Smart liquids for oral controlled drug release: an overview of alginate and non-alginate based systems

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**Abstract**

Sustaining and controlling the rate of drug release is essential in pharmaceutical technology. It can reduce the number of units administered by the patient with subsequent improvement in patient compliance. These technologies can allow controlled liberation of the active pharmaceutical ingredients to correlate with the chronobiology of the diseases. The significance can be hastened if the controlled release technology was adopted in liquid oral dosage form. Numerous approaches have been implemented in development of liquid oral controlled release formulations. These include preparation of sustained release coated microparticles which are fabricated in the form of oral suspension. Application of ion exchange resin showed success with some products available in the market. Alginate based in situ gelling system has gained much interest. This system depends on fabrication of drug in alginate solution in presence of sequestered calcium ions. This system undergoes in- situ gelation immediately after administration due to liberation of calcium ion in the acidic environment of the stomach. The developed gel may be manipulated to float or to perform mucoadhesion. The promise of such technique has been magnified further after combination with chitosan which maintained gel formation in the stomach as well as in the intestinal environment. This article will provide an overview on liquid oral controlled release drug delivery systems with emphasis on the alginate based formulations.

**Key Words:** Alginate, chitosan, *in situ* gel, microparticles, gastro-retentive, sustained release.

1. **Introduction**

Oral drug delivery is the most natural way and convenient option for administration of medication. Usually conventional dosage forms such as tablets and capsules are not appropriate for certain groups of patients as geriatric, pediatric and those showing dysphagia. Additionally, these conventional dosage forms usually produce a wide range of fluctuation in drug concentration in the blood after administration that may lead to either undesirable side effects or poor efficiency. Taken this into consideration together with the need for repetitive dosing had led to the development of oral sustained release drug delivery systems [1]. This delivery system was mainly designed for those drugs with short biological half-life thus eliminate frequent administration and improve patient compliance. A major advantage of these formulations is the ease of administration as a liquid accompanied by modifying drug release pattern. They help to eliminate the problems associated with the administration of solid dosage and enable convenient use.

Many techniques have been employed to develop liquid oral controlled release formulations. One of the early investigated systems employed the preparation of sparingly soluble salts to develop oral sustained release suspensions [2] or formulating controlled release spherical particles [3].

The development of liquid oral sustained release formulations adopting the *in situ* gelation strategy has gained much interest recently as another promising alternative [4]. The concept was to administer a liquid drug solution or dispersion that is capable to convert to gel in the stomach. This switch in consistency results due the exposure to *in situ* gelation triggering factors such as pH shift (example polyacrylic acid), temperature change (example HPMC, MC, poloxamers copolymers and chitosan) or change in the ionic environment (example pectin, alginate and gellan) [5]. Different polymers have been investigated in developing oral *in situ* gelling systems [6-9]. Pectin and gellan gum were among the polymers initially investigated [10]. Combination between the thermosensitive polymers Pluronic F127 and Xyloglucan was employed to prepare liquid oral *in situ* gel of the antiasthmatic drug montelukast sodium, with improved bioavailability [11].

In this review, oral liquid sustained release systems will be broadly classified as either alginate based (*in situ* gel forming system) or non-alginate based techniques. Non-alginate system includes techniques like formation of microparticulate system or drug resinate complex (Figure 1). Compared to non-alginate system, *in situ* gel systems possess potential advantages like simple manufacturing processes, availability of raw materials with reasonable prices. In spite of these benefits, alginate based *in situ* gel systems for oral modified drug release liquids are not in the market yet. Table 1 represents an overview of the different approaches for preparing liquid oral sustained release systems.

**2.Alginate based systems**

Alginate is a natural hydrophilic polysaccharide present in the cell wall of marine brown algae and in capsular polysaccharides of certain bacterial species, such as Pseudomonas. Though microbial fermentation is a feasible procedure, marine brown algae represents the major source of alginates [12]. Alginate biopolymer is biocompatible, biodegradable and non-immunogenic. The industrial and pharmaceutical applications of alginate is due to its unique properties to retain water and formation of hydrogel. Therefore, it is widely used as thickening and stabilizing agent in many pharmaceutical as well as food products [13,14].

Chemically, it is the salt of alginic acid. Alginate constitutes a family of un-branched, linear copolymers. Its backbone structure composed of mannuronic acid blocks (m) and guluronic acid blocks (g). They are arranged as different block copolymers of either mm, gg or alternating m and g residues (m/g) (Fig. 2). Alginates have no regular repeating distribution of the monomers along the polymer chain. The m/g ratio varies largely from 0.19 to 2.26 indicating wide differences in composition among various specious [15]. The chemical composition and sequence of m and g residues within the polymer backbone depends on the source and location of brown seaweed, age and type of tissues used in alginate extraction and the collection season of the year. Such variations are the reason for the presences of over 200 different alginates with varying properties such as viscosity, solubility, gelation capacity, among others [16-18].

Alginate's gelation property arises from the availability of lots of free hydroxyl and carboxylic groups. This gives alginate its polyelectrolyte nature. The ion-triggered gelation property of alginate, which is its ability to form supramolecular networks via electrostatic interaction, is one of its main biofunctional properties [15, 18]. Gel forming property of alginate is driven by the presence of divalent cation that induces association of helical sections of the polymeric chains via connection zones (Figure 2).

It is widely accepted that only g-blocks of alginate are involved in the inter-chain cross-linking in response to divalent cations to form hydrogel [19]. This was reflected by the fact that gels prepared from alginate with a high content of guluronic acid residues exhibit more stiff gel mass than those with a lower residues [20]. However, this proposition was argued later by other researchers who suggested that mannuronic residue can be also involved in gel formation. However this contribution is minor as they form weak connections [18,21].

Despite the variety of cations, calcium (Ca2+) is the most widely used crosslinking ion to produce gel due to its low toxicity and wide availability with low price. This gives alginate polymers their peculiar character of being calcium-responsive polymers. This unique temperature-independent transition of alginate from sol to gel in presence of multivalent cations gives alginate its suitability for the development of biomaterial of wide applications including, for example, tissue engineering, drug delivery and controlled drug release formulations [20, 22].

The mechanism of *in situ* gelation via calcium cross-linking of alginate chains occurs either by diffusion or internal setting method. In the diffusion method, the ions diffuse into the alginate solution from outside surrounding or reservoir. For the internal setting, the ion source is included within the alginate liquid in an inactive form and a trigger factor sets off the ions into the solution. The diffusion method yields gels with a gradient in the crosslinking ion concentration across the thickness of the formed gel, while internal setting gives a uniform ion concentrations throughout the gel [12,19].

Most investigated oral *in situ* gel formation usually based on “internal setting” method where the ion source is situated within the alginate solution. To avoid premature gelation before administration, the divalent ions should be present in an inactive complex form. This complex is usually obtained by the interaction between calcium chloride and sodium citrate to form calcium citrate complex. The triggering factor, such as change in pH value and/ or solubility of the ion source, will set free calcium ions into the solution initiating, thus, crosslinking and gel formation [12,19].

