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REVIEW

POTENTIAL ASPECTS OF CHITOSAN AS PHARMACEUTICAL EXCIPIENT

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Abstract: Interest in use of the polysaccharide chitosan as a pharmaceutical excipient by different dose routes and for a number of applications is not new but it still does not appear to be present in any marketed drugs. Also a novel excipient in a new formulation requires a lot of safety consideration. Published literature showed that chitosan has low oral toxicity and prior human exposure has occurred through use in dietary supplements and food additive, medical device and cosmetic applications. Although systemic exposure to chitosan may be limited, this needs a more careful assessment of its safety as a parenteral excipient. Chitosan has local biological activity in the form of hemostatic action, facilitates platelet adhesion, cholesterol lowering and weight management. Chitosan has become an upcoming research area as a novel excipient in controlled drug delivery, which necessitates us to get an overall information about it.

Keywords: chitosan, polysaccharide, excipient, toxicity, hydrogel

Nowadays it is well known that novel drug delivery systems offer suitable means of site-specific and/or time-controlled delivery of therapeutic agents (1, 2) and for that, among various kinds of polymeric systems, hydrogels are now widely used (3, 4) as drug containers or release rate controlling barriers. They are porous in nature, so drugs can be loaded into the gel matrix and they will release drug at a pre-designed rate. In addition to their inertness and good compatibility, the ability of hydrogels to release an entrapped drug in an aqueous medium and the ease of regulating such drug release make hydrogels particularly suitable as drug carriers for the controlled release of pharmaceuticals (5). Hydroxypropyl methylcellulose (HPMC) (6), a cellulose derivative, is most widely used for delivering drug in the form of hydrogel as it swells when brought into contact with water. Drug will be released through the polymeric matrix at a controlled rate due to diffusion through polymer network and polymer swelling. Small amount of HPMC is good enough to prepare gel having a high viscosity, which is excellent in formative property and also having almost no interaction with medical substance (7). The use of chitosan as biodegradable polymeric carriers for the drug delivery systems has gained a wide interest, mainly for their biocompatibility.

Chitosan

Chitosan is a polysaccharide comprising copolymers of glucosamine (β(1–4)-linked 2-amino-2-deoxy-D-glucose) and N-acetylglucosamine (2-acetamido-2-deoxy-D-glucose) and can be derived by partial deacetylation of chitin from crustacean shells (8, 9). Its discovery has been attributed to Rouget in 1859 when he found that boiling chitin in potassium hydroxide rendered the material soluble in organic acids; Hoppe-Seyler named it chitosan in 1894 (10). However, it took until 1950 for the structure of chitosan to be finally resolved. In the literature, the term chitosan is used to describe chitosan polymers with different molecular weights (50–2000 kDa), viscosity and degree of deacetylation (40–98%) (8). Although not strictly adhered to, it is reported that the generic term chitosan is applied when the extent of deacetylation is above 70% and the generic term chitin is used when the extent of deacetylation is insignificant, or below 20% (11).

The major component of chitosan, glucosamine, is a natural substance produced in the body from glucose and is involved in the manufacture of glycosaminoglycan, which forms cartilage tissue in the body; glucosamine is also present in tendons and ligaments (12, 13). Interest in the use of chitosan as a pharmaceutical excipient is not new

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but it still does not appear to be present in any marketed drugs. However, it is reported as being under investigation for use in a number of pharmaceutical formulations. Although not as a pharmaceutical excipient, established human exposure to chitosan has occurred through its use as a dietary supplement in preparations for obesity and hypercholesterolemia (8, 13).

