DRUG DELIVERY SYSTEMS BETWEEN METAL, LIPOSOME, AND POLYMER-BASED NANOMEDICINE: A REVIEW

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Herein, the drug delivery systems (DDS) based on nanomedicine proofed high potential and wide applicability that have distinct features related to Nano-sized. Enhancement of bioavailability and pharmacokinetics after oral administration via utility of natural/synthetic biodegradable polymeric nanomaterials. Improving biocompatibility, safety, enhanced permeability, better retention time, lower toxicity and efficient transportation of drugs to desired tissues or cells. These nanomaterials based on different types including metallic and polymeric Nano-medicine that can hydride with each other to gain new and unique features increase the efficiency of drug delivery and decrease patient compliance.

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INTRODUCTION

The therapeutic delivery in our bodies can be achieved by temporal and spatial drug delivery systems, which ensure effective and efficient transportation for the drugs into the desired cells and tissues.[1,2] Since 1500 BC, using the pills as a form of administration of drugs had the precedence.[3] Pill administration concept involves swallowing the pill and dissolving it in the stomach which is absorbed in the intestines and goes into circulation. Some limitations have been encountered in this approach, in cases of drugs which can break down in the stomach such as insulin. Consequently, insulin is injected into the fatty tissues and is then absorbed into the systemic circulation.[4] There are several other ways of drug administration such as transdermal, ocular and gastrointestinal or stimuli-reactive routes.[5] The first and second routes were applied, respectively, for avoiding the drawbacks of oral administration of pills. Later on, the sustained release was a desirable objective for developing the therapeutic profile by maintaining the drug levels in blood and tissues by a gradual release of medication for a prolonged interval of time, after single-dose administration.

The sustained-release phenomenon was achieved first in the late 1940s and early 1950s when the pills were coated with a talc-mucilage composition that converts the pills into shape looked alike pearls.[6] These coatings were hydrophobic and non-swelling at acidic pH of the stomach but are converted to ionized form in slightly alkaline pH of the intestinal region of the gastrointestinal tract, then get dissolved and release the drug. The prolonged time of drug release from the stomach to the small intestine, protect the stomach from the drug and protect the drug from being destroyed by digestive enzymes in the stomach.[7] However, these systems had some shortcomings due to their sensitivity for different physiological parameters such as pH, gastric emptying and so on.[8] The trials until the 1950s were unsuccessful to control drug release.

By progressing the drug release process, SmithKline Beecham developed the oral predetermined-release formulation as Spansules®.[9] Spansules® could sustain the release kinetics of dextroamphetamine sulfate (Dexedrine®) up to 12 h. Hence, the term of controlled release was achieved by developing the design of the tablets to prolong the time of therapeutic release through the introduction of different drug release mechanisms (dissolution-controlled, diffusion-controlled, osmosis-controlled, and ion-exchange-controlled mechanisms).

Introducing Spansules® as capsules containing micro-pellets coated with water-soluble wax, developed this design. Then the liposomes were considered as one of the earliest targeted systems, which were discovered in the 1960s. The anticancer agent was discovered as the liposomal-encapsulated formulation of doxorubicin (Doxil) in the 1990s which was approved first by the US Food and Drug Administration (FDA).[10]

The watershed in the drug delivery occurred in 1976 when Robert Langer and Judah Folkman discovered the large molecules could be delivered over days and weeks from polymer matrices.[3] The development was the replacement of waxy coatings with reproducible synthetic and more stable polymers that get gradually dissolved[7, 11] to insure the sustained level of effective drug concentration in the blood and enhance the control on drug release with obviously efficient new DDSs.[12,13]

DEVELOPMENT OF DDSs FROM BENCH-SIDE TO MARKET

Through the rigorous steps of the process of drug development from the laboratory bench to the pharmacies, we can understand the drug discovery and draw attention to

the tremendous amount of scientific effort that goes into the production and development of modern medicines before they reach the pharmacies. There are four stages from bench to the patient as shown: (1) drug discovery, (2) drug development, (3) regulatory review and approval, and (4) marketing.[14]

Drug discovery

The key to both academic biomedical research and the pharmaceutical industry is explicitly associated with the discovery and exploitation of new drug targets. An appropriate target, which can be called 'druggable' is categorized into biomolecule and protein receptors that can be determined according to disease conditions or pathology.[15] This step is followed by confirmation of its impact on disease progression with target validation and identification. To completely understand this aspect, the effect of interaction of another molecule with the target molecule/receptor is studied.

