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SODIUM ALGINATE AS A CARRIER FOR ORAL GASTRORETENTIVE IN- SITU GELLING SYSTEM: AN INSIGHT REVIEW

Vanshika K. Sahu*, Vikrant P. Wankhade, Dattahari N. Dhage, Ninad Burkhande, Sanket Rankhamb

Department of Pharmaceutics, Vidya Bharti College of Pharmacy, Amravati 444602, India.

Abstract:

Over the past ten years, in-situ gelling drug delivery devices have attracted a lot of attention. They are in a sol state prior to delivery, and they get converted to gel when exposed to a wide range of physical stimuli, including changes in temperature, pH, and the presence of ions. One of the natural polymers employed frequently in protein and drug delivery systems is alginate. Oral administration of liquid dosage forms with in situ gelling properties may be beneficial for elderly patients who have difficulty swallowing. Numerous uses for sodium alginate have prompted researchers to concentrate on developing novel in-situ gelling systems. Oral sustained release drug delivery has several advantages over other dosage forms, such as simpler dose administration, increased patient compliance, formulation flexibility, and cost effectiveness, and is therefore receiving more and more attention in the pharmaceutical industry. The chemistry of sodium alginate, the rationale for using alginate as a carrier for oral in-situ gelling systems, the principle of in situ gel formation, the method for preparation of oral Gastroretentive in-situ gel, and a literature survey on alginate-based oral in-situ therapy for various therapeutic agents have been discussed in this paper. This article provides a comprehensive review of alginate's current status and advancement in the sol-to-gel transition phase. The future of alginate polymer applications in pharmaceutical and biomedical research is bright. Alginate's safety, biocompatibility, and ease of preparation are some of its most significant features. The demand for the development of liquid oral controlled-release drug delivery systems increased due to the expected improvement in patient compliance and flexibility of dosing. Overcoming the potential for dose dumping was necessary for the area's advancement. This prompted researchers to use a variety of gastro-retentive techniques to prevent dose dumping once the rigid gel structure in the intestinal environment was destroyed. As a result, researchers must update the developments in alginate-based drug delivery systems, and this review provides advice for future study.

Key words: *In-situ gelling systems, Drug Delivery, Sodium Alginate, pH induced ion gelation, sol to gel transition.*

Corresponding author:

Vanshika K. Sahu,
M.Pharm student,
Vidyabharti College of Pharmacy,
Camp Road, C.K. Naidu Road, Amravati, India 444602
Email: vanshikasahu347@gmail.com

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INTRODUCTION:

The most popular dose forms for oral administration are tablets and capsules, although they might cause issues for elderly or very young patients who have swallowing issues. For instance, 26% of patients over 75 in Norway who participated in a survey reported having trouble swallowing pills. Unfortunately, these issues may cause patients to open capsules or crush tablets, which could negatively impact the formulation's release characteristics, pharmacokinetics, and therapeutic effectiveness. Dysphagia-related issues are getting worse as the percentage of elderly people in the population rises. The use of liquid formulations, which are typically easier to swallow, improves compliance. Liquid dosage forms with in-place gelling capabilities can be given orally to elderly patients who have difficulty swallowing [1]. However, due to the unpredictability of gastric emptying time, conventional liquid formulations are typically linked to variable bioavailability. Formulating liquid dosage forms that gel in the gastrointestinal environment helps to maintain the therapeutic level for a prolonged period of time and increases the residence time in the gastrointestinal system and bioavailability [2]. Any delivery system's objective is to deliver a therapeutic dose of medication to the right region of the body on time frame in order to achieve the desired drug concentration [3].

The peculiarity of the majority of in-situ gelling drug delivery methods is that they must first be in a sol-state before being administered and must then go through gelation in the body. Because of this, they have a reduced administration frequency, improved patient compliance, and maintained drug release at the administration site. They are also characterised by ease of administration, prolonged residence time, and sustained drug release. The fact that these formulations can be taken by a variety of methods to achieve a local or systemic effect of the medication loaded is one of the factors contributing to their enormous success. Moreover, they work well as vehicles for nano- and micro-drug delivery system [4].

One of the key methods for creating successful GRDDSs is to develop buoyant systems, which have a bulk density lower than gastric fluid (1.004 to 1.010 g/mL). In general, adding swelling enhancers or wicking agents, as well as incorporating effervescent combinations, can result in the dosage form's overall floating behaviour [5].

The Gastroretentive in situ oral gel system, which is a floating system, has been extensively utilised to deliver antacid medication. The in situ oral gel system's suspension state ingredient mixture gelates in the stomach as a result of the pH change. In addition to calcium carbonate, calcium chloride, and sodium citrate being employed as cross-linkers, Gellan gum and sodium alginate are widely used as polymers [6].

Floating drug delivery systems have the remarkable ability to prolong drug buoyancy in the stomach without specifically affecting how quickly the stomach empties. This produces the desired prolonged stomach retention duration and delayed drug release rate from the system, which offers effective drug plasma concentration variation control [7].

Antacids and other medications for GIT disorders and infections have been successfully delivered using raft-forming systems, according to reports. According to reports, after coming into contact with stomach liquid, a thick, linked gel forms. In this, every component of the fluid is consistently referred to as a raft. The raft acts as a raft on the gastric juice's surface. These systems often include gel-forming polymers, alkali bicarbonates, and carbonates, which cause the creation of CO2 in the gastric fluid, which is used as an antacid and to treat gastroesophageal reflux by producing an in-situ raft floating system. The floating raft serves as a barrier between the oesophagus and stomach and keeps gastric contents from entering an oesophagus [8].

