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PLANTS AS PHARMACEUTICAL EXCIPIENTS IN ORAL SUSTAINED DRUG DELIVERY SYSTEMS: A REVIEW

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ABSTRACT

Plants and their derivatives have contributed immensely to drug development for their application as medicinal agents or as excipients in the preparation of new drug delivery systems. Their use keeps increasing by the day. The rich, yet-to-be fully tapped vegetation available in the African sub-region gives it great potential as, likely, the next global destination source for pharmaceutical excipient. This work reviews published articles on plants and derivatives that have been employed so far in modifying drug delivery. Published articles from databases of Pubmed, Science direct and Google scholar were sourced. Obtained manuscripts were screened for relevance to the topic and currency after reading through the abstract and scanning the body of the work. Gums and mucilages as plant derivatives in their natural form or as modified forms have been well investigated for use in controlled drug delivery. Some of these have been as functional in modifying drug release as many commercially employed excipients in drug delivery. Many plants and plant-derived polymers are generally regarded as safe, easily cultivated, show good functionality as drug additives and can be modified to improve on any less desirable property. Taking advantage of these positive factors will open doors for optimal use of these naturally endowed pharmaceutical excipients.

INTRODUCTION

Research and Markets in its 2021 report for the global pharmaceutical industry postulated an expected growth from $1.23 Trillion in 2020 to $1.25 Trillion in 2021 at a compound annual growth rate (CAGR) of 1.8 % and to $1.70 Trillion by 2025 at a CAGR of 8 % [1]. Africa, despite that its rich medicinal herbs, some exclusive to the region, was with the least contribution to the global pharmaceuticals market. The fast moving pace of new technologies in drug delivery systems as well as the high cost of new drug discoveries and development has led to a call for new pharmaceutical excipients to improve efficiency of the active pharmaceutical ingredient (API) delivery and bioefficacy amongst other reasons. In Nigeria, the challenge of the importation of over 80 % of the raw materials employed

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in drug production and the consequent high cost of medicines has forced a large number of patients to resort to herbal medicine, who depend on the indigenous plants for healing. Investigations have given a scientific backing to most of the folkloric claims of these plants, and many are now marketed as herbal supplements. Such plants are generally regarded as safe (GRAS) since they are consumed as food by indigents, hence it made for good thinking to study them as sources of raw materials for drug formulation.

The technologies of novel drug delivery systems has created the need for raw materials with specialized features to aid the delivery process while not causing a great economic damage. Sustained drug delivery system has been largely employed with recorded successes in drug formulation and more APIs are being designed as such dosage formulation [2]. The success of any sustained release system is dependent largely on the functional role of the excipients applied in its formulation.

Gums and starches are two classes of polymers that have been found to be suitable in retarding drug release, effecting a sustained drug delivery in physiological systems. Thus new sources of these polymers are required to meet the tailored needs of sustained release formulations and plants have been identified as one of such. The interest in herbal excipients has grown tremendously in the past decade with research focused on indigent plants, consumed as food or traditional herbs that have been used from the beginning of time.

For a region with dense vegetation, tropical Africa could become a primary source for pharmaceutical raw materials with the current trend of sourcing from herbal plants. There is a pressing need then to study indigenous nutraceuticals and their potential as pharmaceutical excipients and not just for their pharmacological properties. Waste products of agricultural crops have severally been processed into raw materials for drug formulations and there is still an abundance of these plants out there that are yet to be investigated [3].

The high cost of drug discovery and development has pushed for a redesigning of delivery system of known active API for optimal drug efficacy, prompting the need for excipients with unique functional features. The call for a cheaper and safer source for pharmaceutical excipient as well as growing interest in natural polymers created the need for this new direction of study. This review thus aims to highlight the potentials of the vegetations in the tropical regions of Africa, its under-utilization; emphasize the need to cultivate crops, not solely for consumption to live, but also to generate revenue from the drug market. The crux of it being to attempt to draw attention to the emerging trend of herbal excipients employed in the design of oral sustained released drug delivery systems with emphasis on native and modified natural gums.