***2.1.Oral in situ gelling alginate system***

The concept of oral liquid controlled release system by *in situ* gelation is to prepare a low viscosity dispersion of alginate with the drug and calcium complex, thus enabling convenient intake. Following administration, the gastric acidity will liberate calcium from its complex that will link the linear alginate chains, by electrostatic interaction, forming the hydrogel network structure. The formed gel should be capable of releasing drug molecules in a sustained manner providing a relatively consistent plasma concentration profile. To maintain the liquid state while in the bottle (i.e. outside the body) while ensuring rapid conversion into gel of reasonable consistency after administration, the concentration of calcium citrate complex had to be optimized by adjusting the concentration of both calcium chloride and sodium citrate [23].

The gelation rate is very important factor in the design of the oral *in situ* gelling systems as it will affect the uniformity and strength of the formed hydrogels. Also it is important if gastroretentive design is in mind. This can be controlled by proper manipulation of the conditions, such as the alginate composition (g to m ratio), controlling the pH-value of the liquid and concentration of the multivalent ions source.

***2.2. Evaluation of the gel forming property***

This parameter is routinely used as a measure of the ability of liquid alginate system to undergo *in situ* gelation when at the proper environment. The test usually conducted by packing 10 ml of liquid alginate in 0.1N hydrochloric acid (pH 1.2) solution kept at 37°C for 24 hours (simulating gastric conditions). After separation of the liquid content of the bag by sieving, the remaining gel is weighed. The higher the gel weight the more the gel forming capacity of the system [23,24]. Other researchers tested *in situ* gelation by the addition of liquid alginate (10 ml) to 500 ml of 0.1 N hydrochloric acid under gentle agitation. Gelation was visually observed and qualified by scoring [10,25].

A more simplified method was used by other researchers by transferring one ml of tested solution to 5ml of 0.1N HCL placed in a test tube maintained at 37 + 0.5 ºC. The gelling capacity was graded according to gel stiffness and time period for which the formed gel keeps its integrity [26,27].

***2.3.Calcium-free alginate system***

It worth noting that the presence of calcium in alginate *in situ* gelling liquids might provide a source for interaction with many drugs. This led to the investigation of calcium free system that depends mainly on the endogenous calcium present in body fluids (i.e. diffusion method of crosslinking). Calcium free alginate and alginate/chitosan *in situ* gelling liquids of the antidiabetic drug nateglinide was investigated. The authors compared gelling capacity of calcium-containing alginate liquid to calcium-free one. In spite of absence of calcium, calcium-free liquid underwent gelation that was comparable to those containing calcium complex. They suggested that gel formation in absence of calcium could be due to the intra-molecular hydrogen bonding, with the protonated carboxylic groups playing a significant role [13]. Physical state characterization of unprocessed alginate and alginate after gelation indicated that the induced gelation in calcium free alginate was due to the liberation of alginic acid with subsequent hydrogen bonding and gel formation [28].

***2.4.Alginate-polymer combinations***

Liquid alginate was shortly compared to other biopolymers. Cimetidine release from different *in situ* gel forming liquids was investigated. The liquids were prepared using either gellan gum, enzyme-degraded xyloglucan (thermo-reversible gel) or sodium alginate with calcium complex. The *in vivo* bioavailability in rabbits showed similar release pattern from the three formulations that was comparable to the commercial cimetidine/alginate suspension [8].

Later on, combination between two biopolymers with different mechanism of *in situ* gelation was investigated. Paracetamol release from Liquid containing xyloglucan (1.5%w/v) and alginate (0.5%w/v) was investigated. The prepared liquid was of suitable consistency ensuring ease of administration. Plasma levels of paracetamol showed more sustained release pattern over 6 h from this polymer mixture compared to xyloglucan (1.5%) only solution [29]. Alginate was also combined with methylcellulose for the delivery of paracetamol with the aim of modifying drug release as well as improving stomach integrity. *In vivo* studies revealed improved sustained release profile of this combination compared to alginate only, methylcellose only and aqueous drug solution [30].

Alginate vehicles with calcium complex are not always capable of sustaining the release of highly water soluble drugs. Meantime, increasing gel mechanical strength by increasing alginate concentration will decrease the fluidity of the liquid formulation and makes it difficult for oral administration. To overcome this problem, especially in the gastric phase, processing the drug prior to incorporation in alginate liquid was an attractive solution. This was can be achieved by preparing solid dispersion of these drugs a polymer of low acid solubility. Methacrylic resins (Eudragits®) polymers were suitable for this purpose due to their compatibility with different drugs and high chemical stability [31].

Additionally, a broad family of the anionic Eudragit® grades that only dissolve above a specific trigger pH-value. Eudragits® S 100 was employed to prepare enteric coated dextromethorphan (highly soluble drug) microparticles to modify the release while in the stomach phase. Eudragits® S 100 has a pH trigger value above 7.0. The drug-polymer microparticles were prepared by the simple solid dispersion using solvent evaporation technique. The microparticles succeeded in reducing drug release while in the gastric phase compared to alginate liquid containing unprocessed drug [32]. A similar strategy was adopted to modify the release of Losartan potassium using Eudragit® L100 with a pH trigger above 5.5 [33].

It should be noted that alginate gel is sensitive to pH change and the formed ionic crosslinked mass would break apart upon shifting the conditions from acidic gastric to the basic intestinal. The rupture of the pH dependent gel in intestinal phase is expected to produce an initial high drug release. This makes drug release largely dependent on gastric emptying rate, which is widely variable both inter- and intra-subject. Additionally, if premature gastric emptying occurs there is a high risk of dose dumping. This drew the attention to the need to enforce the gel mechanical strength by blending alginate with other polymers to overcome the drawbacks of alginate only systems. Chitosan was selected for this purpose [33] Chitosan is a polysaccharide biopolymer derived from chitin. It is polycationic, nontoxic, biodegradable with some antibacterial properties [34]. Hybrid of alginate and chitosan biopolymers combined the good characteristics and can minimize the drawbacks of each polymer [34].

This strategy succeeded in reducing drug release compared to alginate only system when shifting from gastric to intestinal phase. The sustained release pattern was maintained more or less similar in both phases [23,28,33]. This partial gel reservation property upon shifting to high pH value was due to the structure of chitosan that is rich in amine groups giving the polymer pH-sensitive characteristics. In acidic conditions (gastric phase), the polycationic chitosan chains are soluble due to electrostatic repulsion between the protonated amine groups. This can initiate electrostatic interaction with the polyanionic alginate chains resulting in increased gel strength, in addition to the existence of interactive coulomb forces [35]. This is believed to augment the *in situ* gelling capacity and gel strength [36,37]. Upon increasing pH value (intestinal phase), led to formation of a dissociated precipitate that resist rapid disintegration of the gel mass avoiding, thus, dose dumping [38].

