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Designing Polymeric Nanoparticles for Targeted Drug Delivery System

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Outline:

Introduction

New opportunities to prevent and to treat diseases are by emerging the understanding of disease pathways. The intrinsic limitations of therapeutic biomacromolecules, such as proteins and nucleic acids, can be avoid through rationally-designed delivery vehicles. Drug delivery is becoming an increasingly important aspect for medicine field, as more potent and specific drugs are being developed. No longer depending on small-molecule drugs, this field now not only encompasses prolonging the duration of drug release but also focusing on customized systems that are designed to achieve specific spatial and temporal control. With the incorporation of nanotechnology, so-called smart drug-delivery systems integrate biosensing functionalities which support unaided *in vivo* feedback control that resulting in part characteristics of the new term Nanomedicine.

Many biomaterials, primarily polymer- or lipid-based, can be used to this end, offering extensive chemical diversity and the potential for further modification using nanoparticles. The particularly large surface area on the nanoparticles presents diverse opportunities to place functional groups on the surface. Particles can be created by expanding or contracting with changes in temperature or pH, or interact with anti-bodies in special ways to provide rapid ex-vivo medical diagnostic tests.

More practical design extensions have been made in combining inorganic materials with polymers and in combining different classes of polymers together in nanoparticle form. A whole host of new types of polymer particles could be designed into reality with the recent advances in chemistry, processing techniques, and analytical instrumentation. For example now we have particles that are hollow, multi-lobed, conductive, thermo responsive, magnetic, functionalized with reactive groups on the surface, and pH responsive. This could be applied into floating carrier, multiparticulate drug delivery, dual core or multiple layering drugs and more.

Polymeric nanoparticles have been produced for decades for use in a variety of high performance materials such as high impact resistant polymers and specialty coatings for these purposes. Advanced analytical techniques and computer simulations of the events occurring during particle formation allow us to measure structure and develop control strategies to produce structured particles. Our ability to develop new control process strategies such as modified the of carrier shape, chemical composition, internal structure, and morphology of the nanoparticles so as to develop new levels of product performance in the targeted drug delivery system.

Background of study

By year 2050, human population will reach 9,100 million which is about 34% increase in population from present situation. By increasing in this population, it proportionally increases in global demand for foods, feed and energy. Despite on the expected demand on food (and water), several technology should be applied to make a rational use of resources possible. Considering to this situation, nanotechnology could suppose a great tool in solving that demand [1]. Exploration of nanotechnology has brought significantly innovations to the pharmacology fields for over past 30 years [2]. Engineered nanomaterials (ENMs), one of nanotechnology application already became part of human daily life as food packaging agents, drug delivery systems, therapeutics, biosensors, and many more. By European Parliament and Council [3] definition, ‘nanomaterial’ (NM) is any material that is characterized in one

dimension ≤ 100 nm, or comprises of separate functional parts either internal or on the surface, which have one or more dimensions ≤ 100 nm, which include structures, in example, agglomerates or aggregates, which may be larger than 100 nm, but will retain the typical properties of nanoscale [4]. FAO/WHO report [5] that the ENMs have several applications in the agrofood sector include nanostructured food ingredients, nanodelivery systems, organic and inorganic nanosized additives, nanocoatings on food contact surfaces, surface functionnalized NMs, nanofiltration, nanosized agrochemicals, nanosensors, water decontamination, etc. However, in this chapter, authors will highlight on nanodelivery system from history up to its application.

By definition, drug delivery systems are supramolecular assemblies incorporating agents intended to treat a disease. They are used to overcome the shortcomings of the conventional drugs, such as unfavorable pharmacokinetics, poor solubility, instability, high toxicity, drug resistance and low cellular uptake. Drug targeting is defined as selective drug delivery to specific physiological sites, organs, tissues, or cells where a drug's pharmacological activities are required. In fact, a drug distributes uniformly in the whole body when it is entered the blood stream, and the drug that is distributed at sites other than the therapeutic sites may cause toxic side effects. By increasing delivery to the therapeutic sites and reducing delivery to the unwanted sites, an improved therapeutic index can be obtained with enhanced and reduced drug action at the therapeutic and the unwanted sites, respectively [6]. The proposed mechanism of drug delivery or drug carriers is represented in figure 11.1 below;

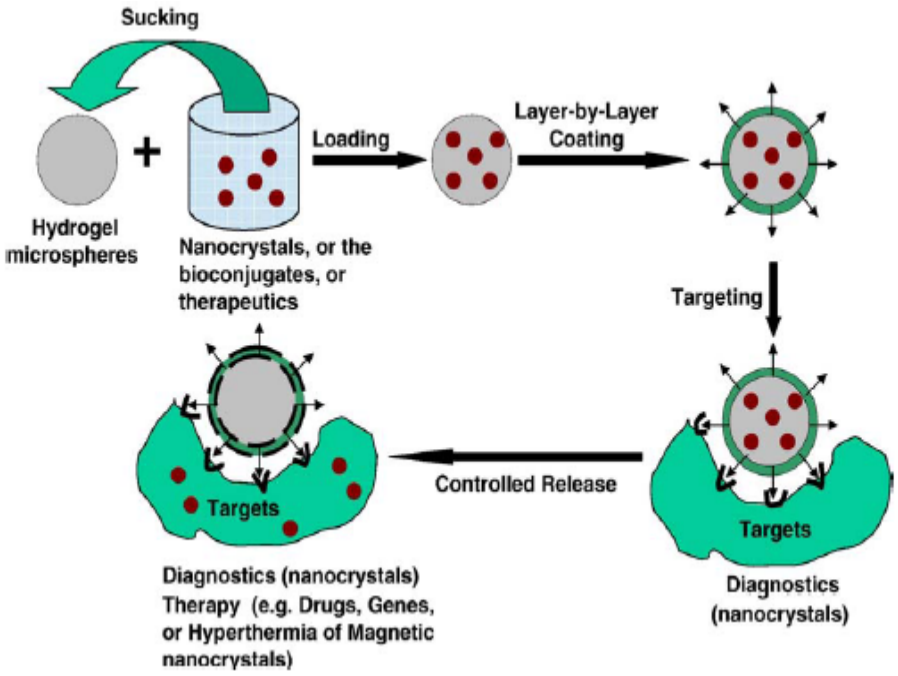

FIGURE 11.1
Drug carriers, drug conjugates and drug-nanosystems can be engineered to control degradation, react to stimuli and be site-specific [7]

There are two general methods for drug targeting; active and passive targeting. Active targeting refers to increasing in the delivery of drugs to a specific target through the use of specific interactions at target sites where a drug's pharmacological activities are applied. These interactions for example include antigen–antibody and ligand–receptor binding. Alternatively, physical signals such as magnetic fields and temperatures that are externally applied to the target sites may be utilized for active targeting respectively. Carriers classified into this methodology include antibodies, transferrin, ferrite containing liposomes, and thermoresponsive carriers.

On the other hand, passive targeting is defined as a method in which the physical and chemical properties of carrier systems increase the target/nontarget ratio of the quantity of drug delivered by adjusting these properties to the physiological and the histological characteristics of the target and nontarget tissues, organs, and cells. Carriers included in this category are synthetic polymers, some natural polymers such as albumin, liposomes, micro (or nano) particles, and polymeric micelles. This is because of the challenges with use of large size materials in drug delivery, some of which include poor bioavailability, in vivo stability, solubility, intestinal absorption, sustained and targeted delivery to site of action, therapeutic effectiveness, generalized side effects, and plasma fluctuations of drugs. Of recent, several researches in nanodrug delivery have been designed to overcome these challenges through the development and fabrication of nanostructures.

It has been reported that, nanostructures have the ability to protect drugs from the degradation in the gastrointestinal tract (GIT), the technology can allow target delivery of drugs to various areas of the body. The technology enables the delivery of drugs that are poorly water soluble and can provide means of bypassing the liver, thereby preventing the first pass metabolism. Nanotechnology increases oral bioavailability of drugs due to their specialized uptake mechanisms such as absorptive endocytosis and are able to remain in the blood circulation for a long time, releasing the incorporated drug in a controlled fashion, leading to less plasma fluctuations and minimized side-effects.

