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An Overview: Sustained-Release Sodium Alginate Beads

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ABSTRACT

Pharmaceutical research and inventions are potentially developed for the design of an ideal dosage regimen in drug therapy of many diseases, which attains therapeutic concentration of drug in plasma and maintains it constant for the entire duration of treatment and also minimizes the side effects. Recent trends in pharmaceutical technology indicate that mucoadhesive microparticles and alginate beads as drug delivery systems are especially suitable for achieving delivery of drugs at a predetermined rate locally or systemically for a prolonged period. The sustained release system was formulated to release a drug slowly over some time in the body. The sustained release system has the more therapeutic activity of a drug when compared to immediate release. The main aim of the present review is to explain the various polymers used, advantages and limitations, properties of alginate, mechanism of drug release from beads, method of preparation of alginate beads, characterization method, application of alginate beads, future perspectives, this review also briefly explained the updated patenting system for the development of sodium alginate beads as a drug delivery system.

INTRODUCTION:

The release of a drug from a micro-particle depends on a variety of factors, including the carrier used to form the microparticle and the amount of drug contained in it[1]. Beads are one of the most commonly used techniques in a sustained release dosage form. These are spherical particles with a size ranging from 50 nm to 2 mm, which contain core substances. The molecular size of the drug particle must be less than 1000 Dalton to formulate as SRDF[2]. Many APIs show problems like low biological availability and repeated dosing due to poor solubility and penetration through lipid membranes[3]. Among them, oral API administration is the most routine way to take medicines. Because of their short $t_{1/2}$ and less absorption through a part of the small intestine, it restricts the use of many APIs. This gives an effect on pharmacokinetic activity which causes frequent dosing of many APIs to achieve their effective dose. This causes pill burden and poor patient compliance. [4]

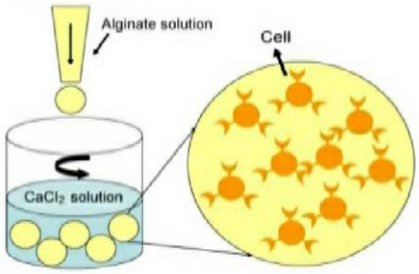

Figure No. 1: Sodium Alginate Beads.

The Particulate API delivery system is one of the approaches to improving the physicochemical properties of API. The particulate API delivery system depends on altering the physical character of the API to alter its characteristics like solubility, permeability, etc. Among the many applications of the particulate system, mucoadhesive activity is important, where API release can be controlled and designed by using repeating units of natural substances such as poliglusam, sodium alginate, and so on. The overall action of API can be controlled by the active ingredients, which have a short $t_{1/2}$ of fewer than 4 hours, which is the main reason for frequent dosing or multiple dosing of medication when using the particulate system of API delivery. The delivery system includes many pellets, beads, lipospheres, microspheres, microcapsules, etc. The various substances (polymers) used as carriers in the microsphere are chitosan, sodium alginate, gum ghatti Hpmc k100m, etc.[5]

The sustained release system was designed to release slowly over some time a drug in the body (organs or tissues). It is a system that delivers a drug to a specific target in the body

with a delay after its administration. Drugs that are easily absorbable in the gastrointestinal tract and have short $t_{1/2}$ will be eliminated quickly from the blood circulation, so they require frequent dosing to control this drawback. The sustained release formulation had been developed to maintain the drug concentration level. And to maintain the effective concentration in the blood for a longer period, in the sustained release dosage form, drug release over a sustained period but should not at a constant rate, whereas in the controlled release dosage form which maintains the drug release over a sustained period at a constant rate. Beads are spherical particles that range in size from 50 nm to 2 mm and contain the core substances. The sustained release beads are the spherical substances that contain the active pharmaceutical ingredient and are designed to release the drug at a predetermined rate at a constant concentration in the body. Khan, Ismail, & Gani, 2014. These beads were used for the modified release of medications, antibiotics, hormones, and vaccines. The oral sustained release beads are polymer-coated.[6]

1. POLYMERS USED IN THE PREPARATION OF SODIUM ALGINATE BEADS:

Natural polysaccharides have advantages over synthetic polymers like they are non-toxic, less expensive, biodegradable, and easily available.