***2.5.Gastro-retentive oral in situ gelling alginate systems***

Drugs with narrow absorption window are those drugs that are absorbed mainly from the upper part of the gastrointestinal tract. Therefore, traditional modified release formulations of those drugs cannot provide a true prolonged release profile. Once the dosage form has passed the absorption site(s) at the specific regions of the gastrointestinal tract, the drug is no longer absorbed from the dosage form and its bioavailability is adversely affected. On the other hand, drugs that are intended to act locally in the stomach, such as antacid, are better kept there for as long as possible. The inability of conventional oral drug delivery systems to retain drugs in the stomach led to the development of gastro-retentive drug delivery systems (GRDDS). These systems increase the residence time of the dosage form in the gastric phase up to several hours. This could hold a promise to improve the bioavailability of these drugs and reduce fluctuations in the plasma drug concentrations. Several Formulation strategies adopted to obtain a successful GRDDS included floating (low density), sedimenting (high density), expanding systems and mucoadhesive systems [39-42]. Considering oral liquid *in situ* gelling formulations, only floating and mucoadhesive systems will be discussed in the following section as they are the only investigated techniques for this system (Figure 3).

***2.5.1.Floating liquid oral in situ gelling system***

Floating drug delivery system (FDDS), also named hydrodynamically balanced system, is one of the most investigated approaches for achieving gastro-retention. FDDS should have a bulk density lower than that of the gastric fluids to remain buoyant in the stomach for long time with a slow drug release at a desired rate. This scenario should occur without affecting the gastric emptying rate (Figure 3). After the release of the drug, the residual system should degrade and pass to the intestine. This system requires sufficiently high level of gastric fluids for the system to float and to maintain buoyant for the required time.

To achieve efficient floating of oral liquid *in situ* gelling (also called raft forming) sodium bicarbonate is usually incorporated in the component of the alginate liquid. Upon interacting with the acidic environment of the stomach, it releases carbon dioxide gas that entrap in the formed gel mass imparting low density with subsequent floating above the gastric content [43]. The *in vitro* floating lag time (time taken for the formed gel to float on the surface) and total buoyancy time are critical parameters and usually taken as a measure for the success or failure of this system [44]. The *in vitro* floating time is usually measured by adding certain volume (usually 10 mL) of the *in situ* gelling liquid to 500 mL of 0.1N hydrochloric acid (pH 1.2) with mild agitation. Floating lag time and total floating time are then determined [45].

Floating gastro-retentive *in situ* gelling liquid of the locally acting H2-antagonist, ranitidine, was investigated. The liquid system was formulated using different grades of sodium alginate (low, medium and high viscosity) and calcium carbonate, in presence or absence of calcium citrate complex (source of calcium for *in situ* gelation of alginate). In absence of calcium citrate, gelation and floatation based mainly on the free availability of a sufficient number of calcium ions and carbon dioxide gas released as a result of interaction of calcium carbonate with the gastric acidity. Changing the concentration of drug, calcium carbonate as well as alginate grade had a great impact on drug release rate. It was concluded that presence of calcium complex is essential for efficient control over ranitidine release rate [46]. Importantly, presence of calcium carbonate showed internal premature gelation during storage [47]. Therefore, presence of small amount of sodium citrate would be beneficial to complex with the possibly freed calcium ions during the shelf life of the liquid. Alternatively, calcium carbonate can be replaced by sodium carbonate. Drug release pattern is highly dependent on the composition as well as concentration of liquid components. For instant, using the same compositions but of different ratios amoxicillin release followed Zero order kinetics [45], while pregabalin showed Fickian diffusion mechanism [48]. This can be argued due to the higher ratio of calcium citrate complex in pregabalin system the led to formation of more structured gel mass.

Combination of alginate with hydroxypropyl methyl cellulose (HPMC) was investigated with a great success. HPMC was used as it has a high water swelling properties that is independence on the pH value [49]. Sodium bicarbonate and calcium citrate complex were also involved in the system to aid rapid floatation. This floating system was able to sustain amoxicillin release over 12h with zero order release kinetics [45]. Meloxicam, was successively formulated into floating oral *in situ* gelling liquid. The solubility of meloxicam was improved by forming ternary solid dispersion with hydrophilic excipients. *In vivo* studies showed significant reduction in the carrageenan induced rat paw edema and reduced ulcerogenic effect in rats' stomach compared to standard meloxicam [50]. Similar strategy of floating *in situ* gel forming oral alginate liquids was adopted for Nizatidine [51], Ofloxacin [26] and Losartan potassium [52] making this approach a practical solution for many problems encountered with these medications.

***2.5.2.Mucoadhesive oral liquid in situ gelling system***

Mucosal drug delivery is an attractive way of drug administration. However, fast drainage from the target mucosal surface, due to rapid mucosal turnover rate, represents a major obstacle as it prevents sufficient drug absorption. *In situ* gelling and mucoadhesive polymers proved to be essential excipients to extend the mucosal residence time of drug delivery systems. Due to this prolonged residence time both local as well as systemic therapeutic efficacy of many drugs can be substantially enhanced. For this system, mucoadhesive strength and force of adhesion are critical parameters and should be carefully evaluated [53].

This technique is widely investigated for ocular [38], vaginal [54], nasal [55] as well as injectable [56] drug delivery systems. To our knowledge, limited research is available concerning liquid oral *in situ* gelling gastroretentive mucoadhesive system.

Alginate is classified as good mucoadhesive agent [57]. However, for efficient mucoadhesion, the used polymeric chain should be able to penetrate the mucus gel layer close to the epithelium cell lining to form an anchor for the delivery system. This is usually cannot be achieved by a single polymer type and combinations of different polymers with *in situ* gelling and mucoadhesive properties are needed to attain the desired duration of mucoadhesion [5]. Additionally, this combination will be more practical to avoid possible liquefaction of the gel layer by the liquid turnover of the gastric mucosa.

Shastri et al. [58] combined sodium alginate, pectin and HPMC K4M to prepare gastro-retentive mucoadhesive system of Cefuroxime Axetil. The results revealed that increasing concentration of sodium alginate increased mucoadhesion power and reduced drug release rate. This system was recently investigated as a tool to overcome problems associated with hospitalized patients who are on nasogastric feeding. Many critical care units treating from complications secondary to aneurysmal subarachnoid hemorrhage are receiving nimodipine therapy that requires frequent administration every 4 hours [59]. Being maximally absorbed from upper gastrointestinal tract, the benefit of the *in situ* gelling liquid is to enable ease of administration through nasogastric tube feeding with reduced dosing frequency due to prolonged residency in the stomach. The liquid system combined sodium alginate and carboxymethyle cellulose (CMC) to maximize mucoadhesion power. The mucoadhesive *in situ* gelling liquids sustained nimodipine release up to 8 hours with proofed gastric retention, as reflected by X-ray radiography in rabbit [42].

