REVIEW

CHITOSAN AS A DRUG CARRIER

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Abstract
The review discusses the latest issues related to using chitosan, a biocompatible and biodegradable polymer derived from chitin, as a carrier in intelligent drug-delivery systems. The continuous development of medicine and rapid technological progress pose new challenges in designing new therapeutic agents. Chitosan has properties that make it suitable for drug-delivery applications, such as its ability to form nanoparticles and its mucoadhesion that enhance drug absorption. Chitosan can be combined with antibiotics, analgesics and other ingredients with specific properties. While chitosan is not medicinal substance, it can be a carrier in controlled drug-release systems.

Keywords: *chitosan, drug-delivery system, antibiotics, painkillers*

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1. Introduction

Chitosan belongs to a group of natural polymers obtained from chitin [1, 2]. It is an essential polysaccharide [2] characterised by a linear structure and high molecular weight (Figure 1a). It can be obtained from plant and animal sources. Chitosan most often occurs in the exoskeleton of crustaceans and molluscs and in fungal biomass [3, 4]. Chitosan is of particular importance in drug-delivery systems (DDS) due to its biocompatibility, low toxicity [5], biodegradability in the biological environment and adhesion to the mucosa [2, 6–9] (Figure 1b).

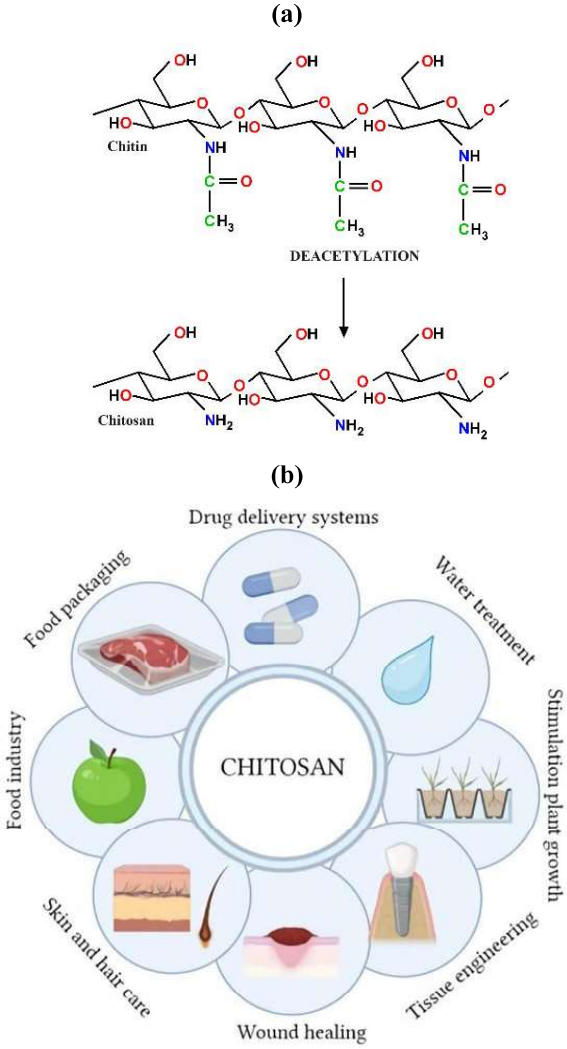

Figure 1. (a) Preparation of chitosan via chitin deacetylation. (b) The physicochemical properties of chitosan-based hydrogel [10]. This figure is distributed under the terms and conditions of a Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

Target DDS are used to administer therapeutic agents to the body in a controlled and target manner. They optimise the therapeutic effects of drugs – increasing the bioavailability

and pharmacokinetics stability – while minimising side effects. They can be classified as oral, intravenous, transdermal or implantable. Chitosan-based drug carriers can improve the pharmacokinetics and therapeutic efficacy of various drugs [11]. In intelligent DDS, chitosan can be in the form of nanoparticles [2, 12, 13], coatings [6, 7, 14, 15], scaffolds [16] or in the form of a hydrogel [17].

