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A REVIEW OF RECENT ADVANCEMENT IN PHARMACEUTICAL DOSAGE FORM

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ABSTRACT

Polymeric drug delivery systems have been achieved great development in the last two decades. Polymeric drug delivery has defined as a formulation or a device that enables the introduction of a therapeutic substance into the body. Biodegradable and bio-reducible polymers make the magic possible choice for lot of new drug delivery systems. The future prospects of the research for practical applications has required for the development in the field.

Main body

Natural polymers such as arginine, chitosan, dextrin, polysaccharides, poly (glycolic acid), poly (lactic acid), and hyaluronic acid have been treated for polymeric drug delivery systems. Synthetic polymers such as poly (2-hydroxyethyl methacrylate), poly (N-isopropyl acrylamide) s, poly(ethylenimine)s, dendritic polymers, biodegradable and bio-absorbable polymers have been also discussed for polymeric drug delivery. Targeting polymeric drug delivery, biomimetic and bio-related polymeric systems, and drug-free macromolecular therapeutics have also treated for polymeric drug delivery. In polymeric gene delivery systems, virial vectors and non-virial vectors for gene delivery have briefly analysed. The systems of non-virial vectors for gene delivery are polyethyleneimine derivatives, polyethyleneimine copolymers, and polyethyleneimine conjugated bio-reducible polymers, and the systems of virial vectors are DNA conjugates and RNA conjugates for gene delivery.

I. INTRODUCTION

The research for polymeric drug delivery has been progressed for a long time since 1980's [1,2,3,4]. The searches for new drug delivery systems approach and new modes of action represent one of the frontier research areas. Those involve multi-disciplinary scientific approaches to provide major advances in an improving therapeutic index and bioavailability at the specific delivery of drugs [5,6]. Whether the drug delivery system relies on a biodegradable implant to deliver medicine subcutaneously or deep within the body, the biodegradable and bio-absorbable polymers provide a safe framework for delivering medicine without harm to the body.

Polymeric drug delivery system has defined as a formulation or a device that enables the introduction of a therapeutic substance into the body. It improves its safety and efficacy by controlling the rate, time, and place of release of drugs in the body. Drug delivery has achieved great development in the last two decades, but it remains a difficult task to regulate drug entry into the body such as brain. However, recent progress in studies of the carrier-mediated transportation of Nano-drug delivery system across the blood-brain barrier is beginning to provide a rational basis for controlling drug distribution to the brain. The transport systems at the blood-brain barrier are the uptake transporters for natural nutrients such as amino acid, peptide, hexose, mono-carboxylate and stem cells [7,8,9]. The present paper has been reviewed for the polymeric drug and gene delivery systems of natural and synthetic polymers to formulate drugs into the backbone structures in various cases. The future prospects of the research for practical applications has been also proposed for the development in the fields. Drug delivery system combines one or more traditional drug delivery systems with engineered technologies. The systems create the ability to specifically targeting point where a drug has released in the body and/or the rate at which it has released.

Biodegradable and bio-absorbable polymers make the magic possible choice for lot of new drug delivery systems. The bio-absorbable polymers like hydrogels such as poly (lactic acid) and poly (glycolic acid), and their copolymers have used to create the delivery component of the systems [10,11].

