# PAMAM DENDRIMERS AND PROSPECTS OF THEIR APPLICATION IN MEDICINE

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Development of drug delivery systems based on branched biocompatible polymers is one of the most promising areas of modern nanopharmaceutics. Researchers have been exploring this area several decades now, and the results of their efforts quickly find their way into production. Dendrimers, a new class of universal synthetic polymers with a highly functional surface, have a number of unique properties: constant size, high degree of branching, multivalence, solubility in water, definite molecular weight, internal cavities. With the release of VivaSol gel, the first dendrimer-based commercialized product, the "model range" of dendrimer carriers has grown significantly. Poly(amide-amine) (PAMAM) dendrimers, which consist of an alkyldiamine core and tertiary amine branches, are believed to be among the most promising compounds that can be used in the development of the new generation drugs. However, they were kept out of the list of clinically acceptable compounds for a long time because of their toxicity, unclear behavior in living systems and pharmacokinetic profile, as well the difficulties associated with establishing a therapeutic dose. This review presents basic information about PAMAM dendrimers and attempts to assess the prospects of their application in treatment of various diseases, including COVID-19.

**Keywords:** dendrimers, drugs, COVID 19, drug delivery systems

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# ДЕНДРИМЕРЫ PAMAM И ПЕРСПЕКТИВЫ ИХ ПРИМЕНЕНИЯ В МЕДИЦИНЕ

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Разработка систем доставки лекарственных веществ на основе разветвленных биосовместимых полимеров — одно из наиболее перспективных направлений современной нанофармацевтики. Исследования в данной области ведут уже не одно десятилетие, а их результаты активно внедряют в производство. Дендримеры — новый класс универсальных синтетических полимеров с поверхностью высокой степени функциональности, — обладают уникальными свойствами: постоянством размера, высокой степенью разветвления, многовалентностью, растворимостью в воде, четко определенной молекулярной массой, наличием внутренних полостей. С выпуском первого коммерческого продукта на основе дендримера — геля VivaSol, «модельный ряд» дендримерных носителей существенно разросся. Поли(амид)аминовые дендримеры, состоящие из алкилдиаминового ядра и третичных аминовых ветвей, считают одними из наиболее перспективных соединений для разработки препаратов нового поколения. Однако их клиническая адаптация долгое время была ограничена вследствие их токсичности, неопределенности поведения в живых системах и фармакокинетического профиля, а также сложности в подборе терапевтической дозы. В обзоре представлены основные сведения о дендримерах PAMAM и сделана попытка оценить перспективы их применения в терапии различных заболеваний, в том числе COVID-19.

**Ключевые слова:** дендримеры, лекарственные препараты, COVID-19, системы доставки

**Вклад авторов:** все авторы статьи в равнозначной степени внесли вклад в поиск и анализ литературы, интерпретацию полученных данных, подготовку и оформление рукописи.

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In the field of pharmaceutical chemistry, the top priority task is the development of drug and vaccine delivery systems. Today, pharmaceutical giants are working on the new systems that would deliver drugs, vaccines and siRNA. Oncology remains one of the leading areas of their practical application. However, since 2019, when the COVID-19 pandemic began, a task considered particularly urgent is the development of targeted drug delivery systems, i.e., those that deliver antiviral and standard therapy drugs to target organs (brain, lungs, intestines). There is a wide range of new delivery systems available nowadays, which necessitates regular systematization of information about their actual applicability in clinical practice. The primary reason behind the interest in three-dimensional branched monodisperse polymer dendrimers is their unique and stable structure [1], which can be designed during stepwise synthesis, something unachievable with other polymers. As a result, their unique geometry and valence properties are completed with the low degree of polydispersity. Constant charge and size enable formation of well-defined complexes with various drugs.

The purpose of this review is to summarize information about the various drug compounds delivery systems based on PAMAM dendrimers that are described in the scientific literature and used by the pharmaceutical industry. A subject that received more attention is the trend of using this type of carriers in the fight against COVID-19.

