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NAVIGATING THE DEEPER ROUTES OF CONTROLLED DRUG RELEASE - AN OVERVIEW OF FLOATING ORAL IN-SITU GEL: A RAISING TIDE IN NOVEL DRUG DELIVERY SYSTEMS

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ABSTRACT:

The current recapitulates erudite regarding the floating oral in-situ gel technique, which comes under the category of gastroretentive drug delivery system and sub-categorized under the floating technique. where the GRFDDS is one of the novel drug delivery systems. The recent biggest problem in the medical field was patient incompliance with the medications they take daily as the frequency of dosage form and stopping taking the medications due to their incompliance, or geriatrics may have the problem of dementia, which leads to patient comorbidity. If it is not treated properly, the condition of patients will become worsen to overcome these problems. The novel drug delivery system was adopted as the frequency of dosage form is reduced, exhibiting prolong effect and site-specific action of dosage form in the body and maintaining its safety and efficacy with their respective limits. Rapid gastric emptying was observed mostly in conventional tablets, which leads to low bioavailability, does not exhibit enough therapeutic activity, and delays the curing time of disease in the patients. We discuss about the critical role of polymers in the formulation of these systems, focusing on their concentration, mechanism and the ideal characteristics of drug candidates, to improve therapeutic outcomes and patient adherence.

Key words: Floating oral-in situ gel, Polymers, Buoyancy, Swelling time, GRT (gastric retentive time)

Introduction:

Persons to reach their destinations require some route maps and vehicles, just as the medication to reach its destinations means a specific target site in the body. It requires route maps, known as routes of administration, because it elicits its therapeutic activity in the body and cures worsening conditions, diseases, and disorders. There are various routes of administration like oral, nasal, topical, ocular, pulmonary, rectal, and vaginal in that mostly oral route of administration is preferred as patients exhibit compliance towards it, and there are different types of dosage forms available: solid like tablets, capsules, powders, and supplements; liquid like solutions, suspensions, emulsions, and gases like aerosols. As the new trends are following novel drug delivery systems in that most frequently solid type of dosage form are used and solids reach stomach and by there its journey starts where one of the revolutionary steps was recently founded few years back was gastro retentive floating drug delivery systems where oral in-situ gels adopted floating nature initially formulated as sol form after administration when it contact to various Ph nature present in body fluids and undergo sol to gel conditions by these its density become low and exhibits its actions by floating mechanism and increases the oral bioavailability as decreasing the gastric emptying time.

Advantages	Disadvantages
Reduces the dose frequency	Perfect storage conditions must be maintained; if not, the product may be degraded.
Sustaining and prolonging release are observed.	prolong exposure to the drug. There may be a chance of dose dumping occurring.
Site-specific action is exhibited	It requires a larger quantity of fluids to exhibit better floating.
Bioavailability was improved and increased.	As the final formulation is sol, there is more susceptibility to microbial growth.

Types of Mechanism/Classification/Floating Oral in-Situ Drug Delivery Systems

Floating mechanism

Effervescent:

The effervescent name indicates that the formation of gas bubbles when in contact with the gastric fluid due to the chemical reaction of formulation and gastric juice (Hcl) leads to the liberation of carbon dioxide gas. mostly sodium bicarbonate is used as effervescent, and citric acid and tartaric Acid is also used as a gas-releasing agent. The base of these systems was Matrix, prepared by using swelling polymers such as methyl cellulose and chitosan. These are further divided into two categories: **gas-generating systems and liquid-volatile systems.**

