Efficacy of Cassava Starch in the Design of Drug Delivery Platforms: From Roots to Polymers

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Abstract

Starch has cropped up as a new attractive biopolymer for use in pharmaceutical applications, owing to its distinctive physical, chemical and functional properties. This biopolymer has a number of potential advantages like being biocompatible, low cost, easily isolated from plant sources and non-toxic in nature. In the field of pharmaceutical science, starch is used as a raw material for the development of various drug delivery platforms. Generally, cassava starch (tapioca) is obtained from swollen roots of the perennial shrub *Manihot esculenta* and it contains a low amount of amylose in contrast to other varieties of starches. Because of this reason, cassava starch exhibits various prime benefits including little gelatinization temperature, higher swelling power and produces relatively high viscosity paste, making it preferable as an excipient for pharmaceutical applications. However, cassava starches in their native form are offensive for many applications due to their inefficiency to withstand various processing requirements like high temperature and diverse pH, but their use is enhanced by starch modification. These functional starches have demonstrated outstanding potential as primary excipients in a number of pharmaceutical formulations. In this article, we discuss the potential application of cassava starches in the pharmaceutical and biomedical fields along with the toxicity assessment of modified cassava starches.

1. Introduction

Biopolymers play a very significant potential in the pharmaceutical field because they are used to design a range of carrier systems suitable for the transport of diverse chemical and biological agents by overcoming the limitations of synthetic or conventional polymers [1]. The main reason for biopolymers have gained much popularity is that they are plentiful in nature, biodegradable, cheap, easily modifying drugs having unfavorable pharmacokinetics or instability and are either derived directly from biological systems or chemically synthesized from biological building blocks [2]. Currently, starch has become a new promising biopolymer or excipient in the pharmaceutical field being its thickening, adhesive, film-forming, gelling, swelling properties, biodegradability, biocompatible and non-toxic in nature. It is one of the most widely and easily available polymers, which can be obtained from various sources such as rice, potato, corn, sago, banana, wheat and starchy tubers or root vegetables like cassava [3, 4].

Cassava (*Manihot esculenta*, belonging to the family Euphorbiaceae) also called manioc or tapioca, is grown annually in tropical and subtropical areas for its eatable nature and its tuberous roots are the tremendous origin of starch [5]. Starch derived from the cassava contains a low amount of amylose (0% in waxy cassava starch) or a high amount of amylose (above 30% in self-pollinated progenies of AMYCS-3 and AMYCS-4) as compared to other types of starch, which supports the various prime benefits including low gelatinization temperature, low retrogradation rates, higher swelling rate and produces comparably high viscosity paste, makes it preferable as an excipient for pharmaceutical applications [6–9]. In addition, starches with a huge content of amylose are more exothermic and capable of forming a more stable gel with higher strength. The significant variation of amylose amount in cassava has a profound effect on starch functional properties [10].
Nevertheless, there are some limitations in cassava starch applications due to its inefficiency to withstand various processing requirements such as their swollen nature, thermal resistance, gelatinized granules cannot retain granular structure as a result, collapsing instantaneously. The application of cassava starch for industrial purposes is also limited by low shear stress resistance, susceptibility to thermal decomposition, high viscosity even at minor concentrations, low process tolerance and strong hydrophilic nature [11, 12]. These deficiencies may be upgraded via various modification techniques or by combining starches with protein moieties or other functional compounds. The techniques for native starch modifications have been extensively divided into four categories i.e., physical, chemical, enzymatical and genetical modifications that aim to produce various novel starch moieties with upgraded physicochemical or functional properties along with potential structural attributes for various medicinal, food, industrial or non-food purposes [13]. Currently, modified starches, e.g. sodium starch glycolate (chemically modified starch) and pregelatinized starch (physically modified starch) are approved by the United States Food and Drug Administration (FDA) for use either as an isolated excipient or as a matrix for drug delivery systems in controlled or sustained-release tablets and capsules, subcutaneous implants, transdermal and ophthalmic systems [14, 15]. Several modified starches have already been used for the development of various novel microparticulate and nanoparticulate drug carriers for the treatment of diverse forms of ailments. However, systematic studies on their properties and excipient functionalities and proper toxicity assessment are still needed. This article highlights the recent application of native cassava starches and modified cassava starches in the biomedical or pharmaceutical fields, either as a material choice or excipients of drug delivery platforms.

2. Methodology For Data Extraction

Considering the significance of this study, a thorough literature survey was conducted through online databases like PubMed, SpringerLink, Science Direct, Scopus, Google Scholar and Research Gate. The title and abstract of articles were searched from previously mentioned databases by using the corresponding keywords, i.e., starch, cassava, biopolymer, excipient, starch modification and drug delivery platforms to understand the recent trends of native and modified cassava starch based material with substantial applications in the pharmaceutical and biomedical field.

3. Geographical Sources Of Cassava Starch

The good agricultural harvest of cassava starch depends upon several climatic factors like an adequate amount of sunlight, rainfall and higher temperatures. These requirements are well fulfilled by the tropics where the mean temperature is always greater than 18°C. Though cassava is a plant of high economic importance and is considered a demanded food by over 800 million people (Food and Agriculture Organization, United Nations), its geographical origins have remained controversial [16–18]. Apart from the commonly known Manihot esculenta which is the broadly harvested cassava, there are various other wild variations of it often referred to as Manihot esculenta subspecies (Manihot esculenta subsp. flabellifolia and Manihot esculenta subsp. peruviana) that widely grow over the neotropics viz., Peru,
Venezuela, Guyana, Brazil, Bolivia and Surinam [19]. Although cassava was predominantly only cultivated in parts of South America, later sailors and explorers recognized its potential as a multipurpose plant and thus eventually with the advancement of agricultural technologies and better communication, cassava cultivation has spread from the American neotropics to the Asian countries as well. As per Food and Agriculture Organization Corporate Statistical (FAOSTAT) 2015 reports, cassava world production raised to > 263 million tons in 2013, a 27% increase in production during the last 10 years. From these, Africa 54.8% (144.2 million), Asia contributed 33.5% (88.2 million tons) and the Americas 11.6% (30.5 million tons). 30 countries which include 18 African, 4 Latin American and 8 Asian were the major cassava growers around the globe [20, 21]. Furthermore, latest FAOSTAT 2019 report, Nigeria stands to be the biggest grower of cassava followed by Congo DR, Thailand, Indonesia, Brazil, Ghana, Angola, Cambodia and Vietnam. While Thailand, Vietnam and Cambodia stand to be the largest exporters of cassava starch and flour, China, Japan and Indonesia beg the place of largest importers of cassava flour and starches [22]. The advancements in cassava productivity, sustainability and quality could be crucial for ensuring food security in Africa and Nigeria, where the population is predicted to double by 2050 than in any other country, but where cassava yields are low. The expansion of cassava manufacturing will need to be critically managed, because huge production of cassava crops may not only cause environmental impacts but also contribute to habitat degradation and soil damage, as forests and other natural biospheres are destroyed and replaced by cassava farms. The dual aims of rising food production and minimizing environmental collisions have led to calls for the “ecological intensification” or “sustainable intensification” of food production by the use of “good agricultural practices” [23]. To support the use of best agricultural formalities, a systematic map of studies about cassava farming is urgently needed.

