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Review Article

POLYMERIC NANOPARTICLES IN DRUG DELIVERY SYSTEMS CRITICAL REVIEW AND CONCEPTS

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Abstract

Nanoparticulate drug delivery systems seem to be a viable and promising strategy for the biopharmaceutical industry. In particular of interest are polymeric nanoparticles have attracted the interest of many research groups and have been utilized in an increasing number of fields during the last decades. They have been used frequently as drug delivery vehicles due to their grand bioavailability, better encapsulation, controlled release and less toxic properties. Various nanoparticulate systems, types of polymers used, fate of the polymeric nanoparticles in vivo, control release and improvement of therapeutic value of nanoencapsulated drugs are highlighted in the current review.

Keywords: Biodegradable polymers, drug delivery, nanocarriers, polymeric nanoparticles,

Introduction

In comparison to solid lipid nanoparticles or nanosuspensions polymeric nanoparticles (PNPs) consists of a biodegradable polymer. Biocompatibility is an essential feature for potential application as tissue engineering, drug and gene delivery and new vaccination strategies. Most biodegradable polymers consists of synthetic polyesters like polycyanoacrylate[1] or poly (D, L-lactide) and related polymers like poly(lactid acid) (PLA) or poly(lactide-co-glycolide) (PLGA) to give a few examples. Latest developments also include natural polymers like chitosan[2], gelatine[3, 4], and sodium alginate[5] to overcome some toxicological problems with the synthetic polymers.

PNPs represent a significant improvement over traditional oral and intravenous methods of administration in terms of efficiency and effectiveness[6]. The advantages of using PNPs in drug delivery are many, the most important being that they generally increase the stability of any volatile pharmaceutical agents and that they are easily and cheaply fabricated

in large quantities by a multitude of methods. Also, PNPs may have engineered specificity, allowing them to deliver a higher concentration of pharmaceutical agent to a desired location. Nanoparticles can be of two types- Nanospheres or nanocapsules. Nanospheres are considered as a matrix system in which the matrix in uniformly dispersed whereas nanospheres are systems where a polymeric membrane surrounds the drug in a matrix core.

PNPs depend on the choice of suitable polymeric system having maximum encapsulation (higher encapsulation efficiency), improvement of bioavailability and retention time. The desired PNPs are generally achieved by hit and trial method (no specific rule) however, the encapsulation process with PNPs are in more advance condition in comparison to other nanoparticle systems. These formulations are superior to traditional medicine with respect to control release, targeted delivery and therapeutic impact. These targeting capabilities of PNPs are influenced by particle size, surface charge, surface modification, and hydrophobicity. Among these, the size and size distributions of nanoparticles are important to determine their interaction with the cell membrane and their penetration across the physiological drug barriers. The size of nanoparticles for crossing different biological barriers is dependent on the tissue, target site and circulation.[7]

The choice of polymer and the ability to modify drug release from polymeric nanoparticles have made them ideal candidates for cancer therapy, delivery of vaccines, contraceptives and delivery of targeted antibiotics. Moreover, polymeric nanoparticles can be easily incorporated into other activities related to drug delivery, such as tissue engineering, and into drug delivery for species other than humans. From the polymer chemistry viewpoint, in future there will be a challenging field to create new polymers matching hydrophilic and lipophilic properties of upcoming drugs for smart formulation.

Polymers used in controlled drug delivery, including nanoparticles, may be classified as either (*i*) natural and synthetic, or (*ii*) biodegradable and non-biodegradable. Examples of naturally occurring biodegradable and biocompatible polymers used to prepare nanoparticles include: cellulose, gelatin, pullulan, chitosan, alginate, and gliadin. The characteristics and performance, particularly in vivo, of nanoparticles prepared using natural polymers may be less predictable as these polymers may vary widely in chemical composition and hence, physical properties. In addition, natural polymers are often mildly immunogenic. Conversely, it is possible to synthesize polymers with precise chemical

composition, resulting in highly predictable physical properties such as solubility, permeability, and rates of biodegradation.