Drug development

The term 'drug candidate' is the best term of identification of the picked compounds through its dosage, efficacy, safety, and toxicity. There are two phases to ensure drug acceptance and confirm its features.[16] Firstly, the preclinical phase, which composed of two ways to study desired compounds pharmacodynamics and pharmacokinetics, features. These are simulated in cells (in vitro) and in animals (in vivo), which confirm the compound's profiles from its absorption, metabolism, excretion, and toxicity. The best and promising compounds have no toxicity, high absorption, effective distribution into desired cells and highly efficient metabolism. Secondly, a clinical phase which investigated in patients through 3 phases as following 1) testing in a small group of healthy volunteers, 2) testing in a small group of patients and finally 3) testing in a large group of patients to show its efficacy.[14]

Regulatory review and approval

Approval, by the food and drug administration agency (FDA), and marketing of the new drugs involve two phases. The first one is pre-approval (pre-market), FDA continues its oversight of drug safety and effectiveness in the drug's proposed use; appropriateness of the proposed labelling; and adequacy of manufacturing methods to assure the drug's identity, strength, quality, and purity. Second, the phase of post-approval (post-marked) that the drug introduced finally in the markets.[17]

NANOMEDICINE IN DRUG RELEASE

Recently developed, the multidisciplinary nanotechnology field has a considerable potential for solving many problems in therapeutic delivery systems. These advanced technologies overcome different therapeutic issues of conventional formulations like its poor bioavailability, drug instability or insolubility.[18] Nanomaterial with size below 350 nm has high efficiency and the ability for enhancing both medical devices and therapeutic areas due to its unique working mechanism and specific properties. There are different types of nanomaterial and their conjugates, for example, polymeric nanomaterial, metallic nanomaterial, metal-metal nanocomposites or hybrids, and metal-polymer nanocomposites.[19] For a clear understanding of the types of nanomaterial, they have been divided into two broad categories.

Metal-based nanomedicine

The noticeable potential of drug release is related directly to nano-carriers for drug transportation into the desired cells and tissues, and this is based on the type of materials used. Metallic composites have high efficacy in the drug delivery and release that depend on the abundance of metals such as gold, silver, porous iron oxide, zinc oxide, nano-titanium dioxide, and nano-silica etc.[20] Various categories of metal-based nano-medicine have great potential and an obvious role in drug release that included the two broad applicable types, carbon nanotubes and mesoporous silica nanoparticles.

Carbon-based nanomedicine

Unique and distinct chemical and physical properties of carbonaceous materials allow them to penetrate the drug release domain. These compounds have variability in their shape and several characters and are able to be an efficient part of active gradients of many therapeutic molecules. At first, the sp^2 hyperdization of carbon materials allowed them to have exclusive features for the drug release, according to its valence.

The different types of carbon-based- materials show different shapes and dimensions ranged from zero, 0D, to 3D dimensions such as 0D fullerenes and graphene clusters, 1D carbon nanotubes (CNTs) and graphene nanoribbons, 2D graphene surface and 3D graphite crystal and nanotube networks.[21] CNTs cylindrical morphology is formed by rolling one or multiple graphene layers. It is classified as single-walled carbon nanotubes (SWCNTs), and multiple-walled carbon tubes (MWCNs). SWCNs consist of one single cylinder of graphite sheet, with a diameter ranging from 0.4 to 3.0 nm.[22] On the other hand, MWCNs are conventionally depicted as an array of tubes that are coaxially aligned around a central hollow with the uniformed distance between layers. The numbers of layers dictate the diameters of MWCNs: the inner diameter can change from 0.4 nm to a few nanometers, while the outer diameter ranges from 2 to 100 nm.[21,23] The drug loading mechanism on CNTs is due to its unique properties of high surface area and spherical shape that ensure the remarkable loading of drug molecules. Hydrophilic or amphiphilic polymeric materials can be used for enhancement of the drug loading of CNTs and can affect the drug loading mechanism.Various approaches can illustrate the drug loading mechanism on CNTs such as encapsulation inside the cavities of the tubes,[24] functionalization of the surface, and adsorption on the wall or among the walls of CNTs.[25]

Mesoporous silica nanoparticles (MSNs)

Platforms based on silica nanoparticles are efficient designs for enhancement of drug release. These platforms

have unique features and characteristics such as robustness, easy surface modification, high surface area large pore volume and its tunable shape provide the drug release profile. For the first time, MCM-41 (Mobil Composition of Matter No. 41) was introduced as a novel drug system in 2001. This material was introduced to develop advanced nano-therapeutics.[26-28]

