Review Article

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Silicon-based particles as a platform for development of antiviral drugs

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Abstract: The growing number of viral infections and viral strains from year to year requires the creation of new, more effective antiviral drugs. One of the cost-effective ways to increase drug efficiency is the development of delivery systems for already known and clinically used drugs in order to overcome the challenges currently limiting their efficiency. This review presents the current status of silicon-based particles in this area. Silicon-based materials consist mainly of silicon and its compounds and can contain other inorganic oxides, i.e. are inorganic in nature. Their inorganic nature provides a number of advantages over organic materials (e.g. polymers, lipids, micelles, etc.) which are widely proposed and already used for the indicated purpose. This review provides information about the structural features of the silicon-based materials, methods of their preparation. It contains studies showing why and how the particles themselves can serve as antiviral agents or, as carriers, can help overcome the disadvantages of active drugs and increase their antiviral efficacy. The review highlights the enormous potential of silicon-based inorganic particles (pristine or modified with various inorganic and organic species) in the fight against widespread viral infections.

Keywords: silicon-based particles; antiviral drug; drug delivery system

1 Introduction

Influenza, coronavirus infection, SARS and other viral infections are at the top of the list of annual diseases of people all over the world. This problem is familiar to almost everyone. According to WHO, worldwide, annual epidemics of influenza are estimated to result in about 3–5 million cases of severe illness, and about 290,000–650,000 respiratory deaths.[1] About 7 million people have died so far from COVID-19 outbreak as of December 8, 2023.[2] Plant viruses cause considerable economic losses due to decreasing both the quality and quantity of food crops.[3,4]

Various drugs are currently used to treat and prevent viral infections in clinical practice or agriculture. However, effective treatment often requires repeated administration of large doses of antiviral agents because of their limited solubility, short half-life in the body or short virus protection window, slow or incomplete absorption, reduced stability. This leads to unavoidable side effects on healthy human cells and tissues, especially in children, and to a decrease in plant resistance to viral infections. These disadvantages limit the widespread use of antiviral drugs and suggest an urgent need to develop new, more effective and safer drugs.

Among the various strategies for improving the pharmacological and consumer properties of drugs, the development of their new formulations based on biologically relevant particles has shown a powerful ability to solve the indicated shortcomings. Particles of different nature and structures are proposed for this purpose: metal and metal oxide particles, metal-organic frameworks, polymeric particles, liposomes and lipid particles, micelles, microemulsions, etc.[5–8] Silicon-based particles, i.e. particles predominantly composed of silicon or its compounds (for example, porous silicon, silica, clay particles, etc.), are also actively proposed as carriers for antitumor, anti-inflammatory, antibacterial drugs, etc. However, unlike the listed above materials, the number of works devoted to the use of silicon-based particles for the development of new antiviral drugs is rather limited. Nevertheless, the works available in the literature have shown the promise of application of silicon-based particles for this purpose. The review contains the studies focused on the use of silicon-based particles both as independent antiviral agents and as carriers of antiviral drugs. This work emphasizes how silicon-based particles can overcome challenges associated with practical application of antiviral drugs.

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2 Why silicon-based particles?

Silicon is the most abundant element in the biosphere after oxygen. Its compounds can be found in the soil (silicon makes up 27.7 % of Earth's crust), plants.[9] Silicon is necessary for birds and animals.[10,11] There is silicon in the human body. Silicon is a vital micronutrient necessary for bone hardness, joint mobility and good condition of the skin and its appendages (hair, sweat and sebaceous glands, nails).[12–14] Thus, the biological role of this microelement in living organisms is very important. A theory has been proposed that silicon could act as an alternative elemental basis in life's origin.[15]

At ordinary temperatures silicon is relatively inactive. When heated, it can react with oxygen and other elements (for example, halogens, metals, carbon, etc.). In nature, silicon is found in many dioxide forms, crystalline or amorphous (such as quartz, sand or opal, diatomaceous earth, etc.) and in uncountable variations of the natural silicates. The natural materials are widely used for biomedical applications. For example, some natural zeolites have been extensively used and showed their potential applications in various biotechnologies and in medicine.[16,17] Natural clays are successfully used in medicine and cosmetology.[18,19] The natural silicon-based materials can serve as precursors for synthetic silicon-based materials.[20,21] Syntheic silicon-based materials are also of a great interest for pharmaceutical and biomedical fields. Moreover, numerous studies show the benefits of synthetic materials compared to natural ones (for example, Refs. 19, 20). Synthetic route makes it possible to obtain materials with controlled characteristics and higher purity. Nevertheless, both natural and synthetic silicon-based materials are relevant for development new, more effective drug formulations due to the unique combination of their biological and physical-chemical properties.

First of all, for the safe functioning of drug delivery systems in the body, it is necessary for drug carriers themselves to be biocompatible and completely removed from the body when "the work is done". Biocompatibility is the ability of a material not to cause harmful effects when in contact with tissues or cells of the body but to induce the cellular or tissue response necessary to achieve an optimal therapeutic effect. The studies of silicon-based materials including porous silicon,[22,23] amorphous silica,[24–26] silicon nitride,[27,28] clays[29] showed that the materials exhibited biocompatibility in biological systems.

Safe removal of the silicon-based particles from the body occurs due to their degradation in the body. One of the degradation products of silicon-containing particles is soluble orthosilicic acid ($Si(OH)_4$) which is usually removed from the body by the kidneys.[30,31] It was shown that even Si_3N_4 powders which have very high mechanical strength are dissolved in blood serum, gastric juice and synthetic medium with pH 7.4, i.e. they are biodegradable materials.[32,33] The indicated properties of the silicon-based materials depend on surface chemistry, textural characteristics, size and concentration of their particles, as well as properties of the environment.

Another very important property of silicon-based materials is their resistance to attacks of pathogens and enzymes in the body. It is well known that most "soft" materials such as polymers, lipids, liposomes, etc., which are frequently used as drug carriers, are easily degraded by enzymes and microorganizms in biological media. This leads to the destruction of the structural integrity of the carrier materials and loaded drug (if it is sensitive to denaturation and loss of structure), appearance of by-products.[34–38] Due to inorganic nature of their matrix, silicon-based materials undergo negligible degradation by enzymes and pathogens which are capable to break down organic matter. Therefore, encapsulation of the drugs susceptible to degradation into silicon-containing materials is able to enhance their resistance to the degradation by enzymes and microorganisms, temperature, pH, irradiation, etc.[39–44] Moreover, it is known that some silicon-based particles themselves counteract pathogenesis, and several possible mechanisms of their antibacterial and antimicrobial action are proposed: deposited on cells particles act as a physical barrier to penetration pathogens into the cells,[45] direct interaction of the particles with microorganisms leading to damage of bacterial membranes,[46,47] the formation of reactive oxygen species (ROS)[48,49] or reactive nitrogen species (RNS).[28]

As for the physical and chemical properties of silicon-based materials, most of them have high mechanical strength and thermal stability, exhibit a diverse morphology and structure.[50–52] Silicon-based particles can form hydrogels, which are a promising basis for the development of soft drug formulations.[53] The high porosity and possibility of easy chemical functionalization of silicon-based particle surface promote efficient drug loading, modification of its release, targeted drug delivery.[17,54,55]

Particulate drug delivery systems are promising in terms of the concept of multivalent binding.[56,57] For effective action, a drug system must be multivalent, i.e. have multiple repeatable receptor sites for enhanced and selective binding to the virus. Like many other particulate delivery systems, the surface of silicon-based particles contains multiple centers that can be modified with the necessary receptor sites to attach to the virus, thus forming a multivalent system.

Taking into account all of the above, it can be concluded that silicon-based materials are a promising basis for development of new antiviral drug formulations.

3 Groups of antiviral drugs, mechanisms of action

In order to understand the principles of action of silica-based particulate antiviral drugs, we briefly review the antiviral mechanisms of existing drugs and their targets. Unlike antibiotics, which break the integrity of the pathogen, the action of antiviral drugs is aimed at inhibiting the development process, not killing viruses.

In general, modern antiviral drugs can be divided into two groups: drugs that targeting the viruses themselves, and drugs that activate or mimic the body's own immune defenses. The drugs of the first group interfere with specific stages of the viral life cycle and thereby prevent the development of viral infection. The group includes the inhibitors of virus attachment, entry, uncoating, viral protein synthesis, assembly and release of virions.[58–60]

At the infection stage, the virus adsorbs on the cell membrane and then penetrates the cell. The virus adsorption is achieved by the interaction of the viral envelope glycoprotein with target cell-surface molecules. The surface glycoproteins and target molecules are different for different groups of viruses. For example, the attachment step of human and avian influenza A virus as well as coronavirus is mediated by the interaction of the viral envelope glycoprotein hemagglutinin (HA) with cell-surface molecules containing sialic acids (SA).[61–63] The herpes simplex virus (HSV) attaches to the host's cell surface receptor, heparan sulfate proteoglycans (HSPGs) via its viral glycoproteins gB and/or gC.[64,65] To prevent this process of attachment the virus to the cell, drugs that directly blocking the receptor-binding domain of the virus or host's cell surface receptors are used, for example, soluble decoy receptors, antibodies to membrane receptors. These drugs prevent infection of the cells at initial stage. If the virus does attach to a cell, its entry into the cell can occur in several ways that depend on the type of virus. The most common ways are endocytosis (in which the membrane folds inward, surrounds the virus and submerges it in its digestive vesicle, then pulls it deep into the cell) and direct fusion of the viral particle with the membrane, as well passage of the viral particle through the membrane through special channels that are formed under the influence of the virus. Inhibitors of virus fusion with the cell membrane, capsid stabilizers, and ion channel blockers are effective at this stage. The next stage is the synthesis of viral components in the infected cell. Entering the cell, the nucleic acid of virus "forces" the cell to synthesize proteins and nucleic acids of the viruses from its cellular materials. Inhibitors of viral components (DNA and RNA polymerases, reverse transcriptase, helicase, etc. are effective at this stage. Following the replication of viral nucleic acids, the assembly of the protein capsids of the daughter virions occurs. This process can be disrupted by the use of structural protein inhibitors. The final step in the life cycle of a virus is the release of new virus particles from the host cell. Different types of viruses exit the cell in different ways: some cause the host cell to rupture (a process called lysis), others exit by exocytosis, and still others take a piece of the plasma membrane with them when they break away. In some cases, the release of new viral particles kills the host cell (e.g., a cell whose membrane ruptures will not survive). In other cases, the cell remains intact so that it can continue to produce even more viral particles. At this stage, for example, inhibitors of neuraminidase are effective because neuraminidase helps mature virions leave the cell.[58–60]

The drugs of the second group do not directly affect the virus itself. They influence the body's immune system by introducing protective proteins (interferons) or stimulating their synthesis (interferon inducers). Interferons can activate a whole cascade of reactions in the body to fight viral infection.[66–68] Immunomodulators, diverse biologically active substances, can change (increase or decrease) immune response and used in combination with antiviral drugs.[69–70]

In recent decades, a large number of effective antiviral drugs have been developed. Most of them target specific pathways of action against viruses. However, due to the high mutation rate of viruses, the effectiveness of many drugs decreases significantly over time. A promising way to solve this problem is to develop drugs that prevent the virus from attaching to the cell membrane. This mechanism is common to various viruses, so drugs aimed at inhibiting this process will have a wide spectrum of action.[71,72]

4 Silicon-based particles for virus inactivation

4.1 Porous silicon particles

Porous silicon has a highly developed 3D porous structure with crystalline silicon skeleton. This sponge-like material can have a variety of structures and morphologies. It can be obtained by different techniques depending on the desired structure and properties of the material. However,

electrochemical etching of crystalline Si wafers in HF-based solutions is the most frequently used technique for the fabrication of nanostructured porous silicon. This technique is rather simple and inexpensive. Anode (Si wafer) and cathode (for example, Pt electrode) are placed in HF solution. The film of porous silicon is formed on the anode when the appropriate voltage/current between the electrodes is applied. The formed film can then be easily processed into a variety of forms including micro and nanoparticles. Different porous structures with distinct pore morphologies and size can be tuned by simply changing fabrication parameters such as the applied current density, wafer resistivity, concentration of HF solution (Figure 1a). The freshly etched porous silicon surface is primary terminated by hydride species (Si–H, Si–H_2, Si–H_3). However, these hydrogen-terminated bonds are unstable in air or water. Therefore, the surface of porous silicon particles can be easily functionalized by various groups and molecules which make tunable drug load and release[51,54,73,74] (Figure 1b). Besides, porous silicon materials are biocompatible and biodegradable.[23,31,54,73,74] Gongalsky et al.[22] synthesized non-porous and porous silicon particles and showed significant difference in their biodegradation lifetimes (20 days for the non-porous particles and only 24 h for the porous particles) which was explained by different size of nanocrystals of the materials. It was also shown that both type of the particles exhibited low *in vitro* cytotoxicity towards MCF-7 and HEK293T cells in concentration up to 800 μg/mL.