Nanoscale size nanostructures are able to penetrate tissues and are easily taken up by cells, allowing for efficient delivery of drugs to target sites of action. Uptake of nanostructures has been reported to be 15–250 times greater than that of microparticles in the 1–10 μm range. Nanotechnology improves performance and acceptability of dosage forms by increasing their effectiveness, safety, patient adherence, as well as ultimately reducing health care costs. It may also enhance the performance of drugs that are unable to pass clinical trial phases. Nanotechnology definitely promises to serve as drug delivery carrier of choice for the more challenging conventional drugs used for the treatment and management of chronic diseases such as cancer, asthma, hypertension, HIV and diabetes [7].

Nanostructured-based drug delivery system

Nanostructured- based drug delivery system is one of the rapidly emerging areas currently that has gained many researchers attention due to the suitable means of both side specific and time controlled drug delivery. Currently nanostructured- based drug delivery system produce many commercially available products that is patient compliance and no side effect. Nanostructured- based drug delivery system offer many advantages, some of which include; (1) they can pass through the smallest and narrow capillary vessels due to their ultra-tiny volume; (2) they can penetrate cells and tissue gap to arrive at target organs such as liver, spleen, lungs, spinal cord and lymph; (3) they can provide

controlled- release for prolong period. These unique properties makes nanostructured- based drug delivery system better choice to delivery drug compare to convectional drug delivery system.

Recently combination of polymeric system with nanostructured- based drug delivery system provides sustained drug release. Among different type of polymeric system, hydrogel consider as a suitable drug carrier for controlled drug release. Hydrogel is cross linked with a three dimensional network that able to absorb large amount of water due to the presence of hydrophilic group in the network such as carboxylic, amidic and others. Hydrogel can significantly use in drug delivery system. Hydrogel can be a suitable carrier for drug delivery system due drug release from its matrix upon swelling, the interaction of the drug with the polymers, and the solubility of the drug in the release media. Hydrogel have capability to protect drugs from hostile environment such as presence of enzymes and extreme pH in the internal organs like stomach. Besides that, hydrogels physical properties make them as good candidates for drug carrier. For example, hydrogels porosity enable drug loading into gel network and consequently drug release at desired site. Hydrogel has capable of exhibiting significant volume changes in response to small changes in pH, temperature and other environmental stimuli.

Types of nanodelivery: natural or synthetic

Two types of polymers can be used in nanodelivery which is natural and synthetic. Natural polymers or biopolymers may be naturally occurring materials which is formed in nature during the life cycles of green plants, animals, bacteria and fungi are polymers or polymer matrix composites. Collagen while synthetic polymers from the ester family. Table 11.1 shows example of natural and synthetic polymers and Table 11.2 shows adavantages and disadvantages of natural and synthetic polymers

TABLE 11.1
Example of Natural and Synthetic Polymers

Natural	**Synthetic**
cellulose, starch, chitosan, carrageenan, aliginates, xantham gum, gellan gum, pectins	poly(lactic acid) (PLA), poly(cyanoacrylates) (PACA), poly(acrylic acid), poly(anhydrides), poly(amides), poly (ortho esters), poly(ethylene glycol), and poly(vinyl alcohol) (PVA) and other like poly(isobutylcynoacrylate) (PIBCA), poly(ethylene oxide) (PEO), poly(å-caprolac- tone) (PCL)

TABLE 11.2
Adavantages and Disadvantages of Natural and Synthetic Polymers

Natural polymers		**Synthetic polymers**
• Less toxic • Biocompatibility • Biodegradable • Easily available	**Advantages**	• Biocompatibility
• High degree of variability in natural materials derived from animal sources • Structurally more complex • Extraction process very complicated and high cost	**Disadvantages**	• Toxic • Non degrable • Synthetic process is very complicated and high cost

Starch

Starch is one example of natural polymers in nanodelivery. Starch is a polysaccharide. It occurs majorly in plants where they act as storage materials. Chemically, it is composed of recurring units of glycopyranose in an alpha D-(1, 4) linkage and on hydrolysis yields the monosaccharide, glucose. The use of starch in pharmaceutics is broad. It is used as co-polymer and excipient in controlled drug delivery as drug carriers, in tissue engineering scaffolds as hydrogels and as solubility enhancers.

Santander-Ortega *et al.*[8] investigated the potential of starch nanoparticles as a transdermal drug delivery system (TDDS). The challenge faced in delivering drug through these systems is that the skin acts as an effective barrier to drug passage and must therefore be overcome for effective drug delivery. Nanoparticles were shown to facilitate drug delivery without interference to the skin's integrity. The method used to prepare the nanoparticles was emulsification-diffusion due to its reproducibility, higher yields, ease of scale-up and control over size of particles and degree of polydispersity. Maize starch modified and un-modified (by the addition of propyl groups) was used as polymeric material to formulate 2 different types of nano-particles. The modified starch nano-particles were shown to be non-toxic using LDH (Lactose dehydrogenase) and MTT assay and resulted in particles of uniform size distribution while the nano- particles formulated from the native starch was not observable. Flufenamic acid, caffeine and testosterone were used as model drugs and their delivery across the skin was analyzed using excised skin from female Caucasian patients who had undergone abdominal plastic surgery. Permeation data obtained for caffeine and testosterone were similar for nano-encapsulated and free drugs while the delivery of flufenamic acid using the nanoparticles was enhanced by about ten-fold.

Chitosan

Chitosan is another example of natural polymer. This polymer is obtained from the partial N-deacetylation of chitin found in the shells of crustacean. It is composed of glucosamine and N-acetyl glucosamine linked by β 1-4 glucosidic bonds and is one of the most widely studied natural polymers for nano-drug delivery. The deacetylation of chitin is both concentration and temperature dependent with optimal yields achieved at temperatures between 600C- 800C using 50%w/w alkali. Nano-particles fabricated with chitosan as co-polymer was used to investigate the controlled release of anti-retroviral drug, lamivudine.

The nano-particles were prepared by emulsion and solvent evaporation technique and characterised using dynamic light scattering. The use of this method resulted in monodispersed particles with asize range of 300-350nm. Two formulations with differences in percentage drug weight (3% and 6%) were made, of which drug release rate was higher from the nano-particles with higher drug loading, though both were able to control drug release fairly well. Drug release kinetics showed that the mechanism of drug release was by diffusion. Conclusions reached suggested that the nano-particles could be applied for gastrointestinal drug delivery because drug release was relatively slower at neutral pH compared to acidic pH and also slower in the acidic pH compare to the alkaline pH.

Carrageenan

Kappa carrageenan is also a natural polymers that widely used in biomedical application currently. K-carrageenan is a sulfated and linear polysaccharide with a repeating d-galactose and 3, 6-anhydro-d-galactose units and is classically used as an agent for several potential pharmaceutical applications such as gelling agent in the food and pharmaceutical industries and controlled drug release. Hezaveh investigated the incorparation of metal nanoparticels such as Ag, MgO and M into kappa carrageenan hydrogel matrix to sustain drug release and avoid burst release [9].

Hybrid approach

An inorganic-organic composite usually comprises an inorganic phase and a film forming organic phase. A typical green approach to developing an inorganic-organic composite involves the selection of film forming organic phase from starches having a degree of polymerization; degree of substitution and viscosity such that the substituted starches are insoluble in water during mixing but dissolve at a higher processing temperature during forming, setting or drying of the composite. Thus, excessive migration of the starch is prevented and the composite is substantially strengthened. There has also been reports on the lab-on-a-chip approach [13-18], which embodies micron- or nano-sized machines composed of sophisticated circuits. Small devices have many advantages including portability/disposability, low cost, high reproducibility, high-throughput screening, and multiple functionalities in a single device.

