

## EXTRACTION, MODIFICATION, AND CHARACTERIZATION OF NATURAL POLYMERS USED IN TRANSDERMAL DRUG DELIVERY SYSTEM: AN UPDATED REVIEW

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### ABSTRACT

The modified/regulated drug delivery system helps to sustain the delivery of the drug for a prolonged period. The modified drug delivery system is primarily aimed at ensuring protection, the effectiveness of the drug, and patient compliance. The transdermal drug delivery system (TDDS) falls within the modified drug delivery system, in which the goal is to deliver the drug at a fixed dose and regulated rate through the skin. Polymers are the backbone of the framework for providing transdermal systems. The polymer should be stable, non-toxic, economical, and provide a sustainable release of the drug. In general, natural polymers used in the TDDS as rate-controlling agents, protective, and stabilizing agents and also used to minimize the frequency of dosing and improve the drug's effectiveness by localizing at the site of action. Nowadays, manufacturers are likely to use natural polymers due to many issues associated with drug release and side effects with synthetic polymers. Drug release processes from natural polymers include oxidation, diffusion, and swelling. Natural polymers may be used as the basis to achieve predetermined drug distribution throughout the body. The use of natural materials for traditional and modern types of dosage forms are gums, mucilages, resins, and plant waste etc. Thus, the main objective of this review article is to give a brief knowledge about the extraction, modification, characterization, and biomedical application of conventional natural polymers used in the transdermal drug delivery system and their future prospective.

**Keywords:** Natural polymer, Polysaccharide, Gums, Mucilages, Extraction, Modification, Characterization, Application, Transdermal drug delivery system.

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### INTRODUCTION

Polymer is an essential part of any matrix drug delivery systems. Polymers are used for the various drug delivery systems, provide thickness, consistency, and volume and also provide multifunctional stability, drug release, proper targeting, improved biological compatibility, and patient compliance [1]. Choosing a polymer because of the inherent complexity of structures requires a comprehensive understanding of the surface and bulk properties of polymers so that it can produce the desired functionality [2]. In the preparation of the transdermal drug delivery system (TDDS), both natural and synthetic polymers can be used. Biodegradable polymers are generally high molecular weight materials from natural sources such as plants, microorganisms, and animals. Natural polymers are preferred compared to synthetic polymer [3] due to its low toxicity, renewability, versatility to modify, biodegradability, and low cost [3]. Natural polysaccharide polymers are hydrophilic, enzymatically degradable, and are capable of maintaining the stability of protein drugs embedded in them and also increasing their therapeutic efficacy [4]. The polysaccharide polymers are biocompatible and interact with living cells, which makes them compliant and appropriate biomaterials for long systemic circulation and targeted drug delivery systems [5]. In general, most natural polymers are considered safe for oral use and therefore find applications in the food and pharmaceutical industries. Extracting and developing polymers from natural sources can reduce regulatory approval requirements [6]. The seasonal result, location/climate, soil variability, and stability as they lack viscosity or distortion during storage, etc., are some of the difficulties of using natural polymers [6]. These problems and the petrochemicals revolution led to the growing use of synthetic polymers, slowly nudged to the background of natural polymers. Synthetic polymers are comfortable and endeavored to drug delivery scientists because of their physicochemical properties [6]. The increasing concern about bio-incompatibility, toxicity, etc., factors led to natural polymers revisited repeatedly in the pharmaceutical field. In recent times, the use of natural polymers has increased due to the support of "green chemistry" and technology materials [6]. Natural polymers are biogenic, and their

biological properties such as cell recognition and interactions, enzymatic degradation, extracellular matrix-like appearance, and chemical stability make them materials of choice for drug delivery [6]. The natural polymers have the varieties of role in the drug delivery system such as emulsification [7], suspension [8], retarding the drug release [9], film coating [10], disintegration [11], solubilization, bioadhesion, gelling, thickening, viscosity modulation, bulking agent [12], drug encapsulation, and mechanical enhancer [13-15]. The use of natural polymers in the targeted drug delivery system is also increasing day by day. Increasing the use of natural polymers in drug delivery means an increase in demand, which indicates the need for research and development into new natural polymers or modification of old polymers for subsequent marketing [15]. This review article gives a piece of detailed information about the extraction, modification, characterization, and biomedical application of conventional natural polymers used in the TDDS and their future prospective.

### DESCRIPTION ABOUT TDDS

The transdermal drug delivery system is characterized as a medicated adhesive patch or film system which is mounted over the skin's surface to deliver a predetermined dose of the drug over an extended period [16]. The delivery of drugs in a controlled manner through the skin is the most challenging field. Thus, the technique for the controlled release of drugs through TDDS is more efficient, appealing, and successful [16]. The transdermal patch shows to be beneficial compared to other drug delivery system, due to the following reasons [16-26]:

- This provides patients with safety, secure, and painless self-administration
- TDDS can be useful in poly-medicated patients
- TDDS provides a constant rate of drug release to an extended period to prevent dose dumping and therapeutic index problems associated with oral dose and parenteral administration
- TDDS patches enhanced the therapeutic effects of different medications by preventing common drug-related problems such as

first-pass metabolism, toxic metabolite formation, poor absorption, gastrointestinal irritation, etc.

- TDDS is useful for medications that have a short half-life to prevent repeated dosing
- Simplified medicines reduce inter and intra-patient variability
- For unconscious patients with dysphagia or constipation, TDDS has a more significant advantage
- Avoiding of pre-systemic metabolism leads to a reduction in the amount and, thus, a reduction in adverse effects in acute liver toxicity
- The absorption of the drug can be terminated by withdrawing transdermal devices at any point in time
- TDDS is usually cost-effective as patches, designed to deliver 1–7-day medications as compared with other treatments
- In comparison with the nasal cavity, it provides a relatively wide range of applications [16-26].

