REVIEW ARTICLE

A Review of Chitosan in Oral Drug Delivery Formulations

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Abstract

In recent decades, the utility of nanoformulations as medication delivery systems has grown. It is not always the best option due to gastrointestinal distress, restricted inadequate absorption, and solubility. The impact of the early hepatic transit is one of the biggest obstacles that drugs must get past to have a therapeutic effect. These materials have attracted a lot of attention because studies have shown that oral delivery can be significantly enhanced by controlled-release systems that use nanoparticles (NPs) made of naturally derived biodegradable polymers. Chitosan (CS) has several applications and qualities in the pharmaceutical and medical industries. The traditional medication delivery method has been completely transformed by NPs' capacity to modify molecules and their structures. In the current environment, CS because of their small size, NPs are a valuable tool for novel drug delivery systems. The process of ionotropic gelation is not the only one used in this field; alternative techniques include solvent evaporation, polyelectrolyte complex, emulsification solvent diffusion, emulsification cross-linking, and microemulsion. Numerous drug delivery applications, such as CS NPs have been found to be beneficial for a range of utilization, encompassing mucosal and controlled administration of drugs, tissue engineering, delivery of non-viral genes, vaccines, ocular drugs, electrodeposition, delivery of drugs that target the brain, enhancement of stability, and efficient delivery of insulin.

Key words: Chitosan, complex coacervation, herbal bioactive, ionotropic gelation, nanoparticles, oral medication administration, patents, solvent evaporation

INTRODUCTION

In recent years, the creation of novel medicine delivery techniques has received more attention. The advantages and disadvantages of drug delivery strategies, the fundamental and physicochemical qualities that could qualify a medication for drug formulation, and the ways for assessing delivery services the environment, toxicology at the point of delivery, and viability will all be covered in this review.[1] Even with all of the research that has been done on medication delivery techniques, ingesting it is still the most effective, least complicated, and safest.[2,3] These limitations have been overcome by the development of nanotechnology, especially in the area of nanomedicine, where nanocarriers are now more widely accepted as oral drug delivery systems. The fundamental principle of nanomedicine, a subfield of nanotechnology, is the use of nanometric particles.[4] As drug carriers, nanoparticles (NPs) are used in many different kinds of drug delivery systems. According to the pharmaceutical industry, NPs can be used to treat conditions such as diabetes, cancer, and HIV.[5,6] NPs were created to enhance therapeutic limitations and membrane crossing. There are worries about whether any of the synthetic substances in these items could be harmful to people's health.[7] Because of their intrinsic adaptability, biological compatibility, and biodegradability, NPs made from polymers, like chitosan (CS) NPs, as well as the infused form of herbal bioactives (curcumin, aloe vera [AV], etc.), have desired features and uses.[8,9] Carrier-mediated medication delivery has become a potent therapy approach for a number of diseases.

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The enhancement of specificity resulting from medication targeting a specific tissue, cell, or intracellular compartment;, regulation of release kinetics; active agent protection; or any combination of these factors all contribute to a rise in the therapeutic effectiveness of both conventional and new treatments. Since their introduction as drug carriers more than 30 years ago, polymer composites have drawn increasing interest, primarily because of their increased loading capacities, stability, and controllable physicochemical characteristics.[1,2] Localized drug release can also be accomplished through systemic injection by placing macroscopic drug depots in close proximity to the target site.

Directed site-proximate mega drug depots are an additional tool for promoting localized drug release in addition to systemic dosing. *In situ*-forming nanomaterials that react to environmental stimuli have garnered significant interest among the various systems examined for this technique because of their superior control over biodistribution, non-invasive nature, and capacity to mitigate adverse effects associated with systemic delivery.[3] Researchers have become more interested in using biodegradable plastics as possible medication delivery system carriers in recent years.

Poly(vinyl alcohol) (PVA) is an artificial polymer that is water soluble, non-toxic, and has the ability to form films in addition to having advantageous chemical and physical properties.[4] This polymer finds utility in numerous applications such as controlled drug delivery systems, membrane production, packaging, and polymer recycling. The process of PVA's dissolution, changes in its crystallization and swelling behavior, and its capacity to physiologically form gels have all been studied.[5] PVA is widely used in the medical field for kidney transplantation, embedded devices for medical purposes, nanofiltration, synthetic pancreas, and synthetic vitreous due to its biological intelligence. CS is a kind of organic polymer that is created in an atmosphere that is alkaline when CS is deacetylated (Cs). Among basic linear polysaccharides, an β-(1, 4)-2-amino-2-deoxy-D-glucopyranose is an unbranched chain.[4,7,9] Because most repeat units have amine functionality, the polymer is hydrophilic and soluble in diluted acid.[10] The culinary, pharmaceutical, and biotechnology sectors all use CS extensively. The biodegradability, bioactivity, biocompatibility, and biological properties of this polysaccharide have led to extensive research in the field of biomaterials.[11-16] Polymer blends are a useful tool for producing novel materials with the required properties. They have experienced tremendous scientific and commercial developments in this field. The rationale for this was the realization that blending can often be completed more rapidly and affordably than creating new materials and that there are situations in which new materials can be obtained without requiring new molecules.[17,18] It is possible to combine a range of polymers, both natural and semisynthetic, to produce NPs with various drug delivery systems.[10] Because of their superior qualities, CS and its derivatives stand out from other polymers and are perfect for oral ingestion.[11] The negative charge of amino groups serves as an adhesive and aids penetration.[12] In addition, these NPs are biocompatible, biodegradable, and non-toxic. The biopolymer CS has garnered considerable interest in the medical domain owing to its exceptional attributes, accessibility, and adaptability. A compound called N and D-glucosamine atoms are randomly repeated and joined with (1 4) glycosidic links to form the linear polymer CS.[13] CS a polymer found in nature that follows cellulose in abundance is derived from chitin. There are several uses for chitin and CS in the food, pharmaceutical, and medical industries (including gene transplantation, tissue repair, and wound healing).[14] The spread of NPs made of CS (CSNPs) in our mouths and eyes is one of its fascinating features. CSNPs are thought to be a workable solution for addressing the inaccuracy and bioavailability of certain active components. CS promotes cellular uptake and retention due to its strong reactivity for the electrically charged mucus barrier.[15]

