NANOMATERIALS:
EVOLUTION AND ADVANCEMENT TOWARDS THERAPEUTIC DRUG DELIVERY (PART II)

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Nanomaterials: Evolution and Advancement towards Therapeutic Drug Delivery *(Part II)*

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FOREWORD

Engineered nanomaterials (ENMs), due to their interesting physicochemical properties such as smaller size, larger surface area, electrical, optical and magnetic properties are being sought in a wide range of applications including technology, cosmetics, food packaging, medical imaging and drug delivery. Carbon nanotubes (CNTs), quantum dots, mesoporous and amorphous nanosilica, nanosilver, nano titanium and zinc oxides are some of the ENMs currently in commerce. Nevertheless, the attractive physicochemical characteristics of the ENMs also create concerns when exposed to, with respect to human and ecosystem health. This book on "nanomaterials" is very timely, and touches upon the different aspects of application of ENMs in drug delivery. The chapters in this book discuss the use of a spectrum of nanomaterials in drug delivery including nano metal oxides, CNTs and lipid nanoparticles, their various nanoforms, synthesis, characterization, efficacy in terms of drug delivery and the need for toxicity testing. Physicochemical characterization is an important aspect in nanotechnology, especially, in the realm of drug delivery. The synthesis of ENMs can introduce batch to batch variation in terms of size, shape, surface characteristics and chemical composition based on source materials and synthetic routes. Moreover, the stability of ENMs can be affected based on storage conditions. This book has thus given an importance to the aspect of physicochemical testing and discusses the different analytical methods to assess morphology, surface functionalities, behavior in solution, stability, etc. This book on "nanomaterials" also identifies the need for toxicity testing of the ENMs in drug delivery. Toxicity testing is a critical component for the selection of safer ENMs for application in drug delivery and to meet regulatory standards. This book has done a fantastic job in familiarizing the reader with the scope and application of the various ENMs and their nanoforms in drug delivery along with some insight into medical imaging and computational aspect of structure-activity relationships. I congratulate the editor Dr. Surendra Nimesh on doing a fantastic job with this book on the application ENMs in drug delivery, which is one of the promising emerging medical technologies.

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PREFACE

Chemically synthesized drugs have been one of the major tools in combating several diseases, including bacterial and viral infections. However, these drug molecules face several barriers, including poor cellular uptake and instability in the physiological environment that masks the therapeutic potential. In order to circumvent these issues, there arises a need to develop vehicles that could effectively and safely transport the drug molecules to the target sites. Nanotechnology has come up as one of the potent and viable strategies. Several candidates have been proposed, such as nanoparticles, liposomes, carbon nanotubes, mesoporous silica nanoparticles, etc. These vectors can be modulated to achieve delivery, including drugs that are highly unstable and face difficulty in reaching sites. This book compilation brings together some of the eminent scientists working in different dimensions of nanotechnology. They have contributed chapters in their domain of knowledge that we believe would be highly useful not only for the young researchers but also for the experts looking for some exhaustive compilations.

Chapter 1 provides a detailed account of the application of lipid-based nanoparticles and nanostructures. This chapter also provides an overview of the recent literature on solid lipid nanoparticles and nanostructured lipid carriers for drug delivery applications. Background information on the origins, composition, characterization parameters, and biological applications of these nanocarrier systems has also been presented.

Chapter 2 provides an exhaustive account of the main route of preparation and applications of MSNs and silica nanomaterials. The chapter also provides insights into the chemistry, structure, and characterization of MSNs, followed by the synthetic strategies, and finally ends with a note on the application of MSNs.

Chapter 3 deals with hydrogels; they are defined as materials composed of water (hydro) and matrix (gel). The chapter discusses the role of polymer and peptide-based hydrogels, their multi-functionality, unique properties, and major uses. Hydrogels can serve as a major tool for human welfare in the future.

Chapter 4 talks about the application of metallic nanoparticles in drug delivery. Metallic nanoparticles have been used for treatment in some life-threatening diseases such as cancer. This chapter introduces gold and silver nanoparticles, nanoshells and nanocages, and their physicochemical properties. It illustrates some of the recent advances in the field of diagnostic imaging and cancer therapy.

Chapter 5 discusses the computational and experimental studies for the interaction of drugs with β-cyclodextrins. This chapter summarizes cyclodextrin's applications in drug delivery research through experimental and computational findings. In addition, it presents the highlights of various techniques of inclusion complex formations, mechanism of delivery systems, and their analytical methods.

Chapter 6 outlines the clinical applications of nanotechnology in various areas, including cancer, CNS disorder, rheumatoid arthritis, thyroid, cardiac diseases, ocular drug delivery, and vaccines. This chapter overviews the current status of pharmacological and clinical studies of nanoparticles in the development process.

Chapter 7 illustrates the scale-up, preclinical, and clinical status of PLGA, along with its copolymers-based drug delivery systems. This chapter summarizes the extensive applications, laboratory, and industrial-scale methods for the production of PLGA nano/microparticles, preclinical, and clinical status PLGA-based drug delivery systems.

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CHAPTER 1

Solid Lipid Nanoparticles and Nanostructured Lipid Carriers for Drug Delivery Applications

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Abstract: Lipid nanoparticles, such as solid lipid nanoparticles and nanostructured lipid carriers, are drug delivery systems in which solid lipids are dispersed in an aqueous phase stabilized by a surfactant layer. The great interest in these nanocarriers in the latest years is due to the biocompatible lipid matrix, associated with the potential for sustained drug release, and easy transposition to the industrial scale. Moreover, these lipid systems present the ability to prevent drug degradation, and to enhance cell uptake, usually increasing drug efficacy. This chapter will provide an overview of the recent literature on solid lipid nanoparticles and nanostructured lipid carriers for drug delivery applications. Thus, some background information on the origins, composition, characterization parameters and biological applications of these nanocarrier systems will be presented.

Keywords: Nanocarriers, Nanoparticles, Nanostructured lipid carriers, Solid lipid nanoparticles.

INTRODUCTION

Nanotechnology is an exciting research field that, year after year, attracts more attention from researchers all over the world. It is defined as the research area that investigates nanometric systems, which are within the 1-1000 nm size range [1, 2].

In nanomedicine, nanoparticles are usually used for imaging, diagnosis and drug delivery purposes. Nanoparticles used for drug delivery are usually called nanocarriers. Nanocarriers can enhance the pharmacological activity, decrease

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toxicity, and allow *in vivo* administration of drugs. There are many types of materials that can be used to produce nanoparticles for drug delivery, which include polymers, inorganic materials, and lipids [3]. In this context, this review focuses on novel lipid nanocarriers that have attracted much interest over the past 25 years: solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC).

Both SLN and NLC are new generations of nanoemulsions (NE), being SLN the first generation (emerged in the 1990s) and NLC the second generation (emerged in the 2000s). Thus, we will discuss in this chapter the origin, key features, characterization and applications of these systems.