DRUG DISCOVERY AND DEVELOPMENT

Drug development is a complex, time consuming and expensive endeavor. A 2020 study by Wouters and coworker estimated the average cost of drug development for a single drug at $1.3 billion using publicly available data [4]. Only about 10 % of the drugs that get to the level of pre-clinical trial make it to the human testing stage. The cost of the failed drugs is not recouped but the successful drugs must compensate for the loss. The high cost of production leads to expensive drugs which has posed a huge problem in disease management in developing countries [5]. There have only been a limited number of drug leads and drug candidates in developing countries owing to the fact that pharmaceutical firms do not foresee a profit from drug sales in such countries because there is lack of purchasing power.

Therapeutically active agents are hardly administered alone but as a mix with other substances to make a dosage form. The added substances, known as excipients are added to the API for various reasons amongst which are [6];

i. Facilitation of dosage form production

Sometimes the quantity of the API required to elicit a desired therapeutic action may be too small for production of a dosage form e.g. successful compaction of the powder blend to give satisfactory tablet dosage form required a minimal quantity; drugs with low therapeutic index require a bulking up to minimal compactable quantity; some APIs may require viscosity imparting agents to keep them suspended long enough to dispense an appropriate dose; etc

ii. Patient acceptability of dosage form encouraging adherence

Drug administration must take into consideration the state of the patient and ability to receive the drug e.g. a baby/toddler cannot be expected to swallow a solid dosage form or an unpleasant tasting liquid or semi-solid dosage form without a lot of fuss; a comatose patient cannot be expected to take an oral dosage formulation. Heavy pill burden discourages adherence but the

technology of delayed release formulation with the aid of release modifying excipients has shown positive outcomes.

iii. Improving stability of the API

Some APIs have been observed to show a poor retention of stability in their pure form or react with packaging materials sometimes leading to hazardous by-products. Such APIs require the aid of other substances to improve their shelf life while keeping them fit for consumption by preventing the undesirable interactions. This will in turn impact the total effectiveness and safety of the API.

iv. Improving bioavailabilty of the drug

At the start of drug production, excipients were included in a formulation just to get the desired consistency and there were considered to be inert. However drug design nowadays involves the use of substances that enhance the bioavailability of the API such as targeted site release, targeted time release, improved solubility of an API in a solvent, nanosizing of drug particles, etc. [7].

Excipients have various origins – animal (gelatin, lactose), plants (starches, cellulose), minerals (silica, talc) and synthesis (polyethylene glycol, povidone). Their origin and use does not automatically confer suitability for use on them and so must undergo analytical control test. In order to meet the numerous current functional requirements for excipients in novel delivery systems, new classes are being made available, sometimes derived from old and new excipients either alone, in combination or after appropriate modification. Compounds originating from food are generally recognized as safe and fall into one category; a second category has compounds that are obtained by the structural modification of already approved substances and in use and a third category has new compounds with growing use in technologies such as modified drug release systems [7].

Aside the use of such foods as herbal nutraceuticals, they are also being explored as potential pharmaceutical excipients. Plant-based materials have found tremendous interest in the drug industry because of their non-toxicity, affordability, ease of accessibility, renewability, constant availability since they are cultivated, biodegradability, biocompatibility, eco-friendliness and ease of modification [8]. Even food waste materials can be used as sources of excipients e.g. cellulose extracted from waste fibers. However, like the benefits listed above, herbal excipients also have their drawbacks [9]:

i. Susceptibility to microbial contamination and degradation
ii. Topographical variations
iii. Inconsistency in constituent composition which may vary with area of cultivation
iv. Slow rate of production since its growth is a natural process dependent on factors present in its environment
v. Increased chances of heavy metal contamination from the environment

The multiple applications of plant based polymers as excipients and their relatively low cost have contributed to the increase in demands for identification of potential new ones. On the basis of their various conventional uses in pharmaceutical formulations, herbal excipients can be categorized into thickeners (gums, mucilages), binders (starches), emulsifiers (acacia gum, tragacanth gum), suspenders (gums, pectin), lubricant, disintegrants (starch) gelling agents (alginate, pectin, agar) flavoring agents (peppermint, nutmeg), diluents, sweetening agents (dates, stevia), coating agents and colouring agents (henna, turmeric). The performance of an excipient in a formulation is partly responsible for the standard of the preparation. The emergence of novel drug delivery systems in a bid to achieve better bioefficacy of a known API means newer and more efficient excipients are required at minimal cost.

