Advances in Colloid and Interface Science 284 (2020) 102251

Contents lists available at ScienceDirect

Advances in Colloid and Interface Science

journal homepage: www.elsevier.com/locate/cis

Historical Perspective

Drug nanodelivery systems based on natural polysaccharides against different diseases

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ARTICLE INFO

Article history:
27 August 2020
Available online 1 September 2020

Keywords:
Natural polysaccharides
Drugs
Nanocarriers
Diagnosis
Cancer
Diabetes
HIV
Malaria
Cardiovascular
Respiratory diseases
Skin diseases

ABSTRACT

Drug nanodelivery systems (DNDSs) are fascinated cargos to achieve outstanding therapeutic results of various drugs or natural bioactive compounds owing to their unique structures. The efficiency of several pharmaceutical drugs or natural bioactive ingredients is restricted because of their week bioavailability, poor bioaccessibility and pharmacokinetics after orally pathways. In order to handle such constraints, usage of native/natural polysaccharides (NPLS) in fabrication of DNDSs has gained more popularity in the arena of nanotechnology for controlled drug delivery to enhance safety, biocompatibility, better retention time, bioavailability, lower toxicity and enhanced permeability. The main commonly used NPLS in nanoencapsulation systems include chitosan, pectin, alginates, cellulose, starches, and gums recognized as potential materials for fabrication of cargos. Herein, this review is centered on different polysaccharide-based nanocarriers including nanoemulsions, nanohydrogels, nanoliposomes, nanoparticles and nanofibers, which have already served as encouraging candidates for entrapment of therapeutic drugs as well as for their sustained controlled release. Furthermore, the current article explicitly offers comprehensive details regarding application of NPLS-based nanocarriers encapsulating several drugs intended for the handling of numerous disorders, including diabetes, cancer, HIV, malaria, cardiovascular and respiratory as well as skin diseases.

Contents

Abbreviations: AIDS, Acquired immune deficiency syndrome; BJO, *Brucea javanica* oil; CAP, Cellulose acetate phthalate; CVD, Cardiovascular diseases; CMC, Carboxymethyl cellulose; CNCs, Cellulose nanocrystals; CS, Chitosan; CF, Cystic fibrosis; DE, Degree of esterification; DDS, Drug delivery system; GIT, Gastrointestinal tract; GRAS, Generally recognized as safe; HAO, Hyaluronan oligosaccharides; HIV, Human immune deficiency viruses; IDF, International Diabetes Federation; NO, Nitric oxide; NPLS, Natural polysaccharides; O/W, Oil in Water; PEG, Polyethylene glycol hydrogel; TB, Tuberculosis; W/O, Water-in-oil; WHO, World health organization.

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https://doi.org/10.1016/j.cis.2020.102251
0001-8686/

1. Introduction

Drug nanodelivery systems (DNDSs) have been now considered as an effective strategy for enhancing the pharmacological and therapeutic attributes of drugs. These systems aid not only to overcome the issues of solubility associated to the drugs but also behave as nanocarriers for handling and transportation of drugs at targeted sites. For getting a desired therapeutic outcome, a drug demands an appropriate delivery system in order to ensure its specific controlled release at specific target. However, nanotechnology-based drug delivery systems offer promising ways out in development of suitable cargos for effective delivery of drugs against several diseases and also for resolving the challenges allied to the drugs including their poor bioavailability, side effects, low solubility, therapeutic potency, poor intestinal absorption mechanism by degradation, and plasma inconsistency of drugs [1]. DNDSs are basically drug cargos such as nanoemulsions, nanoliposomes, nanohydrogels, nanoparticles and nanofibers which have been fetched much attentions for medical purposes due to their capability to entrap or hold the drugs within their core and carry them to the target sites; also they consist of a very high surface to mass ratio which enhances their efficiency. Thereby, DNDSs are widely used for the diagnosis and treatment of infectious diseases [2].

In general, nanoencapsulated cargos are characterized as nanoparticles with sizes < 100 nm [3], also considered as nano-scale cargos mainly in the area of cosmetics and pharmaceutics [4]. These nanocargos entail of at least two constituents; one of which is the bioactive drug and the other as encapsulating material [5]. For successful fabrication of DNDSs such as nanoparticles, selection of encapsulating polymers is an important parameter. Biopolymers provide protection to the drugs from environmental factors that cause degradation in the gastrointestinal tract (GIT) as well as more efficiency while delivering the drugs in different parts of the inflammatory sites [6].

Amongst the biopolymers, NPLS are the most abundant and naturally available polymers which have gained a great popularity over the synthetic polymers because of their diverse functions. In addition, NPLS are documented as generally recognized as safe (GRAS) for targeting delivery because of their superior properties including non-toxicity and non-reactogenicity, easily available at large scale and relatively less expensive remarkable biocompatibility and extraordinarily biodegradability [7] . Because of their unique characteristics, polysaccharides are extensively used as excipients in formulations of nanoencapsulated cargos and also for pharmaceutical and clinical uses [8]. Their physicochemical properties also offer an expedient way for biochemical amendment where needed, as well as permitting comfortable production of nanoencapsulated cargos for transportation of drugs. In addition, particular NPLS are able to afford targeting mechanisms owing to site specific enzymatic degradation, receptors affirmation and binding, environmental trigging, mucosal adhesion and transportation [9].

Furthermore, while using NPLS for DNDSs, drugs can be immersed or bound to the outer layer [10]; thereby, they may have the ability to increase the stability and solubility of therapeutic drugs. So far, researchers are showing their keen interest in using NPLS hardies including chitosan, pectin, alginate, starches, cellulose and gums for fabrication of nanoencapsulated cargos, expressing their unique therapeutic effects for ailments such as cancer, diabetes, HIV, cardiovascular diseases [11,12]. In the current review, we have tried to provide an inclusive enlightenment of the subsequent features: (i) a brief introduction to NPLS as encapsulants/carriers; (ii) a summary of nanoencapsulation techniques applied for fabrication of polysaccharide-based nano-cargos; (iii) a brief illustration of nano cargos such as nanoemulsions, nanoliposomes, nanohydogels, nanoparticles and nanofibers; 4) review of the natural polysaccharide-based nano cargo used for the treatment of several diseases. Overall, this article encompasses the recent literature based on evaluated nanocarriers using NPLS for the treatment of several ailments.

2. Natural polysaccharides used in DNDSs

Advantageously, NPLS are commonly functional macromolecular biopolymers isolated from several origins, including plants (i.e., cellulose, pectin), animals (e.g. chitosan, chondroitin), microbial (i.e., xanthan gum, pullulan, dextran) and algal (e.g. alginate) [3], which are usually composed of more than ten monosaccharide units by glyosidic bonding/linkages in linear or branched chains [13]. They are generally considered highly safe, stable, biocompatible, and inexpensive biomaterials which can be easily modified and processed according to the required designs and structures for further application in several areas including agricultural, food, nutrition, membranes, chemical engineering, biomedical and pharmaceutical [14].

In pharmaceutical and biomedical areas, NPLS have efficaciously gained much considerations because of their distinctive biological activities including antitumor, anti-proliferation, antioxidant, anticoagulant and hypoglycemic properties [15]. Apart from these unique characteristics, NPLS are being used as excipient candidates for DNDSs due to having surface groups (ligands), which play vital roles in binding with the cell receptors and engaged in the controlled and targeted conveyance of therapeutic drugs. Furthermore, NPLS are those biomaterials which have a unique ability (cellular physiology) that is responsible to giving them usually amazing biodegradability, biocompatibility and low toxicity [16]. In short, the capabilities regarding NPLS mentioned above are clearly convincing that they can be exploited in the construction of DNDSs. Additionally, **Fig. 1** depicts several bioactivities of polysaccharides that facilitate numerous health benefits.

As emphasized, because of their surface assemblies including hydroxyl, carboxyl and amino groups, NPLS can be simply modified either chemically or biochemically, ensuing a number of functional derivatives. Particularly, these derivable groups play an effective role in forming non-covalent bonding in combination with living muscles including mucous membranes and epithelia, resulting in bioadhesion [17]. For instance, NPLS include pectin, starch, alginate and chitosan are mainly recognized as excellent bioadhesive matrices. Drug-loaded

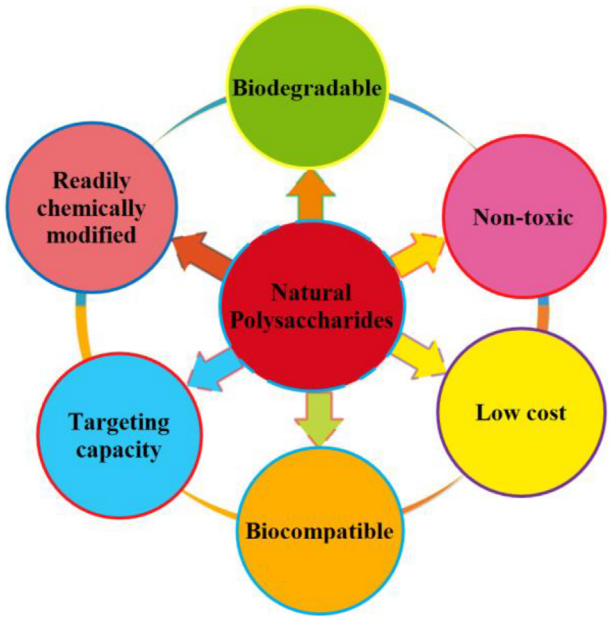

Fig. 1. Some key benefits of natural polysaccharides in the drug delivery systems.

nanocarriers prepared through bioadhesive polysaccharides could enhance the resistance time as well as cellular absorbance/uptake of the drugs. All these accumulated evidences about the superior biological and physiochemical aspects of polysaccharides are convincing that they could be used as promising biomaterials in future [11].

In recent years, many researches have successfully studied NPLS and their derivatives for potent functions (as emulsifiers, stabilizers, and thickener agents) in the formulation of different nanocarriers including nanoemulsions, nanoliposomes, nanohydrogels, nanoparticles, nanofibers, etc [18,19]. NPLS which are predominantly involved in the formation of nano cargos for DNDSs have been discussed below in order to elaborate their physiochemical and molecular characteristics.

2.1. Chitosan

Chitosan (CS), a well-known NPLS extracted from the crabs and shrimp, is a linear cationic hetro-polysaccharide comprised of β-1,4-linked 2-amino-2-deoxy-glucopyranose and 2-acetamido-2-deoxy-β-D-glucopyranose residues [9]. It has been declared well as a GRAS material by the US Food and Drug Administration (FDA) and also considered as second amplest natural biopolymer after cellulose because it has several strong potentials such as biocompatibility, non-toxicity, antibacterial activity, biodegradability, film forming and emulsifying characteristics. Due to these outstanding properties, CS has found extensive pharmaceutical and clinical applications, in wounds curing and drug delivery systems [20]. Therefore, CS has drawn many considerations for DNDSs as well as delivery of bioactive compounds. The amino functional groups in CS structure are of great interest for biochemical adjustments and electrostatic interactions in DNDSs and they are responsible for providing solubility in slightly acidic solutions to this polymer [21].

On the other hand, even though it has amino groups having positive charges, CS holds very little immunogenicity activity instead of synthetic polymers; thereby, is being used as a bioadhesive material that sticks onto the mucosal cells (negatively charged) and also enhances the withholding characteristics as well as penetrates inside the cells [22]. CS positive charges also empowers it to expand the opening of epithelial tightfitting intersections and broaden paracellular passageways corridors, supporting transportation of drugs comprising hydrophilic compounds into the targeting tissues [23].

Recently, CS has been extensively used as a carrier/wall material for fabrication of nanocarriers, used for DNDSs against several diseases. A study demonstrated that curcumin was incorporated into CS-based polyelectrolyte complexes, which showed an enhanced encapsulation efficiency, yield and loading capacity of (64–76%), (50–72%), (20–26%), respectively. These curcumin loaded CS-based nanoparticles have shown significant decline trend in hyperglycemia within a week throughout orally administration [24]. In another study, liraglutide (an antidiabetic drug) was incorporated into CS coated calcium-alginate nanoparticles, which showed fantastic encapsulation efficiency (92.4%) for liraglutide; findings of this study also revealed that CS coated calcium-alginate nanoparticles containing liraglutide had a great potential for management of diabetes [25]. In another research, Saesoo and his team encapsulated curcumin into CS-based nanoliposomes, which exhibited a significant loading of curcumin leading to a better nanostructure than conventional structures of vaginal administration; phospholipid-CS hybrid nanoliposomes encouraging cell entry for drug delivery in contradiction of cervical cancer [26]. However, many studies have been successfully conducted on CS-based nanocarriers encapsulating therapeutic drugs used in the healing of different diseases, e.g. resveratrol loaded into CS-based nanofibers for cervical cancer [10], and phenytoin encapsulated into CS-based nanohydrogels against skin diseases [27].