All the above-mentioned properties make porous silicon particles attractive for creation of new antiviral therapeutics.

Osminkina et al.[75,76] showed that porous silicon particles themselves are an effective universal antiviral agents against pathogenic human viruses of various sizes, shapes, with and without an envelope: H1N1 influenza A, Poliovirus, Human immunodeficiency virus, West Nile virus and hepatitis A virus. The antiviral activity of the particles is based on their high adsorption capacity on relation to the viruses due to microporous structure and high specific surface area. The interaction between the particles and viruses prevents the contact of the virus with host cells that leads to decrease in the infectious titer of all studied types of viruses by approximately 104 times, and corresponded to an inactivation of 99.99 % viruses *in vitro*.

A number of studies indicate that porous silicon particles can serve as effective carriers of various antiviral drugs. A potent antiviral compound against influenza A virus saliphenylhalamide (SaliPhe) is poor soluble in water. To improve its water solubility, reduce side-effects of the antiviral compound and increase its bioavailability, SaliPhe was loaded into thermally hydrocarbonized porous silicon nanoparticles which had a Z-average diameter of 129 ± 10 nm and a pore diameter of 10.7 ± 0.3 nm. The drug loaded particles exhibited low cytotoxicity, increased dissolution rate and steady release of SaliPhe in inorganic solvents compared to the pure drug.[77] Porous silicon particles were investigated as potential carriers of well known antiviral drug acyclovir (ACV). To develop controlled delivery systems of ACV, Maniya et al.[78] used porous silicon micro- and nanoparticles with three surface chemistries (native PSi, thermally oxidized (TOPSi) and thermally hydrosilylated using undecylenic acid UnPSi). The particles exhibited controlled release behavior for several days. UnPSi particles showed slower release than TOPSi and native PSi regardless of the particle size. The authors explained this experimental fact by more stable Si–C chemistry. However, another possible reason that the authors did not consider is covalent attachment of ACV to UnPSi using N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride as linker, while ACV loading into native and TOPSi particles was carried out by immersion method. In other work, the authors compared native, partially and complete thermally oxidized porous silicon films as carriers for ACV. The drug loading was

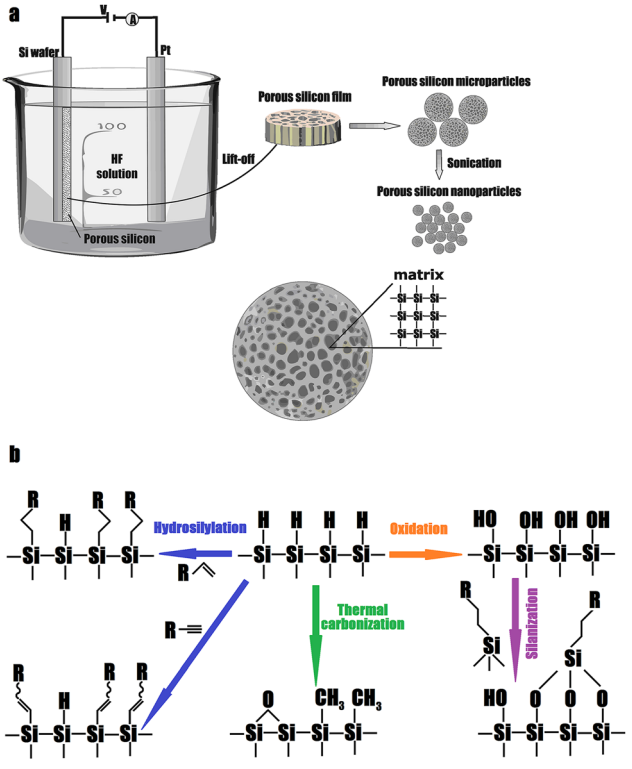

Figure 1: Type of matrix and electrochemical etching method of synthesis of porous silicon particles by electrochemical etching (a) and schematic illustration of surface functionalization of freshly etched porous silicon with various groups by oxidation followed by silanization, thermal hydrosilylation and hydrocarbonization (b).

carried out by immersion method. It was shown that due to amphiphilic surface attributed partially oxidation of Si–H species during drug loading, native PSi film exhibited higher loading as well as slower release of ACV up to 8 h which is controlled by non-Fickian diffusion.[79]

Anti-Malaria drug quinacrine, which has been shown to be active against Ebola Virus and SARS-CoV-2, was loaded in porous silicon particles by sorption. Increasing temperature of the sorption up to 60 °C led to significant increase in efficiency of drug loading. The obtained drug delivery system exhibited prolonged release of the drug.[80]

4.2 Silicon nitride particles

Silicon nitride (Si_3N_4) is a composite consisting of silicon nitride crystalline grains embedded in a matrix of amorphous or partially crystallized glassy phase. In crystal structure of Si_3N_4, each nitrogen atom is surrounded by three silicon atoms, and each silicon atom is tetrahedrally surrounded by four nitrogen atoms. The SiN4 tetrahedra are connected by sharing corners to form a rigid three-dimensional framework. Cristalline silicon nitride has two stable polymorphs at ambient conditions: trigonal α-Si_3N_4 and hexagonal β-Si_3N_4.[81] The repeating structural unit of crystalline Si_3N_4 and crystal structure of β-Si_3N_4 grains are presented in Figure 2. It exhibits excellent mechanical properties comparable to steel, which depend on the size and shape of Si_3N_4 grains, as well as the amount and chemical composition of the grain boundary phases.[28,50,82] In the indicated works, the basic methods of preparation of the materials are detailed. At the same time, a large number of studies have demonstrated biocompatibility of Si_3N_4 (for example, Refs. 27, 28, 83, 84) and its ability to dissolve in aqueous media.[32,33,84] Silicon nitride undergoes hydrolysis in aqueous media and in general, the dissolution process can be written as

$$Si_3N_4 + 6H_2O \rightarrow 3SiO_2 + 4NH_3$$

$$SiO_2 + 2H_2O \rightarrow Si(OH)_4$$

(Du et al.[28]). The hydrolysis processes occurring at surface of silicon nitride particles play a key role in antiviral activity of the Si_3N_4. Pezzoti et al.[85–87] showed that the hemolytic cleavage of Si–N bonds occurring upon hydrolysis at the Si_3N_4 surface triggers a cascade of reactions leading to the formation of NH_4^+/NH_3 and reactive radical nitrogen species, which damage virion RNA structure of single-stranded RNA viruses (ssRNA) such as Influenza A H1N1, Enterovirus 71, Feline calicivirus, SARS-CoV-2 virus. The authors noted that despite of the common mechanisms of action, the kinetics of inactivation of ssRNA viruses by Si_3N_4 particles can be different. In addition to the effect of differences in the genomic structure between different viruses, the kinetics of inactivation depends on the different levels of binding between virions and Si_3N_4 particles. For inactivation, a virion must come into contact with the particles. The contact occurs due to electrostatic interaction between positively charged proteins of viral envelope and membrane and negatively charged Si_3N_4 surface at homestatic pH and then, between negatively charged spike glycoproteins and Si–NH^{3+} sites of Si_3N_4 surface, which resemble cell lysine N-terminal receptors. The stronger the interaction, the faster and better inactivation occurs. Once in contact with the surface of Si_3N_4 particles, the virions are killed by "ammonia poisoning." This two-step antiviral mechanism has been branded as the "catch-and-kill" effect (Figure 3). The antiviral activity of Si_3N_4 particles against Herpes simplex virus 1 has recently been demonstrated. According to the mechanism described above, ammonia and its nitrogen radical byproducts, produced upon Si_3N_4 hydrolysis, directly reacted with viral proteins and irreversibly damaged the virus DNA structure. The authors believe that minor additives of micrometric Si_3N_4 particles into antiviral creams, gels and oral rinses could provide a valid alternative topical antiviral treatment.[88] Simpson et al.[89] studied the antiviral efficacy of Si_3N_4 against SARS-CoV-2 using powders, solids, and embedded nonwoven fabrics (polypropylene fibers). Antiviral efficiencies for all three materials were 99.99 % at ≤5 min, ~93 % in 24 h, and 87–92 % in 120 min, respectively. The study demonstrated that Si_3N_4 embedded fabric is a promising material for commercial masks that not only "catch" but also "kill" the pathogens.

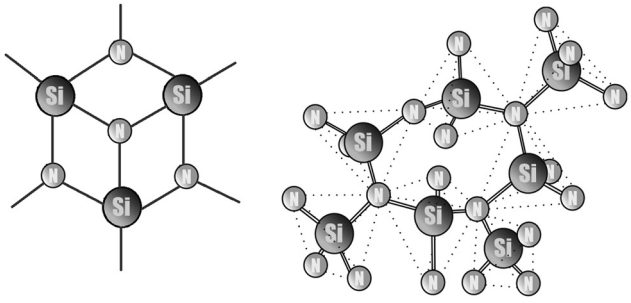

Figure 2: The repeating structural unit of crystalline Si_3N_4 and crystal structure of β-Si_3N_4 grains.

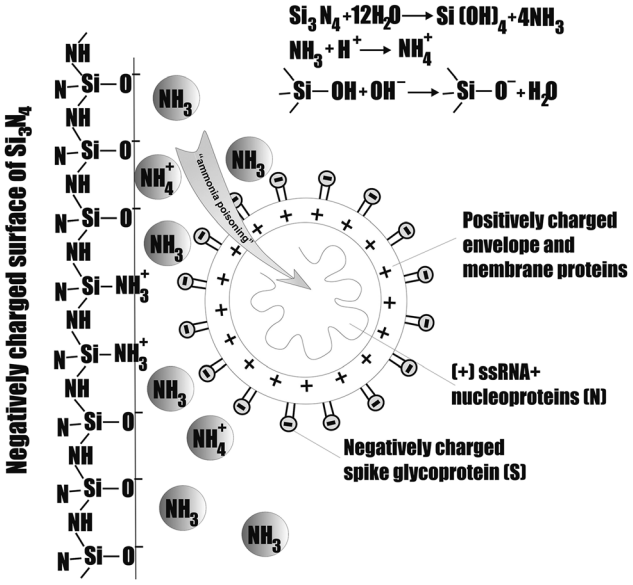

Figure 3: Schematic illustration of "catch-and-kill" antiviral mechanism of Si_3N_4 particles against SARS-CoV-2.

4.3 Silicon-based dendrimers. Carbosilane dendrimers

Dendrimers are highly branched artificial macromolecules with well-defined spherical structure in which a central core (an atom or group of atoms) is surrounded by the symmetric of tree-like branches with terminal functional groups known as dendrons (Figure 4). The geometric repetition of the dendrimeric branches results into the formation of radially centric layers called "generations". Although dendrimers are polymeric molecules, they have some properties of particles, such as high symmetry, three-dimensional spherical structure, narrow polydispersity, surface charge, interior cavity capable to encapsulate drugs, etc. Especially, these properties exhibit dendrimers of a high generation. Therefore, dendrimers are often considered as promising particulate drug carriers.[90–92]

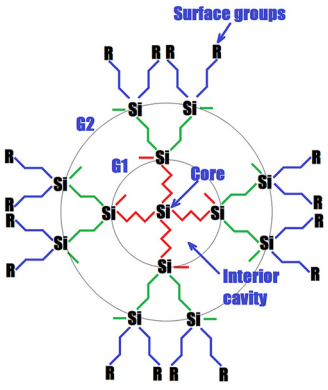

Figure 4: Schematic representation of carbosilane dendrimer components.

Silicon-based dendrimers are a broad family of dendritic materials. Carbosilane dendrimers is the most important class of silicon-based dendrimers. Carbosilanes can contain silicon atom or group of atoms as a core and silicon and carbon in molecular skeleton (Figure 4). The silicon–silicon, silicon–carbon and carbon–carbon bonds leads to high hydrophobicity as well as thermal and hydrolytic stability of the compounds. Depending on the nature of the terminal functional groups, carbosilanes can be divided into three groups: cationic, anionic and neutral dendrimers. The features of preparation, structure and properties of carbosilane dendrimers are described in detail in literature (for example, Refs. 93–96).

