Review article

An overview on recent biomedical applications of biopolymers: Their role in drug delivery systems and comparison of major systems

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Abstract

Polymers are ubiquitous in our daily lives, from workplaces to homes. Biopolymers are becoming more popular as an alternative to petroleum-based polymers because of their lower environmental impact due to their low carbon footprint and easy degradation. The primary aim of developing technology is a better quality of life. Improved therapies and tailor-made treatments are currently the focus of scientists. However, the delivery of drugs has been a long problem in the field of medicine. As a result, many drug delivery systems (DDSs) have been created for this purpose. Among these, nanotechnology-based DDSs, especially nanofibers, hold a promising future. This review focuses on the importance of naturally abundant biopolymers in recent medical applications, especially their role in DDSs, and provides a crucial comparison of the merits and demerits of the major DDSs for researchers to develop tailor-made DDSs.

Keywords:

Biopolymers, Nanotechnology, Drug delivery systems, Nanofibers, Biomedical

Abbreviations

No keyword abbreviations are available

Data availability

Data will be made available on request.

Nomenclature

BNC Bacterial nanocellulose
CNC Cellulose nanocrystal
CNF Cellulose nanofibers
CS Chitosan
CM Convergent method
CMC Critical micellar concentration
DM Divergent method
DDS Drug delivery system
ES Electrospinning
ECM Extracellular matrix
EVs Extracellular vesicles
FDA Food and Drug Administration
GPC Global production capacity
GTA Glycerol triacetate
HMPA 2,2-bis(hydroxymethyl)propanoic acid
HNT Halloysite nanotubes HNT
MTX Methotrexate
NC Nanocellulose
NF Nanofiber
PEG Polyethylene glycol
PVP Polyvinylpyrrolidone
PCL poly-caprolactone
PLA Poly lactic acid
PMS Polymeric micelles

TEMED 2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl

TEC Triethyl citrate (TEC)

1 Introduction

In the past decade, there has been a massive uproar for replacing fossil fuel-based products with green eco-friendly products having sustainability. Due to the industry's continuous growth, the demand for polymers has increased. Previously, petroleum-based polymers were mainly used to cope with the continuous increase in industrial demand and fulfilled the requirements to some extent, but they harm our environment more. Petroleum-based polymers are limited to industrial use only since they lack biocompatibility and degradability and have become significant carbon contributors [3]. Biomaterials are the class of synthetic or natural polymers, composites, ceramics, and metals that can interact with the biological system for various applications [4]. However, biopolymers have gained exceptional importance in this class over the past decade. Biopolymers are produced from natural or plant-based resources such as different bio-wastages, horticulture, and crops, and in the form of by-products. Biopolymers are renewable, biocompatible, cheap, release less carbon, and are ultimately environmentally friendly, with the least harmful impact on the environment in terms of pollution. So, in recent years, the trend has shifted towards biopolymers to fulfill the growing demand [5]. The key features of biopolymers are illustrated in Fig. 1 a. Biopolymers play a crucial role in major industrial sectors (Fig. 1b). The growth of the biopolymer industry and its demand can be understood from the fact that the sales of biopolymers are increasing by 20–30% per year. This sales increase reflects that petroleum-based polymers will be entirely replaced by biopolymers in the coming years [6] (Fig. 1b).

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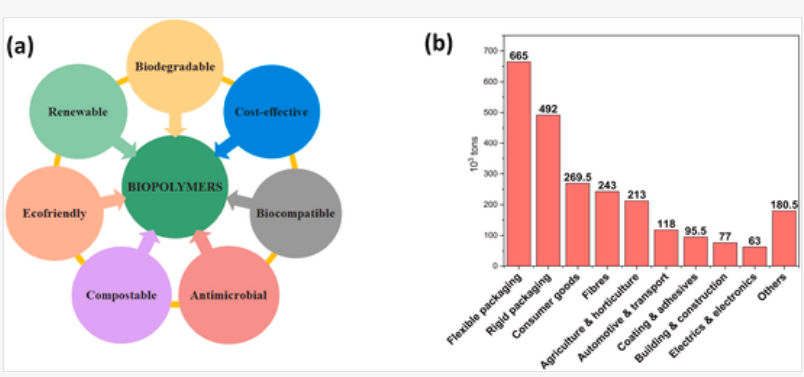
Fig. 1



Key features of biopolymers; (a) Main characteristics, (b) Use in major industrial sectors.

According to the European Bioplastics 2021 report, it is estimated that by 2026 the bio-based/non-biodegradable polymers market will be decreased by 15.08%, while there will be an increase of 8.41% in the biodegradable biopolymers production capacities due to the increasing in demand worldwide. Fig. 2 shows the comparison between overall production and biopolymers production based on biodegradability. The report also estimated that the global production capacity (GPC) of biopolymers would be increased by 214.15% (calculated by the authors based on data from https://ect-center.com/blog/biodegradable-polymers).

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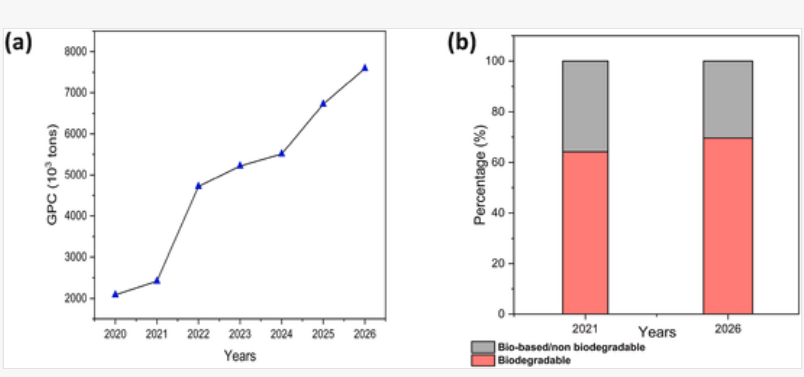
Fig. 2



Predicted biopolymers production; (a) overall volume from 2020 to 2026, (b) volume in 2026 based on biodegradability.

Technology is evolving every day, and the top priority of scientists is the quality of health care. Therapeutics and drug delivery have been a primary concern of scientists for many years because efficient and effective drug delivery has always been a problem. The major issues faced in drug delivery include toxicity, non-specificity, side effects, less bioavailability, short drug delivery, rapid degradation, and the invasive nature [7–9]. Therefore, it is essential to devise new strategies for designing drug delivery systems (DDS) that are nontoxic, specific and can permit sustained drug delivery with increased bioavailability. Biopolymers in DDSs help in overcoming problems associated with biocompatibility and biodegradability. But still, new strategies are required to overcome these problems faced by the DDSs. Nanotechnology has gained the attention of scientists to overcome the issues with conventional DDSs. So, it has been observed that the drug delivery (DD) trend has shifted towards nanotechnology drug delivery systems (NDDSs). The fundamental feature of the success of these systems is that they are designed at the nano-level. Other key features include flexibility in the composition of the system components, free movement due to the nano size, biocompatibility, and non-toxicity [10,11].

This review focuses on the different biomaterials applications in the biomedical field, especially in DDSs. It highlights the progress so far, the major strengths and weaknesses of the systems, and the potential solutions to overcome the issues for various systems in future development. It also focuses on biomaterials based on recent nano DDSs, and critically compares the significant merits and demerits of the most commonly used DDSs, providing a guideline for developing tailormade DDSs.

2 Important biomaterials in biomedical applications

The significant advantage of biopolymers is their natural sources and cost-effectiveness. Here we discuss some of the most biomedically used biomaterials. The abundance and natural properties like biocompatibility and antimicrobial activity make them the optimum option for various biomedical applications ~~[12][252,253]~~[12,252,253].

2.1 Chitosan

Chitosan (CS) is the second abundant, non-toxic biopolymer that comprises glucosamine and N-acetyl glucosamine units (Fig. 3a) [13]. In nature, it is found in the exoskeletons of crustaceans and fungi. CS is obtained by the deacetylation of chitin in alkaline conditions, and this chemical reaction is represented in Fig. 3b. CS is a cationic polyamide that can react chemically with an anionic system [14].