***2.6.Combined alginate and emulsion***

Though multiple emulsion (w/o/w) has been investigated to sustain the release of lamotrigine [60], combination between emulsion and alginate system was also explored. *In situ* gelling emulgel prepared using Gelucire 39/01 and alginate solution was propped as stomach specific floating system of piroxicam. Calcium carbonate was used as buoyancy imparting agent as well as crosslinker [61]. Another *in situ* gelling emulsion was developed in order to reduce mebeverine hydrochloride release from HPMC and alginate system Where Compritol® 888ATO and Precirol® ATO5 were incorporated to impart some hydrophobicity to the system [27]. The produced *in situ* gelling emulsion controlled drug release compared to alginate/HPMC system, and was comparable to the marketed product “Duspatalin®200 SR” tablets.

**3.Non-Alginate oral sustained release liquids**

***3.1.Microparticle systems***

The other method of obtaining modified release oral liquid formulation is by preparing microparticulate system, mostly by adopting the spray-drying technique. It allows the designing of microspheres or microcapsules where the drug is either dispersed in or enclosed by a polymeric matrix [62]. The obtained microparticles are then dispersed in a suitable liquid [63,64]. In this technique, dry powder products are usually obtained by spraying polymeric solution or suspension of the drug and the polymer of choice [65]. Based on the polymer and experimental conditions, microparticles with various sizes and different dissolution profiles can be obtained. Spray dried theophylline with either hydroxyl propyl methyl cellulose phthalate or ethyl cellulose were prepared using different solvents and different polymeric ratios. The prepared microparticles were able to sustain theophylline release that was largely dependent on polymer type and concentration [66].

Amoxicillin loaded gelatin nanoparticles were prepared using the innovative technology, the Büchi Nano Spray Dryer B-90. The aim was to produce nanoparticles with mucoadhesive power for stomach specific delivery with the aim of eradicating Helicobacter pylori. Dry suspension of dual immediate and sustained release amoxicillin was prepared. The gelatin nanoparticles (with average particle size of 571nm) were able to sustained amoxicillin release over 12 hour and were stable for one year under accelerated storage conditions [67].

Alternatively, spray congealing was used to prepare microparticulate system. In this technique, the drug is dispersed or dissolved in a polymeric molten base and sprayed via atomizer into a cooled chamber. Zmax® is a commercially available extended release oral suspension containing azithromycin dehydrate microspheres. It is used as single daily dose for the treatment of sinusitis and pneumonia in adults. The microparticles (50-300µm) are prepared by spray congealing techniques by dispersing the drug in a molten carrier of the block copolymer Poloxamer 407 and glyceryl behenate [68].

**3.2.*Drug-resinate complex***

The use of ion exchange resins to make a complex with ionizable drugs is another alternative technique enabling formulation of modified release oral liquids [69]. It is one of the early investigated strategies to obtain sustained released formulations. Ion exchange resins are cross-linked synthetic polymers with high molecular weight and lots of ionizable head groups. Based on these groups, they are classified as either cation-exchange resins with acidic groups (such as sulfo or carboxyl groups) or anion-exchange resins with basic groups (such as amino, imino, or quaternary ammonium groups). It worth noting that most of the commercially available sustained release liquids for oral administration, especially those for pediatrics, utilize the drug resinate complex formation. The developed resinate complexes are usually incorporated into microcapsules or directly suspended in suspending vehicles.

The most commonly employed ion exchange resins in drug delivery are the cationic type. Indion 244, a cross-linked polystyrene with a free sulphuric acid group, was utilized to prepare extended release chlorpheniramine maleate suspension [70]. Delsym® is dextromethorphan suspension produced by Reckitt Benckiser LLC and usually administered twice daily. Dyanavel XR® (produced by TrisPharma) is a mixed immediate and extended release suspension of amphatmine complexed with sodium polystyren sulfate and coated with the pH dependent polymers povidone and polyvinyl acetate [71]. Quillivant XR® (produced by Pfizer) is another combined immediate and extended release of methlphenidrate marketed in the form of powder for suspension, after reconstitution with water [72].

Other marketed products are MST® Continus® (Napp Pharmaceuticals Limited) and Tussionex®(UCB) are also available for the extended release of morphine and Hydrocodone chlorpheniramine, respectively [73,74].

**Conclusion and future perspectives**

The expected improvement in patient compliance and flexibility of dosing increased the demand for development of liquid oral controlled release drug delivery systems. The number of research articles in this field is increasing with early articles employing non alginate-based systems such as suspensions of slowly dissolving salts or coated particles in addition to ion exchange resins. Recent articles concentrated on development and evaluation of alginate-based formulations which employed alginate solutions which undergo *in situ* gelation in the stomach. The progress in the area required overcoming the possibility of dose dumping. This encouraged researchers to adopt various gastro-retentive strategies to avoid dose dumping after destruction of the firm gel structure in the intestinal conditions. The advancement employed polyelectrolyte complexation between alginate and chitosan to develop a system which undergoes *in situ* gelation in the stomach with promising ability to retain the gel structure for extended period of time even after reaching the intestine. The later effort showed interesting results and allowed the formulator to develop calcium free formulation with minimum possibility of interactions. Unfortunately, the number of publications in this area still small and important factors need to be investigated to encourage researchers to advance this technique through drug development pipelines. One of the most important factors that requires investigation is the effect of food on the gelling capacity and drug release pattern from alginate-chitosan based system. This factor requires extensive work taking into consideration the type of meal and the administration time in relation to meal. Accordingly, a series of investigations must be systematically designed taking into consideration the historical data to shed light on factors affecting drug release pattern from alginate-chitosan liquid oral sustained release preparations. The coming days will determine the success of these investigations and how results can contribute to advancement in this area.

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**Author contributions:** All authors contributed equally to literature review, original draft writing, reviewing and editing

**References:**

[1] M.P. Ratnaparkhi, P.G. Jyoti, [Sustained release oral drug delivery system-an overview](https://pdfs.semanticscholar.org/ec84/3d7dabecf7498324497488d784fe0f845070.pdf), Int. J. Pharm. Res. Rev. 2(3) (2013) 11-21.

[2] K.P. Shah, L. Chafetz, Use of sparingly soluble salts to prepare oral sustained

release suspensions, Int. J. Pharm. 109 (1994) 271-281.

[3] A.J. Ribeiro, G. Silva, D. Ferreira, F. Veiga, Chitosan-reinforced alginate microspheres obtained through the emulsification/internal gelation technique, Eur. J. Pharm. Sci. 25 (2005) 31-40.

[4] H.B. Nirmal, S.R. Bakiwal, S.P. Pawar, In situ gel: new trend in controlled and sustained drug delivery system, Int. J. Pharm. Tech Res. 2 (2010) 1398-1408.

