Polymers and their Nanostructures in Therapeutic Delivery: An Overview

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Abstract

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Polymers and nanoparticles have recently played a vital role in targeted therapeutic delivery. From the beginning of the 20th century, nanomedicines have tremendously grown, driven by the enhancement in chemical engineering. These days, the rational design of polymers and nanoparticles built to perform diverse biological functions and customization for a given drug is the foundation for modern advancements in therapeutic delivery. This review mainly highlights the different types of polymers and their nanocarriers used in targeted drug delivery and their prospective applications and discusses the potential barriers in the field. The most recent advancements in polymers that may direct intracellular distribution are highlighted in this review as the areas pushing the boundaries of medication delivery.

Keywords: polymer, nanoparticles, polymer architecture, nanocarriers, targeted drug delivery

Introduction

In terms of illness diagnosis, treatment, and prevention, the fields of science have begun to change with the development of a broad range of nanoscale technologies. The National Institutes of Health refers to these technical advancements as "nanomedicines" because they can transform molecular findings from proteomics and genomics into numerous advantages for patients. Biochemical processes can be mimicked or changed using nanoparticles. Functionalized carbon nanotubes, nano-machines, nano-fibers, self-assembling polymeric nano-constructs, nano-membranes, and nano-sized silicon chips for drug, protein, nucleic acid, or peptide delivery and release are a few examples of these devices. Biosensors and laboratory diagnostics are also included (Singh & Lillard, 2009).

Over the past few decades, biodegradable polymers have been the subject of substantial research for the creation of therapeutic delivery systems. The development of polymeric nanoparticles for tissue engineering and drug delivery is receiving a lot of attention due to its potential applications in site-specific drug targeting, stabilizing labile molecules from deterioration, and regulating drug release (Kaur & Kaur, 2014). Due to the unique properties of nanoparticles, they have been used in drug delivery, unlike any other materials. The creation of therapeutic agents for the treatment of disease has successfully improved as a result of recent advances in biomedical science. The transport of therapeutic agents to the desired site obstacles the way of the effectiveness of treating numerous diseases. Conventional therapeutic drugs have drawbacks including inadequate bio-distribution, unfavorable side effects, minimal efficacy, and non-selectivity (Yetisgin et al., 2020). As a result, the present focus of research efforts is on designing well-controlled, multifunctional delivery systems using nanoparticles. Delivering a variety of molecules to specific parts of the body through the association of therapeutic medicines with nanoparticles that have distinctive physicochemical and biological properties and engineering their paths for appropriate targeting is a promising strategy (Jahan et al., 2017). Low doses can be utilized because this targeted technique increases the therapeutic agent's concentration in cells and tissues, especially when there is a conflict between the agent's beneficial and harmful effects. By improving the

efficacy and/or tolerance in biological systems, raising the concentration of therapeutic substances in the target area also improves their therapeutic index. Combining water-insoluble medicinal compounds with nanoparticles can enhance their bioavailability and shield them from physiological obstacles. Conversely, when therapeutic nanoparticles are associated with contrast agents, it becomes possible to monitor their delivery location and track their journey in in-vivo systems. Recent advancements in nanotechnology have led to the development of various types of nanoparticles like vesicles, liposomes, dendrimers, carbon nanotubes, and so on, as drug delivery vehicles (Paul & Sharma, 2010). The aforementioned benefits make it possible to use targeted therapeutic nanoparticles in a variety of medical specialties.

Encapsulation of drugs in appropriate nano-carriers is the main aspect of enhancing the efficacy of drugs for targeted therapeutic delivery. Reports are available where various characteristics of nanoparticles as well as the encapsulation of drugs in them are presented (MG et al., 2015; Park, 2014). Therefore, it is essential to have an extensive understanding of their important qualities and their types to acquire the in-depth information needed for their effective application in the pharmaceutical sector. Hence the primary objective of this paper is to outline the types and characteristics of nanoparticles that make them essential tools in nano-medicine and review the previous decade of research on therapeutic nanoparticles and their targeted delivery uses in a range of illnesses, including cancer, neurological diseases, and many others.

Review Method

Polymers and their nanostructures play a significant role in therapeutic delivery. This overview uses a timeframe between 2015 to 2020 and focuses on the rational design and diverse functions of polymer-based nanocarriers, including their methods of encapsulation of medication and their potential uses in various types of illness, like cancer, tumor, gene therapy, and so on. It draws on their applications in targeted drug delivery. Additionally, it addresses potential barriers and highlights recent advances that enhance the use of nano-carriers in therapeutic delivery minimizing their unwanted effects on human health. It takes the following figure as a reference point.

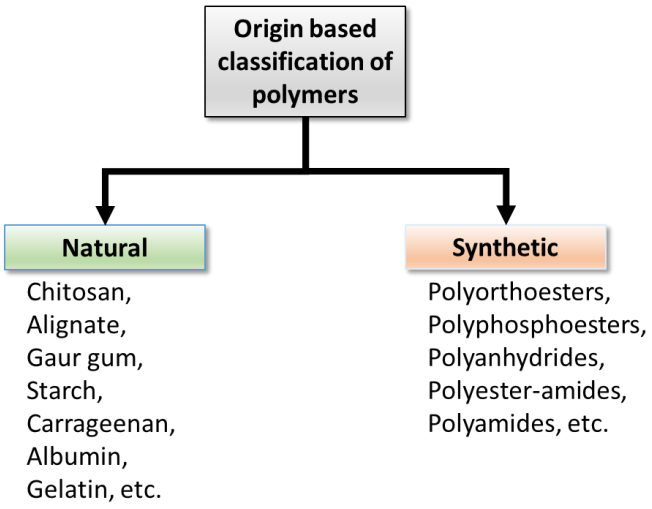
Polymers and Nanotechnology

Source-based Classifications of Polymer

Polymers play a central role in the formulation of drug delivery carriers, and in controlling drug release, which is one of the promising features of drug delivery technologies. Classification of polymers can be a challenging job to do in a drug delivery system. Based on origin, they may be classified as either natural or synthetic. The commonly known classification of polymers based on their origin is given in Figure 1.

Figure 1

Commonly known classification of polymers based on their origin.

