Nanocarriers in modern drug delivery systems

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Introduction

Nanotechnology consists in manufacturing nanometre-sized materials and structures, i.e. up to 100 nm. There is no doubt that it is one of the most dynamically developing branches of science and technology. This is a multidisciplinary branch, as it combines the elements of solid-state physics, chemistry, material science and molecular biology that interpenetrate each other. Nanotechnology is widely used in medical science. Reducing the size of a selected material to a nanometric scale makes it possible to utilise them in numerous potential applications.

Drug carriers can be built of carbon, polymeric and magnetic materials, as well as of their combinations, thus creating complexes – core-shell structures. The main goals of nanopharmacology are the targeted therapy (TT) and the controlled drug delivery systems (DDS). The basic component of the DDS includes using an appropriate carrier that should not be toxic, should bind the drug properly, making it also possible to release it at the target site keeping the therapeutic concentration range. In addition, the role of nanoparticles (NP) used is to improve the therapeutic value of applied drugs by changing their solubility, retention time and the penetration of biological barriers [1]. The bioavailability enhanced by the above-mentioned mechanisms increases the therapy efficacy and minimises side effects resulting from a prolonged administration of medication. The conjugates of nanoparticle–drug offer a lot of advantages: they reduce therapy costs targeted at the proper site by guiding molecules (folic acid (FA), antibody (Ab) or RGD – the integrin recognising peptide - $\alpha_v\beta_3$) – they reduce the general toxicity of pharmaceuticals and increase the drug tolerance in patients. The very process of drug nanoencapsulation increases the efficacy, specificity and the therapeutic index of immobilised active substances [2, 3]. This is not only the carrier biotransformation inside the body that counts, but also its size is of equal importance. The size of molecules affects all the stages of pharmacokinetics, e.g. while the drug penetrates cell membranes (blood vessel walls, epithelia) and is excreted from the body – avoiding accumulation and related side effects. Particular types of nanoparticles show different indications for use depending on the area of the body. As a result, nanocarriers should show specific features necessary to reach a predefined goal, i.e. a properly sized carrier, type of attaching the drug to the NP, surface properties (hydrophilicity/hydrophobicity), the presence of surface functional groups, biodegradability and physical properties because of environmental changes, such as pH, temperature and the features of the very carrier, including surface potential and magnetism [4].

Drug immobilization on nanocarriers is carried out by using physical processes: adsorption, absorption and encapsulation, and chemical processes: covalent bonds, ionic bonds and the van der Waals forces.

Polymeric nanoparticles

Recently the chemistry of polymers has been focusing on utilising them as biocompatible carriers in the controlled drug delivery systems. Widely used in the drug delivery and imaging applications are the polymeric nanoparticles that can be defined as stable, colloidal structures occurring in the form of nanospheres and nanocapsules [5]. Depending on their chemical composition, polymeric nanoparticles can originate from synthetic polymers (e.g. polycaprolactone (PCL), polyacrylamide, poly(methyl methacrylate) and natural ones (e.g. gelatine, chitosan, albumins). The size of nanostructures should range from 5 to 10 nm, with the upper size limit of up to 1000 nm, however, the sizes of the most commonly obtained structures range from 100 to 500 nm.

Because of their low toxicity and negligible side effects, the main materials used in the nanopharmacology include: biodegradable polymers, e.g. CS [6], PLA [7], gelatine [8], HMPA (N-(2-hydroxypropylo) metacrylamide) [9] and their copolymers, e.g. PLGC (lactic and glycol acid copolymer and caprolactone copolymer) [10], PLGA [11]. This is mainly due to its complete degradation inside the human body, making it possible to reach the renal threshold for those substances and excrete them easily. In addition, des Rieux et al. [12] have found that polymeric nanoparticles show stability in blood, do not stimulate the immune system and inflammatory processes, do not activate platelets and neutrophils and are not degraded in the reticuloendothelial system (RES) [12].

There are six classical methods for obtaining polymeric capsules described in the literature. The methods include: nanoprecipitation [13], emulsification-diffusion [14,15], emulsification–coacervation [16,17], double emulsification [18], surface polymerization [19,20] and layer-by-layer polymerization [21]. The multi-structural structures with precisely defined morphology, shape and chain length are obtained using the atom transfer radical polymerization (ATRP). The ATRP is an effective technique for designing and controlling a polymer structure, which is extremely important when using polymers in medical applications [22].

