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TARGETED TRANSPORT AS A PROMISING METHOD OF DRUG DELIVERY TO THE CENTRAL NERVOUS SYSTEM (REVIEW)

A. I. Skorobogatova,[1,2,*] O. A. Terent'eva,[1,2] V. A. Vainshtein,[2] S. V. Okovityi,[1,2] E. V. Flisyuk,[2] and I. A. Narkevich[2]

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Targeted transport systems for drug delivery to the central nervous system (CNS) are reviewed. A modern classification of dosage forms according to generation and characteristic features is presented. The main targeted delivery systems for CNS drugs based on nanocarriers such as liposomes, polymer nanoparticles, polymer micelles, solid lipid nanoparticles, and nanoparticles of chitosan and human serum albumin are examined.

Keywords: targeted transport, central nervous system, blood–brain barrier, drug delivery systems, nanocarriers.

The development of innovative dosage forms (DFs) for new drugs is a fundamental problem of modern pharmaceutical science. The main requirements for DFs are bioavailability, therapeutic efficacy, safety, and drug tolerance. These requirements are responsible for the pharmaceutical approaches to development of the formulation, design, and production technology of a DF for a given drug. According to the SP XIVth Ed., Vol. 2, GPM. 1.4.1.0001.15 "Dosage forms," there are several DF classifications according to aggregate state, dispersion, administration pathway, and type of drug release. Each of the classifications has a certain value for DF pharmaceutical development. For example, classification by aggregate state and administration pathway partly determines the rate of drug action. The effect is felt faster after peroral administration of liquid than solid DFs. An injected solution acts faster than a peroral one. Classification by dispersion determines the drug manufacturing technology and also allows its stability to be predicted (homogeneous systems are more stable than heterogeneous ones). Classification by type of release (ordinary or modified) determines the rate of onset and duration of the drug therapeutic effect.

[1] N. P. Bekhtereva Institute of the Human Brain, Russian Academy of Sciences, 9 Akad. Pavlova St., St. Petersburg, 197376 Russia.
[2] St. Petersburg State Chemical Pharmaceutical Academy, Ministry of Health of the RF, 14A Prof. Popova St., St. Petersburg, 197376 Russia.
[*] e-mail: Anastasiya. Skorobogatova@pharminnotech.come

Classification by drug generation is used to develop DFs for targeted drug delivery to target organs.

1. Traditional DFs (first generation). This group includes ointments, tablets, suppositories, and solutions for injection that are characterized by continuous, inadvertent, and fast drug release. Such DFs have short active times and low bioavailability and are single-use.

The disadvantages of traditional DFs are:

Increased drug consumption because the drug does not reach the intended biological target;

Lack of targeted drug action that leads to side effects and reduced treatment efficacy;

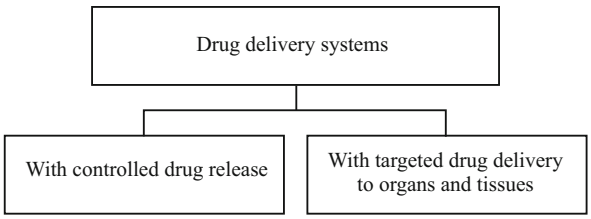
Inability to maintain the optimal therapeutic drug concentration in infected organs.

2. Prolonged-action DFs (second generation). This group comprises DFs with delayed release and increased duration of drug action. Development of prolonged-action DFs is most critical for drugs with short elimination half-lives in order to establish zero-order kinetics; with elimination half-lives 12 h, to smooth drug blood-concentration peaks and improve tolerance to therapy [3].

Second generation DFs include retard- and depot-forms.

Depot-forms create an *in vivo* drug reserve that is released over a long time.

Injectable depot-forms are suspensions (Betaspan depot, Depo-Prover), oil solutions (Moditen™ depo, Clopixol® de-



Scheme 1. Classification of drug delivery systems.

pot), microcapsule suspensions, lyophilizates for preparation of solutions and suspensions for injection (Octreotide depot, buserelin depot).