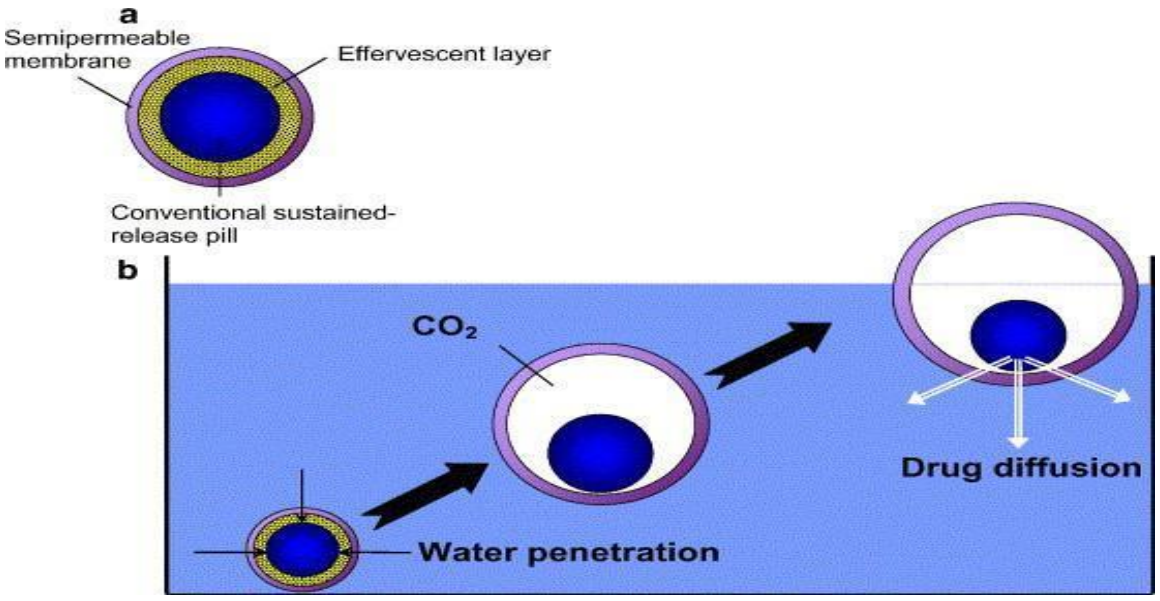

Figure -1: Diagrammatic representation of effervescent type of gastric drug delivery systems

a) gas generating systems

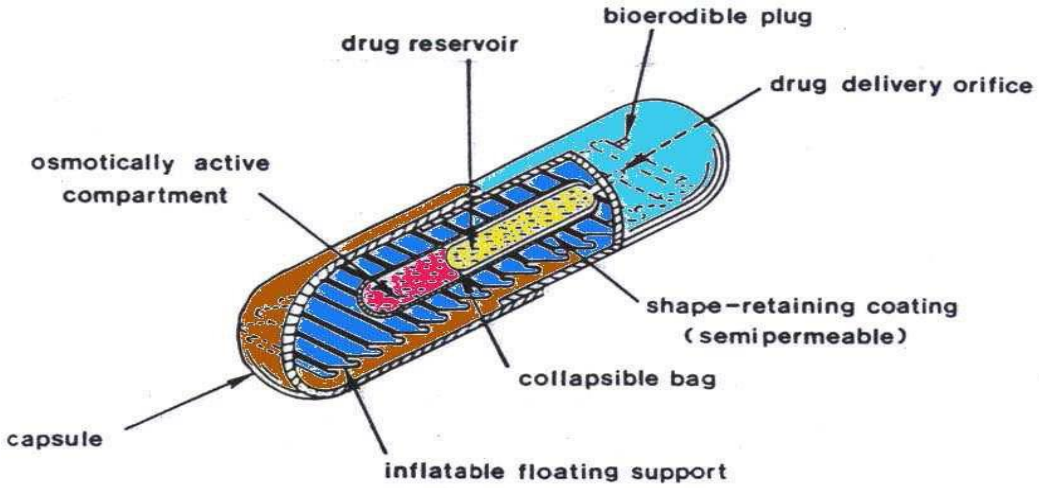

Figure -2: Diagrammatic representation of effervescent type of gastric drug delivery systems

b) liquid volatile systems.[18,19]

Non-effervescent: no generation of gas takes place, and this system is also based on the matrix type, where polymers are used most frequently: swellable cellulosic hydrocolloids, HPMC, SCMC, and polysaccharides. Mostly, the mechanism exhibited here was the swollen entrapment of gas and buoyancy, and these systems are further divided into