#### Limitations of TDDS

- The drug molecule with a large molecular size is not suitable for transdermal delivery (> 1000 Dalton approx.)
- The medication must have specific physicochemical properties for skin penetration, and if the dosage of a drug is high, i.e., it is challenging to deliver more than 10–25 mg/day by transdermal. The preferred average drug dosage is below 5 mg/days
- The drug or the excipients used in the formulations may result in local irritation at the site of administration such as itching, erythema, and local edema
- Clinical trial is required before applying the transdermal patches to the skin surface
- At the site of operation, most patients experience dermatitis due to system components
- The barrier function of the skin changes from one person to another person depending upon the age and the location from where they belong
- Low skin permeability limits the number of medicines available in this way
- TDDS is not an appropriate system to deliver the ionic drug molecules
- Hormones are not the suitable candidates to deliver through the transdermal route [16-26].

#### Building blocks of TDDS

##### Rate controlling membrane

The TDDS regulates the drug release property by dispersing into a matrix of inert polymers. The polymer powder blended physically with drug moiety and then molded to get the desired thickness and surface area [23-26].

##### Selection of model drug

- It is expected to be therapeutically active (dose in mg), with a molecular weight of about maximum 1000 Da.
- The drug should be soluble in the vehicle and the log p value of as much as 5.

Transdermal drug delivery has now become increasingly widespread. For the production of transdermal network, various physicochemical, pharmacokinetic, and pharmacological properties of the drug should be considered because of the skin's permeability, and drugs must be transdermally distributed through the skin by passive diffusion and constrained by several significant restrictions [24].

##### Pressure sensitive adhesive

Pressure-sensitive adhesive makes direct contact between the skin and the transdermal system, and holds the drug in solution or suspension form in the system. The consistency of the drug spreading mainly depends on the applied force [23]. The rapidity of the transdermal device can be achieved by adhesive immune to strain. Examples include polyisobutylene, polyacrylate, and silicones [24].

##### Release liners

A patch is usually protected by waterproof padding which is incorporated during preparation. The release liner is removed only before applying the patch on the skin surface because the release liner is in direct contact with the transdermal system, therefore, both physically and chemically inert. The release liner consists of a base layer that can be non-occlusive (e.g., paper fabric) or occlusive (e.g., polyethylene and polyvinylchloride) and a silicone or Teflon release covering sheet. Specific components used in transdermal patches as release liners include polyester foil and metalized laminate [24-26].

##### Backing laminate

The following points must be taken into account during the formation of the backing layer:

- It must be versatile and non-toxic
- Getting a low transmission rate of water vapor to facilitate hydration of the skin and thus helps to increase the skin permeability of drugs
- This should be consistent with the transdermal device because it is still in use throughout the operation
- It must have strong tensile resistance [24].

For example, polyethylene film, polyester film and polyolefin film, and aluminum vapor-coated layer.

##### Penetration enhancers

The compounds that facilitate penetration of topically used drugs are typically called absorption boosters, accelerators, or penetration enhancers. They are used in a solution to enhance diffusiveness, and solubility, thereby, helps to reduce the skin's barrier resistance reversibly [24].

For example, hydrocarbons, alcohols, acids, amines, amides, esters, surfactant, terpenes, terpenoids, essential oil, sulfoxides, lipids, and miscellaneous such as cyclodextrin derivatives and chitosan.

##### Desired properties for penetration enhancers

- The penetration enhancer must be non-irritating, non-sensitizing, non-phototoxic, and non-comedogenic
- Initiation action should be immediate and the operation period should be consistent and repeatable
- They should not have any pharmacological activity in the body, i.e., should not bind to the surface of the receptor
- When the enhancer withdrew, the upper layer regains its natural barrier properties wholly and automatically
- The accelerants to be used in topical formulations and system should be chemically and physically consistent with all medications and adjuvants
- This should be readily incorporated into preparations for effective dermatological activity. It should have an optimal parameter of solubility that is comparable to that of the skin
- This should stick to the skin surface and spread well when applied [23,24].

##### Plasticizers and solvent

For transdermal formulations, plasticizers ranging from 5% to 20% (w/w, dry base) have also been used. The plasticizers are also responsible for film adhesiveness to other surfaces or membranes and for increasing the film strength along with the film's brittleness and ductility [23,24,26]. For example, 15% w/w of glycerol or sorbitol, dry basis, phosphate, phthalate esters, fatty acid esters, and glycol derivatives such as polyethylene glycol (PEG) 200 and PEG 400 is generally used for plasticity. Solvents are used for product reservoir preparation [23,26]. For example, methanol, chloroform, acetone, isopropanol, dichloromethane, etc.

#### SOURCES OF NATURAL POLYMERS

Natural polymer has undoubtedly become an interest in the drug delivery system due to its physicochemical properties [27]. The

polymers derived from plants (e.g., pectin, guar gum, and mannan), microbes (e.g., dextran and xanthan gum), and animals (e.g., chitosan or chondroitin), has been found in abundance in the atmosphere and can also be readily re-producible using recombinant DNA technology [27]. The monosaccharide polymers have a wide range of beneficial properties such as high stability, non-toxicity, hydrophilicity, biodegradability, gel-forming ability, and chemical modification ease [27]. There is a range of structural compositions of plant polysaccharides that are related not only to different plants but also to the portion of plants they derived from such as leaves, seeds, roots, and tubers. Two particular structural features can clarify the complexity and variety of polysaccharides: First, monosaccharides can be bound differently in  $\alpha$  or  $\beta$  configuration; second, due to the branched side chains [27]. The natural polymers consisting of amino acids are somewhat uniform in size, and there is no variation. Such polymers are said to be homogeneous or monodisperse. In general, the natural polymers made by condensation polymerization techniques. Natural polymers tend to be readily biodegradable, and they show no adverse effects on the environment or human beings [27]. Depending upon the sources, natural polymers classified into three major categories, depicted in Fig. 1.

