



**REVIEW**

## Biodegradable Materials as Nanocarriers for Drugs and Nutrients

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### ABSTRACT

Several important drugs and nutritional supplements are limited by their lack of bioavailability. Nanomaterials display unique beneficial properties that might help improve the bioavailability of drugs and nutritional supplements. Unfortunately, nanomaterials produced from synthetic polymers and metals may have similar difficulties with bioavailability and toxicity. Naturally occurring biopolymers are biodegradable and non-toxic and are adaptable to the synthesis of nanoparticles. Drugs and other substances can be encapsulated or embedded in such particles with an increase in bioavailability. The search for biodegradable nanomaterials is an active research field. This review summarizes the research on nanocrystalline cellulose, starch, lignin, and other biological and environment-friendly nanocomposites which are commonly used as nanocarriers for drugs and nutrients. Further, prospects for the use of biodegradable nanomaterials in targeted therapy, including environmentally responsive therapy, are discussed.

### KEYWORDS

Nanomaterials; biodegradation; classification; application

## 1 Overview of Nanoencapsulation of Drugs and Nutrients

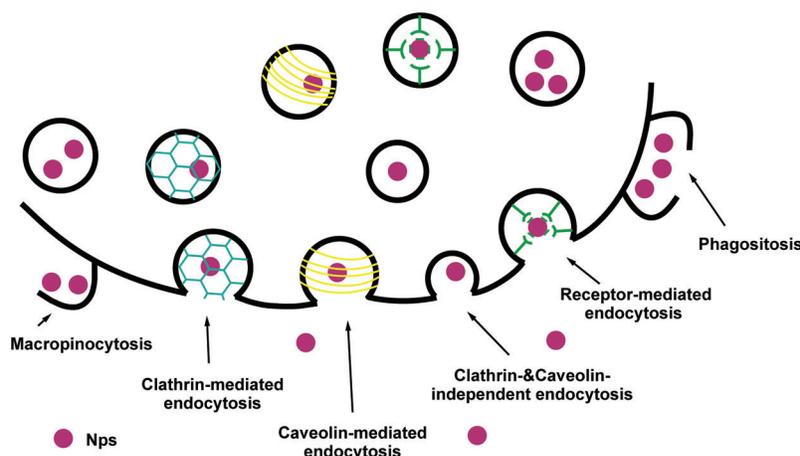
### 1.1 Nanoencapsulation

Many oral drugs, especially anticancer agents, have limitations such as poor chemical stability and low water solubility and bioavailability in the gastrointestinal tract [1], which greatly restrict their clinical application. Additionally, various nutrients such as polyphenols, polyunsaturated fatty acids which are promoted to help prevent chronic disease and prolong lifespan also show low water solubility and stability, resulting in limited bioavailability [2].

Various new carrying systems are now available to overcome these shortcomings and increase the efficacy of drugs and nutrients, and nanoencapsulation is a relatively recent and promising technology [3,4]. Nanoparticles (NPs) exhibit unique surface mass ratios and quantum properties and can be effective carriers for bioactive substances [5,6]. NPs significantly improve the bioavailability of various substances, especially insoluble drugs and nutrients [7–10]. Several modes of entry of nanoparticles into cells are illustrated (Fig. 1). The uptake mechanisms of nanoparticles include phagocytosis, macropinocytosis, and



endocytosis. Nanoparticles are very small and are mainly absorbed through endocytosis which can be divided into subgroups according to various specific protein-receptor interactions, such as clathrin- and caveolae-mediated endocytosis. Successful transformation of clinical drug delivery systems from macro to micro to nano promotes the development of controlled drug release and surmounts pharmacological limitations of traditional dosage forms [11].



**Figure 1:** Schematic representation of NPs' uptake mechanisms [12]

### 1.2 Traditional Wall Materials for Nano-Encapsulation

Traditional capsule wall materials used to embed drugs and nutrients are divided into three main categories: semisynthetic polymer materials, fully synthetic polymer materials, and inorganic materials. Fully synthetic polymer materials display good film-forming properties, high mechanical strength, and stability and are the most widely used capsule wall materials. Fully synthetic polymer materials, such as polyvinyl chloride, polyethylene, polyurea, polyester, and polyurethane, are typically non-biodegradable. Natour et al. [13] utilized interfacial polycondensation between amine and isocyanate monomers in inverse nanoemulsion (water-in-oil). These authors encapsulated ionic liquid-modified magnetite nanoparticles (MNPs) with polyurea nanocapsules (PU NCs) with an average size of 5 nm–20 nm. Hasani-Sadrabadi et al. [14] used self-assembly technology to synthesize nanocapsules composed of a dendritic polyethylene core and Pluronic copolymer shell. The nanocapsules enclosed several hydrophobic anticancer drugs, such as paclitaxel, in the size range of 50 nm–200 nm. However, most polymer monomers in these preparation processes are toxic. Moreover, organic solvents required in these processes are costly and may cause environmental pollution.

Studies on nanoembedded drugs and nutrients using semisynthetic polymer materials are relatively few. Such studies have mainly used cellulose derivatives, such as methylcellulose, ethylcellulose, and cellulose acetate butyrate, and oils, such as 1,3-distearin, and hydroxystearic alcohol. El-Habashy et al. [15] used a solvent evaporation method to prepare ethyl cellulose-based NPs containing piroxicam. These NPs were spherical, with slightly porous surface, and the average particle size was 240 nm.

Inorganic materials are often used in phase-change energy storage materials and are rarely used for the encapsulation of drugs or nutrients. The inorganic materials used for encapsulation include calcium carbonate, phosphate, aluminum, silicate, glass, and clay. Ma et al. [16] prepared sea urchin-shaped hollow  $\text{CaCO}_3$  nanospheres (HCNS) mediated with soybean trypsin inhibitor. These particles displayed a layered porous hollow structure and were used as anticancer drug carriers. The hierarchically porous hollow structure of the carrier realized high loading and continuous release of doxorubicin (DOX).

### 1.3 Shortcomings of Traditional Nanomaterials in Nanoencapsulation of Drugs and Nutrients

Epidemiological studies on urban air pollution suggest that finer particles are more harmful than larger particles. Humans continuously inhale millions of pollutant particles without serious harm. However, an increase of only  $10 \mu\text{g}/\text{m}^3$  can increase the mortality caused by cardiac dysfunction by 1% [17]. The impact of smaller particle size on human health is increasing, suggesting that particles in the nanometer range also produce additional biological effects. The possible use of nanomaterials in food applications increases concerns regarding toxicity. Toxicity assessments need to consider relevant parameters [18], such as materials, structure, surface area, charge, solubility, stability, and aggregation state [19]. Toxic effects of nanomaterials may include inflammatory reactions that worsen airway disease, cardiovascular events caused by hypercoagulability or plaque instability [20], and chronic effects in animal models [21,22]. Nanomaterials used in various fields might eventually enter the human body through the food chain and affect human health, although this possibility is highly speculative. A primary concern among consumers is how nanomaterials are transferred from packaging materials to food products and how the NPs might affect human digestive tract [23].

