Nanotechnology in the Life Sciences

Anand Krishnan · Balasubramani Ravindran · Balamuralikrishnan Balasubramanian · Hendrik C. Swart · Sarojini Jeeva Panchu · Ram Prasad *Editors*

Emerging Nanomaterials for Advanced Technologies

Springer

Nanotechnology in the Life Sciences

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Nano and biotechnology are two of the 21st century's most promising technologies. Nanotechnology is demarcated as the design, development, and application of materials and devices whose least functional make up is on a nanometer scale (1 to 100 nm). Meanwhile, biotechnology deals with metabolic and other physiological developments of biological subjects including microorganisms. These microbial processes have opened up new opportunities to explore novel applications, for example, the biosynthesis of metal nanomaterials, with the implication that these two technologies (i.e., thus nanobiotechnology) can play a vital role in developing and executing many valuable tools in the study of life. Nanotechnology is very diverse, ranging from extensions of conventional device physics to completely new approaches based upon molecular self-assembly, from developing new materials with dimensions on the nanoscale, to investigating whether we can directly control matters on/in the atomic scale level. This idea entails its application to diverse fields of science such as plant biology, organic chemistry, agriculture, the food industry, and more.

Nanobiotechnology offers a wide range of uses in medicine, agriculture, and the environment. Many diseases that do not have cures today may be cured by nanotechnology in the future. Use of nanotechnology in medical therapeutics needs adequate evaluation of its risk and safety factors. Scientists who are against the use of nanotechnology also agree that advancement in nanotechnology should continue because this field promises great benefits, but testing should be carried out to ensure its safety in people. It is possible that nanomedicine in the future will play a crucial role in the treatment of human and plant diseases, and also in the enhancement of normal human physiology and plant systems, respectively. If everything proceeds as expected, nanobiotechnology will, one day, become an inevitable part of our everyday life and will help save many lives.

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Preface

Recent years, the world has perceived the rise of nanotechnology, a fascinating field that creates numerous divisions of the scientific community. The book covers a broad spectrum of the scientific fields such as synthesis techniques, various innovative characterization techniques, and growth mechanisms of nanomaterials, physics and chemistry of nanomaterials, diverse functionalization methods as well as their applications in biological, therapeutic, energy, food and environmental science. Also, it focuses on the applications of nanostructured materials, integrative applications such as nano and microelectronic sensor devices, as well as agriculture and environmental remediation applications. This book comprises a collection of chapters on advances in functionalized nanomaterials and discusses the early stages of development of functionalized nanostructures, including a look at the future of 2D nanomaterials and 3D objects. Further, it includes a chapter on nanomaterial research developments, highlighting work on the life-cycle analysis of nanostructured materials and toxicity aspects. The contents of this book will prove useful for researchers and professionals working in the field of nanomaterials and green technology. Researchers, in the field of nanotechnology from entrants to specialized researchers, in a number of disciplines ranging from biology, chemistry and materials science to engineering and manufacturing in both of academia and industry sectors. The book targets scientists, researchers, academicians, graduates and doctoral students working in biological sciences and waste management.

Our sincere gratitude goes to the contributors for their insights on applications of various nanomaterials in industrial and medical sector.

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(2012). The Radio Rosestad Award for outstanding research and postgraduate teaching in 2017. Hendrik was chair of national and international conferences. He has supervised more than 80 PhD and MSc students successfully in the past with another 20 in progress and has established a National Nano Surface Characterization Facility (NNSCF) containing state-of-the-art surface characterization equipment. A research chair in solid state luminescent and advanced materials was awarded to him from the South African Research Chairs Initiative (SARChI) at the end of 2012, which was renewed for another 5 years at the end of 2017. The main focus of his research group is the improvement of luminescent materials for applications in flat panel displays, solar cells, solid state lighting, dosimetry and thermometry.