## Use of PAMAM dendrimers for drug delivery: prospects

PAMAM dendrimers can be successfully used to solve various biomedical problems. Dendrimers-based delivery systems can be carriers of both hydrophilic and hydrophobic compounds [2]. However, the adoption of unmodified PAMAM dendrimers into clinical practice is limited because of their

toxicity, unpredictable behavior in living organisms, unknown bioavailability, biocompatibility, or pharmacokinetic profile. Moreover, it is hard to establish the effective therapeutic dose of the complex and expensive to produce them.

PAMAM dendrimers are extremely small (1–200 nm), which significantly improves their chances of avoiding capture and destruction by the reticuloendothelial system [3]. One of the downsides of PAMAM dendrimer cations of higher generations is their ability to destroy cell membranes [4].

It is known that dendrimers are capable of passing through the blood-brain barrier, which means they can deliver the carried drugs into the brain. PAMAM dendrimers are most often used in the therapies of brain disorders [5]. For example, there are PAMAM dendrimer and carbamazepine (antiepileptic drug) complexes that are part of the Alzheimer's disease treatment protocols [6]. Caproyl-modified G2 (second generation) PAMAM dendrimers are effective carriers of insulin in a nasal delivery system [7].

A G5 PAMAM dendrimer known for its low solubility in water has the proven capability of delivering haloperidol, a neuroleptic drug, to the brain [8]. A smaller dose of haloperidol-dendrimer complex administered nasally produced a therapeutic effect comparable to that of intraperitoneal administration of this drug.

A group of researchers has analyzed the possibilities of using dendrimers as delivery systems carrying immunogenic peptides into a living organism. Since the bioavailability of peptides is insufficient to induce immunogenic reactions unprotected peptides tend to degrade when acted upon by proteases, there was designed an experimental complex for nasal administration with G4 PAMAM dendrimers as adjuvant and carrier of the pPGT122 peptide epitope [9].

Cationic G5 and G7 PAMAM dendrimers loaded with 14C accumulate in the pancreas, which can be used in the treatment of diabetes mellitus. In addition, these dendrimers have been shown to be rapidly (< 2 h) excreted by the kidneys in the urine [10].

Dendrimers can also be used as systems for delivering proteins into the body: ribonucleases, alcohol dehydrogenases, aldolases etc., including blood plasma proteins, human serum albumin and γ-globulin [11].

*Drugs used in ophthalmology*

Up to 105 million people around the world suffer from glaucoma, a common and severe chronic eye disease that can manifest itself in a variety of clinical forms in people of different ages (including newborns) and races [12]. There are many new glaucoma medications available on the market today, but their choice is still limited.

In a study, PAMAM dendrimers were shown to be capable of delivering antiglaucoma drugs, pilocarpine nitrate and tropicamide [13]. Loading pilocarpine nitrate onto PAMAM dendrimers also increased its bioavailability.

There was developed a hydrogel (mcDH) of G5 PAMAM dendrimer and polyethylene glycol diacrylate (PEG-DA) [14]. Based on the hydrogel, a new brimonidine antiglaucoma drug was designed. The authors of this study have also investigated cytotoxicity of the NIH3T3 delivery system to fibroblasts, brimonidine release kinetics *in vitro*, the ability of this agent to penetrate rabbit's cornea.

A report published in 2017 described a fast-dissolving nanofiber scaffold of PAMAM dendrimer and brimonidine tartrate that, according to the authors, is an alternative to eye drops [15]. The experiment, which lasted three weeks, was designed to compare the response to brimonidine tartrate eye drops and the said scaffold in a brown Norwegian rat model; the response to the two drug forms compared was similar. The researchers have also noted high solubility of the scaffolds, complete biocompatibility and efficient delivery of brimonidine.

A number of in vitro and ex vivo studies have shown that PAMAM-based hydrogels can enhance penetration of anti-glaucoma drugs into eye tissues, which translates into smaller dosages and higher efficacy.

