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POTENTIALS OF CASSAVA STARCH AS PHARMACEUTICAL FORMULATION EXCIPIENT: A REVIEW

[*]Bediako Ango, Kuntworbe Noble, Raphael Johnson and Ofori-Kwakye Kwabena

Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, Ghana.

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***Corresponding Author**
Bediako Ango
Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, Ghana.
bediakoango@yahoo.com
nkuntworbe.pharm@knust.edu.gh
rjohnson.pharm@knust.edu.gh
kokwakye.pharm@knust.edu.gh

ABSTRACT

Cassava (*Manihot esculenta, Crantz*) is a perennial shrub that naturally grows in abundance in the tropics. The swollen roots are rich in Starch and approximately half of the total produce are utilized for Starch production. Recently, cassava starches have been investigated in the pharmaceutical industry as formulation excipients and potential drug delivery carriers like microparticles and nanoparticles. The diversity of these cassava starches concerning physical, chemical, enzymatic, genetic and functional properties modifications has indicated promises of being utilized as substitutes for some commercially available pharmaceutical excipients. Their applications as excipients and drug delivery carriers can add value to this seemingly neglected and underutilized cassava crop and also provide the accompanying modified starches with special properties for specific pharmaceutical formulations. However, literature search indicates only a scanty report on cassava, and thereby, this huge potential of related Starches is yet to be fully pharmaceutically harnessed. In this review, extensive literature search is conducted on available profile of cassava starches within the last decade to create a pool of knowledge to serve as a potential reference source. This review which summarizes the present knowledge on cassava starches, indicates that they shall continue to be materials of cherished importance in pharmaceutical formulation and drug delivery models owing to their excellent characteristic properties like ease of modification, low cost and susceptibility to wider applications. Notwithstanding, the lack of comprehensive toxicity and safety profile studies of cassava starches remains a critical limitation to their commercialization.

KEYWORDS: Cassava, Drug Delivery Carriers, Excipients, Microparticles, Modifications, Nanoparticles.

INTRODUCTION

Pharmaceutical excipient may be regarded as any substance other than the active pharmaceutical ingredient or pro - drug that is included in the manufacturing process or is contained in finished pharmaceutical formulations. Excipients may be classified in accordance with the functions they perform in the related dosage forms or formulations. On this basis they may be classified into categories like fillers, diluents, binders, disintegrants, glidants, lubricants etc.[1] Selecting the right excipients is one of the prime factors governing the efficient production of robust, consistent, reproducible and good - quality pharmaceutical products. Pharmaceutical formulators are thereby continuously researching to improve the manufacturing process and product quality through the use of functional excipients. However, the art of selecting the most optimized excipients is a very critical process that requires a delicate balance between time and cost efficiencies as well as anticipated product performance.

Excipients may also be described as inactive pharmaceutical additives or inactive ingredients that are incorporated to make up medications. They may further include, among others, flavors, colorants, suspending agents, emollients and preservatives. A commonest material that has found wide applications in the pharmaceutical industry as a potential formulation excipient is Starch.

Starch occurs naturally in abundance in plants where they present as carbohydrate reserves in minute granules of diameter ranging from 1 to 100 mm or more. Considerable amounts of Starch may occur in many different parts of the plant including roots and/or tubers, fruits, seeds, flowers and flower – tops etc. and it principally serves as a source of energy. The native starches possess a couple of highly attractive physicochemical properties which facilitate their potential use as excipients. These among others may include related natural abundance and/or availability, accessibility, cheapness and inertness. Furthermore, starches are reported to be highly biodegradable, biocompatible, pollution – free and renewable.[2]

Notwithstanding, starches are also beset with related adverse properties like insolubility in cold water, instability in acidic media, low emulsifying capacity and high susceptibility to dehydration due to which their commercial application remains a huge challenge.[3]

The basic chemical formula of Starch - $(C_6H_{10}O_5)$ n is similar to glucose ($C_6H_{12}O_6$), where 'n' is the number of glucose molecules present. Essentially, Starch is composed of polymerized polysaccharides whose basic unit of glucose molecules are joined by α – d – (1–4) or α – d – (1–6) linkage. Starches may occur in two major polymerized forms namely amylose and amylopectin. Amylose is a linear polymer and occurs mainly as amorphous or solid while amylopectin forms a branched chain and is principally crystalline. Approximately, 70% of the total mass of starch granule is composed of the amorphous section while the remaining 30% constitutes the crystalline portion. The extent of polymerization of amylose is up to 6000, and has a molecular mass ranging between 105 – 106 g/mol. The related chains can easily form single or double structures of helices.

On the contrary, amylopectin has a molecular mass of 107 – 109 g/mol and an extent of polymerization of approximately 2 million. This character renders amylopectin a relatively larger molecule available in nature. Related chain lengths of approximately 20 – 25 glucose units between branch points are typical of amylopectin.[4]

Starch, in the native form is largely employed in the formulation and development of a couple of pharmaceutical products where its particular function depends on the specific formulation in which it is incorporated. Within the pharmaceutical industry, relevant starch functions which are routinely applied are as presented in the following disciplines.

