

Recent Applications of Natural Polymers in Nanodrug Delivery

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Abstract

Natural biopolymers such as starch, chitosan and gelatin have found use in industries as diverse as food, textiles, cosmetics, plastics, adhesives, paper, and pharmaceuticals. The food industry uses these polymers as a thickening agent in snacks, meat products, fruit juices. They are also used in the manufacture of disposable items like fast food utensils and containers. From a pharmaceutical standpoint, these polymers have been extensively used in solid-oral dosage forms, where they have been used as binders, diluents, disintegrant and matrixing agents. In recent times, nanotechnology has started to make significant advances in biomedical applications, including newer drug delivery techniques. There has therefore been considerable research into developing biocompatible, biodegradable submicron devices as drug delivery systems using natural polymers, this is because, they occur widely in nature, generally biocompatible, biodegradable, safe and non-immunogenic. There are reports of these polymers been made into colloidal particles that act as carriers for both large and small drug molecules, conferring on the drug molecules properties which enhance delivery actively or passively, thereby tuning them for use as controlled, ocular, transdermal or intranasal delivery systems. In more advanced areas of drug delivery, these polymers have also been tested for gene therapy and tissue engineering. This review examines the properties and recent applications of three (3) natural polymers; starch, chitosan and gelatin in nano-drug delivery.

Keywords: Natural polymers; Nanotechnology; Drug delivery

Introduction

Although, the initial properties of nanomaterials studied were for its physical, mechanical, electrical, magnetic, chemical and biological applications, recent attention has been geared towards its pharmaceutical application especially in the area of drug delivery. This is because of the challenges with the use of large size materials in drug delivery, some of which include poor bioavailability, in vivo stability, solubility, intestinal absorption, sustained and targeted delivery to site of action, therapeutic effectiveness, generalized side effects, and plasma fluctuations of drugs. Of recent, several publications in Nanodrug delivery have been designed to overcome these challenges due to the development and fabrication of nanostructures. It has been reported that, nanostructures have the ability to protect drugs from the degradation in the gastrointestinal tract, the technology also allows target delivery of drugs to various areas of the body. The technology enables the delivery of drugs that are poorly water soluble and can provide means of bypassing the liver, thereby preventing the first pass metabolism [3,4,8,12,13,16,20,22,24,26,28,37,39,48,49,52,53]. Nanotechnology increases oral bioavailability of drugs due to their specialized uptake mechanisms such as absorptive endocytosis and are able to remain in the blood circulation for a longer time, releasing the incorporated drug in a controlled fashion leading to less plasma fluctuations and minimizing side-effects. It has been reported that, due to the nanoscale size of nanostructures, they are able to penetrate tissues and are taken up by cells, allowing efficient delivery of drugs to target sites of action with the uptake of nanostructures observed to be 15-250 times greater than that of microparticles in the 1- 10 μm range [37]. Nanotechnology improves their performance and acceptability by increasing effectiveness, safety, patient adherence, as well as ultimately reducing health care costs [22]. Nanotechnology may also enhance the performance of drugs that are unable to pass clinical trial phases [22]. It definitely promises to serve as drug delivery carriers for the more challenging conventional drugs used for the treatment and management of chronic diseases such as cancer, asthma, hypertension, HIV and diabetes. Despite the great potentials of nano drug delivery systems in revolutionizing patient treatment,

its safety in humans are of great concern. It has been reported that, smaller nanoparticles show increased toxicity due to their increased surface area [11]. For example, studies have shown that nanotubes are cytotoxic and induce granulomas in lungs of laboratory animals. Metals such as copper, cobalt, titanium and silicon and their oxide nanoparticles have also been reported to have inflammatory and toxic effects on cells [11]. In addition, titanium oxide nanoparticles have been shown to induce DNA damage and chromosomal aberrations, while Hydroxyapatite nanoparticles, a substance closely related to the mineral component of bones and teeth, were found to induce cell death [11]. Many other synthetic/semi-synthetic polymers have been extensively utilized and investigated as the preparation materials of microcapsules [14]. Although the synthetic polymers display chemical stability, their unsatisfactory biocompatibility still limits their potential clinical applications [7,15,40]. Because the natural polymers always show low/non toxicity, low immunogenicity and thereafter good biocompatibility, they have been the preferred polymers in drug delivery systems. Among the natural polymers, alginate has become one of the most common materials used to form microcapsules [17]. Recently, scientists have turned their attention on tuning starch and chitosan for use in nanodrug delivery. One of the ways to avoid the potential hazards of nanodrug delivery may be by using natural polymers. This is because, apart from occurring widely in nature, natural polymers are generally bio-compatible, biodegradable, non-immunogenic and

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safe. This review therefore takes a look at the recent advances made in using three common natural polymers; starch, alginate and chitosan in nanodrug delivery.