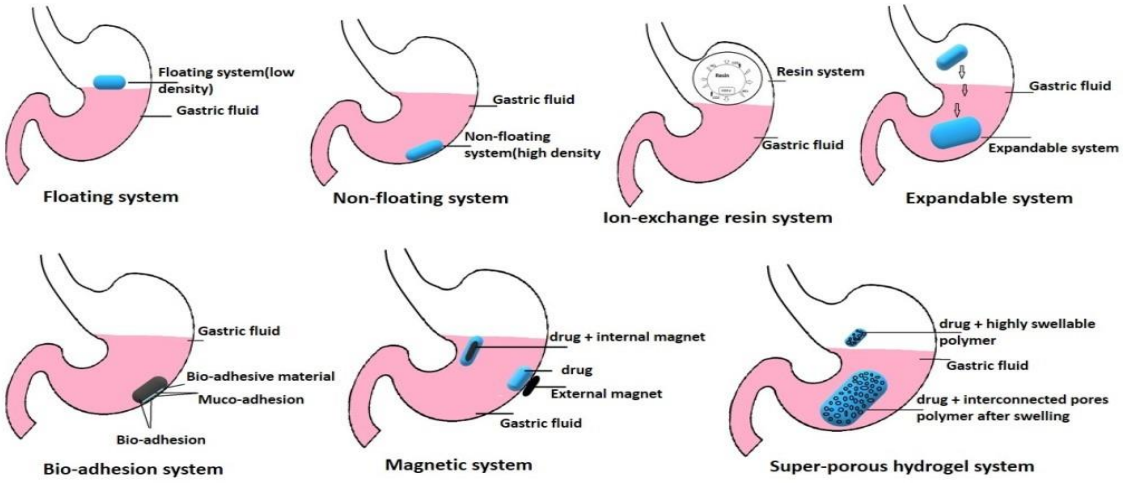

Figure –3: Diagrammatic representation of non-effervescent type of gastric drug delivery systems.[20]

In-situ gel mechanism

- **Thermally triggered:** the formulation remains in sol form below LCST, and after administration into the stomach, after attaining above LCST, it attains gel form and density and starts floating and releasing the drug in a controlled manner.
- The table below contains information about some drugs and polymers that used their key findings in formulation.
- **Ph-triggered:** The formulations maintain sol form at optimal ideal pH 7.4–7.8, and after administration, when contact with their respective surrounding biological fluids of different pH forms, gel and viscosity increase and contact time increases, thereby prolonging their action for a long duration.
- **Ion-triggered: A**fter administration, formulations get in contact with the targeted site biological fluids, which possess ions, either cationic or anionic. This plays a vital role by crosslinking the ions and the sol form of the formulation to form a gel. In the case of ocular formulations, tear fluids contain cations like Na+, Ca2+, and Mg2+ and form a gel, thereby increasing contact time on the surface.
- **Enzymatic cross-linking: t**he enzymes that are present in the body are used as cross-linking agents after contact with the enzymes that are present in the body fluids. Some enzymes act as proteins that are used for gel formation, like casein and hydrocolloids, which exhibit gel mechanisms by unfolding their structure and leading to gel formation as 3-D protein structures are formed after cross-linking.
- **Photopolymerization:** photo means light and polymerization mean formation of polymer molecules as light focus. The monomers units of polymers are formed as gels after administration of formulation at the site of administration. The electromagnetic waves are passed externally from the tissue and breakdown the polymeric structure. The polymeric network is formed and acts as the backbone in gel formations.

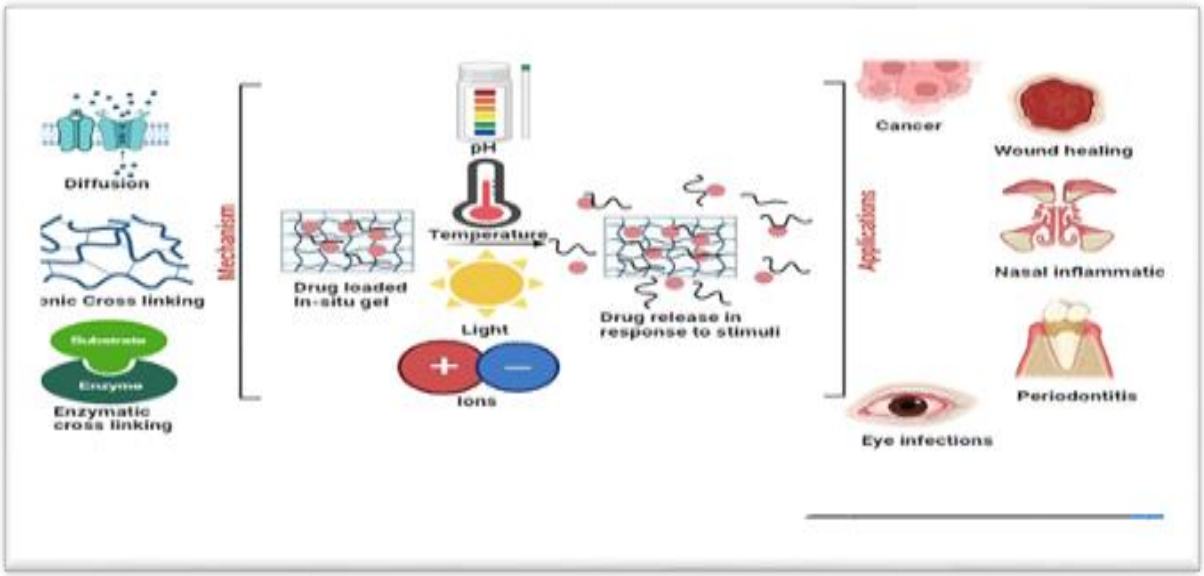

Figure –4: Diagrammatic representation of different mechanism of in-situ gel & its applications.[20]

