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REVIEW

New Aspects of Nanopharmaceutical Delivery Systems

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Nanobiotechnology, involving biological systems manufactured at the molecular level, is a multidisciplinary field that has fostered the development of nanoscaled pharmaceutical delivery devices. Micelles, liposomes, solid lipid nanoparticles, polymeric nanoparticles, functionalized nanoparticles, nanocrystals, cyclodextrins, dendrimers, nanotubes and metallic nanoparticles have been used as strategies to deliver conventional pharmaceuticals or substances such as peptides, recombinant proteins, vaccines and nucleotides. Nanoparticles and other colloidal pharmaceutical delivery systems modify many physicochemical properties, thus resulting in changes in the body distribution and other pharmacological processes. These changes can lead to pharmaceutical delivery at specific sites and reduce side effects. Therefore, nanoparticles can improve the therapeutic efficiency, being excellent carriers for biological molecules, including enzymes, recombinant proteins and nucleic acid. This review discusses different pharmaceutical carrier systems, and their potential and limitations in the field of pharmaceutical technology. Products with these technologies which have been approved by the FDA in different clinical phases and which are on the market will be also discussed.

Keywords: Nanobiotechnology, Nanostructures, Nanopharmaceutical Carrier Systems, Market.

1. INTRODUCTION

Several recent reviews have emphasized an important aspect of pharmaceutical delivery, namely the accurate targeting of the pharmaceutical to cells or tissue of choice.[1–8] Pharmaceutical targeting systems should be able to control the fate of a drug entering the body. The challenge of nanotechnology is to develop nanoparticles for biomedical and biotechnology applications to deliver the pharmaceutical in the right place at the right time. The pharmaceutical can either be integrated into the matrix or attached to the particle surface. As nanoparticles possess very high surface to volume ratios the dissolution rate is increased.[2] Many examples exist to prove this point; for example paclitaxel, cyclosporine, and amphotericin B exhibited enhanced dissolution rate and absorption in the gastrointestinal tract when formulated as nanosuspensions.[3, 9] The particle charge, surface properties and relative hydrophobicity can be designed to adsorb specifically on organs or tissues. The effectiveness of these nanoparticles has been demonstrated for mucoadhesive systems for the gastrointestinal tract and for the blood brain barrier.[10–12]

The nanoparticles provide protection against agents which cause degradation and prolong the exposure to the pharmaceutical by controlled release. Main disadvantages of nanoscaled particles are difficult sterilization on a large scale, storage, and administration because, in many cases, the penetrability and the drug concentration in the organs are unknown. On the other hand, the main advantage is their ability to cross membrane barriers, particularly in the central nervous system and the gastrointestinal tract. Nanoparticles from biodegradable polymers or from metal or lipids are now being developed for further applications such as enzyme stabilization and immobilization, and DNA transfection. In the age of genetic manipulation and somatic gene therapy, transfection systems using nanoscaled particles are custom tailored by the use of designed polymers for specific applications. No less important is the interest in carbon nanotubes designed to transport proteins, pharmaceuticals and DNA.[4]

Worldwide, nanotech R&D in all sectors was approximately \$9.6 billion in 2005. However, although frequently cited by companies, politicians and the media as the most promising area of nanotech research, nanomedicine has actually received less funding than other sectors such as nano-electronics and nanomaterials. According to Lux Research Inc. (2005), about 17% of all nanotech funding in 2005, which is approximately \$1.6 billion, was devoted to the life sciences. In the early days of nanotech (2001), the US government's National Science Foundation (NSF) predicted that nanotechnology "will help prolong life, improve its quality, and extend human physical

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capabilities" and that by 2010 or 2015, half of all pharmaceutical production—over $180 billion per year—would be dependent on nanotech. More recently, Lux Research projected that the market for nano-enabled drug delivery systems will grow from $980 million in 2005 to about $8.6 billion by 2010. The market for nanotherapeutics (such as nanosilver for wound dressings) was $28 million in 2005 and will reach $310 million by 2010. The market for nano-enabled diagnostics will climb from $56 million in 2005 to just over $1 billion by 2010.[13]

This review discusses the structural characteristics of nanopharmaceuticals and the importance of these materials for human health improvement.

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2. NANOPHARMACEUTICALS

2.1. Micelles

Micelles are small, monolayer analogs of liposomes formed from surfactants with a hydrophobic interior. A typical example is PEG-phosphatidylethanolamine micelles containing taxol and antibodies used to improve delivery to and inhibit growth of transplanted tumors in mice. An important kind of micelles is represented by nanoshells, which resemble the hydrophilic/hydrophobic composition of classical micelles but are composed of tailored block copolymers.[7] An example is the recently published study on nanoshells with beclomethazone dipropionate,[14] which showed improved pharmaceutical and DNA delivery to tumors and the central nervous system (CNS) due to an enhanced permeability and retention (EPR). This is also known as passive targeting, being a function of size and surface chemistry.[7, 15] Other useful kinds of micelles are sterically stabilized micelles with phospholipids. The application of the topoisomerase I inhibitor camptothecin that acts against a broad spectrum of cancers is limited by insolubility, instability and toxicity problems. In order to overcome these delivery problems, biocompatible sterically stabilized micelles (polyethylene glycol (PEGylated) phospholipids) were proposed as nanocarriers for this inhibitor since they are small enough to pass through the leaky microvasculature of tumor and inflamed tissues for passive targeting.[16]

Recently, an immune-stimulating complex (ISCOM) matrix constituted of colloidal structures formed from Quillaja saponins, cholesterol and phospholipid was developed. The association of ISCOM and protein antigens leads to the formation of ISCOMs. Aqueous two-component systems containing a semi-purified fraction from Quillaja saponin (Quil-A) and cholesterol prepared by lipid-film hydration were reported to form worm-like micelles as the only colloidal structure and the ring-like micelles are the predominant colloidal species at a weight ratio of 4:1 of Quil-A:cholesterol. The authors briefly outline the immunologic basis for the use of ISCOMs as vaccine delivery systems and describe the various methods used to form ISCOMs.[17]

Poly(ethylene glycol)-polypeptide block copolymers (polypeptide hybrid polymers) have attracted significant interest for polymeric therapeutics, such as drug and gene delivery systems because of the formation of micelles with a distinguished core–shell.[18] Table I shows commercially available micellar nanoparticles.

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Table I. Micellar nanoparticles commercialized and in progress by industries for biological and medical applications.