### 1.4 Advantages of Biodegradable Materials as Nanocarriers

Biodegradable materials are widely used for encapsulating drugs and nutrients owing to their characteristics such as degradability, biocompatibility, and low toxicity. Biodegradable materials refer to polymers that are degraded by the action of microorganisms, such as bacteria and fungi, as per the American Society for Testing Material definition [24]. The definition of biodegradation in medical fields refers to changes in medical devices or biological materials, including loss of integrity or performance under physiological or simulated conditions. The use of biodegradable polymer materials may efficiently solve the problems associated with synthetic polymers and raw vegetable wastes. Thus, the development of biodegradable composites using novel natural polymers that can be degraded into harmless compounds is a priority [25]. Biodegradable nanomaterials are both feasible and safe for use in drug and nutrient encapsulation, with advantages such as high loading efficiency, good stability, biocompatibility, biodegradability, and controlled release [26,27]. This article systematically classifies biodegradable nanomaterials based on source and summarizes their application. Biodegradable nanomaterials exhibit high potential for use in the field of nanomaterials in the future.

## 2 Sources and Preparation of Natural Biodegradable Nanomaterials

Natural biodegradable materials can be divided into the following six categories: (1) Cellulose, chitin, starch, lignin, alginate, and other natural polysaccharide materials; (2) Collagen, fibrinogen, and other natural protein materials; (3) Vegetable oil, animal fat, and other lipid materials; (4) Polyhydroxyalkanoates [PHA, including polyhydroxybutyrate (PHB), polyhydroxybutyrate valerate (PHBV)], polyesters synthesized by bacteria; (5) Polyester, such as polylactic acid (PLA), synthesized from monomers produced by microbial fermentation; and (6) CO<sub>2</sub> copolymers, such as polypropylene carbonate (PPC) prepared from CO<sub>2</sub> and propylene oxide or ethylene oxide (Tab. 1).

**Table 1:** Forms and applications of different natural nanomaterials

Material	Concrete form	Application	Diameter	Loading capacity	Encapsulation efficiency	References
Nanocellulose	Microfibrillated cellulose (MFC)	Drugs encapsulating (methotrexate)	5.78 nm			[28]
	Bacterial nanocellulose (BNC)	Nutrients encapsulating (curcumin)	90 nm–160 nm			[29]
		Drugs encapsulating (serum albumin)	$(0.19 \pm 0.03) \mu\text{m}$			[30]
	Nanocrystalline cellulose (NCC)	Drugs and nutrients encapsulating (adriamycin hydrochloride, curcumin)	$(600 \pm 51) \text{nm}$			[31]
		Nutrients encapsulating (luteolin galuteolin)	50 nm	$(12.9 \pm 1.5) \text{mg/g}$ $(56.9 \pm 0.9) \text{mg/g}$		[32]

(Continued)

**Table 1 (continued).**

Material	Concrete form	Application	Diameter	Loading capacity	Encapsulation efficiency	References
Nanostarch	Starch nanocrystal (SNC)	Drugs encapsulating (indomethacin)	65 nm–75 nm	16%		[33]
	Starch nanoparticle (SNP)	Drugs encapsulating (diclofenac sodium)	21.04 nm		95.01%	[34]
		Drugs encapsulating (5-Aminosalicylic acid (5-ASA))	40 nm–400 nm	0.275 g/g 0.302 g/g		
Nanolignin	Source of lignosulfonate	Nutrients encapsulating (curcumin)	4.9 nm			[36]
	Source of alkali lignin	Drugs encapsulating (adriamycin)	100 nm–500 nm			[37]
Nano-chitosan	Chitosan nanoparticles	Drugs encapsulating (adriamycin)	(213 ± 3) nm (292 ± 42) nm	0.43% (w/w) 1.4% (w/w)	(22.5 ± 1.2)%	[38] [39]
		Nutrients encapsulating (curcumin)	25 nm		93.6%	[40]
		Drugs encapsulating (ciprofloxacin)	260 nm	19%		[41]
Nanocollagen	Collagen nanoparticles	Drugs encapsulating (bovine serum albumin, cytochrome C)	0.2 µm–1.0 µm			[42]
		Nutrients encapsulating ( <i>cucurbitacin B</i> )	41.8 nm–107 nm	>5.8%	>89%	[43]
Nano-poly-lactic acid (PLA)	PLA nanoparticles	Nutrients encapsulating ( <i>aureusidin</i> )	231 nm–376 nm	60%	68%–98%	[44]
		Hypoglycemic drugs encapsulating (repaglinide)	(108.6 ± 3.4) nm~ (220.6 ± 1.2) nm		(81.4 ± 1.8)% ~ (92.7 ± 1.4)%	[44]
		Pesticides encapsulating (azoxystrobin)	130.9 nm, 353.4 nm, 3078.0 nm	15.7%, 17.1%, 18.5%	78.5%, 85.4%, 92.7%	[45]

## 2.1 Nanocellulose Materials

Cellulose is the most abundant natural biopolymer in nature. All plants and some tunicates, algae, and bacteria synthesize cellulose. Cellulose is obtained through selecting material with naturally high cellulose content or extracting pure cellulose from wood and woody plants. In industry, wood pulp and cotton linter are the main cellulose sources.

Biodegradation of cellulose can be complete biodegradation or destructive. For example, cellulose macromolecules are substrates for biological enzymes, and polysaccharide chains are hydrolyzed to produce xylose, glucose, cellobiose, and other simple sugars. The latter are mineralized to carbon dioxide and water [46].

Nanocellulose can be divided into three types based on preparation method, material, and structure: Nanocrystalline cellulose (NCC); bacterial nanocellulose (BNC); and microfibrillated cellulose (MFC). Nanocellulose is primarily prepared from plant materials through controllable chemical, physical, or biological methods. Further, some microorganisms and tunicates are useful sources for preparing nanocellulose. Microfibrillated cellulose (MFC) is mainly prepared by a combination of mechanical methods and enzymatic/chemical treatments, and acid hydrolysis is the main method for preparing nanocrystalline cellulose (NCC). Bacterial nanocellulose (BNC) is prepared by bacterial synthesis [47]. Compared with macro-scale cellulose, nanocellulose displays high specific surface area, high tensile strength, high Young's modulus, high hydrophilicity, and high crystallinity [48]. Nanoscale cellulose exhibits advantageous characteristics of both natural cellulose and nanomaterials. Such properties indicate a new degradable, functional, and sustainable nanomaterial.

## 2.2 Starch Nanomaterials

Starch is a natural polymer found widely in plant tissues. It is highly abundant in nature and has advantages such as low price, high biocompatibility, and biodegradability. However, starch displays poor mechanical properties and water resistance. Starch is produced from  $\alpha$ -D-glucose formed via photosynthesis and converted into the polymer in plant tissues by dehydration and condensation. Starch is a natural biodegradable polymer that is decomposed into glucose by microorganisms and finally metabolized into water and carbon dioxide. Degradation mechanisms of starch remain unclear. Aminabhavi et al. [49] and Maddever et al. [50] suggest that degradation of starch-based polymers occurs via two mechanisms: (1) Starch gradually disappears after being attacked by fungi, bacteria, and other microorganisms to form a hollow structure in the polymer that decreases its mechanical strength and increases its surface area; increased access to the polymer surface favors additional natural decomposition; (2) Starch degradation triggers the release of pro-oxidants and self-oxidants. Long polymer chains are cleaved, causing a decrease in molecular weight; it can then be attacked by microorganisms and eventually mineralized. These two processes are mutually reinforcing.

Application of nanotechnology to starch can improve thermal and mechanical properties of starch without affecting biodegradable and non-toxic properties. Nanostarch constructs include starch nanocrystals and starch nanoparticles [51]. Nanocrystals are typically prepared by acid hydrolysis using starch granules as starting materials. Several methods are used for preparing starch nanoparticles, including precipitation of amorphous starch, combining complex formation and enzymatic hydrolysis, microfluidization and chemical precipitation [51].

