivani College of Pharmaceutical Education and Research, Kopargaon, Maharashtra-423603, India.
[c] Department of Pharmaceutics, Sanjivani College of Pharmaceutical Education and Research, Kopargaon, Maharashtra-423603, India.

ABSTRACT

The simplest and most effective way to administer medication by oral route but due to less residential time in GIT, it cannot release the drug by sustained or controlled rate. The *in situ* floating system is innovative system in the form of a gastro-retardant system. The *in situ* formulation is a liquid solution in nature and gets converted to gel by a different mechanism that floated on the gastric content which results in improved retention time in the stomach. The formed gel matrix releases the drug by the sustained and controlled rate for a longer period of time. It is more beneficial than traditional system such as cost effective and minimum time consuming method it can increase patient compliance, minimum toxicity and adverse effect, easy to swallow and reduced dose dumping.

This review article gives information regarding oral floating *in situ* gel formulation and recent work on drug and polymer used for *in situ* gel.

Key words: Introduction, need, mechanism, approach, recent research work on floating *in situ* gel.

INTRODUCTION

The floating system is a novel process that increases the site-specific uptake and improves absorption rate. The floating system is a lower density system, so it has enough ability to float on the acidic content. Floating system is meant for gastric retention because of sufficient buoyancy and low-density system it can releases drug for longer duration by controlled and sustained rate. The floating system is very useful for the API that has an absorption window in the upper part of the GIT to produce the local stomach effect.[1]

The oral drug delivery system is best route for drug administration. Different oral drug delivery system is prepared as a API reservoir from them active API molecule release over a long period with a predetermined rate as well as controlled & sustained rate. In recent decades the dosage form are designed to be retained in the upper part of GI tract by a different technique such as for example. Raft system, floating system, expanding system, swelling system, bio-adhesive system and low density system. The system offers benefits such as the delivery of medication with short absorption periods in the small intestine and greater resistance duration in the small intestine, which supports the regional effect in the upward part of the small intestine.

Eg: In treating the peptic ulcer disease.[2]

Gastro retentive floating system containing tablet, microbeads, films, capsules, etc. The *in situ* floating gel is a new trend of floating system which have a different route of administration oral, ophthalmic, nasal, rectal, vaginal, peroral. The *in situ* gelling methodology have different benefits such as easy to administered, produce regional action, increase patient compliance, increased bioavailability, reduced dosing frequency, reduced dose dumping, a less complex method for production, cost-effective.[3]

Advantages

1) Reduced dosing frequency.

2) Decreased occurrence of toxicity and intensity of adverse effect.

3) Increase patient compliance.

4) More uniform blood concentration.

5) More consistent and prolonged therapeutic effect.

6) To maintain contineuous concentration of drugs in the blood.

7) Greater selectivity of pharmacological activity.

8) Reduced dose dumping.

9) Improved stomach retention with the slow release of drugs.

10) Regional action and distribution of site requirement directly to the target site.[4,5]

Disadvantages

1) It requires a high level of fluids.

2) Only API that require a small dose may be administered.

3) Difficulty in stabilization responsible for chemical degradation.

4) The solution form of the drug is more susceptible to degradation.

5) In specific for hydrophobic drug, the quantity and consistency of API loading into hydrogel might be reduced.

6) Eating and drinking might be limited up to several hours after placing the drug.

7) Low mechanical intensity can lead to premature dissolution.[5,6]

Suitable Drug Candidate for *In Situ* Floating Gel System

1. Drugs functioning mainly in the region of stomach.

Example: antacids, antibiotics for treatment of ulcers.

2. Drugs may be consumed in the region of stomach.

Example: Albuterol.

3. In acidic pH a drug like weak bases are poorly soluble.

4. Drugs candidate have short window for absorption from gastrointestinal tract.

Example: Absorption of drug from proximal small intestine i.e. riboflavin, levodopa, fursemide, ranitidine hydrochloride.

