Polymeric Nanocarriers: New Endeavors for the Optimization of the Technological Aspects of Drugs

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Abstract : Drug low solubility and stability in physiological environment constitutes a main hurdle in attaining the appropriate bioavailability. Several polymer-based nanotechnologies are being intended in order to optimize the technological (e.g., solubility, stability, bioavailability, etc.) aspects of drugs. Among them, polymeric nanoparticles, dendrimers, polymeric micelles and polymersomes appear as the most attractive and promising. Concomitant with efforts in the academic arena that aim at overcoming these drawbacks and, strongly motivated by a constant search for innovative therapeutic strategies, a very rich intellectual property has been produced in the last years. This phenomenon has been moved forward by the fact that aiming at registering off-patent or about to be off patent products, pharmaceutical companies develop new formulations of old products. Another ambit of research is the design of more sophisticated drug delivery devices (e.g., targeting, localized delivery) in order to minimize adverse effects that make the administration of certain drugs risky or to enhance the patient compliance. A recent report by Cientifica Ltd. foresees a critical expansion in the nano-based drug delivery market from its current $3.4B (about 10% of the total drug delivery market) to about $26B by 2012, being this only a promising beginning for the $220B forecasted by 2015. Given the present circumstances, we are probably witnessing a new revolution in therapeutics that will take treatment to a different dimension. The goal of the present review is to provide a comprehensive and updated patent compilation of the most recent inventions relying on polymer-based nanoparticulated carriers (polymeric nanoparticles, dendrimers, polymeric micellles and polymersomes) for the optimization of the technological aspects of therapeutic agents. This article also includes a thorough review of the patents made public in recent years (2003-2007).

Keywords: Pharmaceutical nanotechnology, polymeric nanocarriers, polymeric nanoparticles, dendrimers, polymeric micelles, polymersomes, drug solubilization and stabilization, enhanced bioavailability.

1. INTRODUCTION

The last century has witnessed a pronounced increase in lifespan. This revolution was mainly led, in early stages, by the discovery of drugs for the treatment of incurable pathologies. An example worth to be stressed was the breakthrough in therapeutics due to the discovery of penicillin by 1928 and the later fast expansion in the design of broad spectrum antibacterial, antiviral and antifungal agents. Later on, this progress was sustained by the rational design and search of novel therapeutic alternatives. Technological and industrial developments allowed the massive production and distribution of formulations and made drugs commercially available to almost every social stratus. However, due to their high hydrophobicity, more than 50% of the drugs approved for use display low aqueous solubility, constituting nowadays one of the main hurdles to attain convenient absorption and bioavailability. Based on their permeability characteristics, the Biopharmaceutic Classification System (BCS) categorizes hydrophobic drugs for oral administration in two major groups: (1) Class II and (2) Class IV. Class II drugs are poorly water-soluble entities with high permeability [1,2]. In this context, enhancement of the solubility of these therapeutic agents usually correlates well with improved bioavailability [3,4]. Class IV comprises poorly water-soluble molecules with low permeability. In this case, a further modification is required to attain appropriate transfer through body membranes. Thus, limited water-solubility represents a serious drawback in the design of formulations not only for oral but also for parenteral and topical administration. Another aspect of concern stems from the limited chemical or biological stability of the drugs in the physiological environment. An example worth to be mentioned is the antitumoral drugs of the camptothecin family [5]. These drugs display a very short $t_{1/2}$ *in vivo* due to the hydrolysis of a lactone group that results in their inactivation. Thus, different technological strategies have been investigated in order to prolong the exposure to the drug [6].

Nanotechnology has opened the possibility of controlling and manipulating structures at the molecular level and led to the creation of novel surface architectures and materials. Traditional biomedical applications incorporated the use of nanotechnology in a broad spectrum of areas. Among them, biosensors, tissue engineering, intelligent systems and nanocomposites are used in implant design and controlled release systems [7]. Several nano-oriented approaches are being intended (e.g. nanoparticle engineering [8-11]) in order to optimize the technological aspects of drugs. The use of these processes has dramatically enhanced dissolution rates *in vitro* and bioavailabilities *in vivo* of many drugs. Another

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important strategy is the design of nanocarriers. From the first liposomes developed by Gregoriadis and colleagues more than three decades ago [12] until the current state-of-the-art, a pronounced increase in the variety of macromolecular-based approaches for drug delivery was observed [13]. Among the technological alternatives, the most broadly implemented are polymeric nanoparticles, dendrimers, polymeric micelles and polymersomes.

Several facts have contributed to the generation of a broad and rich intellectual patrimony available and worth to be revised in the area of polymeric nanocarriers: (1) a constant search for innovative therapeutic strategies aiming at improving not only technological features (e.g. higher patient compliance, targeting, etc.) of a drug but also in order to add technological value to the products and differentiate from the competitors, (2) stronger academia-industry interaction mainly founded on a more compromised involvement of academic scientists as scientific directors and advisors and (3) the high economic impact that a broader intellectual property portfolio has nowadays on a company positioning in the market. This process has gained impulse because in order to register and license off-patent or about-to-be-off-patent products, pharmaceutical companies develop new formulations of old products. Also, the design of more sophisticated drug delivery devices (e.g., targeting, localized delivery) enables administration of certain drugs that display high toxicity or to enhance the patient compliance by the modification of disadvantageous characteristics like bitterness. A recent report by Cientifica Ltd. foresees a critical expansion in the nano-based drug delivery market from its current $3.4 billion (from about $33 billion of the total drug delivery market) to about $26 billion by 2012, representing a ~ 37% annual growth and a promising beginning for the $220B forecasted for 2015 [14]. Given the present circumstances, we are witnesses of a revolution in therapeutics. The goal of the present review is to provide a comprehensive and updated patent compilation of the most recent developments on polymer-based nanoparticulated carriers (polymeric nanoparticles, dendrimers, polymeric micellles and polymersomes) for the improved solubility, stability and bioavailability of therapeutic agents. Every section contains a general descrip-tion and then a table summarizing the most relevant inventions in the period 2003-2007 is included.

