

# Roles of Polysaccharides in Transdermal Drug Delivery System and Future Prospects

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## ABSTRACT

This article reviews various polysaccharides used in transdermal drug delivery system. The system provides continuous controlled delivery of active ingredients through human skin and into the blood stream. Poor penetration of most drugs into the skin has led to numerous studies being conducted to increase the permeability of such drugs. Currently, the interest to utilize natural polysaccharides in transdermal formulations has increased as an alternative to the synthetic materials. Structure modification and polymer blending were carried out among polysaccharides and other materials in order to alter their functional properties. In some cases, the natural polymers provided better controlled release and drug permeation in comparison to the abilities of the synthetic materials. This review focuses on the physicochemical properties of polysaccharides and their effects on drug release profile, skin microstructure, and transdermal drug permeation. The limitations and future prospects of polysaccharides are also discussed.

## INTRODUCTION

A transdermal drug delivery system (TDDS) delivers a specific dose of drugs at a controlled rate through the skin and into the blood stream. This delivery system offers numerous advantages compared to the oral and parenteral routes. The TDDS avoids first-pass metabolism, which is a significant hindrance for oral administration. It overcomes the undesirable characteristics of oral administration and promotes drug bioavailability. The loaded drug could avoid degradation by enzymes and/or by pH-associated deactivation, thus achieve an efficient drug therapy (Saboktakin *et al.*, 2014). TDDS also offers an alternative for unconscious patients or disabled patients who have difficulty in swallowing (dysphagia) (Salinas-Casado *et al.*, 2015).

Additionally, TDDS provides pain-free administration in comparison to the parenteral, hence, raises patients' acceptability

and compliance (Paudel *et al.*, 2010). The method is also convenient because the drug's input can be self-administered and terminated at any point of time by removing the patch. Other than that, the TDDS offers drug release for an extended period of time (up to one week), prolongs the effectiveness of drug biological half-life, and minimizes side-effects (Prausnitz and Langer, 2008). Nevertheless, the biggest concern and challenge for the TDDS is poor permeability due to the skin barrier, specifically the stratum corneum.

In recent years, natural polymers of polysaccharides have become the subject of interest in transdermal formulation. Although many synthetic polymers exist in the market, the recent trend demands a replacement with natural polymers that is low in cost, sustainable, and renewable. Natural polymers have also become more popular because of the favorable properties such as nontoxic, nonpolluting, and potentially degradable (Khairnar *et al.*, 2014). Polysaccharides are generally-recognized-as-safe (GRAS) with respect to their applications in pharmaceutical dosage forms (U.S Food and Drug Administration, 2017). They can be modified using various techniques, which obtain tailor-made materials

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for TDDS, thus is a great alternative to the synthetic materials (Prajapati *et al.*, 2013).

This article aims to review various polysaccharides used by previous researchers in transdermal formulations. The study focuses on the physicochemical properties of the polysaccharides and on their mechanism of drug release and permeation. Related studies were gathered from the following databases—ScienceDirect Freedom Collection (1991–2017), PubMed (1993–2017), SpringerLink (2010–2017), Wiley Online Library (2010–2017), Scopus (2010–2017), and Google Scholar (2010–2017)—using the following keywords: “transdermal drug delivery system”, “polysaccharide”, “natural polymer”, “penetration enhancer”, “controlled release”, and “drug permeation”. Research papers obtained from the database search were carefully assessed and systematically reviewed. The final part of this paper discusses the limitations and future prospects of polysaccharides in TTDS.

### POLYSACCHARIDES IN TDDS

Polysaccharides are complex carbohydrates that are composed of ten to several thousand monosaccharides. Polysaccharides in TDDS are mostly derived from plants, animals, and microbial fermentation. Common polysaccharides used in previous studies are cellulose, chitosan, and starch. Other alternatives were gums and mucilages which are abundant in higher plants. Mucilages are obtained by extraction of the desired plant parts, such as seed endosperms, rhizomes, roots, leaves, and flowers, whereas gums are obtained through the injury of the plant. In other words, mucilages are physiological products whereas gums are pathological products of a plant. Both mucilages and gums are part of carbohydrates; they act as a primary metabolite and is classified as heterogeneous polysaccharides. These polysaccharides hydrocolloids are hydrophilic polymer that produce a viscous solution when in contact with water (Prajapati *et al.*, 2013; Prajapati *et al.*, 2014). Polysaccharides are continuously being explored in the development of new and effective TDDS (Figure 1). Such endeavour nevertheless can be challenging due to the inherent diversity of the polysaccharide structure.

#### Cellulose

Cellulose is the most common material found in the walls of a plant cell. The substance consists of a linear chain of  $\beta$ -(1 $\rightarrow$ 4)-D-glucopyranose units in 4C<sub>1</sub> conformation (Wang *et al.*, 2017; Meng *et al.*, 2017). Cellulose derivatives like carboxymethyl cellulose (CMC), hydroxyethyl cellulose (HEC), and hydroxypropyl methylcellulose (HPMC) are produced by replacing the hydrogen atom of hydroxyl groups in cellulose with alkyl or substituted alkyl groups. Other substances that exist in the walls of a plant cell are hemicellulose and lignin (Taflick *et al.*, 2017; Penttilä *et al.*, 2017).

CMC was reported to exhibit good aqueous solubility. In one experiment, Mandal *et al.* (2017) employed CMC as a nanocomposite hydrogel together with gold nanoparticle, and poly(methacrylic acid) as a crosslinker in transdermal delivery of diltiazem hydrochloride and diclofenac sodium. The hydrogel was noncytotoxic and served as an effective transdermal drug carrier. The drugs were released from the nanocomposite hydrogel in a controlled rate due to the low swelling behaviour and high gel strength. The *in vitro* release study showed that 85% of the

diltiazem and 79% of the diclofenac sodium were released in three days (Mandal *et al.*, 2017).

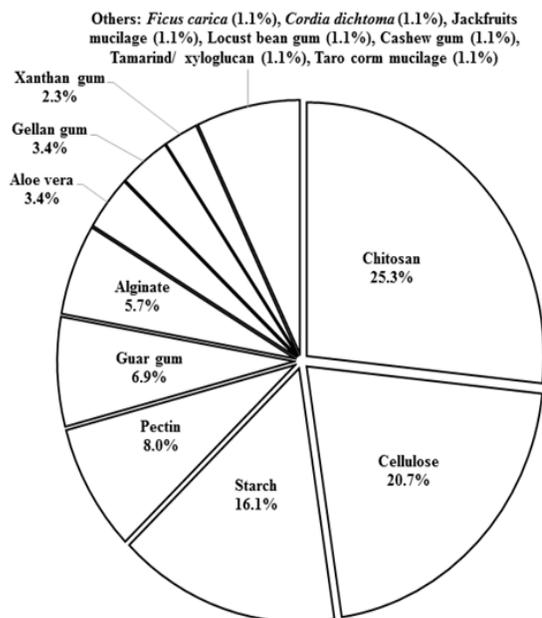


Fig. 1: Polysaccharides in TDDS as reported in previous studies (2003 to 2017).

HEC is a derivative of cellulose with great solubility in water (Kwon *et al.*, 2015; Kong *et al.*, 2016; Taghizadeh and Seifi-Aghjekoah, 2015). In previous studies (Kwon *et al.*, 2015; Kong *et al.*, 2016), HEC and hyaluronic acid (HA) were used to develop a hydrogel for the transdermal delivery of isoliquiritigenin. The HEC/HA hydrogel with a formulation of HEC:HA = 1:3 displayed an optimal transdermal delivery with a drug-release efficiency greater than 70% at pH 7. The high drug permeation was due to the ability of the hydrogel to promote temporary skin swelling hence leads to enlarged pores. Much of the drug permeation occurred via the hair follicles pathway (Kwon *et al.*, 2015). HEC/HA hydrogel has a stable network connection via a strong covalent bond. The hydrogel constitutes of three-dimensional networks of high porosity, thus allowing a large absorption of water or drug. This structure also acted as a reservoir for easy loading and release of drug (Kong *et al.*, 2016).

In Sarkar *et al.*'s (2014) study, HPMC was utilized with natural polysaccharide of taro corm mucilage (TCM), *Colocasia esculenta*, as a transdermal patch for the delivery of diltiazem hydrochloride. HPMC is a hydrophilic swellable polymer, and the HPMC/TCM-based transdermal patch exhibited prolonged and low-cumulative drug permeation compared to that achieved by the formulation without mucilage. The morphology of the drug-loaded HPMC/TCM patch after the *in vitro* release study showed that the patch had a rough surface with several pores, thus explaining the diffusion of the drug from the matrix.