It is noteworthy that there is a large body of research on CS's ability to carry medications that have been released recently. Guadarrama-Waco bar *et al*. recently published CS-based oral administration in 2023, mostly utilizing trial data from 2020. We concentrated on the majority of the study content, which contains references from 2022 and after. The following subheadings have been added to our manuscript upon restructuring: Overview; delivery of oral medications P-gp inhibitors' function in oral medication administration; the use of nanomaterials in delivery systems; the applicability of CS -oriented diverse delivery; oral medication delivery using herbal bioactive-loaded nanoformulations.

Conclusion: The manuscript's writing style is brief and covers the majority of relevant issues, utilizing recent developments centered on different oral nanodrug delivery techniques based on CS.

CS

A mucopolysaccharide that is very similar to cellulose is CS. The main component of crab exoskeletons, chitin, is deacetylated to produce CS. Rouget provided the first descriptions of it in 1859 and 1894. Hoppe-Seyler gave it a formal name.[1,4] Chitin off the crab and shrimp shells are deacetylated by boiling it in sodium hydroxide after it has been decolored with potassium permanganate.[1,4] After oral administration, chitinases break down CS. According to toxicity testing, CS's LD50 in mice was more than 16 g/kg.[4] Lysozymes or intestinal microorganisms release chitinases, which are also found in plant-based dietary items.[5,6] It has also been shown that the physical form of CS's improves their biodegradability.[7] Because of CS's recent FDA approval, inexpensive cost of manufacture, biodegradability, and biocompatibility, its applications in medicines and food have increased dramatically.[8,9]

STRUCTURAL FEATURES

The biopolymer is referred to as chitin when its N-acetylglucosamine unit content is 50% or above; on the other hand, it is called " CS " when its N-acetylglucosamine unit concentration is >50%.[1] The main amine is present around the second position, C-2, of the glucosamine residues, which gives CS's their distinct structural characteristic. There are hardly many biological polymers with such a high primary amine concentration. These amines give CS significant functional qualities that can be used in bio fabrication.[10]

PROPERTIES

The degree of deacetylation, viscosity, and molecular weight all affect CS's characteristics.[1] How much deacetylation there is influences CS's quantity of protonatable amine groups, which in turn influences the molecule's solubility, hydrophilicity, and capacity to communicate electrostatically with polyanions.[11,13] Low-deacetylation (DA) CS has also been shown to exhibit definite dose-dependent toxicity, acting as an absorbing facilitator across both medium and high molecular weights.[14] CS, on the other hand, exhibits no toxic effects at lower molecular weights but is an active promoter at high molecular weights due to its greater DA. Regarding toxicity, it is contingent upon the structural characteristics that define the CS polymers and is not invariably linked to its capacity to enhance absorption. Despite massive efforts to explore the potential application of CS in drug delivery and the abundance of CS producers, it is nevertheless very challenging to find cellulose that has been entirely standardized with respect to its dimensions in molecules that are and certificate of removal for pharmaceutical research.[1]

NANOTECHNOLOGY

According to a working group report published in 2004 by the European Science Foundation, "Nanomedicine" is predicated on complex systems consisting of two or more components and operating at the nanoscale.

A pharmaceutical ingredient that is active is one of the components, and the system as a whole has a specific function that has to do with the identification, treatment, or avoidance of disease.[26] In this context, substances or materials with sizes ranging from 1 nm to 100 s many microns are regarded as being in the nanoscale. For the safe and efficient transportation of active substances to their intended site of action, particles shaped such as nanomedicines-drug transporters, liposomes, dendrimers are essential. Improved drug encapsulation, pharmacokinetics, bioavailability, and therapeutic efficacy are among the extra benefits of NPs above microparticles.[27] The field of drug delivery has entered a new era thanks to nanotechnology.[28]

The polymeric carriers used for the nanoparticulate delivery of drugs should be cheap, easily synthesized, biocompatible, and biodegradable.

CS NPs

According to reports, CS is an excellent choice for creating nano-and microparticles with regulated medication release.[21] Since CS, and CS NPs in particular, has higher stability, lower toxicity, easy and gentle manufacturing methods, many routes of administration, and increased interest as a drug delivery vehicle, they have several benefits.[22] They possess the capacity to regulate the discharge of active substances. Preparation of CS NPs.[23-26]

Ionotropic gelation method

The process is based on an amine group of CS's electrostatic interaction with negatively charged polyanion groups, like tripolyphosphate (TPP).[31,32] By adjusting the ratio of chitosan-to-stabilizer, NPs' shape and surface charge can be modified. The weight ratio of CS to TPP is a crucial processing parameter that needs to be regulated for a high production of NPs. It was discovered that this ratio falls between 3:1 and 6:1.[34,35] In samples exposed to ultrasonic radiation, the average particle size of NPs decreases as solution temperature rises.[36] A volume phase transition occurs when physical-chemical parameters, such as the medium's pH, change.[37] In addition, the diluted alginate (Alg) solution containing insulin was used to produce a calcium counter-ion pre-gel that is ionotropic. Polyelectrolyte complex coating coated with chitin came next.[38,39] Chemokines and amino acids have been loaded using this method,[40] including insulin,[41] Z-DEVD-FMK, a peptide that inhibits caspase,[42] Cycleoxin,[43] FGF, or basic fibroblast growth factor, and siRNA (small interfering RNA).