2. POLYMERIC NANOPARTICLES (NP)

The application of polymer made particles (micro and nano) as means for drug vehiculization was one of the most broadly investigated strategies during the last decades. Particles display interesting features related to the protection/ stabilization of sensitive active compounds and their delivery profiles [15,16]. Due to the higher surface area leading to faster solubilization rates, nano-sized structures usually show higher plasma concentrations and AUC values [17]. However, this phenomenon also depends on the properties of the drug and some studies did not show statistically significant differences [18]. Depending on the production methodology, nanocapsules or nanospheres can be obtained. While the former are vesicular systems where the solid or solubilized drug is surrounded by a polymeric membrane, the later comprise a solid matrix with different levels of porosity where the molecules are homogeneously distributed across the bulk or attached to the surface The different aspects of nanoparticles as well as the biomaterials employed for their production have been comprehensively reviewed by several research groups [19]. The most broadly investigated polymers include the natural chitosan [20,21], alginate [22], gelatin [23] and albumin [24,25] and the synthetic polylactic acid (PLA) [26], poly(lactic-co-glycolic) acid (PLGA) [27], polycaprolactone (PCL) [28], poly(cyanoacrylate) (PCA) [29], poly(methacrylic acid-*co*-ethylacrylate) block copolymer [15,16] as well as combinations with other materials such as poly(ethylene glycol) (PEG) [30]. Also, inorganic nanoparticles have been developed [31,32]. In the case of highly hydrophobic drugs, increased entrapment can be also attained [13]. From a pharmaceutical perspective, the application has been extended to formulations for a broad spectrum of administration routes including intravenous injection and pathologies (e.g., cancer [33,34]). It is worth stressing that microparticles do not enable i.v. administration. Especial emphasis was dedicated to the design of orally administered peptide and protein-loaded preparations [35]. The main advantage stems from the improved stability and absorption of these biologically active molecules in the GI tract. Another area of interest is the drug delivery to the brain. Nanoencapsulation enhances the transfer across the main hurdle: the brain blood barrier (BBB) (for recent reviews read [36,37]). However, nanoparticles are removed from the body by opsonization and phagocytosis [38]. Thus, the modification of the surface with highly hydrophilic chains (e.g., polyethylene glycol) that results in lower recognition by the host and longer circulation times was performed. The profuse academic literature found its parallelism in the patent arena. Prokop patented particles made of oppositely charged polymers such as dextran, derivatives of poly-methacrylamide, PEG and maleic acid [39,40]. Slower release rates are attained by covalently binding the drug to the matrix. Desai and co-workers designed nanoparticles of water insoluble drugs stabilized with a protein coating [41,42]. Oh *et al.* developed a series of drug-polyester complexes obtained by the conjugation of the drug with the polymer, attaining a zero order release profile and preventing the burst effect [43]. Other groups produced biodegradable nanoparticles for local delivery (e.g., bladder [44]) and cell targeting [45-47]. These systems were also investigated in diagnostics, detection and purification of biologically active agents. For example, the group led by Mirkin patented several inventions based on surface-modified gold nanoparticles containing oligonucleotides with sequences complementary to portions of the sequence of a nucleic acid to be detected [48]. Table **1** summarizes the most recent patents pursuing this approach [49-61].

3. DENDRIMERS

Dendrimers are macromolecules combining a number of unique characteristics: (1) a well defined, regularly hyperbranched and three-dimensional architecture, (2) a relatively low polydispersity and (3) a high and tunable functionality. This molecular structure confers the molecule properties substantially different than the linear counterparts. The first family was described by Tomalia *et al.* during the early ´80s and stemmed from a step-by-step synthetic path-

Table 1. Patents Describing the Development of Polymeric Nanoparticles for the Improvement of Technological Aspects of Drugs (Refs 39-61)

Inventors	Patents No. [Ref.]	Polymers	Title	Observations
Prokop, A.	US20036589563 [39]	Dextran, derivatives of poly-methacrylamide, PEG, maleic acid, malic acid, and maleic acid anhydride	Drug delivery system exhibiting permeability control	Enzymatically degradable polymers can be incorporated in otherwise hydrolytically stable particles to provide drug release at particular sites within the body where the enzyme of interest is present.
Prokop, A.	US20046726934 [40]	Polyanions and polycations	Micro-particulate and nano-particulate polymeric delivery system	A method of making a nanoparticle that is stable in a physiological environment for at least a day.
Desai, NP. *et al.*	US20036537579 [41]	Proteins (albumin)	Compositions and methods for administration of pharmacologically active compounds	A formulation useful for the *in vivo* delivery of water insoluble pharmacologically active agents (such as the anticancer drug paclitaxel) in which the drug is delivered in the form of suspended particles coated with protein (albumin).
Desai, NP. *et al.*	US20070092563 [42]	Proteins (albumin)	Novel formulations of pharmacological agents, methods for the preparation thereof and methods for the use thereof	A formulation useful for the *in vivo* delivery of water insoluble pharmacologically active agents (such as the anticancer drug paclitaxel) in which the drug is delivered in the form of suspended particles coated with protein (albumin).
Oh, JE., *et al.*	US20036589548 US20077163698 [43]	Poly(lactic acid), poly(glycolic acid), poly(D-lactic-co-glycolic acid), poly(L-lactic-co-glycolic acid), poly(D,L-lactic-co-glycolic acid), poly(caprolactone) poly(valerolactone) poly(hydroxybutyrate)	Controlled drug delivery system using the conjugation of drug to biodegradable polyester	Sustained controlled release system constructed by the conjugation of drug molecules with biodegradable polyester polymer. The drug release rate can be regulated, resulting in near zero order kinetic profile of release without showing a burst effect.
Leong, KW. *et al.*	US20046797704 [44]	Homopolymer or copolymer comprising one or more monomer repeat units selected from lactic acid, glycolic acid, lactide, lactone, poly(ethylene oxide), and poly(propylene oxide)	Systemic delivery of compounds through non-invasive bladder administration	The biocompatible microparticles or nanoparticles are non-invasively instilled into the bladder and subsequently localized to the lymph node whereupon the therapeutic agent is released from the polymer matrix.
Sung H.-W. *et al.*	US20077265090 [45]	Chitosan and poly-gamma-glutamic acid (gamma-PGA)	Nanoparticles for paracellular drug delivery	The invention discloses the nanoparticles composed of chitosan/poly-gamma-glutamic acid characterized with a positive surface charge and their enhanced permeability through Caco-2 cells for paracellular drug delivery.
Sung, H.-W. *et al.*	US20070116772A1 [46]	Chitosan and poly-gamma-glutamic acid (gamma-PGA)	Nanoparticles for protein drug delivery	The invention discloses nanoparticles of chitosan, poly-glutamic acid, and at least one bioactive agent characterized with a positive surface charge and their enhanced permeability through Caco-2 cells for paracellular drug delivery.

(Table 1) Contd….

