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ALGINATE AS POTENTIAL MUCOSAL DRUG DELIVERY SYSTEM

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ABSTRACT

Alginate is a naturally occurring polysaccharide from marine-sourced brown algae. Its physicochemical properties like solubility, biodegradation, and biocompatibility make it useful in drug delivery. The mucoadhesive property of alginate indicates its use as a potential drug carrier in mucosal delivery systems. In the recent past, delivery of drugs on the mucosal side has been dramatically increased due to prolonged residential time, localised drug action, lower systemic drug concentration, and bypassing of the first pass metabolism. This review article provides an overview of alginate and its use as different drug carriers in mucosal delivery systems.

Keywords: Alginate, Mucoadhesive, Mucosal delivery system, Drug carrier

INTRODUCTION

Mucus is a semi-permeable membrane that allows for the exchange of water, hormones, nutrients, and gasses while also preventing the entry of various pathogens due to its adhesive property and acting as a steric barrier **[1]**. Different organs contain mucus of different compositions and different thicknesses, but the function remains the same. The mucus present in the stomach is the thickest one, and in the case

of the intestine, the mucus gradually thins out **[2-4]**. Mucoadhesion is the process of bioadhesive interaction between formulations and the mucosal epithelium layer **[5]**. The main advantage of a mucoadhesive system is the prolongation of residence time at the site of absorption. The mucociliary clearance system acts as the body's own natural defense mechanism against the deposition of various impurities on the mucosal membrane **[6]**. The water solubility, molecular weight, and chemical stability of drugs also play a major role in the process of mucoadhesion and penetration. The drug molecules, which possess lower hydrophilicity, small molecular size, and neutral surface charge, are able to pass through the mucosal layer easily **[7]**. In recent advancements, drug penetration through the mucosal membrane is influenced by the disruption of the mucosal membrane and achieves greater bioavailability **[8]**.

The mucous membrane is mainly composed of electrolytes, glycoproteins, water, fats, cell components, proteins, immune factors, and enzymes. The pH of the mucus differs from the regional basis of the body. The ocular mucous membrane exhibits a slightly basic, whereas, in the airways section it shows a neutral pH. The luminal surface of the gastric mucus exhibits a highly acidic and the epithelial surface shows a neutral pH **[9-11]**. The mucous layer is composed of mucin fibers which are secreted from the submucosal glands and the goblet cells. Mucins are high molecular weight glycoproteins that consist of threonine, proline, and serine units in a very high amount. These residues are glycosylated with fructose, N- acetyl galactosamine, sialic acids, N-acetylglucosamine and galactose. Because of the presence of the sulfate and carboxyl groups, mucin has a negative charge **[12]**. Mucins are of two types, membrane-bound mucins, or secreted mucins. The properties like signal transduction, pathogen binding, and cellular adhesion are exhibited by the membrane-bound mucins, whereas the viscoelastic property of the mucus is exhibited by the secreted mucins **[9, 13]**. There are 21 genes which encode the whole mucin, and among them, 15 genes are expressed in the gastrointestinal system. The gastrointestinal tract contains MUC2, MUC5AC, MUC5B, MUC6, and MUC7 mucins, among which the MUC2 mucin is the most predominant one. The salivary gland has MUC5B and MUC7 mucins. The mucin in the cervix region is MUC4 and MUC5B. At the ocular site, MUC5AC is found to be the primary mucin. If any mucin gets expressed or localized altered, then it will lead to various pathological conditions, mainly including cancers and ulcerative colitis. Aging also leads to the gradual decrease of the thickness of the

colonic mucus layer as a result of gene expression, which is involved in the biosynthesis of the mucus **[2, 9, 12, 14, 15]**. There are mainly two barriers for drug diffusion across the mucus layer. The first one is the clearance of the mucus, which creates a limited time window for the diffusion of the drug across the membrane. This turnover time is directly proportional to the thickness of the mucus layer. The thinnest mucus layer is present in the eye, so that the turnover time is very much shorter here **[4]**. The second one is the mucin network itself, which acts as a steric barrier by forming a size exclusion filter for compounds with high molecular weights. The average mesh spacing present in the intestinal mucus is close to about 200 nm. It was found that the rate of diffusion of the drug particles across the membrane was inversely proportional to their particle size. Rather than this, the mucous membrane also shows weak Van der Waals interaction with the drug compounds and the functional groups which are produced by the glycans like the sulfate, carboxylic and hydroxyl moieties **[1, 16]**.

