IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

A REVIEW ON GASTRO-RETENTIVE MUCOADHESIVE MICROSPHERES

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Abstract Drugs that are easily absorbed from the gastrointestinal tract (GIT) and have a short half-life are eliminated quickly from the blood circulation and require frequent dosing. To avoid this, and increase the gastric residence time developed GRDDS. The gastroretentive drug delivery system is a novel drug delivery system to prolong gastric retention time thereby targeting the drug to the desired site i.e. to the upper gastrointestinal tract for local or systemic action improving the bioavailability of the drugs. Mucoadhesion is the process whereby synthetic and natural polymers adhere to mucosal surfaces in the body. If these materials are then incorporated into pharmaceutical formulations, drug absorption by mucosal cells may be enhanced or the drug will be released at the site for an extended period. mucoadhesive drug delivery systems generally are the family of hydrogels, such as natural gums, polyacrylates, and cellulose ethers. Microspheres, in general, have the potential to be used for targeted and controlled-release drug delivery. Mucoadhesive microspheres are an ideal targeting system with high safety profile and have been developed for oral, buccal, nasal, ocular, rectal, and vaginal for either systemic or local effects.

Keywords: gastroretentive drug delivery, physiology of stomach, mucoadhesive microsphere preparation, evaluation, current research outcome.

INTRODUCTION

Oral drug delivery systems have dominated other drug delivery systems for human administration due to their various advantages including ease of administration, flexibility in formulation, cost-effectiveness, easy storage and transport, and high patient compliance. However, oral drug delivery systems face challenges such as low bioavailability due to the heterogeneity of the gastrointestinal system, pH of the commensal flora, a gastric retention time of the dosage form, surface area, and enzymatic activity [1]

Conventional drug delivery systems may not overcome the issues imposed by the gastrointestinal tract (GIT) such as incomplete release of drugs, decrease in dose effectiveness, and frequent dose requirement. Therefore, the failure of conventional drug delivery systems to retain drugs in the stomach may lead to the development of novel drug delivery systems, such as the GRDDS. These systems offer several benefits such as prolonged gastric residence time (GRT) of dosage forms in the stomach up to several hours, the increased therapeutic efficacy of drugs by improving drug absorption, and suitability for targeted delivery in the stomach [1,2] GRDDS are feasible for drugs that have low absorption in the lower part of the GIT, are unstable and poorly soluble at alkaline pH, have a short half-life, and show local activity at the upper part of the intestine for eradication of Helicobacter pylori. Several formulation strategies have been used.

The concept of mucosal adhesives, or mucoadhesives, was introduced into the controlled drug delivery arena in the early 1980s.[3] Mucoadhesives are synthetic or natural polymers that interact with the mucus layer covering

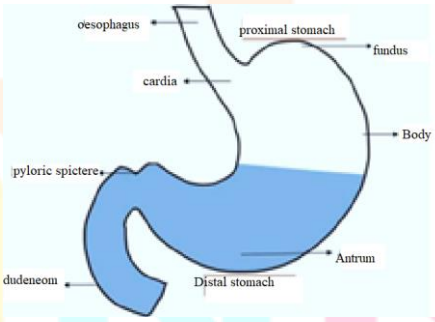
the mucosal epithelial surface and mucin molecules constituting a major part of the mucus. The concept of mucoadhesion has alerted many investigators to the possibility that mucoadhesive polymers can be used to overcome physiological barriers in long-term drug delivery.[4]

Microspheres have become a vital part of such oral systems because of their small size, ranging from 1 to 1000 μm, and high carrier capacity. Microspheres are drug cores with outer layers of an inert polymer. However, the main drawback of these systems is the short residence time.

