BJPS

Brazilian Journal of
Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902022e20802

Article

Applications of polysaccharides in topical and transdermal drug delivery: A recent update of literature

Rabinarayan Parhi[1]*, Suvendu Kumar Sahoo[2], Anik Das[2]

[1]Department of Pharmaceutical Sciences, Susruta School of Medical and Paramedical Sciences, Assam University (A Central University), Silchar-788011, Assam, India, [2]GITAM Institute of Pharmacy, GITAM Deemed to be University, Gandhi Nagar Campus, Rushikonda, Visakhapatnam-530045, Andhra Pradesh, India

The main aim of transdermal drug delivery (TDD) is to deliver a specific dose of drug across the skin and to reach systemic circulation at a controlled rate. On the other hand skin is the target for topical drug delivery. Mentioned drug delivery systems (DDS) have numerous advantages compared to oral and parenteral routes. Avoidance of first-pass metabolism, prevent drug degradation due to harsh environment of the stomach, allow controlled drug delivery, provide patient compliance, and pain-free administration are a few of them. To achieve all of them, a DDS with suitable polymer is the primary requisite. Based on the recent trends, natural polymers have been more popular in comparison to synthetic polymers because the former possesses favourable properties including nontoxic, biodegradable, biocompatible, low cost, sustainable and renewable resources. In this context polysaccharides, composed of chains of monosaccharides bound together by glycosidic bonds, have been successfully employed to augment drug delivery into and across the skin with various formulations such as gel, membrane, patches, nanoparticles, nanofibres, nanocomposite, and microneedles. In this chapter, various polysaccharides such as cellulose, chitosan, and their semisynthetic derivatives, alginate, pectin, carrageenan etc, were discussed with their diverse topical and TDD applications. In addition, various formulations based on polysaccharides and limitations of polysaccharides were also briefly discussed.

Keywords: Polysaccharides. Transdermal drug delivery. Natural polymers. Controlled drug delivery. Hydrogel.

INTRODUCTION

Drug delivery

The main intention behind the use of drug delivery systems (DDS) was to improve not only the pharmacological properties of the active ingredients but also their therapeutic properties. These systems aid to the handling and administration of drugs in addition to overcoming certain shortcomings associated with drugs including low solubility of hydrophobic drugs and poor permeability of hydrophilic drugs across the skin (Santos *et al.*, 2018). The major features of an ideal DDS are to deliver the biological actives in appropriate amount at a constant/suitable rate for a pre-determined period of time and should be able to channel the actives mainly to the site of action in the body (Cirillo *et al.*, 2014). The important basic feature of DDS is to provide plasma drug concentration within the range of therapeutic window (Coelho *et al.*, 2010). The above requirement can only be fulfilled by any DDS due to the presence of suitable drug carriers, usually polymers and other excipients. However, the success of a DDS depends on the properties of drugs and polymers, types of dosage forms, route of administration, and finally, the disease to be treated.

***Correspondence:** R. Parhi. Department of Pharmaceutical Sciences. Susruta School of Medical and Paramedical Sciences. Assam University (A Central University). Silchar-788011, Assam, India. Phone: +91-9052983544E. E-mail: rabi59bls623@gmail.com. ORCID: 0000-0003-4010-4368

Skin structure

Skin is the largest and most easily accessible organ of the human body which performs many critical functions such as regulation of body temperature, protection against the external environment; prevent the entry of microorganisms and other foreign bodies, and homeostasis. Human skin composed of three functionally distinct layers: (i) the epidermis, typically 50-150µm thick, consist of two sub-layers namely lipophilic stratum corneum (SC, 10-20µm thick), the outermost layer of skin, and hydrophilic viable epidermis (usually about 60-80µm thick) composed of four layers (top to bottom) such as stratum lucidum, stratum granulosum, stratum spinosum and stratum germinativum (Figure 1). SC is considered as a non-viable epidermis and composed of aggregated keratin filaments enclosed in a cornified envelope surrounded by lipid bilayer in multiple numbers (Parhi, 2019). (ii) Underneath the epidermis is the dermis, usually a 0.3-5mm thick layer, composed of the outer capillary and the inner reticular layer. Dermis of skin supports hair follicles, sweat glands, connective tissues, a network of capillaries, nerve endings, and lymphatic vessels. (iii) The lowermost layer of skin is subcutaneous that composed of loose, white, fibrous connective tissues with adipose mass. Microvasculature of this layer usually acts as a sink for the drugs which passed the SC (Goyal *et al.*, 2016; Parhi, Suresh, Patnaik, 2015a).

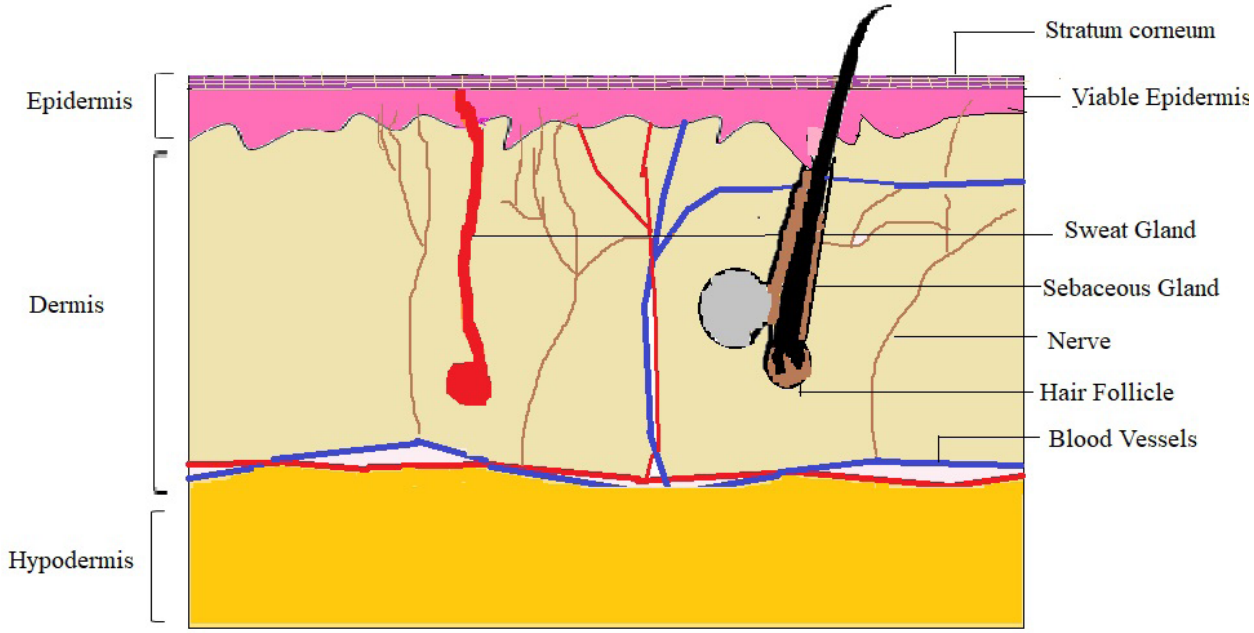

FIGURE 1 -Structure of human skin.

Drug transport pathways across skin

The SC is mainly responsible for the barrier function of the skin leading to the poor absorption of drugs. It is comprised of corneocytes, composed of keratin protein, which is distributed in a continuous matrix of bilipid layer in a particular type of arrangement, popularly known as 'bricks and mortar' structure (Selzer *et al.*, 2013). Bricks indicate corneocytes that provide a high degree of tortuosity to the drug entry, whereas mortar referred to organized lamellar bilipid structure which provides a tight barrier property to the drug permeation across SC (Parhi, 2020a). In order to pass the drug across SC and make the drug reach either deeper part of the skin or to the systemic circulation, either of the following potential routes can be targeted; transepidermal

and transappendageal route. The transepidermal route corresponds to the penetration of drug through corneocytes, called transcellular, or through bilipid layer present between corneocytes, known as intercellular. The penetration of drugs across SC usually happens through intercellular route as the drug has to cross only one type of structure i.e., bilipid layer compared to a repeated layer of corneocytes and bilipid layer in transcellular route (Parhi, 2020b). In the case of transappendageal route, the movement of drugs occurs through eccrine-sweat glands or hair follicles. This route is preferable for high molecular weight (MW) molecules and substances including vesicular and nanoparticles. Therefore, the drugs with certain suitable physicochemical and biological parameters, including MW less than 500 Da, aqueous solubility more than 100 µg/ml and log P values (lipophilicity) between 1 and 3.5, a small dose of the drug (<10mg/day) and lower boiling point (<200°C), are to be kept in mind before selecting any drug molecules for topical and TDD (Parhi, Suresh, Patnaik, 2015a).

Topical and transdermal drug delivery

Topical drug delivery is primarily intended to deliver the drug into different layers of skin for local effect with some distinct advantages: (i) elimination of systemic drug delivery (ii) minimizes the adverse effect due to off-targeting, and (iii) minimum requirement of dose to deliver the drug to the skin. On the other hand, TDD intended to permeate the drug through the skin to reach the systemic circulation in the desired amount that can elicit therapeutic effects (Goyal *et al.*, 2016; Parhi, Suresh, Patnaik, 2015a).

Therefore, the transdermal route is the second most preferred route for drug administration after the oral route and it has been used as alternative routes to oral and parenteral routes. This is because of the superiority of the transdermal route compared to mentioned routes, including avoidance of first-pass metabolism and harsh environment of the stomach, options of self-administration and termination in case of adverse effect, sustained release of drugs, and no pain and risk of infection at the administration site among many (Parhi, Suresh, Patnaik, 2015a).

In case of both topical and TDD, Fick's second law governs drug permeation across the SC (Alvarez-Roman *et al.*, 2004):

$$J = \frac{DCP}{L}$$

Where J is called flux, D is known as the diffusion coefficient of a drug, C is the drug concentration in the DDS, and L is the thickness of the SC. The topically applied drug must penetrate various layers of skin with both hydrophilic and lipophilic domains, in case of topical drug delivery, and beyond the skin layers to the systemic circulation, in case of TDD. Thus, there are several steps in topical and TDD including (i) drug release from the formulation, (ii) drug partition into SC and its diffusion within the SC, (iii) drug partition into the viable epidermis and its diffusion in the viable epidermis, (iv) drug partition into dermis, (v) drug absorption into dermal blood supply, and (vi) drug entry into the systemic circulation (Lane, 2013). The latter two steps are not included in topical drug delivery.

Polymers

Polymers have high MW in which each molecule consist of a huge number of structural units (called monomers) are arranged in a fixed manner (Prajapati *et al.*, 2019). Polymers as carriers have been widely used in the development of delivery systems for diverse classes of biological actives. The DDS includes hydrogel, tablets, capsules, micelles, nanocomposites, microneedles, and particulate systems such as beads, micro-and nanoparticles, etc. Therefore, ideal qualities such as non-toxic, abundant availability, biodegradability, and biocompatibility must be kept in mind before the selection of appropriate polymer(s). Particularly, the latter two qualities of a polymer have the potential to provide the desired rate of drug release as well as the removal of carriers with ease after their administration (Prabaharan, 2008). Encapsulation of drugs and the desire rate of drug release from a polymeric system are due to their three-dimensional existence. To date, numerous polymers

originating from both natural and synthetic sources have been used in various DDS including modified release formulations. However, natural polymers, obtained from plants, animals, fungi, and bacterias, have been increasingly employed not only in traditional but also in controlled drug delivery systems due to their good safety profile, excellent biocompatibility, biodegradability, cheap, ease of chemical modification, and natural abundance (Layek, Mandal, 2020). In recent years, natural polymers of polysaccharides have been seriously considered in the development of transdermal formulations. Polysaccharides are an elaborate form of carbohydrate derivatives composed of chains of monosaccharide sub-units bound together by intermediate glycosidic bonds(Gopinath *et al.*, 2018). The diversified structural properties of polysaccharides are the indicator of their functional properties, including rheological properties and solubility (Guo *et al.*, 2017). Polysaccharides are generally recognized as safe (GRAS) in relation to their application in pharmaceutical dosage forms and can be modified to obtain tailor-made materials for topical and TDD (Saidin, Anuar, Affandi, 2018). They are naturally found in plants, animals, and microbial sources. In this chapter, we have discussed the diverse application of cellulose, chitosan and their semisynthetic derivatives, alginate, pectin, carrageenan, guar gum, gum arabic, gum ghatti, etc.

Various topical and transdermal dosage forms of polysaccharides

Polysaccharides have long been used in diverse fields. However, their applications are more prominent in the biomedical and pharmaceutical field because of their suitable properties such as non-toxic, biodegradable, and biocompatible among many. Their superior qualities in association with their flexibility propel the scientists to engineer them into various pharmaceutical shapes and dosage forms. In this context polysaccharides are being used to develop formulations for topical and transdermal routes, including gels (hydrogel, thermosensitive, and electric responsive), membranes, films, patches and microneedle patches, sponges and their micro-forms, nanoparticles, nanocomposites, and nanofibres, and liposomes and polymerosomes (Figure 2).

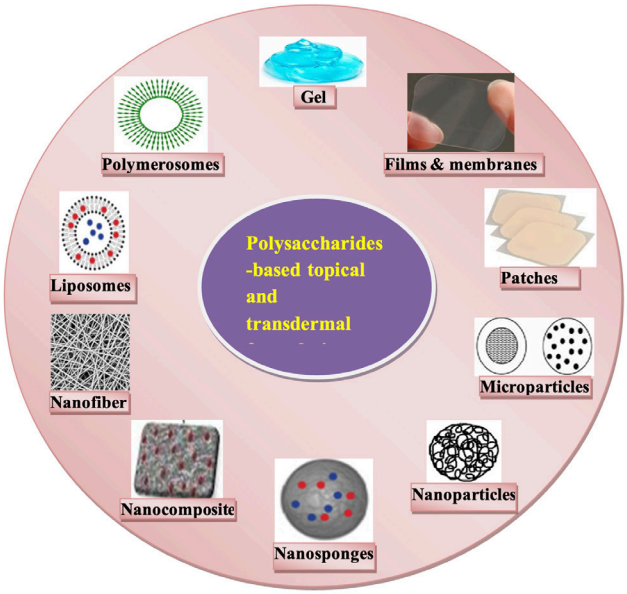

FIGURE 2 - Illustriation depicting different topical and transdermal formulations developed from polysaccharides.

POLYSACCHARIDES

Polysaccharides are quite a diverse group of carbohydrate molecules composed of long chain of polysaccharides unit connected together by glycosidic bonds. Naturally available polysaccharides demonstrate distinct structural features in terms of monosaccharides composition, MW, glycosidic linkage patterns with the type of configuration (α or β), degree of branching and charging properties, etc. These diverse properties influence the functional properties of polysaccharides. Based on mentioned properties, polysaccharides can be classified on a different basis as mentioned in Figure 3 (Alvarez-Lorenzo *et al.*, 2013; Gopinath *et al.*, 2018). Figure 4 illustrates the basic structures of polysaccharides used in topical and transdermal drug delivery.

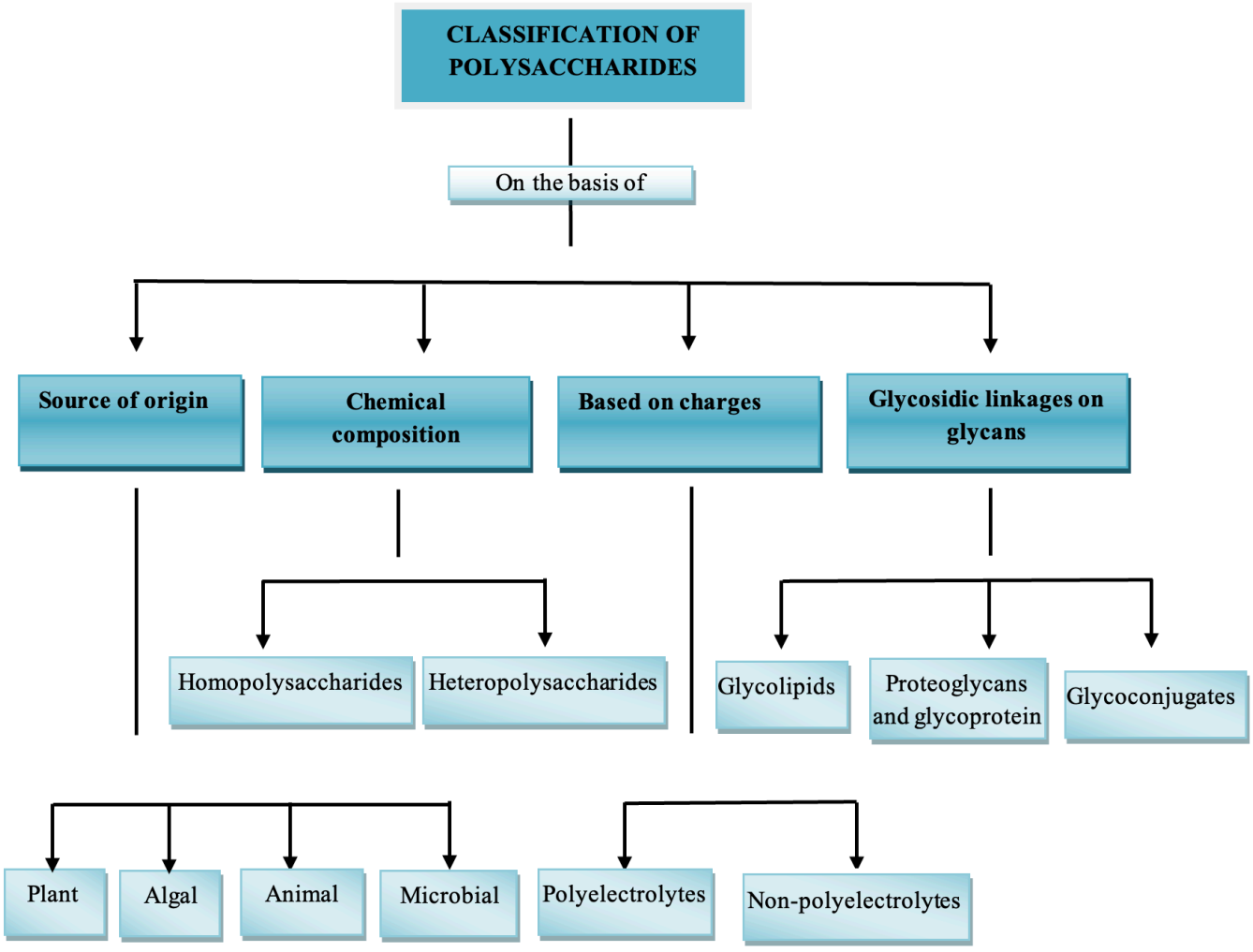

FIGURE 3 - Schematic presentation of polysaccharide classification on different basis.