4. Physicochemical Features Of Cassava Starches As A Drug Delivery Biopolymer

The physicochemical features of cassava starches including organoleptic, structural, crystalline, swelling, gelatinization, pasting, retrogradation and morphological properties are factors of starch quality and can provide a basis for the processing and usage of starch.

4.1. Organooleptic and structural features

Organooleptic features are the important aspects of cassava starch as experienced by the parameters including color, odor, taste and surface texture [24, 25]. These properties are summarized in the Table 1.
Table 1
Organoleptic features of cassava starch.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Parameters</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>01.</td>
<td>Color</td>
<td>White</td>
</tr>
<tr>
<td>02.</td>
<td>Odor</td>
<td>Odorless</td>
</tr>
<tr>
<td>03.</td>
<td>Taste</td>
<td>Tasteless</td>
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<td>04.</td>
<td>Texture</td>
<td>Homogeneous</td>
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Like other types of starch, cassava starch also contains two major molecular components amylose and amylopectin (Fig. 1). Amylose is essentially linear formed by units of D-glucose linked in an α-(1→4), while the amylopectin is highly branched, wherein the D-glycosidic α-(1→6) linkages are responsible for branching points [26]. The physicochemical characteristics are greatly dependent on these two distinct structural polysaccharide fractions i.e., amylose (17–24%) and amylopectin (76–83%) in content. The interaction between amylose and amylopectin improves the viscosity and textural properties of starch, which include cohesiveness and adhesiveness [27, 28]. Compared to other starches like corn, rice, potato and wheat starches, there is a significant variation in the content of amylose (0-30.3%) of cassava starches, which provides superior qualities like bland taste, flavor, high paste clarity and slighter tendency to retrograde [29]. In the case of amylopectin, the distribution of branch chain diameter gives an idea about the swelling power, pasting viscosity and solubility. Thus, it is frequently crucial to measure the concentration of each individual starch component, as well as the overall starch concentration [30].

Space for Fig. 1.

4.2. Crystalline and swelling features

Starch is usually biosynthesized as semicrystalline granules whose shape and size are reliant on the botanical sources. The crystallinity is strongly associated with amylopectin molecules while the amorphous nature mainly represents amylose molecules [31, 32]. The structural crystallinity of starches is identified as type A (Bragg angle 2θ at about 15.3°; 17.1°; 18.2°; and 23.5°), type B (Bragg angle 2θ at about 5.6°; 14.4°; 17.2°; 22.2°; and 24.0°) and type C (Bragg angle 2θ at approximately 5.6°; 15.3°; 17.3°; and 23.5°) using X-ray Diffraction (XRD) analysis [33]. Cassava starches showed prominent peaks (2θ) at 15.2°, 23.4°, and a doublet at 17.2° and 18.2°, which corresponds to the A-type crystallinity. Moreover, relative crystallinity ranged from 36.1 to 41.4%, which is similar, but slightly higher than the values reported for Thai cassava, which averaged 35.8%. These crystallinity variations within cassava starch could be due to the amount of water or moisture content in the starch samples [34, 35].

The swelling capacity and solubility of starch depend on the ability of the starch molecule to hold water through hydrogen bonding by glucan chains. As the thermal energy raises, the bonds among the glucan chain relax and the granules absorb water and swell [36, 37]. The earlier works investigated the swelling capacity and solubility of starches from different sources in the temperature range of 60–90°C. The
swelling power significantly increased steadily with temperature with a twofold change between the temperatures of 60 to 80°C, in the case of all starches [38]. Cassava and potato starches apparently had elevated and lowered swelling capacity as well as solubility. The elevated swelling capacity and solubility of cassava starch are possibly due to a higher content of amylopectin in comparison with potato flour [39]. Although the existence of non-starch constituents (lipids and proteins) in the starch reservoir is one of the most important aspects, having a negative effect on swelling power and solubility. Since cassava starch granules contain fewer amount lipids and protein compared with other forms of starches, this may account for their higher swelling and solubility properties [40, 41].

4.3. Gelatinization and pasting features

Starch is practically insoluble in cold water, however, upon heating the amylopectin structure of starch is getting altered which causes a decrease in the crystallinity and more of the water is absorbed leading to the formation of a gel-like mass. The process of gelatinization is mainly influenced by the breakdown of the intermolecular structure of starch fragments [42, 43]. Gelatinization processes are characterized by the onset temperatures (TO), peak temperatures (TP), conclusion temperature (TC) and enthalpies (ΔHgel) of the phase transitions that vary between the starches from different sources [44]. The earlier investigation reported that potato starches exhibited lower TP (64°C), while cassava starches exhibits higher TP (71°C) respectively. In spite of the fact that, the TO for the two starches are nearly identical and the range of gelatinization for the cassava starch is 9°C wider as compared to the potato starch [45]. The variations in amylose concentration, length of amylopectin chain, non-starch content and degree of crystallinity could be responsible for the discrepancies in gelatinization between different starches. [46–48]. Also, high transition temperatures have been observed due to a high degree of crystallinity, which provides structural stability and makes the granule more resistant to gelatinization. This justification revealed that cassava starches are more stable than other type of starches like potatoes [49].

Pasting usually occurring after gelatinization, resulting in the formation of amylose-amylopectin paste and gel-like a network. The pasting (rheological) features of any starches are investigated in terms of pasting temperatures and viscosities which are characterized as peak, minimum or trough, breakdown, final and setback viscosities [50]. Peak viscosity provides information on the starches ability to bind water, trough viscosity represents the lowest value of viscosity, final viscosity gives the idea regarding the capacity of starch to form a viscous paste or gel after cooking and cooling, breakdown viscosity provides information regarding the rupturing of starch granules and finally, setback viscosity is the indicator for the starch retrogradation during storage [51–53]. Cassava starches are known to have low pasting temperatures because there are a lot of negatively charged phosphate groups in their structures hence, viscosity development starts at the lowest temperatures. In the case of cereal maize, rice and wheat starches, the pasting temperature is very higher, due to the presence of an elevated amounts of proteins or lipids and the subsequent formation of lipid-amylose complex [54, 55]. Cassava starches with low pasting temperatures easily form a paste, which is an advantage for food or non-food industrial processes due to energy cost reductions during the processes of starch production as well as the minimum temperature required to cook the starch sample. However, several factors affect the cassava
starch pasting behavior that are amylose/amylopectin contents and the proportion of ingredients in their matrices [56].

4.4. Retrogradation and morphological features

Retrogradation of starches is a phenomenon that occurs in gelatinized starch as it moves from an initial amorphous form to a more ordered or crystalline state resulting in the loss of its ability to hold water [57]. This process is usually accelerated by a series of physical factors that include an increasing concentration of starch in the paste, increasing amylose content and amylopectin chain length, increasing viscosity of starch paste, degree of crystallinity and finally freeze-storage of starch paste [58,59]. During the retrogradation process, the two main components starch i.e., amylose and amylopectin show various functions. The initial hardness of gel is primarily determined by the re-association of amylose, while retrogradation and long-term gelling capacity are usually influenced by re-crystallization of amylopectin [60]. Moreover, the retrograded starch paste displays lower glass transition temperatures (Tg) and enthalpy than the native starch granules. After the modification of native starch, Tg of the modified cassava starches is found to be 3–6°C which is significantly lower than that of the non-modified starch. This trend was ascribed to the weaker crystallinity of retrograded starch [61,62]. Gomand et al. evaluated the retrogradation properties of cassava starch pastes and reported that cassava starches showed a much lower enthalpy of retrogradation or almost none than that of potato, amylose free and high amylose starches [63]. Because retrogradation is mainly influenced by low temperature, the presence of non-starch components, and polar substances like lipids, proteins, acids and salts. Cassava starches are contains very low amounts of these components and significantly exhibit very low retrogradation, high peak viscosity and produce very stable and transparent gels [64–66].

