Review Article

Chitosan Microspheres as a Delivery System for Nasal Insufflation

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ABSTRACT

Chitosan, a naturally occurring polymer, has gained significant attention in recent years due to its useful qualities as a biomaterial. Its biodegradability, biocompatibility, and non-toxicity make it an ideal candidate for various biomedical applications. Chitosan microspheres have been extensively researched for their potential in drug delivery systems, including oral, nasal, ocular, vaginal, buccal, and parenteral routes. These microspheres can be prepared using various methods, including emulsification-crosslinking, ionotropic gelation, and spray drying. The properties of chitosan microspheres, such as particle size, charge, and loading capacity, can be tailored to suit specific applications. Chitosan has also been explored as a vaccine delivery system and gene delivery vector. Its ability to enhance immune responses and facilitate gene expression makes it a promising tool in the development of novel vaccines and gene therapies.

Keywords: Chitosan, microspheres, Drug delivery, Vaccine delivery, Buccal drug delivery.

INTRODUCTION

The naturally occurring polymer having useful qualities as a biomaterial is chitosan.[1] Chitosan is a polymer mainly from N-acetyl glucosamine and glucosamine copolymers. Chitosan has been utilized in the development of particle drug delivery systems to achieve regulated drug distribution because it is biodegradable and biocompatible. [2] Since chitosan offers advantageous biological qualities such nontoxicity, biocompatibility, biodegradability, and antibacterial activities, it has been thoroughly investigated as a drug carrier for a variety of potential routes of administration. [2,3] Chitosan's physical and chemical characteristics, including its cationic charge in acidic media and its ability to form hydrogen bonds between and within molecules, make it a more desirable polymer for the development of both traditional and innovative medicinal products. To enhance the oral bioavailability of a medicine, chitosan can be used as a coating agent, gel forming, controlled-release matrix, and other beneficial properties like mucoadhesion and permeability augmentation. For site-specific medication delivery, chitosan is a suitable option. [3,4] Microorganisms like yeast and fungus also contain chitosan. [5,6]

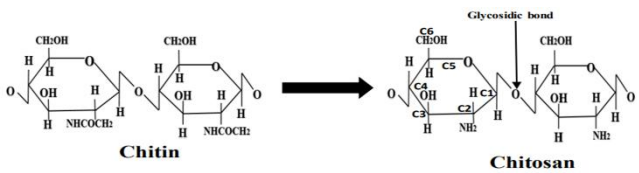

Figure 1: Molecular conversion of chitin to chitosan. [6]

CHITOSAN MICROSPHERES:

Microspheres play a key role in particulate drug delivery systems due to their tiny size and effective carrier properties. [7,8] The use of microsphere-based therapy allows drug release to be precisely customized to the specific treatment location by selecting and formulating various drug-polymer combinations. The overall dose of medicine and the kinetics of release are the variables that can be changed to get the desired outcome.

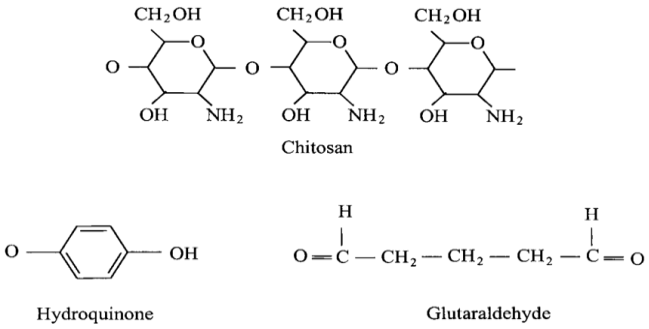

Figure 2: Chemical structure of the materials used for the preparation of chitosan microspheres.[12]