Various polymers are being explored for use in these mucoadhesive drug delivery systems. Among all the polymers, alginate is the most capable one. Alginates are the types of natural polymers that are generally derived from the brown marine algae cell walls and also from brown seaweed for commercial purposes **[17]**. Chemically, the alginates are the salts of various alginic acids and their derivatives. It contains a linear polysaccharide made up of divalent alginic acid salts **[18-21]**. The alginate possesses an egg-box-like structure, which helps with the ionotropic gelation. The cost-effective production and absence of toxic materials in alginate, which eventually leads to easy drug incorporation in the system and easy control of the rate of swellability and release of the drug from the system **[22-24]**. So, in this review we are going to explain how the alginates have the potential to become one of the most promising candidates for the preparation of mucosal drug delivery systems.

SOURCES AND EXTRACTION PROCEDURE OF ALGINATES

Alginic acid salts and their derivatives are known as alginates. The alginates are produced commercially by extraction and purification from the brown seaweeds of the Rhodophyceae, Ascophyllum, Sargassum, Durvillaea, Ecklonia, Laminaria, and Macrocystis classes. Among all the varieties, the Sargassum variety is used for commercial production of alginates due to its higher yield and high quality **[19-21]**. Other than the seaweeds, various algae like Macrocystis pyrifera, Laminaria hyperborea, Laminaria digitata, Laminaria japonica, and Ascophyllum nodosum are also used for the production

of alginates **[25]**. The alginates are found to be produced by bacteria like Pseudomonas putida, Azotobacter vinelandii, Pseudomonas aeruginosa, Pseudomonas mendocina, Pseudomonas syringae, and Pseudomonas fluorescens. Among the bacteria, Azotobacter vinelandii is used for the industrial production of alginates **[26]**.

Extraction of alginate is a series of processes. Washed and dried algae are de-pigmented by 2% formaldehyde and then washed with deionized water. After that, it is treated with a 0.2M HCl solution for 24 hrs. Again, it is washed with deionized water and followed by treatment with 2% sodium carbonate for 5 h with continuous stirring. The supernatant liquid is collected through a centrifugation process, followed by washing with ethanol, methanol, and acetone in an orderly manner. The pure sodium alginate gets precipitated out and that precipitate is collected, dried and stored for the required period of time **[25, 27]**.

CHEMISTRY OF ALGINATES

Chemically, alginates are high molecular weight linear unbranched polysaccharides composed of C-5 epimer, α-L Guluronic acid (G) and β-D mannuronic acid (M) by (1,4) glycosidic bonds. The molecular weight and degree of polymerization of alginates are 20,000-6,00,000 g/M and 100-3,000, respectively **[28]**. The M and G segments are arranged in different sequences and form homopolymer M (MMMMM), G (GGGGG) blocks and heteropolymer M and G blocks (MGMGMG) as shown in **Figure 1**. This type of arrangement was first discovered by Haug in the year 1959; later, with the help of 1H and 13C NMR spectroscopy results, the structures were justified **[22]**. If the G-G blocks are linked together with the help of α-(1,4) glycosidic bonds, it leads to the formation of the 1C4 chair form. The formation of a 4C1 chair occurs when M-M are linked together via a -(1,4) glycosidic bond. Due to the presence of the bulky carboxylic groups in the polymeric chain, it leads to the formation of equatorial/equatorial, equatorial/axial and axial/axial glycosidic bonds in M-M, M-G and G-G, respectively, which results in the formation of buckled stiff polymers in the regions of G-block, flexible ribbon polymers in the regions of M-block and intermediate stiffed regions of MG-block **[22]**. In nature, the alginates are found abundantly in seawater in the form of Sr2+, Mg2+and Na+ metal cations. The degradation of the alginates is higher when the pH ranges are greater than 10.0 and lower than 5.0. Among all the alginate varieties, the sodium salt of alginic acid shows better aqueous solubility and is widely used **[29]**.