In another study, Parhi and Suresh (2016) used HPMC and Eudragit RS100 for the development of diltiazem hydrochloride matrix film. The study revealed that the film made of HPMC alone gave higher drug release compared to the blending of HPMC and Eudragit RS100. Lowering the HPMC concentration resulted

in low percentage of drug release. This finding corroborated that of Mamatha *et al.* (2010), who also used HPMC and Eudragit RS100 for the development of transdermal patch of lercanidipine hydrochloride. In addition, HPMC was utilized as a matrix polymer for transdermal delivery of loratadine (Anuar *et al.*, 2007). The hydrophilic nature of HPMC prompted an initial rapid dissolution of the polymer when in contact with hydrated skin, which led to the accumulation and saturation of drug molecules on the skin surface, hence increased the drug release (Mamatha *et al.*, 2010).

Bacterial cellulose (cellulose produced by bacteria) has also been used in TDDS as a matrix patch (Silva *et al.*, 2014).

Bacterial cellulose membrane is a highly swollen membrane consisting of more than 90% of water content (Silva *et al.*, 2014; Gatenholm and Klemm, 2010). It has a unique property of tridimensional nanofibrillar structure. Oontawee *et al.* (2015) found that the addition of bacterial cellulose can improve a patch's appearance due to the substance's ability to produce a nonwrinkled film. The transdermal bacterial cellulose membrane demonstrated a similar drug permeation rate of diclofenac sodium in comparison to the commercial patch of Olfen® (Silva *et al.*, 2014). Table 1 summarizes the applications of cellulose in TDDS.

**Table 1:** Applications of Cellulose in TDDS.

Polymers	Dosage Forms	Model Drugs	Remarks	References
Carboxymethyl cellulose	Nanocomposite hydrogel	<ul style="list-style-type: none"> <li>Diltiazem hydrochloride</li> <li>Diclofenac sodium</li> </ul>	The drugs were released from the nanocomposite hydrogel in a controlled rate due to the low swelling behaviour and high gel strength.	Mandal <i>et al.</i> (2017)
Hydroxyethyl cellulose/hyaluronic acid	Hydrogel	Isoliquiritigenin	Most of the drug permeation occurred via hair follicles pathway.	Kwon <i>et al.</i> (2015); Kong <i>et al.</i> (2016)
Hydroxypropyl methylcellulose (HPMC)/taro corm mucilage (TCM)	Matrix patch	Diltiazem hydrochloride	HPMC/TCM based transdermal patch exhibited prolonged and low cumulative drug permeation compared to the formulation without mucilage.	Sarkar <i>et al.</i> (2014)
HPMC/Eudragit RS100	Matrix patch	<ul style="list-style-type: none"> <li>Diltiazem hydrochloride</li> <li>Lercanidipine hydrochloride</li> </ul>	Film made of HPMC alone gave higher drug release when compared to the blending of HPMC and Eudragit RS100.	Parhi and Suresh (2016); Mamatha <i>et al.</i> (2010)
HPMC	Matrix film	<ul style="list-style-type: none"> <li>Loratadine</li> <li>Lercanidipine hydrochloride</li> </ul>	The hydrophilic nature of HPMC prompted initial rapid dissolution of the polymer when in contact with hydrated skin which led to the accumulation and saturation of drug molecules on the skin surface, hence increased the drug release.	Anuar <i>et al.</i> (2007); Mamatha <i>et al.</i> (2010)
Bacterial cellulose	Matrix patch	Diclofenac sodium	The bacterial cellulose membrane demonstrated a similar drug permeation rate of diclofenac sodium in comparison to the commercial patch of Olfen®.	Silva <i>et al.</i> (2014)

## Chitosan

Chitosan is the product of deacetylation of chitin, which is derived from the exoskeleton of marine animals such as crab and shrimp (Viyoch *et al.*, 2003; Velmurugan and Ashraf Ali, 2013). It is a cationic polysaccharide made of N-acetyl glucosamine (GlcNAc) and glucosamine (GlcNH<sub>2</sub>) with β-d-(1→4) glycoside linkages (Al-Kassas *et al.*, 2016; Bigucci *et al.*, 2015; Zhou *et al.*, 2010; Ammar *et al.*, 2008). Many chemical and physical modifications have been carried out on chitosan by manipulating its derivative, degree of deacetylation, and molecular weight. The chitosan modifications have overcome its limitations of high molecular weight and low solubility in both water and organic solvents, particularly at the physiological pH and at pH more than 6.5 (Zhou *et al.*, 2010; He *et al.*, 2009).

In He *et al.*'s (2008) experiment, water soluble N-trimethyl chitosan (TMC) with varying degrees of quaternization were synthesized to deliver testosterone transdermally. The *in vitro* and *in vivo* studies in rabbits revealed that the TMCs were able to enhance the drug permeation, and the enhancement effect was

increased with the escalation of quaternization degree. TMCs promoted drug permeation by modifying the secondary structure of keratin in stratum corneum, allowing the structure to become loose.

In a later study, He *et al.* (2009) demonstrated that the drug permeation of chitosan and another derivative of mono-N-carboxymethyl chitosan (MCC) occurred with the increase in water content of stratum corneum, thereby enhancing cells membrane fluidity and decreasing cells membrane potentials. The hygroscopicity and 3D network structure of chitosan and its derivatives allowed water to enter the stratum corneum within a short duration and remained in the skin for a longer period. Changes in the membrane fluidity brought about an alteration in transmembrane transportation, as well as membrane thickness and structure. Chitosan and its derivatives also caused modification in the secondary structure of keratin, resulting in loosening the skin domain. This effect provided freedom for carbon movement, thus increasing the transdermal drug permeation.

In one study (Zhou *et al.*, 2010), various low-molecular-weight chitosan (LMWC) that were soluble in a wide range of pH were used as penetration enhancers for transdermal delivery

of baicalin. LMWC of 1 kDa displayed the highest permeation enhancement effect at pH 7.5 compared to other LMWCs of 1, 2, 3, 4, and 5 kDa, respectively. The pH of the solution was the key factor to its enhancement. At pH 7.5, the amino groups in 1 kDa coexisted as unionized and protonated molecules, which allowed a relatively weak interaction with the carboxylic group (intercorneocyte glycoprotein, and intracorneocyte keratin) of stratum corneum and better transcutaneous permeation. Meanwhile, at a lower pH of 6.5, most amino groups in LMWC of 1 kDa were protonated, and at a higher pH such as 8, the interaction between LMWC of 1 kDa and baicalin was too weak to influence the permeation of baicalin.

In Nawaz and Wong's (2017), LMWC was employed for transdermal delivery of chitosan-5-fluorouracil nanoparticles. The study revealed that the chitosan nanoparticles interacted with skin components of palmitic acid and keratin domains thus facilitated the transdermal drug transport.

An arginine-rich chitosan derivative known as N-Arginine chitosan (N-Arg-CS) was used for the transdermal delivery of adefovir in Lv *et al.*'s (2011) research. In this *in vitro* drug permeation study, the derivative demonstrated a superior enhancing effect compared to that achieved by other penetration enhancers (azone, eucalyptus, and peppermint). The enhancement effect was attributed to the presence of guanidinium group in the N-Arg-CS, as well as the chemical complex between the positive and negative charge in the N-Arg-CS and adefovir. The guanidinium group was reported to be able to open up the tight junctions of stratum corneum hence decreasing the membrane potential (Kosuge *et al.*, 2008).

Chitosan is mostly utilized in the development of matrix-type TDDS. In an *in vivo* study on rats, Pachisia and Agrawal (2012) reported that a chitosan patch containing glimepiride showed higher drug bioavailability compared to the oral suspension of glimepiride in gum acacia. The patch formulation also displayed longer plasma half-life compared to that achieved by oral formulation, indicating that the patch had successfully sustained the drug in the body when administered via TDDS. Another study of chitosan-based transdermal patch using ethinylestradiol (EE) and medroxyprogesterone acetate (MPA) as model drugs demonstrated a controlled release but high drug permeation for both EE and MPA (Agrawal and Pruthi, 2011). The permeation was better than that demonstrated by other polymers of hydroxypropyl cellulose, as well as that by the mixture of HPMC/Eudragit RS100, Eudragit RS100/Eudragit RL100, and ethyl cellulose/polyvinyl pyrrolidone.