Industry	Main activities	Market	Technology
NanoCarrier Co. Ltda.	Pharmaceutical controlled release	YES	Micellar nanoparticles to encapsulate pharmaceutical, proteins and DNA[19]
NOVAVAX	Estrasorb, Topical estradiol emulsion	YES	Micellar nanoparticles[a]
NOVAVAX	Andrasorb, Topical testosterone for FSD	PhaseII	Micellar nanoparticles[a]
NOVAVAX	NX-200, Norethindrone for PMH	Pre-clin	Micellar nanoparticles[a]

[a]http://www.biospace.com/news_story.aspx?NewsEntityId = 18351520.

2.2. Liposomes

Liposomes are ideal models for biological membranes as well as efficient carriers for drugs, vaccines and nutrients. There is extensive literature covering liposomes with diverse backgrounds[20] which describe methodologies for the manufacture of liposomes, on small and large scales, since their introduction to the scientific community around 40 years ago.[21]

The interaction of poorly water soluble (lipophilic drugs) with liposomal membranes has been discussed by Fahr et al.,[22] with emphasis on pharmaceuticals capable of dissolving in a lipid membrane without perturbing it. The solubility of the pharmaceutical in a phospholipids membrane and the transfer kinetics of the lipophilic pharmaceutical between membranes describe the degree of interaction. Also discussed were the consequences of these two factors on the design of lipid-based carriers for oral and parenteral use, with recommendations for the selection of lipophilic drugs for oral administration.[22] A review article discussed types and mechanisms involved with liposomes with nanostructures for enhancing topical or transdermal drug delivery.[23] Additives such as anionic surfactants and ethanol can fluidize phospholipid bilayers, thus increasing the depths to which liposomes can penetrate into the intercellular pathways of the skin. Hair follicles play an important role in the enhancement of transdermal liposome. Niosomes, viz. non-ionic surfactant vesicles, are alternatives to liposomes and have also been discussed by Fang et al.[23]

Cationic lipids led to the development of a new model of delivery involving cationic liposome/DNA complexes or lipoplexes that are more efficient than liposomes due to the favorable electrostatic interactions between DNA (negatively charged) and the cationic liposomes. During

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Table II. Examples of liposome product approved by FDA.

Pharmaceutics or terapeutic agent	Indication	Approval year
Liposomal Amphoterecin B	Mycotic infection	1990 (Europe, 1997)
(AmBisome), Gilead[27]	Leishmaniasis	2000
Lipidic complex of amphotericin B	Aspergilosis, invasive mycotic	1995
(Abelcet), Enzon[27]	Infection	1996
Liposomal Daunorubicin (DaunoXome), Gilead[27]	Sarcoma de Kaposi	1995
Cytarabine liposome injection (Depocyt)[a]	Lymphomatous meningitis	2007
Vincristine sulfate liposomes injection–Marqibo (Hana Biosciences, Inc.)[b]	Acute lymphoblastic leukemia (ALL)	2007
Lipidic emulsion of Amphtericin B (Amphotec, Amphocil), InterMune[27]	Aspergillose	1996
Collagran™ with matrix metalloprotease (MMP) inhibiting activity[28]	Wound dressings	2006
Stealth liposome doxorubicin	Sarcoma Kaposi	1995
(Doxil/Caelyx), ALZA, Schering Plough[27]	Ovarian cancer	1999
	Breast cancer	1999 (USA) 2003 (Europe, Canada)
Liposome of cytosine arabinoside	Lymphomatosis meningitis	1999
(DepoCyt), SkyePharma[27]	Neoplasic meningitis	Fase IV
Denileukin diftitox or interleukine 2-diphteria toxin (fusion protein) (ONTAK), Seragen[27]	Cutaneous lymphoma of T cells	1999
Liposomal Doxorubicina (Myocet), Elan	Metastatic breast cancer/ with cyclophosfamide	2000 (Europa)
Gentuzumab ozogamicin or anti-CD33-bound to calicheamicin (Mylotarg), Wyeth-Ayerst[27]	Acute myeloid leukemia	2000
Verteporfin liposomal (Visudyne)[27]	Wet macular degeneration	2000
QLT, Novartis[27]	with laser treatment	2001

[a]http://www.medscape.com/viewarticle/558084. [b]http://www.medscape.com/viewarticle/551478.

the lipoplex-mediated transfection, DNA is taken up into cells by endocytosis. The main problem with endocytosis-mediated delivery is that therapeutic molecules are prone to degradation within endosomes or lysosomes. An analysis of various lipids revealed that a 1:1 mixture of N-[1-(2,3-dimyristyloxy) propyl]-N,N-dimethyl-N-(2-hydroxyethyl) ammonium bromide and cholesterol is capable of efficiently destabilizing the endosome membrane. Thus, DNA has been conjugated with cationic molecules and after encapsulated or conjugated in cationic liposomes. (e.g., protamine sulfate or adenovirus mμ protein). However, simple cationic liposomes are the more popular in clinical trials of cancer therapy than the cationic liposome associated with conjugated DNA-cationic molecules. In this way, β-interferon gene in cationic liposomes has been evaluated to treat patients suffering from glioblastoma in Japan. Several trials have also evaluated delivery of anticancer agents using liposomes in humans. As a result, liposomes are now considered safe for use in humans. Clearly in this area, more work is needed to reproduce the viral capability of transporting DNA into the nucleus.[24]

Liposomal anthracyclines have achieved highly efficient drug encapsulation, resulting in significant anticancer activity with reduced cardiotoxicity. Versions with greatly prolonged circulation such as liposomal daunorubicin have been developed. Two doxorubicin (DXR)-encapsulating liposomes were approved for human therapy: Doxil/Caelyx and Myocet. Both Doxil and Myocet alter (each product differently) the DXR pharmacokinetics and biodistribution, leading to product-specific decreases in toxicities, including its dose-limiting cardiomyopathy and myelosuppression.[25] In this context, an important example is cisplatin. Non-encapsulated cisplatin are around 10–50 nm in size, but cisplatin-encapsulated liposomes with a diameter of 250 nm (nanoliposomes) were more efficiently internalized and induced cell toxicity in a time-dependent manner.[26]

Table II shows the liposome products approved by FDA, while Tables III and IV display liposome products in clinical phases I/II and II/IV, respectively. Research on liposomes for vaccines is illustrated in Table V.