Chitosan nanoparticles can encapsulate drugs, protecting them against degradation and improving their transport across biological barriers. Such nanoparticles have better antibacterial, anti-inflammatory and antioxidant properties [8, 18]. The kinetics of drug release from such nanoparticles depends on the site of drug targeting, the pH of the environment and the stability of the drug. In laboratory conditions, drug release kinetics is studied based on experimental data obtained during *in vitro* experiments and mathematical models such as the Korsmeyer–Peppas, Higuchi, and zero- and first-order kinetics models [18]. According to recent reports, chitosan nanoparticles are used widely in dentistry, especially in periodontology, implantology and endodontics [8, 15]. Chitosan supports the formation of osteoblasts and the regeneration of bone tissue. In combination with silver and hydroxyapatite nanoparticles, it supports the regeneration of the alveolar ridge. It inhibits the action of oral bacteria such as *Streptococcus mutans* and *Porphyromonas gingivalis* through the action of positively charged silver ions on the negatively charged bacterial cell wall [6, 19].

The use of DDS based on chitosan dressings is a current subject of research by scientists. These dressings allow for the local delivery of drugs – for example, in the case of healing wounds after burns or skin infections, ensuring transdermal transport. This DDS produces a systemic effect by changing the barrier properties of the skin. Chitosan dressings soaked in a medicinal substance create a tight patch–skin connection, facilitating the penetration of drugs. This is due to the mucoadhesive properties of chitosan, extending the contact time of the transdermal preparation with the skin. The therapeutic success of chitosan in transdermal applications depends largely on the type of drug administered, the formulation and the duration of drug delivery. In one study, researchers created a chitosan dressing with fat-soluble clobetasol, which released 80% from the patch within 2 h. The rapid release of the drug resulted in rapid inhibition of the development of bacteries immediately after applying the dressing to the wound [19]. In another study, the authors produced a patch consisting of chitosan, polyvinyl acetate and water-insoluble curcumin with antibacterial properties [20]. The delivery of medicinal substances from chitosan-based dressings resulted in faster healing of wounds and skin surface lesions and reduced the need for more frequent replacement of dressings due to the absorption properties of chitosan.

Chitosan-based hydrogels also demonstrate the ability to release drugs in a controlled manner. They create three-dimensional hydrophilic networks that can absorb and retain water, thus imitating the action of natural tissues in the human body. Chitosan hydrogels enable the use of many types of drugs, peptides and other therapeutic agents. This type of drug carrier can designed to respond to changes in environmental conditions, such as changes in pH and temperature and reaction to enzymes [20].

Drug release kinetics can follow several mechanisms, including diffusion and dissolution. Designing DDS requires knowledge of these mechanisms and absorption times. Understanding the desired release profile, the physicochemical properties of the drug and the intended route of administration is crucial in selecting the appropriate drug release mechanism for a particular formulation. Scientists are constantly exploring innovative DDS to optimise the therapeutic outcomes and to minimise the side effects. The main goal of pharmacological treatment is to obtain and receive the optimal therapeutic dose of the therapeutic drug. The range from the minimum to maximum drug concentration is called the therapeutic window (Figure 2a) [18, 21], which represents the

safe dosage. Figure 2a shows drug release from DDS with immediate release (black curve) and delayed release (blue curve) [21]. Immediate and delayed release from DDS indicate a higher risk of toxicity from the drug [21]. However, the use of prolonged extraction of the drug substance from DDS means that the optimal therapeutic dose is maintained [21]. Conventional oral administration of a drug does not fully utilise its therapeutic dose. When the drug is administered, the dose increases dramatically, reaching a toxic dose. Over time, the therapeutic dose decreases gradually, reaching a dose that is too low to work effectively (e.g. fight bacteria and viruses or reduce pain; Figure 2b) [21]. The use of chitosan in controlled DDS means that the drug dose remains within the therapeutic window for as long as possible.