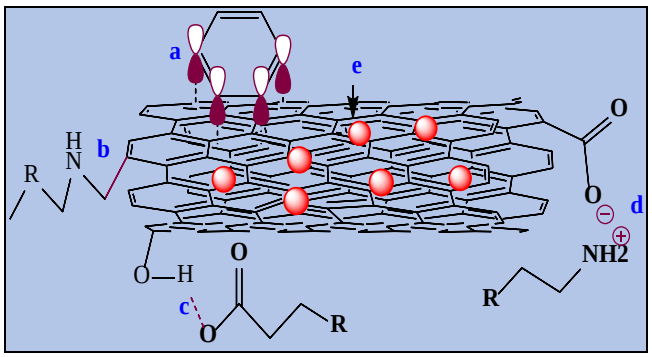

Figure 1. Overall approaches of attaching the drug to the outer surface of CNTs, a) π-π interaction n,b) Covalent bond, c) Hydrogen bonding, d) Ionic interaction and e) encapsulation inside the cavity.

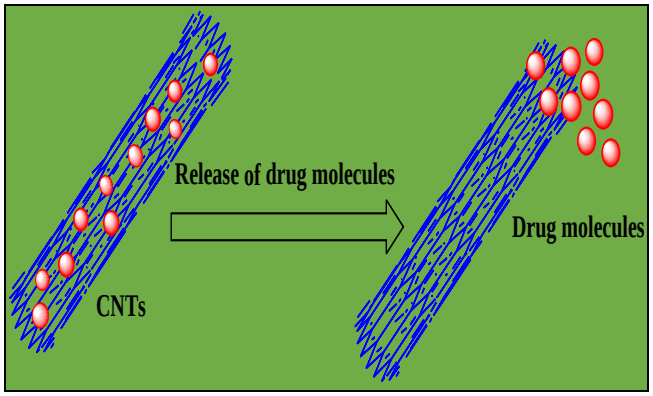

Figure 2. Drug release from carbon nanotubes.

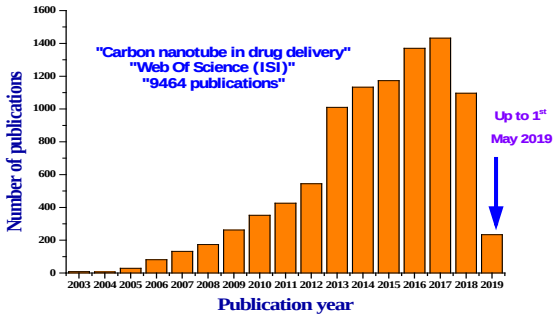

Figure 3. The number of publications per year indexed in the ISI Web of Science on the topic of "carbon nanotube in drug delivery" up to 1st May 2019.

Their therapeutics index and promising features as high drug loading capacity, protection and transportation of drugs to the target site to enhance the drug release. The high surface area of MSNs ensures a high percentage of contact area with guest molecules. MSNs architecture such as tuneable pore diameters, large surface areas and pore volumes, and high chemical and thermal stabilities has a crucial role in their combination therapies and influence the performance of drugs with these nano platforms.[29] Their pore diameter, which acts as a limiting factor, manipulates diffusion processes of drug molecules to the physiological environment. The pore diameter of the mesoporous cavities acts as selector of size of biologically active molecules that are loaded in these cavities. Besides, their Chemical composition and versatile chemistry for surface functionalization make them good hosts for accommodating guests biologically active molecules of various sizes, shapes, and functionalities.[30,31]

Polymer and Liposome-Based Nano-medicine

Polymeric ano-carriers are considered an essential part of manufacture of drug and are of two types, Liposomes and lipid-based polymers, and (2) Carbohydrate and lipid-based polymers

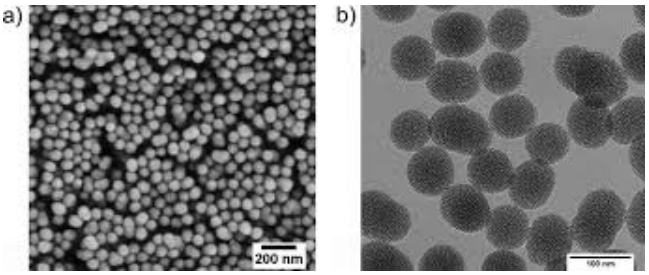

Figure 4. SEM image of mesoporous silica nanoparticles.[1]