As a result, synthetic polymers are also more easily designed for specific applications, such as controlled rates of dissolution, permeability, degradation, and erosion, as well as for targeting. Examples of synthetic biodegradable polymers used to prepare nanoparticles include: polylactide (PLA), poly-(lactide-co-glycolide) (PLGA), polyanhydrides, poly-ε-caprolactone, and polyphosphazene. Biodegradability and biocompatibility are important properties of polymeric materials that are to be injected or implanted into the body. Nonbiodegradable polymeric nanoparticles may be used for controlled drug delivery and also in the complimentary field of diagnostic imaging. Examples of nonbiodegradable, synthetic polymers used in drug delivery include polymethyl methacrylate while polystyrene particles have been used as diagnostic agents[8].

Natural Biodegradable Polymers Used To Prepare Nanoparticles

Alginates

Alginates are linear, unbranched polysaccharides composed of random chains of guluronic and mannuronic acids[9]. In aqueous media, the sodium ions from salts of these anionic, heteropolymers exchange with divalent cations, such as calcium, to form water-insoluble gels[10]. Because of the favorable conditions during manufacture, alginates are ideal carriers for oligonucleotides[11], peptides[12], proteins[13], water-soluble drugs, or drugs that degrade in organic solvents. Alginates are nonimmunogenic and available in a wide range of molecular weights as characterized by their inherent viscosity. Alginate nanoparticles are prepared by extruding an aqueous sodium alginate solution through a narrow-bore needle into an aqueous solution of a cationic agent, such as calcium ions, chitosan, or poly-l-lysine. These cations cross-link the guluronic and mannuronic acids to form an egg-box structure that forms the core of the gel matrix. In vivo, therapeutic agents are released when the matrix redissolves due to the reversible exchange of divalent cations with monovalent ions, especially sodium present in physiological fluid. A disadvantage of the use of alginates is that this reversible ion exchange may result in the rapid release of the therapeutic agent. However, an example of the use of alginate nanoparticles to sustain antibacterial drug levels above the minimum inhibitory concentration in the liver, lungs, and spleen after pulmonary administration was demonstrated using isoniazid, rifampicin, and pyrazinamide[14]. One method to prolong release from alginate particles is to coat them with a cationic polymer, for example, poly-l-lysine or

chitosan. In this application, the mass ratio of alginate to cationic polymer is critical in terms of release characteristics and particle size[15].

Chitosan

Chitosan is a natural polymer obtained by deacetylation of chitin, a component of crab shells. It is a cationic polysaccharide composed of linear β(1,4)-linked d-glucosamine. Chitosan can entrap drugs by numerous mechanisms including chemical cross-linking, ionic cross-linking, and ionic complexation[16, 17].

Gelatin

Gelatin is a natural, biodegradable protein obtained by acid- or base-catalyzed hydrolysis of collagen. It is a heterogenous mixture of single- or multi-stranded polypeptides composed predominantly of glycine, proline, and hydroxyproline residues and is degraded in vivo to amino acids. Gelatin nanoparticles are prepared by a two-step, desolvation process[18]. Gelatin nanoparticles have been used to deliver paclitaxel, methotrexate, doxorubicin, DNA, double-stranded oligonucleotides, and genes. PEGylation of the particles significantly enhances their circulation time in the blood stream[19] and increases their uptake into cells by endocytosis. Antibody-modified gelatin nanoparticles have been used for targeted uptake by lymphocytes[20].

Pullulan

Similar to dextran and cellulose, the glucans in pullulan are water-soluble, linear polysaccharides that consist of three α-1, 4-linked glucose molecules polymerized by α-1,6 linkages on the terminal glucose[21]. Pullulan is a fermentation product of the yeast *Aureobasidium pullulans*. When made hydrophobic by acetylation, these polymers will self-associate to form nanoparticles with a hydrophobic core that will encapsulate hydrophobic drugs. Pullulan nanoparticles have been prepared by dialysis of an organic solution against water. These delivery systems have been used in delivering cytotoxic drugs, genes, and as pH-sensitive delivery systems[22].