Inventors	Patents No. [Ref.]	Polymers	Title	Observations
Turos, E. *et al*.	US20070190160 [47]	One polymerizable hydrocarbon monomer (acrylic monomer, a vinyl monomer, an acrylic resin, or a vinyl resin) and an acrylic or vinyl monomer (acrylonitrile, acrylic acid, maleic acid, methyl acrylate, ethyl acrylate, butyl acrylate, butyl methacrylate, 2-ethylhexyl acrylate, methoxyethyl acrylate, dimethylamino acrylate, methacrylic acid, isobutyl methacrylate, 2-ethyl hexyl methacrylate, lauryl methacrylate, stearic methacrylate, dimethyl amino methacrylate)	Nanoparticles for drug-delivery	This invention relates to polymeric *nanoparticles* obtained by microemulsion polymerization techniques. The drug/target substance is covalently bonded to the novel polymeric nanoparticles to secure them from outer intervention *in vivo* or cell culture *in vitro* until they are exposed at the target site within the cell.
Mirkin, CA. *et al*.	US20036645721 US20046812334 US20046818753 US20046828432 US20056861221 US20056878814 US20056902895 US20056903207 US20056969761 US20066986989 US20067098320 US20077259252 [48]	-	Nanoparticles having oligonucleotides attached thereto and uses therefor	The invention provides methods of detecting a nucleic acid. The methods comprise contacting the nucleic acid with one or more types of particles having oligonucleotides attached thereto. The oligonucleotides are attached to gold nanoparticles and have sequences complementary to portions of the sequence of the nucleic acid.
Sabel, BA. *et al*.	US20030152636A1 [49]	Polyacrylates, Polymethacrylates Polycyanoacrylates, Polyarylamides Polylactates, Polyglycolates, Polyanhydrates Polyorthoesters, gelatin, Polysaccharides albumin, Polystyrenes, Polyvinyls Polyacrolein and Polyglutaraldehydes	Method of treating cancer	Nanoparticles used as a tool to deliver drugs to a specific target within or on a mamalian body.
Alonso, M.J. *et al*.	WO04112758 [50]	Hialuronic acid + Chitosan/Gelatin/Collagen	Hialuronic acid nanoparticles	The inventive nanoparticles comprise hyaluronic acid in salt form, a positively-charged polymer (chitosan), a polyanionic salt and at least one active ingredient.
Reddy, GR. *et al*.	US20050196343A1 WO05089106 [51]	Poly(acrylamide), Poly(2-hydroxyethyl methacrylate), Poly(glycerol monomethacrylate), Poly(acrylic acid) Poly((aminoalkyl)methacrylamides) Poly(sodium acrylate), Poly(vinyl pyrrolidone) and mixtures thereof	Degradable nanoparticles	Polymeric nanoparticles useful in drug delivery, as well as for imaging and diagnosis. The polymeric nanoparticles comprise cross-linkers that, when degraded, leave simple linear polymeric molecules that can be excreted by the body.
Mumper, RJ. *et al*.	US7153525 [52]	Emulsifying wax, Polyoxyethylene sorbitan fatty acid esters, Polyoxyethylene alkyl ethers, Polyoxyethylene stearates, Phospholipids, fatty acids or fatty alcohols or their derivatives, or combinations thereof	Microemulsions as precursors to solid nanoparticles	The microemulsion precursors for solid nanoparticles consist of either alcohol-in-fluorocarbon, liquid hydrocarbon-in-fluorocarbon, or liquid hydrocarbon-in-water microemulsions. The nanoparticles can be made to entrap various materials including drugs, magnets, and sensors.

(Table 1) Contd….

Inventors	Patents No. [Ref.]	Polymers	Title	Observations
Alonso, MJ. *et al.*	US2006134785 [53]	Chitosan + glucomannan	Nanoparticles for the administration of active ingredients, method of producing said particles and composition containing same	The invention relates to nanoparticles used for the administration of active ingredients, the method of producing said nanoparticles with chitosan, glucomannan, at least one active ingredient and, if necessary, an anionic salt, preferably in sodium tripolyphosphate form.
Alonso, MJ. *et al.*	WO06128937 [54]	Chitosan + cyclodextrin	Nanoparticles comprising chitosan and cyclodextrin	System comprising nanoparticles for the release of biologically-active molecules, in which the nanoparticles contain at least 40% chitosan and less than 60% cyclodextrin, whereby both components (a and b) are mixed.
Alonso, MJ. *et al.*	WO06097558 [55]	PEGilated chitosan	Nanoparticles of chitosan and polyethyleneglycol as a system for the administration of biologically-active molecules	Systems for the release of biologically-active molecules comprising chitosan modified chemically with polyethyleneglycol and cross-linked with a cross-linking agent.
Sung, HW. *et al.*	WO06041613 [56]	Poly-gamma-glutamic acid-Poly lactic acid block copolymers conjugated with Galactosamine	Nanoparticles for targeting hepatoma cells	For targeting liver cancer cells, galactosamine was conjugated on the prepared nanoparticles as a targeting moiety.
Pai, C.-M. *et al.*	US20070154559A1 [57]	Methacrylic acid copolymer hydroxypropyl Methylcellulose phthalate hydroxypropyl Methylcellulose acetate succinate, cellulose acetate Phthalate, Shellac, Chitosan hydroxypropyl Methylcellulose Ethylcellulose Methylcellulose Polyvinylalcohol, Sodium alginate and Carbomer	Nanoparticle compositions of water-soluble drugs for oral administration and preparation methods thereof	The invention relates to orally administrable nanoparticles having enhanced entrapping rate of water-soluble drugs within nanoparticles composed of lipids and polymers, and being stable against lipases.
Sung, HW. *et al.*	US20070116772 [58]	Chitosan and poly-gamma-glutamic acid (gamma-PGA)	Nanoparticles for protein drug delivery	The invention discloses nanoparticles of chitosan, poly-glutamic acid, and at least one bioactive agent characterized with a positive surface charge and their enhanced permeability through $CACO_2$ cells for paracellular drug delivery.
Radosz, M. *et al.*	WO07001356 [59]	PEG, PEO, PDMA, PVA (polyvinyl alcohol), or co-polymers thereof	Nanoparticles for cytoplasmic drug delivery to cancer cells	The nanoparticles have a core including the anticancer drug and polymer chains that are soluble at the pH of the cancer cell. The core is surrounded by a layer of polymer chains that are insoluble at the pH of healthy tissue but soluble at the pH of the cancer interstitium. An outside layer is made of water-soluble polymer chains to shield the nanoparticle from RES recognition and give the nanoparticle a long circulation time in the bloodstream of the subject.

(Table 1) Contd….

Inventors	Patents No. [Ref.]	Polymers	Title	Observations
Jon, S. *et al.*	WO07001448 [60]	Biodegradable or non-biodegradable Polymers derivatized with PEG and coated with mucoadhesive polymers like chitosan, Poly(Lysine) Poly(Ethylene imine), lecithin, lectin Polycarboxylic acids, Poly(Acrylic acids), Polysaccharides, Hydrogels monosaccharides, Oligosaccharides oligopeptides, Polypeptides	Coated controlled release polymer particles as efficient oral delivery vehicles for biopharmaceuticals	The composition includes a polymer core encapsulating the active agent and a mucoadhesive coating disposed about the core.
Vila Pena, AI. *et al.*	WO07042572 [61]	Chitosan	Chitosan and heparin nanoparticles	Nanoparticulate systems comprising ionically cross-linked chitosan, heparin and optionally a polyoxyethylenated derivative.

way comprising successive Michael-type addition reactions between methylacrylate and ethylenediamine, rendering the polyamidoamines (PAMAM) [62,63]. The kind of core and number of synthetic cycles determines the generation of the dendrimeric molecule (nomenclature) and also the associated molecular weight, the number of superficial moieties and their nature.

