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# Advances of cassava starch-based composites in novel and conventional drug delivery systems: a state-of-the-art review

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Starch has emerged as a new attractive biopolymer for use in pharmaceutical applications, owing to its distinctive physical, chemical and functional properties. This biopolymer has several potential advantages: it is biocompatible, low cost, non-toxic and easily isolated from plant sources. In the pharmaceutical field, starch is used as a raw material for developing various drug delivery platforms. Generally, cassava starch (tapioca) is obtained from the 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 a low gelatinization temperature, higher swelling power and a relatively high viscosity paste, making it a preferable excipient for pharmaceutical applications. However, cassava starches in their native form are not effective for many applications because of their inefficiency in handling various processing requirements like high temperature and diverse pH. Their applicability can be enhanced by starch modification. These functional starches have demonstrated outstanding prospects as primary excipients in many 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.

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## 1. Introduction

Biopolymers play a very significant role 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, overcoming the limitations of synthetic or conventional polymers.[1] The main reason that biopolymers have gained much popularity is that they are plentiful in nature, biodegradable and cheap, easily modifying drugs that have unfavorable pharmacokinetics and instability. They 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, owing to its thickening, adhesive, film-forming, gelling, and swelling properties, and its biodegradability, biocompatibility and non-toxicity. It is one of the most easily available polymers, and can be obtained from various sources such as rice, potato, corn, sago, banana, wheat, taro, yam, and starchy tubers or root vegetables like cassava (Table 1).[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 edible nature. Its tuberous roots are an excellent source of starch.[5] Starch derived from cassava contains a low amount of amylose (0% in

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Table 1 Various types of starch and their pharmaceutical and biomedical applications

| Sl. no. | Starch | Sources | Applications | Ref. |
|---|---|---|---|---|
| 01. | Potato starch | Root tubers of potato (*Solanum tuberosum*) | Gold nanoparticles for ovarian cancer | 16 and 17 |
| 02. | Rice starch | Endosperm of rice (*Oryza sativa* L.) | Thin films for buccal drug delivery | 18 and 19 |
| 03. | Wheat starch | Endosperm of wheat (*Triticum aestivum*) | Disintegrant in metronidazole tablet formulations | 20 and 21 |
| 05. | Corn or maize starch | Grains of corn (*Zea mays* L.) | Thermoplastic starch films for chlorhexidine delivery | 22 and 23 |
| 06. | Yellow nut-grass starch | Tubers of yellow nut-grass (*Cyperus esculentus* L.) | Binder for the formulation of metronidazole tablets | 24 and 25 |
| 07. | Sago starch | Stem of sago palm (*Metroxylon* spp.) | Excipient for direct compression tablets | 26 and 27 |
| 08. | Banana starch | Pulp of green banana (*Musa paradisiaca*) | Nanoparticles for controlled delivery of curcumin | 27 and 28 |
| 09. | Amaranth starch | Dried seeds of amaranth (*Amaranthus cruentus* L.) | Natural nano starch for medical and chemical industries | 29 and 30 |
| 10. | Taro starch | Tubers of taro (*Colocasia esculenta* (L.) Schott) | Filler for Thiamine Hydrochloride Tablet | 31 and 32 |
| 11. | Yam starch | Tubers of yam (*Dioscorea esculenta*) | Disintegrants for paracetamol tablet formulations | 33 and 34 |

waxy cassava starch) or a high amount of amylose (above 30% in self-pollinated progenies of AMYCS-3 and AMYCS-4) as compared with other types of starch. This low amount of amylose provides starch with various prime benefits including low gelatinization temperature, low retrogradation rates, and higher swelling rate, and produces comparatively high-viscosity paste, making it a preferable excipient for pharmaceutical applications.[6–9] In addition, starches with a large 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 the application of cassava starch due to its poor ability to withstand various processing requirements, such as its swollen nature and thermal resistance, gelatinized granules that cannot retain a granular structure, and the fact that it can collapse 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 low concentrations, low process tolerance and strongly hydrophilic nature.[11,12] These deficiencies may be improved *via* various modification techniques or by combining starches with other functional compounds. The techniques for native starch modifications have been generally divided into four categories, *i.e.*, physical, chemical, enzymatic and genetic modifications. These techniques produce various novel starch moieties with improved physicochemical or functional properties, and also offer 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). These modified starches are used as an excipient or matrix for drug delivery systems, for example, 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, excipient functionalities and proper toxicity assessment are still needed. This article methodically highlights the physicochemical properties, geographical sources, and potential applications of native and modified cassava starches as a material choice in the biomedical or pharmaceutical fields along with the toxicity assessment of modified cassava starches for the first time.

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## 2. Methodology for data extraction

Considering the significance of this study, a thorough literature survey was conducted through online databases such as PubMed, SpringerLink, Science Direct, Scopus, Google Scholar and Research Gate. The title and abstract of articles were searched from the previously mentioned databases by using the corresponding keywords, *i.e.*, starch, cassava, biopolymer, excipient, starch modification, drug delivery platforms and toxicity assessment of modified starch, to understand the recent trends of native and modified cassava starch-based materials 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 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 staple food by over 800 million people (Food and Agriculture Organization, United Nations), its geographical origins have remained controversial.[35–37] Apart from the commonly known *Manihot esculenta*, which is the widely 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*). These species are widely grown over the neotropics, *viz.*, Peru, Venezuela, Guyana, Brazil, Bolivia and Surinam.[38] Although cassava was predominantly cultivated in parts of South America, later sailors and explorers recognized its potential as a multipurpose plant. Eventually, with the advancement of agricultural technologies and better communication, cassava cultivation spread from the American neotropics to the Asian countries as well. As per the Food and Agriculture Organization Corporate Statistical (FAOSTAT) 2015 reports, world cassava production increased to >263 million tons in 2013, a 27% increase in production during the last 10 years. Of this, Africa contributed 54.8% (144.2 million), Asia 33.5% (88.2 million tons) and the Americas 11.6% (30.5 million tons). Thirty countries, which include 18 African, 4 Latin American and 8 Asian, were the major cassava growers around the globe.[39,40] Furthermore, in 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; Thailand, Vietnam and Cambodia stand to be the largest exporters of cassava starch and flour. Furthermore, China, Japan and Indonesia vie for the place of largest importers of cassava flour and starches.[41] Cassava production has shown steady growth for the last six decades from 1961 to 2017 (Fig. 1).

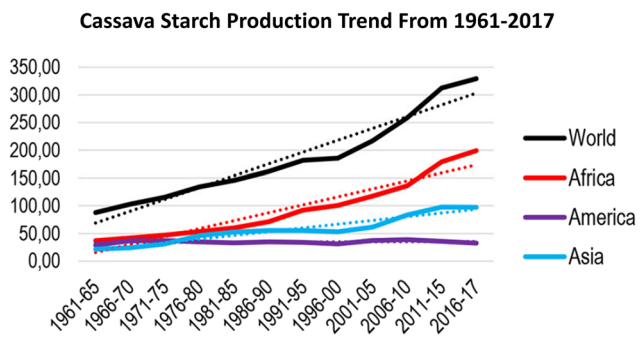


**Fig. 1** Graphical representation of worldwide cassava production. The most dramatic production increase in Africa and Asia is seen from 1996 to 2017, while Latin America showed more restrained increases. Adapted from open access article under Creative Commons license: Amelework *et al.*, 2021.[43]

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, more than in any other country. Hence, a high yield of cassava is very much essential for these regions. 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. Also, forests and other natural biospheres are destroyed and replaced by cassava farms. The dual aims of raising food production and minimizing environmental conflicts have led to calls for the "ecological intensification" or "sustainable intensification" of food production using "good agricultural practices".[42] To support the use of best agricultural practices, a systematic map of studies about cassava farming is urgently needed.

## 4. Physicochemical properties 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 crucial factors of starch quality. This can provide a basis for the processing and usage of starch.

### 4.1. Organoleptic and structural properties

Organoleptic features are important aspects of cassava starch as experienced using parameters including color, odor, taste and surface texture.[44,45] These properties are summarized in Table 2.

Like other types of starch, cassava starch contains two major molecular components, amylose and amylopectin (Fig. 2). Amylose is essentially linear, formed by units of D-glucose linked in an α-(1 → 4) manner, while amylopectin is highly branched, wherein the D-glycosidic α-(1 → 6) linkages are responsible for branching points.[46] 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.[47,48] Compared with other starches like corn, rice, potato and wheat starches, there is a significant variation

**Table 2** Organoleptic properties of cassava starch

| Sl. no. | Parameters | Observation |
|---|---|---|
| 01. | Color | White |
| 02. | Odor | Odorless |
| 03. | Taste | Tasteless |
| 04. | Texture | Homogeneous |

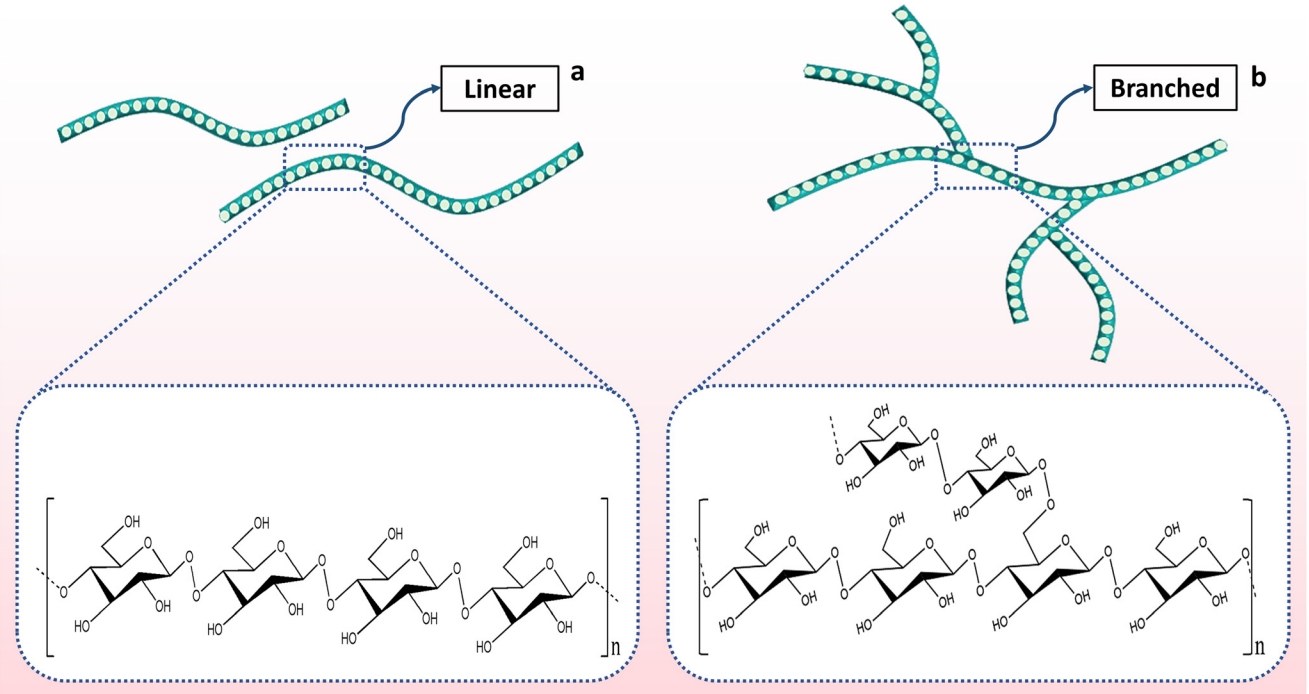


Fig. 2 Chemical structure of the major molecular components of cassava starch. (a) Amylose is predominately made up of long linear chains of α-(1 → 4) glycosidic bonds between two glucose units and has a molecular weight of $10^5$ to $10^6$ Daltons. (b) Amylopectin consists of α-(1 → 4) glycosidic bonds between two glucose units in the straight and α-(1 → 6) glycosidic bonds at the branches, and has a very high molecular weight of $10^7$ to $10^9$ Daltons.