Gliadin

Gliadin is a glycoprotein that, as a component of gluten, is extracted from glutenrich food such as wheat flour. They are slightly hydrophobic and polar. Bioactive molecules of variable polarity can be encapsulated into gliadin nanoparticles. Gliadin nanoparticles can be prepared by a desolvation method that exploits the insolubility of this polymer in water[23].

Gliadin nanoparticles have been used to deliver *trans*-retinoic acid, α-tocopherol, carbazole[24] and vitamin E. Lectins have been conjugated to the surface of gliadin nanoparticles to target the colon and treat *Helicobacter pylori* infections.

Synthetic Biodegradable Polymers Used to Prepare Nanoparticles

Polylactide and Polylactide-co-Glycolide

The hydrophobic PLA may be used alone or copolymerized with poly-glycolic acid to form a range of PLGA of widely varying polymeric ratios and hence physicochemical properties. These FDA-approved polymers have been widely used in drug delivery including nanoparticles. PLA and PLGA polymers degrade by random bulk hydrolysis that is catalyzed in acidic media[25].

Polyanhydrides

Polyanhydrides are biodegradable polymers with a hydrophobic backbone and a hydrolytically labile anhydride linkage. They are synthesized by ring-opening polymerization and degrade by surface hydrolysis. The application of polyanhydrides has been limited to film and microsphere formulation for sustained release of a drug or protein at the site[26].

Poly-ϵ-Caprolactones

Methods used to prepare nanoparticles using poly-ε-caprolatones have been previously reviewed[27] and include emulsion polymerization, solvent displacement, dialysis, and interfacial polymer deposition. These semicrystalline polymers are chemically stable, possess a low glass transition temperature, and degrade slowly. Hence, they have the potential for long-term drug delivery. Poly-ε-caprolactone nanoparticles have been used as vehicles to deliver a wide range of drugs including tamoxifen, retinoic acid, and griseofulvin.

Polyalkyl-Cyanoacrylates

Polyalkyl-cyanoacrylate (PACA) nanoparticles are prepared by the conventional emulsion-evaporation technique. In addition to sustaining drug release, PACA nanoparticles have the ability to overcome multidrug resistance at both the cellular and subcellular levels[28, 29].

Nonbiodegradable Polymers Used To Prepare Nanoparticles

Polymethacrylate (PMA) and polymethyl methacrylate (PMMA) have been widely used in a variety of pharmaceutical and medical applications. Specifically, PMMA Eudragit® nanoparticles can be prepared by nanoprecipitation method

that involves adding hydroalcoholic solution of the polymer to an organic solvent. Incorporation of poly-acrylic acid into nanoparticles increased the transfection efficiency of DNA. The side chain of PMMA can be modified to make these polymers possess pH-dependent solubility and has been used to prepare pH-sensitive nanoparticles to increase the oral bioavailability.

Overview of the Preparation Techniques for Polymer Nanoparticles[30]

PNPs can be conveniently prepared either from preformed polymers or by direct polymerization of monomers using classical polymerization or polyreactions [24]. Methods like solvent evaporation, salting-out, dialysis and supercritical fluid technology, involving the rapid expansion of a supercritical solution or rapid expansion of a supercritical solution into liquid solvent, can be utilized for the preparation of PNP from preformed polymers. On the other hand, PNPs can be directly synthesized by the polymerization of monomers using various polymerization techniques such as micro-emulsion, mini-emulsion, -free emulsion and interfacial polymerization. An illustration of different preparation techniques for PNP is given in Figure. 1. The choice of preparation method is made on the basis of a number of factors such as the type of polymeric system, area of application, size requirement, etc. For instance, a polymeric system that is developed for an application in the biomedical or environmental fields should be completely free from additives or reactants such as surfactants or traces of organic solvents. In this case, techniques like RESS (rapid expansion of a supercritical solution) or RESOLV (rapid expansion of a supercritical solution into a liquid solvent) can be selected, as they do not utilize any surfactant or organic solvent during the PNP preparation. These are just a few of many factors that have to be considered before choosing a particular technique for the PNP preparation. Table 1, below gives a list of drugs investigated for Nanoparticulate Drug Delivery system.

