Review Article

Biopolymeric Nano-based Formulations for Oral Drug Delivery Applications - Need and Concern

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Abstract

This review focusses its attention on biopolymeric drug carriers for oral delivery applications. The review is intended towards upcoming researchers in the area. It provides a detailed introduction to the types of biopolymeric carriers with specific emphasis on chitosan-based and chitosan-coated carriers. The significant advantages and limitations of these carriers have been detailed. Insight into the mechanism of formation of composite hydrogels, chitosan-coated liposomes, and nanoparticles, their oral delivery pathways have been provided. The article also provides an outline of the current trends in oral drug delivery and future prospects.

Key words : Biopolymer, Oral drug delivery, Chitosan, Composite hydrogel, Drug carriers.

Polymers from Natural Resources

Archeological evidence suggests that polymers from natural sources such as cellulose, polysaccharides, lignin and so on existed even 30,000 years ago.[1] Products based polymers of animal sources such as the skin, wool, and fur, etc., have been dated back to 7000 years.[2] The pursuit of humankind to emulate the properties derived out of natural products or those present in live systems, such as animals, in their daily use products has led to the enormous use of polymers and monomers of natural origin. Typical examples of such polymers of natural origin that are finding use in food, agriculture, and healthcare products are polysaccharides, polyesters, polypeptides/proteins and lignin. One of the significant advantages in use of polymers of natural resources is the interdependencies between the functional parameters of the biopolymer and the intrinsic/extrinsic factors. For instance, the change of pH, temperature, and use of acids for protonation, etc., influences the viscosity of the biopolymer. The viscosity of the biopolymer is also interdependent to the ionic strength, solubility, density, and molecular weight of the biopolymer.[3]

Three-dimensional, water-swollen biopolymeric matrices, known as biopolymer hydrogels, have now been extensively used for medicine, personal care products, agriculture, and food industries. It has been suggested that the choice for industrial applications has been based on safety, biocompatibility, biodegradability, abundant availability, and thus the lower price.[4] Amongst the range of biopolymers known, proteins and polysaccharides seem to be the most preferred, either individually or in combination. When proteins and polysaccharides are combined, they are known as interpenetrating networks or simply composite hydrogels. Such hydrogels have the ability to carry larger cargo, better swelling, and elasticity and depending on the choice of protein and polysaccharide, a high immune compatibility.[5] The success of the formation of hydrogels is the crosslinking of one polymeric unit with others. Crosslinking reactions may involve covalent or non-covalent interactions between the biopolymers, or with the external crosslinker molecule.[6] Hydrogels are also classified based on the crosslinking, viz., chemical and physical. Chemical crosslinking refers to covalent networks and physical crosslinking refers to physical entanglements and hydrogen or ionic bonding and hydrophobic interactions.[7]

Depending on the biopolymer choice, an abundance of carboxyl, amine and hydroxyl groups are observed and they, in turn, offer a unique opportunity for attaching targeting ligands or drugs and imaging agents. Chitosan polymers modified with acetyl or dodecyl groups have been reported for the treatment of alpha- and beta-coronaviruses.[8] Similarly, a

pharmaceutical composition of iota-carrageenan and kappa-carrageenan has been reported as a deblocking agent for stuffy nose and as an antiviral agent.[9]

Nanomedicine: Enhanced Interest

The growing interest in nanomedicine, more so for improving drug efficacy, has led to the development of a range of nanoformulations.[10] Liposomes that can encapsulate hydrophilic, hydrophobic and amphiphilic drugs have remained very popular.[11] Liposomes, however, are unstable in the gastrointestinal tract due to the hydrophobicity and membrane fluidity.[12] This has led to a range of nano-based alternatives such as solid dispersions, microemulsions, self-emulsifying systems, nanosuspensions, solid lipid particles, and PEGylated nanoparticles etc.[13]

Nano-formulations of Natural Polymers

Nano-formulation of natural polymers in the last two decades has led to an increased number of health and personal care products. Yaneva et al., in a recent review article suggest that the natural cationic polymer – Chitosan, though known since 1811, has now had a rebirth due to its availability in the form of gels, suspensions, micro- and nanoparticles, and capsules, etc.[3] This has also enabled features such as the ability to carry a wide variety of drugs, enzymes and bioactive and release them in a controlled manner at a given target site.