Biological activity

Conventionally, pharmaceutical excipients have been viewed as ''inert" materials although this view has changed as new proposed excipients cover a range of functions from stabilizing formulations to active roles of enhanced drug uptake and specific drug delivery. However, their role is not to have ''pharmacological" activity. Such a situation appears to be the case for chitosan although its medical device use and wound healing potential has centred on ''biological" activity. A range of studies have shown that chitosan acts as a hemostatic agent. *In vitro* studies with blood have indicated that its hemostatic mechanism seems to be independent of the classical coagulation cascade and appears to be due to an interaction between the cell membrane of erythrocytes and chitosan, with clot formation in the absence of coagulation factors or platelets (14). Furthermore, in the case of blood contacting applications such as drug delivery systems, it has been reported that the positively charged chitosan tends to attract circulating plasma proteins, which adsorb to the material surface, which in turn results in platelet adhesion, activation on the surface of the material and thrombus formation (15). The role of chitosan in the nutritional supplement market as a weight loss aid and cholesterol lowering agent arose from work in the rat showing cholesterol-lowering effects in rats given chitosan diets (16). Although still not fully understood, chitosan's activity has been related to its positively charged nature resulting in binding to free fatty acids (released from consumed fat) and bile salt components which results in disrupted lipid absorption in the gut (8). It has been suggested that chitosan dissolves in the stomach, emulsifying fat and forming a gel in the intestine which entraps fat and prevents intestinal absorption (17, 18). More recently, it has been proposed that chitosan forms a flocculus in the duodenum which entraps dietary oil (19). However, whether chitosan is actually clinically effective in cholesterol control or weight loss remains controversial, with work indicating that chitosan dietary supplementation had no effect on fat absorption or plasma cholesterol levels and had only a minimal, clinically insignificant, effect on bodyweight (20–22). A variety of other biological effects have been attributed to chitosan including antiulcerogenic, antimicrobial, anti-tumor, immune modification, renal protective and osteogenetic actions and use in tissue engineering as a bio-scaffold to allow skin or bone cell growth (17), and is supported by a range of *in vitro* and *in vivo* studies examining potential efficacy.

Pharmacokinetics

A number of studies have examined the *in vitro* and *in vivo* degradation of chitosan, often as films or from implantation, while its fate following oral administration is less well reported. Degradation is dependent on the degree of deacetylation, being less rapid as it becomes higher (23, 24) and minimal degradation of films with very low or high acetylation (25). In discussing tissue implantation use, it is reported that highly deacetylated forms (> 85%) show the lowest degradation rates and may last several months *in vivo*; material with lower levels of deacetylation degrades more rapidly (26). The degradation products are chitosan oligosaccharides of variable length. Although the bioavailability of chitosan after oral administration to animals has not been well investigated, substantial amounts have been shown to be digested in the gut of the rabbit (27, 28). Indeed, chitinolytic enzymes digesting chitosan to generate N-acetylglucosamine (a copolymer of chitosan) are present in the intestinal mucosa of animals as well as in intestinal bacteria. Interestingly, it has also been pointed out (although with no evidence provided) that chitosan is not specifically hydrolyzed by digestive enzymes in man, but limited digestion due to bacterial flora and unspecific enzymes such as amylase and lipase might occur (29). The chitooligomers, which are produced by depolymerization of chitosan, have been reported to have good intestinal absorption (27).

Safety profile

The single dose toxicity of chitosan in rodents is low. There are reports which performed repeated dose toxicity studies with chitosan or related materials in rodents, rabbits and dogs using various parenteral and oral (gavage and dietary) routes. The dietary studies appear to have largely been performed to support the safe use of chitosan materials for food use. In general, results showed no toxicity in rats at up to 2000 mg/kg/day from gavage dosing and at up to 5% (approximately 3000 mg/kg/day) in the diet for durations of up to 3 months. Apparent toxicity was seen at a dietary level of 1% (corre-

sponding to 653–720 mg/kg/day) chitosan oligosaccharide (30). However, it has been suggested that topical findings including erythema/hair loss and swelling of the snout and forelimbs might be due to dermal responses to chitosan oligosaccharide adhering to the skin and fur, which are easily soiled with saliva during grooming, while decreased bodyweight gain and food consumption may be related to feeding difficulties due to the topical lesions on the snout and forelimbs. It is further suggested that increased platelet count, lymphocyte count and differential neutrophil count may be related to the dermal inflammation, although it is not clear if abnormalities in urinalysis and blood chemistry, as well as various organ weight and macroscopic pathology findings, along with vacuolized sertolic cells and decreased germ cells were related only to malnutrition.