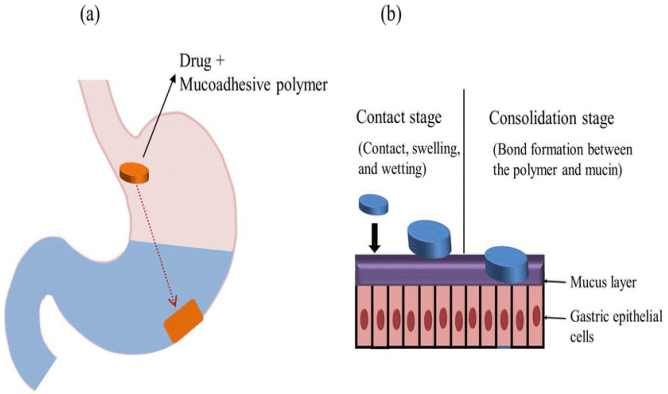
Mucoadhesive microspheres are mucoadhesive-polymer-made micro-particles. [5] Combining bioadhesion properties to microspheres results in mucoadhesive microspheres which resolve this problem by providing enhanced and efficient contact with the absorption membrane. [6] Such microspheres exhibit additional advantages, including more intimate contact with the mucus layer and efficient absorption. Entrapped inside mucoadhesive microspheres, the drug can be continuously released at the mucosal surface, thus achieving higher bioavailability. Therefore, it is conceivable that the drug delivery system that combined nanocrystals with enteric-coated mucoadhesive microspheres could achieve a higher dissolution percentage during the residence time and high drug loading capacity, as well as prolong the residence time of the drug in the intestine, the absorption site. Mucoadhesive microspheres efficiently target drugs to the absorption site by anchoring bacterial adhesions, plant lectins, antibodies, etc. by adhering to any mucosal tissue of eye, nasal cavity, urinary, and GI tract; custom-developed mucoadhesive microspheres offer localized and controlled release of drugs.

Physiology of Stomach

In the GRDDS, the stomach has a crucial role; therefore, a good understanding of the anatomy and physiology of the stomach is a prerequisite for the successful development of the gastroretentive dosage form. Anatomically, the stomach is divided into two parts: the proximal stomach, which consists of the fundus and body; and the distal stomach, which consists of the antrum and the pylorus as shown in the below Figure The main role of the stomach is to store the food temporarily, grind it, and then slowly release it into the duodenum. The fundus and body primarily act as reservoirs for undigested food, whereas the antrum acts as a pump to assist in gastric emptying by a propelling action. The mobility pattern of the stomach is termed as the migrating myoelectric complex (MMC); Gastric emptying occurs in both the fed and fasted states, but the pattern of gastric emptying drastically varies between both states. In the fasted state, an inner digestive sequence of electrical events follows cyclically through both the stomach and the small intestine every 90–120 min.



The mucoadhesive/bioadhesive system was designed to adhere to the gastric epithelial cell surface and prolong the GRT of drug compounds.[7] In this approach, drugs are incorporated in a mucoadhesive agent, which can be either natural or synthetic polymers. Bonding established between the polymer and mucosal surface facilitates the mucoadhesion process, which generally involves two steps: the contact stage and the consolidation stage. Commonly used mucoadhesive polymers include Carbopol, chitosan, sodium alginate, HPMC, polyethylene glycol, and poly (acrylic acid). Mucoadhesive polymers assist in binding drug substances to the mucosal surfaces and prolonging the drug residence time at the application site.



Factors affecting gastric retention

The gastric retention time (GRT) of dosage forms is controlled by several factors. The density and size of the dosage form, Fed and fasted stomach, and dietary components such as fat, certain amino acids, and peptides can slow gastric emptying and intestinal transit. The patents position, posture, age, sex, sleep, and disease state of the individual (e.g., gastrointestinal diseases and diabetes) can also alter motor activity, thus slowing transit time. Certain Drug combinations that contain gastro-kinetic agents such as metoclopramide and cisapride have been marketed and can also affect gastric retention. [8]

Advantages of GRDDS

- Reduced counter-activity of the body.
- Minimization of fluctuations in drug concentration.
- Sustained drug delivery/reduced frequency of dosing.
- Enhanced bioavailability.
- Targeted therapy for local ailments in the upper GIT.
- Effective concentration extended time and then minimized the adverse activity in the colon.
- Enhanced first-pass biotransformation.
- Reduced fluctuations of drug concentration.[9]