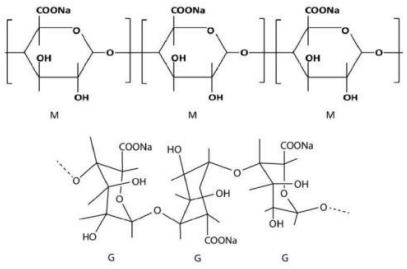

Figure 1: Structure of alginate

MUCOADHESIVE PROPERTY OF ALGINATES

There are two steps in the mucoadhesion process. The first one is the contact stage, where the formulation comes in contact with the mucus membrane, swells and spreads over it and produces a deep contact with the layer **[30]**. The next one is the consolidation step, where the mucoadhesive systems get activated due to the presence of moisture. The plasticization of the system occurs when it comes in contact with moisture, which eventually helps to break the mucoadhesive molecules. It is able to create links through hydrogen bonds and the weak Van der Waals force **[5]**. The consolidation step is properly described by two theories, which are the diffusion theory and the dehydration theory **[31]**. The polymers have to show certain characteristics to be a candidate for the mucoadhesive polymer, like they have to be non-irritant, non-toxic, non-absorbable, have the ability to form strong non-covalent bonds, be able to adhere quickly to the tissues, and have to show better storage usage stability **[32]**. They undergo an aqueous transformation from sol to gel followed by water insoluble salts in the addition of divalent ions like strontium, calcium, and barium. Among all of them, the calcium alginates are generally used for this system, which includes gels, beads, films, sponges, and microparticles **[30]**. In particular, the negatively charged polysaccharides of alginates are widely used in the preparation of mucoadhesive microparticles as the polyanionic mucoadhesive polymers **[33]**.

DIFFERENT MUCOADHESIVE DRUG DELIVERY STRATEGIES

Several alginates-based mucosal drug delivery strategies are shown in **Figure 2**.

Figure 2: Alginate based mucosal drug delivery strategies

Nanoparticles

Due to their small size, nanoparticles are one of the most preferable candidates for mucoadhesive delivery systems. They offer a much greater surface area, and they can be made to adhere to the mucus membrane more efficiently, which results in better absorption. It is also able to protect the peptides from various enzymatic activities and extreme pH values **[34, 35]**. Insulin-loaded mucoadhesive nanoparticles have been successfully prepared using alginate and chitosan by ionotropic gelation of the

alginate followed by a complexation of chitosan polyelectrolyte **[36]**. Poly (lactic-co-glycolic acid) (PLGA) nanoparticles of pilocarpine have been developed by the solvent evaporation method, and mucoadhesive properties have been imparted by coating with sodium alginate **[37]**.

Microspheres

In general, microspheres have great potential to be a targeted and controlled-release mucoadhesive drug delivery system. They also possess higher bioavailability, better biocompatibility, and a wider variety of drug encapsulations, including nucleic acids and proteins. Due to their high surface-to-volume ratio, they are able to produce better intimate contact with the mucous membrane, providing better absorption and bioavailability of the drug **[38]**. Alginate based mucoadhesive microspheres of metformin HCl have been prepared by ionotropic gelation along with Linum usitatissimum mucilage (LSM) for sustained release **[39]**. In another study, mucoadhesive microspheres containing gliclazide were formulated by the same process but tamarind seed polysaccharide (TSP) was employed instead of LSM **[40]**.

Mucoadhesive beads

The mucoadhesive beads are very similar to the microspheres. They possess a high surface area and are able to encapsulate a wide variety of drugs, and show better biocompatibility and higher bioavailability **[41, 42]**. In a research study, the ionotropic gelation process was initiated for the formation of alginate-based mucoadhesive gastro-retentive beads of rebamipide where Carbopol 934 was added as a viscosity modifying polymer **[43]**. Mucoadhesive beads have been formulated following ionotropic gelation using okra (Hibiscus esculentus) gum and sodium alginate for sustained release of glibenclamide **[44]**.