The morphology of starch moieties solely leans on amyloplast or chloroplast biochemistry, as well as plant physiology. Notably, common starches from different plants (corn, rice, wheat, potato and barley) exhibited distinct morphologies ranging from angular, pentagonal, spherical, lenticular, ovoid, irregular or cuboidal-shaped and the average diameter or shape of the starch granule varying from 1-100 µm when viewed by scanning electron microscopy (SEM) [67–69]. However, morphological features of starches obtained from cassava were stated to be ovoid, polygonal and round granules with smooth characteristics and the average granule size ranged from 3–30 µm [70]. It has been observed under an SEM and the surfaces of the starch granules from corn, rice, wheat, potato and barley appear to be limited polished than cassava starch granules. The variations in cassava starch granule sizes were ascribed to differences in the genotype and botanical origin as well as the variety of the crop [71,72].

5. Current Usage Of Cassava Starches In Conventional Drug Delivery Systems

The pharmaceutical excipients are compounds or materials which do not possess any health benefit but help in the manufacturing of pharmaceutical formulations. Starch is the safest excipient among the polymers used in pharmaceutical dosage forms. In several conventional formulations, starch is utilized
as a binder, disintegrant, lubricant, glidant and diluent due to its nontoxic and nonirritant properties [73, 74]. Starches used in the pharmaceutical industry are obtained from various botanical sources like corn, potato, rice, wheat and cassava for several benefits. Compared with corn, potato, rice and wheat starch, the investigation of cassava starch as a medicinal or pharmaceutical biopolymer was not extensively performed although it appears in many standard books [75, 76]. Although, most of the investigations are done in developing countries where cassava is cultivated mainly in South America, India, Philippines, Indonesia, China, Thailand, Malaysia, Vietnam and Indonesia [77]. Conventionally, native cassava starch can be used as excipient or raw material in tablet and capsule formulations owing to its distinct physicochemical and functional properties [78]. The potential applications of cassava starches in conventional drug delivery systems are discussed below (Fig. 2).

Space for Fig. 2.

5.1. Binding agent

Starch is broadly utilized as a binder in the granulation step for massing or screening of materials and components in the fabrication of solid dosage forms like tablets, capsules and so on. As a binder, the starch was converted to a paste, which is generated by heating the starch that causes the smaller formulation particles to clump together to create larger-sized agglomerates resulting in reduced cohesiveness and encouraging flow [79, 80]. The amount of a binder could impart a direct effect on tablet characteristics like crushing strength and friability. As the amount of starch in the formulations increased, the crushing strength is also raised indicating that the starch excipients facilitated tablet binding. A study reported that cassava starch had higher crushing strength values than corn starch and this result is directly correlated with the binding effect [81, 82]. Moreover, cassava starch has been also discovered to possess stronger binding capability when compared to cocoyam starch and maize starch because of the increased gel strength of its mucilage. This explanation indicates that cassava starch provides excellent binding properties and should be explored in pharmaceutical formulations [83].

5.2. Disintegrating agents

A disintegrate is an excipient that is added in a pharmaceutical formulation to achieve the breakup of compressed solid dosage forms to small particles when they come into contact with aqueous matter leading to an increase in surface area for subsequent dissolution [84]. Starch is a cheap and convenient disintegrate which is thought to exert this action by swelling its particles in the body fluids resulting in disruption of confining forces in the dosage form. The usual concentration range of starch as disintegrates in the tablet formulation is 2–10% [85, 86]. Literature reported that starches isolated from cassava offer superior disintegrant qualities over maize starch BP. This could be ascribed that the tensile and crushing strength of the tablets containing cassava starch decreased with an increase in starch concentration (5–10% w/w) leading to easily disintegrated in the aqueous medium in less than 15 minutes. Hence cassava starch provides new insight as to potential disintegrant and is used as a substitute for pharmaceutical dosage forms [87].
5.3. Lubricating agents

Lubricants are the agents that are mixed into tablet or capsule formulations in a very small quantity (usually 0.25–5.0%, w/w) to improve the flowing characteristics by reducing the adhesion and friction among the particles and walls of the die cavity during compression [88]. In the tablet pelleting process, starch acts as a lubricant that aids the flow of particles via pelleting matrix [89]. The role of cassava starch as a lubricant in tablet formulation is comparable. A study reported that cassava starches showed the least flow properties as indicated by the Hausner ratio (HR) as well as Carr's index (IC). Flowing properties of powder or granules are rated based on official HR and IC values. An HR of < 1.11 or CI of < 10 is considered 'excellent' whereas HR > 1.60 or CI > 38 is considered 'very poor' flow. The cassava (tapioca) starch granules have HR value of 1.48 ± 0.03 and an IC value of 28.33 ± 1.53%, thereby granules obtained from cassava starch presented poor flow properties according to the HR and IC values [90, 91]. In addition, size, shape and uniformity of the particles are significantly involved with their flow properties. Particles of cassava starch presented a smaller diameter than that of potato starches. Because larger particles flow better than smaller ones, smaller particles have a large surface area and more surface energy to attract one another to stick together and have more friction to flow. Thus, cassava starch with the lowest cohesiveness would be the starch of choice when fair flowability is desirable [92].

5.4. Glidants

Glidants are inert substances that are combined to tablet formulations to reduce inter particulate friction and to improve the flowing characteristics of granules from the hopper to die cavities during the early stage of compression. They are required at the surface of feed particles and appropriately incorporated into the mixture. Tropical starches have been widely explored as glidants in many conventional tablet or capsule formulations and improved the flow properties of granules at concentrations of 2–10% w/w, thus enhancing the fabrication process and outcome [93, 94]. Literature reported that starches obtained from cassava have shown fair or passable flow properties as indicated by the Hausner ratio (HR) and angle of repose (AoR). The HR and AoR values of cassava starch were found to be 1.44 and 30.82 °. British Pharmacopoeia classifies powder flow as 'excellent' (HR: 1.00-1.11 and AoR: 25–30 °), whereas considered poor (HR: 1.35–1.45 and AoR: 46–55 °). Generally, AoR values below about 30 range are considered to be appropriate for solid dosage from technology. This could be ascribed that observed AoR values for cassava starch are almost similar to the official values suggested by the literature. Hence, these results illustrated that cassava starches may be suitable as an alternative glidant in the field of pharmaceutical formulations [95–97].