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.[49] In the case of amylopectin, the distribution of branch chain diameter gives an indication of swelling power, pasting viscosity and solubility. Thus, it is frequently crucial to measure the concentration of each starch component as well as the overall starch concentration.[50]

### 4.2. Crystalline properties

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 is mainly represented by amylose molecules.[51,52] The structural crystallinity of starches is identified as type A (Bragg angle 2$\theta$ at about 15.3°; 17.1°; 18.2°; and 23.5°), type B (Bragg angle 2$\theta$ at about 5.6°; 14.4°; 17.2°; 22.2°; and 24.0°) and type C (Bragg angle 2$\theta$ at approximately 5.6°; 15.3°; 17.3°; and 23.5°) using X-ray Diffraction (XRD) analysis.[53] Cassava starches showed prominent peaks (2$\theta$) at 15.2°, 23.4°, and a doublet at 17.2° and 18.2°, which corresponds to the A-type crystallinity (Fig. 3). Moreover, relative crystallinity ranged from 36.1 to 41.4%, which is similar to, but slightly higher than the values reported for Thai cassava, which averaged 35.8%. These crystallinity variations within cassava starch may be due to the amount of water or moisture content in the starch samples.[54,55]

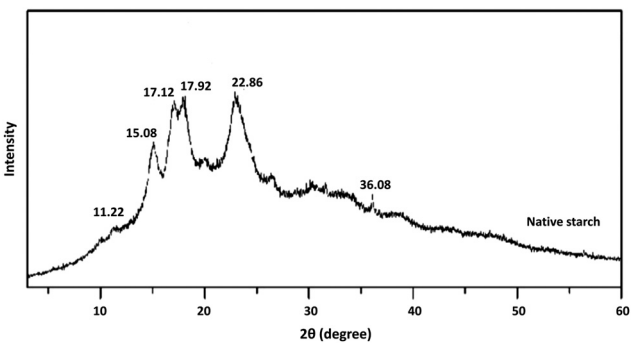


Fig. 3 X-Ray diffraction pattern of native cassava starch. Native cassava starch exhibits three strong diffraction peaks (2$\theta$) at 15.08°, 17.92°, and 22.86°, which indicates a type A crystalline structure. Adapted from open access article under Creative Commons license: Yi *et al.*, 2020.[56]

### 4.3. Swelling and solubility properties

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 rises, the bonds among the glucan chain relax and the granules absorb water and swell.[57,58] 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.[59] Cassava and potato starches had elevated and

lowered swelling capacity and solubility. The elevated swelling capacity and solubility of cassava starch are possibly due to a higher content of amylopectin in comparison with potato flour.[60] However, the existence of non-starch constituents (lipids and proteins) in the starch reservoir is one of the most important aspects, harming swelling power and solubility. Since cassava starch granules contain lower amounts of lipids and protein compared with other forms of starch, this may account for their higher swelling and solubility properties.[61,62]

### 4.4. Gelatinization and pasting properties

Starch is practically insoluble in cold water; however, upon heating, the amylopectin structure of starch is 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.[63,64] Gelatinization processes are characterized by the onset temperatures ($T_O$), peak temperatures ($T_P$), conclusion temperature ($T_C$) and enthalpies ($\Delta H_{gel}$) of the phase transitions, which vary between the starches from different sources.[65] The earlier investigation reported that potato starches exhibited lower $T_P$ (64 °C), while cassava starches exhibited higher $T_P$ (71 °C), respectively. However, the $T_O$ for the two starches are nearly identical and the range of gelatinization for the cassava starch is 9 °C wider as compared with the potato starch.[66] The variations in amylose concentration, length of amylopectin chain, non-starch content and degree of crystallinity may be responsible for the differences in gelatinization between different starches.[67–69] 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 explanation revealed that cassava starches are more stable than other types of starch, such as potato starch.[70]

Pasting usually occurs after gelatinization, resulting in the formation of amylose-amylopectin paste and a gel-like 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.[71] Peak viscosity provides information on the starch's ability to bind water, and trough viscosity represents the lowest value of viscosity. The final viscosity gives an indication of the capacity of the starch to form a viscous paste or gel after cooking and cooling, while breakdown viscosity provides information regarding the rupturing of starch granules, and finally, setback viscosity is the indicator for the starch retrogradation during storage.[72–74] 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 high, due to the presence of an elevated amount of proteins or lipids and the subsequent formation of lipid–amylose complexes.[75,76] Cassava starches with low pasting temperatures easily form a paste, which is an advantage for food or non-food industrial processes. This is also beneficial in the case of energy cost reductions during starch production as well as the minimum temperature required to cook the cassava starch sample. However, several factors affect the cassava starch pasting behavior, including amylose/amylopectin content and the proportion of ingredients in their matrices.[77]

### 4.5. Retrogradation and morphological properties

Retrogradation of starches is a phenomenon that occurs in gelatinized starch as it moves from an initial amorphous form to a crystalline state, resulting in the loss of its ability to hold water.[78] This process is usually accelerated by a series of physical factors, such as increasing concentration of starch in the paste, amylose content and amylopectin chain length, viscosity of starch paste, degree of crystallinity and finally freeze-storage of starch paste.[79,80] During the retrogradation process, the two main components of starch, *i.e.*, amylose and amylopectin, show various functions. The initial hardness of the gel is primarily determined by the re-association of amylose, while retrogradation and long-term gelling capacity are usually influenced by the re-crystallization of amylopectin.[81] Moreover, retrograded starch paste displays lower glass transition temperatures ($T_g$) and enthalpy than the native starch granules. After the modification of native starch, the $T_g$ 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.[82,83] Gomand *et al.* evaluated the retrogradation properties of cassava starch pastes and reported that cassava starches showed a much lower enthalpy of retrogradation and almost none compared with potato, amylose-free and high-amylose starches.[84] Retrogradation is mainly influenced by low temperature, the presence of non-starch components, and polar substances like lipids, proteins, acids and salts. Cassava starches contain very low amounts of these components and significantly exhibit very low retrogradation, high peak viscosity and produce very stable and transparent gels.[85–87]

The morphology of starch moieties depends 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. The average diameter or shape of the starch granule varies from 1–100 μm when viewed by scanning electron microscopy (SEM).[88–90] The morphological features of cassava starches were stated to be ovoid, polygonal and round granules with smooth characteristics.[91] SEM analysis revealed that the surfaces of the starch granules from corn, rice, wheat, potato and barley appear to be limited polished than cassava starch granules. The variation in the sizes of cassava starch granules was ascribed to differences in the genotype and botanical origin as well as the variety of the crop.[92,93] For instance, Toae *et al.*, characterized the starches from nine Thai non-GM bred waxy cassava varieties developed in Thailand and compared them with native cassava starches. The SEM photographs affirmed that the granular morphologies were fairly

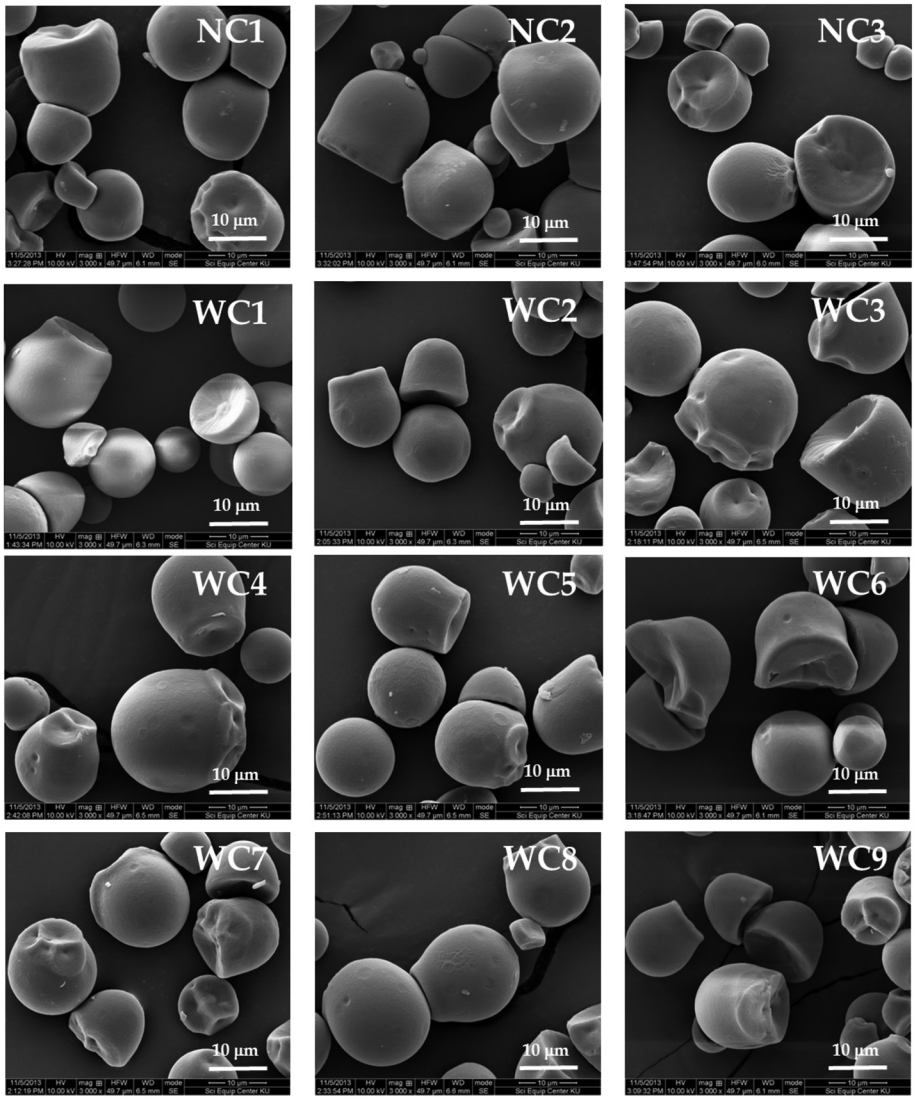


Fig. 4 SEM photographs of Thai non-GM bred waxy cassava starches (WC1–WC9) and wild-type native cassava starches (NC1–NC3). Adapted from open access article under Creative Commons license: Toae *et al.*, 2019.[94]

similar for waxy and native cassava starches (Fig. 4). For waxy cassava starches, the granule sizes ranged from 3–33 μm with an average size of 13.55–16.91 μm, while the sizes of native cassava starch granules were found to be 13.33–14.67 μm.[94]

## 5. Current usage of cassava starches in conventional drug delivery systems

Pharmaceutical excipients are compounds or materials that 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.[95,96] 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 pharmaceutical biopolymer was not extensively performed, although it appears in many standard books.[97,98] 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.[99] Conventionally, native cassava starch can be used as excipients or raw materials in tablet and capsule formulations owing to its distinct physicochemical and functional properties.[100] The potential applications of cassava starches in conventional drug delivery systems are discussed below (Fig. 5).

### 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

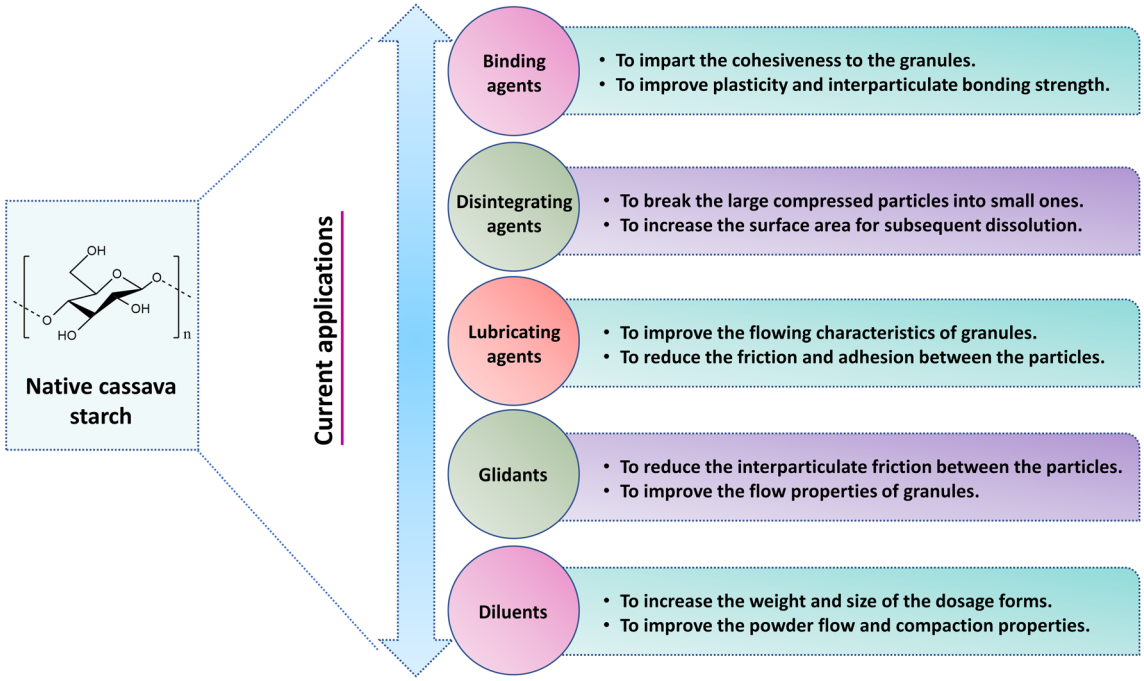


**Fig. 5** Current applications of cassava starches in the design of conventional drug delivery systems like tablets and capsules.

fabrication of solid dosage forms like tablets, capsules and so on. As a binder, the starch is converted to a paste, which is generated by heating the starch, which causes the smaller formulation particles to clump together to create larger-sized agglomerates, resulting in reduced cohesiveness and encouraging flow.[101,102] The amount of a binder can impart a direct effect on tablet characteristics like crushing strength and friability. As the amount of starch in the formulations is increased, the crushing strength is also raised, indicating that the starch excipients facilitate tablet binding. A study reported that cassava starch had higher crushing strength values than corn starch, and this result was directly correlated with the binding effect.[103,104] Moreover, cassava starch has been also discovered to possess stronger binding capability when compared with 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 for use in pharmaceutical formulations.[105]

### 5.2. Disintegrating agents

A disintegrant is an excipient that is added in a pharmaceutical formulation to achieve the breakup of compressed solid dosage forms to small particles when they are in contact with aqueous matter, leading to an increase in surface area for subsequent dissolution.[106] Starch is a cheap and convenient disintegrant that 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 disintegrant in the tablet formulation is 2–10%.[107,108] The literature reports that starches isolated from cassava offer superior disintegrant qualities over maize starch BP. This could be ascribed to the tensile and crushing strength of the tablets containing cassava starch, which decreases with an increase in starch concentration (5–10% w/w), leading to easy disintegration in aqueous medium in less than 15 minutes. Hence cassava starch provides new insight as a potential disintegrant and is used as a substitute for pharmaceutical dosage forms.[109]