HERBAL EXCIPIENTS AND ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEM

Oral delivery of drugs is still the most preferred route since it is convenient, relatively cheaper to produce and package, usually packed as unit doses, The aim of any oral dosage regimen for any disease is to attain an acceptable therapeutic dose at the site of action as soon as possible and maintaining this concentration for the period of the therapy. Using immediate release dosage forms require specific dose size and frequency of dosing to be able to maintain a steady state plasma concentration; that is repetition of dosing is frequently required. There are various problems associated with this manner of dosing starting from plasma concentration fluctuations over several dosing to non-compliance by the patient. Over the years researchers have dedicated a lot to designing a delivery system that will reduce some of these limitations of the conventional drug delivery system. They designed the extended release preparation which also took partial control of drug administration from the

physician and patient. Various terms have been used to describe this system including the following:

i. Delayed release
ii. Repeat action
iii. Prolonged release
iv. Extended release
v. Sustained release
vi. Controlled release
vii. Modified release

Some of these terms are used interchangeably and sometimes there is no distinct line in defining them. The general principle is that they all involve reduced frequency of dosing while maintaining a uniform and adequate plasma concentration of the API for a desired duration [10]. Sustained release drug delivery system (SRDDS) are designed to release an initial dose of the API sufficient to achieve the desired plasma concentration after administration and then a gradual release of the maintenance dose over an extended period with a single dosing of the formulation. The commonest forms of SRDDS are tablets, capsules and granules; although liquid formulations such as suspensions also exist [11]. Table 1 is a compilation of some of the advantages and disadvantages of SRDDS.

Table 1: The advantages and disadvantages of the SRDDS

	Advantages	**Disadvantages**
1	Reduced frequency of dosing	Unpredictable and frequent poor *in vivo- in vitro* correlation
2	Reduced drug dose due to improved drug utilization	Increased chances of dose dumping leading to toxicity
3	Improved patient compliance leading to therapy success	Increased cost of production
4	Uniformed drug release over time giving optimized therapy	Increased chances for first pass clearanc
5	Reduced systemic and local side effect	Additional patient education and counseling required for proper administration
6	Reduced fluctuation of plasma drug concentration leading to uniform pharmacological response	Difficulty in retrieval of drug in case of dose dumping or hypersensitivity reaction
7	Improved drug bioavailability by the protective action of polymer employed against enzymatic inactivation on the API	Reduced potential for dose adjustment where the drug is usually administered in varying strengths
		Complete drug release may not be achieved

Source: [12, 13]

FORMULATION OF ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEM

There are three main mechanism of drug release from SRDDS - diffusion controlled systems, dissolution controlled systems and diffusion- dissolution controlled systems. Other mechanisms of release are ion exchange resin drug complex system, pH dependent formulation system and osmotic pressure controlled systems. In designing any modified drug release system, there are some basic components of the formulation which include:

i. The API
ii. A release controlling agent(s) – matrix formers, membrane formers
iii. A matrix or membrane modifier e.g. wax for hydrophobic matrices and solubilizers for hydrophilic matrices
iv. Density modifiers (optional)
v. Lubricants and flow aid
vi. Supplementary coating agents to extend lag time (optional)

Matrix Controlled Drug Delivery System

In an oral SRDDS design, matrix technology has proved popular due to ease of manufacture, simplicity, raw materials and dosage form stability, reproducibility, ease of product validation and scale-up[14]. Advancement in the area of matrix formulation has contributed immensely to the design of controlled release formulations across a wide variety of drug differing in biopharmaceutical and physicochemical properties. One of the least complicated techniques of SRDDS formulation is the drug-embedded matrix tablet system in which the retardant material and other additives are blended with the drug and compressed into tablets. The retardant material could be either hydrophobic as well as inert (known as plastic matrix system e.g. ethyl cellulose, polyethylene), or hydrophobic but erodible (e.g. polyethylene glycol, castor wax) or hydrophilic (e.g. gums, mucilages, sodium carboxymethyl cellulose).

***Plastic matrix systems*:** Drug release from this system is comparable to leaching from a sponge and release is dependent on drug diffusion in aqueous medium through a network of capillaries formed between compacted polymer particles; however channeling agents could be added to such formulations. Concerns that initiators and residual catalysts used to formulate the matrix polymers could also leach alongside the API were raised as well as concerns by patient on sighting the remains of the insoluble matrix “ghost” in stools.