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Chapter 1
An Insight on Emerging Nanomaterials for the Delivery of Various Nutraceutical Applications for the Betterment of Heath

T. Karpagam, Balasubramanian Balamuralikrishnan, B. Varalakshmi, A. Vijaya Anand, and J. Sugunabai

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1.1 Introduction

An ancient Siddha medicine aphorism "unave marundhu, marundhe unavu" which means food as medicine, medicine as food well emphasizes the importance of diet for disease-free living. The role of food components in inhibiting disease and health enhancement is becoming more apparent to the researchers as well as consumers (Palzer 2009). The relationship between diet and health, and awareness on foods, from a wide range of sources, that either inherently contains health-enhancing active ingredients or included via fortification is important (Taneja and Singh 2012). Thus, there is a demand for a balanced diet and functional food products that focus on specific health benefits. Consumption of functional ingredients enriched foods keeps the body in good health. Diets rich in essential nutrients along with regular exercise decrease threats related to many diseases and maintain body weight. The case of age-related diseases, such as malignancy (e.g., gastrointestinal cancer), cardiovascular diseases, and diabetes, is more prevalent with the increase in life expectancy of humans. Escalating the use of food products from plants delays the development of these chronic diseases, and various health organizations all over the world recommend this. Plant-derived food products show a positive effect on the reduction of chronic diseases due to the presence of phytoconstituents. These are nonnutritive secondary metabolites with widespread biological functions. As bioactive metabolites, these phytochemicals ensure low effectiveness in comparison with pharmaceutical products. However, if regularly ingested in the diet, a perceptible long-term physiological effect can result without side effects (Shampa Sen and Yashwant Pathak 2016). These bioactive components are beneficial to our health and exploited for nutraceutical application. De Felice (1995) defined nutraceuticals as "food or a part of food that provides medical or health benefits, which include prevention and treatment of diseases." The term nutraceutical exists between foods and drugs, and it arose from the combination of nutrition and pharmaceuticals and was framed by Stephen L. DeFelice (Fig. 1.1), in the year 1989 (Kalra 2003). This concept is in modern food science, and the area is beyond the diet, but before the drugs (El Sohaimy 2012).

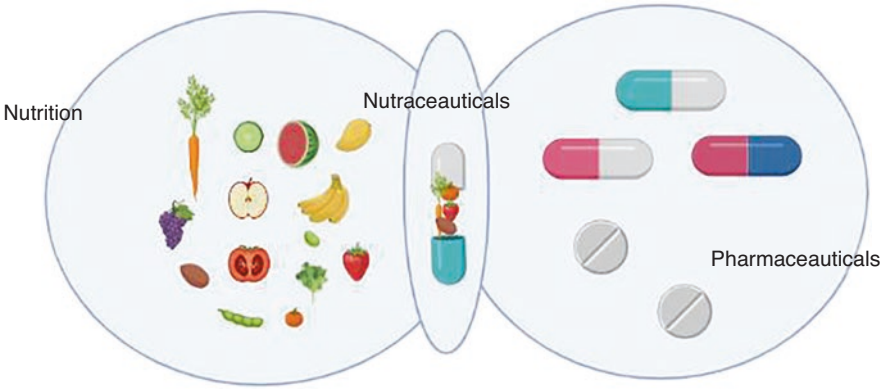

Fig. 1.1 Stephen L. DeFelice definition of nutraceuticals

1.1.1 Role of Nutraceuticals

Nutraceuticals are dietary supplements which deliver nutrients to the body. They are made accessible within a nonfood medium by supplementing phytoconstituents in the health/food product. Nutraceuticals enhance human health by introducing different dosages of active compounds from food in a higher quantity than the amount that can be by the consumption of regular food. Nutraceuticals provide resistance against several diseases and thus contribute significantly to the therapeutic performances. According to the theory of nutritional therapy, the nutraceuticals function by cleansing the body, evading deficiencies due to lack of protective food, reestablishing healthy food practices, and thus restoring healthy absorption of nutrients.

1.1.1.1 The Functional Role of Nutraceuticals

The functional role of nutraceuticals is the enhancement of nourishment for specific groups of people with impaired metabolism, in a specific physical state, who reduce the consumption of certain substances in food.

The following are the categories of nutraceuticals which include foods for special medical purposes (FSMPs):

- Nutrition for newborn and subsequent nourishment for the next stage
- Foods with cereal and foods devoid of cereal for infants and preschool children
- Low-calorie foods for decreasing obesity
- Foods deprived of or lacking phenylalanine
- Foods without gluten
- Nutrition designed for carbohydrate metabolic disorder

- Lactose-lacking foods
- Foods composed of decreased protein
- Foods for sportspersons and persons with augmented physical activity

FSMPs are recommended to consume under the direction of medical persons, and it must hold information regarding their use.