[5] F. Zahir-Jouzdania, J.D. Wolf, F. Atyabib, A. Bernkop-Schnürcha , In situ gelling and mucoadhesive polymers: why do they need each other?, Exp. Op. Drug Del. 15 (10) (2018) 1007-1019.

[6] S. Miyazaki, H. Aoyama, N. Kawasaki, W. Kubo, D. Attwood, In situ-gelling gellan formulations as vehicles for oral drug delivery, J. Control. Release. 60 (1999) 287–295. DOI: 10.1016/S0168-3659(99)00084-X.

[7] S. Miyazaki, W. Kubo, D. Attwood, Oral sustained delivery of theophylline using in situ gelation of sodium alginate, J. Control. Release. 67 (2000) 275–280. DOI: 10.1016/s0168-3659(00)00214-5.

[8] S. Miyazaki, N. Kawasaki, W. Kubo, K. Endo, D. Attwood, Comparison of in situ gelling formulations for the oral delivery of cimetidine, Int. J. Pharm. 220 (2001) 161-168. DOI: 10.1016/S0378-5173(01)00669-X.

[9] W. Kubo, S. Miyazaki, D. Attwood, Oral sustained delivery of paracetamol from in situ-gelling gellan and sodium alginate formulations, Int. J. Pharm. 258 (2003) 55-64. DOI: 10.1016/S0378-5173(03)00163-7.

[10] A. Patel, D. Shah, M. Modasiya, R. Ghasadiya, Development and evaluation of cefpodoxime Proxetil gellan gum based in situ gel, Int. J. Res. Pharm. Biomed. Sci. 1 (2012) 179-190.

[11] R. Mathews, B.P. Rao, K. Abbulu, T.S. Rao, B. Baby, Development of a Sustained Release, Liquid Oral in situ Gelling System of Montelukast Sodium with Improved Bioavailability: Equivalence Testing using Earth Mover’s Distance, Asian J. Pharm. 13(2) (2019) 93-102.

[12] K.I. Draget, C. Taylor, Chemical, physical and biological properties of alginates and their biomedical implications. Food Hydrocoll. 25(2) (2011) 251-256.

[13] K.I. Draget, G. Skjak-Braek, B.T. Stokke, Similarities and differences between alginic acid gels and ionically crosslinked alginate gels, Food. Hydrocoll. 20 (2006) 170-175.

[14] Qin Y, Zhang G, Chen H. The Applications of Alginate in Functional Food Products. J Nutr Food Sci. 3(1) (2020) 1-9.

[15] T. Lopes da Silva, J.M.M. Vidart, M.G. Carlos da Silva, M.L. Gimenes, M.G.A. Vieira, Alginate and Sericin: Environmental and Pharmaceutical Applications In Biological Activities and Application of Marine Polysaccharides, Biological Activities and Application of Marine Polysaccharides, chapter 4 (2017) 57-85. DOI: 10.5772/65257.

[16] [A. Ikeda](https://www.sciencedirect.com/science/article/pii/S0144861799001836?via%3Dihub#!), [A. Takemura](https://www.sciencedirect.com/science/article/pii/S0144861799001836?via%3Dihub#!), [H. Ono](https://www.sciencedirect.com/science/article/pii/S0144861799001836?via%3Dihub#!), Preparation of low-molecular weight alginic acid by acid hydrolysis. Carbohydr. Polym. 42(4) (2000) 421-425.

[17] [S. Bor](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bor%20S%5BAuthor%5D&cauthor=true&cauthor_uid=31624050), [İ.H. Kalkan](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kalkan%20%26%23x00130%3BH%5BAuthor%5D&cauthor=true&cauthor_uid=31624050), [A. Çelebi](https://www.ncbi.nlm.nih.gov/pubmed/?term=%26%23x000c7%3Belebi%20A%5BAuthor%5D&cauthor=true&cauthor_uid=31624050), [D. Dinçer](https://www.ncbi.nlm.nih.gov/pubmed/?term=Din%26%23x000e7%3Ber%20D%5BAuthor%5D&cauthor=true&cauthor_uid=31624050), [F. Akyüz](https://www.ncbi.nlm.nih.gov/pubmed/?term=Aky%26%23x000fc%3Bz%20F%5BAuthor%5D&cauthor=true&cauthor_uid=31624050),[P. Dettmar](https://www.ncbi.nlm.nih.gov/pubmed/?term=Dettmar%20P%5BAuthor%5D&cauthor=true&cauthor_uid=31624050), H. Özen. Alginates: From the ocean to gastroesophageal reflux disease treatment. [Turk. J. Gastroenterol](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6836317/). 30 ( 2019) S109–S136.

[18] K.Y. Lee, D.J. Mooney. Alginate: properties and biomedical applications. Prog. Polym. Sci. 37(1) (2012) 106-126. <http://dx.doi.org/10.er16/j.progpolymsci.2011.06.003>.

[19] S.N. Pawar,K.J. Edgar, Alginate derivatization: A review of chemistry, properties and applications. Biomaterials. 33(11) (2012) 3279-3305.

[20] M. George, T.E. Abraham, Polyionic Hydrocolloids for the Intestinal Delivery of Protein Drugs: Alginate and Chitosan -A Review. J. Control. Release. 114(1) (2006) 1-14. doi: 10.1016/j.jconrel.2006.04.017.

[21] I. Donati, S. Holtan, Y.A. Mørch, M. Borgogna, M. Dentini, G. Skjåk‐Bræk, New hypothesis on the role of alternating sequences in calcium‐alginate gels. Biomacromolecules. 6(2) (2005) 1031–1040.

[22] J.S. Yang, Y.J. Xie, W. He. Research progress on chemical modification of alginate: A review. Carbohydr. Polym. 84(1) (2011) 33-39.

[23] G.M. El Maghraby, E.M. Elzayat, F.K. Alanazi, Development of modified in situ gelling oral liquid sustained release formulation of dextromethorphan, Drug Dev. Ind. Pharm. 38 (2012) 971-978.

[24] K. Itoh, W. Kubo, M. Fujiwara, H. Watanabe, S. Miyazaki, D. Attwood, The influence of gastric acidity and taste masking agent on in situ gelling pectin formulations for oral sustained delivery of acetaminophen. Biol. Pharm. Bull. 29 (2006) 343-347.

[25] A. Sharma, J. Sharma, R. Kaur, V. Saini, Development and Characterization of In Situ Oral Gel of Spiramycin. Biomed. Res. Int. 2014 (2014) 876182.

[26] S. Chaniyara, D. Modi, R. Patel, J. Patel, R. Desai, S. Chaudhary, Formulation and Evaluation of Floatable In situ Gel for Stomach-specific Drug Delivery of Ofloxacin. Am. J. Adv. Drug Deliv. 1(3) (2013) 285-299.