### 5.3. Lubricating agents

Lubricants are agents that are mixed into tablet or capsule formulations in a very small quantity (usually 0.25% to 5.0% w/w) to improve the flowing characteristics, for example reducing the adhesion and friction among the particles and walls of the die cavity during compression.[110] In the tablet pelletizing process, starch acts as a lubricant that aids the flow of particles *via* the pelletizing matrix.[111] The role played by cassava starch as a lubricant in tablet formulation is comparable. A study reported that cassava starches showed the lowest 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.[112,113] 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, resulting in more friction to flow. Thus, cassava starch with the lowest cohesiveness would be the starch of choice when fair flowability is desirable.[114]

### 5.4. Glidants

Glidants are inert substances that are combined with tablet formulations to reduce inter-particulate friction. These materials 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 are appropriately incorporated into the mixture. Tropical starches have been widely explored as glidants in many conventional tablet or capsule formulations. As a result, the flow properties of granules at concentrations of 2–10% w/w improved, thus enhancing the fabrication process and outcome.[115,116] The literature reports 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°. The British Pharmacopoeia classifies powder flow as 'excellent' (HR: 1.00–1.11 and AoR: 25–30°), and 'poor' (HR: 1.35–1.45 and AoR: 46–55°). Generally, AoR values below about 30 are considered to be appropriate for solid dosage forms. Observed AoR values for cassava starch are very similar to the official values suggested in the literature. Hence, these results illustrated that cassava starches may be suitable as an alternative glidant in the field of pharmaceutical formulations.[117–119]

### 5.5. Diluents

Diluents are chemically inactive substances or inert materials that act as fillers in the fabrication of solid dosage forms like tablets or capsules.[120] The diluent solubility in a formulation has been shown to affect the mechanism and rate of tablet disintegration. The main purpose of diluents in pharmaceutical formulations is that some drugs are used at very low dosages, thus making it very difficult to process them. In such circumstances, inert ingredients that do not have a therapeutic drug 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 inert, odorless and digestible nature.[121,122] 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 like Avicel PH 101/PH 102 which promotes rapid wetting. As a result, this produces robust granules for fast-disintegrating tablets. Cassava starch co-processed with Avicel PH 101 improves the diluent effectiveness of starches for direct compression tablets with better flowability, friability, disintegration time and tablet uniformity. In this regard, modified cassava starch is offered as a good diluent for producing quick-dissolving tablets with adequate hardness.[123,124]

## 6. Limitations of the use of native cassava starches 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.[125,126] However, cassava starch in its indigenous form has certain drawbacks like hydrophilic nature, high viscosity and propensity to retrogradation even at minimum concentrations. Other drawbacks like brittleness, thermal instability, poor freeze–thaw stability, gel opacity and low process tolerance prohibit its utilization in various dosage forms.[127] The application of native starch as an excipient in the extended or sustained release dosage form is restricted because of its poor compactibility resulting in the production of weak tablets. Sustained-release tablets or capsules comprising native starches are almost completely broken down by the pancreatic enzymes after oral ingestion. This leads to subsequent absorption from the small intestine, and thus fails to release drug over a prolonged period.[128,129] Also, native starches exhibited higher swelling behavior (42.6 g $g^{-1}$) and solubility (25.4 g $g^{-1}$) over water at 90 °C. This is ascribed to 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 cassava starches showed low thermal transition temperature. Furthermore, native starches offer less structural stability and thermal instability, making the granule more liable to gelatinization. Native cassava starch also exhibited noticeable increases in viscosity followed by considerable paste thinning.[130] Apart from this, 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 limit their use in the formulation of direct compaction or compression tablets.[131,132] These are all major constraints of native cassava starch which can be overcome by starch modification, expanding the utilization of cassava starches as an excipient in pharmaceutical dosage forms.

## 7. Modification of cassava starch and its application in novel microparticulate and nanoparticulate drug delivery

Starch modification means the transformation of the physicochemical properties of the native form to improve its functional properties. This modification stabilizes the starch granules during processing. Several methods including chemical, physical, enzymatic and genetic modifications have been implemented to facilitate its utilization for different purposes

such as tablet excipients, drug carriers, wound dressing materials, transdermal patches and scaffolds.[133,134] The chemical modifications imply the introduction of various functional groups to the structure of starch *via* esterification, etherification, crosslinking, oxidation and so on. Physical modifications are 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.[135,136] In contrast, in enzymatic modification the suspension of starch is reacted with diverse enzymes, mainly hydrolyzing enzymes, which directly attack the amorphous regions and produce highly functional derivatives. In genetic modification, enzymes accountable for starch biosynthesis are genetically modified either by introducing new enzymes from other microorganisms or by silencing the plant RNA.[137,138] After the modification of native starch, various properties like stability, digestibility, cold-water swellability, film formation, and emulsifying capacity are significantly enhanced. This modification also improves the water binding power and gel characteristics; as a result, its applications in the pharmaceutical field have increased.[139] Notably, the most widely used modified starch in the pharmaceutical industry is pregelatinized starch. This modification not only improves the flowability, disintegration and hardness properties, but also provides excellent swelling and wettability in the cold water. Eventually, the amount of pregelatinized starch required is much less than conventional starch for tablet production.[140]

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 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 which acting as hydrophobic inert matrix former in the formulation of tablets. This modified 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.[141] 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.[142] Researchers have also designed two-release rate (2RR) monolithic tablets based on modified calcium carboxymethyl-starch (CaCMS) for controlled delivery of poorly soluble drugs. Their findings suggested that CaCMS-based tablet formulations exhibited an initial fast release of ibuprofen followed by a slow release over a period of 12 hours. This is because the CaCMS complex possesses a high hydration capacity (mainly favored by the swelling of disintegrant crospovidone) leading to a first release. As it is a 2RR tablet, there must be a partial release and even if there is an outer layer that disintegrates, the integrity of the tablets is always maintained and subsequently grants controlled release.[143] 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 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.[144] Furthermore, nanoparticulate carriers were developed by using novel starch composites for topical delivery of flufenamic acid, testosterone and caffeine. 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 more immediate release owing to its hydrophilic nature. The release pattern is mainly controlled by the hydrophobic interactions among the encapsulated macromolecules (hydrophobic propyl-starch derivatives) and the nanoparticle matrix, which showed a remarkable permeation effect across the barriers of skin.[145] A similar controlled-release pattern by polymeric nanoparticles has been formerly investigated by using novel crosslinked reduction-sensitive starch. The results suggested that nanoparticles with disulfide crosslinked starch accelerated the release behavior of 5-aminosalicylic acid in a controlled manner in the presence of reducing agent 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 extended and controlled-release dosage forms.[146] As discussed above, both native and modified cassava starches have been investigated as special carriers for delivering water-soluble and poorly water-soluble drugs. This supportive information shows the feasibility of cassava starches for delivering other active pharmaceutical ingredients, and is discussed in below Table 3.

Apart from the other starch derivatives from diverse sources, modified cassava starches have found great use in the pharmaceutical sectors for the development of various novel and conventional drug delivery vehicles. The modified cassava starches are discussed below and their structural framework is depicted in Fig. 6.

- Acetylated starch was generated by treatment of cassava starch with acetic anhydride under alkaline conditions (a).
- Succinate cassava starch was produced by esterification with succinic anhydride in base atmospheres (b).
- Carboxymethyl starch was developed by etherification of cassava starch with monochloroacetic acid under basic conditions at the start and neutral conditions at the end of the reaction (c).
- Methacrylate cassava starch was obtained by reacting cassava starch with glycidyl methacrylate in alkaline environments (d).

Table 3 Potential of native and modified cassava starch-based formulations for drug delivery

| Sl. no. | Drug name | Applicability for drug delivery system combined with native and modified cassava starches | | Ref. |
|---|---|---|---|---|
| | | Yes | No | |
| 01. | Buprenorphine hydrochloride | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 147 |
| 02. | Nilotinib hydrochloride monohydrate | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 148 |
| 03. | Fexofenadine hydrochloride | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 149 |
| 04. | Hydroxychloroquine sulfate | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 150 |
| 05. | Ibrutinib | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 151 |
| 06. | Riluzole | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 152 |
| 07. | Palbociclib | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 153 |
| 08. | Rivaroxaban | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 154 |
| 09. | Crizotinib | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 155 |
| 10. | Prazosin hydrochloride | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 156 |
| 11. | Pazopanib hydrochloride | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 157 |
| 12. | Metoclopramide hydrochloride | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 158 |
| 13. | Empagliflozin | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 159 |
| 14. | Pantoprazole sodium sesquihydrate | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 160 |
| 15. | Teriflunomide | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 161 |
| 16. | Pholcodine | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 162 |
| 17. | Dasatinib monohydrate | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 163 |
| 18. | Clemastine fumarate | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 164 |
| 19. | Sulfabenzamide | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 165 |
| 20. | Quetiapine hemifumarate | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 166 |
| 21. | Losartan potassium, Cozaar | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 167 |
| 22. | Galantamine | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 168 |
| 23. | Ketoconazole | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 169 |
| 24. | Amlodipine besylate | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 170 |
| 25. | Minoxidil | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 171 |
| 26. | Tamsulosin | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 172 |
| 27. | Triamterene (2,4,7-Triamino-6-phenylpteridine) | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 173 |
| 28. | Sodium valproate | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 174 |
| 29. | Lansoprazole | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 175 |
| 30. | Azathioprine | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 176 |
| 31. | Sorafenib tosylate | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 177 |
| 32. | Sunitinib malate | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 178 |
| 33. | Esomeprazole | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 179 |

Table 3 *(Contd.)*

| Sl. no. | Drug name | Applicability for drug delivery system combined with native and modified cassava starches: Yes | No | Ref. |
|---|---|---|---|---|
| 34. | Repaglinide | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 180 |
| 35. | Oxcarbazepine | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 181 |
| 36. | Sertraline hydrochloride | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 182 |
| 37. | Imatinib mesylate | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 183 |
| 38. | Loratadine | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 184 |
| 39. | Letrozole | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 185 |
| 40. | Ketotifen fumarate | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 186 |
| 41. | Amiodarone hydrochloride | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 187 |
| 42. | Aprepitant | √ (Modified cassava starches had higher water solubility) | × (Native cassava starches had poor water solubility) | 188 |

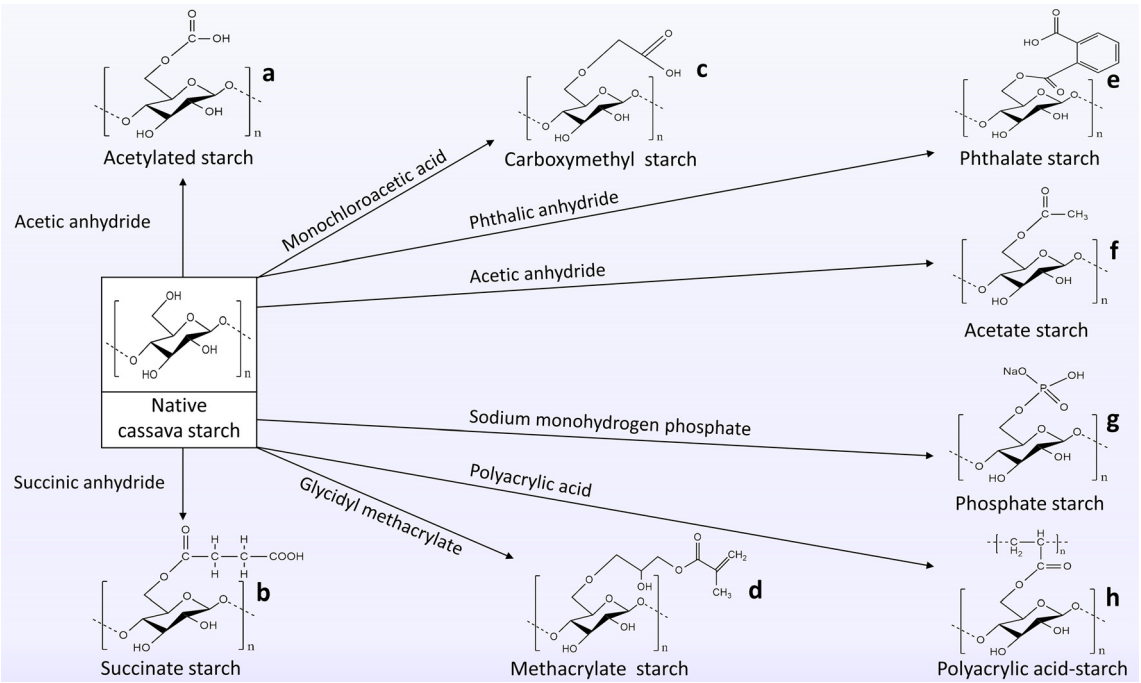


Fig. 6 Modification of native cassava starches to new starch derivatives with special attention to structural illustration. This structural representation of modified cassava starches is provided here according to the information mentioned in Table 4.

• Phthalate cassava starch was developed by esterification of cassava starch with phthalic anhydride under semi-dry conditions (e).

• Acetate cassava starch was produced by esterification of cassava starch by acetic anhydride in an alkaline set-up (f).

