Modified Starch in Targeted Drug Delivery: Methods, Applications and Future Perspectives

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ABSTRACT

Starch is a natural biopolymer which has a huge potential in pharmaceutical applications. There are however, some drawbacks associated with the use of native starch such as poor mechanical properties, fast degradation, low stability, and uncontrolled drug release. To overcome these challenges and facilitate targeted drug delivery, the development of chemical, physical and enzymatic modifications has been emerging as promising strategies. This review covers in detail all the different modifications of starch and their use in drug delivery systems. Significant advances in polymer functionality and drug release rate have been achieved through key modification strategies such as cross-linking, esterification, etherification, oxidation and graft copolymerization. Modified starch-based nanoparticles, hydrogels, microspheres and films have been proven to be very promising for cancer therapy, colon-specific drugs delivery, oral delivery and protein/peptide delivery. Targeted release by pH, temperature, enzymes, and redox potential can be achieved in stimuli-responsive modified starch systems, allowing for precise delivery to disease sites. The analysis of modified starch with other natural polymers demonstrates the unique benefits of modified starch, such as its biodegradability, biocompatibility, cost-effectiveness, and sustainability. Some of the most pressing challenges such as batch variability, reproducibility, stability and limited clinical translation are discussed. Looking ahead, there are a few key perspectives on the future of smart starch biomaterials, AI-driven formulation methods, applying nanotechnology, and adopting green chemistry strategies to optimize clinical utilization. This review aims to give a fresh perspective on how modified starch plays a crucial role in the development of targeted drug delivery technologies.

Keywords: Modified starch, targeted drug delivery, nanoparticles, hydrogels, stimuli-responsive, biocompatibility, clinical applications.

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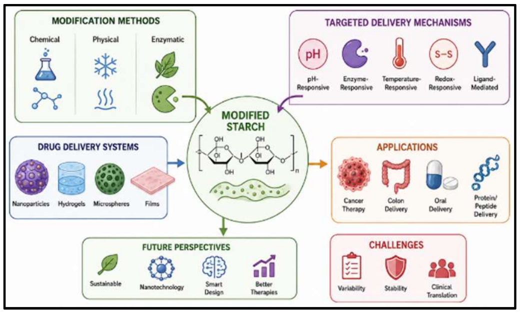

Figure 1: Modified Starch-Based Smart Drug Delivery Systems

1. Introduction

1.1 Drug Delivery Systems: An overview

In pharmaceutical science and medicine, drug delivery systems (DDS) are among the most important field. The general goal of any DDS is to selectively localize therapeutic agents to specific sites of action at specific concentrations whilst reducing exposure of healthy tissues [1]. There are several barriers to conventional oral delivery such as enzymatic degradation in the gastrointestinal tract, poor absorption, extensive first-pass metabolism, and non-site specificity [2]. Parenteral routes do not involve gastrointestinal barriers and involve invasive methods of administration and multiple doses throughout the day, lessening patient compliance [3]. Accordingly, advanced drug delivery systems have been created to overcome these drawbacks and improve therapeutic efficacy while minimizing adverse effects [4].

1.2 Need for Targeted Drug Delivery

A major challenge in the treatment of systemic diseases is the selective delivery of drugs with minimal toxicity towards the normal tissues, especially in the case of cancer, where drugs show dose limiting toxicity in the current chemotherapy treatment [5]. Targeting strategies aim to selectively target therapeutic agents to diseased tissues, while sparing normal tissues, which helps to limit side effects and enhance therapeutic efficacy [6]. This is particularly useful for very potent drugs with limited therapeutic ranges where careful control of drug levels is crucial [7]. Advanced polymeric carriers with particular features are required for both active targeting, based on ligand-receptor interaction, and passive targeting, based on pathophysiological characteristics of disease sites [8].

1.3 Natural Polymers for Drug Delivery

Drug delivery natural polymers derived from biological sources such as polysaccharides, proteins, and nucleic acids have come into the spotlight for their natural biocompatibility, biodegradability, and lack of immunogenic effects [9]. The materials are generally recognized as safe (GRAS) by the regulatory authorities and can be clinically translated [10]. Some of the common natural polymers used are alginate, cellulose, gelatin, chitosan and starch [11]. Starch offers special properties such as great availability, low cost, renewability and environmental friendliness among these.

1.4 Introduction to Starch and Its Limitations

In plants starch is stored in amyloplasts as a glucose polymer, mainly two glucose homopolymers (amylose and amylopectin) [1]. Native starch shows good biodegradability and biocompatibility along with a low cost and is more economical than synthetic polymers [2]. But, there are major drawbacks to unmodified starch which limit its use in pharmaceutical DDS [3]. These constraints are mainly because of the low mechanical strength, high solubility in water, low enzymatic degradation resistance, fast hydration rate that results in burst release kinetic and lack of functionality for active targeting [4]. In addition, native starch is naturally variable from batch to batch and has poor capacity to make stable hydrophobic drug loaded systems [5]. This limits the starch to be systematically modified to achieve new properties while preserving its desirable features [6].