[27] M.A. El Nabarawi, M.H. Teaima, R.A. Abd El-Monem, N.A. El NabarawyNA, D.A. Gaber, Formulation, release characteristics, and bioavailability study of gastroretentive floating matrix tablet and floating raft system of Mebeverine HCl, Drug Des. Devel. Ther. 11 (2017) 1081-1093.

[28] G.M. El Maghraby, A.E. Elsisi, G.A. Elmeshad, Development of liquid oral sustained release formulations of nateglinide: In vitro and *in vivo* evaluation. J. Drug Deliv. Sci. Technol. 29 (2015) 70–77.

[29] K. Itoh, R. Tsuruya,T. Shimoyama, H. Watanabe, S. Miyazaki, A. D'Emanuele, D. Attwood, In situ gelling xyloglucan/alginate liquid formulation for oral sustained drug delivery to dysphagic patients. Drug Dev. Ind. Pharm. 36(4) (2010) 449-455.

[30] T. Shimoyama, K. Itoh, M. Kobayashi, S. Miyazaki, A. D'Emanuele, D. Attwood, Oral Liquid in Situ Gelling Methylcellulose/Alginate Formulations for Sustained Drug Delivery to Dysphagic Patients. Drug Dev. Ind. Pharm. 38(8) (2012) 952-60. Doi: 10.3109/03639045.2011.634809.

[31] E. Mašková, M. Naiserová, K. Kubová, J. Mašek, S. Pavloková, M. Urbanová, J. Brus, J. Vyslouzol, D. Vetchý, Highly Soluble Drugs Directly Granulated by Water Dispersions of Insoluble EudragitD Polymers as a Part of Hypromellose K100M Matrix Systems. BioMed. Res. Int. 2019 (2019) 13.

[32] G.M. El Maghraby, E.M. Elzayat, F.K. Alanazi, Investigation of in Situ Gelling Alginate Formulations as a Sustained Release Vehicle for Co-Precipitates of Dextromethrophan and Eudragit S 100. Acta Pharm. 64(1) (2014) 29-44.

[33] M.A. Amer, E.A. Essa, A.A. Donia, G.M. El Maghraby, Development and evaluation of liquid oral controlled release systems for Losartan potassium. J. Appl. Pharm. Sci. 9(8) (2019) 86-93.

[34] T. Gotoh, K. Matsushima, K.I. Kikuchi, Preparation of alginate‐chitosan hybrid gel beads and adsorption of divalent metal ions. Chemosphere. 55(1) (2004) 135-40.

[35] Y. Vijaya, S.R. Popuri, V.M. Boddu, A. Krishnaiah, Modified chitosan and calcium alginate biopolymer sorbents for removal of nickel (II) through adsorption, Carbohydr. Polym. 72(2) (2008) 261-71.

[36] L. Wang, E. Khor, L.Y. Lim, Chitosan e alginate cacl2 system for membrane coat application. J. Pharm. Sci. 90 (2001) 1134-1142.

[37] A.J. Ribeiro, G. Silva, D. Ferreira, F. Veiga, Chitosan-reinforced alginate microspheres obtained through the emulsification/internal gelation technique. Eur. J. Pharm. Sci. 25 (2005) 31-40.

[38] S. Gupta, S.P. Vyas, Carbopol/chitosan based pH triggered in situ gelling system for ocular delivery of timolol maleate. Sci. Pharm. 78(4) (2010) 959-976.

[39] E.A. Klausner, E. Lavy, M. Friedman, A. Hoffman, Expandable gastroretentive dosage forms. J. Control. Release. 90 (2003) 143–162. Doi: 10.1016/S0168-3659(03)00203-7.

[40] E.A. Essa, F.E. Elkotb, E. EZ Eldin, G.M. El Maghraby, Development and evaluation of glibenclamide floating tablet with optimum release. J. Drug Deliv. Sci. Tec. 27 (2015) 28-36.

[41] K.-M. Hwang, C.-H. Cho, N.-T. Tung, J.-Y. Kim, Y.-S. Rhee, E.-S. Park, Release kinetics of highly porous floating tablets containing cilostazol. Eur. J. Pharm. Biopharm.115 (2017) 39-51. Soi: 10.1016/j.ejpb.2017.01.027.

[42] M. Mamdouh, A. Donia, E. Essa, G. El Maghraby, Preparation of Liquid Oral Mucoadhesive Gastro-retentive System of Nimodipine. Curr. Drug Deliv. 16(9) (2019) 862-871.

[43] M. Tang, K. Alvani, R. Tester, Production and utilization of gastric rafts from polysaccharide combinations to induce satiety: a preliminary study. Nutr. Food Sci. 40 (2010) 155-165.

[44] W. Kubo, S. Miyazaki, M. Dairau, M. Togashi, R. Mikami, D. Attwood, Oral sustained delivery of ambroxol from in situ-gelling pectin formulations. Int. J Pharm. 271 (2004) 233-240.

[45] D.K. Patel, C.N. Patel, Formulation and Evaluation of Floating Oral In Situ Gelling System of Amoxicillin. ISRN Pharmaceutics. 2011 (2011) 1-8.

[46] G. Rohith, B.K. Sridhar, A. Srinatha, Floating drug delivery of a locally acting H2-antagonist: An approach using an in situ gelling liquid formulation. Acta Pharm. 59 (2009) 345-354.

[47] N.A. Abou Youssef, A.A. Kassem, M.A. El-Massik, N.A. Boraie, Develop­ment of gastro-retentive metronidazole floating raft system for targeting Helicobacter pylori. Int. J. Pharm. 486 (2015) 297-305.

[48] J.R. Madan, B.R. Adokar, D. Kamal, Development and evaluation of in situ gel of pregabalin. Int. J. Pharm. Inves. 5(4) (2015) 226-233.

[49] O. Rosenzweig, E. Lavy, I. Gati, Development and in vitro characteriza­tion of floating sustained release drug delivery systems of polyphenols. J. Drug Deliv. 20 (2013) 180-189.

[50] M. Jafar, M. Salahuddin, S.R. Bolla. Gastric floating in-situ gel as a strategy for improving anti-inflammatory activity of meloxicam. J. Appl. Pharm. Sci. 8(11) (2018) 95-102.

[51] S.L. Jadhav, S.K. Banerjee, Formulation and evaluation of floating in situ gel of Nizatidine. Int. J. Res. Pharm. Sci. 4(2) (2013) 250-255.

[52] R. Bashir, S.N. Raza, S. Kawoosa, T.U. Wani, N.A. Khan, Formulation and evaluation of floating oral in situ gelling system of losartan potassium. Int. J. Pharm. Sci. Res. 10(4) (2019) 2045-2053.

[53] C. Atuma, V. Strugala, A. Allen,L. Holm, The adherent gastrointestinal mucus gel layer: thickness and physical state in vivo. Am. J. Physiol. Gastrointest. Liver Physiol. 280(5) (2001) G922-G929.