5.5. Diluents

Diluents are chemically inactive substances or inert materials which perform as fillers in the fabrication of solid dosage forms like tablets or capsules [98]. The diluent solubility in a formulation has been shown to strike the mechanism and rate of tablet disintegration. The main purpose of diluents in pharmaceutical formulations is that, few drugs are used at very low dosages thus making it very difficult to process them. In such circumstances, inert ingredients that do not have the drug's therapeutic effect can be mixed into
the formulation to bulk it up to enable the normal formulation processes. Starch is the widely used diluent or filler in tablet production due to its inertness, odorless and digestible nature [99, 100]. Starches obtained from cassava were found to be a promising diluent for pharmaceutical formulation. However, cassava starch in tablet preparation cannot be utilized as a diluent in direct tablet compression due to its poor compressibility and flow properties. Several modification strategies have been shown to improve these functional properties, by adding other components or agents like Avicel PH 101/PH 102 which promotes rapid wetting as a result produces robust granules for fast disintegrating tablets. Cassava starch co-process with Avicel PH 101 upgrades the diluent effectiveness of cassava starches for direct compression tablets with better flowability, friability, disintegration time and tablet uniformity. As a result, modified cassava starch is offered as a good diluent for producing quick-dissolving tablets with adequate hardness [101, 102].

6. Limitations Of The Use Of Native Cassava Starch In Drug Delivery

Native cassava starch has been explored as a special carrier and conventional excipient for the delivery of various active molecules in pharmaceutical dosage forms as classic tablet disintegrants, binders, glidants and diluents [103, 104]. However, cassava starch in its indigenous form has assertive drawbacks like hydrophilic nature, high viscosity, propensity to retrogradation even at minimum concentrations, brittleness, thermal instability, poor freeze-thaw stability, gel opacity and low process tolerance that prohibit its utilization in various dosage forms [105]. The application of native starch as an excipient or biopolymer in the extended or sustained release dosage form is restricted owing to its poor compactibility resulting in the production of weak tablets. In oral administration of sustained release tablets or capsules comprising native starches are almost completely broken down by the pancreatic enzymes after oral ingestion leading to subsequent absorption from the small intestine and thus fails to drug release for a prolonged period of time [106, 107]. Also, native starches exhibited higher swelling behavior (42.6 g/g) and solubility (25.4 g/g) in excess of water at 90°C, resulting in low water holding capacity which is very unfavorable for the design of pharmaceutical dosage forms. In contrast to thermal stability and pasting profile, the native form of cassava starches showed low thermal transition temperature, which directly provides less structural stability and thermal instability resulting in makes the granule more liable to gelatinization, while native cassava starch exhibited noticeable increases in viscosity followed by considerable paste thinning [108]. Furthermore, native cassava starches have elevated lubricant sensitivity and poor flowability as well as high cohesiveness mainly due to small particle size and large surface area, which limited their use in the formulation of direct compaction or compression tablets [109, 110]. These all are the major constraints of native cassava starch which reduce its uses in pharmaceutical dosage forms. These shortcomings can be overcome by starch modification and expanding the utilization of cassava starches as a biopolymer or excipient in dosage forms.

7. Modification Of Cassava Starch And Its Application In Novel Microparticulate And Nanoparticulate Drug Delivery
The starch modification associates the transformation of physicochemical properties of the native form to upgrade its functional properties and also to stabilize the starch granules during processing. Several methods including chemical, physical, enzymatical, genetical modifications have been implemented to facilitate its utilization for different purposes such as tablet excipients, drug carriers, wound dressing materials, transdermal patches and scaffolds [111, 112]. The chemical modifications basically imply the introduction of various functional groups to the structure of starch via esterification, etherification, crosslinking, oxidation and so on, while physical modifications conferred by physical reinforcement of starch molecules under different hydrothermal conditions, pressure, shear, micronization, irradiation and electric fields without the presence of any chemical or biological reagents [113, 114]. In contrast to enzymatical modification, suspension of starch is reacted with diverse enzymes mostly hydrolyzing enzymes which directly attack the amorphous regions and produce highly functional derivatives, while in the case of genetical modification, enzymes accountable for starch biosynthesis are genetically modified either by introducing new enzymes from other microorganisms or silencing the plant RNA [115, 116]. After the modification of native starch, it has resulted in enhancing the various properties like increased stability, digestibility, cold-water swellability, film formation, emulsifying capacity and finally upgraded the water binding power and gel characteristics due to which its applications in the pharmaceutical field have increased [117]. However, the most widely used modified starch in the pharmaceutical industry is pregelatinized starch, because this modification not only improves the flowability, disintegration and hardness properties but also represents the excellent swelling and wettability in the cold water of the starches and eventually the amount of pregelatinized starch required is much less than conventional starch for the tablet production [118].

In the design of drug carriers, some modified starches are used as excipients for controlling the delivery speed of drug molecules to the desired site because of their low cost, accessibility and good in vivo performance. For example, native starch modified with acetylation was used in the tablet preparation of lamivudine and it was observed that tablets containing a high concentration of acetylated sago starch released the drug in a controlled manner by reducing undesired swelling over time in an aqueous environment and drug release begins when the dissolution media diffuses through the porous matrix [119]. In another study, high-amylose content sodium carboxymethyl starch composites have been developed as excipients for the formulation of tablets with sustained release behavior for the oral delivery of Tramadol HCl. The results revealed that tablets containing modified starch sustained the Tramadol HCl release by preventing undesired disintegration of the tablets in the gastrointestinal tract with consequent dose dumping [120]. Some researchers have also designed two-release rate (2RR) monolithic tablets based on modified calcium carboxymethyl-starch (CaCMS) for controlled delivery of poorly soluble drugs and it was found that CaCMS based tablet formulations exhibited initial fast release of ibuprofen followed by slow release over a period of 12 hours. The reason behind this is that the CaCMS complex possesses a high hydration capacity (mainly favored by the swelling of disintegrant crospovidone) leading to a first release. As it’s 2RR tablets, there must be a partial release and even if there is an outer layer disintegrated, the integrity of the tablets is always maintained and subsequently grants controlled release [121]. Likewise, to improve the mucoadhesive features of native starch, its native structure was
modified by thiol treatment and evaluated as a potential mucoadhesive excipient for the formulations with sustained release behavior. The results indicated that modified starch adhered longest to the goat intestinal mucosa, which might be due to covalent tie-up via disulfide bond construction of the modified starch with the mucus involving thiol exchange reaction and simultaneously sustaining the speed of Irinotecan delivery [122]. Furthermore, nanoparticulate carriers were developed by using novel starch composites or derivatives for topical delivery of flufenamic acid, testosterone, caffeine and obtained results revealed that hydrophobic flufenamic acid and testosterone were released from nanoparticles in a sustained manner without any outburst effect, while the hydrophilic drug caffeine displayed a much immediate release owing to its hydrophilic nature. The release pattern is mainly controlled by the hydrophobic interactions among the encapsulated macromolecule (hydrophobic propyl-starch derivatives) and the nanoparticle matrix and showed a remarkable permeation effect across the barriers of skin [123]. A similar controlled release pattern by polymeric nanoparticles has been formerly investigated by using novel crosslinked reduction-sensitive starch and the results suggested that nanoparticles with disulfide crosslinked starch accelerated the release behavior of 5-aminosalicylic acid in a controlled manner in the existence of reducing agents dithiothreitol due to reductive cleavages of disulfide linkages. Thus, modified starches expand the usefulness of the starches with indigenous form and have provided some outstanding results as matrix-forming excipients for the extended and controlled release dosage forms [124].