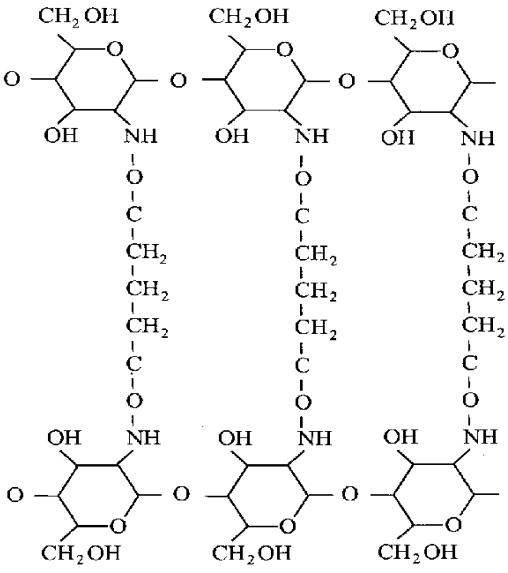

Figure 3: Cross-linking reaction of chitosan with glutaraldehyde. [12]

Microspheres may be built into an ideal drug delivery system with the required release profile by altering the polymer ratios, molecular weight, and other parameters. Microsphere-based devices may extend the life of the encapsulated medicine while also controlling its release. Microspheres, despite their small size, have high surface-to-volume ratios and can be employed for controlled release of insoluble medicines.[9] When creating different pharmaceutical dosage forms that are taken via different channels, such as oral, parenteral, topical, etc., the particle size of microspheres is a crucial aspect. Additionally, it is feasible to localize microspheres in a certain organ or tissue by only altering their size. [10,11]

Chitosan microspheres are frequently used for the delivery of hydrophilic and lipophilic medicines, as well as for the production of biosmers. [13] There are several uses for microspheres in medicine. For many therapeutic compounds, they are often used as carriers and target delivery systems. They may also be used to release medications gradually over the necessary time period to maintain effective drug concentrations at certain biological targets. Furthermore, there are several other uses for microspheres in food, medical equipment, and water purifying methods. [14] Also, microspheres have several uses in pharmaceutical production. They are used for delivering large and fragile molecules, including as proteins, vaccines, antibiotics, hormones, gene therapy, and anticancer treatments. The inclusion of chitosan-loaded anticancer drugs in the formulation of new drug delivery systems can lead to novel characteristics of the nanoparticles, which may be explained partially by the large surface area of the active ingredient delivery over the bulk characteristics. [15]

METHODS FOR PREPARATION OF CHITOSAN MICROSPHERES

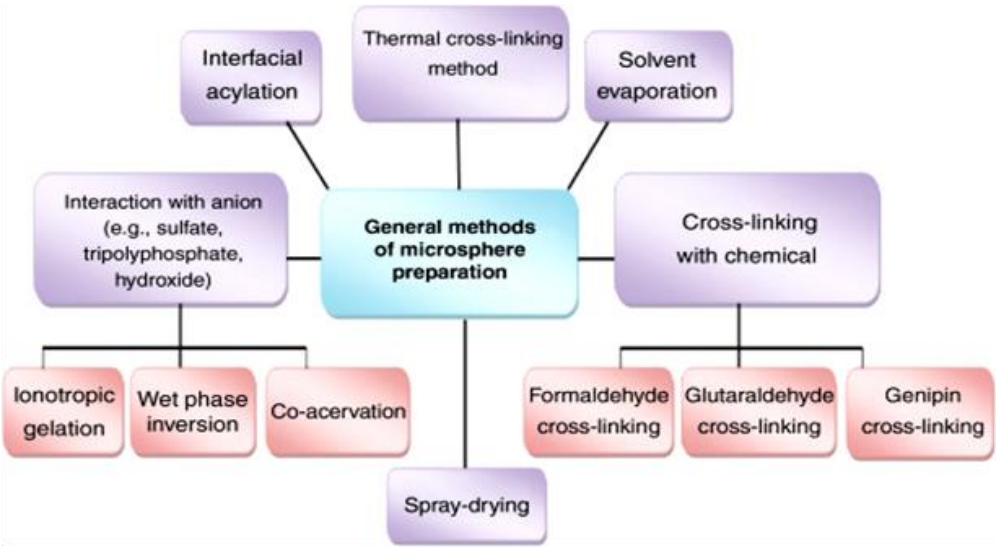

Figure 4: Preparation of Chitosan Microspheres. [16]