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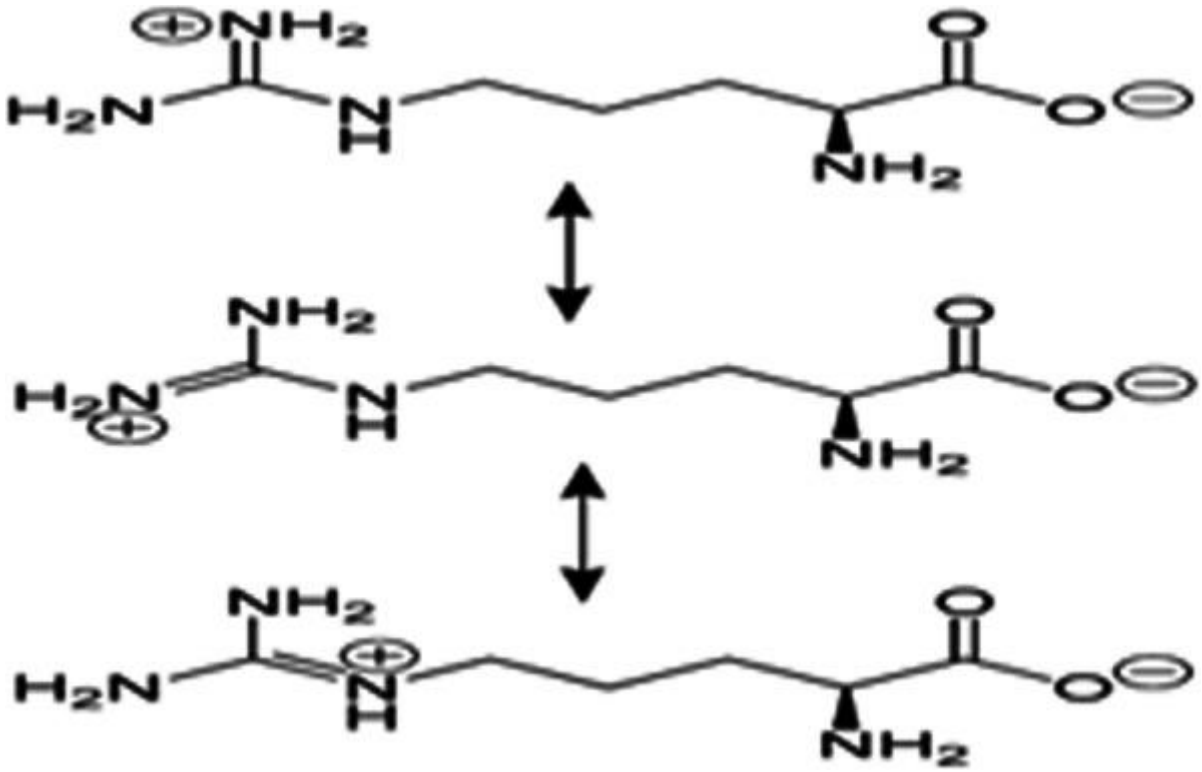
II. NATURAL POLYMERS FOR DRUG DELIVERY

Arginine derivatives

Arginine, also known as L-arginine, is α-amino acid that uses in the biosynthesis of proteins [12]. It contains α-amino group, α-carboxylic acid group, and a side chain consisting of a 3-carbon aliphatic straight chain ending in a guanidino group as shown in Fig. 1. At physiological pH, the carboxylic acid is deprotonated ($-COO^-$), the amino group is protonated ($-NH_3^+$), and the guanidino group is protonated to give the guanidinium form ($-C(NH_2)_2^+$), making arginine a charged aliphatic amino acid [13]. The amino acid side-chain of arginine consists of a 3-carbon aliphatic straight chain, the distal end of which is capped by a guanidinium group, which has a pK_a of 12.48. It is therefore always protonated and positively charged at physiological pH. Because of the conjugation between the double bond and the nitrogen lone pairs, the positive charge is delocalized, enabling the formation of multiple hydrogen bonds in the chemical structures [14].



Chitosan derivatives

Chitosan is one of cationic polysaccharides derived from the natural chitin.

As a cationic polymer with favourable property, it has been widely used to form polyelectrolyte complexes with polyanions for drug delivery [15, 16]. Chitosan is a linear copolymer composed by glucosamine and N-acetyl glucosamine units, via β-(1, 4) linkages, namely 2-amino-2-deoxy-β-d-glucan (Fig. 2a). Chitosan is the product of the deacetylation reaction of chitin (2-acetamido-2-deoxy-β-d-glucan). It has favourable biological properties such as nontoxicity, muco-adhesiveness, biocompatibility and the biodegradability [17,18,19]. The aqueous derivatives of chitosan such as chitosan salts (Fig. 2b), zwitterionic chitosan, and chitosan oligomers have drawn increasing attention due to their water-solubility for biomedical applications [20,21,22,23].