Drug candidate criteria requirements

1. Drugs that are less stable in the intestinal environment and degraded by intestinal and colon bacteria.
2. drugs to prolong oral bioavailability.
3. drugs that exhibit a narrow therapeutic index
4. Drugs that are unionized at the gastric pH are absorbed by multiple gastric sites (stomach, upper, lower, and duodenal).
5. Drugs that are highly acidic are suitable.
6. Drugs that are used to treat diseases in the stomach region by exhibiting their local actions.

Ideal characteristics of floating oral in situ gel

Floating oral in-situ gel is a novel and innovative drug delivery system that is used to retain the drug for some duration in the stomach.

1. Buoyancy and gastric retention as the density of the dosage form is reduced, the product gets buoyant and floats in stomach fluids, and retention time is increased.
2. gelling mechanism as the drug, when contact with gastric fluids, covers its nature by sol to gel.
3. The optimal viscosity of floating oral in-situ gel was 72.67 to 596.33 cps.
4. The optimal pH range for floating oral in-situ gel was 7.44 to 7.88.
5. Usually, the lag time should be 14.67 to 73 seconds.
6. The optimal drug content released by oral in-situ gels was 49.139 to 71.471%.

Factors affecting gastric retention time

1. **1.Density:** Density plays a vital role. If it should be lower than gastric content, it exhibits low density and starts floating at the top of the stomach area, and the optimal density is 1.004 g/mL for optimum drug release.
2. **2.Size:** if the size of the floating oral in-situ gel is greater than 7.5mm (about 0.3 in), it increases gastric retention time as the drug is released in an extended and prolonged manner, or if the diameter is 9.9mm (about 0.39 in) and is considered smaller, this is the optimum range of diameter to maintain the GRT.
3. **3.Shape:** floating oral in-situ is initially designed as a tetrahedron shape, as a ring shape is essential for gel floating and exhibits prolonged release up to 24 hours.
4. **4.Meal composition:** if high-calorie food is consumed, then it contains a greater quantity of fats and proteins and thus remains GRT for up to 4–10 hours. Based on the patient's food intake, the GRT is dependent. The order of caloric content increases; the GRT was fats > proteins > carbohydrates.
5. **5.Food content: in the** fed state, the GRT is high and sustained release of the drug was established, and in the fasting state, the GRT is low and the elimination of the drug from the body is faster.
6. **6.Age:** the GRT is directly proportional to the age increase; the GRT also increases at a young age. And at age > 70 years, I observed very long GRT.
7. **7.Posture: The** GRT rate is delayed when the subject is in a in a supine or left lateral position.
8. **8.Emotion state:** in cases of anxiety or under any other stress conditions, the GRT rate decreased, and in cases of depression, the GRT was retarded.
9. **9.Number of meals: if** the quantity of meals is high, the GRT is prolonged. As the number of meals increases, the amount of food increases.
10. **10.Gender: The** GRT in males was less (3.4) hrs. compared to females (4.6) hrs. These are because of hormonal changes and physiological variations and take time to empty.
11. **11.. Administration of drugs:** administration of some drugs retards the GRT. like atropine belongs to the classification of parasympathomimetic blocks the action of acetylcholine, where (Ach) is a neurotransmitter that stimulates the action of smooth muscles and thus exhibits action on stomach mobility by retarding the gastroretentive time in a prolonged manner.

Ideal characteristics of polymers

1.The polymers should be inert and biocompatible.

2.The polymers must be able to exhibit optimal adherence capacity.

3.It should exhibit non-Newtonian flow and follow pseudo-plastic behavior where the shear rate of the fluid is increased.

4.It should have good tolerance and optical capacity.

5.It should influence tear behaviors, where tear behaviors explain the tear nature of a polymer under stress conditions. If quick or sudden stress is applied, less stress is observed, and if less stress is applied, more stress is observed.