Chitosan promotes sustained release of drug because it mediates prolonged contact with the epithelium via electrostatic interaction between protonated chitosan and anion of the glycoprotein on the epithelial surface, as well as the fixed negative charges in the interior of the tight junction. This electrostatic interaction was found to result in concentration gradient hence allowing the drug to diffuse into the underlying epithelium (Thanou *et al.*, 2000; Yeh *et al.*, 2011). In another study, chitosan was employed as a polymer matrix for transdermal delivery of *Ganoderma lucidum* extract, nortriptyline hydrochloride, and ondansetron, due to its film forming ability, bioadhesiveness, and elasticity (Paul *et al.*, 2015; Escobar-Chávez *et al.*, 2011; Can *et al.*, 2013). Bioadhesion is a crucial factor to drug delivery (Gutschke

*et al.*, 2010; Wokovich *et al.*, 2006), and the bioadhesivity of chitosan leads to a longer residence time on skin and eventually high drug permeation (Kählig *et al.*, 2009).

In one study, chitosan was incorporated into nanoparticles for transdermal delivery application. Chitosan-egg albumin nanoparticles were developed for transdermal delivery of aceclofenac (Jana *et al.*, 2014). The formulation containing chitosan, egg albumin, sodium tripolyphosphate, and Carbopol 940 showed sustained drug release over 8 h across a mouse's skin. The cationic chitosan and anionic egg albumin might have prompted a polyelectrolyte complex and thus controlled the drug release. In another study, Al-Kassas *et al.* (2016) developed chitosan nanoparticles for transdermal delivery of propranolol-hydrochloride. These chitosan nanoparticles were designed by ionic gelation using tripolyphosphate as the cross-linking agent. The nanoparticles were dispersed into a mucoadhesive gel consisting of poloxamer and carbopol. In the *in vitro* and *ex vivo* permeation studies across pig's ear skin, the designed formulation displayed a thixotropic behaviour with prolonged drug release. Chitosan nanoparticles in the form of gel increased the contact time on skin. The morphological study of the treated skin using a scanning electron microscopy suggested that the nanoparticles were able to create drug reservoir within the skin, where it provides the system with a small dose of drug over a long period. Additionally, it was reported that the formulation of chitosan whisker grafted with oligo(lactic acid) nanoparticles containing lidocaine was able to achieve a 100% of drug release in 6 h owing to the product's amphiphilicity and small size attributes (<100 nm) (Engkagul *et al.*, 2017). Table 2 summarizes the applications of chitosan in TDDS.

## Starch

Starch is a hydrophilic polysaccharide mainly found in seeds, fruits, and tubers (Lu *et al.*, 2009). It is composed of two types of polysaccharides namely amylose and amylopectin. Amylose is a linear (1→4)- $\alpha$ -D-glucan while amylopectin is a highly branched macromolecules consisting of the same backbone structure as amylose (1→4)- $\alpha$ -D but with many glucan short chains linked through  $\alpha$ -(1→6) linkages (Paris *et al.*, 1999; Viyoch *et al.*, 2003; Lu *et al.*, 2009; Soares *et al.*, 2013). Usually, the ratio of amylose to amylopectin varies from 10–20% amylose and 80–90% amylopectin depending on the sources (Lu *et al.*, 2009; Viyoch *et al.*, 2003). Viyoch *et al.* (2003) reported that starch with high amylose content of 50–75% is capable of making a strong film while Onofre *et al.* (2009) stated that a modified starch containing 70% amylose produced better controlled drug release in comparison to the conventional starch.

In the study by Santander-Ortega *et al.* (2010), maize starch polymer was used to explore nanoparticulate drug carriers using hydrophobic starch derivatives. Propyl-starch derivatives were synthesized by the reaction of starch with propyl bromide. Nanoparticles were prepared using starch derivatives of two propyl starch with different degrees of substitutions, 1.05 and 1.45 (namely PS-1 and PS-1.45), and these products were loaded with model drugs of flufenamic acid, testosterone, and caffeine. Both PS-1 and PS-1.45 nanoparticles showed high encapsulation efficiency for all three types of drugs. In addition, the drug permeation

profile displayed a clear enhancer effect for flufenamic acid. The delivery of encapsulated flufenamic acid in starch nanoparticles of both PS-1 and PS-1.45 was enhanced for

about 10-fold greater than un-encapsulated flufenamic acid across the human skin. Nonetheless, no such enhancement was observed for testosterone and caffeine.

**Table 2:** Applications of Chitosan in TDDS.

Polymers	Dosage forms	Model drugs	Remarks	References
Chitosan, N-trimethyl chitosan, mono-N-carboxylmethyl chitosan	Gel	Testosterone	Drug permeation through increase in water content of stratum corneum, enhancing cells membrane fluidity and decreasing cells membrane potentials.	He <i>et al.</i> (2008); He <i>et al.</i> (2009)
Low molecular weight chitosan	• Aqueous solution	• Baicalin	The pH of the solution was the key factor to its permeation enhancement.	Zhou <i>et al.</i> (2010)
	• Nanoparticles	• 5-Fluorouracil	Chitosan nanoparticles interacted with skin components of palmitic acid and keratin domains thus facilitate the transdermal drug transport.	Nawaz and Wong (2017)
N-Arginine chitosan	Solution	Adefovir	It demonstrated superior permeation enhancing effect when compared to other penetration enhancers of azone, eucalyptus and peppermint.	Lv <i>et al.</i> (2011)
Chitosan	• Matrix patch	• Glimepiride	Chitosan patch containing glimepiride showed higher drug bioavailability when compared to oral suspension of glimepiride.	Pachisia and Agrawal (2012)
		• Ethinylestradiol • Medroxyprogesterone acetate  • <i>Ganoderma lucidum</i> extract • Nortriptyline hydrochloride • Ondansetron	Chitosan promotes sustained release of drug as it mediates prolonged contact with the epithelium via electrostatic interaction between protonated chitosan and anion of the glycoprotein on the epithelial surface, as well as the fixed negative charges in the interior of the tight junction.  The bioadhesivity of chitosan leads to a longer residence time on skin and eventually high drug permeation.	Agrawal and Pruthi (2011)  Paul <i>et al.</i> (2015); Escobar-Chávez <i>et al.</i> (2011); Can <i>et al.</i> (2013); Kählig <i>et al.</i> (2009)
Chitosan-egg albumin	Nanoparticles	Aceclofenac	The cationic chitosan and anionic egg albumin might have prompted a polyelectrolyte complex, thus control the drug release.	Jana <i>et al.</i> (2014)
Chitosan in mucoadhesive gel	Nanoparticles	Propranolol hydrochloride	Nanoparticles in the form of gel were able to create drug reservoir within the skin, where it provides the system with a small dose of drug over a long period.	Al-Kassas <i>et al.</i> (2016)
Chitosan whisker grafted with oligo (lactic acid)	Nanoparticles	Lidocaine	The formulation was able to achieve 100% drug release in 6 h owing to its amphiphilicity and small size attributes (<100 nm).	Engkagul <i>et al.</i> (2017)

In another study, corn starch was modified into carboxymethylstarch (CMS) with 2-propanol and sodium hydroxide (Saboktakin *et al.*, 2014). The CMS and hyperbranched 1,4-cis polybutadiene (1,4-PBD) were employed as polymer matrix nanoparticles for transdermal delivery of clonidine. The clonidine-loaded CMS-1,4-PBD nanoparticles were able to provide high entrapment efficiency. Besides, starch nanocrystals (SNCs)-based hydrogel was evaluated for the application in the TDDS (Bakrudeen *et al.*, 2016). Hydrogel-based transdermal patches were formulated using three different starches derived from maize, potato, and cassava with SNCs as a drug carrier for acyclovir drug. SNCs are crystalline platelets derived from the hydrolysis of branching point (amorphous lamellae) of starch granules by the acid. SNCs obtained from hydrochloric acid were found to be more stable than those obtained from trifluoroacetic acid. Hydrogel formulated from maize- and potato-based SNCs showed better stability during storage compared to the hydrogel formulated from cassava SNCs.

Cyclodextrins (CDs) are formed naturally by the reaction of bacterial enzymes in starch. CDs are crystalline, torus-shaped cyclic oligosaccharide (Murthy *et al.*, 2004a). They are composed of glucose molecules that consist of 6, 7, or 8 glucopyranose units linked in a ring by  $\alpha$ -1, 4 glycosidic bonds (Mora *et al.*, 2010;

Yang *et al.*, 2008; Yan *et al.*, 2014). CDs have a unique shape of hydrophobic central cavities and hydrophilic exteriors. The shape allows CDs to form inclusion complexes with drugs through van der Waals interactions or hydrogen bonding, thus modify their physicochemical properties (Murthy *et al.*, 2004a; Yang *et al.*, 2008; Berbiciz *et al.*, 2011).