One of the enduring features of drug delivery technology is the central role that polymers play in the control of drug release, and fabrication of drug delivery devices. The need for polymers with specific physical and biological properties has generated continued interest in novel polymer screening from natural resources and synthesis, both from academic and commercial environments. Nano-drug delivery involves the use of carriers of nano-metre range or less to deliver drug molecules to the required site of action. The result of this reduced sizing is a better uptake and retention by target tissues in the human body because nano-sizing, (especially in the range of 10nm-100nm) facilitates passage through cell membrane and reduces the chances of uptake and clearance by the reticulo-endothelial system, the liver and spleen, resulting in enhanced therapeutic effect and a consequent decrease in toxic side effects [19]. In addition, nano sizing results in particles with a large surface area to volume ratio, creating more room for particles to be adsorbed or carried [25]. Natural polymers are of considerable importance because they are generally bio-compatible, bio-degradable, non-toxic and non-immunogenic. They occur widely in nature and are classified into 2 groups; polysaccharides and proteins [45]. Starch, chitosan, alginate, and dextran are examples of commonly used polysaccharides while gelatin and albumin are examples of commonly used proteins. These polymers are applied as colloidal particles of size 10nm-1µm termed nano-particles. In this system, the drug to be delivered could be dispersed within the polymeric matrix or adsorbed on the surface of the carrier in which case they are called nano-spheres or it could be encapsulated within a core surrounded by polymeric membrane and are known as nano-capsules. The method by which they are fabricated into nano-particles for drug delivery depends on their physicochemical properties and the drug to be loaded [42]. In a detailed review by Reis et al. [43], the methods used for preparation of nano-particles can be broadly classified into two:

- a) Polymerization- This could be by emulsion polymerization or by interfacial condensation.
- b) Direct formation from the polymer or solvation of macromolecule- These methods include emulsification followed by solvent evaporation or solvent diffusion, solvent displacement and interfacial deposition, salting out.

Recently, spray- drying with the Buchi nano spray dryerB-90 has been used by Li et al. [31] to prepare nanoparticles. Four out of the 5 polymers used in the study were natural polymers; Arabic gum, whey protein, modified starch and malto dextrin. Yields between 70-90% were obtained, with narrow particle size distribution and particle sizes as low as 350nm.

The loading efficiency of the nano-particle can in turn be influenced by different methodologies. For example, Bilati et al. [2] found that in the formulation of PLGA(poly(lactic-co-glycolic acid) nano-particles using the double emulsion method, more than 80% entrapment efficiency was achieved when sonication was used to create the primary emulsion while the use of a vortex resulted in about 25% entrapment efficiency. This good loading was also attributed to the high molecular weight of PLGA, its hydrophilicity and also its free carboxylate end groups [19]. These properties are also present in natural polymers; in fact the chemical modification of natural polymers is made possible by the presence of free reactive functional groups. This is used to enhance drug therapy by non-covalently attaching ligands that bind specifically to receptors resulting in actively targeted drug delivery. They can also be

passively targeted due to their inherent properties or via the enhanced permeation and retention by surface modification with polyethylene oxide rendering them long- circulating [27,30]. Natural polymers have also been used as carriers of particulate drug carriers, acting as coating agents and surface modifiers [25].

Classes of Natural Polymers

Polysaccharides

These are complex carbohydrates that are made up of repeating monomer units of monosaccharides [41]. They occur widely in nature and of either plant, animal, or microbial origins. They are used widely in drug delivery systems and possess the following advantages [46]. They are biodegradable, thus after drug is depleted the carrier is broken down to components that are readily re-absorbed or eliminated.

- They are bio-compatible and as a result are non-toxic in humans
- They allow for adhesion to target tissues as the presence of reactive functional groups allows the formation of non-covalent bonds to epithelial cells. This helps to enhance residence time and consequently the amount of absorbable drug.
- They also possess specific receptor recognition
- They allow for non-specific protein adsorption as they provide neutral coating with low surface energy
- They possess a high amount of hydroxyl groups on their backbone and allow the incorporation of different specific ligands
- Starch and Chitosan are 2 of the widely studied polysaccharides in nano-drug delivery and thus will be discussed

Starch

Starch is a common polysaccharide. It occurs majorly in plants where they act as storage materials. Chemically, it is composed of recurring units of glycopyranose in an alpha D-(1, 4) linkage and on hydrolysis yields the monosaccharide, glucose (Heller et al., 1990). The use of starch in pharmaceuticals is extensive. It is used as co-polymer and excipient in controlled drug delivery [18,29,56], as drug carriers in tissue engineering scaffolds [35], as Hydrogels [21] and as solubility enhancers [54].

