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Review

Recent applications of starch derivatives in nanodrug delivery

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ABSTRACT

Starch has found use in industries as diverse as food, textiles, cosmetics, plastics, adhesives, paper, and pharmaceuticals. From a pharmaceutical standpoint, starch finds its value in solid-oral dosage forms, where it has been used as a binder, diluent, and disintegrant. However, only recently has the use of starch in nanotechnology started to make significant advances in biomedical applications, including newer drug delivery techniques. There has been a considerable effort to develop biodegradable nanoparticles as effective drug delivery systems. Being cheap, non-toxic, renewable, biodegradable and compatible with many other materials for industrial applications, starch is attracting the interest of drug delivery scientists. We have put together in a short and concise format, recent applications of starch derivatives in the emerging field of nanodrug delivery with the conclusion that a lot still needs to be done.

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1. Introduction

Nanoscience has been variously defined at different fora, books, journals and the web, yet one thing is common; it involves the study of the control of matter on an atomic and molecular scale. This molecular level investigation is at a range usually below 100 nm. In simple terms, a nanometer is one billionth of a meter and the properties of materials at this atomic or subatomic level differ significantly from properties of the same materials at larger sizes. Although, the initial properties of nanomaterials studied were for its physical, mechanical, electrical, magnetic, chemical and biological applications, recently, attention has been geared towards its pharmaceutical application, especially in the area of drug delivery. This is because of the challenges with 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 researches in nanodrug delivery have been designed to overcome these challenges through 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 can allow 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 (Campbell, Qi, Craig, & McNally, 2009; Chorny, Hood, Levy, &

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Muzykantov, 2010; Crommelin et al., 2003; Dziubla, Karim, & Muzykantov, 2005; Farokhzad & Langer, 2009; Ganta, Devalapally, Shahiwala, & Amiji, 2008; Haruyama, 2003; Hughes, 2005; Jin et al., 2009; Kim, Kim, Jeon, Kwon, & Park, 2009; Kunisawa et al., 2005; Panyam & Labhasetwar, 2003; Park, 2007; Singh et al., 2007; Suedee et al., 2010; Thote & Gupta, 2005; Wei et al., 2009). 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 long time, releasing the incorporated drug in a controlled fashion, leading to less plasma fluctuations and minimized side-effects. It has been reported that, due to the nanoscale size of nanostructures, they are able to penetrate tissues and are easily taken up by cells, allowing for efficient delivery of drugs to target sites of action. Uptake of nanostructures has been reported to be 15–250 times greater than that of microparticles in the 1–10 μm range (Panyam & Labhasetwar, 2003). Nanotechnology improves performance and acceptability of dosage forms by increasing their effectiveness, safety, patient adherence, as well as ultimately reducing health care costs (Hughes, 2005). It may also enhance the performance of drugs that are unable to pass clinical trial phases (Hughes, 2005). Nanotechnology definitely promises to serve as drug delivery carrier of choice for the more challenging conventional drugs used for the treatment and management of chronic diseases such as cancer, asthma, hypertension, HIV and diabetes. Although the advantages of nanodrug delivery are many as enumerated above, one of the challenges of this technology is safety.

2. Toxicity of nanodrug delivery systems

Despite the great potentials of nano drug delivery systems in revolutionalizing patient treatment, its safety in humans is of great concern. It has been reported that, smaller nanoparticles show increased toxicity due to their increased surface area (Guzmán, Taylor, & Banfield, 2006). For example, studies have shown that nanotubes are cytotoxic and induce granulomas in lungs of laboratory animals. Nanoparticles of metals such as copper, cobalt, titanium and silicon and their oxides have also been reported to have inflammatory and toxic effects on cells (Guzmán et al., 2006). 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 (Guzmán et al., 2006).