• Phosphate cassava starch was synthesized by phosphorylation of cassava starch with sodium monohydrogen phosphate under alkaline conditions initially and acidic conditions after 2 hours (g).

• Polyacrylic acid blends starch was prepared from cassava starch and polyacrylic acid by esterification reaction (i).

Cassava starch deserves particular attention because of its purity and lack of non-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 drug 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.[189–191]

Notably, modified cassava starches allow the incorporation of various specific ligands, particularly flavor compounds, to obtain inclusion complexes. Hydroxyl groups present in their polysaccharide backbone provide protection during processing and storage since the complexes are resistant to elevated temperatures. Free-flavor compounds are very volatile and susceptible to degradation in the presence of moisture, air, light and high temperatures. Hence by using inclusion complexes, flavor compounds can be suitably released in a controlled manner, and are applied to develop a novel carrier for the entrapment of flavor compounds in treating cardiovascular, liver, and other chronic diseases.[192–195] The potential utilization of modified cassava starch in the design of novel drug carriers, especially nanomaterials and microparticles, as well as various conventional drug carriers including tablets, buccal films and topical gels, is discussed in Table 4 and illustrated in Fig. 7.

Apart from the pharmaceutical applications, some modified cassava starches 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 have already been used for other industrial purposes. Application of these modified starches for industrial purposes includes their use in the food, dairy, beverage, textile, paper, dusting powder, bioplastic composites and agrochemical industries.[214–221] In the food industry, modified cassava starch is used as a stabilizer, thickening agent, emulsifier, texturizer, packaging material and in ice cream formulations, while in the textile industry, it can be used for sizing, finishing, cloth printing, and coating of fabrics.[222–229] Another important purpose for modified cassava starches is that they can be used as coating material, adhesive or binder for paper or non-paper constituents in the paper industry and the adhesive industry. Modified starches are also used as an adsorbent material for the evacuation of dye and heavy metals from water or other materials in chemical and engineering fields.[230–233] Moreover, in many industrial applications, there is competition not only among starches from diverse sources but also between starches and other products. As a result, the development of novel materials has continuously grown and allowed the starch industry to continue its expansion. Given all these potentialities, it seems obvious that nowadays practically all industries use starch and its derivatives in single or multiple forms for precise applications. Hence, the growth of the starch industry in the future appears to be very promising, and it can be predicted that new ventures in starch modification and their diverse applications will endure, being of great interest in applied research.[234,235]

**Table 4** Pharmaceutical applications of newly developed modified cassava starch as an excipient

| Sl. no. | Modified starch | Drug carriers | Purpose | Ref. |
|---|---|---|---|---|
| 01. | Pregelatinized cassava starch succinate | Mucoadhesive microspheres | pH-dependent controlled delivery of propranolol HCl | 196 |
| 02. | Pregelatinized cassava starch | Floating microspheres | Gastroretention of metronidazole for peptic ulcer | 197 |
| 03. | Cassava starch methacrylate | Crosslinked microspheres | Sustained release of curcumin for colonic cancer | 198 |
| 04. | Cassava starch acetate | Crosslinked starch-PEG-gelatin nanocomposites | Controlled delivery of cisplatin for solid tumor treatment | 199 |
| 05. | Acetylated cassava starch | Silver-starch nanocomposite | Extended release of Rifampicin for multi-resistant tuberculosis | 200 |
| 06. | Cassava starch acetate | Starch-polyvinyl alcohol nanocomposites | Controlled and sustained release of paclitaxel for breast cancer treatment | 201 |
| 07. | Crosslinked cassava starch acetate | Starch-polyvinyl alcohol-Closite30b nanocomposites | Controlled release of curcumin for cancer treatment | 202 |
| 08. | Halloysite cassava starch | Starch-based bio-nanocomposites | Controlled delivery of silver sulfadiazine for wound infections | 203 |
| 09. | Hexadecyl cassava starch-grafted PEG | Amphiphilic starch-based nanomicelles | Sustained release of curcumin for cancer treatment | 204 |
| 10. | Pregelatinized cassava starch phthalate | Mucoadhesive buccal films | Enhanced bioavailability of diltiazem HCl for hypertension | 205 |
| 11. | Carboxymethyl cassava starch | Topical gel formulations | Controlled delivery of ibuprofen for inflammatory disease | 206 |
| 12. | Poly(acrylic acid)-cassava starch graft | Hydrogels based on starch-nanostructured hybrid systems | Controlled release of cysteamine for microbial and bacterial disease | 207 |
| 13. | Octenyl succinate cassava starch | Starch-based tablet formulations | Sustained release matrix for theophylline for respiratory diseases | 208 |
| 14. | Pregelatinized cassava starch | Non-effervescent floating mini tablets | Controlled release of ranitidine HCl for acid reflux diseases | 209 |
| 15. | Oxidized konjac glucomannan-cassava starch | Starch-based matrix tablet formulations | Sustained release excipient for bovine serum albumin | 210 |
| 16. | Pregelatinized cassava starch phosphate esters | Starch-based matrix tablet formulations | Controlled delivery of theophylline for respiratory diseases | 211 |
| 17. | Pregelatinized cassava starch | Starch-based fast disintegrating tablets | Immediate delivery of famotidine for geriatric and pediatric patients | 212 |
| 18. | Microcrystalline tapioca starch | Starch-based directly compressed tablets | Delivery of poorly compressible API ascorbic acid and paracetamol | 213 |

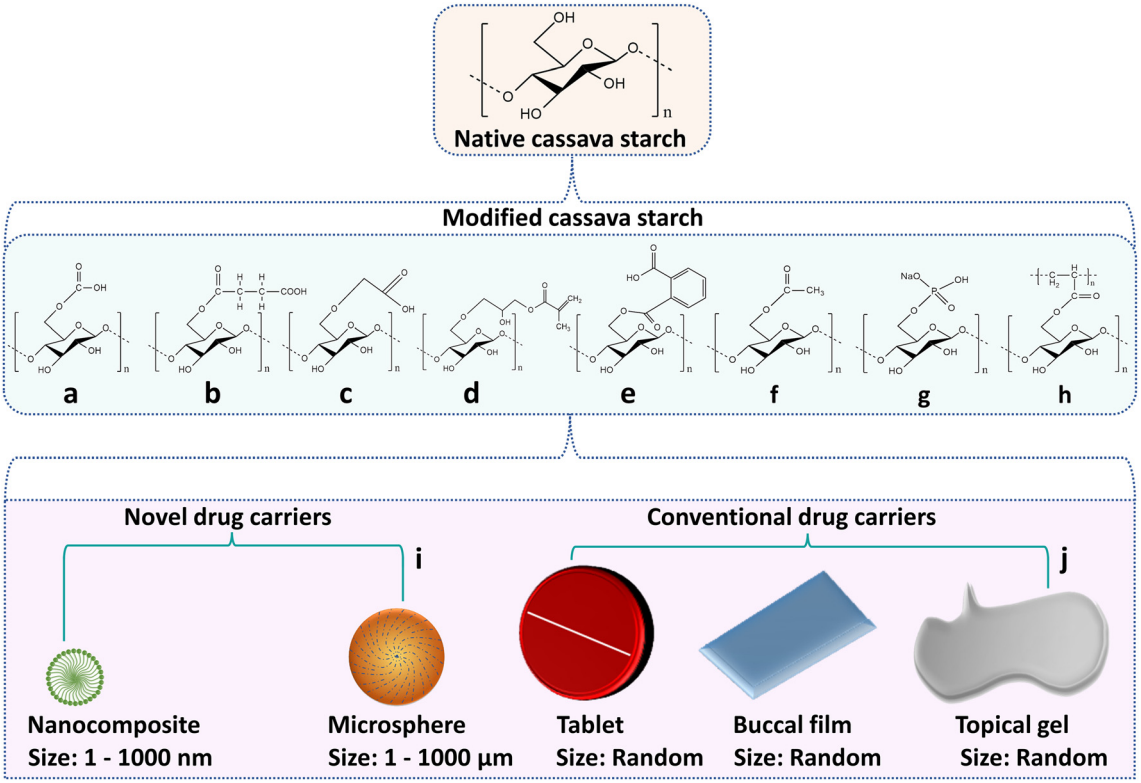


**Fig. 7** Potential applications of modified cassava starches. (a) Acetylated starch. (b) Succinate starch. (c) Carboxymethyl starch. (d) Methacrylate starch. (e) Phthalate starch. (f) Acetate starch. (g) Phosphate starch. (h) Polyacrylic acid-starch blends are utilized in the design of: (i) novel drug carriers and (j) conventional drug carriers.

## 8. Toxicity assessment of modified cassava starch and its derivatives

Over the last decades, starch modification has 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 starches are treated with some chemical or biological agents including acetic anhydride, sodium hypochlorite, sodium trimetaphosphate, ammonium chloride, monochloroacetic acid, hydrochloric acid, chloropropylene glycol, *etc.*, these chemicals are not altogether safe for consumption and may have some harmful effects on human health.[236–242] However, the risks of prolonged use of these chemically modified starches are still unknown. The deep investigation of the safety profile of these modified starches is very crucial concerning 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 that thorough studies must be performed on laboratory animals with the intent of protecting consumer safety.[243] A few toxicological investigations have been carried out with modified starches, and some data have suggested a higher prevalence of structural changes in the kidneys and intestines of mice after prolonged use. It has been also found in long-term studies in rats that consuming high dietary levels of some substituted or crosslinked modified starches resulted in the increased incidence of mineral deposits in the pelvic region of the kidneys along with caecal enlargement.[244,245] Given the interest in these modified cassava starches and their possible use on a large scale, toxicological studies are essential steps in obtaining information on the safe usage of these biopolymers. Various forms of toxicological screening procedure are performed, *viz.*, acute, subchronic, chronic, carcinogenicity and genotoxicity study, as per the Organisation for Economic Co-operation and Development (OECD) guidelines (Fig. 8).

- Acute toxicity study provides preliminary information on the toxic properties of starch moieties which include possible target organ toxicity, acute adverse reactions and dissimilarities in animal growth behavior (a).
- Subchronic toxicity study provides information on gross pathological changes such as differences in biochemical and cardiovascular parameters, linked to earlier acute toxicity studies (short-term toxicity, 90 days) (b).
- Chronic toxicity study provides information on the potential health hazards regarding the long-term effects of test substances in animals, death and toxicity reversibility linked to earlier subchronic toxicity study (long term, 12 months) (b).

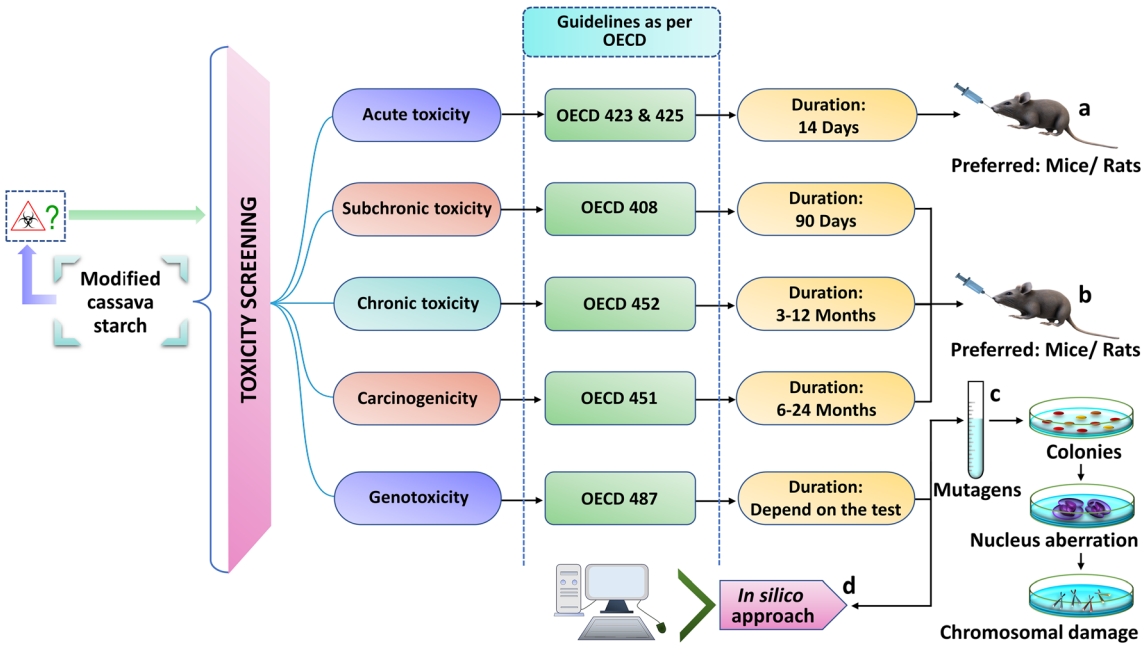


Fig. 8 Toxicity screening methods of modified cassava starch and its derivatives as excipients for pharmaceutical formulations.

• Carcinogenicity testing provides information on the 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 any compound shows inconclusive results in an earlier toxicity study (b).

• Genotoxicity study provides information regarding the mutagenic potential of modified starch. Initially, modified starch derivatives are mixed with bacterial strains as well as mutagenic material and directly transferred to the media with a histidine-containing Petri plate and incubated. After the incubation period, if the compound is mutagenic, colonies are formed and nuclear aberrations are detected. Subsequently, the presence and extent of chromosomal damage is evaluated. Similarly, one control group is prepared and the test carried out in a similar way without mixing any mutagenic materials, resulting in very few or no colonies being formed. Hence, if the test compounds are not mutagenic then the number of colonies on the test plate will be similar to the number of colonies on the control plate (c).