INTERACTION WITH ANIONS

Ionotropic gelation

Low microwaves counter ions (such as pyrophosphate, tripolyphosphate, tetrapolyphosphate, octapolyphosphate, hexametaphosphate, octyl sulfate, lauryl sulfate, hexadecyl sulfate, and cetyl stearyl sulfate) and high MW counterions (such as alginate, κ-carrageenan, and polyalde hydrocarbonic acid) are the two primary types of counterions used in the ionotropic gelation method. In short, dropwise additions of chitosan solution are made to aqueous counterions that are magnetically agitated. Filtration is used to extract the beads from the solution, which are then cleaned with distilled water and allowed to dry. [17] Nasal administration of CMs encapsulated with an atrophic rhinitis vaccine made by ionotropic gelation increased the production of cytokines (tumor necrosis factor-α [TNF-α]) and nitric oxide, which are markers of immune-stimulating activity. [18,19]

Emulsification and ionotropic gelation

The emulsification and ionotropic gelation approach creates a waterin-oil emulsion by adding an aqueous chitosan solution to a nonaqueous continuous phase (isooctane and emulsifier). Ionotropic gelation results from the subsequent addition of sodium hydroxide solution at various intervals. The resulting microspheres are filtered out, cleaned, and then allowed to dry.[20] As spherical microparticles with a diameter of about 10 µm can be created by using a modified technique, it has been suggested that the conventional emulsification and ionotropic gelation method for CM production produces irregular microparticles. One enhanced method uses gelatin, which enables the ionic crosslinking of chitosan/gelatin (water-in-oil emulsion) to occur at low temperatures under coagulation conditions. The surface of chitosan/gelatin microspheres has been modified using a variety of different crosslinking agents. The surface of chitosan/gelatin microspheres crosslinked with sodium sulfate or sodium citrate was extremely smooth,

however chitosan/tripolyphosphate microspheres showed significant gaps. According to certain reports, a tighter size distribution and a drop in diameter result from increasing the stirring speed. [21]

Complex coacervation

After the interionic interaction between oppositely charged polymers, chitosan can be thoroughly coacervated with sodium alginate, sodium carboxymethyl cellulose, sodium polyacrylic acid, and κ-carrageenan to produce microspheres. For example, the formulation of coacervate capsules is achieved by combining potassium chloride and calcium chloride with chitosan-alginate and chitosan-κ-carrageenan. The capsules are subsequently washed and dried after being hardened in a counterion solution. [22,23]

CROSSLINKING METHODS

Emulsion crosslinking method

It is easy to disperse water-insoluble chemicals in chitosan solution and allow the emulsion crosslinking process to capture them. Genipin, formaldehyde, and glutaraldehyde have all been utilized extensively as crosslinking agents in the creation of CMs. The first step in the emulsion crosslinking technique is to dissolve the chitosan in acetic acid to create a chitosan solution. Before a crosslinking agent is applied, this solution is introduced to liquid paraffin that contains a surfactant, creating a water-in-oil emulsion. The resulting microspheres are filtered, cleaned with an appropriate solvent, and then allowed to dry. [24,25,26]

Multiple emulsion method

The most effective technique for improving the target molecule's entrapment efficiency in CMs is most likely the multiple emulsion methods. This technique starts with the formation of a primary emulsion, or oil-in-water, which is a nonaqueous solution that contains the target molecule in a chitosan solution. Following the addition of glutaraldehyde (as a crosslinking agent) or the evaporation of an organic solvent, this primary emulsion is then transferred to an external oil phase to create numerous emulsions (oil-in-water-in-oil). Cellulose microspheres (CMs) loaded with hydrophobic reagents exhibit improved morphological characteristics and yield when prepared by the multiple emulsion method. [27]