BACKGROUND

Oil-in-water emulsions are conventional pharmaceutical dosage forms that are formed by oil droplets dispersed within an aqueous medium. Stabilization of oil droplets occurs by the use of surfactants that concentrate on the oil/water interface. Oil-in-water emulsions have been historically administrated by topical (*e.g*, Diprolene®) and oral (*e.g*, mineral oil emulsion) routes [4].

Since the 1920s, scientists have examined forms of delivering emulsion by the intravenous route. The purpose of intravenous (IV) delivery of emulsions has been to provide energy and nutrients to hospitalized patients who cannot swallow foods normally. Emulsion droplet size can range from some nanometers to few micrometers, but this is not a limiting factor for the peroral and topical administration of emulsions. However, intravenous administration of particles with a size larger than a few micrometers can provoke vessel occlusion [5 - 7].

After years of research, in 1961, an IV fat emulsion (10% soybean oil stabilized with egg phospholipids) (Intralipid®) was released in Europe. The Intralipid® droplet sizes were around 276 nm. These small droplet sizes allowed Intralipid® to be delivered by the i.v. route. Since then, emulsions with narrow nanometric droplet size distribution (NE) started to be used for i.v. delivery of lipids [5, 8, 9].

In the beginning, NE were produced only to allow the delivery of oily components for hospitalized patients. A few years later, many drug-loaded NE arrived in the market (*e.g*, Dizemuls®, Diprivan®, Etomidate-Lipuro®, among others) [10 - 12]. The success of these systems lies in the possibility of delivering hydrophobic compounds intravenously, but with no pain inconvenience [7, 13]. Moreover, NE present advantages such as toxicological safety and facile production on a large scale [14]. Drawbacks of NE systems, however, include low physical stability and low drug retention, leading to fast drug release and low drug stability. These drawbacks are due to the liquid nature of the lipids used in the NE [12, 15].

Liposomes represent another example of drug nanocarriers. Proposed in the 1960s by Bangham and co-workers [16], liposomes are, probably, the most well-known nanocarriers [17]. Phospholipid-based vesicles in the aqueous medium, the liposomes, entered the market in 1986 with Capture®, an anti-aging product by Dior® [18]. Later, the first pharmaceutical liposomes were approved: Alveofact® (1989), Ambisome® (1990), Doxil® (1995) and Daunoxome® (1996). These products explored the strategy of incorporating drugs into liposomal vesicles for some purposes, including better administration of poorly water-soluble drugs, enhancement of drug pharmacological effects and/or reduction of their toxicological effects [12, 18]. The major drawbacks related to liposomes are their low drug loading (DL) for hydrophobic drugs, difficulty in scaled-up production, and high production costs [10, 12, 15].

Polymers are another type of material widely used for nanocarriers production. The major drawbacks of polymeric nanocarriers include cytotoxicity, high cost of biodegradable polymers and scaled-up production difficulties [10, 12, 14, 15]. These drawbacks have hindered the insertion of polymer nanocarriers in the market.

Looking at all those aspects, there was a motivation towards the development of systems that could control drug release similarly to polymeric nanoparticles and liposomes, but without the cell toxicity, typically found in the former, and high production costs, as seen for the latter. In this context, SLN emerged as an alternative that could combine easy scaled-up production, fair costs, and biosafety of NE with the controlled release properties of liposomes and polymeric nanoparticles.

In the beginning of the 1990s, two researchers, Gasco and Müller, started working independently on the production of lipid nanocarriers that later would be called SLN. The first publication about SLN dates back to 1990 from Gasco's group [19]. It was followed by the first publication of Müller's group in 1992 [20]. Westesen's group has also worked on those lipid nanocarriers at that time [21].

Simultaneously with the papers, these researches yielded the first patents on SLN [22, 23]. While Müller's group used the term "solid lipid nanoparticles" since the beginning, Gasco's group used the term "lipospheres" [19, 24, 25] and later, "solid lipid nanospheres" [26 - 32]. Nowadays, the term "solid lipid nanoparticles" and its abbreviation, SLN, are consolidated.

SLN have the same constituents of a NE in a generic way (Fig. **1**). They are formed by lipid droplets dispersed in an aqueous phase stabilized by a surfactant layer. The main difference is that, in the case of NE, the lipids that constitute the droplets are oils, *i.e.*, liquid lipids. In the case of SLN, the lipids used, mainly

CHAPTER 2

Silica Based Nanomaterial for Drug Delivery

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Abstract: The exceptional properties of mesoporous silica nanoparticles (MSNs) promote facile functionalization for improved drug delivery in nanotechnology. Recent advancements in this field have experienced the potential applications of MSNs and porous silicon (PSi). Tunable pore size, large surface area, and better surface properties make the materials possible to hold large amounts of payloads and prevent premature degradation. In this chapter, we will focus on and discuss the main route of preparation and applications of MSNs and silica nanomaterials.

Keywords: Drug delivery, Electron microscopy, Mesoporous silica nanoparticles (MSNs), Nanomaterials, Porous silica (PSi) nanoparticles.

INTRODUCTION

Nanoparticles are those particles whose dimensions range from 1-1000 nm, and small drugs and biological molecules, such as medicine, can be dissolved, entrapped, or bonded in a nanoparticle array. The bioavailability and distribution of nanoparticles can be easily modulated by changing the size range of nanoparticles [1, 2]. In the early 1990s, two independent research groups first invented mesoporous silica. The Mobile Oil Corporation first discovered MSNs in 1992, which were used in different fields due to their versatile textual properties like modifiable pore diameter and size distribution, large surface area, and volume

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of the pores. These attributes allow the encapsulation of a large number of active agents in the porous structure of MSNs [1, 3].

The attachment of various functional groups to the honeycomb-like porous MSNs can be facilitated and help to target drug molecules due to a large surface area as these MSNs are made up of many channels that are organized in a 2-D network. In 2001, Vallet- Regi *et al*. discovered MCM-41 and SBA-15 MSNs as delivery systems for hydrophilic and hydrophobic drugs, and later showed great interest in silica-based materials [4] due to their gate-keeping phenomenon and reactive polymers, which respond faster, and pH-sensitive materials were used to attach to the porous silica material [5]. Wang G and the group studied various processing parameters, such as pore size, connectivity, and geometry of MSNs, and checked how adsorption and release of ibuprofen could be affected [6]. The surface properties of MSNs, having silanol functionalization, could also control the drug loading and release profile of any agent.

MSNs exhibit superior biocompatibility at a suitable concentration for the pharmacological effect to other amorphous silica materials [7]. The highly permeable mesoporous structure of silica-based materials is used for payloads, whereas a hollow mesoporous structure has been widely used in a chemical reaction and controlled release [8].