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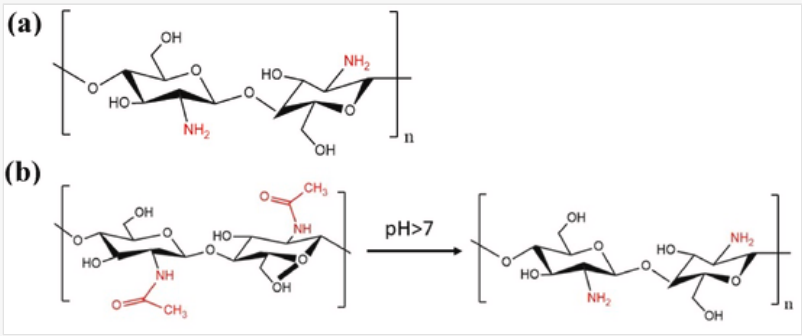
Fig. 3



Chemical structure; (a) chitosan, (b) conversion of chitin to chitosan.

2.1.1 Chitosan advantages and disadvantages

CS is considered a 'magical' polysaccharide for various medical applications. The primary reason is its various natural properties, including biocompatibility, biodegradability, mucoadhesiveness, and its derivability from biomass [15]. Usually, CS is mixed with natural or synthetic polymers. This blending improves physicochemical and mechanical properties [16]. The ability of CS to exist in different physical forms and be soluble in alkaline, acidic, and neutral solutions makes it more applicable compared to chitin [17]. Viscosity is the main parameter to consider for the formation of biocomposites. The viscosity is in direct relation to the concentration of CS. Decreasing the temperature and increasing the degree of deacetylation also increase the viscosity. The deacetylation process of chitin adds primary amino groups that equip CS with antioxidant and antimicrobial properties [18]**.** This addition makes CS a natural choice for medical applications like wound healing due to its homeostatic nature and antimicrobial activities [19].

CS can be refined into nanofibers (NFs), gel, beads, scaffolds, nanoparticles, sponges, membranes, and standalone films [20]. NFs of CS have a large surface area to volume ratios and greater porosities, and they are widely used in biomedical applications such as biological scaffolds, bacterial inhibition, and bone tissue engineering [21, 22]. Using copolymers with the main biopolymer increases the overall abilities of the biocomposite. One of the main biopolymers used with CS is nanocellulose [23]. Chitosan has several benefits, but its poor solubility is its primary downside. Chitosan has the least solubility at the physiological pH of 7.4 because it is a weak base (pka = 6.2–7). The protonated polycation form, $-NH_3^+$ in acidic conditions and hence it is only soluble in acidic medium [24]. The rapid drug release that occurs in drug delivery applications due to CS strong swelling propensity in an aqueous environment is another drawback. The best solution for overcoming these issues is the chemical modification of CS $-NH_2$ or OH group. Mostly CS is modified mostly by adding thiolate or carboxymethyl group [25].

2.1.2 Chitosan applications

CS is the main component for synthesizing biocomposites in many biomedical applications, especially drug delivery [26,27] and tissue engineering [28,29]. CS-based biocomposites can be physically and chemically modified by crosslinking, grafting, impregnation, blending, incorporating rigid fillers, and interpenetration [30].

CS's anti-tumor, antimicrobial and fungal properties make it an appealing material worldwide in pharmaceutical and dentistry fields. It also plays a crucial role in the synthesis of bio-dental materials. These vast potential applications make CS important from an economic point of view because of its current profitable uses in DDSs, treatment of periodontitis, and dentil-pulp regeneration [31]**.** Dinesh and coworkers [32] synthesized cellulose and carboxymethyl modified CS for wound healing. The hydrogels were easily modified into different configurations and showed high injectability potential; they have increased antibacterial activity and proved to be a potential future biomaterial for wound healing. Shagdarova and coworkers [33] used CS and collagen-based hydrogels using Genepin crosslinking for wound healing in mice with diabetes. The hydrogels showed good mechanical and improved biological properties in mouse models but needed to undergo clinical trials. An advanced development was discovered in which CS led to a new DDS by releasing therapeutic components (drugs, growth factors, nanoparticles, and nanostructures) in response to environmental stimuli [34]. CS controls the release of therapeutic components by protecting them from the harsh environment of the body so that the bioavailability of the components can be increased [35]**.**

2.2 Nanocellulose

Cellulose is a linear homopolymer of D-glucose units linked by β-1,4 glycosidic bonds (Fig. 4). It comprises microfibrils with a nano-sized diameter and is surrounded by lignin and hemicellulose [36]. It is the most abundant biopolymer on Earth. Cotton fiber consists of 90% cellulose, while wood has around 45% cellulose [37]. Cellulose in humans is considered a hydrophilic bulking agent for the stools and is often referred to as "dietary fiber" [38].

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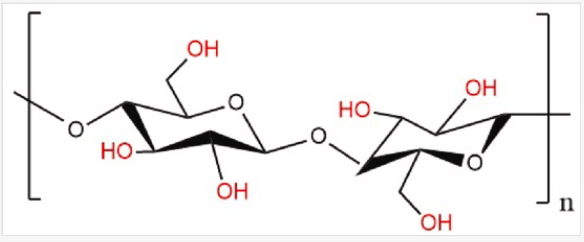
Fig. 4



Structure of cellulose.

Nanocellulose (NC) is a broad term often referring to three types of nano-structured cellulose. These include cellulose nanocrystals (CNC), cellulose nanofibers (CNF), or bacterial nanocellulose (BNC), which is derived from *Gluconacetobacter xylinus* [39–41]. Cellulose nano crystals (CNCs) are obtained by hydrolysis (using sulphuric acid and hydrochloric acid) and have a rod-like structure with a high crystalline index [42]. Young's modulus of CNC ranges from 130 GPa to 250 GPa [43]. CNC based thin films are coated using spin coating and other polymer electrolytes. They can also be used as reinforcing agents due to their biodegradability, high tensile strength, and high aspect ratio [44].

Cellulose nanofibrils (CNFs) are obtained by separation from plant cell walls by homogenization and grinding. Their properties depend on the botanical source and relate to the width of the microfibril in the original plant. Wood based CNFs have a diameter of 10−30 nm. They consist of a crystalline domain in combination with a disordered amorphous region, but because of this structural orientation, their density is relatively low and flexible [45]. They have an advantage in hybrid materials due to their interaction strength with other secondary materials [46]. Bacterial nanocellulose (BNC) gives the highest efficiency production of cellulose and is a nanofibril polymer and is of bacterial origin, obtained by bacterial cultivation. BNCs have ribbon-like structures and a high crystalline index [47]. BNC possesses chemical purity, excellent mechanical strength, superior flexibility, and high absorbency. Due to these properties, BNC has found application in various industries like food, paper, and electronics. In the future, scientists look forward to using BNC in medicine [48].

2.2.1 Nanocellulose advantages and disadvantages

NCs are considered biocompatible nanomaterials and are relatively safe for different biomedical applications. Many common properties among NCs make them a good candidate for medical applications. These properties include low cost, low density, solubility, significant surface area, aspect ratio, mechanical properties, abundance, elasticity, low thermal expansion, and mechanical properties [49]. The modulus and bending strength of cellulose NFs are 150 GPa and 10 GPa, respectively, giving it an advantage of mechanical strength over other biopolymers; hence, it is used in various wound healing dressings [50]. NC is often used with CS, thus improving the mechanical properties of CS-based biocomposites [51]. NC has the attractive capability of undergoing surface chemical modifications. Hydroxyl groups and a high surface area to volume ratio play an important role in introducing different functional groups. These groups can be either charged or hydrophobic moieties that may include oxidation, amination, epoxidation, esterification, silylation, carboxymethylation, sulfonation, and thiol- and azido-functional capabilities [52,53]. NC has a lot of potential properties for biomedical applications, but its use is limited owing to various drawbacks. Due to their significant moisture absorption, poor wettability, and restriction of processing temperature of NC restrict their blending with other biopolymers [54]. However, these problems may be solved by producing NC derivatives through chemical modification processes such as esterification, etherification, or oxidation. NCs usually have immunotolerant potential, but cellulose nanocrystals can induce an inflammatory response. This response can be modulated by the functionalization of CNCs [55,56]. NC can be utilized in coatings, aerogels, hydrogels, films, and membranes for various research areas, from biomedical to material engineering [57].