## 2.3 Lignin Nanomaterials

Lignin is a complex natural polymer produced by higher plants and is a central component of conifers, broad-leaved trees, and grasses. Lignin exhibits environmentally friendly and degradable characteristics. Lignin is primarily extracted from plants by ionic liquids, bases, organic solvents, or ozone [52]. Denatured lignin is divided into four categories, lignosulfonate, sulfate lignin, alkali lignin (KL) and hydrolyzed lignin, based on the production process. In nature, complete degradation of lignin depends on both fungi and bacteria, with fungi playing a major role [53].

Compared with general lignin, nanolignin is a more active adsorbent and surfactant. Further, nanolignin exhibits antibacterial and noncytotoxic properties. Nanolignin is usually classified by lignin processing, as indicated above. Several methods are used for preparing nanolignin, including adding water to a lignin solution as non-solvent and ultrasound-assisted mechanical treatments by high shear homogenization [54].

## 2.4 Chitosan Nanomaterials

Chitosan (CS) is formed by deacetylation of chitin after treatment with concentrated alkali. Chitosan is defined as chitin after  $\geq 55\%$  deacetylation. Chitin is produced by molluscs, crustaceans, insects, and fungi. It is a rare alkaline polysaccharide among natural polymers and is insoluble in water and organic solvents [55]. Chitosan has properties such as biodegradability, low toxicity, good biocompatibility, and mucosal adhesion. This latter property makes chitosan a new type of nanodrug carrier. Chitosan exhibits anti-acid, anti-ulcer, and wound healing properties.

The extraction of chitosan differs with the source. For example, Kumari et al. [56] obtained chitosan from the scales of the fish via treatment with acid and alkali. The chitosan was analyzed by Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), and scanning electron microscope (SEM). Habibi et al. [57] studied submerged fermentation with *Aspergillus terreus* with apple pomace extract as the sole carbon source to produce chitosan. The chitosan produced under optimal condition was characterized and analyzed by FTIR, thermogravimetric analysis (TGA), and differential scanning calorimetry (DSC), and the degree of deacetylation was 88.2%.

Chitosan is easily biodegradable by several microorganisms. Compared with chitosan, chitosan nanoparticles are non-toxic, have good biocompatibility, and are biodegradable. Chitosan NPs as carriers improve the stability of drugs and improve their bioavailability. Chitosan nanoparticles can be prepared by complex coacervation, solvent evaporation [58], covalent cross-linking [59], and ion gelation [60].

### **2.5 Collagen Nanomaterials**

Collagen is a white, opaque, unbranched fibrous protein. It is the basic structural component of the extracellular matrix and accounts for 30% of the body protein in humans. Collagen molecules are connected by hydrogen and covalent bonds and can self-assemble into stable fibers. This highly ordered structure imparts high mechanical strength, thus supporting organs and protecting body function [61–63]. Extraction and preparation of collagen from aquatic animals are accomplished by acid extraction, alkaline extraction, enzymatic extraction, and hot water extraction. The basic principle is to alter the external environment of the protein according to its characteristics and then separate collagen from other proteins [24].

Collagen is a family of proteins, divided into Type I (skin, tendon, and bone), type II (cartilage), and type III (skin and vasculature). All three types are essential to the structure and integrity of the fiber structure. The most common collagen is type I, which is widely used in various applications [64]. Collagen is biodegradable and biocompatible, can improve cell permeability and wound healing, and provide a template for cellular attachment, migration, and proliferation. These properties are the basis for its use as a biomedical matrix material [65–67].

Collagen is made up of several amino acids connected by peptide bonds and is initially degraded into short peptides by extracellular proteolytic enzymes produced and secreted by microorganisms. These peptides are further decomposed into amino acids under the action of peptidases. Nanocollagen is a biologically active nanoscale molecule comprising mixed oligopeptide. The biological activity and skin permeability of nanocollagen are superior to those of collagen. Nanocollagen is mainly produced as nanoparticles.

### **2.6 PLA Nanomaterials**

PLA, also known as polylactide, is a biodegradable polyester with good biocompatibility that also shows good processability and mechanical properties. The material is produced by polymerization of lactic acid. Starting material is obtained from fermented starch, such as corn and rice. It can also be obtained from waste materials, such as cellulose, kitchen garbage, or fish. Currently, PLA is obtained by direct polymerization and ring-opening polymerization of lactide [68]. Direct polymerization method employed melt, melt-solid phase, and solution methods. Ring-opening polymerization is achieved by anionic ring-opening, cationic ring-opening, and coordination opening polymerization. PLA can be decomposed by adding water, and degradation in the human body can be independent of enzymes. It can also be degraded by microbial enzymes in soil and seawater [69]. The intermediate product of degradation is lactic acid that can be mineralized. This polymer is one of a few biomedical materials approved by the US Food and Drug Administration (FDA) [70].

PLA nanomaterials mainly exist in the form of nanoparticles, i.e., PLA block copolymers are directly produced as nanosized particles. Commonly used preparation methods for PLA nanoparticles include solvent evaporation, solvent replacement, and salting out.

## **3 Nanocarriers for Drugs and Nutrients Prepared from Biodegradable Materials**

Drug Delivery Systems (DDS) emerged at the end of the 20<sup>th</sup> century. Such systems rely on the preparation of encapsulated drugs in a carrier that improves efficacy. Advantages of DDS include improved bioavailability and targeting, reduced toxic side-effects, and controlled drug release. The term “nanocarrier” generally refers to carriers with a particle size in the range of 1 nm–1000 nm. Commonly used nanocarriers include liposomes, nanoparticles, micelles, microemulsions, and solid lipid nanoparticles.

Liposomes are phospholipid double-layer enclosed structures with a hydrophilic core and lipophilic properties. The structures bind/encapsulate hydrophobic, hydrophilic, and amphiphilic drugs and nutrients. Hydrophilic substances are encapsulated in the aqueous core; lipophilic drugs and nutrients can disperse in the phospholipid bilayer. This DDS shows strong encapsulation ability. Liposomes can be made to alter the encapsulation efficiency of drugs and nutrients through adjustment of surface charge of phospholipid molecules. Sterically stable liposomes, cationic liposomes, and active targeting liposomes have been developed. Li et al. [71] synthesized thiol derivatized chitosan (CSSH) NPs and utilized them to embed curcumin liposomes. The encapsulation efficiency of CSSH-coated curcumin liposomes was 93.95%, the drug load was 7.95%, and the average particle size was 406.0 nm. Compared with curcumin liposomes, proper liposome coating can improve the stability. Han et al. [72] used d- $\alpha$ -tocopherol polyethylene glycol 1000 succinate (TPGS) as an inhibitor to prepare a surface-modified liposome (TPGS-PTX liposome) to load paclitaxel. The experimental results showed that the average particle size of the delivery system was  $282.6 \pm 20.41$  nm and affected sustained release and inhibition of P-glycoprotein. Hsieh et al. [73] indicated that liposome incorporating lecithin/cholesterol or stearic acid was effective in protecting entrapped  $\alpha$ -amylase from suffering acid (pH 2.8) and pepsin (15 mg/mL). Ghorbanzade et al. [74] used nano-liposomes to encapsulate fish oil and found that yogurt with nano-encapsulated fish oil contained a higher content of DHA and EPA. Essential oil can also be encapsulated in liposome nanoparticles. Khosravi-Darani et al. [75] successfully produced liposomal *Zataria multiflora* Boiss essential oil and found the antibacterial activity was maintained well.