Alginate (ALG), Gellan gum (GG), and pectin (PEC) are examples of several anionic polysaccharides that are ion-sensitive polymers that are cross-linked by monovalent (Na+) and/or divalent (Mg2+ and Ca2+) cations found in a variety of physiological fluids, including saliva, tears, nasal fluid, etc. The sol-gel transition caused by the cross-linking mechanism results in the creation of a robust gel. Cross-linked polymer viscosity and sol-gel transition rate are influenced by the cation type and concentration [4].

Chemistry of Sodium Alginate:

Alginates are among the most adaptable biopolymers and have a variety of uses [9]. Alginates are homopolymeric MM or GG blocks that are interspersed with heteropolymeric MG or GM blocks. Alginates are linear, unbranched polysaccharides that include different units of BD mannuronic (M) and a-L-guluronic acid (G) residues that are 1,4-linked by glycosidic linkages. Molecular structure of Sodium Alginate is depicted in the Fig. 1. Sodium alginate is a natural polymer with biocompatibility and pH-sensitive gel-forming properties [10]. Alginates from various sources have varied block proportions. When alginic acid is hydrated, a high-viscosity "acid gel" is produced as a result of intermolecular interaction. After gelation, the water molecules are still free to

move but are physically restrained inside the alginate matrix. In several applications, such as the use of alginate gels for cell immobilisation or encapsulation, this is of utmost significance [9]. The chemistry, configuration of polymer blocks, and molecular weight of the alginates are crucial elements that affect the physical properties of the gel that is produced. Cross-linkers for the functional groups of alginate chains are divalent cations. Alginate produces stable, reversible gels at room temperature when multivalent cations are present and moderate formulation conditions are used. Gel formation is dependent on ion binding (Mg^{2+} <<Ca^{2+} <Zn^{2+} < Sr^{2+} <Ba^{2+}) and homogeneous gel formation involves considerable cation addition regulation. Although zinc ions have been employed to create alginate particles, calcium is the most commonly used cation because it is thought to be therapeutically safe, practical, and affordable [10]. The most notable characteristic of the alginate molecule, which is primarily related to the current and future uses of alginates, is the sol-gel transition in the presence of multivalent cations, such as Ca^{2+}, which is almost independent on temperature [11]. The biochemical and biophysical characteristics of alginates are consequently determined by their chemical structure, including their gel strength. As a result, different alginates and alginate formulations are likely to behave differently in the GI environment [10].

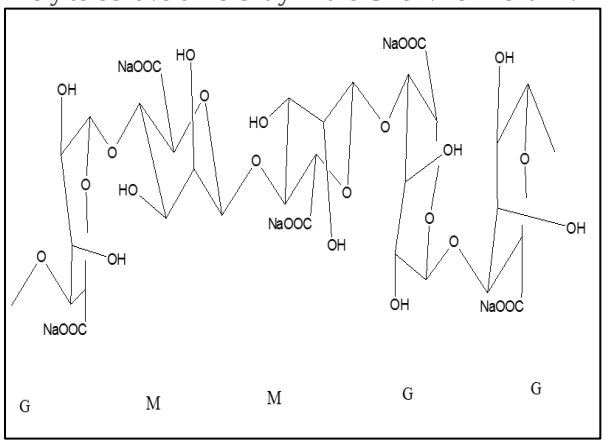

Figure 1: Molecular structure of Sodium Alginate.

Alginate's capacity to gel results from the abundance of free hydroxyl and carboxylic groups that are available. Alginate acquires its polyelectrolyte character as a result. The presence of divalent cations, which encourage the association of helical parts of the polymeric chains via connection zones, is what causes alginate to form gel [12]. Alginate has various features that make it a potential biopolymer suited for the design of controlled-release systems aside from its usage as a food additive. When an alginate matrix is hydrated, it forms a gelatinous layer that can act as a drug diffusion barrier [10].

Due to its special physical characteristics, alginate is a non-toxic gel-forming substance that may primarily be employed as a liquid gel-forming substance. An organic macromolecule called alginate that is non-toxic and biodegradable can be utilised as a scaffold. It is cross-linkable with other compounds and stable in an acidic environment [13].

In both acidic solutions and ethanol (95%), sodium alginate is essentially insoluble. It becomes a gel when dissolved in water and can therefore be used in GDDS. It is marketed in a variety of ways. Several variables, such as % and the presence of specific ions, have an impact on viscosity. Moreover, it diminishes at a high pH. In this review, some researchers discuss their investigations into the involvement of sodium alginate in various in situ gelling drug delivery systems [14].

Gastroesophageal reflux disease symptoms are treated with sodium alginate. Sodium alginate precipitates and turns into a gel when mixed with acid. As a result of the reaction between gastric acid and bicarbonate-containing alginate formulations like Gaviscon, carbon dioxide is released, and the gas is then trapped in the gel precipitate, forming a "raft." On the other hand, if the dosage form has a lower density than that of gastric fluid, which is 1.004 g/cm^3, an alginate formulation without gas production creates a "raft" in the stomach. The raft development seen during esophagogastroduodenoscopy (EGD) is depicted in below Fig. 2 [15].