3. The role of excipients in nano drug delivery

The International Pharmaceutical Excipients Council (IPEC) defines excipients as substances, other than the active pharmaceutical ingredient (API) in finished dosage form, which have been appropriately evaluated for safety, and are included in a drug delivery system to either aid the processing or manufacture, protect, support, enhance stability, bioavailability or patient acceptability, assist in product identification, or enhance other attributes of the overall safety and effectiveness of the drug delivery system during storage or use (Robertson, 1999). They can also be defined as additives used to convert active pharmaceutical ingredients into pharmaceutical dosage forms suitable for administration to patients. Excipients no longer maintain the initial concept of—inactive support; because of the influence they have over both biopharmaceutical aspects and technological factors (Jansook & Loftsson, 2009; Killen & Corrigan, 2006; Langoth, Kalbe, & Bernkop-Schnürch, 2003; Lemieux, Gosselin, & Mateescu, 2009; Li, Lin, Daggy, Mirchandani, & Chien, 2003; Massicotte, Baille, & Mateescu, 2008; Munday & Cox, 2000; Nykänen et al., 2001; Williams, Ward, Culy, Hardy, & Melia, 2010). The desired activity, the excipient's equivalent of the active ingredients efficacy, is called its functionality. The inherent property of an excipient is its functionality in the dosage form. In order to deliver a stable, uniform and effective drug product, it is essential to know the properties of the active pharmaceutical ingredient alone and in combination with all other ingredients based on the requirements of the dosage form and process applied. This underscores the importance of excipients in dosage form development.

The ultimate application goal of any drug delivery system design including nano drug delivery, is to develop clinically useful formulations for treating diseases in patients (Park, 2007). Clinical applications require approval from FDA. The pharmaceutical industry has been slow to utilize the new drug delivery systems if they include excipients that are not generally regarded as safe. This is because, going through clinical studies for FDA approval of a new chemical entity is a long and costly process; there is therefore, a very strong resistance in the industry to adding any untested materials that may require seeking approval. To overcome this reluctant attitude by the industry, scientists need to develop not only new delivery systems that are substantially better than the existing delivery systems (Park, 2007), but also seek for new ways of using old biomaterials. The use of starch (native or modified) is an important strategy towards the attainment of this objective. This is because starch unlike synthetic products is biocompatible, non toxic, biodegradable, eco-friendly and cheap. It is generally a non-polluting renewable source for sustainable supply of cheaper pharmaceutical products.

4. What is starch?

Starch, which is the major dietary source of carbohydrates, is the most abundant storage polysaccharide in plants, and occurs as granules in the chloroplast of green leaves and the amyloplast of seeds, pulses, and tubers (Sajilata, Singhal, & Kulkarni, 2006). Chemically, starches are polysaccharides, composed of a number of monosaccharides or sugar (glucose) molecules linked together with α-D-(1-4) and/or α-D-(1-6) linkages. Starch consists of 2 main structural components, the amylose, which is essentially a linear polymer in which glucose residues are α-D-(1-4) linked typically constituting 15–20% of starch, and amylopectin, which is a larger branched molecule with α-D-(1-4) and α-D-(1-6) linkages and a major component of starch. Amylose is linear or slightly branched with a degree of polymerization up to 6000, and has a molecular mass of 105–106 g/mol. The chains can easily form single or double helices. Amylopectin on the other hand, has a molecular mass of 107–109 g/mol. It is highly branched and has an average degree of polymerization of 2 million, making it one of the largest molecules in nature. Chain lengths of 20–25 glucose units between branch points are typical of amylopectin. About 70% of the mass of starch granule is regarded as amorphous and about 30% as crystalline. The amorphous regions contain the main amount of amylose, and a considerable part of the amylopectin. The crystalline region consists primarily of the amylopectin (Sajilata et al., 2006).

5. Starch microparticles

The use of biodegradable microparticles as a dosage form for the administration of active substances is attracting increasing interest, especially as a means of delivering proteins. Starch is one of the polymers that is suitable for the production of microparticles. It is biodegradable and has a long tradition as an excipient in drug formulations. Starch microparticles have been used for the nasal delivery of drugs and for the delivery of vaccines administered orally and intramuscularly. Bioadhesive systems based on

Table 1
Some microparticulate preparations.