1.5 Objectives and Scope of Review

This systematic review thoroughly explores the different starch modification techniques and their pharmaceutical uses in targeted drug delivery. Chemical, physical and enzymatic modification techniques are discussed, synthesis strategies for modified starch-based DDS such as nanoparticles, hydrogels, microspheres and films are presented, mechanisms of targeted delivery (pH-responsive, colon-targeted and tumor-targeted) are discussed, and clinical applications are discussed in relation to cancer therapy, gastrointestinal delivery and biopharmaceutical delivery, the modified starch is compared with alternative natural polymers, regulatory and safety considerations are discussed, current challenges are discussed and future perspectives for better clinical translation are proposed. This review gives detailed and scientific information to help researchers and practitioners create next-generation modified starch-based drug delivery system.

2. Structure and Properties of Native Starch

2.1 Composition and Structural Organization

Starch is a branched polysaccharide made up of two polymeric glucose molecules in varying proportions, depending on the botanic source [1]. The linear component amylose consists of (1→4)-α-D-glucosidic linked glucose residues with few branches (0.5-1%) [2]. The branched component, amylopectin, has primarily (1→4)-α-glucosidic bonds along the chain and (1→6)-α-glucosidic bonds as branch points, with these occurring at a distance of 20-25 glucose units from each other [3]. The typical starch is composed of 15-35% amylose and 65-85% amylopectin, which have different proportions that are correlated with different physicochemical properties [4]. Amylopectin/amylose ratio is a factor in the level of hydrogen bonding, crystallinity and susceptibility to enzymatic degradation [5].

2.2 Granular Structure and Morphology

The molecules of starch form semi-crystalline spherical aggregates called granules, whose size and morphology are dependent on the botanical origin and are in the range of 3 to 100 μm in diameter [6]. Under the electron microscopy, it is found that it is organized in hierarchy with alternating crystalline and amorphous layers in the form of growth rings [7]. Granules have pits and grooves on the surface which serve as starting points for enzymatic or chemical attack [8]. The interior of the starch granules is lamellar, with amorphous regions (high in branch points) alternating with crystalline regions (linear organized chains), and the starch granules have a relatively smooth surface [9]. This architectural organisation forms semi-crystalline starch structures with ordered and disordered regions, which have a significant impact on the physical properties and responses to modification [10].

2.3 Physicochemical Properties

Native starch exhibits several key physicochemical properties:

a) Hydrophilicity: Native starch is hydrophilic owing to abundant hydroxyl groups, limiting hydrophobic drug loading [1]
b) Biodegradability: Susceptible to enzymatic degradation by amylases, α-glucosidases, and maltases present in biological environments [2]
c) Swelling: Absorbs water and swells significantly above gelatinization temperature, with degree dependent on amylose content [3]
d) Solubility: Insoluble in cold water due to hydrogen bonding but gelatinizes in hot water releasing soluble amylose [4]
e) Crystallinity: Displays crystalline polymorphs (A-, B-, or C-type) with characteristic X-ray diffraction patterns [5]

2.4 Limitations in Pharmaceutical Applications

However, native starch has several drawbacks for DDS applications [1]. The poor mechanical properties restrict the load bearing capacity in solid dosage form [2]. The enzymes rapidly degrade the polymer and water molecules rapidly enter the capsule causing immediate burst release kinetics which are not favorable for sustained release [3]. Thermodynamic instability is a limitation for stability during the processing and storage [4]. Without functional groups, active targeting, surface modifying and covalent drug conformation are not possible [5]. Water absorption and swelling decrease structural integrity [6]. The difficulty of reproducing formulations is a result of botanical variability in batches [7]. Such restrictions require strategic changes to extend pharmaceutical applications [8].

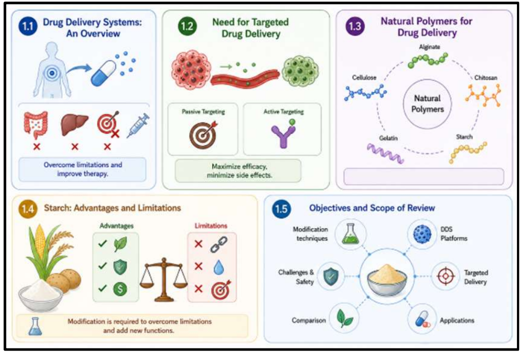

Figure 2: Overview of Targeted Drug Delivery and Modified Starch

3. Techniques for the modification of starch.

3.1 Physical Modification Methods

3.1.1 Heat-Moisture Treatment (HMT)

Heat-moisture treatment is a controlled-heating procedure in the moisture range of 10-30% w/w, but before complete gelatinization [1]. This process results in a structural rearrangement due to an increase in molecular mobility that leads to recrystallization and reassociation of starch chains [2]. HMT reduces swelling and solubility, increases crystallinity and mechanical properties [3]. It is an economical and eco-friendly process which is attractive for pharmaceutical applications [4]. The modified starches have low burst release and high stability [5].