2.2.2 Nanocellulose applications

In recent years, the construction of NC-based biocomposites has become very popular. NC materials have massive potential in photonics, films, foams, surface modifications, nanocomposites, wound dressings, drug delivery, packaging materials, medical devices, optoelectronics, and tissue regeneration scaffolds [58]. NCs also help incorporate desired properties like antimicrobial and antioxidant activities, barrier properties, super-hydrophobicity, or super-hydrophilicity and play roles in the adhesion and brittleness properties during fabrication [57]. Other components used to prepare nanocellulose-based biocomposites include antibiotics, metal oxide, and nanoparticles [59]. One of the primary uses of nanocellulose is in cell culture. Nanocellulose resembles extracellular matrix (ECM) properties with low cytotoxicity. Hence nanocellulose hydrogels are used in 3D cell culture [60]. Rosendahl and coworkers [61] used 3D-printed nanocellulose scaffolds to study breast cancer cells. They used MCF7 and MDA-MB-231 cell lines. Both these cell lines showed increased gene expression of stemness, and migration markers compared to conventional 2D cell culture.

Bone reconstruction has always been challenging for scientists because of the non-availability of biocompatible matrix mimicking ECM. Alginate and gelatin are usually used for the tissue engineering of bone cells as they are highly biocompatible due to their chemical structure [62,63]. In addition to these two biopolymers, various nanomaterials are also used with the alginate and gelatin matrix. However, due to the biocompatibility and natural matrix-like structure, NC is now considered the most compatible biomaterial for tissue engineering [64,65]. It increases the mechanical strength of the matrix by several folds. NC scaffolds may prove to be a potential candidate for drug screening. Dinesh and coworkers [66] prepared 3D-printed alginate–gelatin scaffolds incorporating CNC. The prepared scaffolds showed enhanced swelling properties, improved cell viability (mesenchymal stem cells), and increased mineral deposition. At the genetic level, the upregulation of osteogenic-related genes was also observed. Their results showed that the NC scaffold holds a promising future for 3D-printed tissue engineering.

NC has high mechanical strength, and during wound dressing and cartilage repair, it promotes cell regeneration by acting as a scaffold for tissue engineering. It also allows the targeted delivery of drugs and drives applications in separating biomolecules and cells [67]. Shahriari-Khalaji and coworkers synthesized a dressing for wound healing by using bacterial nanocellulose functionalized by 2,2,6,6-tetramethyl piperidine-1-yl-oxidanyl (TEMPO) oxidation and Poly-L-lysine for the dressing of the infected wound. This functionalization equipped the nanocellulose with high carboxylate content and tensile strength. The developed dressing showed higher antibacterial activity and less toxicity. The rats' wounds recovered faster due to decreased inflammation, higher blood vessel proliferation, and epidermal formation. The dressing could prove to be promising in the future [68]. Zhao and coworkers developed nanofibrils hydrogels with reinforced hyaluronic acid for regenerating cartilage. The synthesized hydrogels showed a high compressive modulus (0.46 ± 0.05 MPa), high strength (0.198 ± 0.009 MPa), and restoring power. High mechanical strength is ideal for strength-bearing tissue like cartilage. The hydrogels also provided an excellent microenvironment for stem cell proliferation and differentiation from chondrogenic cells. They showed a prominent repair effect in rat models with cartilage defects. These hydrogels showed a new way to fabricate scaffolds for cartilage tissue engineering [69].

They are also involved in scaffolds, biosensors for detecting cholesterol, various enzymes and diseases, heavy metal ions in human sweat and urine, general health monitoring, and biomedical implants ~~[254]~~[~~70~~70,254]. The leading edge of the nanocellulose biosensor over the conventional biosensor is its biodegradability [71]. Rao and coworkers formed a dopamine detection biosensor by disrupting the bacterial cellulose pellicle and loading it with palladium nanoparticles. They further modified it with N~~n~~afion and laccase to form the biosensor. The biosensor showed higher sensitivity (5–167 μM) and a lower detection limit (1.26 μM) [72].

Drug solubility in an aqueous medium has become a challenge in recent years. Scientists are trying to find new excipients for DD [54]. CNF is considered a much better excipient due to its remarkable properties like high surface chemistry, high surface area to volume ratio, a barrier to gas in a dry state, negligible toxicity, and high biocompatibility. Kumari and coworkers [73] devised a curcumin delivery system by encapsulating it within the NFs obtained from lemon grass waste. They achieved a drug encapsulation efficiency of 99%. The release mechanism of the nanocomposite was diffusion at all pH. The conserved efficacy of the curcumin was observed in PC3

cell lines, indicating that it could be a good candidate for curcumin in cancer treatment. Pedige and coworkers [74] formed pH-sensitive hydrogels. They oxidized BNC and CNF to form dialdehyde bacterial cellulose (DABC), and then they combined it with CS to form the composite. The composite showed increased mechanical strength in the acidic medium and lowered mechanical strength in the basic medium. The prepared composite can be suitable for biomedical applications, especially DD.

2.3 Poly lactic acid

Poly lactic acid (PLA) is a thermoplastic polyester having the backbone formula $(C_3H_4O_2)_n$ or $[-C(CH_3)HC(=O)O-]_n$ (Fig. 5). It is obtained by condensation of lactic acid with loss of water. The raw material for PLA is obtained by fermenting sugars [75,76]. PLA was approved by the Food and Drug Administration (FDA) as a biomedical material as it is a low cost, biodegradable, biocompatible, compostable, and nontoxic polymer with good mechanical properties [77].

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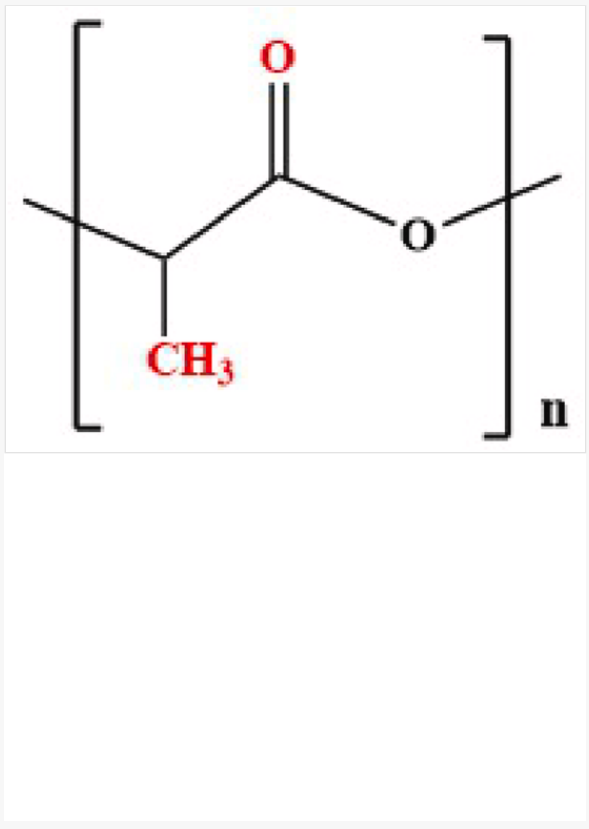
Fig. 5



Structure of poly lactic acid.

2.3.1 Poly lactic acid advantages and disadvantages

PLA is the leading polymer compared to conventional polymers made from petroleum for biomedical applications. PLA has several advantages in the medical and manufacturing sectors [78]. PLA breaks down into L-lactic acid monomers when hydrated. Because they are excreted in the urine, they do not build up in the kidneys or other vital organs. Products made from PLA may enable regulated adsorption and delivery of medicines due to the scaffolds adaptable pore diameter and pore interconnectivity [79]. PLA finds its most widespread usage in the fiber and film industries. These properties make PLA a worthy substitute for petroleum-based polymers.