Polymeric nanoparticles are usually coated with a layer of non-ionic surfactants, such as: poloxamers and poloxamines, used for reducing the carrier opsonisation and phagocytosis and inhibiting intermolecular van der Waals bonding [23]. In addition, surfactants play a significant role during the synthesis of polymeric nanocapsules by taking part in controlling the size of molecules [24]. The key role in the drug delivery process is also played by the topology of a polymeric nanoparticle. Research proves that linear polymers go through the kidneys more easily than branched polymers, and as a result the shape and flexibility of a polymer has a significant impact on pharmacokinetics and the accumulation in the region of neoplastic hyperplasia. It has also been proved that branched polymers with a mass exceeding 30 kDa (renal threshold limit) show considerably longer time of retention in the bloodstream and feature a larger area below the pharmacokinetic curve as compared with linear structured polymers adequate in mass. It results in higher accumulation of branched polymers in the region of a tumour [25].

The active substance immobilization on polymeric nanoparticles can be performed by using the processes of absorption, adsorption,

encapsulation or a chemical reaction (covalent bond). The examples of drug-nanoparticle conjugates are listed in Table 1 [91÷100].

Dendrimers are a specific type of polymers. Unlike linear macromolecules their structure consists of three basic components, i.e.: core (constituting a single atom or a symmetric molecule containing two identical function groups), arms (created of monomers, the number of which corresponds to subsequent generations) and surface functional groups (providing the dendrimer molecule with features) [26]. Dendrimers are built by gradually adding polymer layers around the central core, thus creating subsequent generations; this process is referred to as divergent synthesis.

Particular poly(amido amine) (PAMAM) dendrimer generations can be indentified in terms of size with biologically active substances, e.g. G4 – cytochrome C, G5 – haemoglobin etc. The unique feature typical for those structures is their polyvalence, associated directly with the presence of many functional groups on their surface. Polyfunctionality facilitates the immobilization of drugs and other pharmacokinetic modulators (PEG chain [27], FA [28], RGD peptide [29] etc.) on their surface, modifying it depending on the intended use [30, 31]. There is no doubt that these properties are the main reason for showing significant interest in using the structures as carriers in the drug delivery systems (DDS).

The architecture of those compounds is widely represented in nature, e.g. in the form of tree branch and root system arrangements as well as in the human body, e.g. in the bronchioli structure. At the nanometre level the dendrimeric structures occur in amylopectins and proteoglycans [32]. A lot of advantages have been observed in the fact of utilising dendrimers as the carriers of drugs and other biologically active substances. One of them includes their size allowing them to penetrate through network of vessels to a target site, e.g. to a neoplastic cell. An additional advantage includes a high level of monodispersity and a definite number of surface functional groups, which makes it possible to connect a specified number of drug molecules to the carrier surface at a stoichiometric ratio. The immobilization of active substance on a dendrimer can be performed in two basic ways. The first method consists in binding (covalently or by electrostatic forces) a drug molecule with the surface groups of the dendrimer. The other method consists in incorporating the compound into the dendrimer cavities. Closing the drug inside the carrier is referred to as encapsulation [33]. Both methods have been used to immobilize many drug substances. The examples of those connections are listed in Table 1 [101÷110].

Carbon Nanomaterials

The best described carbon nanomaterials in terms of use as drug carriers are carbon nanotubes (CNTs). It results from the fact that they are susceptible to chemical functionalisation – capacity to immobilize a drug substance on its surface [34]. The nanotube surface functionalisation can be covalent or non-covalent [35]. Additional benefits include their unique physical and chemical properties: large specific surface area, excellent electrical and thermal conductivity and high mechanical strength [36, 37]. Considering their architecture, CNTs are cylindrical structures built of hexagonal carbon rings, hybridised in a trigonal arrangement– sp2. The distance between single atoms equals approximately to 1.4 Å. The nanotube wall is made of a single layer of graphene (single walled carbon nanotubes - SWNTs) or multiple layer of graphene, in the case of multi-walled structures (multi walled carbon nanotubes - MWNTs). At the ends of those structures there are stoppers in the form of a semicircular mesh of carbon atoms – also referred to as flattened fullerenes [35]. Carbon nanotubes can be synthesised in a great number of ways, e.g. using the electric arc method [38], laser ablation [39], and chemical vapour deposition [40].

A basic requirement to be met by a carrier is solubility in aqueous environments (the environment of the digestive system, blood). It is necessary to obtain the basic stages of biodistribution in the human body. In addition, of significance here is the fact of material non-immunogenicity and biocompatibility. In order to provide it the nanotube surface can be modified by: PEGylations [41, 42], adding an amphiphilic copolymer [43], immobilizing the PAMAM dendrimer [44] and by hydroxyapatite-based functionalisation [45].