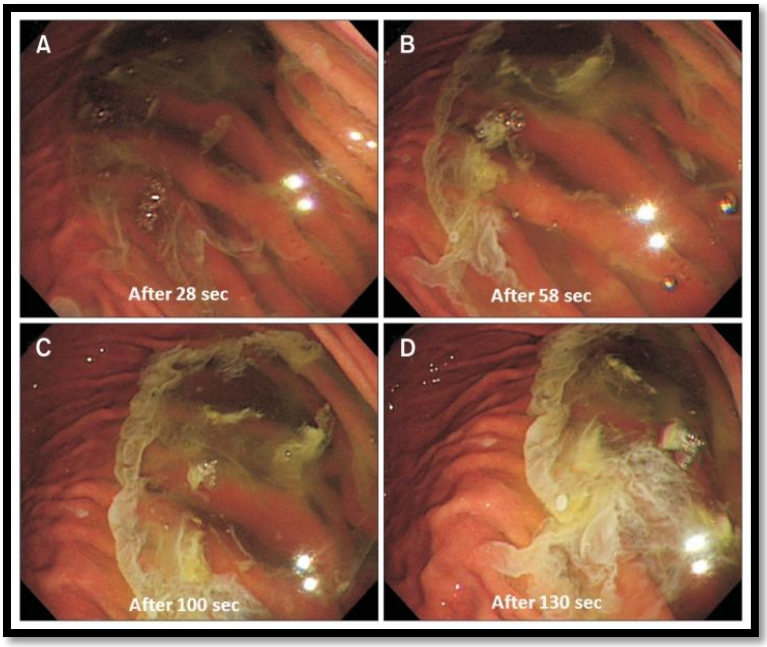

Figure 2: Raft formation of sodium alginate. (A) After 28 seconds of infusion, a precipitate developed. (B and C) A thin membrane-like material formed at the boundary. (D) The membrane floated on the gastric fluid [15].

Rationale for using Alginate as a carrier in Oral Gastroretentive In-situ gel:

As a food or medical-grade material, alginate polymer is biocompatible, inexpensive, and widely available. For several decades, alginate has been widely used in food products and is generally non-toxic. Alginate is widely used as a tablet disintegrant and gelling agent in food and pharmaceutical applications. Alginate has been widely used in a variety of biomedical applications, including tissue engineering, drug delivery, and in some formulations preventing gastric reflux, because of its biocompatibility, biodegradability, non-antigenicity, and chelating ability [10].

Paxman et al. used sodium alginate with high guluronate content because it forms a solid gel in the presence of calcium ions when consumed and to research the efficiency of alginate as a method of appetite control in free-living individuals. The results of the trial demonstrated that daily pre-prandial administration of the sodium alginate formulation led to a significant decrease in mean daily calorie intake, which was supported by decreases in mean daily intakes of carbohydrate, sugar, fat, saturated fat, and protein. The study made a case for a sodium alginate formulation with high gelling properties in the future treatment of overweight and obesity [16]. Harden et al. discovered that an ionic gelling sodium alginate drink significantly reduced post-prandial glycaemic response when compared to an acid-gelling control in self-reported healthy males [17].

Alginates have the following characteristics that make them an ideal matrix for controlled drug delivery.

a) It is easily accessible and reasonably priced.
b) It includes components that are legal food additives.
c) Because it has a protective impact during processing and is non-toxic when taken orally, stability, toxicological, and environmental issues related to solvents can be reduced.
d) It gels at room temperature, reducing the likelihood that sensitive medications would lose their effectiveness at high temperatures.
e) Insoluble gel is created when soluble sodium alginate is cross-linked with a variety of cross-linking agents. This gel is used to delay the release of various medications.
f) The European Pharmacopoeia adopted it.
g) Alginates are not included in the recommended daily intake, the highest categorization for food additives. Alginates now have the generally recognized as safe status from the Food and Drug Administration. The daily permitted amount of sodium alginate for humans is 0 to 50 mg per kg of body weight, according to the joint additive committee of experts from the FAO and WHO. The FAO and WHO eliminated the restrictions on

the amount of alginates that a person may consume daily in 1990.
Many studies have looked into using alginate gels as drug carriers for a variety of drugs [18].

Principle of In-situ gel formation:
Before administration, these are liquids, and they gel under physiological circumstances. Several mechanisms, including ionic cross-linkage, pH change, and temperature variation, make In-situ gel formation conceivable [19].

Sodium alginate (SA) serves as a gelling agent. The formulation acquired is a SA solution that contains sodium citrate, which forms a compound with free Ca^{2+} ions and releases them in the stomach's acid, and calcium carbonate, which serves as a source of Ca^{2+}. The polymeric chains of sodium alginate begin to cross-link as the free Ca2+ ions proceed to bind there, forming the matrix structure. The creation of double helical junction zones, which result in the recomposition of double helical segments into a 3D lattice with cations and hydrogen bonding with water, is required for this gelling [20].

Advantages of In-situ gelling system [21]:
- ✓ Simple administration and patient adherence.
- ✓ Slow medication release and increased stomach retention.
- ✓ Reduces dosing frequency.
- ✓ It acts immediately on the specified area, demonstrating a local action and site specificity.
- ✓ It has less side effects than other pharmaceutical dose forms.
- ✓ Flexibility in formulation.
- ✓ Production is easy.

Disadvantages of In-situ gelling system [21]:
- ✓ Systems for in-situ gel formation are more prone to stability issues due to chemical or microbial breakdown.
- ✓ Degradation may result from pH changes.
- ✓ It necessitates a lot of fluids.
- ✓ It causes deterioration as a result of storage issues.

Method of Preparation of Oral Gastroretentive In-situ gel:
Fig. 3 represents the steps involved in the development of Oral Gastroretentive In-situ gel.

