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Review Article

# Adamantane-containing drug delivery systems

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## Abstract

Adamantane is a weakly functional hydrocarbon widely used to develop new drug molecules to improve their pharmacokinetic and pharmacodynamic parameters. The compound has an affinity for the lipid bilayer of liposomes, enabling its application in targeted drug delivery and surface recognition of target structures. This review presents the available data on developed liposomes, cyclodextrin complexes, and adamantane-based dendrimers. Adamantane has been used in two ways – as a building block to which various functional groups are covalently attached (adamantane-based dendrimers) or as a part of self-aggregating supramolecular systems, where it is incorporated based on its lipophilicity (liposomes) and strong interaction with the host molecule (cyclodextrins). Adamantane represents a suitable structural basis for the development of drug delivery systems. The study of adamantane derivatives is a current topic in designing safe and selective drug delivery systems and molecular carriers.

## Keywords

cyclodextrin complexes, dendrimers, hydrocarbon, liposomes, pharmacophore

## Introduction

Adamantane has limited application in the industry because it is a weakly functional hydrocarbon used in polymer production, and its derivatives are of increasing interest in practice (Hu et al. 2022). Adamantane is applied as a common reference standard for chemical shifts in solid-phase nuclear magnetic resonance (NMR) spectroscopy (Brouwer and Mikolajewski 2023). In color lasers, adamantine can be used to extend the life of the gain medium. Lenzke et al. (2007) proved that adamantane is not photo-ionizable in the atmosphere because its absorption regions are in the vacuum-UV region of the spectrum (Lenzke et al. 2007). Adamantane is an attractive candidate for fuel in spacecraft engines because it is easily ionized, allowing it to be stored in solid form instead of in a pressure tank, and importantly, it is relatively non-toxic (Appliedinosystems (AIS)). Some alkyl derivatives of adamantane have been used as a working fluid in hydraulic systems (Jia et al. 2021). Jeong (2002) developed the first adamantane-based polymers for application as touch screen coatings. Diamondoids such as diamantane, triamantane, tetramantane, and [1(2,3)4]pentamantane are of interest due to their easy availability (Fokin et al. 2006). Their selective functionalization, studied by Weigel et al. (2022) and Yoshihara et al. (2023), provides interest in electronics and nanotechnology (Cameron et al. 2022).

Adamantane is an organic substance comprising four isopropyl groups bonded to a central carbon atom in a cubic configuration (Fig. 1).

This unique structural element, "diamond hydrogen", is very stable and oxid-resistant. Its main advantages as a component of some drug delivery systems (DDS) are as follows: 1) chemical stability, incl. to oxidation; 2) hydrophobicity, providing stability in aqueous solu-

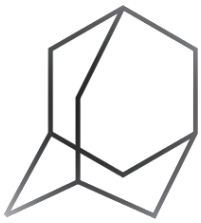

**Figure 1.** Adamantane chemical structure (http://www.chemspider.com/Chemical-Structure.8883.html).

tions; 3) small molecular size, facilitating its incorporation into drug delivery formulations without altering their physicochemical properties; 4) lipophilicity, useful for engineering systems to cross lipid membranes; 5) high adsorption capacity on materials surface makes it suitable for DDS that need to be adsorbed on a specific surface; 6) low toxicity does not cause allergic reactions.

The structural and chemical features of adamantane open new possibilities for developing structural scaffolds or carriers for drug delivery. The substance can be used in two ways: as a building block to which various functional groups are covalently attached (adamantane-based dendrimers) or as a component of self-aggregating supramolecular systems (liposomes) and as a high interaction with the host molecule (cyclodextrins).

Because of its biocompatibility, non-toxicity, low cost, and ease of availability, adamantane provides an ideal structural basis for creating DDS. Liposomes are used as artificial biological membranes; thus, the incorporation of adamantane derivatives into the bilayers provides excellent opportunities to study cellular recognition, based on the possibility of binding different ligands to the adamantane moiety, according to Štimac et al. (2019). As a result, the molecule plays an essential role in comprehending the interactions between manufactured nano-vesicles and particular cellular receptors and elucidating the receptor-targeting process in living cells. Investigating novel adamantane and other diamondoid compounds is an important topic in nanomedicine, particularly in developing safe and selective DDS.

