A REVIEW ON CHITOSAN IN ORAL DRUG DELIVERY FORMULATIONS

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Abstract: In recent decades, nano-formulations have grown progressively more useful as drug delivery systems. Oral administration is the most popular therapeutic delivery strategy, however it is not necessarily the most efficient because of difficulties with swallowing, gastrointestinal discomfort, and other factors like weak absorption and limited solubility. One of the biggest obstacles that drugs must overcome is the effects of the initial hepatic transit to have a therapeutic effect. Studies have revealed that natural polymers made of biodegradable nanoparticles are used in controlled-release systems. These materials considerably enhance oral administration, which is why they have gained major attention. Chitosan serves a variety of purposes in the pharmaceutical industry as well as the healthcare sector. Its two most crucial functions are drug encapsulation and delivery inside the body. Furthermore, by making it easier for drugs to engage with target cells, chitosan can improve medication effectiveness. This review describes recent developments and applications of orally administered chitosan nanoparticle interventions. Based on its physicochemical features, chitosan has the potential to be manufactured into nanoparticles.

Keywords: chitosan, nano-formulations, oral drug delivery.

Introduction

The interest in creating novel medicine delivery techniques has grown over the past few decades. The advantages and disadvantages of drug delivery systems, as well as the fundamental and physicochemical features that can make a drug acceptable for use, will be covered in this article. Pharmaceutical formulation, as well as the methods for evaluating the sustainability of delivery, toxicity at the delivery location and its viability [1]. In spite of the vast amount of research Oral administration is still the most efficient, safest and least complicated to take medications when compared to other techniques [2, 3]. Specifically, the development of nanotechnology and its use of nanocarriers as oral drug vehicles, thereby overcoming these limitations has become more widespread particularly due to science of nanomedicine. Nanoparticles (NPs) are used as medication carriers in numerous types of drug delivery systems. Pharmaceutical companies have discovered that NPs are effective in treating conditions like cancer, diabetes, and HIV [5,6]. NPs were created in order to enhance therapeutic limitations and membrane crossing. There are worries that some of the synthetic substances utilized in these goods could be harmful to people's health [7]. Due to their intrinsic adaptability, biological compatibility, and biodegradability, nanoparticles made from polymers, like chitosan NPs, and the infusion of herbal bioactives (Curcumin, aloe vera, etc.), have desirable features and uses [8,9]. Numerous polymers, both natural and artificial as well as semi-artificial, can be employed to create nanoparticles for different drug delivery systems [10]. Because of its outstanding qualities, chitosan and its derivatives stand out from other polymers and are perfect for oral administration [11]. When amino groups are added, a cationic charge is imparted that improves penetration and serves as a mucoadhesive [12]. These NPs are also biodegradable, biocompatible, and non-toxic. Because of its adaptability, accessibility, and special qualities, the biopolymer chitosan (CS) has attracted a lot of interest in the medical community. N-acetyl-D-glucosamine and D-glucosamine units are randomly repeated and joined by (1→4) glycosidic connections to form the linear polysaccharide chitosan [13]. Chitosan, a naturally occurring polymer that is only second to cellulose in terms of natural abundance, is derived from chitin. The food industry, as well as the medical and pharmaceutical sectors (such as tissue engineering, gene transplantation, and wound healing), employ chitin and chitosan extensively [14]. The fascinating features of chitosan nanoparticles (CSNPs), particularly for ocular and oral distribution, are noteworthy. Some active ingredients are not very bioavailable or stable, however CSNPs are thought to be a promising vehicle for enhancing these characteristics. Chitosan can firmly cling to the negatively charged mucus barrier to improve retention and cellular uptake [15]. It's interesting to see how many research articles on the drug transport capabilities of chitosan have recently been released. Guadarrama-Wacobar et al. reported chitosan-based oral delivery recently, primarily covering 2020 research outcomes, and we focused on most of the research data that includes references from 2022 onwards. The manuscript is constructed in a compact manner that covers the majority of the relevant regions based on recent breakthroughs targeting diverse chitosan-based oral nanodrug delivery systems.