*Drugs used in oncology*

The growing incidence of cancer in the population and the advancements in the methods of treatment of this pathology have increased the rate of development of this area of medical science. Radiation therapy (RT) is one of the most commonly used types of cancer treatment. Its key tasks are to ensure complete resorption of the tumor tissue, inhibit its growth and alleviate symptoms of the disease. This treatment option is not without limitations: in particular, to make RT efficient, it is necessary to very accurately target the radiation and keep it targeted on the tumor throughout the procedure. In this connection, much development effort is now invested into dendrimer-based radiopharmaceuticals. Conceptually, this type of medications are designed to deliver the radioactive nuclide straight into the tumor tissue and in the concentration required, thus protecting healthy tissues from radiation exposure. Radiolabeled dendrimers allow using less radiolabels, which consequently reduces their toxicity and tumor resistance [16]. For example, PAMAM dendrimers can specifically target A549 human lung carcinoma cells overexpressing the avβ3 integrin. The dendrimer, in turn, can be effectively labeled with the 131I radiolabel and subsequently used in radiation treatment of a lung carcinoma that overexpresses the avβ3 integrin [17].

The modern anticancer chemotherapy arsenal includes about a hundred drugs and several groups of substances with similar chemical structure, anticancer action and source of origin. All anticancer drugs aim to inhibit cell proliferation and kill tumor cells. What is promising about dendrimers is they ability to form complexes with chemotherapeutic agents, deliver them to the affected organs and subsequently release in high concentrations. Thus, the main goals of chemotherapy are realized: relapse-free survival of the patient after surgery (adjuvant chemotherapy), reduction of the degree of surgery invasiveness (neoadjuvant chemotherapy), improvement of the quality of life (maintenance chemotherapy).

Anticancer agents with carboxyl groups, such as methotrexate (MTX) or doxorubicin (DOX), interact well with PAMAM dendrimers' core and surface. The rate of incorporation of these agents increases with the generation of dendrimers: for example, 4G PAMAM dendrimer can accommodate up to 26 MTX molecules (with additional polyethylene glycol (PEG) chains).

Doxorubicin is one of the anticancer drugs commonly conjugated to dendrimers [18], the resulting complex applicable in treatments of breast, bladder, stomach cancers and gliomas. PAMAM dendrimers are known to penetrate intestinal epithelial barriers, which makes them usable as carriers in oral delivery systems. In one study, PAMAM dendrimers functionalized with folic acid (widely used as a vector for anticancer drugs) and labeled with isothiocyanate were carrying doxorubicin; the complex proved to be highly efficient [19].

There is a large number of research papers that report on development of drug vectors based on PAMAM dendrimers and designed to deliver antitumor drugs, such as fluorouracil [20], gemcitabine [21], berberine [22], thailandepsin A [23], paclitaxel [24], cisplastin [25], and malloapelta B [26].

A standard chemotherapy drug used against advanced pancreatic cancer is gemcitabine. One of its drawbacks is the short half-life. Most researchers that invest time and effort into development of dendrimer-based gemcitabine delivery systems seek to design an efficient, least toxic complex for cancer treatment [27].

The isoquinoline alkaloid berberine (BBR), a protoberberine, is used in traditional medicine to treat conditions such as type 2 diabetes and hypercholesterolemia. Since BBR inhibits growth of cancer cells and induces apoptosis, it is also used in cancer therapy. A complex of PAMAM dendrimer and BBR was designed and its anticancer activity studied on human breast cancer cells MCF-7 and MDA-MB-468 [22, 28]. The PAMAM-BBR system showed a more potent anticancer effect than BBR alone. Covalent cross-linking of BBR with dendrimer's amino groups allowed increasing the load of the agent carried and even enhance its anticancer activity. The hemolytic toxicity and hypoglycemic effects of BBR were reduced.

Another study demonstrated a complex of trastuzumab and PAMAM dendrimer linked with paclitaxel or docetaxel, which can specifically target SKBR3 HER-2-positive cells. The designed conjugates proved to be even more toxic towards HER-2-positive human breast cancer cells than the agent alone or as part of a simple PAMAM-trastuzumab conjugate [29].

Cis-dichlorodiaminplatin(II) (cisplatin), an anticancer drug, binds DNA via intracavitary cross-links to d(GpG) (dG = deoxyguanosine) and d(ApG) (dA = deoxyadenosine), which impairs DNA replication and transcription and causes cell death. Cisplatin is very effective against many solid tumors, including ovarian cancer. However, tumors become resistant to cisplatin with time and, in addition, it has systemic side effects, nephrotoxicity and neurotoxicity [25]. Compared to uncombined cisplatin, PAMAM–cisplatin complexes showed greater efficacy against all ovarian cancer cell lines, even those resistant to cisplatin. In a variety of cell lines resistant to cisplatin, the G4 PAMAM dendrimer and cisplatin conjugates caused formation of DNA adducts, increased expression of apoptotic genes and high caspase activity while exhibiting better cytotoxicity properties [30].