Table –1: Compare the floating oral in-situ gel over conventional dosage forms

Floating oral in –situ gel	Conventional dosage form
Easy to prepare the formulation as process parameters are less.	Difficult to prepare as process parameters are more.
Patient compliance is more	Patient compliance is less
Less time for formulate a dosage form	More time is consumed to formulate a dosage form
Increases gastric residence time for some drugs	Decreases gastric residence time for some drugs
Suitable to treat local and some systemic diseases	Not suitable to treat all type of local diseases
Little bit of side effect and no risk were observed	High risk and more side effects are observed
Manufacturing investment is less	Manufacturing investment is more

Table -2: Types of polymers

Types of polymers	nature	Conc (%)	mechanism
Xanthan gum	natural	18	Optimized viscosity at low concentrations
Gellan gum	natural	0.4	High gel strength and maintain high strength
Karaya gum	natural	1	Rapidly absorbs water and swells
Psyllium gum	natural	10-20	Maintain the release retardant properties
pectin	natural	0.75	Covert into divalent ions for cross linking
xyloglucan	natural	1.5 w/w	Exhibit swelling properties on heating
chitosan	natural	0-70	Excellent Site-specific delivery
Sodium alginate	natural	2.5 w/v	Form gel when crosslinks with a crosslinking agent
Guar gum	natural	0.5-1	It remains stable at pH 5-7 and not affected by ionic strength or pH
Alginic acid	synthetic	4%w/v	Act as matrix
HPMC	synthetic	0.5-1.5	Dissolution enchaner Extended-release agent
N-polyacrylamide	synthetic	5-20%	Cross linking agents of the gel and collapse around the 32-degree temperature
Carbopol	synthetic	0.8 w/v	Ph dependent stays sol form at gastric pH and low viscous gel at alkaline pH
Poloxamer	synthetic	20%	At room temperature behaves as mobile viscous liquid
Sodium citrate	synthetic	0.5-0.75	Delays in a sugar acid system by reducing the number of hydrogens bonds and accelerates in a sugar -calcium system by reducing electrostatic repulsion
Poly DL-lactic acid	synthetic	Conc independent	Direct condensation of Latic acid monomer and produce PLA used for gel formation
PEG	synthetic	3.5-5 mmol/L	Interact with substances and produces free radicals' polymerization and functional group reaction

Preparation of floating oral-in situ gel: The major ingredient in the preparation of floating oral in situ was a gelling agent, and the gelling polymer was dissolved in distilled water. A crosslinking agent also plays a vital role as the gelling agent forms crosslinking, which leads to gel formation. As the sample was initially in liquid form at room temperature, the final formulation can be powered by using different techniques like lyophilization and spray drying, generally in this preparation, a gum, a semipermeable layer, a crosslinking agent, a polymer matrix, and a drug are present.

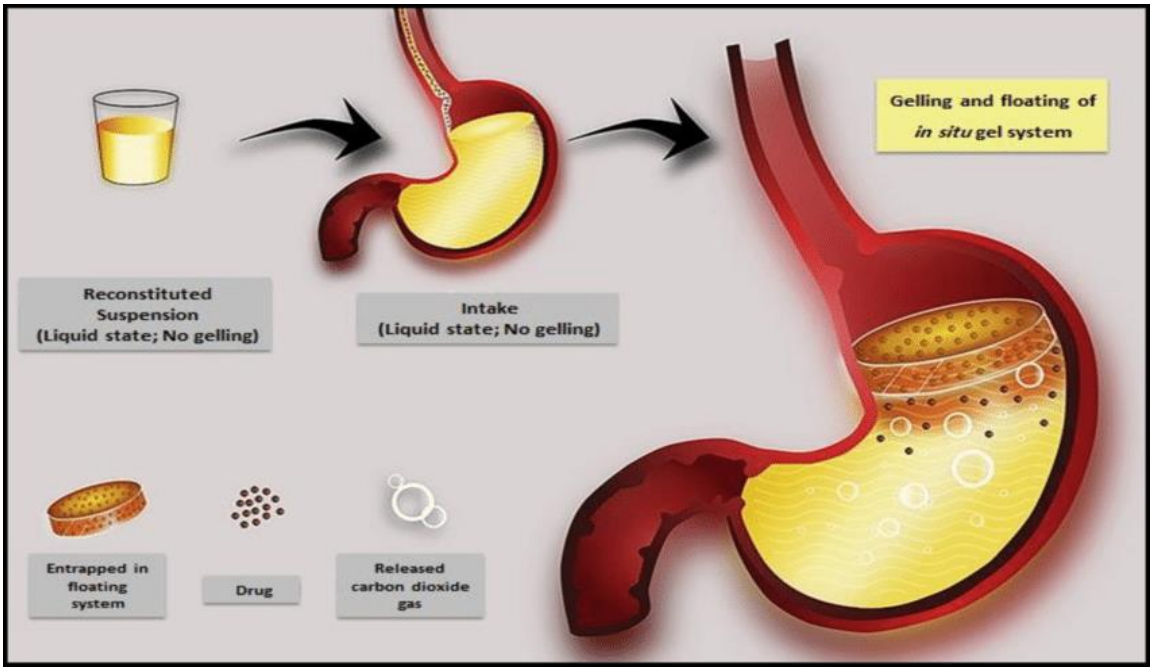

Figure-5: Diagrammatic representations of gelling & floating of in situ gel systems.[21]