Microemulsion method

Glutaraldehyde and the free amino group in CS conjugate By altering the amount of glutaraldehyde, which modifies the degree of cross-linking, particle size can be regulated.

Emulsification-cross linking method

This technique entails creating unique surfactant-polymer NPs for the effective encapsulation and long-term release of medications that dissolve in water.[51] Dioctyl salt sulfosuccinate (Aerosol OTi; AOT) as well as sodium alginate are used to simulate the NPs. AOT is an approved oral, topical, and intramuscular anionic surfactant. The Inactive Ingredients Database maintained by the US Food and Drug Administration claims that AOT is an ionic surfactant excipient that has been authorized for by mouth, topical, and intramuscular usage. Sodium Alg is a polysaccharide that occurs in the environment

polymer that has been thoroughly studied for use in tissue engineering and drug delivery.[52,53] For 4 weeks, the release of medications that are soluble in water, like verapamil and doxorubicin, can be sustained by AOT-Alg NPs.[41]

Complex coacervation method

The rapid formation of CS -DNA NPs is said to be caused by the coacervated of the negatively charged phosphate groups on DNA with the charged amine groups on CS. The weight ratio between the two polymers has a significant effect on the generated NPs number, the charge on the surface, entrapment efficiency, and release. CS-dextran sulfate (DS) NPs physicochemical and release characteristics can be changed by adjusting the ratios of the two ionic polymers.[56,57]

Solvent evaporation method

To precipitate the polymer into nanospheres, this approach necessitates emulsifying the polymer putting the polymer solvent to evaporate after putting the mixture into an aqueous phase. Frontline antitubercular medications have been administered using Alg (a biodegradable and biocompatible co-polymer of guluronic acid and mannuronic acid), including rifampicin, isoniazid, pyrazinamide, and ethambutol as a nanoparticulate delivery system. The US FDA has previously approved alga for use in humans. It is commonly administered by mouth to treat reflux esophagitis.[58]

Coprecipitation method

The coprecipitation process created CS-based NPs with a high degree of size homogeneity that may be employed as a drug carrier for sustained drug release by grafting D, L-lactic acid onto CS. Lactic acid-grafted CS was created by dehydrating the solvent to produce a thin layer of lactic acid-containing CS. LA-g-CS was produced. LA-g-CS was employed to create coacervate drops using a co-precipitation method in ammonium hydroxide, which resulted in the formation of LA-g- CS NPs. The CS and lactic acid-modified CS (LA-g-CS) NPs that were produced had a mean diameter of around 10 nm. They were round and evenly dispersed.[59,60]

APPLICATIONS OF CS NPS: IN PARENTERAL DRUG DELIVERY SYSTEM

Depending on an NPs size, hydrophobicity, and surface charge, its biodistribution can change.[63,64] Particles larger than 100 nm in diameter are quickly absorbed by the reticuloendothelial system, whereas smaller particles typically circulate more slowly. The circulation time of hydrophobic carriers is greatly increased by hydrophilic coating (polyethylene glycol [PEG]) or nonionic surfactant.[6]

In per-oral administration

Research conducted by both human beings and in the laboratory has confirmed that the facilitating uptake properties of CS are caused by cohesion and the mucosal cell membrane's transient tight junction opening.[69,70] In addition, a longer period of contact between the medication and the absorptive surface is made possible by a relationship between the electrically charged CS and the oppositely charged mucin, which facilitates absorption.[71] The research states that CS increases cohesion and lengthens the clearance half-time. Furthermore, studies on the permeation rate of membranes can be increased by CS-induced temporary tight junction opening in Caco-2 cells *in vitro*, especially when it comes to polar medications such as proteins and peptides.[72,73] Moreover, Pan *et al*. demonstrated that providing mice through CS NPs-induced diabetes orally produced a hypoglycemic effect.

In non-viral gene delivery

Mumper was the one who originally suggested CS as a possible gene delivery vehicle.[76] CS polymer is less immunogenic, has no mutational potential and is significantly less hazardous than poly-L-lysine and PEI[22,45,76] It also improves the drug's ability to cross cell membranes. The CS particles had cell targeting ligands affixed to them to boost transfection efficiency. Galactose is widely recognized for liver-focused delivery, hence, prepared glycosylated-CS-graft-dextran DNA complexes to create a liver-targeted delivery system.[77] Similarly, transferrin-chi-tosan-DNA NPs were created by for a specific medication delivery.[76] Since many mammalian cells contain transferrin receptors, transferrin can be taken up through a technique known as receptor-mediated endocytosis. Regretfully, they did not exhibit the desired level of transfection efficiency.[22] Alg-CS NPs exhibited four times the transfection effectiveness of 293 T cells compared to CS NPs in 48 h. Notably, the transfection efficiency was comparable to that of lipofectamines, while also significantly reducing cytotoxicity.