## Pharmaceutical application of adamantane

A particular area of research interest is the development of new adamantane-based drug molecules with improved pharmacokinetic and pharmacodynamic parameters (Korabecny et al. 2019). The role of adamantyl moiety as the main pharmacophore in biologically active compounds is well known. Incorporating the adamantyl core into molecules can significantly affect their lipophilicity, pharmacological and biological properties (Chochkova et al. 2022). Therefore, adamantane can successfully modulate the therapeutic index of parent structures, which is why it has been widely used in constructing agents with various therapeutic fields of application.

To date, numerous adamantane-based compounds with significant biological activities have been synthesized. The review by Lamoureux and Artavia (2010) covers a wide range of substances containing an adamantane structure with pronounced biological effects – antiviral (Shchelkanov et al. 2014), antibacterial (Orzeszko et al. 2000; Chochkova et al. 2022), antimycotic, trypanocidal (Papanastasiou et al. 2008), anti-inflammatory, analgesic, antiulcer, antidepressant, anxiolytic, anticonvulsant, antiparkinsonian, neuroleptic, immunostimulant, antitumor (Wang et al. 2004) hypoglycemic, dilating cerebral vessels, antihypertensive, antioxidant (Worachartcheewan et al. 2014), etc. Some of these adamantane-based compounds have the potential to positively affect multiple sclerosis, peripheral neuropathy, addictions, schizophrenia, neurological and neurodegenerative diseases, asthma, and others. In addition, many analogs bearing an adamantane structure exhibit inhibitory activity against various types of enzymes, for example, 11β-hydroxysteroid dehydrogenase type 1 (Lee et al. 2014), tyrosine kinase (Avramis et al. 2002), glucosyl-ceramide synthase (Bijl et al. 2008), cholinesterase (Spilovska et al. 2013, 2015), glycogen synthase kinase-3 (Goñi-Oliver et al. 2009), steroid sulfatase (Horvath et al. 2004) and tyrosyl-DNA-phosphodiesterase 1 (Munkuev et al. 2021). Upgraded information about the synthesis and biological activities of novel adamantane-containing thiazole compounds was proposed by Warda et al. (2022).

Of interest are the different pharmacotherapeutic applications of the same substance as a component of polypharmacological or multi-target drugs. The latter confirms the versatility of the adamantyl group in drug design.

The concept of adamantane in the role of an "anchor" in the lipid bilayer of liposomes, proposed by Štimac et al. (2017), provides an opportunity for its application in the field of targeted drug delivery and surface recognition of target structures. The results encourage the development of new self-assembled supramolecular systems for basic chemical research and biomedical applications. The use of adamantane and its homologs in nanotechnology is promising. The cage-like structure of the substance allows the incorporation of molecules to be released inside the human body upon matrix breakdown (Mansoori 2007; Ramezani and Mansoori 2007). Also, two separate studies – by Markle (2000) and Garcia et al. (2009), proposed its use as a structural element for the spontaneous formation of molecular crystals. Recently, Yeung et al. (2020) summarized the possibilities for applying hydrocarbon compounds like adamantine with a cage-like structure in nanotechnology, and the prospects of this branch of medicinal chemistry.

## Incorporation of adamantane into liposomes

Multidisciplinary research in chemistry, biology, and medicine helps advance fundamental biomaterial knowledge and the development of novel hybrid products with practical biological applications (Xu et al. 2019; Hu et al. 2020). Lipids are characterized by amphiphilicity and possess diverse chemical properties, making them powerful tools in nanotechnology (Maurya et al. 2022). Liposomes are non-toxic, biodegradable vesicles that can contain both hydrophilic and hydrophobic compounds (Fig. 2).

Muntean et al. (2022) reviewed their use as active principal carriers of active pharmaceutical ingredients (API) in DDS.

Controlling the spontaneous association of lipids was achieved by Antonietti and Förster (2003), allowing the construction of novel lipid-based DDS and biomaterials with better characteristics. The most successful strategy is to utilize targeted liposomes with surface-attached ligands capable of identifying and attaching to target cells. Therefore, passive and active targeting accomplish liposomal drug accumulation in specific tissues and organs.