3.1.2 Microwave Treatment

In the process of microwave treatment, the gelatinization and molecular relaxation of starch suspensions occur selectively due to heating of polar molecules [1]. This technique can rapidly increase the viscosity of starches, and lower the crystallinity in just minutes [2]. The drug loading capacity and porosity of starches treated with microwaves are improved [3]. The modification is fast, energy efficient and organic solvent free [4]. Controlled swelling properties of the product suitable for formulation development [5].

3.1.3 Ultrasonic Treatment

The method of Ultrasonication is based on the principle of acoustic cavitations, which are created by high intensity sound waves, disrupting the hydrogen bonding network and granule structure of starch suspensions [1]. This will result in surface erosion, increase of porosity, and decreases in particle size [2]. The water absorption capacity and the enzymatic accessibility of the sonicated starch is higher and has higher specific surface area [3]. The method is fast and does not generate any chemical residues [4]. Drug encapsulation and the dissolution profile were improved for modified starch [5].

3.2 Chemical Modification Methods

3.2.1 Cross-linking

Cross-linking creates covalent links between chains of starch making it into three-dimensional networks, which significantly enhance mechanical properties and stability [1]. Commonly used cross-linking agents are epichlorohydrin, phosphoryl chloride and adipic acid anhydride [2]. The cross-linked starches are less soluble, have limited swelling and slow release properties [3]. Reagent ratios and reaction conditions can be controlled to achieve the desired degree of crosslinking [4]. Among the starch and starch-based materials, cross-linked starch-based hydrogels have been found to have outstanding stability in diverse pH ranges and biological fluids [5]. These changes reduce burst release significantly and also allow for for predictable delivery profiles [6].

3.2.2 Esterification

Esterification involves the substitution of hydroxyl groups by ester groups by reacting with anhydrides or acid chlorides [1]. The most frequent are the acetylation and the butyration which impart hydrophobicity, thus decreasing water absorption and increasing thermoplasticity [2]. The gelatinization temperature of the starches is lower and their properties of polymer film forming are higher when the starches are esterified [3]. The degree of substitution (DS) determines extent of hydrophobicity and can be precisely controlled [4]. An encapsulation efficiency of lipophilic drugs and a low dissolution rate are significantly increased with esterified starch formulations [5].

3.2.3 Etherification

The introduction of ether groups is achieved by treatment with alkyl halides or epoxides under basic conditions (etherification) [1]. Many water-soluble derivatives are created by substitution with hydroxypropyl (HP) and hydroxyethyl (HE) groups, which render these flexible [2]. Etherified starches retain their hydrophilic properties, but decrease their crystallinity and increase their fragility of granules [3]. The changes are biodegradable and result in bio-compatible products [4]. The hydroxyethyl and hydroxypropyl starches have high solubility, better film-forming ability, and excellent mucoadhesion [5].

3.2.4 Oxidation

Controlled oxidation with permanganate, periodate or hydrogen peroxide introduces the reactive carboxyl and aldehyde groups [1]. Oxidized starches have less viscosity and are more soluble in cold water than other starches, and had improved film properties [2]. These modifications allow efficient covalent drug conjugation, surface modification with targeting ligands and cross-linking with other polymers [3]. Additional hydrogen bonding capacity is exhibited by the oxidized starch derivatives which exhibit improved mucoadhesion. Aldehyde groups can serve as the reaction site for conjugation chemistry and Schiff base formation with drugs containing amino groups [5].

3.2.5 Graft Copolymerization

Graft copolymerization involves the formation of side chains of synthetic or natural polymer with the starch backbone, which is a combination of traits of the two materials [1]. Starch is grafted with vinyl monomers (such as acrylic acid, acrylonitrile) or natural polymers (such as polylactic acid, chitosan) by free radical, ring-opening or coupling chemistry [2]. Grafted copolymers have better mechanical properties, control degradation and have good loading capacity [3]. By grafting poly(acrylic acid) onto starch, the pH-sensitive copolymers for colon delivery are made [4]. Temperature responsive systems are obtained by grafting poly(N-isopropylacrylamide) [5]. The changes allow rational design of multifunctional DDS having tunable properties [6].

3.3 Enzymatic and Biological Modifications

Enzymatic modification involves the use of enzymes as catalyst for modifying starch with high selectivity and biocompatibility [1]. Pullulanase selectively cleaves the branch points to produce linear type starch derivatives with different properties [2]. Cyclodextrin glucanotransferase is an enzyme that transforms starch into cyclodextrins, cyclic oligosaccharides that have hydrophobic cavities which allow the encapsulation of drugs [3]. The formation of covalent bond by transglutaminase results in stable hydrogels [4]. Enzymatic methods are environmentally friendly, mild conditions and safe & FDA approved products [5]. The modifications preserve the biocompatibility of starch and provide advanced functionality [6].