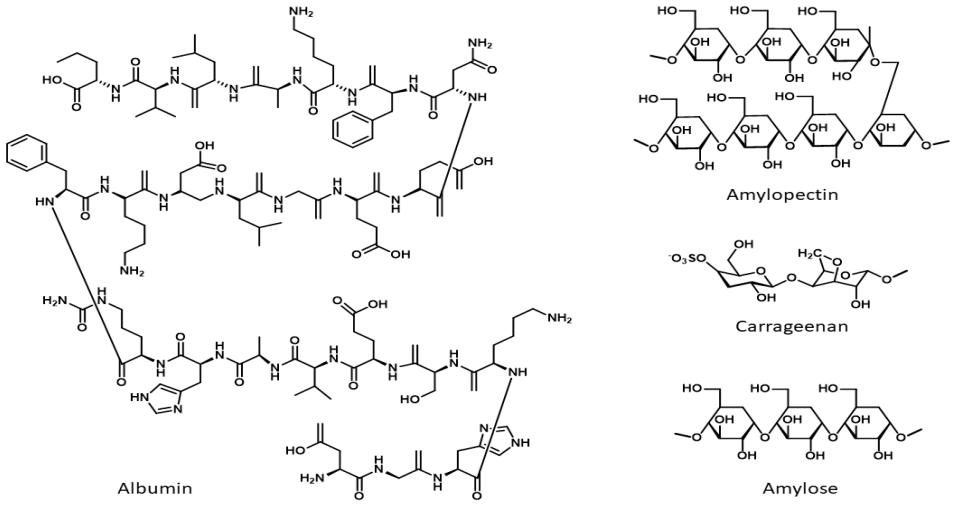


Natural polymers

Natural polymers are broadly utilized in drug delivery systems (DDS) due to their availability in nature in large quantities, biodegradability and compatibility, and lower toxicity. Natural polymers include proteins and polysaccharides. It has some disadvantages like expansive molecular mass arrangements and bunch-to-bunch variableness. Among these polymers, chitosan is broadly utilized due to its ability to blend with various polymers and simple surface modifications, also reduces harmfulness and non-immunogenicity presenting a good fit with cells and tissues (George et al., 2019). The further improvement in the ability of chitosan for targeted drug delivery (DD) was done by Wang et al. (Wang et al., 2015).

Figure 2

Structures of albumin, amylopectin, carrageenan, and amylose (George et al., 2019).



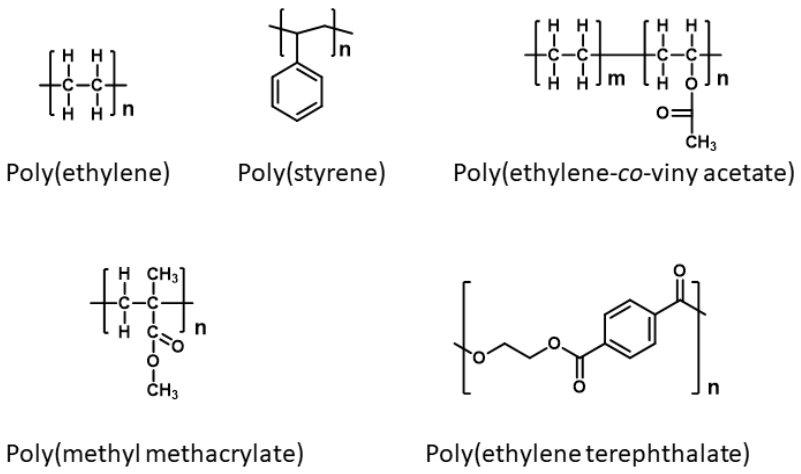
In comparison to chitosan and alginate, many natural polymers like albumin, galactomannan, starch carrageenan, and lignin (Myint et al., 2016) have not been studied adequately.

Synthetic polymers

Around the half-century, the synthesis, development, and use of synthetic polymers for biomedical uses began. Poly(methyl acrylate) (PMMA) was used to develop plastic contact lenses around 1936; and at around 1941, nylon was first used as suture (Hacker & Mikos, 2010). Synthetic polymers are divided into two groups: non-degradable and biodegradable synthetic polymers. The latter has many more advantages over the former one. All artificial polymers can be manufactured in higher grade and clarity and can be designed into multiple structures with required properties but biodegradable polymers have advantages like the capacity to alter mechanical characteristics and rate of degradation to match multiple uses, biodegradable synthetic polymers have diverse medical uses and include dissolvable sutures, DDS and orthopedic fixation (Behravesh et al., 1999). Poly(ethylene), poly(propylene), poly(styrene), poly(ethylene-co-vinyl acetate), poly(tetrafluoroethylene), poly(methyl methacrylate) are some examples of non-degradable synthetic polymers (Hacker & Mikos, 2010).

Figure 3

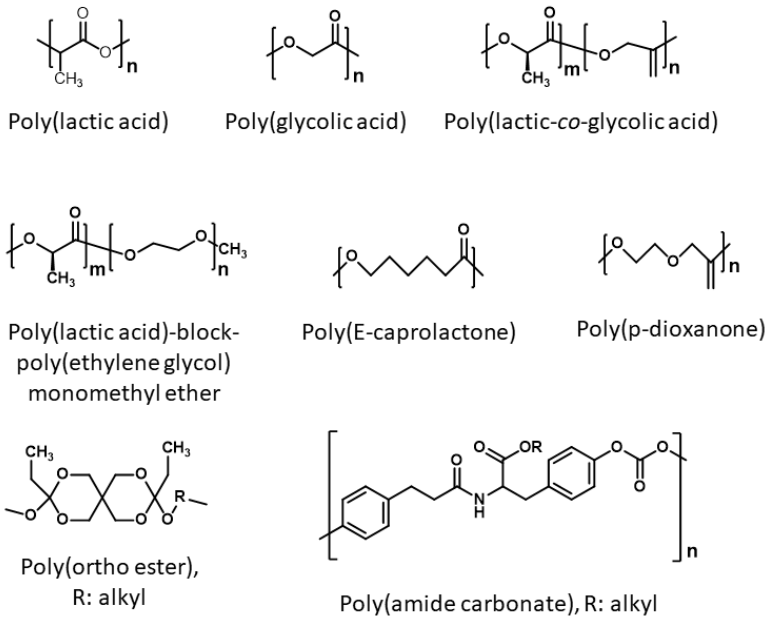
Structures of nondegradable synthetic polymers (Hacker & Mikos, 2010).