Adamantane-containing liposomes (ACLs) have several potential applications in medicine. One of the most promising is drug delivery, where the ACL can be used to encapsulate drugs and target them specifically to the site of the disease. This approach can increase the effectiveness of the drug while reducing adverse effects. Additionally, ACLs have been shown to have antiviral properties and may have potential use in treating viral infections. They may also be helpful in gene therapy, where they can deliver therapeutic genes to specific cells.

One of the approaches for intracellular delivery of proteins and liposomes is based on supramolecular host-guest interaction, including adamantine as a guest molecule for noncovalent supramolecular interaction (Kitagishi et al. 2020). The method aims for a chemical modification to facilitate intracellular delivery, making it suitable for various bioengineering processes, such as protein-based therapy, cell reprogramming, and genome editing.

The adamantyl radical introduction into various drug molecules often increases their biological activity, and studying their mechanism of action broadens the understanding of their pharmacological profiles.

The ability of amantadine to disrupt the fusion of virus particles with the host cell membrane during viral infection was established by Sugrue and Hay (1991). This generated an uprising of research on the interactions of adamantane with liposomes, which serve as cell membrane models. Data from the studies of Štimac et al. (2012) and Šekutor et al. (2014) on adamantyl derivatives – tripeptides, glycopeptides, and guanidines, their incorporation in liposomes and their interaction with the liposomal bilayer in the form of an artificial biological membrane, were the basis for the use of adamantyl radical in the design of new targeted drug-delivery systems. Some of the research focused on the distribution and localization of adamantane and amantadine in lipid bilayers (Ribić et al. 2020; Yang et al. 2021), resulting in which two populations of amantadine found within the phospholipid bilayer – one near the surface and the other much deeper – in the hydrophobic core of the bilayer, with most of the amantadine occupying a surface position. The localization of the compound depends on its initial protonation. In experimental conditions, no changes in the double-layer structure were detected.

Adamantyl tripeptides are a class of chemicals produced from bacterial peptidoglycans (Ribić et al. 2019). They were pentapeptide disaccharide fragments originally extracted from penicillin-treated *Brevibacterium divaricatum* (Ellouz et al. 1974). The structure required for the compounds' immunostimulatory effect was N-acetylmuramyl-L-alanyl-D-isoglutamine (also known as muramyl dipeptide), which can be identified as part of the previously stated peptidoglycan monomer (PGM) (Peroković et al. 2021). Tomašić and Hršak discovered in 1987 that PGM exhibited many biological actions, including antimetastatic and anticancer activity, and enhanced the immune response in experimental animals (Tomašić and Hršak 1987). Ljevaković et al. (2000) investigated for the first time *in vivo* the influence of structural modifications of the parent molecule on biological activity. An adamantyl radical was incorporated into the PGM with comparable biological activity to the parent structure. Vranešić et al. attempted in 1993 to synthesize a novel type of molecule in which the adamantyl residue was connected to a short synthetic peptide, resulting in two diastereoisomers, as pointed out by Levak et al. (2023). The chosen peptide has a comparable construction to the natural peptidoglycan L-alanyl-D-*iso*glutamine. The interaction between two adamantly tripeptide substances and phospholipids in liposomal bilayers was studied for the first time by Frkanec