Recently, combined with other technologies such as optics, single molecular imaging, or cell/protein-based assay systems, biomedical lab on a chip devices have become an important part of drug discovery and diagnosis, but its application in drug delivery systems based on are just beginning to appear. As rightly noted by several authors, to release a drug from a nanodevice is more complicated than to perform assay or screening drug candidates, this is because, successful drug delivery requires at least four components namely; drug reservoir, pump, valve, and sensor. Drugs can be placed either in a fabricated reservoir or in conventional micro- /nanoparticles. Other important organic/inorganic

composites are metal nanoparticles, such as silver, iron oxide, or gold nanoparticles, coated with hydrophilic polymers. Their major application has been as theranostics. Only recently, Hirsch *et al;* developed gold nanoshell, which provided tunable emission light for bioimaging. Importantly, is the fact that, gold nanoparticles can be detected by X-ray and emit thermal energy by excitation making it very useful for medical imaging and thermal therapy (theranostics).

In a related report, Corot *et al;* developed super paramagnetic iron oxide nanoparticles for magnetic resonance imaging (MRI) of the whole body. Mechanistically, these nanoparticles are primarily engulfed by monocyte or macrophage after intravenous administration. However, uptake of super paramagnetic iron oxide by macrophage does not induce activation of nearby cells making it suitable for diagnosis of inflammatory or degenerative diseases. Tao and Desai, 2005 had develop microfabrication as controlled delivery devices. This device provide the capacity to target cells, promote unidirectional controlled release, and enhance permeation across the intestinal epithelial barrier. [19-21].

Factors affecting nanodelivery system

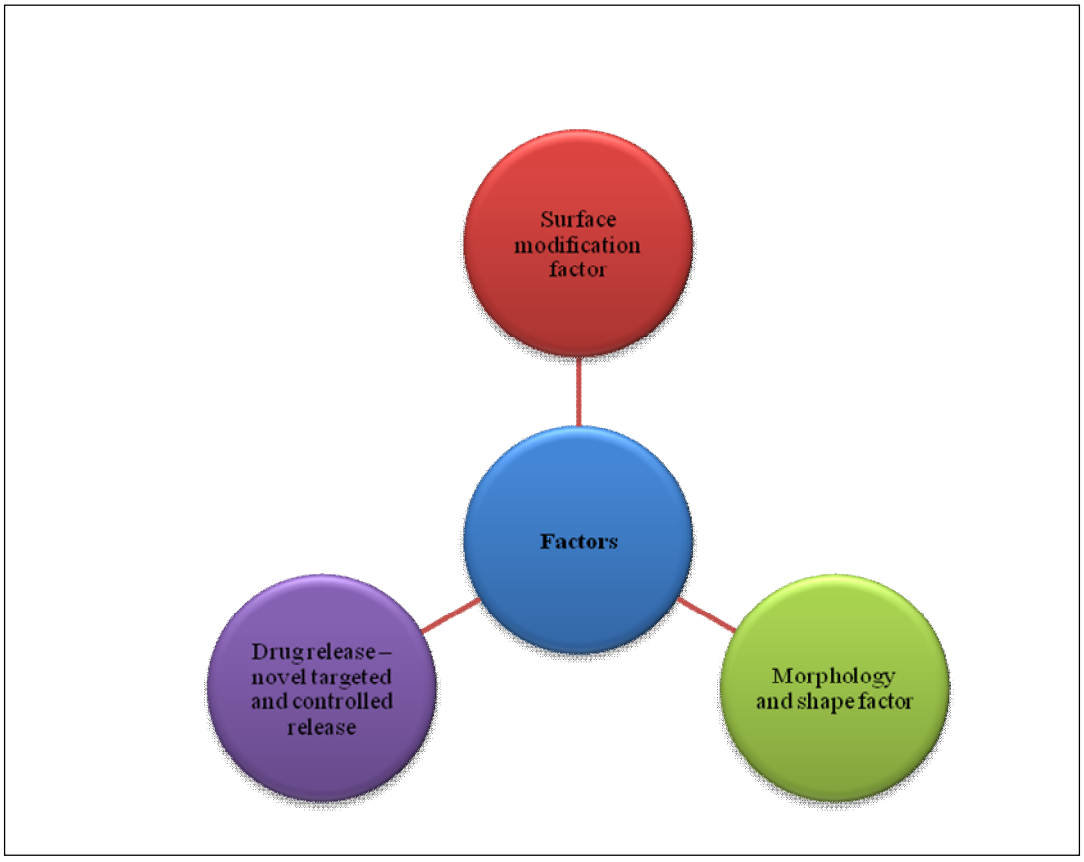

FIGURE 11.2
Factors Affecting Nanodelivery System

Surface modification factor

Nanoparticles can be modified with targeting ligands that selectively recognize and bind to receptors overexpressed on cancer cells. Examples of common ligands include the native ligand to a receptor antagonists, peptides, aptamers, and antibodies or their fragments. Targeting ligands may exert their own therapeutic effects, contributing to treatment efficacy beyond their role in targeting and specificity.
In selecting an appropriate coupling chemistry, the goal is to achieve high coupling efficiency without sacrificing binding activity and specificity of the ligand. Especially where chemical modifications are made on assembled nanoparticles, reactions and processing conditions can disrupt micelle structure or negatively impact drug activity. The required reagents, potential byproducts, temperature, solvent, and necessary purification steps must all be given careful consideration. Ideally, the reaction should proceed under mild conditions, in an aqueous environment, and require minimal post-processing. With desired chemical functional groups in mind, polymers can be chosen or synthesized to provide platforms for simple surface modification protocols.

By preserving binding activity, selective nanoparticle uptake by a target cell population is enabled through receptormediated endocytosis. *in vitro*, actively targeted formulations have a clear advantage over unmodified nanoparticles because greater cell uptake transports greater drug doses to their intracellular targets. However, *in vivo*, functionalizing nanoparticles with targeting ligands often reduces the longer-circulation achieved with PEGylation because the targeting ligands may trigger an immune response. Nevertheless, if cellular uptake can compensate for reduced tumour uptake, overall anti-cancer efficacy may improve. Nanoparticle internalization rates are likely a function of binding strength, which depends on both the intrinsic ligand-target affinity and the ligand density. This further adds to the debate over the optimal ligand conjugation density because increased uptake and decreased circulation may be linked. One approach is to increase ligand mobility so that they can be recruited to a common local area on the nanoparticle surface in the presence of target cells. In this case, multivalent binding would exponentially increase binding strength through avidity without requiring a high conjugation density.

Morphology and shape factor

Morphology and shape factor, especially particle size are the most important characteristics of nanoparticle systems. They determine the *in vivo* distribution, biological fate, toxicity and the targeting ability of nanoparticle systems. In addition, they can also influence the drug loading, drug release and stability of nanoparticles. Many studies have demonstrated that nanoparticles of sub-micron size have a number of advantages over microparticles as a drug delivery system. Generally nanoparticles have relatively higher intracellular uptake compared to microparticles and available to a wider range of biological targets due to their small size and relative mobility. Drug release is affected by particle size. Smaller particles have larger surface area, therefore, most of the drug associated would be at or near the particle surface, leading to fast drug release. Whereas, larger particles have large cores which allow more drug to be encapsulated and slowly diffuse out. Smaller particles also have greater risk of aggregation of particles during storage and transportation of nanoparticle dispersion. It is always a challenge to formulate nanoparticles with the smallest size possible but maximum stability.

Polymer degradation can also be affected by the particle size. For instance, the rate of PLGA polymer degradation was found to increase with increasing particle size *in vitro*. It was thought that in smaller

particles, degradation products of PLGA formed can diffuse out of the particles easily while in large particles, degradationproducts are more likely remained within the polymer matrix for a longer period to cause autocatalytic degradation of the polymer material. Therefore, it was hypothesized that larger particles will contribute to faster polymer degradation as well as the drug release. Additionally, nanoparticle geometry impacts transport properties: discs and rod-shaped nanocarriers have shown improved blood circulation properties over spherical particles [19-21], leading to increased interest in developing drug carriers that circulate a particular geometry and break into smaller nanocarriers for improved tumour accumulation, penetration, and cell uptake. Shape also plays a role, where spherical nanoparticles experience faster uptake than rod-shaped nanoparticles, likely due to changes in local curvature or due to binding sites being blocked when the longitudinal edge of the rods are oriented parallel to the cell membrane.