3.4 Dual and Advanced Modifications

By applying two or more modification techniques, high level materials with improved and complementary properties can be obtained from them [1]. The polymers can be cross-linked sequentially and esterified to provide mechanically strong and water resistant polymers for sustained delivery [2]. The oxidized-carboxyl starch crosslinked chitosan forms ionic complexes for colon targeting [3]. Smart Delivery can be achieved via the use of graft copolymers containing stimuli-responsive polymers that can respond to several environmental stimuli [4]. Hybrid material blends of starch and synthetic polymers (PLGA or PCL) are tunable in terms of both degradation and mechanical properties [5]. These advanced modifications allow to rationally design multifunctional delivery systems targeting complex disease pathologies [6].

Table 1: Types of Starch Modification Methods and Their Effects

Category	Method	Main Effect
Physical	Heat-Moisture Treatment	Improves stability and reduces swelling
Physical	Microwave Treatment	Increases viscosity and porosity
Physical	Ultrasonic Treatment	Reduces particle size and improves drug loading
Chemical	Cross-linking	Enhances strength and sustained release
Chemical	Esterification	Increases hydrophobicity
Chemical	Etherification	Improves solubility and flexibility
Chemical	Oxidation	Adds reactive groups for drug attachment
Chemical	Graft Copolymerization	Creates smart and responsive delivery systems
Enzymatic	Enzymatic Modification	Selective, eco-friendly starch modification
Advanced	Dual Modifications	Produces multifunctional delivery systems

4. Modified Starch-Based Drug Delivery Systems

4.1 Nanoparticles

The modified starch nanoparticles are typically 50-500 nm in size, which are highly effective DDS with lots of advantages [1]. Nanoparticles can be prepared in several ways such as nanoprecipitation, emulsification-solvent evaporation and ionic gelation, allowing control of their size and morphology [2]. Nanoprecipitation is a process in which the starch is dissolved into an organic solvent and the rapid precipitation is carried out in an aqueous medium which results in a particle size that can be tuned [3]. The cross-linked starch nanoparticles exhibit high stability and encapsulation efficiency (EE) of the hydrophobic drugs, more than 80% [4]. Surface modification allows for active targeting, cellular uptake and decreased reticuloendothelial system clearance [5]. Typical surface modification methods include pegylation, chitosan coating, and ligand conjugation [6]. The size of these nanoparticles is much smaller than the scale of the carrier and therefore their penetration effect in cellular barriers is larger than the penetration effect of the macroscale carriers and they will accumulate more in diseased tissues [7].

4.2 Hydrogels

Hydrogels are 3D polymer networks that are able to absorb and retain large amounts of water [1]. Starch is cross linked to form a hydrogel, which has excellent biocompatibility, tunable swelling, and controlled drug release [2]. The physical hydrogels are obtained by hydrogen bonding or van der Waals interactions, and they are reversible and can respond to changes in the environment [3]. Chemical hydrogels with covalent cross-links have excellent mechanical properties and a long release time for drugs [4]. Triggered release can be achieved with stimuli responsive hydrogels containing pH-sensitive or enzyme-sensitive bonds [5]. Other polymers such as chitosan, alginate and hyaluronic acid can be effectively combined with starch to form composite hydrogels which present improved properties [6]. Mucosal delivery, wound healing, and localized therapeutic applications are especially beneficial for these systems [7].

4.3 Microspheres

Starch microspheres (1-1000 μm) have good mechanical properties and small particle size [1]. Drug-loaded microspheres with controlled porosity can be prepared by spray drying, coacervation and emulsification-evaporation techniques [2]. The cross-linked starch microspheres are resistant to breaking up in water and have a delayed release property [3]. Porous microspheres have a huge surface area, which allows high drug loading, and can be used at 70-90% EE for different classes of drugs [4]. In vivo colon-targeted microspheres with sequential chemical modification prepared by sequential chemical modifications are selective for colonic delivery [5]. The modified starch microspheres have a good biocompatibility and low inflammatory response [6]. These systems can be used for parenteral and oral delivery and implantation [7].

4.4 Films and Coatings

Polymer matrices of modified starch films and coatings are suitable for a wide range of pharmaceutical applications as a flexible matrix that is biocompatible [1]. The process of film formation is one of the casting methods from solution or melt processing to produce continuous polymeric structures [2]. Mechanically stiffer films have been obtained from starches that have been esterified and etherified, which have higher elongation at break and less brittleness [3]. Plasticizers (polyols, urea) in films result in greater flexibility and oxygen permeability [4]. Multilayer film coatings allow sequential, targeted release based on layer specific dissolution [5]. The use of edible starch films is less damaging to the environment than the use of synthetic polymer films [6]. The films can be used as coating for tablets, in mucoadhesive patches and targeted delivery to the intestine [7].