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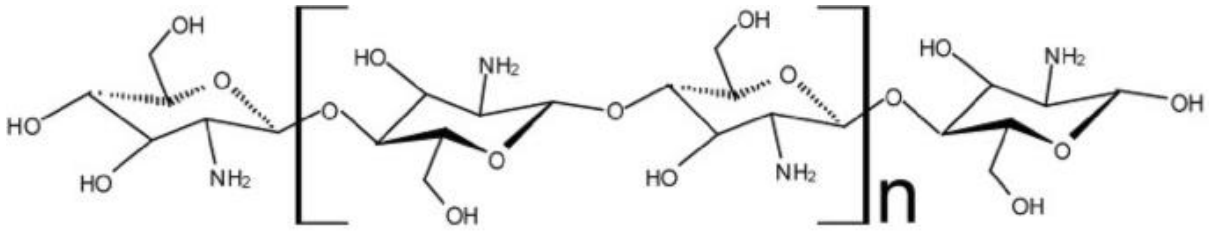
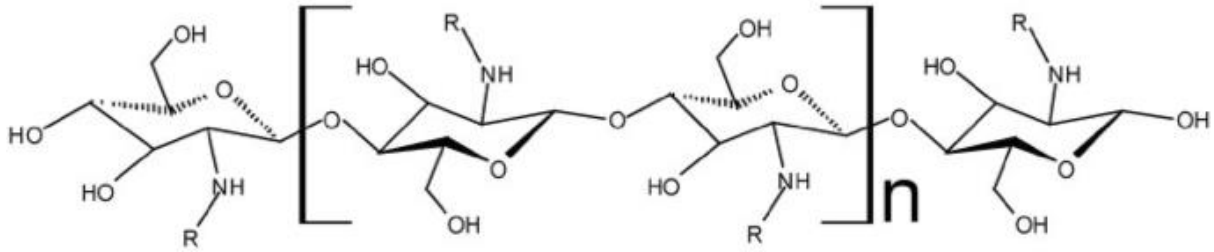


(a) Chitosan



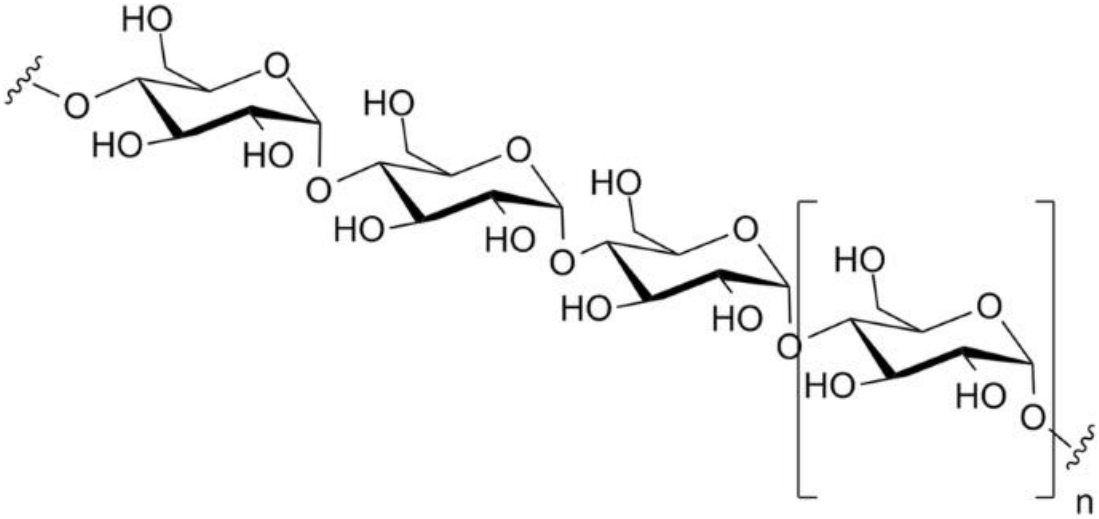
(b) Chitosan salts

(R=-CH_2COOH,-$CH_2CH(OH)COOH$,...)