Loading NPs can change the surface morphology of nanocomposite hydrogel. The addition of nanoparticles has changed the surface morphology of kappa carrageeanan in such a way that the surface bulge is reduced, resulting in a flatter surface. Moreover, it seems that the porosity of nanocomposite is increased. It is also clear that the MgO nanoparticles are finely dispersed in the matrix and a uniform surface is produced. Comparing magnetic nanofillers with Ag nanofillers, magnetic nanofillers formed more compact surface structure. Also, it is clear that nanofillers create a uniform structure when synthesized in the blank matrix which was more obvious in magnetic nanocomposites. Formation of NPs within the hydrogel network results in changing the porosity of hydrogels which can also affect the MB release from nanocomposite hydrogels [9].

Drug release – novel targeted and controlled release

Drug release and polymer biodegradation are important factors to develop a successful nanoparticulate system. In general, drug release rate depends on: (1) solubility of drug; (2) desorption of the surface bound/ adsorbed drug; (3) drug diffusion through the nanoparticle matrix; (4) nanoparticle matrix erosion/degradation; and (5) combination of erosion/diffusion process. Thus solubility, diffusion and biodegradation of the matrix materials head the release process.

In the case of nanospheres, where the drug is uniformly distributed, the release occurs by diffusion or erosion of the matrix under sink conditions. If the diffusion of the drug is faster than matrix erosion, the mechanism of release is largely controlled by a diffusion process. The rapid initial release or 'burst' is mainly attributed to weakly bound or adsorbed drug to the large surface of nanoparticles. It is evident that the method of incorporation has an effect on release profile. If the drug is loaded by incorporation method, the system has a relatively small burst effect and better sustained release characteristics. If the nanoparticle is coated by polymer, the release is then controlled by diffusion of the drug from the polymeric membrane. The membrane coating acts as a barrier to release, therefore, the solubility and diffusivity of drug in polymer membrane becomes determining factor in drug release.

The thickness or geometry does not influence the drug release rate. Furthermore release rate can also be affected by ionic interaction between the drug and addition of auxillary ingredients. When the drug is involved in interaction with auxillary ingredients to form a less water soluble complex, then the drug release can be very slow with almost no burst release effect; whereas if the addition of auxillary ingredients e.g., addition of ethylene oxide-propylene oxide block copolymer (PEO-PPO) to chitosan, reduces the interaction of the model drug bovine serum albumin (BSA) with the matrix material (chitosan) due to competitive electrostatic interaction of PEO-PPO with chitosan, then an increase in

drug release could be observed. Hezaveh used methylene blue (MB) as model drug to test the drug release from nanocomposite hydrogel. It can be seen that by increasing the MgO content of nanocomposites, MB release is significantly increased. By increasing NPs concentration from 0.1 g to 0.2 g, the maximum MB release increases from 0.174 to 0.267 mg/ml. Also, compared to blank hydrogel, the addition of MgO NPs has increased the cumulative release up to 52%, which means that more MB release is achieved [9].

Techniques available

Nanosuspensions

Nanosuspension refers to production of sub-micron-sized particles by subjecting the combination of drug and a suitable emulsifier to the process of milling or high-pressure homogenization. Conventional milling and precipitation processes generally result in particles with sizes that are much greater than 1 mm. As such, a critical step in the nanosuspension preparation is the choice of the manufacturing procedure to ensure production of sub-micron particles. Nanosuspension formulations can be used to improve the solubility of poorly soluble drugs. A large number of new drug candidates emerging from drug discovery programs are water insoluble, and therefore poorly bioavailable, leading to abandoned development efforts. These can now be rescued by formulating them into crystalline nanosuspensions. Techniques such as media milling and high-pressure homogenization have been used commercially for producing nanosuspensions. The unique features of nanosuspensions have enabled their use in various dosage forms, including specialized delivery systems such as mucoadhesive hydrogels.

Nanosuspensions can be delivered by parenteral, per- oral, ocular, and pulmonary routes. Currently, efforts are being directed to extending their applications in site-specific drug delivery. Various particle sizes of spironolactone, a model low solubility drug, have been formulated to yield micro- and nanosuspensions of the type solid lipid nanoparticles and DissoCubes. The DissoCubes nanosuspension yielded highly significant improvements in bioavailability. Particle size minimization is not the major determining factor in the bioavailability improvement. Rather, the type of surfactant used as stabilizer in the formulations is of greater importance. Improvement in drug solubility in the intestine as well as in dissolution rate of spironolactone is the most likely mechanisms responsible for the observed effect, although additional mechanisms such as permeability enhancement may also be involved.

Development of nanoparticle formulations for improved absorption of insoluble compounds and macromolecules enables improved bioavailability and release. Particle size reduction to sizes below 1 mm is usually difficult due to possible particle aggregation and generation of high surface area materials. Milling techniques that have been used to generate nano-sized particles are ball milling or pearl milling that applies milling beads of sizes ranging from 0.4 to 3 mm and these beads may be composed of glass, ceramics or plastics. The time required for milling depends on the hardness and brittleness of the drug material in comparison to milling material and inertial forces set up within the mill. Some of the challenges that milling processes can pose in drug development are

(i) undesirable erosion of the milling equipment components into the drug product;
(ii) the process is usually time consuming, thereby prolonging drug development time;
(iii) milling over a few days may bring the risk of microbiological problems or increases in the cost of production; also

(iv) prolonged milling may induce the formation of amorphous domains in crystalline starting materials or may lead to changes in the polymorphic form of the drug.

The generation of amorphous form of the drug is problematic because these forms may crystallize during the shelf life of the drug leading to changes in solubility and bioavailability of the drug. An example of the conversion of crystalline to amorphous form of the drug was observed in jet milling of albuterol sulfate. Also, the generation of highenergy surfaces that affected wettability was observed with acetylsalicylic acid. Some examples of nano-sized particles produced by milling are

(i) naproxen nanoparticles approximately 200 nm in diameter and
(ii) danazol particles of a mean size of 169 nm.

There were four approved drug products in the USA that are based on NanoCrystal technology:

a) Rapamune (sirolimus) tablets by Wyeth;
b) Tricor (fenofibrate) tablets by Abbott;
c) Emend (aprepitant) capsules by Merck; and
d) Megace ES (megestrol) oral suspension by Par Pharmaceuticals

High pressure homogenization has also been recognized as an effective method of producing nanosuspensions. Again, high-pressure homogenization has been applied commercially with the development of some drug products, such as fenofibrate and paclitaxel. A typical procedure for preparing nanosuspension involves, preparing an aqueous suspension of drug in surfactant solution, this is then passed through a high pressure of typically 1500 bar at 3–20 homogenization cycles. The suspension is then passed through a small gap in the homogenizer of typical width 25 mm at 1500 bar. Due to built up cavitation forces that are created drug particles are broken down from micro to nanoparticles. An example is in the micro fluidization of atovaquone to obtain particles in the 100–300 nm size range . It has been reported that, nanosuspension particles in most cases have an average size ranging from 40 to 500 nm with a small (0.1%) proportion of particles larger than 5 mm. Experts have recognized that, a major challenge in the use of high-pressure homogenization is the possible changes in drug crystal structure that may cause batch-to-batch variation in crystallinity level, and have suggested that, application in drug delivery should include the desired specification by which the quality of each batch will be evaluated.

Polymeric nanoparticles

The polymeric nanoparticles (PNPs) are prepared from biocompatible and biodegradable polymers in size between 10- 1000 nm where the drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. The field of polymer nanoparticles (PNPs) is quickly expanding and playing an important role in a wide spectrum of areas ranging from electronics, photonics, conducting materials, sensors, medicine, biotechnology, pollution control and environmental technology. PNPs are promising vehicles for drug delivery by easy manipulation to prepare carriers with the objective of delivering the drugs to specific target, such an advantage improves the drug safety. Polymer based nanoparticles effectively carry drugs, proteins, and DNA to target cells and organs. Their

nanometer size promotes effective permeation through cell membranes and stability in the blood stream. Polymers are very convenient materials for the manufacture of countless and varied molecular designs that can be inte grated into unique nanoparticle constructs with many potential medical applications.