BINDER

Binders are substances that act as adhesives to bind powders together in the wet granulation process. Furthermore, they offer invaluable assistance in binding granules together during compression. Too little a binding agent inclusion in a formulation results in production of soft granules, while too much a binder inclusion results in large and hard granules production. Starch is one of the most successfully utilized binding agent in the wet granulation process during production of tablets, capsules, and other solid dosage formulations. The granulation process aids to a larger extent, the flow characteristics of active pharmaceutical ingredients - APIs which usually tend to be very cohesive. Solid dosage forms weight consistency and thereby dose variation parameters which are critical in the solids are principally controlled by the flow characteristics of the related granules. Within this domain, the mucilage of Starch becomes the agent of choice as it easily creates large size agglomerates of the powdered ingredients that are characterized with good flow qualities. Furthermore, starch paste, which is produced on heating starch suspension (i.e., gelatinized Starch) is effectively utilized to aggregate particles together to create larger - sized granules that are characterized with good flow qualities. The mechanism underlying this flow improvement quality involves the creation of specific bonds between particles in the powder bed following interaction with the starch paste, which, after drying become solid bridges. There appears to be a direct relationship between the paste viscosity and the solid bridges strength, as reported by some studies. Thus, the higher the viscosity of the paste, the stronger the bridges formed, and the larger the size of the aggregates. Thereby, the starch function as a binder is largely controlled by the starch paste viscosity. Available reports indicate that the source, and thereby, the chemical constituents of the Starch offer significant influence on the degree of related starch paste viscosity.[5]

DISINTEGRANT

A disintegrant is incorporated in solid pharmaceutical formulations to facilitate the fragmentation or break-up of related product such as tablet or granule into smaller discrete particles when exposed to aqueous environment following administration. Disintegration is a relevant step in the process of drug release and absorption. It exposes a larger surface area of the fragmented drug particles to the gastro intestinal - g.i. fluid and thereby promoting easy and quick release of API and related transit into solution. It has been established that the release rate of a drug is greater from disintegrated particles than from the intact tablet or tablet fragments. Thereby, a good disintegrant will quickly break up a tablet into primary particles, facilitating its absorption. Starch has been identified as one of the cheapest and most convenient disintegrant that is commonly utilized in practice. The related mechanism of action has been attributed to the swelling characteristics of its particles on exposure to aqueous environment or water. Specifically, this exposure to aqueous environment leads to disruption of the solid bridges and other binding forces that exist in solid dosage forms. The source and type of the Starch is a principal factor governing the degree of the swelling activity. This observation has further been found to be directly related to the relative proportion composition of the amylose and amylopectin in the particular Starch. The capillary action, which involves formation of channels through which fluids are able to penetrate the solid dosage form and allowing the dissolution of the drug has also been identified as an alternative mechanism of disintegration action of starch.

DILUENT

Diluents or bulking agents, are inert materials that are usually incorporated in certain formulations in sufficient quantities to make a reasonably sized product like tablet. Essentially, some APIs - drugs whose effective therapeutic doses are extremely low, usually less than 50 mg, tend to be very difficult to be pharmaceutically processed into tablets and other required dosage forms. In

an approach to resolving such limitation, bulking materials that do not exert any influence on the therapeutic activity of the API can be incorporated in the formulation. Coupled with other benefits, this may allow for normal formulation and manufacturing processes to be conveniently conducted. Starch is a commonest material that is frequently used for this purpose owing to its characteristic inert, bland, and odorless properties.

ABSORBENT

Absorbents are materials that are included in formulations with the object of holding quantities of fluids in an apparent dry state. Starch which has been established to be hygroscopic and possessing the tendency of absorbing moisture up to 10 – 17 % has been successfully employed as a useful absorbent. Thus, Starch has been frequently used as an absorbent in drug formulations not only to maintain dry state of powdered materials, but to further ensure the stability of drugs against hydrolysis, solvolysis and other related chemical interactions.

GLIDANT/LUBRICANT

Glidants/lubricants are agents that are incorporated in solid formulations to improve the flow properties of granules. Related mechanism of action involves reduction of inter-particulate frictional bonds. Owing to their characteristic slippery and tendency to adhere to surfaces properties, starches have been extensively studied for their glidant and lubricant potentials. Subsequently, starches have been observed to be capable of reducing frictional forces to credible levels and are, thereby, potential and promising glidant and lubricant materials.

Gelatinization and Retrogradation of Starch

Isolated Starch typically occurs as dry, soft and white powder. Generally, it is insoluble in cold water, alcohol, ether and most importantly, in organic solvents. Starch, if kept dry, is stable in storage for indefinite periods. Even so, Starch can be easily disrupted despite the observation that the related granules are physically durable. Starch granules in suspension of aqueous systems readily absorb water when subjected to heating. Thus, the granules under increasing temperature conditions hydrate, increase in size and finally lose their structural integrity. This results in loss of characteristic birefringence – i.e., optical property and opacity, an increase in viscosity, and the eventual formation of a paste or gel. This process is referred to as starch pasting or gelatinization. The temperature at which gelatinization of Starch occurs, referred to as the gelatinization temperature is characteristic and regulated to a larger extent by factors like concentration and pH of the starch suspension, heating rate, salts presence and specific procedure adopted. Gelatinization temperature can thereby be utilized as a standard parameter in classification of starches. The specific arrangement of linkages within the amylose and amylopectin structure regulates to a larger extent, the physical properties of starch granules.[6] Retrogradation of Starch refers to the process whereby the disaggregated amylose and amylopectin chains in a gelatinized starch paste re – associate to form well organized structures as the cooked Starch congeals.[7]