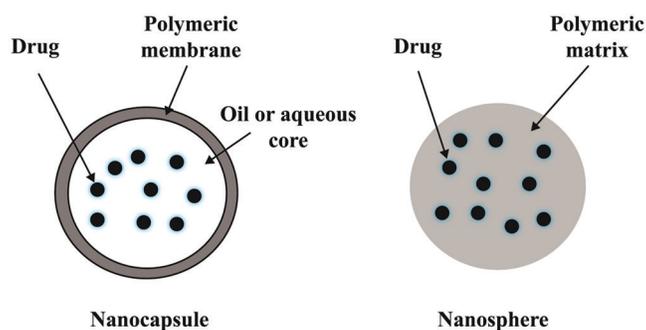
Nanoparticles are a class of solid polymer colloidal particles with a particle size of  $<1$   $\mu\text{m}$ . Drugs and nutrients can be dissolved, coated, or adsorbed on the surface or inside of the particles. Loaded NPs exhibit high carrying capacity and sustained drug release. NPs can be synthesized and modified using various materials for high structural flexibility; however, large amounts of organic solvents are used in the preparation of nanoparticles, and complete removal of these solvents to ensure safety is an ongoing issue.

Nanoparticles can be divided into nanocapsules and nanospheres based on preparation methods and means employed for encapsulating drugs and nutrients (Fig. 2). The characteristics of nanocapsules are membrane wall structure, and aqueous or oil core as a reservoir to accommodate bioactive substances. Differently, nanospheres exhibit a matrix system in which bioactive materials are dispersed in the particles. Simi et al. [33] cross-linked modified starch nanoparticles with sodium tripolyphosphate and used indomethacin as a model drug to observe the morphology of grafted starch nanoparticles and to examine loading and controlled release by scanning electron and atomic force microscopy. The authors used diclofenac sodium (DS) as a model drug to study medical applications of cross-linked starch nanoparticles for transdermal administration [34]. Starch nanoparticles can be used as a DS drug carrier and provide a promising nano-connected system for transdermal delivery of non-steroidal anti-inflammatory drugs. Janes et al. [38] prepared doxorubicin (DOX) chitosan nanoparticles for use in chemotherapy. *In vitro* controlled release was achieved, with stable release maintained for 5 days. Mitra et al. [39] connected low molecular weight dextran (DEX) with the DOX complex to reduce the adverse effects, such as cardiotoxicity and bone marrow suppression, and then produced chitosan nanoparticles. These DOX-loaded NPs showed a significant inhibitory effect on tumor growth. Sriram et al. [40] added naphthalene acetate (NAA) to the chitosan amine group to form a hydrophobic chitosan–NAA drug carrier. Calcium ferrite nanoparticles (CFNP) were embedded in a chitosan–NAA matrix to form a superparamagnetic hybrid nanocarrier for the controlled release of curcumin. Hybrid nanocarrier was successfully employed for targeted drug delivery to tumor cell. Vijayan et al. [76] used chitosan, PLA, and poly aluminum chloride to prepare high-quality biodegradable polymer nanoparticles loaded with repaglinide by solvent extraction. Prepared nanoparticles were spherical, with size ranging from approximately  $108.6 \pm 3.4$  nm to  $(220.6 \pm 1.2)$  nm. Encapsulation efficiency (EE%) was  $81.4\% \pm 1.8\%$  to  $92.7\% \pm 1.4\%$ . A transdermal patch containing repaglinide nanoparticles was 76 times more effective than conventional oral patches.

Besides, nanoparticles are suitable for encapsulating various nutrients. Yuan et al. [77] loaded lutein in zein nanoparticles coated with sophorolipid (ZSLNPs). ZSLNPs were spherical, with a particle size of about 200 nm, and the encapsulation efficiency and loading capacity were 90.04% and 0.82%, respectively. ZSLNPs showed great stability, redispersibility, and increased water solubility of lutein. Luo et al. [78] prepared zein nanoparticles coated with carboxymethyl chitosan (CMCS) to encapsulate vitamin D<sub>3</sub>. The nanoparticles with CMCS coating had a spherical structure with a particle size of 86 to 200 nm. The encapsulation efficiency after CMCS coating was greatly increased to 87.9%. This method was a promising method to enhance chemical stability and controlled release performance. Alishahi et al. [79] fabricated chitosan nanoparticles by adding vitamin C to the tripolyphosphate solution and gradually mixing it into the chitosan solution under stirring. The prepared nanoparticles had a spherical shape, a smooth surface, and maintain the immune-inducing properties of vitamin C. The controlled release of vitamin C was achieved.

PLA requires the use of higher-priced medicinal grade material. PLA currently used in pesticides formulations is prepared with industrial injection molding grade chemical [80]. Yao et al. [45] used an oil/water (O/W) emulsion solvent evaporation to prepare azoxystrobin-PLA microspheres (MS) and showed good dispersibility and spheroidization.

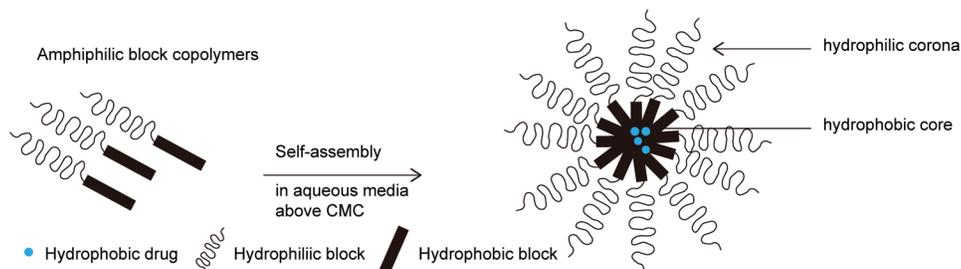
The method of oral delivery of active substances by polymer nanoparticles modified with collagen peptides (CPs) is attractive in Chinese medicine. Tang et al. [43] studied the use of ion-exchange resins to simply separate collagen cation CPs from bovine CPs and modified the surface of mixed nanomicelles (MMs) to improve the oral bioavailability of Cucurbitacin B (CuB). Successful modification of nanomicelles was confirmed. The inhibitory effect of CuB-MMs-CPs on tumors was significantly enhanced. Thus, nanomicelles, co-modified with isolated CPs, could be attractive as carriers for the oral delivery of CuB. Cao-Hoang et al. [81] used the water-in-oil solvent displacement method to encapsulate synthetic and natural  $\beta$ -Carotene into PLA nanoparticles, which offers better protection against oxidation.