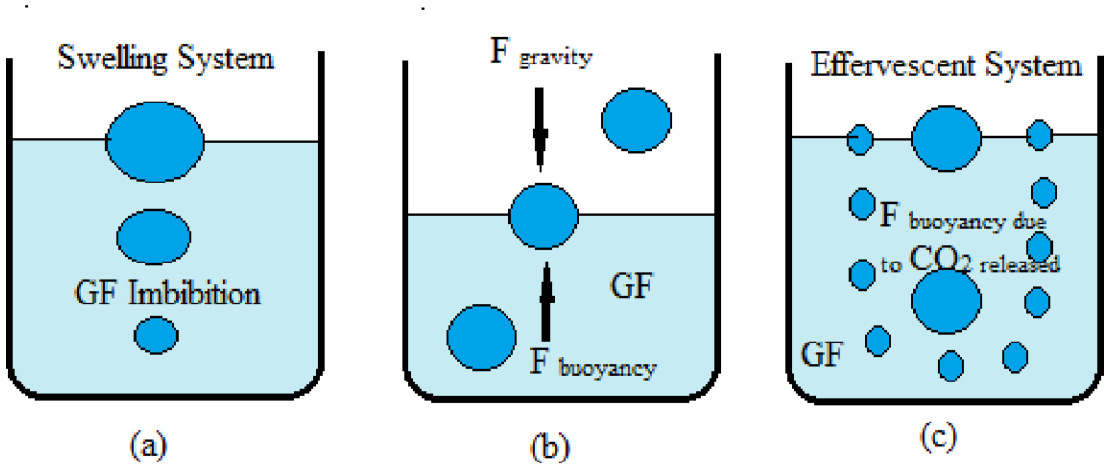

Figure-6: Mechanism of floating oral in situ gel after administration into body .[22]

$$F = F_{buoyancy} - F_{gravity} = (Df - Ds)\, gv$$

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

Table –3: Marketed formulations

s.no	Drug name	Brand name	Manufacturing company	indication	Dosage form	dose
1.	Levodopa +benserazide	Modapar	Roche	Parkinson	Floating controlled release capsule	200-50 mg
2.	misoprostol	Cyto tech	Pharmacia	Stomach ulcers	Bilayer floating capsule	200 mcg
3.	Magnesium antacid	Topalkan	Pierre Fabre drug France	Indigestion heartburn	Floating liquid alginate preparation, suspension	60mcg
4.	Aluminum hydroxide, magnesium carbonate	Liquid gavison	Glaxo smith Kline	Treats occasional Heart burn Indigestion Stomach upsets	Effervescent floating liquid alginate preparation, suspension	254 mg; 237.5 mg
5.	Ferrous sulphate	conviron	Ranbaxy	anemia	Colloidal gel forming FDDS	200 mg
6.	diazepam	Valrelease	Hoffmann -laroche	Anxiety spasticity	Floating capsule	15 mg
7.	Ciprofloxacin	Cifran OD	Ranbaxy	UTI, STD, LRTI	G-2 as generating floating tablets	500 mg
8.	baclofen	Baclofen GRS	Sun pharma	Muscle relaxer	capsule	30 mg
9.	Metformin Hcl - LP	metformin	Galenix	Anti diabetic	tablet	500 mg
10.	Tramadol LP	tramadol	Galenix	Opioid analgesic	tablet	100 mg

Evaluation test :

1.Physical appearance: As initially the formulation is liquid in state, a clarity test needs to be performed. To perform these tests, a white and black background and a tube light are required, and the sample is placed under the two different backgrounds to check for clarity. The sample should also be free from particulate. Thus, the sample passes the test.

2.Ph: The pH is checked using a digital pH meter, and it should be calibrated before and after the test.

3.Isotonic evaluation: any formulation that is in solution and administered into the body should exit isotonicity. Basically, tonicity explains the osmotic pressure the sample exhibits. The ideal isotonicity is equal to body fluids, mostly to maintain isotonicity at 0.9% w/v Nacl solution. If isotoncity is not maintained properly, either hypertonic (increased concentration) or hypotonic (decreased concentration) solutions may not be able to be administered to the body.