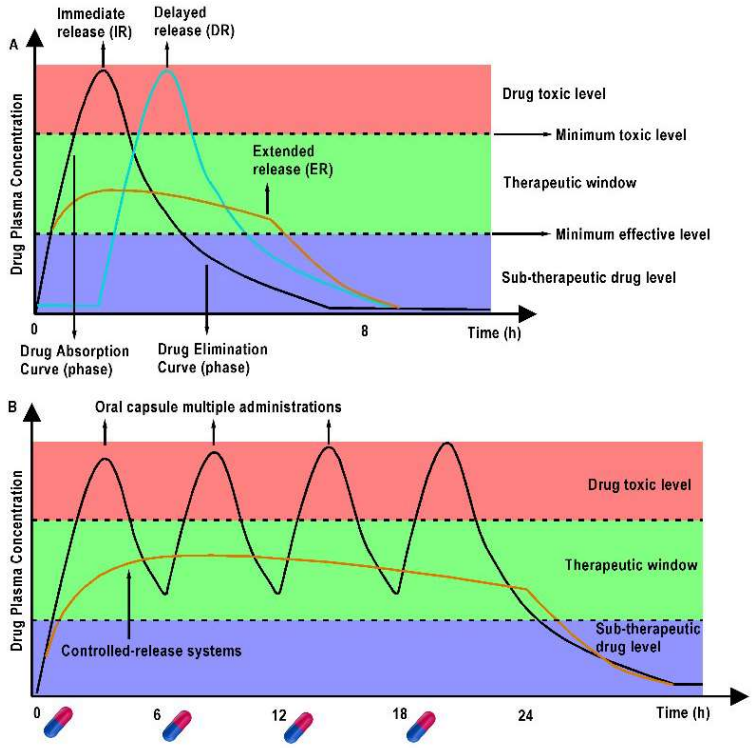

Figure 2. (a) A schematic illustration of the blood concentration of a drug (a) after traditional oral administration and (b) from a controlled drug-release system [21]. This figure is distributed under the terms and conditions of a Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

The choice of a DDS depends mainly on factors such as the nature of the drug, including analgesics [22], anti-inflammatory, antiviral, antibiotics, antihypertensive drugs [23], anticoagulants and natural substances supporting treatment [24]. This review briefly discusses using chitosan as a drug carrier in intelligent DDS to release these compounds.

2. Drug-Delivery Systems Based on Chitosan Carrying Analgesics

Chitosan itself is not an analgesic – a compound that reduces pain – but it can carry other compounds that exert an analgesic action, including paracetamol, ibuprofen, ketoprofen, naproxen and the anaesthetic lidocaine. These are safe preparations provided

that the permissible therapeutic dose is not exceeded; this phenomenon depends on age, weight and comorbidities, among other factors.

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID). It works by inhibiting cyclooxygenases (COX), which produce prostaglandins, hormones responsible for pathogenic processes. Of note, ibuprofen inhibits all COX isoforms; other NSAIDs such as celecoxib can selectively inhibit COX-2 and thus eliminates prostaglandins more effectively [25]. Ibuprofen may cause side effects such as heartburn, nausea and abdominal pain. It has low solubility in the biological environment, fast-acting kinetics and a short period of biological activity [26]. As a result, oral administration of ibuprofen leads to underutilisation of the therapeutic dose of the drug. Despite the potential risk of chitosan inhibiting the action of ibuprofen, using this polymer as a drug carrier could help control the release of ibuprofen, increase its bioavailability and potentially reduce side effects. Such carriers may be designed to release ibuprofen in response to specific conditions in the body [26]. Chitosan-based transdermal patches containing ibuprofen improves the absorption of ibuprofen through the skin, Moreover, chitosan has antibacterial properties, preventing infections at the site where the patch is applied. This local ibuprofen administration system reduces the risk of systemic side effects such as gastric irritation [26].