#### EXTRACTION AND PURIFICATION OF NATURAL POLYMERS USED FOR TDDS

The macerated plant parts (calyxes, leaves, stump barks, roots, seeds, or fruits) are the primary extract that should be warm in water over some time [28]. Then, by filtration technique (using a muslin cloth), the gum or mucilage is separated from the part of the plant. By adding alcohol, the mucilage or gum is precipitated out of water. Absolute ethanol typically used because it precipitates faster and gives higher yields than gasoline: water mixture. Furthermore, ethanol is a preferred solvent for any extraction process and has also approved by the Food and Drug Administration (FDA) [28]. For precipitation, other solvents such as acetone and methanol can also be used effectively. Mucilage is air-dried or oven-dried after precipitation [28]. Seeds of *Mimosa pudica* have macerated for 10 h in sufficient water. The mucilage that was collected, including the seeds, was then dried in the oven for 4–5 h at 50°C. Passing through No. 18 sieve, dried mucilage was isolated from the seed husks. The seed husks were subsequently removed with winnowing by the freeze-drying method rather than heating [29,30].

Mucilage extraction from *Plantago psyllium* seed was successful by adding the seeds to boiling 0.1 M HCl until the seed husk dissolves [31]. Once the color has changed for all the seeds, the filtration is performed and separated. The concentrated filtrate is combined with ethanol to precipitate the mucilage and finally dried [31]. Forsskaolea mucilage obtained by soaking the seed husk in deionized water at 80°C continuously with 2 h ripening [32]. It is then allowed to cool at room

temperature and left overnight. Upon stirring, 0.5 M NaOH is added to separate out the mucilage from the seeds, and the resulting slurry is filtered. The mucilage is precipitated on the filtrate by adding 2 M HCl. Centrifugation of the residue is then carried out to remove the water and acid residues and finally dried [32].

*Sesamum indicum/Sesamum radiatum* mucilage is extracted by proclaiming weighted leaves into hot water for 6 h and is then washed with a bag of muslin. It is then precipitated and cleaned with ethanol [3]. It's dried and milled with salt. Recent extraction in the laboratory indicated that mucilage could be effective when extracted with cold water from the leaves [3]. It has also been found that mucilage browning was less with cold water. In addition, sodium metabisulfite (1% w/v) is used as a bleaching agent/antioxidant during maceration that prevents enzymatic browning [3].

Cashew is an exudate from the *Anacardium occidentale* tree bark. The gum is milled, dissolved in water, and filtered after processing and dried. Alcoholic solvents are generally added in the filtrate to precipitate and then dried in a hot air oven at 45°C [32]. The isolates cashew gum is dissolved in water and centrifuged to obtain precipitation faster. The supernatant stored for drying [32]. First, defatting achieved for parts of the plant, such as tubers with petroleum ether and saponins extracted with methanol before maceration [33].

Nevertheless, some researchers did not attempt to extract saponins from tubers such as *Eulophia campestris* because they preferred to extract mucilage rather than saponins [34]. Mucilage from *E. campestris* tubers extracted by boiling in water for 1 h and then precipitated with acetone, and finally dried the mucilage [34]. It may not be necessary to initially defeat and extract saponins as fat dissolves in acetone and ethanol, which are the common solvents used in mucilage and gum precipitation. In contrast, saponins dissolve in ethanol and a mixture of water and acetone; this means that during precipitation, fat and saponins are separated from the mucilage [34]. Hence, distilled gums and mucilage obtained by water maceration and subsequent precipitation over a while using organic solvents such as ethanol, acetone, and isopropanol, combined with several soakings and washing in organic solvents. This process influenced by various factors such as part of the plant, the position of the mucilage, method of separation, choice of solvents for extraction, and choice of drying technique [34]. The schematic diagram showed in Fig. 2 explained the general process of extraction of natural polymers.

Some washings and precipitations using solvents, including ethanol, acetone, and isopropanol, can able to purify the derived polymer, thus remove impurities [34]. Nevertheless, a liquid chromatography-mass spectrometry purification method used to perform further purification if needed [34]. As far as microbes are concerned, pure ethanol widely

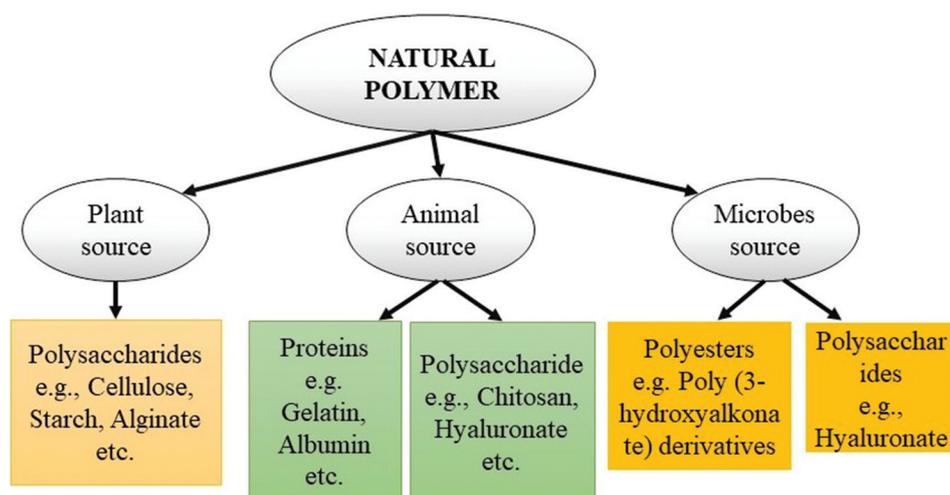


Fig. 1: Based on the sources, classification of natural polymer and their examples