While some biodegradable synthetic polymers are poly(D, L-lactic acid), poly(glycolic acid), poly(l-lactic-co-glycolic acid), poly(D, L-lactic acid)-b-poly(ethylene glycol)monoethyl ether, poly(Ɛ-caprolactone), poly(p-dioxane) and so on (Hacker & Mikos, 2010)

Figure 4

Structures of biodegradable synthetic polymers (Hacker & Mikos, 2010)



Composition-based Classifications of polymer

The shape of a polymer molecule is best explained by the architecture of polymers. All natural or synthetic polymers are categorized into many classes like a star, branched, linear, and so on (Qiu & Bae, 2006). Polymeric nanocarriers have become widely common in drug delivery due to their capability to alter the physical and chemical characteristics of macromolecules. The part played by polymers' architecture in optimizing drug delivery is prime but is not understood (Grayson & Godbey, 2008). Linear polymers are water-soluble polymers and unite polymers and drugs together. Block copolymers applied in the preparation of macromolecules are linear but are categorized as different structures. Branch points and multiple (greater than two) endpoints are present in branched copolymers and are known as the type of polymers somewhere between linear and polymer networks (McKee et al., 2005). Chain hydrophilicity, drug content, molecular weight, electrical charge, solubilizing moiety, backbone, and others are some factors that control the polymer architecture (Qiu & Bae, 2006).

Star polymers

Star polymers have unique structures with a minimum of three arms or chains emerging out from one central part. Because of their peculiar architectures and properties, they have been widely used, and while compared with polymers of similar molecular weight, they possess lower solution viscosity (Wu et al., 2015). These polymers are classified into two groups: regular star polymers and miktoarm star polymers. The former one has similar arms composed of homo or block copolymers, while the latter one is further subdivided into various kinds depending on their structures, topologies, molecular weights, and functional group, and are hoped to be involved in biomedical use (Khanna et al., 2010).

In other words, star polymers are the simplest branched polymers, consisting of several linear chains linked to a central core.

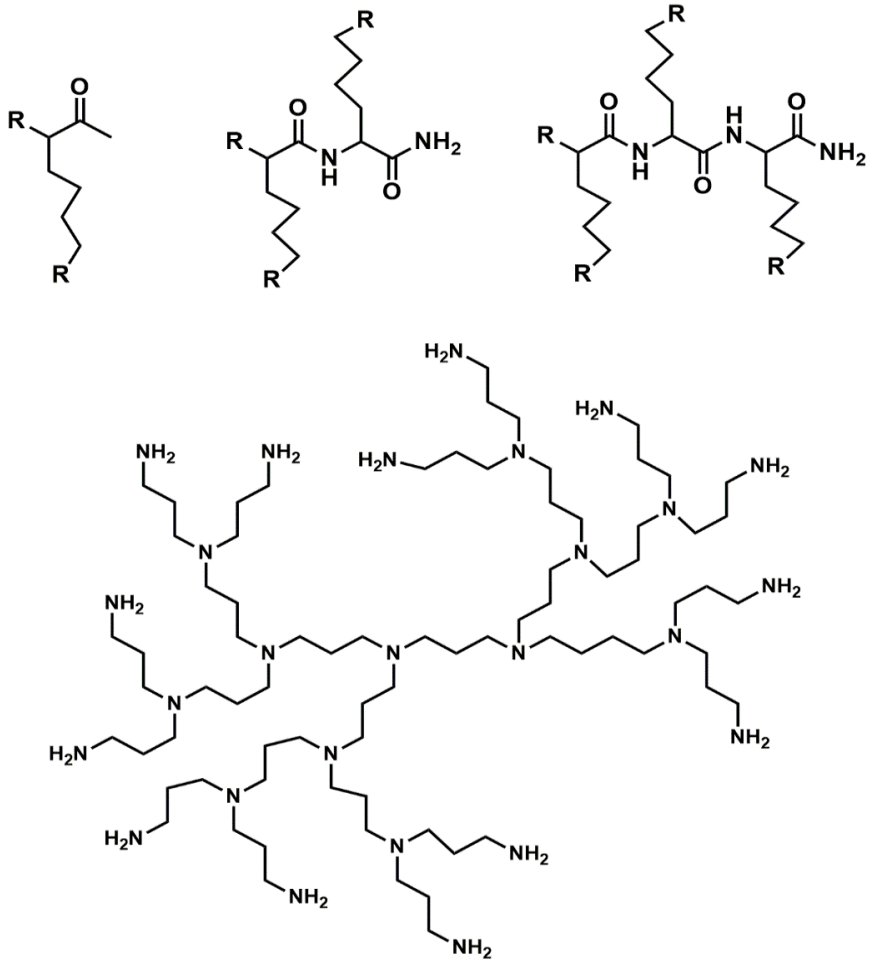
Branched polymers

Branched polymers have side chains or branches composed of the same monomer units as the main chain and these branches are present because of side reactions during polymerization. Branched polymers are further categorized as long-

branched and short-branched polymers. The former one might have comb-like, random, or star-liked polymers. The branches of these polymers do not get connected with another polymer chain (Shrivastava, 2018). Figure 5 is a schematic representation of the structure of the branched polymer.

Figure 5

Schematic representation of the structure of branched polymer (Chen et al., 2001).

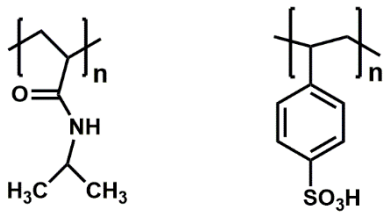


Homopolymer

Homopolymers are obtained by reacting a monomer with itself to form a high molecular weight substance. Homopolymers; polyethylene and polypropylene are obtained by polymerization of ethylene and propylene respectively (Agnihotri & Dhiman, 2017). The structure of poly(N-isopropylacrylamide) and poly(styrenesulfonic acid) are given in Figure 6.

Figure 6

Structure of poly(N-isopropylacrylamide) and poly (styrenesulfonic acid) homopolymers (Urošević et al., 2018)



Ganivada et al. (2017), for the first time, developed a new class of multi-arm homopolymer, poly(ethylene glycol) and doxorubicin attached to 1-6-heptadiene derivative (DoX-peg-RCP polymer). Pinyakit et al. (2020) constructed pH-responsive nanocarriers by post-polymerization of poly(pentafluorophenyl acrylate) (PPFPA) homopolymer.