Paracetamol is another NSAID that is widely used throughout the world due to its antipyretic effectiveness and low risk of side effects. Similarly to ibuprofen, it also inhibits COX to exert analgesic effects, but it does not have anti-inflammatory effects. Paracetamol has a low molecular weight of 151.16 g/mol, which means it can be released in a long-term manner. Indeed, it can be encapsulated in chitosan-coated alginate beads or in nanocomposites as part of DDS [27–30]. This approach is particularly useful for analgesic patches containing it [31]. Chitosan fibre scaffolds obtained from electrospinning act as drug carriers without the need to use additional chemicals [32]. Moreover, chitosan can undergo an encapsulation process, which makes it extremely attractive for use in microspheres with the addition of NSAIDs such as ibuprofen [33–37] and in the form of a hydrogel [38, 39].

Implantation procedures are associated with great pain, which is often alleviated with ketoprofen, another NSAID. Depending on the form, its works for 6–24 h. Ketoprofen, like other NSAIDs, blocks COX and may also irritate the gastric mucosa [25]. In one study, researchers showed that chitosan could be used successfully to form a film to carry ketoprofen [40]. In a rat model of rheumatoid arthritis, this preparation reduced disease-related oedema.

Chitosan can be used to cover anodically oxidised surfaces. Oxide nanotubes are usually produced on the surface of titanium and its alloys [41, 42]. Analgesics can be applied inside the oxide nanotubes and subsequently released rapidly from inside the nanotubes. Covering such a surface with a chitosan coating slows down the release of drugs, which helps achieve therapeutic effects. In one study, the authors compared the effectiveness of analgesic therapy with ibuprofen delivered in the form of microspheres directly into the socket and in a conventional oral manner [36]. The group receiving ibuprofen in the form of chitosan microspheres experienced significantly less pain and visibly less swelling of the operated site compared with the group receiving ibuprofen administered orally. Taken together, chitosan-containing systems that control analgesics such as NSAIDs have the ability to relieve pain and reduce inflammation [36, 37, 43]. The biocompatible properties of chitosan mean that these preparations can be applied directly to the mucous membranes [44].

3. Drug-Delivery Systems Based on Chitosan Carrying Antibiotics

Antibiotics are used to fight bacterial infections: they can kill bacteria or inhibit their growth. There are numerous classes of antibiotics, each with distinct mechanisms of action and spectrum of activity against bacteria. The most common classes of antibiotics are penicillins [45, 46], cephalosporins [47, 48] and tetracyclines. After implantation, there is local inflammation at the site of the implant. In the first days after implantation, growth factors are released locally, and platelets, proteins and blood plasma are released, causing a clot to form. Factors activating the healing process include histamine; prostaglandins; cytokines such as tumour necrosis factor (TNF), interleukin 1 (IL-1), IL-6 and IL-10; chemokines such as chemokine (C-X-C motif) ligand 3 (CXCL3), chemokine (C-C motif) ligand 2 (CCL2), CCL5, CC17, CXCL12 and CXC3CL1; and bone matrix proteins with osteoinductive properties [49]. The pH of the tissues surrounding the implant is reduced from 7–7.35 to approximately 5.2 immediately after implantation, and then returns to the original level after approximately 2 weeks [49]. Such an environment is ideal for developing bacteria, resulting in peri-implant infection and subsequent related complications. Treating such infections requires broad-spectrum antibiotic therapy. Moreover, modifications to the implant surface have been proposed to accelerate their osseointegration and increase biological activity [6, 7]. Controlled DDS are being used with increasing frequency to reduce severe inflammatory reactions by releasing the therapeutic concentration of the drug at the target site [50].