Tablets

Of all the pharmaceutical dosage forms, tablets are the most famous and most widely used because of their higher patient compliance. Due to their greater surface-to-volume ratio, they can also adhere to the mucosal tissue lining of the stomach and can produce localized drug action in a controlled manner **[45]**. Another research finding revealed that the mucoadhesive sustained release tablet of lafutidine was formulated by direct compression where sodium alginate, karaya gum, and xanthan gum were used as matrix formers **[46]**.

***In-situ* gels**

For use in the delivery system, alginate-based gel forming systems or in-situ gel forming systems are extremely advantageous. The cross-linking of the alginate chains occurs via the calcium ions either by the internal setting method or by the diffusion method **[47-49]**. An oral sustained release in situ gelling system of

famotidine based on sodium alginate was studied **[50]**. A mucoadhesive and thermosensitive in situ gel containing nimesulide was studied based on sodium alginate, hydroxypropyl methylcellulose, and poloxamer 407 **[51]**.

Hydrogels

Hydrogels have the ability to hold biological fluids or aqueous solutions in very high amounts due to the presence of 2D or 3D network structures. The presence of hydrophilic groups in the molecular chains means they possess a high affinity for water and show better porosity, elasticity, and swelling capacity **[52, 53]**. An ion-activated mucoadhesive hydrogel system based on sodium alginate and sodium carboxymethyl cellulose has been studied for ophthalmic delivery of gatifloxacin sesquihydrate **[54]**. In another study, administration of oral insulin has been made by hydration of prepared microspheres using alginate and whey protein, where insulin entrapment was achieved by a diffusion mechanism across the hydrogel layer of the microsphere **[55]**.

A few alginate based mucosal delivery of commonly used therapeutic agents are summarized in **Table 1**.

Table 1: Application of alginate in mucosal delivery of drugs

Applications	Polymeric composition	Type of drug carrier	Drug	References
Antibiotic Drug Delivery	Alginate and chitosan	Membrane	Metronidazole	[56]
	Alginate-chitosan	Polyelectrolyte complex film	Clindamycin	[57]
	Sodium alginate, gellan and sodium carboxymethyl cellulose	Ion-activated hydrogel	Gatifloxacin	[54]
NSAID drug delivery	Alginate- sericin	Mucoadhesive particles	Ibuprofen	[58]
	Alginate	Hybrid aerogel microparticles	Ketoprofen	[59]
	Alginate	Hydrogels	Ketorolac	[60]
Anti-diabetic drug delivery	Alginate and ispaghula husk mucilage	Beads	Glibenclamide	[61]
	Alginate and ispaghula	Beads	Gliclazide	[41]
	Alginate and whey protein	Hydrogel microsphere	Insulin	[55]
	Alginate and jackfruit seed starch	Beads	Metformin HCl	[62]
Anti-ulcer drug delivery	Alginate	Beads	Rebamipide	[43]
	Sodium alginate	*In situ* gel	Famotidine	[50]
Miscellaneous	Sodium alginate and the hydroxypropyl methylcellulose	Films	Cetirizine dihydrochloride	[63]
	Alginate, cholesterol and 1,2-dimyristoyl-sn-glycero-3-phosphocholine	Liposomal paste	doxorubicin	[64]
	Alginate	Solid lipid nanoparticles containing *in-situ* gel	Almotriptan	[65]
	Sodium alginate	Microspheres	Metoclopramide	[66]
	Sodium alginate	Microspheres	Carvedilol	[67]

CONCLUSION

The utility of alginate in different forms of drug delivery systems as a drug carrier is summarized in this review. The mucoadhesive property of alginate in formulations like nanoparticles, microspheres, beads, tablets, in-situ gels, and hydrogels causes prolongation of the

residence time of the formulation at the mucosal side and provides slow drug release for a longer period of time. Mucosal drug delivery systems have the potential to reduce systemic drug concentrations, improve local drug action, and avoid pre-systemic drug metabolism. The source, extraction process, and chemistry of alginate are outlined. The favorable compatibility, biodegradation, muco-adhesion, and non-toxic characteristics have aided its versatile application in pharmaceutical and biomedical fields.

REFERENCES

[1] Bandi SP, Bhatnagar S, Venuganti VV, Advanced materials for drug delivery across mucosal barriers, Acta Biomaterialia, 119, 2021, 13-29.