Thermal crosslinking method

Different temperature settings are applied in separate phases to prepare CMs for the thermal crosslinking process. Citric acid used as a crosslinking agent in the thermal crosslinking technique of cellulose microspheres (CMs) synthesis involves several steps. A chitosan solution in acetic acid (2.5% weight/volume) is first cooled to 0°C and treated with citric acid. Maize oil is then added to the solution, forming an emulsion. This emulsion is slowly added to corn oil at 120°C while stirring. The mixture is then stirred vigorously (1000 rpm) for 40 minutes to facilitate crosslinking. The resulting microspheres are then filtered, washed, dried, and sieved. [28]

Crosslinking with a naturally occurring agent

The spray drying approach has also been utilized to create CMs using genipin, a naturally occurring crosslinking agent that offers high sphericity, low crystallinity, and tiny particle size. [29] Genipin-crosslinked cellulose microspheres (CMs) have a slower degradation rate and better biocompatibility compared to glutaraldehyde-crosslinked CMs. Additionally, chitosan-based microspheres used as an injectable drug delivery system exhibit low toxicity. [30,31]

Emulsion droplet coalescence method

To prepare chitosan microspheres (CMs), researchers use the emulsion droplet coalescence technique. This method combines precipitation and emulsion crosslinking concepts. Chitosan droplets coalesce with sodium hydroxide, causing precipitation. To make CMs, liquid paraffin oil is mixed with a stable chitosan emulsion solution. This emulsion is then combined with another stable emulsion containing a sodium hydroxide chitosan aqueous solution. The droplets collide and merge, forming small chitosan particles that precipitate. This technique creates CMs loaded with gadopentetic acid for gadolinium neutron capture therapy. Gadopentetic acid interacts with chitosan's amino groups through electrostatic forces. Unlike traditional emulsion crosslinking, this method produces nanosized particles and achieves high loading of gadopentetic acid. [32]

Precipitation or coacervation method

Since chitosan is insoluble in alkaline pH media, it precipitates when it comes into contact with an alkaline solution. Using a compressed air nozzle, chitosan solution is dropped into an alkaline solution (such as sodium hydroxide, sodium hydroxide–ethanediamine, or sodium hydroxide–methanol) to create coacervate droplets, which is how chitosan particles are made. Prior to thorough washing with hot and cold water, particles are gathered by centrifugation or precipitation. [33] The particle size can be controlled by adjusting the pressure and the diameter of the compressed air nozzle. Additionally, the particles can be hardened using a crosslinking agent, which allows for gradual release. Cellulose microspheres (CMs) are also prepared using a precipitation method with sodium sulfate. To create recombinant human interleukin-2-loaded CMs, a solution of recombinant human interleukin-2 containing sodium sulfate is added dropwise to an acidic chitosan solution. As a result, chitosan precipitates and forms CMs that encapsulate recombinant human interleukin-2. [34]

Reversed micellar method

A stable mixture of oil, water, and surfactants dissolved in organic solvents is called a reverse micelle. To make nanoparticles, an aqueous solution of chitosan and a target molecule is added to this mixture. Then, a crosslinking agent like glutaraldehyde is added. [33] This method is used to produce chitosan nanoparticles that contain medicines, such as doxorubicin attached to dextran. [35]

Sieving method

A technique for creating clozapine-loaded cellulose microspheres (CMs) involves several steps. First, a thick jelly mass of chitosan is made in 4% acetic acid and crosslinked with glutaraldehyde. The crosslinked jelly mass is then passed through a screen to obtain microparticles of the desired size. Next, the non-sticky jelly mass is rinsed with 0.1 N sodium hydroxide to remove excess glutaraldehyde and dried overnight at 40°C. This method achieves a high clozapine loading efficiency of 98.9%. However, the particles have irregular shapes and vary in size, ranging from 543 to 698 µm on average. A major limitation of this method is the uneven size and shape of the particles, which can affect the bioavailability of CMs. Despite this, the method demonstrates controlled and prolonged release of the medication in both in vitro and in vivo studies. [36]