In vaccine delivery

CS is one of the vaccine carriers that has been studied the most. It is believed that by encouraging absorption, it would strengthen the immunological response of the mucosa.[84,85] When vaccinations are administered systemically, CS acts as an adjuvant. Studies have shown that CS absorption occurs before macrophage activation.[85-87] A lot of research has been done on the use of CS in vaccinations for mucosal DNA. A DNA flu vaccine based on CS developed by produced a high number of antibodies when given intranasally to mice.[84] After oral treatment in mice, the pCMVArah2 plasmid encoding the peanut allergen gene was efficiently integrated into CS NP that excellent expression of antigen and good protection.[22,56,88] Vaccines have been linked to various particulate systems as NPs, which have been demonstrated to improve mucosal

lymphoid tissues' ability to absorb antigens and trigger robust mucosal and systemic immune reactions to the antigens.[1]

In ocular drug delivery

Given that as a minimally toxic substance, ocular formulations according to it have demonstrated exceptional tolerance when applied to the rabbit's corneal surface.[89,90] In addition to using CS NP to boost medication transport through the eyes, CS-coated tiny particles are also used because they have the capacity to improve corneal penetration.[89,90] According to research by the rabbits' cornea and conjunctiva retained the CS NP attachment for at least 24 h.[43] A novel delivery method for the sustained topical ophthalmic distribution of the antibiotic gemifloxacin has been explored: Mucous adhesive CS-sodium Alg NPs.[56,91]

In electrodeposition

The selective assembling of NP in space can be mediated by CS suspended within its solution. The 100 nm particles, or fluorescent latex spheres, are organized in an x-y orientation with high lateral resolution on the cathode surface. The control studies demonstrated that the assembly of NPs requires CS. A more thorough investigation revealed that along the z-axis, the NPs got stuck in the CS matrix. Consequently, the electrodeposition method mediated by CS provides a means of assembling microparticles into structures of higher order. Which is a prerequisite to take use of one of the special qualities of NPs. A more thorough investigation revealed that along the z-axis, the NPs got stuck in the CS matrix.[57]

To utilize one of the unique properties of NPs, it is necessary to assemble small molecules into higher-order structures, and this CS -mediated electrodeposition provides a means of doing so.

In stability improvement

Drugs, genes, or proteins have all been successfully delivered through CS-TPP nanogels as drug delivery methods in human fluids. Because of its interactions, the gel network efficiently increases the stability of the particles when they are loaded with medicines or macromolecules.[37] It has also been reported that the CS-ca-senate complex exhibits improved stability. Foods may be modified to have unique textures, unique visual qualities, or greater stabilities due to various situations. Drugs, nutraceuticals, and other bioactive substances have been encapsulated and released under controlled conditions using the NPs that were created as a consequence of the interactions between these biomacromolecules.

In controlled drug delivery

In addition, appropriate for regulated medication delivery systems are CS NPs. CS captures bioactive molecules and condenses them into colloidal particles. It is reported that the mechanisms include chemical crosslinking, ionic crosslinking, and ionic complexation. Chemical modification of CS may provide a viable substitute for regulating drug release by binding bioactive compounds to polymers.

In tissue engineering

CS is a better choice for applications involving tissue[48-50] engineering. CS is a naturally occurring polymer that links as well as is susceptible to the lysozymes that the body of a person contains.

In insulin delivery

Promising insulin as well as other polypeptide carriers have been employed, as have CS-DS s and CS Alg NPs.[46] CS NPs enhance insulin following nasal instillation's systemic absorption.[41] In addition, it has been shown that the insulin-loaded NPs successfully lower blood glucose in a diabetic rat model. The absorption-enhancing properties of CS in powder or solution form were not enhanced by the CS NPs. In the sheep model, CS powder is the most effective formulation for insulin nasal administration.

ORAL DRUG DELIVERY

Before deciding on a dosage, it is essential to take into account any possible interactions; the medication may have with the patient's body.[16] The ideal situation the optimal manner of distribution for optimizing bioavailability and efficacy will depend on the properties of the medication and the rate of absorption. Rather than being prescribed, medication is usually given by medical experts.[17] Drug delivery systems provide features including regulated and focused therapeutic medication distribution.[18] Drug delivery systems, such as nanocarriers, can enhance many of the pharmacokinetic characteristics of free pharmaceuticals. They are often made of lipids or polymers together with associated treatments.[19,20] Nanotechnology is defined by the US as "The creation and implementation of frameworks, equipment (implanted or medicated), and delivery systems that, due to[54] their small dimensions, have unique characteristics as well as functions," "According to the Environmental Protection Agency." This work is focused on the exciting new direction of medication delivery and nanotechnology through the therapeutic use of different kinds of NPs. Oral medication administration takes place in the digestive system in a number of distinct places.[23] The gastrointestinal (GI) tract's natural features support a variety of environments, each with unique benefits and drawbacks. A drug's destiny is largely determined by a number of variables, including its pH, the presence of digestive enzymes, the availability of absorption sites, and the volume of free water.[24] The variable oral absorption site is one of the challenges to be solved. The GI tract's pH is

important for both oral drug administration and medication absorption. There are many areas in the GI tract, and each has a different pH environment.[25]

The oral cavity has a pH between 6 and 7, which is neutral to slightly acidic. Because of the presence of gastric acid, the pH decreases significantly as the medication passes through the stomach, reaching a very acidic range of 1–3. Because of the stomach's low pH, which might affect some medications' durability, enteric-coated formulations are often used to shield pharmaceuticals from deterioration. Afterward, the pH steadily rises to a more alkaline range of 6–7.5 in the small intestine. Because of its wide surface area and plentiful blood flow, this area serves as the main site for drug absorption. The large intestine has a pH between 5.5 and 7, which is mildly acidic to neutral.[26,27] It helps scientists to create medication formulations that are resistant to the stomach's acidic environment and that maximize the release and absorption of the medicine in the intestines.