4.5 Tablets and Capsules

They can be used as functional excipients in the formulation of tablets and as capsule materials [1]. The cross-linked starch derivatives exhibit controlled breakdown and hence, tablets prepared from such substances can be released for a longer duration [2]. Tablet formulations that contain starch exhibit better mechanical characteristics, lower friability and higher hardness [3]. The drugs are released from the enteric coated tablets in the colon due to the dissolution of the coating at a pH of more than 5.5 [4]. Modified starch capsules have been developed with enhanced stability and dissolution rates in comparison to gelatin capsules [5]. Starch based capsule formulations are especially useful for the delivery of proteins and peptides as they have a lower enzymatic exposure [6]. These systems are easy to manufacture and have advanced targeting capability [7].

4.6 Nanofibers

Starch nanofibers (50-500 nm in diameter) produced by electrospinning are used to form high surface area matrices for advanced drug delivery [1]. Continuous ultrathin fibers of starch solutions or blends of starch with polymers can be produced by electrospinning, with controllable properties [2]. By virtue of high drug loading capacity and high surface area, nanofibers can exhibit quick drug release from them [3]. The cross-linked nanofibers have a controlled polymer degradation and thereby show sustained release behavior [4]. Multifunctional delivery systems are chitosan, gelatin, synthetic polymers based composite nanofibers [5]. These materials are extremely useful for wound dressing, tissue engineering and transdermal delivery applications [6].

5. Mechanisms of Targeted Drug Delivery

5.1 pH-Responsive Delivery Systems

pH-Responsive starch systems take advantage of pH changes in the gastrointestinal tract for site-specific delivery [1]. The swelling and dissolution of starch derivatives with ionizable groups, such as carboxylic acids or amines, are pH dependent [2]. Poly(acrylic acid)-grafted starch is stable at stomach pH (~1.5) because the carboxylic acid groups are protonated, and this enables it to resist premature release [3]. Carboxyl groups are deprotonated at neutral and alkaline colonic pH (~6.5-8.0) leading to polymers relaxation and drug release [4]. A pH-sensitive polymer, Eudragit is used to prepare composite carriers for intestinal targeting with starch [5]. Systems for colonic delivery have been found to be more effective than uncoated systems [6]. Mechanism is the osmotic pressure change that occurs due to ionization of polymer functional groups [7].

5.2 Enzyme-Responsive Delivery

The starch enzyme responsive systems take advantage of the natural susceptibility of starch to the degradation by enzymes to achieve targeted release [1]. Colonic amylase and maltase are absent in the proximal gastrointestinal segments, thus colonic targeted systems are based on these enzymes. Selective delivery to the colon is achieved by formulations that are not degraded by pepsin and pancreatic amylase but are degraded by bacterial α-amylase [3]. One way to use a matrix metalloproteinase (MMP) as a targeting agent involves cleaving a peptide linkage between starch and a drug that is linked to the starch by an MMP-sensitive peptide sequence [4]. These mechanisms make these systems biologically selective by themselves, without chemical modification [5]. The in vitro enzymatic degradation studies have been found to be useful in predicting in vivo behavior [6].

5.3 Temperature-Responsive Delivery

The starch copolymers exhibit drastic changes in their properties over very narrow temperature ranges [1]. By incorporating poly(N-isopropylacrylamide) (PNIPAm) or poly(ethylene glycol) into the system, one can obtain systems with lower critical solution temperature (LCST) in the range of physiological temperature [2]. Polymers are hydrophilic and extended in solution below LCST and inhibit drug release [3]. Above LCST, the hydrophobic collapse takes place that leads to fast drug expulsion [4]. External temperature control for on demand release can be achieved by using hyperthermia-activated delivery [5]. These systems are useful for hyperthermia-chemotherapy combinations in cancer therapy in local areas [6].

5.4 Redox-Responsive Systems

Redox-responsive starch systems are made up of disulfide bonds or thioether linkages that are sensitive to reducing environments [1]. High concentrations of glutathione (2-10 mM) are maintained in cancer cells and inside cellular compartments, while the concentration in the extracellular environment is much lower (2-20 μM) [2]. The disulfide-cross-linked starch hydrogels are stable in the extracellular environment, but when exposed to glutathione, they will rapidly degrade and release encapsulated drugs [3]. This would allow for efficient intracellular delivery of the drug, without much leakage of the drug in the extracellular space [4]. A sequential multi-stage release is obtained by hybrid systems that are both redox and pH responsive [5]. These mechanisms can be very useful in the delivery of cytotoxic chemotherapy to the intracellular environment [6].

5.5 Ligand-Mediated Active Targeting

Active targeting nanoparticles functionalized with the ligands that bind to overexpressed disease markers [1]. Folate-conjugated starch nanoparticles are selectively internalized to the tumor and over-express folate receptors in cancer [2]. Integrin receptors in angiogenic vasculature and cancer cells are targeted with incorporation of RGD peptide [3]. The hyaluronic acid conjugation is directed to the receptor CD44 which is present in cancer stem cells [4]. Targeting of transferrin and lactoferrin takes advantage of iron-transport receptors on proliferating cells [5]. These ligand-mediated approaches make for much greater cellular uptake and less off-target toxicity [6]. The dual-ligand systems with targeting and penetration-enhancing ligands maximize the biodistribution [7].