Drug substances can be immobilized in the three basic ways. The first method consists in drug encapsulation inside a nanotube [46] and it surpasses traditional drug immobilization methods, as it provides protection against a premature degradation during the transport to the cell and releases the drug only under specific conditions [47]. The two remaining methods consist in attaching the drug to the nanotube surface. It can be done by creating a covalent bond [48] or a non-covalent bond by electrostatic forces, chemical adsorption [49], etc. The examples of pharmaceuticals conjugated with CNTs are listed in Table 1 [111÷118].

Magnetic Nanoparticles

Many materials show magnetic properties, including: metals (iron, nickel, manganese, cobalt), metal alloys (FePt), metal oxides [50÷54]. By narrowing down the wide scope of magnetic nanoparticle applications to medical applications only, the selection of materials and the method of synthesis become considerably limited. This is mainly due to, among other things, lack of biocompatibility of some materials, inducing cytotoxical reactions in the body as well as the ignorance of biotransformation for certain materials. A nanocarrier used in medical applications should feature a tissue-level and cellular biocompatibility. Amongst all the magnetic nanostructures, this requirement is met only by iron nanoparticles, especially its two oxides (magnetite and maghemite) [55]. Their biocompatibility results from the fact that iron is present in many structures of the human body (liver, spleen, heart) and constitutes a structural base for important biological compounds: haemoglobin, myoglobin and ferritin [56]. The cases of using nickel and cobalt nanoparticles described in literature show the existence of anaphylactic reactions, cellular stress (Fenton's reagent) as well as the induction of acute toxic conditions [57]. Thanks to their magnetic properties, iron nanoparticles are used in a growing number of new branches of medicine. They are used both at the diagnostic and therapeutic level. As a diagnostic tool of the future they can be used for: separating and sorting cells [58], cleaning biological materials [59], immobilizing proteins [60], enzymes [61] and nucleic acids [62], as well as imaging contrast agents in MRI [63]. For therapeutic purposes they are used as drug carriers [64], to induce hypertermia [65], and in a MRI-guided radiotherapy [66]. Currently, many preparations based on iron nanoparticles, and their derivative core-shell structures are at the stage of clinical trials [4].

The literature describes a lot of methods for synthesising magnetic nanoparticles, e.g. Massart's and its modifications [67, 68], Modlay's [69], Sun's [70] by thermal decomposition of an iron pentacarbonyl precursor [71] and as a result of reductive co-precipitation [72]. The majority of the above-mentioned methods for synthesising magnetic nanoparticles use their co-precepitation from the solution of iron salt (II) and iron (III) in an alkaline environment. Depending on the use of the synthesised nanomaterial, a significant role is played by its size, shape and the character of surface functional groups. Laboratory experiments show that the diameter of nanoparticles can be adjusted by a strict control of reaction conditions, including time, temperature and the type of mixing. Furthermore, depending on the production method, reaction conditions and components used, nanoparticles adopt a spherical, disc-like or cubic shape [73].

Magnetic nanoparticles can be simple carriers (non-shelled, nude structures) or be a core part in the complex core-shell type structures. The shell on the magnetic core fulfils a lot of significant functions. Its presence is aimed at improving physical and chemical properties of the carriers. It plays a key role in protecting and stabilising the core against the influence of acid, alkaline and oxidising environments, prevents aggregation, provides the nanoparticle with a surface charge and chemical profile [74]. Additionally enriched by surface functional groups it allows for using subsequent modifications, i.e. makes it possible to covalently bind to a drug substance or immobilize the homing molecules, e.g. monoclonal antibodies, peptides and fluorescence compounds useful in detection [75]. The presence of specific ligands makes nanoparticles multi-functional, which is a key component of modern targeted therapy [76÷78]. The nanostructure combining the features of a biosensor and a drug carrier would make it possible both to provide diagnostic and treatment. This is of importance to obtain a quick progress in the anti-cancer therapy. Implanting such nanoparticles in patients would result in obtaining a synergy of therapy and diagnostics, offering the advantage no need for constant "overloading" the patient's body with different chemical compounds. Furthermore, the presence of imaging contrast agents on the surface of nanoparticles allows for localising them and the lesion in the body. Depending on the compound features, the imaging can be performed using different methods: fluorescent-based, optical, magnetic resonance or nuclear [76]. Combining the imaging diagnostics with a therapy allows us to observe the treatment efficacy and tumour regression in real time [79]. In addition, the surface functionalisation with a polymeric shell prevents from quick excretion of nanoparticles out of the body and their degradation in the reticuloendothelial system (RES), it is also of importance for limiting the toxicity of nanocarriers [80]. A perfect shell should feature high affinity to its core and, what is even more important, should not induce the processes of immune response (primary and secondary). It should also prevent the carrier from opsonisation by the plasma proteins. The literature describes a lot of shell types on the magnetic core that most frequently include: lipid [81, 82], protein [83], polysaccharide [84], dendrimer [85], silicon [86] and polymeric shells [87, 88]. A pharmaceutical can be immobilized using the encapsulation method during carrier synthesis or by using the surface functional groups to covalently bind a drug molecule. The examples of drug-magnetic nanoparticle conjugates are listed in Table 1 [87, 119÷129].