However, the limitations of PLA are its low melting point, slow crystallization rate, limited processability, high brittleness, low mechanical strength, and low service temperature. These limitations are usually overcome by blending PLA with other fillers in the form of biomaterials or biopolymers. These are used to vary the mechanical properties of the PLA. The fillers generally used are triethyl citrate (TEC) and glycerol triacetate (GTA). They enhance ductility, but on the other hand, they reduce mechanical strength. Recently, CS has gained attention for being used as a copolymer with the PLA to increase the tensile strength and tensile modulus [80]. CS/PLA composites also demonstrated good barrier properties against moisture and UV rays [81,82]. However, due to its natural hydrophobic nature is used as a scaffold for tissue engineering and orthopedic implants. Adding PLA to different materials enhances the properties, especially mechanical strength [83]. Still, PLA is becoming the most used biodegradable polymer in clinical applications, ranging from DDSs and tissue engineering to temporary and long-term implantable devices, and constantly expanding to further fields [84,85].

2.3.2 Poly lactic acid applications

PLA is increasingly used in various biomedical applications, including tissue engineering scaffolds, short- and long implants, bone screws, anchors, spinal cages, prostheses, sutures, vascular grafts, and drug delivery [86]. Chen and coworkers [79] prepared bio-composite using PLA, magnesium powder, and calcium phosphate ($PLA-Mg-Ca_3(PO4)_2$). The composite showed increased mechanical strength, negligible cytotoxicity, and biocompatible products after degradation, thus improving the healing of bone tissue. PLA has also been successfully used in numerous DD formulations because of its high biocompatibility, tunable degradation rates, and malleability [87].

Mei and coworkers [88] prepared PLA-methotrexate (PLA-MTX) scaffolds for controlled DD to repress tumor growth. Scaffolds were prepared by using 3D printing. The scaffold showed high suppressive effects on A-549, MCF-7, and 4T1 nano cell lines and a less toxic effect on normal cell line MC3T3-E1. *In vivo* experiments also showed that the scaffolds have no side effects on the organs. Thus, all the results showed that the PLA-MTX scaffold could treat tumors by controlled drug release. Khosraviboroujeni and coworkers [85] prepared a 3D-printed micro needles system based on PLA for the transdermal delivery of estradiol valerate. The size of the needle tip was kept at around 173 μm. The drug release was recorded slowly for up to seven days. The studies also confirmed that the needles could penetrate the skin without reaching dermal nerves and puncturing blood vessels. Thus, this system can be used for the painless delivery of drugs transdermally.

2.4 Lipids

Lipids and fats are critical components for the homeostatic function of the body. It plays an essential role in the most critical functions of the human body, especially in energy storage and maintaining the integrity of the cells. Lipids, by nature, are oily and nonpolar and hence are soluble in organic solvents. Lipids generally comprise phospholipids, fats & oils, waxes, and steroids [89,90]. Since lipids lack the repeating monomer unit, they are considered macromolecular biomaterials, but they are most

compatible with the body as lipids make up 50% of an individual cell. The significant role of these biomaterials in biomedical applications is the drug delivery application [91].

2.4.1 Lipids applications

This class of biomolecules, due to its immense potential properties, makes up the major classes of DDS known as lipid-based drug delivery systems (LBDDS). LBDDS gained major attention due to their delivery of water-insoluble drugs, increased bioavailability of drugs, low antigenicity, high bioactivity, natural biocompatibility, and easy drug transport and release due to fusion with the cell membrane [92]. However, LBDDS lacks the stability and mechanical strength to withstand the harsh body environment during the DD. On the other hand, biopolymers play crucial roles in the DDS, but the significant drawbacks include drug solubility, low biocompatibility, physiological degradation, efficacy, and bioavailability. To overcome these issues, lipids are now used with biopolymers to form lipid-polymers amalgam DDS. These systems show exceptional properties; the individual system lacks [93,94]. Major advantages include increased encapsulation efficiency, enhanced stability, specified kinetics for controlled release, and a precisely tailored release profile are all possible with the hybrid composite [95].

There are three parts to lipid-polymer hybrid nanoparticles: the polymer core, which encapsulates the drug; the lipid monolayer, which surrounds the polymer core and provides control over drug release; and the lipid-polymer layer, for steric stabilization, which offers increased half-life for the therapeutic [96]. Drugs, proteins, DNA, vaccines, anti-ageing compounds, and target ligands may all be encapsulated, adsorbed, or covalently bonded using these hybrid systems [97,98]. Lipids-based drug delivery systems (LBDDS) mainly include liposomes and extracellular vesicles. Some of the commercially available drugs in lipid formulations are included in Table 1. Fig. 6 sums up the common merits and individual drawbacks of the biopolymers discussed, focusing on the DD application.

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Table 1

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Commercially available drugs in lipid formulations [2].

Therapeutic	Marketed product name	Targeted disease	Major role	References
Efavirenz	Sustiva®	HIV/AIDS	Inhibiting the reproduction of HIV by inhibiting the enzyme protease for reproduction	[99]
Saquinavir	Fortovase®			[100]
Ritonavir	Nor-vir®			[101]
Clofazamine	Lamprene®	Hansen's disease (leprosy)	Inhibit bacterial growth by binding to the DNA	[102]
mRNA	Pfizer-BioNTech (BNT162b2; comirnaty)	COVID-19	Immunity against COVID-19	[103]
	Moderna mRNA vaccine			[104]

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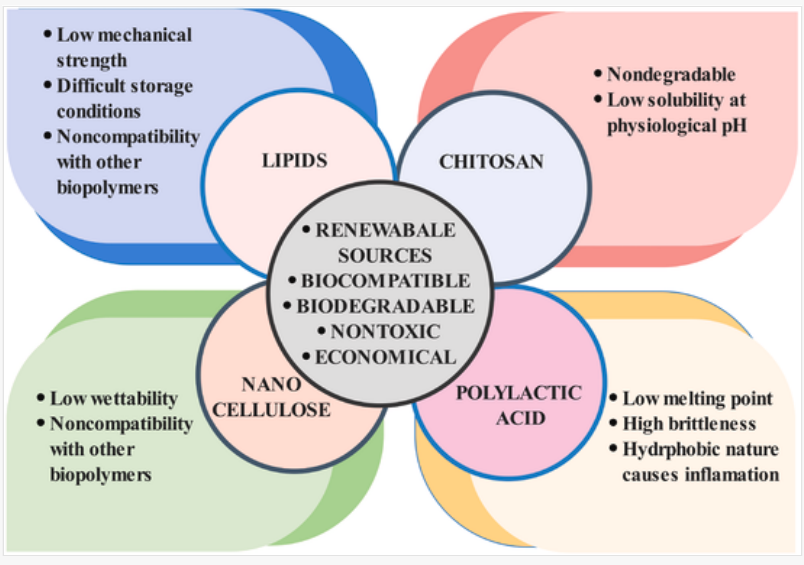
Fig. 6



Comparison of merits and demerits of major biopolymers.

3 Drug delivery systems

Drug delivery systems (DDSs) are approaches, formulations, manufacturing techniques, storage systems, and other technologies to transport a therapeutic substance to the specific target site in the body [105]. Different drug formulations and devices are used for various drug delivery. Nowadays, in addition to pharmaceutical drugs, scientists are looking for the delivery of biomolecules into the body, including peptides, proteins, cells, and genes [106]. The ideal DDS should be target site-specific and should prevent drug degradation in blood circulation. It should also increase the drug's effectiveness and prevent the cellular degradation of the drugs by enzymes native to the cell [107,108]. The significant challenges for the DDSs include controlled drug release, less toxicity, low immunogenic response, site-specific delivery, increased bioavailability after reaching the target site, and delivery of the macromolecule inside the cell [109]. In the past decade, nanotechnology based DDSs have gained much more attention as compared to conventional systems since, without any doubt, they hold the key to the future of therapeutics [110–112]. The system involves designing at a nano-scale level, resulting in efficient therapeutic delivery. Scientists call these smart nanocarriers [113,114], and are primarily used for anti-cancer treatments and therapeutics delivery [115].