Genistein (4,5,7-Trihydroxyisoflavone), found in soybean and chickpea, has a wide range of physiological and pharmacological functions. It is known to inhibit the growth of human melanoma cells at the G2/M transition and has been shown to inhibit DNA strand breaks mediated by $H_2O_2$/Cu(II) by acting as a direct scavenger of reactive oxygen species with an OH group at the C-4 position, which enables its antioxidant activity [31].

Loading of the G4 and G5 PEGylated PAMAM dendrimer with 5-fluorouracil (5FU, anticancer drug) allowed reducing the amount of agent lost in delivery and decreased its hemolytic toxicity [20]. It took 90 molecules of the drug to fully load the G4 PAMAM-NH2 dendrimer. A group of researchers suggested [32] a way to increase the synergistic anticancer efficacy by developing a system for co-delivery of the miR-205 gene vector and the 5FU target drug on an acetylated PAMAM conjugated to an LHRH peptide (LHRH-G5.0NHAC). The optimized co-delivery system was then evaluated for synergistic anticancer effect *in vitro* and *in vivo*.

It is known that folate receptors (FR) are highly expressed in many types of tumor cells (e.g., breast carcinoma) [33]. Polyethylene glycol-modified G4 PAMAM dendrimers were functionalized with folic acid (FA), then the complex was extended with 5FU and 99mTc (technetium-99m) and became the new PEG-PAMAM G4-FA-5FU-99mTc complex. Compared to other nanocarriers and normal cells, the FA-specific complex showed high breast cancer cells penetration capacity.

In one study, PAMAM dendrimer was used to co-deliver miR-21 antisense oligonucleotide (as-miR-21) and 5FU to a human glioblastoma while increasing cytotoxicity of the 5FU antisense therapy [34]. Antisense therapy seeks to stop synthesis of the protein involved in the development of the disease by inhibiting translation of its mRNA with complementary antisense oligonucleotides.

Another study describes a PEG core PAMAM dendrimer-based gemcitabine delivery system that contains anionic carboxylic acid groups modified with PEG chains that were simultaneously conjugated with Flt1 antibodies [35]. Flt1 is the vascular endothelial growth factor (VEGF) receptor 1, which promotes angiogenesis in histomorphological varieties of cancer. Extended with gemcitabine, this system became more efficient in reducing tumor burden in a pancreatic cancer xenograft model. Moreover, this gemcitabine delivery system has also changed the growth dynamics of myeloid cells and decreased their amount in bone marrow.

Dendrimers are also vital components of the anticancer drugs targeted delivery vector systems. The vectors are monoclonal antibodies and tumor-specific proteins that can recognize and bind tumor-specific antigens. Folic acid can be called a promising vector candidate enabling targeted delivery of anticancer drugs. Cell membranes of most tumors (carcinomas, gliomas) have a folic acid receptor. After binding to the receptor, the drug-dendrimer complex enters the cell by means of the receptor-mediated endocytosis and releases the drug.

*Antiviral drugs*

In the last two centuries, viral diseases have been among the most pressing medical and social problems. Some acute viral infections claim the lives of up to 14 million people worldwide each year, according to WHO. Viruses are non-cellular life forms that can infect living organisms by penetration through epithelium of the gastrointestinal tract (enterovirus, adenovirus), epithelium of the respiratory tract (rhinovirus), skin (papilloma virus, chickenpox), mucous membranes, placenta, during blood transfusions, organ transplantation operations, breastfeeding.

One of the key requirements for the newly designed antiviral drugs is the ability to selectively suppress a certain stage of virus reproduction without affecting the vital processes of other body cells; another key requirement is high bioavailability that allows keeping concentration of the drug in target cells at the level needed to cure and counteract development of drug resistance.