[54] [S. Rençber](https://pubmed.ncbi.nlm.nih.gov/?term=Ren%C3%A7ber+S&cauthor_id=27055376), [S.Y. Karavana](https://pubmed.ncbi.nlm.nih.gov/?term=Karavana+SY&cauthor_id=27055376), [Z.A. Şenyiğit](https://pubmed.ncbi.nlm.nih.gov/?term=%C5%9Eenyi%C4%9Fit+ZA&cauthor_id=27055376), [B. Eraç](https://pubmed.ncbi.nlm.nih.gov/?term=Era%C3%A7+B&cauthor_id=27055376), [M.H. Limoncu](https://pubmed.ncbi.nlm.nih.gov/?term=Limoncu+MH&cauthor_id=27055376), [E. Baloğlu](https://pubmed.ncbi.nlm.nih.gov/?term=Balo%C4%9Flu+E&cauthor_id=27055376), Mucoadhesive in Situ Gel Formulation for Vaginal Delivery of Clotrimazole: Formulation, Preparation, and in Vitro/in Vivo Evaluation. Pharm Dev Technol. 22(4) (2017) 551-561.

[55] P. Mura, N. Mennini, C. Nativi, [B. Richichi](https://pubmed.ncbi.nlm.nih.gov/?term=Richichi+B&cauthor_id=29032194), In situ mucoadhesive-thermosensitive liposomal gel as a novel vehicle for nasal extended delivery of opiorphin. Eur. J. Pharm. Biopharm. 22 (2018) 54-61.

[56] J.A.Yang, J. Yeom, B.W. Hwang, [A.S. Hoffman,](https://www.sciencedirect.com/science/article/pii/S0079670014000811" \l "!) [S.K. Hahn](https://www.sciencedirect.com/science/article/pii/S0079670014000811#!). In situ-forming injectable hydrogels for regenerative medicine. Prog. Polym. Sci. 39(12) (2014) 1973-1986.

[57] K. Kesavan, G. Nath, J.K. Pandit, Sodium alginate based mucoadhesivesystem for gatifloxacin and its in vitro antibacterial activity. ScientiaPharmaceutica. 78 (2010) 941-995.

[58] D.H. Shastri, H.D. Dodiya, P. Shelat, A.K. Bhanupriy, Formulation Development and Evaluation of a Gastroretentive in situ oral gel of Cefuroxime Axetil. J. Young Pharm. 8(4) (2016) 324-329.

[59] N.G. Rao, M. Subhan, Development of Nimodipine Fast Dissolving Tablets: Effect of Functionality of Hydrophilic Carriers on Solid Dispersion Technique. J. Pharm. Biomed. Sci. 8(10) (2010) 1-7.

[60] B. Mishra, B.L. Sahoo, M. Mishra, D. Shukla, V. Kumar, Design of a controlled release liquid formulation of lamotrigine. DARU. 2 (2011) 126-137.

[61] A. Saxena, K.A. Mishra, N. Verma, S. Shiv, S.S. Bhattacharya, A. Ghosh, A. Verma, J.K. Pandit, Gelucire Based In Situ Gelling Emulsions: A Potential Carrier for Sustained Stomach Specific Delivery of Gastric Irritant Drugs. BioMed Res. Int. 2013 (2013) 1-11.

[62] M. Trofimiuk, K. Wasilewska, K. Winnicka, How to Modify Drug Release in Paediatric Dosage Forms? Novel Technologies and Modern Approaches with Regard to Children’s Population. Int. J. Mol. Sci. 20(13) (2019) 3200. Soi:10.3390/ijms20133200

[63] M.N. Singh, K.S.Y. Hemant,M. Ram,H.G. Shivakumar, Microencapsulation: A promising technique for controlled drug delivery. Res. Pharm. Sci. 5 (2010) 65-77.

[64] Y. Kojima, T. Ohta, K. Shiraki, R. Takano, H. Maeda, Y. Ogawa, Effects of spray drying process parameters on the solubility behavior and physical stability of solid dispersions prepared using a laboratory-scale spray dryer. Drug Dev. Ind. Pharm.39 (2013) 1484-1493.

[65] K. Cal, K. Sollohub, Spray Drying Technique. I: Hardware and Process Parameters. J. Pharm. Sci. 99 (2009) 575-586.

[66] J. Emami, J. Varshosaz, F. Ahmadi, Preparation and evaluation of a liquid sustained release drug delivery system for theophylline using spray drying technique. Research in Pharmaceutical Sciences. 2 (2007) 1-11.

[67] S. Harsha, Pharmaceutical suspension containing both immediate/sustained-release amoxicillin-loaded gelatin nanoparticles: preparation and in vitro characterization. Drug Des. Devel. Ther. 7 (2013) 1027-1033.

[68] Full Prescribing Information Zmax®. Available online: <https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050797s024lbl.pdf> (accessed 5 April 2019).

[69] I. Singh, A.K. Rehni, R. Kalra, G. Joshi, M. Kumar, H.Y. Aboul-Enein, Ion exchange resins: Drug delivery and therapeutic applications. FABAD J. Pharm. Sci. 32 (2007) 91-100.

[70] U. Kadam, D.M. Sakarkar, P.S. Kawtikwar, Development and Evaluation of Oral Controlled Release Chlorpheniramine-Ion Exchange Resinate Suspension. Indian J. Pharm. Sci. 70(4) (2008) 531-534.

[71] Full Prescribing Information Dyanavel XR®. Available online: <http://dyanavelxr.com/pdfs/pi.pdf> (accessed 5 April 2019).

[72] Full Prescribing Information MST® Continous®. Available online: <https://www.medicines.org.uk/emc/>product/1015/smpc#PHARMACOKINETIC\_PROPS (accessed on 5 April 2019).

[73] Full Prescribing Information Quillivant XR®. Available online: [https://www.fda.gov/downloads/Drugs/Drug Safety/DrugShortages/UCM602794.pdf](https://www.fda.gov/downloads/Drugs/Drug%20Safety/DrugShortages/UCM602794.pdf) (accessed on 5 April 2019).

[74] Tussionex® Drug Information: Description, User Reviews, Drug Side E  
ects, Interactions—Prescribing Information. Available online: <https://www.rxlist.com/tussionex-drug.htm> (accessed on 5 April 2019).