***Hydrophobic but erodible matrix system*:** this is also known as the wax matrix system. The powdered form of the wax, drug and other additives is blended and the dosage form manufactured using direct compression, roller compaction or hot melt granulation techniques. The channeling agent will dissolve in the aqueous medium forming tortuous capillaries on the insoluble matrix which will allow the API access to the aqueous medium for dissolution and diffusion out of the matrix. The pore diffusion and erosion control drug release from such systems.

***Hydrophilic matrix system*:** these systems are also known as the swellable-soluble matrices. It involves the mixture of the API, a water-swellable hydrophilic polymer and other additives. On exposure to the aqueous environment, the formulation will swell; form a gel which will erode gradually allowing for API dissolution. The viscous gelatinous layer will act as the surface barrier that will control drug release and liquid penetration into the matrix system. As it becomes dilute, the outer barrier layer will erode and the erosion rate is dependent on the nature of the polymer.

Membrane Controlled Drug Delivery System

The membrane controlled technology for sustained release formulations involves the release of the drug from the inner reservoir core by a monitoring polymeric encapsulating membrane which will have a specific permeability. The drug will diffuse through this membrane owing to the membrane hydration with water which is present in the GIT or the drug solubility in a membrane component. Unlike the swellable matrix polymer, the membrane polymer does not swell and will not erode. A loading of the membrane could also serve for an initial release of the API on contact with the dissolution medium before the release from the reservoir core which will give a continuous release from an adequate period. An increase in the coat/membrane thickness could also cause a reduction in the release rate while the presence of some polar compounds, when co-encapsulated, can still lower the release rates further. Another way this system differs from the matrix system is that the polymer membrane is found only on the surface of the formulation while the polymer in the matrix system is embedded in the whole formulation. The membrane plays a critical role in the release of the drug and the choice of polymer is just as important. Typically, ethyl cellulose, acrylic co-polymers, zein and shellac are the polymers of choice in this system; however because of inconsistency in quality as natural products, shellac and zein are less often used. Other additives like plasticizers are required to modify the release characteristics of the membrane.

POLYMERS USE IN SUSTAINED RELEASE DRUG DELIVERY SYSTEM

The word "polymer" designates an unspecified quantity of monomer units and a polymer with a large number of monomers is called a high polymer. However, a polymer is not necessarily composed of monomers of same molecular weight, structure or chemical composition. Some natural polymers contain one type of monomer while a lot of synthetic and natural polymers contain at least two types of monomers. Such polymers are called copolymers.

Over the past 30 years, polymer based technologies have found wide biomedical applications. Polymers used as pharmaceutical excipients can be of synthetic or natural origin. Natural polymers or biopolymers occur in nature in the course of the life cycles of animals, green plants, fungi and bacteria; they include starch, alginate, chitosan, dextrins, gellan gum, xanthan gum, pectins and proteins while synthetic polymers include poly-lactide-co-glycolide acid, polylactic acid, polyanhydrides, polyisohexylcyanocrylate , poly (cyanoacrylates), poly(acrylic acid), poly(amides), poly (ortho esters), poly(ethylene glycol), poly(vinyl alcohol) and others such as poly (isobutylcynoacrylate), poly(å- caprolac- tone) , poly(ethylene oxide). The wide utilization of polymers in medical field is because of their biodegradable and biocompatible characteristics since their by-products, glycolic acid and lactic acid, are metabolized.

Drug formulation methods, polymer properties (such as molecular weight, the lactide/glycolide ratio of the copolymers), physicochemical parameters (temperature and pH) are determinants that affect the degradation and consequent release of the associated drug. Table 2 is a summary of the advantages and disadvantages of the use of synthetic and natural polymers as excipients in drug delivery systems.

Batch-to-batch inconsistency and quality is a primary challenge for pharmaceutical suppliers of polymers obtained from natural sources with different assay and qualities. However, the benefits of their use have overshadowed such concerns and there is an increasing interest in the search for new plant based excipients in the design of formulations.

