Chapter

Biomaterials for Drug Delivery: Sources, Classification, Synthesis, Processing, and Applications

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Abstract

A way to avoid or minimize the side effect that could result in drug delivery to cells with increased efficiency and performance in the health rehabilitation process is to use biocompatible and biodegradable drug carriers. These are essentially biomaterials that are metallic, ceramic, or polymeric in nature. The sources of these materials must be biological in its entire ramification. The classification, synthesis, processing, and the applications to which these materials are put are the essential components of having suitable target cell drug carriers. This chapter will be devoted to discussing biomaterials suitable as drug carrier for use in the health-related matters of rehabilitation.

Keywords: biomaterials, drug carriers, cell, drug delivery, health, synthesis, target

1. Introduction

The quest for controlled drug release emanating from side effects associated with the application and delivery of conventional drugs has necessitated the need for materials that can transport drugs to target site without difficulty or problem during and after delivery. Normally, drugs are delivered repeatedly on prescription to the body in measures that will bring about remediation and quick recovery to the patient during the treatment period. In this wise, drug concentration levels will increase and when above the body's tolerance level, the problems associated with over therapeutic concentrations could occur that could result into toxic side [1]. It is also possible that the drug release rate is so fast that therapeutic actions are no longer effective owing to low drug concentrations at the delivery site, which may occur through drug metabolism, degradation, and transport out of the target [1]. Consequently, this phenomenon would result in drug wastage and transport medium loss with high risk offside effects on surrounding body cells, tissues, and organs. The solution to these problems is to

have drug carriers that can provide controlled release rate to the target and would allow for complete therapeutic rehabilitation before degradation and transport of excess concentration of drug and carrier medium [2]. The drug and its carrier in form of capsules are orally administered and may be formulated for parenteral administration [3]. The drug release rate of the capsule can be controlled via the use of cellulose coatings exhibiting slow dissolution, incorporation of drug-complexing elements or compounds which hinder fast dissolution of drug, use of compressed tablets, and the inclusion of emulsion and suspensions. Materials that can permit drug release without changing or decaying over time with longer therapeutic windows (days to years) are required. These carries are such that they can be injected and/or implanted directly to target diseased tissues/cells for enhancing delivery efficiency [4]. To achieve target drug delivery, the use of affinity ligands deposited on biomaterial surfaces to allow for a set retention and usage by infirm tissues and cells have been employed [5]. The design of biomaterials for drug carriers aside permitting surface modification using ligands should also shield drugs from speedy break down and/or degeneracy within the target site.

Thus, the design parameters include: (i) the encapsulation of the sufficient drug of the biomaterial for lengthened release pattern to achieve efficient healing, (ii) sustaining drug stability for effective therapeutics through body transport and at the target site while preserving biological activity, (iii) predictable release rate in the therapeutic period from days to years, (iv) biomaterials and its degradation products must be biocompatible and nontoxic within the body, and (v) the cost of biomaterial synthesis and/or fabrication.

2. Health implications of materials used for drug delivery

Lupron Depot, a poly (lactic-co-glycolic) acid (PLGA) microsphere encapsulating the hormone leuprolide, for the treatment of advanced prostate cancer, and endometriosis [6], PLGA, poly (lactic acid) (PLA), and polyglycolic acid (PGA) materials have FDA approval as micro-particle depot systems as they versatile in controlling material biodegradation time, are biocompatible with nontoxic natural degradation products (lactic acid and glycolic acid). Clinical nanoparticles with FDA approval for cancer nanomedicine treatment of Kaposi's sarcoma (approved 1995) and for recurrent ovarian cancer (approved 1998) is Doxil [7], a poly (ethylene glycol) (PEG) coated (i.e., PEGylated) liposomal encapsulating the chemotherapeutic doxorubicin [8]. This enhances circulation half-life and tumor uptake of the drug, and also reduces its toxicological activity in patients in comparison to the use of free drug [9]. Other approved nanoparticle drug carriers include Marqibo, a liposomal encapsulating vincristine for rare leukemia treatment [10] and Abraxane an albumin-bound paclitaxel nanoparticle for the treatment of breast cancer [11]; Duragesic-transdermal drug delivery system patch containing the opioid fentanyl embedded within an acrylate polymer matrix, in the treatment of chronic pain [12]; and OROS, an osmotically controlled oral drug delivery technology, incorporated into several oral delivery products including Concerta [13]. Implantable biomaterials used include the Gliadel wafer, which consists of dime-sized wafers comprised of the chemotherapeutic agent carmustine and a polymer matrix made of poly (carboxyphenoxy-propane/sebacic acid), which are surgically inserted into the brain post-tumor resection [14–16] use as an adjunct to surgery in patients with recurrent glioblastoma multiforme.