Oral Drug Delivery

The effects of the medication on the patient's body should be considered before administering the dosage [16]. The ideal mode of administration for maximizing bioavailability and effectiveness will be determined by the properties of the medicine and how efficiently it is absorbed. Contrary to drafting prescriptions, medical practitioners often dispense medications [17]. Drug delivery systems include features including regulated drug release and targeted drug distribution [18]. Many of the pharmacologic characteristics of free medications can be improved by drug delivery methods, such as nanocarriers, which are often made of lipids or polymers and related therapies [19]. Sustained-release systems are one type of drug delivery system that serves as a reservoir, whereas other systems are created to alter the pharmacokinetics and biodistribution of the chemicals they distribute [20]. A promising new avenue in drug delivery and nanotechnology, which is at the forefront of this research, is the therapeutic application.
of many different types of nanoparticles [21]. Nanotechnology is described as "the development and implementation of structures, devices (medicated or implants), as well as delivery systems, because of their small size, having distinctive novel features as well as functions" [22] by the United States Environmental Protection Agency.

**Nanotechnology in Delivery Systems**

The polymer is broken down by human enzymes and promotes hemostasis, which speeds up tissue regeneration and promotes wound healing. It has been applied in a number of biological domains, including orthopedics, oral delivery systems, and wound healing systems. It can be fused with other polymeric biomaterials and inorganic bioactive substances to create bone-related tissue engineering materials such as cartilage, intervertebral disks, and bone-related bone graft replacements.

1) **Nanoparticles**

Oral biofilms can be treated using antimicrobial photodynamic therapy (aPDT) using nanomaterials like nanoparticle-loaded oral films, chitosan/sodium alginate, and curcumin (CUR). In 2023, Silvestre and his team created and assessed a unique sodium alginate and chitosan-encapsulated nanoparticle delivery method for the treatment of aPDT. The biofilm was created using solvent evaporation, whereas the NPs were created through polyelectrolyte complexation. Colony-forming units per milliliters (CFU/mL) were used to gauge how effective the photodynamic effect was. Nanoparticles in an artificial saliva medium (in vitro) demonstrated improved control over CUR release when compared to nanoparticles on films. These findings support the notion that aPDT-coupled chitosan/sodium alginate nanoparticles could be beneficial for CUR oral administration. This paves the path for the development of cutting-edge oral delivery systems, which could be utilized to treat dental cavities and infections one day [37]. Fan et al. [38] created mucoadhesive chitosan-based nanoparticles with increased bioavailability and anticoagulant properties for the prevention of deep venous thrombosis.

2) **Liposomes**

Liposomes can be employed as a drug carrier to carry both small compounds and macromolecules. Liposomes usually contain phosphatidylcholine and cholesterol. They are capable of storing substances that can be kept in either water or fat. Liposomes feature a hydrophilic layer or inner cavity that retains soluble molecules and a lipid wall that can store low-water or oil-soluble substances. Liposomes have the potential to allow for regulated and sustained drug release, potentially increasing a medicine's efficacy and therapeutic index. Loading protein medicines into liposome formulations has the potential to improve stability, extend release, reduce degradation, and boost penetration [42]. Liposomes, which are tiny spherical vesicles, are made up of phospholipids and cholesterol. Several liposomal formulations have demonstrated therapeutic activity; nonetheless, liposomes are rarely employed for drug administration orally, in part because of gastrointestinal destabilizing agents and inadequate intestinal absorption. Some of these issues may be overcome using layer-by-layer assembly technique, which has been widely employed to change the surface of various nanoparticulate systems [43]. Sahatsapan's group created chitosan-maleate (CSMHA)-coated liposomes in 2022 to transport proteins across the buccal mucosa. The liposomes were preloaded with fluorescein isothiocyanate-albumin conjugate (FITC-BSA), a protein mimic. Liposomes were created via thin-film hydration, and CSMHA was employed to embellish them. Liposomes coated with CSMHA were evaluated for cytotoxicity against oral fibroblast cells; biocompatibility, mucosahesiveness on porcine buccal mucosa; loading efficiency and capacity, drug release, buccal mucosal penetration, protein integrity, and mucosal permeability. Liposome compositions with sizes ranging from 35 to 166 nm were created. On buccal tissue, CSMHA-coated, FITC-BSA-loaded liposomes had the highest retention. When FITC-BSA was encapsulated in CSMHA-coated liposomes, it proved non-toxic to healthy gingival fibroblast cells and buccal tissue. The results indicate that CSMHA-coated liposomes may be able to boost protein delivery via the buccal route [42].