In another study, *in situ* hydrogels of curcumin and its inclusion complexes of hydroxypropyl- $\beta$ -cyclodextrin (HPCD) were found to produce a stable and efficient TDDS (Sun *et al.*, 2014). The HPCD was capable of increasing more than 20 times water solubility of curcumin as the concentration of HPCD increased from  $10^{-5}$  to  $10^{-2}$  mol/L. The inclusion complex was formed as the two ends of curcumin embedded into the cavity of the HPCD rings. The HPCD enhanced transdermal delivery by increasing the partition of drug into the skin and acted as a drug reservoir to release the curcumin continuously.

In Yang *et al.*'s (2008) study, HPCD was found to increase the transdermal permeation of avobenzone. Without the HPCD, solid avobenzone did not contribute to the TDDS. Meanwhile, in 20% (w/w) HPCD, maximum permeation was achieved by maximizing the amount of free avobenzone to be in equilibrium with complexed avobenzone (avobenzone-HPCD). Further addition of 30% (w/w) HPCD decreased the free avobenzone

available for the TDDS because avobenzone had greater probability to complex with HPCD rather than to get permeated through skin. High HPCD concentration led to sustained release delivery and formation of an avobenzone reservoir on the skin (Yang *et al.*, 2008; Ammar *et al.*, 2008).

In Yan *et al.*'s (2014) study, HPCD grafted with polyethyleneimine was synthesized to develop a cationic polymer that acts as a penetration enhancer. The designed polymer resulted in a 15-fold increase in diclofenac sodium permeation across mice skin when compared to that achieved by the negative control. The interaction between the keratinocyte and the positive charge from amino groups of the polymer created a temporary pathway for drug permeation. Another lipophilic nonpolar drug of propofol complexed with anionic sulfobutyl ether- $\beta$ -cyclodextrin demonstrated that the complexion had enhanced passive permeation across the porcine epidermis (Juluri and Murthy, 2014). The passive flux of propofol from the complexion was almost 4-fold compared to that achieved by the neat propofol. The transport studies across porcine epidermis and dialysis membrane showed that the enhancement was achieved due to the formation of intact complex and the property of sulfobutyl ether- $\beta$ -cyclodextrin, which improved the availability and the thermodynamic activity of the propofol at the dialysis membrane surface.

In Mura *et al.*'s (2014) study, methylated- $\beta$ -cyclodextrin (MCD) was used in the liposomal formulations and microemulsion

formulations for transdermal delivery of clonazepam. The study revealed that the MCD had enhanced skin permeation by increasing the drug solubility and promoting thermodynamic activity. In the liposomal formulation, the MCD was able to extract and form complexion with lipophilic components like cholesterol and triglycerides of the skin, thus temporarily reducing the function of the skin barrier (Mura *et al.*, 2014; Masson *et al.*, 1999). Another study was performed to compare the influence of cyclodextrin complexation on liposomal and nanostructured lipid carrier (NLC) formulations to improve the delivery of oxapropzin (Mennini *et al.*, 2016). The permeation of the oxapropzin-MCD in liposomes and oxapropzin-MCD in the NLC across excised human skin was 24-fold and 12-fold, respectively, when compared to that achieved by the plain drug. The high drug permeation obtained through the liposomes was attributed to its positive charge, which interacted with the negative charge of corneocytes of the stratum corneum and subsequently resulted in a prolonged skin retention, as well as increased penetration ability (Song and Kim, 2006; Jain *et al.*, 2003). Meanwhile, the NLC which contained negative charges was capable of forming an occlusive layer on the skin surface and promoting skin hydration effect, thus contributed to the drug penetration enhancement (Mennini *et al.*, 2016; Pardeike *et al.*, 2009). Table 3 summarizes the applications of starch in TDDS.

**Table 3:** Applications of Starch in TDDS.

Polymers	Dosage Forms	Model Drugs	Remarks	References
Propyl-starch derivative	Nanoparticles	<ul style="list-style-type: none"> <li>Flufenamic acid</li> <li>Testosterone</li> <li>Caffeine</li> </ul>	The delivery of encapsulated flufenamic acid in starch nanoparticles were enhanced for about 10-fold greater than un-encapsulated flufenamic acid across the human skin. Nonetheless, no such enhancement was observed for testosterone and caffeine.	Santander-Ortega <i>et al.</i> (2010).
Carboxymethylstarch 1,4-cis polybutadiene (CMS-1,4-PBD)	Nanoparticles	Clonidine	The clonidine loaded CMS-1,4-PBD nanoparticles were able to provide high entrapment efficiency.	Saboktakin <i>et al.</i> (2014)
Starch nanocrystals (SNCs)	Hydrogel patch	Acyclovir	Hydrogel formulated from maize and potato based SNCs had better stability during storage in comparison to the hydrogel formulated from cassava SNCs.	Bakrudeen <i>et al.</i> (2016)
Hydroxypropyl- $\beta$ -cyclodextrin (HPCD)	• Hydrogel	• Curcumin	HPCD enhanced transdermal delivery by increasing the partition of drug into the skin and acted as drug reservoir to release curcumin continuously.	Sun <i>et al.</i> (2014);
	• Solution	• Avobenzone	High HPCD concentration led to sustained release delivery and formation of an avobenzone reservoir on the skin.	Yang <i>et al.</i> (2008)
HPCD grafted with polyethyleneimine	Solution	Diclofenac sodium	The interaction between the positive charge from amino groups of the polymer and keratinocyte create a temporary pathway for drug permeation.	Yan <i>et al.</i> (2014)
Sulfobutyl ether- $\beta$ -cyclodextrin	Solution	Propofol	The complexion enhanced passive permeation across the porcine epidermis.	Juluri and Murthy (2014)
Methylated- $\beta$ -cyclodextrin (MCD)	<ul style="list-style-type: none"> <li>Liposome and microemulsion</li> <li>Liposome and nanostructured lipid carrier (NLC)</li> </ul>	<ul style="list-style-type: none"> <li>Clonazepam</li> <li>Oxapropzin</li> </ul>	MCD enhanced skin permeation by increasing the drug solubility and promoting thermodynamic activity. The positive charge of liposome interacted with the negative charge of corneocytes of the stratum corneum, and subsequently resulted in a prolonged skin retention, as well as increased penetration ability. Meanwhile, NLC which contained negative charges was capable to form an occlusive layer on the skin surface and promoting skin hydration effect, thus contributed to the drug penetration enhancement.	Mura <i>et al.</i> (2014); Mennini <i>et al.</i> (2016)

### *Aloe vera*

*Aloe vera* is a perennial plant that grows in a hot and dry climate. The genus *Aloe* comprises more than 400 species belonging to the Xanthorrhoeaceae family (Fox *et al.*, 2015). The average molecular weight of *A. vera* gel can be more than 1 MDa (Im *et al.*, 2016). The plant consists primarily of water and other substituents like hemicellulose, pectin, mannose, glucose, L-rhamnose, aldopentose, and uronic acid (Sharma *et al.*, 2015; Cervantes-Martínez *et al.*, 2014). The gel of *A. vera* contains a mixture of polymers of various chain length of  $\beta$ -(1,4)-linked acetylated mannan, known as acemannan, a polysaccharide, which is rich in mannose (Im *et al.*, 2016; Sharma *et al.*, 2015; Cervantes-Martínez *et al.*, 2014; Manna and McAnalley, 1993).

The skin drug permeation study showed that compared to plants such as *A. marlothii* and *A. ferox*, *A. vera* had a better potential as a penetration enhancer. *A. vera* elevated drug

permeation by increasing the partition of drug into the skin (Fox *et al.*, 2015). Some of the *A. vera* constituents were able to exhibit anti-inflammatory effects, penetrate the skin, and provide hydration themselves. The permeation enhancement was dependent on the molecular weight of the co-compound.

In other studies, *A. vera* was reported to act as an effective penetration enhancer for active ingredients of ketoprofen, quinine, oxybutynin, and colchicine with a molecular weight ranging from 254 to 324 Da (Cole and Heard, 2007; Fox *et al.*, 2015) (Table 4). Nevertheless, *A. vera* was also shown to be less permeative towards caffeine, mefenamic acid, and captopril with a molecular weight ranging from 194 to 217 Da (Cole and Heard, 2007; Nair *et al.*, 2013). The permeation enhancement effect of *A. vera* was attributed to a probable pull effect of complexes between the high molecular weight drug and the unidentified enhancing agent within the *A. vera*.