3. Bioresponsive polymers: from design to implementation

An ideal therapeutic drug is expected to treat or cure a disease without resulting to any side effects [17–19]. However, this goal has not been achieved. Many chemotherapeutics are found to destroy both cancerous and healthy cells within the vicinity of the target site [20]. An efficient chemotherapeutics would administer drug, directly to diseased cell populations. Polymers have been found to permit the creation of "responsive" materials within the host environment and can be formulated with drugs to control release [21]. This polymer attribute is due to tuning propensity of the molecular weight of polymers that can be controlled via monomer stoichiometry using controlled polymerization strategies like ATRP [22], RAFT [23], NMO [24], and ROMP [25]. A bioresponsive material is one that can respond to a specific "trigger" inside or outside of the human body. Because the body have unique pathological parameters as pH gradients, temperatures, enzymes, small molecules, etc., the creation of materials that will respond to physiological alterations in both space and time are required.

Triggers include chemical, biological, and physical stimuli [26, 27], the chemical and biological ones are intrinsic to the body, while the physical stimuli are extrinsic to the body can thus be used to quicken sole drug delivery.

4. Redox-sensitive polymers

Bioresponsive materials are initiated by redox potential difference tissue environment and its surrounding [28]. There are materials that can respond to both oxidation and reduction triggers, which are incorporated into responsive polymers, e.g., diselenides with chemical structure like those of disulfides [29]. Diselenides allows for alternative triggers within nano-biotechnology applications [30].

5. pH-responsive polymers

The constituents of the human body such as tissues, fluids, and organelles have varied pH values. Areas like stomach, vagina, and lysosomes display acidic pHs (<7); ocular surface (7.1), the blood (≈7.4), and bile (7.8) [21]. Owing to these varied

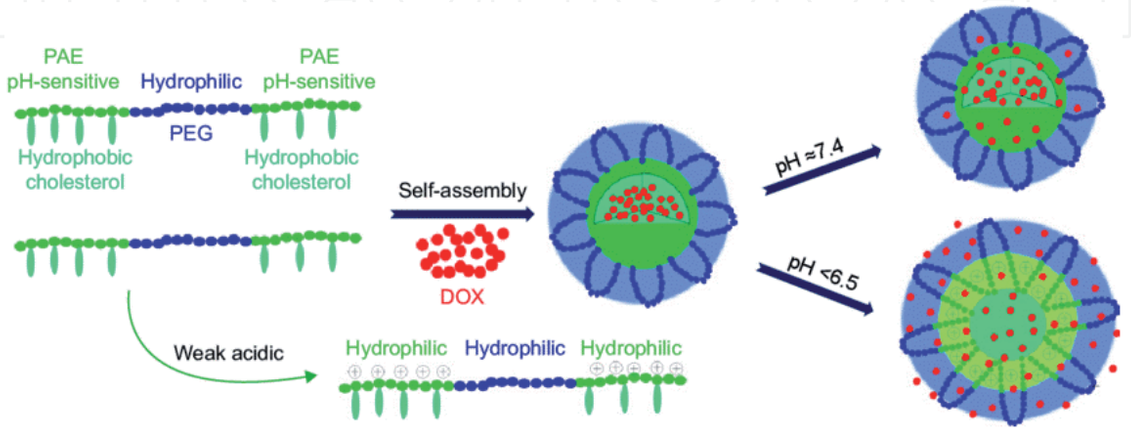

Figure 1.
Schematic illustration of drug loading and controlled release of poly (ethylene glycol) [34]. DOX, doxorubicin; PAE, poly (β-amino esters); PEG, poly (ethylene glycol).

pHs of systems and organs in the body improvement in the efficacy and precision of therapeutic molecules will necessitate the design of polymeric drug delivery systems that are pH specific. pH-responsive materials have been useful in nucleic acid delivery, doxorubicin delivery, and taste masking [31, 32]. The target treatment of tumors has been enhanced using the pH-responsive materials. Such known target delivery includes multifunctional acid sensitive nanocomposites for anticancer drugs and acid-responsive poly(ethylene glycol) derivatives [33] for the controlled release of therapeutics in tumor target treatment (**Figure 1**).