Study title	Reference	Summary
Preparation and characterization of starch-poly-ε-caprolactone microparticles incorporating bioactive agents for drug delivery and tissue engineering applications	Balmayor, Tuzlakoglu, Azevedo, and Reis (2009)	The study suggests starch-poly-ε-caprolactone microparticles containing dexamethasone can be successfully prepared and that these microparticular systems seem to be quite promising for controlled release applications especially as carriers in tissue engineering
Sweet potato starch microparticles as controlled drug release carriers: Preparation and *in vitro* drug release	Liu, Desai, Meng, and Cheng (2007)	*In vitro* release behavior of diclofenac sodium from sweet potato starch microparticles exhibited controlled drug delivery properties. The encapsulation efficiencies of the microparticles formulations were between 95.1% and 98.2% and the mechanism of drug release from the microparticles was Fickian diffusion
Starch-based microparticles as vehicles for the delivery of active platelet-derived growth factor	Silva, Coutinho, Ducheyne, Shapiro, and Reis (2007)	The results demonstrate that starch-based microparticles are suitable vehicles for the incorporation and release of growth factor (GF) and that the incorporation and release did not affect the biological activity of the GFs. This suggests their ability to enhance the regenerating potential of tissue engineering hybrid constructs
Starch-based microspheres produced by emulsion crosslinking with a potential media dependent responsive behavior to be used as drug delivery carriers	Malafaya, Stappers, and Reis (2006)	This study proved that, starch microspheres could be prepared at room temperature to allow for the loading of labile biologically active agents and projects that, this may be useful in the delivery of living cells for improving bone regeneration in tissue engineering
Preparation and characteristics of high-amylose corn starch/pectin blend microparticles	Desai (2005)	Microparticles obtained by blends of high amylose corn starch (HACS)/pectin were effective in targeted drug release to the colon. This process improved the encapsulation efficiency and decreased the drug dissolution and efficient drug release
Starch microparticles as vaccine adjuvant	Rydell, Stertman, and Sjöholm (2005)	This review article focuses on the use of starch, a natural biocompatible and biodegradable polymer for the production of various particulate adjuvant formulations, which can induce mucosal as well as systemic immune responses
Polymer-grafted starch microparticles for oral and nasal immunization	McDermott, Heritage, Bartzoka, and Brook (1998)	A novel silicone polymer-grafted starch microparticle system was developed for the delivery of small quantities of antigen, especially intranasally, and may be useful for the induction of oral tolerance
Novel polymer-grafted starch microparticles for mucosal delivery of vaccines	Heritage et al. (1996)	In this study, a novel microparticle fabrication technique was developed in which human serum albumin (HSA) was entrapped in starch microparticles grafted with 3-(triethoxysilyl)-propyl-terminated polydimethylsiloxane (TS-PDMS). The authors reported that, the microparticles have potential as systemic and mucosal vaccine delivery vehicles
Interferon-γ in starch microparticles: Nitric oxide-generating activity *in vitro* and antileishmanial effect in mice	Degling, Stjärnkvist, and Sjöholm (1993)	Recombinant mouse interferon-γ (mu IFN-) was covalently coupled to polyacryl starch microparticles, a lysosomotropic drug carrier. The microparticle-bound mu IFN was found to activate cultured macrophages for nitrite production and had an anti-leishmanial effect in mice
Inflammatory response to polyacryl starch microparticles, role of arachidonic acid metabolites	Artursson, Ericsson, and Sjöholm (1988)	The effect of polyacryl starch microparticles on arachidonic acid metabolism in macrophage cultures and in mice was studied here. Two of the major metabolites were produced when macrophages were incubated with the microparticles. When the mice were treated with inhibitors of arachidonic acid metabolism, the microparticle-induced hepatomegaly was partly inhibited
Biodegradable microspheres: polyacryl starch microparticles as a delivery system for the antileishmanial drug, sodium stibogluconate	Baillie et al. (1987)	When the drug sodium stibogluconate was covalently bound to polyacryl starch microparticles, it was 100 times more effective than the free form in this murine model of visceral leishmaniasis whereas empty microparticles had no effect on liver parasite

Table 2
Some microcapsule preparations.