5. Drugs have rapid absorption rate in GIT.

6. Drugs shows a potential degradation in the GIT.

Example: amoxicillin

Table 1: Drugs Used For *In Situ* Gel

Bioavailability Obstacle	Therapeutics	Drugs	References
Local activity	Eradication of Helicobacter Pylori	Amoxicillin (Rajinikanth et al., 2007)	[7]
Local activity	Eradication of Helicobacter Pylori	Clarithromycin (Rajinikanth et al.,2007)	[8]
Short half life	Antidiabetic	Mitiglinide calcium (mahmoud et al.,2018)	[9]
Short half-life, short absorption window in upper GIT	Treatment of type II diabetes	Metformin Nagarwal et al.,2009)	[10]
Local activity	Eradication of Helicobacter pylori adjunct	Metronidazole (N.A.H.Abou Youssef et al.,2015)	[11]

Factors Affecting Gastric Retention Time

Density

For gastro retentive action floating behavior vary according to density.

Size and Shape: The formulation containing unit size is in a range between 7.5 to 9.9 mm responsible to improve gastric residual time. The formulation shape is tetrahedron and the ring increases retention time for 24 hours (h) which responsible for drug release for an extended period.

Caloric Content

The food content with high protein and high fats thus the gastric retention time extends up to 10 hours.

With-food and without food

In fasting state the residual period of formulation in the region of stomach are low and meal state the residual period of formulation in the region of stomach is high.

Age

Gastric retention time of stomach is dependent on age factor with respect to increasing age the gastric residual period also increased.

eg. Lower gastric retention time in younger people

Type of meal

Reducing the process of gastric emptying and extending the release of drugs by eating indigestible fatty acid salt polymers will shift motility cycle of stomach into a fed state.

Frequency of feed

As compared to a single meal the successive meal shows high retention time.

Posture

Supine and upright ambulatory condition of the patients are responsible for changing gastric residual time.

Concomitant drug administration

Prokinetic agents such as metoclopramide and cisapride, propantheline opiates such as codeine and anticholinergic drugs such as atropine.[12-14]

Classification of Floating Drug Delivery

Depending on two formulation variable floating system are classified

Effervescent system

Non-effervescent system

Effervescent system

Effervescent compound and swellable polymer prepare the matrix type of system. The effervescent system is prepared by such mechanism so they touched gastric fluid, carbon dioxide release and gas entrapment in the swollen hydrocolloids hence system buoyant for longer duration of time. The effervescent system produces upward motion and maintains buoyancy. In recently the floating pill of multiple unit types developed which generates carbon dioxide gas.[3]

Swellable polymer: methylcellulose, chitosan

Effervescent compound: calcium carbnonate, tartaric acid, and sodium bicarbonate, citric acid, disodium glycerine, citroglycine.[15-17]

Noneffervescent system

Noneffervescent system floating dosage form is used different polymer such as a matrix producing polymer such as polyacrylate, polymethacrylate and gel forming type hydrocolloids, polysaccharides.

It contains a simple technique of mixing gel-forming hydrocolloid with the drug. The noneffervescent system floating dosage form is administered by an oral route so they touched the acidic material then it gets swell and attains <1 bulk density. The swollen matrix of the dosage form contains the air entrapped which increases buoyancy time. Swollen matrix act as a reservoir containing active drug is slowly released to achieve sustained release.[15]

Example of polymer:

1. Cellulosehydrocollids, highly swellable and gel-forming

Eg. Hydroxyethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose.

2. Matrix forming polymer and polysaccharide

Eg. Polystyrene, polyacrylates, polycarbophil.[16]

***In Situ* Gel**

In situ floating gel preparation is suitably delivered by orally as a liquid ' stimuli-responsive ' through a transformation to a gel in the stomach after touch with the gastric fluid. Thus they show a continuous and sustained drug release in recent times, enhanced patient compliance and decreased drug administration intensity compared to traditional drug delivery systems. The *in situ* gel can longer the gastric retention period of drugs. Extending gastric retardant time increases drug solubility, which in high pH is less soluble, increases bioavailability, reduced dose dumping and drug toxicity.[9,10]

Need For Floating *In Situ* Gel

Frequency of drug administration is increased in case of drug with regional action in stomach get quickly emptied and don't get enough retention period in stomach similarly rapid gastric transition from stomach produce low bioavailability for oral dosage form especially in case of API which shows their local action to avoid this problem floating system are produced.