Ideal characteristics of mucoadhesive microspheres

- Good control of active reagent release over a wide time scale.
- Susceptibility to chemical modification.
- Biocompatibility with controllable biodegradability.
- The ability to incorporate reasonably high concentrations of the drug.
- After synthesis stability of preparation with a clinically acceptable shelf life.
- Convert liquid to solid form & mask the bitter taste.
- Decrease dose and toxicity.
- Reduce the dosing frequency and thereby improve the patient compliance
- The drug is protected from enzymatic and photolytic cleavage and therefore found to be wide for drug delivery of protein.[10]

Theories Of Mucoadhesion

1. The Electronic Theory

According to this theory, an electrical double layer is formed on the transfer of electrons between the mucoadhesive and mucosal membranes.

2. The Wetting Theory

This theory applies to liquids and postulates that the lower the contact angle of the liquid on the substrate surface, the greater affinity for adhesion.

3. The Adsorption Theory

According to this theory, the mucoadhesive gets adsorbed on the mucosal surface by intermolecular forces, viz. Vander Waal's forces, hydrogen bonding, etc.

4. The Diffusion Theory
This theory illustrates the forming of a network structure among the mucoadhesive and the mucosal surface by diffusion of the polymer chains present on the mucoadhesive surface.

5. The Mechanical Theory
Explains the formation of an interlocked structure by the diffusion of the liquid adhesives into the micro-cracks and irregularities present on the mucoadhesive substrate resulting in mucoadhesion.

6. The Cohesive Theory
According to this theory, the phenomena of mucoadhesion is mainly due to the intermolecular interactions amongst like-molecules [11]

Mucoadhesive Materials
Mucoadhesive polymers have numerous hydrophilic groups, such as hydroxyl, carboxyl, amide, and sulfate. These groups attach to mucus or the cell membrane by various interactions such as hydrogen bonding and hydrophobic or electrostatic interactions. These hydrophilic groups also cause polymers to swell in water and, thus, expose the maximum number of adhesive sites.[12]

An ideal polymer characteristic for a bioadhesive drug delivery
1. The polymer and its degradation products should be nontoxic and nonabsorbable.
2. It should be non-irritant.
3. It should preferably form a strong noncovalent bond with the mucus or epithelial cell surface.
4. It should adhere quickly to moist tissue and possess some site specificity.
5. It should allow easy incorporation of the drug and offer no hindrance to its release.
6. The polymer must not decompose on storage or during the shelf life of the dosage form.
7. The cost of the polymer should not be high so that the prepared dosage form remains [13,14]

Classification and Examples of Mucoadhesive Polymer
Source
Natural and modified natural Source, synthetic solubility:
Water-soluble
Agarose, chitosan, Gelatin, hyaluronic acid, carrageenan, pectin, sodium alginate.

Cellulose derivatives
Carboxymethylcellulose, Sodium carboxymethylcellulose, thiolated Carboxymethylcellulose, hydroxypropyl methylcellulose, methylcellulose.

Polymers based on poly(meth)acrylic acid
Polycarbophil, Carbopol, polyacrylates, polyacrylic acid, a copolymer of acrylic acid and polyethylene glycol, ethyl hexyl acrylate, a copolymer of methyl vinyl ether and methacrylic acid, polymethacrylate, poly-2-hydroxyethyl methacrylate, a copolymer of acrylic acid and polyalkylcyanoacrylates: polyisobutylcyanoacrylate, polyisohexylcyanoacrylate.