**Table 4:** Applications of *A. vera* in TDDS.

Polymer	Dosage Form	Model Drugs	Remarks	References
<i>A. vera</i>	Gel	<ul style="list-style-type: none"> <li>• Ketoprofen acid</li> <li>• Quinine</li> <li>• Oxybutynin</li> <li>• Colchicine</li> </ul>	<i>A. vera</i> elevated drug permeation by increasing the partition of drug into the skin. Some of the <i>A. vera</i> constituents were able to penetrate the skin and provide hydration themselves, as well as anti-inflammatory effects.	Cole and Heard (2007); Fox <i>et al.</i> (2015)

**Table 5:** Applications of Sodium Alginate in TDDS.

Polymers	Dosage forms	Model drugs	Remarks	References
Conjugated sodium alginate-L-cysteine	Matrix patch	Losartan potassium	Reasonable bursting strength, rapid drug release and increase in drug permeation of the conjugated sodium alginate when compared to the unconjugated counterpart.	Satheesha Babu and Srinivasa Rao (2015)
Sodium alginate	Gel	Nifedipine	The 4.5% (w/w) sodium alginate with nerolidol resulted in permeation rate of 31.70 $\mu\text{g}/\text{cm}^2/\text{h}$ , close to the therapeutic value.	Bektaş <i>et al.</i> (2014)
Alginate/hyaluronate	Microneedle patch	Insulin	The patch showed exceptional mechanical strength and good degradability.	Yu <i>et al.</i> (2017)

### Alginate/Sodium Alginate

Alginate or alginic acid is a polysaccharide derived from brown seaweed with a molecular weight ranging from 213 to 277 kDa (Gómez-Ordóñez *et al.*, 2012). Alginate is composed of D-mannuronate and L-guluronate bonds in varying proportions (Ashikin *et al.*, 2010; Gómez-Ordóñez *et al.*, 2012; Bektaş *et al.*, 2014). It is an anionic, hydrophilic polymer that is insoluble in ethanol and ether (Velmurugan and Ashraf Ali, 2013; Satheesha Babu and Srinivasa Rao, 2015; Gowda *et al.*, 2010). Alginate constitutes a primary amino group at the 2-position of each polymer subunit, and this characteristic facilitates the chemical modification at this site.

Satheesha Babu and Srinivasa Rao (2015) synthesized conjugated sodium alginate-L-cysteine for the development of matrix transdermal patches of losartan potassium. The conjugation of sodium alginate substituted the primary amino group with thiol group, causing the polymer chain to be opened up and form loose matrix, which improved the permeability. The opening allowed a reasonable bursting strength, rapid drug release, and increase in drug permeation of the conjugated sodium alginate when

compared to the unconjugated counterpart.

In addition, a gel composed of sodium alginate and nerolidol as the penetration enhancer was employed in the fabrication of transdermal film of nifedipine (Bektaş *et al.*, 2014). The 4.5% (w/w) sodium alginate with nerolidol resulted in a permeation rate of 31.70  $\mu\text{g}/\text{cm}^2/\text{h}$ , close to the therapeutic value of 33.0–37.5  $\mu\text{g}/\text{cm}^2/\text{h}$ . In another study, a microneedle patch composed of modified alginate/hyaluronate was developed for transdermal delivery of insulin. The patch showed exceptional mechanical strength and good degradability. The *in vivo* transdermal delivery study using diabetic Sprague Dawley rats demonstrated that the relative pharmacologic availability and relative bioavailability of insulin from the prepared patch were  $90.5 \pm 6.8\%$  and  $92.9 \pm 7\%$ , respectively, in comparison to the subcutaneous injection (Yu *et al.*, 2017). Table 5 summarizes the applications of sodium alginate in TDDS.

### Cashew Gum

Cashew gum, which is typically exuded from the stem of *Anacardium occidentale* L., is an anionic, hydrophilic, and

branched acidic heteropolysaccharide (Quelemes *et al.*, 2017; Ribeiro *et al.*, 2016; Pitombeira *et al.*, 2015; Botrel *et al.*, 2017). The main chain of cashew gum contains  $\beta$ -D-galactose 1 $\rightarrow$ 3 linked with side chains of galactose and glucose (de Paula and Rodrigues 1995; de Paula *et al.*, 1998; Pitombeira *et al.*, 2015). Cashew gum is composed of galactose (72–73%), glucose (11–14%), glucuronic acid (4.7–6.3%), arabinose (4.6–5%), and rhamnose (3.2–4%) (de Paula and Rodrigues 1995; de Paula *et al.*, 1998).

Cashew gum has promising applications in TDDS through nanoparticles. Dias *et al.* (2016) formulated

acetylated cashew gum into nanoparticles via dialysis and nanoprecipitation for transdermal delivery of diclofenac diethyl amine (Table 6). The acetylated cashew gum-based nanoparticles (ACG-DDA-NPs) prepared via dialysis resulted in more yields and better colloidal stability compared to that achieved by the nanoprecipitation. The efficiency of drug incorporation for both methods were over 60%. The transdermal permeation of both free drug and ACG-DDA-NPs reached 90%, but the latter demonstrated a more controlled release compared to that achieved by the free drug.

**Table 6:** Application of Cashew Gum in TDDS.

Polymer	Dosage Form	Model Drug	Remarks	References
Acetylated cashew gum	Nanoparticles	Diclofenac diethyl amine	The transdermal permeation of both free drug and acetylated cashew gum-based nanoparticles reached 90%, nevertheless the latter demonstrated a more controlled release when compared to the free drug.	Dias <i>et al.</i> (2016)

**Table 7:** Application of *Cordia dichotoma* Mucilage in TDDS.

Polymer	Dosage Form	Model Drug	Remarks	References
<i>Cordia dichotoma</i> mucilage	Film	Alfuzosin hydrochloride	The <i>in vitro</i> drug release study showed that a greater release of alfuzosin hydrochloride was observed with the increase of concentration of <i>Cordia dichotoma</i> mucilage in the formulation.	Duppala <i>et al.</i> (2016)

**Table 8:** Application of *Ficus carica* Mucilage in TDDS.

Polymers	Dosage Form	Model Drug	Remarks	References
<i>Ficus carica</i> mucilage/ polyvinylpyrrolidone	Matrix patch	Tramadol hydrochloride	The <i>in vitro</i> drug permeation of tramadol hydrochloride could be sustained within the therapeutic range.	Abdul Ahad <i>et al.</i> (2016)

### *Cordia dichotoma*

*Cordia dichotoma* or Indian cherry comprises about 250 species belonging to the family of Boraginaceae (Matias *et al.*, 2015). The fruit contains glucose (67.6%), arabinose (13.2%), and arabinoglucan (Pawar and Jadhav, 2015; Jamkhande *et al.*, 2013), and it has a backbone chain of (1 $\rightarrow$ 3)-linked D-gluco-pyranosyl and (1 $\rightarrow$ 2)-linked L-arabinofuranosyl residues (Basu *et al.*, 1984).

*Cordia dichotoma* fruit mucilage was found to have a film forming property and was employed in the formulation of transdermal film loaded with alfuzosin hydrochloride (Table 7). The *in vitro* drug release study showed that a greater release of alfuzosin hydrochloride was observed with the increase of concentration of *Cordia dichotoma* fruit mucilage in the formulation (Duppala *et al.*, 2016).

### *Ficus carica*

*Ficus carica*, commonly referred as fig, is the largest genus in the Moraceae family (Yang *et al.*, 2015). It has a high proportion of sugar consisting of  $\beta$ -D-glucans with a straight chain having (1 $\rightarrow$ 3)-linked  $\beta$ -D-glucose residues and substituted with a complex structure of branched chains. The side chains show either one D-glucosyl group or di-, tri-, or tetra-D-glucose (Ishurd *et al.*, 2004).

*Ficus carica* mucilage in combination with a synthetic polymer of polyvinylpyrrolidone (PVP) was found to act as a matrix polymer for controlled release of tramadol hydrochloride (Abdul Ahad *et al.*, 2016) (Table 8). *Ficus carica* mucilage-based

patch had a porous surface, and the *in vitro* drug permeation study revealed that tramadol hydrochloride permeation could be sustained within the therapeutic range.

### Guar Gum

Guar gum is exuded from the seed endosperm of the legume plant, *Cyamopsis tetragonoloba* (L) Taub (Prabaharan, 2011; Khairmar *et al.*, 2014). It is a linear non-ionic polymer consisting of (1 $\rightarrow$ 4)- $\beta$ -D-mannopyranosyl units with  $\alpha$ -D-galactopyranosyl units attached by (1 $\rightarrow$ 6) linkages to form short branches (Kulkarni *et al.*, 2012; Prabaharan, 2011; Saurabh *et al.*, 2016). Guar gum is composed of galactomannan, water, protein, ash, and fat (Prabaharan, 2011).