Cytotoxicity of carbosilanes depends on various factors, for example, chemical composition, surface charge, hydrophobicity/hydrophilicity. It is established that cationic dendrimers show high cytotoxicity due to interaction with negatively charged cell membranes resulting in a decrease in their integrity. Neutral and anionic dendrimers are the most compatible.[94,97]

4.3.1 Carbosilane dendrimers as antivirals

Many studies showed that polyanionic carbosilane dendrimers exhibited broad-spectrum antiviral activity.[98] demonstrated that carbosilane dendrimers uniformly functionalized with sialyl lactose moieties (Neu5Acα2 → 3-Galβ1 → 4Glc) exhibited strong inhibitory activities against human influenza viruses (H1N1′ and H3N2).

A special place in this area belongs to a group of Spanish researchers who published a series of works on the use of carbosilane dendrimers as antiviral agents against human immunodeficiency virus (HIV), Herpes Simplex Virus (HSV-2), hepatitis C. They established that sulfated, sulfonated and naphthylsulfonated polyanionic carbosilane dendrimers with a silicon core have shown potent and broad-spectrum anti-HIV-1 and anti-HIV-2 activity. The dendrimers inhibited viral infection at the first step the viruses lifecycle: binding/entry-mediated events. In addition, these dendrimers protected the epithelial monolayer from cell disruption and also reduce HIV-1 infection of activated PBMC. The authors believe that the high antiviral activity of the carbosilane dendrimers is primarily due to their hyperbranched structure that allows multivalent binding to the target, as well as the polyanionic nature of the surface that promotes interaction with viral envelop proteins.[99–102] It was also demonstrated *in vivo* experiments that G2-S16 carbosilane dendrimers inhibited HIV-1 even in

the presence of semen.[103] Thus, the carbosilane dendrimers can inhibit cell-to-cell HIV transmission Comparison of the effects of cationic and anionic carbosilane dendrimers, differing in nature and number of terminal groups, on regulatory T cells that are targets for HIV-1, showed that the anionic dendrimers showed high biocompatibility and activity against viruses, preventing infection of T cells.[104] The studies *in vitro* and *in vivo* have established that the anionic dendrimers G2-S16, G1-S4 and G3-S16 demonstrated highest inhibitory response against Herpes Simplex Virus (HSV-2) infection.[105] The antiviral effects of a series of polyanionic carbosilane dendrimers of a second and third generation with polyphenolic core on hepatitis C virus infection were investigated by Sepúlveda-Crespo et al.[106] The dendrimers inhibited effective virus adsorption of major HCV genotypes. It was established that G2-S24P dendrimer was particularly potent against HCV: it irreversibly destabilized infectious virions at higher concentration. *In vitro* experiments demonstrated that polyanionic dendrimers (G1-S4, G2-S16 and G2-S24P) were also active against human cytomegalovirus (HCMV).[107]

4.3.2 Carbosilane dendrimers as antiviral drugs carriers

As shown in the studies cited above, the antiviral activity of carbosilane dendrimers was significantly enhanced by the use of their combinations with antiviral drugs. For example, polyanionic carbosilan dendrimers exhibited a synergistic activity with tenofovir (TFV) and maraviroc (MRV) in HIV-1 treatment[97] and TFV and raltegravir against HIV-2.[99] A synergetic effect of polyanionic carbosilane dendrimers and acyclovir and TFV against HSV-2 was demonstrated *in vitro* by Ceña-Diez et al.[105] The authors do not specify what the nature of the resulting drug-dendrimer microbicides is, but suggest that such systems can be formed due to drug encapsulation in the internal cavities of the dendrimers or interaction between the drug and the surface of the dendrimer.[97] It was suggested that the synergatic effects of such systems were achieved due to the blocking HIV infections at different stages of the virus life cycle. The dendrimers block viral entry and the subsequent infection of the target cells, whereas antiviral drugs play a decisive role in reverse transcriptase inhibition.

Until now, antiviral effects of polyanionic carbosilanes have been described. However, Perisé-Barrios et al.[108] suggested using polycationic carbosilane dendrimers containing ammonium or amine groups at their periphery as nanocarriers for siRNA for successful gene therapy against HIV-1. The polycationic dendrimers (G2-NN16 and G2-03NN24) form strong complexes with siRNA (dendriplexes) and did not elicit toxicity in CD4 T lymphocytes and macrophages. It was shown that the dendrimers protect siRNA from degradation by RNase The nanoconjugate formed by G2-03NN24/siRNA-Nef presents the highest inhibition of HIV-1 replication. This was explained by more flexible structure of G2-NN16 dendrimer with a silicon core in comparison with G2-03NN24 derived from the polyphenol core. The flexible structure of G2-NN16 dendrimer results in increased cellular uptake by CD4 + T cells.

4.4 Silica particles

Silica is a material having a three-dimensional siloxane (Si–O–Si) network, which is terminated at the silica surface with silanol groups. Nevertheless, it can exist in the form of various structures, have a variety of morphologies, surface properties, and particle sizes (Figure 5). Fairly simple and inexpensive synthesis methods of diverse silica particles and effects of the synthesis parameters on the indicated properties are detailed in reviews.[55,109–111]

Synthetic silica is typically amorphous, i.e. its structure is characterized by the absence of long range periodicity in the network but some short range order remains. Unlike crystalline forms, amorphous silica is recognized by US Food and Drug Administration (FDA) and European Food Safety Authority (EFSA) as safe excipient in dietary supplements and pharmaceutical formulations.[112,113] It is very important for development of novel drug formulations for oral administration. It should be noted that porous silica particles can have ordered pore system and can be considered as crystalline materials in terms of organized porosity. However the pore walls of these particles are created with amorphous silica.

Among silicon-based particles, porous silica particles attract the most attention of researches involved in the development of new drug formulations. Due to their large pore volume and specific surface area, porous silica particles possess a great drug loading capacity and can modify the drug release profile. Their pore structure with tunable pore size and geometry facilitates loading of gust molecules with different nature and size. Moreover, owing to abundant silanol groups on the surface of silica particles, their surface properties can be relatively easy modified by the incorporation of various organic groups and inorganic species. The surface functionalization plays a decisive role in drug-surface interaction, and hence, drug loading and its release kinetics, as well as targeted drug delivery[55,109–111].

Numerous studies have shown that silica particles are biocompatible and biodegradable. However, these very important biological properties depend on structure,

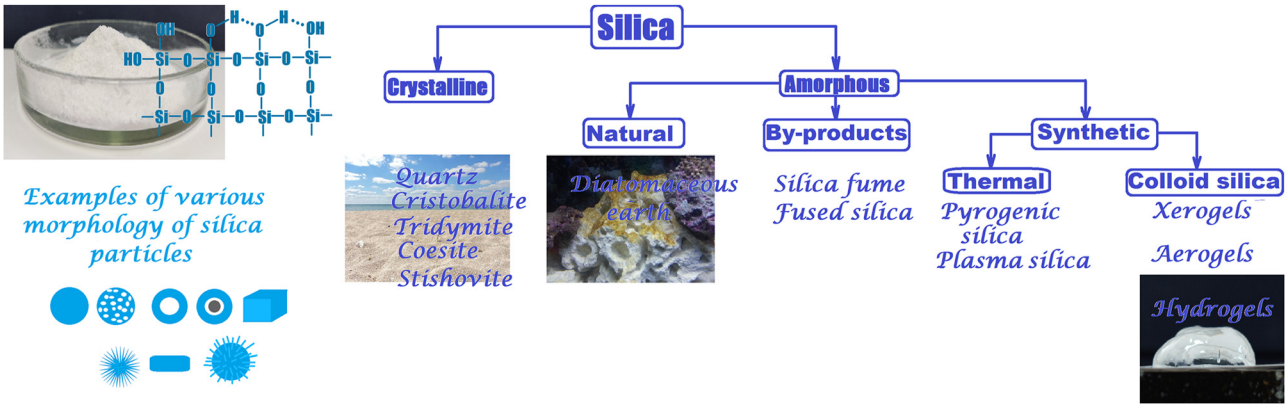

Figure 5: Diversity of silica materials and morphology of their particles.

porosity, surface chemistry, shape, size and even administration routs of silica particles.[55,114,115] As has been mentioned above, due to their inorganic matrixes, silica particles are not subjected to degradation by enzymes and pathogens in living organisms and can protect drugs and cells from attacks of enzymes and microbes in biological media. Moreover, amorphous silica particles exhibit high thermal and mechanical properties[21,116,117] and therefore encapsulation of "fragile" bioactive compounds and objects into silica matrixes can improve their thermal stability, mechanical strength and storage.[118,119]

The studies reported in literature show the promise of using silica particles for the development of antiviral drugs. At the same time, silica particles themselves can exhibit an antiviral effect, and also be carriers for antiviral drugs.

4.4.1 Antiviral effects of silica particles

Some studies show that silica particles themselves may exhibit an antiviral effect. Zschocke et al.[120] compared silica gel with acyclovir cream in the treatment of recurrent herpes labialis and concluded that silica gel relieved all investigated symptoms earlier than acyclovir cream. Therefore, the authors believe that silica gel could prove a useful alternative to topical acyclovir.

At the same time, Nefedova et al.[121] did not find antiviral activity of amorphous silica particles against enveloped (Infuenza A/WSN/1933, SARS-CoV-2, TGEV) and non-enveloped (EMCV) mammalian viruses and bacteriophages (MS2, Φ6). The authors believe that such effect is expected because silica is considered biologically compatible and low toxic.

de Souza e Silva et al.[122] synthesized mesoporous silica particles carrying distinct surface groups (hydroxyl, aminopropyl, glycidyloxypropyl and phenylethyl groups) and studied *in vitro* their cytotoxicity to mammalian cells and inhibitory potential to prevent transduction of the GFP lentiviral vector harboring a VSV-G envelope (vesicular stomatitis virus G glycoprotein) and the GFP lentivector harboring an HIV-gp120 derived envelope. The particles of a few hundred nanometers exhibited uniform spherical shape and smooth surfaces. It was shown that the nanoparticles exhibited no significant toxicity to mammalian cells but reduced the viral transduction ability. The authors found that the inhibitory activity of the silica particles on the viral transduction depended on hydrophobicty/hydrophilicity of the silica particle surface and the virus envelope. The higher reduction of transduction was observed when the surface properties of the silica particles and the virus envelope were similar. The authors proposed that the mechanism of transduction inhibition is associated with the interaction between the virus and nanoparticles: the strong interaction prevents the virus from attaching to the cell necessary for infection, thus giving good transduction inhibition effect.

Cationic quaternary ammonium surfactants are well known as efficient antiviral agents.[123,124] Botequim et al.[125] prepared silica particles coated with a quaternary ammonium cationic surfactant, didodecyldimethylammonium bromide (DDAB) by physical adsorption. The antiviral activity of the prepared particles both in aqueous suspensions and immobilized on glass surface using dopamine was estimated. It was demonstrated that the prepared particles were very efficient against influenza A – H1N1 virus. The authors noted that either in suspension or as a coating, the antiviral activity of the silica particles was not due to the leaching of the surfactant from their surface. The viruses adhere to hydrophobic polycationic surfaces followed by penetration of the polycations into the lipid viral envelope and its damage resulting in release of viral RNA (Figure 6). Commercial silica nano- and microparticles were functionalized with cationic quaternary ammonium surfactants. The surfactants were covalently attached to the silica particles.

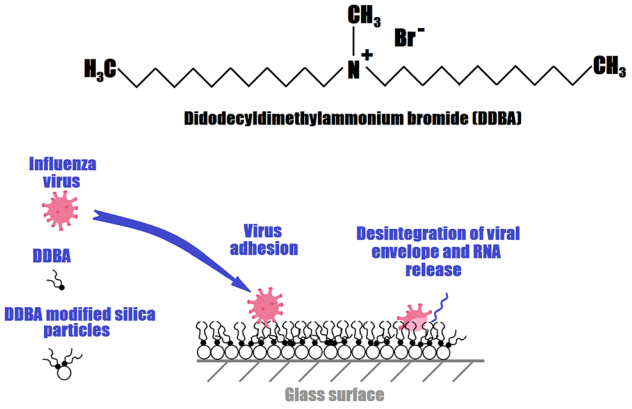

Figure 6: Proposed mechanism of inactivation of Influenza viruses by DDAB modified silica particles onto glass surface.