There are more difficulties to consider, such,[28-32] which areas follow:
Digestion-related proteins in the GI system raise the possibility that the medication being supplied will become unstable. This is a very important issue when working with big compounds such as proteins and nucleic acids. The likelihood of GI cells absorbing macromolecules is minimal. Because the length of time it takes for the stomach to empty is correlated with the amount of food ingested, food intake may affect how well drugs are absorbed. Since the exact delivery site is frequently unknown, controlling the medication release is challenging. Despite oral administration being the most prevalent method, some patients still prefer parenteral or rectal drug delivery. Therefore, three crucial components of a successful oral delivery system are stability against degradation, a controlled drug release profile, and a targeted location of absorption or action.[33]

NANOTECHNOLOGYIN DELIVERY SYSTEMS

Human enzymes break down the polymer, which promotes hemostasis and speeds up tissue regeneration to help heal wounds. It has been applied to several biological domains, including orthopedics, oral delivery methods, and wound healing. It can be combined with different polymeric biomaterials and inorganic bioactive substances to create bone-related tissue engineering materials, cartilage, intervertebral disks, and substitutes for bone grafts.[34,36]

NPs

Antimicrobial photodynamic treatment (aPDT) and for the treatment of oral biofilms, nanomaterials such as NP-coated oral films combined with CS/sodium bentonite and curcumin (CUR) can be utilized. Silvestre and his group are treating aPDT. Created and assessed a new NP delivery system in 2023 that included sodium alginate and CS encapsulated in CUR. Solvent evaporation was used to construct the biofilm, and polyelectrolytic complexation was used to create the NPs. Colony-forming units per milliliters, or CFU/mL, were employed to measure the effectiveness of the photodynamic effect. *In vitro*, the technique using NPs in a synthetic salivary fluid demonstrated better control of CUR release than films filled with NPs. The concept that aPDT-coupled sodium alginate/CS NPs may be beneficial for the oral delivery of CUR is supported by these findings. This opens the door for the development of novel oral administration techniques that could eventually be applied to the treatment of infections and dental cavities.[37,38] These findings support the hypothesis that sodium alginate/CS NPs combined with aPDT might be beneficial for oral CUR delivery. This creates space for the creation of cutting-edge oral delivery methods that might be used in the treatment of tooth decay and infections in the future. To make LMWH-loaded NPs, CS (TCS), negatively charged HP55, and the Ph-TCS/O-CMCS@LMWH were employed. The resulting NPs had a high encapsulation efficacy of 96.6%, a spherical shape, and a normal size of 332 nm at a drug-loading amount of 12.04 IU/mg. Apart from its remarkable colloidal stability and possible mucoadhesive effect, the pH-TCS/O-CMCS@LMWH combination exhibited advantageous pH-responsive drug release characteristics, thereby reducing the premature release of LMWH into the acidic milieu and enhancing its directed release in the intestinal milieu. After oral treatment, pH-TCS/O-CMCS@LMWH demonstrated significant antithrombotic effectiveness and increased bioavailability inside a venous thrombosis model in rats. Therefore, the use using pH-TCS/O-CMCS particles when giving LMWH orally to treat thrombus holds considerable promise. The application of nanotechnology is crucial to multimodal pain relief. In 2023, Wasana *et al.* co-encapsulated chitosan/alginate (CTS/ALG) using the response surface approach curcumin (Cur) and metformin (Met) at their synergistic drug ratio in NPs. What characteristics did the artificial Met-Cur-CTS/ALG-NPs have? 32.6%and 44.2% encapsulating efficiencies, 6.8% and 19.6% drug-loading Met and Cur, 243 nm size of the particle, 21.6 mV electrical potential, and 2.9:1 Met/Cur mass ratio are all present. Met-Cur-CTS/ALG-NPs remained stable after a long storage time in GI fluid simulation. In an *in vitro* examination of artificial digestive fluids, Met-Cur-CTS/ALG-NPs showed sustained release; Cur demonstrated non-Fiskian diffusion while Met demonstrated Fiskian diffusion, in accordance with the Korsmeyer–Peppas model. Caco-2 cells showed notably improved cell uptake or the adhesion in response to Meet-Cur-CTS/ALG-NPs. In BV-2 microglial cells, it was also demonstrated that Met-Cur-CTS/ALG-NPs had more potent anti-inflammatory actions and lipopolysaccharide-stimulated RAW 264.7 macrophages, indicating a higher ability to regulate both the central and peripheral immune processes involved in pain.

LIPOPROTEINS

Liposomes may be employed in medication delivery vehicles for both big and small molecules. Two common liposome components are phosphatidylcholine and cholesterol. Compounds that are stable in fat or water are permitted to be retained. Lipoproteins consist of an interior cavity or hydrophilic layer that contains soluble molecules and a fat wall that may include fewer compounds soluble in water or oil. Drugs' therapeutic index and potency may be raised by the regulated and extended release of medications from liposomes. There may be benefits to using liposome formulations of protein medications, including increased penetration, decreased degradation, extended-release, and improved stability.[42] Liposomes are cholesterol and phospholipid-based tiny spherical particles. Liposomes are tiny spherical vesicles made up of cholesterol and other building blocks. Oral drug delivery is not a common use for liposomes despite the fact that several liposomal formulations have shown clinical efficacy. This is partly because conventional liposomes are prone to absorption in the intestine's issues and stomach destabilizing agents. Several of these problems could be solved with the assembly of layers by layers technique, which has been extensively used to alter different nanoparticulate systems' surfaces.[43] Wang *et al*. (2023) improved the application of electrostatic deposition in the creation of double-layer-coated liposomes containing pectin and CS to enhance GI and consistency of storage. The outcomes suggested that using pectin and CS, double-layer-coated liposomes might be made. Double-layer-coated liposomes were created by Wang *et al*. in 2023. The results indicated that 0.06% pectin and 0.2% CS might be utilized to Pectin and CS double-layer-coated liposomes showed more exact oversight of the release compared to double-layer-coated CS liposomes and liposomes, and they enhanced the intestinal tract's capacity to deliver bioactive substances. This could lead to the creation of more efficient distribution methods for bioactive agents.[44] Delivering 5-fluorouracil (5-FU) to the intestines where colon cancer is most common, and avoiding the release of drugs or disintegration in the stomach or small intestine are the two main problems with the drug's delivery. The discovery of liposomes with the right ligand and encapsulation may make targeted therapy for colon cancer possible.[45] Next, to create nanocapsules, the resultant liposomes were coated once more with a solution of CS and alginate. MTT testing was used *in vitro* to evaluate the cytotoxic of HT-29 that colon cancer cells. The size range of the spherical liposomes and nanocapsules was 120–170 nm. Aptamer-conjugated liposomes caused significantly higher rates of cell death when compared to free medicines or liposomes without an aptamer. To enhance lecithin stability and niacin loading efficiency chitin was added to stabilize the liposome's center.