1) The sodium alginate:

The sodium salt of alginic acid is another widely used mucoadhesive polymer for the designing of various drug delivery systems. It is a linear anionic polysaccharide obtained from biodegradable and biocompatible brown algae. Because of the presence of free carboxyl groups, it has good mucoadhesive properties, allowing the polymer to interact with mucin in the mucous membrane via hydrogen and electrostatic bonding. It has been used as a matrix material in the development of sustained-release formulation. Due to its hydrogel-forming properties, it delivers the drug over a prolonged period. In an aqueous solution and the presence of Ca^2 Al^3, etc, both GG and sodium alginate have properties to undergo ionotropic gelation. In pharmaceutical drug design, the gel-forming property of GG and mucoadhesive behavior of sodium alginate are mainly used for controlled drug delivery applications.[7]

2) Gum ghatti:

It is a complex non-starch polysaccharide obtained as amorphous translucent mucilage from wounds in the bark of the *Anogeissus latifolia* tree which was found in the deciduous forests of India and Sri Lanka. Its emulsification and thickening properties have made it widely used

in food, pharmaceuticals, paper, and other industries. It is a high molecular weight complex polysaccharide that occurs in nature as mixed calcium, magnesium, potassium, and sodium salt. Upon hydrolysis, it gives L-arabinose, D-galactose, D-mannose, D-xylose, L-rhamnose, and D-glucuronic acid. Gum ghatti was marketed in Japan as an existing food additive and was assigned "generally regarded as safe" (GRAS) status by the US FDA. Ghatti gum has also been used for preparing floating drug delivery systems and also as an emulsifying agent. [8]

3) Hydroxypropyl methylcellulose (HPMC):

The most common hydrophilic carrier material used in the preparation of oral controlled drug delivery systems is hydroxypropyl methylcellulose (HPMC). Also known as hypromellose, HPMC belongs to the group of cellulose ethers in which more than one of the three hydroxyl groups from the cellulose glucopyranose units has been substituted, forming ether linkages. The most commonly used polymers in the preparation of sodium alginate beads are hydroxyl propyl methyl cellulose k100m (HPMC k100m), carboxymethyl cellulose, etc. The rate of drug release is maximum from formulations employing CMC sodium salt as the matrix agent and is minimum from formulations employing HPMC K100M as the matrix agent. This shows that the gel formed from HPMC is more viscous and less erodible than the gel formed from CMC. Even though we have used CMC sodium salt of high viscosity, it is clear from the results that the rate of release is maximum with this polymer. [9]

2. CROSS-LINKING AGENTS:

It has been shown in different studies that the cross-linker type has a pronounced effect on the release behavior of drugs from the cross-linked matrix. In general, alginic acid is cross-linked with calcium chloride, resulting in the formation of calcium alginate hydrogel beads, there is a wide variety of physical and chemical methods of cross-linking alginates. [10]

Table No. 1: Cross-linking agents used for the preparation of alginate gel

Sr. No.	Cross-linking agent	Properties	References
A) organic			
1)	Epichlorohydrin	Beads produced are reported to be more elastic than calcium alginate beads. Also after drying and the subsequent reswelling, their pore size and dimensions remain the same.	11
2)	N, N-(3-Dimethyl - aminopropyl)-N-ethylcarbodi- imide (EDC)	Improvement observes in the mechanical properties.	12
3)	Glutaraldehyde	Enhances the mechanical stability but not recommended due to its toxicity	13
B) Inorganic			
1)	Ca^{++}	The most widely used cross-linking agent leads to the production of calcium alginate gel. Beads obtained are compact, but the pore dimensions and volume change after drying and subsequent reswelling widely used cross-linking agent leads to the production of calcium alginate gel. obtained Beads are compact, but the pore dimensions and volume change after drying and subsequent reswelling.	14
2)	Al^{++}	Affects the release profile as well as the morphology of beads.	15
3)	Zn^{++}	Release slowly as compared to calcium beads	16

3. ADVANTAGES AND LIMITATIONS OF SODIUM ALGINATE BEADS:

Table No. 2: Advantages and limitations of Sodium Alginate Beads

Advantages	Limitations
□ ideal pharmacokinetic properties □ enhance homogenous deviation in the body □ minimum dose variation in the combinations of API & less dose-dumping; separate the protect the active ingredients to give better compatibility □ The new system with an increased duration of action *Decrease dosing frequency *Improve patient compliance *Reducing side effect	* Compared to another formulation cost of this system is much higher. □ The use of synthetic polymer gives its an impact on the environment. □ The other component of the system plays a hazardous role in certain areas of human life. □ Reproducibility of preparation is minimal. □ The degradation substance of the repeating unit is produced.

4. PROPERTIES OF ALGINATES:

4.1 Solubility: Sodium alginates are slowly soluble in cold water, forming a viscous, colloidal solution. It is insoluble in alcohol and hydroalcoholic solutions in which alcohol content is greater than 30% by weight. It is also insoluble in other organic solvents such as chloroform and ether, as well as acids where the resulting solution's pH falls below 3.0.

4.2 Viscosity: Different grades of sodium alginates are available, resulting in aqueous solutions with viscosities ranging from 20 to 400 centipoises (0.02-0.4 PaS) in 1% solution at 200°C. Due to its distribution of chain lengths, alginate solutions are not Newtonian and behave as pseudoplastic fluid.