Solvent evaporation method

A polymer solution and an immiscible continuous phase, either aqueous (oil-in-water) or nonaqueous (water-in-oil), combine to produce an emulsion using the solvent evaporation process. Acetone or liquid paraffin can be used for this. After dispersing the target molecule in a chitosan solution with acetone, the mixture is emulsified in liquid paraffin while being stirred. The suspension of microspheres is filtered, cleaned, and dried. One way to avoid agglomeration is to add magnesium stearate. Increasing the quantity of magnesium stearate employed in the preparation seems to reduce the average particle size. [37]

Spray drying method

Spray drying is one of the most widely researched techniques for creating cellulose microspheres (CMs). This process involves spraying a chitosan solution, allowing it to air dry, and then adding a crosslinking agent. CMs are also created by spray drying multiple emulsions, such as oil-in-water-in-oil or water-in-oil-in-water, to entrap drugs like cimetidine and famotidine into microspheres. In contrast to other microspheres made using the oil-in-water emulsion method or conventional spray drying, CMs release the drug in a controlled and prolonged manner. [38]

Nasal drug delivery:

Due to the tremendous potential for administration of medications, the nasal route has attracted a lot of interest from academics in recent decades for systemic drug delivery. The noninvasive nature of nasal medication administration adds to its ease and security. Additionally, compared to oral, sublingual, and transdermal administrations, nasal medication administration has a faster beginning of effect. A few benefits of using the nasal cavity as a site for systemic drug absorption include its relatively large surface area, highly vascularized epithelial layer, porous endothelial basement membrane, high total blood flow per cubic centimeter, ability to avoid first pass metabolism, and ease of access. [39] One of the most significant limiting constraints for nasal medication administration is nasal mucociliary clearance. It essentially eliminates prolonged nasal medication delivery and drastically reduces the amount of time that is permitted for drug absorption to take place. To improve medication absorption, mucoadhesive formulations have been created to lengthen the duration of contact between the dosage form and the nasal cavity's mucosal layers. [40] Thus, to lessen the impact of mucociliary clearance, mucoadhesive microspheres have been created. The medication formulation has a longer residence duration because the microspheres create a gel-like coating that is gradually removed from the nasal cavity. [41,42]

FACTORS AFFECTING THE NASAL ROUTE

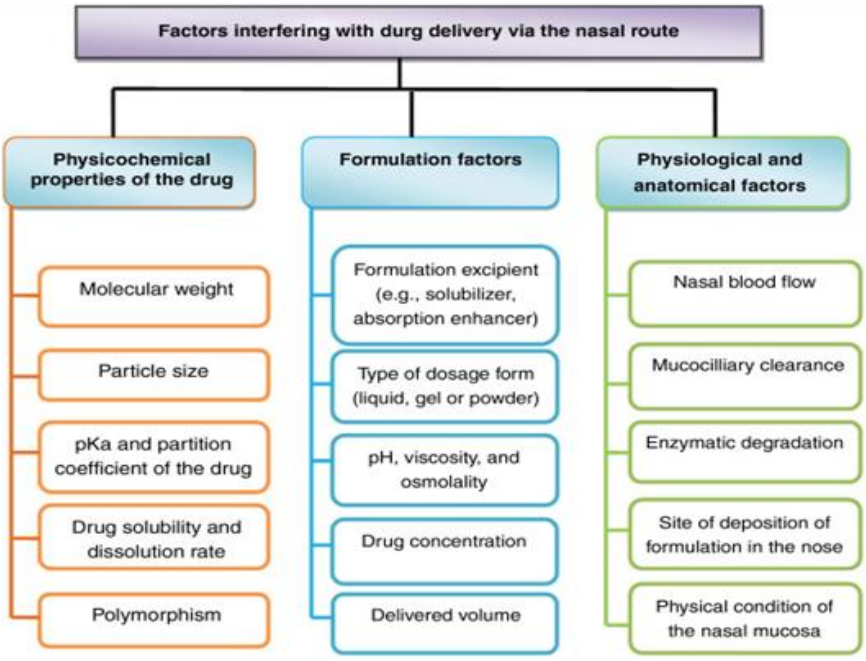

Figure 5: Factor affecting the nasal route. [16]