The alkoxysilanes containing cationic trimethyl quaternary ammonium group with alkyl chains of different length (C18, C14) (aklylated, hydrophobic), as well as alkoxysilane containing only trimethyl quaternary ammonium group (nonalkylated hydrophilic) were used for the functionalization. A series of self-assembled structured surfaces were prepared using bimodal suspension mixtures, containing both the hydrophobic and hydropholic functionalized silica nano/micro-particles. The surfaces exhibited both antiviral and hydrophobic (easy-clean) properties.[126]

Attachment of Herpes simplex virus (HSV) to cell is mediated by the interaction of the viral envelope glycoproteins (gB or gC) with target cell-surface molecules – glycosaminoglycans (GAGs, heparan sulfate proteoglycans) containing negatively charged sulfonate groups. Therefore, Lee et al.[127] synthesized silica particles functionalized with molecules that mimic GAGs which acted as decoy receptors and would interact with viruses, thus preventing their interaction and penetration into cells. Two types of silica particles with diameters of 150–200 nm were prepared: solid silica particles and mesoporous silica particles. Both types of the silica particles were functionalized with benzene sulfonate (Figure 7). The functionalized silica particles exhibited antiviral effect against HSV-1 and HSV-2. However the mesoporous functionalized particles revealed a lower IC_{50} value compared to similar solid particles, which was explained by higher weight % organic content of the mesoporous silica particles. The unfunctionalized solid and mesoporous particles did not show the antiviral activity. Continuing this work, the authors synthesized propyl sulfonate-, propyl-thiol-, zwitterionic sulfonate- and phenyl-functionalized mesoporous silica particles (Figure 7). Negative viral inhibition was observed for propyl-thiol-, zwitterionic sulfonate-functionalized and unfunctionalized mesoporous silica particles. The phenyl-modified particles exhibited a weak antiviral effect. The investigation of their antiviral activity showed that the sulfonate group plays a key role in the antiviral response, which is enhanced by benzene group within the ligand in comparison with propyl group.[128]

A major mechanism of human immunodeficiency virus (HIV) infection involves the interaction of the exterior viral envelope glycoprotein gp120 with the surface receptor of human cells CD4. Cheng et al.[129] designed and prepared silica nanoparticles functionalized with CD4 peptide fragments or whole soluble sCD4 for targeting the HIV-gp120 antigen and potentially the HIV virus itself. The CD4 type receptors were immobilized onto silica particles by two methods: through lysines on the sCD4 or through the glycosidic linkage. It was found that the immobilization through the glycosidic linkage (oxidized sialic acids) enabled CD4 to be attached to a solid surface in a homogeneous manner without loss of any gp120 binding affinity, with nearly complete removal of whole gp120 from solution. The authors believe that particles modified with sCD4 or sCD4 mimics can function as “Trojan horses”, because the external surface can be optimized for binding while at the same time the pores can be loaded with an antiviral agent.

Some studies reported about antiviral activity of silica particles with incorporated inorganic species such as gold and silver nanoparticles, whose antiviral and antibacterial activity is well known. Their incorporation helps to reduce cytotoxic and genotoxic effects of free metal particles, as well as to prevent their aggregation, which could reduce their antiviral capabilities over time. Lysenko et al.[130] prepared two types of silica nanoparticles: (1) core–shell silica particles with gold sphere as core and (2) silica particles with immobilized gold particles on their surface. It was shown that both types of the nanoparticles demonstrated good antiviral effect against adenoviruses. The effect depended on the particle concentration. The particles of the second type exhibited a higher virucidal effect, possibly due to direct interaction of the nanoparticles with virus surface receptors. Assis et al.[131] developed SiO_2–Ag composite immobilized in a polymeric matrix (ethyl vinyl acetate), which exhibited a high virucidal activity towards SARS-CoV-2. The proposed mechanism of enhancement of antiviral activity of the composite is generation of reactive oxygen species (ROS) due to surface plasmon resonance (SPR) effect of Ag nanoparticles anchored onto silica particles in the presence of O_2 and H_2O and the subsequent oxidative stress. Silica nanoparticles (~400 nm in diameter) decorated with silver particles (~30 nm in diameter) displayed their antiviral capability against bacteriophage MS2 and murine norovirus (MNV)[132] as well as Influenza A virus.[133] The authors suggested that the major antiviral mechanism of the particles is the interaction with viral components located at the membrane.

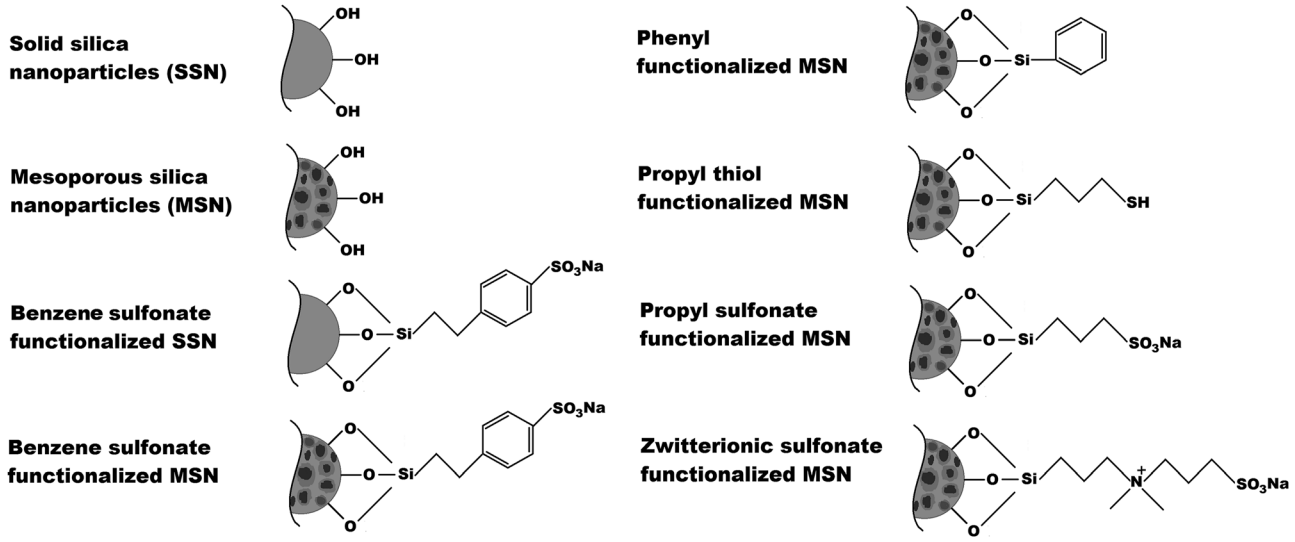

Figure 7: GAG mimetic unfunctionalized and functionalised silica nanoparticles studied by Lee et al.[97,98] as viral entry inhibitors of herpes simplex type 1 and type 2 viruses.

Silica nanoparticles have shown their effectiveness in protecting plants from viral infections.

In vitro and *in vivo* biological experiments have shown antiviral activity of silica nanoparticles against Tobacco mosaic virus (TMV) in host plants at a low concentration (100 μg/ml). The nanoparticles remarkably inhibited virus infection not only due to the direct injury of TMV shell proteins, which prevents viral entry and replication, but also due to the activation of the plant defense mechanisms that leads to plant immunity and growth response. It was found that the antiviral effect of silica particles was higher than that induced by the conventional anti-TMV agent lentinan (a neutral polysaccharide)[134]. Elsharkawy and Mousa[135] studied effects of silica nanoparticles on the systemic expression of certain defense-related genes in cucumber plants infected with *Papaya ring spot virus* (PRSV). The effect of silica particles on expression of defense-related enzymes in tomato plants infected with Tomato Yellow Leaf Curl Virus (TYLCV) was investigated by El-Sawy et al.[136] The obtained results showed that the treatment of cucumber and tomato plants with silica particles significantly suppressed the viral infections via activation of defense mechanisms in the plants. Schematic illustration of antiviral mechanisms of silica particles in plants is presented in Figure 8.

The obtained results showed that the plant treatment with silica suspensions reduced accumulation of the viruses in cucumber and tomato plants and increased defense mechanism against the viruses in the plants.

4.4.2 Silica particles as antiviral drug carriers

Due to highly developed porous structure and surface area, silica particles can serve as reservoirs for accommodation of large quantities of antiviral drugs.

Hirao et al.[137] proposed mesoporous silica particles filled with cetyltrimethylammonium chloride (CTAC), a cationic surfactant with an alkyl chain length of 16, as virus-inactivating material. As mentioned above, cationic quaternary ammonium surfactants exhibit pronounced antiviral activity. The inactivation activity of the loaded particles was tested using model enveloped (bacteriophage Φ6) and nonenveloped (bacteriophage Qβ) viruses. The silica particles demonstrated approximately 4 orders of magnitude of virus inactivation against their respective viruses contact time of 10 min. In aqueous solution, the surfactant loaded silica particles released the antiviral agent and the released surfactant acted on the viruses. The authors suggested that the mechanism of inactivation can be attributed to the interaction of the positively charged cationic surfactant with the lipid membrane and proteins that make up the outermost layer of the virus leading to the membrane disruption and the protein denaturation. A prototype paper containing the silica particles demonstrated approximately a 5 orders of magnitude of virus inactivation.

In vitro and *in vivo* studies showed that the use of spherical mesoporous silica particles with a diameter as drug carriers for ribavirin had significantly improved the efficiency of the drug against largemouth bass virus

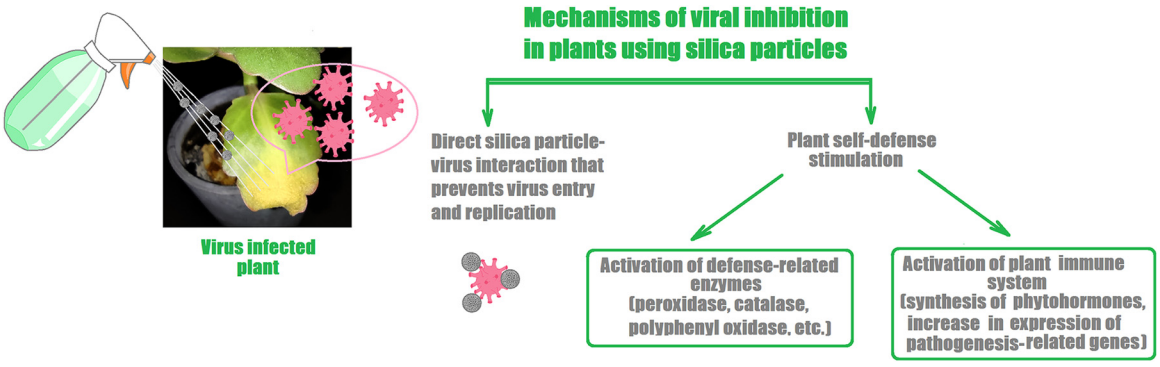

Figure 8: Schematic illustration of antiviral mechanisms of silica particles in plants.

(LMBV).The drug was loaded by physical adsorption (immersion of the silica particles in a solution of ribavirin). The authors noted that ribavirin exhibited significant toxicity to experiment fish when the concentration of ribavirin reached 40 mg/l, while the loaded silica particles did not show significant toxicity at the same ribavirin concentration.[138]

Sol-gel encapsulation of poor water soluble antiviral drug velpatasvir (VLP), effective against hepatitis C virus (HCV), in mesoporous silica nanoparticles (MSN) significantly improved the drug release kinetics in wide range of pH values, i.e., 1.2–6.8. *In vivo* toxicological evaluation and pharmacokinetic results demonstrated that VLP-silica composite is non-toxic and significantly enhanced the bioavailability as compared to pure drug.[139]

Braun et al.[140] developed mesoporous silica particles with a mean size of 170 nm as carries for peptide VIR-576, which has a very short half-life in the body, to improve its stability and delivery. The peptide prevents human immunodeficiency virus 1 (HIV-1) entry and was found to be safe and effective in a phase I/II clinical trial. In model *in vitro* experiments, it was found that the peptide released from the silica particles slow, in active form. However, inhibitory activity of the released peptide was significantly lower compared to free peptide and only after a release time of 48 h, the efficiency of HIV-1 inhibition measured for the free peptide and for the released VIR-576 were very similar. Nevertheless, the release rate in the presence of serum proteins was found to be clearly higher than that observed under protein-free conditions.

In *in vitro* experiment, Akimsheva et al.[141] showed that silica particles could be the basis for developing a new oral formulation of acyclovir. Sol-gel encapsulation of the drug in silica matrix resulted in formation of acyclovir-silica composite which contained only 18.4 mg/g of the composite and was able to maintain the concentration of the drug in different parts of the gastrointestinal tract for 26 h regardless of the acidity of the medium and the time of transit through them. This can contribute to the continuous and permanent therapeutic effect of acyclovir and avoid the multiple taking the drug during the day (Figure 9).