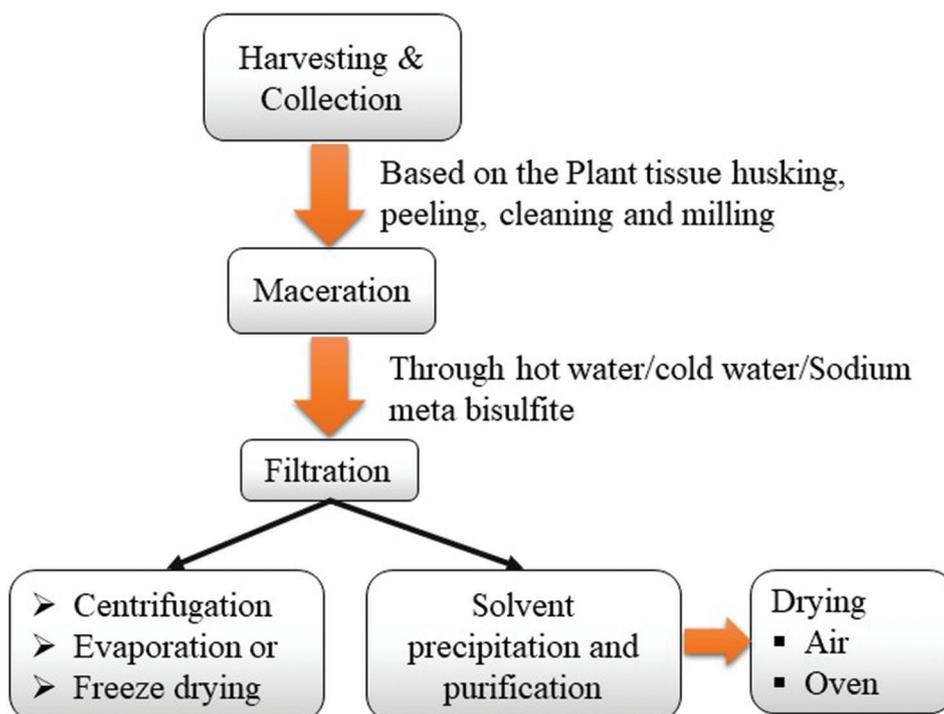


Fig. 2: Schematic diagram for the general extraction process of natural polymers

used for extraction and purification [34]. Absolute ethanol inactivates the bacteria, but the microbes reactivate in the presence of favorable conditions and can contribute to polymer degradation. One of the drawbacks of renewable polymers is microbial degradation [34]. Some of the natural polymers, including chitosan and aloe vera mucilage, exhibit antimicrobial activity so that no microbial contamination can occur. The microbial load can be easily calculated using traditional microbiological measures. Therefore, polymers can be sterilized depending on use [35]. Sterilization methods include filtration, use of ethylene oxide or hydrogen peroxide, 70% ethanol (resistant to hydrophilic viruses and bacterial spores), gamma irradiation, and low-temperature radiofrequency glow discharge plasma treatment can be used for polymer sterilization process [35]. To prevent polymer degradation, morphological changes, chemical damage, the choice of sterilization technique is paramount [35].

#### MODIFICATION OF NATURAL POLYMERS BY VARIOUS TECHNIQUES

Natural polymers improved as a way of overcoming their drawbacks such as viscosity, microbial degradation, and partial or low solubility. Furthermore, altering existing polymers improves their properties and flexibility in the delivery system. Reformation should be made in such a way that the existing polymers do not sacrifice their physical/biological properties. Modification methods include grafting, cross-linking, derivative formation, and blending of polymer-polymers [36].

#### Grafting and Cross-linking

Singh and Chauhan synthesized a polymer network of psyllium husk and methacrylamide (MAAm) with ammonium persulfate (APS) used as an initiator and N, N-methylene-bisacrylamide (N, N-MBAAm) used as a cross-linking agent [36]. The synthesis carried out through a free-radical process followed by chemically induced polymerization. The ammonium persulfate has developed reactive psyllium in MAAm and N, N-MBAAm site chains. The four reactive sites on N, N-MBAAm can be connected to the psyllium and poly radicals (MAAm) to create a three-dimensional (3D) psy-cl-poly (MAAm) hydrogel. Insulin is introduced in the hydrogel with a proper swelling balance process. Afterward, the hydrogel swelled

and dried to obtain an insulin-loaded polymer matrix system. The polymer matrix was evaluated at predetermined time for swelling and release of the drug [36]. The swelling and release of the drug occurred at a higher rate with neutral pH than acidic pH environment, but the release from the hydrogel still modulated with differences in the structure of polymer network and cross-linker used [36].

Moreover, psyllium polymeric network was synthesized by using N-hydroxymethyl acrylamide, and N, N-MBAAm used as cross-linkers, and salicylic acids and tetracycline hydrochlorides used as model drugs [37]. Besides, hydrogels based on psyllium-N-vinylpyrrolidone was also obtained by radiation mediated cross-linking process and 5-fluorouracil was used as a model drug in that preparation [38]. In another study, methacrylic acid and sterculia gum have modified using APS as the initiator, and N, N-MBAAm used as a hydrogel generating cross-linking agent [39].

Sterculia gum and modified sterculia-cl-poly (MAAc) were characterized for swelling ability, drug release, morphological, and structural alteration [40]. A comparison study revealed that sterculia-cl-poly (MAAc) has demonstrated morphological variability as opposed to the smooth and homogenous sterculia gum. The swelling was analyzed according to the parameters of the reaction. The authors noted that sterculia-cl-poly swelling (MAAc) was decreased as the concentration of monomers in the polymer matrix increased [40]. In addition, sterculia-cl-poly (MAAc) swelling was increased with an increase in APS concentration (used as initiator) and decreased with an increase in N, N-MBAAm concentration. Swelling also increased with an increase in sterculia gum [40]. In the aqueous medium, swelling is depending on matrix retention time. In comparison, with an increase in pH, swelling increased and decreased by 0.9% NaCl. While swelling increased as pH grew, drug release rates were higher at lower pH 2.2. This was attributed to the accelerated solubility of the drug ranitidine at lower pH. The authors have changed the sterculia gum with acrylamide (AAm) and used the same initiator and cross-linker [40]. Many natural polymers grafting and cross-linking have been reported so far such as polyacrylamide grafted into Katira gum and Katira gum cross-linked with glutaraldehyde [41,42]; guar-gum cross-linkage with trisodium

trimetaphosphate [43]; and an epichlorohydrin cross-linked with cashew gum [44].