These highly functionalized materials enable drug incorporation into the core of the molecule and drug complexation and conjugation on the surface [64-67], being the ability of the molecules to enter the ramified 3D structure fully related to the size of the dendrimer. Thus, it is assumed that due to sterical hindrance, PAMAMs larger than generation 4 (G4) are only capable of superficial complexation or conjugation and drugs cannot access the inner domains of the molecule. Cytocompatibility investigations suggested the concentration-dependent toxicity of -NH_2-terminated derivatives. The main mechanism is apparently related to the cationization of the molecule and later membrane damage [68]. A similar effect was observed in contact with red blood cells. In contrast, dendrimers with a carboxylic or hydroxyl surface are, in general, less toxic. Regardless some compositional drawbacks of NH_2-terminated PAMAMs, this rationale was capitalized to the design of modifications that led to more compatible materials. For example, poly(ethylene glycol)-containing materials were synthesized by modifying the terminals with PEG chains [69,70] and pro-adhesive peptides like RGD for tissue engineering and drug delivery applications [71]. Similar findings were observed by D´Emanuele and collaborators by modifying the surface with lauroyl and PEG chains [72]. Also, PEG-diamine was used as the initiator to generate novel molecular structures and larger cores [73,74]. Inspired in this technology, other interesting approaches like dendrimer-shape DNA structures were developed [75]. In terms of intellectual property, Dow Chemical Co. and Dendritech Inc. have made a tremendous contribution along the last 21 years. From the first reported PAMAMs (the first patent was published in 1986 [76]) to more innovative and biocompatible modifications to fine tune the properties and applications [77,78] a long way has been transited. For example, in 2003 Tomalia *et al.* patented dendrimers displaying different reactive moieties in the core and the shell that are reactive with each other rather than with themselves [79]. These materials were denomined tectodendrimers. Other noteworthy work is the design of a product (Vivagel®) based on a pharmacologically active dendrimer for prophylaxis or treatment of sexually transmitted diseases and actually investigated as contraceptive [80]. Hubbell *et al.* patented a group of polyethylene glycol/ poly(lysine) (PEG/PLL) tissue coatings showing preventing cell-cell contact and inhibiting post-surgical tissue adhesions, metastasis of tumors and restenosis in damaged blood vessels [81]. A synopsis of patents focused on dendrimer-based approaches is presented in Table **2** [77-95].

4. POLYMERIC MICELLES

Polymeric micelles are nano-structures formed by the self-assembly of amphiphiles in water, above a minimal concentration called the critical micelle concentration or CMC [96]. Polymeric micelles are composed by internal and external zones named *core* and shell, respectively. Due to the high molecular weight of the amphiphiles, they display higher stability (slower dissociation upon dilution) than micelles formed by regular surfactants (e.g., polyethoxylated castor oil or Cremophor® EL, polysorbate 80 or Tween® 80), even at concentrations below the CMC, extending their circulation times in blood [97]. These materials are also safer for parenteral administration [98,99] and display larger cores and hence, result in higher solubilization capacity. The hydrophobic character of the core enables the inclusion of hydrophobic drugs by physical means or chemical conjugation and their dispersion at the molecular level, resulting in enhanced water-solubility [100]. Also, the isolating effect (from the environment) of the polymeric entity can protect molecules sensitive to chemical or biological triggers from degradation and metabolism [101]. Based on the core-drug interactions through chemical and physical forces, drugs display different release profiles. Also, polymeric micelles containing poly(ethylene oxide) as the hydrophilic component evade opsonization and uptake by the macrophages of the reticuloendothelial system (RES), prolonging circulation times in blood [102,103]. Another aspect of relevance is the inhibition of efflux transporters like PGP [104].

Table 2. Patents Describing the Development of Dendrimers for the Improvement of Technological Aspects of Drugs (Refs 77-95)

Inventors	Patents No. [Ref.]	Polymers	Title	Observations
Tomalia, DA. *et al.*	US20067078461 [77]	Poly(propylene imine) (POPAM) and Poly(amidoamine) (PAMAM)	Biocompatible dendrimers	The present invention relates to compositions and methods involving biocompatible *dendrimers* for use in transfection and imaging applications.
Malik, N. *et al.*	US20067005124 [78]	Polyamidoamine (PAMAM) and Polypropylamine	Dendritic-antineoplastic drug delivery system	The antineoplastic agents conjugated to the dendritic polymer may be administered intravenously, orally, parentally, subcutaneously, intramuscularly, intraarterially or topically to an animal in an amount which is effective to inhibit growth of the malignant tumor.
Tomalia, DA. *et al.*	US20036635720 [79]	Polyamidoamine (PAMAM)	Core-shell tectodendrimers	Core-shell tecto (*dendrimers*) useful in biomedicine, pharmaceuticals, personal care products, and in other ways analogous to the known uses for *dendrimers.*
Matthews, BR. *et al.*	US20050008611 [80]	Poly(lysine), polyamidoamine (PAMAM) and polypropylenimine	Agent for the prevention and treatment of sexually transmitted diseases-I	Use of a polylysine, polyamidoamine or polypropylenimine *dendrimer* having naphthyl disulphonate terminal groups as a topically applied agent in prophylaxis or treatment of sexually transmitted diseases.
Hubbell, JA. *et al.*	US20060122290 [81]	Polyethylene glycol/poly(lysine) (PEG/PLL)	Multifunctional polymeric tissue coatings	The systems are useful in inhibiting formation of post-surgical adhesions, protecting damaged blood vessels from thrombosis and restenosis, and decreasing the extent of metastasis of attachment-dependent tumor cells.
Matthews, BR. *et al.*	US20030129158 [82]	Polyamidoamine (PAMAM) dendrimers, PAMAM (EDA) dendrimers, Poly(Propyleneimine) (PPI) dendrimers and Polylysine dendrimers	Anionic or cationic dendrimer antimicrobial or antiparasitic compositions	A dendrimer to inhibit, prophylactically or therapeutically, a bacterial, yeast, fungal, or parasitic agent in a patient.
Weber, M. *et al.*	US20030096280 US7192744 [83]	Polyamidoamine (PAMAM)	Targeted transfection of cells using a biotinylated dendrimer	The present invention relates to processes for the targeted transfection of cells.
Malik, N. *et al.*	US20046790437 [84]	Polyamidoamine (PAMAM) and Polypropylamine	Method of treating cancerous tumors with a dendritic-platinate drug delivery system	The dendritic polymer platinates may be administered intravenously, orally, parentally, subcutaneously or topically to an animal in an amount which is effective to inhibit growth of the malignant tumor.
Goodman, M. *et al.*	WO04009666 [85]	Dendrimers and a biologically active molecule bonded to the dendrimer through a disulfide linkage, an ether linkage, or a thioether linkage, wherein the dendrimer comprises at least one guanidine, Amidine, Ureido, or Thioureido groups	Dendrimers as molecular translocators	Transport molecules consisting of dendrimers with bonded active molecules.
Yu, L. *et al.*	US20056878374 [86]	Poly(ethylene imine), Poly(propylene imine) (PPI), Poly(lysine) and Polyamidoamine (PAMAM)	Biodegradable polyacetals	Biodegradable polymers containing acetal recurring units for using them in polynucleotide delivery applications.

(Table 2) Contd….