Santander-Ortega et al. [46] investigated the potential of starch nano-particles as a transdermal drug delivery system (TDDS). The challenge faced in delivering drug through these systems is that the skin acts as an effective barrier to drug passage and must therefore be overcome for effective drug delivery. Nano-particles were shown to facilitate drug delivery without interference to the skin's integrity. The method used to prepare the nano-particles was emulsification-diffusion due to its reproducibility, higher yields, ease of scale-up and control over size of particles and degree of polydispersity. Maize starch modified and un-modified (by the addition of propyl groups) was used as polymeric material to formulate 2 different types of nano-particles. The modified starch nano-particles were shown to be non-toxic using LDH (Lactose dehydrogenase) and MTT assay and resulted in particles of uniform size distribution while the nano-particles formulated from the native starch was not observable. Flufenamic acid, caffeine and testosterone were used as model drugs and their delivery across the skin was analyzed using excised skin from female Caucasian patients who had undergone abdominal plastic surgery. Permeation data obtained for caffeine and testosterone were similar for nano-encapsulated and free drugs while the delivery of flufenamic acid using the nano-particles was enhanced by about ten-fold.

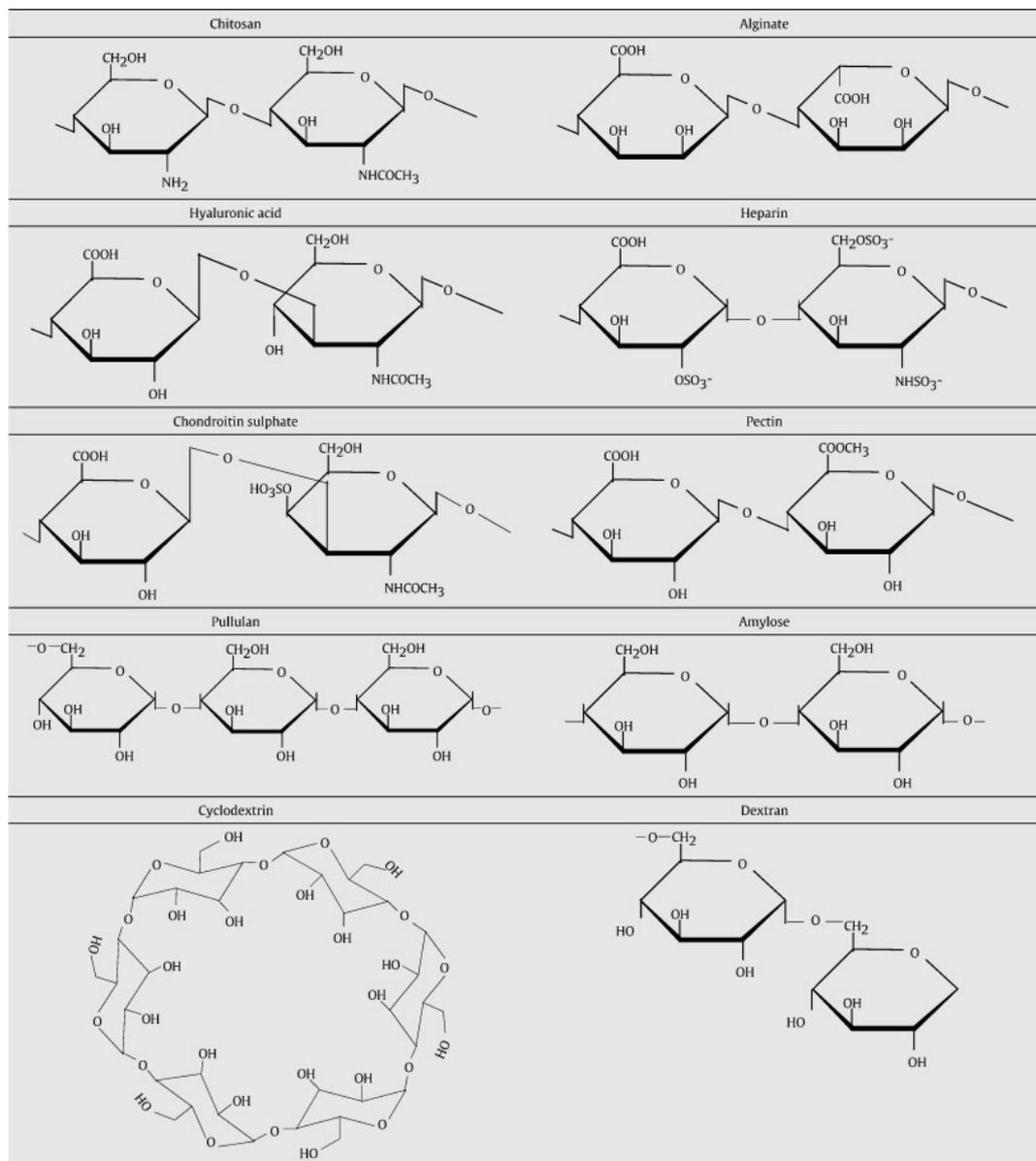


Figure 1: Chemical structures of some polysaccharides showing the presence of available reactive groups (Taken from [32]).