2.2. Alginates

Alginates are non-toxic and linear anionic, soluble in water NPLS, constituted of two uronic acids comprising (1–4)-linked- α-L-guluronate and β-D-mannuronate, which are commonly present in brown seaweed [28]. Alginates are present in the market with various formulations based on the purity for number of usages. Among alginates, sodium alginate and calcium alginate have gained more popularity as encapsulants because they have divalent cations which confer them interesting properties in fabrication of DNDSs. These both are considered a better choice for nanoencapsulation of drugs due to their eco-friendly abilities such as highly safe, easy in production, non-toxic behavior, and excellent biocompatibility [25]. These alginates are highly recognized for production of nanocarriers such as nanohydrogels, exploited as a drug cargo in GIT route [14].

Because of the occurrence of divalent cations, e.g., calcium ions, such biopolymers can produce gel in liquid suspensions at the lowest pH values. Alginate is also able to produce gels due to the potent ionic interfaces among the guluronic acid residues and the calcium ions [29]. Transportation of drugs to the targeted sites thru alginate-based hydrogels is basically a pH-based process. Incorporated drugs inside the alginate (encapsulant) shrink in an acidic environment called gastric environment without releasing inside the stomach. As, it reaches to the abdominal region, the pH upsurges and so ensures of swelling of the biopolymer that enables its quick collapse and the consequent releasing of drug. Recently, alginates are being broadly used alone or blended with other polysaccharides, including chitosan, pectin and carrageenan for numerous DNDSs against a number of diseases. Doxorubicin, is one of the supreme and frequently used chemotherapeutic drugs, which recently has gained much attentions due to its therapeutic potential as anti-cancer agent [30]. As an example, Zhou and his coworkers prepared doxorubicin-loaded alginate nanohydrogels with very narrower size distribution, which exhibited best capacity for controlled release against tumor-specific intracellular triggered release of doxorubicin [14]. Another interesting study described that incorporation of insulin into alginate-based nanoparticles lowered the blood sugar level of diabetic rats up to 40% with a constant hypoglycaemic consequence for 18 h [31].

2.3. Pectins

Pectins are known for anionic and natural biopolymers and one of the most popular linear polysaccharides, which are composed of α-(1–4)-D-galacturonic acid with some methyl esters and L-rhamnose groups. The degree of esterification (DE) is a crucial parameter that affects different attributes of pectins. Pectins are usually classified into two main classes of low methoxyl pectin (LMP, DE<50%) and high methoxyl pectin (HMP, DE > 50%) on the basis of DE as well as number of methoxyl groups. Pectin is recommended as a promising encapsulant/carrier in the nanoencapsulation process, owing to its exceptional characteristics such as an outstanding stabilizer and a virtuous wall material that offers proficient binding abilities [3]. Also, pectin is recognized as non-toxic and non-digested in the upper side of GIT by gastric enzymes and considered less soluble in such conditions. Though, pectin is totally absorbed and digested inside the colon surroundings through pectinolytic enzymes that are formed via colonic microflora [11].

Additionally, pectins also have different hydrophobicity values based on methoxylation; for example, HMP is highly hydrophobic and has the capability to intermingle with hydrophobic bioactive compounds. Therefore, these have successfully been gained much more interest as a carrier and playing an important character in interaction with hydrophobic bioactive compounds; for instance antibiotics belong to the fluoroquinolone's family can improve the entrapment of drugs into the pectin-based carriers and deliver a sustained and controlled releasing profile [32].

The above given illustrations confer role of pectin in development of nanocarriers for transdermal administration of drugs which is considered to be safe. Pectins are widely used in fabrication of drug-loaded nanocarriers i.e. nanoemulsions, nanoliposomes, and nanoparticles for controlled drug release, because it has the ability to constrain the development of cancer cells and encourage their apoptosis, enabling its application in the pharmaceutical industry. Furthermore, pectin-based drug cargoes have also been prepared which are loaded with different therapeutic drugs against several diseases such as nanoemulsions loaded with curcumin for cancer treatment [33], nanoparticles loaded with cefazolin for wound healing [1] and nanoparticles loaded with metformin for diabetes treatments [34].

Neohesperidin is a flavanone glycoside, which has a wide range of strong biological capacities including anticancer, anti-allergic, anti-diabetic, and anti-inflammation properties [35]. As an example, it was concluded that pectin-based nanoliposomes loaded with neohesperidin were found to be an excellent candidate, exhibiting a controlled release of drug inside the GIT environments. These findings also revealed that pectin-based nanoliposomes improved the cellular uptake inside the surroundings of colonic epithelial cells [11]. Curcumin, a polyphenolic compound, is well known for its broad spectrum of medicinal benefits in the last few decades [36], because of its significant biological activities such as anticancer properties [37]. In another investigation, pectin-based nanoparticles comprising curcumin were successfully prepared with encapsulation efficiency around 90%, which exhibited significant intake by cancer cells due to controlled release of curcumin [33].

2.4. Cellulose

Cellulose, one of the extreme acknowledged NPLS in the biosphere, is extensively obtained from the cell walls of many algae, bacteria, plants, and fungi [38]. It is structurally comprised by D-glucopyranose ring components which are organized in a specific way; e.g., C1 atom from one glucose circle and C4 from the head-to-head circle are covalently merged among each other, thereby, it reveals the lowermost energy conformation. Its complete assembly is made via β-1, 4-glycosidic linkages [39]. However, cellulose is vastly documented as a high biocompatible, superior biodegradable, low toxic, and GRAS with remarkable physical, mechanical and chemical characteristics in the arena of medical sciences, which makes it an appropriate candidate for successful entrapment and conveyance of drugs. Nevertheless, natural form of cellulose is still poorly soluble in aqueous-based suspensions, which is a major constraint that limits its further applications in the food and nutraceutical products. By overcoming this problem and enhancing its application as a wall material/carrier, different modified celluloses are prepared through physical, chemical or biochemical methods [40]. A variety of modified celluloses such as cellulose nanocrystals (CNCs), cellulose acetate, methylcellulose, cellulose ethers, nanofibrillar cellulose (NFC), hydroxypropyl celluloses, and carboxymethyl cellulose (CMC) are available in the market for nanoencapsulation of drugs and their delivery on controlled targeted sites against different diseases. Owing to functional attributes, these modified forms of cellulose are being used as thickener agents, stabilizers, binders, and tablet fillers with drug or bioactive compounds as well as used for fabrication of nanocarriers which are loaded with therapeutic drugs against diseases. For instance, Ntoutoume and co-workers fabricated curcumin-loaded CNCs, which exhibited significantly 3-4 times more activity in contradiction of HT-29, PC-3, and DU125 cancer line cells instead of curcumin alone [41].

Phycobiliprotein, a seaweed bioactive compound, is known to have ant-aging, anti-inflammatory, angiotensin and hepatoprotective potentials [42]. In a study, polyethylene adsorbed CNCs were used to fabricate nanoliposomes loaded with phycobiliprotein, which showed controlled release of phycobiliprotein in GIT conditions. It was reported that these CNC-coated nanoliposomes remarkably enhanced stability of drugs in digestive environments [43]. In another investigation, chloroquine was incorporated into sodium CMC-based nanoparticles for treatment of rheumatoid arthritis. This formulation was topically used in disease model rats for one-month study, which significantly exhibited better results than control group. Also, it was concluded that chloroquine-loaded nanoparticles exhibited a significant role in decreasing the bone destruction. It was also identified that this formulation was more effective for treatment of rheumatoid arthritis and it exhibited a wide range of advantageous applications against topical oral chloroquine adverse effects [44].

2.5. Starches

Starches are almost exclusively promising NPLS enclosing a larger molecular weight biopolymer formed by a large chain of glucose units allied through glucosidic bonds [45]. Chemically, starches are classified into two prime kinds: amylopectin and amylose. Amylose is essentially a linear (~99%) starch polymer encompassing α 1, 4- linkages having (~1%) branched joints associated via α-1,6-linkages; however, it subsidizes most of the amorphous piece of starch. On the other side, amylopectin is a highly branched starch consisting of (95%) α-1,4 linked spine and having (5%) α-1,6 linkages of 20-30 glucose units; thus, it supports primarily to the external crystal-like structures of starches capsules [18].

Generally, native starches have attracted applications in controlled release of drugs because of their wonderful advantages such as GRAS materials, excellent biocompatibility, non-toxicity, inexpensive, enhancing drug solubility and storage capacity. However, native starches are less beneficial due to some limitations such as lower emulsifying capability. To circumvent such issues and to achieve desired functionalities of starches, their structures are modified through diverse approaches including enzymatic, biochemical, chemicals and physical methods [46]. Chemical modifications are recognized as significant tools to increase the reactive sites to intermingle with drug molecules and thus, modified starches can easily be absorbed in GIT surroundings. Usually, native starches are easily cross linked, oxidized, acetylated, hydroxypropylated and partially hydrolyzed particles in order to obtain modified starches, which have shown significant outcomes during drug delivery. Several modified starches such as dextrins, maltodextrins, and OSA modified starches are available in the market for DNDSs on controlled targeted sites against different diseases [47,48]. Because of

their well-designed structures, modified starches are being used for fabrication of different nanocarriers which are loaded with therapeutic drugs against diseases in the last decades [49].

2.6. Gums

Gums are mostly water soluble NPLS which are extracted from various sources; such as Arabic gum from plant exudates, guar gum from seed gums, carrageenans from sea weed gums, and xanthan gum from microbial exudates gums [19]. Their structures are comprised of heterogeneous sugar items including xylose, uronic acids, glucose, rhamnose, mannose, arabinose and galactose. There is a wide class of gums which have evoked tremendous intentions especially in the food and pharmaceutical sectors because of their exceptional functional attributes such as biodegradability, non-toxicity, inexpensiveness, biocompatibility, and GRAS materials for human consumption [50].

Gums comprise branched polymeric structures able to produce 3D molecular structure, which can offer outstanding adhesive and cohesive characteristics making them useful to interact with drugs or bioactive compounds [51]. In addition, gums are effectively being used as protective colloids, carriers, thickeners, emulsifiers, stabilizers and tablet binders. Gums are commonly involved with several encapsulating biopolymers to fabricate interpenetrating polymeric complexes that can deliver robust thermal and mechanical qualities to a number of fragile hydrogels. Gums have also been technologically advanced in association with pH-sensitive biopolymers and revealed potent competencies during target release profile via nanodrug delivery. As a result, these have shown inadequate digestion as well as minimum absorption in the *in vivo* models; thereby, gums have the capability to boost up the precise and sustained drug release of DNDSs. Hence, owing to their marvelous properties, gums are being widely applied as encapsulating agents in fabrication of nanocarriers loaded with drugs or bioactive compounds used for treatment of several ailments [52].

For instance, Tan and coworkers [51] encapsulated curcumin into Arabic gum-chitosan based nanoparticles, which exhibited controlled release in stimulated GI surroundings, and they suggested that such model carrier could be used in targeted DNDSs. In an interesting work held in 2011 [53], diverse solvents were used in order to explore a comparative drug loading ability where dichloromethane exhibited exceptional outcomes. This study also demonstrated that cross linked combination of guar gum with glutaraldehyde delayed releasing process of tamoxifen which ultimately made this system more appropriate for sustained delivery of tamoxifen citrate. In another research, apigenin, an antidiabetic drug, was incorporated into hydrogels stabilized by gellan gum-chitosan to evaluate its wound healing effect against diabetes. The findings verified that gellan gum-chitosan hydrogels released 96.11% of apigenin within 24 hours. Also, it was proved that application of fabricated gellan gum-chitosan based hydrogels containing apigenin seemed to be extremely suitable in the case of wound curing due to its awe-inspiring properties of moist nature, biocompatibility, antioxidant effectiveness and biodegradability [50].

3. Fabrication of different polysaccharide-based nanocarriers

Typically, there are two major strategies including top-down and bottom-up approaches, which have gained more recognitions by several researchers and being used for the construction of NPLS-based nanocarriers [17], as summarized in Table 1. Bottom-up methods consist of self-organization of those encapsulating materials used for fabrication of carriers which can be affected through numerous features like ionic strength, dissolving temperature, variations in pH and composition [54]. In this sense, coacervation, nanoprecipitation, inclusion complexion, and layer-by-layer approach are some examples of bottom-up techniques [55]. These techniques are more welcomed in the domain of nanotechnology owing to their better control on particle size as well as on finally structures shaped of carriers; they also need very minute amount of energy for processing [56]. On the other hand, top-down techniques includes the utilization of specific devices that allow physical designing as well as reduction in size of fabricated particles that can be used for needed and useful purposes [54]. There are several practices such as homogenization, sonication, extrusion, and emulsification-solvent evaporation that fall under the shadow of top down techniques. It is obviously proved that the bottom-up approaches are more advantageous instead of top-down processes because of rapid and wide range of rearrangements in these processes leading to the fabrication of nano cargos having minor defects and extra reliable chemical assembly [17].