The tablet/capsule floating formulation is needed to swallow as the whole unit. For the dose adjustment, it cannot break into half as they are designed for control or sustain release and floating ability also depends on the tablet dimension. The liquid floating formulation is not stable in comparison with tablet/capsule floating formulation.

Some children, elder patients, adult patient, and patients with certain state suffer from dysphasia. Hence tablet/capsule floating system are difficult to swallow. The tablet/capsule floating system is needed to available in different strengths for the dose adjustment. Hence the *in situ* gel formulation orally administered in aqueous solution form and gets converted into gel under certain polymeric conformation. Thus viscous gel of lower-density buoyont on gastric layer produces continuous and slow drug release for a longer duration of time. The low-density gel formation is called a raft.[3,18,19]

Mechanism of *In Situ* Gelation

The oral liquid *in situ* floating gel preparation is get converted into gel under environmental condition. Ion cross-linking, change in pH, change in temperature is responsible for *in situ* gel formation. Sodium citrate solution complex with the polymer solution of gellan gum, sodium alginate, pectin contain divalent ions formed complexes is a breakdown in the gastric physiological condition of gastrointestinal tract to release divalent ions (ca++). The ca++ ion is responsible for *in situ* gelation of an orally delivered liquid.

The *in situ* gel system forms a double-helical junction zone triggered by a double-helical segment accumulation to develop a three-dimensional network of cations and hydrogen bonding with water.[20]

Solution = ph or ionic cross linking or temp. Modulation → Matrix of gel

Phase transition system

Mechanism of the Floating System

To increasing retention time of stomach different system are used eg. swelling system, expanding system, high density system, mucoadhesive system, modified-shape system, gastric emptying delaying devices from this system floating drug delivery is mostly used.

Floating system has less bulk density than gastric content hence it float on a surface of gastric content without changing the gastric emptying rate for a longer duration of time. The system is buoyant in the gastrointestinal tract for a longer duration which slowly released the API. After the drug release, the residue emptied from stomach these results in controlling variation in plasma drug concentration as well as improve gastric emptying time.

F = F buoyancy -F gravity = (Df- Ds) gv---------- (1)

Where,

F= total vertical force,

Df = fluid density

Ds = object density

V= volume

G= acceleration due to gravity.[10,20]

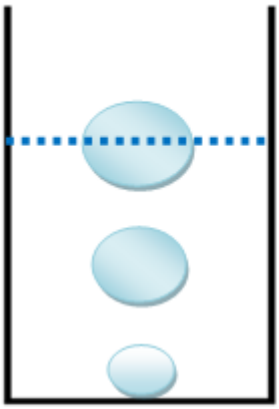

Fig1: Imbibition of gastric fluid

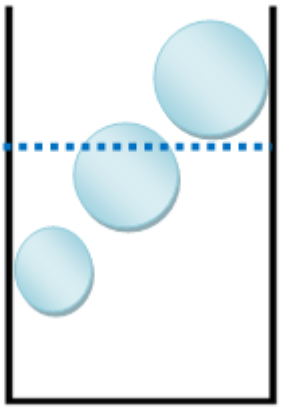

Fig2: Buoyant and swell

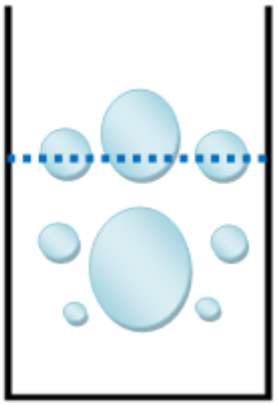

Fig3: Gas generating system (co2 release)