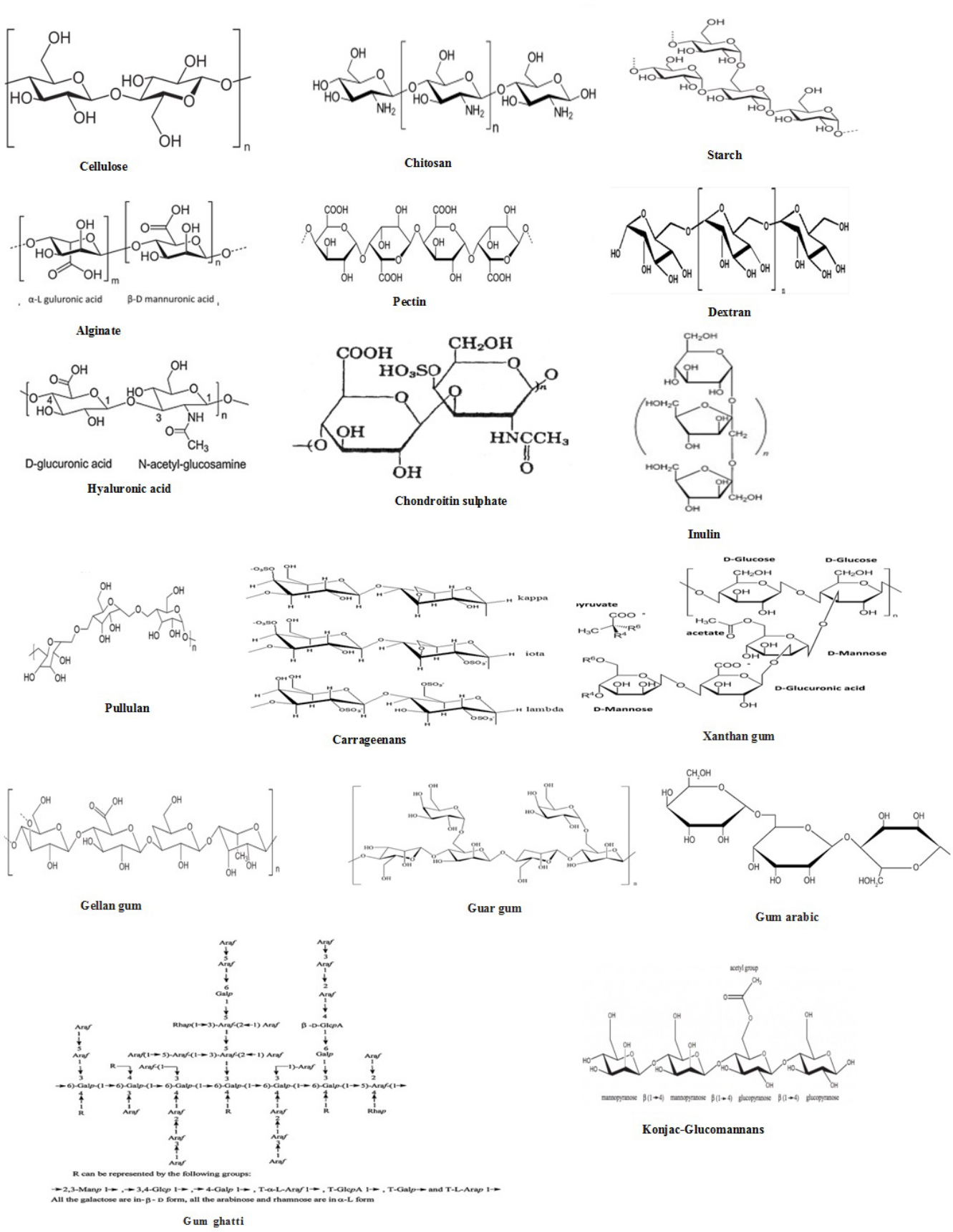

FIGURE 4 - Basic structures of polysaccharides used in topical and transdermal drug delivery.

Cellulose and its derivatives

Cellulose is the most abundant organic polymer in nature and is an important structural component of the cell wall of plants. It is also available in several living species of marine origin including algae, bacteria, fungi, and invertebrates. Cellulose is a linear polysaccharide composed of D-glucose units linked *via* β-1,4-glycosidic bonds (Figure 4) (Dragan, Dinu, 2019). The degree of polymerization of cellulose depends on the origin and separation process. There are a total of three hydroxyl groups at C2, C3, and C6 positions of each glucose unit, which are responsible for the formation of inter- and intramolecular hydrogen bonding. These hydrogen bonds give rise to the crystalline structure of cellulose and therefore, cellulose is virtually insoluble in water as well as in most of the common solvents (Layek, Mandal, 2020). In addition, the hydrogen bonding ability of cellulose is leading to binding with different materials in the matrix of polymer combination. Cellulose has other good qualities such as biocompatibility, biodegradability, high surface area, flexibility, and mechanical stability, which make cellulose a good polymer for DDS (Gopinath *et al*., 2018). Based on particle size, shape, and degree of crystallinity, cellulose has variation in mechanical and pharmaceutical properties and available in various commercial grades. Among all, microcrystalline cellulose, partially depolymerized cellulose, is the most widely used cellulose in the pharmaceutical industry (Thoorens *et al*., 2014). Powdered cellulose and low crystalline powdered cellulose are the other types of pure cellulose that have their applications in the pharmaceutical industry.

However, the presence of multiple hydroxyl groups on the cellulose structure provides enough possibilities for chemical modification to produce modified cellulose with drug delivery specific excipient. Etherification and esterification of hydroxyl groups are the most commonly used cellulose modification. The degree of substitution immensely influences the solubility characteristics of modified cellulose, with a lower degree of substitution (up to 1.0) yields modified cellulose which is only soluble in alkaline medium and a higher degree of substitution (2.3 to 3.0) yields modified cellulose which is soluble in organic solvents. Moderate level of substitution (between 1.0 and 2.3) found to exhibit maximum water solubility (Kamel, 2008). The most commonly used modified cellulose in the pharmaceutical industry are methyl cellulose (MC), ethyl cellulose (EC), carboxy methyl cellulose (CMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), and hydroxypropyl methylcellulose (HPMC). Cellulose esters are obtained by reacting hydroxyl groups of cellulose and alkyl anhydride and then acid hydrolysis with the use of strong mineral acids including sulfuric, nitric, and phosphoric acids. Cellulose acetate (CA), cellulose acetate phthalate (CAP), cellulose acetate succinate (CAS), and HPMC phthalate (HPMCP) are amongst widely used cellulosic esters in the pharmaceutical industry. Based on the physicochemical properties, cellulosic esters are of two types namely, enteric and non-enteric esters. The enteric cellulosic esters are insoluble in acidic conditions but soluble in mildly acidic to an alkaline environment. The solubility depends on the degree of esterification: the higher the degree of substitution of a carboxyl group, lower the solubilization pH. However, non-enteric esters do not exhibit any pH-dependent solubility (Layek, Mandal, 2020).

Any alteration of SC pH (5.5) makes skin vulnerable to multiple skin diseases. Therefore, topical formulations developed for the treatment of any kind of skin disease should not have much variation in pH. In the line of above concept, a pH-responsive smart hydrogel was developed with 2-hydroxyethyl acrylate grafted CMC to deliver one of the major flavonoids naringenin for the treatment of atopic dermatitis. Developed hydrogels demonstrated an increased swelling ratio with the decrease in grafting and cross-linking density. They showed a greater swelling ratio at pH 7.5 and 8.5 rather than at pH 5.5. Further, developed gels exhibited enhanced skin penetration of narigennin (So*et al*., 2018). An advanced hydrogel was developed to treat melanoma in two steps: development of carbohydrate-based prodrug where CMC is bioconjugated with doxorubicin hydrochloride (a potent anticancer drug) by covalent amide bonds followed by cross-linking with citric acid to form hydrogel. It was observed that the degree of carboxylation on the cellulose backbone determines the gel fraction behavior of the developed gel. The results obtained from drug release

kinetics and cytotoxicity study demonstrated that the developed novel bioconjugated hydrogel is effective in the treatment of melanoma (Capanema *et al*., 2018). In another study, hydrogels composed of HEC-hyaluronic acid were developed for effective transdermal delivery of isoliquiritigenin. The stability of the network, suitable viscoelastic behavior, and optimal adhesiveness of resulted gel depend on cross-linker (divinyl sulfone) concentration and swelling media. The improved skin permeation of isoliquirtigenin from the hydrogel is attributed to the high water retention capacity of the hydrogel containing hyaluronic acid that loosens the skin barrier reversibly through skin hydration (Kong, Kim, Park, 2016). Cocaine dependency is a huge public health issue. However, there are still no FDA-approved pharmacotherapies. Therefore, Ganti *et al.* (2018) developed a HPC-based hydrogel of 4-benzylpiperdine, a substitute agonist, to treat cocaine used disorder. Hydrogel based on 2% HPC and 18% of the 4-benzylpiperidine exhibited the best structural stability and excellent passive transdermal permeation across dermatomed human skin in 24 h (Ganti *et al*., 2018).

Our group developed and evaluated gels of diltiazem hydrochloride, aceclofenac, and metoprolol succinate. In one study, cryogels of diltiazem hydrochloride were developed with HPMC and poly(vinyl alcohol) (PVA) and evaluated for bioadhesive strength and in vitro drug release. We observed that the concentration of HPMC was having a more prominent influence on both bioadhesive strength of gel and cumulative percentage of drug release from the gel compared to PVA (Parhi, Suresh, Patnaik, 2015b).

In another study, thermal gels of the same drug were prepared using HPMC K100M and Pluronic F127. Among various combinations, the gels with 1% w/w of HPMC and 25% w/w Pluronic F127 showed better in vitro results. With the incorporation of l-menthol in the optimized gel, it was observed that the antihypertensive activity was prolonged up to 8 hr in a rabbit model (Parhi, Suresh, Patnaik, 2015c).

Bioadhesive thermosensitive topical gel of aceclofenac was developed with HPMC K100M and Pluronic F127 and the results demonstrated that the presence of HPMC in the gel had a more pronounced effect on the bioadhesion than that of Pluronic F127. However, consistency index was influenced by both the polymers. In addition, the cumulative percentage of drug release was negatively influenced by both polymers (Singh, Parhi, Garg, 2011). Another antihypertensitive drug metoprolol succinate, with having first-pass metabolism, was selected as a model drug for the development of thermosensitive gel composed of HPMC and Pluronic F127. The obtained optimized gel was found to be composed of 0.92% w/w of HPMC K100M and 15% w/w of Pluronic F127 with predicted bioadhesive force, viscosity and cumulative percentage drug release (at the end of 8 h) were 41.56 gram force, 48.94 Pa.s and 84.94 mg/cm^2, respectively (Parhi, 2016).

We have fabricated transdermal film-forming gel loaded with etoricoxib using HPMC and eudragit RL100. The optimized gel (composed of 1.12% of HPMC and 0.4% of eudragit) exhibited viscosity of 1549.5 mPa.s and drug permeation of 4639.11 μg/cm^2 at the end of 24 h. Anti-inflammatory study on rats demonstrated better-sustained release (for 8 h) compared to orally administered drug suspension (Parhi, Goli, 2020). In another study, diltiazem loaded transdermal film was fabricated with HPMC K4M and eudragit RS100. It was observed that the drug release was decreased with the decrease in HPMC content in the film due to its hydrophilic nature. The optimized film was found to effectively reduce arterial blood pressure in normotensive rabbits (Parhi, Suresh, 2016). In one study, transdermal films composed of HPMC and invasosomes (phospholipid, ethanol, and D-limonene) loaded with drug avanafil, a selective phosphodiesterase-5 inhibitor, were developed to circumvent poor oral bioavailability of avanafil, first-pass metabolism, and altered absorption in the presence of food. The invasosomes showed higher ex vivo permeation compared to the raw film containing drug with an enhancement factor of 2.51. In addition, the bioavailability of avanafil was found to be higher (4-fold) for the optimized film when the rat model was used for in vivo pharmacokinetic study (Ahmed, Badr-Eldin, 2019). It was reported that film consisting of either neem gum polysaccharide or its carboxymethylated derivative can not be formed. However, acrylamide grafted neem gum can be used successfully to develop transdermal film for the delivery of albumin. The resulted film was found to

have suitable physicochemical and mechanical parameters with drug delivery up to 7h (Malviya, 2020).

Yalcintas *et al.* (2020) developed a dissolvable microneedle array with carbohydrate-based polymers such as CMC, trehalose, maltodextrin, glucose, and hyaluronic acid to study their cytotoxicity and apoptosis-inducing effect. The obtained results demonstrated that dissolvable microneedle was feasible to prepare with all the polymers except glucose at a higher concentration (>50mg/mL). The apoptosis-inducing effect of the above materials was found to be negligible except that of glucose. Therefore, the above base materials can be used to develop dissolvable microneedle to enhance transdermal and intradermal drug delivery without the hindrance of cytotoxicity and apoptosis (Yalcintas *et al.*, 2020).

Ghorani *et al.* (2018) investigated the feasibility of developing cellulose acetate-based nanofibres as a carrier for the delivery of water soluble essential amino acid l-tryptophan. The developed nanofibres were found to be free from structural defects and l-tryptophan release from the fibres follows pseudo-second order kinetic model. Nanofibres with a mean diameter of 720 nm offer both the highest rate constant and initial desorption, which was attributed to low fibre diameter and high relative surface area (Ghorani *et al.*, 2018). In another study, HPC and polyurethane-based nanofibers were successfully prepared to deliver donepezil hydrochloride in the transdermal route. In vitro release of drug from drug/HPC/polyurethane nanofibre mat at a ratio of 1:2:10 demonstrated Korsmeyer-Peppas drug release kinetics with diffusion is the drug release mechanisms. The nanofibre mats of the above composition were found to be well tolerated in in vitro cytotoxicity study and non-irritant to the skin (Gencturk *et al.*, 2017).

Chitin/chitosan and their derivatives

Chitin is serendipity as discovered accidentally during research on mushrooms. Later on, it was extracted from the cell wall of fungus, yeast, green algae, cuticles of insects, and crabs (Einbu, Vayrum, 2008). In comparison, chitosan is available less abundantly in nature and the cell wall of certain fungi is only the natural source (Ribeiro *et al.*, 2020). However, chitosan, only cationic natural polysaccharide, is mostly obtained by alkaline or enzymatic deacetylation of chitin. Chitin is a homopolymer of N-acetyl D-glucosamine and glucosamine which are linked by β- 1-4-glycosidic bonds. Chitosan is composed of one chitin monomer i.e. N-acetyl glucosamine and another chitosan monomer i.e. 2-amino 2-deoxy-β-D-glucopyranose (Figure 4) (Park *et al.*, 2011). The only difference between cellulose and chitosan is the presence of an amino group at C2 position in chitosan instead of a hydroxyl group in cellulose. The physical and biological properties of chitosan and its applications are mainly influenced by the degree of deacetylation and MW. The degree of deacylation of chitosan ranges from 60 to 100%. This led to MW of chitosan vary from 10 to beyond 1000 kD (Layek, Singh, 2017). Both hydroxyl and amino groups are present on the chitosan skeleton endows chitosan with high reactivity towards cross-linking and chemical modifications (Dragan, Dinu, 2019). However, their numbers are determined by the process of deacetylation. Accordingly, there are two hydroxyl groups: primary hydroxyl group responsible for substitution leading to the formation of branched polymer or even copolymers leading to change in their physical and mechanical properties. The secondary hydroxyl group undergoes substitution to improve the solubility of chitosan (Kim *et al.*, 2008). Both hydroxyl and amino groups involve in inter-and intramolecular hydrogen bonding which denying the aqueous solubility of chitosan in addition to solubility in common organic solvents. The pKa value of amino group of chitosan is~6.5 which results in its protonation in aqueous acidic media (Szymańska, Winnicka, 2015). This protonation properties of chitosan lead to its solubility in aqueous acidic solvents including acetic acid, lactic acid, hydrochloric acid, and citric acid (Parhi, 2020). Due to the above remarkable positive qualities, both chitin and chitosan are used in almost every field such as medicines, biotechnology, food processing chemistry, environment, and agriculture, etc. Chitosan also demonstrates bioactivities such as antibacterial, antifungal, antitumour, and antioxidant properties (Cheung*et al.*, 2015). In the pharmaceutical field, it has been widely used as a delivery device for many active

ingredients. Chitosan as a polymer offers flexibility to design different dosage forms such as tablets, capsules, and particulate systems. Regarding topical and TDD, chitosan and its derivatives employed in the development of bioadhesive gels, membrane and films, microemulsion, and more recently, nanoparticle incorporated gel and patches were also developed in order to increase the drug stability and to enhance the drug permeation across the skin (Parhi, 2019).