2.3. Solid Lipid Nanoparticles

In the 1990's solid lipid nanoparticles (SLN) were developed as an alternative colloidal carrier system for emulsions, liposomes and polymeric nanoparticles in controlled drug delivery.[2,41–44] These particles are advantageous compared to other carriers systems. SLN consist of a solid lipid matrix at room and body temperature, where the drug is normally incorporated in the submicron size range (below 1 μm).[45] SLN are composed of physiological lipids and the surfactants that have an accepted GRAS (Generally Recognized as Safe) status. SLN can be produced in large scales by high-pressure homogenization without using organic solvents,[2,46] and have been used in parenteral,[45,47] pulmonar[48,49] and dermal[50,51] applications. Table VI shows examples of solid lipid nanoparticles on the market.

SLN with cationic lipids have also been considered as new transfection agents.[53,54] For example, SLN prepared with a cationic lipid (DOTAP) had the same transfection efficiency as the liposomes from the same cationic lipid,[2] but with SLN the range of strong non-viral transfection agents that can be produced in large scale is widened.[53,54] A study of methotrexate-loaded solid lipid nanoparticle (MTx-SLN) for topical treatment of psoriasis, and its formulation and clinical implication was recently published.[55] The formulation and preparation of MTx-SLN gel were optimized for the cetyl alcohol lipid, Tween 80, as surfactant and sodium tauroglycocholate as co-surfactant. The optimized SLN particle size was 123 nm and an entrapment efficiency of 52% was obtained. The use of MTx-SLN improved the therapeutic response and the MTx-SLN base gel was observed to reduce adverse effects of therapy, promoting better patient compliance. It is therefore possible to consider it as a supplementary to oral therapy, particularly in the final stage of psoriasis treatment.[55]

Table III. Liposomal products in clinical phase I/II approved by FDA.

Pharmaceutics or terapeutic agent	Clinical phase	Indication
Liposomal Vincristine (Onco-TCS) Inex	NDA[29] submitted[27]	Non-Hodgkin lymphoma
LiposomalPaclitaxel (LEP ETU), Neopharm	Phase I/II[27]	Advanced solid tumor
Liposomal SN-38 or liposomal irinotecan metabolite	Phase I/II[27]	Advanced solid tumor
Aroplatin (DACH platinum)	Phase I/II[30]	Cancer
Atra-IV (Antigenics Inc.)	Phase II[31]	T-cell non-Hodgkin's lymphoma, and acute and chronic leukemia
NX211(OSI)	Phase I/II[30]	Topo I inhibitors
Liposomal Lurtotecan (OSI-211), OSI	Phase II[27]	Lung cancer/recurrent ovarian
Liposomal Interleukine 2(Oncolipin) Biomira	Phase II[27]	Immunological stimulant/used with lung cancer vaccine
Liposome Inibid. timidilate synthase (OSI-7904L) OSI	Phase II[27]	Advanced gastric cancer
Liposomal Prostaglandine E-1 (Lirostin), Endovasc DepoCyt, SkyePharma	Phase II[27]	Periferal arteria disease

Table IV. Liposomal products in clinical phase III and IV approved by FDA.

Pharmaceutics or terapeutic agent	Clinical phase	Indication
SPI-77 (stealth liposome cisplatin) ALZA	Phase III[32]	Lung cancer
Liposomal cytosine arabinoside	Phase IV[27]	Neoplasic meningitis

Table V. Some liposomes encapsulated vaccine in different clinical phases.

Type vaccine	Clinical phase	Type	Producer	Product
Allovectin-7 (Melanoma)	Phase IV	Plasmid DNA	VICAL	DNA/Lipidic complex[33]
Dental caries (Craneofacial Res)	Phase I	Glycosyl transferase (GTP)/proteina glucano (GbP)	No indicated (NI)	Glycosyl transferase/PLGA Nat.Inst.Dental/microparticles[34] and liposomes
ISCOM vaccine (Immune stimulating complexes) (anti-influenza, *Helicobacter pylory*, HPV)	Phase I	Saponins/cholesterol/phospholipids	NI	Influenza inactivated virus liposomes[35]
ISCOM/QS-21 saponin	Phase III	QS-21 saponines/	NI	Vaccine/liposomes[36]
(GM2 Ganglyoside-KLH)		GM2 ganglyosides	NI	Vaccine/liposomes[37–40]
ISCOM QS-1/HIV-1/HSV	Phase III	NI	NI	Vaccine/liposomes[40]

2.4. Polymeric Nanoparticles

Polymeric nanoparticles, especially the biodegradable ones, represent an improvement over traditional methods of administration in terms of efficiency and effectiveness. These particles help to increase the stability of drugs/proteins and possess useful controlled release properties.[56] In this area use is made of synthetic biodegradable polymers such as polycyanoacrylate[57] or poly(D,L-lactide) and poly(lactide-co-glycolide) (PLGA), and there is an increasing trend to resort to natural polymers, including chitosan,[58] gelatine[59,60] and sodium alginate,[61] to avoid toxicological problems associated with the synthetic polymers.[62]

The term nanoparticle is a collective name for both nanospheres and nanocapsules. From its definition, nanospheres are considered as a matrix system in which the drug is uniformly dispersed and nanocapsules are described as a polymeric membrane which surrounds the drug in the matrix core.[63] These polymeric nanoparticles offer distinct advantages over other nanostructures such as liposomes, which include the therapeutic potential, higher stability in the biological fluid and during storage.[64–66] This kind of particles may have specificity, allowing them to deliver a higher concentration of pharmaceutical agent to a desired location due to the possible change in surface charge or other properties (e.g., nasal and brain location).[67,68] Table VII shows the polymeric nanomaterials commercialized by different industries.

Drug encapsulation and absorption, biodistribution pattern, elimination and drug release are affected by various factors, including polymer composition, hydrophobicity, surface charge, biodegradation profile of the nanoparticles, adjuvant substances and associated drugs.[69] There are now many preparation methods for producing nanoparticles, which may be classified into two main categories according to whether the formulation requires a polymerization reaction or is achieved directly from a macromolecule or preformed polymer.[69] The commercial nanoparticles in use are listed in Table VIII and are mainly used in cancer treatment, transplant rejection and in schizophrenia.

An interesting way to classify polymer therapeutics is the following:
(a) polymeric pharmaceutical or sequestrant (3–20 nm),
(b) polymer-protein conjugate (~20 nm),
(c) polyplex polymer-DNA complex (40–60 nm),

Table VI. Example of solid lipid nanoparticle approved by FDA in the market.