The dosage must be quantitatively released and dispersed throughout the nasal cavity in order for powder to be delivered by nasal route. It is crucial to examine how the microspheres behave while being delivered from a commercial device because the deposition pattern may undoubtedly impact medication bioavailability. [43,44]

For microparticulate drug delivery systems, a variety of biodegradable materials have been employed as carriers. Chitosan microspheres have drawn a lot of interest lately because of their mucoadhesive, high charge density, toxicity, biodegradability, and biocompatibility. Chitosan's gelling ability has a variety of applications, such as microencapsulation and controlled medication release using microparticulate systems. [45] A variety of techniques, including ionotropic gelation, [46] emulsification-crosslinking, [47,48] thermal crosslinking, [49] solvent evaporations, [50] spray drying, [51,52] and precipitation coacervation have been attempted by different groups to create chitosan microspheres. [53]

Chitosan microspheres are prepared using the emulsification-crosslinking technique. Researchers study how various factors affect the size of these microspheres. These factors include the concentration of chitosan, stirring speed, amount of crosslinking agent, crosslinking time, liquid-to-oil ratio, and DOSS concentration. A study evaluates how well chitosan microspheres are delivered from a nasal device (Miat) and measures the amount of medication released.[11]

Chitosan-mode of action

In both human and animal models, chitosan, a bioadhesive substance, can reduce formulation removal from the nasal cavity.[54,55] Additionally, chitosan has the ability to temporarily relax mucosal membrane tight junctions. [56,57]

APPLICATION OF CHITOSAN MICROSPHERES

1. Oral drug delivery:

Solid dose forms are the preferred distribution method as patients dislike liquid formulations and because medications like peptide medicines have stability issues that must be resolved. Tablets are therefore probably the most advantageous dose form, except from capsules. Many chitosan-based medication delivery systems are based on tablets because they offer a precise dose and are simple to produce and manage. [58,59]

2. Ocular drug delivery:

Chitosan is a good material for designing ocular drug delivery systems because of its physicochemical qualities, benign nature, and ability to enhance penetration. Chitosan-based formulations for ocular drug delivery include hydrogels, [60] nanoparticles [61] and coated colloidal systems. [62] Systems based on chitosan may enhance the biodistribution and retention of medications administered topically to the eye. Utilizing its in situ gelling capabilities, chitosan may be administered and dispersed across the surface of the eye in a nearly liquid state before solidifying into a gel. A longer ocular residence period and enhanced therapeutic effectiveness can be attained in this manner. [60,63]

3. Vaginal drug delivery:

Metronidazole-containing chitosan-based vaginal tablets are made by directly compressing the polymer, which is weakly cross-linked using glutaraldehyde, with sodium alginate and either microcrystalline cellulose or not. In pH 4.8 and pH 7, the tablets demonstrated sufficient release characteristics and provided low swelling index values. Additionally, these tablets demonstrated rather strong adhesive qualities. [64]

4. Buccal drug delivery

The buccal route is an alternate method of delivering medications to the application site since it circumvents hepatic first-pass metabolism and degradation in the stomach and small intestine. Additionally, patients are quite accepting of this method. A buccal delivery system should release the medication in a regulated manner and remain in the mouth cavity for hours. The duration of the drug's residency in the oral cavity is extended by mucoadhesive polymers. [65] Chitosan is a potential polymer for buccal administration because of its mucoadhesive and absorption-enhancing qualities. [66]

5. Parenteral drug delivery

Agarose gel electrophoresis is used to investigate the ability of chitosans to form complexes with DNA. Degradation in the presence of DNaseII is used to evaluate the ability of the complexed polymers to stabilize DNA. Chitosan fractions of varying molecular masses are labeled with a radioactive marker using the Bolton and Hunter reagent to track their distribution in the body. The distribution of chitosan in tissues is assessed after intravenous injection in rats. [67] Fluorescent glycol-chitosan and N-succinyl-chitosan are used in mice to study their pharmacokinetics and tissue distribution. Both chitosans show minimal buildup in tissues and good retention in blood circulation, indicating that chitosan is a useful carrier for medications that are quickly eliminated from the body.