4.3 Degradation and Chemical stability: Degradation of a Ca^{2+} cross-linked alginate gel can occur by removal of the Ca^{2+} ions. This can be accomplished by the use of a chelating agent such as ethylene glycol-bis (b-aminoethyl ether)-N, N, N ', N'-tetra acetic acid (EGTA), citrate, lactate, and phosphate or by a high concentration of ions such as Na^{+} or Mg^{2+}. As Ca^{2+} ions remove the cross-linking in the gel decreased and the gels are destabilized.

4.4 Sterilization: Filtration is the simplest and least detrimental means of aseptization but mostly alginate solutions are sterilized by autoclaving rather than filtration.

4.5 Immunogenicity and Biocompatibility: Biocompatibility and immunogenicity of polymer materials are two cardinal issues for successful application in carriers for drug delivery. The chemical composition and mitogenic contaminants found in alginates, according to most authors, are two major contributors to alginate Immunogenicity.

4.6 Bioadhesion: Bioadhesion was generally defined as the adhesion or contact between two surfaces with one being a biological substratum. If one of the surfaces involved is a mucosal layer, the term mucoadhesion is used. Alginate possesses a bioadhesive property that can serve as a potential advantage in mucosal drug delivery. [17,18]

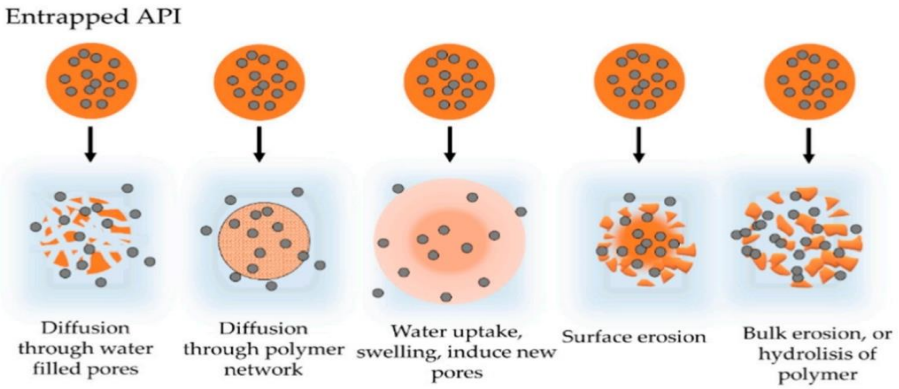

Figure No. 2: Drug Release from beads in Different ways.

The mechanism of drug release from multiparticulate can occur in the following ways:

5. MECHANISM OF ACTION MULTIPARTICULATE FLOATING DRUG DELIVERY SYSTEMS:

1. Diffusion:

When contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution can occur and the drug solutions diffuse across the release coat to the exterior.

2. Erosion:

There are Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle.

3. Osmosis:

In allowing water to enter under the right circumstances, an osmotic pressure could be built up within the interior of the particle. The drug was forced out of the particle into the exterior through the coating.[19]:

6. METHODS OF PREPARATION OF ALGINATE BEADS:

The methods for the preparation of alginate beads or microparticles should be such that they allow for the production of beads with narrow size distribution and has a high production rate. Alginate beads are conventionally prepared by extrusion through needles into calcium solutions. Air-jet, electrical potential, vibration units, etc. have been added to increase the droplet output of syringe-based systems.

1) Air atomization:

Requires an extrusion device with a small orifice through which alginate solutions containing the drug are forced. Beads are 5 to 200 µm particles that can be produced. The size of beads could be controlled by either adjusting gas and liquid flow and operating pressure or the distance between the orifice and the surface of the crosslinking solution.[20]

2) Coaxial bead generator:

Coaxial airstream pulls as droplets from a needle tip into a gelling bath. It can produce spherical beads are ranging in size down to around 400 µm.

3) Dropping method:

It is a simple method. The use of a syringe with a needle or a pipette is required. It is the most extensively utilized method for preparing the > 500 µm particles. The size of beads formed is dependent on the size of the needle used and the viscosity of the alginate solution.[21]

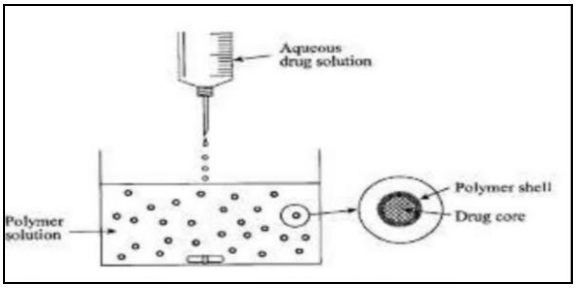

Figure No. 3: Dropping method for preparation of Alginate Beads.

4) Electrostatic bead generator:

The electrostatic force pulls droplets from the needle tip into a gelling bath. This method can generate particles ranging from 150 to 1000 m in size. Bead size depends upon the voltage and distance between the needle tip and the gelling bath, solution viscosity, flow rate of the solution as well as on needle diameter.