In Thakur *et al.*'s (2009) study, tailoring acryloyl guar gum (AGG) was synthesized to develop a guar gum hydrogel for transdermal delivery of pro-drugs L-tyrosine and 3,4-dihydroxy phenylalanine (L-DOPA). Various types of AGG hydrogel were synthesized by grafting reaction with acrylic acid (AAc), methacrylic acid (MAAc), 2-hydroxyethyl methacrylate (HEMA), and 2-hydroxypropyl methacrylate (HPMA). Both pro-drugs showed high loading on these hydrogel materials. The hydrogel materials responded well to physiological stimuli such as pH and ionic strength. The cumulative release of pro drug L-tyrosine was maximum from the AGG containing MAAc, while the L-DOPA had a maximum release from AGG containing AAc in both media of pH 7.4 and 2.2. The AGG hydrogels containing MAAc and AAc showed a porous network structure with uniform shape

and size. On the other hand, the AGG containing HEMA and HPMA showed low drug release even after 12 h. The hydrogels apparently had small pore size and the grafted polymer chains formed aggregates due to the low level of interaction between less hydrophilic HEMA and HPMA with the AGG backbone.

Extensive work has been reported on transdermal diclofenac sodium using guar gum as the main polymer (Giri *et al.*, 2011; Giri *et al.*, 2012; Giri *et al.*, 2013; Giri *et al.*, 2016). Guar gum-chemically-modified multi-walled carbon nanotube hybrid hydrogel and guar gum hydrogel with nanosilica have been synthesized for sustained release of diclofenac sodium. Both formulations showed that the drug exhibited slow but steady release owing to its highly viscous property (Giri *et al.*, 2011; Giri *et al.*, 2012). Additionally, *in situ* nanosilica/acrylic acid grafted guar gum membrane (AAGG) was utilized for controlled transdermal delivery of diclofenac sodium (Giri *et al.*,

2013). In this study, guar gum was grafted with acrylic acid and nanocomposite was prepared *in situ* with nanosilica. The graft copolymer nanocomposite demonstrated excellent controlled drug release property compared to that achieved by the guar gum alone and AAGG due to the hydrophobicity, and better “cage morphology” formed by the grafted unit and drug molecules.

In Murthy *et al.*'s (2004b) study, carboxymethyl guar gum (CMG) was used in the formulation of transdermal terbutaline sulfate (TS). The CMG film was prepared by casting the solution at pH 5 and 10. The *in vitro* diffusion study showed that the release of TS from the CMG film was relatively slower when using pH 5 in comparison to pH 10. The pharmacokinetic study demonstrated that the CMG film of pH 5 had a consistent steady-state concentration of TS and about 50% higher bioavailability compared to that achieved by the pH 10 formulation. Table 9 summarizes the applications of guar gum in TDDS.

**Table 9:** Applications of Guar Gum in TDDS.

Polymers	Dosage Forms	Model Drugs	Remarks	References
Acryloyl guar gum (AGG)	Hydrogel	<ul style="list-style-type: none"> <li>L-tyrosine</li> <li>3,4-dihydroxy phenylalanine (L-DOPA)</li> </ul>	The cumulative release of L-tyrosine was maximum from AGG containing methacrylic acid, while L-DOPA had a maximum release from AGG containing acrylic acid in both media of pH 7.4 and 2.2.	Thakur <i>et al.</i> (2009)
Guar gum	Hydrogel	Diclofenac sodium	Guar gum-chemically modified multi-walled carbon nanotube hybrid hydrogel and guar gum hydrogel with nanosilica showed slow but steady drug release owing to their highly viscous property.	Giri <i>et al.</i> (2011); Giri <i>et al.</i> (2012)
Nanosilica/acrylic acid grafted guar gum (AAGG)	Nanocomposite	Diclofenac sodium	The graft copolymer nanocomposite demonstrated excellent controlled drug release property when compared to the guar gum alone and AAGG due to the hydrophobicity and better ‘cage morphology’ formed by grafted unit and drug molecules.	Giri <i>et al.</i> (2013)
Carboxymethyl guar gum (CMG)	Film	Terbutaline sulfate	The <i>in vitro</i> diffusion study showed that the release of terbutaline sulfate from CMG film was relatively slower when using pH 5 in comparison to pH 10 formulation.	Murthy <i>et al.</i> (2004b)

**Table 10:** Applications of Gellan Gum in TDDS.

Polymer	Dosage Forms	Model Drugs	Remarks	References
Gellan gum	• Gel and hydrogel film	• Diclofenac sodium	Both formulations had higher initial flux and total diclofenac transport when compared to the commercial formulations of Voltaren emulgel and Pennsaid solution in the <i>in vitro</i> transport study.	Carmona-Moran <i>et al.</i> (2016)
	• Hydrogel patch coated with gold nanorods	• Fluorescein isothiocyanate-modified ovalbumin	The combination of gellan gum hydrogel and photothermal effect of gold nanorods had successfully improved the protein delivery.	Haine <i>et al.</i> (2017)

## Gellan Gum

Gellan gum produced by the bacteria *Sphingomonas elodea* is a linear, anionic deacylated exopolysaccharide with a polymer chain of tetrasaccharide repeating units of  $\alpha$ -L-rhamnose,  $\beta$ -D-glucose, and  $\beta$ -D-glucuronate in the molar ratio of 1:2:1 (Xiao *et al.*, 2011; Osmalek *et al.*, 2014; Priyadarshini *et al.*, 2016; Carmona-Moran *et al.*, 2016).

In Carmona-Moran *et al.*'s (2016) study, they investigated semisolid gel and solid hydrogel films using gellan gum as a gelling agent for transdermal delivery of diclofenac sodium. In the *in vitro* transport study, both formulations recorded higher initial flux and total diclofenac transport compared to that achieved by the commercial formulations of Voltaren emulgel and Pennsaid

solution. High initial flux was necessary to achieve the immediate therapeutic effect or quick pain relief when using the transdermal diclofenac sodium. Various concentrations of gellan gum provided different effects to the semisolid and solid hydrogel films. In the semisolid formulation, low gellan gum concentration reduced the diclofenac sodium transport and permeability while reducing the gellan gum concentration in the solid hydrogel film increased the total diclofenac transport. This opposite behaviour was likely to be influenced by the three-dimensional swollen configuration of the polymer.

Gellan gum has also been used in the preparation of hydrogel patch coated with gold nanorods for transdermal protein delivery of fluorescein isothiocyanate-modified

ovalbumin (FITC-OVA) (Haine *et al.*, 2017). The study demonstrated that the combination of gellan gum hydrogel and photothermal effect of gold nanorods had successfully improved the protein delivery. In order to increase the adhesive property, the hydrogel was combined with other anionic polysaccharides of chondroitin sulfate and hyaluronic acid. The gellan gum/hyaluronic acid hydrogel exhibited slower release of FITC-OVA compared to that achieved by gellan gum/chondroitin sulfate. This could be due to the tight polymer networks developed between the hyaluronic acid and gellan gum (Haine *et al.*, 2017). Table 10 summarizes the applications of gellan gum in TDDS.

### Jackfruits Mucilage

Jackfruit or *Artocarpus heterophyllus* Lam belongs to the Moraceae family and has high level of carbohydrate (Jagtap *et al.*, 2011). The fruit pulp consists of glucose, mannose, rhamnose, arabinose, galactose, xylose, and galacturonic acid (Sabale *et al.*, 2012; Zhu *et al.*, 2017). The polysaccharide derived from jackfruit pulp has an average molecular weight of 1,668 kDa (Zhu *et al.*, 2017).

In one study, the mucilage obtained from a ripe jackfruit pulp was found to be a promising polymer for transdermal delivery of acyclovir (Bhoyar *et al.*, 2015) (Table 11). A high concentration of jackfruit mucilage produced excellent drug release property but low folding endurance. Further study needs to be carried out to investigate the transdermal drug delivery mechanism of jackfruit mucilage.

**Table 11:** Application of Jackfruits Mucilage in TDDS.

Polymer	Dosage Form	Model Drug	Remarks	References
Jackfruits mucilage	Film	Acyclovir	High concentration of jackfruit mucilage produced excellent drug release property but low folding endurance.	Bhoyar <i>et al.</i> (2015)

**Table 12:** Application of Locust Bean Gum in TDDS.

Polymers	Dosage Form	Model Drug	Remarks	References
Locust bean gum/alginate	Film	Piroxicam	The study revealed that the optimized ratio of locust bean gum to alginate was about 12:80.5 as it achieved the highest percentage of drug permeation when compared to other compositions.	Keshavarao <i>et al.</i> (2011)

### Locust Bean Gum

Locust bean gum (LBG) is obtained from the endosperm of leguminous plant *Ceratonia siliqua* Linn. LBG has a molecular weight that ranges from 300 to 1,200 kDa (Kaity *et al.*, 2013). It is a hydrophilic polymer and is mainly composed of neutral galactomannan made up of 1,4-linked D-mannopyranosyl backbone, which links to (1,6)  $\alpha$ -D-galactose (Kaity *et al.*, 2013; Keshavarao *et al.*, 2011; Kulkarni *et al.*, 2012; Jana and Sen, 2017).