Starch nano-particles have been employed to deliver insulin via non-invasive routes; Makham [34] investigated the use of chitosan cross linked starch polymers as carriers for oral insulin delivery, manipulating the bio-adhesive and not so adhesive properties of chitosan and carboxymethyl starch to formulate hydrogels loaded with insulin. The authors however noted that, Insulin delivered by this method however faces the challenge of being broken down by proteases.

The nasal route can also be considered as an alternative to the subcutaneous route of administration because it is highly vascularised and is of great benefit in drug delivery as drugs given through this route are not subject to first-pass metabolism. However for effective delivery through this route, it is crucial that barriers to nasal drug delivery which include the lipophilic epithelium and muco-ciliary clearance must be overcome. Jain et al. [23] reports a size dependent

insulin release in rats from starch nano-particles. Potato starch was used to prepare 2 different types of nano-particles by cross-linking with epichlorohydrin and phosphoryl chloride (POCl_3) using both the gel and emulsion methods. These methods however led to the production of polydispersed nano-particles. There were statistically significant differences in mean sizes except in emulsion prepared epichlorohydrin cross linked particles which were smaller and of uniform distribution. In-vitro studies showed that drug release followed first order kinetics and was diffusion controlled along with burst effect, due to the presence of left-over insulin on the surface of the nanoparticles after entrapment. Emulsion cross-linked particles released their drug faster than gel cross linked particles with 85-90% and 81% release in 12 hrs respectively. These differences were attributed to the diffusion path length of the drug within the particles. The smaller the particle size the less distance the drug will travel to be released. Tests carried out on the diabetes induced rats showed a 50-65% reduction in blood

glucose by nano-particles compared to plain insulin formulation which served as control and this lasted for about 6hrs. Permeation enhancers modulated the hypoglycaemic effect and bioavailability of nano-particles, Plasma insulin levels of small sized nano-particles were also found to be significantly higher. Conclusions obtained from the study however recommend that further work would be needed in order to produce a more efficient carrier system.

Simi and Abraham [47] note that the presence of hydroxyl groups on starch enhances its hydrophilicity and confers on it low moisture resistance. This property poses a major constraint in drug delivery as a result of which it is often necessary to modify the polymer before it is made into nano particles as observed above. In their study, starch extracted from cassava tuber was modified by graft co-polymerization using long chain fatty acids before the resulting polymer was made into nano-particles [47]. The nano-particles were prepared by dialysis and subsequently crosslinked using sodium tripolyphosphate. Oleic acid and stearic acid were both used as fatty acids while indomethacin was used as model drug. Findings showed that drug release from both types of nano-particles was effectively controlled. It is however not clear whether there was a significant difference between drug releases in both types of nano-particles. No attempts were also made to formulate the un-modified starch granules into nano-particles though this may have been due to results obtained from differential scanning calorimetry which showed that native starch was less processable than grafted starch.

In addition, magnetised iron-oxide nano-particles coated with starch were used by Cole et al. [6] as a means of targeting brain tumours. Magnetic resonance imaging and histological reports showed that surface modification with polyethylene oxide improved delivery to tumour cells resulting in a greater accumulation of particles in the glioma compared to the rest of the brain.

Chitosan

This polymer is obtained from the partial N-deacetylation of chitin found in the shells of crustacean. It is composed of glucosamine and N-acetyl glucosamine linked by β 1-4 glucosidic bonds and is one of the most widely studied natural polymers for nano-drug delivery. The deacetylation of chitin is both concentration and temperature dependent with optimal yields achieved at temperatures between 60°C-80°C using 50%w/w alkali [44].

Park et al. [38] in a review on chitosan describes its numerous applications in delivering low molecular weight drugs and summarises the reason for its choice being in its physicochemical and biological properties, enabling chemical modification and enhanced residence time respectively. It has been used as both a composite membrane with collagen [50] and a cross linked polymer for transdermal delivery of propranol [51].

Nano-particles fabricated with chitosan as co-polymer was used to by Dev et al. [10] to investigate the controlled release of anti-retroviral drug, lamivudine. The nano-particles were prepared by emulsion and solvent evaporation technique and characterised using dynamic light scattering. The use of this method resulted in monodispersed particles with a size range of 300-350nm. Two formulations with differences in percentage drug weight (3% and 6%) were made, of which drug release rate was higher from the nano-particles with higher drug loading, though both were able to control drug release fairly well. Drug release kinetics showed that the mechanism of drug release was by diffusion. Conclusions reached suggested that the nano-particles could be applied for gastrointestinal drug delivery because drug release was relatively

slower at neutral pH compared to acidic P^H and also slower in the acidic P^H compare to the alkaline P^H .