CHEMISTRY OF MESOPOROUS SILICA NANOPARTICLES

Due to high inertness, stable structure and hydrophilic nature silica-based systems show various advantages over organic polymers. These systems can therefore be easily dispersed in aqueous media and suitable for many water-soluble therapeutic agents [1, 3]. Silica material exhibits special characteristics such as it shows a good conjugation tendency to DNA or protein [9]. Due to the robust Si surface, emission at the Red light due to small size, amorphous silica nanoparticles also result in large oxidative stress cytotoxicity at 10-100µg/ml [10] and shows photostable and modifiable luminescence property [11].

The MSNs are mainly synthesized by chemically synthesized techniques from inorganic precursors such as tetra-alkoxysilanes and sodium silicates. Organic functional groups may also conjugate to the surface of MSNs by performing initial hydrolysis/condensation reactions using a tri-alkoxyorganosilane . Organo silanes such as 1,2-bis(tri-methoxysilyl)ethane and 1,4-bis(tri-ethoxysilyl)benzene react with each other in the synthesis medium of the core-shell of silicon dioxide which forms a surface on the shell after deposition of organosilica species [12].

Chemically, an active honeycomb-like structure facilitates chemical functionalization, and modification of the surface leads to connect different therapeutic agents.

Various pore geometries of MSNs have been shown Fig. (**1**).

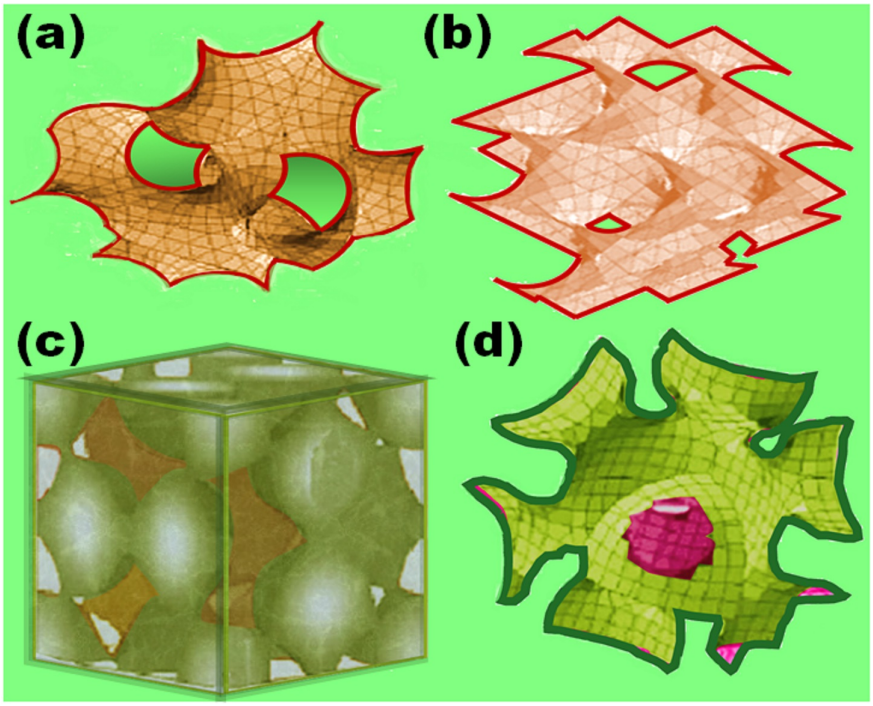

Fig. (1). Geometry of pores in mesoporous silica nanoparticles **(a)** Ia3d type **(b)** cubic pn3m type **(c)** cage type pm3n **(d)** cage type Im3 m.

MSNs show more protectiveness against external response *viz*. degradation and mechanical stress than liposomes, and dendrimers due to strong Si-bonds and it does not require any external stabilization for synthesis [18]. MSNs show different internal structures and orifice diameter represented in Table **1**.

Table 1. Different interior structures and orifice diameter of MSNs.

Type of MSNs	Interior-Structure	Orifice-Diameter (nm)	References
MCM-50	Lamellar	2–5	[13, 14]
SBA-11	3D cubic	2.1–3.6	[14, 15]
SBA-12	3D hexagonal	3.1	[16, 17]
SBA-16	3D cubic structure - cage-like	4.0-9.0	[18]

CHAPTER 3

Hydrogels for Drug Delivery

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Abstract: The term 'Hydrogel' is self-defined, as a material composed of water (hydro) and matrix (gel). The hydrogels do not dissolve in water; rather, absorb water and swell into a volumetric mass due to their smart 3-dimensional network. Over the past few years, hydrogels have served as a multifunctional platform and gained the interest of the scientific community. The unique properties of hydrogels, including flexibility, biocompatibility, and mechanical stability, have made them quite an important research area in different fields like disease treatment, targeted drug delivery, and many others. The current applications of hydrogels include the manufacturing of contact lenses, drug delivery systems, hemostats, wound dressings, biosensors, *etc*. Here, the role of polymer and peptide-based hydrogels, their multi-functionality, unique properties, and major uses have been elaborated, which can serve as a major tool for human welfare in the future.

Keywords: Drug Delivery, Hydrogel, Polyethylene Glycol, Polymer, Nano-crystals.

INTRODUCTION

In this era of developing novel biomaterials, rigorous research is being undertaken to contribute to various biomedical applications, including cell-mediated therapy, tissue regeneration, drug delivery, and so on. One group of these biomaterials that has become a rich area of interest is hydrogels. A highly hydrated 3D fibrous meshwork of peptides and polymers in hydrogels can be engineered to mimic the extracellular matrix (ECM) milieu – to support both *in vivo* and *in vitro* tissue engineering and provide *in vivo* drug delivery platform [1 - 5]. Hydrogel formation involves different types of interactions, *i.e.*, covalent, ionic, and weak

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(including hydrophobic, van der wall forces, *etc*.) interactions. Hydrogels, being majorly composed of water (>90% water), are highly hydrophilic and play multifunctional roles in the hydrophilic physiological environment (Fig. **1**).