Implantable depot-forms are tablets (Naltrexone implant), depot capsules (Espiral), ophthalmic films (Timoptic depot), and intrauterine therapeutic devices (Mirena).

Retard-forms are mainly peroral, sometimes rectal DFs that create an *in vivo* drug reserve and release it slowly into the blood pool.

The advantages of second-generation DFs are:

Ability to reduce the frequency of drug administration;

Lack of drug concentration oscillations;

Maintenance of optimal drug concentration for a long time;

Reduced incidence of side effects (SEs) [1].

3. Drug delivery systems (third generation). DFs of the third generation are innovative DFs with targeted drug delivery to cells and a lengthy, continuous, and regulated release of the drug (Scheme 1).

Therapeutic systems (TSs) are considered DFs with controlled release. TSs are DFs that release drugs at a programmed rate at certain time intervals for a long period (from several days to several months).

TSs consist of components, e.g., drug reservoir, platforms on which the TSs are placed, and a therapeutic program that determines the drug release rate. TS efficacy is determined by the amount of drug released per unit time, which corresponds to zero-order kinetics. The release process itself is independent of physiological or pathological factors (food intake, associated diseases). This enables the development of the therapeutic effect to be predicted.

Targeted drug delivery systems (TDDSs) are systems that deliver the optimal required amount of drug accurately to the target cell. Such systems can increase the therapeutic specificity and efficacy and reduce drug toxic effects.

SEs of many drugs in traditional DFs and their low therapeutic efficacies are due mainly to the difficulty of reaching the target. Targeted drug delivery is one method for solving this problem.

Modern pharmacy uses the following systems for targeted drug delivery: liposomes, polymer nanoparticles (NPs), polymer micelles, solid lipid particles, dendrimers, cyclodextrins, carbon tubes, fullerenes, magnetic particles, silica particles, and albumins. They can be used to increase drug delivery to the disease site, which is especially important in developing antitumor drugs and those for treating CNS disorders such as Alzheimer's, Parkinson's, and neurodegenerative diseases [2, 3].

Methods for drug delivery to the CNS

The main problem facing researchers developing DFs to treat CNS diseases is the need to deliver the drug across the blood—brain barrier (BBB), which is impenetrable for most drugs.

The BBB is based on tight junctions of epithelial cells that form cranial and spinal capillaries and act as the primary barrier [4, 5]. The BBB under normal conditions is poorly permeable to 100% of large molecules and 98% of small ones except for a limited range of lipophilic molecules with mass 400 – 500 Da [6].

Osmotic opening of the BBB was used to treat human brain tumors and was one of the first methods for increasing its permeability to hydrophilic drugs. For this, intracarotid infusion over 30 sec of a hypertonic arabinose or mannitol solution and then a solution of antitumor drug through the same catheter caused dehydration of epithelial cells, which opened tight epithelial junctions and increased the BBB permeability in 10 or 30 min (if Na-Ca channel inhibitors were used). The methotrexate brain concentration increased by seven times as compared to distilled H_2O if arabinose solution (1.6 M) was injected followed by methotrexate solution [7 – 9]. Survival of patients with CNS primary lymphoma and highly malignant glioma increased statistically significantly if mannitol solution (1.4 M) was injected i.v. (carotid) followed by methotrexate and i.v. injection of procarbazine and cyclophosphamide. Tumors disappeared in 24 – 40 months in CNS multiple germinoma patients after osmotic treatment with carboplatin and etoposide [10].

However, injection of hyperosmotic solutions altered the cellular structure of the microvasculature, which initiated apoptotic reactions of epithelial cells. Furthermore, injection in this manner of several antitumor drugs, e.g., doxorubicin, cisplatin, bleomycin, 5-fluorouracil, and vincristine, caused pronounced neurotoxicity in experimental animals. The obvious deficiencies of this method, i.e., the complicated technology, non-selectivity, risk of passing tumors through the BBB into peripheral tissues, and neurotoxicity, make it unattractive for broad implementation into clinical practice [4, 6, 9].