Table 2: Advantages and disadvantages of polymer use in drug delivery systems

Advantages of polymers	
Natural polymers	***Synthetic polymers***
e.g., Starch, cellulose, gelatin	e.g., Poly ethylene glycol (PEG), PLGA (poly (lactic-co-glycolic acid
Less toxic	Biocompatibility
Biocompatibility	
Biodegradability	
Easily available	
Flexibility	
Hydrophilicity	
Disadvantages of polymers	
Natural polymers	***Synthetic polymers***
High degree of variability in natural materials derived from animal sources	Toxic
	Non degradable
More complex structurally	Synthetic process is very complicated and high cost
Extraction process very complicated and high cost	
Low mechanical properties	

Source: [15]

Polymer Use in Matrix Tablets

The use of natural, semi-synthetic and synthetic polymers has been extensively explored in the design of SRDDS [16]. Table 2.3 shows categories and examples of polymers that are utilized in matrix tablet design. Synthetic polymers are relatively expensive, not eco-friendly, toxic, require an extended development time for synthesis but are freely available. However natural polymers have found a more favourable application because they are classed as GRAS, economical, readily available, amenable to modification, ecofriendly, biodegradable and biocompatible.

The popularity of hydrophilic polymers may be linked to their swelling ability, regulatory acceptance, low cost and susceptibility to direct compression in tablet formulation [17]. They form a viscous gel in the presence of water and drug release is through diffusion, dissolution, erosion or a combination of the three mechanisms. Sometimes a combination of hydrophilic polymers may be use in order to increase matrix viscosity and modify drug release pattern. Table 4 is a summary of the advantages and disadvantages of hydrophilic polymers. Natural gums are amongst the most popular hydrophilic polymers that are widely used in the design of sustained release formulations. Starches are another class of polymers that have found wide application in the SRDDS whether as the native or modified form.

Table 3: Categories of polymers used in matrix tablets and examples

	Polymers	**Examples**
1	Natural gums and mucilages	Xanthan gum, karaya gum, guar gum, acacia gum, tamarind gum, neem gum
2	Hydrogels	Polyethylene oxide, cross-linked polyvinyl pyrrolidone
3	Soluble polymers	Polyethylene glycol. Polyvinyl alcohol, hydroxypropyl methyl cellulose
4	Biodegradable polymers	Polylactic acid, polyanhydrides, polycaprolactone
5	Non-biodegradable polymers	Polyethylene vinyl acetate, polyether urethane
6	Mucoadhesive polymers	Polycarbophil, tragacanth gum, sodium carboxymethyl cellulose

Source: [14]

GUMS AND MUCILAGES

It is rather difficult to distinguish gums and mucilages; however gums are produced as a result of a pathological condition which results from injury to the plant or adverse condition of growth leading to changes in its existing cell wall while mucilages are generally products of metabolism, formed within the cell in the absence of any injury. Gums are also readily dissolved in water while mucilages form a slimy mass. These substances are formed in different parts of the plants such as the middle lamella (e.g. algae); cell wall (e.g. seed epidermis, the seed endodermis, cells in the bark); special secretory cells (e.g. squill); in the schizogenous sacs as in the young stem of Rhamnuspurshiana, or by lysiogenous metamorphosis of the cell walls as in tragacanth and acacia[18] .

Gums consist of sugar units linked to create larger molecules and are heterogenous in composition. Most natural gums form three dimensional interlinked molecular structures which are known as gels. The entrapment of water molecules between their chains

and branches lead to the swelling typically observed with gums [19]. On hydrolysis, sugar units such as mannose, xylose, glucose, arabinose are yielded. Table 5 show their classification according to four parameters.

Table 4: Advantages and disadvantages of hydrophilic matrix systems

	Advantages	Disadvantages
1	Comparatively simple concept	Drug release is dependent on two diffusion processes
2	Excipients are generally cheap and generally regarded as safe (GRAS)	Improper erosion of the outer hydrated matrix could complicate the release profile of the drug
3	Capable o sustaining high drug loading	Batch-to-batch consistency required in the raw materials and process parameters
4	Chances of "ghost" matrices are very low since they are erodible	Problematic scale-up process
5	Easy to manufacture using direct compression, roller compaction or wet granulation techniques	Optimal rate-controlling polymers required for various API
6	Different drug release kinetic models are possible	

Source: [10]