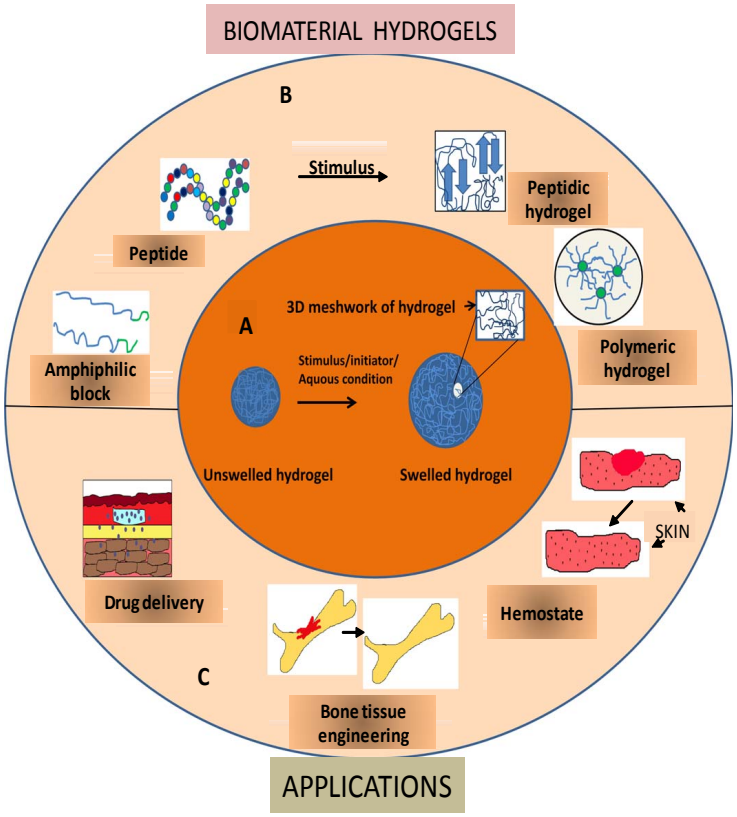

Fig. (1). Representation of hydrogels, their assembly and applications.

Supramolecular self-assembly of peptides and polymers involves many non-covalent interactions that spontaneously and reversibly organizes the different peptides and polymers into functional and novel structures with the desired supramolecular nanoscale morphology. The use of this bottom-up approach for the synthesis of variable nanomaterials serves as a potential application in various fields including biomedical, different types of tissue engineering, and many other areas. The modification of functional groups over peptide building blocks and polymers using different chemical and biological methods followed by hydrogel formation creates an attractive platform for the scientific community to design and develop efficient and potential biomaterials.

Despite their use in different fields, hydrogels have encountered some limitations, *viz.*, poor mechanical strength [6 - 8], low/non-uniform homogeneity, bio-

incompatibility, excessive volumetric swelling [9 - 12], low biodegradability / higher toxicity, expensive synthesis and fabrication [13, 14], which hinder its path to successfully function at the target site. To counter these problems, numerous hydrogels ranging from the long-chain peptide, *e.g.*, RADA16-I [15, 16] and RADKPS [17], to short peptide, *e.g.*, Leu-ΔPhe (Leucine α,β- dihydroxy phenylalanine) [18], contributing as highly regulated drug delivery platforms for both hydrophilic and hydrophobic drugs have been reported in the past few years.

Hydrogels have been categorized based on their origin (natural and synthetic), assembly (spontaneous and stimulus-based), chain length (long [19] and short [20, 21]), and configuration (in case of peptides [22]) (Fig. **2**). Both natural and synthetic polymers have been exploited to assemble into functional hydrogels. Natural polymers include chitosan, hyaluronic acid, sodium alginate, gellan gum, collagen, cellulose and gelatin, while the synthetic category includes polyethylene glycol (PEG), poly-lactic acid (PLA), polyvinyl alcohol (PVA), polyacrylic acid (PAA) and so forth [23, 24]. Broadly, the following sections deal with two types of hydrogels, *viz.*, polymer-based and peptide-based hydrogels.

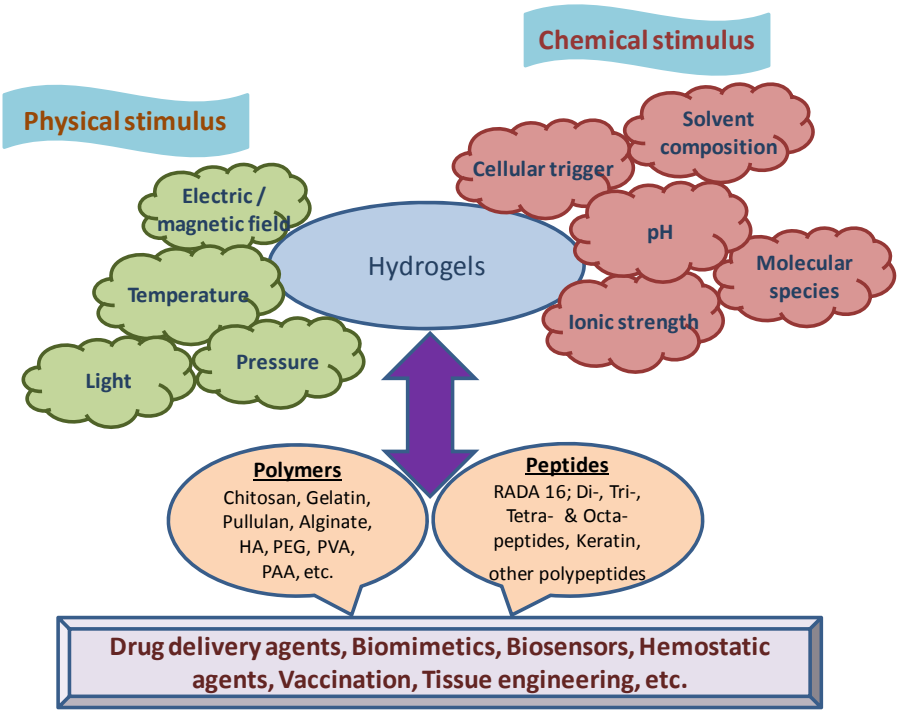

Fig. (2). Types of peptides and polymers used for hydrogel formation under different stimulus conditions and their applications.

CHAPTER 4

Metallic Nanoparticles: Applications in Drug Delivery

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Abstract: In the field of nanotechnology, the synthesis of metallic nanoparticles (NPs) is a demanding task for both modern phytopharmaceutical research as well as academics. These metallic nanostructures, NPs, made of metals such as gold and silver NPs can be used as quantum dots for the applications in Biomedical Science and Technology. Nanomedicine is a newly developed branch that is a boon for modern medicine. Nanotechnology in medicines will increase the production of the intended results and safety of the medicine. Nanoparticles are known for their stability, solubility, absorption and reduced toxicity. Metallic nanoparticles have been used for treatment in some life-threatening diseases such as cancer. This chapter introduces gold and silver nanoparticles, nanoshells and nanocages and their physico-chemical properties, and illustrates some of the recent advances in the field of diagnostic imaging and cancer therapy. Nanotechnology had a great influence on medical science and made a remarkable progress in the field of diagnostics.

Keywords: Cancer therapy, Diagnostic imaging, Metallic nanoparticles, Modern phytopharmaceutical, Nanotechnology.

INTRODUCTION

Nanobiotechnology is the branch of biotechnology that deals with the synthesis and applications of several types of nanoparticles in biological systems. This technology has helped to design and develop better materials for medical applications in the areas of diagnosis as well as therapy. For generations, NPs have found their usage in routine applications such as in pottery and medicines. Nanotechnology has eventually made great progress in distribution and analysis in the field of biomedical science, as summarized in Fig. (**1**).