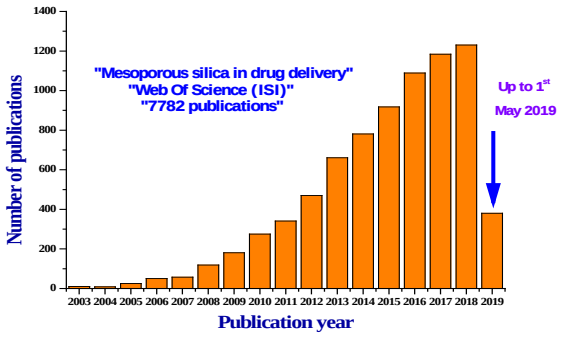

Figure 5. The number of publications per year indexed in the ISI Web of Science on the topic of "mesoporous silica in drug delivery" up to 1st May 2019.

They were discovered by Alec D. Bengham at the University of Cambridge in 1964 and were considered as the most efficient nano-carriers of drugs. Lipid bilayer structure or membrane that surrounds an aqueous compartment is the simple definition of the liposome. Main advantage of the liposomes in drug delivery systems is a core-shell design, for example, a typical phospholipid-based liposome, which allows a better encapsulation strategy for the sustained drug release. Phospholipid-based liposome has smart design as the hydrophilic or aqueous core that allows encapsulation of hydrophilic drugs, while the lipid membrane can encapsulate hydrophobic drugs. Thus, the advantage of the liposomal smart design is the encapsulation proficiency of both hydrophilic as well as hydrophobic drugs.

Table 1. Summary of some drug loaded metal-based nanoparticles together with their properties.

Nano system	Physicochemical properties and drug release efficiency	Synthesis method	Carried Drugs	Ref.
Silica-gold nanoshell and gold nanoparticles	Nanoshell sized in a range about 70-120 nm. Nanoshell drug loading efficiency and drug release profile revealed 87.5 and 99.0 % respectively.	Sol-gel method	Levofloxacin	33-35
Nano diamond-silk fibroin (ND-SF) hybrid	Nanodiamond (ND) is a new member of nanocarbon allotropes with truncated octahedral architecture that are about 2 to 8 nm in diameter. NDs are non-toxic, chemically and biologically inert, biocompatible and highly efficient in drug release.	Co-flow device	Doxorubicin	36
Porous silicon (pSi)	Revealed the tunable and versatile nature of pSi permitting high surface areas (up to 850 m^2g^{-1}), low-cost and reproducible fabrication, large pore volumes (>0.9 cm^3g^{-1}) and exhibited enhanced biocompatibility and biodegradation.	Anodic electrochemical etching in specific mixtures of hydrofluoric acid (HF) and ethanol thus enabling a 'top-down' approach	Doxorubicin and daunorubicn	37
Selenium nanoparticles carried on ruthenium polypyridyl (RuPOP)	Biocompatible, straightforward synthesis, low-toxicity, degradability in vivo, excellent antioxidant activity and chemopreventative effects	Pluronic F-127 surface modification for hydrophobic Ru complexes	5-Fluorouracil (5-FU) and doxorubicin	38, 39
Quantum dots (QDs)	(QDs) are type of stable semiconductor nanoparticles (NPs) such as g CdTe/CdS Q with a size of 2–10 nm that can easily emit strong fluorescence under irradiation. QDs possess great potential in intracellular imaging of living cells, good stability; high quantum yields (QYs), resistance to photobleaching, size-dependent emission spectra, and good biocompatibility.	Ex-situ growth approach	Folic acid (FA)	40, 41
Polyvinylpyrrolidone (PVP)-coated spherically clustered porous gold-silver alloy nanoparticle (PVP-SPAN)	PVP-SPAN provided 10 times higher loading capacity for oligonucleotide than conventional hollow Nanoshells due to increased pore diameter and surface-to-volume ratio	By low temperature mediated, partially inhibited galvanic replacement reaction followed by silver etching process	Doxorubicin	42
Polyethylene glycol-coated metal oxide nanoparticles (Fe_3O_4, NiO, CoO and SnO)	Better physiochemical properties have been achieved by surface modification of magnetic nanoparticles using various polymers, silica, different surfactant, or various organic compounds. Sufficient amount of drug can be loaded onto the stable surfaced nanoparticles with magnetic core shell structure and penetrating into Blood Brain Barrier. Low toxicity and better biodegradability	Precipitation method	Doxorubicin	43, 44
Oxidized multiwalled carbon nanotubes (MWCNT-COOH)	Enhanced delivery efficiency into cancer cells with reduced cytotoxicity. Release profiles demonstrated that approximately 98 % of BA could be released within 22 hours. Biocompatibility studies revealed that MWCNT-BA at concentrations <50 µg mL^{-1} expressed no cytotoxicity	Drug loading on (MWCNT-COOH)	Betulinic acid (BA)	45