Gums and mucilages have a normal equilibrium moisture content of 10 % or more and are susceptible to microbial contamination when exposed to external environment during production process. They act as viscosity imparting agents when introduced to an aqueous system; however on storage they tend to lose some of their viscosity. As pharmaceuticals, natural gums are used as disintegrants and binders in solid dosage forms; in oral liquid and topical formulations they are employed as thickeners, suspending agents and stabilizers. When orally consumed, they are metabolized by the intestinal microflora into their unit sugar components. They also tend to have uncontrolled hydration rates and pH dependent solubility. To overcome some of these drawbacks chemical modification methods are applied, a process that can also enable their suitability for modified drug release systems. Some of these modification processes are:

i. carboxymethylation/carbomoylethylation of gums
ii. gum grafting with polymers
iii. cross linking of the gum

METHODS

In this review, three primary sources of information were employed – a primary, secondary and tertiary source. The primary source included original articles published in scholarly or academic peer reviewed journals and original works on which researches were based; the secondary sources included reference materials such as textbooks, dictionaries, pharmacopoeia and articles that interpret/review the subject area while the tertiary sources included, conference papers, short communications, and newspaper/magazine articles. The search engines that were employed for the review include Google Scholar, Science Direct and PubMed. The time frames for the search for the various search engines varied depending on the default settings as

i.	Google Scholar	Unlimited
ii.	Science Direct	1997 – 2021
iii.	PubMed	1987 – 2021

The search terms applied were sustained release, natural gums, excipients, nutraceuticals, herbal medicine, herbal excipients, natural polymers, matrix tablets. The exclusion criteria for the published materials used in this review were works on polymers from other sources than plants, synthetic polymers and any reference material published before 1987. Also, any repeated published articles from the search engines were excluded.

A Google scholar search on natural gums gave a hit of 19,600 articles with 792 already published in 2021 while a PubMed search found 1,604 articles; further analysis of the results showed a spiked interest in the 2000s which has kept rising to date. When the Science Direct search engine was employed, natural gums found a total of 58,980 articles of which 5,915 were related to the pharmaceutical sciences; 2020 had the highest publication of 4407 articles and over 3000 publications on natural gums in 2021 already. This indicated a rising interest in natural gums. Some examples of natural gums and mucilages that have been studied and found to be potential alternatives to the commercially available excipients are listed in table 4.1. Publications ranged from use of the native gums to their modified versions in various dosage forms especially the novel

delivery systems. Karaya and locust bean gums were studied for their retarding effect as sustained release matrix tablets [21]. The efficacy of drug release was evaluated at the first and twelfth hours; the diffusion exponent and the time taken to release 50 % of the active component. A significant influence of the gum quantity employed on the release pattern was observed; drug-polymer compatibility and sustained release properties were also confirmed. In another study karaya gum was cross linked with trisodium trimetaphosphate and used as a retardant in Isoniazid tablet formulation [22]. This was compared to another formulation with the raw karaya gum. *In vitro* evaluation of the release profile over 12 hours showed the formulated with the highest concentration of the modified karaya gum had a sufficiently slow release profile with about 83 % of Isoniazid being released within 10 hours.

Table 5: Classification of gums and mucilages

Basis	**Class**	**Examples**
According to charge	Non-ionic seed gum	Tamarind, guar, locust bean, xanthan, arabinana, cellulose
	Anionic gum	Tragacanth, arabic, karaya, gellan, agar, carrageenans, pectic acid
According to origin	Plant origin	1. shrubs/ tree exudate e.g. karaya, arabic, ghutti, tragacanth, albizia 2. seed gums e.g. guar, locust bean, starch, amylose, cellulose 3. extracts e.g. pectin, larch 4. tuber and roots e.g. potato starch, cassava starch
	Marine origin	Agar, carrageenaans, alginic acids, laminarin
	Animal origin	Chitin, chitosan, chondroitin sulfate, Hyaluronic acids
	Microbial origin (bacterial and fungal)	Xanthan, dextran, curdian, pullulan, zanflo emulsan, baker's yeast glycan, krestin
According to gelation behaviour	Cold set gels (forms gels on cooling the solution	Gellan gum
	Heat set gels (forms gels on heating the solution	Konjac glucomannan
	Reentrant gels (from which Galactose residues are removed)	Xyloglucans
According to chemical structure	Galactomannans	Fenugreek gum, guar gum, locust bean gum
	Glucomannans	Konjac glucomannan
	Uronic acid containing gums	Xanthan gums