[2] Boegh M, Nielsen HM, Mucus as a barrier to drug delivery–understanding and mimicking the barrier properties, Basic & Clinical Pharmacology & Toxicology, 116(3), 2015, 179-86.

[3] Murgia X, Loretz B, Hartwig O, Hittinger M, Lehr CM, The role of mucus on drug transport and its potential to affect therapeutic outcomes, Advanced Drug Delivery Reviews, 124, 2018, 82-97.

[4] Lai SK, Wang YY, Hanes J, Mucus-penetrating nanoparticles for drug and gene delivery to mucosal tissues, Advanced Drug Delivery Reviews, 61(2),2009, 158-71.

[5] Swain S, Behera A, Beg S, N Patra C, C Dinda S, Sruti J, EB Rao M, Modified alginate beads for mucoadhesive drug delivery system: an updated review of patents, Recent Patents on Drug Delivery & Formulation, 6(3), 2012, 259-77.

[6] Carvalho FC, Bruschi ML, Evangelista RC, Gremião MP, Mucoadhesive drug delivery systems, Brazilian Journal of Pharmaceutical Sciences, 46(1), 2010, 1-7.

[7] Araújo F, Martins C, Azevedo C, Sarmento B, Chemical modification of drug molecules as strategy to reduce interactions with mucus, Advanced Drug Delivery Reviews, 124, 2018, 98-106.

[8] Das Neves J, Sarmento B, Technological strategies to overcome the mucus barrier in mucosal drug delivery, Advanced Drug Delivery Reviews, 124, 2018, 1-2.

[9] Leal J, Smyth HD, Ghosh D, Physicochemical properties of mucus and their impact on transmucosal drug delivery, International Journal of Pharmaceutics, 532(1), 2017, 555-72.

[10] Pezzulo AA, Tang XX, Hoegger MJ, Abou Alaiwa MH, Ramachandran S, Moninger TO, Karp PH, Wohlford-Lenane CL, Haagsman HP, Van Eijk M, Bánfi B, Reduced airway surface pH impairs bacterial killing in the porcine cystic fibrosis lung, Nature, 487(7405), 2012, 109-13.

[11] Clarke MA, Rodriguez AC, Gage JC, Herrero R, Hildesheim A, Wacholder S, Burk R, Schiffman M, A large, population-based study of age-related associations between vaginal pH and human papillomavirus infection, BMC Infectious Diseases, 12(1), 2012, 1-9.

[12] Dhanisha SS, Guruvayoorappan C, Drishya S, Abeesh P, Mucins: Structural diversity, biosynthesis, its role in pathogenesis and as possible therapeutic targets, Critical Reviews in Oncology/Hematology, 122, 2018, 98-122.

[13] Jonckheere N, Skrypek N, Frénois F, Van Seuningen I, Membrane-bound mucin modular domains: from structure to function, Biochimie, 95(6), 2013, 1077-86.

[14] Elderman M, Sovran B, Hugenholtz F, Graversen K, Huijskes M, Houtsma E, Belzer C, Boekschoten M, De Vos P, Dekker J, Wells J, The effect of age on the intestinal mucus thickness, microbiota composition and immunity in relation to sex in mice, PloS One, 12(9), 2017, 184274.

[15] Sovran B, Hugenholtz F, Elderman M, Van Beek AA, Graversen K, Huijskes M, Boekschoten MV, Savelkoul HF, De Vos P, Dekker J, Wells JM, Age-associated impairment of the mucus barrier function is associated with profound changes in microbiota and immunity, Scientific Reports, 9(1), 2019, 1-3.

[16] Bajka BH, Rigby NM, Cross KL, Macierzanka A, Mackie AR, The influence of small intestinal mucus structure on particle transport ex vivo, Colloids and Surfaces B: Biointerfaces, 135, 2015, 73-80.

[17] Hasnain MS, Jameel E, Mohanta B, Dhara AK, Alkahtani S, Nayak AK, Alginates: sources, structure, and properties In Alginates in Drug Delivery, Academic Press, 2020, 1-17.