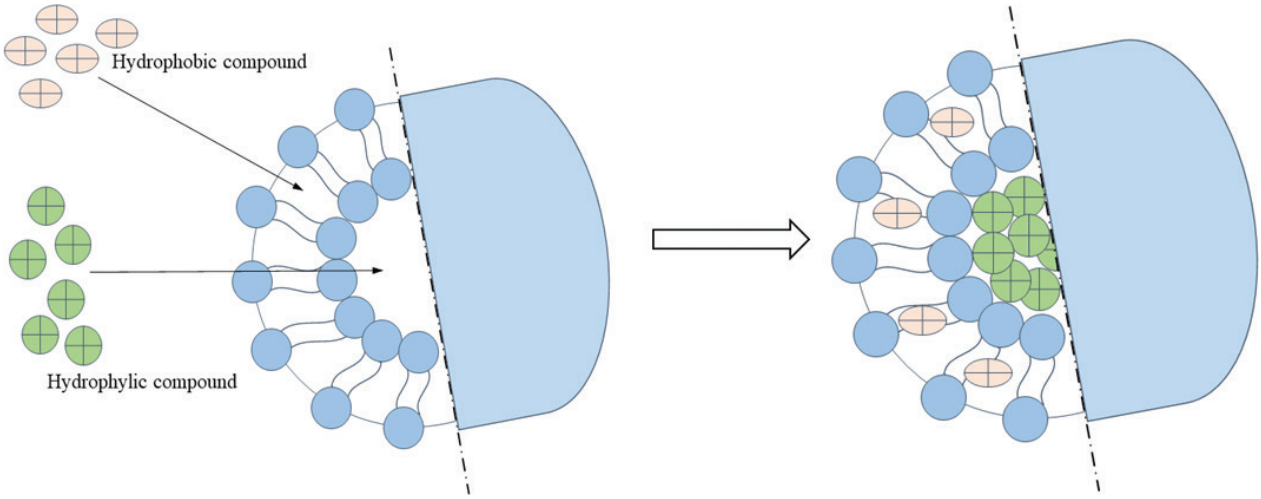


**Figure 2.** Incorporation of hydrophobic and hydrophilic compounds in liposomes.

et al. (2023). The liposomal bilayer structure included egg phosphatidylcholine, cholesterol, and diacetyl phosphate, as well as labeled fatty acids (n-doxyl stearic acid) with a paramagnetic nitroxide moiety located at various carbon atoms (at 5, 7, and 16 carbon atoms). Consequently, all spin-labeled lipids in the liposomes tested in the study, including 16-doxyl stearic acid in the liposomes' hydrophobic core, changed their mobility characteristics after the entrapment of the substances.

Mannose conjugates of 1-amino adamantane and adamant-1-yltripeptides were synthesized in other studies by Ribić et al. (2011, 2012). Their target was the mannose receptors expressed on the cell surface of many immunocompetent cells, including macrophages and dendritic cells. The influence on the specific immune response was evaluated *in vivo*. These compounds were also incorporated into liposomes and characterized by Štimac et al. (2012) using additional physicochemical methods. Because of its lipophilic qualities, the adamantyl group was found in the lipid core of the bilayer, whereas the contained mannose hydrophilic portion was found on the liposomal surface. The presented liposomal system with included adamantyl glycoconjugates served as the foundation for flexible carbohydrate-containing targeted DDS, with the adamantane moiety operating as an anchoring framework for different carbohydrate molecules of interest. According to Štimac et al. (2017), this method can also be used to analyze protein interactions with membrane receptors.

Šekutor et al. (2014) reported the successful incorporation of adamantyl aminoguanidine derivatives into liposome model membrane systems combining in one molecule the highly polar guanidine group and the lipophilic "anchoring" adamantyl radical. The guanidine group was a key structural motif associated with hydrophilic cell-penetrating peptides (Zhang et al. 2019; Fernández Caro 2020). Based on the adamantyl moiety's affinity for the lipid bilayer, adamantyl aminoguanidines were membrane-compatible. The guanidine subunit remained on the exterior side of the lipid bilayer, facing outwards. At the same time, the molecules were integrated into multilamellar liposomes, and the vesicle thus generated was implicated in surface recognition (Rozas et al. 2013). Liposomes containing adamantyl aminoguanidine were similar in size to the empty liposomes, but their surface charge was substantial. When studying their interaction, liposomes containing only phosphate groups and those with adamantyl-guanidine derivatives were mixed, and the guanidine fragments on the surface successfully interacted with the complementary liposomes, leading to liposome recognition and subsequent aggregation (Šekutor et al. 2014).