Source: [19, 20]

Lakshmi and Swain, 2018 extracted the gum of *Moringa oleifera* and formulated solid dispersions of indomethacin with polyethylene glycol as a carrier by solvent evaporation and melting methods[46]. In vitro release profile study shows the gum was capable of a 12 hour sustained release unlike the synthetic and semi synthetic polymers it was compared against. Ibuprofen was formulated as a matrix tablet using the gum of *Sida acuta* as a retardant for sustained release [50]. This formulation was compared against another natural gum, guar. Following zero order kinetics the *Sida acuta* gum tablet batch released 96.82 % of the drug within 8 hours while guar gum batch released 94.55 % within the same time frame. Its potential as a sustained release agent was further promoted when the formulated tablets conformed to compendial standards.

Pure and modified cashew gums were used to formulate sustained release matrix tablets of diclofenac [51]. Modification of the gum was by crosslinking and microcrystalline cellulose was selected as the reference retardant agent. Tablets were prepared by direct compression and they satisfied compendial limits on evaluation. Drug release by the 12th hour ranged between 97.35 % to 100 % for the various batches and kinetic analysis showed a zero order release. Stability studies also showed no significant changes in drug content and appearance across all formulations.

Table 6: Some examples of natural gums and mucilages that have been investigated as pharmaceutical excipients

S. No	Herbal Excipient	Source	Herbal Use	Use as a Pharmaceutical Excipient
1	Locust bean gum	*Ceratonia siliqua*	Diarrhea, diabetes, antioxidant	Controlled Release agent [23]
2	Okra gum	*Hibiscus esculentus*	Diuretic, emollient, syphilis, antiscorbutic, antispasmodic	Sustained release agent [24] Binder [25, 26]
3	Sterculia gum	*Sterculia foetida*	Antiepileptic, diuretic, laxative, rheumatism	Controlled release agent [27, 28]
4	Aloe mucilage	*Aloe barbadensis*	Antibacterial, antiviral, antiseptic, burns, oral health	Sustained release agent [29, 30]
5	Fenugreek mucilage	*Trigonella foenum-graceum*	Antibacterial, diabetes, anorexia, gastri stimulant	Disintegrant [31]
6	Ocimum mucilage	*Ocimum americanum*	Tonic, diarrhea, bronchitis, conjunctivitis	Disintegrant [32]
7	Neem gum	*Azadirachta indica*	Leprosy, antihelminthic, fever, nalaria, skin ulcer	Binder [33]
8	Khaya gum	*Khaya grandifoliola*	Gonorrhea, skin diseases, gastric ulcer	Controlled release agent [34]
9	Cassia tora	*Cassia tora*	Stimulant, carminative and tonic	Suspending agent [35]
10	Agar	*Gelidium amansii*	Gelling agent in food, constipation	Suspending agent [36]
11	Albizia gum	*Albizia zygia*	Opthalmia, female sterility, purgative, aphrodisiac	Suspending agent [37]
12	Karaya gum	*Sterculia Urens*	Laxative, aphrodisiac, food stabilizer	Sustained release agent [38]
13	Ghatti gum	*Anogeissus latifolia*	Post-delivery tonic for women	Modified release agent [39]
14	Copal gum	*Bursera bipinnata*	Headache, burns, fever and stomachache	Sustained release agent [40]
15	Tamarind gum	*Tamarindus indica*	Wound healing, malaria, diarrhea, fever	Sustained release agent)[41]
16	Hupu gum	*Cochlospernum gossypium*	Antimicrobial, hepatoprotective, sedative, anticarcinogenic	Mucoadhesive agent [42]
17	Honey locust gum	*Gleditsia triacanthos*	Rheumatoid arthritis, whooping cough, blood disorders	Sustained release agent [43]
18	Leucaena leucocephata gum	*Leucaena leucocephata*	Stomachache, abortifacient, antiheminthic, antidiabetic	Emulsifying agent [44]
19	Tara gum	*Caesalpinia spinosa*	Food thickener and stabilizer	Controlled release agent [45]
20	Moringa oleifera gum	*Moringa oleifera*	Antiepileptic, antiulcer, antitumour, antioxidant	Sustained release agent [46]
21	Psyllium husk	*Plantago ovata*	Diarrhea, constipation, hemorrhoids, high blood pressure	Sustained release agent [47]
22	Lepidium sativum mucilage	*Lepidium sativum*	Respiratory disorders, memory booster, aphrodisiac	Controlled release agent [48]
23	Bhara gum	*Terminalia bellerica*	Colic, cough, diarrhea, anaemia	Controlled release agent [49]