Nanotechnology

Nanotechnology has become an integral part of our lives, and this science has become an absolute necessity in almost every sector, from medicine to electronics, beauty products to food business, etc. In drug delivery science, it is now well-recognized that a drug carrier can be as important as the drug itself. A carrier has a significant contribution to achieving the full benefit of a drug: it can protect the drug from harsh environments, enhance lifetime in the circulatory system, facilitate targeted delivery, restrict side effects, control release in terms of time and location, etc. and thereby contribute to the improvement of both the pharmacokinetics and pharmacodynamics. Thus, designing need-based strategies for the development of drug-specific therapeutic carriers is gaining unprecedented attention in the pharmaceutical industry. Researchers are always looking at carriers of different sizes, forms, and materials; carriers with nanoscale dimensions are among them as they have enhanced the ability to contribute to overcoming various challenges that the micro-sized carriers frequently fail to meet. There is a growing number of literature reviewing various types of carriers, their necessities, material choice, function, etc. However, a lack of systematic review work, particularly on the design strategies of nanocarriers, has been strongly felt which has prompted us to loom this work.

Nanocarriers

Nanocarriers are nanomaterials being utilized to transport another material, for example, a drug. Regularly utilized nanocarriers incorporate micelles, polymers, carbon-based substances, liposomes, and other materials (Qian et al., 2012). Nanocarriers' sizes vary from diameter 1–1000 nm (R. Singh & Lillard, 2009), anyway because of the diameter of microcapillaries being 200 nm, nanomedicine frequently refers to carriers <200 nm (Singh & Lillard, 2009). As a result of their small size, nanocarriers can convey medications to in any case difficult-to-reach destinations around the body. Because nanocarriers are so small, it is regularly hard to give huge medication portions utilizing them. The achievements in nanomedicine have encouraged researchers to calculate its utilizations in a countless number of medical complications with the prime objective of getting a high degree remedial.

The interest in the study of polymer nanostructures emerged out because of easy bioavailability and controlled drug release from a single dose, and permitting risk-less delivery until delivered to the necessary site (Rizvi & Saleh, 2018). Due to several problems such as continuous administration of the medicine with a shorter half-life, diminished patient consistency, high and ordinary peak-valley plasma concentration-time profile, and so on in traditional medication a consistent-state medicine (drug) concentration and particularity of target release can't be accomplished, which gives rise to the improved and targeted medication structure. Modern sophisticated methods of treatments are slowly overcoming the traditional ways, for which polymers are considered the primary backbone for building up an improved and targeted therapeutic delivery system (Sur et al., 2019).

Polymer nanostructures are solid colloidal structures ranging from 1 to 1000 nm in size and are derived from natural, synthetic, or semi-synthetic sources (Pugazhendhi et al., 2018). Polymer nanostructures can load themselves with drug, protein, or DNA particles and carry them to the target site. Depending on the various modes of their preparations, the matrix of nanoparticles, the drug, or any other compounds can get dissolved, attached, entrapped, or encapsulated (Conde et al., 2014). Polymeric nanostructures are usually nanocapsules or nanospheres, which are represented in Figure 8 (Mozafari et al., 2009).

Because continuous use of non-biodegradable polymeric nanostructures causes a series of serious issues like long-term toxicity and high pathological problems, which

were resolved by utilizing biodegradable polymeric nanostructures (Ramkumar et al., 2017).

In the 20th century, after the invention of sophisticated instruments like high-resolution microscopy, the door to nano-medicine was brusquely opened. Already in the 19th century, nanoporous ceramics filters were in use to filter viruses, and years before the development of the high-tech devices, at around 1900, Einstein and Max Planck gave theoretical proof for the existence of tiny matters that follow their laws (MG et al., 2015). After this, immediately in 1920, Richard Zsigmondy and Henry Siedentopf developed an ultra-microscope, which successfully detects particles smaller than 4nm (Mappes et al., 2012).

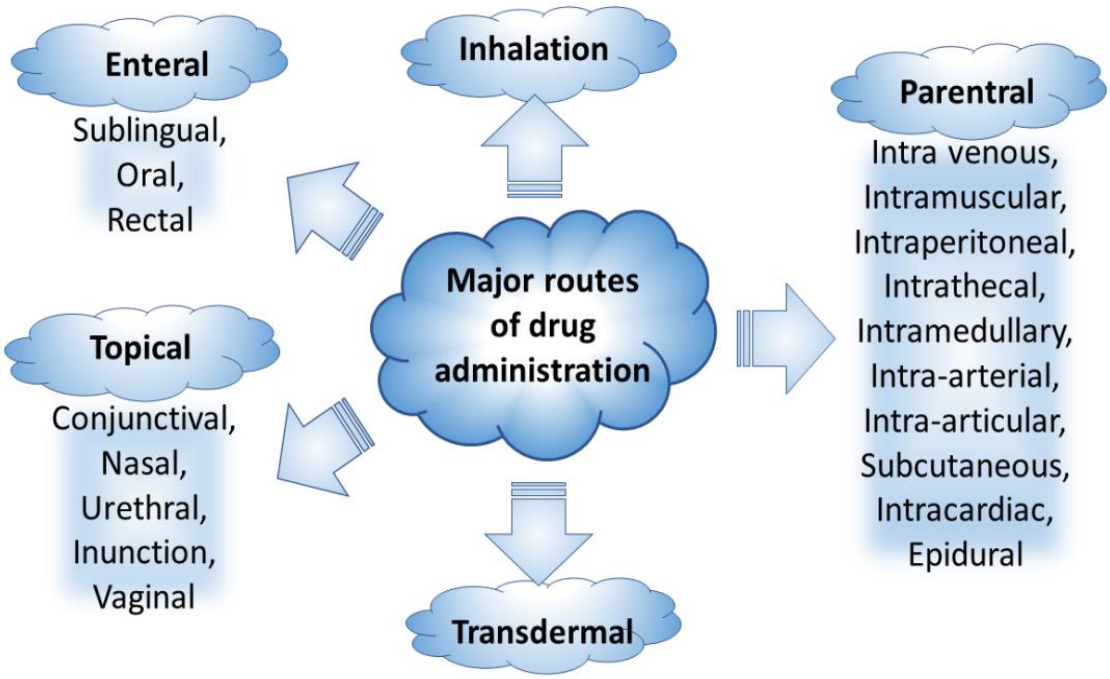
Zsigmondy got a patent for the immersion ultra-microscope in the year 1912, and since 1931, after the development of TEM by Max Knoll; better resolutions were obtained in the study of colloidal particle behavior (Mappes et al., 2012). Later in 1936, Erwin Muller developed FEM which makes the study possible in the atomic range and after further improvement of FEM in the year 1951, the study of individual atoms and their arrangement on the surface becomes possible (Yamamoto et al., 2013). Also, the development of scanning probe microscopy in 1980, STM in 1981, and AFM in 1986 made the study more specific (Yamamoto et al., 2013). In 1974, Norio Taniguchi coined the term "nanotechnology" (Taniguchi, 1974). Peter Paul Speiser, in the late 1960s, obtained nanoparticles for targeted drug delivery for the first time (Kreuter, 2007). Georges Jean Franz Kohler and Cesar Milstein, in the year 1970 developed monoclonal antibodies (Köhler, G., Milstein, 1975). Since 1994, polymer nanostructures came into the field (Sur et al., 2019).