In one study nanogels of aceclofenac were developed in two steps: in the first step nanoparticles of aceclofenac were developed using chitosan and egg albumin as polymers and then the resulted nanoparticles were dispersed in carbopol 940 based gel base. The resulted nanogel exhibited sustained permeation of aceclofenac over 8h when excised mouse skin was used as a model membrane. The permeation flux of aceclofenac from developed nanogel was significantly higher compared to marketed gel and its anti-inflammatory effect was also higher than that of marketed gel over 4h in carrageenan-induced rat paw edema (Jana *et al*., 2014). In another study, chitin-based nanogel (120-140 nm) incorporated with 5-fluorouracil was developed. The resulted nanogel exhibited pH-responsive swelling and drug release. The steady-state flux of drugs from the nanogel and their retention in the deeper layer of skin was found to be the same and 4-5 times compared to control, respectively (Sabitha *et al*., 2013). Nanogels of anti-psoriatic model drug clobetasol with the particle size of 132±14 nm were prepared using chitin. These nanogels showed enhanced transdermal flux which was attributed to the loosening of epidermal layers resulted from fragmented SC. Additionally, these nanogels exhibited a significant anti-inflammatory activity at a concentration 0.35 mg/mL (Panonnummal, Jayakumar, Sabitha, 2017). In order to avoid first-pass metabolism of orally administered propranolol hydrochloride and thereby improving its systemic bioavailability, chitosan-based nanogels of the drug were prepared by ionic gelation method. The prepared uniform nanogel demonstrated thixotropic behavior and released the drug for a prolonged period across pig ear skin. In addition, chitosan nanoparticles were found to create a drug reservoir after being entered into the skin (Al-Kassas *et al*., 2016). Nanoparticles based on chitosan whisker grafted with oligo(lactic acid) in water were prepared to encapsulate and transdermally deliver model drug lidocaine. The particle size and amphiphilic properties of the developed nanoparticles depend on the oligo(lactic acid) chain length. The results depicted that both the unencapsulated and lidocaine encapsulated were capable of diffuse through the demis layer (Engkagul *et al*., 2017).

In an interesting investigation chitosan-coated liposomes of indocyanine green, a promising candidate for the treatment of topical melanoma photodynamic therapy were developed to avoid its instability in an aqueous medium and to enhance its skin permeation. The chitosan coating was successful as it has increased the size of liposomes and able to convert the zeta potential from negative to positive value. Chitosan coated liposomes not only resist the degradation of indocyanine green but also skin permeation of indocyanine was found to be significantly enhanced. In addition, these coated liposomes exhibited increase cellular uptake and photocytotoxicity significantly in melanoma cells (Lee, Lim, Lee, 2019). Polymerosomes were prepared with polystyrene and poly(acrylic acid) and then these vesicles were coated with chitosan. The mentioned decorated polymerosomes interacted strongly with skin components compared to naked polymerosomes because of the positive charge vesicle surface in the presence of chitosan. In addition, decorated vesicles showed enhanced drug penetration into the skin followed by accumulation of the drug in the skin layers, particularly in hair follicles (Caon *et al*., 2014).

In one study O/W based microemulsion of olive leaf extract containing polyphenol was developed for possible topical or transdermal delivery. In this, microspheres of olive leaf extract with chitosan were developed and then converted into O/W microemulsion. The microspheres exhibited pH-dependent drug release with 100% release of polyphenol at pH 7.4 after 6 hr of study and capable of providing stability for 3 months (Acosta *et al*., 2015). Clotrimazole incorporated chitosan coated microemulsion was fabricated for its topical delivery against *Candida albicans*. The resulted microemulsion demonstrated a positive surface which attributed to the presence of

chitosan on the surface of microemulsion leading to a higher degree of bioadhesion and better retention on the skin surface. This resulted in sustained release and higher permeation of drug present in chitosan coated microemulsion compared to uncoated microemulsion. In addition, the coated emulsion exhibited a higher zone of inhibition compared to uncoated microemulsion indicating the combination effort of drug and chitosan (Kumari, Kesavan, 2017). More recently, Luesakul *et al.*(2020) fabricated nanoemulsion using *Plai* extract as both active ingredients and oil phase and then modified with chitosan coating and modified chitosan (quaternized form of chitosan) coating. Quaternized chitosan coating on emulsion demonstrated improved stability of *Plai* extract during 28 days of study by acting as a protective layer. An increased anticancer, anti-inflammatory activities and in vitro permeability of the *Plai* extract was observed for quaternized chitosan coated emulsion compared to uncoated and chitosan coated nanoemulsion. It was attributed to the fineness of nanoemulsion and the permanent positive charge exerted by the presence of quaternized chitosan (Luesakul *et al*., 2020).

Polymeric nanoparticles composed of chitosan, poly(N-isopropylamide-co-acrylic acid, and cellulose laurate were prepared to employ a microfluidic technique for transdermal delivery of tretinoin and clindamycin phosphate. These nanoparticles (diameter between 200nm and 300nm) demonstrated desired transdermal permeation for both drugs with decreased erythema potential compared to a bulk mixture of drug and drug solution. In addition, there was a sustained release of model drugs with minimum inhibitory and bacterial concentrations than the formulations developed by bulk mixing method. These results were attributed to the increased residence time of the above nanoparticles on the skin surface due to the presence of chitosan (Shamsi *et al*., 2017). Another polymeric nanoparticles (small particle size with low polydispersity index) based on chitosan was developed with the successful inclusion of curcumin for transdermal delivery. Ex vivo permeation of the above nanoparticles using full-thickness mice skin has proven their ability to deliver curcumin across the skin with reaching a maximum flux of 5.14±1.31g/cm2h. The penetration route of the developed nanoparticles was observed to be mainly through the appendageal route (Abdel-Hafez, Hathout, Sammour, 2018).

Reshmi *et al*. (2018) fabricated composite electrospun membranes of curcumin with nanochitosan and poly(-caprolactone) nanofibres and observed that nanochitosan with a concentration of 15% in composite membrane demonstrated excellent bioavailability, sustained release of curcumin at different pH conditions along with improved cell adhesion and proliferation. These results were attributed to their increased hydrophilcity, lower average fiber diameter, and high surface area to volume ratio (Reshmi *et al*., 2018). In another investigation, a cross-linked chitosan based transdermal film was developed by incorporating zidovudine and different chemical penetration enhancers. The results demonstrated that film containing 5% oleic acid had higher flux compared to the film containing other penetration enhancers such as cineole, menthol, and tween 80 (Singh, Upasani, 2013).

One investigation reported that the transdermal patch of metoprolol tartrate, fabricated with chitosan and polyvinyl pyrrolidone (PVP) as polymers, exhibited control release and effective skin permeation of the drug. Furthermore, the developed patches showed higher tensile strength and swellability with higher PVP concentration (Gandhi *et al*., 2014). A transdermal patch of rivastigmine based on chitosan microparticles was developed and observed that the loading of drug between 7-42% in microparticles showed better drug stability without surface irregularities. Loading of drug beyond 42% resulted in enhanced drug release, but the microparticles showed distorted surface with increased surface drug presence. These microparticles were then incorporated in acrylic adhesion in different ratios. Among all, the patch with 15% of microparticles demonstrated a higher rate of drug permeation across cellulose filter membrane over 6-days compared to rivastigmine salt-based patch. The lower release in the latter case was attributed to the formation of rivastigmine crystals in the adhesion patch which was not evident in the former case (Sadeghia *et al*., 2016).In another study, nanocrystals of gibenclamide were engineered and then incorporated directly into chitosan polymeric base to obtained nano- and microcrystal-based patches. The

results of drug release and ex vivo permeation (across rat skin) studies demonstrated higher release and cumulative permeation for the nanocrystal-based patch compared to the microcrystal-based patch. In vivo study in Wister rats revealed the enhanced efficacy of nanoparticle-based patch in reducing blood glucose levels and able to counteract the induced hyperglycemia associated with oral therapy in tested animals compared to microparticle-based patch (Ali, Hanafy, 2017).

Starch

Starch is a major natural polysaccharide present in various plants, green and red algae. Among all renewable sources of biodegradable polymers, starch is one of the promising natural biodegradable polymers because of its biodegradable, biocompatible, non-toxic, edible, relatively inexpensive, and abundantly occurring in nature. It is composed of two main components; a linear or slightly branched amylase (10-30%) with α-(1-4)-D-glucopyranose and a highly branched macromolecules amylopectin (70-90%) with α-(1-4)-D-glucopyranose backbone linked through α-(1-6)-branch linkages (Figure 4) (Fu *et al*., 2018). Starch is synthesized as a granular form by green plants and acts as an energy reserve. Both crystalline (lamella region) and amorphous (low lateral order regions) regions are coexisting in starch granules. During starch solution preparation, initially amorphous region hydrolyzed leading to the formation of solution and thereafter crystalline region converted into stable suspension by vigorous mechanical agitation. The first step of solubilization depends on factors such as amylase content granule size and pores on the surface, whereas second step solubilization is influenced by amylopectin content, distribution of α-(1-6) branches between amorphous and crystalline regions and degree of packing of the double helices within the crystallites (Bakrudeen, Sudarvizhi, Reddy, 2016). Despite all the above, starch has limitations in applications as they extremely brittle resulting in poor processability, inherently poor water-resistant along with intrinsic mechanical, thermal, and biological properties. Therefore, various methods including blending of starch with other material, adding functional plasticizers, crosslinking them by employing heat treatment, chemical agent of photo-irradiation, and using nanocomposites have been used to improve their physical properties and processability (Tak *et al*., 2019). Modifications in starch are linked to primary and secondary hydroxyl groups and the process involved are etherification, esterification, oxidation, and graft copolymerization (Gopinath *et al*., 2018).

Presently, more emphasis is being given to starch-based nanocrystals as they can be utilized as filler materials to develop various stable formulations. For instance, starch nanocrystals can reinforce and form a good biomembrane with the support of other suitable polymers leading to the formation of formulation with perfect stability for longer duration. Bionanocomposite, the blending of starch nanocrystals in different biopolymer matrices, is one such formulation which has the tremendous potential to deliver different drugs. In this regard, starch nanocrystals were obtained from different sources such as maize, potato, and cassava, and then incorporated into different polymer matrices to form hydrogel patches including poly(N-isopropylacrylamide) (PNIPAM). The model drug incorporated in the nanocomposite was acyclovir, which was prescribed in the treatment of *Herpes simplex* infection such as genital herpes and cold sores. The stability of hydrogels from potato and maize starch nanocrystal demonstrated better stability in storage conditions. Among all, more stable potato-based starch nanocrystals were incorporated in PNIPAM loaded with acyclovir. The drug release was found to be 95% in 17 hr for the above hydrogel patch (Bakrudeen, Sudarvizhi, Reddy, 2016). In another study starch obtained from mungbean was used along with PVA to develop biodegradable biomaterial films of sulindac employing UV irradiation technique as a cross-linking method. The optimum time for the UV irradiation-based cross-linking was found to be 30 min. The developed film was having a binding site for sulindac that was verified by the recognition ability test. The release property of sulindac from the films was found to be influenced by pH, temperature, and type of plasticizer. The results demonstrated that the release of drug at pH 10 and 45°C was higher than that of release at pH 4.0 and 25°C. The release rate of drug across artificial skin from the film

was increased at a relatively steady rate for 20 days. The difference in drug release was attributed to the types of plasticizers used in the film development (Tak *et al.*, 2019).

Saboktakin, Akhyari and Nasiro (2014) synthesized modified starch carboxymethyl starch and then formed nanoparticles by combining it with hyperbranched 1,4-cis polybutadiene for the delivery of clonidine across the skin. Both the average particle size and drug encapsulation efficiency in nanoparticles were found to be increased with clonidine loading density. The results demonstrated that the drug release was increased to 100% at the end of 10 hr of study (Saboktakin, Akhyari, Nasiro, 2014). Maize starch based nanoparticles of diclofenac sodium were developed using nanoprecipitation method and the optimized nanoparticles were found to be stable (zeta potential of -35.3mV) and small in diameter (21.04nm). The drug release was found to be sustained up to 6 hr and was safe and non-irritant when studied on rat skin (El-Naggar *et al.*, 2015). Zimon *et al.* (2018) developed a complex of micro-RNAs-197 (miR-197, which has proven to be a better treatment option for psoriasis) and quaternized starch as a carrier. Then, in order to further the drug permeation across the skin, a physical penetration enhancement method called ultrasound was employed. The resulted complex was found to decrease the expression of the miR-197 target proteins along with the significant reduction in psoriatic activity markers. Thus, the resulted complex could be a potential carrier for the topical skin treatment of psoriasis (Zimon *et al.*, 2018).

Alginate

Alginate is a naturally occurring linear polysaccharide mainly extracted from brown algae such as *Laminaria hyperborean*, *Macrocystis pyrifera*, *Ascophyllum nodosum*, and *Laminaria digitata*. Alginate is also produced by certain bacteria belonging to genera *Azotobacter* and *Pseudomonas*. It is composed of varying proportions of β-D-mannuronic acid (M block) and α-L-guluronopyranosyl (G block) units linked by the 1,4-glycosidic bond (Figure 4). It has both homopolymeric sections with either only G or M blocks and heteropolymeric sections with alternate blocks of G and M (Poly-MG). The overall property of alginate depends on the molar ratio and distribution of M and G blocks, and their MW. The poly-G blocks show gel-forming ability, whereas poly-M and poly-MG blocks provide flexibility (Ribeiro *et al.*, 2020). Molar ratio of M and G blocks gives rise to two groups of alginates: high G and high M. High M category of alginates are commercially available and mostly used in the pharmaceutical industry. Low pH leads to the formation of a highly viscous gel layer because of the hydration of matrix, which can serve as a diffusion barrier for the drug. Similarly, a high viscous layer is also produced by the presence of cations which act as cross-linker between carboxyl groups available in the alginate backbone (Jain, Bar-Shalom, 2014). Alginate is one of the most extensively studied polysaccharides in biomedical and pharmaceutical applications because it has suitable properties including easy availability, low toxicity, biodegradability, biocompatibility, and comparatively inexpensive. The presence of M and G-blocks on alginates affects the sensitiveness of alginate to pH and polyvalent cations such as Ca++ or Ba++ because of the different relative positions of the carboxylic acid group in each block (Alvarez-Lorenzo *et al.*, 2013).

In one investigation, matrix type of transdermal films of donepezil was successfully developed with alginate as matrix former. The resulted transdermal film possessed suitable properties such as high bioadhesiveness, good mechanical strength, and enhanced permeability across pig skin (Galipoğlu, Erdal, Güngör, 2015). Most recently, a hydrophilic polyelectrolyte multilayer film of ciprofloxacin hydrochloride using an alternate layer of sodium alginate and poly(4-vinylpyridine) was developed. It was observed that several layers and the nature of the outer layer governed the physicochemical properties, drug loading, and drug release bahaviour of the films. The three-layered film with poly(4-vinylpyridine) in the middle and sodium alginate layer on either side (surface) was found to have the most favourable properties compared to other films, including lowest contact angle, lower roughness, highest drug loading capacity, and drug loading efficiency (Alshhab, Yilmaz, 2020).

Ahmed *et al.* (2020) developed nanoparticles of dapoxetine with alginate and chitosan, and then incorporated them in HPMC-based film for transdermal delivery. The obtained nanoparticles were able to penetrate deeper into skin layers with enhanced permeation of dapoxetine across the abdominal skin of rats. Moreover, ex vivo study demonstrated a sustained release profile of the drug (Ahmed *et al.*, 2020). In another study, Abnoos *et al.* (2018) investigated the possibility of developing sodium alginate and chitosan-based nanogel of pirfenidone for transdermal delivery. Ex vivo permeation of developed nanoparticles across mouse skin demonstrated significant enhancement in permeation and sustained release during 24 h of study. It was concluded that the resulted nanoparticles have promising TDDS for pirfenidone to treat pulmonary fibrosis (Abnoos *et al.*, 2018). In order to avoid a higher degradation rate at the acidic pH, nanoparticles of rabeprazole with alginate core and coated chitosan were developed and then incorporated in HPMC and HPC based transdermal patch. The optimized nanoparticles were found to provide sustained release across rat skin. The developed patches exhibited minimum patch-to-patch variability and provided controlled drug release (Ahmed, El-Say, 2014).

Pectins

Pectin is a branched heteropolysaccharide present in almost all fruits or other plant tissues. However, pectin is commercially obtained from the peel of citrus fruits such as lemon, lime, and orange or apple pomace (Nesic, Seslija, 2017). Pectin is a complex polysaccharide composed of poly (D-galacturonic acid) linked by α-(1,4) bonds and a wide variety of neutral sugars including rhamnose, arabinose, etc (Figure 4). The number of sugar units present in the pectin chain is about 100 to 1000 that resulting average MW of pectin between 50, 000 and 15,000 Da. It can be found in various forms such as esterified, free acid, simple salt. The degree of methyl-esterification of D-galacturonic acid is a crucial parameter that determines various properties of pectin such as its solubility, gelling and film-forming ability. The factors influencing the degree of esterification are the source, extraction method, and environment. The degree of esterification of pectin is generally ranged from 60 to 90%. However, the degree of esterification can be modified during the extraction process. Moreover, the commercial pectins are available in two forms: low ester pectins with a degree of esterification less than 50 (LM pectin) and high ester pectins with a degree of esterification more than 50% (HM pectin). However, commercial varieties are having esterification between 20-40% for LM pectins and between 60-75% for HM pectins (Chomto, Nunthanid, 2017). These two categories of pectin exhibit different mechanisms for gel formation. The LM pectins form gels in the presence of divalent cations such as Ca++, Ba++, etc, which act as a link between pairs of carboxylic groups of two different chains (Alvarez-Lorenzo *et al.*, 2013). The potential to form gel can further be improved by amidation that necessitates low Ca++ concentration to form a gel, whereas, HM pectin forms a gel by reacting with different sugars (eg. sucrose) in the presence of acidic pH (pH <3.5) (Alvarez-Lorenzo *et al.*, 2013). Hydrogen bonding between free carboxylic groups of pectin molecules and hydroxyl groups of surrounding pectin molecules is responsible for the gelation of HM-pectins. At neutral or slightly acidic pH, most of the carboxylic groups of pectin bear a negative charge, and therefore, repulsion between the pectin molecules occurs that prevents the formation of the gel network. However, the carboxylic groups remain unionized at acidic pH which decreases both repulsions between pectin molecules and attraction between pectin and water molecules. But the addition of sugar molecules forms an environment of low water activity that leads to chain-chain interaction rather than chain-solvent interactions.