Loading of antiviral drugs on dendrimers enables delivery to target organs and prolongation of action of the drugs, which in turn ensures efficacy of drug therapy. The most common antiviral drugs are interferon derivatives, inhibitors of viral RNA, enzymes (neuraminidase) that release new virions. Scientists have been designing interferon-dendrimer complexes for several years now. In one of the studies, researchers have successfully formed a complex of arginine-modified PAMAM dendrimer and interferon beta used in glioblastoma therapies, which was then studied in mice [36]. Authors of another work managed to create a PAMAM dendrimer-based transdermal delivery system with interferon regulatory factor 3 (IFN 3).

In the literature, there are solitary mentions of designed complexes of a dendrimer and an antiviral drug, for example, acyclovir [37].

**PAMAM dendrimers and COVID-19**

There are five classes of drugs that are used in the standard COVID-19 treatment protocol: anti-inflammatory (non-specific

anti-inflammatory drugs), systemic corticosteroids (glucocorticosteroids), vitamins, antivirals and anticoagulants. Targeted delivery can soften the systemic effects drugs have on the body, increase their bioavailability, reduce the dose and toxic load on the organs that eliminate them from the body.

Combination drug therapy relying on delivery systems is one of the promising ways of treatment of complicated COVID-19 cases. It allows not only to reduce the dosage of the administered drugs, but also to achieve several therapeutic goals. For example, COVID-19-induced inflammation in the lungs calls for non-specific anti-inflammatory, antiviral drugs, corticosteroids and anticoagulants. These medications are administered parenterally and act systemically, which significantly increases the number of side effects and iatrogenic complications associated with their use.

*Antivirals in COVID-19 therapies*

PAMAM dendrimer cations themselves are known to possess antiviral properties and act against herpes virus (HSV) and influenza [38]. Cationic dendrimers with NH2 and OH groups interacted with negatively charged envelope of the MERS-CoV virus and thus blocked it [39]. Another study investigated antiviral activity of G1 polyamidoamine dendrimers conjugated with 3'-siallactose or 6'-sialyllactose; the targets were various strains of the influenza virus [40]. The authors noted that the complexes prevented penetration of the virus into cells. The analysis of hemoglutination inhibition data revealed that human and swine influenza viruses were inhibited by (6SL)-PAMAM dendrimer complexes and, to a lesser extent, (3SL)-PAMAM dendrimer complexes.

Brain is one of the organs affected by the new coronovirus infection. The main problem in establishing the therapeutic dose of a drug designed to work in the brain lies with the need to pass the blood-brain barrier. This fact underpins the importance of development of systems capable of reaching the focus of the disease through the physiological barriers of the body and releasing a therapeutic dose of the drug carried in the tissue affected by the virus.

*Anti-inflammatory drugs in COVID-19 therapies*

Severe post-COVID-19 complications develop because of the systemic inflammatory response of the body with excessive production of cytokines. Tumor necrosis factor alpha (TNFα) plays a central role in most inflammatory lung diseases, such as chronic obstructive pulmonary disease, asthma, acute respiratory distress syndrome and acute lung injury. Theoretically, TNFα is a promising target for siRNA-based therapy against acute and chronic lung inflammation. Authors of one of the studies used G3 PAMAM dendrimers to deliver TNFa-targeted siRNA to the lungs [41]. They investigated the efficacy and safety of the resulting complex (dendriplex) in a mice model of acute pneumonia. Dendriplexes were shown to efficiently deliver the agent, ensure high transfection efficacy and high uptake of RAW264.7 by macrophages.

There was described a G2 PAMAM dendrimer and dexamethasone-based heme oxygenase 1 (HO-1) delivery system designed to treat ischemic stroke [42]. HO-1 is an antioxidant enzyme that has anti-inflammatory and immunomodulatory effects. Dexamethasone, an anti-inflammatory corticosteroid drug, is a common component of treatment protocols for a variety of acute inflammatory diseases. In particular, it is used to alleviate cerebral edema in ischemic stroke. Therefore, the combined delivery of the HO-1 gene and dexamethasone may have an additive effect on ischemic brain structures.