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Biocompatibility of metals can be enhanced with coatings of nanoparticles as nanofilms are known to have better interaction with living cells since nanoparticles films have a positive impact on cell adhesion and proliferation.

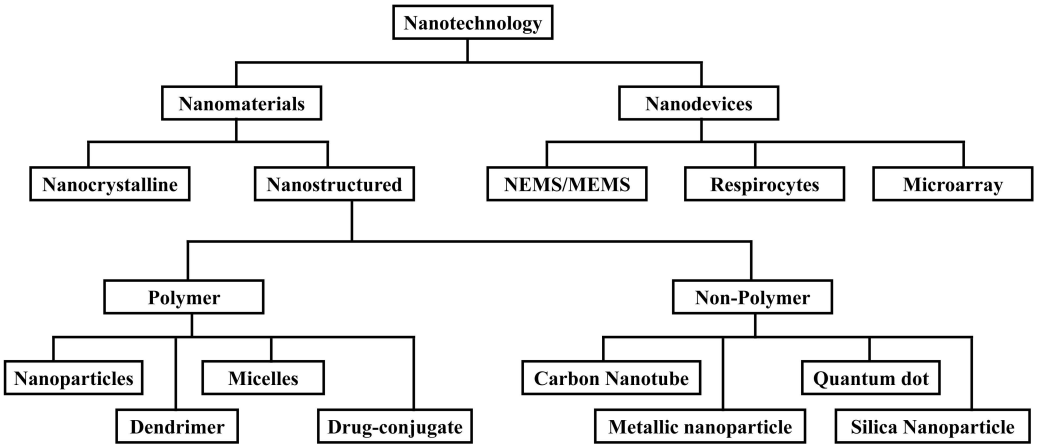

Fig. (1). Schematic diagram of various types of nanosystems in the field of drug delivery and diagnostics.

Nanoparticles are small in size, select a diseased site with the benefit of consuming only small amounts, thus producing fewer side effects. Nanoparticles in various forms and shapes such as micelles,vesicles and dendrimer capsules, have been utilized as drug delivery vehicles (Fig. **2**). Nanotechnology has given the benefit of manipulating metals to the nanoscale range with remarkable properties and enhanced medical applications. Any structure designed and developed in the size range of 1 nm to 100 nm, in any one dimension is considered as nanoparticle [1].

ADVANTAGES OF NANOPARTICLES-BASED DRUG DELIVERY

There are many advantages of using nanoparticles as drug carriers, as these increase the therapeutic efficiency and pharmacological features of drugs. For example, poor water-soluble drugs solubility could be improved by nanoparticles.The distribution of two or more drugs at once for the treatment of amorphous control and release of metabolic and therapeutic compounds might be enabled with the usage of nanoparticles [2, 3].

Nano-carriers for drug delivery system have several merits attached to them, such as:

1. Being very less volumetric, nanoparticles can easily move across the narrow capillaries.

2. Nanocarriers can penetrate the inter junction gap in between cells and tissues to reach the target organ.
3. The release of drugs can be controlled and therefore, drugs can be effective for a prolonged period.

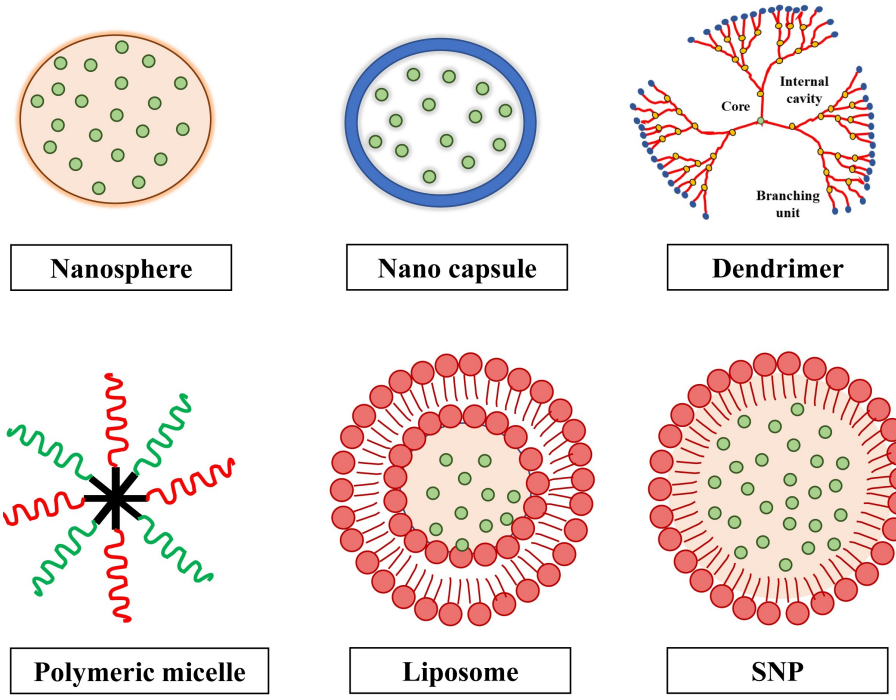

Fig. (2). Various nanocarriers as drug delivery vehicles.

Owing to these features nano-based drug delivery vehicles have become favorable as carriers for the delivery of drugs than the conventional system [4]. The most important advantage of nanoparticles is in the preservation of pharmacological activity of the drug in which high doses of the drug can be incorporated without worrying about any modification due to chemical reactions [5].

APPLICATIONS

- Achievement of targeted drug delivery therapy that can be used as a treatment for organs such as the brain and in diseased conditions like cancer;
- To deliver drugs and genes
- For detection of pathogens
- Proteins can be identified
- To map biomarkers
- Probing of DNA structure

CHAPTER 5

Computational and Experimental Binding Interactions of Drug and β-Cyclodextrin as a Drug-Delivery Vehicle

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Abstract: cyclodextrins are primarily used to enhance the aqueous solubility and stability of drug molecules and they can be chemically modified to display functional groups on their primary or secondary rim. It belongs to the cyclic polymers (α-1,4) - linked oligosaccharides of α-glucopyranose units with hydrophobic inner core and hydrophilic outer surface. This combination of functionality and guest binding ability makes Cyclodextrin is an important scaffold to design functional supramolecular systems. Due to its structural characteristics, it can interact with appropriately sized drug molecules to form an inclusion complex. Inclusion into the Cyclodextrin's cavity alters the physicochemical properties of an included compound, especially on increasing its dissolution rate and sometimes in increasing the drug inhibition rate. Structural factors raise favor for this non-covalent inclusion complex and offer a variety of pharmaceutical applications that may be used in many industrial products. The negligible cytotoxic effects of cyclodextrin are an important attribute in applications such as drug carriers, food and flavors, cosmetics, packing, textiles, separation processes, environment protection, fermentation, and catalysis. Through this chapter, we aimed to summarize Cyclodextrin's applications in drug delivery research through experimental and computational findings. In addition, we tried to present the highlights of various techniques of inclusion complex formations, mechanism of delivery systems and their analytical methods.