In general, nanoencapsulation systems show surprising benefits in the field of food and pharmaceuticals [4]. They are able to encapsulate amphiphilic compounds i.e., both hydrophobic and hydrophilic compounds. Regardless of their fabrication methods, polysaccharide-based nanocarriers are mainly divided into following; nanoemulsions, nanoliposomes, nanofibers, nanohydrogels, and nanoparticles. These nanocarriers exhibit succeeding advantages such as less toxicity and GRAS material, higher emulsifying abilities and improved encapsulation efficiency, targeted delivery and controlled release as well as able to facilitate intestinal absorption of loaded drugs. [57]. They are briefly described in following sections.

3.1. Polysaccharide-based nanoemulsions

Nanoemulsions are colloidal mini-sized cargos, comprising two or more immiscible phases such as oil, water, and emulsifier (polysaccharide) having diameter dimensions regularly reaching from 10 to 200 nm [3] as shown in Fig. 2A. The purpose of used polysaccharides as emulsifiers is to minimize the interfacial tension among the aqueous phases and the lipid phase which ultimately reduces the droplet size [72]. They are able to stabilize the nanoemulsions for long term stability by means of steric hindrance and electrostatic forces. Therefore, polysaccharide-based nanoemulsions are recognized as efficient conveyance cargos for food functional compounds and drugs [5]. They retain extraordinary characteristics such as dynamic stability, large surface area, biodegradability, transparency, biocompatibility, tunable rheology and it is easy to prepare DNDSs for therapeutic drugs [73].

In the case of combining two immiscible phases of nanoemulsions, various approaches such as ultrasonication, homogenization, shear mixing and microfluidization are being used. As described in the previous literature, nanoemulsions are categorized into two leading classes: single emulsions and double emulsions Double emulsions ($W_1/O/W_2$) encompasses W_1/O droplets spread in a peripheral continuous water section of W_2 [3]. In such type of suspensions in which W_1 has the ability to absorb hydrophilic therapeutic bioactive compounds or drugs including colors, amino acids, polyphenols, vitamins, and minerals, displaying a number of biological activities. The most important parameter that defines the stability of nanoemulsion is droplet size; it is understood that a smaller droplet size offers more stability to the nanoemulsion system. Also, both hydrophilic and hydrophobic drugs/bioactive compounds can be nanoencapsulated within nanoemulsions fabricated via NPLS as encapsulants [74]. In broad-spectrum, various kinds of emulsions fabricated by numerous emulsification techniques reveal physiochemical properties, differences in efficiency, encapsulation and controlled release of drugs against different diseases. As an example, capsaicin, a bioactive drug consumed for curing of pain was encapsulated into chitosan and alginate-based nanoemulsions to explore *in vivo* pharmacokinetic effects in rats. Compared to control groups, the bioavailability of capsaicin-loaded nanoemulsions was significantly higher. It was also concluded that as compared to double layered nanoemulsions, triple layered nanoemulsions showed slightly increased volume of distributions [75].

In another interesting study, finasteride, an extensively used drug for treatment of benign prostatic hyperplasia was encapsulated into chitosan and polystyrene-β-poly (acrylic acid)-based nanoemulsions to

Table 1
A detailed summary on nanoencapsulated approaches used to produce polysaccharide-based nanocarriers

Approaches	Nanoencapsulation techniques	General principles	Benefits	Drawbacks	References
	Nanoprecipitation	Basically, depends on the spontaneous way of emulsification of an organic phase (inner) comprising organic solvent, bioactives and encapsulant (polymer), into the liquid phase suspension (external).	Comparatively low-priced, simply adjustable and delivers multilayers to the fabricated nanoparticles.	A very little amount of polymer is used as encapsulant, which may produce difficulties while production of final nanocarriers in the concluding suspension	[58]
	Enzymolysis and recrystallization	Involves two kinds of irregular stages: incubating polysaccharides through unbranched enzymes and retrogradation.	A simplistic and efficient practice, able to produce nanocarriers.	It has restricted applications at lab scale	[59]
	Layer by layer deposition	Widely applied in fabrication of nanocarriers composed by several multilayers and comprises alternated deposition with diverse charged polyelectrolytes round about a stimulating model.	Reasonable, a simply adoptable assembly practice; offers improved safety to lipophilic bioactives.	Very limited use at industrial level	[58]
	Coacervation	Infers liquid-liquid separation inside any suspension encompassing charged macroions, providing a phase with plenty of polymers. Polymer separation from supernatant is judged through deposition of resulted coacervate covering polymers, besides the drugs.	Provides maximum encapsulation efficacy	Over acidic circumstances, this method may degrade concentration of entrapped bioactive compounds	[60]
Bottom up methods	Polyelectrolyte complex formation	relies on the suspension made by a combination of natural polymers and polyelectrolytes with reverse charges in an aqueous suspension and their subsequent complexation is achieved by ionic bonding.	It is biocompatible and more sensitive to variations in eco-friendly circumstances.	Non-uniformity of the surface charge leads to disturbances on adsorbing properties of the PEs.	[61]
	Supercritical fluid extraction	Includes the sound mixing of cholesterol-phospholipid into the supercritical CO2 as well as precipitation method used to produce the fine lipid particles.	Accessible, safe, and cost-effective	Offers very minor yield even after employing of maximum pressures typically > 350 bar, which is not acceptable during encapsulation of mostly bioactives	[54]
	Self-assembly	Using of an enzyme pretreatment is necessary for production of short chain linear molecules which have higher molecular mobility at suitable conditions and following incubation of pretreated suspension at fixed heating temperature for rearrangement the order of molecules	Profitable, and easily available at commercial level	It has restricted applications at industrial scale	[62]
	Inclusion complexation	Usually, used for entrapment of a supra-molecular in combination with entrapped bioactive into an encapsulate (coating material) by van der Waals force and hydrogen bonding	Convenient for entrapment of unstable bioactive compounds as well as provides sophisticated encapsulation efficiency	This technique only permits limited compounds to accomplish positively encapsulation	[60]
	Ultrasonication	US is followed by the perturbation of the O/W interface and subsequent creation of fine droplets, driven by a cavitation phenomenon.	Effective, compatible and economical method at lab-scale, Offer narrow size emulsion	Limited applications at industrial scale.	[63]
	Nano spray drying	It has an advanced ultrasonic atomizer and its working principle is based on vibrating network equipment that can generate smaller particle size with smooth and fine distribution, obtained from nozzles of spray dryer.	Modest, quick, and comparatively low-priced approach	Because of few restrictions for volatile bioactives, it has restricted applications at lab scale	[64]
	Extrusion gelation techniques	In this technique, biopolymer-based suspensions pass through a nozzle and enter into gelling environment. In lab scale, the biopolymer-based suspensions are loaded into a syringe and permits across a needle inside the gelling environment to achieve gelation.	A convenient tactic that can be used for loading of both hydrophobic and hydrophilic molecules, Can be used at industrial scale	Gives larger size to the droplets, restricted applications at industrial scale	[55]
Top down methods	Membrane emulsification	Pre-emulsion is passed through a micrometric membrane with continuous flow, in order to confirm narrow size distribution.	Low shear and low energy procedure, provide smoothness distribution among particles	Low flux of the dispersed phase.	[65]
	Electrospraying	It is a technique used for production of fiber like droplets via providing an electric field.	Modest and economical approach; high loading efficiency and time saving method	Have some restrictions that limits its application on industrial scale	[66]
	Electrospinning	In this approach, electrostatic forces play an important role in development of nanosized fibers produced by electrically stimulating jet of polymeric suspensions due to the deposition on top of grounded collector.	Modest, inexpensive and versatile approaches as well as greater encapsulation proficiency.	Restrictions for their use on large scale production or on industrial scale	[66]
	Solvent demixing	Organic solvents are quickly diffused into the aqueous phase, thereby nanoemulsion is formulated in a single phase at low energy level but they offer extraordinary output of encapsulation.	Low-intensity method, reliable for creating nanometric droplets of the nanoemulsion	Relatively high concentration of surfactants is needed for this process	[67]

Table 1 (*continued*)

Approaches	Nanoencapsulation techniques	General principles	Benefits	Drawbacks	References
	High shear homogenizers	The emulsion is passed through the fine slot among the rotor and stator, drop breakage occurs because of intense shearing. Further emulsion passes through the colloid mill allow the drop size to be more reduced.	More profitable and easily scalable approach of emulsification, applied on highly viscous emulsion.	Provide limited particle size of emulsion	[68]
	Emulsion phase inversion	A method which is applied to overturn the (W/O) emulsion into (O/W) emulsion or vice versa.	Easy in use, low energy cost and are more capable to produce fine emulsion	High used quantity of oils and surfactants	[69]
	Microfluidization	This technique is basically based on the mechanism of separating an emulsion into two mainly streams that are then made to impinge on each other in the heart of the microfluidizer.	Considered an effective method and offered nanosized particle, tremendous emulsification power	High energy method, time consuming, wastage of coarse emulsion	[70]
	High-pressure homogenization	A fluid is passed through a micrometric homogenization chamber, where high pressure (50–400 MPa) is applied to compress the fluids.	Reproducibility, simple operating tools, industrial scalability, and efficient output	Demands large amounts of energy to process the fluid, high-cost	[71]

examine the retention of finasteride in dermis and epidermis pathways. Different layers of polystyrene-β-polyacrylic acid and chitosan presented polyelectrolyte constituted nanoemulsions of 350–400 nm size range. Also, they improved the drug retention in diverse skin layers and reduced finasteride passageway through the dermis [76]. Metformin, a well know antidiabetic drug, was loaded into sodium alginate-based nanoparticles, which presented outstanding drug release (100 %) within 30 min instead of bare metformin while performing *in vitro* study. Authors also claimed that metformin-loaded nanoparticles exhibited three times higher efficiency than free metformin when administrated orally in diabetic animals [29]. Similarly, metformin-loaded gum Arabic and chitosan-based nanoparticles revealed anti-hyperlipidemic and anyiglycemic effects even at a lower dose (9.2 mg metformin) instead of free metformin (150 mg/kg) during 21 days study in diabetic rats [77].

3.2. Polysaccharide-based nanoliposomes

By definition, liposomes may comprise spherical structural shapes having one or two layers wherein the internal cavity is composed by molecules (hydrophilic in nature) directed towards water suspension and bilayer membrane is composed of lipophilic ends comprising phospholipids, for example soy lecithin. In addition, liposomes are primarily categorized into two leading classes on the behalf of lipid bilayer. Those liposomes which have single lipid bilayer are called as unilamellar, and those compiled with two or more lipid bilayers are known as multilamellar [3]. Nanoliposomes are nanometric cargos (Fig. 2B), which have diametric sizes < 200 nm having a greater surface area than conventional forms of liposomes; thereby, higher energy is needed to fabricate them [78].

Various tactics (i.e., mechanical, non-mechanical) have been proposed by several researchers for the production of nanoliposome systems. For instance, non-mechanical methods encompass freeze thawing, reduction of various cleansing agent lipid micelles, injection method, freeze drying-rehydration, and reverse-phased evaporation. On the other hand, mechanical approaches include colloid mills, ultrasonication, high pressure homogenization, microfluidization and extrusion [79,80]. Additionally, modern methods including dense gas practice, cross-flow purification method, freeze-drying doubly technique, dual asymmetric centrifugation, membrane contractor technology and supercritical fluid technology are also being used to produce nanoliposomes [74].

As carriers, nanoliposomes are not very stable, as may show fluctuation in distribution of droplet size, rapid oxidation phenomenon and escape of entrapped bioactives, which limits their application. These kinds of drawbacks can be overwhelmed through coatings of biopolymeric and bio-adhesive materials nearby the nanoliposomes [81]. Furthermore, there may be several factors that could be helpful to understand how polysaccharide conjugation on the outer layers of nanoliposomes can behave as a barrier against degradation of liposomal membranes in the GIT surroundings: (i) these polysaccharides coated onto the outward layer of liposomes are able to retard the fluidity of nanoliposomal membranes, and thus improving their colloidal steadiness as well as having the capability to manage drugs release profile; (ii) polysaccharides working efficiency is based on the function of pH or enzyme sensitivity phenomenon, for instance, chitosan is poorly soluble at intestinal pH and easily soluble at gastric pH, but pectin is less soluble inside the gastric environment and easily breaks down via colonic enzymes. This mechanism is able to protect nanoliposomal cargos from gastro-intestinal surroundings or enzymatic degradation and in that way governing drugs delivery; (iii) the development of electrostatic networks among polysaccharide conjugation and phospholipids is able to retard the permeability of nanoliposomal membranes leading towards lower drug leakage [82]. Therefore, NPLS being non-toxic, biocompatible and biodegradable, such as pectin, chitosan, alginate, etc. can be applied as coatings to enhance the stability of nanoliposomes. Consequently, polysaccharide-based nanoliposomes can be applied in case of delivering the drugs on infectious spots inside the body [11]. Owing to high charge density and mucoadhesive attributes, polysaccharide-based nanoliposomes are being used as nanocarriers to enhance the stability and targeted delivery of drugs. In a research work, Haghighi and coworkers [83] fabricated pectin-based nanoliposomes encapsulating phloridzin (bioactive compound), which exhibited a greater encapsulation and stability rather than simple nanoliposomes. Also, these authors reported that pectin-based nanoliposomes loaded with phloridzin could be used as promising cargos for application in food as well as pharmaceutical industries. In another interesting study, Shishir and his colleagues successfully prepared chitosan and pectin-based nanoliposomes encapsulating neohesperidin drug in order to enable its precise conveyance inside the GIT environment. The particle size of fabricated nanoliposomes was attained having a range around 87-225 nm. They also determined that these fabricated polysaccharide-based nanoliposomes were successfully able to encapsulate 72-78% of incorporated drug in GIT surroundings as well as exhibited controlled release. These polymeric nanoliposomes enhanced the cellular uptake in the colonic epithelial cells and showed perfect biological activities [11].