A novel core-shell microcapsule incorporated with berberine was successfully developed with bovine serum albumin gel as microcapsule core and alternating multilayers of calcium cross-linked pectin hydrogel as shell (coating). This is followed by the formation of a polyelectrolytic complex between pectin and chitosan. The resulted complex microcapsules exhibited a pH dependant prolonged release of berberine and showed promising antibacterial effect against acne-

causing bacteria *Cutibacterium acnes* (Paşcalău*et al*., 2020).

In one investigation, a novel pectin-based silver nanocomposite was developed and then its drug delivery potential was studied with donepezil as a model drug. The resulted nanocomposite released 94.33±2.12% of the drug in phosphate buffer saline during 5 days period. In addition, the film released about 92 kcps silver nanoparticles that showed promising antimicrobial activity against *Staphylacoccus aureus* and *E. coli*. Released silver nanoparticles were able to resist the growth of mentioned microbes on the skin during the film application (Kodoth *et al.*, 2019).

Hadebe *et al*. (2014) developed a pectin-based hydrogel patch containing insulin for possible controlled release of insulin in the transdermal route. The developed patches elevated plasma insulin concentration of streptozotocin-induced diabetic rats. In addition, it was observed that the elevation of plasma insulin concentration was comparable to those in subcutaneous insulin-treated rats (Hadebe *et al.*, 2014).In another study, pectin isolated from leaves of plant *Cissampelos pareira* was used to develop a matrix layer of transdermal patches of nicotine, and the resulted matrix layer was found to be brittle. However, flexibility and mechanical strength of the patch were improved with the addition of deproteinized natural rubber latex. With increasing rubber latex content, the hydrophilicity was found to be decreased. The drug release and permeation depend on the hydrophilicity of the patches. The above patch showed a higher in vitro drug release and permeation profile of nicotine compared to commercial formulation Nicotinell TTS-20 (Suksaeree*et al.*, 2018).

Zhou *et al*. (2014) developed liposomes of vitamin C using combined techniques (thin film evaporation and dynamic high-pressure microfluidization) and then the resulted liposomes were coated with high methoxyl pectin and low methoxyl pectin. Coated liposomes showed an increase in average diameter, decrease zeta potential, prevent aggregation, minimization of the oxidation of lipid, and prevented the leakage of vitamin C with similar drug entrapment efficiency to both types of pectin to that of control. Low methoxyl pectin-coated liposomes exhibited higher physicochemical stability than its counterpart. Skin permeation was found to be improved by 1.7-fold for high methoxyl pectin and 2.1-fold for low methoxyl pectin compared to control (Zhou *et al.*, 2014). A novel base for the fabrication of microneedle array incorporating bovine serum albumin was carried out with pectin. The resulted microneedle arrays showed its replication precision of ±0.39% for the needle height, ±0.97% for base diameter, and ±0.32% for the inter-base spacing. The loading and release of bovine serum albumin were found to depend on its interaction with pectin (Demir, Kerimoglu, 2015).

Dextran

Dextran is a common natural polysaccharide composed of D-glucopyranose units linked by an α-1,6-glycosidic bond in the main chain and α-1,3 glycosidic bond in branched chains (Figure 4) (Chen, Huang, Huang, 2020). Dextran has qualities such as biodegradability, biocompatibility, excellent water solubility, can aid to the stability of DDS, and prevent aggregation in blood circulation (Anirudhan, Binusree, 2016). In addition, it possesses a large number of hydroxyl groups on its backbone which can be chemically modified to form various drug carriers including prodrugs, nanomaterials, nano-micelles, and so on. Esterification, oxidation, terminal amination, etc are the processes used for the chemical modification of dextran (Patil *et al.*, 2019). Dextran is a suitable polymer for the preparation of topical/transdermal preparations as it can act as an agent for the improvement of skin activity (Lorenzo *et al.*, 2017).

Patil *et al.* (2019) developed an electro-responsive TDDS with polyacrylamide grafted dextran as a reservoir for model drug rivastigmine tartarate and cross-linked dextran-PVA blend film as rate-controlling membrane. They observed little drug permeation from the system in the absence of electrical stimuli, while in the presence of electrical stimuli the flux was increased by 1.6-fold. They also observed that drug permeability

decreased with the increase in the concentration of cross-linker. In addition, the drug permeability was enhanced when the strength of the applied electric current increased from 2 to 8 mA (Patil *et al*., 2019).

Ning *et al*. (2020) fabricated double-layered microneedles of insulin with methacrylated hyaluronic acid-derived core microneedles and homogenous combination of cyanine 5 and fluorescein isothiocyanate (FITC)-dextran as coated material. The mechanical properties of the core microneedles were found to be unchanged with coating. The resulted microneedles performed dual functions: effective delivery of insulin into the systemic circulation of mice for controlling the blood glucose level and allowed the extraction of skin interstitial fluid for analysis of the glucose biomarker (Ning *et al*., 2020). Recently, Chen *et al*.(2020) developed self-degradable microneedle composed of hyaluronic acid integrated with pH sensitive dextran nanoparticles to encapsulate zinc phthalocyanine and anti-CTLA4 antibody. This novel microneedle was developed to deliver the effect of both photodynamic therapy and immunotherapy, simultaneously and observed that the microneedles demonstrated photodynamic therapy that exerts its effect to kill tumor cells and trigger the immune responses, followed by the effect of immunotherapy with an immune checkpoint inhibitor (Chen *et al*., 2020). In another study FITC-dextran of different MWwere considered for their transdermal delivery across porcine skin using hydrogel-forming microneedle composed of Gantrez S-97, sodium carbonate, and polyethylene glycol. The result showed that the amount of lower MW dextran (10 kDa) permeated across the skin sample was significantly higher than that of higher MW dextran (150 kDa) in 24 hr of study (Hutton *et al*., 2020).

A composite nanofibrous transdermal patch of tetracycline composed of dextran and polycaprolactone as polymeric base and graphene oxide as nanocomposite was fabricated. The resulted patch demonstrated good mechanical properties and released the drug in a sustained manner due to the presence of graphene oxide nanosheets. Finally, the nanocomposite patch was found to control infectious bacteria such as *E. coli* and *S. aureus* and thus could be useful in the treatment of chronic infectious lesions (Nematpour *et al*., 2020).

Hyaluronic acid

Hyaluronic acid is an anionic, non-sulfated glycosaminoglycan with disaccharide repeating units of β-1,-4-linked D-glucuronic acid, and β-1,-3-linked N-acetyl-D-glucosamine (Vasvani, Kulkarni, Rawtani, 2020). It is a critical component of the extracellular matrix in hydrated tissue (Figure 4). Carboxylic groups of hyaluronic acid exhibit a pKa value of 3-4, leading to their ionization at pH 7.4 (physiological condition). Thus, present in the form of a polyanion called hyaluronan. MW and conformation are the two critical factors of hyaluronic acid influencing its nature in water solution. The MW of hyaluronic acid varies between 20kDa and 4000 kDa and the use of hyaluronic acid in the pharmaceutical field is based on their MW. It exists in random-coil conformation when present in solution. In this conformation, hyaluronic acid is hydrophilic and forms hydrogen bonds with surrounded water molecules. Thus, high MW and random coil conformation converting the hyaluronic solution to a highly elastic and viscous one. Hyaluronic acid has the qualities that make it a suitable candidate for pharmaceutical application as a whole and topical/transdermal application as particular, including nontoxic, biodegradable (easily degraded in the human body by enzyme hyaluronidase), biocompatible, nonimmunogenic, and its inherent interactions *via* hyaluronic acid receptors which present in various organs of our body (it avoids an additional step in modifying the polymer with targeting ligands for their interactions to the receptor) (Kim *et al*., 2017). In addition, hyaluronic acid can be commercially modified by cross-linking or conjugation reactions to make it suitable for advanced use in biomedical and pharmaceutical fields (Tripodo *et al*., 2015).

Chatterjee*et al*. (2020) developed a dual-responsive (pH and temperature) nanocomposite hydrogel delivery system incorporating gallic acid with alanine conjugated hyaluronic acid and chitosan. Pluronic F-127 hydrogel was used to incorporate the above conjugated nanoparticles. The resulted hydrogel demonstrated higher mechanical stability and sustained drug release property when studied in simulated skin pH conditions (pH = 6.4). In addition, the hydrogel showed low toxicity with or without gallic acid

(Chatterjee*et al*., 2020). A complex pH sensitive hydrogel based on hyaluronic acid and HEC was developed to incorporate antimicrobial compound isoliquiritigenin and then, deliver the drug through transdermal route. The pH functionality was provided by hyaluronic acid and cellulose component served as a scaffold to build hydrogels. Hydrogel composed of hyaluronic acid:HEC (3:1) showed optimal adhesive and rheological properties. The drug release was found to be influenced by pH; drug release was more than 70% at pH 7.0. This result was attributed to the larger pore size in the developed hydrogel. The optimized hydrogel at above pH demonstrated the highest antimicrobial activity against *Propioibacterium acnes* (Kwon, Kong, Park, 2015).

To avoid complications involved in wound healing, intelligent transparent bilayer films with PVP and antiseptic neomercurocromo® in the inner layer (to be in contact with SC), and PVP and hyaluronic acid with antibiotic ciprofloxacin in the outer layer were developed. The inner layer of the resulted bilayer film showed good adhesion to the skin and release the antiseptic at a faster rate. In the outer layer, the interaction between PVP and hyaluronic acid *via* hydrogen bonds ensured the sustained release of ciprofloxacin over 5 days that helped in maintaining an aseptic wound bed during the healing process. In addition, no toxic effects on the wound were observed in in vivo mice full-thickness wound model (Contardi*et al*., 2019). In order to provide a predictable and extended duration of activity and to avoid the first-pass metabolism when administered orally, transdermal films of thiocolchicoside based on hyaluronic acid and chitosan were developed by polyelectrolyte complex formation. The film based on the equal proportion of polymers exhibited lower water uptake ability compared to other films prepared with different weight ratios. This lower water uptake leads to low drug diffusion across the films and thereby, higher drug penetration across the skin (Bigucci *et al*., 2015).

More recently, Huerta-Ángeles *et al*. (2020) synthesized and characterized all-trans retinoic acid and hyaluronan conjugates. They observed that the shelf-life stability of the resulted conjugates was improved with a degree of substitution. The addition of antioxidant morin into the conjugate had further improved the photostability. Furthermore, the photodegradation of conjugate had not produced any toxic products. Thus, this conjugate could be used as a vehicle to deliver drugs and cosmeceuticals (Huerta-Ángeles *et al*., 2020).

Yang *et al.* (2019) developed a hyaluronic-based dissolving microneedle that was complexed with doxorubicin-loaded transferosome to enhance lymphatic delivery. The resulted microneedles had sufficient mechanical strength to efficiently insert into rat skin and thereafter, released doxorubicin-loaded transferosomes in the dermis *via* self-dissolution. Above microneedles improved doxorubicin accumulation in lymph nodes significantly and increased its plasma bioavailability compared to epidermal diffusion of drugs (Yang *et al*., 2019).

Franzé *et al.* (2018) developed hyaluronic acid decorated flexible transferosomes and ethosomes of nifedipine using egg phosphatidylcholine with tween 80 and ethanol, respectively. The presence of hyaluronic acid on the transferomes surface was found to be essential for efficient penetration of nifedipine into the skin in dose dependent manner. However, a higher amount of hyaluronic acid on the vesicle surface significantly affected the flexibility of the vesicles by increasing the packing order of the bilayer followed by reduction of the structural rearrangement of the vesicles. This resulted in a decrease in vesicle penetration across the skin. The stiffening effect of hyaluronic acid was counterbalanced by the addition of ethanol (transethosomes) as a fluidizing agent by maintaining the highest concentration of hyaluronic acid (Franzé *et al*., 2018). In another study, hyaluronic acid-based ethosomes containing model drug rhodamine B were developed for TDD. The improved stability of the ethosomes was due to the three-dimensional network structure of hyaluronic acid. Furthermore, hyaluronic acid contributed to the enhanced penetration of model drug across rat dorsal skin compared to ethosomes without hyaluronic acid. This was attributed to the hydrophilic structure of hyaluronic acid leading to its diffusion into the epidermis through hydration with the SC (Xie *et al*., 2018).

In ordered to improve the permeability of bupivacaine across the skin, nanostructured lipid carriers (NLCs) modified with hyaluronic acid were developed to

encapsulate bupivacaine. The resulted modified NLC has a small particle size (150nm) and zeta potential of -40 mV, indicating higher stability of NLC. In vitro study of the hyaluronic acid-modified NLC demonstrated sustained release behavior of bupivacaine until 72 h and 2.5-fold increase in percutaneous penetration enhancement compared to free bupivacaine (Yue, Zhao, Yin, 2018).

Chondroitin sulphate

Chondroitin sulphate is an animals-form linear disaccharide composed of (1-3)-β-N-acetyl-D-galactosamine and (1-4)-β-glucuronic acid (Figure 4). It is anionic due to the presence of functional groups such as sulfates, hydroxyl, and carboxylic acid groups on its backbone (Gul *et al.*, 2018). Thus, chondroitin sulphate can form cross-linking with other cationic polymers such as chitosan to form hydrogels and nanocarriers.

A novel nanoparticle-loaded emulgel was successfully developed for transdermal delivery of ketoprofen. Nanoparticles were fabricated with chondroitin sulfate-chitosan by polyelectrolyte complex formation or complex coacervation and then loaded in argan oil-based emulgel in order to impart desired viscosity to the formulation. The emulgel demonstrated significant skin penetration enhancement of ketoprofen compared to marketed gel when mice skin was used as model membrane. In addition, the argan oil synergizes the anti-inflammatory effect of formulation and thereby promoted skin penetration of ketoprofen (Gul*et al.*, 2018).

A hydrogel-based transdermal patch composed of poly(acrylamide)-grafted-chondroitin sulfate copolymer as a drug reservoir and chitosan cross-linked PVA film as the rate-controlling membrane was fabricated. The drug permeation across the rate-controlling membrane was decreased with an increase in the cross-linking agent (glutaraldehyde) and thickness of the membrane. However, the drug permeation was found to be increased with the increase in electric stimulus from 2-8mA, and nearly 3-fold higher flux was exhibited with the application of electric stimulus compared to the absence of an electric stimulus (Birajdar *et al.*, 2020).

Qian *et al.* (2014) fabricated a drug-free microneedle patch with chondroitin sulfate and PVA employing a casting molded method and then, used the resulted microneedle patch to create micropores on the rabbit skin surface. Thereafter, they developed gel and microemulsion-based gel of sinomenine (an anti-inflammatory agent) to apply on the microporated skin. Higher bioavailability of199% and 243% for simple gel and microemulsion-based gel, respectively, were observed when the rabbit model was used. In addition, Cmax values were found to be significantly improved compared to rabbits not treated with microneedle. The results were attributed to the formation of microconduit with the application of microneedle on the skin, thus improving the permeability of drugs by bypassing the SC of the skin (Qian *et al.*, 2014).Yet in another study sinomenine loaded dissolving microneedles were fabricated using chondroitin sulfate and PVP. Compared to sinomenine-based gel, microneedles incorporated with sinomenine demonstrated higher cumulative permeation (5.31-fold) and permeation rate (5.06-fold). Similarly, values of area under the curve after skin administration was found to 1.43-fold than that of gel, which was comparable to sinomenine injection (1.63-fold) (Shu *et al.*, 2020).In another study, Fukushima *et al.*(2010), developed insulin incorporated dissolving microneedle patch with chondroitin sulfate and evaluated for pharmacodynamic effect on shaved abdominal skin of dogs. The results showed a dose-dependent hypoglycemic effect and the bioavailabilities of insulin from microneedles were 72.1±11.6% and 72.4±8.3% for two patches and four patches, respectively (Fukushima *et al.*, 2010). Naito *et al.*(2012) fabricated antigen-loaded dissolving microneedle array patches using chondroitin sulfate mixed with model antigen, ovalbumin. The resulted microneedle effectively delivered a significant amount of antigen into the skin within 3 minutes of application and was found to induce robust antigen-specific antibody responses in the sera of mice (Naito *et al.*, 2012).

Inulins

Inulins are a group of natural polysaccharides present as an energy reserve in plants such as wheat, chicory, bananas, garlic, etc. However, inulins obtained from chicory plants are available commercially

(Roberfroid, 2013). It is composed of chain-terminating glucose units and repetitive fructose units linked through β-(2-1) glycosidic bond (Figure 4). The degree of polymerization of standard inulin ranges from 2 to 60, but more than 10 is commercially considered as inulin (Nair, Suman, Thompkinson, 2010). Its higher solubility in water makes it suitable in the preparation of gel and also can improve the stability of the emulsion.

Sarphie *et al.* (1997) evaluated a novel transdermal powdered delivery method (using PowderJet® device) following delivery of radiolabelled inulin to hairless guinea pigs. It was observed that the device efficiently ejected drug i.e, 83% of the starting dose impacting the skin and 33% of the starting dose of inulin found to be delivered into the hairless skin. In addition, there was a significant increase in inulin delivered with the increase in particle size, while washing the skin immediately after the injection decreased the amount of inulin delivered (Sarphie *et al.*, 1997).