Overview of Cassava – Manihot esculenta

Cassava (*Manihot esculenta, Crantz; Euphobiaceae*) is a perennial shrub and a critical industrial crop that is available in abundance in many tropical and subtropical areas including South America (e.g. Brazil), Africa (e.g. Nigeria, Ghana, Cote D'Ivoire) and Asia (e.g. Thailand).[8] The swollen tubers of cassava are rich in Starch and approximately half of the total roots produced are utilized for Starch production. Although maize has been the leading crop for Starch production (more than 80% of the world starch production), cassava production for Starch is increasing rapidly; over 3% annually and accounting for about 7% of global Starch produced.[9] Owing to their outstanding physicochemical and functional properties, cassava starches are gradually assuming a couple of substantial benefits of pharmaceutical interest over some of the other traditional crop starches. These pharmaceutical significances and benefits are related to, among others, their higher starch accumulation capacity, all-year-round availability, biocompatibility, biodegradation ability and favorable economic price. Others are the cassava plant's suitable resilience to drought, poor soil factors, pests and diseases, and relatively simple Starch extraction technique.[10,8]

A couple of cassava varieties have been identified and authenticated globally, however, the most popular or commonest accession is the Manihot esculenta, crantz. Thus, apart from this variety, other related wild variations that are often referred to as Manihot esculenta subspecies have also been identified.[11,12] Available reports indicate that thirty - 30 countries comprising of eighteen – 18 African, four – 4 Latin America and eight – 8 Asian were selected as principal growers of a couple of varieties of cassava in the world in 2010.[13]

In Ghana, notable varieties of cassava that have been developed and introduced for adoption may include All improved cassava, Abrabopa, Ampong, Sika bankye, Bosome nsia, Ankrah, Nkabom and Esam Bankye. Others are Doku Duade, Afisiafi, Bankye hemaa, Duadekpakpa and Amansen varieties as per reports of the Council for Scientific and Industrial Research – Crops Research Institute i.e., (CSIR – CRI). Various scientific studies on these cassava varieties regarding yield, physicochemical, functional etc. properties of the related starches have been conducted and documented. A study conducted by Tappiban et al., 2020, investigated the influence of cassava variety on the related starch properties including potential as pharmaceutical formulation excipient. The study indicated that the cassava – starch based pharmaceutical excipient character is variety – sensitive and could thereby influence cassava starch utility in this technology.[14] In a

separate study conducted by Adjei, K. F. et al., significant alterations in the related starch properties of the respective cassava varieties was reported.[15] William, G et al., (2019), investigated the influence and effects of maturity and thereby time of harvest of cassava accessions on related starch properties and functions. It was reported that the maturity significantly affects starch yield, composition and pasting properties of all the selected cassava varieties. Thereby, the maturity and time to harvesting is a relevant factor worthy of due consideration during utilization of cassava starch for both specific food and non – food industrial applications, especially in the pharmaceutical formulation discipline.[16]

Chemical constituents of cassava starch.

Like other Starches, the chemical constituents of cassava starch are dominated by amylose and amylopectin. However, other chemical constituents that have been identified in cassava starch may, among others, include 0.06 – 0.75 % protein, 0.03 – 0.29 % ash, 0.01 – 1.2 % lipid, 0.0029 – 0.0095 % phosphorous and 0.11 – 1.9 % fibrous materials.[17]

Retrogradation and gelatinization properties of cassava starch have been reported to be similar to the other starches derived from different sources. However, cassava starch exhibits lower gelatinization temperature, and higher water – binding capacity, viscosity and shear resistance. These exceptional qualities make it an excipient of choice over the other starches in certain specific disciplines in the pharmaceutical industry, notably in the binding and disintegrating characters.

Rheological properties of cassava starch which may involve the pasting property, viscosity and characteristics of its related gel have also received considerable attention. It has been reported that aqueous gel of cassava starch exhibits pseudoplastic or shear thinning properties and is, thereby, Non – Newtonian.[18]

Modification of Starches

A couple of pharmaceutical techniques are available for modification of native starches including cassava starch, to produce modified versions with significantly improved functional characteristics. These may among others include physical, chemical, enzymatic and genetic bioengineering mechanisms. The chemical modification may involve introduction of various functional groups to the structure of native Starch through various chemical processes like esterification, etherification, crosslinking, oxidation and grafting.[19] Physical modification usually involves subjection of the native starches to a variety of physical reinforcement under different conditions of temperature, humidity, pressure, shear, micronization, irradiation and electromagnetic fields in the absence of any biological or chemical reagents.[20] In the enzymatic modification technique, a suspension of Starch is subjected to interactions with diverse enzyme systems, especially hydrolyzing enzymes, which directly react with the amorphous regions resulting in the production of highly functional derivatives.[21] Relative to genetic bioengineering model, specific enzymes that are responsible for starch biosynthesis are modified via genetic engineering concepts (producing recombinant enzymes) by either introducing new enzymes from other microorganisms or by silencing the plant RNA.[22] These modifications of native starches, result in significant improvement in various characteristic properties like stability, digestibility, biocompatibility, film formation, and emulsifying capacity of the modified versions.

Furthermore, this modification improves the water binding and gelling tendencies of starches; which eventually leads to significant broadening of the related pharmaceutical applications.[20] Invariably, in the pharmaceutical industry, one of the most utilized modified Starch is the pregelatinized version. In this modified format, significant improvement in characteristic properties of flow, disintegration and hardness; as well as swelling and wettability in cold water are achieved. Eventually, pregelatinized starch requirement shall be much less than that of conventional starch requirement for tablet production.[23]

Applications of Cassava Starches

Native cassava starch has found many useful applications in the food industry. These may include its utilization in the production of sweeteners like (high-fructose syrup, glucose, dextrin and monosodium glutamate), tapioca pearls, bakery and pastry products, noodles, soups, soft drinks, ice creams, and yoghurts. It has also been successfully applied in the production of feedstock as well as in microbial fermentation procedures; such as in bioethanol, butanol, L-lactic acid and trehalose production.[24] Cassava starches are also increasingly finding wider applications in non - food industries like textile, adhesive, paper, cardboard, leather etc. and more importantly and interestingly in the pharmaceutical industry.[25,24,26]