Chitosan combination was also used by Menon et al. [36] for therapeutic drug delivery. Nano-complexes of chitosan and polyoxometalates (POM) were tested as anti-cancer preparation. Since POM's though toxic have shown promise in being used as anti-viral and anti-tumour agent, the role of chitosan was to minimise the toxicity associated with POM, by modifying its surface properties. Mono-dispersed particles with size 200nm were produced using ionotropic gelation technique and the use of probe sonication was shown to control particle size and distribution compared to ultrasonication. In-vitro studies showed that the nano-complex was able to sustain drug release with enhanced anti-tumour activity at much lesser doses than the POM alone.

Similarly as with starch nano particles, Luo et al. [33] used chitosan oligosaccharides (COS) to coat lipid based carriers in order to enhance ocular drug delivery. This material is obtained from the decomposition of chitosan, but it is more soluble in water than chitin and chitosan. Drug introduced into the eye have minimal residence times as they are quickly washed away and have to be re-administered regularly. But in this study, COS enhanced permeation and adhesion of the cornea. There was a 7.7 fold and 2.8 fold retention of the model drug, flubiprofen by the COS coated nano lipid carriers compared to the phosphate buffer solution and uncoated nanolipid carriers which were attributed to the mucoadhesive properties of COS. The use of COS was also found to be non-irritating to the eye, a property which is of utmost importance in the choice of a suitable eye formulation.

Proteins

Proteins are made up of numerous units of amino acids joined by peptide linkages. They are found in humans, animal and plants where they exist as structural units.

Gelatin

Gelatin is obtained from the breakdown and hydrolysis of collagen, obtained from the connective tissues, bones and skins of animals. It is a known matrixing agent drug delivery. Bajpai and Shoubey [1] describes a process for the controlled release of sulphamethoxazole using 2 different gelatin nano-particles {Type A (porcine skin) and type B gelatin(bovine skin)} and cross linked with gluteraldehyde; Nano-particles of varying gelatin concentrations were prepared by solvent evaporation techniques and drug release kinetics evaluated using appropriate kinetic models. Findings from this system suggest that this system could be of use in targeted drug delivery such as colon drug delivery where P^H is an important consideration. Drug release was found to increase following increased swelling of the nanoparticles. In addition, swelling was further enhanced by an increase in P^H with greater drug release occurring at P^H 7.5 than at P^H 1.8. The nano particles were also not degraded in simulated gastric fluid thereby showing their stability under acidic conditions. An increase in concentration of the cross linker led to an increase in swelling and drug release up until a certain concentration(10.6mM) when swelling began to decline. This relationship between the amount of cross linker and the polymer has also been reported by Das et al. [9]; In their case, nano-particles composed of gelatin blended with montmorillonite (MMT) were loaded with the anti-cancer agent paclitaxel. These nano-particles were prepared by the same method of solvent evaporation and produced similar results. Increase in gluteraldehyde concentrations was reported to increase swelling and consequently drug release up until a certain point, when further increases in concentration of the cross linker led

to decreased swelling and drug release. There was also a cumulative increase in drug release with increased P^H . 80% of the drug was released within 8hrs at P^H 7.4 while there was less than 44% drug release within 4 h at P^H 1.2. Increasing concentration of the loaded drug also led to an increase in drug release.

The use of proteins as nano carriers is also employed in gene therapy. Viral and non-viral vectors are used for the transfection of DNA into cells, because, the injection of naked DNA into living tissue results in enzymatic degradation and reduced cellular uptake due to repulsion between the negatively charged DNA and cell membrane. In this domain, Coester et al. [5] used avidin modified gelatin nanoparticles for the delivery of biotinylated PNA (Peptide nucleic acids) in order to investigate their use as anti-sense therapy. Zwiorek et al. [57] suggests that gelatin nano- particles have the potential to be used for effective non-viral gene delivery and are a safer alternative to the use of viral vectors. A 2 step desolvation process was used to prepare cationized particles of uniform size distribution and low polydispersity and comparisons between polyethyleneimine- DNA complexes and the gelatin particles showed that the latter is effective in facilitating gene expression, has less toxic and better tolerated.