Lipophilic prodrugs were the next attempt to increase targeted drug delivery to the brain. For example, levodopa, which passes through the BBB into brain neurons and is decarboxylated into dopamine during the process, is currently used to relieve the symptoms of Parkinsonism. A drawback of this method is the active metabolism of levodopa in the intestines [4, 6].

The deficiencies of the aforementioned methods do not allow them to be widely used in clinical practice. This necessitated a search for other methods for delivering drugs to the CNS. TDDS was one of the most promising methods.

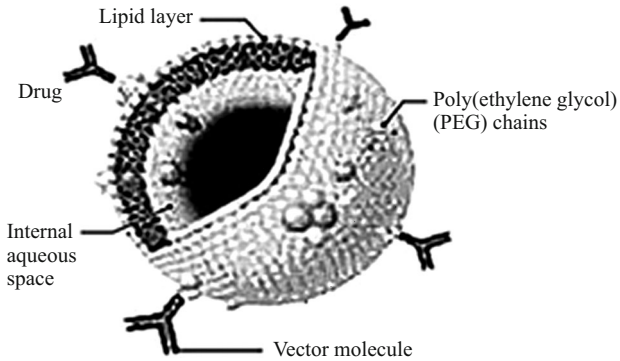


Fig. 1. Liposome structure [13].

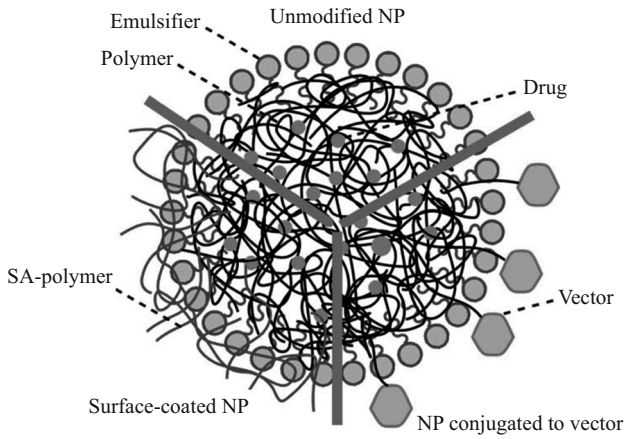


Fig. 2. Polymer nanoparticle (NP) structure.

TDDS for treating CNS diseases.

TDDS increase the specificity and therapeutic efficacy and also reduce drug toxicity by delivering drugs to the given target.

The most important requirement for carriers for CNS TDDS is their capability for biodegradation over several days. This requirement excludes the use of dendrimers, carbon nanotubes, fullerenes, silica particles, and magnetic particles for brain delivery. Nanocarriers are the most promising TDDS for CNS drug delivery.

Nanocarriers form a broad group of solid colloidal particles of sizes 1 – 1000 nm (1 μm) consisting of macromolecular materials in which the active ingredient is dissolved, incorporated, encapsulated, or bonded and adsorbed to the surface [11].

Biodegradability over several days, low toxicity, and biocompatibility are important parameters for selecting a material for CNS TDDS development. Also, surface functional groups and the ability to affect the drug release rate are important. The most promising TDDS for drug delivery to the CNS are liposomes, polymer NPs, solid lipid NPs, and polymer micelles [11, 12].

Liposomes

Development of liposomes as TDDS began in earnest in the 1970s. Liposomes are closed spherical structures of one or several concentric lipid bilayers with an aqueous phase within (Fig. 1).

Liposomes have low toxicity, are biocompatible and biodegradable, and have high affinity for cell membranes. Therefore, they can be used to deliver hydrophobic (in the lipid bilayer) or hydrophilic molecules (in the aqueous phase).

The U. S. Food and Drug Administration (FDA) has registered several liposome preparations, i.e., Doxil® (doxorubicin), DepoCyt® (Cytarabine), Marqibo® (Vincristine), AmBisome® (Amphotericin), Onivyde® (Irinotecan), Visudyne® (Verteporfin), and DaunoXome® (Daunorubicin).