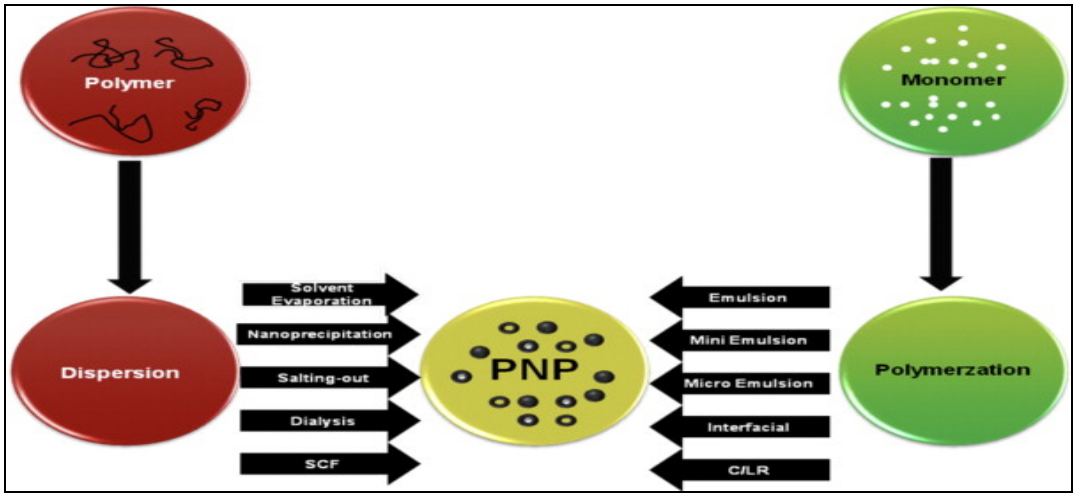

FIGURE 11.3
Schematic representation of various techniques for the preparation of polymer nanoparticles [10]

PNPs can be conveniently prepared either from preformed polymers or by direct polymerization of monomers using classical polymerization or polyreactions [11]. Methods like solvent evaporation, salting-out, dialysis and supercritical fluid technology, involving the rapid expansion of a supercritical solution or rapid expansion of a supercritical solution into liquid solvent, can be utilized for the preparation of PNP from preformed polymers. On the other hand, PNPs can be directly synthesized by the polymerization of monomers using various polymerization techniques such as micro-emulsion, mini-emulsion, surfactant-free emulsion and interfacial polymerization. An illustration of different preparation techniques for PNP is given in Figure 11.3. The choice of preparation method is made on the basis of a number of factors such as the type of polymeric system, area of application, size requirement and others [10].

Advantages of polymeric nanoparticles

- Increases the stability of any volatile pharmaceutical agents, easily and cheaply fabricated in large quantities by a multitude of methods.
- They offer a significant improvement over traditional oral and intravenous methods of administration in terms of efficiency and effectiveness.
- Delivers a higher concentration of pharmaceutical agent to a desired location.
- The choice of polymer and the ability to modify drug release from polymeric nanoparticles have made them ideal candidates for cancer therapy, delivery of vaccines, contraceptives and delivery of targeted antibiotics.
- Polymeric nanoparticles can be easily incorporated into other activities related to drug delivery, such as tissue engineering.

Mechanisms of drug release of polymeric nanoparticles the polymeric drug carriers deliver the drug at the tissue site by any one of the three general physicochemical mechanisms. (1) By the swelling of the polymer nanoparticles by hydration followed by release through diffusion. (2) By an enzymatic reaction resulting in rupture or cleavage or degradation of the polymer at site of delivery, there by releasing the drug from the entrapped inner core.(3) Dissociation of the drug from the polymer and its deadsorption/release from the swelled nanoparticles [12].

Biodegradable nanoparticles have been used frequently as drug delivery vehicles due to its grand bioavailability, better encapsulation, control release and less toxic properties.It also can be used as carrier for gene delivery. The development of safe and efficient vectors or carriers for *in vivo* gene transfer has been one of the key challenges in fulfilling the promises of gene therapy. Viral vectors, while efficient in many gene transfer applications *in vivo*, pose safety concerns that are unlikely to abate in the near future, rendering synthetic carriers attractive alternatives. The synthetic vectors including cationic liposomes and polycations, while offering better safety profile, continue to suffer from low gene transfer efficiency. Mechanistic studies are essential to identify the rate-limiting steps in the non-viral gene transfer process. Controlled and systematic studies are needed in order to reveal the structure-function relationship.

Hai-Quan Mao have designed and synthesized a series of biodegradable polyphosphoramidate (PPA) gene carriers with the same backbone but different structural parameters (type and structure of charge group, charge density, side chain spacer, etc.) in an effort to elucidate the structure-activity relationship. The aim of this study is to investigate the structure-transfection efficiency relationship of PPA gene carriers; and to investigate the effect of PPA structure on DNA compaction ability of PPA, stability of PPA/DNA nanoparticles in physiological medium, cellular uptake efficiency, intracellular trafficking, DNA unpacking, and nuclear translocation. More importantly, the biodistribution of PPA/DNA nanoparticles and transport of nanoparticles in the liver will be correlated to the structure and gene transfer efficiency of the PPA/DNA nanoparticles.

Poly (ethylene glycol) (PEG) has often been used to confer to these drug carriers the desired stability during the extracellular delivery phase. The incorporation of PEG to lipo- or polyplexes has been proven effective in reducing undesired effects such as immune response, unspecific interactions, and degradation. PEGylation can be implemented by using PEGylated components in the initial complex formation. Alternatively, PEG shielding can be applied to preformed complexes in a secondary processing step by using either electrostatic self-assembly or chemical grafting. While PEGylation is a necessity to improve extracellular stability and circulation half-life, it often decreases the transfection efficiency due to reduced specificity and inhibited cell association and uptake.

Incorporating receptor targeting orusing bioresponsive linkers to release PEG have proven useful to overcome these intracellular barriers to efficient delivery. Previous work with a copolymerprotected gene vector (COPROG), consisting of a branched polyethylenimine (bPEI)/ DNA polyplex subsequently shielded with a copolymer consisting of both PEG and anionic peptides (P6YE5C), showed the presence of the copolymer, which provides steric stabilization, protection from opsonization, and allows freeze-drying of the vector with little loss of activity. COPROG particles have proven to be effective gene delivery vectors with decreased cellular toxicity without impairing gene transfer. The decreased toxicity of COPROG is likely a result of the removal of unbound polycation by the excess anionic copolymer emphasizing the potential role of binding stoichiometry in three-component complexes. Likely due to their stabilizing and opsonization- inhibiting properties, COPROGs have proven advantageous in

promoting the tranfection capacity of polyplexloaded sponges upon subcutaneous implantation, and when colyophilized with fibrinogen, are a simple means to achieve an injectable fibrin gene-activated matrix.

At the level of research, many synthetic DNA particles have been prepared for transfection in cell cultures and in animal studies. However, several authors are of the opinion that, certain issues must be addressed in the development of DNA particles with cationic polymers. These are

(i) potential toxicity of cationic polymers especially when administered at high concentrations;
(ii) instability of particles on storage;
(iii) instability of DNA particle size and particle size distribution leading to undesirable particle aggregation;
(iv) poor transfection efficiency;
(v) poor stability in blood circulation; and
(vi) high cost of scaling up the process to achieve reproducible product quality.

Solid-lipid nanoparticles

Solid lipid nanoparticles (SLN) are particles made from solid lipids with mean diameters ranging between 50–1000nm and represent an alternative to polymeric particulate carriers. The main advantage offered by lipid carriers in drug delivery is the use of physiological lipids or lipid molecules with a history of safe use in human medicine, which can decrease the danger of acute and chronic toxicity. Sufficient data are available for the use of drug-loaded lipid nano and microparticles for oral delivery, the main mechanism of lipid particulate materials translocation across the intestine being the uptake via Peyer's patches.

Research reported shows that SLN constituted of stearic acid and phosphatidylcholine were evidenced in lymph and blood after duodenal administration to rats: the small diameters of SLN may facilitate their uptake by the lymphatics. Up until today, only a few methods are described in the literature for SLN preparation, including high pressure hot homogenization and cold homogenization techniques microemulsion-based preparation and solvent emulsification/evaporation method. Particularly, the emulsification/evaporation method concerns the preparation of nanoparticles dispersions from O/W emulsions: the lipophilic material is dissolved in a water-immiscible organic solvent that is emulsified in an aqueous phase.