[18] Karmakar S, Manna S, Kabiraj S, Jana S, Recent progress in alginate-based carriers for ocular targeting of therapeutics, Food Hydrocolloids for Health, 2022, 100071.

[19] Andersen T, Melvik J E, Gåserød O, Alsberg E, Christensen B E, Ionically gelled alginate foams: physical properties controlled by operational and macromolecular parameters, Biomacromolecules, 13(11), 2012, 3703-3710.

[20] Sari-Chmayssem N, Taha S, Mawlawi H, Guégan JP, Jeftić J, Benvegnu T, Extracted and depolymerized alginates from brown algae Sargassum vulgare of Lebanese origin: Chemical, rheological, and antioxidant properties, Journal of Applied Phycology, 28(3), 2016, 1915-1929.

[21] Manna, S., & Jana, S. Marine polysaccharides in tailor-made drug delivery. Current Pharmaceutical Design, 28(13), 2022, 1046-1066.

[22] Onsøyen E, Alginates. In Thickening and gelling agents for food, Springer, 1997, 22-44.

[23] Smrdel P, Bogataj M, Mrhar A, The influence of selected parameters on the size and shape of alginate beads prepared by ionotropic gelation, Scientia Pharmaceutica, 76(1), 2008, 77-90.

[24] Racoviţă S, Vasiliu S, Popa M, Luca C, Polysaccharides based on micro- and nanoparticles obtained by ionic gelation and their applications as drug delivery systems, Revue Roumaine de Chimie, 54(9), 2009, 709-18.

[25] Manna S, Mal M, Das S, Mandal D, Bhowmik M, Ionically Gelled Alginates in Drug Delivery, In Ionically Gelled Biopolysaccharide Based Systems in Drug Delivery, Springer, 2021, 29-53.

[26] Trujillo-Roldán MA, Moreno S, Espín G, Galindo E, The roles of oxygen and alginate-lyase in determining the molecular weight of alginate produced by Azotobacter vinelandii, Applied Microbiology and Biotechnology, 63(6), 2004, 742-7.

[27] Fertah M, Belfkira A, Taourirte M, Brouillette F, Extraction and characterization of sodium alginate from Moroccan Laminaria digitata brown seaweed, Arabian Journal of Chemistry,10, 2017, S3707-14.

[28] Aprilliza M, Characterization and properties of sodium alginate from brown algae used as an ecofriendly superabsorbent, IOP Conference Series: Materials Science and Engineering, 188, 2017, 012019.

[29] Goh CH, Heng PW, Chan LW, Alginates as a useful natural polymer for microencapsulation and therapeutic applications, Carbohydrate Polymers, 88(1), 2012, 1-2.

[30] Asati S, Jain S, Choubey A, Bioadhesive or mucoadhesive drug delivery system: a potential alternative to conventional therapy, Journal of Drug Delivery and Therapeutics, 9(4-A), 2019, 858-67.

[31] Andrews GP, Laverty TP, Jones DS, Mucoadhesive polymeric platforms for controlled drug delivery, European Journal of Pharmaceutics and Biopharmaceutics, 71(3), 2009, 505-18.

[32] Vinod KR, Rohit Reddy T, Sandhya S, David Banji VR, Critical review on mucoadhesive drug delivery systems, Hygeia- Journal for Drugs and Medicines, 4(1), 2012, 1-5.

[33] Mortazavi SA, Moghimi HR, Effect of surfactant type and concentration on the duration of mucoadhesion of carbopol 934 and HPMC solid compacts, Iranian Journal of Pharmaceutical Research, 20(4), 2010, 191-9.

[34] Al-Dhubiab BE, Nair AB, Kumria R, Attimarad M, Harsha S, Formulation and evaluation of nano-based drug delivery system for the buccal

delivery of acyclovir, Colloids and Surfaces B: Biointerfaces, 136, 2015, 878-84.

[35] Mansuri S, Kesharwani P, Jain K, Tekade RK, Jain NK, Mucoadhesion: A promising approach in drug delivery system, Reactive and Functional Polymers, 100, 2016, 151-72.