In recent times, much research and development have been done in the area of targeted drug delivery systems. There are numerous systems successfully working on this recently, however, some remaining difficulties need to be resolved and sophisticated technology for target drug delivery is required to be developed. So, nanotechnology has been studied recently to improve the system of drug delivery (Patra et al., 2018). Nanostructures have been broadly studied for drug delivery and hence are the most sophisticated technology in the field of their uses due to their significant likeability to alter characteristics like solubility, drug release ability, diffusion capacity, and bioavailability and immunity response. This takes the pharmaceutical field to the next level (Patra et al., 2018).

Polymeric nanostructures were introduced to remove the dull methods of synthesis of nanoparticles. Due to many benefits over normal nanoparticles, polymeric nanostructures have gained much attention from researchers. Their large surface area permits to display of a greater number of ligands and their small size allows them to move through tiny capillaries and easily reach the target cell (Dey et al., 2016). Natural polymers like protein (albumin and gelatin) and polysaccharides are widely used as matrix-based nanostructures in therapeutic delivery because of their most basic properties like biocompatibility, degradability, and easy surface modifications (Kakkar et al., 2017). A protein like albumin is highly versatile with its high solubility in water, the number of binding sites, and highly sensitive surface groups, which make it a suitable candidate for drug delivery (Elzoghby et al., 2012). For delivery of drug to the required location, the paths (routes) employed are important factors during treatment and these paths may show different results depending on their applied ways. Usually, the delivery is systematic but depending on the seriousness of disease or lethalness, drugs are applied directly to the affected part. The various routes of drug management are shown in Figure 7 (Begines et al., 2020).

Figure 7

Various anatomic routes for drug delivery.



Tacrolimus (TAC), is an immunosuppressant with important use in ophthalmology, yet, because of its limited corneal penetration capacity various nanocarriers were developed. Castro et al. (Castro et al., 2020) prepared positively charged NPs to enhance the deep ocular insertion of TAC after surficial use. With their mean diameter of 104±1 nm, positive zeta potential and muco-adhesive properties make TAC-NPs very effective for ocular use. The improved TAC-NPs do not cause any irritation and presented itself as an alternative for drug delivery of tacrolimus in the treatment of anterior segment inflammatory situations. (Ryu et al., 2019) proposed a quick-dissolving tablet consisting of dexamethasone encapsulated with polylactic-glycolic acid nanoparticles PLGA, to improve the availability of ocular medicinal products, consisting of dexamethasone encapsulated with polylacticglycolic acid nanoparticles PLGA. Preocular application was employed for healthy and easy management of an exact drug dose. They further obtained an improvement in the ocular drug bioavailability by 2.6 times compared to maxidex^{R} by using an alginate system made up of PLGA-NPs. Further, Wu et al. (B. Wu et al., 2018) presented Gadolinium polymeric nanoparticles (GdNPs) particularly engineered for magnetic resonance imaging (MRI)/CT/photoacoustic imaging (PAI) guided photothermal therapy. NPs were prepared bismuth-based (GD-PEG-Bi). NIR light was absorbed by these NPs and changed that light into heat, as a result, the temperature rose to 40ºC and progressive removal of the tumor as well as its removal from root, was observed. NPs and quantum dots (QDs) were joined together by Belletti et al. (Belletti et al., 2017) and synergy was developed. Because of the low solubility and low bioavailability of this agent, it shows low efficiency in cancer treatment. By loading these NPs in PLGA, the above-mentioned properties are enhanced, and the percentage of curcumin retained by the organism. For the imaging agent, QDs were loaded to NPs, obtaining theranostic utilization.

Recently albumin has been of great use in preparing NPs and DDS because of its intrinsic characteristics like stability, solubility, acidic nature, non-immunogenic property, non-toxicity, and biodegradability. Further, it has longer binding areas and 19 19-day long half-life. (Jiang et al., 2017). Currently, many nutraceuticals are used to decrease cardiovascular risk agents, for example, blood glucose, hypertension, and high levels of cholesterin (Rivellese et al., 2019). In the case of osteoarthritis, traditional

medications to relieve pain and repair joints are not safe for long-term use. So, nutraceuticals can be an effective alternative (Wang et al., 2018).

Various Structures of Nanocarriers

Nanobiotechnology has provided several basic and applied developments in the health sector. For successful drug delivery and effective diagnostic instruments, nanocarriers have been developed recently. Nanocarriers lower the side effects during the treatment by effective and targeted biomolecular interactions (Chamundeeswari et al., 2019). Nanocarriers have a high surface area to volume ratio, and the capability to modify basic characteristics and bioavailability of drugs. Some properties of nanocarriers like low toxicity, upgraded pharmacokinetics and biodistribution, controlled and targeted drug delivery, and high solubility and stability can be applied in drug delivery (How et al., 2013). Most importantly, by changing the shapes, sizes, composition, and surface properties of nanocarriers, their physiochemical properties can be adjusted (Sun et al., 2014). Nanocarriers include nanoparticles, liposomes, micelles, vesicles, microparticles, and some other structures.

Nanoparticles

Solid colloidal particles of dimensions 10nm to 1000nm are known as nanoparticles (Rao & Geckeler, 2011). Nanospheres and nanocapsules are collectively called polymer nanoparticles (PNP). The molecules are either adsorbed or loaded within the solid nanoparticles (i.e. matrix particles). Generally, a nanosphere is spherical but is not mandatory (Vauthier & Couvreur, 2000). While encapsulated molecules in nanocapsules are bound to either an oil or water core cavity (Couvreur, Dubernet, & Puisieux, 1995).