6. Hydrolysis and enzymatically responsive polymers

Hydrolysis prone materials can be degraded by body fluid via nucleophilic addition of water into an electrophilic functional group on a polymer. The electrophilic functional groups often used on polymers include esters and anhydrides [35]. The Gliadel wafer consisting of chemotherapeutic Carmustine impregnated within a polyanhydride material has been demonstrated as hydrolysis-sensitive materials for drug delivery [36] in the treatment of brain tumors. Enzyme-responsive polymers such as matrix metallo-proteins, hyaluronidases, phospholipases, and prostate-specific antigen [21] have been incorporated into polymers for target drug delivery in areas like tumor imaging, doxorubicin delivery, and minimization of inflammation in the colon [37].

7. Temperature-responsive polymers

Another drug delivery vehicle is the temperature-sensitive polymers that can operate at both human body temperature of 37°C and at ambient temperature such as 25°C [38]. These polymers include poloxamers, poly(N-alkyl acryl amides), poly(N vinyl caprolactams), cellulose, xyloglucan, and chitosan. These thermo-responsive polymers can be modified via [39] varying the ratio of monomers, end-group modifications, and post-polymerization modifications to make them suitable for varying applications [40].

8. Magnetic-responsive polymers

Magnetic-responsive polymers are therapeutic drug-loaded polymers that work under the influence of magnetic resonance imaging (MRI) to delivery its drug to the target [41]. These include the following: systematic release of dopamine from alginates impregnated with magnetic beads; targeted plasmid delivery to the lung via chitosan nanoparticles; and insulin delivery [42].

9. Light-responsive polymers

Light-responsive polymers are used as external drug delivery systems that use noninvasive and painless techniques [26, 43–48] as drugs are delivered by light UV- and visible-wavelength irradiation stimulation. In this technique, a remote-activated approach without direct patient contact is used [49]; this includes the release of drugs from a light-responsive azobenzene modified amphiphilic block copolymer to target melanoma cells [50].

10. Swelling and contracting polymers

There are polymers that can swell or shrink in response to external stimuli [51]. This phenomenon can have stemmed from changes in porosity occasioned as ionic cross-linking molecules are leached, resulting in alteration of the diffusion pathways for sensing molecules. Alginate is a commonly employed polymer that is isolated from seaweed, is relatively biocompatible, and has been used for sustained delivery of vascular endothelial growth factor (VEGF) to a target within the body.

11. Biomaterial-based drug delivery systems

While a limited number of affinity-based delivery systems have been developed for the delivery of neurotrophic factors, we also examine the broad spectrum of reservoir-based delivery systems, including microspheres, electrospun nanofibers, hydrogels, and combinations of these systems.

Drug delivery systems transport biological active agents, such as growth factors and genetic material, into the desired location to promote beneficial effects for the treatment of diseases and disorders [52], osmotic pumps for the delivery of neurotrophic factors [53] to target site, affinity-based delivery systems (ABDS) in which drug loading and controlled release are achieved through the interactions of therapeutic drug and the delivery system, and reservoir-based delivery systems, where a polymer structure encapsulates the drug while its release is controlled via the material properties.

12. Affinity-based delivery systems (ABDS)

ABDS operate through the noncovalent interactions between device material and target drug [54] in a similar pattern to the interactions that occur in the extracellular matrix where the delivery of proteins and other biomolecules are controlled [55]. ABDS include molecular imprinting, cyclodextrin-based delivery, and heparin-based delivery [56]. Molecular imprinting uses polymer networks synthesized via a precursor molecule that is removed to reveal an imprint that acts as an affinity binding zone. In cyclodextrin-based delivery systems, small hydrophobic drugs are attracted to the hydrophobic center of an oligosaccharide cyclodextrin torus, which permits the complexes formation with enhanced solubility when compared to the drug itself. ABDS is observed to be superior to traditional reservoir-based systems as the release characteristics are dependent on the activities occurring between the drug and the matrix in a way not affected by the matrix properties [57].

13. Reservoir-based delivery systems (RBDS)

Reservoir-based delivery systems (RBDS) are porous with drug release rate controlled by diffusion [58]. In RBDS, the drug is immersed or dissolved in a polymer solvent/reservoir. The drug penetrates via the biodegradable polymer structure to control the initial release followed by another release as surface and bulk erosion

occurs in polymer reservoir. RBDS include nanogels, nanoparticles, micelles, hydrogels, microspheres, and electrospun nanofibers.