3.1 Hydrogels drug delivery system

Hydrogels are polymers with a 3D network. They naturally absorb water and swell under certain conditions without deformation and being dissolved. They have applications in various fields like tissue engineering [116], drug delivery [117], and wound dressings [118]. However, the application of DD has gained much attention in the last decade. The two main features of this DDS include its insolubility in aqueous media and flexibility in the adjustment of porosity. The insolubility of hydrogels is due to the physical or chemical crosslinking in the 3D network. The crosslinked networks mean that the hydrogels may be formed from a single polymer or a blending of polymers to produce hydrophilic hydrogels. The groups mainly responsible for the hydrophilic nature include sulphonic, hydroxyl, and carboxyl. In some instances, the copolymerization of hydrophilic and hydrophobic polymers yields semi-interpenetrating or interpenetrating networks [119]. The porosity of hydrogels is tunable since the affinity of hydrogels for aqueous media and the density of polymers can be adjusted to fine-tune their porosity. The porosity ultimately plays an essential role in drug trapping and subsequent release. Hydrogels can also be developed into various sizes and shapes, from film and beads to slabs, depending upon the application [120,121].

3.1.1 Methods of hydrogels formulation

The 3D hydrogel network is crosslinked by physical and chemical means. Hydrogels are said to be physically crosslinked if the non-covalent interaction holds the network chains. These hydrogels are considered less toxic and do not require crosslinker aid [122]. But the drawbacks of these hydrogels include the disruption of the gels in the presence of varying physical conditions like stress, pH, and change in ionic strength [123].

In chemical crosslinking, the primary force for crosslinking is the covalent interaction between the

polymeric network [124,125]. Chemically crosslinked hydrogels are more stable and have more mechanical strength than physically crosslinked hydrogels [126]. Different methods for chemically crosslinked hydrogels are mentioned in Table 2, while methods used to prepare physically crosslinked hydrogels are shown in Table 3.

alt-text: Table 2

Table 2

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Different strategies to prepare chemically cross-linked hydrogels.

Techniques	Methods	Advantages	Disadvantages	References
Radical polymerization	This method revolves around the crosslinkers for the polymerization of monomers. This method is rapid and easy	Hydrogels can be formed rapidly at room temperature and physiological pH	Uncontrollable reaction causing the uneven distribution of polymerization resulting in non-uniform hydrogels	[127,128]
Chemical reaction crosslinking	This method utilizes the natural chemical reaction between different functional groups	Utilizes the naturally occurring functional groups, mainly –OH groups, for the cross-linking	Toxic crosslinkers are mostly used and are not suitable for the biomedical applications	[129]
Enzyme crosslinking	This method makes use of enzymes for the fabrication of hydrogels.	Maximum crosslinking is achieved due to enzyme specificity, non-toxic	Enzymes are costly, and it is not easy to have specific enzymes for specific reactions	[130]

alt-text: Table 3

Table 3

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Different strategies to prepare physically cross-linked hydrogels.

Techniques	Methods	Advantages	Disadvantages	References
Cooling or heating of the solution	The hot polymer solution is cooled to synthesize hydrogels	Easy method, no cross linker required	Addition of salt for the formation gel results in unwanted ions affecting the application.	[131,132]
Ionic interaction	The polymer is crosslinked by adding a divalent or trivalent ion of the opposite charge	Good mechanical strength, independent of necessity for biopolymers to have ionic groups	Addition of salts for the gelling of solution limits the utilization in biomedical applications	[133]
Coacervation of complex	The mixing of poly-ions having opposite charges forms coacervates gels	Uses the natural opposite ions interaction of the biopolymers involved, ecofriendly	Too much dependency upon the pH of the solution and polymers concentration	[134]
Freeze–thawing method	These gels are fabricated by the repetition of freeze-thaw cycles. The major mechanism behind the formation of crosslinking is microcrystals and H-bonding	Ecofriendly, nontoxic, highly porous, and elastic hydrogel formation	Low mechanical strength in aqueous medium since the only link involve is hydrogen bonding	[135]

3.1.2 The applications of hydrogels

In recent years, scientists have been moving towards developing biopolymer-based hydrogels for DD that are stimuli-responsive and are named “smart hydrogels” [136]. Fig. 7 shows the overall theme for the stimuli responsive based mechanism of smart hydrogels. They are usually responsive to stimuli like pH [137,138], temperature [139], antigens [140], light [141,142], and glucose [143]. Table 4 enlists some of the recent DD applications of biopolymer based smart hydrogels.

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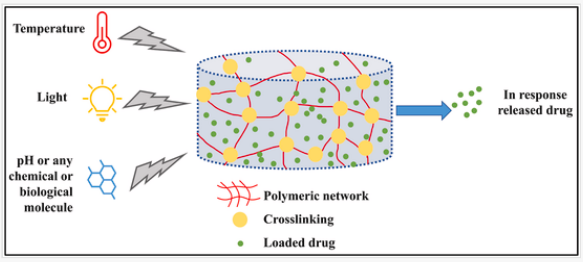
alt-text: Fig. 7

Fig. 7



Smart hydrogels drug delivery illustration.

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Table 4

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Recent biopolymers-based hydrogels drug delivery systems.

Hydrogels composition		Role of biopolymers	References
Biopolymer	**Drugs**		
Alginate	Insulin	Sustained release of drug	[144]
CS and cellulose	Amoxicillin	Controlled drug release, high-loading capacity	[145]
Mesona chinensis polysaccharide and CS	Curcumin	High mechanical stability and pore distribution	[146]
CS and cellulose	5-fluorouracil	Increase drug loading capacity and entrapment efficiency	[147]
CS and PVP/PEG	Acyclovir hydrochloride	Sustained release, skin-friendly and high mechanical strength	[148]

3.2 Nano drug delivery systems

3.2.1 Lipid-based nano drug delivery systems

The use of nanoparticles in the biomedical and pharmaceutical industries has revolutionized healthcare administration [149]. Biopolymer nanoparticles, which are in the nanosized size range, have a critical role in the controlled release of pharmaceuticals. The relevance of nanoparticles in biological signaling pathways may be traced back to their ability to reach intracellular and cellular targets and even the blood-brain barrier. Their tiny particle size is responsible for their high therapeutic efficacy, easy absorption, and subsequent circulation in the body [150]. Nanoparticle medication delivery based on biopolymers has attracted scientists' attention because of its potential benefits. Including biopolymers in nanoparticles has led to essential modifications that increase their effectiveness. Many bioactive molecules, including proteins, peptides, enzymes, immunomodulating agents, and nucleotides (e.g., DNA), have been successfully surface-immobilized using biopolymers in nanoparticle manufacturing [151–153]. In order to achieve the aims of targeted delivery of therapeutics, a fused form of lipid polymer amalgam is used [153,154]. Major lipid-based nano DDSs include liposomes and extracellular vesicles, which are discussed in the following sections.

3.2.1.1 Liposomal drug delivery system

Liposomes are spherical-shaped, colloidal vesicles composed of one or more lipid bilayers in an aqueous medium. A typical liposomal structure is shown in Fig. 8. They were first described in 1965 [155], and since then, liposomes have found their potential as DDSs. Their natural permeability and retention make them potential candidates for DD [156]. Based on their size, liposomes are divided into three main categories but the optimal size for liposomal drug delivery is 50–200 nm. Table 5 enlists the major types of liposomes based on their sizes [157].

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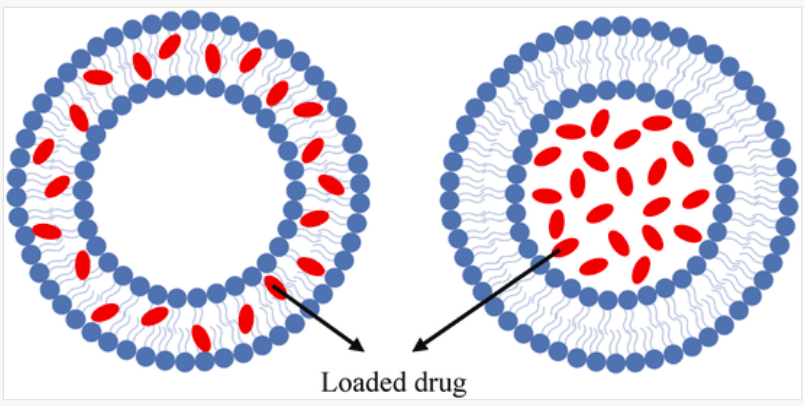
alt-text: Fig. 8

Fig. 8



Structure of liposomes loaded with drug, (a) Hydrophilic drug, (b) Hydrophobic drug.