APPROACHES

Physical Mechanism

Swelling

Swelling is a physical type of approach. Water is absorb by polymer and expands to achieve the desired space to form a *in situ* gel. Glyceryl mono-oleate (myveol 18-19) substance is a 1400 polar lipid in nature that swell in water to form a crystalline phase structure of lyotropic liquid. Bio adhesive property are responsible for degradation by enzymatic action.[3]

In this type of approach, the polymer is present in an external environment which results in swelling from inside to outside and slowly release the API for a longer duration of time.[5]

Diffusion

Diffusion is a physical type of approach. Diffusion process occurs in polymer solution in which diffusion of solvent to surrounding tissue forms a precipitation and solidification of polymer matrix.

eg. N-methyl pyrrolidone is useful for the diffusion system.[3,5]

Chemical Reaction Mechanism

Ionic cross linking

The phase transition process occurs in the polymer in the existence of different ions. The polysaccharide is belonging to the class of ion-sensitive. Gellan gum is anionic polysaccharide which easily available as gelrite® it undergoes to *in situ* gelation in existence of mono and divalent cation such as ca++, k+, mg++ and sodium.

In the existence of divalent cations, the sodium alginate completes the gelation of *in situ* gel. The divalent cation is responsible for gelation of low methoxy pectin similarly gelation of alginic acid in existence of polyvalent or divalent cation.

eg. Ca++, block in alginate chain because of reaction with glucuronic acid.

Sodium alginate undergoes a *in situ* gel formation in presence of calcium chloride. Gellan gum go through *in situ* gelation in existence of sodium citrate.[3,21,22]

Enzymatic cross-linking

Enzymatic cross-linking is most convenient approach to form *in situ* gel. Body fluid contains an enzyme which is responsible for constructing *in situ* gel by enzymatic cross-linking. The body fluids containing the enzyme which causes cross-linking to develop a *in situ* gel. It is the most suitable approach for the preparation of *in situ* gel.[5,21]

Photo polymerization

The *in situ* gel is formed by using electromagnetic radiation. Electromagnetic radiation application was used to develop a gel by administering into a tissue site a mixture of monomers or reactive macromers and initiators. Polymerizable functional groups or acrylates are used on macromers and monomers because in the presence of photoinitiator they rapidly undergo photo-polymerization.

The polymer which containing a polymerisable functional group that undergoes the dissociation in existence of photo-initiators such as acrylates or the polymer has the long visible and ultraviolet wavelength. The biologically harmful wavelength is not used such as short wavelength.

Ketone like 2, 2-dimethoxy-2-phenyl acetophenone is initiator in ultraviolet polymerization approach. The visible light systems use camphorquinone and ethyl eosin as initiators.[5,22]

Physiological Stimuli Mechanism

Temperature-induced in situ gel system

Three Types of temperature in this system

1. Negatively thermosensitive type

Eg: Poly (N-isopropylacrylamine)

2. Positively thermosensitive type

Eg: Polyacrylic acid

3. Thermally reversible type

Eg: Pluronic, tetronics, poloxamer

In this type of system, body temperature is required for gelation no external heat is required. The temperature-induced system contains the thermoresponsive polymer or temperature-responsive polymer which has their own physical properties which undergo drastic and discontinuous change with the temperature. This system is used the stimuli-responsive polymer which can change their properties with the surrounding environment.

This polymer exhibits a miscibility gap at low or high temperature an lower or upper critical solution temperature exist. The range is 0-100ºc to exist as a solution at the upper critical solution temperature. In this type of system at room temperature the polymer solution are liquid in nature and converted to a gel in contact with body fluid by body temperature.