Keywords: Drug Delivery, Drug, Drug-Polymer Interactions, Drug Carriers, β-Cyclodextrin, Inclusion Complex, SEM, TEM.

INTRODUCTION

The classical natural-based drug development is an incredibly tedious process and so the current revolution in drug discovery is driven by functional genomics, pro-

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teomics, high throughput screening and *in silico* drug designing. Recently, several strategies have attempted to improve drug safety and efficacy, such as individualization of drug therapy, dosing, monitoring and controlled administration [1, 2]. The selective distribution of drug molecules in their position should increase their efficacy while minimizing adverse side effects. Referable to the solubility, distribution and duration of action, the delivery of some drug molecules becomes challenging and the continuous actions may be modified by a combination of drug vehicle molecules. Drug delivery vehicles are also designated as drug carriers that act as the most important entity required for the successful passage of loaded drug molecules. The ideal drug delivery vehicle would be targeting all individual cells and should possess unique characteristic features such as biocompatible and virtually 100% reliable, able to cross blood-brain barriers and also known by the target cells and must preserve the specificity surface ligands [4, 5].

Currently, various carrier molecules such as liposomes, monoclonal antibodies, fragments of modified plasma proteins, microspheres, lipoproteins and nanoparticles are constantly intended to overcome the intelligible properties of drug particles. Liposomes are small artificially designed vesicles composed of bi-lipid membrane specially designed to bind and rapidly taken by macrophages for passive drug delivery (Fig. **1**); they have been extensively used in non-viral vector-mediated gene therapy [5]. Monoclonal antibodies are a type of glycoprotein that include polypeptide and carbohydrate according to the ratio of 82:18 and 96:4, respectively. The drug complex with monoclonal antibody provides selective targeting for tumor cell masses or lymphomas. Modified plasma proteins are a unique method of transporting drugs due to their solubility and relatively small molecular weight. It can be easily modified by attaching different molecules such as peptides, sugars and other ligands to an appropriate mode of drug delivery. Microspheres are soluble polymers ideally having a particle size less than 200 μm and well planned to subdue some of the troubles of conventional therapy and enhance the healing efficacy of drugs. Microspheres are classified into two characters, namely synthetic polymers and natural polymers. Various techniques for the carrier particles that include solubilization solid dispersion are effectively applied to enhance the bioavailability and drug solubility [6 - 8]. Even though these methods show reliable applications and have some disadvantages such as low drug loading and heavy doses. Moreover, the complexation of drug-polymer interactions came up with the Drug-cyclodextrin inclusion complex as a novel and alternate method for drug delivery system [9, 10]. Cyclodextrins are cyclic oligosaccharides having lipophilic inner cavities that can trap or encapsulate other molecules and hydrophilic outer surfaces capable of interacting with a big assortment of molecules to make non-covalent inclusion complexes to lead a host-client type of complexity that can change or improve the

physical, chemical and biological properties of guest molecules.

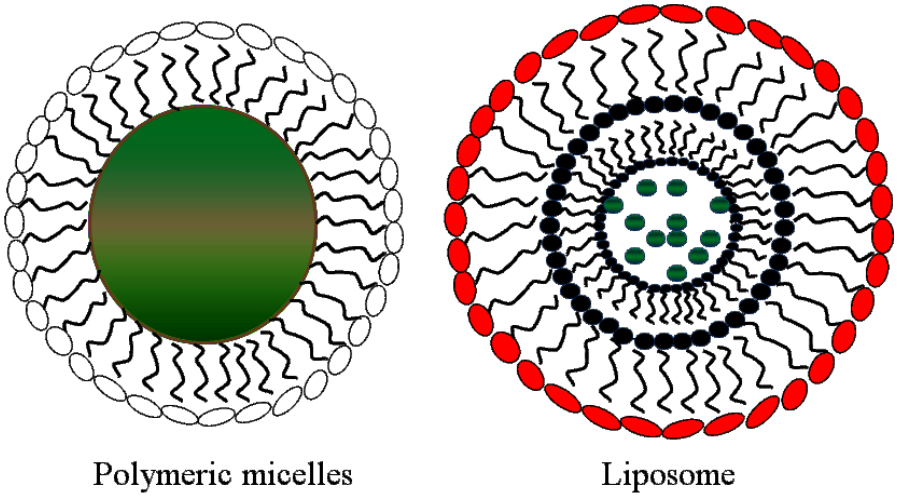

Fig. (1). Cartoon representation of typical polymeric micelles and liposomes.

Chronological Evolution of Cyclodextrin

The discovery of cyclodextrin was investigated in the late 19th century by Antonie Villiers during his research on the action of enzymes on various carbohydrates, particularly using the butyric Bacillus amylobacter on potato starch. Through this research, he revealed that under suitable conditions with incubation treatment, potato starch could ferment and produce dextrin because of the action of Bacillus microbes. In summary, he also discovered other byproducts that can be obtained after a few days of incubation, a highly crystalline substance with a composition of starch and dextrin. When examining the properties of dextrin, there are many similarities to cellulose, called cellulosin, which is resistant to acid hydrolysis and the absence of reducing sugars [11, 12]. Subsequently, manipulation of experimental conditions resulted in the two new distinct crystallised cellulosins, alpha-dextrin (α-cyclodextrin) and beta-dextrin (β-cyclodextrin). From 1853 to 1920, Franz Schardinger studied heat-resistant microorganism that can contribute to food poisoning and he found a type of extremely heat resistant microorganism that can dissolve starch from crystalline byproducts remarkably like the cellulosine reported by Villiers [13, 14]. He was the first person who explained the underlying properties of dextrins and later he proposed that dextrins were cyclic polysaccharides. Freudenberg confirmed long predictions of dextrin in the form of cyclic polysaccharides after 30 years, because these were cyclic oligosaccharides [15]. In 1911, Hans Pringsheim, a German chemist, played a critical role in research on dextrins and repeated the same experiments of Schardinger and isolated pure alpha dextrin and beta dextrins and

CHAPTER 6

Clinical Milestones in Nanotherapeutics: Current Status and Future Prospects

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Abstract: An aging population and poor clinical solutions for several diseases have propelled the rapid emergence of nanotherapeutics. Advanced drug delivery has turned out to be an important aspect of the medical field. A targeted delivery system transports the drug to the place of action hence, minimizing its adverse side effects on other vital tissues. Cell-specific targeting can be achieved by coupling drugs to specially framed carriers. Various nanoparticles, including solid lipid nanoparticles, nanosuspensions, nanoliposomes, micelles, polymeric nanoparticles, magnetic nanoparticles, dendrimers, carbon nanotubes, and fullerenes have been developed as carriers in drug delivery systems. In this chapter, the aforementioned nanocarriers and their clinical milestones achieved in various arenas including cancer, CNS disorder, rheumatoid arthritis, thyroid, cardiac diseases, ocular drug delivery, and vaccines so far, are scrutinized. This chapter outlines the current status of pharmacological and clinical studies of nanoparticles in the development process.