Factors Affecting Mucoadhesion
Mucoadhesion may be affected by several factors, including hydrophilicity, molecular weight, cross-linking, swelling, pH, and the concentration of the active polymer.[15]
- Hydrophilicity
- Molecular Weight
- Cross-linking and Swelling
- Spatial Conformation
- pH
- The concentration of Active Polymer
- Drug/Excipient Concentration

Method and preparation of mucoadhesive microsphere

Microspheres can be prepared by using different techniques

- Complex coacervation
- Hot melt microencapsulation
- Single emulsion techniques
- Double emulsion method
- Solvent removal
- Ion tropic Gelatin
- Phase inversion method
- Spray drying. [16]
-

Complex coacervation:

The principle of this method is under the suitable condition when a solution of two hydrophilic colloids was mixed, resulting in a separation of the liquid precipitate. In this method, the coating material phase is prepared by dissolving immiscible polymer in a suitable vehicle and the core material is dispersed in a solution of coating polymer under constant stirring. Microencapsulation was achieved by utilizing one of the methods of phase separation, that is, by changing the ph of the medium, by adding a salt or an incompatible polymer or a non-solvent to the polymer solution; by including a polymer-polymer interaction. Generally, the coating is hardened by thermal cross-linking or desolation technique, to form a self-sustaining microsphere [17]

Hot melt microencapsulation

This method was first used by Mathiowitz and Lengerto to prepare microspheres of polyanhydride copolymer of poly (P-carboxy phenoxy) propane anhydride) with sebacic acid. In this method, the polymer was first melted and then mixed with solid particles of the drug that had been sieved to less than 50µm. the mixture was suspended in a non-miscible solvent (like silicon oil), continuously stirred, and heated to 5 °C above the melting point of the polymer. When the emulsion stabilized it was left for cooling until the polymer particles solidified.

The resulting microspheres were washed with petroleum ether. The main objective for developing this method was to develop a microencapsulation process suitable for the water labile polymers, e.g., polyanhydride. Microspheres with a diameter of 1-1000 µm could be obtained and the size distribution could be easily controlled by changing the stirring rate. The major limitation of this method is that it is not suitable for thermolabile substances [18]

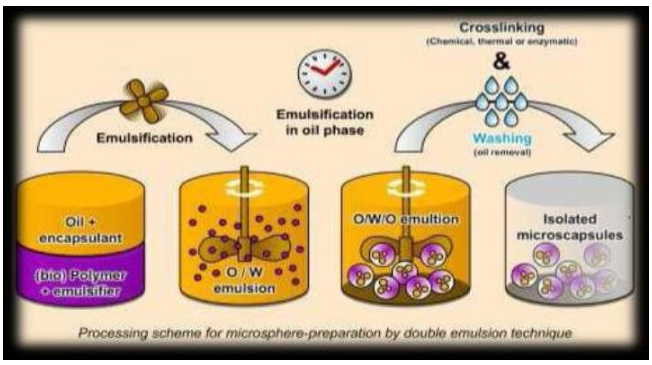
Single emulsion technique: Generally, by this technique carriers of natural polymers like protein and carbohydrates are prepared. The natural polymers are dissolved or dispersed in an aqueous medium followed by dispersion in non-medium-like oil. Next cross-linking of the dispersed globule is carried out. The cross-linking can be achieved either using heat by using chemical cross-linkers. The chemical cross-linking agent used is glutaraldehyde, formaldehyde, Diacid chloride, tetra phthalate chloride, etc (Sinha first step in next step cross-linking is carried out by two methods.

- **Cross-linking by heat:** by adding the dispersion into heated oil, but it is unsuitable for the thermolabile drugs.
- **Chemical cross-linking agent:** by using agent i.e. formaldehyde, die acid chloride, Glutaraldehyde, etc. but it is having the disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifuge, washing, and separation. chitosan solution (in acetic acid) by adding to liquid paraffin containing a surfactant resulting formation of w/o emulsion (Jayaprakash, 2007 hydrochloride microsphere are prepared by using glutaraldehyde 25% solution as cross-link [19]

Double emulsion technique: Double emulsion method of microsphere preparation involves the formation of the emulsion of type w/o/w and is best suited for water-soluble drugs, peptides, proteins, and vaccines. This method can be used with both natural as well as synthetic polymers