TiO_2 film on TLM alloy	(TLM) alloys are Ti–25Nb–3Mo–2Sn– 3Zr consisting of biocompatible elements Nb, Mo, Sn, and Zr has good mechanical properties and biological compatibilities	Two-step anodization	Dexamethasone (DXM)	46
Single-walled carbon nanotubes (SWCNTs)	SWCNT provides enhanced biocompatibility, stability, and solubility in physiological solutions.	SWCNT complexes	Curcumin, gambogicacid and doxorubicin	47-49
Mesoporous silica nanoparticles (MSNs) and organic-inorganic hybrid on mesoporous silica nanoparticles	Excellent vehicle to carry drugs molecule. high thermal/chemical stability, tunable biocom-patibility/degradability and resistance to corrosion under extreme condition	Co-condensation and post –grafting method	Ibuprofen, hydrophilic and hydrophobic anticancer drugs	50-52
Mesoporous bioactive glass nanoparticles	Bioactive glass nanoparticles (BGn) have recently gained potential usefulness to load and deliver therapeutic molecules (drugs and particularly genes). Spherical BGn with sizes of 80–90 nm were produced to obtain 3–5 nm sized mesopores	Sono-reacted sol–gel process	Chemical drug (Na-ampicillin) and gene (small interfering RNA; siRNA)	53

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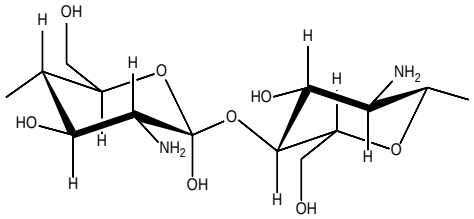
Secondly, carbohydrate and protein-based polymers type have promising clinical progress and results. This type containing polysaccharide polymers can be natural or synthetic such as cellulose, gelatin, chitosan, heparin, polylactic acid, polyglycolic acid, and their copolymer poly (lactic-co-glycolic acid) (PLGA). Natural degradation by the enzymes in the body and highly biocompatibility are the most inherent features of carbohydrate based polymers. Combining two or more polymers to form a core-shell design of polymeric micelles by is an alternate strategy used in the formulation of polymeric nano-medicine, which are currently under clinical investigations.

Classification of Polymers

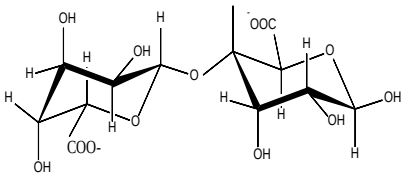
Natural and synthetic classes are the essential two categories of polymeric materials that are used in the drug delivery system with broad applicability. Natural polymers are classified into two subdivisions as polysaccharide-based and protein-based polymers, which synthetic polymers have different subdivisions as polyesters, polyether, poloxamers, and recombinant protein-based polymers.[54]

Natural polymers in drug delivery

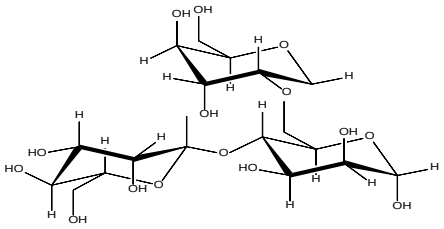
Natural polymers have an important role in drug release and in delivering therapeutic agents to the target tissue. Special features of natural polymers that are attractive in drug delivery are their biodegradability, lack of toxicity, inexpensive, great economic features and safety. There are various sources for natural polymers, mainly polysaccharides, including plants, microbes, algae, and fungus. Chemical character of some polymers is neutral and the carboxylate or sulfate groups have negative charges (Carrageenan, Chondroitin, and Dermatan) but Chitosan is the only cationic polysaccharide currently known. Various origins of natural polymers are described below:



Chitosan



Alginate

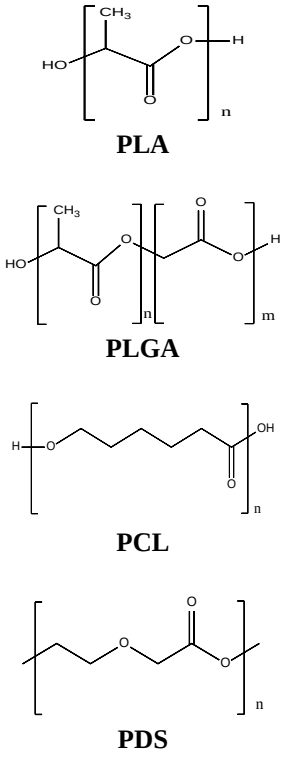


Guar gum

Figure 6. Structures of some natural polymers.