Transfection with the aid of gelatin nanoparticles was also used by Xu et al. [55] for the delivery of DNA plasmids encoding for insulin growth like factor 1 (IGF-1) into chondrocytes. In order to incorporate the plasmids into the gelatin nano-particles, complex coacervation was employed because it is an easy, fast and particularly useful method for the incorporation of large molecules. The authors proved that, cationized gelatin particles were of smaller sizes than non- cationized particles, this they attributed to the condensation of the cationized particles. Fluorescence spectroscopy showed that the cationized gelatin nano-particles were successfully transfected and expressed the gene while the reverse was the case for the non-cationized gelatin particles. This is probably due to enhanced endocytosis, occurring as a result of interactions between the positive charge on the former and the negative charge on the cell membrane. A 5-fold increase in growth factor production was observed in cells containing these nano-particles. Findings also showed that over expression of the gene was maintained steadily for up to 2 weeks when they were grown in collagen (type II) -glycosaminoglycan scaffolds in 3D culture. Since a prolonged and localized release of IGF-1 was achieved in this study, and IGF-1 is known to promote growth in skeletal muscle, cartilage and bones and numerous other tissues in the body tissue, this approach shows potential applications in gene therapy and tissue engineering.

Perspectives and Conclusions

From the foregoing, it is obvious that natural polymers such as starch, gelatin and chitosan are no longer mere traditional excipients for use as binders, disintegrant or diluents, but are now being applied widely as therapeutic drug carriers. The efficiency of delivery and release of bioactive molecules from these systems is influenced by factors such as polymer type, drug loading, polymer breakdown, molecular weight, particle size, interactions between the drug and polymer and several other technological and pharmacotechnical factors. Natural polymers may not for now enjoy the robustness of easy amenability to formulation design as compared to synthetic polymers, but their excellent biocompatibility and safety makes them very important in the preparation of various drug delivery systems with the potential to achieve the formulator's desire for target or protected delivery of bioactive agents. However, increasing works needs to be done in the near future on these polymers. It is important to note that apart from being

safe, natural polymers are relatively very cheap. A major limitation to the use of some of the natural polymers such as starch appears to be its higher sensitivity to acid attack; however, modification has been proved to impart acid-resistance to the products. It is therefore important to optimize the process of transition of these polymer granules from their native micro- to the artificial submicron levels in greater detail and also pay greater attention to the toxicological profiles of the nanoscale polymer-derivatives. This is because, although generally regarded as safe, derivatives of these natural polymers and in fact at submicron levels may pose some safety challenges especially as carriers in drug delivery systems. The physicochemical properties of polymers depend largely on their botanical or biological source, therefore, there is a greater need now than ever before for scientists to begin to source for even cheaper polymers from our natural environment; plants, animals and microorganisms alike. Conclusively, if the Pharma Industries, governments and donor agencies will take the risk of investing more in natural product research in nanodrug delivery, then the answer to the current "saftetyphobia" by regulatory agencies may soon be at hand.

References

1. Bajpai AK, Choubey J (2005) Release study of sulphamethoxazole controlled by swelling of gelatin nanoparticles and drug-biopolymer interaction. J. Macromol. Sci. 42: 253-275.
2. Bilati U, Allemann E, Doelker E (2005) Poly(D,L-lactide-co-glycolide) protein-loaded nanoparticles prepared by the double emulsion method—processing and formulation issues for enhanced entrapment efficiency. J Microencapsul. 22: 205-214.
3. Campbell K, Qi S, Craig DQM, McNally T (2009) Paracetamol-loaded poly (ϵ -caprolactone) layered silicate nanocomposites prepared using hot-melt extrusion. J Pharm Sci. 98: 4831-4843.
4. Chorny M, Hood E, Levy RJ, Muzykantor VR (2010) Endothelial delivery of antioxidant enzymes loaded into non-polymeric magnetic nanoparticles. J Control Release. 146: 144-151.
5. Coester C, Kreuter J, Von BH, Langer K (2000) Preparation of avidin-labelled gelatin nanoparticles as carriers for biotinylated peptide nucleic acid (PNA). Int J Pharm. 196: 147-149.
6. Cole AJ, David AE, Wang J, Galbani CJ, Yang VC (2011) Magnetic brain tumor targeting and biodistribution of long-circulating PEG-modified, cross-linked starch-coated iron oxide nanoparticles. Biomaterials 32: 6291-6301.
7. Coviello T, Matricardi P, Marianecchi C, Alhaique F (2007) Polysaccharide hydrogels for modified release formulations. J Control Release 119: 5-24.
8. Crommelin DJA, Storm G, Jiskoot W, Stenekes R, Mastrobattista E et al. (2003) Nanotechnological approaches for the delivery of macromolecules. J Control Release 87: 81-88.
9. Das PR, Nanda RM, Behara A, Nayak PR (2011) Gelatin blended with nanoparticle cloisite30B (MMT) for control drug delivery of anticancer drug paclitaxel. International research journal of biochemistry and bioinformatics 1: 35-42.
10. Dev A, Binulal NS, Anitha A, Nair SV, Furuie T et al. (2010) Preparation of poly (lactic acid)/chitosan nanoparticles for anti-HIV drug delivery applications. Carbohydr Polym 80: 833-838.
11. Guzman KAD, Taylor MR, Banfield JF (2006) Environmental Risks of Nanotechnology: National Nanotechnology Initiative Funding, 2000–2004. Environ. Sci. Technol. 40: 1401-1407.
12. Dziubla TD, Karim A, Muzykantor VR (2005) Polymer nanocarriers protecting active enzyme cargo against proteolysis. J Control Release 102: 427-439.
13. Farokhzad OC, Langer R (2009) Impact of Nanotechnology on Drug Delivery. ACS Nano, 3: 16-20.
14. Freemantle M (2005) Polymers Exploited for Drug Delivery. Chemical & Engineering News 83: 45-47.
15. Fritz HG, Widmann B (1993) Native Starch Used For Modification of Synthetic-Polymers. Starch-Starke 45: 314-322.