In Keshavarao *et al.*'s (2011) study, LBG was used with another polysaccharide of alginate to develop a transdermal film loaded with piroxicam (Keshavarao *et al.*, 2011) (Table 12). The study revealed that the optimized ratio of LBG to alginate was about 12:80.5 as it achieved the highest percentage of drug permeation compared to that achieved by other compositions. However, further understanding is required on how this gum interacts and its mechanism in TDDS.

### Pectin

Pectin is obtained by the acid hydrolysis located primarily in the middle lamella between cells in the tissues of higher plant. Pectin is a linear, anionic polysaccharide with a predominant structural feature of 1 $\rightarrow$ 4 linked  $\alpha$ -D-galacturonic residues interrupted by 1, 2-L- rhamnose residues (Saha *et al.*, 2016; Soares *et al.*, 2013; Kulkarni *et al.*, 2012). The sources for pectin production are generally from orange, mango, apple, sugar beet, banana, and pomegranate (Saberian *et al.*, 2017; Wang *et al.*, 2016; Wikiera *et al.*, 2016; Guo *et al.*, 2017; Oliveira *et al.*, 2016;

Pereira *et al.*, 2016). The composition of pectin depends on the botanical sources (Cárdenas *et al.*, 2008).

In Güngör *et al.*'s (2008) study, pectin was used to develop a matrix type transdermal film for the delivery of verapamil hydrochloride. The *in vivo* percutaneous absorption study showed that the verapamil hydrochloride transdermal patches, with and without the penetration enhancers, were capable of achieving the desired therapeutic effect of lowering the systolic blood pressure. Another study conducted by Bektaş, *et al.* (2014) used pectin to develop a transdermal film of nifedipine. The textural analysis of the gel's formulation revealed that the formulation, which contained 3.5% (w/w) of pectin, was suitable for the fabrication of transdermal film. Further study is necessary to improve the formulation of pectin-based transdermal film of nifedipine in order to achieve the therapeutic effect.

In another study, low-methoxyl-pectin (LMP)- and high-methoxyl-pectin (HMP)-coated liposomes were used for transdermal delivery of vitamin C (Zhou *et al.*, 2014). The LMP and HMP were found to increase the permeation of vitamin C by 2.1- and 1.7-fold, respectively, when compared to that achieved by uncoated nanoliposomes. The permeation enhancement was attributed to the bioadhesive property of the pectin, which promoted skin contact for an extended period. Additionally, the anionic property of pectin contributed to the negatively-charged nanoliposomes hence increased drug flux and diffusion coefficient.

In Hadebe *et al.*'s (2014) study, amidated pectin was used to formulate a hydrogel matrix patch for transdermal delivery of

insulin. The immunohistochemical study revealed that the pectin hydrogel patch had the potential to deliver insulin transdermally. The patch evoked changes in blood glucose and plasma insulin concentrations. It had the potential to offer a controlled release of insulin with a concomitant alleviation of some diabetic symptoms. The amidated pectin has also been used in TDDS to manage malaria disease. Transdermal chloroquine was developed using amidated pectin in the form of matrix patch as an alternative to oral administration (Musabayane *et al.*, 2003). In another study, asiatic acid-pectin hydrogel matrix patch was developed to investigate its effect on parasitemia suppression and inflammation reduction that was induced by *Plasmodium berghei* (Alfrd Mavondo and Tagumirwa, 2016). The results were compared with transdermal chloroquine patch. The asiatic acid-pectin hydrogel patch showed better efficacy and was able to reduce parasitemia and inflammation more significantly than the transdermal chloroquine patch. Table 13 summarizes the applications of pectin in TDDS.

**Table 13:** Applications of Pectin in TDDS.

Polymers	Dosage Forms	Model Drugs	Remarks	References
Pectin	Matrix patch	Verapamil hydrochloride	The <i>in vivo</i> percutaneous absorption study showed that verapamil hydrochloride transdermal patch, with and without penetration enhancers were capable of achieving the desired therapeutic effect of lowering the systolic blood pressure.	Güngör <i>et al.</i> (2008)
Low methoxyl pectin and high methoxyl pectin	Liposomes	Vitamin C	Low methoxyl pectin and high methoxyl pectin increased the permeation of vitamin C by 2.1 and 1.7 fold respectively, when compared to uncoated nanoliposomes.	Zhou <i>et al.</i> (2014)
Amidated pectin	Matrix patch	• Insulin • Chloroquine	The immunohistochemical study revealed that pectin hydrogel patch had the potential to deliver insulin transdermally. Transdermal chloroquine was developed using amidated pectin in the form of matrix patch as an alternative to oral administration.	Hadebe <i>et al.</i> (2014) Musabayane <i>et al.</i> (2003)
Asiatic acid-pectin	Matrix patch	-	The asiatic acid-pectin hydrogel patch was able to reduce parasitemia and inflammation more significantly than transdermal chloroquine patch.	Alfrd Mavondo and Tagumirwa (2016)

**Table 14:** Application of Tamarind/Xyloglucan in TDDS.

Polymer	Dosage Form	Model Drug	Remarks	References
Tamarind/xyloglucan	Patch	Clindamycin	The designed patch showed controlled release and excellent antimicrobial property.	Duangjit <i>et al.</i> (2014)

**Table 15:** Application of Xanthan Gum in TDDS.

Polymer	Dosage form	Model drug	Remarks	References
Grafted xanthan gum	Matrix film	Atenolol	Atenolol, a hydrophilic drug exerted an interaction with the hydrophilic xanthan gum, which led to swelling and large pores formation, thus promoting drug loading and higher release rate.	Mundargi <i>et al.</i> (2007)

## Xanthan Gum

Xanthan gum is an exopolysaccharide that is mainly produced by the bacterium *Xanthomonas campestris*. It is an anionic polymer with a molecular weight of 200 Da to 2,000 kDa (Han *et al.*, 2017). Xanthan gum is a water-soluble polymer that readily disperses in cold and hot water (Palaniraj and Jayaraman, 2011; Nur Hazirah *et al.*, 2016). The primary structure of xanthan gum consists of repeated pentasaccharide units formed by two

## Tamarind/Xyloglucan

Tamarind (*Tamarindus indica*) is a leguminous tree in the family of Fabaceae. Tamarind seed can contain up to 72% mucilage with a molecular weight around 720 to 880 kDa (Alpizar-Reyes *et al.*, 2017; Kaur *et al.*, 2012; Freitas *et al.*, 2005). It is composed of polysaccharide called xyloglucan, which is classified as hemicellulose and contains glucose, xylose, and galactose units (Freitas *et al.*, 2005; Alpizar-Reyes *et al.*, 2017). Tamarind has a backbone chain of (1→4) β-D-glucans-like cellulose but the side chain is substituted with α-D-xylopyranose linked (1→6) to glucose residues (Oontawee *et al.*, 2015; Kaur *et al.*, 2012; Khounvilay and Sittikijyothin, 2012). In Duangjit *et al.*'s (2014) study, tamarind seeds were used as a gelling agent in the formulation of clindamycin transdermal patch. The designed patch showed controlled release and excellent antimicrobial property (Table 14). Further study is required to understand the function and mechanism of tamarind in TDDS.

D-glucose, two D-mannose, and one D-glucuronic acid units (Nur Hazirah *et al.*, 2016; García-Ochoa *et al.*, 2000). The main unit which is composed of β-D-glucose linked at the 1 and 4 positions is identical to cellulose (García-Ochoa *et al.*, 2000; Palaniraj and Jayaraman, 2011).

In Mundargi *et al.*'s (2007) study, grafted xanthan gum was employed as a matrix film for transdermal delivery of atenolol (Table 15). Acrylamide was grafted onto the xanthan gum by free radical polymerization. The matrix film was synthesized using

various concentrations of acrylamide and atenolol. The *in vitro* release study indicated that a low grafting ratio of acrylamide (xanthan gum:acrylamide = 1:7.5) resulted in a high drug release compared to that achieved by other grafting ratios. The high drug

loading in the matrix film also elevated drug release. Atenolol, a hydrophilic drug, exerted an interaction with the hydrophilic xanthan gum, which led to swelling and large pores formation, thus promoting drug loading and higher release rate.