Ursula Scheffel carried out the first experiment with polymer nanoparticles, which was initiated by Paul Ehrlich. During the period of the late 1960s and early 1970s, large numbers of contributions were performed by Peter Speiser *et al*. (S. C. Khanna & Speiser, 1969). Since then, PNPs have been extensively researched as drug carriers in the medicinal field.

As a drug carrier, PNPs have huge advantages like higher efficiency in drug entrapping, higher intracellular uptake, higher stability of encapsulated particles, and biocompatibility. Most crucially, PNPs are meant to deliver drugs accurately to improve treatment outcomes, decreasing the side effects (Hoffman, 2008). Despite these advantages, there are some disadvantages, too. They leave unsafe solvent wastes behind and are non-biodegradable, delicate, and pricey to produce. Among these, minimizing the toxicity of PNPs is most important (Singh & Nalwa, 2007).

Vesicles

Polymeric capsules are polymeric vesicles, also referred to as polymersomes consisting of a bilayered membrane (Figure 12). Its size varies from nano- to micrometer. These are composed of amphiphilic copolymer (Brinkhuis et al., 2011). Due to their similarities to liposomes, Discher et al. (Discher et al., 1999) conducted the first scientific study in 1999 and coined the term polymersomes. The duration of blood circulation, RES identification, biodistribution, and the process of cell absorption are all significantly impacted by the size of vesicles.

In comparison to liposomes, polymersomes have a higher molecular weight of copolymer than lipids and thus have higher stability. Lipid MWs are typically less than 1 kDa, although copolymer MWs can reach 100 kDa. By choosing the right polymer, appropriate MW values, and the right ratio of hydrophobic to hydrophilic sections, one can alter the many physicochemical features of polymersomes. Nevertheless, its low entrapment efficiency is reliant on the concentration of the solution (García, 2018).

Vesicles evolved from simple hollow spheres in the beginning to considerably more complex bio-inspired nanostructures, such as multi-compartment vesicles. Polymeric vesicles are designed to respond to stimuli and are used in a variety of applications, such as biosensors, catalysts, nanoreactors, and biomedicine. Even with these benefits, they are not without restrictions. Vesicle monomers must be both biocompatible and biodegradable. According to Zhu et al. (Zhu et al., 2017), the vesicles ought to possess various functions, and a fitting synthesis procedure ought to be utilized for large-scale manufacturing

Polymeric Micelles

Widely researched polymeric micelles (PMs) are produced when amphiphilic polymers self-aggregate. They are made up of a hydrophilic polymer corona and a hydrophobic polymer core (figure 11). Their sizes vary from 20-200nm (Cagel et al., 2017). Because polymeric micelles are more stable than surfactants due to their lower critical micelle concentration (CMC), they are more suited for drug delivery.

Drugs are either physically entrapped into the core of micelle drug delivery (Mandal et al., 2017). The encapsulation of the drug has significantly increased the solubility of the drug and also the availability of active particles in medicines. Additionally, it lessens the lethal consequences of the drug (Abandansari et al., 2017) and also plays an important role in increasing the life of medications. The susceptibility to elevated ionic strength and low stability when diluted by bodily liquids are the drawbacks of PMs. These two lead to the medications' early release (Felber et al., 2012).

Microparticles

The spherical particles composed of a polymer matrix with a diameter ranging between 1-1000 μM are known as polymeric microparticles. Microparticles may be microspheres or microcapsules. Microspheres are made up of a solid homogeneous polymer matrix, while microcapsules have a core that can be solid, liquid, or even empty (Ju & Chu, 2019).

If the active core particles are encapsulated within a solid matrix of irregular shell particles, then those materials are microspheres (Dubey et al., 2009). Microcapsules can be spherical or non-spherical in shape but have distinctive structures (Ghosh, 2006). Microcapsules are categorized as single-core (mono-core or mono-nuclear) and multi-core (poly-core or mono-nuclear). Mono-core microcapsules consist of a central core and outer shell whose thickness can be 10%-90% of the total capsule volume, while poly-core microcapsules have several distinct cores with various sizes (Whelehan & Marison, 2011), generally formed by emulsion. The general structure of microparticles is shown in Figure 12 (Urbas et al., 2017).

Microparticles exhibit high drug loading efficiency and comparatively high stability and morphological integrity (Eltaher et al., 2018), but are not able to overcome the biological barriers, and are mostly delivered directly to the target site (Kohane, 2007). Some other limitations include macromolecule entrapping, minimizing burst release, increasing release time, enhancing loading of the macromolecule, entrapping small hydrophilic particles, and so on (Kohane, 2007).

Table 1

Different nanocarriers with their size, properties, and application.

Nanocarriers	**Size (nm)**	**Properties**	**Applications**
Solid lipid nanocarriers	50-100	Colloidal carrier, better stability, ease of upgradeability, biodegradable, low drug loading capacity, burst release	In vivo and in vitro drug delivery to liver cells, gene vector carrier, topical use, targeted drug conveyance to solid tumors, anti-tubercular chemotherapy
Liposome	50-100	Phospholipid bilayer vesicle, Biocompatible, biodegradable, low toxicity	Entrap hydrophilic and hydrophobic drug, bestconveyance of biologically active matter
Dendrimer	1-10	Symmetrical about the axis, similar, clearly defined, uniform-sized highly branched particles	Drug conveyance targeted to liver, photodynamic therapy, neutron capture treatment, imaging, gene conveyance
Polymeric nanocarriers	10-100	Successful cell membrane penetration, stable in blood, decomposable (ecofriendly)	High concentrations of drug conveyance, active and passive medicine conveyance, volatile pharmaceutical agent are stable