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Table 5

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Different categories of liposomes based on size.

Name	Particle Size (nm)	Lamellae number
Unilamellar vesicle (small)	200–100	1
Unilamellar vesicle (Large)	>100	1
Multilamellar vesicle	>500	>5
Oligolamellar vesicle	100–1000	2–5
Multi vesicular vesicles	>1000	1

Despite so many natural features of liposomes, a few drawbacks limit the use of liposomes as the DDS. The main three disadvantages of this system include the retention of the entrapped molecule, rapid clearance by the immune system, and delivery of therapeutic effects across the cell membrane. The retention problem is solved by adding cholesterol and sphingomyelin to the lipid bilayer, reducing the leaking issue [158]. Secondly, when liposomes enter the bloodstream, they are taken up by the phagocytes cell of the spleen and liver. This cause a tremendous decrease in the therapeutic material's efficacy and bioavailability. This problem can be overcome by coating the liposome with polyethylene glycol. This strategy decreased liposome uptake by the monocytes, increasing their half-life [159]. The specific site delivery drawback can be overcome by using receptor-mediated endocytosis by covering the surface of the liposome with the antibody [160].

Several liposomal formulations for various drugs application are also commercially available, while many drug delivery formulations are in different phases of trials. Some of the commercially available liposomal-based drugs are listed in Table 6.

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Table 6

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Different commercially available liposomal-based therapeutics [1].

Disease	Drug	Administration route	Benefits
Fungal infection	Amphotericin B	IV infusion	Less toxic, improved stability
Asthma	Terbutaline sulfate	Subcutaneous injection	Enhanced drug efficacy, fewer side- effects
Keratitis	Amphotericin B	Ocular	Effective local and sustained drug release
Cancer therapy	Cytarabin	IV injection	Local targeted delivery
Breast neoplasm	Doxorubicin	IV injection	Targeted delivery, drug stability

3.2.1.2 Extracellular vesicles drug delivery

Extracellular vesicles (EVs) are nano-sized particles released by almost all cells in the body. They are involved in cell communication. EVs comprise lipid membranes and aqueous compartments that include many biomolecules like proteins, nucleic acids, and small soluble molecules [161]. EVs are usually confused with liposomes. Liposomes are artificial vesicles made up of a lipid bilayer and lack biological origin, while EVs are vesicles secreted by the cells [162]. EVs are very stable in different biological fluids and carry various biomolecules, making them a worthy candidate for the DDS [163].

For the isolation of EVs for a DDS, it is necessary to keep in mind that the method used should be able to preserve its structure. Secondly, the selected source should allow the garnering of the vesicles specific to the target cell or the organ [164]. EVs are conventionally isolated by exploiting their properties like size and density. The practical techniques involved are ultracentrifugation [165], microcentrifugation [166], and gel filtration [167]. Some isolation methods involve the modulation of solubility properties by using polyethylene glycol [168] or sodium acetate [169].

There are two main strategies for drug loading into EVs. The first is loading the drugs before EVs are isolated or manipulating the parent cell. For this strategy, the parent cell should be compatible with the drug. The second strategy is to load the drugs/therapeutic after EVs isolation. For this strategy, the structure of the vesicle should be preserved for proper functionalization [161]. Various DD applications of EVs for treating cancer and different diseases are listed in Table 7.

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Table 7

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Recent application of EVs in drug delivery.

Disease/Condition	Animal model	Therapeutic	Route of administration	References
Breast cancer	Mouse	PH20-hyaluronidase & Doxorubicin	IV	[170]
Melanoma	Mouse	TNF-a	IV	[171]
Triple negative breast cancer	Mouse	Verrucarin A	IV	[172]
Gastric cancer	Mouse	Lipocalin-type prostaglandin D2 synthase (L-PGDS)	Subcutaneous	[173]

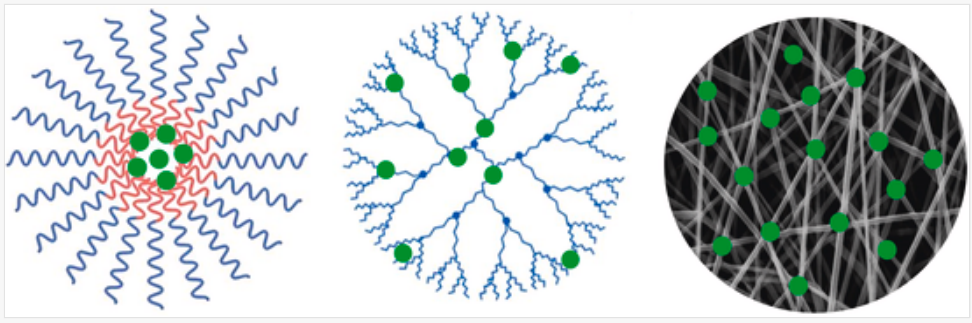
Lung cancer	Mouse	TNF-a	IV	[174]
Acute myocardial infarction	Rat	miR-223	Local	[175]
Alzheimer's disease	Mouse	Curcumin	IP	[176]
Parkinson's disease	Mouse	Anti-alpha synuclein shRNA minicircle	IV	[177]
Rheumatoid arthritis	Mouse	miR-21	IV	[178]
Acute kidney injury	Mouse	siRNAs	IV	[179]
Acute liver failure	Mouse	TNF-a	IV	[180]
COVID-19	Only *in vivo* study	Tetraspanin and CD63	Only *I in vivo* study	[181]
Neuroinflammation	Mice	Bryostatin-1	Local	[182]

3.3 Non lipid-based nano drug delivery systems

Various nano DDSs that utilize other biomaterials blends and offer a wide range of biomedical applications are also developed. This category consists of three major systems micelles, dendrimers, and nanofibers, as illustrated in Fig. 9.

alt-text: Fig. 9

Fig. 9



Major nanotechnology based drug delivery structures, (a) Polymeric micelles, (b) Dendrimers, (c) Nanofibers.

3.3.1 Polymeric micelles

Polymeric micelles (PMs) are nanoscopic structures (>100 nm). They are colloids formed mainly by the self-aggregation of block copolymers [183]. The solvent affinity for each block of copolymer (also known as block selectivity) drives the self-assembly of the copolymer in solution exclusively by thermodynamic forces [184]. They have a unique property known as the critical micellar concentration (CMC) for self-aggregation. Below the CMC, the structure exists as disassembled single molecules; above this concentration, they form micelles [185].

A typical micelle consists of a hydrophobic core by the hydrophobic blocks and a hydrophilic corona generated by hydrophilic blocks on the outer side [186]. Employing hydrophobic interactions, hydrogen bonds, and sometimes ionic connection, the hydrophobic building blocks of amphiphilic block copolymers join together to make a “reservoir” where additional hydrophobic molecules may be solubilized. Additionally, the core shields sensitive therapeutic agents from harsh physiological conditions. Polyethylene glycol (PEG) is the micelle's most universally used hydrophobic block [187].

The micelle structure is stabilized at the solvent-core boundary due to the corona. The corona's polymer must be easily dissolved in the solvent to retain the core structure there [188]. By reducing the contact area and extending into the solvent phase immediately surrounding the core, the corona's polymer chains may reduce the free energy of the hydrophobic core-solvent interaction. The corona interacts with the primary biological factors like various antibodies or proteins, which is critical in therapeutic delivery. PEG and PVP are mainly used as corona in the micelle structure [189,190]. Other than the self-aggregated method, various techniques for forming micelles are summarized in Table 8.

alt-text: Table 8

Table 8

Various techniques for the synthesis of polymeric micelles.