Polysaccharides

Natural polymers have been in use for many years with the aim of facilitating the efficiency of drugs and their delivery. Biodegradable polymers are widely being studied as a potential carrier material for specific drug delivery because of their non-toxic, biocompatible nature. Natural polysaccharides have investigated for application in drug delivery industry as well as in biomedical fields. Modified polymer has found its application as a support material for gene delivery, cell culture, and tissue engineering. Nowadays, natural polymers have modified to obtain novel biomaterials for controlled drug delivery applications.

Polysaccharides are long chains of carbohydrate molecules, specifically polymeric carbohydrates composed of monosaccharide units bound together by glyosidic linkages as shown in Fig. 3. This carbohydrate can react with water-hydrolysis using amylase enzymes at catalyst, which produces constituent sugars (monosaccharides or oligosaccharides). Natural saccharides are generally of simple carbohydrates called monosaccharides with general formula $(CH_2O)_n$ where n is three or more. Examples of monosaccharides are glucose, fructose, and glyceraldehyde [24]. Those natural polymers have used as biomaterials for drug delivery systems. Starch is a glucose polymer in which glucopyranose units have bonded by alpha-linkages. It has made up of a mixture of amylose and amylopectin. Amylose consists of a linear chain of several hundred glucose molecules and amylopectin is a branched molecule made of several thousand glucose units [25].



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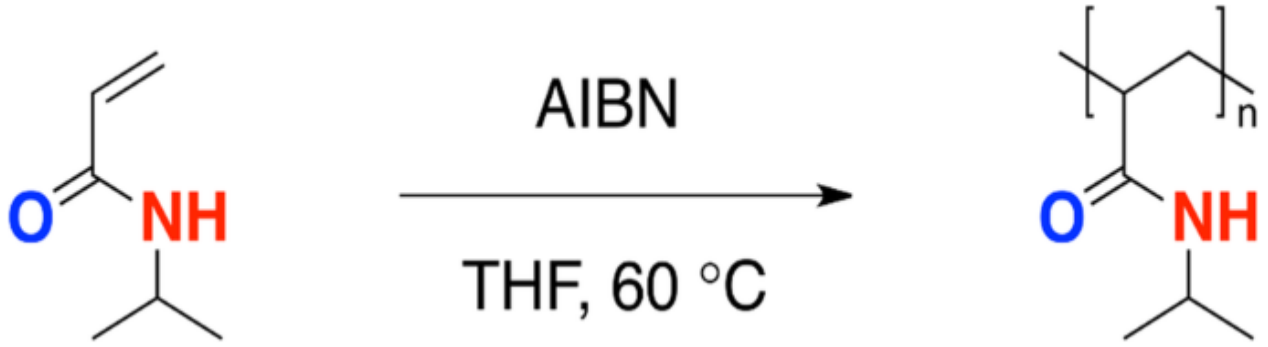
III. SYNTHETIC POLYMERS FOR DRUG DELIVERY SYSTEMS

Poly (2-hydroxyethyl methacrylate)