Solution is liquid in form at lower critical solution temperature form a gel by hydrogen bonding mechanism between polymer and water. Polymer-polymer interaction leads to change a polymer solubility with the use of suitable polymer.[5]

PH triggered system

In this system, a gel is formed by a change in pH. This system uses pH sensitive and pH responsive polymer. PH sensitive polymer is also called polyelectrolytes because they have an acidic or ionizable functional group. The polyelectrolyte mechanism for the formation of *in situ* gel is they can increase the external pH which causes hydrogel swelling to form a *in situ* gel

Polymers are used in the pH triggered system have an anionic group.

eg. Carbomer and derivative

Cellulose acetate phthalate (CAP)

Polyethylene glycol (PEG)

Pseudo latexes and ply methacrilic acid (PMC)

The polymers with a anionic group leads to an increase in pH which increases the swelling.

The polymer with a cationic group leads to an increase in pH which decreases the swelling.[5,21]

Table 2: Recent patents for *In situ* gel

US patent	Formulation	Reference
US20190167839	Absorbable *in situ* gel forming system, method of making and use thereof.	[23]
US20170266294	Pharmaceutical formulation that form gel *in situ*.	[24]
US20150099751	*In situ* gel loaded with phosphodisterase type v inhibitors nanoemulsion.	[25]
US20150111834	Recipe for *in situ* gel and implant, drug delivery system formed thereof.	[26]
US20150268193	Composition and method for gel electrophoresis with *in situ* calibration.	[27]
US20110082128	*In situ* gel ophthalmic drug delivery system of estradiol or other estrogen for prevention of cataracts.	[28]
US20070213453	Polyvinyl alcohols gels, especially *in situ* gelling gels.	[29]
US 20030143274	Medical uses of *in situ* formed gels.	[30]

Table 3: Marketed preparation of *In situ* gel

Drug	Technology	Product	company	Reference
Alginic acid & sodium bicarbonate	Effervescent system	Liquid gaviscon	Reckitt benckiser healthcare, UK	[31]
Antacid	Floating liquid form	Almagate flatcoat	_	[32]
Ferrous sulphate	Floating system of colloidal gel	Conviron	Ranbaxy, India	[31]
Aluminium & magnesium	Alginate floating liquid	Topalkan	Pierre fabre medicament, france	[31]

Table 4: Recent research work on floating *In situ* gel

Drug	Category	Treatement	Year	Reference
Moxifloxacin hcl	Antibiotic	Periodontitis	2019	[33]
Nifedipine	Calcium channel blocker	Preeclampsia	2019	[34]
Paracetamol	Analgesic & antipyretic	Dysphagic patient	2019	[35]
Ciprofloxacin	antibiotic	Helicobacter pylori infection & urinary tract infection	2019	[36]
Losartan potassium	Angiotensin receptor blocker	Hypertension	2019	[37]
Mitiglinide calcium	Antidiabetic	Type-II diabetis	2018	[9]
Meloxicam	NSAID	Improving anti-inflammatory action	2018	[38]
Azithromycin	Macrolide antibiotic	Peptic ulcer	2015	[39]
Metronidazole	antibiotic	Gastritis, peptic & duodenal ulcer	2015	[11]
Diltiazem hcl	Calcium channel blocker	Angiana and hypertension	2016	[40]

CONCLUSION

In situ gel are novel and commercially applied technique which can form a gel matrix from which drug molecule is released by controlled and sustained rate as compared to the conventional dosage form. It can improves the retention period of the stomach, increases the bioavailability of the drug, site-specific delivery (upper part of the stomach) which can increase the therapeutic index. It is a simple method for preparation, cost-effective and minimum time-consuming methods.

The *in situ* floating system is used for the drug which has a narrow window of absorption in GI and shows systemic as well as the local therapeutic effect in the stomach. The above mention type of drug available in tablet/capsule dosage form is suitable for the floating *in situ* gel. Hence it is the most suitable method than conventional dosage form.

ABBREVIATIONS

API: active pharmaceutical ingredient, GIT: gastro intestinal tract.

REFERENCE

Rathod HJ, Mehta DP, Yadav JS. A review on stomach specific floating in-situ gel. Int J Pharm Res. 2014;6(4):19–30.