Since 1990, chitosan-based on its film-forming ability has been used in controlled drug delivery.[14] The properties of chitosan, such as its ability to increase the cell chemotactic activity, activity against yeast and fungus, promoting IgM production by lymphocytes and enabling bone formation to have been successfully employed by researchers to develop multifunctional platforms.[15] From the mid-1990s, chitosan self-assemblies or nanoparticle forming chitosan have found wide applications.[16] Nanoparticles of chitosan, in addition to the properties of chitosan also have favorable and tunable characteristic features such as half-life, toxicity, time of circulation and release profile.[17] Chitosan nanoparticles are prepared by conjugating hydrophobic units to nitrogen and oxygen atoms of the chitosan backbone. They also self-assemble in aqueous medium (Fig. 1) into polymeric micelles.[18] This reaction generally happens in acidic pH conditions.

When chitosan dissolved in acetic acid is reacted with glutaraldehyde, an ethylenic double bond forms between glutaraldehyde and chitosan, as established through NMR and Raman spectroscopy. The mechanism of this reaction has been detailed as one between the free pendant amine group of chitosan polymer interacting with the aldehydic group of the glutaraldehyde to form stable imine bonds on account of a resonance in adjacent double ethylenic bonds. The crosslinked unit has non-uniform chain length and terminal unities and involves two chitosan unities from the same or different polymeric chains. As glutaraldehyde concentration increases, the degree of crystallinity and particle size decreases.[20]

When chitosan is modified to contain N-palmitoyl and other similar groups, then the self-assembly process happens even in neutral or alkaline pH.[21] Ionic gelation technique based chitosan nanoparticles is reported to be taken up by the gut epithelial cells, while those prepared by self-assembly processes are avidly taken up by the gut cells and translocated to liver and gall bladder.[22, 23] In the preparation of chitosan hydrogels, when the conventional glacial acetic acid is replaced by Li/K hydroxide and urea mixture, then an in situ reduction of Ag+ ions to Ag, leading to chitosan-Ag hydrogels is possible. Such hydrogels have antibacterial properties coupled with mechanical properties.[24] The enhancement in antibacterial and mechanical properties is reported to higher when silver nanoparticles are crosslinked to chitosan through siloxane, with nanoparticle release under acidic conditions. Such acidic release specificity provides for the chitosan carriers applications in treatment of digestive disorders.[25] Similar observations have been made with other polysaccharides as well.[26] Polysaccharide hydrogels are ideal carriers for hydrophobic

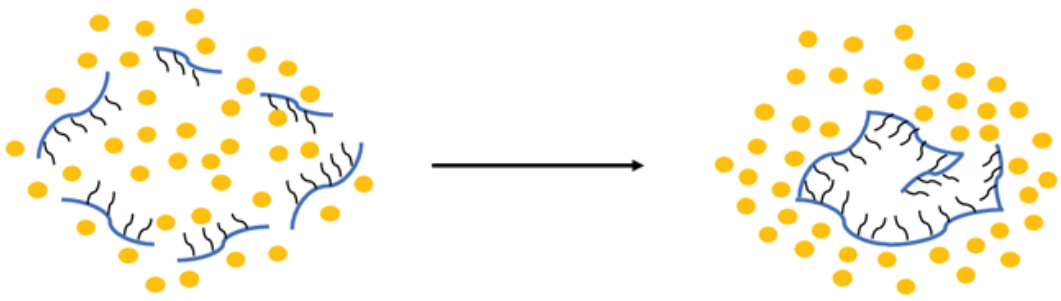

Figure 1: Self assembly of chitosan.[19]

drugs such as riboflavin and have been found to have long circulating times, leading to the lowering of drug dosage.[27] The release rate of drugs from polysaccharide matrices such as chitosan is attributed to the rigid and hydrophobic environment that it provides. Based on this approach drug nanoformulations are coated with chitosan to reduce the release rate.[28]