Neufurth et al.[142] in *in vitro* experiments showed that inorganic physiological polymer (polyphosphate) exhibits strong antiviral effect against SARS-Cov-2 virus. They demonstrated that the polymers with different chain length, $PolyP_3$ and $PolyP_{40}$, efficiently inhibited the binding SARS-CoV-2 spike (S)-protein to host cell ACE2 recerptor at physiological pH due to strong interaction between the polyphosphates and Arg amino acids at the surface of RBD (receptor binding domain of the spike (S)-protein). Since the polyphosphate are subject to enzymatic degradation, they were encapsulated in silica particles with a size of 100–200 nm. However, as the results of the study showed, the encapsulation contributed to a decrease in the toxicity of the particles loaded with polyphosphates compared to empty silica particles, but did not lead to an increase in the inhibitory effect of the polyphosphates released from the particles. The inhibitory activity of the encapsulated and free polyphosphates was found to be approximately the same.

Modification of silica particle surface with various polymers, groups and species is a powerful tool to control structure and properties both silica particles themselves (for example, porosity, surface charge, degradation, cytotoxicity, etc.) and created drug delivery systems (for example, drug loading, phase state, release kinetics, targeted delivery, etc.).

LaBauve et al.[143] investigated lipid-coated mesoporous silica particles with hexagonal pore structure as carriers for ML333. The lipid coating promoted enhancement of colloidal stability and circulation time of the silica particles, their biocompatibility, protection of the cargo. The authors concluded that the silica particles are promising drug delivery vehicles to treat Venezuelan equine encephalitis virus (VEEV) infection because they significantly inhibited VEEV and did not exhibit cytotoxicity. Lipid-coated

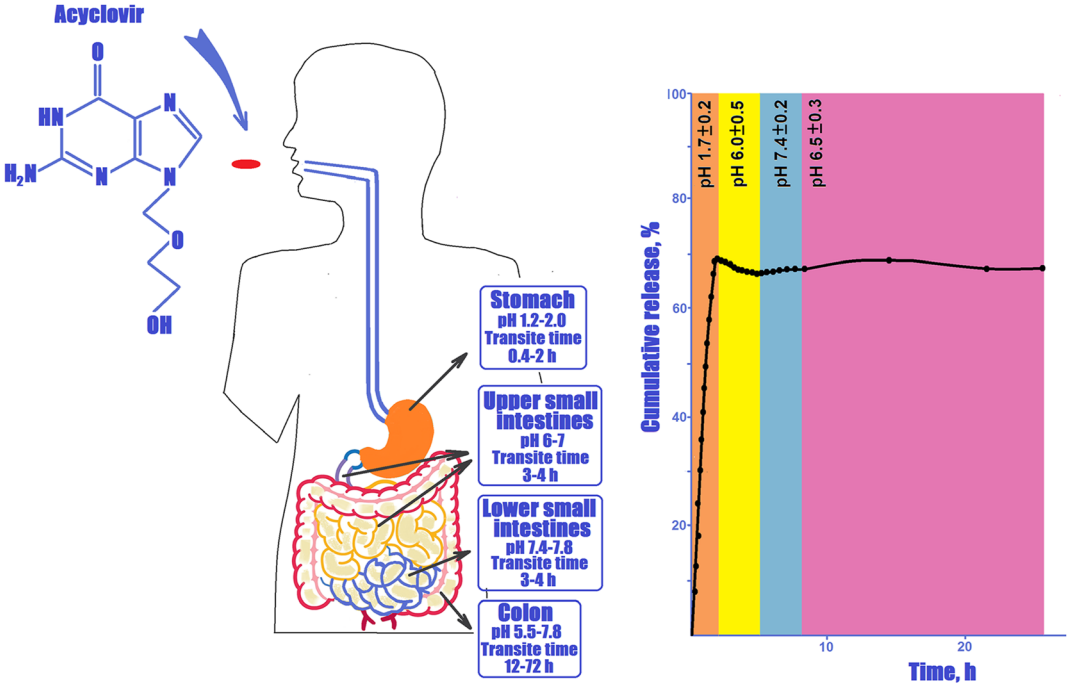

Figure 9: Cumulative release of acyclovir from acyclovir-silica composites in accordance with the transit conditions in the GIT.

mesoporous silica particles with varying morphology (hexagonal, stellate, dendrimeric) and size were also studied as carries for CRISPR-Cas9 ribonucleoproteins (RNP) that target host genes necessary for Ebola virus (EBOV) infection. The stellate particles were found to be the most suitable for this purpose. The particles successfully delivered CAS9 RNP cargo intracellulary with minimal cell toxicity. *In vitro* and *in vivo* studies have demonstrated potential use of the developed formulation to prevent the viral infection.[144]

Encapsulation of curcumin in mesoporous silica particles coated with temperature-responding polymers (PEGMA) has enabled the development of new antiviral formulation against Zika virus.[145] Due to the polymer coating, release of curcumin significantly increases when the temperature is higher than the critical temperature (38 °C, the temperature of fever). The authors noted that the antiviral ability of the formulation was higher compared to free drug. The particles were also doped magnetic and phosphorescence imaging metal ions (Eu3+ and Gd3+) for imaging function, which can help to understand the position of the carrier in the body.

Polydopamine-coated mesoporous silica nanoparticles were used for co-loading anti-inflammatory Ziyuglycoside I (ZgI) and antiviral oseltamivir (OST). Such drug delivery system was designed for achievement of synergistic therapeutic effects of ZgI and OST viral pneumonia, that is, rapid killing of influenza viruses by OST and effective control of the virus-induced hyperinflammatory response by ZgI. ZgI was loaded into the pre-synthesized silica particles by adsorption, then the particles were coated with polydopamine (PDA), and OST was incorporated into the PDA coating. PDA was used as pH-responsible polymer for direct targeted treatment of viral pneumonia. *In vitro* and *in vivo* experiments showed rapid antiviral effect of OST and effective control of the inflammatory response by ZgI.

Poorly soluble in aqueous media antiviral drug niclosamide (NIC) was encapsulated into ordered mesoporous MCM-41 and SBA-15 silica particles coated with mucoadhesive non-ionic polymer Tween 60 to induce high drug solubility and eventually enhanced bioavailability *in vivo*. *In vitro* studies of release kinetics showed significantly enhanced release of the encapsulated NIC compared to free drug. However, the modeling the drug release process using kinetic sorption models is unlikely to provide information on the release rates and its mechanism. Nevertheless, these *in vitro* studies and *in vivo* studies of pharmacokinetics of NIC showed that the encapsulation of the drug significantly enhanced NIC release and improved its oral absorption in the gastrointestinal tract compared to free drug due to the synergetic effect of the mesoporous carriers and surfactant. The authors demonstrated that the mesoporous silica carriers are promising materials for improvement of the efficacy of orally administrated poorly soluble drugs, such as NIC.[146]

AbouAitah et al.[147] used mesoporous silica particles functionalized with amino groups by grafting for loading of natural prodrugs: shikimic acid, quercetin or both. The

synthesized drug loaded silica particles exhibited higher antiviral activity against avian influenza H5N1 virus compared to free prodrugs and unloaded silica particles. The effect depends on the concentration of nanoparticles in the nanoformulation. Shikimic acid was particularly efficient in the virus inhibition, even for low loading into the silica nanoparticles, in comparison with quercetin. The proposed mechanisms of antiviral activity of the nanoformulations against avian influenza H5N1 are direct (virucidal mechanism) and indirect (immunomodulatory effects).

Hydroxychloroquine (HCQ) is considered as promising drug for treatment of respiratory syndrome caused by SARS-CoV-2. However, the clinical trials have shown numerous side effects of the drug. In order to reduce the side effects of HCQ and to deliver this drug in a controlled manner Olejnik and Goscianska,[148] proposed to encapsulate HCQ into unfunctionalized (SBA-15 and SBA-16) and functionalized with amino groups and copper mesoporous silica particles. HCQ interacted with unfunctionalized silica particles through hydrogen bonding, while in the case of the functionalized particles the complexes with drug molecules were formed. It was found that the drug loading depended mainly on total pore volume of the synthesized materials rather than the surface functionalization. However the presence of functional groups affected the amounts of released drug. The authors showed that the encapsulation of HCQ into the silica particles resulted in sustained release, which was controlled by quasi-Fickian diffusion and was also dependent on pH conditions, textural parameters, surface charge of the particles.

A number of studies have focused on development of delivery systems for acyclovir based on surface functionalized silica particles. Dolinina et al.[149] synthesized composites of acyclovir with mercaptopropyl functionalized silica particles and phenyl functionalized silica particles[150] and studied release kinetics of the drug in solutions with pH mimicking pH of different segments of gastrointestinal tract (GIT). Although the composites of acyclovir with the organomodified particles showed controlled release according to zero-order law, they were found to be unsuitable for further development of oral acyclovir formulations because the release properties of the drug were highly dependent on pH of release medium, i.e. the release properties (the release rate, the amount of released ACV)can change dramatically during transition of the composites through various segments of GIT.

The mentioned above mesoporous silica particles functionalized with sodium benzene sulfonate as glycosaminoglycan (GAG) mimetics were loaded with acyclovir.[128] It was shown the prepared silica particles functionalized with sodium benzene sulfonate and loaded with acyclovir were able to target two herpes simplex virus (HSV) infection pathways: extracellularly, the attached GAG mimetic bound the majority of virions and inhibited their entry and the release acyclovir and intracellularly, the released acyclovir inhibited viral DNA replication.

Mukherjee et al.[151] developed mesoporous silica particles as carriers for targeted delivery of shDNA against the RNA of a hepatitis C virus to inhibit its replication. The silica particles were coated with amine and galactose for specific targeting liver cells. The obtained drug delivery system showed significant reduction of viral RNA level (about 94 %) in HCV-JFH1 infectious cell culture due to the successful delivery and action of the shDNA.

Hybrid microcontainers made of silica nanostructures and polypeptide/polysaccharide (poly-L-arginine/dextran sulfate) with encapsulated anti-viral siRNAs (NP-1155, NP-717 and NP-1496) were synthesized by Timin et al.[152] as antiviral formulations against influenza A (H1N1) virus infection. The authors used the integration of sol-gel method with layer-by-layer technique to fabricate the non-toxic microcontainers with improved mechanical properties and low permeability protecting the bioactive molecules from the decomposition before reaching the target cells. Because the microcontainers were made of biodegradable polymers and silica, the siRNA can release due to the degradation of the microcapsule structure. *In vitro* study showed that siRNA released from the microcapsules significantly decreased the level of viral nucleoprotein in the infected A549 and MDCK cells. All the tested siRNA demonstrated the inhibition activity against the virus in dose-dependent manner. The decrease in the virus titer was observed for NP-717. The authors concluded that microencapsulation technology has great potential for development of RNA delivery systems against influenza virus infection.

Mesoporous silica particles with dendritic structure to deliver siRNA were proposed for treatment of SARS-Cov-2 infection. Due to large pore structure, the dendritic particles showed a high siRNA loading and its protection from nuclease-mediated degradation. The particles were decorated with SARS-Cov-2 S protein for targeting the infected host cells and specific recognition of the protein by ACE2 receptor on the cell surface. *In vitro* experiments showed that the particles possessed high biocompatibility, released siRNA slowly and continuously for 30 h and exhibited its targeted delivery to the ACE-2 overexpressed cells. The cells treated with the particles demonstrated inhibition effect on the transfected SARS-Cov-2 RdRp gene expression, and this effect was higher compared to free siRNA.[153]

Complex of quercetin as a potent inhibitor of SARS-CoV-2 with virus-like core–shell silica-ZnO-Ag particles has demonstrated antiviral activity against bacteriophage upon

irradiation by NIR laser. Due to the biomimetic morphology, the virus-like nanoparticles showed greatly superior cellular uptake property, unique internalization pathways, and extended blood circulation duration. Under the radiation, hyperthermia generated by the silica particles resulted in increasing Ag^+ release and disruption of virus membranes. Synergistic effect of quercetin and silica-ZnO-Ag under NOR laser irradiation was achieved.[154]

Arkaban et al.[155] synthesized Fe(III)-doped mesoporous silica particles loaded with antiviral drug remdesivir and coated with polydopamine as gatekeeper for theranostic purposes. *In vitro* magnetic resonance imaging (MRI) and MMT tests showed applicability of the nanoformulation as MRI contrast agent and the biocompatibility of the nanocarrier. *In vitro* release study demonstrated that the encapsulation of remdesivir with a short circulation time into the silica particles dopped with Fe(III) resulted in release of 75 ± 2 % of the drug in a medium with pH 7.4 during the first 90 h. This result is significantly higher compared to release of the drug from undoped particles because doping of Fe in SiO_2 makes them degradable.