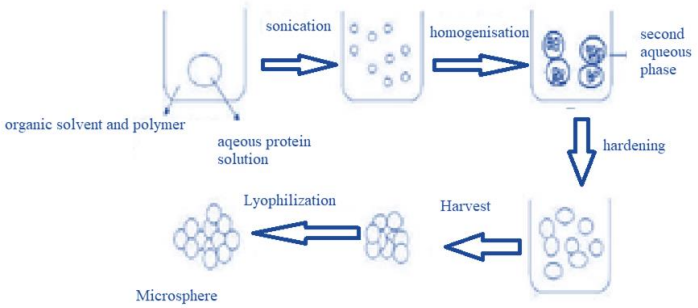
The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain active constituents. The continuous phase generally consists of the polymer solution that eventually encapsulation the protein contained in the dispersed aqueous phase. The primary emulsion is subjected then to the homogenization of the sonication before addition to the aqueous solution of the polyvinyl alcohol (PVA). This results in the formation of the double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction. Several hydrophilic drugs like luteinizing hormone-releasing

hormone (LH-RH) agonists, vaccines, proteins /peptides, and conventional molecules are successfully incorporated into the microspheres using the method of double emulsion solvent evaporation extraction. [16]



microspheres preparation double emulation techniques

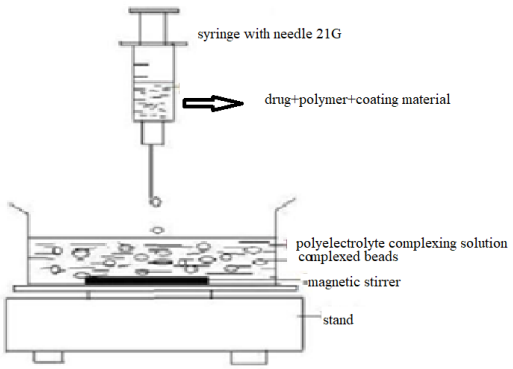
Solvent evaporation/ removal: This is a non-aqueous method of microencapsulation and is most suitable for water-labile polymers such as poly anhydrides. The method involves dissolving the polymer into a volatile organic solvent and the drug is dispersed or dissolved in it, this solution is then suspended in the silicon oil containing span 85 and methylene chloride under stirring. Then petroleum ether is added and stirred until the solvent is extracted into the oil solution the obtained microsphere was then subjected to vacuum drying [20]



solvent removal/ evaporation method microspheres preparation

Ionotropic gelation technique: sodium alginate and the mucoadhesive polymer is dispersed in purified water (50 ml) to form a homogeneous polymer mixture. The drug is added to the polymer matrix and mixed thoroughly to form smooth viscous dispersion. The resulting dispersion is then sprayed calcium into chloride (10% w/v) solution by continuous stirring. Produced droplets are retained in the calcium chloride solution for 15 minutes to complete the curing reaction and the thus separated are washed repeatedly with purified water to remove excess calcium impurity deposited on the surface of the microsphere and then dried at 45 °C for 12 hrs

Mechanism: The microsphere prepared by the ionotropic gelatin technique mechanism involves electrostatic interaction between amine groups of the polymer and negatively charged groups of polyanion such as tripolyphosphate. The chemical reaction between sodium alginate and calcium chloride to form calcium alginate was utilized for microsphere formation. As calcium ions are being released by ion exchange with sodium ions in the medium, electrostatic repulsion between the carboxylate anions further accelerates the swelling and erosion of alginate gels. On account of short time release in alkaline media, alginate was not found to be an ideal sustained release wall material for microencapsulation



by ion tropic gelation method for microspheres preparation

Phase inversion method: The method involves the addition of the drug into a dilute polymeric solution, in ethylene chloride; and the resultant mixture is poured into an unstirred bath of strong non-solvent, petroleum ether, in a ratio of 1:100. Microspheres produced are then clarified, washed with petroleum ether and air dried.[20]

EVALUATION OF MUCOADHESIVE MICROSPHERES

The microspheres are evaluated for the following parameters.