Poly (2-hydroxyethyl methacrylate) [poly (HEMA)] is a polymer that forms a hydrogel in water or aqueous solution [26]. Poly (PHEMA) hydrogel for intraocular lens material was synthesized by solution polymerization using 2-hydroxyethyl methacrylate (HEMA) as raw material, azobis isobutyronitrile (AIBN), ammonium persulfate or sodium pyrosulfate (APS/SMBS) as catalyst, and ethylene glycolmethacrylate (EGDMA) or tri-ethylene glycolmethacrylate (TEGDMA) as cross-linking additive [27]. Poly (HEMA) is commonly used to coat cell culture flasks in order to prevent cell adhesion and induce spheroid formation, particularly in cancer research. Older alternatives to pHEMA include agar and agarose gels [28,29]. Equilibrium swelling, structural characterization and solute transports in swollen poly (HEMA) gels cross-linked with tripropyleneglycol diacrylate (TPGDA) were investigated for a wide range of TPGDA concentrations for drug delivery systems [30]. The physical and chemical properties of pilocarpine from poly (HEMA) hydrogels were investigated to elucidate the mechanism of drug–polymer interaction and the effect on drug release behaviour of controlled release polymeric devices [31]. Poly (HEMA) hydrogels are widely used for biomedical implants. The extreme hydrophilicity of poly (HEMA) confers resistance to protein fouling, making it a strong candidate coating for ventricular catheters [32].

Poly (N-isopropyl acrylamide) s

Aqueous solution of poly (N-isopropyl acrylamide) (PNIPAAm) shows a lower critical solution temperature (LCST). The temperature-responsive polymer has investigated in the 1960's [33]. They have established 32 C as the LCST of thermos-sensitive poly (N-isopropyl arylamide). The thermodynamic property of the system has evaluated from the phase diagram and the heat absorbed during phase separation by entropy effect [34]. The process of free radical polymerization for a single type of monomer, in this case of N-isopropyl-acrylamide, find to form the polymer known as a homo-polymerization. The initiator of azobis isobutyronitrile (AIBN) has commonly used in radical polymerization.



Thermo-responsive polymers have attracted much attention because of their potential biological and medical applications such as drug and gene delivery [35,36,37]. The swelling of cross-linked poly (N, N′-alkyl substituted acrylamides) in water was studied in relation to temperature changes. The thermo-sensitivity of water swelling has attributed to the delicate hydrophilic/hydrophobic balance of polymer chains and has affected by the size, configuration, and mobility of alkyl side-chain groups [38].

The cell culture surface of the polymer has readily prepared by the technique reversibly into hydrophilic and hydrophobic coatings of PNIPAAm-grafted polymers [39]. Temperature/pH sensitive hydrogels were prepared by copolymerizing N-isopropyl acrylamide (NIPAAm) and acrylic acid (AAc) [40]. The influence of polyelectrolyte on the LCST of temperature/pH sensitive hydrogels had investigated in the pH range of swelling ratio. The swelling ratio of the hydrogels in the presence of poly (allyl amine) (PAA) as a polyelectrolyte was also measured at the same conditions [41]. It has briefly discussed about the tumor micro-environmental responsive Nano-particles in situ stimuli responsive such as pH, redox responsive, hypoxia sensitive, etc.