3.3. Polysaccharide-based nanohydrogels

Nanohydrogels are known for their three-dimensional structure made by nanosized polymeric networks have the capacity to grasp huge amounts of liquids inside their arrangements [84], as shown in **Fig. 2C**. Nanohydrogels encompass a wide range of ever-interesting

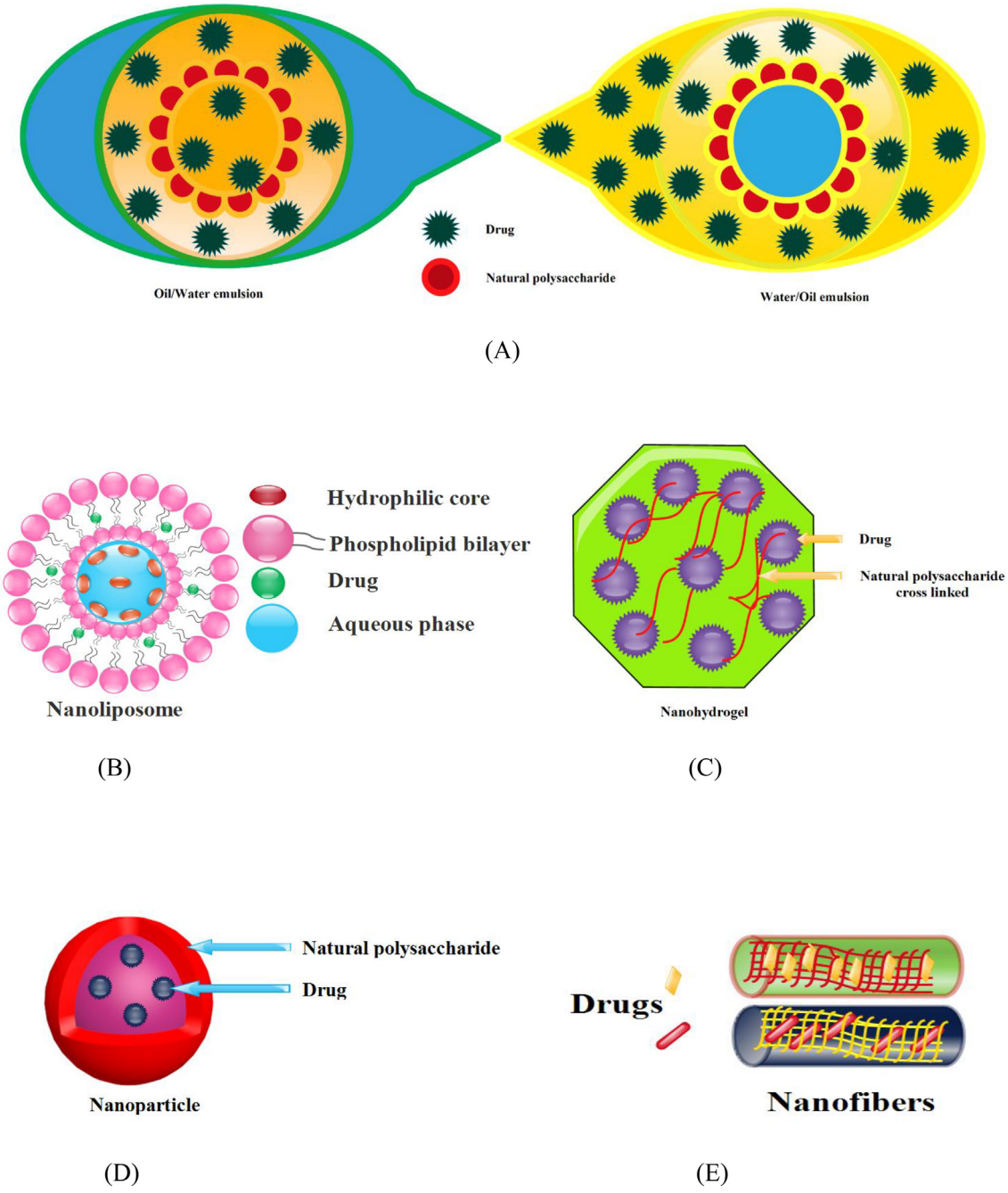

Fig. 2. Different forms of drug-loaded polysaccharides: (A) nanoemulsions; (B) nanoliposomes; (C) nanohydrogels; (D) polymeric nanoparticles; (E) nanofibers.

attributes such as higher mechanical stability, tremendous loading capability for drugs or bioactives, and controlled-release smooth responses to eco-friendly stimuli, which make them more suitable choices for different applications in numerous fields. Natural polysaccharide-based nanohydrogels have successfully received massive attentions as DNDSs because of their unique capabilities including biodegradability, low cost production, non-toxic behavior, biocompatibility, efficient releasing of drugs, and resemblance to macromolecular constituents of the extracellular matrix [85]. In nanohydrogel structures, NPLS intermingle with each other by different kinds of cross-linkers including glutaraldehyde, methylene-bis-acrylamide and byproducts of ethylene-glycol-di(meth)acrylate, etc. These cross-linkers comprise active sites which interact with hydroxyl groups of NPLS resulting in the highly compacted coil like matrix [86]. Furthermore, different polysaccharides consist of several kinds of functional groups that can be applied for advanced bioconjugation resulting in novel nanohydrogels, offering specific applications [87]. Various kinds of approaches comprising diverse mechanisms, are usually being used for fabrication of polysaccharide-based nanohydrogels such as chemical cross linking, radiation cross linking, physical cross linking, and polymerization grafting [17].

Polysaccharides-based nanohydrogels have opened an innovative paradigm in the realm of drug delivery and have been used as nanocarriers for incorporating diverse drugs against infectious diseases by many researchers. For instance, paclitaxel and prednisolone are recognized as anti-cancer and anti-inflammatory drugs, respectively; both drugs were incorporated into nanohydrogels stabilized by gellan gum, which were used for cancer treatment. In this work, it was determined

that gellan gum-based nanohydrogels enhanced the effectiveness of drugs, improved solubility of incorporated drugs, and also significantly increased their cytotoxic impact *in vitro* on different kinds of cancer cells because of potent therapeutic effects of anticancer and anti-inflammatory drugs [88]. In another research, acrylic acid-loaded nanohydrogels stabilized by bacterial CNCs were produced for skin wound curing. It was concluded that these cellulose-based nanohydrogels sustained the morphology and activity of human dermal fibroblasts, limited cells migration, promoted rapid cells proliferation and affected nine gene expressions associated with wound healing [85]. In another interesting study, Wang and his coworkers used 5-fluorouracil, an anti-cancer drug, in fabrication of nanohydrogels coated by konjac glucomannan, sodium alginate, and graphene oxide to analysis its anti-cancer effect. They found that these polysaccharide-based nanohydrogels exhibited 38.02% releasing rate of 5-fluorouracil at pH= 1.2 and 84.19% at pH= 6.8 after 6 and 12 h, respectively [89].

3.4. Polysaccharide-based nanoparticles

Nanoparticles are known to be nano cargos consisting particle sizes up to 100 nm [3] as shown in **Fig. 2D**. In order to fabricate nanoparticles, NPLS are considered as safe matrices because they are easily modified; consequently, can have diverse derivatives by their utilization due to holding many functional groups including amino, sulfate, hydroxyl, ester, and carboxylate groups [4]. Various techniques have been used to fabricate natural polysaccharide-based nanoparticles which confirm appropriate and targeted delivery of drugs properly. For example, these nanoparticles have been assembled through nano spray drying, self-assembly, electrospraying and anti-solvent precipitation. Thanks to their non-toxicity, biocompatibility, mucoadhesiveness and bioavailability, polysaccharide-based nanoparticles have been emerged as multifunctional cargos for protection of drugs, their smooth delivery on inflammatory sites, and for enhancing their therapeutic index [90].

In recent years, many researchers have successfully fabricated polysaccharide-based nanoparticles encapsulating drugs for the treatment of severe diseases. For instance, Mosafer and his coworkers produced inactivated PR8 influenza-loaded nanoparticles stabilized by sodium alginate and trimethyl chitosan. It was proved that sodium alginate (anionic polymer) altered the immunostimulatory attributes of fabricated nanoparticles as well as increased their stability. They also demonstrated that these inactivated PR8 influenza-loaded nanoparticles were more effective to assess the degree of immune-adjuvant through the nasal vaccination [91]. In another work held in 2018, quercetin (an antidiabetic bioactive) was incorporated into nanoparticles stabilized by alginate and succinyl chitosan, which were used for diabetes treatment during orally administration to diabetic rats. It was concluded that quercetin-loaded nanoparticles did not show any kind of toxicity during *in vivo* study. Also, these prepared nanoparticles exhibited an efficient mechanism for releasing of quercetin during *in vivo and in vitro* studies, and also a significant hypoglycemic response was monitored during orally administration to diabetic rats [92]. These studies are highly appealing that such kind of carriers could be used for treatment of several diseases.

3.5. Polysaccharide-based nanofibers

Nanofibers (NFs) are comprised of nano structures with 100 nm diameter approximately as shown in **Fig. 2E**, offering a broad arrangement of permeable networks because of their ultrahigh surface to volume proportion which can be simply optimized during generation [93,94]. NFs can be fabricated through different techniques including template synthesis, flash spinning, phase separation, self-assembly, melt-blowing, bicomponent spinning, and salt leaching; but the most riveting approach is electrospinning which is being widely used to produce the nanofibers because of its competence, offering nanosized fibers, high loading capacity, ease in processing, cost-efficacious, and simple parameters. Several hundreds of polymers are available in nature, but NPLS have become more qualified candidates for fabricating NFs in last decades, owing to their extraordinary abilities including biodegradability, lack of toxicity, and biocompatibility [95]. Polysaccharide-based NFs are accomplishing great concerns in recent times due to their remarkable attributes, e.g., a great porosity, high surface region, and smaller pore size; thereby, these nano cargos have notable applications in the arena of drugs conveyance, tissue engineering, bone regeneration, and wound dressings. Among vast prospective applications, natural polysaccharide-based NFs are being applied for safe delivery of drugs to overcome the risks of numerous diseases [95].

For instance, resveratrol was loaded into chitosan and gellan-based NFs where these NFs revealed a superior antioxidant potential rather than bare resveratrol. Additionally, chitosan and gellan-based NFs showed excellent release of resveratrol and also significantly enhanced the cytotoxic effect *in vitro* against HT29 cancer cells [10]. In another investigation, curcumin was incorporated into chitosan-based nanofibers, which exhibited a great potential to inhibit the infections due to *S. epidermidis* and Methicillin-resistant *Staphylococcus* up to 88% and 94%, respectively. Furthermore, it was concluded that these chitosan-based NFs encapsulating curcumin also exhibited anticancer potential when explored on L929, MCF-7 and HEP G2 cell lines during *in vitro* cell toxicity analysis [96]. In another work, bromelain (anti-inflammatory drug) was encapsulated into chitosan-based NFs where release and activity of bromelain in the induced burn wounds in the rats were accessed for 21 days. It was indicated that bromelain-loaded chitosan NFs (with 2% w/v chitosan formulation) exhibited a better release profile and physiochemical properties as well as lower cytotoxicity compared with those NFs with 4% w/v chitosan. It was also reported that bromelain-loaded chitosan NFs (with 2% chitosan) were more effective in healing burn skin as compared to chitosan NFs alone [95].

4. Application of polysaccharide-based nanocarriers loaded with drugs against various diseases

In this section, we have mainly focused on the application of polysaccharide-based drugs encapsulating therapeutic drugs for the treatment of several diseases. As, it is proved that these nanocarriers are easily absorbed, excreted and simply break down within our body without any kind of surgical measures. A large number of polysaccharides include chitosan, alginates, cellulose, pectins, starches and gums have been considered as safe for fabrication of nanocarriers and to deliver drugs and also used for their sustained controlled release as shown in Fig. 3. In this regard, chitosan and alginates are highly recommended as plentiful NPLS.