MICELLES

Encasing hydrophobic drugs is a typical application for polymeric micelles, which are nano systems with a hydrophilic outside and a hydrophobic center. Because these systems can improve drug stability and protect oral administration strategies are viable methods for administering medication from the harsh GI tract. The ability of polymeric micelles to rapidly reach a therapeutic dose without causing side effects or interfering with the epithelium efflux pumps is another advantage of their excellent drug encapsulation capacity. Because it is easily converted into an amphiphilic polymer that can self-assemble, CS is widely used to make polymeric micelles. CS improves the absorption of drugs in the intestines due to its mucoadhesive properties and ability to temporarily relax the tight links of the epithelium,[47] i.e., creating drug delivery devices with 3D printing technology has opened up new applications for tailored therapy. In nanomedicine, it is critical to be able to create personalized drug-loaded structures and delivery systems with the right amount of medication. Almeida *et al*. (2021) linked nano systems for 3D printing (print fills) that are sealed with an enteric layer and loaded with calprotectin (CPT) using CS-based polymeric micelles. This protects the nanosystems from the harsh environment of the GI tract. Only in the colon did the print fills release their micelles; otherwise, they remained stable at a pH that resembled the simulated gastric juice in the stomach. In a 3D intestinal cell-based model, CS micelles were found to enhance CPT permeability compared to the free medications, exhibiting an apparent permeability coefficient of approximately 9 10−6 cm/s. To simulate intestinal absorption, the dissolving medium was then employed. Polymeric micelles that are released specifically for the colon may be used to stop drug-specific or systemic breakdown throughout the intestinal tract and enhance gut absorption using 3D printing and nanotechnology.

CS exhibits several limitations, including its incapacity to create micelles and its inability to enhance drug bioavailability despite being extensively employed to augment oral drug delivery through permeation. Tu *et al*. created the novel CS derivative GA-CS-TPGS (gallic acid- CS-D-tocopherol PEG 1000 succinate) in 2020. The goal of Kumar *et al*., novel polymer, a form of oleic acid grafted on low-molecular-weight carboxymethyl CS (OA-CMCS), is to enhance the biopharmaceutical performance of poorly water-soluble pharmaceuticals. Analytical methods such as 1H-NMR and FT-IR spectroscopy were used to design this polymer, synthesize it through amination reaction, and assess the final product. Incorporating rifampicin and moxifloxacin into micelles changes the fluorescence characteristics. The maximum fluorescence emission shifts in the long-wavelength region and the hydro-dynamic volume of the spinning fragment containing the fluorophore significantly increases, causing an increase in fluorescence anisotropy. Using the pyrene label, critical micelle concentrations varied from 4 to 30 nm depending on the polymer selected. By facilitating the absorption of antibiotics by bacteria and enveloping them in a protective layer, micellar systems enhance their efficacy. Research on the pharmacokinetic of moxifloxacin in micellar systems revealed that the medication's maximum

blood concentration increased by two times and that it was 1.7 times more efficient than it was in the free form.[52]

APPLICABILITY OF CS-ORIENTED MULTIFARIOUS DELIVERY

Gene delivery methods through oral non-viral, such as CS-zein hybrid systems, the copolymer consists of poly(ethylene glycol)-poly(ε-caprolactone) tiny particles, hybrids of halloysite nanotubes and carbon dots, and CS -p-hydroxyphenyl (CH-pHP) have been assessed to the efficiency in administration by mouth for a variety of pathological conditions, such as osteoarthritis caused by trauma, diabetes mellitus, weight gain, and inflammatory bowel disease. The nucleic acids such as siRNA, miRNA, and DNA, and nucleotide can be combined to create straightforward and affordable systems, which are more conventional than conventional modes of delivery.[55] For example,[56] created an inexpensive orally nanoparticulate system based on plasmid DNA (pDNA) that delivers vaccines using CS-coated, NPs of superparamagnetic ferrous oxide derivatized with ascorbic acid (SPION). They came to learn that the pDNA release had reached 45% and was favorable after 48 h. Thus, CS can efficiently encapsulated DNA in the environment of the extremely acidic GI, permitting release during passing through the target alkali intestine cells.[65,66] After methylation or thiolation, structurally modified CS significantly enhanced the adhesion of and penetration behavior by efficiently transferring proteins and peptides and opening tight connections between epithelial cells.[58] These macromolecules have a larger given parenterally or subcutaneously, have a higher molecular weight, and exhibit greater hydrophilicity despite their inherently weak structure. In addition, research is being done on giving them orally [Figures 1-4].[38] A number of investigations assessing the movement of proteins and peptides, including insulin from humans, parathyroid hormone, calcitonin, exenatide, desmopressin, vasopressin, hormone leptin interferon, and ovalbumin, have been carried out using different polymers.[59-62] For an oral diabetes medication delivery system, CS is actually the subject of active research because it is more patient-friendly and less costly than injectables.[63] For approximately 96% of the time, sugar was maintained at GI pH in the case of PLGA-modified tiny particles and thereafter showed intestine-sustained release. Blood glucose levels were calculated to decrease to 27% for particles containing CS-modified PLGA, 35% for CS through gold NPs, and 38% for natural CS NPs in animal trials, indicating a hypoglycemic impact.