[36] Sarmento B, Ribeiro A, Veiga F, Sampaio P, Neufeld R, Ferreira D, Alginate/chitosan nanoparticles are effective for oral insulin delivery, Pharmaceutical Research, 24(12), 2007, 2198-206.

[37] Yoncheva K, Vandervoort J, Ludwig A, Development of mucoadhesive poly (lactide-co-glycolide) nanoparticles for ocular application, Pharmaceutical Development and Technology, 16(1), 2011, 29-35.

[38] Kumari N, Aggarwal G, Harikumar SL, Mucoadhesive microspheres: A review. Journal of Drug Delivery and Therapeutics, 4(5), 2014, 48-54.

[39] Ghumman SA, Noreen S, tul Muntaha S, Linum usitatissimum seed mucilage-alginate mucoadhesive microspheres of metformin HCl: Fabrication, characterization and evaluation, International Journal of Biological Macromolecules, 155, 2020, 358-68.

[40] Pal D, Nayak AK, Novel tamarind seed polysaccharide-alginate mucoadhesive microspheres for oral gliclazide delivery: in vitro–in vivo evaluation, Drug Delivery, 19(3), 2012, 123-31.

[41] Nayak AK, Hasnain MS, Beg S, Alam MI, Mucoadhesive beads of gliclazide: Design, development, and evaluation, Science Asia, 36(4), 2010, 319-25.

[42] Nayak AK, Pal D, Pradhan J, Hasnain MS, Fenugreek seed mucilage-alginate mucoadhesive beads of metformin HCl: Design, optimization and evaluation, International Journal of Biological Macromolecules, 54, 2013, 144-54.

[43] Kashid P, Doijad R, Shete A, Sajane S, Bhagat A, Studies on Rebamipide Loaded Gastroretentive Alginate Based Mucoadhesive Beads: Formulation & In-vitro, In-vivo Evaluation, Pharmaceutical Methods, 7(2), 2016.

[44] Sinha P, Ubaidulla U, Nayak AK, Okra (Hibiscus esculentus) gum-alginate blend mucoadhesive beads for controlled glibenclamide release, International Journal of Biological Macromolecules,72, 2015, 1069-75.

[45] Rajput GC, Majmudar FD, Patel JK, Patel KN, Thakor RS, Patel BP, Rajgor NB, Stomach specific mucoadhesive tablets as controlled drug delivery system–A review work, International Journal of Pharmacy and Biological Research, 1(1), 2010, 30-41.

[46] Patil S, Talele GS. Gastroretentive mucoadhesive tablet of lafutidine for

controlled release and enhanced bioavailability, Drug Delivery, 22(3), 2015, 312-9.

[47] Essa EA, Elebyary TT, Abdelquader MM, El Maghraby GM, Elkordy AA, Smart liquids for oral controlled drug release: An overview of alginate and non-alginate-based systems, Journal of Drug Delivery Science and Technology, 61, 2021, 102211.

[48] Draget KI, Taylor C, Chemical, physical and biological properties of alginates and their biomedical implications, Food Hydrocolloids, 25(2), 2011, 251-6.

[49] Pawar SN, Edgar KJ, Alginate derivatization: A review of chemistry, properties and applications. Biomaterials, 33(11), 2012, 3279-305.

[50] Modasiya MK, Prajapati BG, Patel VM, Patel JK, Sodium alginate based in situ gelling system of Famotidine: preparation and in-vivo characterizations, Journal of Science and Technology, 5(1), 2010, 27-42.

[51] Yuan Y, Cui Y, Zhang L, Zhu HP, Guo YS, Zhong B, Hu X, Zhang L, Wang XH, Chen L, Thermosensitive and mucoadhesive in situ gel based on poloxamer as new carrier for rectal administration of nimesulide, International Journal of Pharmaceutics, 430(1-2), 2012, 114-9.

[52] Hanafy NA, Leporatti S, El-Kemary MA, Mucoadhesive hydrogel nanoparticles as smart biomedical drug delivery system, Applied Sciences, 9(5), 2019, 825.

[53] Vashist A, Vashist A, Gupta YK, Ahmad S, Recent advances in hydrogel-based drug delivery systems for the human body, Journal of Materials Chemistry B, 2(2), 2014, 147-66.