#### Formation of derivatives

Natural polymeric derivatives have found better physicochemical properties such as hydrophilicity, solubility, swell ability, drug release, stimulus-response, and film formation [14,45]. The natural polymeric derivative can be formed by various chemical techniques such as carboxymethylation, carbamoylethylation, cyanoethylation, acetylation, deacetylation, sulfation, phosphorylation, and esterification [14]. Carboxymethylation increases their solubility by adding carboxymethyl groups to the existing polymers. Natural polymers such as cashew gum [46], xyloglucan gum [47], locust bean gum [48], starch [49], hemicelluloses [50], konjac glucomannan [51], xylan [52], guar gum, and tara gum [53] have been carboxymethylated to increase their solubility [45]. Carboxymethylation was carried out by using aqueous and non-aqueous method [47,53]. The process of carboxymethylation using the aqueous method is determined by solvent structure, solvent composition, sodium hydroxide, monochloroacetic acid concentration, reaction time, and temperature of the reaction [47]. At the presence of sodium hydroxide, carbamoylethylation of mucilage and gum is done with AAm. The reaction parameters that affect the carbamoylethylation process include the gum-liquor ratio, sodium hydroxide, AAm concentrations, and reaction temperature [54]. Carbamoylethylation increases the properties of the gum, including water solubility, consistency, and clarity of solution [55]. For example, carbamoylethylated polysaccharides (mucilage and gum) include guar gum [54] and the cassia tora gum [53]. Cyanoethylation is another method used to alter the natural polymers and improve their solubility and chemical stability. In the presence of sodium hydroxide, the cyanoethylation process is performed with acrylonitrile. Thus, acrylonitrile and sodium hydroxide concentrations, temperature, and time of reaction are the parameters that affect the process [56]. Some of the examples of natural cyanoethylated polymers are cassia tora gum [56], tamarind kernel powder [57] etc.

#### Polymer-polymer blending

Polymer-polymer blending is an easy and comfortable way to change polymeric nature or form new polymers without the chemical reaction/synthetic process [58]. The blending may occur due to physical bonding between two or more polymers at a time [58]. The mixing may also be due to chemical bonding, or covalent bonding (cross-linking) or ionic bonding interacting between the two or more polymers. Blending polymers is a way to boost the properties of the participating polymers [58]. A mixture of alginate, sapwood bean gum, and xanthan gum in microspherical drug delivery system improved the efficacy in drug trapping and further delayed the drug release compared to alginate and sapwood bean or alginate and xanthan gum mixture [58]. Microbeads made with an alginate and Irvingia gum combination have significantly improved the efficiency of drug loading and controlled the drug release over 7 h compared to alginate microbeads [59]. Natural and synthetic gum composites have also been used to create hydrogels, including carboxymethyl cellulose (CMC)/locust bean gum and methacrylate copolymers [60]. However, its interaction with CMC developed a hydrogel that enhances the mechanical strength of CMC [60].

#### CHARACTERIZATION OF NATURAL POLYMER

Plant mucilages and gums are mostly polysaccharides in nature. The structure, physicochemical, physicochemical, and drug delivery properties need to thoroughly elucidate to advance the use of mucilages and gums from bench to pilot scale. It is also essential to distinguish between each natural polymer with others. The comprehensive characterization of a natural polymer can show its uniqueness and improve its use in pharmaceutical applications [61].

#### Structural elucidation of natural polymers

The identification of the polymer is usually done by determining the structure of the polymer. The properties of polymers depend on their

chemical structure and chain conformations. While to fully elucidate a polymer's structure and chain conformation, a wide range of techniques are available to describe and classify a polymer systematically [61]. Fourier transform infrared spectroscopy, liquid state nuclear magnetic resonance (NMR) (one and two dimensions), solid-state NMR, Raman spectroscopy, gas chromatography (GC), GC-mass spectroscopy (GC-MS), and high-performance liquid chromatography are used to classify and identify the polymeric structures [61]. Polysaccharide chain conformations in solutions are elucidated by static and dynamic light dispersion, viscosity analysis, circular dichroism analysis, atomic force microscopy (AFM), single-molecule force spectroscopy based on AFM, fluorescence correlation spectroscopy, and NMR spectroscopy [61].

#### Identification of sugar constituents

The mucilage or gum is hydrolyzed with dilute acids to determine the sugar constituents [14]. Chromatographic techniques, including size exclusion chromatography with multi-angle laser light scattering, GC can able to isolate the various monosaccharides from gum and mucilage. Structural elucidation can also be done with NMR spectroscopy and MS [14]. Methylation, periodate, and lead tetra-acetate oxidation is elucidate the process of monosaccharide-monosaccharide bonding in polymer chemistry [14].

#### Polymorphism determination

An alteration in the polymeric structure can also change its degree of crystallinity, which further affects their properties such as solubility, stability, and drug release [29]. Various analytical techniques have been used to determine polymorphism such as gel electrophoresis, differential scanning calorimetry (DSC), wide-angle X-ray diffraction (XRD), and powder XRD [29]. However, the X-ray diffraction is the primary technique which is used to determine the degree of crystallinity of a polymer. Characteristic peaks reflect the degree of crystallinity in the obtained spectrum [29]. The lack of characteristic spectrum peaks is indicative of the polymer's full amorphous existence [29]. The majority of natural polymers are either amorphous or semi-crystalline. The polymer, which is high-crystallinity in nature, is more soluble and vice-versa [62].

#### Determination of molecular weight and polydispersity index

The determination of polysaccharide's molecular weights may be challenging due to their heterogeneity and polydispersity behavior [63]. Polysaccharide fractions of mucilage and gums can be observable by preparative chromatography, for example, scale exclusion chromatography (SEC), GC, and viscometer rheometric technique generally used for molecular weight and polydispersity determination [64]. The determination of viscosity gives a brief knowledge about the molecular weight as it is a direct molecular weight representation. The multi-angle laser light scattering is faster and more reliable when combined with chromatographic techniques, such as, Size exclusion chromatography (SEC) [65]. Summers *et al.* recently promotes the advanced polymer chromatography system that provides a better polymer distribution resolution with a shorter time-span to determine molecular weight distribution [65]. Nevertheless, the system also appears to be advocated for samples of low molecular weight polymer [65].