Upon evaporation of the solvent, a nanoparticle dispersion is formed by precipitation of the lipid in the aqueous medium. Depending on the composition and the concentration of the lipid in the organic phase, very low particle sizes can be obtained, ranging from 30–100nm, but a clear disadvantage of this method is the use of organic solvents, whose toxicity cannot always be neglected. Recently, an emulsification–diffusion technique was developed using non-toxic and physiologicallycompatible solvents and monoglycerides or waxes as components of the disperse phase of oil-in-water emulsions obtained at 50 °C. The solvent-in-water emulsion–diffusion technique was before described in the literature mostly for the obtainment of polymeric micro- and nanoparticles and only a few authors proposed its application in the production of SLN.

According to the moderate water solubility of the solvents employed, the dilution of the emulsions determined the diffusion of the organic solvent from the droplets to the continuous phase with the

consequent instant solidification of lipophilic material. The emulsion compositions and process parameters used were the results of a formulative study aimed to develop optimized nanosphere formulations, whose mean sizes were below 200nm. The possibility of incorporating a peptide drug such as insulin in the SLN obtained with the developed method was considered, aiming to protect it from chemical and enzymatic degradation, as it is well-known that the incorporation of peptides in polymeric or non-polymeric particles should exert a certain protection of the drug against the proteolytic enzymes present in the gastrointestinal tract. Indeed, the use of lipids as matrix materials for sustained-release formulations for peptides and proteins has been reported only by few authors, owing to the hydrophobic nature of the lipid matrix that can be more appropriate to incorporate lipophilic drugs rather than hydrophilic proteins.

An adequately high solubility of the drug in the lipid melt is therefore the pre-requisite to obtain a sufficient SLN loading capacity. Considering that the solubility of insulin in most commonly employed solvents and lipids is quite low, a specific solvent medium of the peptide was required. Isobutyric acid, a partially water-miscible solvent with low toxicity, revealed a totally unexpected high insulin-solubilization capacity at 50 °C, further increasing when the solvent was water-saturated. Solid lipid insulin-loaded microparticles were therefore produced using isobutyric acid as a solvent. Preliminary analysis of microparticles content after processing showed an insulin-high encapsulation efficiency; moreover, insulin in SLN did not undergo any chemical modification and its in vitro release from the microparticles was very low, with an initial burst effect of 20% of the dose.

Of recent, SLN has become a popular drug delivery system for ophthalmic application. It is gaining prominence as promising approach to improve the poor ocular bioavailability of biomolecules. In particular, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC), regarded as the first and second generation of lipid nanoparticles are currently being applied. NLC was developed due by combining the advantages of SLN and avoidance of their limitations such as low drug loading capacity, poor long term stability and early drug expulsion caused by lipid polymorphism.(107, 108) NLC consist of a mixture of spacially different solid and liquid lipids molecules, resulting in a structure with more imperfections in crystal lattice to accommodate drugs. As drug delivery devices, NLC show great promise for the eye, due to their better biocompatibility, modified drug release kinetics, reduction of drug leakage during storage, avoidance of organic solvents during production process and feasibility of large scale production.

To prepare particles using the homogenization method, the drug is dissolved or solubilized in the lipid that has been melted and heated to a temperature approximately 5–10 °C above its melting point. For the hot homogenization technique, the drug dissolved in the lipid melt is dispersed under stirring in a hot aqueous surfactant solution of identical temperature. The obtained pre-emulsion is homogenized to produce nanoemulsions that are subsequently cooled to room temperature. Solid lipid nanoparticles are obtained upon lipid recrystallization at room temperature. Some of the process variables that will affect the particle size of nanoparticles as well as drug loading are

(i) the type of homogenization technique;
(ii) speed of homogenization; and
(iii) rate of cooling in hot homogenization.

Cold homogenization is applied for highly temperature-sensitive drugs and hydrophilic drugs. For the cold homogenization technique the drug containing lipid melt is cooled and ground to obtain lipid

particles. The lipid particles are dispersed in a cold surfactant solution that is homogenized at or below room temperature. The process avoids or minimizes the melting of lipids and therefore minimizing the loss of hydrophilic drugs to the water surface. Solid lipid nanoparticles can also be prepared by using microemulsions as precursors.

Mechanism of nanodelivery inside human body

One of example that has been proposed by [9] was about the mechanism of alginate-enclosed chitosan-calcium phosphate-iron-saturated bovine lactoferrin nanocarrier (AEC-CP-Fe-bLf NCs) internalization and its action inside human body. From the figure, it shows that the alginate coating of orally directed AEC-CP-Fe-bLf NCs is degraded in the alkaline environment offered in the small intestine (A). Then, the alginate coating free C-CP-Fe-bLf NCs enter the blood circulation via endocytosis and/or transcytosis (B). After that, C-CP-Fe-bLf NCs are released in the tumor site by making use of the enhanced permeability retention effect(C). Finally, the uptake of C-CP-Fe-bLf NCs in to the cancer cells is based on oligosaccharide and/or lactoferrin receptor-mediated endocytosis(D).

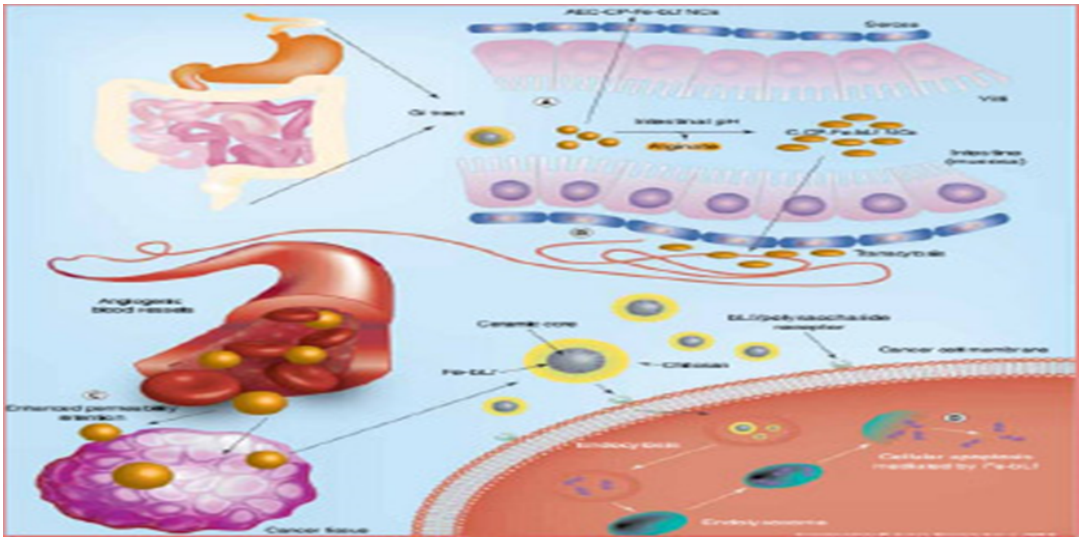

FIGURE 11.2
Example of mechanism of nanodelivery inside human body
Legend: AEC: Alginate-enclosed chitosan; C: Chitosan; CP: Calcium phosphate; Fe-bLf: Iron-saturated bovine lactoferrin; NC:Nanocarrier [9]

Nanodelivery applications

Nanodelivery system has been applied previously in many applications for human body [10]. Figure 11.3 below shows a summary of nanodelivery application in the body.