Keywords: Alzheimer's disease, Cancer, Carbon nanotubes, Central nervous system, Clinical trials, Drug delivery, Fullerenes, Magnetic nanoparticles, Nanosuspensions, Nanoparticles, Nanoliposomes, Parkinson's disease, Vaccine.

INTRODUCTION

Nanotherapeutics is one of the most advanced controlled drug delivery systems (CDDS) [1]. Nanoformulations are definitely among the promising carriers for the new era of drug delivery systems where therapeutic agents can be delivered selectively to target sites. Nanoformulations offer the advantages of being longer acting, rapidly soluble, less toxic, less immunogenic, and better than controlled-release formulations [2]. Targeted delivery in nanotechnology can be achieved by two approaches bottom-up and top-down fabrication at a nano-level with size and functional group modifications [3]. The therapeutic combat the disease at a

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minimum required dosage without causing significant adverse events, thereby improving the quality of life (QoL) of the patient. All these objectives could be met with the application of nanotechnology to therapeutic agents. Stability and safety are the major concerns for these nanoformulations. The blood-brain barrier (BBB) is the most critical barrier in designing drugs for the central nervous system (CNS) targeting. With the advancement in nanotechnology, newer techniques have been developed to stabilize these molecules and also make them more selective hence, reducing their toxicity [1, 2]. Trials dedicated to the toxicology of these agents should be carried out as a part of preclinical studies as well as clinical studies to establish the safety of these formulations.

DRUG TARGETING

The optimization of the nanotherapeutic agent depends on the conjugation of the drug to the carrier. A drug molecule could be covalently attached to the carrier, adsorbed on to the carrier, or encapsulated into the carrier. For the cell-specific targeting, covalent linking provides advantages over other strategies as the amount of drug (number of drug molecules) attached can be controlled. Either passive or active mechanisms could be used for cell-specific drug targeting. Passive drug targeting can be achieved through enhanced permeability and retention (EPR). Effective drug targeting is a function of the altered physical stimulus (viz. pH, temperature, and magnetism) [1, 4]. It can be achieved by targeting cell-specific ligands and receptors. At the target sites, drugs are released from the carriers and the release of the drugs could be controlled by altering the physiological parameters, *e.g*., pH, osmolarity, temperature, and enzymatic activity [4]. The ultimate aim of the targeted drug delivery is to ensure prolonged, localized, and protected drug action within impaired tissue.

CARRIERS FOR NANOTHERAPEUTIC FORMULATIONS

Nanotherapeutic formulations are better than conventional delivery systems due to enhanced site-specific delivery owing to the size of nanoparticles (NPs) [4]. Cell-specific drug targeting can be achieved by a combination of specially designed carriers and drug molecules [1]. The uptake of nanocarriers by cells is dependent on the physicochemical and biological properties of these carriers. Optimized nanocarriers have better penetration into the cell and have a targeted delivery compared to the larger molecules. A wide range of advanced nanocarriers have been used in therapeutics viz. solid lipids nanoparticles, polymeric nanoparticles, liposomes, micelles, dendrimers, nanosuspensions, carbon nanotubes, fullerenes, and magnetic nanoparticles [1, 4]. The scope of clinical applications of these nanoparticles has been described in detail.

Solid Lipids Nanoparticles

Solid lipid nanoparticles (SLNs) have been characterized as an alternative drug delivery system to other colloidal carriers, such as emulsions, liposomes and polymeric micro- and nanoparticles. Lipids mainly comprise triglycerides (tricaprin, trilaurin, and tripalmitin), partial glycerides (Imwitor), fatty acids (palmitic acid, stearic acid), steroids (cholesterol), and waxes (cetyl palmitate). Numerous emulsifiers could be used to stabilize the aqueous lipid dispersion according to their molecular weight and charge. The quality and quantity of the surfactant elected to depend upon the selected lipid and route of administration. Commonly used surfactants include egg lecithin, soybean lecithin, sodium cholate, and Poloxamer 188 [5]. From a regulatory perspective, the delivery system used should be chemically and physically stable. SLNs offer several advantages of being easy to prepare; chemically and physically stable, and control release properties due to the EPR effect [6]. They can carry a variety of molecules to the target location including proteins, antigens, nucleotide, and small drug molecules [7]. SLNs have shown significant efficacy for drug targeting to the brain as these molecules can easily cross BBB [8]. SLNs are also potential vehicles for gene therapy due to their chemical stability. SLNs can be used for transdermal drug delivery to selective skin layers due to its drug modulation properties [9]. Nanostructured lipid carriers (NLC) are advanced SLNs that have better physicochemical properties than conventional SLNs. A large number of SLNs with a variety of anticancer drugs (doxorubicin (DOX), camptothecin (CPT), etoposide, paclitaxel (PTX), idarubicin, retinoic acid, and SN-38 [irinotecan analog]) have been prepared and tested in animals; however, clinical trial of these formulations has to be carefully designed to establish safety and efficacy in humans [6]. Manjunath and Venkateswarlu conducted a study in which tripalmitin SLNs were loaded with clozapine and after intravenous (IV) administration in mice, there was a significant increase in drug concentration in the brain compared to clozapine suspension. Similarly, after intraperitoneal administration of tripalmitin SLNs of etoposide, increased brain drug levels were observed compared to conventional etoposide [10]. In a study by Yang and coworkers, Stearic acid SLNs stabilized with Poloxamer 188 and loaded with CPT showed targeted drug delivery to the brain by crossing BBB both *via* intravenous and oral routes. Maximum serum concentration (C_{max}), Area under the curve (AUC)/dose and mean retention time were higher by 180%, 10.4 folds and 4 folds, respectively than the drug solution [11]. Singh and coworkers achieved increased drug targeting of docetaxel to brain tumors with excellent safety and efficacy by conjugation of Lactoferrin (*Lf*) on SLNs surface [12]. SLNs could be used for drug delivery to the lungs. Dry powder formulations and aerosols for inhalation could be prepared using spray drying with lactose as excipient [13, 14].