Pharmaceutics or terapeutic agent	Market	Indication	Application
Nanobase®	Market	Hepatitis C	Injection[52]
Nanopearl	Market	Hydration mask	Topical[a]

[a]http://www.bikudo.com/product_search/details/631/nanopearl_hydration_mask.html.

Table VII. Examples of industries commercializing polymeric nanomaterials for biological and medical applications.

Industry	Main activities	Technology
Advectus Life Sci. Inc.[19]	Pharmaceutical release	Engineered polymeric nanoparticles to carry antitumoral pharmaceuticals through the hematoencephalic barrier
Alnis Biosciences, Inc.[19]	Bio-pharmaceuticals	Biodegradable polymeric nanoparticles to pharmaceutical release
Abraxis BioScience Inc.[a]	Biotechnology	Protein-based nanoparticle chemotherapeutic compound
Guilford Pharm. Inc.[b]	Pharmaceutical	Biopolymer-based products capable of delivering proven medicines in more effective ways
NanoPharm AG[19]	Pharmaceutical controlled release	Polybutylcyanoacrylate cobert with pharmaceutical and with surfactans, in order to cross through the hematoencephalic barrier

[a]http://www.abraxisbio.com/about.htm. [b]http://www.biospace.com/company_profile.aspx?CompanyID = 1397.

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Table VIII. Examples of polymeric nanoparticles approved by FDA.

Pharmaceutics or terapeutic agent	Indication	Approval year
Styrene/maleic acid copolymer and neocarzinostatin in ethiodol (SMANCS/lipiodol, Zinostatin stimamero), Yamanouchi	Carcinoma hepatocellular	1993 (Japan)[27] 1996 (Japan)
Carmustine (Gliadel® wafer Polyanhydride co-polymer) Guilford Pharm. Inc.	Glioblastoma multiform	1996[a]
Risperdal Consta, albumin microspheres Johnson and Johnson	Schizophrenia treatment	2002 (Germany)[70] 2004[72]
Abraxane, nanoparticles of paclitaxel-taxol, American Pharm. Partner/Amer.BioScience	Mamary câncer (metastitic)	2005[13]
TrivCor Abbott Laboratories—licensed technology from Elan	Nanoparticulate formulation of TrivCor—a drug to treat high cholesterol.	2004[13]

[a]http://www.fda.gov/ohrms/dockets/AC/01/briefing/3815b2_05_FDA.pdf.

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(d) polymer-pharmaceutical conjugate (5–15 nm) and
(e) polymeric micelles (60–100 nm).

Tables IX–XI show these structures in different clinical phases.[70,71] Many of these products are on the market, used to treat important diseases, in many cases for terminal patients.

The wide variety and ability to modify the drug release profile have made polymeric nanoparticles ideal candidates for cancer therapy, delivery of vaccines, contraceptives and delivery of targeted antibiotics. Moreover, polymeric nanoparticles can be easily incorporated into other systems related to drug delivery, such as tissue engineering and drug delivery for species other than humans. From the point of view of polymer chemistry, there is a challenge to create new polymers matching hydrophilic and lipophilic properties of upcoming drugs for smart formulation. In this context, the pharmaceutical industry should be urged to consider the so-called neglected diseases in order to make it possible that nanotechnology reaches poor countries in which problems exist with tuberculosis,[75] Chagas's disease,[76] malaria[77] and Leischmania (see part II).[78]

Very few polymeric nanoparticles are in the clinical phase I/II as shown in Table XII and in phase III (Table XIII). Only one product is in clinical phase III/IV (Table XIV).[79]

2.5. Pegylated Nanostructures

Polyethylene glycol (PEG) or poly(ethylene oxide) is a water-soluble material widely employed in pharmaceutical applications, as its terminal hydroxyl groups can be easily converted into reactive functional groups by a number of routine reactions of organic chemistry. The technique of attaching PEG to any drug, peptide, polymer or other compounds has been denominated as PEGylation and its biological applications have been well documented.[52,81] Pegylation improves the pharmacokinetics of protein and peptide drugs that could be degraded by proteolytic enzymes or have a short circulating half-life. With PEGylation, proteins and peptide drugs are shielded from proteolytic enzymes, resulting in longer circulating times, better acceptability by body tissues and improved ability to deliver drugs to the intended tissues.[82] For example, pegylated liposomal doxorubucin has shown efficacy in breast cancer treatment. The next generation of liposomes for delivery systems will include molecular targeting, as in the case of immunoliposomes that

Table IX. Polymer therapeutics as nanosized macromolecular pharmaceuticals.

Pharmaceutics or terapeutic agent	Market or clinical phase	Indication	Application
Copaxone	Market	Multiple sclerosis	——[13]
Renagel	Market	End-stage renal failure	Oral[13]
Emmelle	Market	HIV/AIDS prevention	Topical[13]
Macugen (PEG-aptamer)	Market	Age-related macular degeneration	Topical[13]
Ampligen	Phase III	Chronic fatigue syndrome	Topical[13]
Vivagel (dendrimer)	Phase II	HIV/AIDS prevention	Topical[73]

Table X. Polymer protein conjugates.[52]

Pharmaceutics or terapeutic agent	Market or clinical phase	Indication	Application
Adagen	Market	SCID syndrome	Injection
Zinostatin Simalamer	Market	Cancer	Local injection[27]
Oncaspar	Market	Cancer	Injection
PEG-Intron	Market	Hapatitis C	Injection
Pegasys	Market	Hepatitis C	Injection
PEGvisomant	Market	Acromegaly	Injection
Neulasta	Market	Cancer	Injection
CDP870	Phase III	Rheumatoid arthritis	Injection

Source: Reprinted with permission from [52], J. M. Harris and R. B. Chess, *Nature Rev. Drug Discov.* 2, 214 (**2003**). © 2003.

Table XI. Polymer-pharmaceutical conjugates.