6. Applications of Modified Starch in Drug Delivery

6.1 Cancer Therapy

Modified starch nanoparticles are an outstanding candidate for the drug delivery system for chemotherapy because of the critical limitations of free drugs [1]. When encapsulated in folate-conjugated starch nanoparticles, doxorubicin (DOX), a topoisomerase II inhibitor, exhibits 95% EE and selective uptake in the tumor in folate-receptor-positive cancer xenografts [2]. In vivo data show that it exhibits a much less cardiotoxic (a significant limitation of DOX) and has therapeutic efficacy [3]. The problem of poor aqueous solubility is addressed by encapsulating paclitaxel in the starch nanoparticles [4] that are hyperhydrophobic. Intracellular delivery of drugs in multidrug resistant cancers is achieved by using pH and redox-responsive starch systems, which allow the release of the drug in the intracellular environment, bypassing the drug efflux pumps [5]. Therapeutic response can be increased when combination therapy of chemotherapy and immune checkpoint inhibitors (ICI) is administered via modified starch [6]. There are currently several formulations under clinical trials based on starch as a carrier [7].

6.2 Colon-Specific Delivery

Colon-targeted therapy is used for inflammatory bowel disease (IBD), colorectal cancer and infectious colonic diseases [1]. Colonic-specific formulations are also based on the presence of colonic bacterial flora and gradients in the pH and the absence of these conditions in other parts of the gastrointestinal tract [2]. The cross-linked starch tablets are not broken down by pepsin and pancreatic enzymes in the stomach and small intestine respectively so that they remain intact [3]. Native bacterial enzymes in colon quickly break down starch, leading to the release of the drug at the disease site [4]. This results in significantly decreased systemic exposure and associated side effects, which increases tolerability [5]. Conventional formulations of mesalamine, a commonly used IBD therapeutic, have been shown to have improved efficacy and safety with colon targeted systems using starch as the carrier [6]. These systems are especially useful for local acting agents that are not very systemic tolerant [7].

7.3 Oral Protein and Peptide Delivery

Protein and peptide therapeutics are highly effective, but have significant challenges for gastrointestinal delivery such as enzymatic degradation and intestinal permeability [1]. Proteins are protected from the proteolytic enzymes of stomach and small intestine by modified starch matrices [2]. The insulin encapsulation in starch nanoparticles shows enhanced bioavailabilities in animal model (40-50%) compared to bioavailability of free insulin (5%) [3]. Vitamin B12-starch conjugates have increased intestinal absorption due to increased mucosal retention and cellular uptake [4]. Only starch degraded by enzymes is absorbed in the colon [5]. The use of mucoadhesive starch derivatives increases the residence time of the pharmaceuticals in the intestine, thus improving the permeation [6]. Once-daily oral peptide delivery is achieved by these methods, resulting in enhanced patient compliance [7].

7.4 Vaccine Delivery

A vaccine adjuvant system based on modified starch nanoparticles has been developed, which is an effective carrier and adjuvant for vaccine antigens [1]. The recognition of polysaccharide patterns as pathogen-associated molecular patterns (PAMPs) by antigen-presenting cells (APCs) is also enhanced in particle uptake [2]. Antigens delivered by oral starch-based vaccine carriers are introduced into the gut-associated lymphoid tissue (GALT), which leads to generation of both mucosal and systemic immune responses [3]. Starch nanoparticles containing model antigens (OVA) can enhance the antibody level of IgG and IgG antibody level of IgA in comparison with administration of free antigens [4]. Surface mannose or lectin modification increases the APC uptake and immunogenicity [5]. These systems do not require the cold chain that is required with traditional vaccines, which makes them more accessible in resource-limited areas [6]. The current focus of development is on vaccine candidates for COVID-19 and influenza [7].

7.5 Wound Healing and Tissue Engineering

Controlled growth factor delivery and tissue regeneration support are key features of matrices based on modified starch that foster wound healing [1]. Starch hydrogels keep the wound areas moist and aid in gas exchange, thereby facilitating the process of epithelialization [2]. The incorporation of antimicrobial agents (such as silver nanoparticles and essential oils) can help prevent infection, which is important in the management of chronic wounds [3]. The fibroblast proliferation and collagen deposition are stimulated by growth factor-loaded starch scaffolds [4]. Three-dimensional porous starch matrix is used as structural support in tissue engineering [5]. Biopolymer products are glucose or short chain saccharides which are used as the nutritional source for cellular metabolism [6]. It is used in clinical situations such as diabetic ulcers, burn wounds, and healing after surgery [7].