16. Ganta S, Devalapally H, Shahiwala A, Amiji M (2008) A review of stimulus-responsive nanocarriers for drug and gene delivery. *J Control Release*. 126: 187-204.
17. Gåserød O, Jolliffe IG, Hampson FC, Dettmar PW, Skjåk-Bræk G (1998) The enhancement of the bioadhesive properties of calcium alginate gel beads by coating with chitosan. *Int J Pharm*. 175: 237-246.
18. Geresh S, Gdalevsk GY, Gilboa I, Voorspoels J, Remon JP et al. (2004) Bioadhesive grafted starch copolymers as platforms for peroral drug delivery: a study of theophylline release. *J Control Release*. 94: 391-399.
19. Goldberg M, Langer R, Jia X (2007) Nanostructured materials for applications in drug delivery and tissue engineering. *J Biomater Sci Polym Ed*. 18: 241-268.
20. Haruyama T (2003) Micro- and nanobiotechnology for biosensing cellular responses. *Adv Drug Deliv Rev*. 55: 393-401.
21. Heller J, Pangburn SH, Roskos KV (1990) Development of enzymatically degradable protective coatings for use in triggered drug delivery systems: derivatized starch hydrogels. *Biomaterials* 11: 345-350.
22. Hughes GA (2005) Nanostructure-mediated drug delivery. *Nanomedicine* 1: 22-30.
23. Jain AK, Khar RK, Ahmed FJ, Diwan PV (2008) Effective insulin delivery using starch nanoparticles as a potential trans-nasal mucoadhesive carrier. *Eur J Pharm Biopharm*. 69: 426-435.
24. Jin Y, Ai P, Xin R, Tian Y, Dong J et al. (2009) Self-assembled drug delivery systems: Part 3. In vitro/in vivo studies of the self-assembled nanoparticulates of cholesteryl acyl didanosine. *Int J Pharm*. 368: 207-214.
25. Jong WH, Borm PJA (2008) Drug delivery and nanoparticles: Applications and hazards. *Int J Nanomedicine*. 3: 133-149.
26. Kim S, Kim JH, Jeon O, Kwon IC, Park K (2009) Engineered polymers for advanced drug delivery. *Eur J Pharm Biopharm*. 71: 420-430.
27. Kumari A, Yadav SK, Yadav SC (2010) Biodegradable polymeric nanoparticles based drug delivery systems. *Colloids Surf B Biointerfaces*. 75: 1-18.
28. Kunisawa J, Masuda T, Katayama K, Yoshikawa T, Tsutsumi Y et al. (2005) Fusogenic liposome delivers encapsulated nanoparticles for cytosolic controlled gene release. *J Control Release*. 105: 344-353.
29. Levina M, Rajabi-Siahboomi AR (2004) The influence of excipients on drug release from hydroxypropylmethyl cellulose matrices. *J Pharm Sci*. 93: 2746-2754.
30. Li D, Zhong X, Zeng Z, Jiang J, Li L et al. (2009) Application of targeted drug delivery system in Chinese medicine. *J Control Release*. 138: 103-112.
31. Li X, Anton N, Arpagaus C, Belleiteix F, Vandamme TF (2010) Nanoparticles by spray drying using innovative new technology: The Büchi Nano Spray Dryer B-90. *J Control Release*. 147: 304-310.
32. Liu Z, Jiao Y, Wang Y, Zhou C, Zhang Z (2008) Polysaccharides-based nanoparticles as drug delivery systems. *Adv Drug Deliv Rev*. 60: 1650-1662.
33. Luo Q, Zhao J, Zhang X, Pan W (2011) Nanostructured lipid carrier (NLC) coated with chitosan oligosaccharides and its potential use in ocular drug delivery system. *Int J Pharm*. 403: 185-191.
34. Mahkam M (2010) Modified Chitosan Cross-linked Starch Polymers for Oral Insulin Delivery. *J Bioact Compat Polym*. 25: 406-418.
35. Malafaya BP, Stappers F, Reis RL (2006) Starch-based microspheres produced by emulsion crosslinking with a potential media dependent responsive behavior to be used as drug delivery carriers. *J Mater Sci Mater Med*. 17: 371-377.
36. Menon D, Thomas RT, Narayanan S, Maya S, Jayakumar R et al. (2011) A novel chitosan/polyoxometalate nano-complex for anti-cancer applications. *Carbohydr Polym*. 84: 887-893.