5) Emulsification:

Used only for stable drugs because it involves the use of harsh chemical reagents to remove oil at the end of the process. Particles with sizes ranging from 1 to 150 m could be created by this method. The size of microbeads produced depends upon stirring speed and the rate of the addition of the thess-linking solution.

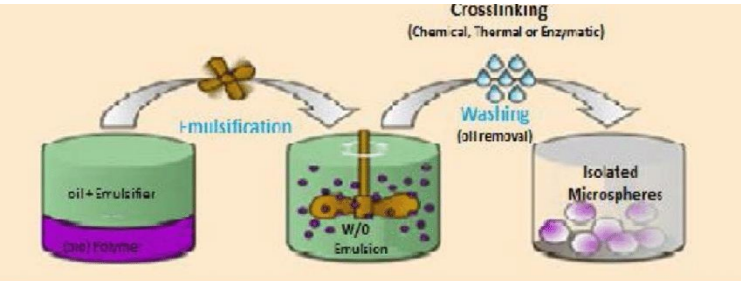

Figure No. 4: Microbeads prepare by Emulsification Methods.

6) Laminar jet breaks up technique:

A device depends on a laminar jet break up induced by applying a sinusoidal frequency with the defined amplitude to the nozzle. Normally, 300 to 600 mm particles have been produced.

7) Mechanical cutting:

Bead formation was accomplished using a rotating cutting tool that cuts the jet into uniform cylindrical segments that form spherical beads due to surface tension as they fall into a gelling bath. 150 µm to 3 mm particles can be produced.

8) Spinning disk atomization:

Bead formation was achieved by a specially designed spinning disk atomizer. These are suitable for 300 to 600 µm size particles.

9) Vibrating nozzle technique:

This encapsulation technique is based on the harmonically vibrating nozzle. More than 200 m particles can be produced using this method.[22]

10) Complex coacervation:

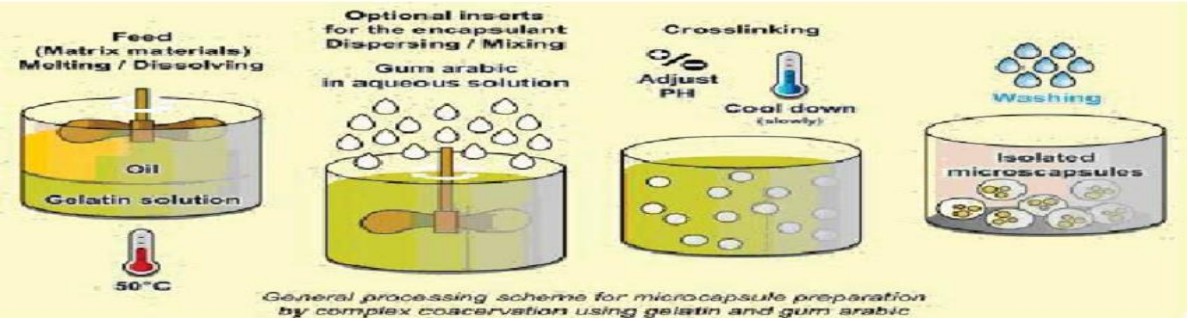

Figure No. 5: Microbeads prepared by complex conversation method using gelatin and gum Arabic.

Under specific conditions of polyion concentration, pH, and ionic strength, the polyelectrolyte mixture could separate into two distinct phases; a dense coacervate phase which can contain the microbeads, and a dilute equilibrium phase. Oppositely charged complex poly-electrolytes had been commonly used. The optimal conditions for the maximum coacervate yield are a pH of 3.9, ionic strength of 1 mM, and a total polyion concentration of 0.15% w/v.[23]

Sodium alginate beads are commonly prepared using the following methods:

1. Ionotropic Gelation Method:

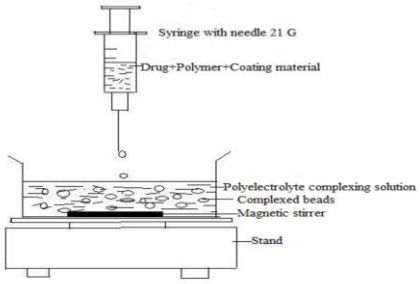

Figure No. 6: Sodium alginate beads by Ionotropic Gelation methods.

For bead formation, 50 mL of a 2-2.5 % w/v aqueous solution of sodium alginate was added dropwise from a glass syringe with a size-22G needle into 100 mL of an aqueous calcium

chloride solution being stirred at 400 rpm. The concentration of $CaCl_2$ in the solution ranged from 1% w/v to 3% w/v. The stirring should be continued for one hour and the calcium alginate beads are harvested by filtration, washed with distilled water, and air-dried overnight. The sequential method and the simultaneous method are used to load the drugs.