**Figure 2:** Drug loading methods for nanocapsules (reservoir system) and nanospheres (matrix system) [82]

Micelles show particle sizes of >10 nm in a narrow size distribution. These structures self-assemble via microphase separation of amphiphilic block copolymers in selected solvents. The micelles with hydrophilic shells and hydrophobic cores can spontaneously form polymer micelles after dissolving in water (Fig. 3). Commonly used hydrophilic blocks include polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), poly (N-(2-hydroxypropyl) methacrylamide) (PHPMA), and poly (n-isopropyl acrylamide) (PNIPAM). Micelles are characterized by the solubilization of hydrophobic drugs, good stability, ease of modification, and significant drug loading capacity. Zhang et al. [83] prepared transferrin-modified paclitaxel-loaded polyphosphoester hybrid micelles (TPM). These micelles formed a core-shell structure with high encapsulation efficiency ( $89.9\% \pm 3.4\%$ ) in an aqueous medium. Chen et al. [84] attached paclitaxel to the C-6 position of the N-acetyl-D-glucosamine (GlcNAc) residue of hyaluronic acid (HA)

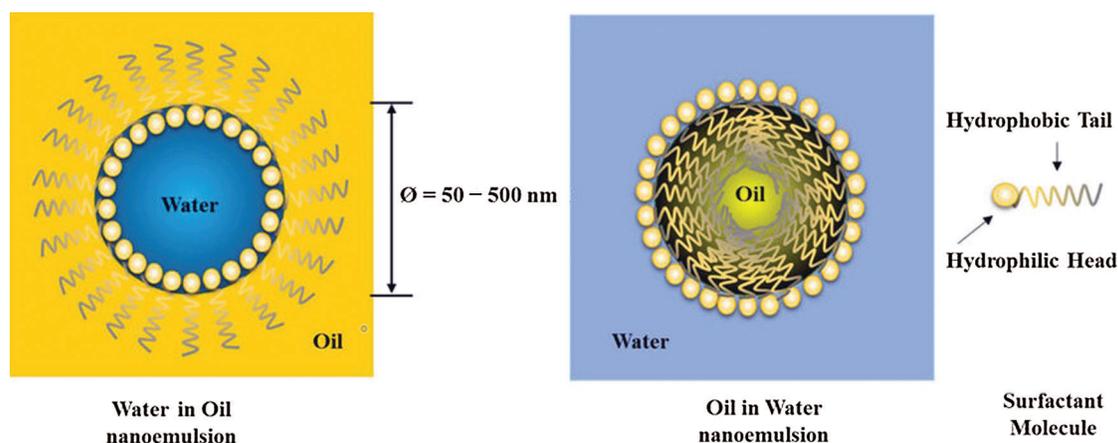
using hexamethylene diamine as a linker to produce a new type of drug conjugate, HA-6-PTX. With a drug loading capacity of 21.8%, increased drug release was observed. Harada et al. [85] used PEG polyglutamate block copolymers to encapsulate granulocyte colony-stimulating factor (G-CSF); G-CSF encapsulated in polymeric micelles of diameter 60 nm–70 nm displayed a longer half-life and enhanced efficacy. Tang et al. [86] enclosed paclitaxel (PTX) into a dual pH-sensitive micelle with an acid-cleavable anionic shell, a pH-sensitive core, and a PEG corona. Inhibition of tumor growth and lung metastasis with these particles was achieved, with values of 77.7% and 88.3%, respectively, without significant toxicity. Wang et al. [87] designed and prepared an amphiphilic carboxymethyl chitosan–quercetin (CQ) conjugate that increased water solubility of paclitaxel (PTX) to improve oral bioavailability. The critical micelle concentration of the CQ conjugate was low, and it was self-assembled into polymer micelles in an aqueous solution. Drug loading and encapsulation efficiency were  $33.62\% \pm 1.34\%$  and  $85.63\% \pm 1.26\%$ , respectively. The system was a good carrier for oral non-water-soluble anticancer drugs. Ghasemi et al. [88] fabricated natural casein micelle nanocapsule to encapsulate fish oil by means of pH changes and ultrasound. The encapsulation efficiency was 92%–97%. The technology proposed in this study can be used as an effective method for wrapping and transporting unsaturated fatty acids, oils and other hydrophobic compounds in milk, other foods, and medicines to improve the health of the general population. Levinson et al. [89] prepared VD<sub>3</sub> loaded re-assembled casein micelles to solubilize VD<sub>3</sub> in a fat-free food system and protect it from degradation throughout production, shelf life and digestion. The experimental results showed that VD<sub>3</sub> re-assembled casein micelles successfully delivered VD<sub>3</sub> and improved the rheology of yogurt without affecting the taste.



**Figure 3:** Drug-loaded polymeric micelles formed from self-assembly of amphiphilic block copolymers in aqueous media [90]

Nanoemulsions are transparent or semi-transparent dispersion systems with a particle size of 20 nm–200 nm. These emulsions are produced by mixing water phase, oil phase, surfactants, and co-surfactants in an appropriate ratio (Fig. 4). Emulsions display low viscosity and isotropic thermodynamic and dynamic stability. Nanoemulsions generally require the use of higher concentrations of surfactants, which may limit their application. For example, clinical applications may cause toxicity. Further, the high energy requirement for the preparation of nanoemulsions involves more expensive equipment, resulting in higher production costs. Severino et al. [91] compared minimum inhibitory concentrations of carvacrol, mandarin, bergamot, and lemon Eos nanoemulsions. Carvacrol nanoemulsion was selected for incorporation into modified chitosan to form a bioactive coating. This modified chitosan-based coating increased the radiosensitivity of *Escherichia coli* and *Salmonella typhimurium* by 1.32 times and 1.30 times, respectively, without modified atmosphere packaging. Lin et al. [92] prepared positively charged nanoemulsion particles with amoxicillin, chitosan, and heparin using water-in-oil emulsification. Nanoemulsion particles were spherical and displayed controlled release of amoxicillin for targeting *Helicobacter pylori* infection sites. Najlah et al. [93] used two nanoemulsion preparations (Clinoleic 20% and Intralipid 20%) as drug carriers for paclitaxel (PX) and characterized particle size, zeta potential,

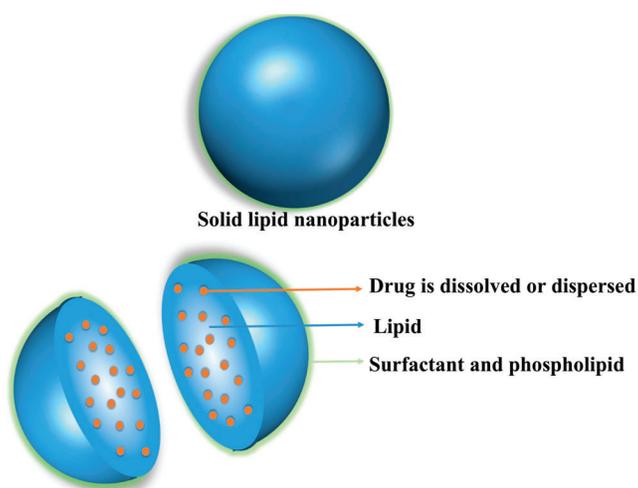
loading rate, and pH. Particle sizes were uniform and stable, and the pH range of the monoclinic oil was slightly higher than that of the lipid formulation. Chaiyana et al. [94] used essential oil from *Zingiber cassumunar* rhizome (EO)/Tween 20 and propylene glycol (2:1)/water system to develop an EO nanoemulsion. Internal droplet size displayed a range of  $211.5 \pm 63.3$  nm to  $366.7 \pm 77.8$  nm. The nanoemulsion significantly enhanced the anti-inflammatory effects of the EO without obvious toxicity in human peripheral blood mononuclear cells. As for nutrients, polyphenols, such as procyanidins, have many desired biological effects, their use in oral preparations is also limited by some structural features. Cerda-Opazo et al. [95] fabricated O/W nanoemulsion and used it to encapsulate avocado peel extract, which was a promising source of procyanidins. The resulting spherical nanoemulsion had a particle size of about 160 nm and had good stability. Costa et al. [96] developed lipid-based nanoemulsions collected from de microalga *Spirulina sp.* LEB18, and incorporated with biopeptides obtained from this same microalga. The antioxidant activity was evaluated. The average droplet diameter of nanoemulsions was at the range of  $222.9 \pm 3.4$  nm to  $466.9 \pm 5.3$  nm. Raikos et al. [97] used oil-in-water beverage emulsions for lycopene encapsulation, and the most favorable formulation containing a mixture of long-to short-chain triglyceride at a ratio 75:25.