In order to avoid the risk of thermal effect from the higher intensity or the duration of the ultrasound treatment, dual low- and high-frequency in the range of 20kHz to 3 MHz was employed to enhance skin permeability of model drug glucose and inulin. Aluminum foil pitting experiments were performed to quantify the number of pits, pit radius and the total pitted area observed in dual as well as single frequency ultrasound experiments. A higher number of pits was observed for dual frequency ultrasound. Subsequently, in vitro testing on porcine skin showed higher localized transport regions for dual frequencies compared to single frequency. Finally, passive delivery of both inulin and glucose to and through the skin was found to be significantly enhanced with dual frequency ultrasound (Sarphie *et al.*, 1997). In another study, low frequency sonophoresis (58 kHz) was used to investigate the possibility of permeation enhancement of hydrophilic permeants such as mannitol, luteinizing hormone-releasing hormone, dextran, and inulin across pig skin. The results demonstrated that the permeability-resistivity correlation for each permeant is related to its size. In addition, the tortuosity of the permeant within the skin also depends on its size with larger permeant experience less tortuosity (Tezel, Sens, Mitragotri, 2003).

Kushner, Blankschtein and Langer (2007) used both theoretical and experimental methods to evaluate parameters such as porosity, tortuosity, and hindrance factor of the aqueous pore channel present in the skin as a function of (i) radius of the model permeants (inulin, urea, mannitol, and raffinose) and (ii) the skin perturbation extent in the skin at a low dose and high dose of ultrasound (20 kHz) with simultaneous application of sodium lauryl sulfate. They observed that porosity increased over 100-fold over the range of skin perturbation examined, tortuosity decreased and only the hindrance factor for inulin was significantly <1 over the range of permeant radii tested. This result indicated that surface related phenomenon induced by the application of both ultrasound and sodium lauryl sulphate was mainly responsible for the mentioned enhancement in the transdermal permeability of hydrophilic permeants (Kushner, Blankschtein, Langer, 2007). Same author in a separate investigation revealed that porosity and tortuosity of aqueous pore channels in the skin were assumed to be independent of permeant radius and hindrance factor was statistically larger in the localized transport regions than non-localized transport regions. They also revealed that porosity was 3.8-fold higher in the localized transport regions compared to non-localized transport regions when infinitely large aqueous pores were assumed, while for tortuosity the difference was found to be very little for both the regions (Kushner, Blankschtein, Langer, 2008).

Pullulan

Pullulan is a natural non-ionic exo-polysaccharide produced by yeast-like polymorphic fungus *Aureobasidiumpullulans*. It is composed of maltotriose units linked through α-(1-6) glycosidic bonds and branched through α-(1-4) glycosidic bonds (Figure 4) (Singh, Kaur, Kennedy, 2015). This unique α-linkages pattern provides various physical properties to form a film that is flexible, mechanically strong, water-soluble, transparent, and low permeability to oxygen. Other desirable qualities of pullulan are non-hygroscopic, biodegradable, non-toxic, non-immunogenic, non-mutagenic, tasteless, colourless, and stable at a wide range

of pH and maximum temperature of 250-280°C (Coltelli*et al.*, 2020). However, its solution in water produces low viscosity compared to other polysaccharides. The water solubility of pullulan can be modified by modifying the hydroxyl groups on its skeleton (Singh, Kaur, Kennedy, 2015). Due to the above properties, pullulan is considered as a potential polymer for the topical/TDD with films, patches, and microneedles (Vora *et al.*, 2020).

A novel topical film fabricated with *Rhus verniciflua* extract-loaded pullulan hydrogel was developed to treat atopic dermatitis. The film demonstrated significant attenuation in dermatitis score, epidermal thickness, mast cell infiltration, and serum myeloperoxidase activities compared to plain gel and non-treated rat groups. The results revealed that the film inhibits atopic dermatitis through exerting dual roles: *Rhus verniciflua* extract mediated pharmaceutical and pullulan-mediated physical actions (Jeong *et al.*, 2019). Vishwanath *et al.* (2012) developed a transdermal film of metoprolol succinate with the blend of pullulan and poly(acrylamide). They revealed that the developed blend polymer exhibited good film-forming property and released the drug fast, thus suitable for formulating TDDS for the immediate release of incorporated drugs (Vishwanath *et al.*, 2012).

Patil *et al.*(2020) successfully synthesized an electrically responsive copolymer composed of poly(acrylamide) and pullulan and then used it for the fabrication of a hydrogel reservoir for rivastigmine tartarate. In addition, a rate-controlling membrane composed of pullulan and PVA was developed for on-demand drug release. The drug diffusion was found to be enhanced by 1.68-folds when electric stimulation was applied compared to without it. The permeation rate was observed to augment with the increase in electric stimulus from 2 to 8 mA and the opposite is observed with the increase in crosslinking agent concentration (Patil *et al.*, 2020).

Vora *et al.*(2020) reported for the first time, the fabrication and characterization of dissolving microneedle incorporating FITC-bovin serum albumin and insulin as model molecules using rapidly dissolving carbohydrate pullulan. The resulted microneedle showed stability for the incorporated molecules in addition to good mechanical strength and biocompatibility. Furthermore, microneedles successfully delivered the model drugs across excised neonatal porcine skin (Vora *et al.*, 2020). Fonseca *et al.*(2020) used pullulan to fabricate dissolving microneedle patches for insulin and the resulted microneedle arrays showed good thermal stability and mechanical properties that helped the microneedle penetrating skin up to 381 μm depth. The microneedle was dissolved inside human abdominal skin in vitro within 2 h and releasing up to 87% of insulin, after application. The microneedles showed stability at different temperatures for 28 days with retaining secondary structure of insulin and not exhibited cytotoxicity towards human keratinocytes (Fonseca *et al.*, 2020).

Carrageenans

Carrageenans or carrageenins are a family of linear high MW sulphated polysaccharides which are extracted from certain species of red edible seaweeds belonging to the family Rhodophyceae (Guo *et al.*, 2017; Li *et al.*, 2014a). However, most of the commercial carrageenans are now extracted from *Educheuma denticulatum* and *Kappaphycus alvarezii*. It is consisting of chains of β-D-galactose and 3,6-anhydro-α-D-galactose linked by α-(1,3) and β-(1,4) glycosidic bonds. Based on the MW (generally varies between 100-1000 kDa), number and position of sulfate groups and 3,6-anhydro-α-D-galactose content, carrageenans are classified into various types including lambda (λ with three sulfate group per dimer), iota (t with two sulfate group per dimer) kappa (k with one sulfate group per dimer), μ (mu), ν (nu), θ (theta) and ξ (Ksi) (Figure 4) (Yee *et al.*, 2016). The first three types of carrageenan are widely used in biomedical and pharmaceutical fields. The k-carrageenan was found to produce firm, rigid gels in the presence of potassium ions. However, t-carrageenans forms soft, elastic gels in the presence of calcium ions as it contains two sulfate groups per dimer. Contrary to this, λ-carrageenan is highly sulfated which less likely to form a gel structure (Layek, Mandal, 2020; Guo *et al.*, 2017).

An unique hydrogel based on carrageenan as matrix and guar gum, potassium citrate, and glycerin

as additives was developed for the delivery of tocotrienol-rich palm-based vitamin E into the skin. The strength and flexibility of the hydrogel were found to be increased with the inclusion of additives in the hydrogel. In addition, permeability of the drug across the polysulfone membrane and its bioavailability showed improvement with the inclusion of polyethyleneglycol-40 and hydrogenated castor oil mixture (Yee *et al.*, 2016). Kaur *et al*. (2019) fabricated biocomposite films composed of carrageenan (k variety)/locust bean gum/ montmorillonite for TDD of curcumin. The addition of montmorillonite improved the mechanical properties of developed films and the drug release was observed to be sustained with the increasing concentration of locust bean gum and montmorillonite. In comparison to control carrageenan film, film composed of carrageenan with locust bean gum and the combination of carrageenan with both locust bean gum and montmorillonite demonstrated faster wound healing property when the rat model was adopted (Kaur *et al.*, 2019). In another study, Rebouh *et al*.(2019) fabricated matrix type transdermal films of metformin with chitosan and carrageenan (k variety). The mechanical strength was found to be increased with the increase in carrageenan concentration in film. This was attributed to the formation of polyelectrolyte complex. The ex-vivo permeation displayed high drug flux with a good permeation enhancement effect (Rebouh *et al.*, 2019).

Xanthan gum

Xantham gum is an exopolysaccharide produced by the fermentation of carbohydrates obtained from *Xanthomonas campestris*. It is consisting of β-(1,4)-D-glucose based backbone and β-D-mannose-(1,4)-β-D-glucuronic acid-(1,2)-α-D-mannose side chain at every alternate glucose unit. The mannose at the terminal position may carry pyruvate residues at positions C-4 and C-6, and the internal mannose is found to be partially acetylated at C-6 (Figure 4) (Alvarez-Lorenzo *et al.*, 2013; Bejenariu *et al.*, 2008). Moreover, the percent composition of xanthan gum desirable for industrial use is: 43.4% of mannose, 37% of glucose, 19.5% of glucuronic acid, 4.5% of acetate, and 4.4% of pyruvate. Xanthan gum is a high MW polysaccharide gum that is soluble in both cold and hot water. In an aqueous solution, xanthan gum undergoes a conformational transition from an ordered helical shape (at temperature relevant to the human body and salt concentration) to a conformation with chain disorderliness (at low ionic strength and elevated temperature). In addition, this transition can be modified by external variables that result in the formation of physical gels (Alvarez-Lorenzo *et al.*, 2013). It has also other pharmaceutical uses such as suspending, stabilizing, and thickening agents. However, it is more popular because of its controlled drug release characteristics which are proceded by polymer hydration (Rajesh, Siddaramaiah, 2009).

Nanoparticles-loaded xanthan gum and HPMC gels were developed for tetracaine. The drug possesses a positive charge on its surface and the silica nanoparticles express negative charges on their surface leading to interaction with the drug. HPMC-based gel delivered the drug more efficiently compared to xanthan gum when porcine skin was used as a model membrane. However, nanoparticle-loaded HPMC-based gel showed a 10-fold higher flux of drug compared to equivalent nanoparticle-loaded xanthan gum gel. The above result was attributed to the consequence of the dehydration mediated diffusional restriction imparted on the drug by xanthan gum. In contrast, HPMC demonstrated viscosity independent interactions with the drug (Cai, Mesquida, Jones, 2016). Shin *et al.* (2018) developed curcumin-loaded solid lipid nanoparticles by ultrasonic homogenization and then, these nanoparticles were introduced in thermoresponsive hydrogel made up of pluronic F68 and F127 to obtain thermoresponsive nanogel of curcumin. They reported that the skin adhesiveness and adhesive strength of the hydrogel with the addition of 0.2% of xanthan gum were increased compared to gel without xanthan gum. The cumulative amount of curcumin permeation was significantly increased with gel compared to curcumin ethanol solution (Shin, Park, 2018).

With the intention to circumvent limited oral bioavailability, a microemulsion formulation of repaglinide was developed and then incorporation of the resulted microemulsion in xanthan gum gel base. The in vitro drug permeation across rat skin displayed

higher permeability of drug for microemulsion and microemulsion gel compared to a plain drug suspension. The increased fluxes for microemulsion and microemulsion gel were found to be 12.30-fold and 10.97-fold, respectively, compared to repaglinide suspension. Between microemulsion and microemulsion gel, the former showed higher cumulative drug permeation. In vivo oral glucose tolerance test on rats demonstrated that the microemulsion gel had significant hypoglycemic activity than that of oral repaglinide suspension (Shinde, Modani, Singh, 2018).

To avoid chemical instability, a novel nanocrystal suspension of montelukast was developed and the resulted suspension was incorporated into xanthan gum-based hydrogel. The stability study on nanocrystal hydrogel displayed reduced degradation under visible exposure, generating only 30% and 50% amount of cis-isomer and sulfoxide as the major degradation products, as compared to the alkaline solution of drug. Moreover, there was no marked pharmacokinetic difference between the nanocrystal and conventional hydrogels, when administered topically in rats (Im *et al*., 2019). Ngan *et al*. (2014) fabricated O/W nanoemulsion of fullerene followed by its incorporation in xanthan gum and beeswax-based hydrogel. The stability of fullerene was found to be dependent on xanthan gum content in nanoemulsion gel and displayed stability up to 90 days of storage at elevated temperature (Ngan *et al*., 2014).

Bhunia *et al*.(2013) fabricated transdermal membranes of diltiazem hydrochloride composed of xanthan gum and high/low MWPVA blends irradiated under the low dose electron beam. Irradiation converts amorphous PVA in the irradiated state to the crystalline phase. The crystals of PVA were observed to be fibrillar at low xanthan gum content with the high MW, while similar orientation at higher xanthan gum content with low MWPVA. Membrane obtained from both varieties of PVA demonstrated slow and sustained release of diltiazem hydrochloride, but higher MWvariety induced slightly higher release despite low drug encapsulation efficiency because of its better wet mechanical strength(Bhunia *et al*., 2013). Matrix polymeric membrane of domperidone composed of xanthan gum and sodium alginate were developed and the in vitro drug release study showed controlled release of drug from the membrane, with a decrease in drug release with the increase in xanthan gum concentration in the membrane. In addition, it was observed that there was no significant change in drug content after 3 months of study indicating that the membranes were stable (Rajesh, Siddaramaiah, 2009).

Gellan gum

Gellan gum is an anionic exopolysaccharide produced by *Pseudomonas elodea*. It is a tetrasaccharide with two residues of D-glucose, one each of D-rhamnose and D-glucuronic acid (Figure 4). It is a water soluble and high MW polymer with excellent gelling and mechanical properties. Gellan gum easily disperses in aqueous media to produce good stability and high gel strength at lower concentrations in the presence of gel-promoting cations. This variable gelling strength of gellan gum is due to the formation of a coaxial triangular 3-fold double helix (Alvarez-Lorenzo *et al*., 2013). In addition to the above, gellan gum has excellent biocompatibility, biodegradability which made it a suitable polymer for the development of transdermal formulations including gels, hydrogel films, patches, and nanogel (Carmona-Moran *et al*., 2016; Nair *et al*., 2019).

Carmona-Moran *et al.* (2016) fabricated semisolid gel and solid hydrogel film formulations with gellan gum and their reformulated forms (homogenized) to enhance the transdermal penetration of diclofenac sodium. The reformulated gel and film displayed significantly higher diclofenac flux compared to commercially available gel and solution formulations. The solid hydrogel with entrapped temperature-responsive nanogel (reformulated gel) showed 6-fold higher flux when surface temperature increased from 22°C to 32°C (Carmona-Moran*et al*., 2016). In one investigation, ibuprofen and chitosan nanoconjugates were developed, and then, they were incorporated into gelling base of gellan gum. It was observed that there was a strong interaction between the carboxylate ion of ibuprofen and protonated amino group of chitosan results in the formation of an eutectic product with a significant decrease in particle size. The size reduction induced the formation of an

amorphous form of the drug from crystalline form. There was a 4-fold increase in ibuprofen release from chitosan-ibuprofen-gellan conjugate nanogel across pig skin compared to gellan gel containing ibuprofen under identical conditions (Abioye, Issah, Kola-Mustapha, 2015). Hydrogel-based transdermal system of nebivolol composed of gellan gum and carbopol was developed and observed that the influence of carbopol concentration in gel viscosity was more pronounced compared to gellan gum. The optimized gel demonstrated a biphasic release pattern and the release rate was found to be influenced by the concentration of gellan gum. The in vivo study on rats indicated that transdermal administration of optimized gel showed 2-fold higher activity compared to oral administration (Nair *et al*., 2019).

Guar gum

Guar gum is a natural polysaccharide extracted from the seeds of *Cyamopsis tetragonoloba*, family leguminosae (Pegg, 2012). It chemically belongs to the galactomannan family as it is composed of both galactose and mannose (Guo *et al*., 2017). It has a linear backbone of (1-4) linked mannose residue and side chains of D-galactose attached to the linear backbone at the alternate position by α-(1-4)-glycosidic bond (Figure 4). The various commercially available guar gum differs in particle size, viscosity, and rate of hydration. Guar gum forms highly viscous pseudoplastic solutions in cold water. In addition, it rapidly dissolves or swells in polar solvents with forming strong hydrogen bonds; however, it forms weak bonds in nonpolar solvents (Layek, Mandal, 2020).

Shankrayya, Basavaraj and Sreenivasa (2016) fabricated a transdermal patch of aceclofenac with sodium carboxymethyl hydroxypropyl guar and various synthetic polymers. They observed that the patch developed with 2% guar derivatives demonstrated better sustained release profile up to 24 hr compared to all other patches developed with synthetic polymers (Shankrayya, Basavaraj, Sreenivasa, 2016). A novel polymeric nanocomposite based TDDS of diltiazem hydrochloride was fabricated with guar gum-g-polyacrylamide copolymer and nanosilica. The patch containing 1% nanosilica exhibited the most hydrophobic characteristics and the same patch showed the highest in vitro drug release patterns. In addition, the nanocomposite patch displayed non-irritant behavior with good cytocompatibility (Dutta *et al*., 2017). In another study, Giri *et al*.(2014) fabricated *in situ* composite membranes of diclofenac sodium with 2-hydroxyethyl methacrylate grafted carboxymethyl guar gum- functionalized multi-walled carbon nanotube. The membrane with lower nanocomposite concentration showed better polymer and nanocomposite interaction and better orientation of nanocomposite in the polymer matrix compared to their higher concentrations. The resulted nanocomposite membrane displayed efficient drug encapsulation and sustained release of the drug. The drug release was mainly influenced by the viscoelastic relaxation behavior of the device and all the membranes showed a significant increase in the half-life of drug molecules (Giri *et al*., 2014).

Gum arabic

Gum arabic a highly branched natural polysaccharide derived from the exudates of *Acacia trees*. The main chain of gum arabic is composed of 1,3-linked β-D-galactopyranosyl units with other carbohydrates including rhamnose, glucuronic acid, and arabinose, usually forming complexes with ions such as magnesium, calcium, or potassium (Figure 4). It exhibited excellent water solubility, up to 30% at ambient temperature, with 30% gum arabic solution have a lower viscosity than that of 1% solution of xanthan gum (Guo *et al*., 2017; Alvarez-Lorenzo *et al*., 2013.