Silica particles have been proposed as RNA containers to inhibit plant viral infections. Amine functionalized silica nanoparticles loaded with double-stranded RNA (dsRNA) have shown great potential for suppressing viral infections in plants. Three types of nanoparticles, including amino-propyl modified silica nanopowder (ASNP), were studied as carriers of double-stranded RNA (dsRNA) for inactivation of Potato virus Y. It was investigated whether ASNP could deliver dsRNAs capable of silencing the target gene expression and affecting the virus resistance of plants. The plants were treated with the nanoparticles by infiltration, spraying and root soaking methods. It was found that ASNP-dsRNA nanoparticles effectively silenced genes in plants for at least 14 days. The nanoparticles were recommended for root soaking, which is considered the most effective method of antiviral compound application.[156] Sangwan et al.[157] investigated the possibility of using amine functionalized mesoporous silica nanoparticles as a dsRNA delivery platform in plants to control Tomato leaf curl New Delhi viral infection. They synthesized the mesoporous silica nanoparticles with average sizes ~10, ~ 32 and ~ 66 nm, loaded them with dsRNA targeting AC2 gene of the virus and studied delivery into plant leaf and root tissues. It was found that the highest antiviral effect exhibited the particles with an average size of ~ 32 nm probably due to better internalization into the plant system and high loading capacity. In addition, it is shown that amino functionalized silica particles protected dsRNA from nucleases degradation.

4.5 Aluminum silicates

4.5.1 Zeolites

Zeolites are hydrated crystalline porous aluminosilicates with rigid ordered 3D structure. The regular structural frameworks of zeolites are made up of three primary components, namely oxygen, silicon, and aluminium. Their primary building blocks are TO_4 tetrahedra (T being silicon or aluminum). The tetrahedra are connected to each other into a corner-sharing network through bridging oxygen atoms and formed 3D framework with regular distribution of pores. The different orientation of tetrahedra results in a wide range of crystalline structures with internal micro and mesoporous and channels along the entire crystalline structure. The presence of the trivalent aluminum infers an anionic character to the framework. The charge is balanced by the presence of exchangeable extra-framework cations (usually, ions of alkali and alkaline earth metals) (Figure 10). Zeolites are the most important inorganic cation exchangers.[16,17] The studies of biosafety of zeolites have shown that their cytotoxicity and biocompatibility depended on Si/Al ratio, particle size and morphology.[158,159]

4.5.1.1 Virucidal properties of zeolite particles

Some studies show that zeolite particles in pure form may exhibit antiviral effects. Grce and Pavelić evaluated the antiviral activity of micronized naturally occurring zeolite clinoptilolite against human adenovirus 5, herpes simplex virus type 1 and human enterovirus (coxsackievirus B5 and echovirus 7). The obtained results showed inhibitory effect of viral proliferation, but very high doses of the zeolite were need for an efficient treatment. This makes clinical use of clinoptilolite difficult. However, according to the authors, the zeolite could be used in purification of drinking water from different viral particles.[160] Mikloska et al.[161] developed antiviral composition containing synthetic zeolite mordenite as active substance, carrier (organic gel, water, oil, cream, liposome and liposome-based systems) and vitamins for prophylaxis, therapy, pre- and post-treatment of diseases caused by the infections with Herpes simplex virus type 1 and/or 2. Thermo-mechanically activated clinoptilolite in composition with propolis and/or colostrums exhibited antiviral effect due to inhibitor activity towards nucleotide and non-nucleotide analogue reverse transcriptases, protease and as entry inhibitor. It was shown that this pharmaceutical composition may be used for prophylaxis and treatment of human immunodeficiency virus (HIV) and

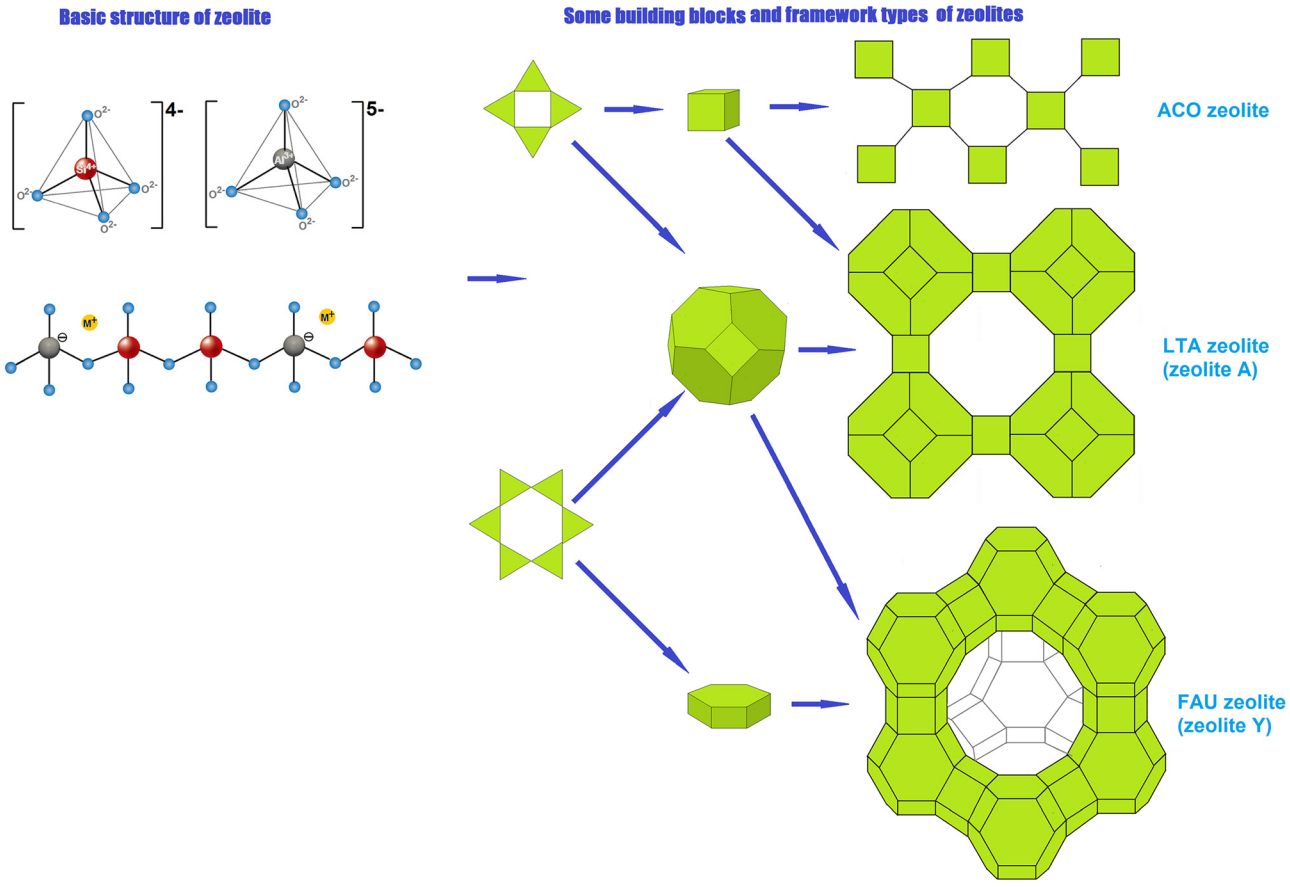

Figure 10: Illustration of basic structures, principles of zeolite formation and some examples of their framework types.

diseases caused by infection of herpes simplex virus type 1 and type 2.[162] The mineral complex based on natural clinoptilolite zeolite ("AZEOMED") administrated orally showed a high antiviral activity against a highly pathogenic strain of avian influenza virus A. In addition, clinic trials demonstrated effectiveness of the zeolite drug in the treatment of diseases associated with viral infections, along with their standard therapy. For example, candidiasis which is common in HIV/AIDS. It was shown that the mineral complex is highly effective for treating all groups of patients with chronic diseases (for example, diabetes, cardiovascular diseases) identified as patients with the highest risk of COVID-19 infection and mortality.[163]

A series of works was devoted to investigation of antiviral properties of zeolites containing transition metal ions. The antiviral activity of such zeolites was studied both in suspensions and in the form of coatings in various materials. The antiviral effects of suspensions of zeolite powders containing Ag, Ag/Cu, Ag/Zn/ZnO ions in PBS as well as the Ag/Cu zeolite incorporated into plastic against human coronavirus 229E and feline infectious peritonitis virus (FIPV; feline coronavirus) were studied by Bright et al.[164] Unfortunately, the authors did not indicate the type of zeolite. Nevertheless, among the studied zeolites, Ag/Cu zeolite, both in the suspension and incorporated into plastic, has shown effectiveness against all tested viruses. The authors believe that zeolite powders containing antiviral heavy metals have many potential application, including development of various materials with antiviral properties (plastics, paints, fabrics).

Cotton textile with antiviral properties was developed by incorporation of containing Cu^{2+} ions zeolite A on the cotton fibers. The zeolite rapidly and effectively inactivated the H5 subtype avian influenza viruses (AIVs), however different sensitivity of different viral strains to Cu^{2+} containing zeolites was observed.[165] The authors supposed that possible mechanism of antiviral activity of the textile with the incorporated zeolite was a direct, close, and efficient contact of the viruses with the Cu^{2+} on the surface of zeolites incorporated in the dense cotton fibers.

Guerrero-Argueroet al.[166] studied antiviral properties of Ag^{+}/Zn^{2+} and $Ag+/Cu^{2+}$ containing faujasite-type zeolites along or in combination with quaternary ammonium compound (benzalkonium nitrate (BZN)) against SARS-CoV-2

virus. The antiviral activity was studied both in suspensions and as coatings in cotton and polyester fabrics. The obtained results showed that inactivation of SARS-CoV-2 was high and exhibited a strong time- and dose-dependent effect in the zeolite suspensions as well as the textile samples. The effect for textiles maintained even after washes, repeated SARS-CoV-2 exposures or treatment with soil-like materials. Addition of the quaternary ammonium compound enhanced the effect. The authors hypothesized that the higher antiviral activity of the combination of the metal ion containing zeolite with quaternary ammonium compound was achieved due to their synergetic effect, i.e. the quaternary ammonium compound facilitates access of transition metal ions to the interior of the virus.

Virucidal activity of the colloids consisting of Ag-ion releasing zeolite (the type of zeolite is not specified), fumed silica and surgical guide VI resin against SARS-CoV-2 and HIV-1 was evaluated to develop 3D printed materials with antiviral properties The composites decreased the half-life of SARS-CoV-2 by 47.24 % and HIV-1 by 62.8 %. As has been suggested, the inhibitory activity of the synthesized composites may be associated with the interaction of silver ions released from the composites with the viral envelope proteins. The inclusion of zeolites and fumed silica significantly increased the mechanical properties of the composite, which are very important for creation of 3D printable materials.[167]

4.5.1.2 Zeolites as antiviral drug carriers

Due to their 3D well-defined porous structure, zeolites are widely proposed as carriers for delivery of various drugs with anti-inflammatory, antitumor, antioxidant, antibacterial activity, etc. However, only one study focusing on the development of a zeolite carrier for a drug with antiviral activity was found in literature. Olejnik et al.[168] showed zeolites can serve as carrier for delivery of hydroxychloroquine, an antimalarial and immunomodulatory agent exhibiting antiviral activity. It was suggested that delivery of the drug in a controlled manner from the carrier would reduce side effects of hydroxychloroquine. The drug loading in the synthesized microporous Na-A and Na-X zeolites was carried out by adsorption. It was shown that the release process was affected by particle size distributions, morphological forms, and chemical compositions of the zeolites. The authors showed that for most synthesized composites, the release followed the Korsmeyer–Peppas model and was controlled by non-Fickian diffusion (diffusion exponent n values were bellow 0.5). However, in numerous studies reported in literature, the $n < 0.5$ indicates pseudo- (quasi-, hindered) Fickian diffusion mechanism (for example, Refs. 169, 170, 171, 172).