**Figure 4:** Schematic diagram of water-in-oil (W/O) and oil-in-water (O/W) nanoemulsions composed of surfactant micelles [98]

Solid lipid nanoparticles were first reported in the 1990s as natural/synthetic lipids or lipids as carriers encapsulated or embedded in a lipid core. This nano-DDS shows a particle size of 50 nm–1000 nm (Fig. 5). Solid lipid nanoparticles improve bioavailability, reduce toxicity, and increase drug stability. However, their biggest advantages are that organic solvents are not required and they can be produced on a large scale [99]. This nanocarrier is suitable for delivering fat-soluble drugs and nutrients and has a high encapsulation rate; however, hydrophilic drugs and nutrients are generally not suitable. Further, this DDS is susceptible to drug leakage and increased particle size during storage. Wang et al. [100] prepared tilmicosin-loaded hydrogenated castor oil solid lipid nanoparticles (SLNs) using hot homogenization and ultrasound to enhance the antibacterial activity of SLNs. Particle size was  $343 \pm 26$  nm, and encapsulation efficiency was  $60.4\% \pm 3.3\%$ . Shi et al. [101] used soybean lecithin as a solid lipid to prepare an aqueous dispersion of SLNs encapsulating frankincense and myrrh essential oils using high-pressure homogenization. SLNs exhibited a core with a lower ordered structure. The particle size was  $113.3 \pm 3.6$  nm, and the drug encapsulation efficiency was  $80.60\% \pm 1.11\%$ . Shtay et al. [102] used cocoa butter as a lipid core and sodium stearyl-2-lactate (SSL) and mono- and diglycerides of fatty acids (MDG) as emulsifiers and surfactants to prepare SLN. Particle characteristics, stability in suspension, and effects of

different cooling conditions on the performance and stability of SLNs during storage were reported. Cocoa butter SLN showed a particle size of 112.7 nm, which is suitable for a food-grade SLN. Yang et al. [103] prepared fish oil-loaded hollow solid lipid micro- and nanoparticles according to atomization of the CO<sub>2</sub>-expanded lipid mixture. The received particles were spherical and free-flowing. Fish oil loading efficiency was accomplished at 92.3% (w/w). Through this method, the bioavailability of EPA and DHA was significantly increased from 9.7% to 18.2%. Shtay et al. [104] prepared Epigallocatechin-3-gallate-loaded solid lipid nanoparticles (EGCG-SLN) made of a mixture of cocoa butter and food-grade surfactants by a hot homogenization method. This system can introduce EGCG into food. The average particle size of EGCG nanoparticles was 108 nm–122 nm and the maximum packaging rate was 68.5%. Zardini et al. [105] loaded lycopene on nanostructured lipid carriers and solid lipid nanoparticles by high shear homogenization and ultrasonic treatment. The particle size of the developed nanocarriers was between 74.93 nm and 183.40 nm.



**Figure 5:** Drug loading methods for SLNs [106]

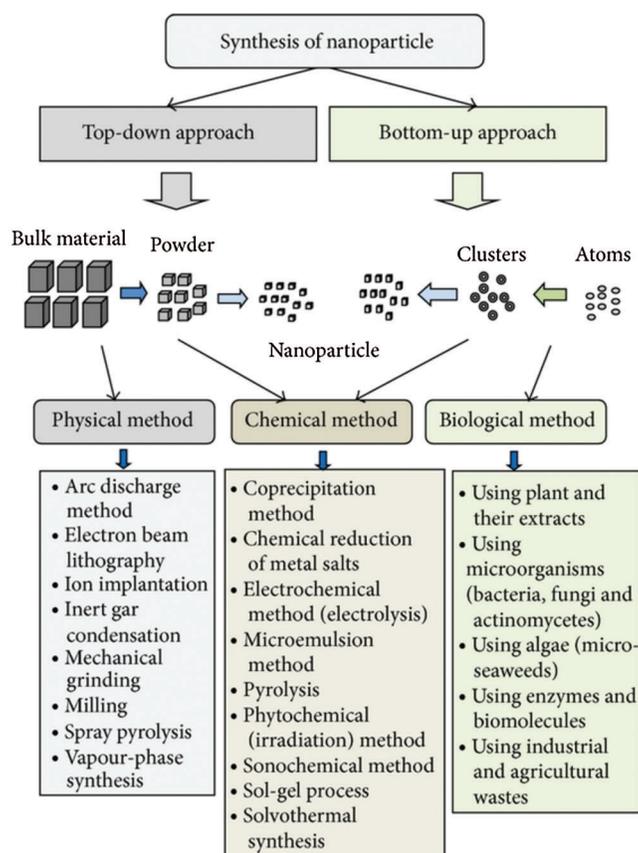
## 4 Development Trends of the Use of Biodegradable Nanomaterials as Drug and Nutrient Carriers

### 4.1 Green Preparation Technology

Public demand is increasing for environmental protection and sustainable development. Researchers now consider both development of biodegradable nanomaterials and environmentally friendly methods for the preparation of these materials. Green preparation of nanomaterials focuses on renewable solvents, pollution-free reducing agents, and non-toxic protective agents to avoid adverse environmental impacts.

Traditional nanomaterial preparation methods use either top-down or bottom-up methods (Fig. 6). Top-down methods transform materials into nanoparticles through external mechanical forces. Bottom-up refers to the formation of nuclei through chemical changes with gradual generation of nanomaterials, and it is preferred to produce nanoparticles [107,108]. Green preparation methods mainly involve plant and microbial synthesis. Plant preparation refers to the use of plants as reducing agents for the synthesis of nanomaterials or plant extracts, such as proteins, amino acids, phenols, saponins, terpenes, and vitamins, to be used as reducing and capping agents for synthesis. Microbial synthesis [109] refers to the use of microalgae, bacteria, and other microorganisms to adsorb and reduce metal ions *in situ* to obtain nanoparticles. Roychoudhury et al. [110] used *Lyngbya majuscula* as a biological agent for the synthesis of NPs. These cyanobacteria were first mixed with gold and silver ions in solution, and a bimetallic gold-silver nano-alloy was formed under appropriate conditions. This method is similar to plant synthesis