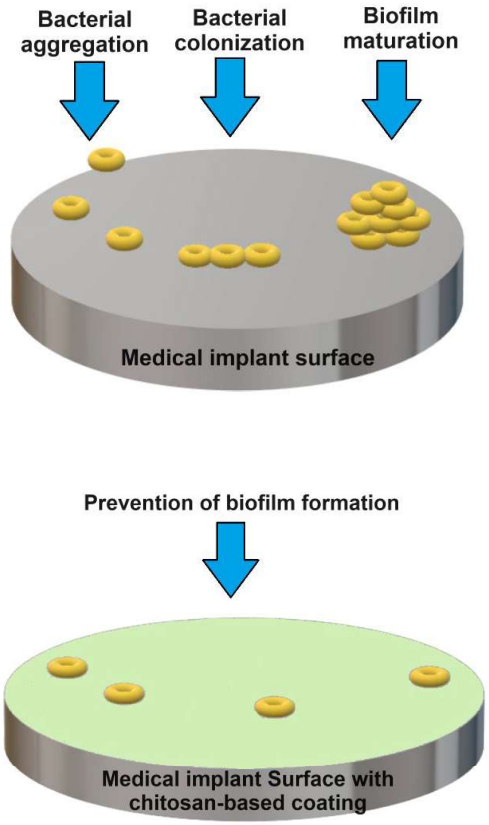

Figure 3. A schematic illustration of the process of bacterial colonisation on (a) the surface of implants without a chitosan coating and (b) an implant covered with a chitosan coating, which prevents the adhesion of bacteria.

According to the World Health Organization, a major problem in medicine is the overuse of antibiotics, which has resulted in increased antibiotic resistance among bacteria. In the human body, a biofilm forms on the implant surface; this coating consists of microorganisms that adhere closely to each other. It comprises polysaccharides, proteins and lipids, which makes it difficult for the antibiotic to reach and penetrate bacterial cells. Implants could be covered with coating containing biopolymers such as chitosan [51]. The use of biopolymer coatings based on chitosan supports the early stage of inhibiting bacterial growth by disturbing the development of biofilm (Figure 3) [52]. Chitosan coatings combined with an antibiotic inhibit the adhesion of bacteria to a natural biofilm that does not contain bacterial cells. This effect is due in part to the natural antimicrobial properties of chitosan [53].

Penicillin is a broad-spectrum antibiotic that disrupts the synthesis of bacterial cell membranes. It inhibits the enzyme transpeptidase, which is involved in cross-linking peptidoglycan chains in bacterial cell walls. This inhibition weakens the cell wall and thus inhibits bacterial growth [46]. However, many bacteria have developed resistance to penicillin-based antibiotics, which is why DDS that use chitosan to carry these antibiotics are being developed less and less frequently.

A recent study demonstrated the increased effectiveness of antibiotics loaded into chitosan magnetic microspheres. These microspheres ensure prolonged release and targeted delivery of the antibiotic to bacteria [47]. The magnetic properties of the microspheres enable external control over the movement of particles and their location in the human body. This method of targeted drug delivery is particularly beneficial to ensure the highest antibiotic concentration occurs at the site of infection, thus increasing its effectiveness and simultaneously minimising systemic side effects.

4. Drug-Delivery Systems Based on Chitosan Carrying Other Medicinal Substances

As mentioned above, the widespread use of antibiotics had led to the development of drug-resistant bacterial strains. One of the possibilities to overcome this issue is to increase the antibiotic dose, but this approach can disrupts the natural bacterial microflora of the treated person and lead to toxicity. An alternative approach is to use other bactericidal agents such as chlorhexidine [54], peptides, organic and inorganic substances.

Chlorhexidine, a commonly used antiseptic and antibacterial agent, is used in oral hygiene products and/or to inhibit bacteria responsible for inflammation in the mouth [55, 56]. The combination of chitosan as an adhesive agent with chlorhexidine enhances the antimicrobial effects, inhibits the formation of biofilm and thus reduces the risk of bacterial growth, in particular streptococci [57, 58]. Researches developed chlorhexidine-releasing liposomes containing chitosan that showed high cell compatibility and reduced inflammatory reactions by 60% in murine macrophages [54].

The latest research focuses on the search for new antibacterial agents based on antimicrobial peptides. These natural molecules affect the cell membrane of bacteria, inhibiting their further development. Chitosan-based hydrogel systems saturated with peptides are also being generated. One of them is histidine, which in the human body stimulates the immune system to combat viruses and bacteria [59]. There are also known natural products with antibacterial activity such as honey, propolis and bee pollen. The latest research shows the possibility of isolating jelleine-1, a bactericidal compound, from royal jelly. The use of this peptide applied in a carrier such as chitosan inhibits the release of pro-inflammatory cytokines and thus reduce inflammation (Figure 4) [59–62].