14. Microspheres

Microspheres are usually used as controlled drug release systems for stereotactic injections to isolated disease or injury sites in medicine and pharmacology [59]. Drugs like neurotransmitters, hormones, and neurotrophic factors have been encapsulated using microspheres obtained from biodegradable polymers [60]. These polymers include poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and poly(ε-caprolactone) (PCL). Microsphere-based drug delivery uses localized surgical injection to circumvent the blood-brain barrier; this is better in performance to orthodox methods like intravenous injection and oral drug delivery. The parameters of the microsphere such as the particle size, polymer degradation rate, and method of erosion (bulk versus surface degradation) can be utilized to control the rate of drug delivery rates [61]. PCL has been found useful as a microsphere for the carrier of sustained long period drug delivery as it demonstrates the slowest degradation rate [62]. The double emulsion method is often used in synthesizing of microspheres. The method involves dissolving the desired polymer in a nonpolar solvent to form an oil emulsion. The hydrophilic compound that is to be encapsulated is dissolved in an aqueous solution and then emulsified with the dissolved polymer-solvent solution to give a water-in-oil emulsion. After this the solvent evaporates, the polymer solidifies as it forms microspheres that encapsulated the inner aqueous solution [63].

15. Electrospun nanofibers

Electrospinning process involves the application of an electric potential to draw out thin nanometer to micrometer diameter polymer fibers (natural or synthetic). A viscous solution of the polymer is prepared (at room or elevated temperature), then pumped via a spinneret nozzle (positive terminal) into an electric field such that the applied force due to the high voltage counters the surface tension leading to the formation of fiber droplets onto a collector plate that serves as negative terminal. The nanofibers produced are often used as drug based-reservoir delivery systems as the pores in the matrix serves as receptive sites for bioactive agents [64]. This fiber production process advantages include surface flexibility with respect to function or application, reduced initial burst release, and the possibility of producing different fiber configuration depending on usage [65]. Drugs are embedded in the pores of electrospun nanofibers by emulsion electrospinning; the target drug is dissolved in a desired polymer solution [64] such as in diclofenac sodium (DS) and human serum albumin (HSA) [66]. Electrospun nanofibers show some draw backs that include formation of drug aggregates during encapsulation along nonsmooth fibers, maintaining uniform fiber size distribution, the use of toxic solvents to form polymer-drug emulsion in drug delivery and its attendant health concerns. Despite these drawbacks, advances in the development of less toxic electrospun fibers, which contain extracellular matrix components such as keratin and collagen, have been developed for wound healing application. The biocompatibility potential of PVA with the bioactive nature of keratin, CoQ10, and antimicrobial mupirocin has been

evaluated for wound care due to its ability to support the growth of keratinocytes and hasten skin regeneration [67].

16. Hydrogels

Hydrogel is a hydrophilic network of cross-linked polymer chains with swelling capability but does not dissolve in aqueous solution in the presence of water to create a three-dimensional gel-like structure. The synthesis of hydrogels is through polymerization [68], its properties, and drug release mechanism that depend on the polymer type used. The mechanisms involved in the drug delivery of hydrogel may be diffusion controlled, chemical controlled, swelling controlled, and modulated release systems. The use of acetyl-(Arg-Ala-Asp-Ala)4-$CONH_2$ self-assembling peptide hydrogel to carry model factors such as lysozyme, trypsin inhibitor, BSA, and IgG [69] reveals the potential of these hydrogels carriers of therapeutic agents with the preservation of protein activity. An agarose hydrogel has been found capable of delivering sustained bioactive lysozyme release [70] and was used for the local delivery of BDNF in adult rat models.

17. Surface-modified biomaterials

The biomaterial surface chemistry and topography impact protein adsorption, cell interaction, and host site response. Monocyte adhesion in vitro [71] have been shown to be altered by its surface chemistry, while in vivo surface chemistry does not significantly influence the foreign body reaction. Polymeric, ceramic, or metallic-based biomaterials exhibit variability in surface properties such as hydrophilic to hydrophobic; hard to soft in vivo [72].

18. Surface specificity

Cell adhesion to adsorbed proteins is achieved via integrin and other receptors in the cell membrane and the occurrence of this triggered intracellular signaling events. Thus, the control of protein adsorption on biomaterials surfaces is crucial to controlling and directing cell responses. Oligopeptides with specific binding sites have been incorporated to control cell adsorption to the protein surface and these include short oligopeptide, e.g., adhesive oligopeptide is an arginine-glycine-aspartic acid (or RGD) [73] that is found in a number of different extracellular matrix proteins, such as fibronectin [74], laminin [75], collagen [76], and vitronectin [77]. Short oligopeptides are less expensive, easy to synthesize, and has greater flexibility for surface modification compared to bulky and labile intact proteins. To a surface modified using nonfouling PEG (99%) and RGD (1%), the protein adsorption was minimal (2 ng/cm2) leaving the sufficient RGD sites for fibroblast cell adhesion [78]. Structure and conformation of oligopeptides influence modulating cell adhesion as demonstrated with the use of immobilized cyclic RGD peptide which increased human bone marrow stromal cell adhesion to that of linear RGD peptides [79] (**Table 1**).