Flexible liposomes or transfersomes are a class of lipid based nanoparticles that have a phospholipid and a single chain surfactant. The surfactant provides for flexibility for the nanoparticles and makes them ultra-deformable. The transfersomes trespass intact skin spontaneously under the influence of transcutaneous hydration gradient.[29] Chitosan coating of transfersomes, led to sustainable drug release but with a reduced flexibility.[30] Chitosan coated transfersomes are considered ideal for intranasal delivery of drugs with low oral bioavailability.[31, 32] Chitosomes have mucoadhesive property and thus stay in the stomach for a longer time.[10]

The lipid molecule glycerol monooleate can form liquid crystalline phases such as cubes with a non-lamellar liquid crystal internal structure in biological fluids. This provides an opportunity for modifying drug release properties. Cubosomes are prepared by top-down approaches and carry amphiphilic proteins and block copolymers as stabilizers. Compared to liposomes, cubosomes have better stability and special liquid crystalline structure.[33, 34] While cubosomes have sustained-release properties in vivo, in GIT, the lipases destabilize them through compromise of liquid crystalline structure. Surface cross linking of cubosomes with chitosan enables to overcome the lipase digestion, has a slower in vitro release of drugs and enhanced oral bioavailability. Spray-dried chitosan-coated cubosomes were reported to be better than chitosan coated cubosomes. This methodology is an ideal one for highly lipophilic drugs.[35]

Adsorption of chitosan to the surface of liposomes occurred through electrostatic interactions between positively charged amino groups of chitosan and negatively charged phospholipids alongside hydrophobic interactions and hydrogen bonding.[36] An o-palmitoyl chitosan synthesized from chitosan and palmitoyl chloride in a methane sulfonic acid solvent medium resultant in a liposomal formulation for encapsulating drugs with higher intestinal absorption,[37, 38] Mechanistically, it has been demonstrated that the mixing of chitosan to dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), followed by its hydration, affected the thermotropic behavior of DPPC without changing its phase transition temperature. Chitosan tuned the intermolecular interaction between neighboring lipid molecules.[39]

Oral Drug Delivery

Non-invasive routes for drug administration includes oral, nasal, transdermal and pulmonary.

Oral drug delivery is the most popular method due to its non-invasive and safer character. It is also popular due to its patient friendly character. Fig. 2 details the main barriers for non-invasive administration of drugs.

More specifically to oral drug delivery, unpredictable adsorption, more so with macromolecular drugs, inactivation of the drug in the gastrointestinal tract are some of the disadvantages.[41] This inactivation of drugs is considered to be due to extreme pH conditions and the presence of digestive enzymes and biliary salts.[42] Drug dependent pharmacodynamic studies, which are carried out alongside pharmacokinetics studies, help in the understanding of biochemical and physiological effects of a drug. The pharmacokinetic studies, on the other hand, provide information on the concentration of the active ingredient of the drug molecule in bodily fluids as a function of time.[43] The pharmacokinetic studies