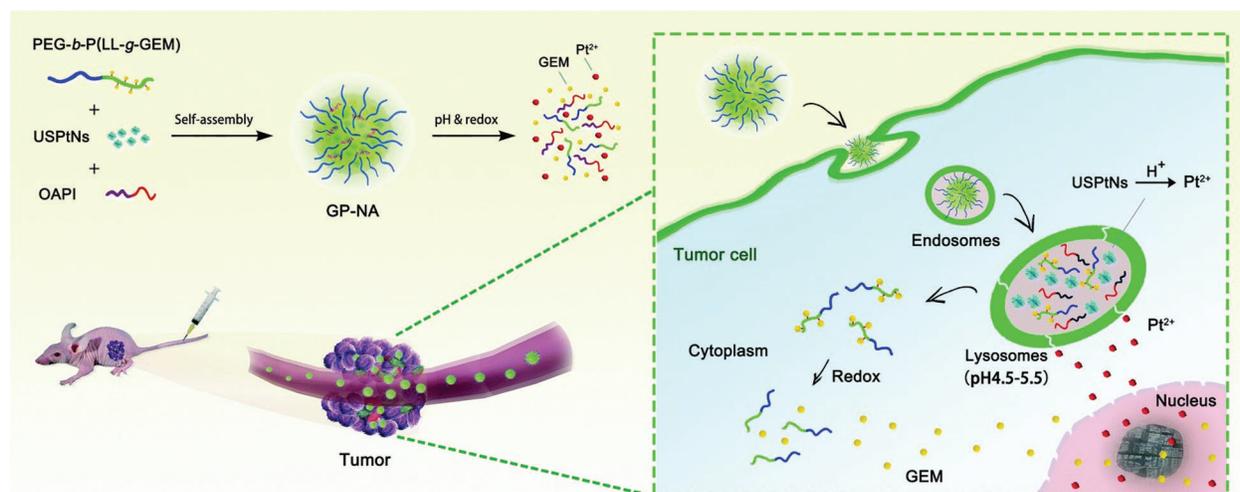
method and directly uses extracts of microorganisms, such as polysaccharides, proteins, polyphenols, etc., as reducing agents and stabilizers for the synthesis of nanoparticles. For example, Netala et al. [111] used a water extract of endophytic fungi to reduce  $\text{AgNO}_3$  and obtain spherical silver nanoparticles with a particle size of 3 nm–40 nm. In addition, environmentally friendly and sustainable processing technology is also the focus of research. Water and supercritical carbon dioxide are seen as interesting alternatives to traditional organic solvents. As for conventional heating, hydrothermal approaches, microwave energy and focused sunlight are popular green strategies.



**Figure 6:** Preparation methods of nanomaterials [107]

#### 4.2 Environmentally Responsive Nanomaterials

Environmentally responsive materials release active ingredients in response to changes in environmental stimuli, such as enzymes, pH, redox, and ionic strength. Such materials are of great interest in medicine, food processing, and environmental engineering [112–116]. Application of environmentally responsive materials in medicine focuses on the development of tumor microenvironmental stimulus-responsive nanodrug delivery systems and is a core technology for tumor-targeted therapy [117–119]. Reported tumor microenvironmental stimulus–response signals include low pH, tumor tissue, endosomes and lysosomes; lysosomal enzymes; tumor extracellular matrix metalloproteinases; reactive oxygen species generated by mitochondria; and reduced glutathione (GSH) in tumor cells. These stimuli allow targeting of drug release from nanoparticles to kill cancer cells (Fig. 7) [120].



**Figure 7:** Tumor microenvironmental stimuli in response to biological signals [120]

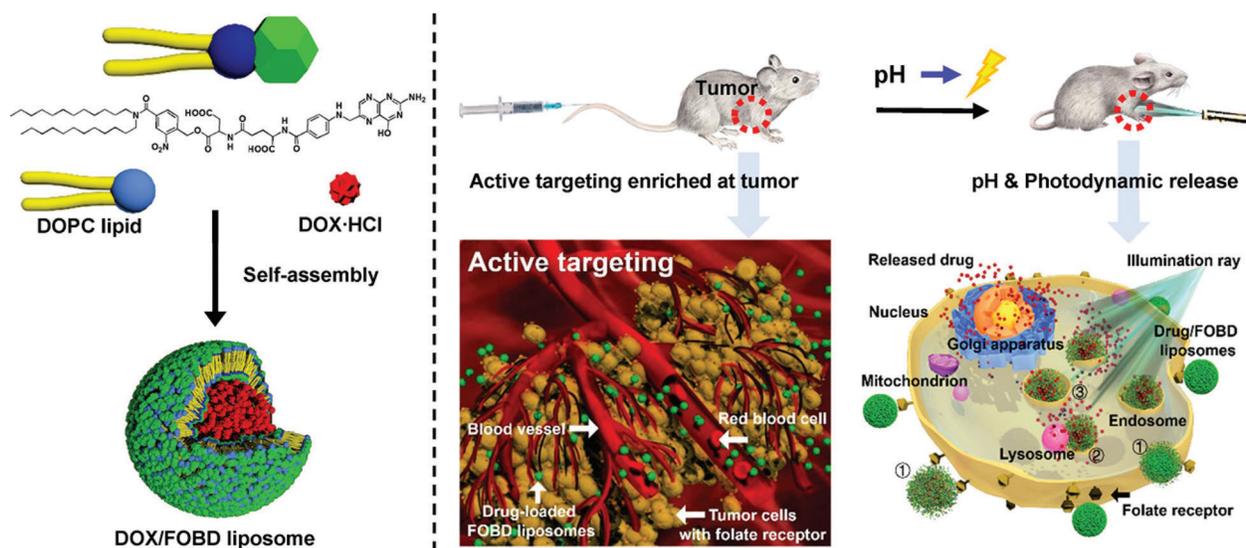
Five categories of stimuli are recognized: Enzyme-responsive, pH-responsive, redox-responsive, light-responsive, and temperature-responsive. For example, Wang et al. [121] developed a hydrogen peroxide ( $\text{H}_2\text{O}_2$ )-triggered nanomaterial (LV-TAX/Au@Ag) for combined chemo-photothermal therapy. When LV-TAX/Au@Ag reaches the tumor, endogenous  $\text{H}_2\text{O}_2$  in the tumor microenvironment triggers combination therapy by etching silver on the surface of AuNRs. It was observed that these NPs caused extensive necrosis and apoptosis in tumor tissues and greatly inhibited the proliferation of solid tumor cells. Xu et al. [122] developed an original strategy for simultaneous pesticide encapsulation based on emulsion and surface modification of mesoporous silica nanoparticles with carboxymethyl chitosan. pH-responsive release was controlled by carboxymethyl chitosan, and a satisfactory loading (21%) was achieved. Yu et al. [123] first synthesized poly(lactic acid)-graft-acetaldehyde/PEG (PLA-g-ALD/PEG) through a chemical reaction and then synthesized a polymer-drug conjugate nanodrug delivery system. The nano-DDS has remarkable pH sensitivity.

### 4.3 Nanomaterial Targeting

Use of nanotechnology to target tumor stem cells is currently an active field of research that seeks controlled release from nanoparticles for targeted cancer treatment (Fig. 8) [124]. Targeted DDS are generally divided into passive and active targeting, and more finely categorized into passive [125], physical [126], active [127], and bionic targeting [128] based on the underlying targeting principle (Fig. 9) [129]. Passive targeting is based on the physiological and pathological characteristics of the treatment site and intrinsic properties of the nanodrug delivery system to achieve accumulation of the DDS at the treatment site. Passive targeting does not actively identify specific sites. Current passive targeted drug delivery strategies include EPR effect [130], intelligent regulation of particle size to decrease or increase aggregation [131,132], intelligent adjustment of surface properties [133], reduction of interstitial tumor pressure [134], and drug release in response to reaching the target site [135]. Li et al. [136] modified PLGA with PEG to prepare two types of biodegradable nanoparticles loaded with salinomycin and docetaxel for sustained release of drugs. Tumor suppression is enhanced compared with single and dual drugs.