S/No.	Drug delivery systems	Biomaterial	API	Significance of the study	Reference
	ORAL DRUG DELIVERY SYSTEMS				
	Silk Nanoparticles	Silk and fibrin	Celecoxib and curcumin	Silk fibroin nanoparticles were seen to promote anti-inflammatory properties of celecoxib or curcumin and could be exploited for oral osteoarthritis management since a controlled drug release was achieved by varying the drug loading	[80]
	Electrospun fibers	Polylactic acid	Metronidazole	PLA nanofibers associated with metronidazole (MNZ) were used to control microbiological proliferation during periodontitis treatment, inhibiting bacteria growth during the treatment	[81]
	OCULAR DRUG DELIVERY SYSTEMS				
	Nanocomposite hydrogel	Hyaluronic acid	Latanoprost	The hyaluronic acid nanocomposite hydrogels, with controlled degradation properties and sustained release, could serve as potential drug delivery systems for many ocular diseases as they controlled the release of latanoprost in vitro	[82]
	Hydrogel contact lens	Silicone	Ofloxacin and Chloramphenicol	The drug release from the lenses was directly proportional to the amount of drug loaded and the lenses at the different loading concentrations showed transmittance of 95–97%. The silicone hydrogel contact lenses can be used to control drug delivery to the eye and is an alternative ocular delivery technique in the treatment or prevention of corneal infections	[83]
	PULMONARY DRUG DELIVERY SYSTEMS				
	Porous particles	Poly(lactide-co-glycolide) (PLGA)	Celecoxib	Large porous celecoxib-PLGA microparticles prepared using supercritical fluid technology exhibited sustained drug delivery and antitumor efficacy, without causing any significant toxicity	[84]
	Nanoparticles	Nanopolymeric particles consisting of hydroxyl propyl methylcellulose (HPMC), poly-vinylpyrrolidone (PVP)	Fluticasone	The in vitro antibacterial studies showed that HPMC-PVP-FLU nanoparticles displayed superior effect against Gram-positive bacteria compared to the unprocessed FLU and positive control	[85]

S/No.	Drug delivery systems	Biomaterial	API	Significance of the study	Reference
IV	**IMPLANT DRUG DELIVERY SYSTEMS**				
	Silk disc implants	Silk fibrin	IgG antibody or human immunodeficiency virus (HIV) inhibitor 5P12-RANTES	SF was formulated into insertable discs that can encapsulate either IgG antibody or human immunodeficiency virus (HIV) inhibitor 5P12-RANTES. The water vapor annealing showed a sustained release for 31 days and this released protein could inhibit HIV infection in both blood and human colorectal tissue	[86]
	Bone biomaterials implant	Hydroxyapatite	Doxorubicin-loaded cyclodextrin	Hydroxyapatite-cyclodextrin-doxorubicin chemotherapeutic strategy enhanced the drug-targeting effect on tumor cells while protecting the more sensitive healthy cells after implantation. A successful integration of such a drug delivery system might allow healthy cells to initially survive during the doxorubicin exposure period	[87]
V	**SYSTEMIC DRUG DELIVERY**				
	Polylactide scaffold hydrogel injections	Cholesterol-modified poly(ethylene glycol)–polylactide	Chondrocytes	The formulation shows lower critical gelation temperature, higher mechanical strength, larger pore size, better chondrocyte adhesion, and slower degradation compared to plain polylactide scaffold gels. The hydrogel serves as a promising chondrocyte carrier for cartilage tissue engineering and gives an alternative solution to surgical cartilage repair	[88]
	ANG-(1–7) functionalized plant chloroplast	Lyophilized lettuce cells (ACE2/ANG-(1–7))	Lyophilized lettuce cells (ACE2/ANG-(1–7))	Toxicology studies showed that both male and female rats tolerated ~10-fold ACE2/ANG-(1–7) higher than efficacy dose. The efficient attenuation of pulmonary arterial hypertension with no toxicity augurs well for the clinical advancement of the first oral protein therapy to prevent/treat underlying pathology for this disease.	[89]
VI	**VAGINAL DRUG DELIVERY SYSTEMS**				
	Organogel	Palm oil and hyaluronic acid	Maraviroc	There was a 2.5-fold increase in the percentage of maraviroc release in the presence of hyaluronidase, hence the effectiveness of hyaluronidase enzyme acting as a trigger. This shows the potential use of palm oil/hyaluronic acid-based organogel for the vaginal delivery of anti-HIV microbicide for HIV prevention	[90]
	Vaginal rings	Silicone matrix polymer	Dapivirine	A monthly vaginal ring containing dapivirine reduced the risk of HIV-1 infection among African women, with increased efficacy in subgroups with evidence of increased adherence	[91]