4.Viscosity: the viscosity of sol to gel is determined by using a Brookfield viscometer, either cone or plate model. The sample is placed, and based on the requirements, the speed of the spindle is fixed at a certain rpm, and the viscosity is determined as the sample exhibited thixotropic and rheological properties. Plays an important role in the ease of administration.

5.Gel strength: gel strength basically depends upon the gelling agent we used in the formulation. The gel strength is measured by a rheometer, where gradually the load is placed on the aqueous gel and the change in strength is determined. If gel exhibits higher and lower strength, it indicates less stability, durability, loss of buoyancy, and inadequate drug release.

6.Gel capacity: a suitable buffer is prepared, and 2–5 ml (about 0.17 oz) of sample is taken in a vial. The dying agent is used as an indicator for the final detection of gel, and if the result

(+) gel form after a few minutes and disperse rapidly.

(++) Gelation occurs immediately and lasts for several hours.

(+++) immediately gelation occurs, remains extended period. (7)

7.Floating study: the suitable stimulated dissolution medium is selected and poured into the dissolution vessel type II, and 10 ml (about 0.34 oz) of sample is placed. The time taken by the sample to float is denoted as floating time. In this floating study, we can study both FLT (floating lag time) and DOF (duration of floating).

Result :

1. Low gelling capacity = (+) FLT-immediate gelation; DOF <12 hrs.

2.immediate gelling capacity (++) FLT: immediate gelation; DOF<12 hrs.

3.high gelling capacity (+++) FLT: immediate gelation; DOF: >24 hrs.

8. **In vitro drug release: a** suitable buffer is prepared, a dissolution apparatus type is used, the sink condition is maintained, and samples are withdrawn based on the time interval points. The samples are then subjected to UV visible spectroscopy. The lambda max is fixed based on the drug used, and the purpose of spectroscopy is to determine concentration by predicting the drug release with respect to the time interval.

9.**Stability**: stability is used to predict the (t90) shelf life of a product. where the samples are exposed to different temperatures and the degradation of the product is determined. For a product, the expiration date is fixed before the time it should be used. According to the ICH guidelines, the stability test was conducted, and samples were collected and subjected to analysis. Storage can be predicted with respect to time.

10.Texture analysis: The purpose of texture analysis is to provide information about the mechanical properties of a formulation, mainly hardness, compressibility, and adhesiveness. These properties can be directly correlated with sensory parameters, like in vivo, and therefore, the obtained information is used in the development of products with desirable attributes that contribute to patient acceptability and compliance. The consistency, firmness, and cohesiveness of an in-situ gelling system are assessed using a device called a texture profile analyzer. Higher values of adhesiveness in gels are needed to maintain intimate contact with the mucus surface.

11.Swelling index: the quantity at which the gel was formed is taken, and now remove the excess quantity of buffer after the gel forms and note the weight, which is considered the initial weight of the sample. Now place the sample in the distilled water and leave it for hours. Again, reweigh the gel and consider it the final weight. By these, we can determine the fraction of water observed or water required for swelling.

12.Spreading coefficient: The spreading coefficient was determined by a device or an apparatus. The device consists of a ground glass slide that was fixed to the wooden block. Each formulation, weighing about 2 g, was placed on the ground slide. On top of these, another glass slides of the same dimensions are placed, with the second slide containing a hook. A weight of 1 g was placed on top of the two slides for 5 minutes to expel air and provide a uniform film of gel between the two slides. The measured quantity of weight was placed in the pan attached to the pulley with the help of a hook. The time (in seconds) required by the top slide to separate from the ground slide was noted. A shorter interval indicates a better spreading coefficient. The result is calculated by using the following formula:

$$S = (M \times L) / T$$

Whereas;

S = spreading coefficient; M = weight tied to the upper slide; L = length of the glass slides.

T = time taken to separate the slides (7)

Application

1.Sustainable and controlled formulations can be formulated there by prolonging release, reducing dose frequency, and improving patient compliance.

2.Targeted drug delivery can be achieved as the drug is released at a specific site and reduces the disease.

3.Local effects were exhibited by the floating oral drug delivery system to treat the diseases present in the stomach upper and lower regions.

4.Floating oral in situ gels are used for various diseases like peptic ulcers, helicobacter, gastroenteritis, gastritis, hiatal hernia, atrophic gastritis, gastric cancer,

5.Drugs with a narrow therapeutic index can be formulated as in situ gels.