4.1. Cancer

Cancer can be defined as a multifactorial, heterogeneous disease affecting humans which is occurred due to abnormality in the apoptosis and leads to the uncontrolled cell division [97]. It is mainly of two types: malignant and benign tumors. Malignant tumors have the ability to flow with blood or lymph system and can travel to remaining portions of the body, encounter other tissues and generate novel tumors there. Benign tumors don't have the ability to move and they just grow at their originated place. Today, one of the main health challenges and major death causing diseases is cancer. Cancer is not a name of one disease, it is a collection of related diseases and has more than 277 types which may occur by many possible factors. [98]. Most fatal types of cancers are especially lungs cancer, breast cancer, colorectal cancer and prostate cancer. According to a research conducted by US National Cancer Institute, the most studied factors which may increase the risk of cancer are age, diet, hormones, alcohol, obesity, radiation, cancer causing substances, chronic inflammation, sunlight, immunosuppression, infectious agents, and tobacco.

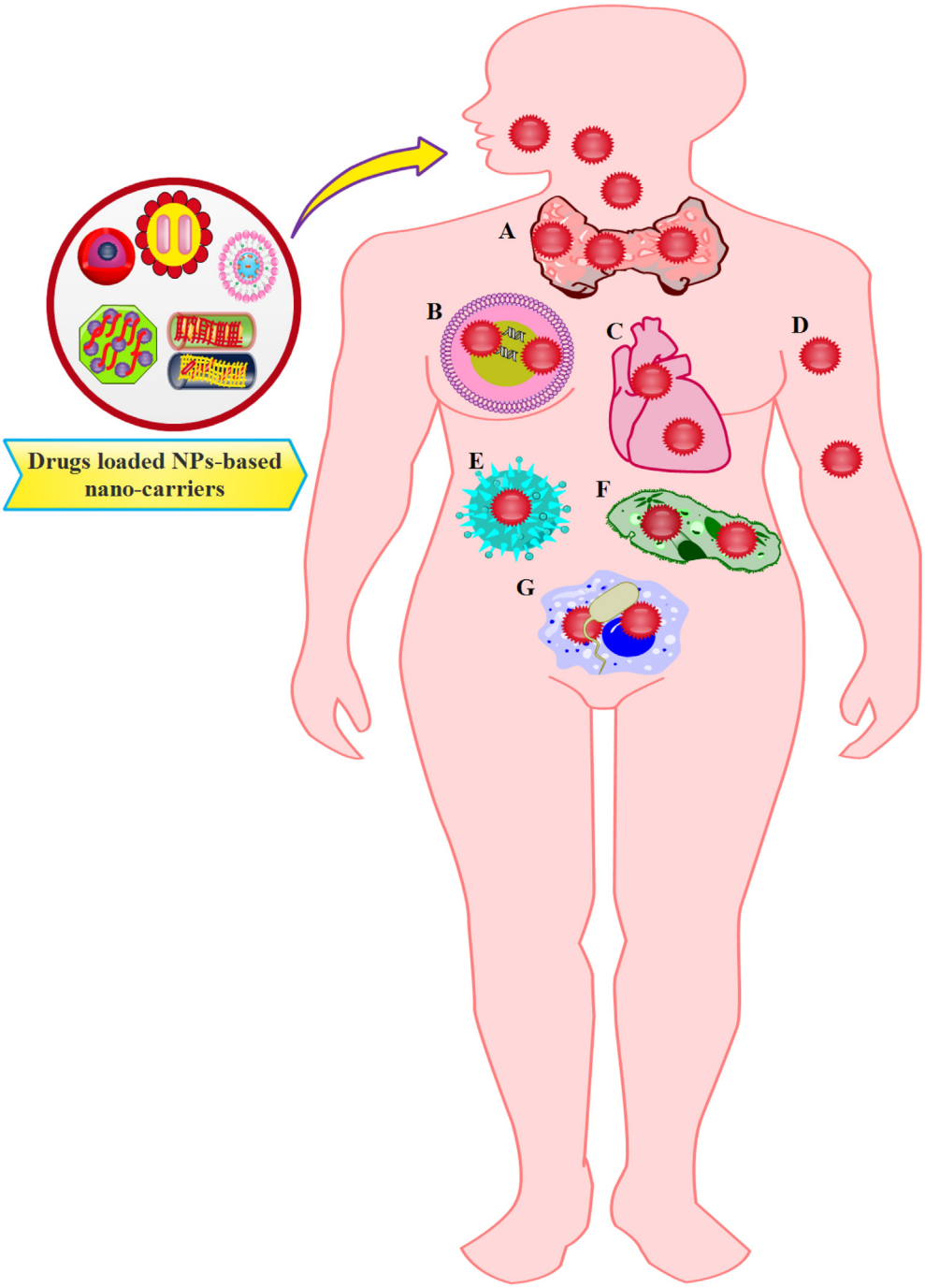

Fig. 3. Application of natural polysaccharide (NPs)-based nanocarriers loaded with different drugs for the treatment of several diseases. A- respiratory diseases; B- Cancer; C- Cardiovascular diseases; D- Skin diseases; E- HIV; F- Malaria; G- Diabetes.

Cancer is a growing disease and according to WHO, it is known to be the second most death causing disease worldwide; cancer has killed 8.8 million people in 2015 and an estimated 9.6 million deaths in 2018. Around 1,762,450 new cases and 606,880 deaths are claimed by the United States in 2019. The recent and expected high death rate is due to the unavailability of proper and suitable treatment methods to fight against advanced stages of cancer [99]. Researches have estimated that around 13.1 million individuals are going to be affected by cancer in 2030. Recently, treatments which are used to cure cancer are surgery, chemotherapy, hormone therapy, radio therapy and immunotherapy or combination of them. After these single or combined treatments, patients have much possibility to relapse and metastasis of malignant cells may occur again. Chemotherapeutic drugs not only kill cancer cells but also have negative effects on healthy cells and after their persistent use on tumor cells, develop resistant in addition to the side effects on other organs and tissues [100].

As cancer is a dreadful disease and there is no proper treatment which can manage it successfully, so scientists are still finding and exploring new methods. The development of new drugs alone is not sufficient for confirming improvement in drug therapy. For the anticancer drug delivery, the most important goals which need to be achieved are high intra tumor drug concentration and minimum exposure of the drug to the normal cells. To overwhelmed the shortcomings associated with the conventional chemotherapy procedures and to

accomplish above mentioned goals, nanotechnology has evolved nanocargos for the treatment of cancer [101]. Efforts are under progress to combine nanotechnology with DNDSs to indorse potential nanoformulation strategy for preparing anticancer drugs.

In particular, NPLS such as chitosan and pectin are extensively investigated due to their wide range of biological activities such as drug transporters, bioremediation and anticancer property. They have exhibited a potent capacity to fight against pancreatic, bladder, breast, melanoma, metastatic, colon and lungs cancers [100]. A novel double barrier nanomaterial, carboxymethyl-hexanoyl chitosan-dodecyl sulfate nanoparticles loaded with H3TM04 (1-(5-(napthalen-2-yl)-3-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl) ethanone) scattered inside the nanofibers for controlled drug release against skin cancer were prepared. The *in vitro* release of H3TM04 through dual layered nanomaterial was continuous up to 120 h. Drug encapsulation and formation of nanoparticles decreases the IC_{50} values by 50% once competed with non-encapsulated H3TM04. The *ex-vivo* skin permeation findings showed that encapsulation of H3TM04 improved both skin composite retention and permeation. This study demonstrated a novel approach to confirm the stable as well as persistent transport of H3TM04, and also exhibited useful application of PEO chitosan nanofiber mats in chemotherapy [16]. In another interesting investigation, pectin mediated gold nanoparticles (p-GNPs) were equipped by using anionic pectin obtained from banana peels and its effectiveness as an anticancer vehicle was assessed. p-GNPs induced apoptosis which was manifest from the upsurge in G1 environment, DNA mutilation in comet test and maintenance of Annexin V-FITC/PI dual stain through the cells. These consequences have exposed novel outlooks for *in-vivo* analyzing of p-GNPs which can be further used to explore for its cancer therapy [102]. More relevant studies have been summarized in **Table 2**.

4.2. Diabetes

Diabetes mellitus (DM) also known as 'diabetes', can be defined as the high sugar content or high glucose level in the blood for a long period of time [103]. Its initial symptoms include persistent urination, increased thirst and increased hunger. Negligence and disregarding at the start of the disease can lead to the serious and long term complications to the patient and can damage other parts of the body e.g. cardiovascular system, kidneys, eyes, nerves and feet. Individuals who are suffered in diabetes have increased risk of osteoporosis [104].

Diabetes can occur either due to the abnormal function of pancreas or lack of enough insulin production in the body. Mainly it is of three types; (i) Type 1 diabetes, resulting from the abnormal function of pancreas due to loss of beta cells and not producing enough insulin. Its cause is unknown. (ii) Type 2 diabetes, occurs because of the resistance of body cells or their fail to respond to the insulin properly. Excessive body weight and insufficient exercise together are the most common cause of this type. (iii) Gestational diabetes, occurs only in the women during pregnancy when the blood sugar level rise up [103].

If the disease is untreated and not well managed at the initial stages, it can lead to the acute, chronic morbidity and death stages. According to the current situation, researches have estimated that it will affect around 693 million people in 2045. In details, according to International Diabetes Federation (IDF) around 5 million people with age > 20 were died in 2017 because of the diabetes worldwide and, it was estimated that global healthcare spends around USD 850 billion on diabetes [124]. Yet, so far, still much investigations are required to find the proper solutions for the management of DM as well as for preventing the diabetic patients from developing diabetes related to complications and premature mortality.

As the diabetic patient does not have sufficient insulin, so the administration of insulin externally is necessary to lower the glucose level of blood. In particular, insulin is a 5800 Da peptide hormone containing 51 amino acids organized in two major chains that are connected by disulfide bridge [125]. Insulin plays a crucial part in the breakdown of carbohydrates, proteins and fats through encouraging the cellular uptake of marginal glucose and the formation of proteins, hepatic, fatty acids and glycogen. Presently, intravenous route is used for the direct administration of insulin into the diabetic patient by repeated subcutaneous injections. The insulin injection can reduce the blood glucose level ranging from 14-15 to 3.5-7.0 mmol/L. But this method has disadvantages: for instance insulin resistance, poor compliance, local infection, fat deposits at injection site, resulting in patient discomfort, and non-effective treatment [126]. All these disadvantages let the researches to find other ways that would be used for insulin therapy, such as nasals, pulmonary and oral delivery of insulin along with intravenous infusion [104]. Oral delivery, among all delivery systems, is considered the most preferable owing to its many advantages: convenient, slight insensitivity and patient obedience in both long- and short-term treatment. Besides its numerous advantages, orally delivered insulin faces many challenges. As insulin is very sensitive, its stability can be affected through acidic environment, high temperature, ions, organic chemicals, solvent media and additionally it can be degraded chemically or enzymatically in the GIT leading to the poor therapeutic effects to the patients. For resolving such shortcomings, many efforts have been proposed for the active orally conveyance of insulin. [127].

During the past decade, nanotechnology has got much interest by the pharmacologists in diabetes treatment. NPLS such as chitosan, pectin, alginate etc. are biodegradable, biocompatible, safe, easy to use and have better physiological stability [125]. Polysaccharide-based DNDSs bear several complications and deliver an appropriate road map for the delivery of insulin. The wound healing efficacy of silver nanoparticles impregnated chitosan-polyethylene glycol (PEG) hydrogel which was evaluated in this research that was conducted on diabetic rabbits. *In-vitro* studies showed antimicrobial and antioxidant properties of silver nanoparticles permeated hydrogel as well as high porosity, high degree of swelling and high water vapor transition rate as compared to simple chitosan-PEG hydrogel I diabetic rabbit. The hydrogel revealed a sustained release of silver nanoparticles over 7 days exhibiting slow biodegradation of developed hydrogels. These results indicated that the silver nanoparticles impregnated chitosan-PEG hydrogels can be a great approach for wound healing in chronic diabetic wounds [128]. In another study, pH-sensitive calcium alginate hydrogels loaded with protamine nanoparticles and hyaluronan oligosaccharides (HAO) were developed and their wound healing effect was examined in diabetic mice. The results showed great suppression effect on both G+ and G- bacteria with the arbitration of anti-bacterial protamine nanoparticles; thus, it controlled the further inflammation by inhibiting the bacterial population at the wounds spot and improved wounds curing effect. *In-vitro* results revealed that the addition of HAO also promoted the secretion of VEGF, capillary alike cylinder construction and human umbilical vein endothelial cells migration. It may leave positive influences during the wound healing by encouraging the growth of blood vessels at the sides of wound sites. Thus, these results verified that the developed protamine nanoparticles hydrogels and HAO promoted the quick curing of diabetic injuries on the surface of skin, and it could be a promising approach for managing diabetic ulcers [12]. Table 3 provides more details about some other recent studies in this field.