#### Surface characteristics of natural polymers

The surface morphology of a polymer or its derivative can affects the rate and mechanisms of drug release from the polymer [66]. The surface modification of a polymer is used to screen the drugs [66]. A polymer (modified or natural polymer) morphology also affects the degree and length of its circulation through blood, polymer-drug interaction, or nano or micro-particle-cell interactions or cell encapsulation [67]. Hence, an understanding of the morphology of natural polymers such as shape, scale, and surface chemistry is imperative and can able to determine with scanning tunnel microscopy, transmission electron microscopy (TEM), scanning electron microscopy (SEM), and atomic force microscopy (AFM) [68]. TEM offers a two-dimensional view of a substance while SEM provides a 3D view and by exposing the molecular surface and mechanical properties, AFM takes it much further. TEM revealed that the particle is a nanocapsule with the inner ring display and SEM verified with the

hollowness display [68]. The application of technologies such as AFM and Raman spectroscopy improves polymer surface characterization. The topographical, electromagnetic, thermal, and near-field optical properties elucidated on the molecular scale are provided with high-resolution data of both chemical and morphological structures [68].

#### Thermal behavioral analysis

The physical and chemical changes of the polymer are generally identified by the DSC during the thermal processes. The polymer exposed by a range of temperatures and helps to identify the glass transition, crystallization, and decomposition nature of the polymer. Polymers act differently above and below their temperatures of glass transition [69]. The mechanical properties of the polymer also depend

on the transition temperature [70]. Polymer thermal activity is distinct, and so each polymer is supposed to show a specific thermogram. Dynamic mechanical thermal analysis, thermally stimulated current spectroscopy, and dilatometry are other techniques used to analyze the polymeric thermal behavior [71].

#### Rheological behavior analysis of natural polymer

Another property based on molecular weight is the viscoelastic nature of the polymer. Viscoelastic properties of material contribute, for example the strength of the substance, stiffness, release of the drug, suspendability, and spreadability [72]. However, the rheometer measures the viscosity/flux as well as other parameters such as the impact of shear on polymer flow property, the effect of different

**Table 1: Biological source, composition, and uses of common natural polymers in drug delivery systems**

Polymer	Biological source	Main component/s	Uses in drug delivery systems	Reference
Gum Arabic/ Gum Acacia	<i>Acacia senegal</i> (Family-Leguminosae) or <i>Acacia arabica</i> (Family-Combretaceae)	Composed of 1, 3-Galactopyranosyle $\beta$ -D components, arabinose, glucuronic acid, rhamnose, and monosaccharide sugars	Suspending agent, emulsifying agent, binding agent, adhesive agent, emollients for cosmetics	[74-77]
Agar	<i>Gelidium amansii</i> (Family-Gracilariaceae)	Combination of agarose and agaropectin	Suspending agent, emulsifying agent, supportive gelling agent, surgical lubricant, disintegrating agent, bacterial culture fluid, laxative medium	[71,78]
Tamarind Gum	<i>Tamarindus indica</i> (Family-Leguminosae)	Consists of (1, 4)- $\beta$ -D-glucan, $\alpha$ -D-xylopyranose	Hydrogel, mucoadhesive agent, binding agent, emulsifying agent, suspending agent, high thermal stability	[79]
Moringa gum	<i>M. oleifera</i> (Family-Moringaceae)	Arabinose, galactose, and glucuronic acid	Gelling agent, binder, release retardant, lightweight, <i>M. oleifera</i> butter is used for baby products to provide a free, radical-resistant, emollient	[80]
Guar Gum	<i>Cyamopsis tetragonolobus</i> (Family-Leguminosae)	Polysaccharide made up of (1 to 4)-Diequatorially associated $\beta$ -Dmannoses monomers, $\beta$ -1,4 connected- D-mannopyranoses	Controlled release property, tablet excipient, release retardant	[81]
Tragacanth	<i>Astragalus gummifer</i> (Family-Leguminosae)	Tragacanthin (composed of Tragacanthic acid and arabinogalactan), Orin, D-galacturonic acid, D-xylose, L-fructose, D-galactose	Emulsifier, thickening agent, and suspending agent	[82]
Locust Bean Gum	<i>Ceratonia siliqua</i> (Family-Leguminosae)	Galactomannan (80%), albumin and globulin (32%), glutelin (68%)	Binders, viscosity enhancers, stabilizers, matrix formers, drug release modifiers, coatings, disintegrators, solubilizers, emulsifiers, suspending agents, gelling agents, and bioadhesives	[83]
Jackfruit Mucilage	<i>Heterophyllous artocarpus</i> (Family-Moraceae)	Rhamnose, xylose, arabinose, glucose, galacturonic acid, pectic acid proteins, fats, calcium, and phosphorus	Bio adhesives, binder for tablets, strong insulator, absorption of water and swelling properties, film-forming ability	[84]
Rosin	<i>Pinus toeda</i> (Family-Pinaceae)	Abietic acid, Pimaric acid	Film coating agent, film-forming agent, release modifier, binding agent	[85]
Gum copal	<i>Agathis coranthifolia</i> (Family-Araucariaceae)	Agathic acid, diterpenoid, Lobdane, cis-communicated acid, trans-communicated acid	Binders, drug release modifiers, film coater, viscosity enhancers, stabilizers, disintegrates, solubilizes, emulsifiers, suspending agents, gelling agents, and bioadhesives	[86]
Gum Damar	<i>Shorea wiesneri</i> (Family-Dipterocarpaceae)	$\alpha$ -resin (40%), $\beta$ -resin (22%), Dammarolic acid (23%)	Binding agent, film-forming agent, bioadhesive agents, release retardant	[87]
Pectin	<i>Citrus limon</i> (Family-Rutaceae)	Ester of a (1 $\rightarrow$ 4) linked (+) - polygalacturonate sequences interrupted with (1-2) - (-) - rhamnose residues, (+) - galactose, (-) - arabinose, (+) - xylose, and (-) - fructose	Drug delivery, gene delivery, wound healing, tissue engineering, TDDS, hydrogel formation	[88,89]
Alginates	<i>Macrocystis pyrifera</i> , <i>Laminaria digitata</i> , and <i>Laminaria saccharina</i> (Family-Laminariaceae)	Copolymer of D-mannuronic acid (M) and L-guluronic acid	Drug delivery, tissue engineering, wound healing, release retardant, disintegrating agent	[90,91]
Xanthan Gum	<i>Xanthomonas campestris</i> (Family-Xanthomonadaceae)	D-glucosyl, D-mannosyl, and D-glucuronyl acid residues	Cosmetics, drug delivery, water treatments, TDDSs	[92,93]