• *In silico* computational approaches predicting genotoxicity based on chemical structures, diverse datasets and quantitative structure–activity relationships (QSAR) prediction methodologies are recognized as alternative cost-effective toxicity estimation tools (d).

### 8.1. Acute toxicity

Acute toxicity studies are carried out to determine the temporary side effects of starch derivatives when given in single or multiple dosages over 24 hours and subsequently daily 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.[246,247] Moreover, the measurement of $LD_{50}$ has now been utilized as a major criterion in assessing acute toxicity and is the initial procedure for basic screening of pharmacological agents as well as excipients, mainly starch and polymers, for toxicity.[248,249] Aside from mortality, other parameters, mainly duration or time of onset, length of recovery of surviving 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 guide in the selection of doses for the investigation of long-term toxicity and also other investigations that involve the usage of animals.[250] 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.[251,252] In a study, assessment of the acute oral toxicity of modified cassava starch acetate was performed on thirty male and thirty female rats. Animals were separated into 6 different groups and treated with single individual doses of cassava starch acetate (dose range 5, 50, 300, 2000 and finally 5000 mg per kg body weight). After the treatment, all these animals were closely observed for any sign of toxicity for up to 29 days. The results revealed that rats treated with cassava starch acetate did not exhibit any sign of clinically adverse reactions, abnormality, or death. These results may further contribute as a reference safety study which is required for the large-scale commercialization of modified cassava starch.[253]

### 8.2. Subchronic toxicity

Subchronic toxicity studies are usually advised for 3 months (90 days), but may be advised to run for up to 12 months in

single rodent and non-rodent breeds according to OECD guideline 408. During the study period, all 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 subjected to histopathological analysis to observe the gross pathological changes like differences in biochemical and cardiovascular parameters. Moreover, the results obtained from this study can help to predict the accurate dosages of the starch derivatives for future chronic or long-term toxicity studies.[254,255] In a research investigation, 90 days of acute oral toxicity assessments of biodegradable film from acetate cassava starch were investigated in Wister rats (dose range 3, 30, and 300 mg per kg body weight). The obtained results revealed that cassava starch acetate (300 mg per kg body weight) does not cause obvious signs of toxicity or changes in relative organ weight. Histopathological evaluations did not show much difference in comparison with the control group (water), which further indicates the safety of these acetate cassava starch-based biofilms. However, further studies in this area are essential for the exploration of suitable safety efficacy of modified cassava starch.[256]

### 8.3. Chronic toxicity

In general, studies on chronic toxicity are performed to describe the profile of starch derivatives 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 information on the possible health hazards regarding the long-term effects of test substances in animals, toxicity reversibility, death and potential target organ toxicity.[257,258] It has also been 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 show 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.[259] However, no such information has been reported for the modified version of cassava starches in animal models, hence the execution of a chronic toxicity study is very important for further investigation of the safety profile of these starches.

### 8.4. Carcinogenicity

The carcinogenicity study measures the tumorigenic role played by various materials such as starch derivatives, 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 information from other origins indicates a propensity for tumor initiation, and is typically conducted in mouse or rat models. The duration of the study is generally 2 years; however, these studies should be performed if the expected clinical use of the materials would be continuous for at least 6 months or more than that.[260,261] Pharmaceuticals provided for a brief period, for example, anesthetics, antibiotics, and radio-tagged imaging materials and diagnostic aids do not require carcinogenicity tests unless there is a reason for concern. Moreover, completion of rodent carcinogenicity testing is not necessary before the commencement of a large 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 before the market clearance, but tests should be carried out after approval. 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. 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 earlier chronic toxicity study or the animal models.[262,263]

### 8.5. Genotoxicity

Genotoxicity testing is intended to identify genetic damage such as gene mutations, DNA damage and chromosomal aberration, which may be reflected in 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.[264] Genetic toxicity testing of chemicals is performed using various *in vitro* approaches which provide information regarding the initial genetic toxicity, and *in vivo* approaches are suitable for estimating secondary genotoxic reactions like oxidative stress and inflammation. There are several technological preferences in and out of the field of genetic toxicology, including flow cytometric analysis, 3D culture systems, micronucleus tests and high-throughput methods of gene expression assay. This technological approach measures the diverse parameters or effects on the genome leading to cancer as well as mutation, and finally interprets the genotoxicity test outcomes.[265,266] 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. No genotoxicity studies were available for these starches or for 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.[267] It should be noted that if there is any cause for 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 intersections of information technology, engineering, biotechnology, medicine and

Table 5 Recent patents published for the cassava starch-based invention (2017–2022)

| Sl. no. | Inventors | Title | Patent no. and year | Ref. |
|---|---|---|---|---|
| 01. | Gao Yuanyuan & Co-inventor | Method for preparing essential oil microcapsules by taking cassava starch alcohol-free esterification mixture as wall material | CN114190507 (A) & 2022 | 273 |
| 02. | Xue Xingyong & Co-inventor | Preparation method and application of phosphoric acid-based geopolymer/starch composite porous microsphere adsorption material | CN114950355 (A) & 2022 | 274 |
| 03. | Hanchett Douglas & Co-inventor | Thermally inhibited waxy cassava starch | AU2022209338 (A1) & 2022 | 275 |
| 04. | Yan Kailiang | Cassava starch residue-liquid separation device | CN217490061 (U) & 2022 | 276 |
| 05. | Lin Rihui & Co-inventor | Preparation method and application of kaempferol starch nanoparticles | CN113577307 (A) & 2021 | 277 |
| 06. | Huang Lijie & Co-inventor | Cassava residue nanocellulose-cassava starch film and preparation method thereof | CN113831563 (A) & 2021 | 278 |
| 07. | Lu Yefei & Co-inventors | Long-term storage and recovering method of cassava crossbred capsules | CN112514751 (A) & 2021 | 279 |
| 08. | Su Shaozhen & Co-inventor | Preparation method of intercalation modified montmorillonite/cassava starch composite film | CN113150393 (A) & 2021 | 280 |
| 09. | Liao Bo | Antiseptic process for preparing cassava starch | CN111205373 (A) & 2020 | 281 |
| 10. | Lin Rihui & Co- inventor | Starch nanoparticles with controllable crystallinity as well as preparation method and application thereof | CN112321853 (A) & 2020 | 282 |
| 11. | Li Yilun & Co-inventor | Method for improving viscosity of cassava starch | CN111808205 (A) & 2020 | 283 |
| 12. | Ou Wenjun & Co-inventor | Cassava preservative | CN111543476 (A) & 2020 | 284 |
| 13. | Chen Hui | Levonorgestrel tablet and preparation method thereof | CN109276550 (A) & 2019 | 285 |
| 14. | Li Heping | Preparation method for aminated cross-linked AA/MA/EA grafted xanthogenated cassava starch magnetic imprinted microspheres | CN109280187 (A) & 2019 | 286 |
| 15. | Luo Mingchang & Co-inventor | Preparation method of oxidized hydroxypropyl starch for pharmaceutical capsules | CN109400726 (A) & 2019 | 287 |
| 16. | Shi Xiaodan & Co-inventor | Method for producing succinic acid-modified cassava starch through ultra-high-pressure microfluidization method | CN109957035 (A) & 2019 | 288 |
| 17. | Li Changying | Method for preparing cassava starch microspheres | CN107814880 (A) & 2018 | 289 |
| 18. | Ma Xianli & Co-inventor | Preparation method for cassava oxidized starch-based adhesive | CN107603513 (A) & 2018 | 290 |
| 19. | Li Heping & Co-inventor | Preparation method for magnetic cross-linked AA/AM graft esterified cyanoethyl tapioca starch microspheres | CN107722533 (A) & 2018 | 291 |
| 20. | Lin Ooi Poh & Co-inventor | Starch extraction | WO2017025482 (A1) & 2018 | 292 |
| 21. | Swaile Frederick David & Co-inventor | Aerosol composition comprising particulate tapioca starch | JP2017061543 (A) & 2017 | 293 |
| 22. | Yin Xiulian & Co-inventor | Method for preparing roxithromycin sustained release tablet through phosphorylated porous cassava starch | CN106727394 (A) & 2017 | 294 |
| 23. | Li Changying | Preparation method of cassava starch microspheres | CN106389345 (A) & 2017 | 295 |
| 24. | Zhifeng Ren & Co-inventor | Method to synthesize graphene-based amphiphilic Janus nanosheets | US20200377675 (A1) & 2017 | 296 |

pharmaceutical sciences are triggering new routes in research & development (R & D) or commercialization. In this regard, intellectual property rights (IPR) play a very important role both in the economic and social development of mankind. Intellectual property not only gives licensed rights to inventors and industries, but also provides authority and protection to transfer their right to use to other people lawfully. One system to guarantee IPR is patenting processes and products.[268,269] Patents are one of the most significant inventive parameters attempted to devise the intrinsic value of an original invention and encourage creativity.[270] In recent times, patents on starch and starch-based materials have opened 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. The total annual income from the starch sector is approximated to be €15 billion.[271] Additionally, the significant role played by cassava starch used as a biopolymer in pharmaceutical and other fields has gained much attention due to the increasing number of publications and patents issued every year by the Patent and Trademark Office.[272] The patents relevant to cassava starch-based inventions applied in drug carriers or as excipients were searched in various databases like Google Patents and Espacenet. After conducting screening processes, patents registered 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 Table 5.

## 10. Conclusions and outlook

Starches from cassava have found a wide array of uses in pharmaceutical formulations as a safe excipient. However, some of their intrinsic physicochemical properties make them less efficient as a multifunctional excipient, and need a few technical modifications to qualify as a potential pharma-

ceutical excipient. A large library of modified cassava starches is currently being developed for the design of drug delivery carriers, as they can control the delivery speed of drug molecules to the desired site with relatively low cost, accessibility and good *in vivo* performance. Various types of modified cassava starch 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. A few toxicological investigations have already been conducted on the modified starches obtained from cassava. The obtained results suggested that the 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 their utility in diverse fields of knowledge and futuristic materials for dosage form design. Finally, systematic studies on cassava starches are suggested to obtain better understanding of their properties, which will be helpful for their timely application as pharmaceutical excipients.

## Authors contribution

S. D. conceptualized, writing-original draft, reviewed and edited to all aspects of the article. M. K. D. reviewed and edited the revised version of the article. T. J., B. B., R. M., P. K. Y., N. R. G. B., T. D., D. R., B. S., B. D., I. D., K. P., A. R., A. C., P. S., D. S., D. B., B. K. J., D. T., N. G., B. K. and S. M. discussed and contributed equally throughout the article. S. D. additionally contributed to drawing all the chemical structures by using ChemDraw. S. D., M. K. D. and S. M. substantially contributed to drawing, visualization and drafting all the figures and tables.

## Conflicts of interest

The authors declare that they have no known conflicts of interest that could have appeared to influence the work reported in this paper. All the tables are self-made and original. Some figures are self-made and original and some are adapted from open-access articles under the Creative Commons license agreement (citation mentioned throughout the figures caption).

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## References

1 S. Gopi, A. Amalraj, N. P. Sukumaran, J. T. Haponiuk and S. Thomas, *Macromol. Symp.*, 2018, **380**, 1800114.
2 E. A. Hassan, J. Bai and D. Dou, *Egypt. J. Chem.*, 2019, **62**, 1725–1737.
3 B. J. Bordoloi, B. Kalita and D. Shil, *Int. J. Curr. Pharm. Res.*, 2019, **11**, 54–59.
4 S. W. Horstmann, K. M. Lynch and E. K. Arendt, *Foods*, 2017, **6**, 29.
5 Y. Yang, X. Luo, W. Wei, Z. Fan, T. Huang and X. Pan, *Sci. Rep.*, 2020, **10**, 14197.
6 S. M. Chisenga, T. S. Workneh, G. Bultosa and A. M. Alimi, *J. Food Sci. Technol.*, 2019, **56**, 2799–2813.
7 A. Rolland-Sabaté, *et al.*, *Food Hydrocolloids*, 2012, **27**, 161–174.
8 A. Rolland-Sabaté, *et al.*, *Carbohydr. Polym.*, 2013, **92**, 1451–1462.
9 A. Karlström, F. Calle, S. Salazar, N. Morante, D. Dufour and H. Ceballos, *Front. Plant Sci.*, 2016, **7**, 604.
10 I. Cornejo-Ramírez, O. Martínez-Cruz, C. L. Del-Toro-Sánchez, F. J. Wong-Corral, J. Borboa-Flores and F. J. Cinco-Moroyoqui, *CyTA – J. Food*, 2018, **16**, 1003–1017.
11 Z. Wang, P. Mhaske, A. Farahnaky, S. Kasapis and M. Majzoobi, *Food Hydrocolloids*, 2022, **129**, 107542.
12 L. D. Pérez-Vergara, M. T. Cifuentes, A. P. Franco, C. Pérez-Cervera and R. Andrade-Pizarro, *NFS J.*, 2020, **21**, 39–49.
13 Ziauddin, H. Xiong and F. Peng, *Crit. Rev. Food Sci. Nutr.*, 2017, **57**, 2691–2705.
14 M. A. V. T. Garcia, C. F. Garcia and A. A. G. Faraco, *Starch/Staerke*, 2020, **72**, 1900270.
15 N. Charoenthai, T. Sanga-Ngam and S. Puttipipatkhachorn, *Pharm. Sci. Asia*, 2018, **45**, 195–204.
16 J. Li, *et al.*, *Inorg. Chem. Commun.*, 2023, **155**, 111002.
17 H. Gujral, *et al.*, *Int. J. Biol. Macromol.*, 2021, **186**, 155–162.
18 S.-Y. Chan, J. Y. Lau, Y. C. Tiew and T. Balakrishnan, *Int. J. Pharm.*, 2019, **562**, 203–211.
19 S. Xing, *et al.*, *PLoS One*, 2016, **11**, e0168467.
20 M. A. Odeniyi and J. O. Ayorinde, *Polim. Med.*, 2014, **44**, 147–155.
21 K.-H. Kim and J.-Y. Kim, *Plants*, 2021, **10**, 2282.
22 V. M. Queiroz, I. C. S. Kling, A. E. Eltom, B. S. Archanjo, M. D. Prado and R. A. Simão, *Mater. Sci. Eng.*, 2020, **112**, 110852.