Source: Compiled by the Researcher (2021)

Terminalia mantaly gum was modified by microwave irradiation at various times and investigated as sustained release and mucoadhesive agents of naproxen by direct compression [52]. The native gum was also used to prepare another batch and evaluated alongside the modified gums. Fourier-transform Infrared Spectroscopy (FTIR) spectra showed drug-excipient

compatibility while irradiation improved the mechanical properties of the formulation. A sustained release rate increasing with irradiation time was observed. The formulations with native terminalia gum had a release range from 57.43 % to 54.97 % for polymer concentration range of 5 – 10 % while the modified gum had a range of 65.36 – 74.64 %. bioadhesion was also observed to increase with rise in irradiation time.

Gums from two plants, *Enterolobium cyclocarpum* and *Cedrela odorata* were evaluated for their bioadhesive and sustained release properties in metformin microsphere formulations [53]. Hydroxypropy methyl cellulose (HPMC) was applied as the standard for evaluation. A 92 - 98 % microspheres yield was obtained, and FTIR spectra of the various formulations showed drug-excipient compatibility. After an initial burst yield over the first 30 minutes, a steady release was observed for 5 hours followed by a slow release over 5 days with the *E. cyclocarpum* gum showing highest sustained release while *C. odorata* showed the least sustained release. However release profile of both gums was almost the same as the HPMC containing formulation.

Ketoprofen matrix tablets were formulated using the mucilage of *Hibiscus rosa-sinensis* leaves and HPMC was used as the reference for evaluation as well as a commercial brand of sustained release ketoprofen tablet [54]. The tablets were prepared using direct compression method and were reported to pass of the stipulated physical tests. A sustained drug release for up to 24 hours was recorded comparable to the commercial brand. At 40 % concentration hibiscus mucilage was reported to give a release profile (78.3 %) which was comparable to the commercial brand. Sometimes the natural gum may be used as a co-excipient to a natural or synthetic polymer. The gum of *Lasianthera africana* was extracted and used as a co-excipient to guar gum at a concentration of 20 %w/w in the formulation of theophylline sustained release tablets using the wet granulation method [55].

The matrix tablet was able to sustain theophylline release for up to 8 hours and it followed a zero order release kinetics through a non-Fickian diffusion mechanism. Wadher and coworkers formulated metformin hydrochloride sustained release tablets using a hydrophilic polymer, Eudragit alone and in combination with damar and copal gums using wet granulation method [56]. When used alone, the Eudragit could not sustain the drug release while the addition of the co-excipients was able to sustain the release for more than 12 hours.

Pharmaceutically, herbal excipients have found a wide application, other than their use as release retarding agents in drug design technology. From the regulatory view, compounds that originate from the food industry fall within the first category of approved excipients [7]. Safety has always been considered as the most important requirement of any API while ignoring the safety of the excipient. However, this expansion of the role of excipients has raised a need for established safety profile as well as quality.

CONCLUSION

The established generally safe for consumption status of plants consumed as food and their potential as raw materials for the pharmaceutical industry means stringent safety tests will be eased and the period from discovery to the market will be relatively short. Their ease of cultivation and abundance, sometimes growing as weeds, means they will be cheaper to produce eliminating the bottlenecks of importation. Their amenability to modification means they can be bioengineered for better drug delivery thus leading to better bioeffectivity. The functionality of excipients is fast replacing the requirement for therapeutic efficacy from the API. The abundance of natural polymers and their ease of modification is ensuring the possibility of efficacious drug delivery systems with lower risk of biotoxicity. Nature has played its role to place these potential pharmaceutical raw materials at our disposal; it is up to us as a country to bridge the gap with the right funding and open doors. An intentional change of attitude to the dying drug production in Nigeria is required of the custodians of the industry.

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Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Uwah T O and Akpabio E I conceived this review and designed the framework of the work. Uwah T O prepared the first draft. Effiong D E prepared the final draft of the manuscript. All authors read and gave approval for the final manuscript.

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