Active targeting is the combination of specific molecules, such as proteins, peptides, nucleic acids, antibodies, and small molecules, on the surface of the nanodrug delivery system that interact at the target site to increase effects in target tissues. Currently, active targeted drug delivery strategies involve [130] targeting tumor cells, tumor stem cells, tumor neovascularization, tumor-associated macrophages, other

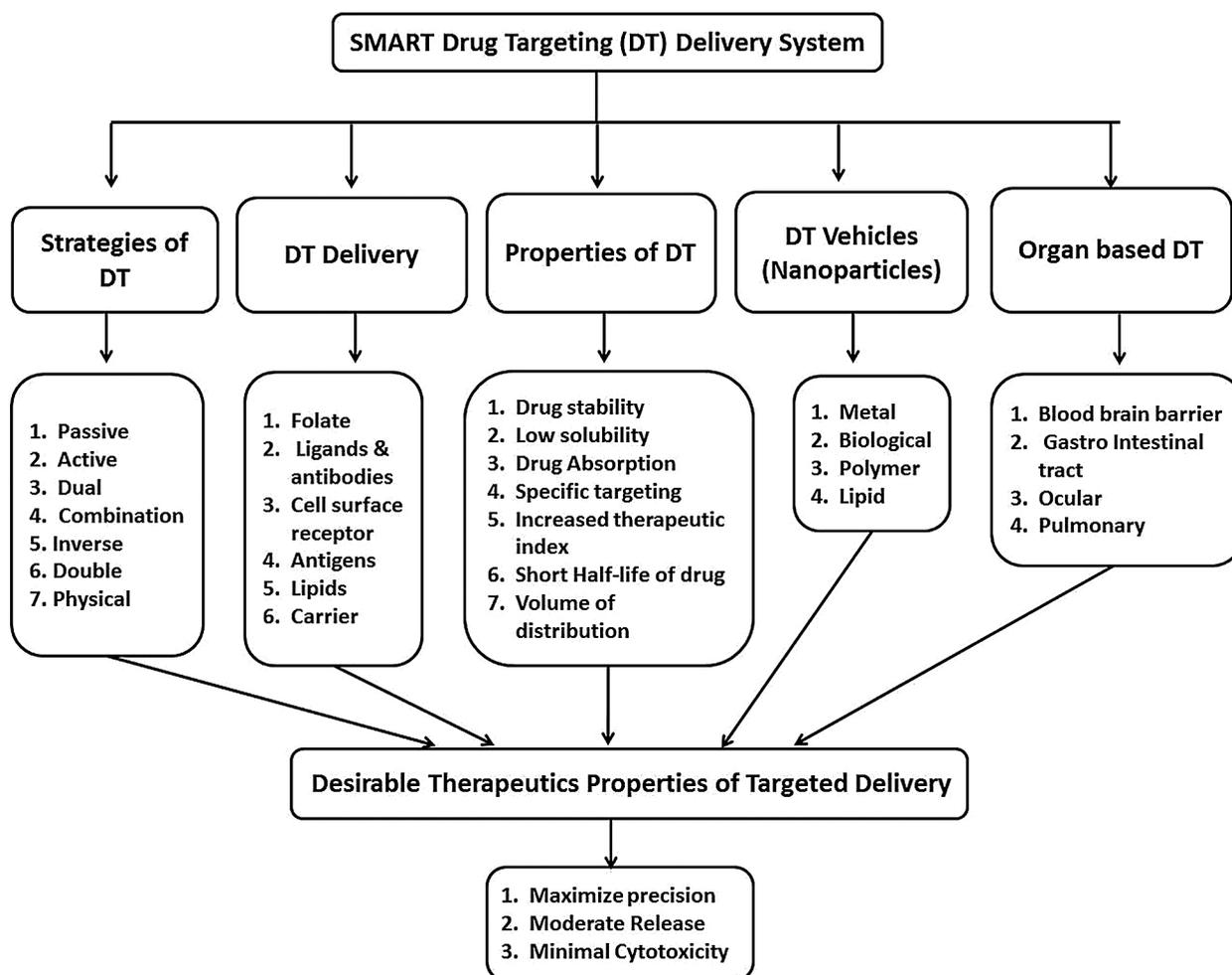
stromal cells, and various other cells. Yang et al. [137] prepared PLGA biodegradable nanoparticles loaded with curcumin and paclitaxel and included modified HA on the surface of the nanoparticles to interact with CD44 receptor on the surface of breast cancer stem cells to stimulate release specifically in breast cancer stem cells and breast cancer cells.



**Figure 8:** Controlled release nanoparticles for the targeted treatment of cancer [124]

## 5 Problems and Prospects

Nature provides abundant materials to meet various needs. The use of natural polymers as described above to synthesize degradable nanomaterials from natural resources and novel nanocomposite materials are widely studied in various research fields. Such research has important practical significance in the context of establishing an environment-friendly society. Development of biodegradable nanomaterials is challenging in terms of scaling production from patents to markets [138]. Challenges come from several aspects. The mechanical properties of degradable materials are still insufficient, and chemical modification is usually required. The application scenarios of biodegradable materials are limited. The current main applications in the biomedical and food fields are drug delivery and food packaging materials/storage containers. In biomedicine, through the chemical modification of polymers, degradable materials are expected to be used in bio-imaging, targeted drug delivery, implantation and tissue engineering. *In vitro* research and clinical trials are also areas that need to be expanded. In terms of food, degradable materials are expected to be used in new foods, food and feed additives, biocides, pesticides, and food contact materials. The production cost is related to the manufacturing process. The most widely studied silicon nanostructures used in biomedical applications are porous silicon particles and nanosilicon quantum dots, which usually require a multi-step preparation process and lack a convenient preparation process. Black phosphorus, which has recently attracted attention, can be prepared by liquid phase exfoliation to prepare several layers of black phosphorus, which is relatively simple and low in cost and is very advantageous for the production of layers and the biological applications of several layers of two-dimensional black phosphorus nanoparticles [139]. Thus, exploring new nanomaterials is a feasible solution strategy. It is important to show sufficient cost savings to make up for the large amount of early cost investment.



**Figure 9:** Schematic representation of smart drug targeted strategies [129]

Further, with the development of nanomaterials, human beings are increasingly exposed to nano-level exogenous objects. Even biodegradable nanomaterials need to be evaluated for their safety. Development of packaging materials is one the main applications of nanotechnology in food industry. However, nanoparticles may migrate to food through the mass transfer process, thereby affecting human health. Further research is needed to clarify the migration mechanism. In addition to paying attention to the impact of nanomaterials on human health, it is also necessary to evaluate its impact on ecology. Nano packaging materials or products added with nanoparticles may undergo various modifications such as photochemical conversion, oxidation, reduction, and biodegradation after microbial metabolism. Therefore, attention should be paid to their potential accumulation in the environment. The antibacterial activity of various nanoparticles has been confirmed, but the effect of the antimicrobial effect after treatment on the microbial community in soil and water is still unclear. This requires us to conduct ecotoxicity testing and find more powerful analysis techniques [140]. Lack of standards for nanomaterials introduces the issues of quality control and supervision. These problems place high demands on researchers to move innovations with these materials from the laboratory to general use for the benefit of society. Identification and development of non-toxic, sustainable, and environment-friendly biodegradable nanomaterials will continue to attract substantial interest in the field of polymer materials.

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