With a pharmacologic bioavailability of 6.57%, this method demonstrated favorable outcomes in an animal tests on type 1 diabetes and a comparable pH release profile for insulin.

Inhibitors of permeability-glycoprotein (P-gp.) are essential for improving the oral administration of medications prepared in NP systems.[70] The GI tract contains a membrane transporter protein called P-gp., which actively pumps medications out of

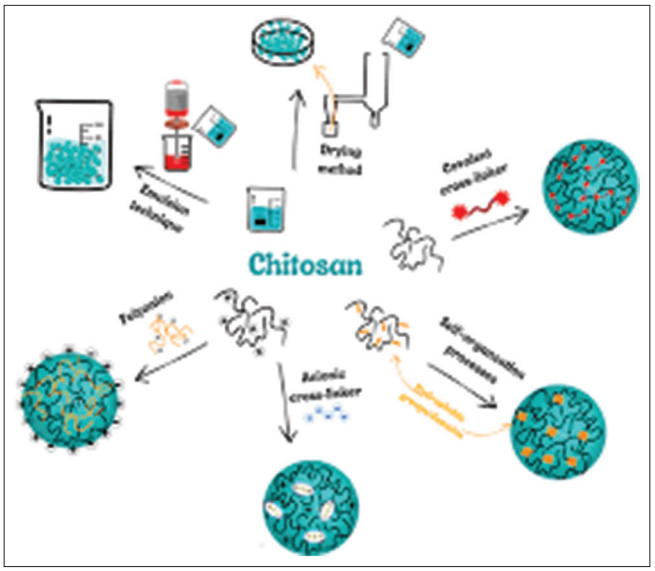

Figure 1: Chitosan

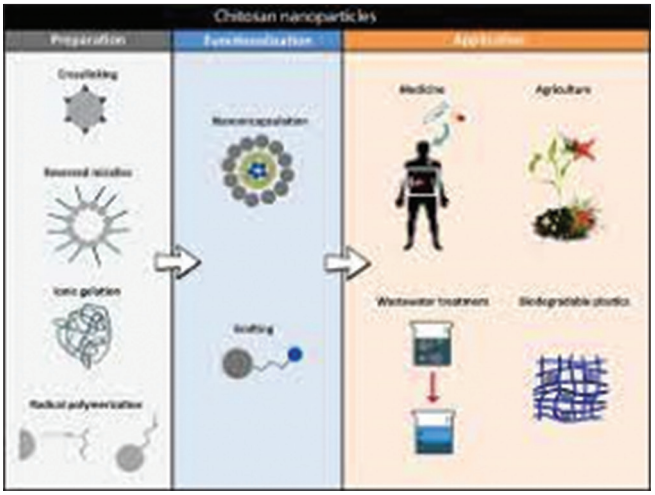

Figure 2: Applications of chitosan

enterocytes to reduce absorption and bioavailability. Because they can enhance drug solubility, stability, and target-specific delivery, nanoformulations including lipid-based carriers and polymeric NPs have drawn a lot of interest as oral drug delivery vehicles.[71,72] P-gp. inhibitors reduce P-gp's efflux activity when given with nanoformulated medications, which increases drug absorption and improves therapeutic results. These inhibitors increase the length of time that medications spend in the absorption site by inhibiting P-gp, which delays the quick removal of medications from the stomach and improves absorption efficiency.[73-75]

HERBAL BIOACTIVE LOADED NANO FORMULATIONS FOR ORAL DELIVERY

Approximately 80% of the world's population receives their medical treatment from traditional herbal medicines due to

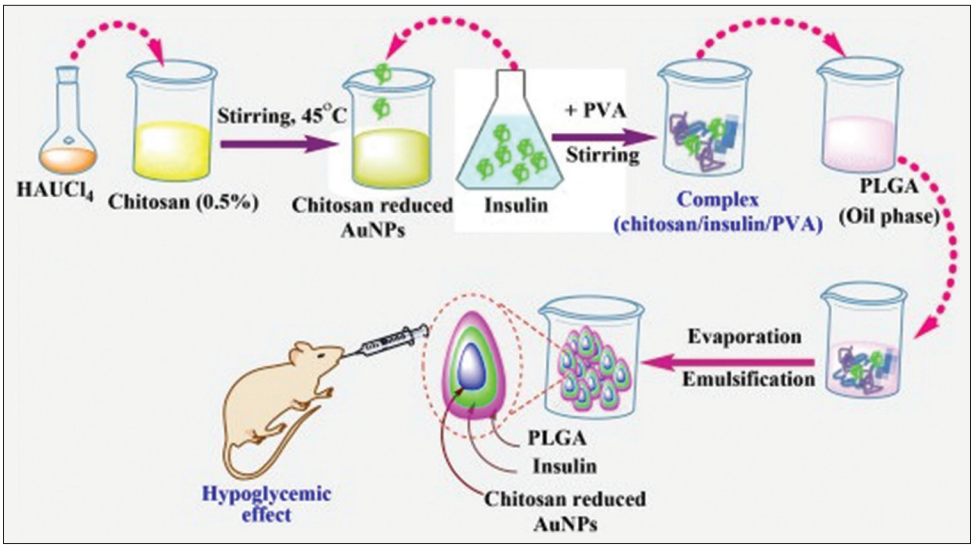

Figure 3: Diagrammatic depiction of the on-site manufacturing of gold particles on a surface PLGA NPs updated with chitosan in light of insulin delivery by vocal administration (Adapted from,[67] Elsevier permission granted)