Liposomes in the blood stream are rather quickly captured by reticular-endothelial system (RES) cells and accumulate in the liver and spleen. Liposomes that circulate for long times in the blood stream and can deliver drugs to the brain can be created by decreasing their size to d nm or modifying their surface with poly(ethylene glycol) (PEG). Liposomes conjugated to PEG are not quickly captured by RES cells and circulate longer in the blood stream [8, 13].

Vectors can be attached to liposome surfaces to modulate their biodistribution by binding to certain sites of actual cells and tissues. For example, BBB epithelial cells have surface receptors for transferrin, lactoferrin, apolipoprotein E (APOE), insulin, and epidermal growth factor. Liposomes can be modified for targeted CNS delivery by using vectors such as APOE, transferrin, lactoferrin, and antibodies to transferrin and lactoferrin receptors. PEG-liposomes conjugated to transferrin increased brain delivery of docetaxel by 14.58 times as compared with FDA-approved Docel™ [14].

Penetrating peptide TAT, which transports liposomes through membranes without interacting with receptors, was also used as a vector for brain delivery of drugs. An analysis of rats with glioma showed that survival was much longer in groups that received TAT-PEG-liposomes of doxorubicin than in those receiving the free drug and PEG-liposomes (Table 1) [15, 16].

Polymer NPs

Polymer NPs consist of slightly water-soluble biocompatible and biodegradable copolymers. The polymers used to design NPs for CNS delivery are:

Poly(butyl cyanoacrylate) (PBCA);

Poly(lactic acid) (PLA);

Poly(lactide-co-glycolide) (PLGA).

NPs of PLA and PLGA are produced mainly by emulsification-diffusion and precipitation; of PBCA, by emulsion polymerization and nanoprecipitation. Studies found that NPs of PBCA had the greatest dissolution rate because of the low molecular mass [5, 26 – 28].

TABLE 1. Several Liposomal Drug Delivery Systems for Brain

Drug	Liposome surface modification	Preparation method	Application	Ref.
Prednisolone	PEG	Film extrusion	Multiple sclerosis	[17]
Doxorubicin	PEG	Thin film hydration	Glioma	[15, 16]
	PEG + lactoferrin	Thin film hydration		[18]
	PEG + TAT	Remote loading using an ammonium sulfate gradient		[19, 20]
	Transferrin + TAT peptide	Remote loading using an ammonium sulfate gradient		[21]
5-Fluorouracil	Transferrin	Film casting	Brain tumor	[22, 23]
Docetaxel	Transferrin	Solvent spraying	Brain tumor	[14]
Resveratrol	PEG—Transferrin	Thin film hydration	Glioblastoma	[24]
Senktide	PEG + lactoferrin, PEG + antibody to lactoferrin receptors	Thin film hydration	Dopamine production stimulated by brain nuclei	[25]

Unmodified NPs, like liposomes, are quickly captured by RES cells and accumulate in the liver. The circulation time of NPs in the blood stream can be increased by decreasing their size or modifying their surface. The second pathway appeared more efficacious. For this, surfactants (SAs) such as Polysorbate 80 or Poloxamer 188 were adsorbed on NP surfaces and PEGs were covalently linked to them. Coating NPs with Polysorbate 80 increased not only their circulation time in blood but also their capture by brain endothelial cells. A possible mechanism for the increased delivery of SA-coated NPs is adsorption on them of apolipoprotein E or A-1 followed by receptor-mediated absorption of the particles by brain capillary endothelial cells.

Prolonged and significant analgesic effects were observed in test animals after i.v. injection of NPs with loperamide that were coated with Polysorbate 80. However, this effect did not develop for NPs not coated with Polysorbate 80 [29]. Figure 2 shows structures of the three main types of polymer NPs.