Study title	Reference	Summary
An intelligent multicompartmental system based on thermo-sensitive starch microspheres for temperature-controlled release of drugs	Fundueanu, Constantin, Ascenzi, and Simionescu (2010)	Here, starch microspheres with thermo-responsive properties and possessing strong anionic functional groups (–SO_3H), capable of binding electrostatically to drugs, was reported
Study of high amylose corn starch as food grade enteric coating in a microcapsule model system	Dimantov, Greenberg, Kesselman, and Shimoni (2004)	The potential use of high amylose corn starch coatings as food grade enteric coatings for protection of core materials from dissolution in the stomach and release in the small intestine was demonstrated in this study
Biodegradable cross-linked starch/protein microcapsules containing proteinase inhibitor for oral protein administration	Larionova, Ponchel, Duchêne, and Larionova (1999)	In this study, starch/bovine serum albumin mixed-walled microcapsules were prepared using interfacial cross-linking with terephthaloyl chloride. The microcapsules were loaded with native or amino-protected aprotinin by incorporating protease inhibitors in the aqueous phase during the cross-linking process. Microcapsules could be degraded in the presence of α-amylase
A note on the microencapsulation of pancreatic protease for protection against gastric digestion	Lin and Lee (1993)	Here zeolite, cellulose acetate phthalate (CAP) and maize starch were used as the coating materials for encapsulating pancreatic protease, which was proposed as an additive to enhance the food efficiency and growth rate of weanling pigs
Effect of opsonins on the macrophage uptake of polyacrylstarch microparticles	Artursson and Sjöholm (1986)	In this study, macrophage uptake of polyacryl-starch and polyacrylamide microparticles was investigated *in vitro*. The results suggested that polyacrylstarch microparticles were rapidly phagocytosed by macrophage monolayers

polysaccharide microparticles have been reported to significantly enhance the systemic absorption of conventional drugs and polypeptides across the nasal mucosa, even when devoid of absorption enhancing agents. A major area of application of microparticles is as dry powder inhalation formulations for asthma and for deep-lung delivery of various agents. It has also been reported that, particles reaching the lungs are phagocytosed rapidly by alveolar macrophages. Although phagocytosis and sequestration of inhaled powders may be a problem for drug delivery to other cells comprising lung tissue, it is an advantage for chemotherapy of tuberculosis. Phagocytosed microparticles can deliver larger amounts of drug to the cytosol than oral doses. It is also opined strongly that, microparticles have the potential for lowering dose frequency and magnitude, which is especially advantageous for maintaining drug concentrations and improving patient compliance. This is the main reason this dosage form is an attractive pulmonary drug delivery system. A summary of some microparticulate preparations is given in Table 1.

6. Starch microcapsules

Microencapsulation is the process of enclosing a substance inside a membrane to form a microcapsule. It provides a simple and cost-effective way to enclose bioactive materials within a semi-permeable polymeric membrane. Both synthetic/semi-synthetic polymers and natural polymers have been extensively utilized

Table 3
Some nanoparticle preparations.