1. Particle Size and Shape

Light microscopy (LM) and scanning electron microscopy (SEM) both can be used to determine the size, shape, and outer structure of microspheres. [18]

2. Surface Characterization of The Mucoadhesive Microspheres

Data from scanning electron microscopy, scanning tunneling microscopy and electron microscopy provides insight into the surface morphology of microspheres and the morphological changes produced through the degradation of polymer. Changes in the surface morphology occurring through the degradation of polymer can be studied by incubating the microspheres in the phosphate buffer saline at different intervals of time. It was found that microspheres with the coarser surface improve adhesion through stronger mechanical interactions, while the smooth surface of the microspheres leads to weak mucoadhesive properties. [21]

3. Surface Charge Study

From photon correlation spectroscopy data the surface charge (zeta potential) of the mucoadhesive microspheres can be determined. The surface charge can be determined by relating measured electrophoretic mobility to zeta potential with in-built software based on the Helmholtz– Smoluchowski equation. Zeta potential is an indicator of particle surface charge, which can be used to predict and control the adhesive strength, stability, and mechanisms of mucoadhesion. [22]

4. Entrapment Efficiency

The entrapment efficiency of the microspheres or the percent entrapment can be determined by keeping the microspheres in the buffer solution and allowing lysing. The lysate obtained is filtered or centrifuged and then subjected to the determination of active constituents as per the monograph requirement. The percent entrapment efficiency is calculated using the following equation 12: % Entrapment = Actual content/Theoretical content x 100

5. Swelling Index

The swelling index illustrates the ability of the mucoadhesive microspheres to get swelled at the absorbing surface by absorbing fluids available at the site of absorption, which is a primary requirement for the initiation of mucoadhesion.[23] The percent swelling value can be determined using the following equation.

Percent swelling = DT - D0 / D0 × 100

Where, D0 = weight of dried microspheres

DT = weight of swelled microspheres. [24]

6. In Vitro/Ex Vivo Methods

To evaluate the mucoadhesive strength of the microspheres, various in vitro/ex vivo methods are employed as follows:

a. Shear strength measurement

The shear stress measures the force that causes a mucoadhesive to slide concerning the mucus layer in a direction parallel to their plane of contact. The CAHN dynamic contact angle analyzer has been modified to perform adhesive microforce measurements. The system consists of an IBM-compatible computer and a microbalance assembly. The microbalance unit consists of a stationary sample, tare loops, and a motor-powered translation stage. The instrument measures the bioadhesive force between mucosal tissue and a single microsphere mounted on a small diameter metal wire suspended from the sample loop in a microtensiometer. [25]

b. In- Vitro Release Study

Standard IP/BP/USP dissolution apparatus is used to study in-vitro release profile in the dissolution media that is similar to the fluid present at the absorption site as per monograph, using a rotating basket or paddle-type dissolution apparatus. [26]

c. Ex-Vivo Mucoadhesion Study

The mucoadhesive property of the microspheres is evaluated on the goat's intestinal mucosa by using phosphate buffer, as per the monograph. Weighed microspheres are spread onto wet rinsed tissue specimens and immediately thereafter the slides are hung onto the arm of a USP tablet disintegrating test machine with suitable support at 370C. The weight of microspheres leached out at different intervals is measured. The % mucoadhesion is calculated by the [27]

Literature review on mucoadhesive microspheres in gastro retentive delivery systems