## Incorporation of adamantane into cyclodextrin complexes

Organic polymers, colloids, or biomolecules, including DNA, proteins, and lipids, can also create nano-devices. Carbohydrates, mainly polysaccharides, receive special attention. Cyclodextrins (CDs) have multifunctional features that enable them to be employed in a wide range of drug delivery routes, such as oral, transdermal, or ocular administration (dos Passos Menezes et al. 2019). The publication of Lachowicz et al. (2020) reviewed cyclodextrin products with different administration routes. Cyclodextrins' structural features were described by Szejtli and Osa (1996) and later further studied by Biwer et al. (2002). Cyclodextrins' most stable three-dimensional molecular configuration was a hollow truncated cone, also known as a "doughnut-shaped structure." The primary hydroxyl groups are orientated towards the top edge of the truncated cone, while the secondary hydroxyl groups are oriented towards the lower edge (Fig. 3).

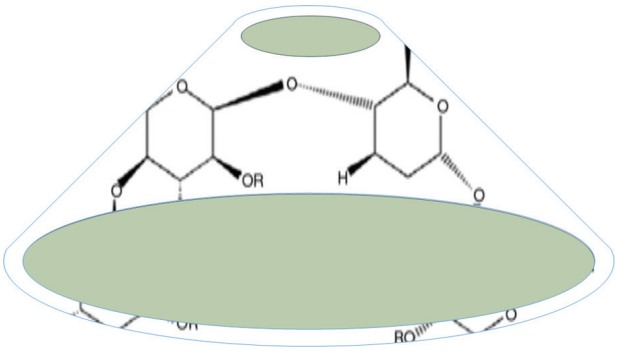


**Figure 3.** Cone-shaped cyclodextrin structure.

The outside surface of cyclodextrins is hydrophilic due to the presence of hydroxyl groups, but the cavity containing glycosidic oxygen is hydrophobic. The hydrophobic interior determines the possibility of CDs being used as carriers – for inclusion or partial encapsulation of organic and inorganic compounds (guests) without forming a covalent bond. The ability to form complexes has been well studied in the studies of Khan et al. (1998) and Li and Loh (2008). In their paper, Poulson et al. (2022) reviewed the recent achievements in the capabilities of cyclodextrins and their derivatives to encapsulate and transport various molecules.

Their large size and hydrophilicity limit the ability to cross membranes, respectively, the application in pharmaceutical practice. Cyclodextrins do not attach to drug molecules effectively enough, causing them to be lost in the cavity of the "doughnut" before being delivered to the target. Natural CDs are typically derivatized to improve their usability (Dhiman and Bhatia 2020). At the turn of the century, many independent investigations discovered that amphiphilic cyclodextrins may spontaneously form aggregates such as bilayers, micelles, and bilayer vesicles (Liu et al. 2020; Muankaew et al. 2020; Araújo et al. 2022). These aggregates, particularly bilayer vesicles, can solve the issues above while acting as drug-delivery vehicles with hydrophobic and hydrophilic affinities. Numerous pieces of research revealed that cyclodextrins may form complexes with various guest molecules, including medicines, surfactants, and polymers (Araújo et al. 2021; Mohamadhoseini and Mohamadnia 2021; Pandey et al. 2021).

The ability of cyclodextrins to interact with diverse chemicals serves as the foundation for novel drug delivery strategies based on supramolecular recognition of nanoparticles

made up of amphiphilic cyclodextrin and a guest molecule. Among the numerous chemical groups that can interact with CDs, the adamantyl moiety serves as a model guest molecule. It has a strong association constant ($10^{-3} \div 10^{-5}$ $M^{-1}$) and fits nicely into the β-cyclodextrin cavity (Musumeci et al. 2020). Based on this interaction and the easy formation of a "host-guest" complex between adamantane and CDs, many self-aggregating cyclodextrin DDS have been developed, as well as those for fluorescent sensing and bioimaging (Narayanan et al. 2022). In addition, carbohydrates are adequate ligands for cellular receptors, for example, lectins, which stimulate molecular transport across biological membranes. Binkowski et al. (2005) discovered that adamantylated monosaccharides are a novel family of chemicals that may be utilized to modify the surface of CDs. Voskuhl et al. (2010) created new carbohydrate-adamantane conjugates to investigate their complexes with CDs and interactions with specific lectins, and Vico et al. (2011) transformed amphiphilic β-cyclodextrin vesicles with maltose and lactose when the host molecule interacted with adamantane. The artificial glycocalyx on the surface of amphiphilic cyclodextrin vesicles was used in research with lectins, including maltose, concanavalin A, and lactose with peanut agglutinin. Amphiphilic CDs have also been implemented as artificial receptor units in liposomes, as reported by Kauscher et al. (2013).