Study title	Reference	Summary
Nanoparticles made from novel starch derivatives for transdermal drug delivery	Santander-Ortega et al. (2010)	Propyl-starch nanoparticles were reported to show high encapsulation efficiency for three model drugs (flufenamic acid, testosterone and caffeine) intended for transdermal delivery
Effective insulin delivery using starch nanoparticles as a potential trans-nasal mucoadhesive carrier	Jain, Khar, Ahmed, and Diwan (2008)	In this study, mucoadhesive starch nanoparticles (NPs) for trans-nasal insulin delivery were prepared and investigation showed an enhanced concentration gradient
Dialdehyde starch nanoparticles: Preparation and application as drug carrier	Yu, Xiao, Tong, Chen, and Liu (2007)	Here, dialdehyde starch nanoparticles were shown to be effective for controlled release of doxorubicin. The study also demonstrates that the nanoparticles possess good thermal stability, small particle size, low biological toxicity, and slowly released the anticancer drug
Preparation of folate-conjugated starch nanoparticles and their application to tumor-targeted drug delivery vector	Xiao et al. (2006)	Folate modified with PEG was conjugated to the surface of starch nanoparticles to obtain the folate-conjugated starch nanoparticles (FA-PEG/StNP). The study showed that, FA-PEG/StNP is a potential carrier for targeted delivery of the anticancer drug, doxorubicin

and investigated as the preparation materials of microcapsules. Although the synthetic polymers display chemical stability, their unsatisfactory biocompatibility still limits their potential clinical applications. Because the natural polymers always show low/non toxicity, low immunogenicity and therefore good biocompatibility, they have been the preferred polymers used in microencapsulation systems. Among the natural polymers, alginate is one of the most common materials used to form microcapsules; however, starch derivatives are now gaining attention. For instance, starch nasal bioadhesive microspheres with significantly extended half-life have been reported for several therapeutic agents including insulin. Improved bioavailability of gentamycin-encapsulated starch microspheres as well as magnetic starch microspheres for parenteral administration of magnetic iron oxides to enhance contrast in magnetic resonance imaging has been reported: A summary is presented in Table 2.

7. Starch nanoparticles

Nanoparticles are solid or colloidal particles consisting of macromolecular substances that vary in size from 10 to 1000 nm. The drug may be dissolved, entrapped, adsorbed, attached or encapsulated into the nanoparticle matrix. The matrix may be biodegradable materials such as polymers or proteins or biodegradable/biocompatible/bioasborbable materials such as starch. Depending on the method of preparation, nanoparticles can be obtained with different physicochemical, technical or mechanical properties as well as modulated release characteristics for the immobilized bioactive or therapeutic agents. Some of the recent studies in this area are presented in Table 3.

8. Starch combined with other polymers

Native starch is almost completely broken down by pancreatic enzymes after oral ingestion, with subsequent absorption from the small intestine into the systemic circulation. Usually, a certain proportion of starch, called resistant starch, escapes digestion in the small intestine and undergoes fermentation by bacteria in the colon. To inhibit or reduce the enzymatic degradation taking place in the stomach in order to allow adequate amount of the therapeutic agent to be absorbed, starch has been combined with other polymers to impart this desired property. For example, cross linked starch–protein microcapsules containing proteinase inhibitor has been reported to allow the oral administration of peptide drugs such as insulin or proteins. The protective effect of microcapsules with aprotinin for bovine serum albumin has also been demonstrated. A summary of some applications of starch/polymer combinations is presented in Table 4.

9. Other starch derivatives and starch scaffolds

Starch at submicron sizes is also finding application in tissue engineering. The general requirements for a scaffold material to be considered suitable for tissue engineering are; biocompatibility, appropriate mechanical properties, controlled degradation rate and appropriate pore size and morphology. These properties which

Table 4
Some applications of starch/polymer combinations.