In the pharmaceutical industry, starches from cassava including native and modified versions are widely used in a variety of development and formulation techniques. They may be utilized in regulation of characteristic properties like moisture content, consistency, rheological and shelf life of both active pharmaceutical ingredients and related formulations. They have also been reported to be useful regulators in disintegration, clarity, texture, tensile and coating procedures of pharmaceutical formulations. Furthermore, starches have been utilized in emulsion stabilization and oil resistant films design. Indeed, starches including brands from cassava serve as multifunctional ingredients in many a pharmaceutical industry.[27]

Within the pharmaceutical discipline, cassava starch has indicated the promises to possessing great potential as excipient for many a solid dosage form design and

development. This is principally attributed to its unique characteristic properties of abundant availability and accessibility, high purity and ability to easily undergo physical, chemical, enzymatic and genetic modifications. These cumulatively, lead to easy alterations in their structures and thereby improving its related functional properties.

Cassava starch has demonstrated to deform mainly by plastic flow during compression, a character which favorably compares with that of official corn starch. This is an indication that cassava starch could be utilized as suitable alternative to corn starch as binder in tablet formulation. From literature, cassava starch has been documented to be possessing a lowest shape factor quality. This implies that cassava starch may serve as ingredient of choice in production of granules intended for tablet and capsule development and manufacture as they possess the tendency of promoting closer packaging of granules per the lowest shape factor quality.[28] In a comparative study, cassava starch demonstrated better binding qualities than gelatin BP in formulation of paracetamol tablet.[29] A couple of reports are also available on the potential use of cassava starches as fillers, granulators, glidants, thickeners, disintegrants, consistency modifiers, adhesives as well as gelling, bulking, and water retention agents.[30] The modified versions of cassava starches have also found wide applications in a variety of other pharmaceutical delivery systems. In this domain, modified cassava starches among others, have been successfully utilized as carrier for solid dispersions, direct compressor - filler, matrix forming agent for control release and a carrier for mucoadhesive microspheres.[31]

In a typical evaluation study conducted by Zhao et al., cassava starch was modified by the cross - link technique in the presence of alkaline sodium trimetaphosphate solution. Another batch of cassava starch was subjected to the acid hydrolysis - modification technique by exposure and interaction with 6% w/v HCl solution at room temperature for 192 hours. These modified cassava starches and the native version were subjected to spray-drying that enabled production of agglomerated starch granules which were characterized with better flowability and direct compressibility qualities. It was found out that crosslinking did not increase the relative crystallinity or the melting enthalpy of cassava starch while acid hydrolysis resulted in an increase in the crystallinity of both starches by removal of the amorphous regions. The natural and cross- linked cassava starches produced tablets with very low crushing strength, while the acid modified starch produced tablets with higher crushing strength.[32] Acid - modified and cross-linked cassava starches demonstrated improved qualities as fillers in direct-compression tablet preparation.[33] These studies and several others appear to indicate that modified cassava starches have a potential to be utilized as valuable pharmaceutical excipients and drug delivery carriers. However, systematic and detailed studies on their properties and excipient functionalities remain to be fully investigated and or conducted and are thereby urgently and critically needed.

Nduele, M., has reported on the successful utilization of cassava starch as a filler in hard gelatin capsule formulations. In this study, starches of potato, cassava and corn were mixed with model phenacetin, and the powder mixes formulated as hard gelatin capsules. On subjection to disintegration time analysis, formulations composed of 20% and 50% starch could not comply with the test. However, the formulation that was composed of 80% cassava starch demonstrated the shortest disintegration time. The dissolution profile of the formulations was observed to be dependent on the powder bed's degree of porosity and the cassava starch - filled formulation stood out as the most outstanding product in this discipline.[34,35]

Suruni Silvia, has documented the use of pregelatinized cassava starch as useful enteric polymer excipient for the formulation of enteric coated – tablets. In this study, cassava starch in the native form was esterified in a basic aqueous medium with phthalic anhydride. The resulting pregelatinized cassava starch phthalate – PCSPh was observed to possess improved coating characteristics qualities like better thermal and solubility properties; improved stability and/or non- disintegration quality in acidic medium; improved dissolution profiles of related products etc. This study has among others, demonstrated the promising potential of utilization of PCSPh as enteric polymer excipient for the formulation of enteric – coated products.[36]

Significant work has been documented on the utilization of cassava starches as potential excipient in liquid and semi – solid dosage forms, specifically in suspensions, emulsions, creams and ointments as well as in parenteral. Generally, cassava starch has been reported to be composed of low amount of amylose, in contrast to other varieties of starch composition.[12] Because of this quality, cassava starch exhibits various prime benefits including little gelatinization temperature, higher swelling power, and produces relatively high viscosity paste making it preferable as an excipient for many a liquid pharmaceutical formulation. In this discipline, both the native and modified cassava starches have been used as thickeners, suspending agent, wetting agent, stabilizers etc. with considerable level of successes. Starch mucilage has been successfully applied onto the skin as an emollient, utilized as a base in some enemas formulation and successfully used in the treatment or management of iodine poisoning.[37]

Furthermore, starch has been extensively investigated as an excipient in nasal drug delivery systems for nasal, oral, periodontal, and other targeted delivery systems.[38]

A study conducted by Atuilik, S. A. and Odetsei, V. at the Entrance University College of Health Sciences,

Pharmaceutics Laboratory, reported of a favorable comparison of the suspending agent properties of a locally available cassava starch - native and Compound Tragacanth Powder.