A) In the sequential method: calcium alginate beads were prepared as described in the previous paragraph. The wet beads were then immersed and stirred for 1 hr in a solution containing an anti-diabetic drug (concentration ranging from 2-3% w/v), filtered, and washed with distilled water. Antidiabetic drug-loaded calcium alginate beads were obtained by subsequent drying.

B) In the simultaneous method: the gelation of beads by calcium ions occurred simultaneously with the drug loading into the beads. The sodium alginate solution was introduced dropwise into $CaCl_2$ solutions (concentration ranging from 1-3% w/v) which also contained anti-diabetic drug (concentration ranging from 2-3% w/v). After 1hr of these beads were removed from the counter ion solution. The drug-loaded beads were washed and dried like that of blank beads (beads without drug).[24]

2) Emulsion Gelation Method:

The oil-entrapped calcium alginate beads were created using the emulsion gelation technique. The polymer was dissolved in water while being stirred at a speed of 100 rpm. Selected oils (2.5 ml) were added to the polymer solution. The drug 50 mg was added to it. With gentle agitation of 37°C 0.5°C at room temperature, the homogenized or non-homogenized mixture was extruded into a 5% calcium chloride solution. The formed beads are allowed to stand for 5 min in the solution and then decanted, filtered, and finally dried overnight at room temperature.[25]

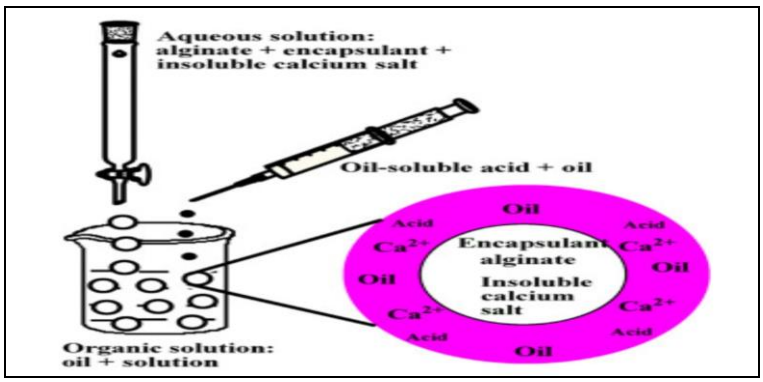

Figure No. 7: Emulsification Gelation Methods

3) Emulsion cross-linking method :

The medication was dissolved in the gelatine solution in this form, which has previously been heated at 40^0C for 1 hr. The solution was added drop by drop to liquid paraffin while at 35^0C, resulting in w/o emulsion, this mixture was roused at 1500 rpm for 10 minutes. Optional stirring should at 15^0C for 10 min. In 5 mL of aqueous glutaraldehyde saturated toluene solution at 28^0C for 3 hours for cross-linking, the spherically shaped beads were washed three times with acetone and isopropyl alcohol, respectively, air-dried and discrete. Then formed beads with a 100 mL 10 mm glycine solution containing 0.1 percent w/v between 80 and 370C are preserved for 10 min to lump unreacted glutaraldehyde. [26]

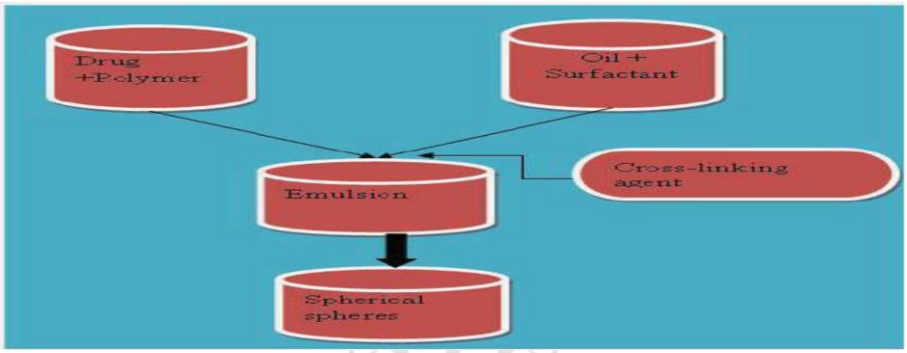

Figure No. 8: Emulsion cross-linking methods for the formation of beads.

7. CHARACTERIZATION METHODS:

1) Fourier Transform Infra-Red Spectroscopy:

The compatibility between pure drug and polymer was detected by FT-IR spectra obtained. Samples were reduced to powder and analyzed as KBr pellets by employing a Fourier transform-infrared (FTIR) spectroscope (Perkin Elmer Spectrum RX I, USA). The pellet was placed within the sample holder. Spectral scanning was taken within the wavelength region between 4000 and 400 cm^{-1} at a resolution of 4 cm^{-1} with a scan speed of 1 cm/s. [27]

2) Surface Morphology Analysis by Scanning Electron Microscopy (SEM):

Drug-coated beads were mounted on a brass stub using double-sided adhesive tape and sputtered with a tiny layer of gold (3–5 nm) under vacuum in an ion sputter for 75 s and at 20 kV to make them electrically conductive, and their morphology was observed using a scanning electron microscope (ZEISS EVO 40, Japan).