Inventors	Patents No. [Ref.]	Polymers	Title	Observations
Jiménez, O. *et al.*	US20050175669 [87]	Polyamidoamine (PAMAM)	Highly lubricious hydrophilic coating utilizing dendrimers	Hydrophilic coating for a medical device comprises a mixture of colloidal aliphatic polyurethane, an aqueous dilution of PVP and specific dendrimers to enhance the physical integrity of the coating, to improve adhesion and to covalently bind or load one of an antithrombolitic drug or an antibiotic drug within the dendrimer.
Brechbiel, MW. *et al.*	US20056852842 [88]	Diaminobutane (DAB) and Polyamidoamine (PAMAM)	Methods for functional kidney imaging using small dendrimer contrast agents	Small dendrimer-based MRI contrast agents are disclosed to accumulate in renal tubules. The accumulation enables visualization of renal structure and function, permitting assessment of structural and functional damage to the kidneys.
Frechet, JJ. *et al.*	US20067097856 [89]	Polymers: Poly(alkylene oxides), star Poly(alkylene oxides) polysaccharides, poly(amino acids) and Poly(hydroxystyrene) Synthetic organic polymer Poly(vinylphenol) Poly(hydroxymethacrylate), poly(*N*-2-hydroxypropylmethacrylamide) Poly(diallylamine), Poly(lactic acid) and Poly(hydroxymethylcaprolactone) Poly(4-hydroxyethylcaprolactone)	Dendrimeric support or carrier macromolecule	The present invention provides a family of dendrimers that are useful as supports, vectors, carriers or delivery vehicles for the delivery of drugs, genetic material, imaging components or other functional molecule to which they can be conjugated.
Kobayashi, H. *et al.*	US20060204443 [90]	Diaminobutane (DAB), poly(lysine) and polyamidoamine (PAMAM)	Methods for tumor treatment using dendrimer conjugates	The dendrimer conjugate comprises an effective amount of an anti-tumor agent. The anti-tumor agent is selectively concentrated in the lymphatic system to treat metastatic disease.
Liskamp, RMJ. *et al.*	WO06135233 [91]	Amino acid based dendrimers	Dendrimers multivalently substituted with active groups	Relates to dendrimers multivalently substituted with active groups such as peptides, carbohydrates and drug molecules, and processes for the preparation thereof based on microwave assisted reactions, and to the use of such multivalent dendrimers.
Tomalia, DA. *et al.*	WO06105043 [92]	PAMAM dendrimers, PEHAM dendrimers, polylysine dendrimers dendrigraft dendrimers, Random hyperbranched dendrimers hyperbranched dendrimers and other dendritic polymers. Preferably at least one of the dendrons in the Janus dendrimer is a PEHAM dendrimer	Janus dendrimers and dendrons	New Janus dendrimers where at least two dendrons are attached at the core, and where at least two of the dendrons have different functionality. Specific targeting entities for diagnostic and therapeutic applications can be attached to the dendrimer.
Paleos, C. *et al.*	US2006204472 [93]	Diaminobutane poly(propylene imino) dendrimer (DAB) or other dendrimeric molecules of similar structure, e.g. PAMAM dendrimers	Multifunctional dendrimers and hyperbranched polymers as drug and gene delivery systems	Synthesis of multifunctional dendrimeric and hyperbranched polymers for application as drug delivery systems of bioactive pharmaceutical compounds and as gene delivery systems.

(Table 2) Contd….

Inventors	Patents No. [Ref.]	Polymers	Title	Observations
William, B. *et al.*	US20070041934 [94]	Polyamideamine (PAMAM) and Polypropylamine (POPAM)	Dendrimer based compositions and methods of using the same	The present invention is directed to dendrimer based compositions and systems for use in disease diagnosis and therapy (e.g., cancer diagnosis and therapy).
Chauhan, AS. *et al.*	US20070014757 [95]	Polyamidoamine, Polypropylene Polyethyleneimine, Carbohydrate based dendrimer, peptide based dendrimer Glycopeptide dendrimer, Poly aryl amine polyamide, Poly (alkyl amine), Polyamido alcohol, Polyether, Polythioether Polysiloxane, Dendritic aryl ester Perchlorinated dendrimer	Compositions and complexes containing a macromolecular compound as potential anti-inflammatory agents	A composition exhibiting anti-inflammatory activity comprising of a monodisperse macromolecular polymers such as dendrimer having a plurality of terminal groups or such molecules bound/complexed to drug moieties having anti-inflammatory activity.

The most broadly studied amphiphiles are derivatives of poly(ethylene oxide)-poly(propylene oxide) (PEO-PPO-PEO) block copolymers [105-107]. However, the bio-stability of these derivates and relatively high CMC values motivated the design and development of counterparts displaying enhanced features. Among them, it is worth mentioning the replacement of PPO by more hydrophobic polymeric segments based on, styrene oxide and butylene oxide and conjugates of hydrophilic poly(ethylene glycol) segments with hydrophobic blocks of phospholipids [108], poly(L-amino acid)s [109-112] and polyesters [113, 114]. In the last years, these strong investigative efforts gave place to a profuse number of amphiphilic polymers based on these block combinations.

Rapoport and co-workers registered polymeric micelles made of a variety of acrylamide derivatives, acrylic and methacrylic acid [132] and other materials [133] for the encapsulation of antitumoral drugs like paclitaxel and doxorubicin. These systems incorporated an innovative feature, ultrasound, that resulted in micellar disruption and increased delivery. This phenomenon reverts as the radiation is turned off, and the substance is re-encapsulated. Kwon *et al.* have developed a vast platform of thermo-responsive amphiphiles belonging to all the described families for drug solubilization, stabilization and delivery [134-138]. Another group with a tradition in the design of this kind of carriers is the one led by J-C Leroux at the University of Montreal. Materials display pH-dependency and associate or dissociate depending on the pH of the medium [139]. Heller and collaborators introduced the versatile poly(orthoesters) that allow degradation rates from a few hours to several months. In this context, fine tuning of the compositions (e.g., incorporation of PEG) rendered novel micelle-forming materials [140]. Regardless the higher stability upon dilution, a gradual de-assembly of the micelles takes place at concentration below the CMC. Thus, several scientists developed stable core or shell-crosslinked micelles. For example, Bronich and Kabanov patented a diversity of core-stabilized micelles for the delivery of drugs, proteins and DNA [141]. Table **3** concentrates the main patents relying on this technology [115-141].

5. POLYMERSOMES

Polymersomes, defined as polymeric vesicles made of amphiphilic block copolymers that self-assemble in aqueous medium forming a bilayer that surrounds a liquid aqueous core, were described in recent years [142]. The formation of these structures is constrained to a very narrow hydrophilic/ hydrophobic ratio [143]. For example, polystyrene-poly-acrylic acid block copolymers are among those displaying polymersome-forming tendency [144]. Since these derivatives are not biodegradable, molecules combining PEG and polyesters like PLA and PCL were designed. Thus, lipophilic drugs can accommodate across the membrane and water-soluble ones within the core. Discher *et al.* combined two anticancer drugs with different solubility: doxorubicin (core) and taxol (membrane) in order to attain improved activity against solid tumors [145]. Due to the relatively short way these entities have gone, a limited number of patents is available (Table **4**) [146-151], most of them by Discher *et al.*

6. CURRENT AND FUTURE DEVELOPMENTS

The present work has reviewed the most recent intellectual property on polymer-based nanotechnolgical strategies for the design of optimal drug delivery devices. This is an effervescing area, with large investment volumes being poured by both public and private sectors [152]. Most of the novelties still remain as experimental enterprises and are dealing with regulatory agencies to get approval. A few have reached clinical studies or were approved (see Table **5**) [12, 153-160].