[54] Kesavan K, Kant S, Pandit JK, Therapeutic effectiveness in the treatment of experimental bacterial keratitis with ion-activated mucoadhesive hydrogel, Ocular Immunology and Inflammation, 24(5), 2016, 489-92.

[55] Déat-Lainé E, Hoffart V, Garrait G, Jarrige JF, Cardot JM, Subirade M, Beyssac E, Efficacy of mucoadhesive hydrogel microparticles of whey protein and alginate for oral insulin delivery, Pharmaceutical Research, 30(3), 2013, 721-34.

[56] Tentor F, Siccardi G, Sacco P, Demarchi D, Marsich E, Almdal K, Bose Goswami S, Boisen A, Long lasting mucoadhesive membrane based on alginate and chitosan for intravaginal drug delivery, Journal of Materials Science: Materials in Medicine, 31(3), 2020, 1-2.

[57] Kilicarslan M, Ilhan M, Inal O, Orhan K, Preparation and evaluation of clindamycin phosphate loaded chitosan/alginate polyelectrolyte complex film as mucoadhesive drug delivery system for periodontal

therapy, European Journal of Pharmaceutical Sciences, 123, 2018, 441-51.

[58] Freitas ED, Vidart JM, Silva EA, da Silva MG, Vieira MG, Development of mucoadhesive sericin/alginate particles loaded with ibuprofen for sustained drug delivery, Particuology, 41, 2018, 65-73.

[59] Gonçalves VS, Gurikov P, Poejo J, Matias AA, Heinrich S, Duarte CM, Smirnova I, Alginate-based hybrid aerogel microparticles for mucosal drug delivery, European Journal of Pharmaceutics and Biopharmaceutics, 107, 2016, 160-70.

[60] El Moussaoui S, Fernández-Campos F, Alonso C, Limón D, Halbaut L, Garduño-Ramirez ML, Calpena AC, Mallandrich M, Topical Mucoadhesive Alginate-Based Hydrogel Loading Ketorolac for Pain Management after Pharmacotherapy, Ablation, or Surgical Removal in Condyloma Acuminata, Gels, 7(1), 2021, 8.

[61] Nayak AK, Pal D, Santra K, Plantago ovata F. Mucilage-alginate mucoadhesive beads for controlled release of glibenclamide: development, optimization, and in vitro-in vivo evaluation, Journal of Pharmaceutics, 2013,151035.

[62] Nayak AK, Pal D, Formulation optimization and evaluation of jackfruit seed starch–alginate mucoadhesive beads of metformin HCl, International Journal of Biological Macromolecules, 59, 2013, 264-72.

[63] Pamlényi K, Kristó K, Jójárt-Laczkovich O, Regdon G, Formulation and Optimization of Sodium Alginate Polymer Film as a Buccal Mucoadhesive Drug Delivery System Containing Cetirizine Dihydrochloride, Pharmaceutics,13(5), 2021, 619.

[64] Shtenberg Y, Goldfeder M, Prinz H, Shainsky J, Ghantous Y, El-Naaj IA, Schroeder A, Bianco-Peled H, Mucoadhesive alginate pastes with embedded liposomes for local oral drug delivery, International Journal of Biological Macromolecules, 111, 2018, 62-9.

[65] Abou Youssef NA, Kassem AA, Farid RM, Ismail FA, Magda Abd Elsamea EM, Boraie NA, A novel nasal almotriptan loaded solid lipid nanoparticles in mucoadhesive in situ gel formulation for brain targeting: preparation, characterization and in vivo evaluation, International Journal of Pharmaceutics, 548(1), 2018, 609-24.

[66] Gavini E, Rassu G, Sanna V, Cossu M, Giunchedi P, Mucoadhesive microspheres for nasal administration of an antiemetic drug, metoclopramide: in-vitro/ex-vivo studies, Journal of Pharmacy and Pharmacology, 57(3), 2005, 287-94.

[67] Patil SB, Sawant KK, Development, optimization and in vitro evaluation of alginate mucoadhesive microspheres of carvedilol for nasal delivery, Journal of Microencapsulation, 26(5), 2009, 432-43.