Bohm et al. (2011) explored the high stability of cyclodextrin-adamantane complexes in the synthesis of tubular vesicles from cyclodextrin and adamantyl-modified hyperbranched poly(ethyleneimine) that self-aggregate with the modified fluorescent dye calcein (Fig. 4).

The disclosed supramolecular arrangement possesses long-term stability over a wide pH range, indicating a significant potential for developing novel materials with better characteristics (Ippel 2019).

Zhang et al. (2018) developed a self-assembled supramolecular polymeric DDS based on guest-host interaction for combined photothermal antitumor chemotherapy. It comprises β-cyclodextrin functionalized hyaluronic acid and an adamantane-linked camptothecin/IR825 dye that absorbs in the near-infrared (NIR) region. Hyaluronic acid provides colloidal stability and biocompatibility of the complex, and the disulfide bridge in the camptothecin/dye conjugate is cleaved upon reduction, with subsequent release of the pharmacological agent and recovery of fluorescence emission. At the same time, the dye converts locally absorbed light into heat, making the system suitable for photothermal therapy. In an in vitro study with three types of cancer cell lines, the nano platform was found to rapidly enter and release camptothecin, followed by their successful destruction upon NIR irradiation. Application to mice with experimental tumors resulted in significant tumor regression, revealing the potential of this nano platform to provide a targeted combined photothermal chemotherapy.

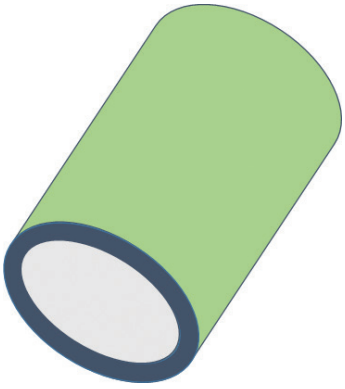

**Figure 4.** A schematic view of tube-shaped cyclodextrin complex.

Tumor-associated macrophages (TAMs) are overexpressed in solid cancers. They have an immunosuppressive function, which supports the growth of the tumor and avoids the immune reaction. Current studies are focused on discovering agents (drugs, nanomaterials) that rewire TAMs to a tumor-suppressive type. However, reducing systemic side effects and delivering API to the macrophages is a challenge. Rodell et al. (2019) developed an adamantane-modified derivative of the Toll-like receptor (TLR) agonist resiquimod. Adamantane interacts with cyclodextrin nanoparticles (CDNPs) as a guest, allowing for the provision of a drug in the form of an aqueous solution and its TAM-targeted administration. In a study of therapeutic effectiveness and systemic adverse effects in the MC38 cancer mouse model, the molecule retained macrophage function by agonizing TLRs, and the adamantane moiety increased drug affinity for CDNPs. The possibility of strong nanoparticle-drug interactions to minimize the systemic toxicity of TLR agonists while retaining therapeutic effectiveness and reducing tumor development was proven in this work.

In a study by Kitagishi et al. (2020), the carrier molecule β-cyclodextrin was modified with octa arginine (R8), a cell-penetrating peptide. Different proteins (green fluorescent protein, β-galactosidase, and IgG) were partially modified by binding to adamantane residues and successfully delivered into HeLa cells by supramolecular host-guest interactions. Such results were also obtained with liposomes of 100 nm size, with adamantane residues on their surface.

In treating cancer diseases, the main goal of modern nuclear medicine is to reduce the radiation dose to a minimum. This branch of medicine uses macromolecules for pretargeting, but significant problems include a need for biocompatibility and in vivo stability. Jallinoja et al. (2023) designed complexes of cucurbit[7]uryl and adamantane as the foundation for antibody-based pretargeted PET. The two chemicals were biocompatible, tolerated well, and interacted on a host-guest basis. The researchers developed three 64Cu-labeled adamantane guest ligands and tested them in human pancreatic cancer BxPC3 and MIAPaCa-2 mice xenografts. The study showed that this approach is suitable for pretargeted PET because of the proven stability of the adamantane complexes and their specific and high uptake by tumor cells.