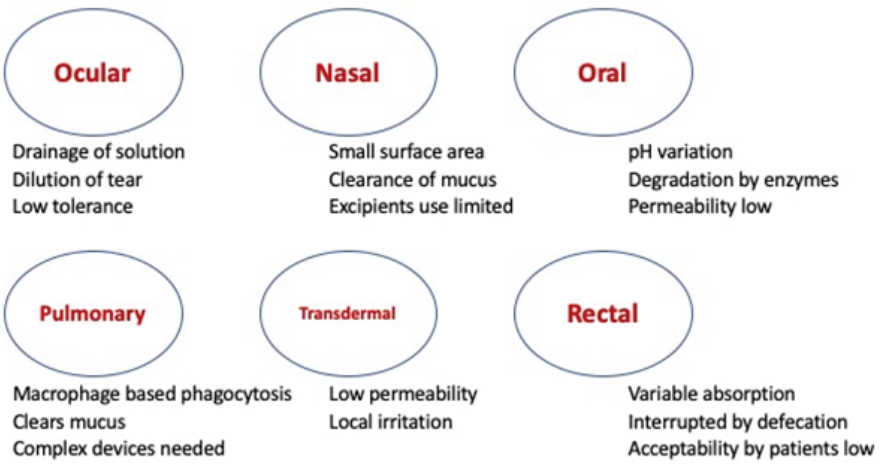

Figure 2: Main barriers in drug administration through non-invasive routes[40]

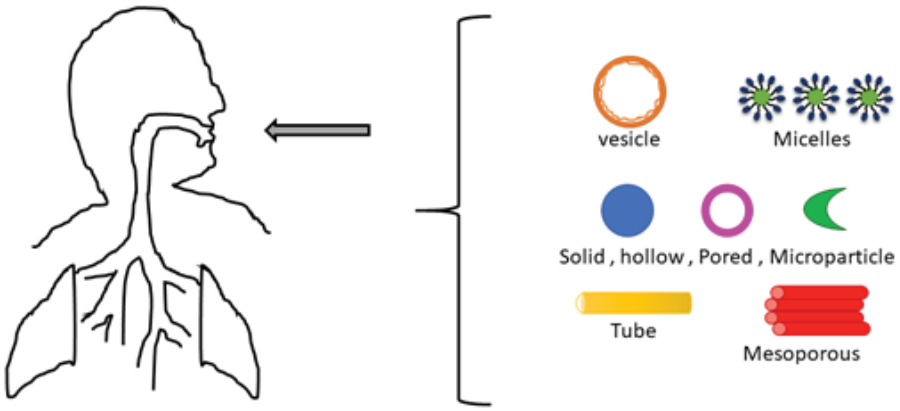

Figure 3: Possibilities for oral drug delivery[44]

utilize the advancements made in the fields of mass spectroscopy, chromatography, radioimmunoassays etc. to estimate the amount of the active ingredient.[23]

Encapsulation of the drug in nanocarriers such as micelles, dendrimers, etc. has been suggested.

Effective oral delivery of nanoparticles requires efficient transport of the nanoparticle-drug complex (either as a whole or drug alone after dissociating from the nanoparticle). While most drug nanocarriers offer drug protection and controlled release, many of them on encountering the protective mucus layer of the gut mucosal surface get trapped in the mucus, a process known as mucoadhesion.[45] Mucoadhesion involves physicochemical interactions between nanoparticles and mucins leading to the formation of gel-like structures in the mucus. Mucus permeating properties are thus required for the nanocarriers to reach the drug to the absorptive membrane of the mucosal epithelium. Functionalization of the nanoparticles with slippery surfaces, proteolytic enzymes etc., have been suggested for obtaining mucus permeating properties. Subsequent to mucus permeation, the nanocarriers either adhere to the gut cell surface or enter the absorptive cell and remain in circulation.[41] Yet another concern for nanocarriers that permeate through the mucus layer is that they may damage the protective mucus structure. In a similar manner, the interaction of the nanocarrier with the gut cells may result in loss of drug viability and potential side effects during subsequent translocation during the circulation in bloodstream.[41] Fig. 4. details the steps involved in the oral drug delivery using nanoparticles.