An interesting hybrid bioadhesive in the form of an array of microscale pillers was proposed for the transdermal delivery of antibiotic kanamycin A. Array of microscale pillers were made up of PDMS and the adhesive property was imparted by gum arabic. The resulted hybrid adhesive displayed higher adhesive property and biocompatibility compared to the sample made of PDMS alone or sample with a flat surface (Wang, Lu, 2018).In another study, microcapsules of salicylic acid were prepared with gum arabic and maltodextrin for transdermal application. The optimum gum arabic/

maltodextrin was found to be 1:1 with enhanced water solubility. In vitro permeation study demonstrated that the developed microcapsules had lower permeability within 19 h without initial burst permeability. In addition, higher retention of salicylic acid on the skin surface and lower skin retention were observed (Huang *et al.*, 2014). The same authors reported the preparation of fragrance (obtained from *Osmanthus* flower) microcapsules with fragrance as core and matrix combination of maltodextrin and gum arabic as shell material. There was higher retention of fragrance in the microcapsules for the condition of long heating time (one week) at a low temperature of 60°C compared to high temperature (80-120°C) after the short heating time of 30 minutes. In vitro permeation study displayed longer residence of fragrance in the microcapsules on the skin surface than that of pure fragrance oil (Li *et al.*, 2014b).

Gum ghatti

Gum ghatti is another polysaccharide with a highly branched structure. The main branched sugar residues in gum ghatti are galactose, galacturonic acid, arabinose, and mannose (Figure 4). It shows excellent water solubility which is attributed to the presence of 1-6 linked glycosidic bonds (Guo *et al.*, 2017).

Birajdar *et al.* (2019) fabricated an electric stimulus-based reservoir type of patch for quetiapine fumarate with a reservoir composed of polyacrylamide-grafted-gum ghatti copolymers and a rate-controlling membrane composed of gum ghatti and PVA. There was a 2-fold enhancement of drug flux after the application of electric stimulus than that of patches without the application of an electric stimulus. Furthermore, the drug permeation increased with the increase in electric stimulus from 2 to 8 mA (Birajdar *et al.*, 2019).

Glucomannans

The glucomannans belong to the mannan type of natural polysaccharides. It consists of random distribution of β-(1-4)-linked D-glucose and β-(1-4)-linked D-mannose in the backbone (Figure 4) (Gopinath *et al.*, 2018).

Zhang *et al.*(2010) fabricated gel film of acyclovir with konjac glucomannan and xanthan gum. The optimized film composed of konjac glucomannan and xanthan gum at a ratio 2.36:1 (v/v) displayed optimal adhesive ability. The release of the drug from the optimized film showed a peak at 4.5 h and could maintain for 3-7 h. Thus, the above film had good bioadhesive property along with controlled-release abilities (Zhang *et al.*, 2010). Types of polysaccharides with various formulations, incorporated drugs, and used for the treatment are presented in Table I.

TABLE I - Types of polysaccharides with various formulations, incorporated drugs, and used for the treatment

Types	Name of the polymer(s)	Type(s) of formulation	Drug	Used for the treatment	References
Cellulose and its derivatives	CMC and 2-hydroxyethyl acrylate	pH responsive smart hydrogel	Naringenin	Atopic dermatitis	So, Hyuk, Soo, 2018
	CMC	Hydrogel	Doxorubicin hydrochloride	Melanoma	Capanema *et al*., 2018
	HEC and hyaluronic acid	Hydrogel	Isoliquiritigenin	Antibacterial activity	Kong, Kim, Park, 2016
	HPC	Hydrogel	4-benzylpiperdine	Cocaine used disorder	Ganti *et al*., 2018
	HPMC and PVA	Cryogel	Diltiazem HCl	Hypertension	Parhi, Suresh, Patnaik, 2015b
	HPMC K100M and Pluronic F127	Thermosensitive gel	Diltiazem HCl	Hypertension	Parhi, Suresh, Patnaik, 2015c
	HPMC K100M and Pluronic F127	Thermosensitive gel	Aceclofenac	Osteoarthritis	Singh, Parhi, Garg, 2011
	HPMC and Pluronic F127	Thermosensitive gel	Metoprolol succinate	Hypertension	Parhi, 2016
	HPMC and eudragit RL100	Film-forming gel	Etoricoxib	Musculoskeletal disorders	Parhi, Goli, 2020
	HPMC K4M and eudragit RS100	Film	Diltiazem HCl	Hypertension	Parhi, Suresh, 2016
	HPMC and (phospholipid)	Film and (Invasosomes)	Avanafil	Erectile dysfunction	Ahmed, Badr-Eldin, 2019
	Neem gum polysaccharide or its carboxymethylated derivative	Film	Albumin	-----	Malviya, 2020
	CMC, trehalose, maltodextrin, glucose and hyaluronic acid	Dissolvable microneedle array	---	----	Yalcintas *et al*., 2020
	Cellulose acetate	Nanofibres	l-tryptophan.	---	Ghorani *et al*., 2018
	HPC and polyurethane	Nanofibres	Donepezil hydrochloride	Alzheimer disease	Gencturk *et al*., 2017

TABLE I - Types of polysaccharides with various formulations, incorporated drugs, and used for the treatment

Types	Name of the polymer(s)	Type(s) of formulation	Drug	Used for the treatment	References
Chitin/chitosan and their derivatives	Chitosan, egg albumin and carbopol 940	Nanogel	Aceclofenac	Pain and inflammation	Cheung *et al.*, 2015
	Chitin	Nanogel	5-fluorouracil	Melanoma	Jana *et al.*, 2014
	Chitin	Nanogel	Clobetasol	Psoriasis	Sabitha *et al.*, 2013
	Chitosan, carbopol and poloxamer	Nanogel	Propranolol hydrochloride	Cardiovascular conditions such as hyper-tension, angina pectoris and cardiac arrhythmia	Panonnummal, Jayakumar, Sabitha, 2017
	Chitosan whisker grafted with oligo(lactic acid)	Nanoparticles	Lidocaine	---	Al-Kassas *et al.*, 2016
	Chitosan	Chitosan-coated liposomes	Indocyanine green	Melanoma	Engkagul *et al.*, 2017
	Chitosan, polystyrene and poly(acrylic acid)	Chitosan coated polymerosomes	----	----	Lee, Lim, Lee, 2019
	Chitosan	O/W based microemulsion	Polyphenol of olive leaf extract	---	Caon *et al.*, 2014
	Chitosan	Chitosan coated microemulsion	Clotrimazole	Candidiasis	Acosta *et al.*, 2015
	Chitosan and Quaternized chitosan	Chitosan and Quaternized chitosan coated nanoemulsion	Plai extract	Anticancer and Anti-inflammatory activity	Kumari, Kesavan, 2017
	Chitosan, poly(N-isopropylamide-co-acrylic acid and cellulose laurate	Polymeric nanoparticles	Tretinoin and clindamycin phosphate	-----	Luesakul *et al.*, 2020
	Chitosan	Polymeric nanoparticles	Curcumin	Various tumors	Shamsi *et al.*, 2017
	Nanochitosan and poly(-caprolactone) nanofibres	Composite elctrospun membranes	Curcumin	Wound healing (Antibacterial)	Abdel-Hafez, Hathout, Sammour, 2018
	Cross-linked chitosan	Film	Zidovudine	Antiviral	Reshmi *et al.*, 2018
	Chitosan and PVP	Patch	Metoprolol tartarte	----	Singh, Upasani, 2013
	Chitosan	Micrparticles incorporated Patch	Rivastigmine	Mild to moderate Alzheimer's disease	Gandhi *et al.*, 2014
	Chitosan	Nano- and microcrystal based patch	Gibenclamide	Diabetes	Sadeghia *et al.*, 2016

TABLE I - Types of polysaccharides with various formulations, incorporated drugs, and used for the treatment

Types	Name of the polymer(s)	Type(s) of formulation	Drug	Used for the treatment	References
Starch	Starch and poly(N-isopropylacrylamide) (PNIPAM)	Hydrogel patches	Ayclovir	Herpes simplex Infection such as genital herpes and cold sores	Fu *et al*., 2018
	Starch obtained from mungbean and PVA	Films	Sulindac	Inflammation	Bakrudeen, Sudarvizhi, Reddy, 2016
	Carboxymethyl starch and 1,4-cis polybutadiene	Nanoparticles	Clonidine	----	Tak *et al*., 2019
	Maize starch	Nanoparticles	Diclofenac sodium	Rheumatoid disorders and other chronic inflammatory diseases	Saboktakin, Akhyari, Nasiro, 2014
	Quaternized starch	Complex	miR-197	Psoriasis	El-Naggar *et al*., 2015
Alginate	Alginate	Matrix film	Donepezil	Alzheimer's disease	Jain, Bar-Shalom, 2014
	Sodium alginate and poly(4-vinylpyridine)	Polyelectrolyte multilayer films	Ciprofloxacin hydrochloride	Wound healing	Galipoğlu, Erdal, Güngör, 2015
	Alginate, chitosan and HPMC	Nanoparticles incorporated film	Dapoxetine	Depression	Alshhab, Yilmaz, 2020
	Sodium alginate and chitosan	Nanogel	Pirfenidone	Pulmonary fibrosis	Ahmed *et al*., 2020
	Alginate chitosan HPMC and HPC	Nanoparticles incorporated patch	Rabeprazole	Erosive gastroesophageal reflux	Abnoos *et al*., 2018
Pectins	Bovine serum albumin, pectin and chitosan	Core-shell microcapsule	Berberine	Acne	Chomto, Nunthanid, 2017
	Pectin, poly(2-acrylamido-2-methyl-1-propanesulfonic acid-co-acrylamide) and silver	Silver nanocomposite film	Donepezil	Antimicrobial	Paşcalău *et al*., 2020
	Pectin	Hydrogel patch	Insulin	Diabetes	Kodoth *et al*., 2019
	Pectin and natural rubber latex	Matrix patch	Nicotine	Smoking cessation	Hadebe *et al*., 2014
	High and low methoxyl pectin	Pectin coated liposomes	Vitamin C	Photoprotection, reducing melanin, eliminating free radicals, and promoting collagen biosynthesis	Suksaeree *et al*., 2018
	Pectin.	Microneedle array	Bovine serum albumin	----	Zhou *et al*., 2014

TABLE I - Types of polysaccharides with various formulations, incorporated drugs, and used for the treatment

Types	Name of the polymer(s)	Type(s) of formulation	Drug	Used for the treatment	References
Dextran	Polyacrylamide grafted dextran (reservoir) and dextran-PVA blend (rate controlling membrane)	Electro-responsive TDDS	Rivastigmine tartarate	---	Anirudhan, Binusree, 2016
	Methacrylated hyaluronic acid-derived (core) and cyanine 5 and flurescein isothiocyanate (FITC)-dextran (Coating)	Double-layered microneedles	Insulin	Controlling the blood glucose level and allowed the extraction of skin interstitial fluid for analysis of the glucose	Patil *et al*., 2019
	Hyaluronic acid integrated with pH sensitive dextran nanoparticles	Self-degradable microneedle	Zinc phthalocyanine and anti-CTLA4 antibody	Photodynamic therapy and immunotherapy	Lorenzo *et al*., 2017
	Gantrez S-97, sodium carbonate and polyethylene glycol.	Microneedle	FITC-dextran	----	Ning *et al*., 2020
	Dextran and polycaprolactone, and grapheme oxide	Composite nanofibrous transdermal patch	Tetracycline	Chronic infectious lesion	Chen *et al*., 2020
Hyaluronic acid	Chitosan, hyaluronic acid, alanine, and pluronic F127	Dual-responsive (pH and temperature) nanocomposite hydrogel	Gallic acid	Atopic dermatitis	Tripodo *et al*., 2015
	Hyaluronic acid and HEC	complex pH sensitive hydrogel	isoliquiritigenin	Antimicrobial activity	Chatterjee *et al*., 2020
	PVP (inner layer), and PVP and hyaluronic acid (outer layer)	Intelligent transparent bilayer films involving	Ciprofloxacin	Chronic and non-healing wounds or burns	Kwon, Kong, Park, 2015
	Hyaluronic acid and chitosan	Polyelectrolyte complex based films	Thiocolchicoside	Muscle relaxant, anti-inflammatory and analgesic properties	Contardi *et al*., 2019

TABLE I - Types of polysaccharides with various formulations, incorporated drugs, and used for the treatment

Types	Name of the polymer(s)	Type(s) of formulation	Drug	Used for the treatment	References
	All-trans retinoic acid and hyaluronan	Conjugates	Antioxidant morin	Vehicle to deliver drugs and cosmeceuticals	Bigucci *et al*., 2015
	Hyaluronic acid	Dissolving microneedle that was complexed with transferosome	Doxorubicin	Tumor metastasis.	Huerta-Ángeles *et al*., 2020
	Hyaluronic acid and egg phosphatidylcholine	Transferosomes and ethosomes	Nifedipine	Raynaud's syndrome	Yang *et al*., 2019
	Hyaluronic acid	Ethosomes	Rhodamine B	-----	Franzé *et al*., 2018
	Hyaluronic acid	Nanostructured lipid carriers (NLCs) modified with hyaluronic acid	Bupivacaine	Postoperative pain or other acute and chronic pain	Xie *et al*., 2018
Chondroitin sulphate	Chondroitin sulfate and PVA	Microneedle patch, gel and microemulsion-based gel of	Sinomenine	Rheumatoid arthritis	Birajdar *et al*., 2020
	Chondroitin sulfate and PVP	Dissolving microneedles	Sinomenine	----	Qian *et al*., 2014
	Chondrioitin sulfate	Dissolving microneedle patch	FITC-insulin	Dose-dependent hypoglycemic effect and the bioavailabilities of insulin	Shu *et al*., 2020
	Chondriotin Sulfate mixed with model	Dissolving Microneedle array patches	Ovalbumin	Percutaneous vaccination	Fukushima *et al*., 2010
Inulins	----	Transdermal powdered delivery method (using PowderJet® device)	Radiolabelled inulin	----	Nair, Suman, Thompkinson, 2010
	----	----	Glucose and inulin	----	Sarphie *et al*., 1997
	---	----	Mannitol, luteinizing hormone releasing hormone, dextran and inulin	----	Sarphie *et al*., 1997
	---	---	Inulin, urea, mannitol and raffinose	Permeability enhancement	Tezel, Sens, Mitragotri, 2003

TABLE I - Types of polysaccharides with various formulations, incorporated drugs, and used for the treatment

Types	Name of the polymer(s)	Type(s) of formulation	Drug	Used for the treatment	References
Pullulan	Pullulan	Dissolving microneedle	FITC-bovin serum albumin and insulin	----	Coltelli *et al*., 2020
	Pullullan	Hydrogel	*Rhus verniciflua* extract	Atopic dermatitis	Vora *et al*., 2020
	Pullulan and polyacrylamid	Film	Metoprolol succinate	----	Jeong *et al*., 2019
	Poly(acrylamide) and pullulan copolymer (reservoir) and pullulan and PVA (rate controlling membrane)	Electrically-responsive hydrogel patch	Rivastigmine tartarate	Alzheimer's disease	Vishwanath *et al*., 2012
	Pullulan	Dissolving microneedle patches	Insulin	Diabetes mellitus	Patil *et al*., 2020
Carrageenans	Carrageenan and guar gum	Hydrogel	Tocotrienol-rich palm-based vitamin E	Prevent free radical damage in skin	Li *et al*., 2014a
	k-carrageenan /locust bean gum/montomorillonite	Biocomposite films	Curcumin	Antibacterial properties	Yee *et al*., 2016
	Chitosan and k-carrageenan	Matrix type films	Metformin	Diabetes	Kaur *et al*., 2019
Xanthan gum	Xanthan gum and sodium alginate	Matrix membrane	Domperidone	Hypertension	Bejenariu *et al*., 2008
	Xanthan gum and HPMC	Nanogel	Tetracaine	Local anesthesia	Rajesh, Siddaramaiah, 2009
	F68 and F127, and xanthan gum	Themoresponsive nanogel	Curcumin	----	Cai, Mesquida, Jones, 2016
	Xanthan gum	Microemulsion gel	Repaglinide	Hypoglycemic activity	Shin, Park, 2018
	Xanthan gum	Nanocrystal hydrogel	Montelukast	Chronic asthma and symptoms of seasonal allergies	Shinde, Modani, Singh, 2018
	Xanthan gum and beeswax	O/W nanoemulsion gel	Fullerene	Oxidative stress-related diseases	Im *et al*., 2019
	Xanthan gum and PVA	Membranes	Diltiazem hydrochloride	Angina pectoris and anal fissure	Ngan *et al*., 2014
Gellan gum	Gellan gum	Semisolid gel and solid hydrogel film	Diclofenac sodium	Pain management in osteoarthritis	Bhunia *et al*., 2013
	Gellan gum, carbopol and polyethylene glycol	Hydrogel	Nebivolol	Hypertension	Carmona-Moran *et al*., 2016
	Chitosan and gellan gum	Nanoconjugates	Ibuprofen	Pain, fever, symptoms of rheumatoid arthritis and osteoarthritis	Nair *et al*., 2019

TABLE I - Types of polysaccharides with various formulations, incorporated drugs, and used for the treatment

Types	Name of the polymer(s)	Type(s) of formulation	Drug	Used for the treatment	References
Guar gum	Sodium carboxy methyl hydroxyl propyl guar	Patch	Aceclofenac	------	Shankrayya, Basavaraj, Sreenivasa, 2016
	Guar gum-g-polyacrylamide copolymer	Polymeric nanocomposite	Diltiazem hydrochloride	---	Dutta *et al*., 2017
	2-hydroxyethyl methacrylate grafted carboxymethyl guar gum	Composite membranes	Diclofenac sodium	Rheumatoid arthritis	Giri *et al*., 2014
Gum arabic	PDMS and gum arabic	Array of microscale pillers	Kanamycin A	----	Wang, Lu, 2018
	Gum arabic and maltodextrin	Microcapsules	Salicylic acid	----	Huang *et al*., 2014
	Fragrance (as core), and maltodextrin and gum arabic (as shell)	Microcapsules		----	Li *et al*., 2014b
Gum ghatti	Polyacrylamide-grafted-gum ghatti copolymers (reservoir) and composed of gum ghatti and PVA (rate controlling membrane)	Electric stimulus based reservoir type of patch	Quetiapine fumarate	---	Birajdar*et al*., 2019
Glucomannans	Konjac glucomannan and xanthan gum.	Film	Acyclovir	----	Zhang *et al*., 2010

LIMITATIONS OF POLYSACCHARIDES

Polysaccharides, particularly natural ones, have been in the center of drug delivery research because of their suitable properties. However, natural polymers suffer due to their primary limitations including microbial contamination, low mechanical strength, reduced viscosity during storage, poor stability, thickening, and uncontrolled rate of hydration (Dias *et al*., 2016). In addition, variation in the drug release profile is observed due to diverse physicochemical properties and varied purity of polysaccharides associated with batch-to-batch variations, due to the physical and environmental factors (Layek, Mandal, 2020). To circumvent the above problems associated with polysaccharides following measures are currently being undertaken; (i) modification of polysaccharides with grafting, cross-linking, and blending with other polymers of natural/semisynthetic/ synthetic origin, resulting in improvement of physical, chemical, and functional properties, and (ii) stringent control of the quality control of natural polysaccharides is necessary for pharmaceutical applications (Layek, Mandal, 2020).