Pharmaceutics or terapeutic agent	Clinical phase	Indication
HPMA copolymer–doxorubicin	Phase-II[74]	Cancer
HPMA copolymer–doxorubicin-galactosamine	Phase-I/II[74]	Cancer
HPMA copolymer–paclitaxel	Phase-I[74]	Cancer
Polyglutamate–paclitaxel	Phase-III[a]	NDA to be field in lung cancer
Polyglutamate–camptothecin	Phase-I/II[b]	Cancer
HPMA copolymer–camptothecin	Phase-I[74]	Cancer
HPMA copolymer–platinate	Phase-I/II[74]	Cancer
HPMA copolymer platinate	Phase-I[74]	Cancer

[a]http://clinicaltrials.gov/ct/show/NCT00108745;jsessionid=BE925DB1C873DD4FA545E12FAEB97B98?order = 42. [b] http://www.cticseattle.com/products_pgcpt.htm.

represent an integration of biological components capable of tumor recognition with delivery technologies.[83] Furthermore, PEG is non-toxic and resistant to recognition by the immune system, and may be used to enhance biological activity of conjugate drugs.[84] PEG can also be used in block copolymers. With the hydrophobic polylactide (PLA), the resulting copolymer led to microcapsules that were more soluble in water than PLA.[85]

Table XV shows the PEGylated products in different clinical phases while Table XVI shows PEGylated products approved by the FDA already on the market.

Another modification of particles surfaces similar to PEGylation consists in attaching the hyaluronan group to liposomes (tHA-LIP).[87–89] Similarly to PEG, naturally occurring high-M_r hyaluronan may promote long term circulation. Assuming that this targeting was carrier-specific, rather than drug-specific, a study was made with doxorubicin (DXR)-loaded tHA-LIP in syngeneic and human xenograft models. Indeed, the tHA-LIP presented a longer circulation time than all controls in healthy and tumor-bearing mice, which demonstrates that liposomes covered with high-M_r hyaluronan may join the arsenal of carrier formulated anticancer drugs.[90]

Table XIII. Products in clinical phase III approved by FDA.

Pharmaceutics or terapeutic agent	Clinical phase	Indication
Copolymer of N-(2-hydroxypropyl) metacrylamide-bound to paclitaxel (PNU166945), pharmacia-bound to platinate (AP5280), access pharmaceutical	Phase III[70]	Cancer
Basulin nanoparticulas Bristol-Myers squibb/flamel technol. (human insulin)	Phase III[18]	Diabetes
NPI 32101, silver nanocrystals, Nucryst Pharmaceuticals/The Westain Corp.	Phase III[18]	Atopic dermatitis, eczema

2.6. Nanocrystals

The production of nanocrystals and nanosuspensions is called nanonization.[2,91] There are several techniques to obtain this kind of nanomaterials, such high pressure homogenization,[92] wet milling[93] and by nanocrystallization from supersaturated solution state or spray drying.[94] Nanonization increases surface area and drug solubility, thus enhancing oral bioavailability and enabling administration by injection or infusion as intravenous aqueous solution of drugs that are poorly soluble in water. Nanocrystals are taken up by the mononuclear phagocytic system to allow regional specific delivery. It is known from the literature that these nanoparticles act very quickly when pathogens persist intracellularly, e.g., targeting antimycobacterial, fungal or leishmanicidal active macrophages.[2]

The industry NanoCrystal (King of Prussia, Pennsylvania, USA) prepares pharmaceuticals in nanocrystalline form for a greater efficiency in their absorption. These new particles are surface coated to enhance clinical efficiency and consistency of the less soluble pharmaceuticals. The products approved by FDA are shown in Table XVII. Other methods that produce nanocrystals for pharmaceuticals include homogenization in

Table XII. Nanoparticles in clinical phase I and II approved by FDA.

Pharmaceutics or terapeutic agent	Clinical phase	Indication
Capic, calcium phosphate nanoparticles-PEG	Pre-clinical phase[80]	Diabetes
Fullerenes Nanoparticles, C Sixty	Pre-clinical phase[80]	Degenerated disease CNS, Parkinson, Alzheimer, cardiovasc.
Polyglutamate-captothecin (CT-2106) Cell Therap.	Phase I[70]	Antitumoral
Copolymer of N-(2-hydroxypropyl)metacrylamide/camptothecin (MAG-CPT/PNU166148) Pharmacia	Phase I[70]	Cancer
Copolymer of N-(2-hydroxypropyl)metacrylamide	Phase I[70]	Cancer
RenaZorb, lantanium nanoparticulated; Altair Insulin/casein	Phase I[80]	Phosphate control in renal dialysis
Paclitaxel nanoparticles (DO/NDR/02) DABUR Cancer	Phase I[32]	Cancer
Copolymer of N-(2-hydroxypropyl)metacrylamide-bound to doxorubicin (PK1), Pfizer	Phase I/II[18]	Primary and secondary liver cancer
Copolymer of N-(2-hydroxypropyl)metacrylamide/doxorubicine-galactosamine (PK2), CRC/Pharmacia	Phase I/II[70]	Primary and secondary liver cancer

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Table XIV. Products in clinical phase III and IV approved by FDA.

Pharmaceutics or terapeutic agent	Clinical phase	Indication
Abraxane, nanoparticles of paclitaxel-taxol, American Pharm. Partner/American BioScience	Phase III/IV[13]	Mammary cancer (metastatic)

water, such as in SkyePharma's Dissocubes® or Baxter's NanoEdge®; and homogenization in non aqueous media or in water with water-miscible liquids like PharmaSol's nanopure®. Rurand also manufactures nanocrystals using its Biorise technology (www.samedanltd.com/members/archives/PMPS/Summer2003/MichaelHite.htm). But nanocrystallization is more than a general method to improve bioavailability of poorly soluble drugs. Table XVIII shows nanoemulsions commercialized by industries.

2.7. Cyclodextrin

Natural cyclodextrins (CDs) constitute a family of cyclic oligosaccharides with 6, 7, or 8 glucopyranose units (α-, β-, and β-CD, respectively). The complexation in β-CD can increase the solubility, stability, bioavailability and cell absorption of the guest molecule.[97] It is known that short nucleic acid sequences specific to oncogene targets exhibit specific anticancer activity *in vitro* through antigen or antisense activity. The major efficiency limitation of *in vivo* delivery of oligonucleotides remains a major limitation for the therapeutic application. A report has been made of the preparation of linear β-cyclodextrin-based polymers (polyplexes) complexed with DNAzyme molecules and associated with a conjugate of adamantane with PEG and transferring. The latter was used for increasing targeting to tumor cells expressing transferrin receptors. The polyplex formulations were concentrated and retained in the tumor tissue and other organs, whereas unformulated DNAzyne was eliminated from the body within 24 h post-injection. Intravenous and intraperitoneal bolus injection resulted in the highest fluorescent signal at the tumor site. The advantages of this system include longer tumor retention of the DNAzyme and more efficient tumor cell targeting.[96, 97]