3) **Micelles**

Polymeric micelles, which are nanosystems made up of a hydrophobic core and a hydrophilic shell, are commonly used to encapsulate hydrophobic medicines. These systems are viable oral delivery strategies due to their capacity to protect the medicine from the harsh GIT environment and boost drug stability. Polymeric micelles’ high drug encapsulation capacity is particularly advantageous since a therapeutic dose can be achieved quickly while reducing undesired side effects and evading epithelial efflux pumps. Chitosan is commonly employed in the manufacture of polymeric micelles because it may be easily converted into an amphiphilic polymer with self-assembly properties. Chitosan's mucoadhesive qualities and capacity to temporarily open the epithelium's tight connections increase drug absorption in the intestines [47]. Drug delivery methods using 3D printing technology have advanced, as have uses for customized treatment. The ability to construct personalized structures filled with medications and delivery systems with appropriate drug dosage is of special importance in nanomedicine. Almeida and colleagues (2021) coupled chitosan-based polymeric micelles loaded with camptothecin (CPT) with 3D printing systems (printfills) sealed with an enteric layer to protect nanosystems from the harsh GIT environment. The printfills were stable at a pH equivalent to that of simulated stomach gastric juice and only released micelles in the colon. In a 3D intestinal cell-based model, intestinal absorption was replicated using dissolving media and chitosan micelles, which greatly improved CPT permeability compared to free pharmaceuticals, with an apparent permeability coefficient (Papp) of roughly $9 \times 10^{-6}$ cm/s. The use of 3D printing and nanotechnology to deliver polymeric micelles to the colon has the potential to improve intestinal absorption while limiting systemic or drug-specific degradation throughout the gastrointestinal tract [48].

4) **Applicability of Chitosan-Oriented Multifarious Delivery**

With respect to oral non-viral gene delivery systems, halloysite nanotubes-carbon dots hybrids, chitosan-zein hybrid systems, chitosan-p-hydroxyphenaclyl (CH-pHP), and poly(ethylene glycol)-poly(ε-caprolactone) copolymer (PEG-PCL) nanoparticles have
been evaluated for effective oral delivery for many pathological conditions, including inflammatory bowel disease, diabetes mellitus, obesity, and post-traumatic osteoarthritis [53,54]. Among the many forms of nucleic acids, DNA, siRNA, miRNA, and oligonucleotides can be combined to create simple and low-cost systems when compared to other administration routes [55]. For example, Jabali et al. [56] developed a low-cost plasmid DNA (pDNA)-based oral nanoparticulate system for vaccine delivery that uses ascorbic acid-derivatized, chitosan-coated superparamagnetic iron oxide nanoparticles (SPIION). They found that pDNA release was beneficial, reaching 45% after 48 hours. As a result, chitosan can successfully encapsulate pDNA in the highly acidic stomach environment while allowing release while passing through the target alkaline intestines. Wang et al. [57] investigated chitosan-based triphospholipidate (CSTPP) nanoparticles for dual photodynamic gene transfer using methylene tetrahydrofolic dehydrogenase 1-like shRNA (Short hairpin RNA)(MTHFD1L) and 5-aminolevulinic acid (ALA). The effect of shRNA/photosensitizer administration on gene expression in oral squamous cell carcinoma cells was studied, and it resulted in apoptosis and the formation of reactive oxygen species.Because of its capacity to break down tight connections between epithelial cells and effectively distribute proteins and peptides, structurally modified chitosan dramatically improved mucoadhesion and penetrating behavior [58]. These macromolecules are delivered parenterally or subcutaneously despite having a weak structural foundation and having a higher molecular weight and greater degree of hydrophilicity. Studies are currently being done to administer them orally [38]. There have been numerous studies done to assess the delivery of peptides and proteins using various polymers, including thryptophin-releasing hormone, octreotide, desmopressin, vasopressin, uroguanferin, calcitonin, exenatide, human insulin, parathyroid hormone, leptin, interferon, and ovalbumin [59]. To distribute proteins, a variety of chitosan-based delivery methods, including microparticles, nanoparticles, liposomes, and niosomes, have been created [60–62]. In fact, chitosan is being actively researched as a vehicle for oral insulin medication delivery since it is more cost-effective and patient-friendly than injectables [63]. Self-assembled nanoparticles arise as a result of electrostatic interaction between the positively charged chitosan and the negatively charged insulin. Due to mucoadhesiveness and reversible tight junction opening, this method facilitates paracellular intestinal uptake from enterocytes and helps to protect the core insulin molecules from enzymatic degradation within the stomach [64]. Modified chitosan nanoparticles have also led to the development of novel techniques for enhanced targeting and sustained delivery [65].