TABLE 2. Several Polymer NPs Used for Drug Delivery to Brain

Polymer	Drug	NP surface modification	Preparation method	Application	Ref.
Poly(butyl cyanoacrylate)	Gemcitabine	Polysorbate 80	Polymerization emulsion	Brain tumor	[31]
	Dalargin	Polysorbate 80	Polymerization emulsion	Pain syndrome	[32]
	Loperamide	Polysorbate 80	Polymerization emulsion	Pain syndrome	[29]
	Methotrexate	Polysorbate 80	Polymerization emulsion	Brain tumor	[33]
	Rivastigmine	Polysorbate 80	Polymerization emulsion	Alzheimer's disease	[34]
	Tacrine	Polysorbate 80	Polymerization emulsion	Alzheimer's disease	[35]
	Nerve growth factor	Polysorbate 80	Anionic polymerization	Growth factor	[36]
Poly(lactide-co-glycolide)	Diazepam	-	Nanoprecipitation	Epilepsy, schizophrenia	[37]
	Doxorubicin	Polysorbate 80	Nanoprecipitation	Glioma	[38]
	Loperamide	Poloxamer 188	Nanoprecipitation	Pain syndrome	[38]
		PEG + poly(lactide-co-glycolide) + polysorbate 80	Nanoprecipitation		[39]
	Olanzapine	-	Nanoprecipitation	Schizophrenia	[40]
	Paclitaxel	PEG + glutathione	Nanoprecipitation	Brain tumor	[41]
	Temozolomide	PEG + transferrin	Emulsification-diffusion	Brain tumor	[42]
	Urocortin	PEG + lactoferrin	Emulsification-diffusion	Parkinson's disease	[43]
Poly(lactic acid)	Amphotericin B	PEG + Polysorbate 80	Nanoprecipitation	CNS fungal infections	[44]
	Ritonavir	TAT peptide	Emulsification	HIV	[45]
	Sulpiride	PEG	Emulsification	Psychoses	[46]

NPs are conjugated with vectors to increase CNS drug delivery. Transferrin, lactoferrin, antibodies to transferrin and lactoferrin receptors, APOE, and TAT peptide are used as vectors [11, 29]. Development of TDDS based on polymer NPs for intranasal administration has been an active area for the last decade. The CNS has a few sections without a BBB or with increased barrier permeability, e.g., olfactory nerves and the floor of the cerebral ventricle, through which drugs can be transported. Drugs are transported from the nasal cavity through olfactory and trigeminal nerves, bypassing the BBB [30]. Currently, TDDS based on PLGA for diazepam and olanzapine are being studied *in vivo* (Table 2).

Polymer micelles

Polymer micelles are amphiphilic systems consisting of block copolymers with the hydrophobic part facing within and the hydrophilic part on the outside to form a spherical structure (Fig. 3).

Advantages of micelles are their small sizes (10 – 60 nm), unique structure, biocompatibility, biodegradability, simple syntheses, and high stability. Unmodified polymer micelles are not captured by RES cells and circulate for a long time in the blood pool because of their small sizes [47]. Micelles can be modified for targeted drug delivery, like other NPs, by using a SA or conjugating a copolymer of PEG and vectors. The cyclic peptide arginine-glycine-asparagine, which binds to integrins that are over-expressed in glioma cells, was used as a vector to deliver platinum drugs using polymer micelles [48]. Polymer micelles are used for intranasal delivery of zolmitriptan to the brain (Table 3).

Other carriers for CNS drug delivery

Solid lipid particles (SLPs) are colloidal particles ~200 nm in size that consist of lipids and are stabilized by SAs. The lipids can be tri-, di-, and monoglycerides. SLPs pass easily and quickly through the BBB because of their lipid structure. However, use of unmodified NPs has been associated with development of extrapyramidal disturbances due to nonspecific action. SLPs can be modified to decrease SEs by coating the surface with SAs such as Polysorbate 80, stearic acid, and Poloxamer 188 [53 – 55]. The free carboxylic acid in stearic acid allows SLPs to be conjugated to vectors, e.g., lactoferrin, for targeted delivery of drugs to the brain [53].

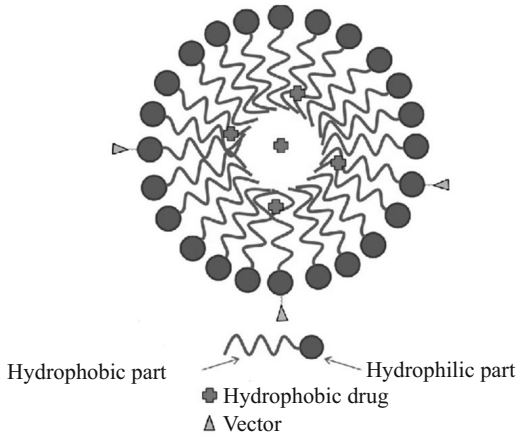


Fig. 3. Micelle structure.