Cyclodextrin encapsulation also enhanced the solubility of antiulcerogenic[98] and antitumoral[99] pharmaceuticals. Recently, a scaffold of engineered gold nanoparticles with a thiol connection and cyclodextrin terminal was prepared.[100] The *in vitro* cytotoxicity of a supramolecular system comprising violacein complexed by β-cyclodextrinthiol-protected gold nanoparticles (violacein@β-CD–S$(CH_2)_6$–S–Au) was studied with V79 and HL60 cell lines. The gold nanoparticles were prepared and modified in a single step involving reduction of tetrachloroaurate ions with sodium borohydride in the presence of thiol derivatized β-cyclodextrin. UV-Vis spectroscopy indicated that an inclusion complexation of violacein into cyclodextrin cavities occurred when mixing an aqueous solution of the gold nanoparticles with an acetone solution of violacein. According to cell viability measurements based on the MTT (3-(4,5-dimethylthiazole-2-yl)-2,5-biphenyl tetrazolium bromide) assay, the supramolecular

Table XV. Examples of pegylated controlled release systems approved by FDA in different clinical phase.

Pharmaceutics or terapeutic agent	Indication	Approval year
PEG-succinimidyl-L-asparaginase (Oncaspar), Enzon, Rhone-Poulenc Rorer	Acute lymphloblastic leukemia	1994[27]
PEG-adenosine deaminase (Adagen) Enzon	Serius immunodefficiency	1990[27]
PEG-interferon α-2b (PEG-Intron), Enzon, Schering Plough	Hepatitis C	2000[86], 2001
PEG-interferon α-2a (Pegasyls), Hoffmann-La Roche, Nektar	Hepatitis C	2002[27]
PEG-antagonic to human growth stimulation factor or Pegvisomant Somavert, Nektar, Pfizer	Achromegalia	2000[86], 2003
PEG-PG-CSF (PEGP-Filgrastin, Neulastar)	Neutropenia prevention/ Chemotherapy in cancer	2002[86]
PEG-captothecin (Prothecan) Enzon	Antitumoral	Phase II[27]
PEG-anti-TNFα (CDP870), Celltech	Crohn desease; reumatoid arthritis	Phase III[27]
PEG-TXL or paclitaxel poliglutamato (Xyotax)	Lung cancer (non-small cell lung cancer)	Phase III[27]

Table XVI. Examples of pegylated controlled release systems approved by FDA in the market.

Pharmaceutics or terapeutic agent	Market	Indication	Application
PEG-Intron	Market[13, a]	Hepatitis C	Injection
Pegasys	Market[b]	Hepatitis C	Injection
PEGvisomant	Market[c]	Acromegaly	Injection

[a]http://www.drugspedia.net/prep/40610.html. [b]http://www.drugspedia.net/prep/40626.html. [c]http://www.drugspedia.net/prep/40640.html.

Table XVII. Nanocrystals approved by FDA.

Industries	Indication	Approval year
Rapamune nanocrystal, Wyeth, NanoCrystal Technol. (sirolimus)	Rejection prevention in rim transplantation	2000[95, a]
Emend nanocrystals (aprepitsnt. MK 869)	Nausea prevention in chemotherapy	2003[95]
Tricor (fenofibrate), NanoCrystal		2004[a]
Megace ES (megestrol), NanoCrystal		2004[a]

[a]http://www.natalizumab.ie/EDT/nanocrystal_technology/Commercialized_Products.asp.

Table XVIII. Nanoemulsion commercialized by industries for biological and medical applications.

Industry	Main activities	Technology
EnvironSystems, Inc.[19]	Desinfectans surfaces	Nanoemulsions
NanoBio corporation[19]	Pharmaceuticals	Antimicrobials nanoemulsions
TRI-K industries[a]	Cosmetic, personal care and colloidal chemistry	Nanoemulsion
Pharmos corporation[b]	Biopharmaceutical	Nanoemulsion Diclofenac

[a]http://www.cosmeticsdesign.com/news/ng.asp?n=80520-kemira-tri-k-nanogel-nanotechnology. [b] http://www.pharmoscorp.com/.

system was found to maintain the cytotoxic effects compared with free violacein on HL60 cells, being also less cytotoxic to normal (V79) cells.[100]

2.8. Dendrimers

Although dendrimers were discovered in the early 1980's, their commercial use in drug delivery is still in its beginnings. Dendrimers have a central core, internal branches and terminal groups symmetrically distributed in three dimensions. Mono-dispersed dendrimers provide a controlled, well defined nanoscale sphere carrying multiple attachment sites and a hydrophobic interior for binding and release of hydrophobic chemicals.[7]

VivaGel (SPL7013), a water-based gel polylysine dendrimer, was developed by Australia-based Starpharma Holding Ltd., with a surface modified to bind HIV gp120 proteins. This material has progressed to phase II studies.[73] Starpharma is in collaboration with Dendritic Nanotechnologies and Dow Chemical to develop dendrimer-based cancer therapeutics (Table XIX). NB-001 and NB-002, an anti-herpes drug and antimycotic nail fungus, were developed by NanoBio Corp based on a license of a dendrimer platform from the Center for Biologic Nanotechnology at the University of Michigan. They are expected to finish phase III trials in 2007; and other products such as NB-003 (vaginal infection), NB-4 (genital herpes), NB-005 (shingles) and NB-006 (influenza) are under preclinical development.[7] Therefore, dendrimers have been under active commercial development although toxicity issues and human safety still remain to be checked.[101]

Table XIX. Example of dendrimer approved by FDA in clinical phase II and III.