1.1.2 Role of Phytonutrients

Phytonutrients have a biological function which enhances health. They generally help plants to thwart competitors, predators, or pathogens – phytochemicals in food work by acting as a substrate and cofactors for biochemical reactions. As inhibitors of biochemical reaction, it removes the unwanted component in the intestine and augments the absorption and stability of vital nutrients. Also, they function as a selective growth factor for good flora and as inhibitors of infectious bacteria. They also deactivate harmful chemicals and act as ligands to antagonize the receptors that are present either extracellular or intracellularly (Baby Chauhan et al. 2013).

1.2 Classification of Nutraceuticals

Nutraceuticals are dietary component with health benefits. Examples include diets rich in fiber, probiotics, prebiotics, PUFA, antioxidants, vitamins, minerals, polyphenols, and spices. Natural sources, chemical nature of components, nature of the reaction, and pharmacological functions form the basis of nutraceutical classification.

The broad classifications of nutraceuticals are as follows:

(a) Potential nutraceuticals
(b) Established nutraceuticals

Clinical data on the medical benefits are needed to make the potential nutraceutical to established nutraceuticals (Pandey et al. 2010).

Classification of nutraceuticals based on its composition/functions (Akobundu et al. 2004):

1.2.1 Nutraceuticals with nutrients
1.2.2 Nutraceuticals with herbals or phytochemicals
1.2.3 Nutraceuticals with dietary supplements

1.2.1 Nutraceuticals with Nutrients

Nutraceuticals with nutrients are foods rich in nutrients and do the nutritive function, e.g., carbohydrates, fatty acids, amino acids, vitamins, and minerals. Foods comprising of carbohydrates, proteins, and lipids are necessary for the appropriate functioning of the body and its calorific requirements. Vitamins and minerals are not synthesized within the human body and play the role as protective foods. Hence they must be supplied via diet for the appropriate functioning of the body. Nutraceuticals play the role to improve health by combating against some chronic diseases (Mc Clements 2012).

1.2.2 Nutraceuticals with Phytochemicals

Nutraceuticals with phytochemicals possess herbs or botanical products. Intake of plant-based food offers enormous benefits to human health. Plants contain various phytochemical compounds, mostly polyphenols. These polyphenols are responsible for the beneficial activity. Pharmaceutical products with active ingredient have appeared in health products. These active ingredients are phytoconstituents with bioactivity (Espín et al. 2007). Important phytochemicals are anthocyanins, resveratrol, isoflavones, and polyphenols like ellagic acid, proanthocyanins, and flavanones.

1.2.3 Nutraceuticals with Dietary Supplements

Nutraceuticals act as dietary supplements composed of probiotics, prebiotics, antioxidants, and enzymes. They deliver bioactive constituents to the body, which is a mixture of several ingredients, metabolites, or constituents in the form of liquid, capsule, or tablet. The subclassification includes extracts from plants, supplements from herbs, proteins, vitamins, and minerals.

1.3 Sources of Nutraceuticals

Sources of nutraceuticals include plants, animals, and microbial.

Plant sources: Some significant plant sources include beta-glucan, ascorbic acid, gamma-tocotrienol, luteolin, cellulose, quercetin, gallic acid, indole3carbinol, pectin, perillyl alcohol, glutathione, potassium, allicin, D-limonene, daidzein, genistein, lycopene, hemicellulose, lignin, capsaicin, alpha-tocopherol, and zeaxanthin.

Animal sources: Some significant animal sources include conjugated linoleic acid (CLA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), selenium, and zinc.

Microbials: Some significant microbial sources include yeast, *Bifidobacterium*, *Lactobacillus*, and *Streptococcus*. Nowadays, the intake of foods is not only to satisfy the energy needs but also combat diseases and augment both physical and mental health (Menrad 2003).