Micelle	10-100	Biostability, dynamic system, colloidal collection of amphiphilic molecules	Either hydrophobic or hydrophilic drug is loaded
Carbon nanotubes	0.4-3	Hexagonal structure, crystalline,allotropic carbon sheet, single or multiple layer, dynamic toughness, distinct electrical and elastic characteristics	Gene and medicine conveyance, peptide delivery, synthetic implants, tissue engineering, identification of cancer cell
Gold	1-100	Multi-surface capability, multifunctional, magnificent biocompatibility, less poisonous, surface plasmon resonance (SPR)characteristics, Fluorescence resonance energy transfer event	Biosensing, functionalized AuNPs enhance drug delivery, imaging
Magnetic nanocarriers	1-100	Superparamagnetism, chemicallystable, high colloidal stability,	Magnetic separation, MRI, targeted therapeutic delivery, hyperthermia, magnetic fluid, biosensing, thermoablation
Quantum dot	2-10	Distinct electronic characteristics, luminescence properties, narrow emission spectra, continuous absorption spectra, high light stability	Macromolecules tracking, labeling cells and organelles, bioimaging, Biomarker detection

Mesoporous silica	1-100	Multiple (more than 100) pores with honey-comb architecture, biocompatible, greater loading ability, thermally and chemically stable, manageable pore, flexibility for drug encapsulated with hydrophilic and lipophilic properties	Sustained drug delivery, peptides and protein delivery
Hybrid nanocarriers	1-100	Chemical and physical properties are developed based on nanostructure and spatial arrangements of particles	synergetic therapy, targeted drug conveyance, biosensing, imaging

Note. Re-drawn from Chamundeeswari et al. (2019).

Nanostructures for Targeted Delivery

Since 1908, after Paul Ehrlich (a Nobel Prize laureate for medicine) proposed the idea of a "magic bullet": a drug that tears down the infected cells but is no harm to healthy cells (Strebhardt & Ullrich, 2008), many researchers have tried to obtain that goal, mainly for cancer treatment (J. Shi et al., 2011). Nanoparticles have huge possibilities for high efficiency in drug delivery because of their high extent of biocompatibility. Also, for biomedical uses, they should be eco-friendly, bear a high half-life in the bloodstream, not join together or cause a negative effect in the cells and tissues, and be cheap. The effectiveness of such particles widely depends on the chemical, physical properties, and drug-loading techniques (Nikezić et al., 2020). More importantly, the fact that nanotoxicity differs from the current toxicity standard should not be neglected (Kumar et al., 2017). However, in the context of cancer treatment, there are a few difficulties regarding specific targeting and drug delivery. In some cases,

few targeted particles were found in both cancer and healthy cells. Thus, to remove these problems, concurrent targeting of multiple tumor constituents is required (Duncan et al., 2010).

NPs are employed for multiple purposes based on their size, structure, and physicochemical properties, and are divided mainly into Organic and Inorganic. Further, carbon-based NPs are taken as separate types (De Matteis & Rinaldi, 2018). Silica and gold, quantum dots, and fullerenes are considered inorganic NPs, while liposomes, dendrimers, micelles, nanospheres, and nanocapsules are organic NPs. Thus, polymer conjugates, nanotubes, micelles, dendrimers, and liposomes are usually employed for drug delivery (Sharma, Keservani, & Kesharwani, 2018). Depending on the type of drug employed for treatment and the method of loading, an appropriate carrier is taken by considering their morphology and composition.

Orive et al. (2010) used micelles by functionalizing their surfaces with different ligands and peptides, thus permitting the extended governing of medications. These micelles are very significant while loading anti-cancer drugs in blood, particularly for tumors because micelles are capable of overcoming the blood-brain barrier. Moreover, micelles might be an appropriate option for drugs like Amphotericin-B and paclitaxel which are not completely soluble in the aqueous phase, because micelles core allows drugs solubility (Lu & Park, 2013). The Zidovudine and Stavudine, used in HIV treatment are encapsulated in liposomes with a size range between 120-200 nm, which in terms increases the half-life of drugs (Mamo et al., 2010). Thus, free ends of the branches of dendrimers with a diameter of 10-100 nm are used in the administration of medicine.

Carbon nanotubes can also be used in controlled and targeted drug delivery because of their peculiar physicochemical characteristics and their appropriate structure (Heilmann,1983). Nanotubes can be used to attach drugs to their outer wall, active ingredients can be loaded into its mesh by applying porous adsorbent, or they can be used as nano-catheters (Foldvari & Bagonluri, 2008). Quantum dots are used in the administration of drugs because of their large surface area which is sufficient to attach therapeutic agents (Kaji et al., 2007). However, because of their low physiological stability and biocompatibility, they are not of choice in biomedical utilizations. These

structures might become toxic, might have a low half-life, could aggregate, and could be caught in non-specific links, if not combined with an appropriate ligand. Currently, their applications primarily depend on nano-crystals of Cd, but also of Pb and Hg as highly toxic elements (Kaji et al., 2007). Thus, the development of ecology is of great necessity.

Currently, gold nanoparticles (AuNPs) have drawn much attention in the field of biomedical applications, especially for targeted delivery. AuNPs are the subject of choice because they are inert, non-toxic, biocompatible, stable, and highly dispersed (Khan et al., 2014). Furthermore, their definite and peculiar optical and chemical properties, small size, area/volume ratio, facile synthesis, and surface Plasmon response built up interest in them (Laban et al., 2016; Pal et al., 2013). The effectiveness of nano-drug preparation dependent on biologically prepared AuNPs for enhanced drug ability was studied by Shittu et al. (Shittu et al., 2017). Thus, PEG was covalently bonded with AuNPs and entrapped with an antibiotic (Lincomycin), and release ability was increased by the availability of AuNPs also the growth of bacteria was inhibited for a long time when compared to non-nanodrug. Further, the stability, cellular uptake, and drug loading capacity of AuNPs can be increased by decorating their surface with different biocompatible polymers (Farooq et al., 2018). Farooq et al. (2018) combined two anticancer drugs (doxorubicin and bleomycin) to load AuNPs, which enhances the stability and anti-cancer activities in HeLa cells. It was observed that this nanodrug increased the curative effects via active targeting of HeLa cells and blocking their cancer cell cycle.

However, drug-loaded AuNPs require intense research as there is no detailed knowledge regarding their possible ways of absorption, circulation, distribution, toxicity, metabolism, targeted area, and removal from the body. Thus, intensive studies in medicine and in vivo are of great significance.