Cassava starches have been observed to possess a couple of physical and chemical properties which make them first choice excipient in formulation of some pharmaceutical topical products. It has been reported that cassava starches possess unique properties that enhances moisturizing function of creams and ointments. It has the ability to absorb and retain water which is important for moisturizing the skin. Additionally, cassava starch can form films that are resistant to water vapor and thereby providing a barrier that helps to prevent moisture loss from the skin. Furthermore, the hydrophobicity character of cassava starch can be enhanced through the esterification chemical modification technique. This modification reduces water absorptivity and solubility potentials of the starch, rendering it more effective as a moisturizer. The cross linking – oxidized cassava starch, in particular, has been found to have a good paste stability and enhanced retrograded properties which further enhance its moisturizing capabilities. These unique properties of cassava starch make it a promising excipient as a moisturizer in the cream and ointment industry[12] Furthermore, cassava starch has indicated the promise of being used in preparation of other topically applied products such as dusting powders for its absorbency and as a protective covering in ointments.[39] However, complete utilization of these highly promising pharmaceutical potentials of cassava starch requires further and detailed studies.

Starch has registered a remarkable benchmark in the delivery of parenteral formulations, where they are usually utilized in the form of drug – loaded carriers in microparticles and nanoparticles models. The use of microparticles and nanoparticles as pharmaceutical drug delivery systems is attracting growing interest, especially as a means of delivering site – specific and/or targeted medications. Starch is one of the polymers that has proven to be most suitable for the production of microspheres and nanoparticles to which the modified cassava starch is highly promising and thereby a potential. It is biodegradable to an acceptable extent and has a long tradition tag as an effective pharmaceutical formulation excipient.[40] Starch microspheres have been successfully used for nasal delivery of drugs and for the delivery of vaccines that may be administered per the oral and intramuscular routes. Many of the studies on starch microspheres have been carried out on sphere microspheres which are prepared by cross – linking soluble starch with epichlorohydrin or on starch particles produced by the polymerization of acry lated starch in a water-in-oil emulsion. These are all, invariably, starch microspheres that are intended for subcutaneous injections. In an improved technique, the microspheres were prepared by using an aqueous two – phase system consisting of two structurally different polymers, PEG and starch, and utilizing the ability of starch to crystallize as a method of cross-linkage. The resulting starch microspheres, when loaded with active ingredients and then coated with poly lactic – co – glycolic Acid (PLGA) resulted in a product with improved sustained release qualities.[41] A human growth hormone formulated in PLGA – coated starch microsphere has been successfully developed and clinically applied. Thus, cassava starch possesses the potential of being harnessed in the microsphere and nanoparticle drug delivery technique in parenteral drug formulation. However, systematic and comprehensive development of the abundantly available cassava starch in this technology continues to remain silent, thereby rendering the material hugely under - utilized.

Related limitations

However, the native form of cassava starches is not suitable for many a formulation application owing to their inability to withstand various processing conditions like high temperatures, high humidity, diverse pH etc., but their use may be enhanced by the starch modification technique. Furthermore, only a scanty report is available on the practical utilization of these excipient potentials of cassava starches. The source and specie specifications of cassava starch are further challenges requiring urgent resolution measures to achieve full utilization of the excipient potentials of cassava. Other identifiable gaps in formulation development involving cassava starch may include lack of standardization, misuse and over use of the material. In this article, the applications of cassava starches as potential excipients and drug delivery carriers in the pharmaceutical industry, against the background of the enumerated challenges above, were extensively investigated and thereby constituted the focus and primary objective of the study.

Recent developments in the Cassava Starch Technology

To harness the pharmaceutical formulation excipient and drug delivery - carrier potentials of cassava starch to the maximum level, researchers are persistently pursuing advanced and complex studies with the sole intention of realizing this primary objective. Principal limitations that are related to conventional drug delivery systems may include drug – specific or target organ factors and parenteral administration challenges. Other unfavorable issues may be related to bioavailability, biocompatibility and biodegradation characteristics. However, the introduction of the microparticle and nanocomposite delivery systems model, to which cassava starch plays a potent role, has emerged as a panacea to this burden of the conventional drug delivery systems. Subsequent to this, a couple of studies in these domains have been extensively conducted some of which have led to revelation of new discoveries and concepts in the cassava starch industry. This industry is thereby attracting deep pharmaceutical interests some of which are briefly presented herein.

In a recent study, native cassava starch was subjected to a complex – modification technique via interaction with ferulic acid. The resulting modified Starch was observed to be characterized with a number of improved physicochemical properties, the most prominent among which was the antioxidant quality. This observation implies an interesting potential use of the modified cassava starch as antioxidant in the cosmetic industry. Essentially, this is a promising indication of the possible utilization of cassava starch as relevant excipient in antiaging formulations.[42]

Thah, H. and Hung, V., have reported the successful development of curcumin – loaded cassava starch nanoparticle formulation which has demonstrated improved pharmaceutical benefits including better efficiency, loading capacity, cellular absorption, sustained release characteristics etc. over the conventional curcumin formulations.[43]

In a separate study, Sivamaruthi et al., developed nanoparticles from cassava starch using a nanoprecipitation technique to encapsulate insulin for nasal delivery. The nanoparticle formulation exhibited good stability, better mucoadhesive properties, and enhanced insulin release in simulated mucus conditions compared to free insulin. Furthermore, this study demonstrated the potential of cassava starch-based nanoparticles as biodegradable and biocompatible carrier for targeted drug delivery in parenteral routes like nasal administration; and thereby potentially offering a cost-effective alternative for specific drug delivery.[44]