1.4 Recent Trends of Nutraceuticals in the Global Market

Due to the enormous change in living style, the incidence of lifestyle-associated diseases is also growing. Life expectancy with these diseases is also growing. After gaining knowledge regarding the underlying cause of disease, now the consumers across the world are shifting from disease-causing chemical products to preventive healthcare products like nutraceuticals. Hence, the growth of the nutraceutical market is also rising. The value of global nutraceutical market was 205.39 billion USD in 2016 and is foreseen to elevate to around 294.79 billion USD by 2022, at 6.3% compound annual growth rate (CAGR) from 2017 to 2022 (Mordointelligence.com, 2017). Last year (2019), the global nutraceutical market was at 382.51 billion USD, at 8.3% CAGR which was higher than the estimation (https://www.grandviewresearch.com/industry-analysis/nutraceuticals-market, 2020). In forthcoming years, the market is expected to reach 423.2 billion USD by 2025, at a CAGR of 6.8% during 2020–2025. The tremendous increase in the global nutraceutical market is due to the increased utility of nutraceuticals by the people around the world. Improved delivery of nutraceuticals is may be one cause.

1.5 Bioavailability of Bioactive Compounds of Nutraceuticals

The efficiency of nutraceuticals depends on its bioavailability. With the increasing knowledge and understanding of the protective role of nutraceuticals, its availability into the body has become a significant concern. This essential factor must be considered by the manufacturers when producing nutraceuticals (Rapaka and Coates 2006). The quantity of a functional/bioactive compound that enters the blood circulation is called bioavailability (Esfanjani et al. 2018). Decreased bioavailability lowers the benefits of nutraceuticals inside the body. The route of administration/intake of nutraceuticals is oral, and they pass through GIT to reach the blood. Various constrain and obstructions like inadequate gastric retention, reduced permeability, solubility in the gut, and unstable conditions encountered in the GI tract reduce the activity and hence availability of nutraceuticals (Bell 2001). Apart from decreased bioavailability, it is necessary to regard other challenges like poor solubility, instability, and crystallization before incorporating these bioactive molecules into

products while manufacturing (Augustin and Sanguansri 2012). To overcome the physiological limitations of the body and to enhance the bioavailability and absorption of nutraceutical compounds as nutritionally and pharmacologically important one, the bioactive compound needs to be conjugated with the suitable delivery system, thus enhancing its bioavailability.

1.5.1 Enhancing the Bioavailability of Nutraceuticals by Nanotechnology

Many proposed targeted delivery systems have not been considered globally as a pertinent system for the delivery of bioactive compounds since each bioactive compound has its typical molecular structure requiring different systems. Nanotechnology-based targeted delivery systems are now booming to evade problem raised in the bioavailability of bioactive compounds. Development of delivery systems with nanomaterials is to boost the biological availability of functional components present in nutraceuticals. The encapsulation of bioactive compounds combats the acidity and breakdown by enzymes present in the GIT. These delivery systems offer an increased surface area and enhance the bioavailability. Reducing the particle size of delivery systems improves its efficiency, solubility, and biological activity of the compounds due to the availability of greater surface area per unit molecule (Prasad et al. 2019).

1.6 Nanotechnology

Employing and handling materials, at the nanometer scale, is called nanotechnology (Fathi et al. 2012). A nanometer is one-millionth of a millimeter. The dimensions of nanoparticles (NPs) are roughly between 1 and 100 nm (Prasad et al. 2016, 2017a, 2018). Nanotechnology shows the excellent possibility of enhancing the delivery of nutraceuticals. It facilitates controlled release, improves bioavailability, and protects the nutraceuticals during processing, storage, and distribution.

1.6.1 Nanocarriers as Nano Delivery System

The material used for the synthesis of nanoparticles (NPs) or nanocarriers is of organic or inorganic material (Bhushan et al. 2014) or a mixture of both (Fig. 1.2). Nanocarriers synthesized from organic material are comprised of polymeric and lipid-based nanoparticles, and those that are synthesized from inorganic materials are from metallic nanostructures such as quantum dots (Prasad et al. 2017b).