23 C. P. Palanisamy, B. Cui, Z. Hong-Xia, S. Jayaraman and K. M. Gothandam, *Polymers*, 2020, **12**, 2161.
24 R. V. Manek, P. F. Builders, W. M. Kolling, M. Emeje and O. O. Kunle, *AAPS PharmSciTech*, 2012, **13**, 379–388.
25 R. T. Widodo, A. Hassan, K. B. Liew and L. C. Ming, *Polymers*, 2022, **14**, 3050.
26 C. Du, J. Fan, W. Jiang, W. Ge and S. Du, *Int. J. Biol. Macromol.*, 2020, **164**, 1785–1793.
27 L. Acevedo-Guevara, L. Nieto-Suaza, L. T. Sánchez, M. I. Pinzón and C. C. Villa, *Int. J. Biol. Macromol.*, 2018, **111**, 498–504.
28 H. Marta, Y. Cahyana, M. Djali and G. Pramafisi, *Polymers*, 2022, **14**, 3092.
29 R. Zuo, *et al.*, *Int. J. Biol. Macromol.*, 2024, **260**, 129525.
30 F. Zhu, *Crit. Rev. Food Sci. Nutr.*, 2015, **57**, 313–325.
31 P. M. Lestari, A. Widayanti and H. Afifah, *Open Access Maced. J. Med. Sci.*, 2019, **7**, 3827–3832.
32 N. Sit, S. C. Deka and S. Misra, *J. Food Sci. Technol.*, 2015, **52**, 4324–4332.
33 N. Nattapulwat, N. Purkkao and O. Suwithayapan, *AAPS PharmSciTech*, 2009, **10**, 193–198.
34 O. A. Odeku and B. L. Akinwande, *Saudi Pharm. J.*, 2012, **20**, 171–175.
35 A. M. Fermont, P. J. A. Van Asten, P. Tittonell, M. Van Wijk and K. E. Giller, *Field Crops Res.*, 2009, **112**, 24–36.
36 K. Kawano, in *Hybridization of Crop Plants*, ed. W. R. Fehr and H. H. Hadley, ASA, Madison, 1st edn, 1980, ch. 13, pp. 225–233.
37 S. Latif and J. Müller, *Trends Food Sci. Technol.*, 2015, **44**, 147–158.
38 A. C. Allem, *Genet. Resour. Crop Evol.*, 1994, **41**, 133–150.
39 H. Ceballos, E. Okogbenin, J. C. Pérez, L. A. B. López-Valle and D. Debouck, in *Root and Tuber Crops: Handbook of Plant Breeding*, ed. J. Bradshaw, Springer, New York, 2010, vol. 7, ch. 2, pp. 53–96.
40 P. Chavarriaga-Aguirre, *In Vitro Cell. Dev. Biol.: Plant*, 2016, **52**, 461–478.
41 O. A. Otekunrin and B. Sawicka, *Acta Sci. Agric.*, 2019, **3**, 194–202.
42 G. E. Shackelford, N. R. Haddaway, H. O. Usieta, P. Pypers, S. O. Petrovan and W. J. Sutherland, *Environ. Evid.*, 2018, **7**, 30.
43 A. B. Amelework, M. W. Bairu, O. Maema, S. L. Venter and M. Laing, *Front. Sustain. Food Syst.*, 2021, **5**, 617783.
44 T. A. Dada, L. I. Barber, L. Ngoma and M. Mwanza, *Food Sci. Nutr.*, 2017, **6**, 395–399.
45 A. Edhirej, S. M. Sapuan, M. Jawaid and N. I. Zahari, *Polym. Compos.*, 2018, **39**, 1704–1715.
46 P. Tappiban, D. R. Smith, K. Triwitayakorn and J. Bao, *Trends Food Sci. Technol.*, 2019, **83**, 167–180.
47 A. L. Charles, Y. H. Chang, W. C. Ko, K. Sriroth and T. Huang, *J. Agric. Food Chem.*, 2005, **53**, 2717–2725.
48 D. O. Oni, J. Mwero and C. Kabubo, *Open J. Civ. Eng.*, 2020, **14**, 289–301.
49 F. Zhu, *Carbohydr. Polym.*, 2015, **122**, 456–480.
50 M. Raphael, *et al.*, *J. Plant Breed. Crop Sci.*, 2011, **3**, 195–202.
51 D. Lourdin, J. L. Putaux, G. Potocki-Véronèse, C. Chevigny, A. Rolland-Sabaté and A. Buléon, in *Starch: Metabolism and Structure*, ed. Y. Nakamura, Springer, Tokyo, 1st edn, 2015, ch. 3, pp. 61–90.
52 R. Bajaj, N. Singh, A. Kaur and N. Inouchi, *J. Food Sci. Technol.*, 2018, **55**, 3799–3808.
53 S. M. Chisenga, T. S. Workneh, G. Bultosa and M. Laing, *AIMS Agric. Food*, 2019, **4**, 939–966.
54 N. Morante, *et al.*, *Food Hydrocolloids*, 2016, **56**, 383–395.
55 M. K. Mtunguja, *Starch-Starke*, 2016, **68**, 1–14.
56 T. Yi, *et al.*, *Processes*, 2020, **8**, 329.
57 T. Sasaki and J. Matsuki, *Cereal Chem.*, 1998, **75**, 525–529.
58 L. M. Nwokocha, N. A. Aviara, C. Senan and P. A. Williams, *Carbohydr. Polym.*, 2009, **76**, 362–367.
59 E. Nuwamanya, Y. Baguma, E. Wembabazi and P. Rubaihayo, *Afr. J. Biotechnol.*, 2011, **10**, 12018–12030.
60 H. Kusumayanti, N. A. Handayani and H. P. Santosa, *Procedia Environ. Sci.*, 2015, **23**, 164–167.
61 M. R. Debet and M. J. Gidley, *Carbohydr. Polym.*, 2006, **64**, 452–465.
62 J. A. Montagnac, C. R. Davis and S. A. Tanumihardjo, *Compr. Rev. Food Sci. Food Saf.*, 2009, **8**, 181–194.
63 W. S. Ratnayake and D. S. Jackson, *Adv. Food Nutr. Res.*, 2009, **55**, 221–268.
64 M. C. Garcia, C. M. L. Franco, M. S. S. Júnior and M. Caliari, *J. Therm. Anal. Calorim.*, 2016, **123**, 919–926.
65 B. Y. Ritika, B. S. Khatkar and B. S. Yadav, *Int. J. Food Prop.*, 2010, **13**, 1339–1354.
66 J. Da Cruz Francisco, J. Silverio, A. Eliasson and K. Larsson, *Food Hydrocolloids*, 1996, **10**, 317–322.
67 J. Jane, *et al.*, *Cereal Chem.*, 1999, **76**, 629–637.
68 S. Varavinit, S. Shobsngob, W. Varanyanond, P. Chinachoti and O. Naivikul, *Starch/Staerke*, 2003, **55**, 410–415.
69 A. L. Charles, Y. H. Chang, W. C. Ko, K. Sriroth and T. Huang, *J. Agric. Food Chem.*, 2005, **53**, 2717–2725.
70 S. C. Alcázar-Alay and M. A. A. Meireles, *Food Sci. Technol.*, 2015, **35**, 215–236.
71 W. Berski, *et al.*, *Carbohydr. Polym.*, 2011, **83**, 665–671.
72 Q. Sun, *PLoS One*, 2014, **9**, e95862.
73 K. S. Sandhu and N. Singh, *Int. J. Food Prop.*, 2005, **8**, 481–491.
74 I. L. Batey and B. M. Curtin, *Cereal Chem.*, 2000, **77**, 754–760.
75 J. Waterschoot, S. Gomand, E. Fierens and J. A. Delcour, *Starch/Staerke*, 2015, **67**, 14–29.
76 O. O. Oladunmoye, O. C. Aworh, B. Maziya-Dixon, O. L. Erukainure and G. N. Elemo, *Nutr. Food Sci.*, 2014, **2**, 132–138.
77 T. Thanyasiriwat, *et al.*, *Plant Biol.*, 2014, **16**, 197–207.
78 S. Park, Y. Na, J.-W. Kim, S. D. Kang and K.-H. Park, *Food Technol. Biotechnol.*, 2018, **27**, 299–312.
79 S. Wang, C. Li, L. Copeland and Q. Niu, *Compr. Rev. Food Sci. Food Saf.*, 2015, **14**, 568–585.