Another study reported by Sanjoy, D et al., involved 'Cassava Starch as a Binder in Lyophilized Formulations: Development and characterization of injectable microspheres containing docetaxel prepared with cassava starch as a binder'. This study investigated the use of pregelatinized cassava starch as a binder in docetaxel-loaded microspheres for injectable suspensions. The microspheres with cassava starch binder exhibited good stability, drug loading capacity, and sustained drug release profiles when compared to a formulation designed with polyvinylpyrrolidone (PVP), a synthetic binder. This study suggested the potential of cassava starch as a natural and potentially less immunogenic binder in lyophilized formulations for parenteral administration, offering a possible alternative for specific drug delivery systems.[12,45]

Another separate study conducted by Raj and Prahba involved investigation of the in vitro drug release profile of cisplatin - loaded Cassava Starch Acetate CSA – polyethylene glycol PEG – gelatin G nano composite model. A significantly improved controlled delivery of cisplatin potential of this polymeric cross - linked CSA – PEG – G nano composite was revealed in this study.[46]

However, majority of these studies presented above are still at the preclinical stage, and further research and regulatory approvals are thereby required before such relevant cassava starch-based formulation applications can be used in marketed parenteral formulations.

Limitations of the Cassava Starch Technology

Notwithstanding the above - mentioned pharmaceutical significance and huge potential of the cassava starch technology, it is also beset with a couple of practical challenges and limitations. Potential adverse physicochemical properties with which cassava starches are characterized such as poor solubility in cold water, ease of dehydration, low emulsifying power and instability in acidic medium are critical hindrances to commercialization of these starches. In an effort to resolving some of these challenges, the native cassava starch is subjected to a couple of technical modifications whereby the physical, chemical and functional properties of the modified versions are significantly improved. The modified cassava starches have indicated potentials as better and more useful pharmaceutical formulation excipients and thereby presents as a discipline requiring further and advanced exploration and research. Thus, cassava starch modification techniques such as cross-linking, gelatinization, acid – acid - modification, grafting, esterification, etherification, enzymatic alterations, genetic modifications etc. still remain a discipline yet to be fully explored, and thereby, a huge gap in the commercialization of the ingredient. Cassava species, source and standardization of related starches are also major areas of concern. Coupled with a higher degree of wide applications of starches, including cassava starch, in a variety of pharmaceutical formulations, the urgent need for further research to developing newer excipients possessing appropriate functional properties to satisfy needy pharmaceutical cases based on Starch becomes a necessity to the pharmaceutical drug formulator.

Toxicity and Safety Profile of Cassava Starches

In recent times, concerns related to toxicity and safety profiles of cassava starches have been assuming wider dimensions as a result of the growing pharmaceutical interests expressed in utilization of these starches as both excipients and carriers in drug delivery systems. The utilization of modified cassava starches is on the increase. However, related risks on their long - term use are scanty and appear to remain largely unknown in available literature. This thereby demands the urgent need for extensive and deeper investigations into the toxicity and safety profiles of these modified starches. Even so, a couple of such studies have been conducted in animal models with the sole aim of investigating these critical requirements. A toxicological study involving long – term administration of chemically modified cassava starch in mice resulted in structural changes in the intestines and kidneys.[47] In a separate long – term toxicological study, following prolonged administration of cross-linked or substituted modified cassava starches in rats, higher levels of mineral deposits in the kidney pelvic regions coupled with enlargement of the caecum

were observed.[48] These are ample evidence of the critical need for deeper toxicological studies to be conducted regarding consumer safety, should the envisaged large – scale use or commercialization of these starches is to become a reality. Relevant toxicological screening tests to be conducted may among others include acute, sub – chronic, chronic, carcinogenic and genotoxic assessments. These may be performed in accordance with the Organization for Economic and Co-operative Development – OECD guidelines.

Outlook of the Cassava Starch Industry

This current review has revealed that cassava starches including both the native and modified versions, have emerged as promising excipients in the pharmaceutical formulation technology. This is attributed principally to their favorable unique properties and characteristics which are further readily adaptable. However, systematic and extensive studies on their properties and excipient functionalities, especially on modified cassava starches, are required so as to assist in fully harnessing these potentials. Additionally, further research in assessment and evaluation of cassava starches capabilities and limitations in different pharmaceutical formulations, especially in micro and nano formulated systems, is an urgent necessity. For a comprehensive understanding of the limitations of cassava starches as pharmaceutical excipients, further research in consultation with requisite stakeholders like experts in the field may also be recommended.

This review summarizes, to a greater extent, available documented information on cassava starches and their related applications as pharmaceutical formulation excipients and drug delivery carriers. This has been designed with the intent to developing a resource center that can promote cassava starch as a potential formulation excipient in the pharmaceutical industry, and thereby creating ingredient alternatives and a wide variety of related products. Furthermore, this is with the view to providing suggestions for further and needed research studies to be adopted so as to fully harness the formulation excipient and drug delivery carrier potentials of cassava starches concerning pharmaceutical technology. With high levels of accuracy in drug delivery to target organs coupled with formulation benefits of excellence in vivo performance, readily availability and accessibility, low cost etc. cassava starches are currently attracting higher demands for development as drug delivery carriers. Concerning the design of microparticles, nanocomposites, buccal films, nasal and topical gel formulations, cassava starches have demonstrated credible qualities and invaluable successes to which adequate documentation is available. Notwithstanding, related toxicity and safety profiles are only scanty or even non available, rendering their commercialization a huge challenge. However, a few toxicological studies conducted on modified cassava starches suggested their patient safety as they do not appear to show any sign of serious clinical toxicity. Modified cassava starches have further proven to be utilized in a variety of disciplines as promising materials for design of drug delivery carriers and formulation excipients based on their huge versatility factor. Finally, detailed and systematic investigations of cassava starches shall be conducted to facilitate acquiring a better understanding of related characteristics and enable the total development of the material.