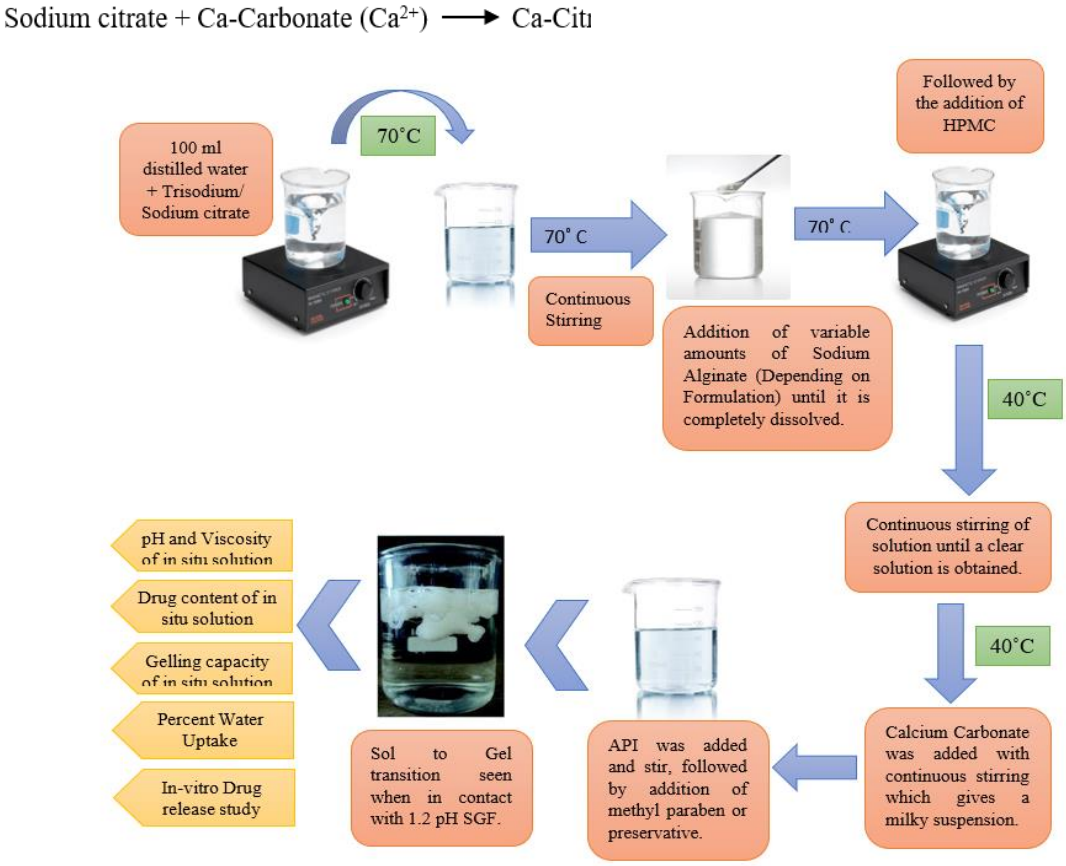

Figure 3: Schematic Representation for Method of Preparation of Alginate based In-situ gel and its Evaluation

Applications of Alginate Based Oral Gastroretentive In-situ gel:

Alginate based oral In-situ gel of different therapeutic agents are summarized in Table1.

Table 1: Alginate Based Oral In-Situ Gel of Different Therapeutic Agents.

Sr.No.	Model Drug	Use	In-situ Activation	Conclusion Remarks	References
1.	Nicardipine Hydrochloride	Anti-Hypertensive	Ionic cross-linking	Optimized formulation showed a slow drug release of 96.44 % up to 12 hours.	[23]
2.	Valsartan	Anti-Hypertensive	pH induced ion gelation	Observed the pH-dependent drug release from the dissolution study where it released the drug faster in less acidic media.	[24]
3.	Propranolol HCl	Anti-Hypertensive	pH induced ion gelation	The selected formulations (A7, P7 and G3) rapidly formed gels and floated in the acidic medium with a sustained release pattern of propranolol over an 8 h period.	[25]
4.	Ropinirole Hydrochloride	Anti-Parkinson	pH induced ion gelation	Optimized formulation showed a slow drug release of 96.10% up to 12 h.	[22]
5.	Leflunomide	Anti- rheumatic	pH induced ion gelation	Formula C4 showed good gel formation ex vivo study.	[26]
6.	Lornoxicam	Anti- rheumatic	Ionic cross-linking	Optimized formulation F11 released 99.52% of the drug over a 12 h extended period.	[27]
7.	Mitiglinide calcium	Anti-diabetic	Ionic cross-linking	The formula exhibited in vivo sustained release manner	[28]

				of MTG over 24 h and improved the bioavailability of the drug.	
8.	Metformin hydrochloride	Anti- diabetic	Ionic cross-linking	Pharmacodynamic studies showed a significant reduction in blood glucose levels in Wistar rats.	[29]
9.	Spiramycin	Antibiotic	pH triggered In-situ gel	During antimicrobial studies, we found that the formulation containing spiramycin showed good zone of inhibition against different microbial strains (Staphylococcus aureus and Escherichia coli).	[30]
10.	Neratinib	Anti- Cancer	pH induced ion gelation	The in vitro gelation of an in-situ gel formulation showed immediate gelation, and the gel was retained for an extended period of time.	[31]
11.	Celecoxib	Anti-inflammatory	pH induced ion gelation	F3 exhibited a significantly higher percentage of paw oedema inhibition at 8 h compared with the reference drug ($p < 0:05$).	[32]
12.	Lafutidine	Anti-ulcer	pH induced ion gelation	All the formulations were able to	[13]

				float instantaneously and kept floating for more than 12 h and all the tests' values were observed within range with sustained release up to 12 h.	
13.	Minocycline Hydrochloride	Anti-ulcer	Ionic cross linking	Formulation F8 was found to be optimum with sodium alginate (2%w/v) and HPMC K100M CR (1.5%w/v), shows release up to 12 hours.	[33]