37. Panyam J, Labhasetwar V (2003) Biodegradable nanoparticles for drug and gene delivery to cells and tissue. *Adv Drug Deliv Rev*. 55: 329-347.
38. Park JH, Saravanakuma G, Kwangmeyung K, Kwon I (2010) Targeted delivery of low molecular drugs using chitosan and its derivatives. *Adv Drug Deliv Rev*. 62: 28-41.
39. Park K (2007) Nanotechnology: What it can do for drug delivery. *J Control Release*. 120: 1-3.
40. Passl WJ (1989) Synthetic polymers in modern pharmacy. *Prog Polym Sci*. 14: 629-677.
41. Prabakaran M (2011) Prospective of guar gum and its derivatives as controlled drug delivery systems. *Int J Biol Macromol*. 49: 117-124.
42. Rangasamy M (2011) Nano Technology: A review. *J.App.Pharm.Sci*. 1: 8-16.
43. Reis CP, Neufeld RJ, Ribeiro AJ, Veiga F (2006) Nanoencapsulation I. Methods for preparation of drug-loaded polymeric nanoparticles. *Nanomedicine*. 2: 8-21.
44. Sabnis S, Block L (2000) Chitosan as an enabling excipient for drug delivery systems. I. Molecular modifications. *Int J Biol Macromol*. 27: 181-186.
45. Sailaja A, Amareshwar P, Chakravarty P (2011) Different techniques used for the preparation of nanoparticles using natural polymers and their application. *Int J Pharm Pharm Sci*. 3: 45-50.
46. Santander-Ortega MJ, Stauner T, Loretz B, Ortega-Vinuesa JL, Bastos-González D et al. (2010) Nanoparticles made from novel starch derivatives for transdermal drug delivery. *J Control Release*. 141: 85-92.
47. Simi CK, Abraham TE (2007) Hydrophobic grafted and cross-linked starch nanoparticles for drug delivery. *Bioprocess Biosyst Eng*. 30: 173-180.
48. Singh P, Prasuhn D, Yeh RM, Destito G, Rae CS et al. (2007) Bio-distribution, toxicity and pathology of cowpea mosaic virus nanoparticles in vivo. *J Control Release*. 120: 41-50.
49. Suedee R, Jantarat C, Lindner W, Viernstein H, Songkro S et al (2010) Development of a pH-responsive drug delivery system for enantioselective-controlled delivery of racemic drugs. *J Control Release*. 142: 122-131.
50. Thacharodi D, Panduranga Rao K (1996) Collagen-Chitosan composite membranes controlled transdermal delivery of nifedipine and propranolol hydrochloride. *Int J Pharm*. 134: 239-241.
51. Thacharodi D, Panduranga Rao K (1995) Development and in-vitro evaluation of chitosan-based transdermal drug delivery systems for the controlled delivery of propranolol hydrochloride. *Biomaterials* 16: 145-148.
52. Thote AJ, Gupta RB (2005) Formation of nanoparticles of a hydrophilic drug using supercritical carbon dioxide and microencapsulation for sustained release. *Nanomedicine*. 1: 85-90.
53. Wei X, Gong C, Gou M, Fu S, Guo Q et al. (2009) Biodegradable poly([var epsilon]-caprolactone)-poly(ethylene glycol) copolymers as drug delivery system. *Int J Pharm*. 381: 1-18.
54. Wu C, Zhongyan W, Zhi Z, Jang T, Zhang J (2011) Development of biodegradable porous starch foam for improving oral delivery of poorly water soluble drugs. *Int J Pharm*. 403: 162-169.
55. Xu X, Capito RM, Spector M (2008) Delivery of plasmid IGF-1 to chondrocytes via cationized gelatin nanoparticles. *J Biomed Mater Res A*. 84: 73-83.
56. Yamini K, Chalapathi V, Lakshmi Narasimha Reddy N, Lokesh KV, Praveen Kumar Reddy S (2011) Formulation of diclofenac sodium tablets using tapioca starch powder- A promising binder. *J.App.Pharm.Sci*. 1: 125-127
57. Zwiorek K, Kloeckner J, Wagner K, Coeste C (2004) Gelatin nanoparticles as a new and simple gene delivery system. *J Pharm Pharm Sci*. 7: 22-28.