CONCLUSIONS

Cassava starches have indicated the promise of being utilized as pharmaceutical excipients and carriers in drug delivery in a wide variety of formulations. However, their potential use as multifunctional excipient is limited by some of their adverse characteristic physicochemical properties. In an approach to resolving this challenge, native cassava starch may be subjected to a variety of technical modifications that invariably improve their quality as pharmaceutical excipients and drug delivery carriers. A couple of modified cassava starches have been established among others, to be useful in the formulation of microparticles, nanocomposites, tablets, buccal films and topical gels. This review appears to indicate that cassava starch shall continue to be a material of cherished importance in pharmaceutical formulation and drug delivery model owing to its possession of excellent characteristic properties like ease of modification, low cost and susceptibility to wider applications. Even with these potential benefits, lack of credible and systematic toxicity and safety profile studies of cassava starches are a critical limitation to their commercialization.

REFERENCES

1. Chaudhari SP, Patil PS. *Pharmaceutical Excipients: A Review.* Int J Advances in Pharmacy, Biology & Chemistry., 2012; 1(1): 21 - 32.
2. Builders P, Arhewoh MK. *Pharmaceutical Applications of Native Starch In Conventional Drug Delivery.* Starch - Starke, 2016; 68(9 -10).
3. Hu A, Jiao S, Zheng J, Zhang Z. *Ultrasonic Frequency Effect on Corn Starch and its Cavitation.* LWT Food Sci & Tech., 2015; 60: 941-947.
4. Rodrigues A, Emeje M. *Recent Applications of Starch Derivatives in Nanodrug Delivery.* Carbohydrate Polymers, 2012; 8: 987-994.
5. Hartesi B, Sriwidodo T, Abdassah M, Chaerunisaa AY. *Starch as Pharmaceutical Excipient.* Int J Pharm Sci Rev & Res., 2016; 41(2): 56-64.
6. Musah H, Ochu SN, Bhatia PG. *Evaluation of the Tablet Binding Properties of Barley (Hordeum vulgare) Starch.* Int J of Applied Pharmaceutics, 2010; 2(4): 4 - 7.
7. Punia S, Kidwai MK, Kawaljit SS, Dhull SB, Kaur M. *Oat Starch: Physicochemical, Morphological, Rheological characteristics and its applications - A Review.* Int J of Biological Molecules, 2020; 154(2020): 493 - 498.
8. Nweke F, Haggleblade S, Zulu B. *Recent Growth in Africa Cassava.*, in *2020 Vision Briefs*, F. Nweke, Editor. 2020, EconPapers from IFPRI.: International