1. Anti-hypertensive drug delivery:

- To treat hypertension, Desai et al. 2022 created a gastro-retentive In-situ gelling system of nicardipine hydrochloride using sodium alginate as the gelling polymer, HPMC K100M as the release retard polymer, calcium carbonate as the cross-linking agent, and trisodium citrate as the fluidity enhancer agent. Ionic cross-linking formed the basis for the flotation mechanism. For pre- and post-formulation evaluation, numerous experiments were conducted. Based on the findings, a white, viscous solution with a consistent consistency was produced. In terms of having the ability to regulate long-term medication release, Batch B1 was very well equipped. It was determined that the drug concentration was greater than 97%, the viscosities were within acceptable limits for swallowing, and the pH ranged from 7.33 to 7.68, which was adequate for oral digestion. Utilizing Design Expert 13 software, interactions and responses were determined based on polymer concentration and statistical analysis. Batch B1 (0.6% w/v and 0.5% w/v HPMC K100M) of the improved formulation demonstrated a delayed drug release of 96.44% for up to 12 hours. The best match model for drug release was the Higuchi model, which stated that drug release occurred via the Fiskian process, i.e., a combination of diffusion and erosion. The in-situ gel prepared can ultimately provide prolonged release, enhance the bioavailability of the drug, and increase patient compliance [23].
- Permana et al. 2022 formulated a Valsartan in solid dispersion-floating gel in-situ delivery system. Valsartan (VAL), a BCS class II medication with low solubility and high permeability, frequently has issues with limited bioavailability in various formulations. With improved formulation, such as adding it to a solid dispersion system, its low bioavailability can be increased (SD). Gastroretentive systems can improve the absorption even further. Here, we created a brand-new combined delivery method using SD and floating in-situ gel. VAL was combined with PVP and PEG 6000, a polymer carrier, and then its solubility was assessed. The research discovered that VAL-SD had PVP K-30 as the drug's carrier, with a PVP K-30 ratio of 1:3 demonstrating the drug's greatest solubility in various liquids. Moreover, analyses using DSC and XRD showed that VAL changed from crystal to amorphous after SD formulation.

  The SD was then formed into floating in-situ gel preparations utilising HPMC as the controlled release matrix and sodium alginate as the gel forming agent. The physical characteristics and drug release profile of the VAL-SD floating in-situ gels were assessed. As a result of the usage of HPMC in floating in-situ gel, the in vitro release of VAL was able to be sustained for 24 hours in biorelevant medium, according to the results of all physical evaluations of the formula. Significantly,

the impact of meal intake on VAL release was also examined, demonstrating for the first time that the VAL release in fasted-state simulated gastric fluid could be modulated in 2 hours and onwards. Hence, it is conceivable that the VAL release after two hours in an empty stomach environment was unaffected by food ingestion. Following up on these findings, in vivo research using an animal model should be done to better evaluate this system's effectiveness [24].

- Wiwattanapatapee et al. 2017 developed in situ gel forming systems incorporating propranolol HCl were formulated using different type of polymer base (alginate, pectin and Gellan gum). Propranolol is entirely absorbed in the gastrointestinal tract, however due to its short half-life and rapid first pass metabolism, its oral bioavailability is quite low. Thus, the gastro-retentive dose form is chosen to increase propranolol's oral bioavailability. 1 The obtained formulations underwent testing for viscosity, ability to gel, floating characteristics, and in vitro drug release. All formulations instantly began to gel, float on the surface of the acidic medium in less than a minute, and continue to float for more than eight hours. According to the drug release trial, HPMC K4M was the best additional polymer because it had a sustained release pattern and released a greater quantity of medications than PEG 4000 and Carbopol 934. The formulations with the highest percentage of drug release (80–90%) over an 8-hour period, made up of 0.25% Gellan gum without extra polymer (G3), 2% pectin with 1% HPMC K4M, and 2% alginate with 1% HPMC K4M (A7), were chosen as the most acceptable formulations. Also, they were simple to pour out of the container [25].

2. Anti-Parkinson drug delivery:

- Masareddy et al. 2021 created an in-situ solution that, after gelation, floats in the stomach and is appropriate for sustaining the release of the medication. In the current study, ropinirole hydrochloride, an anti-drug for Parkinson's, was employed to develop an in-situ gel for long-lasting activity. The gel matrix is made of sodium alginate, a natural polymer, and calcium carbonate, which serves as both a source of Ca^{2+} ions for the sol to gel transition and a source of CO_2 entrapped in the matrix for gel floatation. HPMC K100M was studied as a release-retarded polymer. Ion gelation triggered by pH was the cause of the gel's flotation. Different assessment parameters were applied to the formulated In-situ solution. The drug content was determined to be >87%, the viscosities were in the acceptable range suitable for swallowing, and the pH was determined to be in the range of 7.35–7.87, which was suitable for oral ingestion. Based on the results, a pale-colored, viscous solution of uniform consistency was obtained. Utilizing Design Expert 12 software, interactions and responses were calculated based on polymer concentration and statistical analysis. The optimised formulation F5 (0.75 mg SA and 0.5 mg HPMC) exhibited a delayed drug release of 96.10% up to 12 h. The best model fit the drug release was the Korsmeyer-Peppas model, which described drug release on imbibition of water from the environment by polymer matrix. The development of a once-daily dosage form as opposed to multiple doses of tablets can ultimately provide prolonged release, improve the drug's bioavailability, and increase patient compliance; as a result, the in-situ gel preparation can be seen as a promising dosage form for increased therapeutic action [22].