TDDS: Transdermal drug delivery system, *M. oleifera*: *Moringa oleifera*

Table 2: Various natural polymers function, characteristics, limitations, and biomedical application in TDDS

Natural polymer	Active components	Dose	Polymer location/ function	Characteristic	Limitations	Applications	Reference
Gum acacia	-	-	Release modifier/ retardant	Emulsifying property is present	Solution viscosity is high at solid concentration	-	[94]
Agar	Eserine and Pralidoxime chloride	-	Role of agar in TDDS as a nutrient for bacterial growth to conduct Ames and Whitfield spot test	High gel strength at low concentrations and nutrient for bacterial growth	A swelling behavior is present	Eserine is used in glaucoma and pralidoxime chloride is used as an antidote to treat poisoning	[95]
Tamarind Gum	Clindamycin	1% w/w	Role of extracts from Tamarind seeds as a novel gelling agent for TDDS and it works as release retardant	It has excellent physical properties such as binding, stabilizing, plasticizing, thickening and gelling abilities	A high viscous solution is formed when dissolved in water	Clindamycin phosphate is the most common topical. antibiotic used in the treatment of acne vulgaris	[96]
Moringa gum	Tizanidine Hydrochloride	6 mg	Good film-forming and adhesive property	Drug release modifier	Sticky in nature	Centrally acting myotonolytic skeletal muscle relaxant	[97]
Guar Gum	Carvedilol	1.30% w/w	Achieved controlled release and improved bioavailability	Non-toxic, biodegradable, bioadhesive	Microbial contamination and thickening of gum	Hypertension, congestive cardiac failure, and angina	[98]
Tragacanth	Gentamicin and Lidocaine	-	Gel forming ability	Hydrogel forming capability, release modifier, higher mechanical strength	Solidified in high concentration, needs external pressure to dissolve	It has antioxidant and wound healing activity	[99]
Locust Bean Gum (LBG)	Curcumin	25 mg or 25% w/w	Increasing the concentration of LBG helps to sustain the release of drug from the polymer composite transdermal films	Higher mechanical properties	Solubility is one of the major drawbacks to be controlled under defined conditions	Wound healing, anti-inflammatory agent, anti-bacterial agent	[100]
Jackfruit Mucilage	Acyclovir	20 mg	Film-forming agent	It has good film-forming and binding capability	Skin irritancy, moisture absorbs	Antiviral agent	[101]
Rosin	Diltiazem hydrochloride	10% w/w	Film-forming ability	Excellent biocompatibility and degradation features are present	Slightly dermal toxicity is present that can be altered by chemical modification	Treatment of arrhythmia, angina pectoris, and hypertension	[102]
Gum copal	Verapamil hydrochloride	2% w/v	Rate controlling membrane in transdermal patch	Yellow-colored transparent hydrophobic materials, useful for topical wound healing	Gum copal films are very much brittle in nature	Antianginal reduces high blood pressure and effective in migraine treatment	[103]
Gum Damar	Diltiazem hydrochloride	20% w/w	Matrix forming agent	Emulsifying, stabilizing, strong water-resistant, high binding capacity	Gum damar films are brittle when dried	Treatment of arrhythmia, angina pectoris, and hypertension	[104]
Zein	Ovalbumin	40 mg	Film coating is the main function of zein in this patch	It is hydrophobic in nature, but it is made up of alcohol-soluble protein of corn	Zein films are found to be brittle in the absence of plasticizers	Ovalbumin is an antigen that can be used to induce cystitis by initially sensitizing animals to the antigen	[105]

(Contd...)

Table 2: (Continued)

Natural polymer	Active components	Dose	Polymer location/ function	Characteristic	Limitations	Applications	Reference
Pectin	Nicotine	2.5% w/w	Good film-forming ability and release modifier	It works as a gelling agent, thickening agent, emulsifying agent, stabilizing agent and a good source of dietary fiber	-	Nicotine is a stimulant and potent parasympathomimetic alkaloid	[106]
Alginates	Domperidone	10 mg	Release modifier (Controlled release property)	Gel forming, thickening and stabilizing abilities	Low mechanical property (e.g., gel strength)	Antiemetic properties and antihypertensive agent	[107]
Xanthan Gum	Propranolol	2.5 mg	Control drug release through polymer hydration process	Thickening, gelling, emulsifying and stabilizing agent	Concerning their colloidal stability	Hypertension and angina	[108]
Modified Starch	Clonidine	10 mg	Maintain the stability of patch	High swelling ability, high thickening, binding, stabilizing and improve the solubility	-	High blood pressure, prevents the ADHD	[109]
Carrageenan	Acetylsalicylic acid	2.5% w/w	Conductive polymer or hydrogel to prepare matrix	Non-toxic, gelling agent with viscosity building properties	External stimulant is needed to increase its ability	Antipyretic and analgesic effects	[110]
Agarose	Progesterone	0.3 ml	As a matrix in transdermal patch	Release retardant, release modifier	Low-gelling and low melting properties are present	Hormone replacement therapy	[111]
Cellulose-Based Polymers	Furosemide	24.64–26.22% w/w or 4.52 mg/cm <sup>2</sup>	Ethylcellulose has a good film-forming property	Ethylcellulose (EC) is regarded as non-toxic, nonallergic, and nonirritating material	Low water permeation property	It is commonly used in the treatment of the cardiac and pulmonary disorders in premature infants and neonates	[112]
Poly lactide	TS	1 g (64 µg of TS per 0.64 cm <sup>2</sup> )	Good controlled release property and high film-forming capability	Biocompatible, biodegradable, and erosion profiles are present	Dose dumping and incompetent drug release property	NSAIDs and topical analgesic effects	[113]
PHA	Ketoprofen, clonidine, and tamsulosin	5 mg of each drug	PHA works as a matrix and helps to release the drug	Homopolymer, Biodegradable, and thermoplastic in nature	Permeation enhancer is needed	ketoprofen (nonsteroidal anti-inflammatory drug,) and clonidine (anti-hypertension drug, anionic) as well as tamsulosin (selective α adrenoceptor antagonist)	[114]
Natural Rubber	Ketoprofen	23.94 mg	Suitable membrane to release the drug from patch	Biocompatibility, flexibility, mechanical stability, and well permeation capabilities are present	Swelling can be occurred	Analgesic in chronic pain conditions and for the acute and long-term treatment of rheumatoid arthritis and colonic adenocarcinoma	[115]

TTDS: Transdermal drug delivery system, TS: Trolamine salicylate, PHA: Polyhydroxyalkanoates

frequencies or temperatures on polymers, and helps to understand the capacity of the polymer to behave as a viscous fluid, paste, gel, or a 3D network [72].