An understanding of the travel map of the nanoparticle or the active ingredient of the drug starting from the GI tract mucus lining to the gut wall and the blood vessels is essential for understanding the drug bioavailability in the target organ. Confocal Raman microscopy or Coherent anti-Stokes Raman scattering microscopy are ideal techniques for such studies as they are dependent on the vibrational structure of the molecules within the sample volume.[46] Employing this

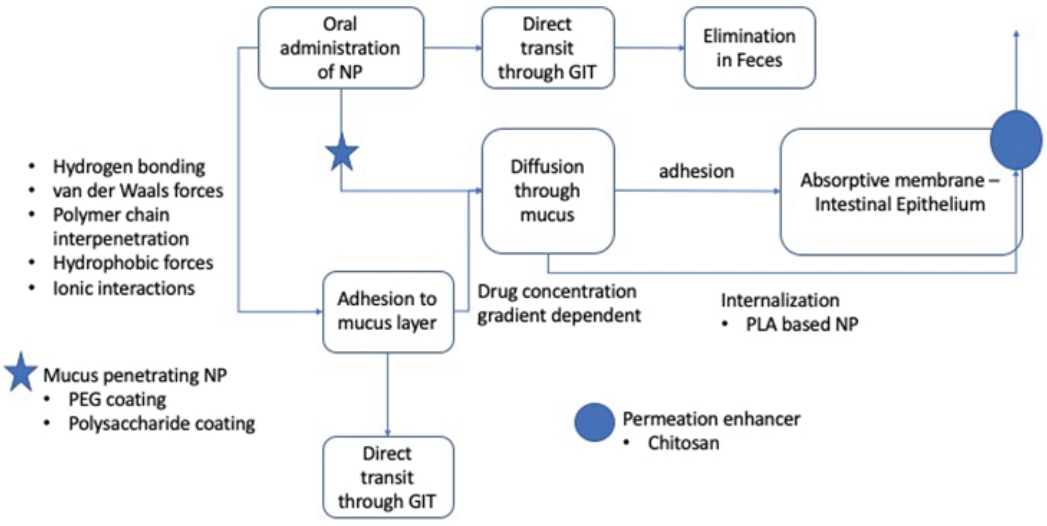

Figure 4: Pathway for orally delivered nanocarrier based drugs

technique, Quaternary Ammonium Palmitoyl Glycol Chitosan (GCPQ)[47] has been reported to have an order of magnitude higher uptake compared to conventional chitosan nanoparticles. This increase has been attributed to the ability of the GCPQ to self-assemble into micelles and encapsulate drugs, leading to oral absorption of hydrophobic and hydrophilic drugs.[48] There are now strong experimental evidence to suggest that GCPQ nanoparticles move through the enterocytes in the villi to the blood stream before being transported to the hepatocytes and hepatocellular spaces of liver. This is followed by recirculation via bile in gall bladder to the small intestine.[23] The recirculation, in turn, improves the drug absorption.

Similar observations have also been made with hybrid pastes of liposomes, alginate and calcium, where a 1.7 fold greater mucosa retention, a controlled drug release in the oral cavity has been reported.[49]

Optimizing Oral Drug Delivery Systems

Computational methods are widely used in the formulation of drug delivery systems. The studies include selection of optimal excipients, prediction of drug/carrier toxicity, carrier stability, and biological performance of the drug delivery system.[50] Molecular modeling, molecular mechanics and discrete elemental modeling etc., are employed alongside pharmacokinetic studies. The advantage of computational modeling is the reduction in time and cost for predicting the parameters.[51]

Recent Advances in Oral Drug Carriers with Emphasis on Chitosan

The field of natural polymer-carriers, more so those based on chitosan nanocarriers, is growing rapidly. An assessment of the publications that have emerged in the area of chitosan for oral drug delivery indicates that about 2500 publications being available during the last twenty years, with about 70 publications in 2020 itself. Some of the research works that have attracted interest owing to their ability to enhance the encapsulation of drugs and also provide for a sustained release are detailed below:

a. Pectin and chitosan microspheres for controlled release of acetaminophen on oral administration, where pectin interacted with the drug while chitosan had no interaction with the drug at the molecular level.[52]

b. Chitosan coated nanoemulsions carrying water-soluble drugs such as repaglinide had a higher oral bioavailability than those without the coating.[53]

c. Overcoming the limited enhancement of oral drug bioavailability and inability to form micelles through gallic acid – chitosan – D-α-tocopherol polyethylene glycol 1000 succinate copolymers.[54]