80 S. Wang, C. Li, X. Zhang, L. Copeland and S. Wang, *Sci. Rep.*, 2016, **6**, 20965.
81 M. A. Ottenhof and I. A. Farhat, *Biotechnol. Genet. Eng. Rev.*, 2004, **21**, 215–228.
82 T. Tran, K. Piyachomkwan and K. Sriroth, *Starch/Staerke*, 2007, **59**, 46–55.
83 X. Lian, K. Cheng, D. Wang, W. Zhu and X. Wang, *Int. J. Food Prop.*, 2017, **20**, 3224–3236.
84 S. Gomand, L. Lamberts, R. G. F. Visser and J. A. Delcour, *Food Hydrocolloids*, 2010, **24**, 424–433.
85 M. Achor, J. Y. Oyeniyi, M. H. Musa and M. S. Gwarzo, *J. Appl. Pharm. Sci.*, 2015, **5**, 126–131.
86 M. C. Garcia, T. M. Elias, K. De Oliveira Ribeiro, M. S. S. Júnior and M. Caliari, *Food Sci. Technol.*, 2018, **39**, 803–809.
87 T. P. R. D. Santos, C. M. L. Franco, M. M. Mischan, D. De Souza Fernandes, M. S. DelBem and M. Leonel, *Aust. J. Crop Sci.*, 2019, **13**, 1486–1494.
88 S. Pérez and E. Bertoft, *Starch-Starke*, 2010, **62**, 389–420.
89 M. Gupta, A. S. Bawa and A. D. Semwal, *Int. J. Food Prop.*, 2009, **12**, 587–604.
90 H. S. P. Lizarazo, R. Hurtado and C. L. F. Rodríguez, *Agron. Colomb.*, 2015, **33**, 244–252.
91 W. Wang, C. Hostettler, F. F. Damberger, J. Kossmann, J. R. Lloyd and S. C. Zeeman, *Front. Plant Sci.*, 2018, **9**, 1562.
92 S. A. Oyeyinka, A. A. Adeloye, S. Smith, B. O. Adesina and F. F. Akinwande, *Agrosearch*, 2019, **19**, 28–45.
93 S. Mishra and T. Rai, *Food Hydrocolloids*, 2006, **20**, 557–566.
94 R. Toae, *et al.*, *Plants*, 2019, **8**, 447.
95 Y. Hong, G. Liu and Z. Gu, *Drug Delivery*, 2016, **23**, 12–20.
96 P. Juneja, B. Kaur, O. A. Odeku and I. Singh, *J. Drug Delivery*, 2014, **2014**, 827035.
97 O. A. Odeku, *Starch-Starke*, 2013, **65**, 89–106.
98 W. Abotbina, *et al.*, *Materials*, 2022, **15**, 6992.
99 A. I. Malik, *et al.*, *Breed. Sci.*, 2020, **70**, 145–166.
100 C. Siriwachirachai and T. Pongjanyakul, *Pharmaceutics*, 2022, **14**, 1245.
101 N. Visavarungroj, J. Herman and J. P. Remon, *Int. J. Pharm.*, 1990, **59**, 73–78.
102 L. Vandevivere, *et al.*, *Int. J. Pharm.*, 2019, **571**, 118760.
103 M. V. Lawal, M. A. Odeniyi and O. A. Itiola, *Asian Pac. J. Trop. Biomed.*, 2015, **5**, 585–590.
104 J. I. Ordu and J. I. Onyemelukwe, *Int. J. Life Sci. Res.*, 2018, **4**, 1834–1843.
105 D. B. Abdallah, N. A. Charoo and A. S. Elgorashi, *Pharm. Biol.*, 2014, **52**, 935–943.
106 D. Markl and J. A. Zeitler, *Pharm. Res.*, 2017, **34**, 890–917.
107 O. A. Odeku and B. L. Akinwande, *Saudi Pharm. J.*, 2012, **20**, 171–175.
108 J. T. Ingram and W. Lowenthal, *J. Pharm. Sci.*, 1968, **57**, 393–399.
109 F. K. Adjei, Y. A. Osei, N. Kuntworbe and K. Ofori-Kwakye, *J. Pharm.*, 2017, **2017**, 2326912.
110 J. Li and Y. Wu, *Lubricants*, 2014, **2**, 21–43.
111 P. G. Surdi de Castro, *et al.*, *Sci. Rep.*, 2021, **11**, 900.
112 J. B. M. Fernandes, *et al.*, *An. Acad. Bras. Cienc.*, 2019, **91**, e20180094.
113 R. B. Shah, M. A. Tawakkul and M. A. Khan, *AAPS PharmSciTech*, 2008, **9**, 250–258.
114 Md. M. Hasan, S. Rana and S. S. Chowdhury, *Bangladesh Pharm. J.*, 2015, **17**, 128–134.
115 L. L. Augsburger and R. F. Shangraw, *J. Pharm. Sci.*, 1966, **55**, 418–423.
116 B. S. Agboola, T. O. Ajala and O. A. Odeku, *Starch/Staerke*, 2018, **70**, 1700047.
117 O. Adeoye and G. Alebiowu, *Pharm. Dev. Technol.*, 2014, **19**, 901–910.
118 J. Chitedze, M. Monjerezi, J. D. K. Saka and J. Steenkamp, *J. Appl. Pharm. Sci.*, 2012, **2**, 31–37.
119 H. P. Goh, P. W. S. Heng and C. V. Liew, *Int. J. Pharm.*, 2018, **547**, 133–141.
120 N. Nagpal, P. Kaur, R. Kumar, S. Rahar, R. Dhawan and M. Arora, *Bull. Pharm. Res.*, 2016, **6**, 45–49.
121 S. G. Late and A. K. Banga, *AAPS PharmSciTech*, 2010, **11**, 1627–1635.
122 P. M. Lestari, A. Widayanti and H. Afifah, *Open Access Maced. J. Med. Sci.*, 2019, **7**, 3827–3832.
123 M. Landín, M. González, C. Souto, A. Concheiro, J. L. Gómez-Amoza and R. Martínez-Pacheco, *Drug Dev. Ind. Pharm.*, 1993, **19**, 1211–1220.
124 Y. Wicaksono and N. Syifa, *Indones. J. Pharm.*, 2008, **19**, 165–171.
125 C. E. Bos, G. K. Bolhuis, H. Van Doorne and C. F. Lerk, *Pharm. Weekbl.*, 1987, **9**, 274–282.
126 V. C. Orsi, M. M. D. C. Vila, V. M. Hanai-Yoshida, M. V. Chaud, V. M. Balcão and J. M. De Oliveira, *Ars Pharm.*, 2019, **60**, 205–211.
127 R. S. Ayu, K. Abdan, H. A. Saffian, K. Zaman, M. Jawaid and C. H. Lee, *Polymers*, 2018, **10**, 1187.
128 H. J. Prado, M. C. Matulewicz, P. R. Bonelli and A. L. Cukierman, *Carbohydr. Res.*, 2009, **344**, 1325–1331.
129 R. C. Mundargi, N. B. Shelke, A. P. Rokhade, S. A. Patil and T. M. Aminabhavi, *Carbohydr. Polym.*, 2008, **71**, 42–53.
130 C.-L. Lin, J.-H. Lin, J.-J. Lin and Y. Chang, *Molecules*, 2020, **25**, 5528.
131 Y. Zhang, *et al.*, *Starch/Staerke*, 2013, **65**, 461–468.
132 A. Getachew, Z. Yilma and S. Abrha, *Adv. Pharmacol. Sci.*, 2020, **2020**, 2708063.
133 A. Golachowski, W. Dróżdż, M. Golachowska, M. Kapelko-Żeberska and B. Raszewski, *Foods*, 2020, **9**, 1311.
134 M. Labelle, P. Ispas-Szabo and M. A. Mateescu, *Starch/Staerke*, 2020, **72**, 2000002.
135 Q. Chen, *et al.*, *RSC Adv.*, 2015, **5**, 67459–67474.
136 A. O. Ashogbon and E. T. Akintayo, *Starch-Starke*, 2014, **66**, 41–57.
137 S. Park, Y. Na, J.-W. Kim, S. D. Kang and K.-H. Park, *Food Sci. Biotechnol.*, 2017, **27**, 299–312.
138 K. H. Hebelstrup, D. Sagnelli and A. Blennow, *Front. Plant Sci.*, 2015, **6**, 247.

139 K. Bashir and M. Aggarwal, *J. Food Sci. Technol.*, 2019, **56**, 513–523.
140 S. Lefnaoui and N. Moulai-Mostefa, *Saudi Pharm. J.*, 2015, **23**, 698–711.
141 A. V. Singh and L. K. Nath, *Saudi Pharm. J.*, 2013, **21**, 193–200.
142 T. Nabais and G. Leclair, *ISRN Pharm.*, 2014, **2014**, 391523.
143 T. C. Le and M. A. Mateescu, *Drug Delivery Transl. Res.*, 2017, **7**, 516–528.
144 A. B. Ahmed and I. Bhaduri, *Int. J. Pharm. Pharm. Sci.*, 2017, **9**, 132–137.
145 M. J. Santander-Ortega, *et al.*, *J. Controlled Release*, 2010, **141**, 85–92.
146 J. Yang, Y. Huang, C. Gao, M. Liu and X. Zhang, *Colloids Surf., B*, 2014, **115**, 368–376.
147 G. Sodeifian, M. A. Nooshabadi, F. Razmimanesh and A. Tabibzadeh, *Arabian J. Chem.*, 2023, **16**, 105196.
148 H. Nateghi, G. Sodeifian, F. Razmimanesh and J. M. N. Abad, *Sci. Rep.*, 2023, **13**, 12906.
149 G. Sodeifian, H. Bagheri, M. A. Nooshabadi, F. Razmimanesh and A. Roshanghias, *J. Supercrit. Fluids*, 2023, **200**, 106000.
150 G. Sodeifian, C. Garlapati, M. A. Nooshabadi, F. Razmimanesh and A. Tabibzadeh, *Sci. Rep.*, 2023, **13**, 8112.
151 G. Sodeifian, L. Nasri, F. Razmimanesh and M. A. Nooshabadi, *J. Chem. Thermodyn.*, 2023, **182**, 107050.
152 M. Abadian, G. Sodeifian, F. Razmimanesh and S. Z. Mahmoudabadi, *Fluid Phase Equilib.*, 2023, **567**, 113711.
153 G. Sodeifian, C.-T. Hsieh, A. Tabibzadeh, H.-C. Wang and M. A. Nooshabadi, *Sci. Rep.*, 2023, **13**, 2172.
154 G. Sodeifian, M. M. B. Usefi, F. Razmimanesh and A. Roshanghias, *Arabian J. Chem.*, 2023, **16**, 104421.
155 G. Sodeifian, C. Garlapati and A. Roshanghias, *Sci. Rep.*, 2022, **12**, 17494.
156 G. Sodeifian, R. S. Alwi, F. Razmimanesh and F. Sodeifian, *J. Mol. Liq.*, 2022, **362**, 119689.
157 G. Sodeifian, R. S. Alwi, F. Razmimanesh and A. Roshanghias, *J. Supercrit. Fluids*, 2022, **190**, 105759.
158 G. Sodeifian, C.-T. Hsieh, R. Derakhsheshpour, Y. Chen and F. Razmimanesh, *Arabian J. Chem.*, 2022, **15**, 103876.
159 G. Sodeifian, C. Garlapati, F. Razmimanesh and H. Nateghi, *Sci. Rep.*, 2022, **12**, 9008.
160 G. Sodeifian, C. Garlapati, F. Razmimanesh and H. Nateghi, *Sci. Rep.*, 2022, **12**, 7758.
161 G. Sodeifian, L. Nasri, F. Razmimanesh and M. Abadian, *J. CO2 Util.*, 2022, **58**, 101931.
162 G. Sodeifian, R. S. Alwi and F. Razmimanesh, *Fluid Phase Equilib.*, 2022, **556**, 113396.
163 G. Sodeifian, R. S. Alwi, F. Razmimanesh and M. Abadian, *J. Mol. Liq.*, 2022, **346**, 117899.
164 G. Sodeifian, C. Garlapati, F. Razmimanesh and M. Ghanaat-Ghamsari, *Sci. Rep.*, 2021, **11**, 24344.
165 G. Sodeifian, C. Garlapati, F. Razmimanesh and F. Sodeifian, *J. Mol. Liq.*, 2021, **335**, 116446.
166 G. Sodeifian, R. S. Alwi, F. Razmimanesh and K. Tamura, *Fluid Phase Equilib.*, 2021, **537**, 113003.
167 G. Sodeifian, L. Nasri, F. Razmimanesh and M. Abadian, *J. Mol. Liq.*, 2021, **331**, 115745.
168 G. Sodeifian, S. M. Hazaveie and F. Sodeifian, *J. Mol. Liq.*, 2021, **330**, 115695.
169 G. Sodeifian, S. A. Sajadian, F. Razmimanesh and S. M. Hazaveie, *Sci. Rep.*, 2021, **11**, 7546.
170 G. Sodeifian, C. Garlapati, F. Razmimanesh and F. Sodeifian, *J. Chem. Eng. Data*, 2021, **66**, 1119–1131.
171 G. Sodeifian, N. S. Ardestani, F. Razmimanesh and S. A. Sajadian, *Fluid Phase Equilib.*, 2021, **522**, 112745.
172 S. M. Hazaveie, G. Sodeifian and S. A. Sajadian, *J. Supercrit. Fluids*, 2020, **163**, 104875.
173 G. Sodeifian, C. Garlapati, S. M. Hazaveie and F. Sodeifian, *J. Chem. Eng. Data*, 2020, **65**, 4406–4416.
174 G. Sodeifian, N. S. Ardestani, M. R. Golmohammadi and A. Fazlali, *J. Chem. Eng. Data*, 2020, **65**, 1747–1760.
175 G. Sodeifian, S. A. Sajadian and R. Derakhsheshpour, *Fluid Phase Equilib.*, 2020, **507**, 112422.
176 G. Sodeifian, F. Razmimanesh, N. S. Ardestani and S. A. Sajadian, *J. Mol. Liq.*, 2020, **229**, 112179.
177 G. Sodeifian, F. Razmimanesh, S. A. Sajadian and S. M. Hazaveie, *J. Chem. Thermodyn.*, 2020, **142**, 105998.
178 G. Sodeifian and F. Razmimanesh, *J. Mol. Liq.*, 2020, **297**, 111740.
179 G. Sodeifian, R. Detakhsheshpour and S. A. Sajadian, *J. Supercrit. Fluids*, 2019, **154**, 104606.
180 G. Sodeifian, S. M. Hazaveie, S. A. Sajadian and N. S. Ardestani, *J. Chem. Eng. Data*, 2019, **64**, 5338–5348.
181 G. Sodeifian, S. M. Hazaveie, S. A. Sajadian and F. Razmimanesh, *Fluid Phase Equilib.*, 2019, **493**, 160–173.
182 G. Sodeifian and S. A. Sajadian, *J. Supercrit. Fluids*, 2019, **149**, 79–87.
183 G. Sodeifian and F. Razmimanesh, *J. Supercrit. Fluids*, 2019, **146**, 89–99.
184 G. Sodeifian, F. Razmimanesh and H. S. Panah, *Fluid Phase Equilib.*, 2018, **472**, 147–159.
185 G. Sodeifian, *J. Supercrit. Fluids*, 2018, **133**, 239–252.
186 G. Sodeifian, N. S. Ardestani and H. S. Panah, *Fluid Phase Equilib.*, 2018, **458**, 102–114.
187 G. Sodeifian and F. Razmimanesh, *Fluid Phase Equilib.*, 2017, **450**, 149–159.
188 G. Sodeifian and N. S. Ardestani, *J. Supercrit. Fluids*, 2017, **128**, 102–111.
189 S. T. Tene, J. M. Klang, S. C. N. Houketchang, G. T. Boungo and H. M. Womeni, *Food Sci. Nutr.*, 2019, **7**, 1190–1206.
190 A. R. Rajan and T. E. Abraham, *Bioprocess Biosyst. Eng.*, 2006, **29**, 65–71.
191 E. C. Ibezim, in *Biopolymers in Drug Delivery: Recent Advances and Challenges*, ed. M. U. Adikwu and