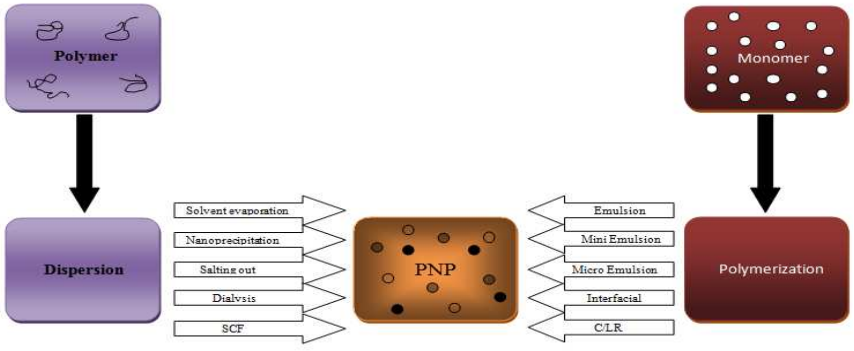

Figure 1. Schematic representation of various techniques for the preparation of polymer nanoparticles.
SCF* Supercritical fluid technology, C/LR* Controlled/ living radical.

Table 1: List of drugs investigated for Nanoparticulate Drug Delivery system.

Sr. no.	Name of the drug	Carrier References	Reference no.
1.	Xanthone	PLGA	31
2.	Triclosan	Submicron emulsion and NCs	32
3.	Tobramycin	SLN	33
4.	Tamoxifen	Polycaprolactone NPs	34
5.	Praziquantel	PLGA NC	35
6.	Mitoxantrone	Magnetic NPs	36
7.	Loperamide	Polysorbate 80-coated PBCA NPs	37
8.	Isoniazide	PLGA NC	38
9.	Indomethacin	SLN	39
10.	Flurbiprofen	Nanosuspension	40
11.	5-Fluorouracil	Colloidal NPs	41
12.	Cyclosporine	SLN	42
13.	Clozapine	SLN	43
14.	Cisplatin	Polymeric micelles	44
15.	Budesonide	PLA NPs	45
16.	Betamethasone	Calcium carbonate NPs	46
17.	Adriamycin	PBCA NPs	47

NC* Nanocapsules; NPs* Nanoparticles; PBCA* Polybutylcyno acrylate; PLGA* Poly-lactic-co-glycolic acid; SLN* Solid–lipid nanoparticles.

Pharmacokinetics and Biodistribution of Nanocarriers Administered Orally

As discussed, size, composition, surface characteristics and architecture of the polymeric nanocarrier are determinant for the optimization of oral formulations: they influence nanocarrier stability and uptake by enterocytes or M cells. After absorption, drug and/or drug loaded can be included in cytoplasmic vesicles or diffuse in the cytoplasm and be discharged in the serosal spaces to gain access to the mesentheric lymph or blood. Water-insoluble polymers forming stable nanocarriers (e.g. PLGA) are more likely to be absorbed as particles whereas polymers forming less stable particles forming polyelectrolyte complexes (e.g. chitosan) or polymeric micelles will partly dissociate and will not be completely absorbed as a particle. Whether the polymer itself will be absorbed will depend on the physicochemical properties of the polymer e.g. its molecular weight, conformation, and hydrophobicity. When taken up byMcells, nanoparticles will be transcytosed close to immune cells and are more likely to be delivered to the GALT and lymphoid cells[48]. In contrast, nanoparticles, micelles or drugs taken up by absorptive enterocytes will be mainly delivered in the blood. The characterization of both M cells and enterocytes absorption and crossing to the blood and lymph vessels has not been systematically analyzed. Once absorbed in the blood, the chemical and physical properties of the nanoparticleswhich are essential parameters for oral absorptionwill also affect pharmacokinetics and biodistribution.