5) Herbal Bioactives Loaded Nanoformulations for Oral Delivery
Because traditional herbal remedies can be used to treat a wide range of diseases, they are used by about 80% of the world's population for healthcare. Plants are responsible for around 25% of modern medicines, according to the World Health Organization. Herbal bioactive drug delivery systems have emerged as a viable oral drug delivery strategy. These systems take advantage of the therapeutic potential of natural chemicals originating from plants, which have a wide range of biological functions. These bioactive chemicals’ stability, bioavailability, and targeted administration can be increased by encapsulating them within delivery systems such as nanoparticles, liposomes, or micelles. Herbal bioactive drug delivery systems have a number of advantages, including better solubility, prolonged release, lower toxicity, and improved therapeutic efficacy. These methods can also be adapted to specific plant extracts, enabling for personalized treatment approaches. Continued study in this area has the potential to lead to the development of safe and effective oral medication delivery systems.

Future Perspectives
Future paths in pharmaceutical research now look bright thanks to recent developments in chitosan nanoformulations for oral drug delivery systems. Having strong biocompatibility, biodegradability, and mucoadhesive qualities, the natural polymer chitosan, produced from chitin, is a prime candidate for boosting drug absorption and bioavailability. In the future, scientists can concentrate on perfecting chitosan nanoformulations to get around the drawbacks of traditional oral drug delivery systems. This include looking for ways to increase drug stability, controlled release kinetics, and drug loading effectiveness. Furthermore, there is a lot of potential in the development of multifunctional chitosan nanoparticles that can deliver several medications at once or target particular areas in the gastrointestinal system. Additionally, efforts might be made to better comprehend how chitosan nanoparticles interact with biological barriers in the gastrointestinal tract. This would entail looking into things like cellular absorption methods, mucus penetration, and possible toxicity issues. Oral medication delivery methods may be further revolutionized by merging chitosan nanoformulations with other cutting-edge technologies, including nanotechnology, biotechnology, and personalized medicine. To achieve site-specific drug release, this may entail using stimuli-responsive or intelligent systems, delivering medications and imaging agents simultaneously with nanoscale carriers, or combining chitosan nanoparticles with targeted therapeutic strategies.

Conclusion
Despite the fact that medications must pass through many barriers and avoid biological processes that reduce their bioavailability and efficacy, oral administration remains the favored mode of drug delivery for both patients and clinicians. The use of biocompatible polymers in nanoformulations or nanoparticulate drug delivery systems has sparked considerable attention. Their physicochemical features make them appropriate for alternative dosage strategies. Furthermore, they allow for the vector processing of therapeutic molecules with low solubility and bioavailability, improving their interaction with target organs or cells via various routes of administration. Chitosan-based NPs are commonly used in unconventional treatment due to their low cost, high efficiency, and capacity to contain peptides, medicines, and DNA to disrupt certain biological processes. Because chitosan NPs can get past physical and biological barriers to boost medication bioavailability, which leads to increased efficacy with fewer side effects, this can be done orally without the need for invasive or painful routes of administration.

References


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