It is important to compare this natural polymer with the other natural polymers.The comparative analysis with other natural polymers is important.
Modified starch is a competitor to a wide variety of natural polymers for drug delivery. This section systematically compares the key performance parameters.

Polymer	Key Advantages	Limitations	Applications
Modified Starch	Cost-effective, abundant, biodegradable, multifunctional, FDA-approved [1]	Batch variability, burst release tendency, mechanical properties [2]	Colon delivery, oral peptides, cancer, vaccines [3]
Chitosan	Antimicrobial, mucoadhesive, cationic, biocompatible [4]	Limited solubility, source variability, cost [5]	Gene delivery, wound healing, oral delivery [6]
Alginate	Biocompatible, gelation with divalent ions, low cost [7]	Poor mechanical strength, burst release, instability [8]	Microencapsulation, oral delivery, tissue engineering [9]
Cellulose	Abundantly available, inert, easy modification [10]	Limited intrinsic bioactivity, slow degradation, brittleness [11]	Tablet coating, film formation, hydrogels [12]

In addition to being less expensive and more readily accepted by regulatory authorities than chitosan, modified starch also has greater mechanical property and sustained release performance than alginate, and can be biodegraded more effectively than cellulose [1]. Starch has better chemical stability and improved storage at room temperature as compared to gelatin [2]. The selection of the polymer is tailored to the application's needs, the target organ, the properties of the drug and regulatory/commercial factors [3].

8. Toxicity, Biocompatibility, and Regulatory Considerations

8.1 Biocompatibility and Cytotoxicity

The results of modified starch showed good biocompatibility when tested with different cell types and tissue models [1]. The in vitro cytotoxicity data obtained from MTT and LDH assays shows that the majority of starch formulations are safe, with dose-dependent behavior and IC50 values > 500μg/mL [2]. It has been found that cross-linked starch nanoparticles have a very low cellular uptake and no cytotoxicity at all even at high concentration of 1000 μg/mL [3]. Acute toxicity, hepatotoxicity, nephrotoxicity and hematological abnormalities have not been observed in vivo upon intravenous administration of 1000 mg/kg in mice and rats [4]. Major organs are normal by histopathological examination, with no inflammatory infiltration [5]. Starch is GRAS recognized by FDA, has minimum allergic potential and is used in a variety of FDA approved drugs [6].

8.2 Biodegradation and Metabolism

Modified starch can be degraded in predictable manner by enzyme reactions similar to those of starch in the diet [1]. Mammalian amylases break native starches down to glucose and maltose and these are then metabolized in the normal glucose pathway [2]. Cross-linked starch also possesses delayed enzymatic degradation properties and thus provides for sustained delivery of the starch units while ultimately degraded to glucose units [3]. The hydrophilicity and enzymogenic accessibility of the oxidized starch are improved because of the increase of the carboxylic groups, which makes the degradation process faster [4]. Complete clearance has been shown in vivo with 14C-starch, where respiratory CO2 is the main route of elimination (48-72 hours) [5]. The absorption of intact starch in the systemic circulation is very low as extensive starch degradation occurs in the gastrointestinal tract before absorption [6]. Endogenous metabolites (glucose, short-chain fatty acids from colonic fermentation) are produced in the body in the absence of bioaccumulation [7].

8.3 Regulatory Pathway and Approval Status

The pharmaceutical formulations containing modified starch excipients have been well established and have well-known pathways for regulation [1]. Numerous marketed formulations contain the excipients of the following: Pregelatinized starch, cross-linked starch, and sodium starch glycolate are all approved by the FDA [2]. Physically modified starch (HMT, microwave) is a food additive that is generally recognized as safe by FDA for direct food use [3]. Chemically modified starch (cross-linked, esterified) is processed through well-known pharmaceutical excipient approval procedures, including documentation of its safety. Oxidized and etherified starches have been approved in certain countries based on their proven safety profiles [5]. Preclinical toxicology (acute, subacute and chronic studies), genotoxicity and immunotoxicity assessment are carried out on novel starch modifications [6]. EMA has offered guidance regarding excipient evaluation in Quality Overall Summary (QOS) [7]. Novel starch formulations are advanced into clinical translation via the IND/CTA pathway along with pharmacology and toxicology data [8].

8.4 Scale-up and Manufacturing Considerations

Scale-up of the starch formulations is challenging and needs to be optimized if the formulation is a modified starch [1]. Strict quality control is required because of the natural polymer source variability [2]. The final product properties are strongly influenced by the process parameters such as temperature, turbulence and residence times [3]. Process validation is necessary to ensure consistent performance when going from a laboratory to pilot and commercial scale [4]. For pharmaceutical applications, good manufacturing practice (GMP) compliance is critical [5]. Waste management, solvent recovery and energy use are environmental concerns that need to be assessed [6]. Depending on the method of modification, sterilization compatibility can differ: Some formulations are not compatible with autoclaving but can be processed by other methods (gamma irradiation or filtration) [7]. Most starch formulations do not require cold-chain storage, making distribution easier [8].