Synthetic polymers in drug delivery:

Synthetic biodegradable polymers have a wide and distinct impact on drug delivery and tissue engineering fields. Synthetic polymers, due to their structure, are devoid of certain disadvantages of natural polymers such as microbial contamination. Many natural polymers are exposed to external environment and there are chances of microbial contamination. Industrial production is a controlled procedure with definite quantities of ingredients, while the natural polymers are dependent on environmental and seasonal factors.[60] Unstable climate conditions and differences in the regions lead to an uncontrolled rate of hydration and different times of harvest collection of natural materials. There are commonly used synthetic polymers in drug delivery such as PLA (polylactic acid), PGA (polyglycolic acid), PCL (poly (e-caprolactone)), PHB (poly hydroxybutyrate), PLGA (Poly (lactide-co-glycolide), PDS (Polydioxanone) and Polyamide etc. Biocompatibility and degradability are the required important features of the polymers, which are selected for incorporation into the drug delivery system. Biocompatible polymers offer a highly efficient transition of desired drugs into the tissues or organs without issues in biological systems. Biodegradable polymers disintegrate with the cleavage of covalent bonds between the drug molecule and the polymer. This erosion of the polymer is due to the dissolution of linking chains without causing any change in the chemical structure of the drug molecule.



PLA

PLGA

PCL

PDS

Figure 7. Structures of some synthetic polymers.

Table 2. The origins of some natural polymers.

Polymer origin	Examples of polymers	Composition of polymers	Ref.
Plant origin	Starch, hemicellulose, cellulose, agar, pectin, guar gum	Guar gum is natural polysaccharide composed of the sugar's galactose and mannose. Pectin is a natural, non-toxic and anionic polysaccharide extracted from cell walls of most plants	55
Microbial origin	Curdlan, gellan, xanthan	Xanthan is an extracellular heteropolysaccharide produced by fermentation of the bacterium Xanthomonascampestris. Gellan gum is a bacterial exopolysaccharide commercially prepared by aerobic submerged fermentation of *Sphingomonas elodea.*	55
Algal origin	Alginate, carrageenan	Alginate is cross-linked as Ca salt; It incorporated in different application, their derivatives such as polyethylene glycol–anthracene modified alginate, photocross-linked heparin-alginate hydrogels, alginate–guargum hydrogel, micelles/sodium alginate composite gel beads and chitosan-Ca-alginate microspheres.	56-58
Fungal origin	Chitin, pullulan, scleroglucan	Chitosan is linear polysaccharide composed of -1,4-linked 2-amino-2-deoxy-*D*-glucose (N-acetyl glucosamine). It is insoluble at high pH conditions. Chitosan itself is nontoxic, biodegradable, and biocompatible	55, 59

Table 3.Methods of preparation of polymeric nanomedicine

Method of preparation	Definition	Examples	Ref.
Coacervation or ionic gelation of hydrophilic polymers	Coacervation is an electrostatic interaction between two aqueous media in which the liquid-to-gel (i.e., ionic gelation) transition occurs at normal conditions.	The cationic (amino groups of chitosan are positively charged) interaction with anions (tripolyphosphates are negative charged) to form coacervates.	61-63
Interfacial polymerization	The interfacial polymerization of two reactive monomers in two different phases (i.e., disperse and continuous) with the cross-linking of interfacial reactions.	Radical polymerization, polycondensation, or polyaddition	64, 65
Emulsification-solvent evaporation	Two-step process consists of polymeric emulsification in an aqueous medium followed by solvent evaporation from the polymer and nanoparticle precipitation.	Poly(lactic-co-glycolic acid) (PLGA), poly-*D*,*L*-lactic acid (PLA), poly(ε-caprolactone) (PCL), ethyl cellulose, poly(β-hydroxybutyrate) etc.	66
Salting out	This phenomenon based on separation of the water-miscible phase (solvent) from the aqueous phase by the salting-out method	PLA, poly (methacrylic) acids, and ethyl cellulose nanospheres.	62, 67

Some smart platforms of polymeric Nanomedicine in drug delivery systems

Polymeric nano-materials have distinct characteristics that qualify them to be good sources for sustained and controlled release. These materials offer required perquisites, which ensure the efficient drug delivery system such as biocompatibility, biodegradability, high accuracy and efficiency, a high loading capacity of the desired drug and finally temporal and spatial directing of the drug into the desired cell or tissue with limited cytotoxicity and side effects.