CONCLUSIONS

This chapter reviewed and analyzed the background information and detailed application of various polysaccharides such as cellulose, chitosan and their semisynthetic derivatives, alginate, pectin, carrageenan, guar gum, gum arabic, gum ghatti, etc to deliver drugs into and across the skin. These polysaccharides have the potential to be used not only in the preparation of conventional dosage forms (e.g. gel) for topical and TDD but also the development of controlled-release formulations such as nanoparticles and microneedles etc. This is possible

because of quality attributes of polysaccharides including biocompatibility, poly-functionality, biodegradability, bioadhesion capacity, non-toxicity, benign to the environment, and finally sustainability and renewability for the source of energy. In addition, the efficacy of these biomolecules is related to mentioned properties. For instance, semisynthetic derivatives of cellulose and pectin have been extensively used to develop film and patch-related formulations due to their good film-forming capabilities. In addition, chitosan and its derivatives are widely used in the development of particulate material such as micro-and nanoparticles because of the presence of charges on their surface that allows the use ionic gelation method. On most occasions, the combination of polymers, preferably one polysaccharide with synthetic polymer with complementary properties, is essential to accomplish the desired formulation criteria for the transdermal and topical drug delivery.

CONFLICT OF INTEREST

The author declares that this article content has no conflict of interest

ETHICAL ISSUES

Not applicable.

REFERENCES

Abdel-Hafez SM, Hathout RM, Sammour OA. Tracking the transdermal penetration pathways of optimized curcumin-loaded chitosan nanoparticles *via* confocal laser scanning microscopy. Int J Biol Macromol. 2018;108:753-64.

Abioye AO, Issah S, Kola-Mustapha AT. Ex vivo skin permeation and retention studies on chitosan–ibuprofen-gellan ternary nanogel prepared by in situ ionic gelation technique-a tool for controlled transdermal delivery of ibuprofen. Int J Pharm. 2015;490(1-2):112-30.

Abnoos M, Mohseni M, Mousavi SAJ, Ashtari K, Ilka R, Mehravi B. Chitosan-alginate nano-carrier for transdermal delivery of pirfenidone in idiopathic pulmonary fibrosis. Int J Biol Macromol. 2018;118(Pt A):1319-25.

N, Sánchez E, Calderón L, Cordoba-Diaz M, Cordoba-Diaz D, Dom S, et al. Physical stability studies of semi-solid formulations from natural compounds loaded with chitosan microspheres. Mar Drugs. 2015;13(9):5901-19.

Ahmed OAA, Badr-Eldin SM. Development of an optimized avanafil-loaded invasomal transdermal film: *Ex vivo* skin permeation and *in vivo* evaluation. Int J Pharm. 2019;570:118657.

Ahmed TA, Alay AMS, Okbazghi SZ, Alhakamy NA. Two-step optimization to develop a transdermal film loaded with dapoxetine nanoparticles: a promising technique to improve drug skin permeation. Dose-Response. 2020;18(2):1-15.

Ahmed TA, El-Say KM. Development of alginate-reinforced chitosan nanoparticles utilizing W/O nanoemulsification/internal crosslinking technique for transdermal delivery of rabeprazole. Life Sci. 2014;110(1):35-43.

Ali HSM, Hanafy AF. Glibenclamide nanocrystals in a biodegradable chitosan patch for transdermal delivery: engineering, formulation, and evaluation. J Pharm Sci. 2017;106(1):402-10.

Al-Kassas R, Wen J, Cheng AE-M, Kim AM-J, Sze S, Liu M, et al. Transdermal delivery of propranolol hydrochloride through chitosan nanoparticles dispersed in mucoadhesive gel. Carbohyd Polym. 2016;153:176-86.

Alshhab A, Yilmaz E. Sodium alginate/poly(4-vinylpyridine) polyelectrolyte multilayer films: Preparation, characterization and ciprofloxacin HCl release. Int J Biol Macromol. 2020;147:809-20.

Alvarez-Lorenzo C, Blanco-Fernandez B, Puga AM, Concheiro A. Crosslinked ionic polysaccharides for stimuli-sensitive drug delivery. Adv Drug Deliv Rev. 2013;65(9):1148-71.

Alvarez-Roman R, Naik A, Kalia YN, Guy RH, Fessi H. Skin penetration and distribution of polymeric nanoparticles. J Control Release. 2004;99(1):53-62.

Anirudhan TS, Binusree J. Dextran based nanosized carrier for the controlled and targeted delivery of curcumin toliver cancer cells. Int J Biol Macromol. 2016;88:222-35.

Bakrudeen HV, Sudarvizhi C, Reddy BSR. Starch nanocrystals based hydrogel: Construction, characterizations and transdermal application. Mater Sci Eng C Mater Biol Appl. 2016;68:880-889.

Bejenariu A, Popa M, Cerf D, Picton L. Stiffness xanthan hydrogels: synthesis, swelling characteristics and controlled release properties. Polym Bull. 2008;61(5):631-41.

Bhunia T, Giri A, Nasim T, Chattopadhyay D, Bandyopadhyay A. Uniquely different PVA-xanthan gum irradiated membranes as transdermal diltiazem delivery device. Carbohyd Polym. 2013;95(1):252-61.

Bigucci F, Abruzzo A, Saladini B, Gallucci MC, Cerchiara T, Luppi B. Development and characterization of chitosan/hyaluronan film for transdermal delivery of thiocolchicoside. Carbohyd Polym. 2015;130:32-40.

Birajdar RP, Patil SB, Alange VV, Kulkarni RV. Electro-responsive polyacrylamide-grafted-gum ghatti copolymer for transdermal drug delivery application. J Macromol Sci Part A: Pure Appl Chem. 2019;56(4):306-15.

Birajdar RP, Patil SB, Alange VV, Kulkarni RV. Synthesis and characterization of electrically responsive poly(acrylamide)-grafted-chondroitin sulfate hydrogel for transdermal drug delivery application. Int J Polym Mater Polym Biomater. 2020;69(3):148-57.

Cai XJ, Mesquida P, Jones SA. Investigating the ability of nanoparticle-loaded hydroxypropyl methylcellulose and xanthan gum gels to enhance drug penetration into the skin. Int J Pharm. 2016;513(1-2):302-8.

Caon T, Porto LC, Granada A, Tagliari MP, Silva MAS, Simões CMO, et al. Chitosan-decorated polystyrene-b-poly(acrylic acid) polymersomes as novel carriers for topical delivery of finasteride. Eur J Pharm Sci. 2014;52:165-72.

Capanema NSV, Mansur AAP, Carvalho SM, Carvalho IC, Chagas P, de Oliveira LCA, et al. Bioengineered carboxymethyl cellulose-doxorubicin prodrug hydrogels for topical chemotherapy of melanoma skin cancer. Carbohyd Polym. 2018;195:401-12.

Carmona-Moran CA, Zavgorodnya O, Penman AD, Kharlampieva E, Bridges Jr SL, Hergenrother RW, et al. Development of gellan gum containing formulations for transdermal drug delivery: Component evaluation and controlled drug release using temperature responsive nanogels. Int J Pharm. 2016;509(1-2):465-76.

Chatterjee S, Hui PC-L, Wat E, Kan C-W, Leung P-C, Wang W. Drug delivery system of dual-responsive PF127 hydrogel with polysaccharide-based nano-conjugate for textile-based transdermal therapy. Carbohyd Polym. 2020;236:116074.

Chen F, Huang G, Huang H. Preparation and application of dextran and its derivatives as carriers. Int J Biol Macromol. 2020;145:827-34.

Chen SX, Ma M, Xue F, Shen S, Chen Q, Kuang Y, et al. Construction of microneedle-assisted co-delivery platform and its combining photodynamic/immunotherapy. J Control Release. 2020;324:218-27.

Cheung RCF, Ng TB, Wong JH, Chan WY. Chitosan: an update on potential biomedical and pharmaceutical applications. Mar Drugs. 2015;13(8):5156-86.

Chomto P, Nunthanid J. Physicochemical and powder characteristics of various citrus pectins and their application for oral pharmaceutical tablets. Carbohyd Polym. 2017;174:25-31.

Cirillo G, Hampel S, Spizzirri UG, Parisi OI, Nevio PN, Iemma F. Carbon nanotubes hybrid hydrogels in drug delivery: a perspective review. BioMed Res Int. 2014;2014:17.

Coelho JF, Ferreira PC, Alves P, Cordeiro R, Fonseca AC, Góis JR, et al. Drug delivery systems: Advanced technologies potentially applicable in personalized treatments. EPMA J. 2010;1(1):164-209.

Coltelli MB, Danti S, Clerk KD, Lazzeri A, Morganti P.Pullulan for advanced sustainable body- and skin-contact applications. J Funct Biomater. 2020;11(1):20.

Contardi M, Russo D, Suarato G, Heredia-Guerrero JA, Ceseracciu L, Penna I, et al. Polyvinylpyrrolidone/hyaluronic acid-based bilayer constructs for sequential delivery of cutaneous antiseptic and antibiotic. Chem Eng J. 2019;358:912-23.

Demir YK, Kerimoglu O. Novel use of pectin as a microneedle base. Chem Pharm Bull (Tokyo). 2015;63(4):300-4.

Dias SFL, Nogueira SS, de França DF, Guimarães MA, Pitombeira NA de O, Gobbo GG, et al. Acetylated cashew gum-based nanoparticles for transdermal delivery of diclofenac diethyl amine. Carbohydr Polym. 2016;143:254-61.

Dragan ES, Dinu MV. Polysaccharides constructed hydrogels as vehicles for proteins and peptides. A review. Carbohyd Polym. 2019;225:115210.

Dutta K, Das B, Mondal D, Adhikari A, Rana D, Chattopadhyay AK, et al. An ex situ approach to fabricating nanosilica reinforced polyacrylamide grafted guar gum nanocomposites as an efficient biomaterial for transdermal drug delivery application. New J Chem. 2017;41(17):9461-71.

Einbu A, Vayrum KM. Characterization of chitin and its hydrolysis to GlcNAc and GlcN. Biomacromol. 2008;9(7):1870-5.

El-Naggar ME, El-Rafie MH, El-sheikh MA, El-Feky GS, Hebeish A. Synthesis, characterization, release kinetics and toxicity profile of drug-loaded starch nanoparticles. Int J Biol Macromol. 2015;81:718-29.

Engkagul V, Klaharn I, Sereemaspun A, Chirachanchai S. Chitosan whisker grafted with oligo(lactic acid) nanoparticles via a greensynthesis pathway: Potential as a transdermal drug delivery system. Nanomedicine. 2017;13(8):2523-31.

Fonseca DFS, Costa PC, Almeida IF, Dias-Pereira P, Correia-Sá I, Bastos V, et al. Pullulan microneedle patches for the efficient transdermal administration of insulin envisioning diabetes treatment. Carbohydr Polym. 2020;241:116314.

Franzé S, Marengo A, Stella B, Minghetti P, Arpicco S, Cilurzo F. Hyaluronan-decorated liposomes as drug delivery systems for cutaneous administration. Int J Pharm. 2018;535(1-2):333-9.

Fu L, Zhu J, Zhang S, Li X, Zhang B, Pu H, et al. Hierarchical structure and thermal behavior of hydrophobic starch-based films with different amylose contents. Carbohydr Polym. 2018;181:528-35.

Fukushima K, Yamazaki T, Hasegawa R, Ito Y, Sugioka N, Takada K. Pharmacokinetic and pharmacodynamic evaluation of insulin dissolving microneedles in dogs. Diabetes Technol Ther. 2010;12(6):465-74.

Galipoğlu M, Erdal MS, Güngör S. Biopolymer-based transdermal films of donepezil as an alternative delivery approach in Alzheimer's disease treatment. AAPS PharmSciTech. 2015;16(2),284-92.

Gandhi A, Jana S, Paul A, Sheet S, Nag R, Sen KK. Metoprolol tartrate containing glutaraldehyde cross-linked chitosan-polyvinyl pyrrolidone matrix transdermal patch: preparation and characterization. J PharmaSciTech. 2014;3(2):72-6.

Ganti SS, Nguyen HX, Murnane KS, Blough BE, Banga AK. Transdermal formulation of 4-benzylpiperidine for cocaine-use disorder. J Drug Deliv Sci Technol. 2018;47:299-308.

Gencturk A, Kahraman E, Güngör S, Özhan G, Özsoy Y, Sarac AS. Polyurethane/hydroxypropyl cellulose electrospun nanofiber mats as potential transdermal drug delivery system: characterization studies and in vitro assays. Artif Cells Nanomed Biotechnol. 2017;45(3):655-64.

Ghorani B, Goswami P, Blackburn RS, Russell SJ. Enrichment of cellulose acetate nanofibre assemblies for therapeutic delivery of l-tryptophan. Int J Biol Macromol. 2018;108:1-8.

Giri A, Bhunia T, Mishra SM, Goswami L, Panda AB, Bandyopadhya A. A transdermal device from 2-hydroxyethyl methacrylate grafted carboxymethyl guar gum–multi-walled carbon nanotube composites. RSC Adv. 2014;4(26):13546-56.

Gopinath V, Saravanan S, Al-Maleki AR, Ramesh M, Vadivelu J. A review of natural polysaccharides for drug delivery applications: Special focus on cellulose, starch and glycogen. Biomed Pharmacoth. 2018;107:96-108.

Goyal R, Macri LK, Kaplan HM, Kohn J. Nanoparticles and nanofibers for topical drug delivery. J Controlled Release. 2016;240:77-92.

Gul R, Ahmed N, Ullah N, Khan MI, Elaissari A, Rehman A. Biodegradable ingredient-based emulgel loaded with ketoprofen nanoparticles. AAPS PharmSciTech. 2018;19(4):1869-81.

Guo MQ, Hu X, Wang C, Ai L. Polysaccharides: Structure and Solubility. InTech. 2017. DOI:10.5772/intechopen.71570.

Hadebe SI, Ngubane PS, Serumula MR, Musabayane CT. Transdermal delivery of insulin by amidated pectin hydrogel matrix patch in streptozotocin-induced diabetic rats: effects on some selected metabolic parameters. PLoS One. 2014;9(7):101461.

Huang Y, Li Y, Fan H, Xia Q. Preparation and characterization of salicylic acid-loaded microcapsules as delivery systems for cosmetics. Integr Ferroelectr. 2014;152(1):22.

Huerta-Ángeles G, Brandejsová M, Štěpán P, Pavlík V, Starigazdová J, Orzol P, et al. Retinoic acid grafted to hyaluronan for skin delivery: Synthesis, stability studies, and biological evaluation. Carbohyd Polym. 2020;231:115733.

Hutton ARJ, McCrudden MTC, Larrañeta E, Donnelly RF. Influence of molecular weight on transdermal delivery of model macromolecules using hydrogel-forming microneedles: potential to enhance the administration of novel low molecular weight biotherapeutics. J Mater Chem B. 2020;8(19):4202.

Im SH, Jung HT, Ho MJ, Lee JE, Kim HT, Kim DY, et al. Montelukast nanocrystals for transdermal delivery with improved chemical stability. Pharmaceutics. 2019;12(1):18.

Jain D, Bar-Shalom D. Alginate drug delivery systems: application in context of pharmaceutical and biomedical research. Drug Dev Ind Pharm. 2014;40(12):1576-84.

Jana S, Manna S, Nayak AK, Sen KK, Basu SK. Carbopol gel containing chitosan-egg albumin nanoparticles for transdermal aceclofenac delivery. Coll Surf, B. 2014;114:36-44.

Jeong JH, Back SK, An JH, Lee N-S, Kim D-K, Na CS, et al. Topical film prepared with Rhus verniciflua extract-loaded pullulan hydrogel for atopic dermatitis treatment. J Biomed Mater Res B Appl Biomater. 2019;107(7):2325-34.

Kamel S. Pharmaceutical significance of cellulose: a review. Polym Lett. 2008;2(11):758-78.

Kaur R, Sharma A, Puri V, Singh I. Preparation and characterization of biocomposite films of carrageenan/locust bean gum/montmorrillonite for transdermal delivery of curcumin. BioImpacts. 2019;9(1):37-43.

Kim H, Jeong H, Han S, Beack S, Hwang BW, Shin M, et al. Hyaluronate and its derivatives for customized biomedical applications. Biomaterials. 2017;123:155-71.