9. Current Challenges and Future Prospects

9.1 Current Challenges

Critical challenges limiting current clinical translation of modified starch formulations include:

a) Batch Variability: Starch source heterogeneity creates inconsistent physicochemical properties limiting reproducibility [1]
b) Molecular Characterization: Complex polymeric structures challenge thorough characterization, complicating regulatory approval [2]
c) Mechanical Properties: Despite improvements, modified starch exhibits inferior mechanical strength versus synthetic polymers [3]
d) Stability Issues: Chemical instability under accelerated conditions limits shelf-life and storage compatibility [4]
e) Limited Clinical Data: Few completed clinical trials establish safety and efficacy

in humans versus many preclinical studies [5]

f) Scale-up Manufacturing: Transition from laboratory to commercial production presents technical and regulatory hurdles [6]

g) Off-Target Effects: Lack of selectivity can result in undesired accumulation in healthy tissues, limiting efficacy/safety [7]

h) Cost-Effectiveness: While starch is inexpensive, formulation development, modification, and characterization increase costs [8]

9.2 Future Perspectives

Smart Starch Biomaterials and Intelligent Delivery Systems

Multi-responsive starch systems with pH, temperature, enzyme and redox sensitivity allow for more advanced and intelligent delivery systems to respond to multiple stimuli in the microenvironment of each disease [1]. New and promising systems are based on starch, where the integrated biosensors allow for real-time monitoring as well as adaptive drug release [2]. The application of starch nanofiber based smart textiles for drug delivery and monitoring would meet the requirements for personalized medicine [3].

AI Assisted Formulation Design and Optimization.

Optimal modification parameters predicted from machine learning and artificial intelligence—with minimal experimental testing [1]. Novel starch modifications with desired properties are rationally designed using computational chemistry [2]. Robotic systems with AI can be used for high throughput screening, which accelerates development and costs [3].

Integrating nanotechnology and hybrid systems

The multimodal imaging and therapy using starch-metal nanoparticle hybrids with polymeric and inorganic character is available [1]. Starch-lipid nanoparticle systems are more effective in encapsulation of hydrophobic drugs and genetic materials [2]. Optimizing biocompatibility and mechanical properties by using core-shell nanoparticles, where the core is made from a synthetic material and the shell is made from starch, can be achieved [3].

Green Chemistry and Sustainable Manufacturing

Enzymatic modification strategies replace chemical synthesis and thus do not generate hazardous waste and do not consume energy [1]. Bio crosslinkers with renewable origins are used in place of toxic chemical crosslinkers [2]. Formulation processes with minimal impact on the environment, such as solvent-free and aqueous. This sustainability enhancements make for better looks in pharmaceutical and nutraceutical uses [4].

Personalized Medicine and Precision Therapeutics

Drug formulations focused on the pharmacogenomics profile of each individual can optimize drug efficacy [1]. Biomarker-guided formulation selection brings the starch formulation to the patient that is best suited for the benefit-risk profile [2]. The emerging possibilities of 3D bioprinting with starch-based inks are on-demand, patient-specific manufacturing [3].

Clinical Translation and Regulatory Harmonization

Across the FDA, EMA and ICH regulatory agencies, there are harmonized guidelines to facilitate the clinical approval of new starch formulations [1]. Greater investment in demonstration of human safety and efficacy data in clinical trials will establish translational potential [2]. Development and commercialization process will be speeded up through industry-academic collaborations [3]. There are regulatory pathways for natural polymer modifications that are becoming clearer, and have less uncertainty in approval [4].

10. Conclusion

This is no small feat of a biomaterial that is inherently biocompatible, biodegradable and sustainable, and can deliver intricate, targeted drug delivery [1]. The limitations of native starch can be overcome by chemical, physical, and enzymatic modification techniques to develop a range of different functions including pH responsiveness, enzyme sensitivity, mucoadhesiveness, and active targeting [2]. Nanoparticles, hydrogels, microspheres, films and fibres modified with starch are effective in cancer therapy, gastrointestinal delivery, protein/peptide delivery, vaccines and tissue engineering [3]. Comparative analysis has shown that there are certain advantages over other natural polymers such as being cost effective, having mechanical properties, and being acceptable for regulatory reasons [4]. There are presently some problems associated with batch variation, stability and the lack of clinical data, which necessitate systematic research [5]. Future outlook focuses on smart starch materials, AI-driven design, integration of nanotechnology, green manufacturing, as well as on the harmonization with regulations and personalised medicine [6]. Future clinical translation of starch formulations will be faster when strategically researched to overcome identified challenges, which will revolutionize targeted drug delivery and enhance therapeutic efficacy in patients with various diseases [7]. In the future, modified starch can be expected to play an even more prominent role in the development of new generations of pharmaceutical products, especially in the context of sustainability and personalized medicine in healthcare [8].

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