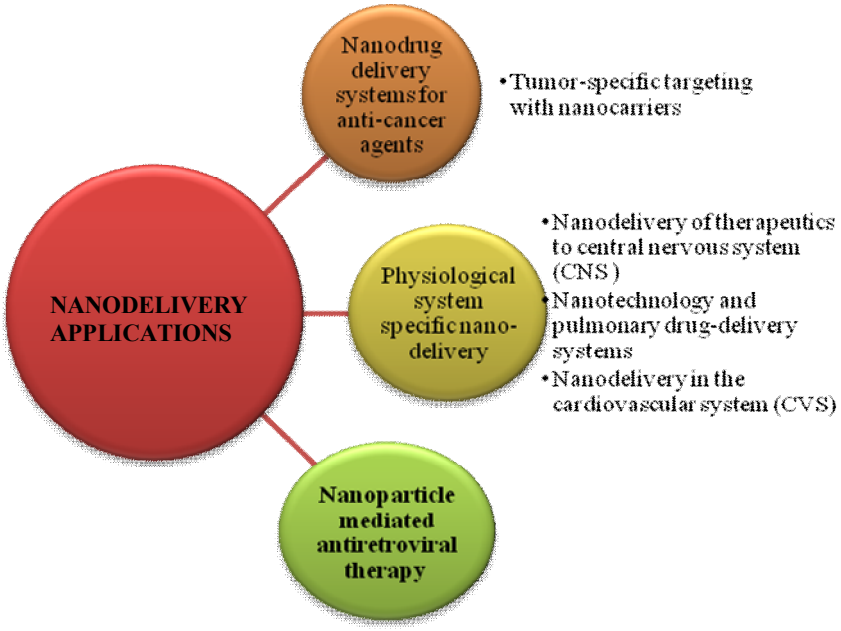

FIGURE 11.3
A summary of nanodelivery applications in the body

Nanodrug delivery systems for anti-cancer agents

Many researchers have used different approaches and techniques for formulating nanoparticles for anti-cancer agents. Some of these studies along with their prominent findings are mentioned here.

TABLE 11.3
Different types of anti-cancer agents and their mode of action against cancer cell

Hydrophobic properties				Hydrophilic properties			
Anti-cancer agents	Techniques	Mode of actions	Findings	Anti-cancer agents	Techniques	Mode of actions	Findings
Paclitaxel	Albumin-bound paclitaxel (ABI-007, Abraxane®; Abraxis BioScience and AstraZeneca).	natural carrier of endogenous hydrophobic molecules such as vitamins, hormones and other water-insoluble plasma substances.	help endothelial transcytosis of protein-bound and unbound plasma constituents through	Pluronics	Incorporated with doxorubicin and other anticancer agents	interact with multi-drug resitance (MDR) cancer cells	drastic sensitization of cancer cell
		stabilize the			inclusion of		improve

		drug particle and prevents any risk of capillary obstruction and does not require any specific infusion systems or steroid/antihistamine premedication before the infusion.	binding to a cell-surface		paclitaxel in liposomal formulations (LEP-ETU)		the drug's antitumor efficacy
	Albumin-bound paclitaxel ABI-007	colloidal suspension derived from the lyophilized formulation of paclitaxel and human serum albumin diluted in saline.	higher penetration into tumor cells with an increased anti-tumor activity, compared with an equal dose of standard paclitaxel	Endostatin	20 kDa internal fragment of the carboxy terminus of collagen XVIII	inhibit the growth of a variety of human tumors by inhibiting neovascularization	unstable or expensive, thus, limits their clinical application
			maximum tolerated dose of ABI-007 on patients with solid tumors and breast cancer	Endostar	novel recombinant human endostatin	inhibit endothelial cell proliferation, migration, and vessel formation	approved by the Chinese State Food and Drug Administration for the treatment of non-small cell lung cancer in 2005 and has a broad spectrum of activity

							against solid tumors
			antitumor activity in patients with metastatic breast cancer, with a good overall response rate and less side effects		endostar-loaded PEG-PLGA nanoparticles	maintain adequate concentrations of endostar in plasma and tumor	improving its antitumoreffect and better anticancer effect
	micellar nanoparticle formulation of paclitaxel (NK105	Paclitaxel was incorporated into the inner core of the micelle system by physical entrapment through hydrophobic interactions between the drug and the block copolymers for paclitaxel	NK105 increased plasma AUC				caused slower growth of tumor cell xenografts, and prolonged tumor doubling time.
			potent antitumor activity against a human colorectal cancer cell line HT-29 xenograft	CPX-1	novel liposome-encapsulated formulation of irinotecan and floxuridine	prolong in vitro optimized synergistic molar ratios of both drugs following infusion	well tolerated, and had significant antitumor activity
			decreased in neurotoxicity	MCC-465	immunoliposomeencapsulated doxorubicin tagged with polyethylene glycol (PEG) and the F(ab) fragment	positively reacts to >90% of cancerous stomach tissues but	cytotoxic activity against several human stomach
Osteonectin	bind albumin	present in some	facilitate intra-				

(secreted protein acid rich in cysteine (SPARC))		neoplasms (breast, lung, and prostate cancer), leading to the accumulation of albumin in some tumors	tumor accumulation of albumin-bound drugs		of human mAb GAH (goat anti-human)	negatively to all normal tissues.	cancer cells compared with doxorubicin or doxorubicin-incorporated PEG liposomes

Other than above agents, polymeric micelles also can be utilized to increase the accumulation of drugs in tumor tissues utilizing the enhanced permeability and retention (EPR) effect and to incorporate various kinds of drugs into the inner core by chemical conjugation or physical entrapment with relatively high stability. There are several anticancer drug-incorporated micelle carrier systems under clinical evaluation, these include;

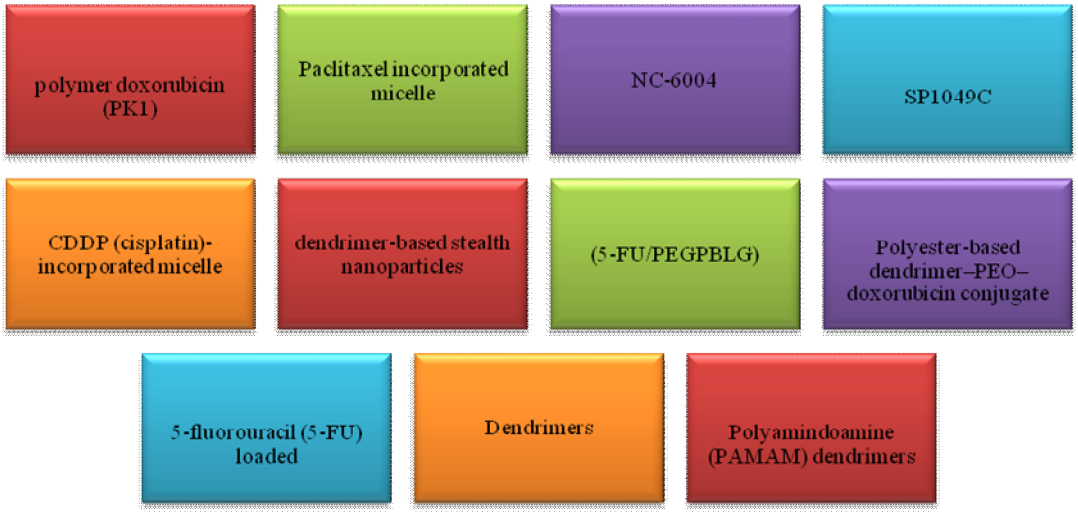

FIGURE 11.4
Several anticancer drug-incorporated micelle carrier systems

Tumor-specific targeting with nanocarriers

Tumors have different features from normal tissues. They can be either leaky tumor blood vessels or defective lymphatic drainage, which promotes the delivery and retention of particles called enhancing permeability and retention (EPR) effect. Nanoformulation, one of technique reported by researchers can settle this problem by entering and accumulate within tumor cells. This technique can deliver higher doses of the drug, thus, increasing its anticancer effects besides decreasing the side effects associated. However, by using this technique, there are many variable factors may affect the delivery of drug like clearance of nanoparticles by kidneys and uptake by reticuloendothelial cells, which at the end will retain anticancer nanoparticles in tumor. To overcome these problems, targeted drug delivery

was introduced. Targeted delivery of therapeutic agents penetrated into cancer cell has important roles for detection, diagnosis and therapy of cancer. Biomarkers, one of targeted delivery were applied to differentiate between cancerous tissue and normal tissues. One example of biomarker is ligands. Ligands were applied by studies for tumor-specific targeting. There are many types of ligands employed to serve this purposes (see Table 11.4 below);