S/No.	Drug delivery systems	Biomaterial	API	Significance of the study	Reference
VII	**TOPICAL DRUG DELIVERY SYSTEMS**				
	Electrospun fibers	Polylactic acid and collagen	Collagen and silver sulfadiazine	The electrospun fibers were nontoxic to the cells and provided favorable substrates for the neonatal epidermal keratinocytes cells to undergo cell attachment and proliferation, hence its potential for use in chronic wound management	[92]
	Hydrogel	Polyvinyl alcohol and carbopol	Diclofenac diethylamine	In vitro skin permeation for 10 h showed that the enhancement ratios of the flux of diclofenac was higher compared to the marketed formulations. The study highlighted the advantage of the experimental transdermal hydrogel over the hydrogel with microsized drug particles	[93]

Table 1.
Drug delivery systems showing the significance of the biomaterials utilized in delivering active pharmaceutical ingredients at their biological target site.

19. Nonfouling surfaces

Poly (ethylene glycol) (PEG), or poly(ethylene oxide) (PEO) having nonfouling surfaces demonstrates protein and cell resistance capabilities. PEG have been attached to materials in such a manner to render them nonfouling through processes like covalent immobilization, adsorption, or interpenetration. PEG has been covalently attached to mussel adhesive protein to form a nonfouling and a sticky segment copolymer [94] with gold and titanium surfaces attached to the sticky segment, while the PEG chains occur at the new interface. It should be noted that the nonfouling ability/attribute of PEG is dependent on the surface chain density that is prone to oxidants damaged. However, the use of plasma deposition of tetra ethylene glycol dimethyl ether (tetraglyme) on PEG will reduce protein surface adsorption [95]. Other materials with nonfouling surfaces include phospholipid surfaces [96] and saccharide surfaces [97], and these biomaterials ensure increased compatibility issues between the drug carrier systems and biological systems to which they are introduced to elicit a pharmacological activity.

20. Smart biomaterials

Materials which respond to environmental changes are attractive particularly in vivo as these can be utilized to control drug release, cell adhesiveness, mechanical properties, or permeability. These environmental changes can be brought about by stimulants like pH [98], temperature [99], and light [100]. The body employs changes in pH to facilitate a range of different processes. For example, along the gastrointestinal track, food is broken down into nutritive substances in the stomach under acidic pH ~ 2 and subsequently absorbed in the small intestine (pH ~ 7). Patient often prefers the oral drug delivery requiring routine, periodic delivery of drugs and for effectiveness, the drug must resist the stomach acidic pH. The pH-sensitive materials that are mindful of gastrointestinal tract pH variation have been developed to transport drugs successfully through the stomach to the small intestine. Such successful materials include pH responsive hydrogels prepared from poly(methacrylic acid) grafted with poly(ethylene glycol) (PMAA-g-PEG) that swells in response to pH. For instance, the gel shrinks by trapping the drug cargo pH ~ 2 as interpolymer complexes are formed, but at physiological pH ~ 7, the gel can swell 3–25 times based on its composition as it releases its cargo in the target site [101]. Insulin-loaded PMAA-g-PEG gels have been orally delivered to diabetic mice with a significant decrease in glucose levels as protein function is protected in acidic and digestive enzymes environments [102].

20.1 Self-assembled biomaterials

Self-organization or self-assembly is based on the formation of weak noncovalent bonds, like hydrogen, ionic, or Van der Waals bonds or hydrophobic interactions [103]. In amphiphilic molecules, there are hydrophobic and hydrophilic segments that self-assemble to form nanometer 3D structures like micelles, vesicles, and tubules, which depend on the molecule's length and composition [104–107]. When any of these are dispersed in aqueous solvent, the hydrophobic segments agglomerate and water is expelled to produce a well-ordered structure useful in biomedical applications. Phospholipid a naturally occurring amphiphilic molecule that is largely compose of cell membrane is one such amphiphilic molecules while an oligomer, a polymer of amino acids, can be synthesized to have hydrophobic, hydrophilic, charged, etc., regions that can self-assemble into a macroscopic hydrogel [108]. The self-assembled biomaterials can be engineered for use in nanotechnology, tissue engineering for drug and cell carriers.