A key feature is to understand and internalize that due to the multidisciplinary nature of this area a convergence of different professionals is demanded to bring a product to the market [152]. Dr. Robert Langer, a renowned and pioneering figure, scientific leader and mentor in emerging disciplines like biomaterials, Tissue Engineering, bio and nanotechnology recently expressed that "the intersection of materials science and biotechnology is in my mind one of the most interesting, dynamic emerging fields today. Broadening our ability to predict and engineer nanotechnology and nanoscale materials at that interface is a critical next step" [161]. Following this vision, the best is probably still to come.

Table 3. Patents Describing the Development of Polymeric Micelles for the Improvement of Technological Aspects of Drugs (Refs 115-141)

Inventors	Patents No. [Ref.]	Polymers	Title	Observations
Ranger, M. *et al.*	US20026780428 [115]	Poly([poly(ethylene glycol)] Methacrylate)-block-poly(ethyl methacrylate-co-tert-butyl methacrylate) and Star-Poly([poly(ethylene glycol)] methacrylate)-block-poly(ethyl methacrylate-co-methacrylic acid)	Unimolecular polymeric micelles with an ionizable inner core	Loaded drugs can be physically retained in the *micelles* when the pH of the surrounding medium favors interactions with the core. Upon a change in pH, modification in the ionization state of the core will decrease the interactions between the drug and the inner core and facilitate the release of the micellar contents.
Hubbell, JA. *et al.*	US20030059906 US20067132475 [116]	Poly(ethylene glycol), Poly(ethylene oxide), Poly(ethylene oxide)-co-Poly(propylene oxide), Poly(N-vinyl pyrrolidone), Poly(ethyloxazoline) Poly(acrylic acid), Poly(ethylene-co-vinyl alcohol), Poly(acrylamide), Poly(*N*-alkyl or *N,N*-dialkylacrylamides), Poly(acrylates) Poly(peptides), and Poly(saccharides)	Block copolymers for multifunctional self-assembled systems	Polymers with novel block structures, containing spatially separated hydrophobic and hydrophilic parts. These features allow the preparation of carriers for bioactive lipo- or water-soluble materials having the benefits of incorporation into such structures, including enhanced cellular targeting because of the presence of antibodies or adhesion peptides on the surface.
Allen, C. *et al.*	US20030176406 [117]	Polycaprolactone-b-poly(ethylene oxide) (PCL-b-PEO)	Polycaprolactone-b-poly (ethylene oxide) copolymer non-cross-linked micelles as a delivery vehicle for steroid	The drug delivery system (micelles) maintains the release of the steroid compound in a patient having a deficient steroid level.
Jackson, JK. *et al.*	US20040234472 US20060189785 [118]	Polyanhydrides, Polyglycolic acids, Polybutrylactones, Polyhydroxybutyrates, polylactic acids Polylacaprolactones, Polyethylene glycol (PEG) and Methoxypolyethylene glycol (MePEG)	Micellar drug delivery systems for hydrophobic drugs	A drug delivery system comprising a hydrophobic drug, a biocompatible micelle forming polymer, and a biocompatible water-soluble polymer.
Seo, M.-H. *et al.*	US20040253195 [119]	Polylactides, Polyglycolides, polydioxan-2-one, Polycaprolactone, Polylactic-co-glycolide, Polylactic-co-caprolactone, Polylactic-co-dioxan-2-one	Polymeric micelle composition with improved stability	Polymeric compositions capable of forming stable micelles in an aqueous solution, comprising an amphiphilic block copolymer of a hydrophilic block and a hydrophobic block, and a polylactic acid derivative wherein one end of the polylactic acid is covalently bound to at least one carboxyl group.
Seo, M.-H. *et al.*	US20040247561 [120]	D,L-polylactic acid, a copolymer of D,L-lactic acid and mandelic acid, a copolymer of D,L-lactic acid and glycolic acid, a copolymer of D,L-lactic acid and caprolactone, and a copolymer of D,L-lactic acid and 1,4-dioxane-2-one	pH responsive biodegradable polylactic acid derivatives forming polymeric micelles and uses thereof for poorly water soluble drug delivery	Polylactic acid derivatives capable of forming micelles in an aqueous solution with a pH of 4 or above. The polylactic acid derivatives may be applied as a drug delivery system in various forms since poor water soluble drugs can be entrapped inside the micelles.
Lavasanifar, A. *et al.*	WO05118672 [121]	Poly(ethylene oxide)-b-poly(ε-caprolactone) (PEO-b-PCL)	Polymer based nano-carriers for the solubilization and delivery of hydrophobic drugs	Novel PEO-b-PCL micelles and micelles containing cyclosporine A or analogs thereof are provided as well as a novel method for making said micelles that reduces aggregation and enhances delivery, the toxicity profile and biodistribution of hydrophobic drugs.

(Table 3) Contd….