4.5.2 Clays

Clay minerals are hydrated aluminum silicates which can contain variable amount of inorganic ions like iron, magnesium, alkali metals, alkaline earth metals and other cations. They are typically characterized by a layered, sandwich-type structure. Their layers are formed from tetrahedral sheets in which a silicon atom is surrounded by four oxygen atoms and octahedral sheets in which a metal such as aluminum or magnesium is surrounded by six oxygen atoms or hydroxyl groups. Such structure is characterized by strong bonds (i.e. covalent bonds) between the atoms forming the layers and weak noncovalent bonding (i.e., hydrogen bonding, van der Waals forces) between the layers, which allows some of them to be exfoliated into few-layered two-dimensional nanosheets (platelets) through physical or chemical means. Depending on a number of tetrahedral and octahedral sheets and their arrangement, clays are divided into several groups. Like zeolites, in general, clays exhibit cation-exchange ability. However, unlike zeolites, some clays are able to swell in an aqueous environment due to interlayer space. The swelling behavior depends on the side of interlayer space: greater the interlayer space, more change will be in swelling behavior. The individual particles of these minerals are mainly of platy form. However their different arrangement, which is related to layer-type crystal structures of clays, results in formation of the materials with different morphology (i.e. layered, fibrous, tubular).[19,173,174] (Figure 11). It was shown that clay materials are biocompatible and do not exhibit significant toxicity.[175–177]

4.5.2.1 Antiviral activity of clay particles

Due to highly developed surface area, negatively charged surfaces, and cation exchange capacity, clays exhibit high affinity to proteins and protein objects including viruses. Therefore, the works devoted to the adsorption of various viruses on clays and the study of their activity aroused great interest.

Very early studies reported that some viruses adsorbed onto clays retained and even increased their infectivity compared to free viruses (for example, Refs. 178, 179). Block et al.[180] assumed that apparent reduced infectivity level of influenza A H1N1 virus adsorbed on montmorillonite compared to free virus was a result of action of each virus-clay aggregate as a single infectious unit rather than a reduction in individual virus infectivity, although it was found that the adsorbed virus was readily deformed. Das and Tadikonda[181] showed that due to exclusive sorption properties, montmorillonote and kaolinite were very efficient clay-based barriers for viral pathogens (SARS-CoV,

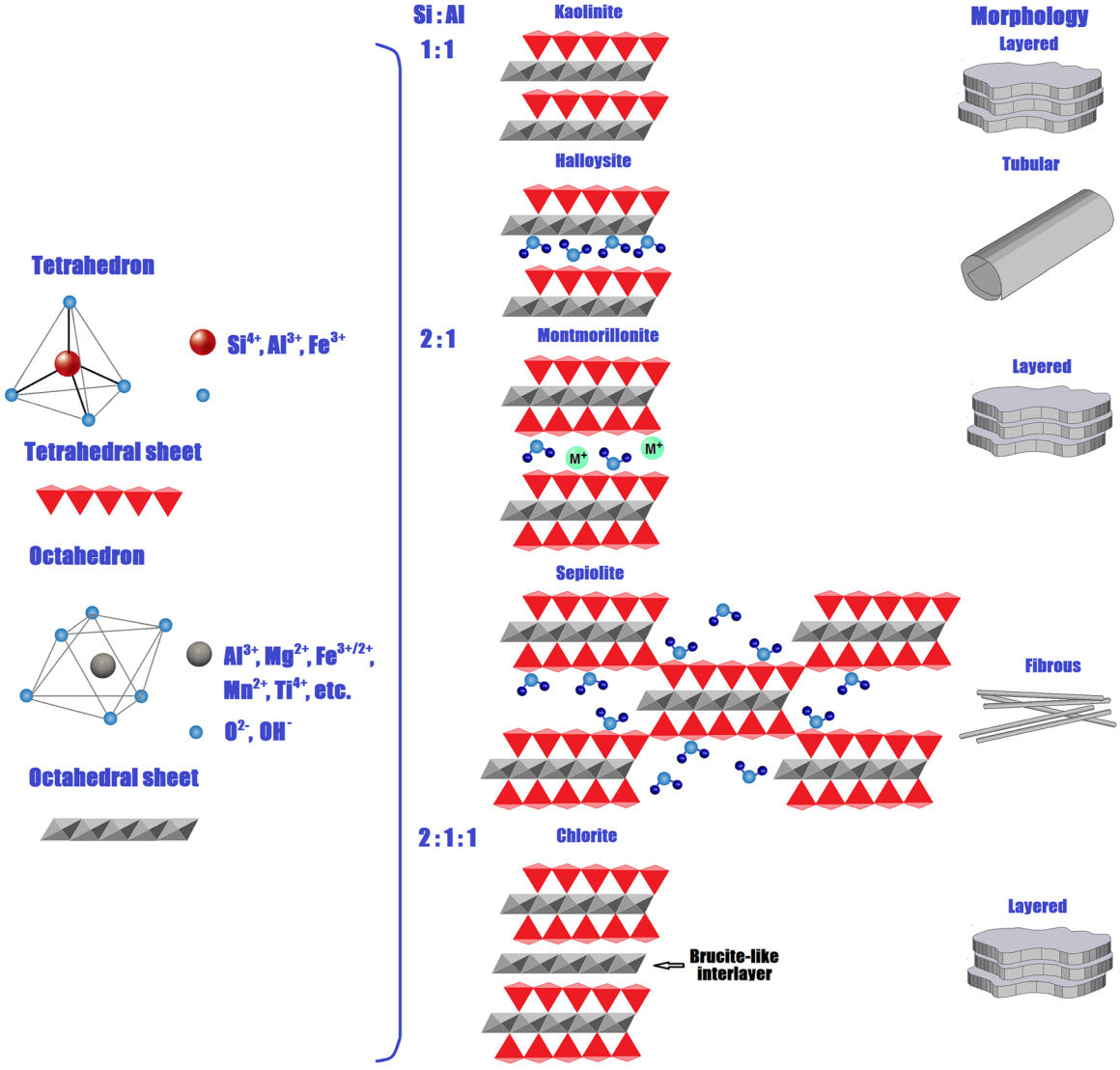

Figure 11: Illustration of diversity of structures and morphology of clay particles.

poliovirus, reovirus) and bacteriophages (MS2 and φx-174). The clay barrier 2–3 mm thick can contain the studied pathogens for 50 years. The authors proposed the use of a bentonite paste for hand sanitization. When applied on the hands, the paste will adsorb all viruses from the skin, and the clay particles with adsorbed viruses can be removed by washing. Such cleansing not only provides complete antiviral protection but also improves the skin condition.[182] The use of bentonite particles in drug-free nasal spray (AM-301) as a barrier against SARS-CoV-2 and its Delta variant was suggested by Fais et al.[183,184] It was hypothesized that bentonite particles that exhibit a high ability to absorb viruses could protect against SARS-CoV-2 and other airborne pathogens. The prepared nasal spray really showed a high antiviral activity. However, it was shown that bentonite particles are not responsible for this effect, which may rather be due to the viscosity of the preparation. Due to the presence of bentonite particles, AM-301 has thixotropic properties permitting its easy application with a nasal spray pump, which results in a protective film once it contacts the nasal epithelium. This safe, non-pharmacological, easy-to-use nasal spray could reduce the risk of infection from SARS-CoV-2 and potentially from other airborne viruses by acting as an "intranasal mask". It should be noted that the efficiency of nasal spray AM-301 (marketed as Bentrio®) against symptoms of allergic rhinitis was tested clinically with participation of 36 allergic rhinitis patients. It was shown that the nasal spray was well tolerated and was considered safe for human use.[184,185] Bai et al.[186] developed nasal spray based on montmorillonite particles for prevention anti treatment of SARS-CoV-2 infection. *In vitro* and *in vivo* experiments showed that the nasal spray has no stimulating

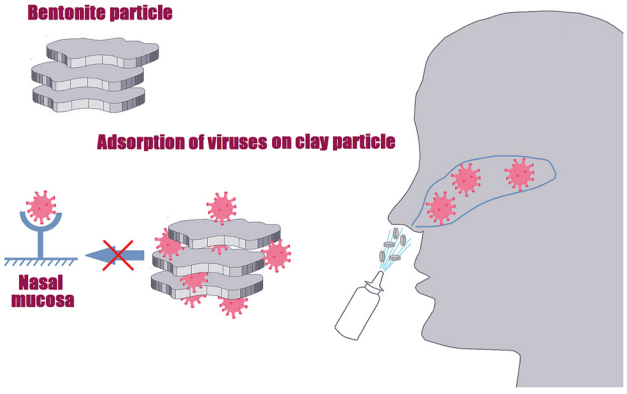

Figure 12: Mechanism of antiviral effect of drug-free nasal spray based on montmorillonite particles.

effect on the respiratory tract and is effective against the viruses. The authors assumed that the antiviral effect is not associated with biological activity of the clay particles, but is due to physical adsorption of the viruses on the clay particles, which mechanically prevents the virus from contacting the nasal mucosa (Figure 12).

Correction note: Correction added 21 May 2025 after online publication 23 January 2025: The sentence “However, it was shown that bentoniteparticles are not responsible for this effect, which may rather be due to the viscosity of the preparation” from paragraph 1, page 17 was deleted.

Nevertheless, some clays have been found to exhibit biological inhibitory effect on various viral infections. Kaolin minerals showed promising inhibitory activity against hepatitis C virus (HCV). The clays causing 28–77 % decrease in HCV RNA, when applied to infected Huh-7 cell lines.[187] To elucidate pathway and mechanism of inhibitory effect of kaolinite particles on HCV, Awad et al.[188] simulated interactions between a protein-fragment extracted from the glycoprotein E1 in the transmembrane domain (TMD) of hepatitis C virus capsid and kaolinite surface by means of molecular modeling based on atomistic force fields and molecular dynamic (MD) simulations. The computational results showed that the studied protein-fragment adsorbed on the kaoline nanoparticles mainly due to hydrogen bonds and electrostatic ones. The adsorption induced conformational changes of the peptide ligands altered dysfunctions of the TMDs causing viral inhibition.

According to the studies published in literature in recent years, clays have a high potential in inhibiting COVID-19. Molecular-level simulations and modeling of interaction of coronavirus spike with human angiotensin-converting hACE2 protein with and without nano-clays (Na-montmorillonite and palygorskite) showed that cohesive energy density (CED) between SARS-CoV-2 and the nano-clays is significantly higher compared to the former and hACE2 due to strong van der Waals attraction fields formed during the virus adsorption on the clays. Thus, the clays can prevent SARS-CoV-2 from interacting with the hACE2 and spread of viral infection.[189] Experimental works *in vitro* and *in vivo* confirmed the ability of clay particles to inhibit SARS-CoV-2 vitus. *In vitro* experiments allowed Poeta et al.[190] to evaluate the rationality of using diosmectite for the treatment of diarrhea in patients with COVID-19. They showed that the clay bound the spike protein RBD and SARS-CoV-2 preparation, and inhibited interaction of the spike protein RBD with ACE2 receptors on the Caco-2 cell surface, as well as NF-kappaB activation and CXCL10 secretion induced by the viral components. Therefore, diosmectite is promising intestinal adsorbent for treatment of COVID-19-associated diarrhea.

Antiviral properties of clay particles may be improved by modification of their surface by various organic and inorganic species. Liang et al.[191] tested the antiviral potentials of Na-montmorillonite nanoplatelets against Japanese encephalitis virus (JEV), dengue virus (DEN) and influenza A virus. The silicate nanoplatelets were modified with cationic and anionic surfactants as well as silver nanoparticles. It was shown that the surfactant-modified particles were less cytotoxic. The authors demonstrated that only the nanoplatelets modified with anionic surfactants could block the infection with the viruses. Electrostatic interaction between the negatively charged nanoplatelets and the positively charged virus particles was the predominant factor in antiviral action. The *in vivo* antiviral activity of the particles modified with anionic surfactant against JEV and DEN was demonstrated using mouse models.

Kaolinite containing silver or copper oxide nanoparticles was found to be effective against vesicular stomatitis virus (VSV), influenza virus, coronaviruses SARS-CoV-2, herpes simplex virus type I (HSV-1). The kaolinite particles were classical polyhedral-shaped platelets with an average size of 9 ?m. Virucidal properties of the clay particles were explained by a direct interaction of the materials with viruses as well as inactivation by the presence of virucidal elements in the material lixiviate.[192]

4.5.2.2 Clay particle as carriers for antiviral drugs

The studies reported in literature indicate that clays can serve as carriers for antiviral drugs. Francis et al.[193] developed delivery system for Acyclovir (ACV) based on Red clay (RC). Although the aim of this work was to develop a delivery system for improving the therapeutic effect of acyclovir in the treatment of skin cancer, the information obtained in this work may be of interest in creating an antiviral drug system based on clay particles, since acyclovir is a well-known antiviral drug. Therefore, this study was included in this overview. Red clay is a natural aluminosilicate material consisting of a mixture of natural minerals and is rich in iron oxide. The prepared ACV-RC-SS (sucrose

stearate, a good emulsifier) particles had a size of 426 ± 31 nm. The authors explained the high encapsulation efficiency and drug loading capacity by interlayers of the RC and electrostatic interactions of ACV in the interlayers due to the ion exchange capacity of the clay. It was found that the encapsulation of ACV resulted in enhanced thermal stability of the drug. *In vitro* studies showed an enhanced permeation and release of ACV. This was explained by enhancement of solubility of ACV, a BCS class III drug, by its encapsulation in RC-SS material.