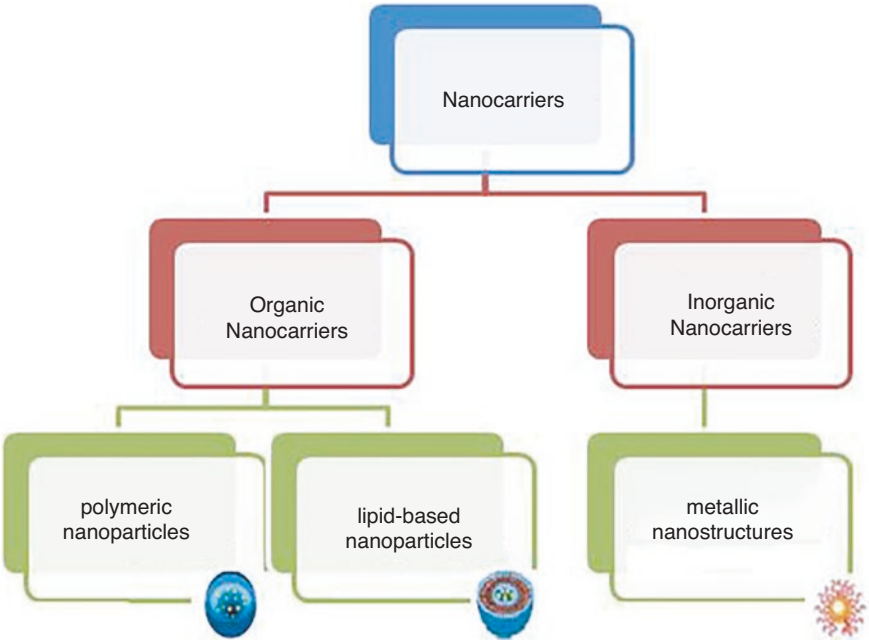

Fig. 1.2 Nanocarriers

1.6.2 Synthesis of Nanoparticles

Nanoparticles can be produced either by top-down methods (fluidization, dispergation, emulsifying technologies, or homogenization methods) or by bottom-up methods (precipitation or condensation, controlled sol-gel syntheses, evaporation) (Fig. 1.3) (Brayner et al. 2013). The size of the mechanical method of production of nanoparticles yields 100–1000 nm, while the size of nanoparticles from the chemical and bottom-up method yields 10–100 nm (Acosta 2009). Various biodegradable natural biopolymers for nanoencapsulation are frequently used (Jampilek and Kralova 2017).

Application of nanotechnology in nutraceuticals has enhanced the properties of nutraceuticals. They alter the difficulties encountered during delivery inside the body. The increased surface area of nutraceuticals is due to the decrease in size of a prepared nutraceutical, which in turn enhanced the desired delivery process inside the body. In a study by Javed et al. (2011), reformulation of silymarin into nanoliposomes increased its bio-absorption. The unique properties, such as size, shape, and internal structure, are essential while designing and fabricating nanomaterials. The fabrication monitors not only the incorporation of bioactive compounds but also on their stability, entrapment and release behaviors, and biological function (de Souza Simo˜es et al. 2017). Thus, nanotechnology offers an essential role in the delivery systems of a nutraceutical (Acevedo-Fani et al. 2017). Some of the