The factors that influence their pharmacokinetics have been recently reviewed[49]. They include (i) surface modification with PEG to avoid uptake by the reticulo-endothelial system (RES) and prolong circulation half-life, (ii) small size to decrease uptake by RES and allow diffusion in the tissues and (iii) neutral charge. Therefore, whether the drug is absorbed either free or encapsulated is essential to assess. Compared to the high amount of in vitro studies described in literature, the oral delivery of peptides and proteins or vaccine using polymeric nanoparticles in vivo has been less described. Moreover, most of the studies, in particular insulin, focus on the evaluation of the plasma pharmacokinetics of the drug and/or its therapeutic or immune response. The fate of the nanoparticles and the polymers is neither well understood nor investigated. Nevertheless, recently published papers using advanced imaging and analytical technologies give new insights on their fate. Data cannot be compared and lead to sometimes controversial conclusions. A few selected examples indicate that the techniques are now available for a better understanding of the fate of particles. Oral delivery of pH-responsive nanoparticles composed of chitosan and poly-glutamic acid loaded with aspart-insulin was studied by single-photon emission computed tomography. Insulin was absorbed into the systemic circulation while the carrier chitosan was mainly retained in the oral tract[50]. PLGA nanoparticles delivered orally were detected after 7 days in several organs including liver, spleen, lungs, brain and kidneys. Most of the particles were located in the liver. PEGylated PLGA-based nanoparticles were rapidly taken up by peritoneal macrophages[51]. Multilayered nanoparticles showed co-localization in the small intestinal mucosa of insulin and alginate.

Oral application of polymeric micelles is not commonly studied and the fate of micelles is generally not investigated as the majority of micellar systems are being developed for injections rather than oral administration. Due to their dynamic structure, themechanisms of drug absorption after oral delivery of drug loaded polymeric micelles differ from nanoparticle uptake. Indeed, both the micelles and the free drug released from the micelles can be absorbed. Above the critical micellar concentration (CMC,) the drug encapsulated in micelles and the free drug can be absorbed whereas below CMC, the drug is released by micelle disassembly. Hence, bothmicelles and unimers can be absorbed in the systemic circulation. Oral delivery of PEG-p (CL-co-TMC) resulted in 40% absorption of the polymer. Pluronic-PAA copolymers demonstrated that these molecules are excreted when administered orally and do not absorb into the systemic circulation[52].

The process of opsonization is one of the most important biological barriers to controlled drug delivery. Injectable polymeric nanoparticle carriers have the ability to revolutionize disease treatment via spatially and temporally controlled drug delivery. However, opsonin proteins present in the blood serum quickly bind to conventional non-stealth nanoparticles, allowing macrophages of the mononuclear phagocytic system (MPS) to easily recognize and remove these drug delivery devices before they can perform their designed therapeutic function. To address these limitations, several methods have been developed to mask or camouflage nanoparticles from the MPS. Of these methods, the most preferred is the adsorption or grafting of poly (ethylene glycol) (PEG) to the surface of nanoparticles. Addition of PEG and PEG-containing copolymers to the surface of nanoparticles results in an increase in the blood circulation half-life of the particles by several orders of magnitude. This method creates a hydrophilic protective layer around the nanoparticles that is able to repel the absorption of opsonin proteins via steric repulsion forces, thereby blocking and delaying the first step in the opsonization process[53].

Table 2: Marketed Nanotechnology Based Approaches to Improve Bioavailability.