Methods	Common solvents	Advantages	Disadvantages	References
Dialysis	Ethanol, acetone, dimethylformamide, dimethyl sulfoxide, dimethylacetamide	Reproducible, narrow range size distribution	Dependence on organic solvent for the formation and difficulty to completely removing the solvent	[191]
Solvent-in-water emulsion	Ethyl acetate, dichloromethane, chloroform	Minimum leaking of the hydrophobic drug	Difficult to completely remove the organic solvent traces	[192]
Solvent evaporation	Acetone	The solvent can be removed efficiently	Low productivity	[193]
Salting-out	Acetone	No requirement for a stabilizer	Only high water miscible solvents can be used	[194]

They have been the most used nanocarriers in the past few years. The key features include easy preparation, smaller size, high efficacy in internalization, and excellent carrier for hydrophobic therapeutics, compared to conventional liposomes that require complex, lengthy, and costly preparation [195]. Most polymeric micelles develop in water reasonably promptly and once reach a particular size they become kinetically “frozen” [15]. As a result, very little polymer chain exchange takes place, which restricts the drug's equilibrium partitioning. To overcome kinetic restrictions and make it easier to load extremely hydrophobic medicines.

3.3.2 Dendrimers

Dendrimers are nanostructures made up of synthetic polymers. The main characteristics of dendrimers include a highly branched structure. Dendrimers have three main parts: a central core consisting of two or more reacting groups, interior layers made up of branching units attached to the core, and the outer surface having terminal functional groups [196].

Biodegradable dendrimers are usually synthesized step-by-step, iteratively [197]. Two methods are usually employed to synthesize dendrimers; one is the convergent method (CM), and the other one is the divergent method (DM). In DM, the dendrimer is grown around the core. The main disadvantage of this method is the construction of defective dendrimers, mainly because of the side reactions. Excessive reagents usually overcome this issue by not allowing any or, to a minimal extent, side reactions [198]. In CM, the starting point is the periphery, which proceeds towards the core. CM has many advantages over DM, including fewer chances of side reactions, pure product, proper structures of dendrimers obtained, and a lesser quantity of reagents required. This method has some disadvantages, like difficulty achieving surface functionalization and the stearic barrier due to the many layers [197]. The main advantages of the dendrimers include high compatibility with biological systems, the ability to carry a variety of therapeutics [199], and a stable structure [200]. The primary downsides of dendrimers are their non-degradability in the physiological environment, which has limited their application. Therefore, scientists are looking to synthesize biodegradable dendrimers [201,202]. Table 9 enlists some of the major categories of biodegradable dendrimers along with their merits and demerits.

alt-text: Table 9

Table 9

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Major categories of biodegradable dendrimers.

Categories	Major components	Advantages	Disadvantages	References
Polyester dendrimers	HMPA monomers, polyester dendrimers based on alternating monomers, and other polyester dendrimers	Degradable linkages and stable structures since cleavage is done under specific conditions, degradation at the physiological pH range	Specific conditions for the cleavage sometimes result in the non-degradability	[203]
Polyacetal dendrimers	Acid-labile polymers having acetal/ketal monomers	High pH sensitivity, good water solubility	Highly complex synthesis method	[204]
DNA dendrimers	DNA units	High immunostimulatory potency and cell internalization efficiency	High dependence on DNA-ligase enzyme for the formation	[205]

3.3.3 Nanofibers

Nanofibers (NFs) are a term that refers to a fiber having a diameter ranging from 50 to 300 nm. NFs are nanomaterials possessing many unique features that make them useful in various applications. Key features include a high surface area to weight ratio, less density, high pore volume, smaller pore size, and high stiffness and tensile strength [206,207]. There are many different conventional methods for NFs preparation, but the conventional methods have drawbacks. Table 10 lists conventional methods for preparing NFs and their drawbacks [212].

alt-text: Table 10

Table 10

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Major issues with the conventional nanofibers fabrication methods.

Methods	Major materials	Advantages	Drawbacks	References
Drawing method	Viscoelastic materials	Simple process, continuous nanofibers in multidirectional arrangement can be produced	It produces discontinuous fibers and cannot be used to produce only continuous fibers	[208]
Template synthesis	Polymeric, metallic, semiconductors, or ceramics based	Nanofibers with varying diameters can be produced	It can produce fibers only with some specific diameters	[209]
Phase separation method	PLA and poly glycolide only	Simple process with minimum equipment requirement, controllable mechanical strength	Restricted to only two polymers	[210]
Self-assembly method	Only small active molecules that can self-assemble	Optimal technique for fabricating nanofibers lower than 100 nm	Lengthy, elaborative, and complex method, low productivity	[211]

Due to these drawbacks, the trend has shifted towards electrospinning (ES) to produce NFs. ES can produce NFs ranging from nano to micron. The main advantage of ES over conventional methods is that it is simple, versatile, and cost-effective [213]. ES is used for producing NFs of various biopolymers with many applications. Some of the recent biomedical applications of the major biopolymers nanofibers are summarized in Table 11.

alt-text: Table 11

Table 11

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Recent biomedical applications of major biopolymers-based nanofibers fabricated by electrospinning.

Biopolymers	System composition	Applications	References
Cellulose	Cellulose-AuNP-AgNP	Wound healing	[214]
	Cellulose acetate/Pramipexole	Wound healing	[215]
	Cellulose-camptothecin	Sustained DD	[216]
	Cellulose acetate/nano cellulose/tranexamic acid	Drug delivery	[217]
Chitosan	MOF-5/CS/polyethylene oxide	Air filter (PM 2.5 removal)	[218]
	Polyvinyl alcohol/CS/AgNP	Dye removal and antibacterial	[219]
	CS/polyvinyl alcohol/halloysite nanoclay/cephradine	Drug delivery	[220]
	CS/polyethylene oxide	Sustained drug delivery	[221]
	CS/CuS/fucoidan	Tissue engineering	[222]
	Polyurethane modified CS/linezolid	Wound healing	[223]
Polylactic acid	PLA	Mask filter	[224]
	PLA/bacitracin/zataria multiflora	Antibacterial	[225]
	CS/PLA/chondroitin sulfate/AgNP	Antibacterial	[226]
	PLA/PCL/magnetic nanoparticle/tetracycline hydrochloride	Drug delivery	[227]

4 Trends in the major drug delivery systems

Current research trends for DDSs were analyzed by the literature using the ScienceDirect database for the last 5 years (2017–2021). Fig. 10a provides an overview of the major biopolymers based DDSs based on the data published in the last 5 years. Table 12 shows the recent patents and ongoing clinical trial stages of major DDSs for various treatment applications. Lipids-based nano drug delivery systems, including liposomal and EVs, are the most researched DDS, followed by hydrogels and nanofibers. On the other hand, NFs based DDS shows exponential growth, as illustrated in Fig. 10b. The increase in attention is due to the significant features of NFs that help to overcome the limitations in the previous DDSs, which are discussed in the next section. However, nanofibers showed the least number of clinical trials and the patents availability (Source: https://clinicaltrials.gov). Fewer numbers show that despite the increase in interest in the nanofibers, the DDS lacks in depth study required for the commercial development of this DDS. Table 13 sums up the significant merits and demerits of major DDSs.

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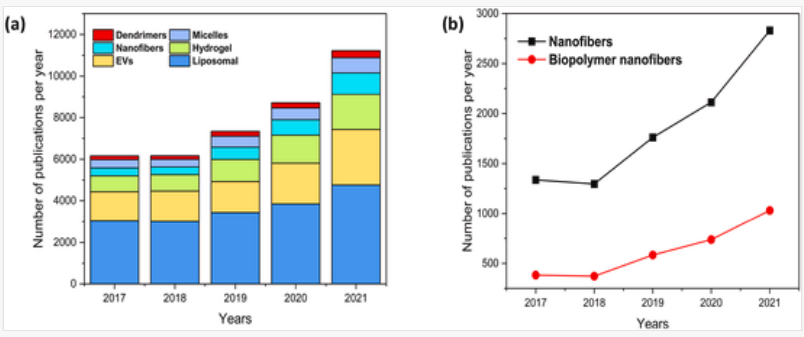
alt-text: Fig. 10

Fig. 10



Literature analysis of major drug delivery systems (ScienceDirect 2017–2022), (a) Overall systems comparison, (b) Nanofibers based biopolymeric systems.

alt-text: Table 12

Table 12

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Ongoing clinical trials and patents of major drug delivery systems.