Apart from the other starch derivatives from diverse sources, modified cassava starches including acetylated, succinate, phthalate, acetate, phosphate, methacrylate, carboxymethyl and polyacrylic acid blends starch have found great use in the pharmaceutical sectors for the development of various novel and conventional drug delivery vehicles (Fig. 3).

**Space for Fig. 3.**

Cassava starch deserves particular attention because of its purity and lack of no starchy compounds like lipids, proteins and ash as distinguished from other origin starches. The modified versions of cassava starch are not only used as a good matrix for delivery systems but also can protect the bioactive compounds with a short half-life from degradation and carry the drug molecules to the desired site [125–127]. Notably, modified cassava starches allow the incorporation of various specific ligands particularly flavor compounds to obtain inclusion complexes, being a large number of hydroxyl groups present in their polysaccharide backbone and will provide protection during processing and storage since the complexes are resisting at elevated temperatures. Because free flavor compounds are very volatile and susceptible to degradation in the existence of moisture, air, light and high temperatures, hence by using inclusion complexes flavor compounds are suitably released in a controlled manner and eventually imparted light shed to develop a novel carrier for entrapment of flavor compounds in treating cardiovascular, liver and other chronic diseases [128–131]. However, the potential utilization of modified cassava starch in the design of novel drug carriers especially microparticles and nanoparticles, as well as various conventional drug carriers including tablets, buccal films and topical gels are discussed in the below Table 2 and Fig. 4.
### Table 2
Pharmaceutical applications of newly developed modified cassava starches as an excipient.

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<tr>
<th>Sl. No.</th>
<th>Modified Starch</th>
<th>Drug Carriers</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>01.</td>
<td>Pregelatinized cassava starch succinate</td>
<td>Mucoadhesive microspheres</td>
<td>pH-dependent controlled delivery of propranolol HCl [132]</td>
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<tr>
<td>02.</td>
<td>Pregelatinized cassava starch</td>
<td>Floating microspheres</td>
<td>Gastroretention of metronidazole for peptic ulcer [133]</td>
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<tr>
<td>03.</td>
<td>Cassava starch methacrylate</td>
<td>Crosslinked microspheres</td>
<td>Sustained release of curcumin for colonic cancer [134]</td>
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<tr>
<td>04.</td>
<td>Cassava starch acetate</td>
<td>Crosslinked starch-PEG-gelatin nanocomposites</td>
<td>Controlled delivery of cisplatin for solid tumors treatment [135]</td>
</tr>
<tr>
<td>05.</td>
<td>Acetylated cassava starch</td>
<td>Silver-starch nanocomposite</td>
<td>Extended release of Rifampicin for the multi-resistant tuberculosis [136]</td>
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<td>06.</td>
<td>Cassava starch acetate</td>
<td>Starch-polyvinyl alcohol nanocomposites</td>
<td>Controlled and sustained release of paclitaxel for breast cancer treatment [137]</td>
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<tr>
<td>07.</td>
<td>Crosslinked cassava starch acetate</td>
<td>Starch-polyvinyl alcohol-Closite30b nanocomposites</td>
<td>Controlled release of curcumin for cancer treatment [138]</td>
</tr>
<tr>
<td></td>
<td>Halloysite cassava starch</td>
<td>Starch based bio-nanocomposites</td>
<td>Controlled delivery of silver sulfadiazine for wound infections [139]</td>
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<tr>
<td>08.</td>
<td>Hexadecyl cassava starch-grafted PEG</td>
<td>Amphiphilic starch based nanomicelles</td>
<td>Sustained release of curcumin for cancer treatment [140]</td>
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<tr>
<td>09.</td>
<td>Pregelatinized cassava starch phthalate</td>
<td>Mucoadhesive buccal films</td>
<td>Enhanced bioavailability of diltiazem HCl for hypertension [141]</td>
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<tr>
<td>10.</td>
<td>Carboxymethyl cassava starch</td>
<td>Topical gel formulations</td>
<td>Controlled delivery of ibuprofen for inflammatory disease [142]</td>
</tr>
<tr>
<td>11.</td>
<td>Poly(acrylic acid-cassava starch graft</td>
<td>Hydrogels based on starch-nanostructured hybrid systems</td>
<td>Controlled release of cysteamine for microbial and bacterial disease [143]</td>
</tr>
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<td>12.</td>
<td>Octenyl succinate cassava starch</td>
<td>Starch based tablet formulations</td>
<td>Sustained release matrix for theophylline for respiratory diseases [144]</td>
</tr>
<tr>
<td>13.</td>
<td>Pregelatinized cassava starch</td>
<td>Non-effervescent floating mini tablets</td>
<td>Controlled release of ranitidine HCl for acid reflux diseases [145]</td>
</tr>
<tr>
<td>14.</td>
<td>Oxidized konjac glucomannan-cassava starch</td>
<td>Starch based matrix tablet formulations</td>
<td>Sustained release excipient for bovine serum albumin [146]</td>
</tr>
<tr>
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</tr>
<tr>
<td>15.</td>
<td>Pregelatinized cassava starch phosphate esters</td>
<td>Starch based matrix tablet formulations</td>
<td>Controlled delivery of theophylline for respiratory diseases [147]</td>
</tr>
<tr>
<td>16.</td>
<td>Pregelatinized cassava starch</td>
<td>Starch based fast disintegrating tablets</td>
<td>Immediate delivery of famotidine for geriatric and pediatric patients [148]</td>
</tr>
<tr>
<td>17.</td>
<td>Microcrystalline tapioca starch</td>
<td>Starch based directly compressed tablets</td>
<td>Delivery of poorly compressible API ascorbic acid and paracetamol [149]</td>
</tr>
</tbody>
</table>

Apart from the pharmaceutical applications, some modified cassava starch and their derivatives like crosslinked cassava starch phosphate, hydroxypropyl cassava starch, citrate esterified cassava starch, dialdehyde cassava starch, cassava ethyl-O-starch, konjac glucomannan modified cassava starch, crosslinked cassava starch and enzyme hydrolyzed cassava starch has already been used for other industrial purposes including food, dairy beverage, textile, paper, dusting powder, bioplastic composites and agrochemical industries [150–157]. In the food industry modified cassava starch is used as a stabilizer, thickening agent, emulsifier, texturizer, packaging materials and ice cream formulations, while in the textile industry it can be used for sizing, finishing, cloth printing, coating of fabrics [158–165]. Another important purpose of the modified cassava starches is that they can use as coating material, adhesive or binder for paper or non-paper materials in the paper industry as well as the adhesive industry and as an adsorbent for evacuation of dye and heavy metals from water or other materials in chemical and engineering fields [166–169]. Moreover, in abundant industrial applications, there is competition not only among starches from diverse sources but also between starches and other products as a result development of novel materials has continuously grown and allowed the starch industry to persist in its expansion. In view of all these potentialities, it seems obvious that nowadays, practically every industry in existence uses starch and its derivatives in one form or another for precise applications. Hence, the growth of the starch industry in the future appears to be very promising, which can be predicted that new ventures in starch modifications and their diverse applications will endure being of great interest in applied research [170–171].

Space for Fig. 4.