4.3. Cardiovascular diseases

Cardiovascular diseases (CVDs) are a cluster of heart or blood vessel disorders which can be classified into mainly two large parts: (i) heart dysfunction includes heart attack and arrhythmias; (ii) vessel dysfunction e.g. atherosclerosis and ischemia. CVDs include several diseases such as high blood pressure, stroke, pulmonary hypertension, heart valve disease, endocarditis, various arrhythmias, venous disease, coronary artery disease, and peripheral artery diseases [34]. CVDs are renowned cause of morbidity and mortality reported in all over the globe and the numbers are increasing especially in the middle and developing countries [138]. According to WHO, 17.7 million people died

Table 2
Application of polysaccharide coated nanocarriers for the entrapment of drugs and their use against cancer.

Natural polysaccharide	Nanocarriers	Drugs	Size (nm)	Zeta potential (mV)	Encapsulat-ion efficiency (%)	Conclusive remarks	Ref
Chitosan	Nanoemulsion	Piplartine	90.7-73.1	5.8-6.9	Not reported	(i) Both formulations exhibited excellent potential for intraductal administration. (ii) This formulation is recommended against cancer.	[105]
Chitosan	Nanoparticles	Coumarin	110.3-452.9	-4.3 to 9.4	78.4	Results showed that coumarin-containing chitosan nanoparticles with pH and photo-responsive properties recommended for cancer therapy application.	[106]
Chitosan	Nanofibers	Doxorubicin, paclitaxel, and 5- fluorouracil	210	Not reported	86-96	The consequences of this investigation exposed the excessive activity of tri-layered nanofibers against killing of breast cancer cells.	[107]
Chitosan	Nanoparticles	Quinoline	141 to 174.8	-2.4 to -14.1	65.8 to 77	(i) Results indicated that utilization of quinolone laden chitosan nanoparticles crosslinked with 3-formylquinolin-2 (1H)-one and 2-chloro-3- formylquinoline *in vitro* study exhibited the faster drug release at low pH, highly recommended for treatment of cancer. (ii) When was compared with non-encapsulated quercetin, the quercetin–loaded chitosan nanoparticles displayed remarkable cytotoxic effect in contradiction of HeLa cells.	[108]
Chitosan	Nanoparticles	*Ginkgo biloba* leaf Polyphenols	45.9 to 177.6	49.7-51.6	91.5 to 92.9	Prepared formulation named (ginkgo biloba leaves Polyprenol and TiO_2 loaded into folic acid-coupled chitosan)-based nanoparticles showed excellent inhibition activity on HepG2 cells and lower cytotoxicity as well as genotoxicity on HL-7702 cells by using low concentration of TiO_2.	[109]
Chitosan	Nanoparticles	Doxorubicin	33.39 to 52.92	13.83 to 29.63	45.89	Doxorubicin loaded chitosan nanoparticles inhibited cells that cause liver cancer thru encouraging apoptosis as well as obstructing cell cycle at G2/M segment by p53/PRC1 way.	[110]
Chitosan and gellan	Nanofibers	Resveratrol	~ 129-232	Not reported	92	This study proved that chitosan and gellan-based nanofibers loaded with resveratrol offered a great potential for delivery of resveratrol in GIT surroundings for treatment of infections.	[10]
Gellan gum	Nanohydrogel	Prednisolone & Paclitaxel	285 to 340	-20.7	47.1 to 82.7	(i) Gellan gum-based nanohydrogel enhanced drug potential, behaved as solubility enhancer for paclitaxel and prednisolone and supporting the uptake of drugs inside the cells. (ii) Furthermore, gellan gum-based nanohydrogel endorsed an improved cytotoxic influence *in vitro* on numerous kinds of cancer cells because of synergistic combined effect of anti-cancer and anti-inflammatory drugs.	[88]
Alginate	Nanoparticles	Doxorubicin	39.2 to 102	-32.72 to -35.37	90.1 to 92.2	(i) Doxorubicin-loaded alginate nanoparticles exhibited outstanding anti-cancer effects, accessed via tumor regression. (ii) They concluded that these doxorubicin-loaded nanoparticles had great potential against breast cancer.	[111]
Sodium alginate	Nanohydrogel	Doxorubicin	135	Not reported	90.5 to 91.3	The formulation with particle size 135 nm, showed the lowermost doxorubicin escape and the prime alteration in accumulative release at varied pH media, as well as displayed a continuous drug release profile.	[14]
Sodium alginate	Nanoparticles	Exemestane	197	-18.3	98	*In vitro* drug release, this study reveals that exemestane-loaded alginate–based nanoparticles showed an effective and controlled delivery of exemestane for cancer treatment.	[112]
Alginate	Nanoparticles	Cisplatin and gold nanoparticles	~1 to 44	-35.1	Not reported	(i) Prepared formulation exhibited an improved chemotherapy efficiency as compared to the unentrapped cisplatin and revealed substantially superior inhibition rate of tumor. (ii) Because of its chemotherapy efficacy, alginate coated nanoparticles intensely inhibited tumor growth up to 95% of control and distinctly elongated the survival rate of animal.	[113]
Sodium alginate	Nanoparticles	Doxorubicin hydrochloride and paclitaxel	9-25	-10 to 25.1	79	The drugs loaded nanoparticles showed higher toxicity even greater than the free drugs in contradiction of HeLa and MCF-7 cells.	[114]
Alginate/ Chitosan	Nanoparticles	Curcumin diglutaric acid	212 to 552	-17.2 to -29.2	28.3 to 78.2	(i) The fabricated nanoparticles embedded by chitosan and alginate encapsulating curcumin diglutaric acid had successfully exhibited greater and effective *in vitro* cellular uptake in human epithelial colorectal adenocarcinoma (Caco-2 cells) and superior anticancer potential in contradiction of human hepatocellular carcinoma (HepG2), Caco-2 and human breast cancer (MDA-MB-231) cells. (ii) Finally, this formulation is recommended as capable tactic for orally administration of curcumin diglutaric acid for cancer treatment.	[115]
Alginate/Chitosan	Nanoparticles	Doxorubicin	80.6	-27.4	8.3	Doxorubicin loaded alginate and chitosan- based nanoparticles solutions displayed extreme sufficient proportion of drugs to encourage a beneficial outcome once exploited in contradiction of the 4 T1 murine breast cancer cell lines *in vitro*.	[116]

Table 2 (*continued*)

Natural polysaccharide	Nanocarriers	Drugs	Size (nm)	Zeta potential (mV)	Encapsulat-ion efficiency (%)	Conclusive remarks	Ref
Pectin	Nanoparticles	Honokiol	640.50	−14.9	52.89	(i) Exploration of the *in vitro* release profile showed that pectin-based nanoparticles encapsulating honokiol displayed a sophisticated and sustained drug releasing flow as compared to free honokiol. (ii) Cytotoxicity, cellular uptake and cell apoptosis findings had established that these nanoparticles offered superior cytotoxicity instead of bare honokiol on HepG2 cells.	[117]
Pectin	Nanoparticles	Oxaliplatin	100-200	35.27	55.2	Authors studied the cytotoxicity influence of oxaliplatin loaded pectin-based nanoparticles on MIA-PaCa-2 cancer cell line linked with pancreas, where the GI50 amounts were found to be ˜5 mg/mL, exhibiting superior cytotoxic effect around 10 folds as compared to the correspondent proportion of control sample.	[118]
Pectin	Nanoparticles	Curcumin	78-114	−31.81	90	Pectin loaded nanoparticles consisting curcumin enhanced the drug ingestion through cancer cells owing to the constant and controlled drug releasing behavior.	[33]
Pectin and chitosan	Nanoparticles	Curcumin	200	32.8	64	This study indicated that pectin loaded curcumin could be used to cure the colon cancer.	[119]
Pectin and alginate	Nanoparticles	Gentamicin	350	Not reported	~80	This study revealed that gentamicin loaded pectin nanoparticles can be used in order to handle with both kinds of infected injuries (acute and chronic).	[120]
Pectin and chitosan	Nanoliposomes	Neohesperidin	87-225	-19.2 to -24.4	64.25	(i) These nanoliposomes had significantly controlled the neohesperidin while releasing profile and 72–78% of the entrapped drug were found to be inside the GIT environments. (ii) Authors also found that these fabricated nanoliposomes can improve the cellular uptake of the epithelial cells belong to colon region.	[11]
Cellulose	Nanofibers	Metformin	83.27	−29.80	Not reported	(i) Cellulose-based nanofibers entrapped with metformin considerably inhibited the movement of melanoma cells. (ii) In addition, adequate adhesion of the melanoma cells on the metformin loaded cellulose-based nanofibers can decline melanoma cells invasion.	[121]
Cellulose	Nanofibers	Etoposide and methotrexate	62.5	Not reported	Not reported	In this study, the cytotoxicity of etoposide and methotrexate was improved when both drugs were incorporated into the nanocomposites instead of their pure form.	[122]
Hydroxyethyl starch	Nanoparticles	Doxorubicin	134.1 to 156.2	−5.2 to −24.0	96.27	This study revealed that doxorubicin loaded nanoparticles successfully overpower the development of liver cancer, by means of a tumor inhibition rate of 73.1%, and remarkably relieved the negative influences allied with doxorubicin.	[123]
Carboxymethyl-hexanoyl and chitosan	Nanofibers	Pyrazoline H3TM04	~ 197	Not reported	84.11	The entrapment of H3TM04 into the fabricated nanofibers had improved its cytotoxicity in the direction of B16F10 melanoma cells.	[16]

globally because of CVDs in 2015 and the number is estimated to rise up to 23.6 million by 2030 [139]. It is also a serious problem in USA and has affected around 85.6 million Americans. In the Eastern Mediterranean region, the mortality rate due to CVDs was 34.1% in 2015 [140]. So, there is a high need to find appropriate solutions and discover efficient techniques against CVDs. Recently, application of cardiovascular biomaterials in CVDs treatment has gained much attention. In this treatment, an apparatus, made up of medical-grade metallic alloys, called coronary artery stent is placed inside the patient by surgery. It provides powered support to the narrowed vessels and greatly improves the treatment for heart attack. In USA, around 560,000 patients were treated with cardiovascular biomaterials in 2007 [141]. Till now, these biomaterials have not got enough progress to provide target drug delivery, CVD diagnosis, and regeneration of cardiac tissues.

The application of polymers for the precise and accurate release of drugs at the targeted sites against CVDs is considered to be a better substitute of conventional stent method. For instance, Cabrales and his colleagues prepared chitosan-based nitric oxide (NO) hydrogel nanoparticles. It was observed that the release of NO by NO-nanoparticles (NO-NPs) decayed inflammation as compared with control-NPs (control-NPs without nitrite). These data suggested that NO-released from NO-NPs were more beneficial as compared to other NO-releasing compounds because they were independent of composition or else enzymatic catalysis; these were merely governing through the hydration rate. This study demonstrated that NO-NPs had the ability to control blood pressure and enhance vascular relaxation. Additionally, NO reduced the hypertension and opened a stenosis vessel that causes heart pain which leads to atherosclerosis and heart attack [142]. In another work, metformin was entrapped into pectin and chitosan-based NPs for healing of CVDs (Chinnaiyan et al., 2019). They reported that metformin-loaded NPs enhanced the HDL level as compared to the control rate leading to prevent cardic diseases. In addition, the protective effects of applied formulation was observed remarkably in the cardiomyocyte, hepatocytes, pulmonary capillary endothelium and myofibrils [34]. In other research, guar gum-based NPs containing selenium were fabricated to evaluate their effect against cardiac disease. It was concluded that these NPs had a great potential in protection of H9c2 cardiac cells as of IR wound by enlightening the ETC efficiency in H9c2 cells [143].

4.4. Malaria

Malaria is a parasitic disease that affects humans worldwide; its early symptoms include fever, tiredness, vomiting, headaches and, if unchecked may leads to yellow skin, seizures, coma or death of the infected person. A single-cell microorganism which belongs to the plasmodium group, is responsible for causing the disease and, it is mostly transmitted by the infected female Anopheles mosquito [144].

Table 3
Application of polysaccharide embedded nanocarriers for the entrapment of drugs and their use against diabetes.