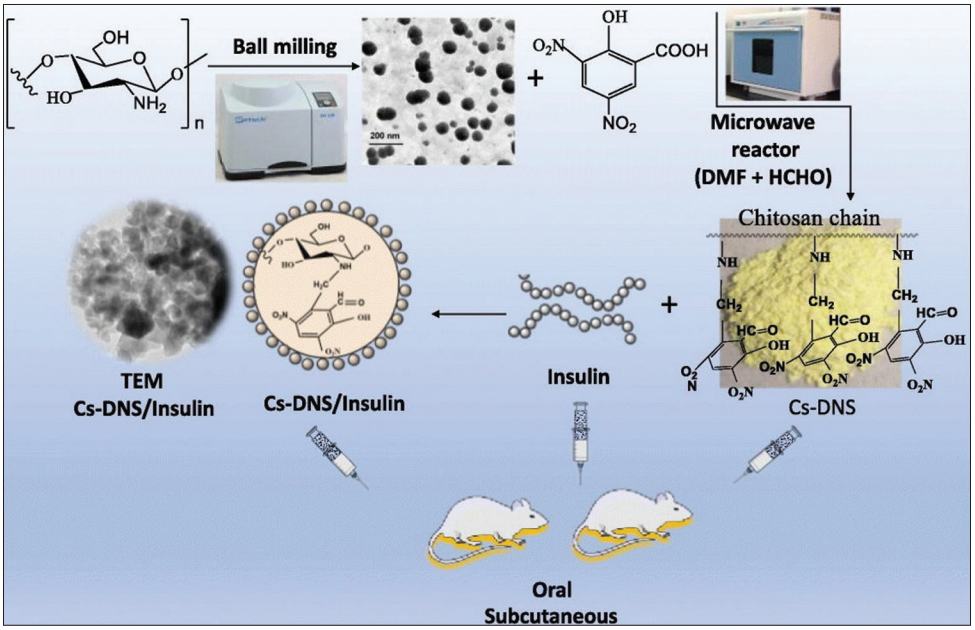

Figure 4: Diagram showing how reduced chitosan (Cs) modified with dinitro salicylic acid (DNS) is made for oral insulin by microwave irradiation (Adapted from,[68] Elsevier permission granted)

its broad variety of therapeutic applications.[78-81] Roughly 25% of contemporary medications are plant-based, according to the World Health Organization.[82] One promising method for oral medicine administration is the use of herbal bioactive drug delivery systems. These systems take advantage of the natural substances found in herbs that have a variety of biological actions.[83]

The security, bioavailability, and targeted administration of these bioactive substances can be enhanced by encapsulating them in delivery systems such as liposomes, NPs, or micelles. Improved solubility, prolonged release, less toxicity, and increased therapeutic efficacy are just a few benefits of using natural bioactive drug delivery systems. In addition, by customizing these systems to certain herbal extracts, personalized medical techniques are made possible.[84,85] There is a lot of potential for creating safe and efficient oral medication delivery systems with continued study in this area.

AV

AV belongs to the Liliaceae family, of which the most popular is the Aloe Barbadensis Miller species.[86] AV extract functions as a good bioenhancer and aids in increasing oral bioavailability lists additional uses for AV in addition to its ability to cure

conditions such as metabolic, cardiovascular, neoplastic, and oral illnesses.[88] Herbal medications were compared and assessed for their intercanal antibacterial activity by Patri *et al*. Eighty removed human premolar teeth were decoronated to produce six-millimeter blocks of the midfoot; for this investigation, the samples were exposed to *Enterococcus faecalis* for 21 days.[91] They were further classified as having or not having CS in Groups 1 (paste with three antibiotics for control), 2 (turmeric), 3 (propolis), and 4 (AV gel).[92] Propolis showed similar antimicrobial properties and efficacy (P = 0.598), according tousing Tukey's *Post hoc* analysis and one-way ANOVA. The three-antibiotic paste formulation, which contains a conjugated CS-curcumin, demonstrated the best results (P = 0.963), as well as AV, showed the worst results. However, the antimicrobial efficacy significantly increased (P = 0.000) following the addition of CS. Since AV performed poorly when combined with CS, the antibacterial activity was increased, making it a potentially useful drug delivery agent.

CONCLUSIONS

For regulated medication distribution, mucosal drug delivery, drug stability enhancement (for medicines, either amino acids or DNA if manufactured as CS NPs), and superior uses for tiny particles of CS in biological engineering are the most appropriate. In addition, the CS NPs are an effective additive used to administer vaccines. These show promise as a non-viral gene delivery vector since they aggregate in many cancers and contain anti-tumor agents. They also function as superior carriers of insulin and other therapeutic polypeptides and have outstanding corneal surface tolerance. Oral administration is still the recommended drug delivery technique even though drugs have to get past a variety of obstacles or steer clear of biological reactions, which lower their efficacy as well as bioavailability. Much interest has been shown in the application of polymers that are biocompatible in drug delivery systems such as nanoformulations and NPs. Their physicochemical characteristics allow them to be used as alternatives to conventional dosing techniques. Moreover, they make it possible to vector process medicinal molecules with limited bioavailability and solubility, which improves their contact with the intended organs or cells through various delivery methods. Because CS-based NPs are inexpensive, highly effective, and may incorporate medicines, peptides, and DNA to disrupt certain biological processes, they are frequently used in unconventional therapy. CS NPs can be administered orally without the need for invasive or uncomfortable methods because they can improve drug absorption and lessen adverse reactions by overcoming physical and biological barriers.

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