Applications in controlled drug delivery

Chitosan is under investigation and its use has been reported in various pharmaceutical formulations like in different types of drug delivery techniques. The chitosan gel bead first received attention as an oral drug delivery vehicle for controlled-release preparations. Chitosan beads containing piroxicam were prepared by a polyelectrolyte complexation of sodium tripolyphosphate and chitosan. The interaction of positively charged chitosan molecules with the anionic counterion caused the formation of gelled spheres (31). Chitosan was also formulated in a controlled-release protein delivery system using bovine serum albumin (BSA) as a model drug. Chitosan was reacted with sodium alginate in the presence of tripolyphosphate for bead formation (32). In order to prepare stabilized chitosan, microspheres by cross-linking agents such as formaldehyde and glutaraldehyde have been used as stabilizing agents (18). However, these chemical cross-linking agents have the possibility of inducing undesirable effects. For example, glutaraldehyde can cause irritation to mucosal membranes because of its toxicity (19, 20). To overcome this disadvantage of chemical cross-linking, ionic cross-linking interaction has been applied to emulsion and syringe method (33). Similarly chitosan microspheres were prepared by using different range of polymer, one of them extensively used is alginate. Beads containing sodium diclofenac were examined and the different influence of Ca^{2+} or Al^{3+} ions on the microsphere morphology and the influence of different amounts of chitosan on the release of diclofenac are shown (34). Also investigations are performed on the influence of chitosan coating on drug release properties from calcium alginate gel beads (CAGB) prepared by three methods, i.e., by dropping alginate solution into $CaCl_2$/chitosan solution, or into chitosan solution then gelled by $CaCl_2$, or into $CaCl_2$ solution then coated by chitosan. The morphology of beads, the chitosan content of beads surface, the swelling and stability of beads in release media were also studied (35). Experiments are made to design a new extended release gastroretentive multiparticulate delivery system for verapamil (VP) by incorporation into hydrogel beads made of chitosan (36). Among the different approaches to achieve colon-specific drug delivery, the use of chitosan provides great promise due to its non-solubilty at pH values higher than 6.5, which prevail in the jejunum and the ileum of the gut, whereas the colonic pH value is in the range of 5.5–6.0 and chitosan then gets soluble again and will release the incorporated drug substances (37). In its hydrated form, chitosan also shows good mucoadhesive properties.

Parenteral administration of proteins/peptides requires repeated injections because of their extremely short biological half-life. Daily multiple injections are highly risky and require close medical supervision. Therefore, the delivery of proteins and peptides by routes other than parenteral route has gained much attention in recent years. As a drug delivery route, nasal cavity offers several possible advantages. Chitosan microspheres were prepared for non-invasive delivery of insulin (38), amlodipine (39) and ondansetron (40) for nasal administration with the aim of avoiding the first pass effect. A range of chitosans are having the ability to act as nasal peptide absorption promoter. These microspheres, after spraying onto the nasal mucosa, can hydrate creating macro adhesive gel (41). Microspheres prepared from suspensions and with higher chitosan content were more bioadhesive than those prepared from emulsions, regardless of the same polymeric composition. The spray-drying method is found to be useful to produce bioadhesive loratadine-loaded microspheres (42). The gel of 2% medium molecular weight of chitosan with EDTA caused an increase in insulin absorption and reduction in the glucose level by as much as 46% of the intravenous route (38). A recent research resulted in chitosan microspheres used as a nasal vaccine delivery system, which was developed by modifiying microspheres through their concomitant use with adjuvants or immunomodulators for an additive and a synergistic effect, and through the mannosylation of chitosan for receptor-mediated targeting antigen-presenting cells (43).

From the above findings it may be concluded that chitosan is a potential pharmaceutical excipient

but still its use is very much limited but it can be effectively used in targeted drug delivery systems.

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