#### **In vivo characterization of natural polymers**

Some of the mucilages and gums can be edible, and some made from non-eating plant components. For instance, cashew nuts and fruits are consumed, but cashew gum is derived from bark. Toxicity and histopathology testing should be done to determine the safety and therapeutic efficacy of those gums and mucilages. The natural polymers used in the transdermal drug delivery system should be characterized *in vivo* before exposed to the skin surface. The transmucosal delivery of Hakea gum tablet was tested *in vivo* for their mucoadhesive properties [73]. The mucoadhesive property was tested *ex vivo* also, by which the

tablet detachments were determined after pre-defined contact times between the tablet and hydrated intestinal mucosa from the newly excised rabbit intestinal mucosa. The strength required for detachment increased with contact time and the concentration of Hakea gum [73]. To assess the transmucosal distribution, the rabbits were anesthetized, Hakea buccal tablets were applied, and blood samples were collected from a cannula inserted into the marginal ear at fixed time intervals of more than 5 h. The chlorpheniramine (CPM) release was managed by Hakea gum and spread throughout 5 h. Moreover, during this time, a high concentration of CPM was given and sustained [73]. Nevertheless, the more concentration of Hakea gum, the more controlled the release and the subsequent reduction of  $C_{max}$  and bioavailability of the incorporated drug [73]. The *in vitro* and *in vivo* characterization of the polymer must be studied before regulatory authorization for marketing [73].

Various natural gums and mucilage can be used as a natural polymer in biomedical applications, as mentioned in Table 1 and their application in the TDDS listed in Table 2.

### ENVIRONMENTAL IMPACTS OF BIOPOLYMERS

Engineers are trying to integrate environmental considerations directly into material selection processes to increase awareness among the people about the necessity of environment in our society and its protection issues [116]. Manufacturing of polymeric materials through using renewable resources can be performed in two ways. First, there are two ways that are available such as natural cycles or intentional intervention by humans to replace the utilization of feedstocks. The second way is a biodegradable end product produced during the manufacturing of biopolymers from renewable feedstocks. At last, the biopolymeric materials are sent to the landfills for decomposition purposes because the degradation of biopolymers can be quickly processed rather than plastic, which is harmful to our environment [116].

### FUTURE TRENDS

There are various beneficial advantages present for natural polymers over synthetic polymers such as natural polymers that are readily available, much cheaper than synthetic polymers, biodegradable, and chemical modification can be easily performed. Hence, the importance of natural polymers is increasing so rapidly in the drug delivery system for their beneficial effect rather than synthetic polymers [117]. Polymeric drug delivery system has the most exciting factor because drugs can be delivered through this process to the bloodstream at measured volume [117]. Some important macroscopic, microscopic structural, and chemical features are present in the natural polymers. Hence, most of the development in the controlled drug delivery system is focusing on the production and utilization of biopolymers [117].

Researchers or scientists want to increase the use of biopolymers not only in innovative drug delivery systems but also in other various sectors such as potential linings for artificial organs using as a substrate for cell growth or chemical reactors, as agents in drug targeting and immunology testing, also in biomedical adhesives, as separation membranes, and as substances in mimic biological systems. Hence, these newly modified biomaterials made up of tailor-made copolymers with desirable functional groups are rapidly manufactured by the researchers [118].

Production of novel supramolecular structures made up of polyethylene oxide copolymers and dendrimers is increasing rapidly because of their massive importance in the delivery of genes and macromolecules [118]. Finding the information about the chemical nature and physical structure of these new materials of biopolymers is very beneficial to increase the application of novel combinations of polymers in the new drug delivery system in the future [118]. The people of society always prefer safe materials and suitable processing methods from the initial synthesis of raw materials to the final disposal of a product that is very important in a product's life cycle. Hence, a movement is growing among scientists and engineers to minimize or slash down the environmental impact of polymer composite production [118].

### CONCLUSION

Biodegradable polymers are essential to delivering a wide range of active ingredients at the target site efficiently because biopolymers have profound side effects, the cost of production is low, and their potency is high in developing a new, advanced and effective drug delivery system. There are some upcoming modern mechanical techniques available to deliver the active ingredients through the transdermal system at the targeted area effectively, for example, X-ray lithography and LIGA (lithography, electroplating, and molding), mechanical array, electro oration, ultrasound, etc. Several issues found in the use of synthetic polymers for making a transdermal patch such as rash, inflammation,

and crystallization of the active ingredients in the rate-controlling membrane during the permeation of drugs through the skin. Thus, more investigations are needed to perform on these types of polymers before they put out for commercial use. Polymers are the backbone of the TDDS, and some care needs to be taken during the production of the transdermal patch, such as toxicity determination, compatibility interaction studies between the polymer and drug molecule and also the degradation pattern before the selection of a polymer in the transdermal patch. The extraction, purification, and production of the natural polymer are less cost-effective than the synthetic polymer and may modify at a time to time. The degradation process of the natural polymer has easily occurred in the soil after its use in the transdermal patch. This article will help to improvise the knowledge about natural polymers used for the TDDS and create interest among the researchers to remodel the conventional natural polymers for future aspects.

### AUTHORS' CONTRIBUTIONS

All the authors contributed equally for the manuscript preparation, and especially edited and final revised by Mr. Sourav Mohanto.

### CONFLICTS OF INTEREST

The authors declare no conflicts of interest, financial, or otherwise.

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