Hydrogel delivery system for anti-COVID-19 repurposed drug Rifampicin (RIF) based on laponite entrapped in a poly(vinylalcohol) (PVA) matrix was developed by Teodorescu and Morariu.[194] The developed hydrogel exhibited well defined porosity, mechanical stability, adequate swelling. Based on molecular docking simulations, the authors suggested a synergistic inhibitory effect of the drug delivery system on the infection due to Rif activity against SARS-CoV-2 main protease ($3CL^{pro}$) and interaction of the clay particles with SARS-CoV-2 S proteins.

A series of works was devoted to the development of oral formulations of Niclosamide (NIC) based on various clay particles: montmorillonite (MMT),[195] synthetic exfoliated layered double hydroxides (X-LDH),[196] dehydrated hydrotalcite (DHT).[197] The NIC-clay hybrid particles were coated with polymers: Tween 60 to improve solubility and bioavailability under gastrointestinal condition and/or Eudragit S100 (ES100) to make the hybrid responsive at precisely the intestinal pH of 6.8 or hydroxypropyl methyl cellulose (HPMC). XRD peaks of crystalline NIC were observed for the prepared hybrids. In the *in vivo* experiments, it was shown that the pharmacokinetic parameters of the developed formulations were significantly higher compared to free NIC or its commercially available formulation (Yomesan®). Thus, this series of works showed prospects of application of clay particles for development of new oral formulations of poorly soluble NIC with the improved bioavailability. Jermy et al.[198] synthesized nanocomposites of clay halloysite (Hal) with zinc ferrite ($ZnFe_2O_4$) or nickel ferrite ($NiFe_2O_4$) (30 %) and dexamethasone (DEX) coated with polyethylene glycol (PEG) as potential pulmonary drug formulation with magnetic resonance imaging property for treatment of COVID-19. DEX is used in drug regimen for treatment of COVID-19 but has a low bioavailability leading to hypertoxicity of the drug. The aim of the work was to develop a formulation delivering the drug in slow and controlled manner at acidic pH (SARS-CoV-2 fusion, entry into the cell occurs at pH 5.5). *In vitro* study of release kinetics showed that the $ZnFe_2O_4$/Hal/DEX/PEG composite was more effective in releasing drug Dex at pH 5.6. The MTT cell viability assay used the human embryonic kidney cells HEK293 cell lines demonstrated a statistically significant improvement in the cell viability for the composite compared to free Dex, that is the composite prevented the toxic effect of DEX. The authors concluded that the developed composit has a great potential to act as pulmonary drug delivery system for targeted lung infection therapeutics.

Sheet-like clay nanoparticles, namely layered double hydroxide (LDH) particles, were used as a carrier of antiviral agents for prolonged and effective protection against plant viruses. The double-stranded RNA (dsRNA) loading in LDH resulted in an enhanced stability of dsRNA under environmental conditions, including enzymatic degradation and washing, sustained release on the leaf surface over a longer period compared to free dsRNA. Single spray of dsRNA loaded on LDH afforded protection against pepper mild mottle virus (PMMoV) and cucumber mosaic virus (CMV) for at least 20 days (instead of 5–7 days for free dsRNA).[199] Liu et al.[200] used LDH nanosheets for immobilization of recombinant DNA plasmids (pDNAs) and its delivery into plants for inhibition of Tomato yellow leaf curl virus (TYLCV). It was found that the immobilization led to an increased stability of pDNA. The treatment of the infected leaves by pDNA-LDH complex promoted improvement of amiRNA-mediated resistance in plants against TYLCV. Slow release of pDNA extended the period of effectiveness and assured long-lasting protection of plants against viral infection.

4.5.3 Aluminum silicate geopolymers

Geopolymers are inorganic polymers formed by covalently bonded mineral molecules. Typically, geopolymers have a 3D aluminosilicate structure and may be amorphous or crystalline. Geopolymers can be prepared by reaction of a solid aluminosilicate, which can be natural or synthetic, with an alkaline solution or alkali silicate solution. Various kinds of aluminosilicate materials can serve as precursors for preparation of geopolymers including zeolites and clays[201–203] (Figure 13).

Nikolov et al.[204] used natural zeolite tuff from Beli Plast deposit (Bulgari) modified with silver and copper ions as precursor to prepare geopolymer paint with antiviral properties. TiO_2 and ZnO were used as pigments. The prepared geopolymer paints were highly homogenous and showed excellent adhesive properties. The cytotoixicity of the fresh geopolymer paints based on TiO_2 was the lowest compared to the samples modified siliver and copper ions. The weakest cytotoxicity was observed for carbonated samples (artificially aged in CO_2 for 7 days). However, the carbonated samples did not any antiviral effect on MDBK (Madin-Darby Bovine Kidney) cells infected with Herpes

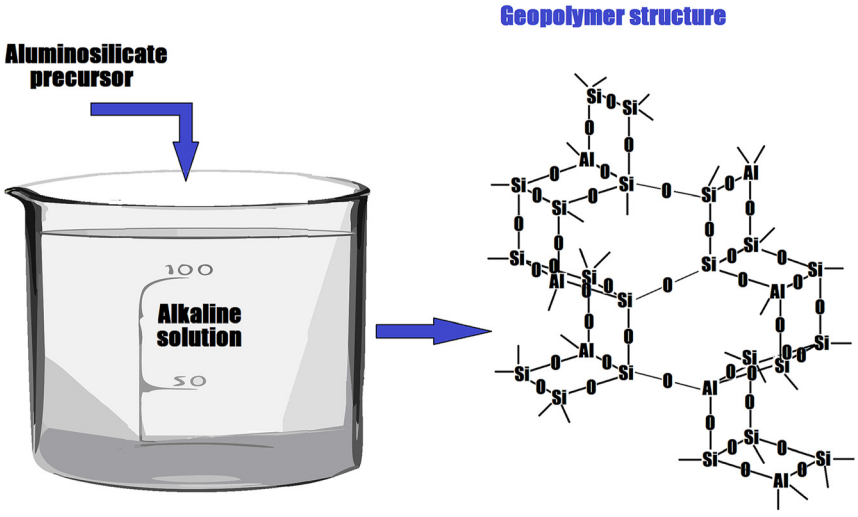

Figure 13: Simple method of preparation of aluminosilicate geopoymer and an example of its 3D structure.

simplex virus type 1, Victoria strain (HSV-1). The time-dependent antiviral effect was found for the fresh samples. The authors believe that the fresh geopolymers have more charged ions which release from the geopolymer paints and interact with the viral supercapsid preventing the attachment and entry of the virus into the host cell.

Synthetic chrysocolla based on nanomodified geopolymers with copper and zinc ferrite ($Cu_{0.5}Zn_{0.5}Fe_2O_4$) as a potential material for antiviral face mask filters was prepared and studied by Silva et al. The aluminosilicate precursor for the geopolymer was clay, metakaolinite, a product of kaolinite calcination. The chrysocolla was obtained by immersing the clay-based cured geopolymer in aqueous copper chloride dehydrate. The obtained materials possessed crystalline structure and magnetic properties. A mild antiviral effect against bacteriophages of the materials was explained by the presence of copper ions, incorporation of copper and ferrites as well as their porous structure.[205]

The clay-based geopolymer with mesoporous structure was studied as a carrier for Niclosamide (NIC) having multiple pathways to inactivate the SARS-CoV-2.[146] Its mesoporous (MCM-41) structure was formed by adding CTAB during dissolving metakaolin in an alkaline solution, followed by removal of the pore-forming agent by calcination. NIC was loaded in the geopolymer by solven evaporation method. The ordered structure of the geopolymer was confirmed by PXRD method. The nanohybride NIC-geopolymer particles were coated with Tween 60 to enhance the drug bioavailability. *In vivo* pharmacokinetic tests showed that NIC-geopolymer hybrid might be good formulation since it improved both T_{max} and $t_{1/2}$ parameters. The encapsulation of NIC in the geopolymer can improve the efficiency from orally administered, poorly-soluble drugs such as NIC.

5 Pre-clinical and clinical studies of silicon-based antiviral particles and drugs

Based on the studies reported in literature, application of silicon-based particles for development of novel drug formulations including antiviral drugs seems not only feasible but also has enormous potential for the creation of a variety of antiviral drugs, i.e. drugs that act on various stages of viral life cycle, drugs causing an appropriate immune response when the virus enters the body, drugs aimed at suppressing a specific viral infection, as well as broad-spectrum antiviral drugs.

It is well known that before a drug is approved for practical use, its development must go through certain stages. Following the synthesis and study of physicochemical properties, the pre-clinical phase of *in vitro, ex vivo* tests involving *in vivo* animal studies demonstrates the efficacy, safety, and toxicity profile and identifies appropriate dose range. Many antiviral silicon-based particles as well as the drug delivery systems based on them have been studied in pre-clinical phase. For example, non-cytotoxicity and antiviral activity of montmorillonite particles modified with surfactants against Japanese encephalitis virus and dengue virus was confirmed by *in vivo* tests using mice as animal model for viral infection.[191] The pharmacokinetics of the composite of antiviral drug niclosamide (NIC), effective against SARS-CoV-2, with anionic clay particles (LDH) was tested *in vivo* and showed prolonged elimination half-life on NIC compared to free drug even with a very low dosage of the drug.[196] In *in vivo* tests, the velpatasvir (VLP)-mesoporous silica composite showed its non-toxicity and significantly enhanced bioavailability.[139] Topical vaginal and rectal

administration of carbosilane dendrimers G1-S4 or G2-S16 prevented herpes simplex virus type 2 transmission in BALB/c mice in values close to 100 %.[105]

Unfortunately, despite many excellent articles and reviews devoted to antiviral silicon-based particles and drug delivery systems and pre-clinical studies, their clinical trials are practically absent. Only one study containing clinical tests of direct antiviral activity of formulations based on silicon-containing particles were found in literature. The comparative investigation of efficacy and tolerability of silica gel and acyclovir cream involving 74 patients with recurrent herpes labialis was carried out, and it was concluded that silica gel was as effective in the treatment of recurrent herpes labialis as acyclovir.[120]

A clinical investigation of a drug based on zeolite particles, which is effective for treatment of diseases associated with viral infections, was also found in literature. Drug "AZEOMED" is mineral complex based on natural clinoptilolite zeolite. Based on the analysis of long-term clinical and laboratory tests, it was shown that the drug was effective for treatment of candidiasis which is common in HIV/AIDS. The mineral complex showed effectiveness for treating all groups of patients with chronic diseases (for example, diabetes, cardiovascular diseases) identified as patients with the highest risk of COVID-19 infection and mortality.[163]

Some formulations based on silica particles that have been clinically tested are not directly related to antiviral drugs. However, information about them can be used in the development of the systems with antiviral properties in which an active substance is poorly soluble in aqueous media at physiological pH. In order to improve the solubility and dissolution rate of poorly soluble fenofibrate, it was encapsulated in mesoporous silica particles. Clinical study involving 12 adults showed that the bioavailability of fenofibrate was improved by 54 %, compared with the commercially available fenofibrate formulation.[206] Dissolution and oral bioavailability of poor water-soluble ibuprofen dispersed in silica-lipid formulation increased by 1.95 times in comparison with a commercial tablet product (Nurofen®) and the pure drug powder. The clinical trials were performed in 16 clinically healthy men aged from 18 to 52 years under fasting conditions.[207]

6 Summary

As follows from this review, silicon-based particles provide ample opportunities for creation formulations with improved pharmacological and consumer properties for treatment and prevention of various viral infections affecting both humans and plants. Due to the diversity of structures, sizes, surface chemistry, porosity, as well as due to the most important biological properties, silicon-based particles can solve almost any problem associated with the properties of a drug, which limit its wide practical application. The studies have shown that biocompatible silicon-based carriers were able to protect antiviral drugs from environmental conditions, to increase bioavailability of antiviral drugs, contributed to their controlled and prolonged release, targeted delivery to the desired sites. All this helps to reduce drug doses and minimize their side effects. In addition, the studies reported in literature, have shown that the particles themselves can exhibit antiviral properties. It should be noted that antiviral action of many silicon-based particles is associated with prevention of virus adhesion to the cell membrane. This mechanism is common to many types of viruses. Therefore, the particles are a promising basis for the creation of broad-spectrum antiviral drugs, which are very important in the context of genetic mutation of viruses. Thus, taking the aforementioned into account, the design of new antiviral drugs using silicon-based particles is an effective approach to control viral infections.

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