Inventors	Patents No. [Ref.]	Polymers	Title	Observations
Lee, SC. *et al.*	US20050158271 [122]	Poly(ethylene glycol)-block-poly(2-(4-vinylbenzyloxy)-*N*,*N*-diethylnicotinamide), Poly(ethylene glycol)-block-poly(2-(4-vinylbenzyloxy)-*N*-picolylnicotinamide), poly(ethylene glycol)-block-poly(2-(4-vinylbenzyloxy)-nicotinamide) Poly(oligoethylene glycol methacrylate-co-poly(2-(4-Vinylbenzyloxy)-*N*,*N*-Diethylnicotinamide) Poly(oligoethylene glycol Methacrylate-co-poly(2-(4-vinylbenzyloxy)-*N*-Picolylnicotinamide) and Poly(oligoethylene glycol Methacrylate-co-poly(2-(4-vinylbenzyloxy)-nicotinamide).	Pharmaceutical applications of hydrotropic polymer micelles	Hydrotropic polymer micelles are formed in solution from copolymers that comprise a hydrophilic polymer and a hydrophobic polymer having pendant hydrotropic agents. A hydrophilic chain comprises polyethyleneoxide (PEG) and a hydrophobic chain comprises hydrotropic monomer units derived from nicotinamide. The micelles are found to be much more effective in solubilizing poorly soluble drugs and exhibit an excellent long-term stability even at high loading of drugs.
Tsai, B.-H. *et al.*	US20050019303 [123]	Polycaprolactone (PCL) and Polyethylene glycol (PEG)	Biodegradable copolymer, and polymeric micelle composition containing the same	The micelles possess good drug and bioactive agent delivery characteristics and are suitable for use in drug delivery or cosmetic applications.
Seo, MH. *et al.*	US20050201972 [124]	Monoacetoxypolyethylene glycol Polyethylene glycol, polyethylene-co-Propylene glycol, polyvinyl Pyrrolidone, polylactides, Polyglycolides, polycaprolactone, Polydioxan-2-one, polylactic-co-Glycolide, polylactic-co-dioxan-2-one Polylactic-co-caprolactone and Polyglycolic-co-caprolactone	Amphiphilic block copolymer and polymeric composition comprising the same for drug delivery	The present invention relates to polymeric compositions capable of forming stable micelles in an aqueous solution, comprising the amphiphilic block copolymer and a polylactic acid derivative wherein one or more ends of the polylactic acid are covalently bound to at least one carboxyl group.
Torchilin, VP. *et al.*	US20060216342 [125]	Polyethylene glycol and phosphatidylethanolamine	Micelle delivery system loaded with a pharmaceutical agent	A drug delivery system comprising a targeted form of a polyethyleneglycol (PEG)/lipid-conjugated micelle, which is capable of stabilizing poorly soluble pharmaceutical agents.
Seo, M.-H. *et al.*	US7153520 [126]	Polyethylene glycol Monoalkoxypolyethylene glycol and Monoacyloxypolyethylene glycol Polylactides, polycaprolactone Poly(lactide-co-glycolide) Poly(lactide-co-caprolactone) Poly(lactide-co-p-dioxanone) Polyorthoesters, polyanhydrides Poly(amino acid) and polycarbonates	Composition for sustained delivery of hydrophobic drugs and process for the preparation thereof	A composition for the sustained delivery of a drug comprising an amphiphilic diblock copolymer. When administered into a particular body site, the composition forms an implant containing the drug and drug containing polymeric micelles, which are slowly released from the implant for an extended period of time.
Breitenkamp K. *et al.*	US20060240092 [127]	Propyne-aryl-poly(ethylene glycol)-b-Poly(aspartic acid)-b-[Poly(phenylalanine)-co-Poly(tyrosine)]	Polymeric micelles for drug delivery	The present invention relates to the field of polymer chemistry and more particularly to multiblock copolymers and micelles comprising the same.

(Table 3) Contd….

Inventors	Patents No. [Ref.]	Polymers	Title	Observations
Kim, S-H. *et al*.	WO07021142 [128]	Polyethylene glycol (PEG), Polyvinylpyrolidone or polyoxazolin.	siRNA-Hydrophilic polymer conjugates for intracellular delivery of siRNA and method thereof	The present invention relates to conjugates between siRNA (small interfering RNA) molecules and hydrophilic polymers, which can effectively be used for gene therapy for treatment of cancers and other infectious diseases.
Chowdhury, DFH.	WO07042833 [129]	Polyoxypropylene (POP) or Polyoxyethylene (POE), Polyoxyethelyne glycol (PEG), Lecithin, Phosphatidylethanolamine (PE) and poloxamers.	Amphiphilic nanotubes and micelles comprising same for use in the delivery of biologically active agents	The nanotube may have magnetic properties. A therapeutic agent may be incorporated in the micelle. The micelle may be coated to form a capsule and can be introduced to the human or animal body for treatment of tumors or targeted drug delivery when a magnetic field or near-IR radiation is applied.
Uhrich, KE. *et al*.	US20077262221 [130]	Poly(ethylene glycol) (PEG) and Poly(ethylene imine) (PEI)	Amphiphilic star-like macromolecules for drug delivery	The present invention provides polymeric compounds that can form micelles in solutions. These compounds have a hydrophobic, core that is coupled to a plurality of hydrophilic moieties.
Jeong, JH. *et al*.	US20070041932 [131]	Polyethylene glycol, Polyvinylpyrrolidone and Polyoxazoline. Polyethylenimine, Polyamidoamine, polylysine, Diethylaminoethyldextran and Polydimethylaminoethyl Methylacrylate	Conjugate for gene transfer comprising oligonucleotide and hydrophilic polymer, polyelectrolyte complex micelles formed from the conjugate, and methods for preparation thereof	A conjugate for gene transfer, which is capable of being used for treatment of incurable diseases, comprising an oligonucleotide intended to be transferred into target cells.
Rapoport, N. *et al*.	US20036649702 [132]	*N*-isopropylacrylamide, *N*,*N*-Diethylacrylamide *N*,*N*-Diethylmethacrylamide, *N*-Isopropylmethacrylamide, *N*-n-Butylacrylamide, other mono- and di-Alkyl substituted acrylamides, acrylic acid and methacrylic acid	Stabilization and acoustic activation of polymeric micelles for drug delivery	The micelle comprises molecules of a block polymer having a hydrophobic block and a hydrophilic block. A drug can be incorporated into the dense inner core of the micelles. When subjected to ultrasound, the micelles release the substance, and then reversibly revert to a stable dense core and re-encapsulating the substance when the ultrasound is turned off.
Rapoport, N.	US20050003008 [133]	Poly(L-amino acid)-co-poly(ethylene oxide) diblock copolymer, Poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) triblock copolymer, PEGylated Diacylphospholipid and mixtures thereof.	Method of *in vivo* drug targeting to solid tumors via acoustically triggered drug delivery in polymeric micelles	A method for administering a drug to a selected site in a patient includes (a) administering a composition including a micellar drug carrier having a hydrophobic core and an effective amount of the drug disposed in the hydrophobic core; and (b) applying ultrasonic energy to the selected site such that the drug is released from the hydrophobic core to the selected site.
Kwon, GS. *et al*.	US20056939561 [134]	Poly (ethylene oxide) – block – poly (N-hexyl stearate L-aspartamide).	Methods and compositions for polyene antibiotics with reduced toxicity	Methods for formulating hydrophobic therapeutic agents such as polyene antibiotics, especially amphotericin B, such that toxicity is reduced. The antibiotic is incorporated within micellar structures of block polymers.

(Table 3) Contd….