Kim IY, Seo SJ, Moon HS, Yoo MK, Park IY, Kim BC, et al. Chitosan and its derivatives for tissue engineering applications. Biotechnol Adv. 2008;26(1):1-21.

Kodoth AK, Ghate VM, Lewis SA, Prakash B, Badalamoole V. Pectin-based silver nanocomposite film for transdermal delivery of Donepezil. Int J Biol Macromol. 2019;134:269-79.

Kong BJ, Kim A, Park SN. Properties and in vitro drug release of hyaluronic acid-hydroxyethyl cellulose hydrogels for transdermal delivery of isoliquiritigenin. Carbohydr Polym. 2016;147:473-81.

Kumari B, Kesavan K. Effect of chitosan coating on microemulsion for effective dermal clotrimazole delivery. Pharm Dev Technol. 2017;22(4):617-26.

Kushner J 4th, Blankschtein D, Langer R. Evaluation of hydrophilic permeant transport parameters in the localized and non-localized transport regions of skin treated simultaneously with low-frequency ultrasound and sodium lauryl sulfate. J Pharm Sci. 2008;97(2):906-18.

Kushner J 4th, Blankschtein D, Langer R. Evaluation of the porosity, the tortuosity, and the hindrance factor for the transdermal delivery of hydrophilic permeants in the context of the aqueous pore pathway hypothesis using dual-radiolabeled permeability experiments. J Pharm Sci. 2007;96(12):3263-82.

Kwon SS, Kong BJ, Park SN. Physicochemical properties of pH-sensitive hydrogels based on hydroxyethyl cellulose-hyaluronic acid and for applications as transdermal delivery systems for skin lesions. Eur J Pharm Biopharm. 2015;92:146-54.

Lane ME. Skin penetration enhancers. Int J Pharm. 2013;447(1-2):12-21.

Layek B, Mandal S. Natural polysaccharides for controlled delivery of oral therapeutics: a recent update. Carbohydr Polym. 2020;230:115617.

Layek B, Singh J. Chitosan for DNA and gene therapy. In: Jennings JA, Bumgardner JD, editors, Chitosan Based Biomaterials. Woodhead Publishing: 2017. p. 209-44.

Lee EH, Lim SJ, Lee MK. Chitosan-coated liposomes to stabilize and enhance transdermal delivery of indocyanine green for photodynamic therapy of melanoma. Carbohydr Polym. 2019;224:115143.

Li L, Ni R, Shao Y, Mao S. Carrageenan and its applications in drug delivery. Carbohyd Polym. 2014a;103:1-11.

Li Y, Huang Y-Q, Fan H-F, Xia Q. Heat-resistant sustained-release fragrance microcapsules. J Appl Polym Sci. 2014b;131(7):40053.

Lorenzo FD, Silipo A, Molinaro A, Parrilli M, Schiraldi C, D'Agostino A, et al. The polysaccharide and low molecular weight components of Opuntia ficus indica cladodes: structure and skin repairing properties. Carbohydr Polym. 2017;157:128-36.

Luesakul U, Puthong S, Sansanaphongpricha K, Muangsin N. Quaternized chitosan-coated nanoemulsions: A novel platform for improving the stability, anti-inflammatory, anti-cancer and transdermal properties of Plai extract. Carbohydr Polym. 2020;230:115625.

Malviya R. Non-invasive drug delivery system for the delivery of protein/peptide using neem gum and its derivatives. Biointerf Res Appl Chem. 2020;10(3):5460-55.

Nair AB, Shah J, Aljaeid BM, Al-Dhubiab BE, Jacob S. Gellan gum-based hydrogel for the transdermal delivery of nebivolol: optimization and evaluation. Polymers (Basel). 2019;11(10):1699.

Nair KK, Suman K, Thompkinson DK. Inulin dietary fiber with functional and health attributes-A review. Food Rev Int. 2010;26(2):189-203.

Naito S, Ito Y, Kiyohara T, Kataoka M, Ochiai M, Takada K. Antigen-loaded dissolving microneedle array as a novel tool for percutaneous vaccination. Vaccine. 2012;30(6):1191-7.

Nematpour N, Farhadian KN, Ebrahimi OS, Arkan E, Seyedi F, Khaledian S, et al. Sustained release nanofibrous composite patch for transdermal antibiotic delivery. Colloids Surf, A. 2020;586:124267.

Nesic AR, Seslija SI. The influence of nanofillers on physical–chemical properties of polysaccharide-based film intended for food packaging. In: AM Grumezescu, editor, Food Packaging. Academic Press: 2017. p. 637-97.

Ngan CL, Basri M, Tripathy M, Karjiban RA, Abdul-Malek E. Physicochemical characterization and thermodynamic studies of nanoemulsion-based transdermal delivery system for fullerene. Sci World J. 2014;2014:219035.

Ning X, Wiraja C, Chin D, Lio S, Xu C. A double-layered microneedle platform fabricated through frozen spray-coating. Adv Healthc Mater. 2020;9(10):2000147.

Panonnummal R, Jayakumar R, Sabitha M. Comparative anti-psoriatic efficacy studies of clobetasol loaded chitin nanogel and marketed cream. Eur J Pharm Sci. 2017;96:193-206.

Parhi R. Chitin and Chitosan in Drug Delivery. In: Crini G, Lichtfouse E, editors. Chitin and Chitosan Applications in Food, Agriculture, Pharmacy, Medicine and Waste water treatment. Cham: Springer International Publishing; 2019. p. 175-240.

Parhi R, Goli VVN. Design and optimization of film-forming gel of etoricoxib using research surface methodology. Drug Deliv Translation Res. 2020;10(2):498-514.

Parhi R, Suresh P, Patnaik S. Formulation optimization of PVA/HPMC cryogel of Diltiazem HCl using 3-level factorial design and evaluation for ex vivo permeation. J Pharm Investig. 2015b;45(3):319-27.

Parhi R, Suresh P, Patnaik S. Physical means of stratum corneum barrier manipulation to enhance transdermal drug delivery. Cur Drug Deliv. 2015a;12(2):122-38.

Parhi R, Suresh P, Patnaik S. Transdermal delivery of diltiazem hydrochloride from Poloxamer-HPMC Gel: in vitro, ex vivo, and in vivo Studies. Drug Deliv Lett. 2015c;5(3):163-72.

Parhi R, Suresh P. Transdermal delivery of diltiazem HCl from matrix film: Effect of penetration enhancers and study of antihypertensive activity in rabbit model. J Adv Res. 2016;7(3):539-50.

Parhi R. Development and optimization of pluronic® F127 and HPMC based thermosensitive gel for the skin delivery of metoprolol succinate. J Drug Deliv Sci Technol. 2016;36:23-33.

Parhi R. Drug delivery applications of chitin and chitosan: a review. Environ Chem Lett. 2020a;18:577-94.

Parhi R. Recent Advances in the Development of Semisolid-dosage forms. In: Beg S, Rahman M, Imam SS, Alruwaili NK, Al Robaian M, Panda SK, editors. Pharmaceutical Drug Product Development and Process Optimization, Boca Raton: Apple Academic Press (CRC); 2020b. p. 125-90.

Park JK, Chung MJ, Choi HN, Park YI. Effects of the molecular weight and the degree of deacetylation of chitosan oligosaccharides on antitumor activity. Int J Mol Sci. 2011;12(1):266-77.

Paşcalău V, Bogdan C, Pall E, Matroş L, Pandrea S-L, Suciu M, et al. Development of BSA gel/Pectin/Chitosan polyelectrolyte complex microcapsules for Berberine delivery and evaluation of their inhibitory effect on *Cutibacterium acnes*. React Funct Polym. 2020;147:104457.

Patil SB, Inamdar SZ, Das KK, Akamanchi KG, Patil AV, Inamadar AC, et al. Tailor-made electrically-responsive poly(acrylamide)-graft-pullulan copolymer based transdermal drug delivery systems: Synthesis, characterization, in-vitro and ex-vivo evaluation. J Drug Deliv Sci Technol. 2020;56(Part A):101525.

Patil SB, Inamdar SZ, Reddy KR, Raghu AV, Soni SK, Kulkarni RV. Novel biocompatible poly(acrylamide)-grafted-dextran hydrogels: Synthesis, characterization and biomedical applications. J Microbiol Methods. 2019;159:200-10.

Pegg AM. The application of natural hydrocolloids to foods and beverages. In: Baines D, Seal R, editors, Natural Food Additives, Ingredients and Flavourings. Cambridge; Woodhead Publishing: 2012. p. 175-96.

Prabaharan M. Chitosan derivatives as promising materials for controlled drug delivery. J Biomater Appl. 2008;23(1):5-36.

Prajapati SK, Jain A, Jain A, Jain S. Biodegradable polymers and constructs: A novel approach in drug delivery. Eur Polym J. 2019;120:109191.

Qian S, Chen Y, Gui S, Wang J, Zhou Y, Chen L. Enhanced penetration of sinomenine fomulations following skin pretreatment with a polymer microneedle patch. Lat Am J Pharm. 2014;33(3):464-9.

Rajesh N, Siddaramaiah. Feasibility of xanthan gum-sodium alginate as a transdermal drug delivery system for domperidone. J Mater Sci Mater Med. 2009;20(10):2085-9.

Rebouh S, Lefnaoui S, Bouhedda Yahoum MM. Artificial neural network-genetic algorithm based prediction of metformin diffusion from transdermal films based on biopolymers for diabetes disease treatment. Published. In: 2019 International Conference on Applied Automation and Industrial Diagnostics (ICAAID), Date of Conference: 25-27 Sept. 2019.

Reshmi CR, Suja PS, Manaf O, Sanu PP, Sujith A. Nanochitosan enriched poly -caprolactone electrospun wound dressing membranes: A fine tuning of physicochemical properties, hemocompatibility and curcumin release profile. Int J Biol Macromol. 2018;108:1261-72.

Ribeiro DML, Carvalho Júnior AR, Vale de Macedo GHR, Chagas VL, Silva LS, Cutrim BS, et al. Polysaccharide-based formulations for healing of skin-related wound infections: lessons from animal models and clinical trials. Biomolecules. 2020;10(1):63.

Roberfroid MB. Introducing inulin-type fructans. Br J Nutr. 2003;93(Suppl 1):13-26.

Sabitha M, Rejinold NS, Nair A, Lakshmanan VK, Nair SV, Jayakumar R. Development and evaluation of 5-fluorouracil loaded chitin nanogels for treatment of skin cancer. Carbohydr Polym. 2013;91(1):48-57.

Saboktakin MR, Akhyari S, Nasirov FA. Synthesis and characterization of modified starch/polybutadiene as novel transdermal drug delivery system. Int J Biol Macromol. 2014;69:442.

Sadeghia M, Ganjia F, Taghizadehb SM, Daraei B. Iranian preparation and characterization of rivastigmine transdermal patch based on chitosan microparticles. Iran J Pharm Res. 2016;15(3):283-94.

Saidin NM, Anuar NK, Affandi MMRMM. Roles of polysaccharides in transdermal drug delivery system and future prospects. J Appl Pharm Sci. 2018;8(3):141-57.

Santos LF, Correia IJ, Silvaa AS, Mano JF. Biomaterials for drug delivery patches. Eur J Pharm Sci. 2018;118:49-66.

Sarphie DF, Johnson B, Cormier M, Burkotha TL, Bellhouse BJ. Bioavailability following transdermal powdered delivery

(TPD) of radiolabeled inulin to hairless guinea pigs. J Control Release. 1997;47(1):61-9.

Selzer D, Abdel-Mottaleb MMA, Hahn T, Schaefer UF, Neumann D. Finite and infinite dosing: Difficulties in measurements, evaluations and predictions. Adv Drug Deliv Rev. 2013;65(2):278-94.

Shamsi M, Zahedi P, Ghourchian H, Minaeian S. Microfluidic-aided fabrication of nanoparticles blend based on chitosan for a transdermal multidrug delivery application. Int J Biol Macromol. 2017;99:433-42.

Shankrayya M, Basavaraj S, Sreenivasa GM. Evaluation of semi synthetic guar gum derivative for the development of transdermal patches of aceclofenac. Res J Pharm Biol Chem Sci. 2016;7(6):2485-91.

Shin LGH, Park HJ. Solid lipid nanoparticles loaded thermoresponsive pluronic-xanthan gum hydrogel as a transdermal delivery system. J Appl Polym Sci. 2018;135(11):46004.

Shinde UA, Modani SH, Singh KH. Design and development of repaglinide microemulsion gel for transdermal delivery. AAPS PharmSciTech. 2018;19(1):315-25.

Shu Z, Cao Y, Tao Y, Liang X, Wang F, Li Z, et al. Polyvinylpyrrolidone microneedles for localized delivery of sinomenine hydrochloride: preparation, release behavior of in vitro &in vivo, and penetration mechanism. Drug Deliv. 2020;27(1):642-51.

Singh N, Upasani CD. Skin permeation of zidovudine from crosslinked chitosan film containing terpene enhancers for transdermal use. Middle East J Sci Res. 2013;16(8):1027-1036.

Singh RS, Kaur N, Kennedy JF. Pullulan and pullulan derivatives as promising biomolecules for drug and gene targeting. Carbohydr Polym. 2015;123:190-207.

Singh S, Parhi R, Garg A. Formulation of topical bioadhesive gel of aceclofenac using 3-level factorial design. Iran J Pharm Res. 2011;10(3):435-45.

So HP, Hyuk SS, Soo NP. Novel pH-responsive hydrogel based on carboxymethyl cellulose/2- hydroxyethyl acrylate for transdermal delivery of naringenin. Carbohydr Polym. 2018;200:341-52.

Suksaeree J, Karnsopa P, Wannaphruek N, Prasomkij J, Panrat K, Monton C, et al. Use of isolated pectin from a cissampelos pareira-based polymer blend matrix for the transdermal delivery of nicotine. J Polym Environ. 2018;26(9):3531-9.

Szymańska E, Winnicka K. Stability of chitosan-a challenge for pharmaceutical and biomedical applications. Mar drugs. 2015;13(4):1819-46.

Tak HY, Yun YH, Lee CM, Yoon SD. Sulindac imprinted mungbean starch/PVA biomaterial films as a transdermal drug delivery patch. Carbohydr Polym. 2019;208:261-4.

Tezel A, Sens A, Mitragotri S. Description of transdermal transport of hydrophilic solutes during low-frequency sonophoresis based on a modified porous pathway model. J Pharm Sci. 2003;92(2):381-93.

Thoorens G, Krier F, Leclercq B, Carlin B, Evrard B. Microcrystalline cellulose, a direct compression binder in a quality by design environment-A review. Int J Pharm. 2014;473(1-2):64-2.

Tripodo G, Trapani A, Torre ML, Giammona G, Trapani G, Mandracchia D. Hyaluronic acid and its derivatives in drug delivery and imaging: Recent advances and challenges. Eur J Pharm Biopharm. 2015;97(Pt B):400-16.

Vasvani S, Kulkarni P, Rawtani D. Hyaluronic acid: A review on its biology, aspects of drug delivery, route of administrations and a special emphasis on its approved marketed products and recent clinical studies. Int J Biol Macromol. 2020;151:1012.

Vishwanath B, Shivakumar HR, Sheshappa RK, Ganesh S, Prasad P, Guru GS, et al. In-Vitro release study of metoprolol succinate from the bioadhesive films of pullulan-polyacrylamide blends. Int J Polym Mater Polym Biomater. 2012;61(4):300-7.

Vora LK, Courtenay AJ, Tekko IA, Larrañeta E, Donnelly RF. Pullulan-based dissolving microneedle arrays for enhanced transdermal delivery of small and large biomolecules. Int J Biol Macromol. 2020;146:290-8.

Wang PH, Lu W. Biomimetic PDMS-gum Arabic hybrid biopolymer adhesive for drug delivery, 22nd International Conference on Miniaturized Systems for Chemistry and Life Sciences, MicroTAS, 2018. p. 544-6.

Xie J, Ji Y, Xue W, Ma D, Hu Y. Hyaluronic acid-containing ethosomes as a potential carrier for transdermal drug delivery. Colloids Surf, B. 2018;172:323-9.

Yalcintas EP, Ackerman DS, Korkmaz E, Telmer CA, Jarvik JW, Campbell PG, et al. Analysis of in vitro cytotoxicity of carbohydrate-based materials used for dissolvable microneedle arrays. Pharm Res. 2020;37(3):33.

Yang H, Wu X, Zhou Z, Chen X, Kong M. Enhanced transdermal lymphatic delivery of doxorubicin via hyaluronic acid based transfersomes/microneedle complex for tumor metastasis therapy. Int J Biol Macromol. 2019;125:9-16.

Yee CM, Hasan ZAA, Ahma N, Hazimah AH. Development of carrageenan hydrogel as a sustained release matrix containing tocotrienol-rich palm-based vitamin E. J Oil Palm Res. 2016;28(3):373-86.

Yue Y, Zhao D, Yin Q. Hyaluronic acid modified nanostructured lipid carriers for transdermal bupivacaine delivery: In vitro and in vivo anesthesia evaluation. Biomed Pharmacother. 2018;98:813-20.

Zhang YQ, Xiong WD, Mi ZY, Ma Z, Li XL. Adhesive and in vitro release properties of the konjac glucomannan and xanthan gum mixture gel film, 4th International Conference on Bioinformatics and Biomedical Engineering, ICBBE. 2010; 5516579.

Zhou W, Liu W, Zou L, Liu W, Liu C, Liang R, et al.Storage stability and skin permeation of vitamin C liposomes improved by pectin coating. Colloids Surf B Biointerfac. 2014;117:330-7.

Zimon RL, Lerman G, Elharrar E, Meningher T, Barzilai A, Masalha M, et al. Ultrasound targeting of Q-starch/miR-197 complexes for topical treatment of psoriasis. J Control Release. 2018;284:103-11.

Received for publication on 02nd September 2020
Accepted for publication on 14th March 2021