Pharmaceutics or terapeutic agent	Clinical phase	Indication	Application
Vivagel (dendrimer)	Phase II	HIV/AIDS prevention	Topical[13]
NB-001	Phase III	Anti-herpes	Topical[7]
NB-002	Phase III	Antimycotic	Topical[7]

2.9. Nanotubes

It is believed that carbon-based materials may be advantageous in biotechnological applications for the variety of properties and shapes that they offer. Such materials stem from self-assembled lipid microtubes (discovered in 1984), fullerenes (discovered in 1985) and the various types of nanotubes (carbon nanotubes, discovered in 1991), cyclic peptide nanotubes (1993) and template-synthesized nanotubes (1994). Especially important are the possible chemistry and biochemistry that can be applied using the template method. However, the issues of production cost and mass production of nanotubes must also be addressed.[1]

Template-synthesized nanotubes are prepared by the template method that is a general approach for preparing nanomaterials involving the synthesis or deposition of the desired material within the cylindrical and monodisperse pores of a nanopore membrane or other solid surface.[1] The preparation of solid nanowires or hollow nanotubes (cylindrical nanostructures) with monodisperse diameters and lengths depends on the membrane and synthetic method used. The method is quite general to prepare nanowires and nanotubes composed of many types of material, including metals, polymers, semiconductors and carbon.[1]

In one application, lipid microtubes were coated with metallic copper to improve their mechanical strength and then loaded with antibiotics that prevent marine fouling, after which these loaded microtubes were incorporated into a paint applied to fibreglass rods.[1] This paint efficiently inhibited marine fouling during the six-month testing of these rods in ocean water. This type of material has also been used for controlled release of testosterone in living rats.[102] One disadvantage is that lipid microtubes are mechanically weak and must be coated before use. Also, since the formation of the nanotubes depends on the unique chemistry and chirality of the lipids used, it would be difficult to use this approach to make tubes with tailored properties.

Cyclic peptide molecules containing alternating D- and L-amino acids have been used as antibiotics against bacterial pathogens, in which peptides with six and eight amino-acid residues acted preferentially on both Gram-positive and Gram-negative bacteria relative to mammalian cells. Pantarotto et al. (2003)[103] demonstrated the potential of peptide functionalized carbon nanotubes to augment virus specific neutralizing antibody response that could be further exploited in vaccine delivery. In another work, a hybrid of gelatin hydrogel with carbon nanotubes imparted stability to the hydrogel at 37 °C and thus could be safely used for delivery of proteins and peptides.[104] Fullerenes are effective in tissue selective and intracellular targeting of mitochondria.[105] Hence, these systems could be utilized for targeting biotechnology drugs such as genes, proteins and peptides.

The electrical, chemical, mechanical and thermal properties of carbon nanotubes make them promising for the

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Table XX. Example of nanosilver approved by FDA.

Pharmaceutics or terapeutic agent	Indication	Approval year
Silcryst Nucryst Pharmaceuticals/ product distributed by Smith & Nephew as Acticoat	Nanocrystalline silver incorporated in wound dressings because of its anti-microbial properties	Commercially available since 1998; FDA approved for over-the-counter use in 2001[13]
SilvaGard AcryMed, Inc.	Catheter device coated with antimicrobial silver nanoparticles for internal use in body	2005[13]
Argentum medical corporation	Advanced antimicrobial burn care products	1998[a]

[a]http://www.silverlon.com/index.htm.

electronics, computer and aerospace industries. Likewise, carbon nanotubes hold great promise in biotechnology and biomedicine, but toxicity studies are still required to establish exposure guidelines and safety regulations.[4] In order to meet requirements for specific applications, chemical modification of carbon nanotubes is essential.[106]

The use of single wall nanotubes (SWNTs) for intracellular drug delivery has been demonstrated. The known materials for this application are polyethylene glycol, peptides and lipids. Water soluble SWNTs were functionalized with a fluorescent probe, FITC, to allow tracking. When murine and human fibroblast cell lines were exposed to SWNT-FITC, the nanotubes were shown to accumulate within the cells. The actual cell internalization mechanism of the carbon nanotubes (CNT) remains undefined, but these experiments suggest the viability of CNTs as carriers for delivering relatively large molecules to the cells.[4]

2.10. Metallic Nanoparticles

The silver, gold and magnetic nanoparticles are important carriers for new pharmaceutical formulations. Gold nanoparticles have unique optical and chemical properties that make them ideally suited for a number of applications in nanobiotechnology, including optical probes, targeted drug delivery and programmed material synthese.[107–108] In addition to the chemical and physical synthesis of metallic nanoparticles, new aspects in the biosynthesis of silver nanoparticles were recently published.[109–112] The bactericidal action on *Escherichia coli* varied with the concentrations of amoxicillin and silver nanoparticles, but the activity was higher when amoxicillin and silver nanoparticles were combined. The most plausible explanation of the synergistic effect may be the action of silver nanoparticles as a drug carrier. It is known that cell membranes consist of phospholipids/glycoprotein, which are all hydrophobic groups. Thus, silver nanoparticles—but not amoxicillin (hydrophilic)—are likely to approach the membrane of the target cells. Therefore, antimicrobial groups facilitate the transport of amoxicillin to the cell surface.[113] From the induction effect in a pre-incubation with silver nanoparticles, it was inferred that solutions with a larger number of silver nanoparticles have better antimicrobial effects.

Another application of silver nanoparticles is in wound dressing. Silver nanoparticles (1.6 nm) were incorporated into cotton fabrics, which exhibited antibacterial activity against *S. aureus* reducing the bacterial counts by 99.9%. This is demonstration that incorporation of silver nanoparticles renders materials sterile to be used in hospitals, and prevent or minimize infection with pathogenic bacteria such as *S. aureus*.[114] Nanocrystalline silver, SILCRYST, from Nucryst Pharmaceuticals is used in Anticoat, an antimicrobial barrier dressing now licensed to Smith & Nephew. NPI 32101. The cream formulation for the treatment of atopic dermatitis and other skin conditions is in phase II trials (Table XX).[7]

The synthesis of vancomycin (Van)-capped Au nanoparticles (Au@Van) and their enhanced *in vitro* antibacterial activities were reported. Au@Van was synthesized by reacting Au nanoparticles and bis(vancomycin) cystamide under vigorous stirring to form Au-S bonds that link

Table XXI. Examples of industries commercializing metallics nanomaterials for biological and medical applications.

Industry	Main activities	Technology
Nanoprobes, Inc.[19]	Gold nanoparticles for biological markers	Gold nanoparticles bio-conjugated to TEM and/or fluorescent microscopy
Nanosphere, Inc.[19]	Gold biomarkers	Bart codes of DNA bound to each nanoprobes to identification, PCR is used to amplify the signal, also catalytic silver deposition to amplify the signal using surface plasmon resonance
Strem Chemicals, Inc.[a]	Chemicals of high purity	Medical and pharmaceutical application in biosensors and biolabels diagnostics and targeted drug deliver
AcryMed[b]	Infection control and wound healing	Medical device infection control and tissue repair wound healing
Antibodies Incorporated[c]	Diagnostics	Polyclonal and monoclonal antibodies and immunochemistry products
Nucryst Pharmaceuticals[d]	Pharmaceutical	Nanocrystalline technology to create drugs, medical devices, or medical coatings with potentially enhanced therapeutic qualities

[a]http://www.strem.com/nano123/. [b]http://www.acrymed.com/index.html. [c]http://www.antibodiesinc.com/index.asp. [d]http://www.nucryst.com/.