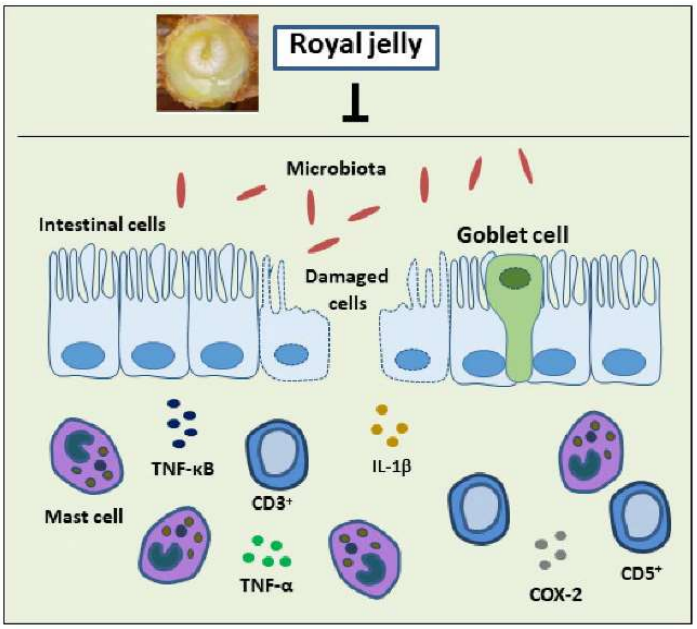

Figure 4. A schematic illustration of the inhibition of lymphocyte growth and pro-inflammatory cytokines by the peptide jelleine-1, which is isolated from royal jelly [62]. Abbreviations: CD, cluster of differentiation; COX, cyclooxygenase; IL, interleukin; TNF, tumour necrosis factor. This figure is distributed under the terms and conditions of a Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

Chitosan combined with copper, silver or gold nanoparticles has antibacterial properties against *Staphylococcus aureus, Listeria monocytogenes, Escherichia coli* and *Salmonella Typhimurium*. The most commonly used chitosan–metal complexes contain silver in the form of ions or nanoparticles. In one study, researchers examined chitosan coatings saturated with silver nanoparticles or silver ions as a bactericidal agent against *S. aureus* and *E. coli* [63]. A chitosan coating saturated with 1% (w/w) silver nanoparticles or 2% (w/w) silver ions exerted a bactericidal effect. Their research showed that the chitosan–silver complex had better antibacterial properties than silver nanoparticles or its ions alone.

The combination of chitosan with micelles takes advantage of the mucoadhesion of chitosan and could be used to treat inflammatory eye diseases [64]. The development of the production of antibacterial agents by mixing chitosan with a copolymer of ethylene and vinyl alcohol is also being investigated [55]. Vinyl alcohol is a synthetic polymer with excellent barrier properties. Mixing these two polymers creates a composite with high antibacterial activity and increased mechanical and barrier properties.

5. Models of Drug Release From Chitosan-Based Carriers

Polymer materials used in the human body are exposed to bodily fluids as well as changes in temperature, pH and the oxygen concentration. Polymer-based drug carriers degrade in the biological environment. Indeed, chitosan swells and degrades in bodily fluids due to breakage of the polymer chain and alterations in the position and number of bonds [65].

This degradation allows the release of the carried drug to the target site. The rate of drug release depends on the type of matrix in which the drug is embedded. The use of chitosan as a drug carrier in controlled DDS requires knowledge of the kinetics of the release of the drug from the polymer. The drug release process has multiple stages. The primary stage in the case of polymers is the diffusion process [65].