Sl no	Drug	Polymers	Outcome
1	Acyclovir	Sodium Alginate	*In vivo* studies showed a gastric residence time of more than 4 h which revealedthat optimized formulation could be a good choice for a gastro retentive system. [28]
2	Atenolol	HPMC K 15M, Carbopol 1974p	In vivo, radio imaging studies in rabbits showed the residence of Mucoadhesive microspheres for 6-8 h in the upper part of GIT.[29]
3	Famotidine	Sodium CMC, Sodium Alginate	With the increase in polymer concentration the mucoadhesion increases. [30]
4	Acyclovir	Ethyl cellulose and Carbopol974P	The bioavailability of acyclovir was greatly improved due to the prolonged retention of ACV in the gastrointestinal tract. [31]
5	Delapril hydrochloride	Polyglycerol esters of fattyacids	The mean residence time of the drug is increased and the plasma concentration of activemetabolite is sustained. [32]
6	Erythromycin	Gelatin	Erythromycin-loaded microspheres were prolonged compared with that of erythromycin without gelatin microspheres. [33]
7	Metoclopramide	Chitosan	Showed good Mucoadhesion up to 8 hrs. [34]
8	Dextran	Thiolated chitosan	Effective mucoadhesive potential. [35]
9	Clarithromycin	Chitosan	Enhanced bioavailability with sustained release. [36]
10	Amoxicillin/ Clarithromycin	PAA[a] with PVP[b]	The dissolution rate of complex microspheres was significantly slower than that ofPVP-alone microspheres. [37]
11	Enorfloxacin	Chitosan-PAA	Enhanced mucoadhesive potential than chitosan alone.[38]
12	Theophylline, Thymine disulfide	Dextran derivative, CAB[c]	Improved bioavailability of the drug.[39]
13	Furosemide	Sodium alginate Chitosan	In vitro, release studies indicated that there was a slow and sustained release of drug for all the formulations. [40]
14	cefpodoxime proxetil	chitosan	Inferences show gastroretentive mucoadhesive microspheres, a potential delivery system for cefpodoxime proxetil in improving bioavailability. [41]
15	Ranitidine	HPMC K100 EUDRAGIT RS 100 sodium carboxymethylcellulose	mucoadhesive microspheres containing the polymer (Sodium alginate) and copolymer (SCMC) in the ratio of 3:1 showed maximum drug release .[42]

16	Atorvastatin calcium	Sodium Alginate Carbopol 934	The pharmacokinetic study like bioavailability was increased in rabbits due to extensive gastric residence time. [43]
17	Atorvastatin calcium	Ethylcellulose, hydroxy propyl methyl cellulose, and carbopol 940	The higher drug content and entrapment efficiency were observed as the concentration of HPMC K100M increased. [44]
18	Simvastatin	Sod. Alginate Carbopol (940) HPMC (K100M) Ethylcellulose	Simvastatin mucoadhesive microspheres were slow and extended over up to 8h and depended on the composition of the coat. [45]
19	Pioglitazone Hydrochloride	HPMC Sodium Alginate sodium carboxymethylcellulose	Pioglitazone HCl microspheres are used to decrease side effects, reduce dosing frequency and improve patient compliance [46]
20	Metformin	Carbopol Ethylcellulose	The concentration of Carbopol 934 and ethyl cellulose affected the dependent variable such as percentage of mucoadhesion, drug entrapment efficiency, etc. [47]

Conclusion

A new approach investigated to override normal gastric emptying is the use of mucoadhesive microspheres for gastroprotection. Based on this approach mucoadhesive microspheres in gastroretentive delivery systems present a promising area for continued research. Mucoadhesion is the property that can be used to adhere the microparticulate drug delivery system to the mucosal membrane. Mucoadhesive microspheres have emerged as promising drug carrier systems in the pharmaceutical industry. Mucoadhesion certainly opens up new possibilities for drug administration but given that much of the work in the field is still at the theoretical and experimental stages, the willingness and enthusiasm of the pharmaceutical industry to develop new formulations will be paramount From this review, we could conclude that various types of preparation methods along with its pharmaceutical application are being used for Microspheres as a drug delivery system for delivering the definite amount of medications in a controlled manner. It may include oral, targeted, sustained, or topical Furthermore by combining various other strategies, mucoadhesive microspheres will find a significant place in novel drug delivery.

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