6.Through in situ gel, not only oral administration, but also novel drug delivery systems like occult, vaginal, rectal, and nasal.

Current challenges :

Every problem has a solution, and to reach that solution, the research faces some hurdles and obstacles to reach the extent and formulate an optimized dosage form. As the article discussed the floating oral in situ gel during the formulation time, the researcher faced some challenges like

1. gastric retention time: as the formulations that are in solution form rapidly undergo the GRT and lead to less bioavailability, to overcome this challenge, floating oral in situ gels are formulated and increase the GRT by forming a gel and floating on the surface of the stomach. The bioavailability of the drug increases.

2.Bioavailability enhancement: the drug's bioavailability is increased by the floating oral in situ gel as the sol form is converted into gel form, the contact time of the drug in the stomach region increases, elimination phases are reduced, and the drug exhibits a longer duration of action.

3. Stability **issues:** as the formulation is in solution form at room temperature, an attack of microorganisms may occur, and a change in pH also leads to product degradation.

4. **Fluid requirements:** to form the gel, the sol requires enough fluid to float at the surface and exhibit a prolonged duration of action.

5. **Storage**: any pharmaceutical formulation needs to be stored in proper conditions until its expiry date and needs to be stored as specified by the manufacturer. The manufacturer. The storage of liquid dosage forms is more tedious than the storage of solid dosage forms. To prevent the degradation of the product, floating oral in situ gels are stored in leak-proof bottles.

Future prospective :

The possibility that thi**s** can happen in the future by overcoming the challenges and setting up the new revised trends, as well as meeting the market specification on time based on the customer's criteria and demand, some of the possible outcomes that can be obtained as future prospects for floating oral in situ gels are

1. **Enhanced gastroretention:** to develop more dosage forms that exhibit a narrow therapeutic index as the formulation initially forms in sol form and, after administration, gel formation occurs and maintains the buoyancy of the gel, the sample floats at the surface and exhibits a longer duration of action in the body.

2. **Herbal medicaments:** as the herbs are the boon from the god and these are the traditional medicines that have treated many problems, the herbs are also following the new trends, and as a novel approach, the herbs are also formulated as floating oral in situ gels, which enhances the drug delivery under the division of herbs.

3. **Water-soluble polymers:** using water-soluble polymers in the preparation of floating oral in situ gel enhanced the acceptability, controlled the release pattern of drug delivery, maintained its stability, and improved the gel responsiveness as exposed to external stimuli.

4.L**iquid oral with sustained release:** Floating in situ gel systems have set a new trend in the development of liquid oral dosage forms with sustained and controlled release, which are typically poorly water-soluble or unstable in intestinal fluids.

Conclusion :

Based on this bibliography, we would like to conclude that floating oral in situ gels took an innovative step for the future and paved a path under novel drug delivery systems, especially in the case of precise targeting, prolonging the duration of drug action, reducing the frequency of doses, and improving patient compliance. As the technique exhibit some of the ambivalent characters leads to the limitations at present researches are more focused to overcome these issues by collaborating with (R & D) department and these wings fully realize their clinical utility and follows the rules of conduct for deliverance to the market.

Few recent research and review works on floating oral in situ gel

1. Formulation, Development and Evaluation of Floating Oral In-situ gel containing Ivabradine. (2021)
2. The development of an in-situ biopolymer-based floating gel for the oral delivery of metformin hydrochloride. (2023)
3. Floating Drug Delivery System: Applications Based on In Situ Gel. (2022)
4. Development of Oral in Situ Gelling Liquid Formulations of Garcinia Extract for Treating Obesity (2023)
5. Preparation and In-Vitro Evaluation of Floating Oral In-Situ Gel of Montelukast Sodium. (2022)
6. Formulation and Evaluation of Gastroprotective. In Situ Gelling System of Ketoprofen. (2023)
7. Preparation, in vitro and in vivo characteristics of floating in situ gel of carvedilol using semi-synthetic and natural polymers to enhance the oral bioavailability (2023)
8. Formulation Design & Development & In-Vitro Evaluation of Dyslipidemia statin drug of floating oral in-site gels using pH dependent natural polymers by SOL-GEL transfer technique. (2023)
9. Formulation Development & In-Vitro Evaluation of Gastro Retentive Drug Release of Floating Oral Liquid In – Situ Gels Contains HMG-CoA Reductase inhibitor Fluvastatin by using Natural polymers (2023)
10. Floating oral insitu gel: A review. (2024)
11. A review of polymers for in situ drug delivery systems. (2024)

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