N-acetylcysteine is a mucolytic expectorant anti-inflammatory drug prescribed in cases of infectious and respiratory diseases of the upper and lower respiratory tract. A group of researchers has found that PAMAM-COOH anionic dendrimer and N-acetylcysteine (NAC) conjugates can efficiently address neuroinflammations [43]. The antioxidant and anti-inflammatory potency of the PAMAM-(COOH)-(NAC) complex was assessed in microglial cells in vitro. Compared to NAC alone, the complex proved to produce a more intense antioxidant effect [44]. In addition, microglial cells (resident macrophages of the central nervous system) were used to investigate cytotoxicity, cellular uptake and the efficacy of the delivery system. The cellular uptake of dendrimers was rapid, with a well-defined drug release rate.

Delivery of the PAMAM dendrimer and methylprednisolone complex to the lungs is a promising pattern in drug therapy of COVID-19. With G5 PAMAM dendrimer as a carrier for methylprednisolone and the complex administered nasally, the dendrimer was demonstrated to persists in the lung for five days [45]. Repeated daily administrations over the next five days showed that the complex did not cause any observable non-specific inflammatory reactions in the lungs.

It is known that COVID-19 may be accompanied by an aggressive inflammatory response of the body with active release of inflammatory cytokines. Such response is called a cytokine storm. It is an uncontrolled overactive reaction of the immune system to the infecting SARS-CoV-2 virus; the result is extensive lung damage combined with multiple organ failure. Cytokine storm is one of the main causes of death of COVID-19 patients. The countermeasures adopted in the clinical practice involve administration of immunosuppressants, recombinant humanized monoclonal antibodies to interleukin IL6 and IL1 receptors: tocilizumab, sarilumab, levilimab, olokizumab, canakinumab. Development of the target delivery systems for these drugs is an important task in the context of treatment of complicated new coronovirus infection cases.

*Anticoagulants in COVID-19 therapies*

Intravascular thrombosis is one of the formidable complications associated with COVID-19. To arrest its development, standard treatment protocols always include administration of drugs that inhibit coagulation hemostasis and prevent formation of blood clots. PAMAM dendrimers can be used as antithrombotic agents in anticoagulant therapy [19]. Arginine- and FA-modified G4 and G5 dendrimers carrying coumarin-3-carboxylic acid showed a good antithrombotic effect, high hemocompatibility, hemocompatibility and stability. Another dendrimer-based complex suggested for treatment of venous thrombosis is the complex of PAMAM dendrimer and enoxaparin, the efficacy of which was demonstrated in mice model experiments [46].

The PAMAM dendrimer-heparin complexes can be formed both by incorporating the drug into the dendrimer and by electrostatic interaction with functional groups. It was discovered that such a complex created through electrostatic interactions improves biocompatibility of the dendrimer itself while reducing the cytotoxicity [47]. A G3 PAMAM dendrimer was used to carry enoxaparin to the lungs, which ultimately resulted in prevention of thrombosis in blood vessels [48].

*Immunobiological drugs*

Since interfering RNA therapy has been shown effective in treatment of the new coronavirus infection, development of

siRNA and mRNA vaccines became an increasingly popular activity. Inhaled PAMAM dendrimer-siRNA complex may be a much more specific and safe therapeutic agent against COVID 19.

## CONCLUSION

It is obvious that the interest in development of dendrimer-based delivery systems (employing their various classes of dendrimers) will continue to grow. In this connection, it seems promising rely on such systems to improve the methods of delivery of the already registered drugs used in the treatment standards. The advantages that underpin the importance of the respective efforts include targeted effect on the organs, accumulation of high therapeutic concentrations of drugs in the lesions, reduced side effects and complications from the treatment. Today, many of the drugs based on dendrimers are already commercially available and approved for clinical use.

The scientific community pays special attention to the development of delivery systems not just for cancers but also for COVID-19. In the fall of 2020, Starpharma announced the completion of testing of a nasal spray against SARS-CoV-2 based on the SPL7013 dendrimer. The G4 SPL7013 consists of a divalent benzylhydrylamine core, outgoing from the core of L-lysine branches with 32 surface groups of naphthalenesulfonic acid (DNAA), which impart hydrophobicity and a high anionic charge to the dendrimer surface [49].

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