3) Bead Size Measurement:

The particle size of 100 dried beads from every batch was measured by optical microscopic technique for average particle size using an optical microscope (Olympus). The ocular micrometer was formerly calibrated by a stage micrometer. [58]

4) Measurement of Buoyancy property:

The evaluation of floating property was determined by placing 100 beads in 100 ml of gastric simulated pH of 7.4. The mixture was stirred at 50rpm with a magnetic stirrer for 2 hours. After 2 hours, the floating ability of the beads was measured by visual observation. The preparation was considered to have buoyancy when all the beads remain floating in the test solution. The layer of floating beads was collected and the buoyancy was determined by using the following formula.[28]

$$\text{Buoyancy} = \frac{\text{Weight of floating beads}}{\text{the initial weight of beads}} \times 100$$

5) Drug content of the beads:

beads (20 mg) in 20 mL of PB (pH 6.8) in amber-colored vials were sonicated for 15 min and mixed at 750 rpm for 4 hr in the dark for complete extraction of the drug. The dispersion was then centrifuged at 5000 rpm for 15 min at 15°C. The drug content of the supernatant of each sample was then measured using a validated UV method at 232 nm.[29]

6) Loose surface crystal study:

The drug-loaded microcapsules were evaluated for loose surface crystal study to calculate the excess amount of drug present on the surface of microcapsules. For that, 100 mg of microcapsule were shaken in 20 ml of pH 7.4 phosphate buffer for 5 min and filtered through a 0.45 µm membrane filter. The amount of drug present in the filtrate was determined by spectrophotometrically, which yields the total drug content. [30]

7) Percent moisture loss:

The microcapsules were evaluated for percentage moisture loss, which gives an idea about the hydrophilic nature. The weighed amount of microcapsules (W1) was initially kept in a desiccator containing calcium chloride at 37° for 24 h. The final weight (W2) was noted

when no further change in the weight of the sample was observed. Finally, the percent moisture content was determined by the following formula.

Percent moisture loss= (W1-W2/W1) ×100 ..... [31]

8) Differential scanning calorimetry (DSC):

DSC was performed for the pure drug, physical mixture of drug with polymers, and optimized microcapsules in DSC apparatus (Shimadzu DSC 60, Tokyo, Japan). Samples were heated from 30 to 300°C at the heating rate of 10°C/min in the nitrogen atmosphere (flow rate, 20 ml/min).

9) Swelling index:

The swelling index was determined by keeping the prepared microcapsules in pH 7.4 phosphate buffer solution for 12 h. After overnight wetting, these swollen microcapsules were collected and their weight was noted. From that weight of the microcapsules before and after wetting, the swelling index was calculated by the following formula.

Sw= (Wt-Wo/Wo) ×100,

where Sw=percent swelling of microcapsules,

Wt=weight of the microcapsules at time t,

Wo=initial weight of the microcapsules.

10) Determination of DEE:

100 mg of beads were taken and crushed using pestle and mortar. The crushed powders of drug-containing beads were placed in a very 250 ml volumetric flask and volume was made up to 250 ml by phosphate buffer, pH 7.4, and kept for 24 h with infrequently shaking at 37 ± 0.5^0 C. After the specified time mixture was stirred at 500 rpm for 20 min using a magnetic stirrer (Remi Motors, India). The polymer debris fashioned after the disintegration of the bead was removed by filtering through Whatman® filter paper (No. 40). The drug content within the filtrate was determined using a UV–vis spectrophotometer (Shimadzu, Japan) at 233 nm against an acceptable blank. The DEE (%) of these prepared beads was calculated by the subsequent formula.

DEE (%) =actual drug content in beads/Theoretical drug content in beads×100.. [32]

11) In Vitro Drug Release Studies.

The release of the drug from numerous beads was tested using dissolution equipment USP (Campbell Electronics, India). The baskets were enclosed with 100-mesh nylon cloth to stop the seepage of the beads. The dissolution rates were measured at 37 ± 1^0C under 50 rpm speed. Accurately weighed quantities of beads containing Vildagliptin equivalent to 100 mg were added to 900 ml of 0.1 N HCl (pH 1.2). The test was carried out for 2 h and then continued in phosphate buffer (pH 7.4) for the next 8 h. 5 ml of aliquots was collected at regular time intervals, and therefore the same quantity of fresh dissolution medium was replaced into the dissolution vessel to keep the sink condition throughout the experiment. The collected aliquots were filtered and suitably diluted to determine the absorbance using a UV–vis spectrophotometer (Shimadzu, Japan) at 233 nm against a suitable blank. [33]