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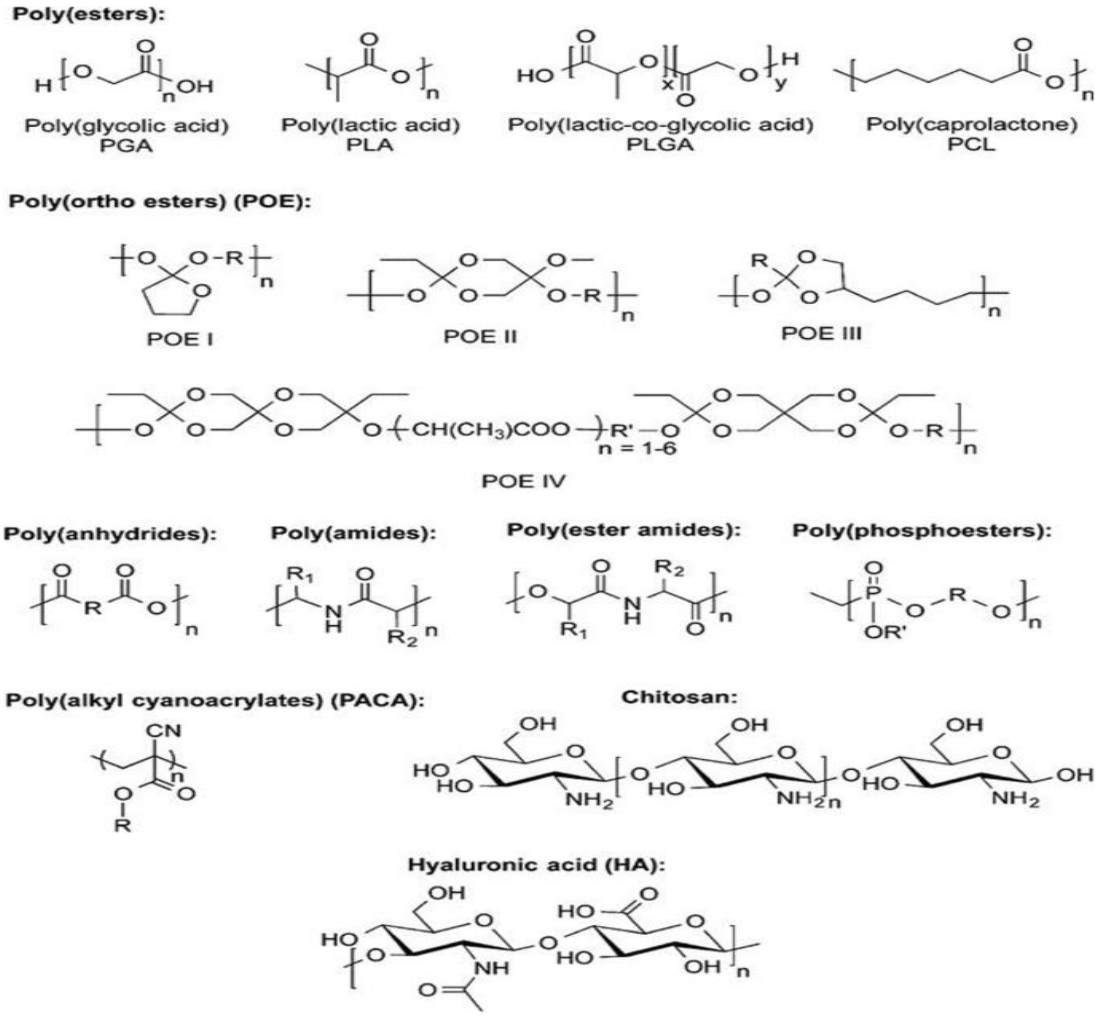
IV. BIODEGRADABLE AND BIO-ABSORBABLE POLYMERS

Bio-absorbable drug delivery systems are a better choice for the application of drug carriers where only the temporary presence of the implant is needed [42]. Among the synthetic and biodegradable polymers, aliphatic polyesters such as poly (glycolic acid), poly (lactic acid), poly (caprolactone) and polydioxanone, are most commonly used and applied to drug delivery systems. As shown in Fig. 8, the several classes of polymers such as poly (esters), poly (ortho esters), polyanhydrides, and biodegradable polycarbonates have also been introduced as potential implant materials for drug delivery [43,44,45].

Biodegradable polymers commonly used include the α-hydroxy acids, polyanhydrides, poly (amides), poly (ester amides), poly (phosphoresces), poly (alkyl cyanoacrylates), poly (hyaluronic acids) and natural sugars such as chitosan, in addition to many other types of degradable polymers as shown in Fig. 7 Synthetic biodegradable polymers are favoured in drug delivery systems, as they have immunogenicity as compared to biodegradable polymers from natural polymers [46,47,48].



V. TARGETING POLYMERIC DRUG DELIVERY

The therapeutic targeting of biomimetic chitosan-PEG-folate-complexed oncolytic adenovirus has examined for active and systematic cancer gene therapy [49]. The oncolytic adenovirus coated with multi-degradable bio-reducible core-cross-linked poly (ethyleneimine) for cancer gene therapy had been also applied [50]. Hepatoma targeting peptide conjugated bio-reducible polymer complexed with oncolytic adenovirus for cancer gene therapy were investigated [51]. Despite considerable advances in tumor-targeting technologies, the lack of selectivity towards tumor cells is still the primary limitation of current cancer therapies. A novel strategy for targeted drug delivery to cancer cells had developed through the formation of a physical conjugate between

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doxorubicin (Dox) and the A10 RNA aptamer that binds to the prostate-specific membrane antigen (PSMA) [52].