Inventors	Patents No. [Ref.]	Polymers	Title	Observations
Kwon, GS. *et al.*	US20040005351 [135]	Methoxy poly(oxyethylene)-block-Poly(epsilon-caprolactone) and methoxy poly(oxyethylene)-Poly(ethylene glycol)-block-poly(N-hexyl-L-aspartamideacyl ester).	Polymeric micelle formulations of hydrophobic compounds and methods	Compositions for improving the solubility of hydrophobic compounds, such as anticancer drugs, polyene antibiotics, antilipidemic agents for reducing the toxicity of Amphotericin B (AmB), and therapeutics such as paclitaxel, tamoxifen, by incorporating these agents within *micelles*.
Kwon, GS.	US20040116360 WO04034992 [136]	Monomethoxy poly(ethylene glycol)-phospholipid.	Encapsulation and deaggregation of polyene antibiotics using poly(ethylene glycol)-phospholipid micelles	The *micelles* can be reconstituted with the Amphotericin B (or other hydrophobic compound) in a deaggregated state and safely used in therapy for fungal infections of humans or animals, especially for systemic fungal infections, or other desired application.
Lavasanifar, A. *et al*.	WO05118672 [137]	Poly(ethylene oxide)-b-poly(ε-caprolactone) (PEO-b-PCL)	Polymer based nano-carriers for the solubilization and delivery of hydrophobic drugs	Novel PEO-b-PCL micelles and micelles containing cyclosporine A or analogs thereof are provided as well as a novel method for making said micelles that reduces aggregation and enhances delivery, the toxicity profile and biodistribution of hydrophobic drugs.
Kwon, GS. *et al.*	US20060251710 [138]	Polyethylene glycol (PEG), and a hydrophobic domain such as Poly(propylene glycol), Poly(L-amino acid), Poly(ester), and Phospholipids	Micelle composition of polymer and passenger drug	*Micelles* extend the time period the drug remains in the *micelles* to improve drug circulation time. Hydrophobic drugs for micelle encapsulation may include rapamycin, geldanamycin, and paclitaxel. Administration of these micelle compositions does not require Cremophor EL or Tween 80, avoiding serious side effects associated with these products.
Sant, V. *et al.*	US20067094810 [139]	Poly (ethylene oxide) - block - poly (n-butyl acrylate-co-methacrylic acid)	pH-sensitive block copolymers for pharmaceutical compositions	The supramolecular assemblies or *micelles* formed from said polymers associate or dissociate reversibly upon changes in the environmental pH.
Ng, SY. *et al.*	US20030152630 [140]	Poly(ethylene glycol) (PEG) and Poly(ortho ester) (POE)	PEG-POE, PEG-POE-PEG, and POE-PEG-POE block copolymers	PEG-POE, PEG-POE-PEG, and POE-PEG-POE block copolymers have both hydrophilic and hydrophobic blocks. They form *micelles* in aqueous solution, making them suitable for encapsulation or solubilization of hydrophobic or water-insoluble materials.
Bronich, TK. *et al.*	US20040228823 [141]	Polymethylacrylic acid, Polyacrylic acid, Poly(phosphate), Polyamino acids, Polymalic acid, or Polylactic acid and Polyetherglycols, Poly(ethylene oxide), copolymers of ethylene oxide and Propylene oxide Polysaccharides, Polyvinyl alcohol Polyvinyl pyrrolidone Polyvinyltriazole, N-oxide of Polyvinylpyridine, HPMA, Polyortho esters, Polyglycerols	Cross-linked ionic core *micelles*	The present invention provides polymer micelles with cross-linked ionic cores as delivery vehicles for therapeutics, diagnostics, nucleic acids, proteins, small molecules and the like. The present invention provides additionally methods of synthesis and uses for such micelles.

Table 4. Patents Describing the Development of Polymersomes for the Improvement of Technological Aspects of Drugs (Refs 146-151)

Inventors	Patents No. [Ref.]	Polymers	Title	Observations
Discher, DE. *et al.*	US20046835394 [146]	Polyethylene oxide (PEO) Poly(ethylethylene) (PEE) Poly(butadiene) (PB or PBD), Poly(styrene) (PS) and Poly(isoprene) (PI)	Polymersomes and related encapsulating membranes	Biocompatible vesicles comprising semi-permeable, thin-walled encapsulating membranes, and which comprise one or more synthetic super-amphiphilic molecules can controlled the encapsulation or release of materials from the vesicle by modifying the composition of the membrane.
Discher, DE. *et al.*	US20050003016 [147]	Polyethylene glycol (PEG) Polylactic acid (PLA), PEG-PLA, polycaprolactone (PCL), PEG-PCL and Polybutadiene	Controlled release polymersomes	The present invention provides methods for preparing stable, purely synthetic, self-assembling, controlled release, polyethylene oxide (PEO)-based polymersome vesicles, and the resulting PEO-based polymersomes capable of such controlled release, and methods of use therefor for the controlled transport and delivery of encapsulatable active agents contained therein.
Discher, DE. *et al.*	US20050048110 US20070218123 US20077217427 [148]	Polyethylene oxide (PEO) Poly(ethylethylene) (PEE) Poly(butadiene) (PB) Poly(styrene) (PS) and Poly(isoprene) (PI)	Polymersomes and related encapsulating membranes	The vesicles cross-linking provides mechanical control and long-term stability, thereby also providing a means of controlling the encapsulation or release of materials from the vesicle by modifying the composition of the membrane.
Hammer, DA. *et al.*	US20050019265 [149]	Poly(ethylene oxide)-Polyethylethylene Poly(ethylene oxide)-Poly(butadiene) Poly(ethylene oxide)-Poly(epsilon-caprolactone) or Poly(ethylene oxide)-Poly(lactic acid)	Polymersomes incorporating highly emissive probes	The instant invention concerns compositions comprising polymersomes, visible or near infrared emissive agents, and optionally a targeting moiety associated with a surface of the polymersome. The invention also relates to use of these compositions in the treatment of disease and in imaging methodology.
Therien, MJ. *et al.*	WO07038763 [150]	Poly(ethylene glycol)-Polycaprolactone diblocks and copolymer of Polyethyleneoxide and Polycaprolactone	Self-assembled biodegradable polymersomes	The invention concerns biodegradable polymersomes, more particularly, polymersomes made of poly(ethyleneoxide)-b-polycaprolactone diblock copolymers.
Qin, S. *et al.*	WO07075502 [151]	Poly(ethylene oxide-*O*-*N*-isopropyl-acrylamide (PEO-6-PNIPAAm)	Thermo-responsive block co-polymers, and use thereof	The thermo-responsive polymersomes display cold-controlled encapsulation near the physiological temperatures. Below the lower critical solution temperature (LCST), the thermo-responsive block displays hydrophilic properties, such that the polymersome dissociates, providing fast release of an active agent encapsulated therein.

Table 5. Marketed Products Utilizing Polymer-Based Nanotechnological Strategies for the Optimization of the Technological Aspects of Drugs

System	Trade name	Company	Application	Ref.
Dextran-nanoparticles	Feridex®	Advanced Magnetics Inc.	These long-circulating ultrasmall superparamagnetic iron oxides (USPIO) have applications in angiography, including tumor angiogenesis imaging, and it was recently demonstrated that USPIO may be used for magnetic resonance lymphograpy to detect cancer metastasis.	[153]
Silicone-nanoparticles	Lumirem®	Guerbet S.A.	Used in magnetic resonance imaging (MRI) to distinguish the loops of the bowel from other abdominal structures and physiology.	[154,155]
Albumin-nanoparticles	Abraxane®	American Bioscience, Inc.	The FDA approved paclitaxel albumin-bound particles for injectable suspension for the treatment of metastatic breast cancer after failure of combination chemotherapy or relapse within six months of adjuvant chemotherapy.	[156,157]

(Table 5) Contd….

System	Trade name	Company	Application	Ref.
Polyisohexylcyanoacrylate (PIHCA)-nanoparticles	Transdrug®	Bio-Alliance Pharma.	Doxorubicin Transdrug® has been approved by the FDA for the multi-centre randomised Phase II/III clinical trial for the treatment of hepatocarcinoma.	[158]
L-lysine dendrimer	VivaGel™	Starpharma.	VivaGel™ is a vaginal microbicide gel under development for the prevention of sexually transmitted infections (STIs). The first clinical trial under this new dendrimer-based drug was completed in 2004.	[159,160]

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