Product	Drug application	Method	Licensed to/Technology
Vivage	Microbicide/Virucide	Dendrimer	Starpharma
Doxii	Doxorubicin, anticancer	Liposomes	Centocor Ortho Biotech Inc
DaunoXome	Doxorubicin, anticancer	Liposomes	Gilead Scuiences/Diatos
AmBisome	Amphotericin B, antifungal	Liposomes	Gilead sciences/Astellas Pharma
Amphotec	Amphotericin B, antifungal	Liposomes	Three Rivers Pharmaceuticals
Neolipid	Delivery platform, anticancer drugs	Liposomes	Neopharm
Superfliuids	Delivery platform	Liposomes	Aphios Corporation
Taxosomes	Paclitaxel	Liposomes	Aphios Corporation
ALERT	Delivery platform	Liposomes	Azaya therapeutics
FloidCrystal	Delivery platform	Lipid nanoparticles	Camurus AB
Estrasorb	Transdermal deliveery	Micelle	Graceway Pharmaceuticals
Nanocarrier	Delivery platform	Micellar nanoparticles	Nanocarrier
Nanoviricida/Ther acour	Antiviral drugs	Micelle	Nanoviricides inc
Medusa platform	Delivery platform/various drugs	Nanogel	Flamel Technologies
Rapamune	Sirolimus	Naocrystal	Wyeth/Elan
Emend	Aprepitant	Naocrystal	Merck/Elan
TriCor	Fenofibrate	Naocrystal	Abbott/Elan
Megace* ES	Megestrol acetate	Naocrystal	Par Pharmaceutical Inc/Elan

Abelcet	Amphotericin B	Naocrystal	Sigma-Tay Pharmaceuticals/Elan
Triglide	Fenofibrate	Naocrystal	First Horizon Pharmaceutical/Skyepharma
Bioral	Delivery platform, Amphotericin B	Naocrystal	Biodelivery Sciences International
Biosilicon	Delivery platform, antifungals (Amphotericin B)	Nanoporous siliconBiosa	pSivida Corp
BioAir, BioOral BioVant, BioLook	Delivery platform	Calcium phosphate (CaP) nanoparticles	BioSante Pharmaceuticals
NanoDRY NanoCOAT NanoQUAD	Delivery platform	Nanopowders	Nanotherapeutics
Protein Stabiliced Nanoparticles	Delivery platform	Polymeric nanoparticles	Azaya Therapeutics
Abraxane	Paclitaxel	Polymeric nanoparticles	Abraxis Biosciences inc
Transdrug	Delivery platform, Doxorubicin Transdrug	Polymeric nanoparticles	Bioalliance Pharma
Oaclitaxel (Genexol-PMP), protein delivery and others	Delivery platform	Polymeric micelles (genexol-PM) Polymeric nanoparticles	Samyang
Biorise	Delivery/drug bioavailability platform	Polymeric network	Eurand
ONCASPAR	Pegylated L-asparaginase for treatment of acute lymphoblastic leukaemia	Polymeric nanoparticles	Sigma-Tau Pharmaceuticals
Various drug applications	Delivery platform	Solid lipid nanoparticles (SLN) and hybrid lipid-polymer nanoparticles (HLN)	Alpharx

Conclusion

During the last years, polymeric nanocarriers have been studied for oral drug delivery at preclinical level to establish proof of concept that they can be useful to deliver drugs by the oral route. The reasons for this increasing interest result from the unfulfilled medical needs that must be addressed. Oral delivery of biopharmaceutical macromolecules (proteins, monoclonal antibodies, and vaccines) by nanoparticles could offer a promising alternative to parenteral administration for a patient-friendly, needle-free delivery. Indeed, many publications and patents demonstrate that

polymeric nanoparticles enhance the bioavailability of biopharmaceuticals in preclinical model. The field of polymeric nanoparticles is now changing from a nascent stage to an emerging stage and requires lot of focus on fundamental research to develop new functional materials, using these captivating particles. Future research work should be focused on the development of techniques that provide precise control over the particle size and morphology, which are the key determinants of the properties and applications of these particles. These efforts will speed up the commercial utilization of polymeric nanoparticles. However whether these delivery systems could be marketed as effectively as conventional ones still remains a mystery to be solved.

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