The entrapment of the drug either physically or covalently bound to the polymer matrix is controlled by the method of preparation and the final shape and properties of the materials. Hyperbranched macromolecules (dendrimers), Polymeric micelles (amphiphilic core/shell) and drug-conjugates are the different shapes of polymeric nanomaterial conjugated with the drug.

Dendrimers

These three-dimensional, well-organized nanoscopic and highly branched polymers of less than 10 nm size were was discovered in 1978 by Vogtle as a novel and highly efficient nanotechnology platforms for drug delivery.[68] Their constructions take place via two different approaches, a divergent method and a convergent approach. A typical dendrimer structure consists of mainly three parts that are core molecule, multiple layers or generations of branched molecules and surface molecules.[69]

Encapsulation or loading mechanism of the drug within the dendrimers is through two ways that are as shown in figure 9. Drug molecules can be loaded both in the interior of the dendrimers as well as attached to the surface groups (terminal groups). Dendrimers are highly efficient vehicles for drug molecules either by encapsulating drugs within the dendritic structure or by inter-acting with drugs at their terminal functional groups via electrostatic or covalent bonds.[70]

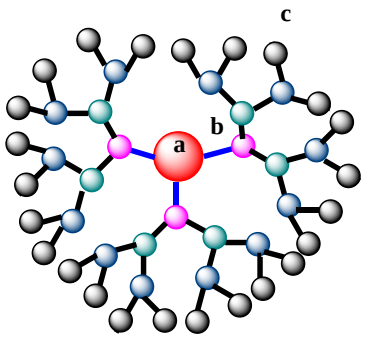


Figure 8. Dendrimer shape consists of a) core, b) multilayers (generations) and c) surface groups.

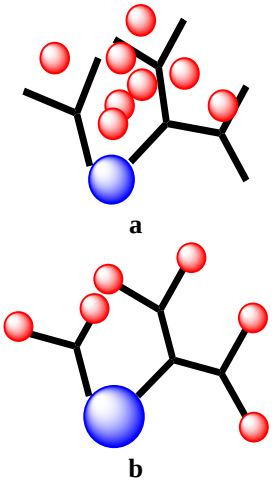


Figure 9. Dendrimer molecule with drug molecules a) Encapsulated within branches and b) loaded at terminal surface of branches.

Micelles (core-shell)

Micelles represent spherical lipid NSs consists of two parts (hydrophobic and hydrophilic parts) like a sheet folded back onto itself. According to the surrounding medium, micelle or reverse micelle can be arranged. Micelle remains with hydrophobic chains on the inside with the polar heads on the outside when the surrounding is an aqueous medium. However, if the surrounding medium is organic, then the components of the micelle are reversed-hence the name becomes reverse micelle. The polar heads are in interior, and the hydrophobic chains are outside.[71]

Polymeric micelles are emerging as a powerful design in the field of nano-medicine for drug release and act as a carrier for different drugs due to their tunable size, in vivo stability, and efficiency in solubilizing water-insoluble drugs, small particle size, good thermodynamic stability in solution and extended-release of various drugs.[72]

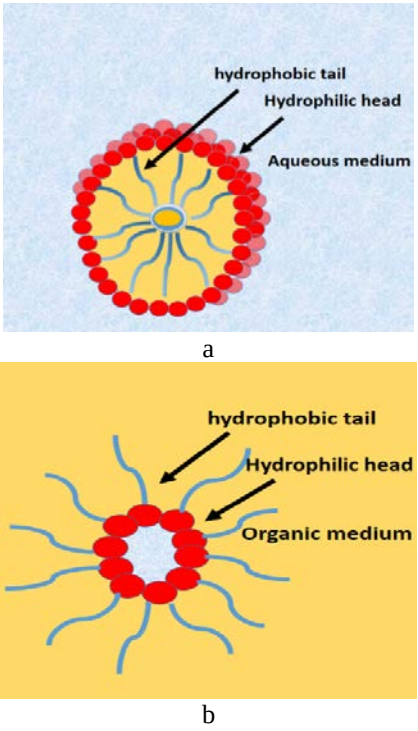


Figure 10. Structure of (a) micelle and (b) reverse micelle.