Food Policy Research Institute – IFPRI Washington.
9. OECD/FAO. *Agriculture in Sub - Saharan Africa: Prospects and Challenges for the next decade.* Starch Production - 2016 2016 [cited 2024 15th September.]; Available from: oecd-ilibrary.org/2016.
10. Sugih AK, Christabella L, Kristianto H, Prasetyo S. *Effect of different types of phosphorylating reagents on the synthesis of modified tapioca starch.* in *IOP Conference Series.* 2010. Material Science and Engineering: IOP Publishing.
11. Allem AC. *The Origin of Manihot esculenta, Crantz (Euphorbiaceae).* Genet Resour Crop Evol., 1994; 41: 133 - 150.
12. Sanjoy D, Jamatia T, Yadav PK, Bhattachery B, Sinha B. *Efficacy of Cassava Starch in the Design of Drug Delivery Platforms.* Polymeric Biomaterials, 2022; (2022).
13. Ceballos H, Okogbenin E, Perez JC. eds. *Handbook of Plant Breeding*. Root and Tuber Crops: ed.
14. J. Bradshaw. Springer: New York 2010; 7: 53 - 96.
15. Tappiban P, Sraphet S, Srisawad N, Bao J, Han H. *Effects of Cassava variety and growth location on Starch fine structure and physicochemical properties.* Food Hydrocolloids, 2020; 108(2020).
16. Adjei KF, Asantewaa YO, Kuntworbe N, Ofori-Kwakye K. *Evaluation of the Disintegrating properties of Native Starches of 5 New Cassava Varieties in Paracetamol Tablet Formulations.* J Pharm (Cairo), 2017.
17. Williams G, Ansah KO, Agbenorhevi JK, Oduro IN, Bobobee E. *Characterization of Starch from New Cassava Accessions at Different Maturity.* J Food Security, 2019; 7(5): 170 - 174.
18. Zhu S, Liu B, Wang F, Huang B, Zhong F, Li Y. *Characterization and in vitro digestion properties of cassava starch and epigallocatechin - 3 - gallate (EGCG) blend.* LWT - Food Sci & Tech., 2021; 137(2021): 110398.
19. Ojewumi ME, Emetere ME, Obinna O, Baloju E. *Rheological properties of cassava and corn starches.* Int Res J Applied Sci, Engineering and Tech., 2019; 5(2): 1 - 11.
20. Chen Q, Yu H, Abdin Z, Chen Y, Chen X. *Recent Progress in Chemical Modification of Starch and its Applications.* RSC Adv., 2015; 5: 67459-67474.
21. Bashir K, Aggarwal M. *Physicochemical, Structural and Functional Properties of Native and Irradiated Starch: A Review.* J. Food Sci Technol, 2019; 56(2): 513-523.
22. Park S, Na Y, Kim JW, Kang SD, Park JH. *Properties and Applications of Strach Modifying Enzymes for use in the Baking Industry.* Food Sci Biotechnol, 2018; 27(2): 299-312.
23. Hebelstrup KH, Sagnelli D, Blennow A. *The Future of Starch Bioengineering: GM Microorganisms or GM Plants?* Frontiers Plant Sci., 2015; 6: 2015.
24. Lefnaoui S, Moulai-Mostefa N. *Synthesis and Evaluation of the Structural and Physicochemical Properties of Carboxymethyl Pregelatinized Starch as a Pharmaceutical Excipient.* Saudi Pharm J., 2015; 23: 689-711.
25. Li S, Cui Y, Zhou Y, Luo Z. *The Industrial Applications of Cassava: Current Status, Opportunities and Prospects.* J Sci Food & Agric., 2017; 97(8).
26. Wang W, Hostettler CE, Damberger FF, Kossmann J, Lloyd JR, Zeeman SC. *Modification of Cassava Root Starch Phosphorylation Enhances Starch Functional Properties.* Front Plant Sci., 2018; 9: 1562.
27. Abotbina W, Sapuan SM, Llyas RA, Sultan MA. *Recent Developments in Cassava based Biocomposites and their Potential Industrial Applications: A Comprehensive Review.* Materials, 2022; 15(19): 6992 - 6999.
28. Shubo L, Yuah Z, Yanyan C, Zhiting L. *The industrial applications of cassava: Current status, opportunities and prospects.* Journal of the Food and Agriculture, 2017; 9(8): 1030 - 1072.
29. Itiola OA, Odeku OA. *Packing and Cohesive Properties of Some Locally Extracted Starches.* Tropical J Pharm Res., 2005; 4(1).
30. Varghese N, Komala M. *Natural Starches as Pharmaceutical Excipients: A Review.* World J Pharm Sci., 2020; 9(10): 1065 - 1081.
31. Du Preez WC. *Cassava starch as modified release excipient in selected gliclazide oral dosage forms.*, in *Pharmaceutics*, 2015; North - West: USA.
32. Charoenthai N, Thiraphong S, Satit P. *Use of Modified Tapioca Starches as Pharmaceutical Excipients.* Int J Pharm Sci., 2018; 45(4): 195 - 204.
33. Zhao Y, Zheng Z, Zhao Y, Tang S, Chen Y. *Cross linked modification of tapioca starch by sodium trimetaphosphate: An influence on its structure.* Food Chemistry, 2024; X.
34. Atichokudomchai N, Varavinit S. *Characterization and Utilization of Acid Modified Cross - linked Tapioca Starch in Pharmaceutical Tablets.* Carbohydrate Polymers, 2003; 53(1): 263 - 270.
35. Nduele M, Ludwig A, Ootegham VM. *The use of Cassava Starch in the Formulation of Gelatin Capsule.* J Pharm Belg., 1993; 48(5): 325-334.
36. Zhang Z, He X, Zeng C, Li Q, Xia H. *Preparation of Cassava Starch - Gelatin Yolk - Shell Microspheres by Water - in - Water Emulsion Method.* Carbohydrate Polymers, 2024; 323(1).
37. Suruni S. *Preparation and Characterization of Pregelatinized Cassava Starch Phthalate as pH - sensitive Polymer for Enteric Coated Tablet Formulation.* Int J Pharm & Pharm Sci., 2014; 6.
38. Shalin S. *Advantages and Applications of Native Excipients.* Asian J Pharm Res., 2012; 2(1): 30 - 39.
39. Lukeva P, Katsarov P, Pilideva B. *Application of Starch, Cellulose and their Derivatives in the Development of Microparticle Drug-Delivery Systems.* Polymers, 2023; 15(17): 3615.
40. Sanjoy D, Jamatia T, Bhattachery B, Mazumder R, Mandal S. *Advances of cassava starch - based composites in novel and conventional drug delivery*

systems: a state-of-the-art review. RSC Pharm., 2024; 1: 182 - 203.
41. Xie X, Zhang Y, Zhu Y, Lan Y. *Preparation and drug - loading properties of amphoteric cassava nanoparticles.* Nanmaterials, 2022; 12(4): 598 - 603.
42. Elfstrand L, Ellison A, Wahlgren M. *Changes in starch structure during manufacturing of starch microspheres for use in parenteral drug formulations: Effects of Temperature Treatment.* Carbohydrate Polymers, 2009; 75(1): 157 - 165.
43. Fang EF, Xie C, Schenkel JA. *A research agenda for ageing in China in the 21st Century.* Ageing Res Rev., 2020 Dec; 101174.
44. Thah H, Hung V. *Characterization of curcumin loaded starch nanoparticles from native cassava and potato starches.* J Sci Tech & Food., 2021; 21(2): 3 - 11.
45. Sivamaruthi BS, Nallasam PK, Suganthy N, Kesika P, Chaiyasut C. *Pharmaceutical and Biomedical applications of starch - based drug delivery system. A review.* J Drug Deliv. Sci & Tech., 2022; 77(Nov 22).
46. Torres GF, Troncoso OP. *Starch based Polymers of Drug Delivery Applications.*, in *Polysaccharides in Advanced Drug Delivery*, 2020; CRC Press. 24.
47. Til HP, Feron VJ, Immel HR, Vogel WF. Toxicity and safety status of cassava starches. Food Chem Toxicol, 1986, 24: 825 – 834.
48. Worzberg OB. Evaluation of natural, cross – linked and acid – modified cassava starches. Nutr Rev., 1986; 44: 74 – 79.