8. Toxicity Assessment Of Modified Cassava Starch And Its Derivatives

Over the last decades, starch modification had a spectacular evolution for providing novel derivatives with a plethora of applications in very diverse fields ranging from biomedical to food or non-food purposes. In parallel to the growth and ever-increasing utilization of modified starches, concerns regarding the safety and toxicity of these starches may have arisen, both during and post-administration. Though at the time of modification, native starch have treated with some chemical or biological agents including acetic anhydride, sodium hypochlorite, sodium trimetaphosphate, ammonium chloride,
monochloroacetic acid, hydrochloric acid, chloropropylene glycol, etc. which are not altogether safe for consumption and may pose some harmful effects on people health [172–178]. However, the risks of prolonged use of these chemically modified starches are still unknown. The safety profile of these modified starches is very crucial for deeply investigated with respect to the toxicological facet. In this regard, the International Toxicological Committee along with the Joint Expert Committee on Food Additives (a combined board of the WHO/FAO) have demanded thorough studies must be performed on laboratory animals with the intent of protecting the consumer’s safety [179]. Few toxicological investigations have been carried out with modified starches and some data suggest a higher prevalence of structural changes in the kidneys and intestines of mice after prolonged use. It has been also found that the long-term studies in rats consuming high dietary levels of some substituted or crosslinked modified starches resulting in the increased incidence of mineral deposits in pelvic region of the kidney along with caecal enlargement [180, 181]. Given the attention of these modified cassava starches and their possible use on a large scale, various form of toxicological studies are essential steps in obtaining information on the safe usage of these biopolymers (Fig. 5).

Space for Fig. 5.

8.1. Acute toxicity

Acute toxicity studies are carried out to determine the temporary side effects of starch derivatives when given in a single or multiple dosages in the course of 24 hours and daily consequently for a total of 14 days. This study solely provides information regarding LD$_{50}$ (intermediate lethal dose), therapeutic index, the safety profile of starch derivatives and safe acute doses for humans [182, 183]. Moreover, the measurement of LD$_{50}$ has now been utilized as a major criterion in assessing acute toxicity and also the initial procedure for basic screening of pharmacological agents as well as excipients mainly starch and polymers for toxicity [184, 185]. Aside from mortality, the other parameters mainly duration or time of onset and length of recovery on survived animals, relative organ weight and hematological parameters are also imperative in the evaluation of acute toxicity. Hence, the results obtained from the acute toxicity study act as a mentor in the selection of doses for the investigation of long-term toxicity and also other investigations that involve the usage of animals [186]. Notably, different methods (Miller and Tainter method, Karber’s method, Lorke’s method, Fixed dose method, Up-/Down method, Acute Toxic Class method) and guidelines (OECD 423 and OECD 425) have been developed and adopted for the testing of acute toxicity [187, 188]. In a study, acute toxicity (oral) of modified cassava starch acetate was performed on thirty male and thirty female rats. Animals were separated into 6 different groups and treatment with single distant doses of cassava starch acetate (dose range 5, 50, 3000, 2000 and finally 5000 mg/kg body weight). After the treatment, all these animals were closely observed for any sign of toxicity for up to 29 days and the found results revealed that rats treated with cassava starch acetate did not exhibit any sign of clinical adverse reactions, abnormality as well as death also. These results may further contribute as a reference safety study which is required for large-scale commercialization of modified cassava starch [189].
8.2. Subchronic toxicity

Subchronic toxicity studies are usually counseled for 3 months (90 days), but may be counseled for up to 12 months (1 year) in single rodent and non-rodent breeds according to OECD guideline 408. During the study period, all these animals are observed for the various pathological conditions that have been linked to behavioral changes and weight variations. Finally, at the end of the experiment, all the animals are killed and the tissues are inflicted to histopathological analysis for observing the gross pathological changes like biochemical and cardiovascular parameters differences. Moreover, the results obtained from this study can help to predict the accurate dosages of the test substance or starch derivatives for future chronic or long-term toxicity studies [190, 191]. In a research investigation, 90 days acute oral toxicity assessments of biodegradable film from acetate cassava starch were investigated in Wister rats (dose range 3, 30, and 300 mg/kg body weight) and results revealed that cassava starch acetate (300 mg/kg body weight) does not cause obvious sign of toxicity as well as relative organ weight and histopathological evaluations did not show much difference in comparison to control group (water), which further indicates the safety of this acetate cassava starch based biofilms. However, further studies in this area are very essential for the exploration of suitable safety efficacy of modified cassava starch [192].

8.3. Chronic toxicity

In general, studies on chronic toxicity are basically performed to describe the profile of test substance or starch derivative in a mammalian breed (especially rodents and non-rodents) for a period of 3 months to 1 year following repeated and prolonged exposure. The results of the chronic toxicity study provide reports on the possible health hazards, interference regarding the long-term effects of test substances in animals, toxicity reversibility, death and also the potential target organ toxicity [193, 194]. It has been also reported that the chronic toxicity study is crucial for new molecular entities (new drug formulations, polymer derivatives, starch derivatives) and should be started when phase II clinical trials illustrate the efficacy of the same. Simultaneously, these studies could be performed with Phase III clinical trials and should be used to reinforce the safety of long-term clinical trials and marketing approval [195]. Though there is no such information has been reported for the modified version of cassava starches in the animal modes, hence the execution of a chronic toxicity study is very much important for further investigating the safety profile of these starches.

8.4. Carcinogenicity

The carcinogenicity study measures the tumorigenic role of various materials like starch derivatives or plant extracts or small molecule pharmaceuticals likely to appear from continuous exposure for a period lasting up to the whole lifetime of the test animals used. Carcinogenicity testing should be carried out only if the information from other origin indicates a propensity for tumor initiation and are typically conducted in mice or rat models. The duration of the study is generally 2 years, however, these studies should be performed if the materials expected for clinical use would be continuous for at least 6 months or more than that [196, 197]. Pharmaceuticals provided intermittently or for a brief period of time, for
example, anesthetics, antibiotics and radio-tagged imaging materials, diagnostic aids do not require carcinogenicity tests unless there is a reason to be concerned. Moreover, finished rodent carcinogenicity testing is not necessary prior to the commencement of a massive clinical study, unless there is a specific consideration for the patient group. For pharmaceuticals that are used to treat fatal or severely disabling disorders, a carcinogenicity test is not required since the market clearance, but tests should be carried out after approval. Although if such material is designed to be provided to people on a long-term basis, a chronic toxicity test (up to 1 year) may be necessary to detect early tumorigenic effects. The new materials or derivatives that show inconclusive results from in vitro analysis and limited in vivo bioassays should be considered for carcinogenicity studies. The carcinogenic potential of modified cassava starches is unexplored because there is no such information available from the earlier chronic toxicity study or the animal models [198, 199].

8.5. Genotoxicity

Genotoxicity testing is intended to identify genetic damages like gene mutations, DNA damage and chromosomal aberration, which may be reflected inheritable or tumorigenic mutation potential of the drug or novel molecular compounds. This study is a crucial part of the preclinical safety assessment of new drugs and is mainly required just before Phase I/II clinical trials [200]. Genetic toxicity testing of chemicals is assessed by various in vitro approaches which provide information regarding the initial genetic toxicity, whilst in vivo approaches are suitable for estimating the secondary genotoxic reactions like oxidative stress and inflammation. There are several technological preferments in and out of the field of genetic toxicology including flow cytometric analysis, 3D culture systems, micronucleus test and high throughput methods of gene expression assay that allowed measuring the diverse parameters or effects on the genome leading to cancer as well as mutation and finally interpreting the genotoxicity test outcomes [201, 202]. However, evaluation of genotoxicity of the modified starch derivatives from other sources (namely oxidized starch, monostarch phosphate, acetylated starch, acetylated distarch phosphate, hydroxypropyl starch, starch sodium octenyl succinate) was evaluated only via in silico study, since no genotoxicity studies were available for these starches as well as modified cassava starches too. The in silico investigations of modified starch substructures revealed no evidence of genotoxicity, hence, these modified starches do not raise concern for genotoxicity [203]. Noteworthy, if there is arising any cause of concern, the genotoxicity study is a crucial step for further safety assessment of modified starches.