## Incorporation of adamantane into dendrimers

Dendrimers are highly branching macromolecules with many functional groups expressed on the dendritic framework (Malkoch and Gallego 2020). They are spherical poly-

mers having a core and a sequence of chemical shells. Each shell is called a generation, and each branch is referred to as a dendron. Dendrimers have a multivalent surface, inner shells that surround the core, and a core with dendrons attached. Higher-generation cores, shielded from the outside by the dendrimer surface, provide unique nano-environments suitable for including guest molecules. The various functional groups on the surface of dendrimers can be transformed further, resulting in variations in dendrimer features (Priyadarshi et al. 2021; Sharma et al. 2022).

Polyethyleneimine and polyamidoamine-containing dendrimers are effective non-viral transfection agents that can deliver genetic material into the cell, according to Saeed et al. (2022). Since the research by Duncan and Izzo (2005) revealed some undesirable dose-dependent cytotoxic effects, to reduce cytotoxicity, Lamanna et al. (2011) designed a new type of polycationic dendron based on tetra-functionalized adamantane. In a study of polycationic adamantane dendrons of different generations, Grillaud et al. (2014) reported no cytotoxicity. Paolino et al. (2013) described other adamantyl-functionalized forming host-guest supramolecular complexes with CDs. Modifying the dendrimer surface significantly reduced the toxicity of polypropylene imine dendrimers and made them suitable for DDS. A novel class of fourth- and fifth-generation hybrid dendrimers with adamantyl moieties (hydrophobic guest groups) and maltose or maltotriose units (biocompatible groups) on their surfaces have been synthesized. The number of adamantyl radicals on the surface of the glycodendrimer determined the host-guest interaction in the generated supramolecular complexes. Other uses for adamantane-containing dendrons involve functioning as carriers and scaffolding for the multi-presentation of bioactive peptides (Bevilacqua et al. 2021; de Souza et al. 2022).

## Conclusion and future perspectives

Adamantane is a primary structural unit for creating various DDS such as its polymers and nanoparticles (liposomes and dendrimers).

Adamantane-based polymers can create materials with controllable mechanical, physicochemical, and biological properties. These polymers are utilized as drug delivery matrices to improve bioavailability, decrease adverse effects, and enable controlled drug release. In cancer diseases, adamantane-based polymer drug carriers provide more effective drug distribution to afflicted tissues while minimizing the toxicity of the pharmaceuticals to healthy tissues and organs. Furthermore, for central nervous system illnesses such as Alzheimer's and Parkinson's, adamantane polymers can carry medications across the blood-brain barrier.

Adamantane nanoparticles can potentially increase the bioavailability and efficacy of API. They can also be used as molecular markers to help visualize and diagnose pathological conditions. Because of their tiny size, nanoparticles may pass through many barriers in the body, such as the blood-brain barrier or the cell membrane, making them appropriate for use as DDS in the treatment of various disorders. Adamantane nanoparticles can also boost medication resistance to enzymatic breakdown and minimize toxicity. ACLs are a form of lipid drug nanocarriers. One of the primary uses of ACLs is drug delivery to the brain, making them helpful in treating neurological diseases. Another application area is cancer diseases, where these carriers increase the efficacy of treatment by delivering drugs directly to the afflicted cells and tissues, resulting in lower drug dosages. Adamantane strengthens their structure, making them more resistant to deterioration and effective. ACLs can be employed as direct delivery systems to cancer cells or to treat infections and illnesses of the nervous system, thus providing better-targeted therapy.

Adamantane-containing DDS are a new generation of drug carriers that employ adamantane as a component to enhance the biopharmaceutical characteristics of API. These systems are biocompatible and may be used to serve a variety of medical purposes, including drug delivery to particular organs and tissues. Although they have the potential to be used in therapeutic treatment, they are currently being researched and developed. Despite their potential advantages, ACL and dendrimers are not yet widely used in medical practice. More study is needed to establish the optimum manner to utilize them as well as to validate their safety and efficacy in treating various disorders.

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