Even though inorganic or metal nanoparticles offer fabulous benefits in almost all fields of science and engineering, however, their non-biodegradability and direct or indirect toxicity are always a great threat and limit their unrestricted applications (Fadeel & Garcia-Bennett, 2010). On the other hand, there is a high possibility that polymeric nanoparticles can be engineered as biocompatible and biodegradable;

however, lack of the rigidity of such polymer nanoparticles also limits its application (Bae et al., 2010), however, there is a possibility that the rigidity of polymer nanoparticles can be improved by increasing the intra- and inter-chain attraction, crosslinking (Barbosa et al., 2017), etc. Also, in many cases, the toxicity of metal nanoparticles is substantially reduced when their surfaces are functionalized by biodegradable polymers. The functionalization of such particles by polymers also introduces various functional groups into such metal nanoparticles, allowing them to introduce their dispersity both in hydrophilic and hydrophobic solvents (Kango et al., 2013). Thus, there is a long way to go to improve the various properties of polymer nanoparticles.

Biodegradable Polymers in Nanocarrier Design

In comparison to other nanoparticles, the entrapping of the drug within the polymer is in a more developed stage (Van Vlerken et al., 2007), and significantly, the molecular weight has shown its effect on the releasing phenomena of the drug of the nanoparticles (Dhandayuthapani et al., 2011). The retention time of the drug is directly related to the molecular mass of the polymer. Biodegradable PNPs have minimum side effects and transport the drug-targeted cells or tissues and in this way, they enhance the therapeutical aid. Nanoparticles based on high molecular weight biodegradable polymers (HMWBP) have performed a primary role as an effective carrier for drugs, nucleic acids, and proteins for the last many years (Liu et al., 2008). However, HMWBP NPs show a slow rate of degradation in vivo leading to the possible outcome of aggregation in the cells, so low molecular weight biodegradable polymer (LMWBP) has acquired significant interest as probable conveyance system as they are highly soluble, permeable, and effectively associated because of their lower dimensions of (Ghosh & Pramanik, 2010).

Chitosan is the broadly employed natural biodegradable polymer in therapeutic delivery. Chitosan is at the top of the list because of its extensive background in the science of drug delivery. Not only this but also its derivatives as well as its hybrid forms are used in multiple fields like cell entrapping, gene delivery, wound dressing, contact lenses, and implants (Shariatinia, 2019). Because of minimum toxicity, protein-based

NPs have gained a lot of importance and are utilized as potential drug carriers (Verma et al., 2018). Among proteins; albumin (Hoogenboezem & Duvall, 2018) and gelatin (Madkhali et al., 2019) have obtained a significant role in the formulation of nanomedicine.

Among many synthetic biodegradable polymers, poly(lactic acid) (PLA) and poly(glycolic acid) (PGA) (polymers of the polyester family) and their copolymers, for example, PGLA, are broadly used and extensively researched and have many uses like dissolvable sutures, surgical fixation instruments, and drug delivery instruments. Poly(dioxanone) is another widely used biodegradable polymer that has applications in sutures. Biodegradable polymers like PLA, PGA, poly(decalactone), poly(lactic-co-glycolide), and poly(Ɛ-caprolactone) are extensively investigated in drug delivery and have formed a significant role in controlled drug release (Middleton & Tipton, 2000).

Biodegradable polymers put forth many advantages such as the capability to tailor the mechanical characteristics, the rate of degradation, and the capability to change shapes. The primary advantages of these polymers are their degradability, which resolves the need for surgical removable, and are time and cost-friendly (Gunatillake et al., 2006). However, the development of degradable polymers can also lead to problems. Biodegradable polymers, like α-hydroxy acid and polydioxanones, are too rigid and incompliant making them unequipped for reversible distortion. Also, they are quite different than human soft tissues and they can cause inflammation, irritation, and scar tissue formation (Madan et al., 2009).

Future Perspective

For more than a decade, the most promising subject in drug delivery has been nanoparticles. This is because of intensive help and funding provided by government agencies on nanotechnologies since 2010 (Park, 2013). Many improvements and accomplishments have been obtained in the field of targeted drug delivery, primarily in the treatment of tumors, and cancer and also in gene therapy. The improvements that will take place during the next 40-50 years are quite impossible to predict. Despite much development in technologies, the patients to cure and difficulties to remove for improved drug delivery will not be removed from our daily needs.

In the future, the modern drug delivery system may have some following challenges to overcome. They are modulated insulin delivery with on-off switching ability, anticancer agents or SiRNA to the tumor are to be delivered to targeted tissues/cells and long-term delivery systems i.e. ranging from 6-12 months with the minimal initial burst effect and in vivo-in vitro release study (Park, 2014). The development of multifunctional nanocarriers is another exciting challenge in delivery. For example, by combining antiangiogenic and DNA intercalating agents, much higher therapeutic activity can be obtained compared to the single addition of each compound (Sengupta et al., 2005). Another example can be a combination of drug and imaging agents in the nanoparticle to get treatment and diagnosis simultaneously (Arias et al., 2011).

Above mentioned models don't have an entire focus on drug delivery across the different scales. They have low applicability in the pharmaceutical business because of their poor ability to predict and poor truthfulness. To cover these limitations, multiscale designing of NPs is required (Nikezić et al., 2020). Shi et al. (2015) synthesized nanocarrier by combining molecules docking and dynamics simulations and they were verified experimentally afterward. Further, the consequences of some physical and chemical properties on the transport of NPs in tumor microvasculature (Li et al., 2016; Shen et al., 2016) are to be studied.

There have been lots of studies to develop the simplest view of nano-robots or nano-devices with the full remote control to diagnose tissue and their repair process, but this has not been achieved till now and perhaps be attained very soon. Self-healing polymers with nanomaterials are sustainable, safe, and long-lasting. So, biodegradable polymers with self-healing properties are required in the future to overcome all challenges.

Conclusion

This review has focused mainly on the different types of polymers, nanoparticles, and then nanocarriers based on polymers as drug carriers. Over the past decades, a wide range of NPs has been witnessed having diversity in quality,

characteristics, composition, and functionalization. Over recent years, nanotechnology has brought a great change in the field of pharmaceutical and biomedical. Nanoparticles have noble characteristics that are a necessity for new technology, and they help to improve the characteristics and efficiency of particles compared to traditionally used particles. Thus, NPs are the materials required to meet the demands of the modern scientific community. More and more efforts are being put into the design of various nanocarriers based on patients' requirements. Advancements in technology and better architecture of these systems will reach translational development step-by-step.

To conclude, the possibility to produce a great variety of nanomaterials with tunable characteristics that can associate in a remarkable style with biological frameworks is giving thrilling new occasions to planning advanced NPs for therapeutic uses.

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Conflict of Interest

The author declares no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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