TABLE 11.4
Ligands employed for tumor-specific targeting and its function

Types of ligands	Functions
Folate	• nonimmunogenic
Folate nanoparticles	• involved in human growth and development, cell division and DNA synthesis
Folate-mediated targeting	• used to deliver protein toxins, low-molecular weight chemotherapeutic agents, liposomes containing chemotherapeutic drugs and immunotherapeutic agents to cancer cells
Folate-conjugated nanoparticles	• used on human cervical carcinoma cells
Transferrin	• essential role in iron homeostasis and cell growth
Transferrin receptor	• initiates receptor mediated endocytosis and internalization of transferrin
Transferrin mediated targeting	• enhancement of anticancer activity
Transferrin conjugated nanoparticles	• enhance the antitumor activity and also contributes to the photo stability and sustain release of drug
Vasoactive intestinal peptide receptors (VIP-R)	• angiogenesis
Polymer-conjugated angiogenesis inhibitor TNP-470 (caplostatin)	• inhibits hyperpermeability of tumor blood vessels
Integrin avb3	• used targeting moiety on nanovectors
PLGA nanoparticles	• for delivering natural products like curcumin, that significantly reported has anti-cancer effects.
Chitosan nanoparticles	• inhibition of tumor growth and induction of tumor necrosis

One significant benefit of tumor therapy with nanoparticles as a drug carrier is to prolong the duration of the drug in the body. This will significantly increase the exposure of the tumor to the chemotherapeutic drug agent, and also prolongs the exposure of the remainder of the body to the drug. Active targeting of tumor tissues can be achieved by chemically arraying ligands on the surface of nanoparticles that can recognize and selectively bind to receptors specifically expressed on tumor cells and vessels. The high surface area to volume ratio of the nanoparticles leads to high local density of ligands for targeting. Using high-affinity ligands for these transporters along with nanoparticles can lead to site-directed delivery of drugs.

Physiological system specific nano-delivery

Nano-scale drug-delivery systems are being created in order to regulate the sustained release especially in pharmacokinetics, pharmacodynamics, solubility, immunocompatibility, cellular uptake, biodistribution and to minimize toxic side effects, thus enhancing therapeutic impact on traditional pharmaceuticals. Nanoparticle mediated drug delivery, has potentially contribute to improve the drug development process which has relied on conventional formulation strategies that are often inadequate. An underlying concept in drug development process is to establish a link between in vitro potency, physicochemical properties and absorption, distribution, metabolism, excretion and toxicity characteristics of a drug candidate which is often cited as a major contributing factor in the failure of drug functional. Meanwhile, the nanoparticle mediated sustained release of drugs offers an obvious therapeutic advantage. The targeted delivery of drugs in the body is required to prevent the release of therapeutics at non-specific sites as well as to protect from any unwanted side effects. Table 11.5 below shows examples of nanodelivery drugs that have been tested by researchers in physiological systems.

TABLE 11.5
Physiological system with specific example of nano-delivery drug

Physiological systems	Examples of nanodelivery drugs
Central nervous system (CNS)	Amitriptyline, polybutyl-cyanoacrylate nanoparticles coated with polysorbate-80, dalagrin, kytorphin, neuromuscular blocking agent tubocurarine, GLUT1 transporter, choline transporter, insulin, transferrin, beta-endorphin peptides, OX26, Doxorubicin, Transferrin-liposomes, folates, Doxorubicin-loaded folic acid-PEG-PLGA micelles, Paclitaxel-loaded PCL/MPEG micelles decorated with folic acid, Cationized bovin serum albumin (CBSA), Polysorbate 80-coated atovaquone-loaded SLN, dipalmitoylated apoE-derived peptides, camphotericin, dalargin, diminazene diaceturate, paclitaxel
Pulmonary system	Beclomethasone dipropionate loaded polymeric micelles, liposomes, synthetic lung surfactant Alveofact®, Liposomal aerosols, non-phospholipid vesicles loaded with beclomethasone dipropionate, Levonorgestrel encapsulated liposomes, Liposomes modified with cell-penetrating peptides, antennapedia, the HIV-1 transcriptional activator, and octaarginine, Liposomes of EYPC-cholesterol (CHOL) incorporating dexamethasone palmitate (DEXP), prednisolone, diazepam, camptotecin, rifampicin, isoniazid, pyrazinamide, low molecular weight heparin (LMWH)–dendrimer complex, pegylated dendrimers (mPEG–dendrimer), Pulmospheres™, 9-nitrocamptothecin (9NC) encapsulated into DLPC liposomes, Lectins, Mucoadhesive nanoparticles coated with mucoadhesive polymers, Poly-lactide-co-glycolide (PLGA), alginate and solid lipid nanoparticles
Cardiovascular systems (CVS)	Resveratrol-loaded nanoparticles [22], micelles with a clot-binding peptide, cysteine-argininеglutamic acid-lysine-alanine (CREKA), magnetofluorescent nanoparticles, paramagnetic liquid perfluorocarbon nanoparticles incorporated a peptidomimetic victronectin antagonist, modified chitosan nanoparticles with a peptide targeting ligand [23],

Nanoparticle mediated antiretroviral therapy

One of the biggest global threats today is Acquired Immunodeficiency Syndrome, also known as AIDS. AIDS is the disease presented with lack of treatment. Despite on standard therapy reported, AIDS couldn't be treated with any treatment available in the world. The current clinical therapy called 'highly active antiretroviral treatment' (HAART), has made significantly contribute to reducing mortality rate. However, it should be noted that HAART is not effective method of treatment since it can bring back a few negative effects to the patient and yet, the drug applied also has a limitation like poor drug stability under gastric condition. Owing to this, nanodelivery drug was introduced in order to improve

drug release and prevent drug limitation. Nanoparticles can provide a target specific and sustained release of these drugs, thus improving their bioavailabilty and protect patient from associated side effects. Examples of nanoparticle drugs used for AIDS therapy are summarized in the table below;

TABLE 11.6
Examples of nanoparticle drugs used for AIDS therapy and its functions in summary

Examples	Functions
Poly (isohexyl cyanate) nanoparticles of zidovudine	for targeting the lymphoid tissue in the gastrointestinal tract
Polyhexylcyanoacrylate nanoparticles	for the delivery of zidovudine thus improving its bioavailability
Zidovudine-loaded poly(isohexyl cyanate) nanoparticles	Accumulated in the cells of the reticuloendothelial system
Poly(epsilon-caprolactone) nanoparticles loaded with saquinavir	for targeting the phagocytic mononuclear system
Stavudine, zidovudine and lamivudine entrapped in polybutylcyanoacrylate (PBCA) and methylmethacrylatesulfopropylmethacrylate (MMA-SPM) nanoparticles	for brain targeting
Dendrimers	deliver antiretroviral drugs
Tuftsinconjugated poly(propyleneimine) dendrimers loaded with efavirenz	for targeted delivery to macrophages and enhanced cellular uptake by mononuclear phagocytic cells
Stavudine loaded into mannosylated and galactosylated liposomes	greater cellular uptake by cells of the mononuclear phagocytic system and greater accumulation in organs of the reticuloendothelial system
PLGA nanoparticles containing ritonavir, lopinavir and efavirenz	increased uptake of the drugs by macrophages
PHCA nanoparticles containing zidovudine	higher drug concentration in the organs of the reticuloendothelial system
PPI dendrimer-based nanocontainers	for targeting of efavirenz macrophages

Conclusions

Nanodelivery systems such as nanosuspensions, polymeric nanoparticles, and solid-lipid nanoparticles, provide a broad range of techniques and strategies that can optimize the delivery of drug into the targeted cell. They were very well functioning in releasing the drugs inside human body as well as manage the time to protect the apopotosis cancer cell, increase the bioavailability and biocompatibility of potential therapy. Furthermore, the carcinogenicity of the drugs might also be detected in early stage before releasing to upscale. Moreover, the use of nanodelivery can enhance the physiologically and specific site of targeted cell. Hence, it may conclude that, nanodelivery drug can be applied at all stages of drug development, from formulations until therapeutic applications for optimal delivery in clinical trials.

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