Natural polysaccharides	Nanocarriers	Drugs	Size (nm)	Z-potential (mV)	Encapsulation efficiency (%)	Conclusive remarks	Ref
Succinyl chitosan and alginate	Nanoparticles	Quercetin	~ 91.58	−19.83 to −35.55	95	A noticeable hypoglycaemic outcome as well as competent protection of glucose homeostasis was observed in diabetic rat after peroral conveyance of fabricated quercetin loaded alginate and succinyl chitosan-based NPs compared to non-encapsulated quercetin.	[92]
Alginate	Nanoparticles	Metformin	60 to 150	+27.3	78	The consequences of *in-vitro* drug releasing profiles and *in-vivo* efficiency investigations proved improved proficiency and response of metformin loaded alginate-based nanoparticles relative to pure metformin.	[29]
Alginate	Nanoparticles	Naringenin	137 to 322	-24.2 to – 39.22	91.4	This study report that momentous hypoglycemic influence was observed afterward oral administration of the alginate-based nanoparticles having naringenin to streptozotocin-induced diabetic rats.	[129]
Alginate and chitosan	Nanoemulsions	Insulin	488	-60	47.3	Alginate and chitosan based nanoemulsion comprising insulin had exhibited hypoglycemic impacts for both usual and diabetic rats.	[130]
Alginate and chitosan	Nanoparticles	Insulin	90-110	−9.34 to + 49.5	63 to 94	(i) Distinctive properties of insulin loaded alginate and chitosan-based nanoparticles had perceived in both *in vivo* and *in vitro* analysis. (ii) Above than 90% encapsulation efficacy, sustained inflammation, and precise drug release from mucoadhesive nanoparticles was observed in current study.	[131]
Alginate and chitosan	Nanoemulsions	Insulin	488-575	−0.97 to −70.30	Not reported	*In vitro* release analysis showed well maintained reliability of the chitosan and alginate-based nanoemulsions in simulated gastric juices. Furthermore, highly significant extended hypoglycemic impacts afterward orally administration of insulin-loaded nanoemulsions instead of subcutaneous insulin.	[130]
Chitosan	Nanoparticles	Ferulic acid	51.2 to 213.41	+14.2 to 31.4	15.31 to 56.45	This study revealed that encapsulated ferulic acid into chitosan-based nanoparticles showed extended plasma retention time and maximum plasma concentration was recorded at 60 min which implied four times augmentation of T_{max} than free ferulic acid.	[132]
Chitosan	Nanoparticles	Insulin	527 to 1577	+11.5 to -20.6	Not reported	It was concluded that insulin loaded chitosan nanoparticles successfully decreased basal serum glucose levels of diabetic rats.	[133]
Folic acid modified chitosan	Nanoemulsions	Insulin	169.5 to 252.4	− 11.3 to +34.2	41.85	After orally administration of insulin-loaded nanoemulsions to the diabetic rats, a realistic hypoglycemic impact was attained instead of subcutaneous insulin.	[134]
Cellulose acetate	Nanofibers	Silver nanoparticles	5.79	Not reported	Not reported	Cellulose acetate nanofibers being complex dressings were more useful for construction of collagen led towards potent wound treatment than simple cellulose dressings.	[135]
Starch	Nanoparticles	Catechin	322-615	-21	59	This study depicts that interestingly upon subjecting catechin loaded starch nanoparticles to intestinal digestion and simulated gastric, the properties of entrapped drug were encouragingly reserved than bare catechin.	[136]
Cellulose nanocrystals (NCs)	Nanohydrogels	Silver nanoparticles	18-272	Not reported	Not reported	(i) Authors recognized a declining trend in the levels of pro-inflammatory cytokines IL-6 and TNF-α directing towards a reduction in swelling of NCs treated mice.	[137]

The parasites are present in the saliva of the infected mosquitoes and when these mosquitos bite a person, they enter into the blood of that person. Via blood, they move towards liver where they develop and imitate themselves. Malarial transmission also depends on the weather conditions such as temperature, humidity and rainfall. People with less immunity have greater chances of the infection when they migrate towards the high transmission area [144]. Globally, malaria causes significant morbidity and mortality mostly in the African regions. According to a survey, about 217 million people infected by malaria were reported in 2016, while in 2017 the number was relatively higher and

219 million cases were reported. Out of all cases reported in 2017, almost 92% cases were reported from WHO African regions, 5% from WHO South East Asian regions and 2% from WHO Eastern Mediterranean Region [145]. As many countries are struggling and working on malaria elimination goals, but it's still a worldwide challenge because of different disease management, diagnosis, epidemiology and treatment factors.

There are many methods for the diagnosis and treatment of malaria. As mosquitoes are agents which are responsible for the transmission of parasite, therefore the most important step in managing malaria is to control the vector, particularly at the larval stage by numerous insecticides. The use of insecticidal coated mosquito nets and mosquito sprays are effective methods recommended by WHO. However, there are still many issues raised while controlling malaria, such as resistance to sulfadoxine composites and quinine. To overcome the current issues and to eliminate the malaria in 2030, WHO started a plan called "Global Technical Strategy for Malaria 2016-2030" [146]. However, there is still needs to improve the various therapies and treatment methods for effective control.

Nanotechnology-based delivery of the malaria drugs is one of the finest approaches to enhance the efficiency and therapeutic effects of the drugs [147]. Polysaccharides are very effective biopolymers comprising awe-inspiring advantages especially for the conveyance of proteins, drugs and DNA molecules at the targeted sites [148,149]. Chitosan NPs containing lemon grass oil were prepared as nano-gels by incorporating acrylate as a thicker. The results of post-fifteen washing demonstrated that the gel loaded with acrylate had a 75% mosquito repellency, in comparison with non-acrylate which only showed 51% repellency. Furthermore, the nanogel did not show any toxic effects even after repeated application on Swiss albino mice. Therefore, this design is appropriate to saturate dress of the army people and those who have field duty where there is a more risk of mosquito biting [147]. In another study, by using the mixture of polyvinyl pyrrolidone and hydroxyl propyl methyl cellulose, curcumin-loaded nanohydrogels were successfully developed. The purpose of this study was to explore the prepared nanocarriers size and their hydrophilic nature to increase the absorption and extend the quick clearance of entrapped curcumin because of the conceivable avoidance of the reticulo-endothelial structure. *In-vitro* data demonstrated the noteworthy larger action of nanoformulations as compared to control sample signifying that the developed system could be engaged as an anti-malarial therapy along with the standard therapy. Moreover, orally it is safe which is confirmed by the acute and subacute toxicity studies [150]. Other relevant studies are reviewed in Table 4.

4.5. Human immune deficiency viruses (HIV)

Two species of viruses belonging to the Lentivirus, cause HIV infection and acquired immune deficiency syndrome (AIDS). In addition, AIDS in humans affect the body's self-defense system and causes gradual failure of the immune system which allows other serious complications and body infections and can lead to death. An untreated HIV patient can survive an average of 9-11 years after infection. HIV can transmit via body fluids; mostly it is transmitted sexually e.g. by the transmission of semen, blood, vaginal fluids and pre-ejaculate. As, non-sexual transmission includes the transfer of HIV from infected mother to her child during pregnancy, during birth and through breastmilk [156]. The target cells of HIV infection in human immune system are vital cells including dendritic cells, macrophages and helper T cells ($CD4^{+}$T cells). On the onset of HIV infection, many mechanisms

Table 4
Application of polysaccharide embedded nanocarriers for the entrapment of drugs and their use against malaria diseases.

Natural polysaccharides	Nanocarriers	Drugs	Size (nm)	Zeta potential (mV)	Encapsulation efficiency (%)	Conclusive remarks	Ref
Ethylcellulose	Nanofibers	Citriodiol	~437	Not reported	Not reported	The effectiveness of these novel citriodiol loaded ethylcellulose nanofibrous mats to repel mosquitoes was assessed in this study.	[151]
Hydroxyl propyl methyl cellulose	Nanohydrogels	Curcumin	100	Not reported	72	(i) This study reveals that antimalarial potential of encapsulated curcumin in nanohydrogels had improved remarkably after loading in hydroxyl propyl methyl cellulose nanohydrogel. (ii)The findings of this study investigated the anti-malarial potential of fabricated nanocarrier that could be used for treatment of malaria.	[150]
Chitosan	Nanoparticles	Artesunate	Less than 300	Not reported	90	Their findings reveal that improved *in vivo* antimalarial potential in case of a smaller amount of parasitemia was detected in infected *Plasmodium berghei* mice by orally delivery of these fabricated nanoformulations.	[152]
Chitosan	Nanoparticles	Ribonucleic acid	100-200	10-13.5	Not reported	This research was conducted to access the *in vitro* parasite inhibition activity against *P. falciparum* K1 strain over 48 h. Also, consequences showed that 71% growth inhibition was achieved by using 10 mg/ml dose for PfTOP2 chitosan/ dsRNA nanoparticles.	[153]
Chitosan	Nanoparticles	Chloroquine	150–300	+32.9	54.72	(i) In this study, authors penetrated different concentration of nanoencapsulated doses (100, 250, and 500 mg/kg bw/day) into Swiss mice and their effect was calculated against *P. berghei* infection, in order to ascertain the true value of its use in the treatment of malaria (ii) They observed the supreme influence of chloroquine at 250 mg/kg bw concentration during storage of 15 days.	[154]
Chitosan	Nanoparticles	Chloroquine	150–300	+32.9	54	Authors revealed that the chitosan-tripolyphosphate conjugated chloroquine competently recovered the liver apoptosis.	[155]

happen which tend to decreases the level of $CD4^+$T cells gradually such as straight assassination of infected cells and killing of $CD4^+$T cells via $CD8^+$ cytotoxic lymphocytes, apoptosis of uninfected bystander cells, pyroptosis of abortively infected T cells recognized as infected cells [157]. Below perilous stage, cell-mediate immunity is misplaced as well as body becomes more vulnerable to numerous disorders and complications, leading to AIDS.

According to a survey, the total number of alive people having HIV in 2017 were about 37 million worldwide [158]. In accordance with a survey conducted by Centers for Diseases Control and Prevention, around 1.1 million individuals having age ≥13 years in USA have faced HIV infection by 2015. With the increase in awareness worldwide, the occurrence of HIV infection had decreased annually and was about 1.8 million in 2016. The access of Highly Active Antiretroviral Therapy (HAART) to the patients has been increased. Even though many efforts have been made and researches are still struggling for better and more better treatment, yet one million people die annually from AIDS-related complications [158]. The use of combined antiretroviral drugs (cART) or HAART can suppress the viral replication in the plasma to an undetectable level. Even after these therapies and medication, the virus is still in the long term cellular reservoir and rebound when the treatment stops; so there is no therapy which can eradicate it completely. Additionally, lifetime cART therapy is costly and also may generate severe side effects that can disturb cardiovascular, nervous and liver systems [159].

Because of the complex pathogenesis of HIV, more efficient, advanced therapeutic combination and novel targeted DNDSs are needed for the optimization of current approaches and eliminating the latently infected cells. Polysaccharide-based nanocarriers are novel approaches which considered ideal with targeting HIV reservoir and eradicating or curing the disease. As an example, saquinavir is a powerful protease inhibitor, incorporated into chitosan-based NPs and used against AIDS. The results demonstrated that chitosan-based NPs had a higher saquinavir loading potential with superior cell targeting efficacy leading to effectual controller of the virus-related propagation in target T-cells. It was also concluded that the saquinavir-loaded chitosan NPs had a superior potency than the free drug even in nanogram levels [160]. In another interesting study, Huang and his co-workers developed tenofovir-loaded cellulose acetate phthalate (CAP) nanofibers, which successfully behaved as HIV-1 entry inhibitor. These CAP-based nanofibers were found to be more tolerated by vaginal epithelial cells as well as through vaginal microflora. It was demonstrated that CAP-based nanofibers successfully sustained integrity in acidic pH environment. Furthermore, incorporation of tenofovir into CAP nanofibers considerably enhanced its antiviral activity [161]. In another work, anti-HIV siRNA loaded chitosan-based NPs were fabricated, which noticeably enhanced cell viability and siRNA efficiency without any significant cytotoxicity as compared to control cells as well as reduced the RNA and protein expression of HIV-1 *tat* in both stable cells [162]. Varshosaz and her fellows incorporated nevirapine (anti-HIV drug) into cellulose acetate butyrate nanoparticles (CAB-NPs) for treatment of HIV. Their studies revealed that CAB-NPs were efficaciously up-taken through macrophage cells, and could be used as potent transporters for efficient conveyance of anti-HIV drugs [163].