Pareek R, Sharma PK, Sharma V. Contemporary Development in Floating Oral In-Situ Gel: A Review. Pharm Biosci J. 2019;7(3):1.

Bashir R, Majeed A, Ali T, Farooq S, Khan NA. Journal of Drug Delivery and Therapeutics Floating Oral In-Situ Gel : A Review. 2019;9(2).

Kumar S, Yagnesh N. An Update on Gastroretentive Floating Systems. World J Pharm Pharm Sci. 2016;5(11):476–525.

Sarada K, Firoz S, Padmini K. In-situ gelling system: A review. Int J Curr Pharm Rev Res. 2015;5(4):76–90.

Mohanty D, Bakshi V, Simharaju N, Haque MA, Sahoo CK. A Review on in situ Gel: A Novel Drug Delivery System. Int J Pharm Rev Res. 2018;50(1):175–81.

Rajinikanth PS, Balasubramaniam J, Mishra B. Development and evaluation of a novel floating in situ gelling system of amoxicillin for eradication of Helicobacter pylori. Int J Pharm. 2007;335(1–2):114–22.

Rajinikanth PS, Mishra B. Floating in situ gelling system for stomach site-specific delivery of clarithromycin to eradicate H. pylori. J Control Release. 2008;125(1):33–41.

Mahmoud DB, Shukr MH, ElMeshad AN. Gastroretentive Cosolvent-Based In Situ Gel as a Promising Approach for Simultaneous Extended Delivery and Enhanced Bioavailability of Mitiglinide Calcium. J Pharm Sci [Internet]. 2019;108(2):897–906. Available from: https://doi.org/10.1016/j.xphs.2018.09.020

. Nagarwal RC, Srinatha A, Pandit JK. In situ forming formulation: Development, evaluation, and optimization using 33 factorial design. AAPS PharmSciTech. 2009;10(3):977–84.

. Abou Youssef NAH, Kassem AA, El-Massik MAE, Boraie NA. Development of gastroretentive metronidazole floating raft system for targeting Helicobacter pylori. Int J Pharm [Internet]. 2015;486(1–2):297–305. Available from: http://dx.doi.org/10.1016/j.ijpharm.2015.04.004

. Shah DP, Jani GK. A newer application of physically modified gellan gum in tablet formulation using factorial design. Ars Pharm. 2010;51(1):28–40.

. Peppas NA, Bures P, Leobandung W, Ichikawa H. Hydrogels in pharmaceutical formulations. Eur J Pharm Biopharm. 2000;50(1):27–46.

. Qiu Y, Park K. Environment-sensitive hydrogels for drug delivery. Adv Drug Deliv Rev [Internet]. 2012;64(SUPPL.):49–60. Available from: http://dx.doi.org/10.1016/j.addr.2012.09.024

. Soppimath KS, Kulkarni AR, Rudzinski WE, Aminabhavi TM. Microspheres as floating drug-delivery systems to

increase gastric retention of drugs. Drug Metab Rev. 2001;33(2):149–60.

. Mohite S, Shah R, Patel N. Research journal of pharmaceutical dosage forms and technology. [Internet]. Vol. 10, Research Journal of Pharmaceutical Dosage Forms and Technology. 2018. p. 10–2. Available from: http://www.indianjournals.com/ijor.aspx?target=ijor:rjpdft&volume=10&issue=1&article=002

. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: A review. AAPS PharmSciTech. 2005;6(3):372–90.

. Xiao SH, Liu YY, Wei LH, Guo Y, Sheng Li Ke Xue Jin Zhan. [Advancement in researches of mast cell]. 2011;42(2):104–7.

. Bhatt P, Khatri N, Kumar M, Baradia D, Misra A. Microbeads mediated oral plasmid DNA delivery using polymethacrylate vectors: An effectual groundwork for colorectal cancer. Drug Deliv. 2015;22(6):849–61.

. Shendge RS, Jamdhade AA, Pande V V. Novel strategy in controlled gastroretentive drug delivery: In-situ floating gel. Int J Drug Deliv. 2014;6(3):230–43.