d. Composite hydrogel cylinders of cellulose nanocrystals and chitosan had higher mechanical and chemical stress resistance as against chitosan hydrogels which degraded through enzyme digestion. The cylinder design and fabrication, ensured drug erosion in the vertical axis.[55]

e. Multiple units of chitosan-functional liposomes (FCL) conjugated to folates served as carriers for chemotherapeutics like Gefitinib and quantum dots such as ZnO. Encapsulation of the FCL cores in a beta-1,3-d-glucan porous microcapsules FCL@GPM capsules that had a 1.47 fold increase in antitumor efficacy, targetability through folate and co-delivery of cellular imaging probes and drugs.[56]

f. Fucoidan has bioactivity against various diseases and its applications in theranostics and oral delivery of drugs is enhanced through preparation of chitosan-fucoidan mixtures.[57]

g. Chitosan-Xanthan gum based hydrogels as potential carriers for antiviral drugs with pH sensitive release profile.[58]

h. Collagen-chitosan sponges as a porous mucoadhesive vehicle for dexamethasone used in the treatment of oral mucositis.[59]

i. Small interfering RNA (siRNA) is employed for improving gene silencing efficiency. Knowledge on designing nanoparticle carriers for siRNA in the areas of release kinetics and inflammation therapy is limited. A mannose-modified trimethyl chitosan-cysteine containing TNF-alpha siRNA has been prepared through ionic gelation technique leading to sustained siRNA release, prolonged RNA interference efficiency in an oral delivery model.[60]

j. State of art information in chitosan coated nanoparticles for biomedical applications have been reviewed by Frank et al. recently. The review provides details on the coating of chitosan on polymer, lipid and metal materials. The advantages of chitosan coating such as physico-chemical stability, controlled release, improved bioavailability have been detailed.[61]

Toxicity Aspects

Using zebra fish model the toxicity of chitosan nanoparticles have been studied by several researchers. In several instances, dose-dependent decrease in the hatching rate has been observed. The LC_{50} value varied from >280 mg/L to 25 mg/L and was

predominantly size-dependent, with lower sized nanoparticles exhibiting a higher LC_{50} value.

Future Outlook and Conclusions

Oral drug delivery of drugs has received a tremendous boost through nanoparticle drug carriers. Preparation methods, size and charge of the nanoparticles, ability to load drugs, drug- nanoparticle interactions, etc. are essential parameters for the sustained release and bioavailability of the drug. Chitosan-based nanomaterials have been extensively studied and reported to have a distinctive positive effect over several other biomaterials. Loading capacity and sustained drug release properties have been improved through composite hydrogels, cubosomes, flexible liposomes and so on. Chitosan nanoparticles with polymeric or metal nanoparticle matrices have been reported for overcoming the limitations of pristine chitosan nanoparticles, more so with respect to antimicrobial properties, aggregation and dissolution in the presence of enzymes. Computational techniques have furthered the optimization of design, drug release and targetabilty of the chitosan carriers.

The challenge in nanoscience research is the lab to market transition. An evaluation of the potential for nanoparticle based oral drug carriers to be made available in the market through the popular methods such technology readiness levels would indicate that several of these studies are limited to laboratory level research. Inputs on engineering and plant design for upscaling nanoparticle drug carriers is required as synthesis of nanoparticle and other nanocomposites with limited size variabilities in large scale and in a reproducible manner is still challenging.

The literature on toxicity of chitosan coated nanocarriers is still scanty. Synthesis procedures in several cases may not comply with sustainable production strategies more so in bulk production as no evaluation of yield and quantum and characteristics of wastes generated has been made.

Nevertheless, it is now time of biopolymeric carriers for oral drug delivery to take center stage as the advantages and positive effects are far more than the shortcomings. An interdisciplinary research involving chemists, biologists, nanotechnologists, engineers and medical professionals is now required to take biopolymer carriers from laboratory to the market.

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