21. Controlled drug delivery

Polymers are large molecules formed from simple monomers and may be synthetic or biopolymers that are the constituents of living organisms like proteins, nucleic acids, and sugars. Biopolymers are active in controlling and regulating many biochemical and biophysical functions of living cells, and thus can participate in cooperative interactions, resulting in nonlinear response to external stimuli. The cooperative interaction mechanism of biopolymers is utilized in producing synthetic polymers that are similar in behavior to biopolymers, which are used as biomaterials with ability to interface with biological systems for a variety of living cells functions.

Polymeric, biodegradable materials are often useful in biomedical applications, as the polymers degrade into normal metabolites of the body or eliminated from the body with or without further metabolic transformation [109, 110]. Developed polymeric biomaterials have physical and chemical properties that are maintained and are not tampered with during synthesis. The use of synthetic polymeric biomaterials includes artificial corneal substitute, blood contacting devices, hip joint replacements, and formation of intraocular lenses [111, 112]. Biodegradable polymers are either natural or synthetic. Natural polymers are derived from natural resources and have potential to be considered for biomedical and pharmaceutical applications owing to biocompatibility, biomimicking environments, unique mechanical properties, and biodegradability. Natural polymers are prone to viral infection, antigenicity, and unstable material supply, which limit biomedical application. On the other hand, synthetic polymers are flexible in synthesis procedure technique with excellent reproducibility which made them useful for surgical and short-term medical application, orthopedic applications that may slowly transfer the load as it degrades [113].

The drug administration into the body is either via an oral or intravenous route with repeated administration done to increase concentration and performance. But this may reach an extreme level before it declines rapidly especially when the elimination rate from the body is high. A too low or too high drug concentration in the body will not benefit the patient because of the side effects. This phenomenon then becomes a concern requiring the use of controlled drug release mechanism which can only be offered by biomaterials [114]. For controlled drug release, the therapeutic and bioactive agents are enveloped or encapsulated in an insoluble biodegradable subnano, nano, micropolymer matrix cavity where the therapeutic agents are released in a controlled fashion.

22. Various drug delivery systems

Widely used drug delivery systems include a liposomal drug delivery system [115, 116] that consists of phospholipids, i.e., fatty acid esters and fat alcohol ethers of glycerol phosphatides; they are negatively charged at physiological pH due to their phosphate groups. Cationic liposomes are prepared using lipid molecules having a quaternary ammonium head group. Because cellular membranes carry negative charges, cationic liposomes interact with these cellular membranes [117]. The stability of liposomes in biological environment is improved with steric stability that can extend its blood circulation time after being administered [118]. Biodegradable polymers are usually used to enhance the steric stability of the liposomes. Natural biodegradable polymers that are suitable for drug delivery systems include proteins (collagen, gelatin, albumin, etc.) and polysaccharides (starch, dextran, chitosan, etc.) [119].

22.1 Polysaccharides

Polysaccharides are many monosaccharide repeating units with high molecular weight. It is biodegradable, biocompatible, and water soluble which make suitable for drug delivery. There are several different types of polysaccharides having different functional groups, which are as follows:

22.2 Alginic acid or alginates

Alginic acid is a linear hetero polysaccharide, nonbranched, high-molecular-weight binary copolymer of (1–4) glycosidic linkage with β-D-mannuronic acid and α-L guluronic acid monomers [120, 121]. Natural alginic acid can be obtained from the cell walls of brown algae. Its acidic nature helps in its spontaneous formation of salts and later gels in the presence of divalent cations like calcium ions. This occurs by the interaction of divalent cations with guluronic acid blocks present on other polysaccharide chains. The gel property paves way for the encapsulation of molecules that can act as drugs within alginate gels with negligible side effects. The drug delivery mechanism of alginates is hinged on the drug polymer interaction and chemical immobilization of the drug on the polymer backbone via reactive carboxylate groups [122–124].

22.3 Starch

Starch, which is a carbohydrate source can be isolated from corn, wheat, potato, tapioca, rice, etc., and consists of two glucosidic macromolecules: 20–30% of linear molecule—amylase and 70–80% of branched molecule—amylopectin. The products of starch processing include thin films, fibers, and porous matrices. It is an important polymer for thermoplastic biodegradable materials due to its low cost, availability, biocompatibility, biodegradability, and having renewable resources [125]. The products of starch degradation include fructose and maltose that are low molecular weight sugar [126]. Microspheres from starch have bioadhesive drug delivery system potential for nasal delivery of proteins [127].