**Table 16:** Physicochemical Properties of Polysaccharides.

Polymer	Physicochemical Properties	References
Carboxymethyl cellulose	Hydrophilic, high chemical stability	Mandal <i>et al.</i> (2017)
Hydroxyethyl cellulose (HEC)/hyaluronic acid (HA)	HEC/HA: Stable viscoelastic, bioadhesive HEC: Hydrophilic HA: Excellent water retention, pH dependent	Kwon <i>et al.</i> (2015); Kong <i>et al.</i> (2016)
Hydroxypropyl methylcellulose	Hydrophilic, high swelling behaviour, viscoelastic, film forming ability	Sarkar <i>et al.</i> (2014); Anuar <i>et al.</i> (2007)
Bacterial cellulose	High swelling behaviour, bioadhesive	Silva <i>et al.</i> (2014)
Chitosan	Cationic, low water solubility, film forming ability, bioadhesive	Paul <i>et al.</i> (2015); Escobar-Chávez <i>et al.</i> (2011); Can <i>et al.</i> (2013)
Low molecular weight chitosan	Water soluble, pH dependent	Zhou <i>et al.</i> (2010)
Arginine-rich derivative of chitosan	Water soluble	Lv <i>et al.</i> (2011); Gao <i>et al.</i> (2008)
Chitosan whisker grafted with oligo (lactic acid)	Amphiphilic, molecular weight of < 100 nm	Engkagul <i>et al.</i> (2017)
Guar gum	Non-ionic, hydrophilic, pH-dependent	Thakur <i>et al.</i> (2009)
Acryloyl guar gum	pH dependent, ionic dependent	Thakur <i>et al.</i> (2009)
Carboxymethyl guar gum	Anionic, hydrophilic, hygroscopic, pH dependent, film forming ability	Murthy <i>et al.</i> (2004b)
Starch	Hydrophilic	Lu <i>et al.</i> (2009)
Propyl-starch derivative	Hydrophobic	Santander-Ortega <i>et al.</i> (2010)
Hydroxypropyl-β-cyclodextrin	Hydrophobic central cavities and hydrophilic exteriors, high solubility	Berbicz <i>et al.</i> (2011)
Hydroxypropyl-β-cyclodextrin grafted with polyethyleneimine	Cationic, bioadhesive	Yan <i>et al.</i> (2014)
Sulfobutyl ether-β-cyclodextrin	Anionic	Juluri & Murthy (2014)
<i>Aloe vera</i>	High water retention	Im <i>et al.</i> (2016); Cervantes-Martínez <i>et al.</i> (2014)
Alginate	Anionic, hydrophilic, insoluble in ethanol and ether	Gómez-Ordóñez <i>et al.</i> (2012); Satheesha Babu and Srinivasa Rao (2015)
Cashew gum	Anionic, hydrophilic	Ribeiro <i>et al.</i> (2016)
<i>Cordia dichotoma</i>	Film forming ability	Duppala <i>et al.</i> (2016)
Gellan gum	Anionic, film forming ability	Xiao <i>et al.</i> (2011)
Jackfruit mucilage	Hydrophilic, film forming ability, bioadhesive	Bhoyar <i>et al.</i> (2015); Sabale <i>et al.</i> (2012); Zhu <i>et al.</i> (2017)
Locust bean gum	Non-ionic, hydrophilic	Kaity <i>et al.</i> (2013)
Pectin	Hydrophilic, anionic, bioadhesive	Anuar and Wong (2014); Zhou <i>et al.</i> (2014); Wong and Anuar (2012)
Tamarind/xyloglucan	Hydrophilic, high thermal and chemical stability, bioadhesive	Alpizar-Reyes <i>et al.</i> (2017)
Xanthan gum	Anionic, hydrophilic, hygroscopic	Palaniraj and Jayaraman (2011); Bhunia <i>et al.</i> (2013); Nur Hazirah <i>et al.</i> (2016)

## LIMITATIONS OF POLYSACCHARIDES AND FUTURE PROSPECTS

Natural polysaccharides exhibit excellent physicochemical properties (Table 16). Several mechanisms of drug permeation enhancement by polysaccharides were reported by researchers (Figure 2). However, they have certain drawbacks including microbial contamination, reduced viscosity during the

storage, thickening, and uncontrolled rate of hydration (Motiwala *et al.*, 2015; Prajapati *et al.*, 2013; Kaity *et al.*, 2013; Dias *et al.*, 2016). Natural materials are also associated with batch-to-batch variations, depending on the environment and several physical factors. The modification of polysaccharides such as by grafting, cross-linking, and blending with other natural/synthetic/semi-synthetic polymers is usually necessary to improve the physical,

chemical, and functional properties of the substance. Examples of polysaccharides blend in TDDS that are not mentioned previously include chitosan/gellan gum (Abioye *et al.*, 2015), chitosan/HPMC (Siddaramaiah *et al.*, 2006; Wahid *et al.*, 2008), chitosan/alginate (Ahmed and El-Say, 2014), chitosan/alginate/ $\beta$ -cyclodextrin (Anirudhan *et al.*, 2017), chitosan/starch (Viyoch *et al.*, 2003; Viyoch *et al.*, 2005),  $\beta$ -cyclodextrin with chitosan/HPMC/HPC/Carbopol (Ammar *et al.*, 2008; Behin *et al.*, 2014; Ahmed *et al.*, 2014), cellulose/guar gum/polyvinyl alcohol (Anirudhan *et al.*, 2017), methylcellulose/pectin (Saha *et al.*, 2016), xanthan gum/polyvinyl alcohol (Bhunia *et al.*, 2013), HPMC/polyethylene glycol (Nair *et al.*, 2013; Badawi *et al.*, 2016), HPMC/Eudragit RS100 (Parhi and Suresh, 2016), and ethyl cellulose/polyvinyl pyrrolidone (Amnuakit *et al.*, 2005).

Clearly, the use of polysaccharides in TDDS formulations, either on its own or in combination with other

polymers, have shown many positive outcomes. Nevertheless, further investigations need to be carried out to optimize the formulations and to fully understand its mechanism of drug release and permeation enhancement. Such studies will significantly contribute to the development of superior TDDS that are safe and environmentally friendly, and with the desired therapeutic effects.

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#### CONFLICT OF INTEREST

The authors report no conflict of interest.

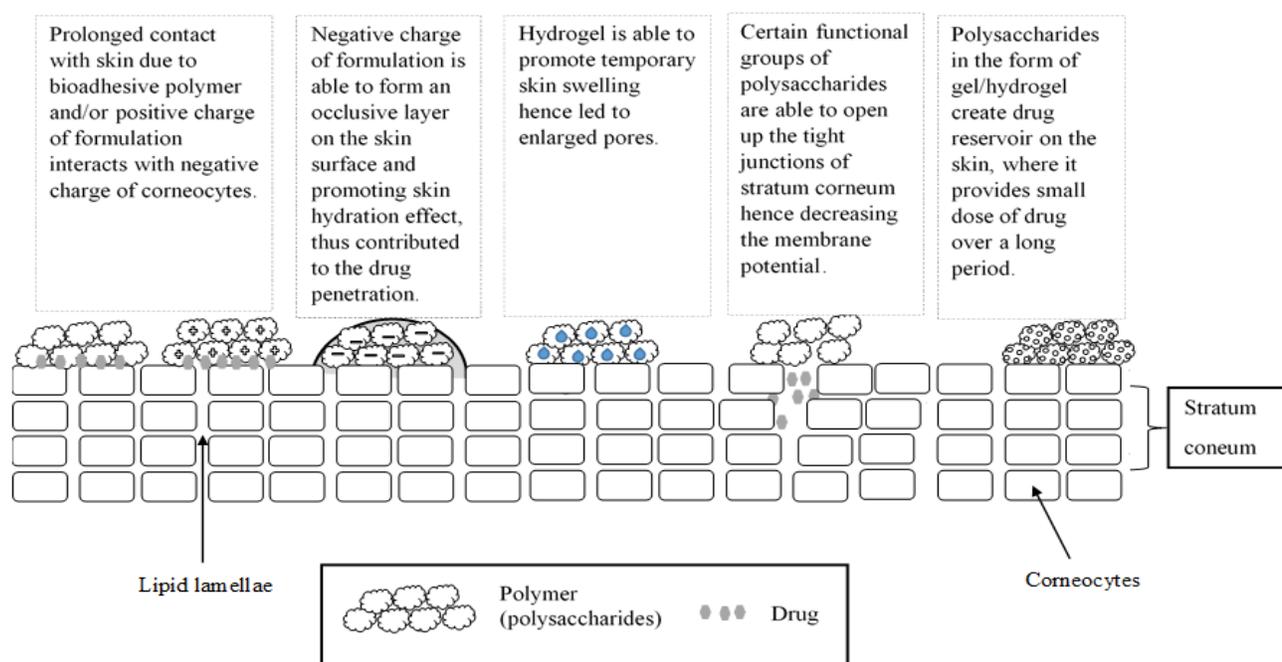


Fig. 2: Mechanisms of drug permeation enhancement across the stratum corneum.

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