4.6. Respiratory diseases

Respiratory (lung) diseases are a cluster of diseases which affect the respiratory tract or the respiration system of an individual. These diseases can be ranged from moderate, for example cold, to severe health issues such as pulmonary arterial hypertension, asthma, tuberculosis, cystic fibrosis, idiopathic pulmonary fibrosis, acute lung injury, human respiratory syncytial virus infection and lung cancer [164]. **Asthma** is illustrated as the irregular airflow blockage and its symptoms include dyspnea, cough and bronchial hyper responsiveness [165]. At present, there is no healing method existing for curing asthma [166]. **Pulmonary arterial hypertension (PAH)** is a severe and death causing disorder which is illustrated by an increase in mean pulmonary artery pressure, >20 mm Hg. The elevation in the mean pulmonary artery pressure may push towards the right heart failure that becomes a major cause eventually death of the patient; the cellular and molecular mechanism for pulmonary vascular remodeling are still not completely understood [167]. **Tuberculosis (TB)** is known for one of the main death illnesses globally caused by a bacterial pathogen *Mycobacterium tuberculosis* [168]. According to a survey conducted by WHO, TB affected around 10 million people in 2017; 1.67 million people die every year due to TB infection [169]. **Cystic fibrosis (CF)** is a genetically inherited several-organs disease which mostly affect the respiratory system. The CF creates a mucous-build up environment which favors the colonization of many pathogenic bacteria and fungi [170]. Its symptoms include difficult breathing, cough with mucous, fatty stool, lung infection and infertility in most males. Idiopathic pulmonary fibrosis (IPF) is more in older people usually above 50 years, as it is an age related disease [171]. It is symbolized as the gradual decrease in the lung function after an irreparable injury of the lung structure [172]. Acute Lung Injury is characterized by severe respiratory distress after an identifiable injury. Its symptoms include dyspnea, hypoxemia refractory to supplementary oxygen, diffuse chest radiographic infiltrates and reduced lung compliance [173]. Human respiratory syncytial virus causes severe infection of lungs and respiratory system especially in the early of childhood [174]. Until now, no specific and suitable treatment method is available. Fever, cough, runny nose, irritability and rapid breathing are its symptoms. Lung cancer is the major reason of cancer death with 1.6 million deaths every year, which is accountable intended for about 20% of all cancer deaths globally [175] . The main cause is tobacco epidemic and aging population. Worldwide, these diseases are the foremost reason of the death particularly in the developing nations where the unclean environment and polluted air favors the respiratory diseases [23].

The use of different NPLS in fabrication of nanoencapsulated systems incorporating drugs for healing of various respiratory infections has been expanding endlessly. For instance, Nafee and team developed chitosan-based NPs comprising 20-O-Methyl-RNA (OMR), acknowledged being a great inhibitor of lung cancer. They revealed that OMR reduced 50% of the telomerase action in A549 lung cancer cell lines [176]. In another investigation, Kumar and co-workers encapsulated the IFN-γ (a potential candidate for asthma therapy) into chitosan-based NPs for treatment of prophylaxis and asthma. On intranasal management, these NPs were taken up by bronchial epithelial cells as well as macrophages that played a main part in immunomodulation. They also concluded that these chitosan-based NPs reduced the airway hyperresponsiveness (AHR) and normalized the lung morphology that might be due to STAT4 signaling pathway [177]. In another investigation, Liu and his research team entrapped *Brucea javanica* oil (BJO) into chitosan-based nanoemulsions which its effect against lung cancer was evaluated. They found that bioavailability of BJO was relatively improved by 1.6-times, and also revealed that chitosan-based nanoemulsions had a great potential in hindering the lung tumor in *in vivo* animal models as compared to the free nanoemulsion [178]. For getting therapeutic results against tuberculosis, Amini and his colleagues incorporated ESAT-6 antigen into chitosan NPs for the safe delivery to female BALB/c mice where they exhibited sturdier capability to induce IL-4, IgG, and IFN-gama antibody level as compared to the control groups [179]. Consequently, these studies are highly convincing that polysaccharide-based nanocarriers could be more appealing candidates for the transportation of drugs in order to handle the respiratory diseases.

4.7. Skin diseases

Skin is the most visible structure of the body, weighing over 5 kg and covers the surface area of around 2 m^2. It delivers a physical fence to the body against peripheral atmosphere. Skin is like a lamination and it consists of multiple layers. It not only provides mechanical protection but

Table 5
Application of polysaccharide-based nanocarriers for the encapsulation of drugs and their use for treatment of skin diseases.

Natural polysaccharides	Nanocarriers	Drugs	Size (nm)	Z-potential (mV)	Encapsulation efficiency (%)	Conclusive remarks	Ref
Carboxymethyl chitosan (CMCS)	Nanoemulsion	Astaxanthin (ASX)	< 100	-6.87	Not reported	This study concluded that the ASX chemical stability and skin permeability increased in the following order: ASX solution control < ASX-NE< CMCS-ASX-NE	[185]
Chitosan	Nanoparticles	Antisense oligonucleotides	221	+20.5	Not reported	(i) This study reveals that β-galactosidase expression was inhibited in approximately 82–85% with transfection of nanoparticles containing 30μg AsODNs at 6 days. (ii)Thus, chitosan nanoparticles are useful carrier for delivery of antisense oligonucleotides into skin cells of rats.	[186]
Chitosan	Nanoparticles	Heparin and basic fibroblast growth factor (bFGF)	206-272	+17.9 to +22.1	97	Sustained release of bFGF from the nanoparticles enhanced the proliferation of human foreskin fibroblast cells (HFF) and angiogenic tube formation by human umbilical vein endothelial cells (HUVEC), suggesting the retaining of bFGF mitogenic activity.	[187]
Chitosan	Nanohydrogels	Phenytoin	128-161	-9.1 to -15.7	95.2	*In vitro* skin permeation studies exposed that phenytoin permeation to the receptor section, and subsequently the risk of systemic absorption, is reduced by nanoencapsulation without any change in the *in vivo* performance of phenytoin in the wound healing process in rats.	[27]
Chitosan	Nanoparticles	Melatonin	113.7 to 331.5	4.6 to 31.2	Not reported	It was demonstrated that chitosan-based NPs can be applied to skin cells at levels up to 200 mg/mL without inducing plasma membrane damage or cell viability decrease.	[188]
Chitosan	Nanoparticles	Aciclovir	350	+31	14	These studies demonstrated that incorporation of aciclovir into chitosan-based nanoparticles significantly improved its chemical stability. Moreover, skin diffusion studies *in vitro* showed enhanced permeation of aciclovir from the nanoparticle system, especially from nanoparticles with higher chitosan content.	[189]
Chitosan	Nanoparticles	Spantide II (SP) and ketoprofen (KP)	172-183	+5.34 to +10.43	Not reported	(i) This study demonstrated that surface modification of chitosan nanoparticles with oleic acid improved skin permeation of fluorescent dye containing nanoparticles by translocating the nanoparticles across the deeper skin layers with higher intensities. (ii) Additional, surface modification of KP and SP nanoparticles with oleic acid exhibited notable increase in skin permeation which was further responsible for improved response in allergic contact dermatitis model.	[190]
Chitosan	Nanoparticles	Clobetasol-17-propionate (CP)	250	+34	92.2	These results indicated that chitosan-based nanoparticles are more suitable to induce epidermal targeting and to improve the risk–benefit ratio for topically applied CP.	[191]
Chitosan	Nanoparticles	DNA	140-260	+16.4 to +34	98	Obtained NPs successfully retained DNA and protected it from nuclease degradation.	[192]
Tamarind gum	Nanoemulsion	Apigenin	183.31	+31.9	Not reported	(i) Results showed toxicity on melanoma (A341) in a concentration range of 0.4–2.0 mg/mL, but less toxicity toward HaCaT cells. (ii) The carbopol and tamarind gum-based nanoemulsion gel formulation loaded with apigenin had a higher penetrability across goatskin compared to marketed formulation.	[193]
High methoxyl pectin (HMP) and low methoxyl pectin (LMP)	Nanoliposomes	Vitamin C	66.9 to 128.9	+2.3 to −35.5	49	HMP and LMP-based nanoliposomes displayed an obvious enhancement in storage stability, with lower aggregation, oxidation of lipid and leakage ratio of vitamin C from liposomes; LMP-based nanoliposomes revealed better physicochemical stability. Furthermore, skin permeation of vitamin C was improved 1.7-fold for HMP-L and 2.1-fold for LMP-L after 24 h, respectively, compared with vitamin C nanoliposomes.	[81]
Sodium alginate	Nanofibers	Ciprofloxacin	200-300	Not reported	98	A faster wound area reduction was found with the treatment of ciprofloxacin loaded formulation compared to the non-loaded group.	[194]
Cashew gum	Nanoparticles	Alkaloid epiisopiloturine	107 to 154	-17.4 to -32.6	76	These gum-based formulation showed a great potential for treatment of skin diseases.	[195]
Xanthan gum	Nanohydrogel	Liranaftate	93.40	Not reported	Not reported	The results suggested that obtained formulation played a key role in enhancing permeability and skin retention effect of liranaftate. The skin permeation ability of HLM-3 increased significantly as compared to the saturated solution of drug.	[196]

also protects the body from external chemicals and microbes, provide cutaneous immunity, etc. Our skin structure is made up of numerous proteins and any mutation in the genes encoding these proteins can lead to the genetic skin disorder. Different types of skin diseases are found in humans; some are very common such as eczema, psoriasis, acne, tinea, warts skin cancer and skin infections [180]. Mostly skin diseases are not very poisonous or life threatening, but can lead to considerable morbidity. Some important skin diseases include **Acne:** acne vulgaris is the most common skin disorder globally in adults and its main cause is a bacterium, named *pionibacterium acnes;* the other forms of acne might be due to creams, greases, oils and dyes. Antibiotics are used for its treatment but in some condition surgery or laser surgery is done. **Psoriasis:** is a skin inflammation which affects around 0.6-4.8% people globally and is characterized by erythematous papules and plaques with usually silver color scale. Petroleum jelly and thick creams are usually used for its treatment. Eczema: is a genetically inherited

chronic skin infection mostly found in adults. Most affected sites on the body are scalp, face, trunk and extremities. Its common treatments include cyclosporine given orally or UV light therapy. Keloids: is a tumor like fibrous growth which is developed as a result of altered wound healing. For its treatment, excision or the combination of different therapies can be used [180]. Rosacea: is quite similar with acne and mostly occurs in older adults. It is a vascular dilation of the central face and its cause is unknown. Usually antibiotics are used for its treatment. Alopecia Areata: is not a noninfectious and noncontagious disease. It attacks the follicles of the hairs and may cause complete hair loss. Many patients can recover without treatment while topical steroids are used for its treatment [181]. Some important viral diseases of skin are measles, rubella, erythema and herpes simples.

Application of different polysaccharide-based nanocarriers incorporating drugs for healing of various skin diseases has been expanding recently. As for example, baicalin was entrapped into gellan-based nanohydrogels successfully, which exhibited excellent inhibiting effect of particular inflammatory markers including oedema, tumor necrosis factor-α, and myeloperoxidase. *In vitro* analysis also confirmed the capacity of produced nanohydrogels to favor the deposition of baicalin in the epidermis [182]. In another research, ibuprofen-loaded cellulose acetate nanofibers were successfully fabricated and they exhibeted improved permeability in the porcine skin as compared to the casting membrane. It was reported that non-woven assemblies revealed superior breathability as well as displayed strong potential in transdermal delivery [183]. In another interesting work, methotrexate-loaded chitosan NPs offered inferior cytotoxicity as compared to the free methotrexate. In skin permeation studies, these chitosan-based NPs infused inside the pig ear skin barrier where they showed relatively higher efficiency up to 3.3-fold maximum than free methotrexate [184]. Table 5 provides more details on relevant studies.

5. Conclusion and future remarks

In recent era, NPLS are recognized as encouraging candidates for fabrication of novel drug delivery systems owing to their wonderful merits including GRAS materials, excellent biocompatibility, non-toxicity, inexpensive, enhancing drug solubility and storage capacity. Recently, many researchers have showed their deep interest on the construction of polysaccharide-based nanocarriers because of their wider productive purposes like encapsulating various drugs for treatment of different diseases including cancer, diabetes, HIV, malaria, cardiovascular, respiratory and skin diseases. The splendid biocompatibility, presence of functional groups, efficient mechanical characteristics, tremendous bioaccessibility and lowest cytotoxicity of polysaccharides make them ideal materials for development of potential nanoencapsulated systems. To sum up, different nano-vehicles such as nanoemulsions, nanohydrogels, nanoliposomes, nanofibers, and nanoparticles are efficient cargos for controlled release of drugs on targeted/infected sites because of their perfect stability in GIT surroundings. Future in-depth studies are needed to explore NPLS for innovative biomedical applications. It is need of time to understand the multidimensional functions of those nanoencapsulated systems which are fabricated with two or more types of NPLS. Furthermore, it is also essential to evaluate the degradation design of polysaccharide-based nanocarriers after degradation inside the body. Herein, it is highly anticipated by several studies that these NPLS-based delivery systems encapsulating several drugs could be used because of their great potential for carefully transportation of drugs as well as for increasing their solubility and bioaccessibility, and even they have the capability to uphold their stability during the GIT surroundings.

Declaration of Competing Interest

All authors declared that they have no any kinds of conflicts.

Acknowledgement

The authors are grateful to the International Education School at Jiangnan University and Chinese Scholarship Council (CSC) for financial support throughout the study. The author Abdur Rehman would like to thanks Jiangnan University and Chinese Government Scholarship for giving opportunity, support and stay in China for carrying study.

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