22.4 Dextran

Dextran is a natural polysaccharide of large glucose molecules with long and branched chains of varying lengths from 3 to 2000 Kd at 1,6- and partly at 1,3-glucosidic linkages. It is synthesized from sucrose via lactic-acid bacteria like *Leuconostoc mesenteroides*, *Streptococcus mutans*, and lactic acid bacterium *Lactobacillus brevis*. It is colloidal and hydrophilic in nature; it is inert to the in vivo environment with no effect on cell viability [128]. Dextran is used as an antithrombotic (antiplatelet), to reduce blood viscosity, and as a volume expander in anemia [129]. Dextran can be degraded by enzyme dextranase in the colon and thus can serve as a colonic drug delivery system.

22.5 Pullulan

Pullulan occurs naturally as linear homopolysaccharide polymer with maltotriose units of 3-glucose or D-glucopyranose units which are linked by α-(1 → 4) glycosidic linkages. It is edible, bland, and tasteless and thus is added to food and beverages. It serves as a coating agent in pharmaceutics, breath fresheners, or oral hygiene products [130]. Consecutive maltotriose units are linked to one another via

α-(1 → 6) glycosidic bond. The pullulan backbone structure is similar to dextran, as both are plasma expanders. Pullulan is commercially synthesized via fermentation process involving the growth of fungus *Aureobasidium pullulans* on a carbohydrate substrate, which is then harvested. This process is followed by the rupture of cell using either an enzyme or a physical force, and pullulan is then extracted via simple water extraction method [130]. This method does not constitute any threat to the environment and therefore it is ecofriendly. This then makes pullulan suitable as a drug delivery vehicle. Pullulan hydrogel micro and nanoparticles are employed in oral administration of gastro-sensitive drugs.

22.6 Hyaluronic acid

Hyaluronic acid also a natural occurring negatively charged linear polysaccharide made of repeating disaccharide units of D-glucuronic acid and 2-acetamido-2-deoxy-D-glucose monosaccharide units. It exists majorly in articular cartilage, connective tissues, synovial fluids of mammals and the mesenchyme of developing embryos. It is water soluble and forms highly viscous solutions and therefore suitable for use as wound dresser as it can act as scavenger for free radicals in wound sites to modulate inflammation [131]. Its use in tissue repair application include to protect delicate tissue in the eye in removal of cataract, corneal transplantation, and glaucoma surgery, as vitreous substitute in retina re-attachment surgery, to relieve pain and improve joint mobility in osteoarthritis (knee) patients suffering and accelerate bone fracture healing [132].

22.7 Chitin and chitosan

Chitin a natural occurring polysaccharide of 1 → 4 β-linked glycan containing 2-acetamido-2-deoxy-D-glucose is a component of shells of crustaceans, cell walls of fungi, etc. When chitin is deacetylated chitosan a semi-crystalline linear copolymer polysaccharide is produced with (1 → 4) β-linked D-glucosamine and some N-acetyl glucosamine groups. The degree of deacetylation (DD) of chitosan may be from 70% and 90% and the MW is in between 10 and 1000 k [133]. While chitin is insoluble in regular solvents, chitosan is fully soluble in aqueous solutions with pH <5.0 [134]. Chitosan degrades in vivo enzymatically via lysozyme to nontoxic products [134]. Chitosan is easy to process and applied, oxygen permeability, water absorptivity, hemostatic property, and ability to induce interleukin-8 from fibroblasts. It uses include wound and burn dressing material, drug delivery and controlled drug release.

22.8 Polyurethane

Polyurethane is a polymer with a chain of organic units linked by carbamate (urethane), which is formed from two or several bi- or higher-functional monomers, one having two or more isocyanate functional groups (–N=C=O) and the other with two or more hydroxyl groups (–OH) [135]. It is a material with similar elasticity to rubber, possess toughness and durability comparable to metal, and is chemically inert. Polyurethane micelles are suitable drug delivery systems.

23. Conclusion

Advances in medical research have led to the exploration of various materials as drug carriers for suitable delivery. Biomaterials are currently well explored in recent

years as a result of their ubiquitous nature, ease of accessibility, biodegradability, and biocompatibility with living tissues. They have been singly used or blended with other materials as composites. This chapter has thus discussed the different biomaterials with their functionalities in the area of drug release. More biomaterials can be explored by processing and characterizations from natural origin to ensure effective performance and limit health complications associated with drug release.

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