3. Anti-rheumatic drug delivery:

- For the treatment of juvenile rheumatoid arthritis (JRA), Esmaeil et al. 2020 developed and evaluated an oral floating In-situ gel of leflunomide (LEF) as a liquid Gastroretentive drug delivery system. The goal was to increase patient compliance, increase gastric residence time, and lessen variations in the drug concentration in plasma. LEF is a disease-modifying anti-rheumatic medication (DMARD) that significantly lessens the symptoms of rheumatoid arthritis (RA) in adults and active juvenile rheumatoid arthritis (JRA) in children. To create floating in-situ gels, various concentrations of calcium carbonate and sodium alginate were used. Viscosity, drug content, pH, density, in-vitro gelling capacity, floating lag time, floating duration, gelling strength, and an in-vitro release study were all used to evaluate the produced gels. The formula C4, which contains 1.5% w/v sodium alginate and 1% w/v calcium carbonate, was found to be the best formula since it had the best viscosity (295.4 cps), gel strength (45 sec), shortest floating lag time (40 sec), and best drug release (98%) for more than 6 hours. This combination was therefore chosen for additional ex vivo research in rats to look for gel development in the stomach. Ex vivo examination of Formula C4 demonstrated good gel formation. Therefore, the floating In-situ gelling system of LEF is regarded as an innovative strategy to improve patient compliance and prolong the drug's duration in the stomach, which will maintain its plasma level [26].
- In-situ gel formulations of lornoxicam for prolonged release were developed by Padmasri et

al. 2022 in order to decrease the frequency of dosing for the treatment of rheumatoid arthritis. This work employed the ion-sensitive in-situ gel production technique. As a biodegradable gel-forming polymer, sodium alginate was required to develop lornoxicam In-situ gel formulations. $CaCl_2$ was used as a cross-linking agent, and chitosan, $HPMCK_4$, $HPMCK_{15}$, guar gum, Gellan gum, xanthan gum, and pectin were used as drug release rate-regulating polymers. The viscosity, in vitro gelling capacity, pH, in vitro drug release, and drug content of the formulations F11–F18 were evaluated. Studies on the pure drug and optimised formulation of lornoxicam were done using FTIR, DSC, and in vivo drug kinetics. The optimal viscosity for administration and swallowing was demonstrated in the formulations. All formulations floated for 12 hours with a pH range of 6.7 to 7.3 and a floating lag time of 2 to 3 seconds. The commercial sustained-release formulation of lornoxicam released 99.92% of the drug in 8 hours, according to in vitro drug release experiments, while the optimised formulation F11 released 99.52% of the medication over a longer period of time (12 hours). According to FTIR investigations, no interactions between the drugs and excipients were found. The higher performance of the optimised formulation is being supported by the findings of in vivo kinetic experiments. The same thing is confirmed by the values of C_{max}, T_{max}, $t_{1/2}$, and AUC. A promising strategy for the treatment of rheumatoid arthritis in a convenient dosage form with greater patient compliance and therapeutic response involves using lornoxicam oral In-situ gel that contains chitosan as a drug release controlling polymer [27].

4. Antidiabetic drug delivery:

- Mahmoud et al. 2019 developed a novel liquid sustained-release drug delivery system, i.e., In-situ gels that undergo ion cross-linking. Poorly water-soluble medications like the novel anti-diabetic medication Mitiglinide Calcium are not suited for these systems (MTG). In order to both increase its bioavailability and sustain its release, our objective was to determine whether the cosolvency technique might be used to formulate a Gastroretentive In-situ gel of the short-half-life MTG. Propylene glycol was used as a cosolvent to dissolve MTG in the polymer solution, and MTG In-situ gel formulations were produced as a result. These formulations were then characterised for their viscosity, gel strength, floating ability, in vitro MTG release, and pharmacokinetic evaluation. The optimised formulation, which consisted of 1% Gellan gum, 0.75 percent sodium alginate, 0.75 percent calcium carbonate, and 7.5 percent propylene glycol, had a reasonable viscosity before being added to simulated gastric fluid, where it quickly solidified into a firm gel that floated over the top and held its buoyancy for 24 hours. The formula enhanced the drug's bioavailability and demonstrated the sustained in vivo release of MTG over a 24-hour period. Cosolvency is a promising method for delivering hydrophobic medicines in liquid formulations for sustained release. With better disease management, these formulations will increase the compliance of diabetic patients by removing the need for frequent dosage [28].
- The goal of Mathew et al. 2019 was to statistically design, optimise, and evaluate a liquid oral, floating In-situ gel of Metformin hydrochloride (MH) to prolong and control the drug's release behaviour and increase gastric residence time (the absorption window being the upper part of the duodenum). There are currently no liquid oral SR preparations of MH on the market. For the formulation, a straightforward mixing-based ionic cross-linking approach was employed. The impact of sodium alginate and three category levels of HPMC (K4M, K100M, and E50) on the response variables was investigated using a two-square factorial design. In simulated stomach fluid, the improved formulation immediately gelled and demonstrated >24-h flotation. A substantial sustained release of the medication for 12 hours was followed by a release of 37.98% in 1 hour. In pharmacodynamic trials, wistar rats had significantly lower blood glucose levels. An absence of toxicity to pancreatic tissues was found in short-term preclinical safety trials. On the other hand, the group that received the improved formulation showed faster regeneration of the islets of Langerhans' cells. A two-year shelf life was determined through stability experiments. Metformin hydrochloride could be formulated as a sophisticated, needle-free, In-situ gelling, SR liquid oral, with drug release controlled in accordance with regulatory guidelines for MH SR formulations. This would be a fascinating substitute for elderly people who have trouble swallowing large medications [29].