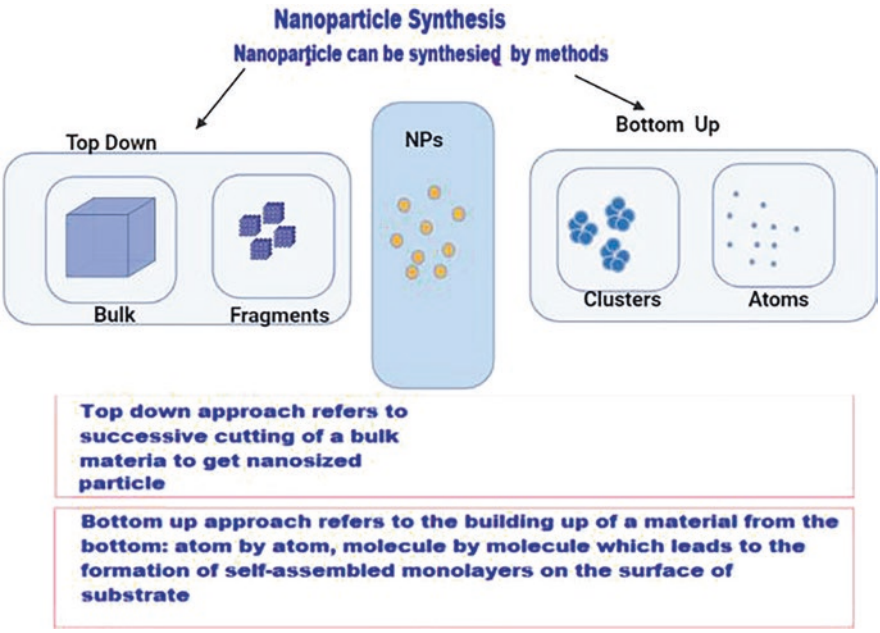

Fig. 1.3 Synthesis of nanoparticles

fabrication techniques of nanomaterials are emulsification, solid dispersion, spray drying, spray freeze drying, electro-spraying process, anti-solvent precipitation, complex coacervation, and layer-by-layer (LbL) deposition. The microscopically developed instruments that characterize nanomaterials help in better understanding of structures in nano-size and interpretation of their role (Tolles and Rath 2003). The nano-architecture endows protection and bioavailability of nutraceuticals by modifying the extent of solubility and its release (Ezhilarasi et al. 2013). Liquid crystalline mesophase is known as lyotropic formed by amphiphilic substances such as lipids along with surfactants and copolymers dispersed in a polar solvent. Under appropriate conditions, hydrophobic interactions cause them to self-assemble into stable crystals in nanometer size. Examples include micelles, hexagonal structures, lamellar structures, and cubosomes, which retain a high degree of molecular orientation in a liquid state.

1.6.3 Scenarios of Nanotechnology in Nutraceuticals

In the present scenario, nutraceutical delivery systems need to be familiar with the location, the load needed to be delivered, a decision on release, and feedback control. Advances in nanotechnologies revolved this by aiding its delivery. Aforementioned can be compared to the "smart drug delivery" presently under

medical research. Thus, nanoscience, engineering, and technology guaranteed the proper delivery of nutraceuticals. Innovation in encapsulated formulations and bioavailability of nutraceuticals are considerably augmented. Even though nanotechnology aids in the delivery of nutraceuticals, however, the essential step necessary is the selection of the loading materials for the delivery systems, which plays a vital role in the encapsulation efficiency and stability, and the available option of materials is also limited. Loading of bioactive ingredients into nanotechnology-based delivery systems is essential. The nanotechnology-based nutraceuticals can attain commercialization by overcoming the boundaries related to them (Augustin and Hemar 2009), by using food grade-based nanomaterials which offer uniformity, flavor, taste, and texture (Prasad et al. 2017c; Chausal et al. 2021).

1.7 Food-Grade Nanomaterials

Various food-grade nanomaterials for delivery of nutraceuticals are as follows:

1.7.1 Lipids as nanomaterials
1.7.2 Polymer as nanomaterials
1.7.3 Cellulose as nanomaterials
1.7.4 Protein as nanomaterials
1.7.5 Polysaccharide as nanomaterials

1.7.1 Lipid as Nanomaterials

Lipids have a tremendous capability for encapsulating nutraceuticals. Some of the examples of lipid-based nanoparticles (Fig. 1.4) are solid-lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, nanoemulsions, and nanoliposomes systems. They encapsulate majority of the natural bioactive compounds. A high dose of different molecules can be encapsulated and used on distinct sites using these lipid-based nanomaterials.

Solid-lipid nanoparticles (SLNs): The first-generation lipid-based nanocarriers are solid-lipid nanoparticles (SLNs). The lipids used in the synthesis are fatty acids, monoglycerides, diglycerides, and triglycerides. They remained in the solid state at body temperature and are stabilized by emulsifying agents (Müller et al. 2000). The SLNs are highly lipophilic, which enables the transportation of core material. Synthesis of SLNs is shown in Fig. 1.5, and list of constituents necessary for the synthesis of nutraceuticals encapsulated in SLNs is shown in Table 1.1.

Advantages of solid-lipid nanoparticles: Solid-lipid nanoparticles have a combination of advantages of liposomes, nanoemulsions, and polymeric nanoparticles. SLNs have good tolerance, high bioavailability, and biodegradability. There is no formation of toxic breakdown products in SLNs (Cacciatore et al. 2016). Therapeutic