9. Recent Patents Issued In The Area Of Cassava Starch Research

Technological innovations at the divergence of information technology, engineering, biotechnology, medicine and pharmaceutical sciences are triggering new routes in research & development (R & D) or commercialization. In this regard, intellectual property right has a very important role both in the economic and social development of mankind. Intellectual property not only gives licensed rights to the inventors and industries but also provides authority and protection to transfer their right to use to other people in a legal way. One system to guarantee intellectual property rights (IPR) is patenting processes
and products [204, 205]. Patents are one of the most significant inventive parameters attempted to devise the intrinsic value of an original invention and encourage creativity [206]. In recent days, patents on starch and starch based materials opens a new route for the development of biocompatible or biodegradable pharmaceutical excipients. According to the statistical data from 2000, the global market consisted of around 48.5 million tons of starch including native as well as modified starch from diverse plant sources. It is not only food for humans but also a renewable and biodegradable polymer with a variety of industrial applications and the total annual income from the starch company is approximated to be €15 billion [207]. The significant role of cassava starch used as a biopolymer in pharmaceutical and other fields have gained much attention due to the increasing number of publications and patents issued every year by the Patent and Trademark Office [208]. The patents relevant to cassava starch stationed inventions applied in drug carriers or as excipients were searched in various databases like google patents and Espacenet. After conducting screening processes, patents stationed on excipients, drug delivery, nanoparticles, microspheres, tablets and topical gels as well as other industrial purposes are included in the patent analysis and summarized in the below Table 3.
Table 3
Recent patents published for the cassava starch based invention (2017–2021).

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Inventors</th>
<th>Title</th>
<th>Patent No. and Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>01.</td>
<td>Lin Rihui &amp; Co-inventor</td>
<td>Preparation method and application of kaempferol starch nanoparticles</td>
<td>CN113577307 (A) &amp; 2021 [209]</td>
</tr>
<tr>
<td>02.</td>
<td>Huang Lijie &amp; Co-inventor</td>
<td>Cassava residue nanocellulose-cassava starch film and preparation method thereof</td>
<td>CN113831563 (A) &amp; 2021 [210]</td>
</tr>
<tr>
<td>03.</td>
<td>Lu Yefei &amp; Co-inventors</td>
<td>Long-term storage and recovering method of cassava crossbred capsules</td>
<td>CN112514751 (A) &amp; 2021 [211]</td>
</tr>
<tr>
<td>04.</td>
<td>Su Shaozhen &amp; Co-inventor</td>
<td>Preparation method of intercalation modified montmorillonite/cassava starch composite film</td>
<td>CN113150393 (A) &amp; 2021 [212]</td>
</tr>
<tr>
<td>05.</td>
<td>Liao Bo</td>
<td>Antiseptic process for preparing cassava starch</td>
<td>CN111205373A (A) &amp; 2020 [213]</td>
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<tr>
<td>06.</td>
<td>Lin Rihui &amp; Co-inventor</td>
<td>Starch nanoparticles with controllable crystallinity as well as preparation method and application thereof</td>
<td>CN112321853 (A) &amp; 2020 [214]</td>
</tr>
<tr>
<td>07.</td>
<td>Li Yilun &amp; Co-inventor</td>
<td>Method for improving viscosity of cassava starch</td>
<td>CN111808205 (A) &amp; 2020 [215]</td>
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<tr>
<td>08.</td>
<td>Ou Wenjun &amp; Co-inventor</td>
<td>Cassava preservative</td>
<td>CN111543476 (A) &amp; 2020 [216]</td>
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<td>09.</td>
<td>Chen Hui</td>
<td>Levonorgestrel tablet and preparation method thereof</td>
<td>CN109276550 (A) &amp; 2019 [217]</td>
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<td>10.</td>
<td>Li Heping</td>
<td>Preparation method for aminated cross-linked AA/MA/EA grafted xanthogenated cassava starch magnetic imprinted microspheres</td>
<td>CN109280187 (A) &amp; 2019 [218]</td>
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<tr>
<td>11.</td>
<td>Luo Mingchang &amp; Co-inventor</td>
<td>Preparation method of oxidized hydroxypropyl starch for pharmaceutical capsules</td>
<td>CN109400726 (A) &amp; 2019 [219]</td>
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<td>12.</td>
<td>Shi Xiaodan &amp; Co-inventor</td>
<td>Method for producing succinic acid-modified cassava starch through ultra-high-pressure microfluidization method</td>
<td>CN109957035 (A) &amp; 2019 [220]</td>
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<tr>
<td>13.</td>
<td>Li Changying</td>
<td>Method for preparing cassava starch microspheres</td>
<td>CN107814880 (A) &amp; 2018 [221]</td>
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<tr>
<td>14.</td>
<td>Ma Xianli &amp; Co-inventor</td>
<td>Preparation method for cassava oxidized starch based adhesive</td>
<td>CN107603513 (A) &amp; 2018 [222]</td>
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<tr>
<td>15.</td>
<td>Li Heping &amp; Co-inventor</td>
<td>Preparation method for magnetic cross-linked AA/AM graft esterified cyanoethyl tapioca starch microspheres</td>
<td>CN107722533 (A) &amp; 2018 [223]</td>
</tr>
<tr>
<td>Sl. No.</td>
<td>Inventors</td>
<td>Title</td>
<td>Patent No. and Year</td>
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<tr>
<td>17.</td>
<td>Swaile Frederick David &amp; Co-inventor</td>
<td>Aerosol composition comprising particulate tapioca starch</td>
<td>JP2017061543 (A) &amp; 2017 [225]</td>
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<tr>
<td>18.</td>
<td>Yin Xiulian &amp; Co-inventor</td>
<td>Method for preparing roxithromycin sustained release tablet through phosphorylated porous cassava starch</td>
<td>CN106727394 (A) &amp; 2017 [226]</td>
</tr>
<tr>
<td>19.</td>
<td>Li Changying</td>
<td>Preparation method of cassava starch microspheres</td>
<td>CN106389345 (A) &amp; 2017 [227]</td>
</tr>
</tbody>
</table>

### 10. Conclusion And Future Directions

Starches from cassava have found a wide array of utilizations in pharmaceutical formulations as a safe excipient. Though, some of its intrinsic physicochemical properties make it less efficient as a multifunctional excipient, which needs a few technical modifications to qualify them as a potential pharmaceutical excipient. A large library of modified cassava starches is currently being developed in the design of drug delivery carriers as they are controlling the delivery speed of drug molecules to the desired site because of relatively low cost, accessibility and good in vivo performance. Various types of modified cassava starches are well documented in the literature for their efficacy in the formulation of microspheres, nanocomposites, tablet formulations, buccal films and topical gels, etc. Despite the promising benefits offered by these modified starches, their safety and toxicity assessment are the major concerns. Few toxicological investigations have already been conducted on the modified starches obtained from cassava and results suggested that modified starch did not show any sign of clinical toxicity which further supports their safe or biocompatible nature. This versatility of modified cassava starches allows its utility in the diverse fields of knowledge and futuristic materials for dosage form designs. Still and all, systematic studies on cassava starches are suggested to obtain more understanding of their properties which will be helpful in their application as pharmaceutical excipients.