Study title	Reference	Summary
Nanoparticles of anionic starch and cationic cyclodextrin derivatives for the targeted delivery of drugs	Thiele et al. (2011)	This study found new modular concept for the formation of nanoparticles from poorly soluble drugs using readily available building blocks. Stable spherical nanoparticles (NPs) were formulated mixing aqueous solutions of the anionic copolymers and of a cationic thioether of β-cyclodextrin (β-CD). The starch/β-CD NPs could be loaded with hydrophobic guest molecules like 1,4-dihydroxyanthraquinone (DHA), which served as a model for the important class of anthracycline antibiotics used in cancer therapy
Controlled release of metformin hydrochloride through crosslinked blends of chitosan–starch	Kumari and Rani (2011)	The authors reported that metformin-loaded chitosan (CHI) and starch (ST) blended beads prepared by cosslinking possess suitable controlled release properties
pH-responsive polysaccharide microcapsules through covalent bonding assembly	Jia et al. (2010)	Here, biocompatible, biodegradable, stable, nontoxic, autofluorescent and pH-responsive microcapsules were successfully prepared using dialdehyde heparin (DHP) and dialdehyde starch (DAS) as the wall components to crosslink with chitosan for the fabrication of the microcapsules. The results confirmed that the method used could be applicable over a wide range of polysaccharides
Preparation and characterization of coacervate microcapsules for the delivery of antimicrobial oyster peptides	Zhang, Liu, Wu, and Chen (2009)	The results in this study suggest that Oyster peptides-loaded alginate/chitosan/starch microcapsules could be a suitable copolymeric carrier system for intestinal protein or peptides delivery in the intestine
Synthesis and evaluation of starch–urea–borate as rate controlling matrix for controlled release	Chowdary and Murali Krishna (2008)	Starch–urea–borate was synthesized and evaluated for controlled release properties in matrix tablets of diclofenac and gliclazide. The authors reported that, starch–urea–borate is a better release rate controlling polymer than HPMC and sodium CMC
Engineering a bifunctional starch–cellulose cross-bridge protein	Levy, Paldi, and Shoseyov (2004)	A novel polysaccharide cross-bridging protein comprising of a cellulose-binding domain from *Clostridium cellulovorans* (CBDclos) and a starch-binding domain from *Aspergillus niger* B1 (SBDAsp) was designed. The two genes were fused in-frame via a synthetic elastin gene to construct a cellulose/starch cross bridging protein (CSCP). Recombinant CSCP was expressed in *Escherichia coli*, and successfully refolded from inclusion bodies. CSCP demonstrated cross-bridging ability in different model systems composed of insoluble or soluble starch and cellulose

Table 5
Some applications of starch in scaffolds development.