Chitosan-based NPs are a promising modality for targeted drug delivery because of their biodegradability, low toxicity, biocompatibility, and simple production. Chitosan is a mucopolysaccharide with a structure close to cellulose but containing free amines to which vectors can be attached for targeted delivery. The main methods for preparing chitosan-based NPs is ionotropic gelation, microemulsification, emulsification-diffusion of solvent, polyelectrolyte complexation, and emulsification. Chitosan-based TDDS for i.v. and intranasal drug delivery to the brain are currently being designed.

The surface of chitosan NPs can also be modified to increase drug delivery to the brain. Pramipexol accumulated in brain more after i.v. injection of chitosan-based pramipexol NPs coated with Polysorbate 80 than after i.v. injection of uncoated NPs [57].

Conjugation of antibodies to transferrin receptors to chitosan NPs increased intranasal delivery of RNA to the CNS as compared to unmodified NPs.

Chitosan NPs for intranasal delivery are currently being designed. NPs for intranasal delivery of bromocriptine, ropinirole, and buspirone to the brain were tested *in vivo*.

TABLE 3. Several Polymer Micelles Used for Drug Delivery to Brain

Drug	Copolymer	Preparation method	Application	Ref.
Doxorubicin	Dextran – b-poly(DL-lactide-co-glycolide)	Thin polymer film method	Brain tumor	[49]
Paclitaxel	PEG-phosphatidylethanolamine	Thin polymer film method	Brain tumor	[50]
Ciprofloxacin	PEG-cholesterol + TAT peptide	Thin polymer film method	Brain bacterial infections	[51]
Platinum drug	PEG – b-poly(L-glutamic acid) + cyclic peptide	Thin polymer film method	Brain tumor	[48]
Zolmitriptan	Poloxamer	Thin polymer film method	Migraine	[52]

TABLE 4. Several TDDS for Brain

Carrier	Drug	Surface modification	Preparation method	Application	Ref.
SLP	Docetaxel	Lactoferrin	Emulsification	Brain tumor	[53]
	Temozolomide	Polysorbate 80	Hot homogenization	Glioblastoma	[54]
	Bromocriptine	Poloxamer 188	Emulsification	Epilepsy	[55]
	Rosmarinic acid	Polysorbate 80	Hot homogenization	Huntington's disease	[56]
Chitosan	Pramipexole	Polysorbate 80	Ionotropic gelation	Parkinson's disease	[57]
	Bromocriptine	-	Ionotropic gelation	Parkinson's disease	[58]
	RNA	Antibody to transferrin receptors	Ionotropic gelation	HIV	[59]
	Rivastigmine	-	Ionotropic gelation	Alzheimer's disease	[60]
	Ropinirole	Polysorbate 80	Emulsification	Parkinson's disease	[61]
	Tacrine	-	Emulsification	Alzheimer's disease	[62]
	Buspirone	-	Ionotropic gelation	Anxiety disorders	[63]
Serum albumin	Loperamide	Transferrin, Antibody to transferrin receptors	Desolvation	Pain syndrome	[64]
	Gabapentin	Polysorbate 80	Coacervation	Epilepsy	[65]
	Obidoxime	Apo E	Desolvation	Organophosphorus compound poisoning	[66]

Human serum albumin (HSA) is another promising carrier for creating NPs. It is highly biodegradable, has low toxicity, and is biocompatible. The surface of albumins can also be modified by conjugating vectors for targeted delivery to the brain (Table 4) [64].

Thus, TDDS are promising DFs for treating CNS diseases. They can be used to deliver a drug through the BBB to the CNS target, to increase the treatment specificity and efficacy, and to diminish drug SEs. Surface modification of nanostructures by coating with SAs and conjugating to PEG and vectors can make therapy even more specific and safe.

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