5. Antibiotic drug delivery:

- The study by Sharma et al. 2014 focuses on spiramycin oral In-situ gel optimization, formulation, and characterization. As cross-linking and viscosifying agents, sodium alginate and hydroxypropyl methylcellulose were utilised, respectively. The floating agent was sodium bicarbonate. The melting point, pH, and partition

coefficient were discovered to be 133°C, 9.5, and 0.193, respectively, in Preformulation studies. The drug's retention period in high-performance liquid chromatography was around 2.65 minutes. During our research on the compatibility of drugs with all polymers, we noticed that there were no changes in the FTIR spectra of a mixture of drugs and polymers. Every formulation demonstrated good pourability. The total floating time was more than 12 hours, and the floating time was less than 30 seconds. In investigations on in vitro drug release, the medication was around 80–100% released from the formulation for 12–16 hours. We revealed through TEM examination that the drug molecules were tightly bound to the polymer and released gradually over the course of up to 12 hours. We observed in these investigations that sodium alginate and HPMC content significantly influenced floating lag time, gelling capacity, and cumulative percentage drug release. During antimicrobial experiments, we found that the spiramycin-containing formulation effectively inhibited a variety of bacterial strains (Staphylococcus aureus and Escherichia coli) [30].

6. Anti-Cancer Drug Delivery:

- Hani et al. 2022 developed an oral raft-forming in situ gelling system of NTB. Breast cancer is treated with neratinib (NTB), an irreversible tyrosine kinase inhibitor of the pan-human epidermal growth factor receptor (HER-2). It's extremely low oral bioavailability at increasing pH and poor water solubility cause the therapeutic benefits in the GIT to decline. The major goal of the study was to develop an oral raft-forming in situ gelling system of NTB that would enhance gastric retention, release the medication in a regulated manner, and float for a lengthy period of time in the stomach. In this study, solid dispersions (SDs) based on polyethylene glycol (PEG) were used to increase NTB solubility, and a two-factor at three-level (3^2) factorial design was used to construct and optimise an in-situ gelling system. The results were analysed to determine the effects of two independent variables, sodium alginate [A] and HPMC K4M [B], on the responses, including floating lag time, percentage (%) water uptake at 2 h, and percentage (%) drug release at 6 h and 12 h. Formulation 1:3 demonstrated the maximum drug solubility across other SDs made with PEG 6000. No interactions between the medication and the polymer were seen in the FT-IR spectra. In NTB SDs, the drug content ranged from 96.22 to 1.71% to 97.70 to 1.89%. The pH value of the created in situ gel compositions was around 7. The in-situ gel formulation showed quick gelation and was held for a longer period of time in an in vitro gelation investigation. The 3^2 factorial designs' findings showed that all of the components were significantly correlated with the response of choice, demonstrating the accuracy of the design strategy used for optimization. To improve retention in the stomach and achieve sustained drug release through floating, the established oral raft-forming in situ gelling method of NTB can therefore be a potential and alternative technique, increasing the therapeutic efficacy of NTB [31].

7. NSAID delivery:

- Rasool et al. 2020 developed and tested a CXB In-situ floating gelling system for sustained oral administration. The current study aimed to improve CXB aqueous solubility using a cosolvency technique in order to improve CXB oral bioavailability and reduce administration frequency. The nonsteroidal anti-inflammatory medication celecoxib (CXB) is used to treat various inflammatory disorders and discomfort. It is COX-2-selective. Due to its weak water solubility, CXB has a low oral bioavailability and a slow dissociation rate. To solubilize CXB, three cosolvents—PEG 600, propylene glycol, and glycerine—were employed at various concentrations. To verify that CXB was soluble in the solutions, particle size analysis was done. The CXB solution was subsequently incorporated into sodium alginate solutions (0.25, 0.5, and 1% w/v) to create the floating In-situ gel formulations. Formulations in gel form were assessed for their floating behaviour and in vitro drug release investigations, whereas formulations in sol form were in vitro described for their physical appearance, pH, and rheological behaviours. The interaction between drugs and polymers was investigated using FTIR spectroscopy. The biological effectiveness of the optimised formula's analgesic and anti-inflammatory properties were assessed. The in-situ gel formulation was improved using the results that showed the less-polar solvent PEG 600 at 80% v/v had the maximum solubilization potential. The optimised formula (F3) had the best sustained release profile when using the Higuchi model release kinetics and had the greatest sodium alginate concentration (1% w/v). The FTIR spectroscopy research found observable molecular interactions between the medication and the polymer. Furthermore, at 8 hours, F3 showed a significantly higher percentage of paw oedema inhibition than the reference medication ($p<0:05$). Additionally, it demonstrated continuous analgesia throughout the duration of the experiment [32].