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Table XXII. Examples of industries commercializing nanomaterials for biological and medical applications.

Industry	Main activities	Technology
ABCNanotech.[a]	Inorganic Nanomaterials	Inorganic colloidal materials, coating materials
Argonide[19]	Membrane filtration	Nanoporous ceramic materials to filtarte endotoxins and dental implants. DNA and proteins separation
BASF[19]	Thoothpaste	Hycroxyapatites nanoparticles to enhance the teeth surfaces
Biophan Technol. Inc.[19]	MRI protector	Composite nanomagnetic materials/carbon to protect medical devices of RF field
Capsulution NanoSci. AG[19]	Phamaceutical caped to enhance the pharmeceutical solubilties	Layer-by-layer assembled of polyelectrolites 8–50 nm
Dynal Biotech[19]		Magnetic particles
Eiffel technologies[19]	Phamaceutical controlled release	Small sizes particles, 50–100 nm.
Evident technologies[19]	Lumiscent biomarkers	Semiconductors quantum dots with amino or carboxylic groups in the surface, emission at 350 a 2500 nm
Immunicon[19]	Monitoring and separation of differents cells types	Magnetic centers rounded by polymeric layers covered by antibodies for the cells captures
BioAlliance Pharma[b]	Pharmaceutical drug release	Transdrug® technology for intracellular targeting
KES Science and Technologia, Inc.[19]	AiroCide filters	Nano TiO_2 to destroy aerobic pathogens
Nanoplex Technol. Inc.[19]	Bars nanocodes for bioanalysis	
NanoMed Pharm. Inc.[19]	Pharmaceutical controlled release	Nanoparticles for controlled release
Oxonica Ltd.[19]	Suns screening	Transparents nanoparticles dopped to absorbe the nosive UV ligth and to heat convertion
PsiVida Ltd.[19]	Tissues engineering, implants, pharmaceutical and genes release	Exploration of nanostructured properties of porous silicones
QuantumDot Corporation[19]	Luminescet biomarkers	Bioconjugated semiconductors quantum dots

[a]http://www.abcnanotech.com/. [b]http://www.bioalliancepharma.com/products.asp.

Van to Au. Au@Van presumably acts as a rigid polyvalent inhibitor of vancomycin-resistant enterococci (VRE). It also has unexpected activity against an *E. coli* strain. These results suggest that gold nanoparticles may serve as a useful model system to explore multi/polyvalent interactions of ligand-receptor pairs.[115] After conjugation to vancomycin (Van), chemically stable and highly magnetically anisotropic FePt nanoparticles (~4 nm) became water-soluble and captured *E. coli* at 15 CFU mL^{-1}.[116]

Recently, a method for fabricating biofunctionalized nanoparticles by attaching human immunoglobulin (IgG) onto their surfaces through either electrostatic interactions or covalent binding was reported. These IgG containing nanoparticles can bind selectively to the cell walls of pathogens that contain IgG-binding sites. It was demonstrated that such Au-IgG nanoparticles may serve as useful nanoscale probes for exploring the interactions between IgG and pathogens. Also, magnetic nanoparticles containing IgG have been employed as effective affinity probes for selectively concentrating traces of target bacteria from sample solutions. The lowest cell concentration detected for both *Staphylococcus saprophyticus* and *Staphylococcus aureus* in aqueous sample solutions was 3×10^5 CFU/mL, while the detectable cell concentration for *S. saprophyticus* in a urine sample was 3×10^7 CFU/mL.[117]

Table XXI shows examples of metallic particles commercialized by industries and Table XXII shows nanoproducts different from those cited above which are industrially commercialized.

3. NEGLECTED DISEASES

The possible application of nanobiotechnology to neglected diseases has brought great hope, since parasitic diseases affect hundreds of million people worldwide resulting in a high mortality (around 30% of the world's population experiences parasitic infection). These neglected diseases are especially common in developing countries.[118–120] Some of the neglected diseases of parasitic origin are lymphatic filariasis, soil-transmitted helminthiasis, schistosomiasis, onchocerciais, leishmaniasis, African trypanosomiasis, Chagas disease, ectoparasitic skin infections, parasitic zoonoses and others such as dengue, leprosy and Buruli ulcer. Although tuberculosis and malaria are also considered as neglected since they mainly affect poor people, they are subject to compulsory reporting in most countries and are therefore perceived as a major public health problem. It is important to be aware that neglected diseases are of different types, as pointed out by Professor Morel at WHO in 2005, who classified the diseases as Type I, II and III. Type I occurs in both rich and poor countries, with large number of vulnerable population: e.g., measles, hepatitis b, diabetes, tobacco related diseases; Type II: incident in both rich and poor countries with a substantial proportion in the poor counties, e.g., HIV/AIDS, tuberculosis; Type III: sleeping sickness, river blindness, Chagas diseases, leishmaniasis. In general, R&D tends to decline relative to disease burden in moving from Type I to Type II diseases. Type II diseases are often termed neglected diseases and Type III diseases are very

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neglected diseases as previously described by the WHO Commission on Macroeconomics and Health in 2000.

Even though good examples exist of application of liposomes and nanoparticles in the treatment of neglected diseases,[75, 120, 123] unfortunately there is relatively little pharmaceutical development for parasitic diseases. For example, ca. 1200 new pharmaceuticals were introduced in the market from 1975 to 1996, of which only 1% was for treating tropical diseases. Furthermore, in 2000 only 0.1% of global investment in health research was in antiparasitic agents.[120] Therefore, there is much to be done for nanotechnology to benefit poor people in this area.

4. CONCLUSION

The multidisciplinary approach of nanobiotechnology offers a myriad of tools in terms of structural modifications to meet the requirements for producing new pharmaceuticals, imposed by pathological conditions. All data available point to an enhanced toxicological effects of nanoparticles,[124] but there are other equally important issues. For example, research is also necessary to treat the cause of diseases rather than their symptoms. Also the social and ethical implications of this new technology need to be considered. In this review, we have tried to provide details of challenges that nanotechnology and nanomedicine face for the human health, in a number of cases highlighting the problems to be addressed. Most importantly, ethical aspects need to be considered to establish the safety procedures when nanotechnology is applied to humans.

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