The zero-order drug-release model describes a system in which the drug release rate does not depend on its concentration in the system. The drug is released slowly from the system. However, the drug adsorption rate depends on its concentration [66]. In the case of drug release from a flat/solid surface, the kinetics mainly follow the Higuchi model [67]. Specifically, the drug concentration used is much higher than the solubility of the drug in the carrier. The drug concentration gradient in the matrix and the resulting diffusion process occur in the direction perpendicular to the interface of the carrier and the therapeutic agent. Therefore, classic, one-dimensional diffusion occurs. Drug release from hydrogel coatings or hydrogels is mainly based on Fickian diffusion. In such a case, when the active substance is surrounded by a polymer, the drug release model is based on Fick's first law, defined by equation (1) [66]:

$$N_A = -D_{AB} \frac{dC_A}{dx} \tag{1}$$

The terms in equation (1) mean the following:

N_A – stream of active agent [kg·A/(m^2·s)];
D_{AB} – drug diffusion coefficient [m^2/s];
C_A – drug concentration [kg·A/m^3];
x – dimensional coordinate [m].

If the drug is incorporated into the pores formed on the surface of the coating, then the diffusion of the drug follows Fick's second law, described in equation (2) [66]:

$$\frac{\partial C_A}{\partial x} = \frac{\partial}{\partial x}(D_{AB}\,(C_A)\frac{d^2C_A}{dx^2}) \tag{2}$$

Currently, the Peppas model is frequently used to describe drug diffusion [67]. It is represented in equation (3):

$$\frac{M_t}{M_\infty} = kt^n \tag{3}$$

The value of n depends on the geometry of the carrier and the release mechanism (Table 1) [67]. k is a constant whose value depends on the structure of a given drug carrier.

Table 1. The value of the exponent n according to the Peppas model for various geometries of the drug-release system [67].

Exponent n / geometry			Release mechanism
Flat plate	**Cylinder**	**Ball**	
0.5	0.45	0.43	Fick's diffusion
0.5 < n < 1.0	0.45 < n < 0.89	0.43 < n < 0.85	Anomalous diffusion
1.0	0.89	0.85	Polymer swelling

The mechanism of drug release strongly depends on the wettability of a given release coating. Chitosan coatings have a strong ability to absorb bodily fluids, leading to faster desorption of the drug substance from the coating (Figure 5).

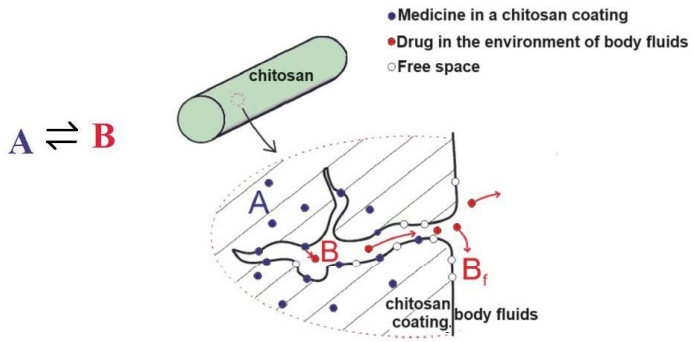

Figure 5. A schematic illustration of the mechanism of drug release from fibres.

Drug-release models from coatings are important for verifying experimental data. In the case of dental implants, it is necessary to release the drug gradually over approximately 14 days. A thorough analysis of the amount of the drug released enables the appropriate selection of the drug dose.

6. Conclusions

Chitosan is a universal carrier of various types of medicinal substances. There has been an increase in research on chitosan-based preparations that carry medicinal substances because chitosan has antibacterial properties, low toxicity, mucoadhesion and low allergenic potential. A controlled and targeted DDS is an excellent way to deliver the optimal therapeutic dose of a drug to the required place, bypassing the oral route and reducing side effects. Chitosan-based drug carriers can increase the solubility of insoluble drugs by creating a stable complex, and thus ensure better biodistribution of drugs. However, there is a need for further research into using chitosan as a carrier for medicinal substances and a detailed determination of their biocidal and therapeutic properties.

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