The effective polymers have designed specifically for gene delivery, and much has learned about their structure–function relationships. With the growing understanding of polymer gene-delivery mechanisms and continued efforts of creative polymer scientists, it is likely that polymer-based gene-delivery systems will become an important tool for human gene therapy [53].

Nanoparticle-based therapeutics in lung cancer is an emerging area and covers the diagnosis, screening, imaging, and treatment of primary and metastatic lung tumours. Innovative engineering on polymeric Nano-carriers allows multiple anticancer drugs and gene delivery to site-specific targets [54]. The targeted drug delivery and gene therapy through natural biodegradable nanoparticles is an area of major interest in the field of nanotechnology and pharmaceuticals [55].

VI. BIOMIMETIC AND BIO-INSPIRED POLYMERS

The biomimetic and bioinspired systems improve biocompatibility during drug delivery application. The success of such a drug delivery system depends on parameters like shape, surface, texture, movement, and preparation methods. The systems have great influence on the biological systems owing to their less toxicity, high biocompatibility, significant interaction, and so on [56,57,58]. The novel developments of dendritic polymers-based targeting nanoscale drug delivery vehicles described here provide great potential to achieve better therapeutic indexes in cancer therapy as well as low side effect [59,60,61]. Although synthetic drug carriers have developed for many applications, it remains important to examine natural particulates, which range from pathogens to mammalian cell's mechanisms. Biocompatible polymeric nanoparticles are considerably promising carrier candidates in delivery of drugs and genes because of their unique chemical and physical properties [62,63,64].

VII. DRUG-FREE MACROMOLECULAR THERAPEUTICS

Drug-free macromolecular therapeutics induce apoptosis of malignant cells by the crosslinking of surface non-internalizing receptors. The receptor crosslinking has mediated by the bio-recognition of high-fidelity natural binding motifs. Those have grafted to the side chains of polymers or attached to targeting moieties against cell receptors. This approach features the absence of low-molecular-weight cytotoxic compounds. Macromolecular therapeutics, also referred to as polymeric Nano-medicines, are a diverse group of drugs characterized by their large molecular weight (MW), including polymer-drug conjugates, polymeric micelles, and polymer-modified liposomes [65,66].

VIII. CONCLUSION

The development of drug delivery carriers based on natural and synthetic polymers are rapidly emerging field. It takes advantages of the remarkable delivery mechanism, which has used by pathogens and mammalian cells, such as selective targeting and prolonged circulation by evasion of the immune systems. The biomimetic and bio-inspired systems have a bright future ahead with a lot of potentials to solve any obstacles encountered in polymeric drug delivery. The fruitful progress will have made in the application of biocompatible and bio-related copolymers and dendrimers to cancer treatment, including their use as delivery systems for potent anti-cancer drugs such as cis-platin and doxorubicin. The unique properties of dendrimers such as their high degree of branching, multi-valence, globular architecture, and well-defined molecular weight make them promising new scaffolds for polymeric drug delivery systems.

The micro-processes that are required for the development of such carriers, such as genetic engineering or in vivo treatments to incorporate therapeutic substances, make it difficult to maintain the integrity of natural and synthetic polymers with cells in a body. The gap between synthetic and biological systems has traditionally been very large. Recent advances in the synthesis of novel biomaterials and understanding of biological systems have paved the way towards bridging this gap. Polymeric drug delivery carriers that have based on pathogens such as bacteria and viruses are potentially immunogenicity for human body. A certain degree of immunogenicity can be ideal if pathogen-based carriers have intended for vaccine delivery, owing to their adjuvant ability. Combining perspectives from the synthetic and biological fields will provide a new paradigm for the design of polymeric drug delivery systems in near future.

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