6. Vaccine delivery

By prolonging the duration of contact between pertussis antigens and the relevant tissue or by enhancing transport across the membrane, chitosan may have a "adjuvant" effect on the immune response. This could improve the presentation of antigens to the immune cells of the mucosal epithelial and nasal associated lymphoid tissue (NALT). [69] It is anticipated that chitosan polymers would make excellent oral vaccine candidates. A coacervation/precipitation process was used to create chitosan microparticles, which were then studied in relation to oral vaccination. Light microscopy, confocal laser scanning microscopy (CLSM), and scanning electron microscopy were used to assess the microparticles shape. We looked at the model antigen ovalbumin's size, charge, loading, and release properties. Additionally, CLSM was used to visualize the first in vivo

absorption experiments of fluorescently tagged chitosan microparticles by mouse Peyer's patches. [70]

7. Gene Delivery System:

Genetic delivery can be used to treat a variety of multigenetic diseases and inherited problems. Viral vectors, cationic liposomes, polycation complexes, and microencapsulated systems are examples of gene delivery techniques. Chitosan has been employed in gene delivery applications as a DNA carrier. [71,72] Because of its ability to stick and move through the GI system, chitosan may also be a helpful oral gene carrier. In order to produce a luciferase gene in the intestinal tract. [72] demonstrated that chitosan and depolymerized chitosan oligomers could carry plasmid DNA containing a luciferase reporter gene and a cytomegalo virus promoter sequence in vivo. [4]

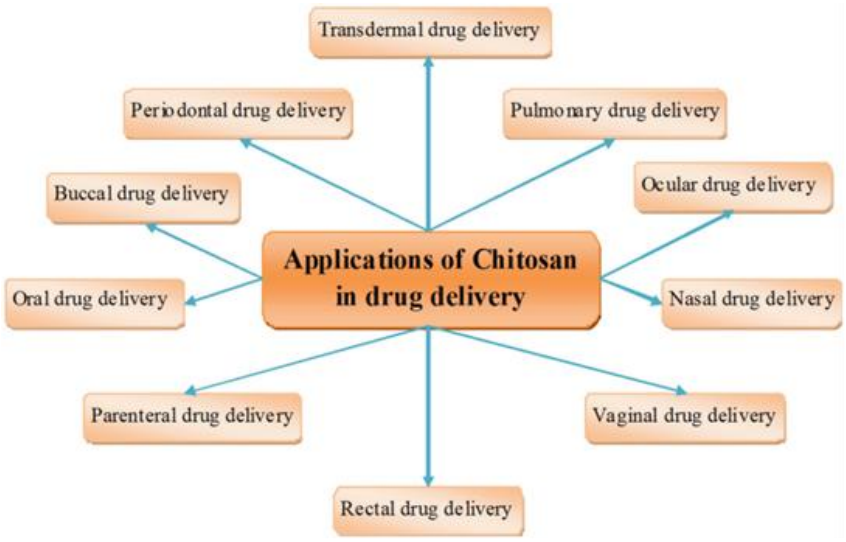

Figure 6: Chitosan used in various drug delivery. [73]

CONCLUSION

Chitosan microspheres have demonstrated significant promise as a nasal medication delivery method. They are a viable choice for both local and systemic drug administration because of their capacity to stick to the nasal mucosa, enhance drug absorption, and avoid first-pass metabolism. Various formulation methods, including spray drying and ionotropic gelation, have been investigated to maximize their effectiveness for regulated and prolonged drug release.

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