12) Stability study:

The stability studies of the optimized microcapsules were carried out as per the ICH guidelines. This microcapsule was suitably packed in the high-density plastic bottles and stored at 40°C/75% RH for 3 months in the stability chamber. This microcapsule was evaluated for physicochemical properties, drug content, and in vitro drug release at specified periods (0, 1, 2, and 3 months) to assess the stability. [34]

8. PATENT LITERATURE INSTANCES ON MUCOADHESIVE MICROPARTICLE DRUG DELIVERY SYSTEMS.

Table No. 3:

Sr. No.	Type of formulation	Year of patent	Patent number	Title of the Patent	Criteria of the Selection of Patent	References
1	Microspheres	May 2001	US6235313 B1	Bioadhesive microspheres and their use as drug delivery and imaging systems.	To establish the correlation between chemical nature, surface	35

					morphology, and the dimensions of drug-loaded microspheres on one hand and bioadhesive forces on the other hand.	
2	Microspheres	February 2003	US0027780 A1	Multiparticulate formulation	Nanoparental multiparticulate formulations are capable of transporting the therapeutic prophylactic and diagnostic agent across mucosal membranes.	36
3	Nanoparticle	May 2003	US6565873 B1	Biodegradable bioadhesive controlled release system of nanoparticles for oral care products.	Site-specific controlled release delivery over the extended period for active ingredients or sensory	37

					markers	
4	Nanoparticle	July 2003	US6565873 B1	Biodegradable bioadhesive controlled release system of nanoparticles for oral care products	Site-specific controlled release delivery over an extended period for active ingredients or sensory markers	38
5	Multiparticulate	February 2007	US0026082 A1	Multiparticle pharmaceutical dosage form containing a mucoadhesive formulated peptide or protein active substances method said pharmaceutical dosage form.	Pharmaceutical dosage form containing a mucoadhesive formulated the peptide or protein active substances method said pharmaceutical dosage form	39
6	Multiparticulate	August 2007	US0196443 A1	Pantoprazole Multiparticulate formulations	To avoid sticking to nasogastric and gastronomy tubes with the sub coating of hypromellose.	40
7	Multiparticul	Decembe	US028100	Mucoadhesive	To increase	41

	ate	r 2007	7 A1	oral formulations of high permeability and high solubility drugs.	the oral bioavailability of BCS Class-1 drugs.	
8	Nanocomposite	September 2009	US0232899 A1	Mucoadhesive nanocomposite delivery system.	Delivery of the drug by addition with chitosan or silica nanocomposite during the in-situ gelation of colloidal silica.	42
9	Multiparticulate	November 2009	US0280183 A1	Multiparticulate form of administration, comprising nucleic acid-containing mucoadhesive active ingredients and method for producing a said form of administration.	The invention relates to the multiparticulate pharmaceutical form comprising mucoadhesive formulated nucleic acid ingredients and to process for producing the pharmaceutic	43

					al form.	
10	Nanoparticles	December 2010	US 0323977 A9	Mucoadhesive nanoparticles for Cancer treatment	Chitosan, glyceryl mono fatty acid, and cancer therapeutics agent have based nanoparticles that target cancer.	44
11	Multiparticulate	April 2011	US 0086095 A1	Bioadhesive polymers	To improved bioadhesive, properties increased residence time at tissue surface and increased the bioavailability of a drug.	45

9. APPLICATIONS OF SODIUM ALGINATE BEADS:

Particulate spheres were developed using repeating units of substance that exhibit favorable biological behavior such as bioadhesion, penetration-enhancing activities.

1. Oral API Delivery: The ability of particulate spheres that containing repeating units of substance to form films allows for formulation application as opposed to the solid dosage form.

2. Gene Delivery: Particulate spheres help in the gene carrier system. eg. Poliglusam, Gelatin, viral vectors, cationic lipoid system, polycations system & gene therapy along with DNA vector & also transport of insulin. It is helpful in vaccine delivery.

3. Repeating units of substance-based API delivery systems: such as particulate, lipoid systems & gels have been demonstrated to have good bioadhesive nature & gain size easily when in contact with the nasal skin enhances the bioavailability & residence periods of the API to the nasal way. eg. Starch, Poliglusam, Gelatin 40

4. Cancer & Local API Delivery: To deliver drug-like paclitaxel at the cancer site at therapeutically acceptable concentration, repeating units of substance films are designated. API mixtures, such as gelatin, PLGA, and poliglusam, have the potential to be used in controlled delivery in the oral cavity.

5. Buccal API Delivery: Because it has muco/bio attachment properties and can act as an absorption-increasing substance, a repeating unit of substance is a very good candidate for using a repeating unit of substance for the buccal target. Poliglusam, Sodium alginate.