**Table 1:** An overview of alginate and non-alginate based approaches for preparing oral liquid controlled release formulations.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug** | **Use** | **Design** | **Polymer** | **Reference** |
| Cefpodoxime Proxetil | Antibiotic | Liquid oral *in situ* gelling | Pectin and gellan | [10] |
| Montelukast sodium | Antiasthmatic | Pluronic F127 and Xyloglucan | [11] |
| Nateglinide | Antidiabetic | Calcium free alginate and alginate/chitosan | [13] |
| Cimetidine | H2-antagonist | Gellan gum, enzyme-degraded xyloglucan or sodium alginate | [8] |
| Paracetamol | Anti-inflammatory | Xyloglucan (1.5%w/v) and alginate (0.5%w/v) | [29] |
| Paracetamol | Anti-inflammatory | Alginate and methylcellulsose | [30] |
| Levetiracetam | Antiepileptic | Drug-Eudragit® solid dispersion in alginate | [31] |
| Dextromethorphan | Antitussive | [32] |
| Losartan potassium | Antihypertensive | [33] |
| Ranitidine | H2-antagonist | Floating gastro-retentive *in situ* gelling liquid | Sodium alginate and calcium carbonate | [46] |
| Amoxicillin | Antibiotic | Alginate with hydroxypropyl methyl cellulose | [45] |
| Pregabalin | Anti-neuropathic pain | [48] |
| Nizatidine | H2-antagonist | [51] |
| Ofloxacin | Antibiotic | [26] |
| Losartan potassium | Antihypertensive | [52] |
| Meloxicam | Anti-inflammatory | Solid dispersion with hydroxypropyl beta-cyclodextrin and diethylamine in sodium alginate dispersion | [50] |
| Cefuroxime Axetil | Antibiotic | Gastro-retentive mucoadhesive system | Sodium alginate, pectin and hydroxypropylmethyl cellulose | [58] |
| Nimodipine | anti-ischemic | sodium alginate and carboxymethyle cellulose | [42] |
| Piroxicam | Anti-inflammatory | Emulsion-based system | Gelucire 39/01, alginate solution and Calcium carbonate | [61] |
| Mebeverine hydrochloride | Antispasmodic | HPMC and alginate | [27] |
| Theophylline | Antiasthmatic | Micro and nano particles-based modified release systems | Hydroxyl propyl methyl cellulose phthalate or ethyl cellulose | [66] |
| Amoxicillin | Antibiotic | Gelatin | [67] |
| Azithromycin | Antibiotic | Poloxamer 407 and glyceryl behenate | [68] |
| Chlorpheniramine maleate | Anti-histaminic | Drug Resin Complex | Indion 244, crosslinked polystyrene with a free sulphuric acid group | [70] |
| Amphatmine | CNS stimulant | Polystyren sulfate acoated with povidone and polyvinyl acetate | [71] |

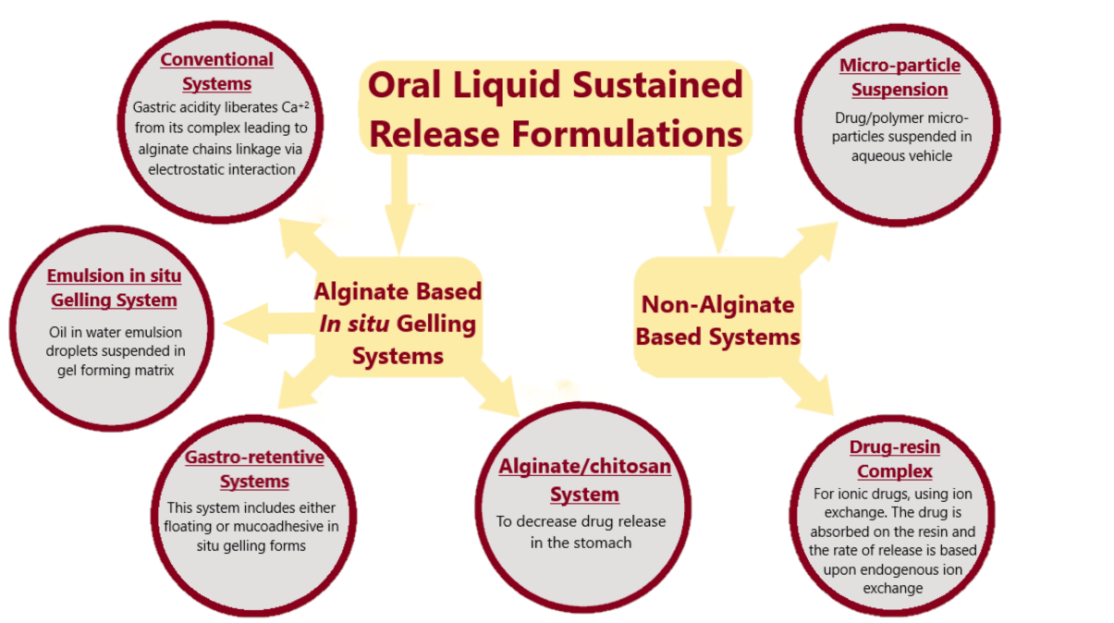
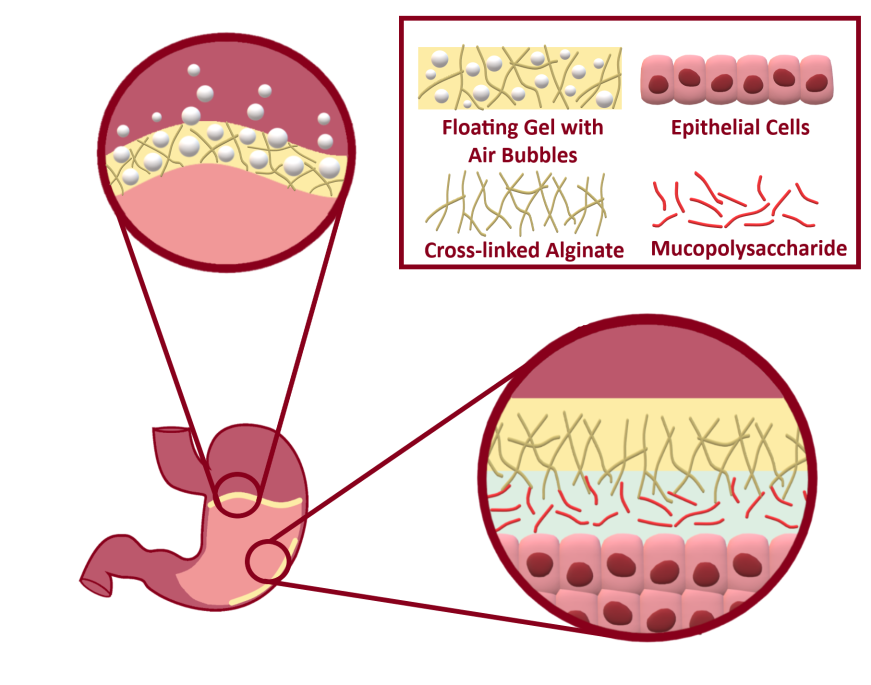
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Fig 1



**Fig 2**



**Fig 3**

**Figure legend**

**Figure 1:** Illustration of the common techniques adopted to formulate oral liquid controlled release formulations.

**Figure 2:** Illustration of the backbone structure of alginate chains showing possible arrangement of mannuronic and guluronic acid blocks (a), together with crosslinking mechanism with calcium ions (b).

**Figure 3:** Schematic illustration of different mechanisms of gastro-retentive liquid oral drug delivery system.