Hydrogels

Hydrogels are biocompatible hydrophilic networks that can be constructed from both natural and synthetic materials. Some unusual properties of hydrogels make them more attractive and efficient for drug delivery and tissue engineering. Their high-affinity for water and high swelling property, relatively low cytotoxicity, injectability, biodegradability, mucoadhesiveness, and tuneable bioadhesive properties are the most beneficial property of hydrogel for enhancement of drug delivery system.[73] Some widespread polymers used to synthesize hydrogels are poly(N-isopropyl acrylamide), poly(L-lactic-co-glycolic acid), poly ethylene glycol), methacrylated poly (glycerol succinic acid) dendrimers, and hen egg-white lysozyme.[74,75] (N-isopropyl acrylamide) (pNIPAm)-based microgels are stimuli-responsive microgels that reversible pNIPAm's volume phase transition temperature (VPTT) at 32 °C. "Breathing-in" technique is the most effective encapsulation of insulin as one of the hydrogel applications in the drug delivery system when compared to more common encapsulation methods in which the gel is re-hydrated in the aqueous solution of the desired material. Its permeability is controlled by lowering the temperature or increasing pH that increases the swelling degree of the desired drug.[73]

Molecularly imprinted polymer (MIP)

Recently, the investigations of new drug delivery vehicles have been directed on the development of some "intelligent" drug delivery devices that can increase the transportation efficiency of the desired drug and decrease patient non-compliance. MIPs have high potential and selectivity for drug delivery to desired tissue and cells without exposure of another cells, which has definite and selective cavities to the desired material. The molecular imprinting phenomenon is related to three steps of synthesis that started with the creation of a pre-polymerization complex of selected functional monomer(s) and a template molecule. It is followed by cross-linking of the complex via polymerization process and finally removing the template from the matrix leaving the well-defined three-dimensional cavities,[76,77] attaching the template with MIPs via a covalent or non-covalent approach. The non-covalent approach is the most widely adopted in the case of a drug delivery system in which, there are no interactions between the template and the functional monomers that ensure the efficiency of the drug release.

CONCLUSION AND FUTURE PERSPECTIVES

From this review, it can be shown that there are various methods for the preparation of DDS that have different potential and impacts in the release efficiency and desired requirements for efficient DDS. Nano-medicine is highly sophisticated and triggered vehicles for enhancement of DDS efficacy that has definite features as biocompatibility, efficient cargo of desired drugs, transportation efficiency that help in decreasing the administration times of drug and reducing the patient compliance. Types of nanomaterial include metallic and polymeric based nanomedicine, which refers to a wide range of applicability of nanomaterial, hence there are different preparation methods and different properties of synthesized materials. Therefore, it can be expected that there is tremendous development in DDS and therapeutic recognition and monitoring according to the new trends and objectives.

Hybrid polymeric smart platforms such as fibrous material, dendrimer, micelle (core-shell), stimuli-responsive hydrogel and MIPs with metallic nanomaterial can ensure the best behaviour and unique properties of DDS. These hypotheses can be studied for further objectives and able to have new trends and prove to be promising biomedical devices in the future.

Table 4. Some applications of molecular imprinted polymers in DDS.

Matrix	Polymerization	Functional monomer/s	Cross- linker	Template	Ref.
MIP- bromhexine	bulk polymerization	MAA	EGDMA	Bromhexine	[78]
MIP- tramadol	bulk polymerization	MAA	EGDMA	Tramadol	[79]
MIP-S-propranolol	copolymerisation	MAA	EGDMA	S-propranolol	[80]
β-cyclodextrin (β-CD)-grafted chitosan (CS) (CS-g-β-CD) microsphere/MIP	bulk polymerization	MAA	EGDMA	Sinomenine hydrochloride (SM)	[81]
MIP- glycyrrhizic acid	bulk polymerization	MAA, dimethylamino-ethyl methacrylate and hydroxyethyl methacrylate	EGDMA	glycyrrhizic acid	[82]
Acetylsalicylic acid-loaded polyDEGDMA in supercritical carbon dioxide	supercritical polymerization	EGDMA	In CO2	Acetylsalicylic acid-	[83]
Magnetic MIPs- aspirin	co-polymerization	MAA and trimethylolpropane-trimethacrylate (TRIM)	-	Aspirin	[84]
Polystyrene-MIP- S-naproxen	precipitation polymerization	MAA	EGDMA	S-naproxen	[85]
MIP- Sulpiride	bulk polymerization	itaconic acid	EGDMA	Sulpiride	[86]
5-FU imprinted microspheres MIP-CS-g-PMMA	free radical polymerization	methyl methacrylate	-	5-fluorouracil (5-FU)	[87]

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