6. Gastroscopy API Delivery: Repeating unit of substance granules having internal formulations formed by deacidifying, when added to acid or neutral component are found buoyant & support a sustained release of the API eg. Eudragit, methylcellulose + Carbopol, Gelatin.

7. Skin API Delivery: Repeating unit of substance has good film-producing properties. The API release from the structure is affected by the thickness & cross-linker of the matrix. eg. Poliglusam, Monoclonal antibodies, also known as targeting particulate spheres, are biologically immune particulate spheres. This type of sphere is used to get selective targeting to characteristic sites of the body part. Monoclonal Antibodies are specific molecules that bind to the characteristic part of the body through which absorption occurs. Viable adsorption & structural.

8. Imaging: The size of particulate spheres plays an important role in determining the imaging of specific areas using already labeled particulate spheres having radioactivity. The particulate spheres given via the IV route differ from the vein will usually become entrapped in the area of the lungs. This phenomenon is specifically used for scintigraphic imaging of tumor masses in lungs using human serum albumin particulate spheres.

9. Topical Porous Particulate spheres: Micro sponges are porous particulate spheres having a size range of 5 to 300 µm. These sponges possess the capacity to entrap various APIs such as emollients, which can be used as a topical application.

10. Physiological Application: Release of high molecular weight substance over a longer period. Passive targeting toward leaky tumor vessels, active targeting of cancer cells, antigens, by I.V. route.

11. Radio starts application: It can be used to embolize various chemical and spleen cancers that are used for synovectomy of local chemotherapy, RA, imaging of the liver, red bone marrow, local chemotherapy, and even imaging of deep vein thrombosis.

12. Vaginal API Delivery: Repeating unit of substance, modified by the introduction of thioglycolic acid to the primary amino groups of the repeating unit of substance is widely used for the treatment of mycotic infections of the genitourinary tract e.g. Poliglusam, Gelatin, PLGA (3). [46,47]

10. FUTURE PERSPECTIVE:

Recent developments in sustained-release beads:

* Calcium alginate beads of acetazolamide for sustained release:

It is an excellent type of formulation for administering vocally due to its exceptional properties such as little immunogenicity, non-toxicity, pH sensitivity, biodegradability, and bioavailability.

* Multi-loaded ceramic beads for sustained release:

HAP or TCP beads are formulated by the extruder method combined with ionic gelation with the presence of calcium ions as defined by (Klein, Treccani, Rezwan, and Franks (2012).

* Iron cross-linked carboxymethylcellulose gelatine coacervate beads:

Coacervation is a mechanism that divides the macromolecular solution into weak colloids and rich colloids, i.e. when two opposite charged molecules begin to interact.

* Liposome in alginate beads containing oyster hydrolysate:

Liposomes are microscopic phospholipids with a bilayer membrane. Different methods have been studied for the drug delivery of protein hydrolysate.

*Ofloxacin interpenetrating polymer beads to taste masking for sustained release:

Masking the taste of unpleasant medications is an important factor in the advancement of drug therapy. Masking the taste of the drug is a difficult task to develop orally administered APIs.

* ALG-Based Three-Dimensional (3D) Cell Culture Systems. 3D culture systems: prepared from using natural, synthetic polymers or their composites, with the ability to reflect the native extracellular matrix and natural physiological conditions have been regarded as advanced technology for complex cellular physiology investigations, drug evaluation, and tissue engineering.

* Cell-Based Microparticles for Therapeutic Applications.

Immobilization of living cells or cell-inducing factors in the ALG matrix is a commonly used technique in tissue and cartilage engineering. [48]

11. PHARMACOKINETIC ADVANTAGES:

Sodium Alginate beads have various pharmacokinetic advantages such as,

a) Increase AUC

b) Sustain drug concentration

c) Enhance nasal absorption

d) Efficient delivery of drugs like insulin into the systemic circulation,

e) Enhance bioavailability

f) Increase mean residence time (MRT) of drugs etc.[49]

12. CONCLUSION:

Sodium alginate beads as drug delivery systems provide several advantages, including greater flexibility and adaptability of dosage forms. alginate beads were easily and successfully formulated by employing the ionotropic gelation technique. It had been observed that the loose network of beads results in a major limitation of drug leakage through the pores during the gelation process. Because of the additional Hpmc k100m polymer, drug release is delayed and can last up to 12 hours. The spherical shape of the particulate drug delivery system was increased with an increase in the concentration of cross-linking agents such as

aluminum chloride Particulate spheres can solve the poor bioavailability problem of curcumin drugs, which is hydrophobic & poorly soluble in aqueous solutions. The production technique such as ionic gelation is simple and cost-effective and also applicable for both industry and laboratory work. This technique consists of the use of natural originating repeating units of a substance. Hence, sodium alginate beads can be one of the effective techniques for targeted drug delivery. [50]

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