Nanoparticle transport mechanisms

The process of binding a drug with its carrier is frequently associated with the change in its distribution. The change in distribution is advantageous, if it results in a higher drug accumulation inside the target cell, e.g. in the neoplastic tumour. There are two main target transport mechanisms: active and passive. In the case of the active transport, the nanocarrier shell is modified with a specific guiding ligand. They can include macromolecular compounds: monoclonal anti-bodies or active peptides, proteins and aptamers [89], and micromolecular ones, e.g. monosaccharides, folic acid. The role of these compounds is to bind to the receptor in a specific and affinity-based way on the surface of a lesion tissue, e.g. by neoplastic hyperplasia. The passive transport mechanism uses the phenomenon of enhanced permeability of capillary endothelium cells (EHR) at the site of neoplastic process. It results from the unique anatomic structure of vessels and the process of intense angiogenesis within the tumour as well as the trend to retain micro- and macromolecular substances within a lesion tissue [90].

Table 1

Using nanoparticles as drug carriers (including the type of nanoparticles and the method of drug substance immobilization)

POLYMERIC NANOPARTICLES				
Drug	**Therapeutic group**	**Carrier**	**Immobilisation method**	**Literature**
Camptothecin (CPT)	anti-neoplastic	PLGA	Encapsulation Nanoprecipitation	[91]
Celecoxib	anti-inflammatory	PLGA	Encapsulation Emulsification-evaporation and salting out	[92]
Cisplatin	antineoplastic	PLGA-mPEG	Encapsulation Cross-linking using carboxymethylcellulose	[93]
Doxetaxel	anti-neoplastic	PAL-PCL	Encapsulation nanoprecipitation	[94]
Triptorelin	hormonal	PLGA	Encapsulation Double emulsification-evaporation	[95]
Dexametasone	hormonal, anti-inflammatory	PLGA	Encapsulation, Evaporation	[96]
Haloperidol	psychotropic	PLGA/PAL	Encapsulation, Emulsification-evaporation	[97]
Clonazepam	psychotropic	PNPCL	Encapsulation, Evaporation	[98]
Doxorubicin +curcumin	anti-neoplastic	PBCA	Co-encapsulation Emulsion and interphase polymerisation	[99]
Low molecular weight heparin (LMWH)	anti-thrombotic	CS	Encapsulation Ionic gelation/ ionotropic gelation	[100]
DENDRIMERS				
Drug	**Therapeutic group**	**Carrier**	**Immobilisation method**	**Literature**
5- aminosalicylic acid (5-ASA)	anti-inflammatory	PAMAM G3	Covalent bond using PABA and PAH	[101]
Propranolol	Hypotensive, antiarrythmic	PAMAM G3, laurylo-PAMAM G3	Covalent bond	[102]
Ketoprofen	anti-inflammatory	PAMAM	Encapsulation	[103]
7-ethyl-10-hydroxycamptothecin (SN-38)	anti-neoplastic	PAMAM G4	Ionic forces	[104]
Doxorubicin	anti-neoplastic	PAMAM	Encapsulation	[105]
Cisplatin	anti-neoplastic	PAMAM-COONa	Covalent bond	[106]
Naproxen	anti-inflammatory	PAMAM G0	Amide or ester covalent bonds	[107]
Ibuprofen	anti-inflammatory	PAMAM G4	Amide or ester covalent bonds	[108]