### Declarations

#### Authors contributions

Sanjoy Das conceptualized, wrote, contributed, reviewed and edited to all aspects of the article. Bireswar Bhattacharya contributed to the geographical sources of cassava starch. Taison Jamatia, Bibek Sinha and Biplajit Das contributed equally to the physicochemical features of cassava starches as a drug delivery biopolymer. Rishav Mazumder, Ichudaule and Kishan Paul contributed equally to the current usage of cassava starches in conventional drug delivery systems. Ankita Roy and Ankita Choudhury
contributed equally to the limitations of the use of native cassava starch in drug delivery. Pinkan Sadhukhan, Dibyojyoti Sarmah and Dhritiman Bhargab contributed equally to the modification of cassava starch and its application in novel microparticulate and nanoparticulate drug delivery. Bani Kumar Jana, Nayan Ranjan Ghose Bishwas and Dubom Tayeng contributed equally to the toxicity assessment of modified cassava starch and its derivatives. Pradip Kumar Yadav contributed to the recent patents issued in the area of cassava starch research. Sanjoy Das additionally contributed to drawing all the chemical structures by using ChemDraw. Sanjoy Das substantially contributed to drawing and drafting all the figures and tables.

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Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest. All the tables and figures are self-made and original.

References


190. OECD guideline for the testing of chemicals (2018) Repeated dose 90-day oral toxicity study in rodents. Section 4: Test No. 408.


203. EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) (2017) Re-evaluation of oxidised starch (E 1404), monostarch phosphate (E 1410), distarch phosphate (E 1412), phosphated distarch phosphate (E 1413), acetylated distarch phosphate (E 1414), acetylated starch (E 1420), acetylated distarch adipate (E 1422), hydroxypropyl starch (E 1440), hydroxypropyl distarch phosphate (E 1442), starch sodium octenyl succinate (E 1450), acetylated oxidised starch (E 1451) and starch aluminium octenyl succinate (E 1452) as food additives. EFSA J 15:e04911.


Figure 1

Chemical structure of the major molecular components of cassava starch. a Amylose is predominately made up of long linear chains of α-(1→4) glycosidic bonds between two glucose units and has a molecular weight of 105 to 106 Daltons. b Amylopectin consists of α-(1→4) glycosidic bonds between two glucose units in the straight, while α-(1→6) glycosidic bonds at the branching and has a very high molecular weight 107 to 109 Daltons.
Current applications of cassava starches in the design of conventional drug delivery systems. **a** binding agents that draw or hold other components of the formulation together to form a cohesive whole chemically, mechanically or as an adhesive. **b** disintegrating agents that added solid dosage forms to promote rapid disintegration of large components into small particles after administration for promoting dissolution into the gastrointestinal fluid. **c** lubricating agents that added in the tablet and capsules formulations to improve the powder processing properties as well as flowability of blends and aid unit operations. **d** glidants that are added to the powder or granules just before the compression as a result enhance the flowability of tablet granules by reducing the inter-particulate friction, cohesion and surface charge. **e** diluents are acting as filler or inert ingredients in pharmaceutical tablet formulations that can significantly improve the content of uniformity as well as increase the weight of dosage form.
Figure 3

Modification of native cassava starches to new starch derivatives with special attention to structural illustration. **a** acetylated starch generated by treatment of cassava starch with acetic anhydride under alkaline conditions. **b** succinate starch produced by esterified with succinic anhydride in base atmospheres. **c** carboxymethyl starch was developed by etherification of cassava starch with monochloroacetic acid under basic conditions (initially) and neutral conditions (at the end of reaction). **d** methacrylate starch obtained by reacting of cassava starch with glycidyl methacrylate in alkaline environments. **e** phthalate starch developed by esterification of cassava starch with phthalic anhydride under semidry conditions. **f** acetate starch produced by esterification of cassava starch by acetic anhydride in alkaline set-up. **g** phosphate starch synthesized by phosphorylation of cassava starch with sodium monohydrogen phosphate under alkaline conditions (initially) and acidic conditions (after 2 hours). **h** polyacrylic acid-cassava starch blend prepared from cassava starch and polyacrylic acid by esterification reaction. This structural representation of modified cassava starches is provided here according to the information mentioned in the Table No. 2.
Figure 4

Potential applications of modified cassava starches. a acetylated starch. b succinate starch. c carboxymethyl starch. d methacrylate starch. e phthalate starch. f acetate starch. g phosphate starch. h polyacrylic acid-starch blend are utilized in the design of: i novel drug carriers including nanomaterial (Crosslinked starch-PEG-gelatin nanocomposites, Silver-starch nanocomposite, nanomicelles, bio-nanocomposites, Starch-PVA nanocomposites, starch-PVA-Closite30b nanocomposites, nanostructured hybrid systems) and microsphere (floating, crosslink and mucoadhesive microspheres). j conventional drug carriers namely tablet (Non-effervescent floating mini tablets, matrix tablets, compressed tablets and fast disintegrating tablets); buccal film (mucoadhesive buccal films) and topical gel formulation (hydrogels).
Figure 5

Toxicity screening methods of modified cassava starch and its derivatives as excipients for pharmaceutical formulations. **a** represent the toxicity sign and to confirm whether the materials are toxic or safe, for that various screening procedure are performed which include acute, subchronic, chronic, carcinogenicity and genotoxicity study as per the OECD guidelines. **b** provides the preliminary information on toxic properties of starch moieties which include the possible target organ toxicity, acute adverse reactions and dissimilarities in animals growth behavior. **c** provides the information on the gross pathological changes like biochemical and cardiovascular parameters differences linked to earlier acute toxicity study (short-term toxicity, 90 days); the potential health hazards, interference regarding the long-term effects of test substances in animals, death, toxicity reversibility linked to earlier subchronic toxicity study (long term, 12 months) and tumorigenic potential of starch derivatives likely to arise from repeated exposure over a period of 6 to 24 months. These carcinogenic assays are usually performed just before a compound can be marketed or if the any compound that show inconclusive results in an earlier toxicity study. **d** modified starch derivatives are mixed with the bacterial strains as well as mutagenic material and directly transfer to the media with histidine containing Petri plate and incubate it. After the incubation period, if the compound is mutagenic, colonies are formed and nucleus aberrations is detected or subsequently evaluate the presence and extent of chromosomal damage. Similarly, one control group was prepared and the test was carried out similar way without mixing of any mutagenic materials resulting in very less or no colonies are formed. Hence, if the test compounds are not mutagenic then number of colonies on test plate is equal to the number of colonies on the control plate. **e** in silico computational approaches for predicting genotoxicity based on chemical structures, properties, diverse
datasets and QSAR prediction methodologies that are recognized as an alternative cost-effective toxicity estimation tools.

**Supplementary Files**

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