8. Anti-Ulcer drug delivery:

- Srinivas et al. 2022 formulated and evaluated raft forming gastro retentive floating drug delivery systems of Lafutidine for improving gastric residence time and sustained drug release for an extended time. Making use of the Box-Behnken experimental design 17 formulations of lafutidine GRDDS were created and tested for a variety of factors, including their physical appearance, pH, in vitro gelling and buoyancy tests, viscosity and density measurements, gel strength, drug content, acid neutralisation ability, and neutralisation profile. They were also subjected to in vitro dissolution, release kinetic, stability, and release testing. The buoyancy lag time ranged between 14.76 and 25.84 seconds, the formulations remained buoyant for more than 8 hours with a gelling time of 12 hours, the drug content ranged from 98.96 to 99.55%, and the in vitro release was 86.86 to 99.34% by the end of 12 hours. All evaluations were performed, and it was found that the values were within range. The drug release was found to be followed by the matrix diffusion process, according to the release kinetics, which were zero-order with respect to Higuchi's model. The most effective formulation was F3, which was further described using FTIR, DSC, and stability investigations. They revealed that there were no interactions between the medication and excipients, no significant changes in the formulation, and that F3 was stable [13].
- Mercy et al. 2018 formulated the floating In-situ gelling system of minocycline HCl by using the ionic cross-linking method. Anti-ulcer medication must be administered locally in the stomach to treat a condition related to a peptic ulcer. We can provide paediatric and geriatric comfort with improved stomach residence time by developing floating In-situ gelling technology. To optimise the concentration of sodium alginate, calcium carbonate, and different grades of HPMC, trial batches were created. The viscosity, gel strength, pH, drug content, in vitro buoyancy, and in vitro drug release of the prepared formulations were assessed. The effect of changing the concentrations of HPMC K100M CR (X2) and sodium alginate (X1) on the dependent variables of viscosity, gelling strength, time needed for complete release, and floating lag time was examined using a 3^2-factorial design. Analyses of variance, regression, and drug release kinetics were carried out. Trial batches T1 to T4 demonstrate the ideal range of sodium alginate; T5 to T7 optimise the concentration of calcium carbonate; and B1 to B12 demonstrate HPMC K100 M CR's maximum sustaining ability in addition to uniform raft production. With sodium alginate (2% w/v) and HPMC K100M CR (1.5% w/v), Formulation F8 was determined to have the best release for up to 12 hours. Utilizing sodium alginate as the gelling polymer and HPMC K100M CR as the release retardant polymer, a floating In-situ gelling system was successfully formulated [33].

Evaluation of Sodium Alginate Based In-Situ Gelling System:

1. **Physical appearance and pH determination:** In-situ solutions produced using sodium alginate were all examined for clarity and solution type [34]. Using a calibrated digital pH metre at 27 °C, the pH was determined in each of the sodium alginate-based In-situ solutions. Each data set's pH was measured three times, and the average values were computed [35].
2. **Drug content:** In a volumetric flask, precisely 5mL of the suspension were taken and briefly dissolved in 0.1N HCl. On further complete solution dissolve, 100 mL of 0.1N HCl were added to the volume. To assess the amount of medication present, 1mL of this solution was collected, diluted to 10mL, and the absorbance at a particular wavelength was measured using a UV spectrophotometer [36].
3. **Spreadability:** One gram of the gel was placed in the middle of a glass plate (20 × 20 cm) to test its Spreadability. Another glass plate of the same size was placed on top of this one. The gel was then spread out between the plates by carefully applying a weight of 1000g to the upper side of the plate. The weight was taken off after a minute, and the spread area's diameter (in cm) was then measured. This evaluation was done in triplicate [36].
4. **Determination of gel strength:** Texture profile analysis is a useful method for determining the properties of the polymeric system. It makes use of a TA-XT2 Texture Analyzer. The gels were positioned in a standard Beaker beneath a 7.6cm aluminium probe during the experiment, which was conducted at ambient temperature. The gelling strength test was selected as the test mode, and the test speed was set at 1.0 mm/s. A trigger force of 5g and an acquisition rate of 50 points per second were used. The gel strength, measured in grams, was used to calculate the force necessary to penetrate the gel [36].
5. **Gelling capacity study:** The gelling capacity was assessed by adding a drop of the system to a vial containing 2mL of newly made, 37°C equilibrated 0.1N HCl (pH 1.2), observing the gelation

process, and recording the time it took for the gel to dissolve. According to the gel integrity, weight, and rate of formation of gel, several grades were assigned [36].

6. **In-vitro drug release study:** Using a cellophane membrane, drug release tests from the in-situ gel were conducted. The apparatus was made in accordance with the literature; a glass tube measuring 10.5 cm in length and 2.1 cm in diameter was used. A known amount of in situ gel was poured to the lower base, which was then tied with cellophane membrane. This was then put in a beaker with 100 mL of phosphate buffer pH 1.2 as the diffusion medium, which is kept at 37°C with 50rpm. Up until the gel was entirely eroded, samples (5mL) were taken from the reservoir at various intervals of time (3h). The spectrophotometric approach was used to calculate the cumulative percent drug release [36].
7. **Measurement of the rheological properties of sol and gel:** This is a vital parameter for the evaluation of the in-situ gels. The viscosity and rheological properties of in situ-formed drug delivery systems can be measured using the Brookfield rheometer or another type of viscometer, such as Ostwald's viscometer. These formulations' viscosities should be such that no problems are anticipated when the patient administers them, particularly during parenteral and ocular administration [37].
8. **Water uptake by gel:** A thermogravimetric analyzer is used to measure the water absorption by gel. In this test, an in-situ gel made in 40 ml of pH 1.2 and 0.1 N HCl is used. The buffer's gel part is collected in a Petri dish, and any extra buffer is cleared away with tissue paper. 10 ml of distilled water are added once the initial weight of the gel is determined. Water is decanted, and the weight of the gel is measured every 30 minutes. The weight difference demonstrates how much water the gel has absorbed [38].

CONCLUSIONS:

This article provides a comprehensive review of alginate's current status and advancement in the sol-to-gel transition phase. The future of alginate polymer applications in pharmaceutical and biomedical research is bright. Alginate's safety, biocompatibility, and ease of preparation are some of its most significant features. The demand for the development of liquid oral controlled-release drug delivery systems increased due to the expected improvement in patient compliance and flexibility of dosing. Overcoming the potential for dose dumping was necessary for the area's advancement. This prompted researchers to use a variety of gastro-retentive techniques to prevent dose dumping once the rigid gel structure in the intestinal environment was destroyed. As a result, researchers must update the developments in alginate-based drug delivery systems, and this review provides advice for future study.

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