Methotrexate	anti-neoplastic	PAMAM	Amide covalent bonds, coupled with DCC	[109]
Erythromycin	antibiotic	PAMAM	Ester covalent bond	[110]
NANOTUBES				
Drug	**Therapeutic group**	**Carrier**	**Immobilisation method**	**Literatura**
Doxorubicin	anti-neoplastic	SWNT	Non-covalent bond	[111]
Cisplatin	anti-neoplastic	SWNT	Covalent bond Coupled with EDC	[112]
Paclitaxel	anti-neoplastic	SWNT- PEG	Ester covalent bond	[113]
Sulfametoxazole	antibiotic	f-CNTs	Non-covalent bond	[114]
Amphotericin B	antibiotic	f-CNTs	Covalent bond	[115]
Diclofenac	anti-inflammatory	MWNT-CMG	Encapsulation	[116]
Daunorubicin	anti-neoplastic	SWNT	Encapsulation	[117]
Gemcitabine	anti-neoplastic	SWNT	Encapsulation	[118]
MAGNETIC NANOPARTICLES				
Drug	**Therapeutic group**	**Carrier**	**Immobilisation method**	**Literature**
Cisplatin	anti-neoplastic	MNP@PLC	Encapsulation , emulsification	[119]
Gemcitabine	anti-neoplastic	MNP@PLC	Encapsulation Emulsification-diffusion	[87]
Doxorubicin	anti-neoplastic	MNP@PS-b-PAA	Encapsulation Micro emulsification	[120]
Doxorubicin	anti-neoplastic	MNP@ PEG-PAL-PEG-acrylate	Encapsulation, Double emulsification	[121]
Cisplatin, siRNA	anti-neoplastic	MNP@PPI G5	Encapsulation	[122]
Methotrexate	anti-neoplastic	MNP@APTMS	Amid covalent bond	[123]
Methotrexate	anti-neoplastic	MNP@PEG	Amid covalent bond	[124]
Dopamine	b-adrenomimetic	MNP@SiO_2	Covalent bond	[125]
Ciprophloxacin	antibiotic	MNP@PEG-PMMA	Encapsulation free radical polymerisation and precipitation	[126]
5-fluorouracil	anti-neoplastic	MNP@EC	Encapsulation Emulsification-evaporation	[127]
Ftorafur and 5-fluorouracil	anti-neoplastic	MNP@PBCA	Encapsulation- anionic polymerisation and adsorption	[128]
t-PA	fibrynolytic	MNP@TEOS/ PEG	Covalent bond	[129]

Abbreviations: PLGA (poly(lactic-co-glycolic acid); mPEG (monomethoxy-poly(polyethylene glycol) PAL(***poly(lactic acid***)); PCL(poly(ε-caprolactone) PNPCL(poly(Nisopropylacrylamide)-b-poly(ε-caprolactone)); PBCA- (poly(butyl cyanoacrylate)): CS – chitosan; PAMAM (polyamidoamine) ; PABA (p-aminobenzoic acid); PAH (p-aminohippuric acid); DCC(dicyclohexylcarbodiimide) - N,N'-dicykloheksylokarbodiimid; EDC (1-(3-(dimethylamino) propyl)-3-ethylcarbodiimide hydrochloride); SWNT (single walled carbon nanotubes), MWNT (multi walled carbon nanotubes); CNT (carbon nanotubes); fCNT (functionalized carbon nanotubes); CMG (carboxymethyl guar gum); MNP (magnetic nanoparticles); Fe_3O_4; PS-b-PAA (poly (styrene-block-allyl alcohol)); FA / methoxy PEG-PAL-PEG-acrylate (triblock copolymers R (R = methoxy or folate (FA))-PEG(114)-PAL(x)-PEG(46)-acrylate); PPI(Poly(Propyleneimine))–Poli(propylenoimina);APTMS((3-aminopropyl)trimethoxysilane); PEG (poly(ethylene glycol)); SiO_2 – silica; PMMA (polymethyl methacrylate); EC (ethylocellulose); TEOS (tetraethyl orthosilicate); t-PA (tissue plasminogen activator).

Summary

The recently observed dynamic development of nanotechnology has introduced innovations in many branches, including medical sciences. The nanoparticles used in biomedical applications (DDS, targeted therapy) must be persistent, non-toxic and cannot be susceptible to the influence of the surrounding environment. Therefore, so important is the chemical composition of their shell. It is associated with selecting an appropriate and biocompatible shell for the cells of the human body, aimed at protecting metallic molecular cores against oxidising, and at the same time making it possible to attach specified functional molecules: drugs, guiding molecules and contrast agents. The most promising seem to be magnetic iron-based nanoparticles, as this element is a natural component of living organisms. The magnetic properties enrich them with additional capacities. As compared with other nanocarriers, whose pharmacokinetics and side effects cannot be fully predicted, their benefits and side effects are well known. Nanoparticles have already been in use in nanopharmacology, diagnostics (in vitro and in vivo) and medical analytics, but their huge application potential remains still unleashed.

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