C. O. Esimone, Bentham Science Publishers, United Arab Emirates, 1st Ed, 2009, ch. 4, pp. 39–56.
192 T. Itthisoponkul, J. R. Mitchell, A. Taylor and I. A. Farhat, *Carbohydr. Polym.*, 2007, **69**, 106–115.
193 A. Madene, M. Jacquot, J. Scher and S. Desobry, *Int. J. Food Sci. Technol.*, 2006, **41**, 1–21.
194 Md. K. Saifullah, M. R. I. Shishir, R. Ferdowsi, R. T. Rahman and Q. V. Vuong, *Trends Food Sci. Technol.*, 2019, **86**, 230–251.
195 C. Zhao, Y. Cao, Y. Zhang and Y. Qiao, *Int. J. Mol. Sci.*, 2019, **20**, 752.
196 S. Surini, V. Anggriani and A. Effionora, *J. Med. Sci.*, 2009, **9**, 249–256.
197 O. A. Odeku, A. A. Aderogba, T. O. Ajala, O. D. Akin-Ajani and A. Okunlola, *J. Pharm. Invest.*, 2017, **47**, 445–451.
198 A. G. B. Pereira, A. R. Fajardo, S. R. Nocchi, C. V. Nakamura, A. F. Rubira and E. C. Muniz, *Carbohydr. Polym.*, 2013, **98**, 711–720.
199 V. Raj and G. Prabha, *J. Assoc. Arab Univ. Basic Appl. Sci.*, 2016, **21**, 10–16.
200 C. Isimi and A. D. C. C. Rodrigues, *J. Nanomed. Nanotechnol.*, 2016, **7**, 1–8.
201 S. Mohanty, *J. Adv. Nanobiotechnol.*, 2017, **1**, 16–24.
202 D. P. Mohanty and S. K. B. Al, *Int. J. Pharm. Biol. Sci.*, 2017, **8**, 5–11.
203 G. L. P. Da Silva, L. C. De Assunção Morais, J. B. Olivato, J. Marini and P. C. Ferrari, *J. Biomater. Appl.*, 2021, **35**, 1096–1108.
204 Z. Kou, *et al.*, *Int. J. Biol. Macromol.*, 2020, **145**, 655–662.
205 S. Surini, F. Gotalia and K. S. S. Putri, *Int. J. Appl. Pharm.*, 2018, **10**, 225–229.
206 T. Gabriel, A. Belete and T. Gebre-Mariam, *J. Drug Delivery Ther.*, 2013, **3**, 1–10.
207 M. Palencia, A. L. Tulio and M. C. Enrique, *Curr. Chem. Biol.*, 2017, **11**, 28–35.
208 G. K. Athira and A. N. Jyothi, *J. Pharm. Sci. Res.*, 2015, **6**, 200–211.
209 G. N. A. D. Putra, R. Murwanti, A. Rohman and T. N. S. Sulaiman, *Int. J. Appl. Pharm.*, 2019, **11**, 32–40.
210 C. Liu, J. Li, K. Li, C. Xie and J. Liu, *Int. J. Biol. Macromol.*, 2020, **156**, 1045–1052.
211 E. Anwar, H. Khotimah and A. Yanuar, *J. Med. Sci.*, 2006, **6**, 923–929.
212 A. Zaki, E. Anwa and S. Surini, *Int. J. Appl. Pharm.*, 2017, **9**, 71–73.
213 A. O. Shittu, A. R. Oyi, A. B. Isah, S. Kareem and M. Ibrahim, *Int. J. Pharm. Sci. Res.*, 2012, **3**, 2180–2190.
214 E. H. Nabeshima and M. V. E. Grossmann, *Carbohydr. Polym.*, 2001, **45**, 347–353.
215 L. Z. Jaekel, M. Schmiele, R. Da Silva Rodrigues and Y. K. Chang, *J. Food Sci. Technol.*, 2015, **52**, 7305–7312.
216 K. Oltramari, *et al.*, *Starch/Staerke*, 2017, **69**, 11–12.
217 R. Wongsagon, S. Shobsngob and S. Varavinit, *Starch/Staerke*, 2005, **57**, 166–172.
218 O. Adewoyin, *Br. J. Pharm. Res.*, 2015, **8**, 1–7.
219 B. A. Harsojuwono, S. T. Mulyani and I. W. Arnata, *J. Appl. Hortic.*, 2019, **21**, 13–19.
220 A. N. Jyothi, S. N. Moorthy and K. N. Rajasekharan, *Starch/Staerke*, 2006, **58**, 292–299.
221 R. M. Collares, *et al.*, *J. Zhejiang Univ., Sci., B*, 2012, **13**, 579–586.
222 M. Iwe, G. O. Okereke and A. An, *Agrotechnol*, 2014, **4**, 1–6.
223 H. J. J. K.-V. Putten, *et al.*, *Transgenic Res.*, 2012, **21**, 39–50.
224 F. Hosseini and S. Ansari, *J. Food Sci. Technol.*, 2019, **56**, 5374–5385.
225 P. Mhaske, Z. Wang, A. Farahnaky, S. Kasapis and M. Majzoobi, *Crit. Rev. Food Sci. Nutr.*, 2021, **8**, 1–27.
226 D. De Souza Fernandes, M. Leonel, M. S. Del, M. M. Mischan, E. A. Garcia and T. P. R. D. Santos, *J. Food Sci. Technol.*, 2017, **54**, 1357–1367.
227 R. Wongsagonsup, *et al.*, *Carbohydr. Polym.*, 2014, **101**, 656–665.
228 M. Y. Naz, S. A. Sulaiman, B. Ariwahjoedi and K. Z. K. Shaari, *Sci. World J.*, 2014, **2014**, 375206.
229 W. Li, Z. Xu, Z. Wang and J. Xing, *Polymers*, 2018, **10**, 1110.
230 S. Wang, F. Zhang, F. Chen and Z. Pang, *Bioresources*, 2013, **8**, 3574–3589.
231 Z. Wang, *et al.*, *Int. J. Biol. Macromol.*, 2019, **126**, 603–611.
232 W. Murdianto, S. Anggrahini, S. Sutardi and Y. Pranoto, *Pak. J. Nutr.*, 2019, **18**, 471–478.
233 L. Ekebafe, *Afr. J. Environ. Sci. Technol.*, 2012, **6**, 275–282.
234 S. Jobling, *Curr. Opin. Plant Biol.*, 2004, **7**, 210–218.
235 R. N. Tharanathan, *Crit. Rev. Food. Sci. Nutr.*, 2005, **45**, 371–384.
236 V. D. Trela, A. L. Ramallo and O. A. Albani, *Braz. Arch. Biol. Technol.*, 2020, **63**, 1–13.
237 L. H. Garrido, E. Schnitzler, M. E. B. Zortéa, T. De Souza Rocha and I. M. Demiate, *J. Food Sci. Technol.*, 2014, **51**, 2640–2647.
238 K. Heebthong and K. Ruttarattanamongkol, *Starch/Staerke*, 2016, **68**, 528–540.
239 A. G. G. Issola, A. N. Kamlo, A. M. C. Yona and M. K. Ndikontar, *J. Renewable Mater.*, 2018, **6**, 642–650.
240 H. Qiu and L. He, *Polym. Adv. Technol.*, 1999, **10**, 468–472.
241 L. P. Cordoba, *Braz. J. Therm. Anal.*, 2013, **2**, 6–11.
242 C. S. Schmitz, K. N. De Simas, K. M. O. D. Santos, J. J. João, R. D. De Mello Castanho Amboni and E. R. Amante, *Int. J. Food Sci. Technol.*, 2006, **41**, 681–687.
243 G. Pifferi and P. Restani, *Farmaco*, 2003, **58**, 541–550.
244 H. P. Til, V. J. Feron, H. R. Immel and W. F. Vogel, *Food Chem. Toxicol.*, 1986, **24**, 825–834.
245 O. B. Wurzburg, *Nutr. Rev.*, 1986, **44**, 74–79.
246 E. Chinedu, D. Arome and F. S. Ameh, *Toxicol. Int.*, 2013, **20**, 224–226.
247 E. Walum, *Environ. Health Perspect.*, 1998, **106**, 497–503.
248 J. E. LeBeau, *Regul. Toxicol. Pharmacol.*, 1983, **3**, 71–74.
249 P. J. Vit, *Arch. Toxicol.*, 1989, **63**, 343–344.
250 M. Porwal, N. A. Khan and K. Maheshwari, *Sci. Pharm.*, 2017, **85**, 29.

251 E. O. Erhirhie, C. P. Ihekwereme and E. E. Ilodigwe, *Interdiscip. Toxicol.*, 2018, **11**, 5–12.
252 R. L. Lipnick, *et al.*, *Food Chem. Toxicol.*, 1995, **33**, 223–231.
253 D. R. Jesus, T. B. L. Prando, D. C. Dragunski, F. M. Gasparotto, E. L. B. Lourenço and A. Gasparotto Jr., *Lat. Am. J. Pharm.*, 2015, **34**, 1154–1161.
254 OECD Guideline for the Testing of Chemicals, Repeated dose 90-day oral toxicity study in rodents, 2018, **section 4**, Test No. 408.
255 S. Parasuraman, *J. Pharmacol. Pharmacother.*, 2011, **2**, 74–79.
256 D. R. Jesus, *et al.*, *J. Evidence-Based Complementary Altern. Med.*, 2015, 390416.
257 OECD Guideline for the Testing of Chemicals, Chronic toxicity studies, 2018, **section 4**, Test No. 452.
258 R. Zepeda, M. Candiracci, N. Lobos, S. Lux and H. F. Miranda, *Mar. Drugs*, 2014, **12**, 5055–5071.
259 J. B. Colerangle, in *A Comprehensive Guide to Toxicology in Nonclinical Drug Development*, ed. A. S. Faqi, Academic Press, London, 2nd edn, 2017, ch. 25, pp. 659–683.
260 R. Corvi, *et al.*, *Toxicol. In Vitro*, 2017, **45**, 278–286.
261 OECD Guideline for the Testing of Chemicals, Carcinogenicity studies., 2018, **section 4**, Test No. 451.
262 G. Jena, C. L. Kaul and P. Ramarao, *Indian J. Pharmacol.*, 2005, **37**, 209–222.
263 A. S. Faqi and J. S. Yan, in *A Comprehensive Guide to Toxicology in Nonclinical Drug Development*, ed. A. S. Faqi, Academic Press, London, 2nd edn, 2017, ch. 30, pp. 813–823.
264 K.-M. Wu, J. Dou, H. Ghantous, S. Chen, A. Bigger and D. Birnkrant, *Regul. Toxicol. Pharmacol.*, 2010, **56**, 1–3.
265 H. Türkez, M. Arslan and Ö. Özdemir, *Expert Opin. Drug Metab. Toxicol.*, 2017, **13**, 1089–1098.
266 OECD Guideline for the Testing of Chemicals, *In vitro* mammalian cell micronucleus test., 2016, **section 4**, Test No. 487.
267 A. Mortensen, *et al.*, *EFSA J.*, 2017, **15**, e04911.
268 B. Medeiros-Neves, M. C. Nemitz, F. N. S. Fachel and H. F. Teixeira, *Recent Pat. Drug Delivery Formulation*, 2019, **13**, 192–202.
269 H. Jj, D. P. Es, L. Mirjam, M. Margherita, R. H. Michael and H. Michal, *J. Clin. Transl. Res.*, 2017, **3**, 250–259.
270 J. L. Tidwell and L. A. Liotta, *Methods Mol. Biol.*, 2012, **823**, 391–408.
271 H. Wang, T. Feng, H. Zhuang, Z. Xu, R. Ye and M. Sun, *Recent Pat. Food Nutr. Agric.*, 2018, **9**, 23–30.
272 S. Li, Y. Cui, Y. Zhou, Z. Luo, J. Liu and M. Zhao, *J. Sci. Food Agric.*, 2017, **97**, 2282–2290.
273 G. Yuanyuan, *et al.*, *Patent China*, 2022, CN114190507, A.
274 X. Xingyong, X. Yuanyuan, H. Yaocong, S. Qiaoqiao, L. Songyang and M. Chen, *Patent China*, 2022, CN114950355, A.
275 H. Douglas, *et al.*, *Patent Australia*, 2022, AU2022209338A1.
276 Y. Kailiang, *Patent China*, 2022, CN217490061U.
277 L. Rihui, S. Yonggui, Y. Xianchao and J. Siyu, *Patent China*, 2021, CN113577307A.
278 H. Lijie, *et al.*, *Patent China*, 2021, CN113831563A.
279 L. Yefei, *et al.*, *Patent China*, 2021, CN112514751A.
280 S. Shaozhen, H. Lijie, H. Xiaoxue, S. Shaoxin and L. Ping, *Patent China*, 2021, CN113150393A.
281 L. Bo, *Patent China*, 2020, CN111205373, A.
282 L. Rihui, F. Yanye, Z. Lihong, Z. Yijun and Y. Xianchao, *Patent China*, 2020, CN112321853A.
283 L. Yilun and L. Xiangdong, *Patent China*, 2020, CN111808205A.
284 O. Wenjun, *et al.*, *Patent China*, 2020, CN111543476A.
285 C. Hui, *Patent China*, 2019, CN109276550A.
286 L. Heping, *et al.*, *Patent China*, 2019, CN109280187A.
287 L. Mingchang, L. Jingli and Z. Huangqiang, *Patent China*, 2019, CN109400726A.
288 S. Xiaodan, S. Ancheng and J. Xiachao, *Patent China*, 2019, CN109957035A.
289 L. Changying, *Patent China*, 2018, CN107814880A.
290 M. Xianli, L. Fangyao and L. Hanfu, *Patent China*, 2018, CN107603513A.
291 L. Heping, *et al.*, *Patent China*, 2018, CN107722533A.
292 P. L. Ooi, V. Malayalam, A. Guha, A. Dasgupta and S. D. Prabhakar, Patent World Intellectual Property Organization, 2018, WO2017025482A1.
293 S. F. David, R. V. T. Jazmin and T. E. Michael, *Patent Japan*, 2017, JP2017061543A.
294 Y. Xiulian, Y. Qinghong, W. Miaomiao, Z. Xuejuan and Z. Xinghai, *Patent China*, 2017, CN106727394A.
295 C. Li, *Patent China*, 2017, CN106389345A.
296 Z. Ren, D. Luo and F. Wang, *Patent United State*, 2017, US20200377675A1.