CHAPTER 7

Scale-up, Preclinical and Clinical Status of Poly (Lactide-Co-Glycolide) and its Copolymers based Drug Delivery Systems

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Abstract: Poly(lactide-co-glycolide) or PLGA is a kind of a synthetic polymer that has been approved by USFDA for its use in humans. PLGA nano/microparticles have proved to offer controlled as well as the sustained release of several medicinal moieties. PLGA is chemically synthesized by direct polycondensation of glycolic acid (GA) with lactic acid (LA) and different factors like LA: GA ratio, storage temperature, the initial molecular weight of the monomers, and exposure time to water influences the physical properties of PLGA. Similarly, various factors like morphology, crystallinity, molecular weight, shape, size molecular, hydrophobicity, chemical structure, physicochemical properties, glass transition temperature are some of the crucial factors responsible for the biodegradation of PLGA. PLGA based micro/nanoparticles are generally prepared by the oil-in-water emulsification process. On the other hand, spray drying is one of the industrial methods for the production of PLGA particles. In this chapter, we have summarized the extensive applications, laboratory, and industrial-scale methods for the production of PLGA nano/microparticles, preclinical, and clinical status PLGA based drug delivery systems.

Keywords: Industrial scale-up, Microparticles, Nanoparticles, Physicochemical properties, Poly(lactide-co-glycolide), Preclinical and clinical status, Scaffolds, Vaccine adjuvant.

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INTRODUCTION

Recently, extensive consideration has been given to the utilization of polymers in drug delivery. Polymers such as polycaprolactone, alginate, and chitosan have been discovered and widely utilized for drug delivery. Polymers are obtained both from natural and synthetic origins and possess different merits and demerits. Merits of natural polymers include good cell adhesion and cell function in comparison to synthetic polymers while limited purity and allergenic reactions are the demerits of natural polymers. In contrast, among natural [1 - 6] and synthetic polymers, synthetic polymers viz. poly (amide), poly (amino acid), and poly (ester) are extensively used in the customization of drug delivery carriers [7, 8]. Poly (lactide-co-glycolide) (PLGA), is a kind of synthetic polymer that has been extensively explored to achieve desired effects or targets in drug delivery. Additionally, PLGA possesses the unique merit of being a biodegradable polymer, which is synthesized through direct polycondensation of glycolic acid (GA) with lactic acid (LA). Random opening of ring and copolymerization of monomers like cyclic dimer (1,4-dioxane-2,5-diones) of lactic acid and glycolic acid, in the company of catalyst especially tin (II) 2-ethyl hexanoate, tin (II) alkoxide, or aluminum isopropoxide results in the formation of PLGA [9, 10].

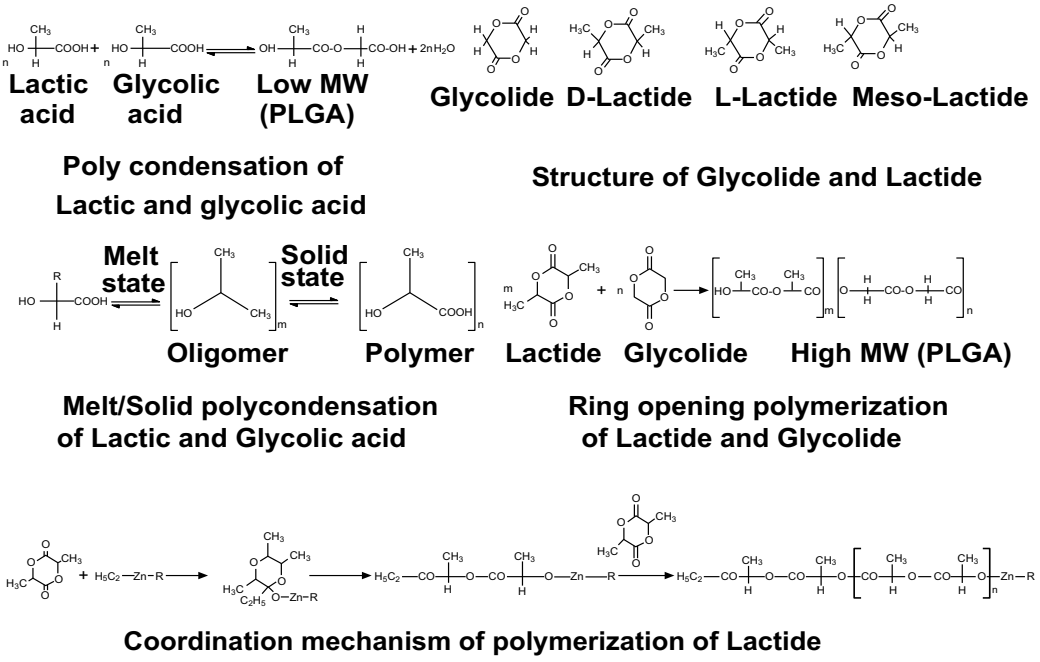
Foremost work was carried out on PLGA in the area of biomedicine from 1960 to 1970 period. Subsequently, the investigation of polymer led to its extensive use in several fields, *e.g* vascular graft, dental and fracture repair, gene delivery, and cancer therapy [11, 12]. Furthermore, USFDA approved PLGA for its use in various drug delivery systems *i.e.* microspheres, microparticles, implants, nanoparticles, and *in-situ* gel formation. PLGA microparticles are used for tendering controlled and sustained release of Human Growth Hormone (HGH) and for the treatment of cancer, cardiovascular diseases, infection, and inflammation [13, 14].

CHEMISTRY AND PHYSICO-CHEMICAL PROPERTIES OF PLGA

PLGA Synthesis

Poly (lactide-co-glycolide) is synthesized by the method of direct polycondensation of glycolic and lactic acid (Scheme **1**). The polycondensation reactions are responsible for the solution and the melted or solid-state of the polymer. The manufacturing of high molecular weight polymer requires a high degree of dehydration which is difficult to accomplish and hence, polycondensation is considered as an incomplete method to get high molecular weight polymers [15]. However, synthesis of high molecular weight (160 kDa) PLGA was achieved by azeotropic dehydration glycolic acid and L-lactic acid

solution in diphenyl ether at 130°C in presence of tin powder as a catalyst for 20-40 h [16]. For the complexity and purification of the end product, the solvents were introduced; hence, polycondensation is performed to obtain the melting state of the polymer. The melt polycondensation method possesses two equilibria: the ring/chain equilibrium for the formation of cyclic diester and hydration/dehydration for the formation of ester. However, in typical melt polycondensation, glycolide, and cyclic diesterslactide (Scheme **1**) are synthesized by the depolymerization method. The specific condition of this reaction *i.e.* high temperature under vacuum, can not only produce dehydration but also forms cyclic diesters in equilibrium with the polymer. This reaction repulses the excessive growth of the chain of the polymer, and thus it cannot be employed for high molecular weight polymer. To surmount this problem, the method involving melt/solid polycondensation was recently developed to achieve a specific objective (Scheme **1**) [17].



Scheme 1. Steps involved in the synthesis of poly (lactide-co-glycolide, PLGA).

In the first step, dehydration of monomers can formulate the oligomers, followed by the second step, where oligomers are under vacuum (10 Torr), and tin chloride dehydrate/p-toluenesulfonic acid or zinc acetate dihydrate can be used as a

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