. Shinde SR, Sable P, Lodhi BB, Khan S. A novel approach of gastroretentive drug delivery : in situ gel. J Innov Pharm Biol Sci. 2014;1(1):39–59.

. Nirmal HB, Bakliwal SR, Pawar SP. In-Situ gel: New trends in controlled and sustained drug delivery system. Int J PharmTech Res. 2010;2(2):1398–408.

. Shalby S, Olbrich J, Corbett J. Absorbable *in situ* gel forming system, method of making and use thereof. US Pat Appl Pub.2019

. Baldwin JJ, Wei G. Pharmaceutical formulation that form gel *in situ*. US Pat Appl Pub.2015

. Mosli HAM, Attleiah AG, Bassossy HM, Helaal MHAM. *In situ* gel loaded with phosphodisterase type v inhibitors nanoemulsion. US Pat Appl Pub.2015

. Cheng F, Lu MJM, Ko Y, Lin M, Chou S. Recipe for *in situ* gel and implant, drug delivery system formed thereof. US Pat Appl Pub.2015

. Guadagno P, Erin S. Composition and method for gel electrophoresis with *in situ* CAlibration. US Pat Appl Pub.2015

. Adeyeye MC, Davis VL, Kotreka UK. *In situ* gel ophthalmic drug delivery system of estradiol or other estrogen for prevention of cataracts. US Pat Appl Pub.2011

. Muller R, Innerebner F. Polyvinyl alcohols gels, especially *in situ* gelling gels. US Pat Appl Pub.2007

. Viegas TX, Reeve LE, Henry RC. Medical uses of *in situ* formed gels. US Pat Appl Pub.2003

. Mandal UK, Chatterjee B, Senjoti FG. Gastro-retentive drug delivery systems and their in vivo success: A recent

update. Asian J Pharm Sci [Internet]. 2016;11(5):575–84. Available from: http://dx.doi.org/10.1016/j.ajps.2016.04.007

. Pawar VK, Kansal S, Garg G, Awasthi R, Singodia D, Kulkarni GT. Gastroretentive dosage forms: A review with special emphasis on floating drug delivery systems. Drug Deliv. 2011;18(2):97–110.

. Swain GP, Patel S, Gandhi J, Shah P. SC. J Oral Biol Craniofacial Res [Internet]. 2019; Available from: https://doi.org/10.1016/j.jobcr.2019.04.001

. Karemore MN, Avari JG. * Address for Correspondence. J Drug Deliv Sci Technol [Internet]. 2019; Available from: https://doi.org/10.1016/j.jddst.2019.01.025

. Sharma S, Sarkar G, Srestha B, Chattopadhyay D, Bhowmik M. International Journal of Biological Macromolecules In - situ fast gelling formulation for oral sustained drug delivery of paracetamol to dysphagic patients. Int J Biol Macromol [Internet]. 2019;134:864–8. Available from: https://doi.org/10.1016/j.ijbiomac.2019.05.092

. Pashikanti S, Jyothsna B. FORMULATION AND EVALUATION OF FLOATING IN SITU GEL OF CIPROFLOXACIN. 2019;11(1):2–8.

. Potassium L, Khan NA, Assistant S. No Title. 2019;10(4):2045–53.

. Jafar M, Salahuddin M, Bolla SR. Gastric floating in-situ gel as a strategy for improving anti-inflammatory activity of meloxicam. 2018;8(11):95–102.

. Jahangir MA, Muheem A, Saleem S. Formulation and Evaluation of Novel floating In Situ Gelling System of Macrolide Antibiotic Using different Gelling Polymers RESEARCH ARTICLE FORMULATION AND EVALUATION OF NOVEL FLOATING IN SITU GELLING. 2015;(September).

. Bobade NN, Pande SD. Formulation and evaluation of controlled release gastro-retentive in situ gel for diltiazem hydrochloride. Indian J Pharm Educ Res. 2016;50(3):S254–65.