Study title	Reference	Summary
Evaluation of glutinous rice starch based matrix microbeads using scanning electron microscopy	Sachan, Ghosh, and Bhattacharya (2010)	Good quality microbeads were prepared by an industrially feasible micro orifice ionotropic-getation method using glutinous starch from Assam Bora rice, and sodium alginate backbone. Drug release properties from the prepared micro devices were excellent
Development of porous HAp and β-TCP scaffolds by starch consolidation with foaming method and drug-chitosan bilayered scaffold based drug delivery system	Kundu et al. (2010)	Here, a novel approach of forming hydroxyapatite (Hap) and pure beta-tri calcium phosphate (β-TCP) based porous scaffolds by applying together starch consolidation with foaming method was developed. The ability of these starch-based scaffolds to release drugs suitably for osteomyelitis was confirmed *in vitro*
Preparation of starch-based scaffolds for tissue engineering by supercritical immersion precipitation	Duarte, Mano, and Reis (2009)	The authors reported highly porous and interconnected starch-based scaffolds using supercritical immersion precipitation technique to prepare scaffolds of a polymeric blend of starch and poly (L-lactic acid) for tissue engineering purposes
Porous scaffold of gelatin-starch with nanohydroxyapatite composite processed via novel microwave vacuum drying	Sundaram, Durance, and Wang (2008)	Hydroxyapatite (HA) is a fundamental mineral-based biomaterial, used for preparing composites for bone repair and regeneration. A gelatin–starch blend reinforced with HA nanocrystals (nHA) gave biocompatible composites with enhanced mechanical properties in this report
Novel starch-based scaffolds for bone tissue engineering: cytotoxicity, cell culture, and protein expression	Salgado, Coutinho, and Reis (2004)	In the work, new scaffolds based on a 50/50 (wt%) blend of corn starch/ethylene-vinyl alcohol (SEVA-C) were prepared. After characterization, cytotoxicity evaluation, direct contact assays, cell viability assay and Western b lot analysis, the authors concluded that, the starch-based scaffolds should be considered as an alternative for bone tissue-engineering applications in the near future
Microwave processing of starch-based porous structures for tissue engineering scaffolds	Torres, Boccaccini, and Troncoso (2007)	Starches obtained from potato, sweet potato, corn starch, and non isolated amaranth and quinoa starch were used to produce porous biodegradable scaffolds suitable for tissue engineering
Bone tissue engineering constructs based on starch scaffolds and bone marrow cells cultured in a flow perfusion bioreactor	Gomes, Ribeiro, Malafaya, Reis, and Cunha (2001)	This study reports the suitability of starch based three-dimensional scaffolds exhibiting distinct porous structures for the proliferation and osteogenic differentiation of rat bone marrow (RBM) stromal cells in tissue engineering
Scaffold development using 3D printing with a starch-based polymer	Lam, Mo, Teoh, and Hutmacher (2002)	In this study, a unique blend of starch-based polymer powders (cornstarch, dextran and gelatin) was developed for the 3DP process. Cylindrical scaffolds of five different designs were fabricated and post-processed to enhance the mechanical and chemical properties
Alternative tissue engineering scaffolds based on starch: processing methodologies, morphology, degradation and mechanical properties	Gomes, Godinho, Tchalamov, Cunha, and Reis (2002)	Here, various alternative methodologies are described for preparation of starch scaffolds. Therefore, scaffolds obtained from these using these methodologies may constitute an important alternative to the materials currently used in tissue engineering
New partially degradable and bioactive acrylic bone cements based on starch blends and ceramic fillers	Espigares et al. (2002)	This work reports the development of new partially biodegradable acrylic bone cements based on corn starch/cellulose acetate blends. The developed systems show a range of properties that might allow for their application as self-curing bone cements, exhibiting several advantages with respect to other commercially available bone cements
Porous starch-based drug delivery systems processed by a microwave route	Malafaya, Elvira, Gallardo, San Román, and Reis (2001)	A new simple processing route to produce starch-based porous materials was developed based on a microwave baking methodology. This processing route was used to obtain non-loaded controls and loaded drug delivery carriers, incorporating a non-steroid anti-inflammatory agent
A new approach based on injection moulding to produce biodegradable polymeric scaffolds: morphology, mechanical and degradation behavior	Gomes et al. (2001)	This paper describes a preliminary study on the development of a new method to produce biodegradable scaffolds from a range of corn-starch-based polymers. The scaffolds could be moulded into complex shapes, and the blowing additives do not affect the non-cytotoxic behavior of the starch-based materials

can easily be imparted on starch by modification have made it very useful as carriers in tissue engineering. Porosity, pore size and pore structure are important factors that are associated with nutrient supply to transplanted and regenerated cells. It has been reported that, small diameter pores are preferable to yield high surface area per volume. Some of the applications of starch in scaffolds development are presented in Table 5.

10. Perspectives and conclusions

From the foregoing, it is obvious that starch is a very important excipient with potentials for use in the preparation of various drug delivery systems, intended to achieve the formulator's desire for target or protected delivery of bioactive agents. It is important to note that apart from the low cost of starch, it is also relatively pure and does not need intensive purification procedures like other naturally occurring biopolymers, such as celluloses and gums. A major limitation to starch use appears to be its higher sensitivity to acid attack; however, modification has been proved to impart acid-resistance to the product. It is important to optimize the process of transition of starch granules from its native micro- to the artificial submicron levels in greater detail and also pay greater attention to the toxicological profiles of the nanoscale starch-derived products. Most of the studies did not evaluate the safety profiles. Although starch is generally regarded as safe, its derivatives and in fact at submicron levels, it may pose some safety challenges especially as carriers in drug delivery systems. It was also observed in the course of this review that, most of the starches used were obtained from corn, rice or potato. Since the physicochemical properties of starch depend largely on its botanical or biological source, other sources of starch should be investigated. It is possible to conclude that, although there have been a number of applications of starch, especially its derivatives in nanodrug delivery, there is still a lot to be done on starch nanoparticles.

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