Drug delivery system	Product name/Sponsor	Major biopolymer	Therapeutic	Application	Patent identifier/Clinical phase	References
Hydrogels	Catasyn™ Hydrogel	Chitosan	Silver Sulfadiazine	Superficial burns treatment	NCT04601532/Phase 4	[228]
	HemCon bandage	Chitosan	N/A	Coronary angiography	NCT00716365/Phase 4	[229]

	Dextenza®	PEG N-hydroxysuccinimidyl glutarate	Dexamethasone	Conjunctivitis	NCT04708821/Phase 3	[230]
	ProCore Ltd.	Hyaluronic acid	Fibrinogen	Osteoarthritis	NCT02188771/Phase 2	[231]
Liposomes	Celsion	Lipids	Doxycycline	Anticancer	US10251901B2	[232]
	Syncore Biotechnology	Lipids	Paclitaxel	Anticancer	US10413511B2	[233]
	University of Rome Tor Vergata	Lipids	Liposomal lactoferrin SOC therapy	COVID-19 treatment	NCT04475120/Phase 3	[234]
Extracellular vesicles	University of Louisville	Grape based exosomes	Curcumin	Colon cancer	NCT01294072/Phase 1	[235]
	Tel-Aviv Sourasky Medical Center	T-REx™-293 cells exosomes	CD24	COVID-19 peneumonia	NCT04747574/Phase 1	[236]
	Isfahan University of Medical Sciences	Mesenchymal cells exosomes	miRNA-124	Cerebrovascular disorders	NCT03384433/Phase 2	[237]
Micelles	Asan Medical Center	Polymeric micelles	Paclitaxel/carboplatin	Ovarian cancer treatment	NCT00886717/Phase 2	[238]
	Samyang Biopharmace-uticals Corporation	Polymeric micelles	Genexol-PM	Advanced pancreatic cancer	NCT00882973/Phase 1	[239]
Dendrimers	Starpharma Pty Ltd	Poly-L-lysine	1% w/w SPL7013 Gel	Bacterial vaginosis	NCT01577537/Phase 3	[240]
	National Institute of Allergy and Infectious Diseases	Poly-L-lysine	3% w/w SPL7013 Gel	Herpes simplex ii	NCT00331032/Phase 1	[241]
	Ashvattha Therapeutics, Inc.	Poly-amidoamine dendrimers	D-4517.2	Macular degeneration/diabetic macular edema	NCT05387837/Phase 2	[242]
Nanofibers	Esfahan University of Medical Sciences	NA	Ciprofloxacin, metronidazole and clindamycin	Endodontics procedures	NCT03690960	[243]

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Table 13

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Comparison of major drug delivery systems.

Drug delivery systems	Advantages	Disadvantages	Reference
Hydrogels	• Cost-effective	• Not always biocompatible and biodegradable	[244,245]
	• Biocompatible	• Difficult to synthesize biopolymers-based hydrogels	
	• High stability	• Requires toxic crosslinker	
	• Several routes of administration	• Releases the drug at once	
	• Drug release can be controlled depending on the need	• Reactivation required	
		• Nonspecific	
		• Not suitable for hydrophobic drug delivery	
Liposomal	• High efficacy	• Expensive	[246,247]
	• Enhanced therapeutic index	• Short half-life	
	• Biocompatible and Biodegradable	• Less solubility	

	• Nontoxic and non-immunogenic	• Leakage results in reduced efficacy	
	• It can be used for hydrophilic as well as hydrophobic drug	• Side reactions may occur, resulting in non-specificity	
	• High loading efficiency		
Extracellular vesicles	• Only DDS with a biologic origin, hence highly biocompatible	• Overall expensive	[248]
	• Innately non-immunogenic and nontoxic	• ECVs are challenging to isolate and purify	
	• Good stability	• Less loading efficiency	
	• Good specificity	• Difficult to upscale production	
Micelle	• Excellent for hydrophobic drugs	• Low productivity	[249]
	• Good reproducibility	• It depends on the thermodynamic forces for the folding and hence requires specific combinations of starting materials	
	• Better specificity by easy incorporation of other biomolecules	• Mainly organic solvents are required, which are difficult to remove and hence contaminate the end products	
Dendrimer	• Highly compatible	• Mostly non-degradable	
	• Stable structure in the physiological environment	• Complex synthesis process	
	• Can work with a wide range of therapeutics		
Nanofibers	• Cost-effective	• Complexity in process designing	[250,251]
	• Easy fabrication process	• Drug loading is difficult to measure	
	• High surface area hence better for absorption and release of drug	• Fabrication procedure results in the deactivation of active biological molecules for delivery	
	• Highly flexible in making different combinations of biocomposites	• The setup is bulky and nonportable	
	• Biocompatible and biodegradable		
	• Increased bioavailability of the drug		

5 Conclusions and future perspectives

Different DDSs are available for various applications, with their merits and demerits. The selection of the DDS mainly depends upon the nature of the therapeutic, the required route of administration, and the release mechanism, followed by the bioavailability and efficacy. However, nowadays, scientists are mainly interested in developing

non-invasive DDSs that can be administered by patients, making them more user-friendly. Among the major DDSs discussed, lipids-based DDSs are the major studied DDS. However, lipid base DDSs do not hold a wide range of DD applications since the major drawbacks are limited application routes, lack of mechanical strength, incompatibility with other biopolymers and sensitive storage conditions. But still, owing to their maximum compatibility and ability to deliver a wide range of therapeutics, they are mainly used for DD applications. They most recent use of this system is the COVID-19 vaccine for the delivery of mRNA. Micelles and dendrimers-based DDSs are limited because of their complex synthesis methods and high reliance on the thermodynamic forces to form the complex.

Among all the DDSs, hydrogels DDSs can be tailormade by combining with different biopolymers and have maximum routes of administration among all DDSs. But hydrogels mostly lack the surface area, natural interaction between biopolymers, and biocompatibility required for drug delivery application. Nanofibers can overcome the major limitations of the previous DDSs since they have a much greater surface area than hydrogels and high flexibility in combining different biopolymers. However, the drawback for the NFs lies in their production by electrospinning (ES). The primary issue with the ES process is its procedure complexity as it depends upon various parameters like voltage, temperature, solvent nature, viscosity, and spinning distance for the fiber morphology, thus making the procedure complex, and causing variable results from batch to batch. Therefore, designing the fabrication process using ES is a tedious task. The variability from batch to batch results in the inaccurate measurement of the loaded drug and hence is the major hindrance in the commercialization of nanofibers. Scientists should be looking for smaller handheld versions of electrospinning setups, and the drug loading issue can be overcome by developing precise and accurate assays for the measured loaded drug. However, more clinical trials and drug administration studies using NFs are required to explore more potential of this system.

Declaration of competing interest

The authors state that no potential conflicts of interest or personal ties might have influenced the work reported in this research.

Authors contribution

All authors contributed towards drafting and critically revising the paper and agree to be accountable for all aspects of the work. The authors confirm that this manuscript has not been previously published and is not currently under consideration by any other journal.

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The corrections made in this section will be reviewed and approved by a journal production editor. The newly added/removed references and its citations will be reordered and rearranged by the production team.

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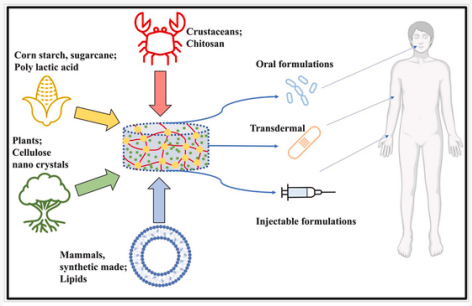

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