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Review article

Cyclodextrins in the antiviral therapy

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ABSTRACT

The main antiviral drug-cyclodextrin interactions, changes in physicochemical and physiological properties of the most commonly used virucides are summarized. The potential complexation of antiviral molecules against the SARS-Cov2 also pointed out the lack of detailed information in designing effective and general medicines against viral infections. The principal problem of the current molecules is the 3D structures of the currently active compounds. Improving the solubility or bioavailability of antiviral molecules is possible, however, there is no universal solution, and the complexation experiments dominantly use the already approved cyclodextrin derivatives. This review discusses the basic properties of the different cyclodextrin derivatives, their potential in antiviral formulations, and the prevention and treatment of viral infections. The biologically active new cyclodextrin derivatives are also discussed.

1. Introduction

Cyclodextrins (CDs) are natural oligosaccharides of cyclic structures, in which the glucopyranoside (Glcp) units are connected with α(1 → 4) glycosidic bond. The 5–9 membered natural CDs have more or less symmetric cavities. In the <5 membered CDs no real holes, while in the >9 membered macrocycles more distorted, many times more cavities exist. The most common CDs have a unique structure where the secondary hydroxyl region of the Glcp units forms a very strong, and the more flexible primary hydroxyls form a slightly less hydrophilic barrier for the significantly less hydrophilic cavity as shown in Figs. 1 and 2.

Although the cavity is only less hydrophilic and less polar than hydroxyl rims, it can form complexes with geometrically suitable very hydrophilic or polar groups, too. CDs can capture neutral molecules, various inorganic and organic salts, acids, or bases by a full or partial inclusion through coordination with CD hydroxyls. Strong bases can form salts with CD hydroxyls. The hollow structure of CDs allows the formation of inclusion complexes, but a real inclusion can frequently exist in crystalline structures only. In solutions, usually, the guest molecule freely moves in- and outward the cavity since the complexation process is a dynamic equilibrium. The composition and (apparent) complex stability constants - derived from the complex equilibrium equation (Eq. (1)) - characterize the inclusion complexes. Due to mathematical limitations, the calculated complex stability constant is always apparent because the calculations neglect the less abundant other complex compositions.

$$x\ CD + y\ Guest \rightleftarrows CD_x\ Guest_y \Rightarrow K_{xy} = \left[CD_x\ Guest_y\right] / \left(\left[CD_{free}\right]^x \left[Guest_{free}\right]^y\right) \quad \text{Eq. 1}$$

where *x* and *y* refer to the stoichiometry and [CD_x $Guest_y$], [CD_{free}]' [$Guest_{free}$] are the concentrations of the species in mol/L (M) unit.

Although the GRAS list [1] of food additives contains numerous CDs, only a few are accepted for pharmaceutical uses, particularly in the parenteral drug compositions.

The apparent complex stability constants of the most common, 1:1 complexes are in the range of 300–800 M^{-1} [2]. It means, to put it simply, that a 'complexed' guest molecule stays for an average of 300–600 times longer close to the CD cavity than when solvated freely in the solvent. Various tricks can shift this dynamic equilibrium to get the drug molecules more complexed than free.

Natural CDs form numerous crystalline complexes with various blood components [252], making them more suitable for topical or oral administration than for parenteral administration. Currently, among the derivatized CDs, (2-hydroxy)propylated βCD (HPβCD) and 4-sulfobutylated (SBβCD or SBECD) are permitted for parenteral drug carriers only. For topical administration, the European Medical Agency (EMA) approved the randomly methylated βCD (RAMEB), too [3].

The number of antiviral drugs is more limited than the antibiotics and is actually just over 100. Most antiviral medicines are administered

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in topical or parenteral formulations. A common problem with these compounds is that they are poorly soluble in water or physiologically buffered saline (PBS) and usually have poor gastrointestinal absorption. The low water solubility is usually associated with moderate to high logP values (logarithm of 10 of octanol-water concentration distribution ratio, which characterizes the molecular lipophilicity). The logP values can be calculated in computers, and the fit of the whole or partially (in the case of large molecules) into the cavity needs geometrical considerations. Although in silico calculations can help the scientist in the a priori selection of an appropriate guest for complexation, the best complexing CD derivatives are the statistically derivatized CDs, which are poorly suitable for computer simulations.

In general, the comparison of various publications (articles, proceedings papers, or patents) is complicated, and many times difficult to figure out the depth of the mentions upon the first look at the publication. It is particularly true for the filed patents in which practically all new potential drug formulations mention CDs, blocking their future use, independently from the usefulness. In the literature analysis, to reduce crowdedness in Figs. 1–4, patents have been removed, and the graphs show only relative numbers due to the many overlaps. The absolute numbers have few meanings in comparison. Our literature survey used the major internet databases, namely ScienceDirect®, SciFinder®, and Web of Science®.

The CDs can serve.

a) as additives, either as solubility and bioavailability enhancers or drug stabilizers [4].
b) as analytical aid in drug analysis [5].
c) as a virucidal agent [6–9].
d) destruction material for virus protein/lipid shell [10–13].
e) as multivalent antigen vector [14–16].
f) vaccine adjuvant [17–22].
g) antibody stabilization [22].

The line between categories is not sharp, and many authors often set up similar groups or possibly create other subcategories in technical papers. Although both CD and viral literature are enormous, their intersection is minimal. The dominant part of articles and patents deals with the antiviral drug/CD complexes, and to a somehow less extent, antiviral drug analysis. The last four categories together, which show the direct effect of CDs in antiviral therapy, account for less than 3% of all CD publications. Fig. 3a shows the literature distribution of CD publications within the direct antiviral use of CDs (patents not included). If we dig a little deeper and remove the reports on the analytical applications, the picture is even worse, not only for the whole CD literature but also within these subgroups, as shown in Fig. 3b. Although some CD-lipid/membrane interaction has been known for a long time, the most known is the cholesterol-CD interaction. The effect of CDs on these viral and cell constituents is still unclear or not entirely understood.

In the articles, pharmaceutical and medical applications play a leading role, and the appearance of CDs in antiviral formulations is less pronounced. It is also true that many accepted antiviral molecules are usually soluble in water, poorly absorbed from oral formulations, or owing to their chemical structures like the nucleoside or nucleotide subunits, less suitable guests for complexation with the most common/accepted CDs. Another weakness is that some of the molecules are prodrugs, and the parenteral administration is the only available route. Although near one hundred accepted chemicals are available for antiviral treatments, only less than half of these compounds have experimented with CDs. The currently most serious pandemic conditions set the focus on the weaknesses of antiviral therapy. Complexes of potential anti-SARS-Cov2 candidates are virtually invisible, as shown in Fig. 4, even when guest molecules from other therapeutic areas supplement this set. At the time of the manuscript preparation, the outcome of the intensive coronavirus research is unknown. This paper aims to demonstrate the role of CDs in the treatment of antiviral infections. With this aspect in mind, the CD applications in various drug analyses are

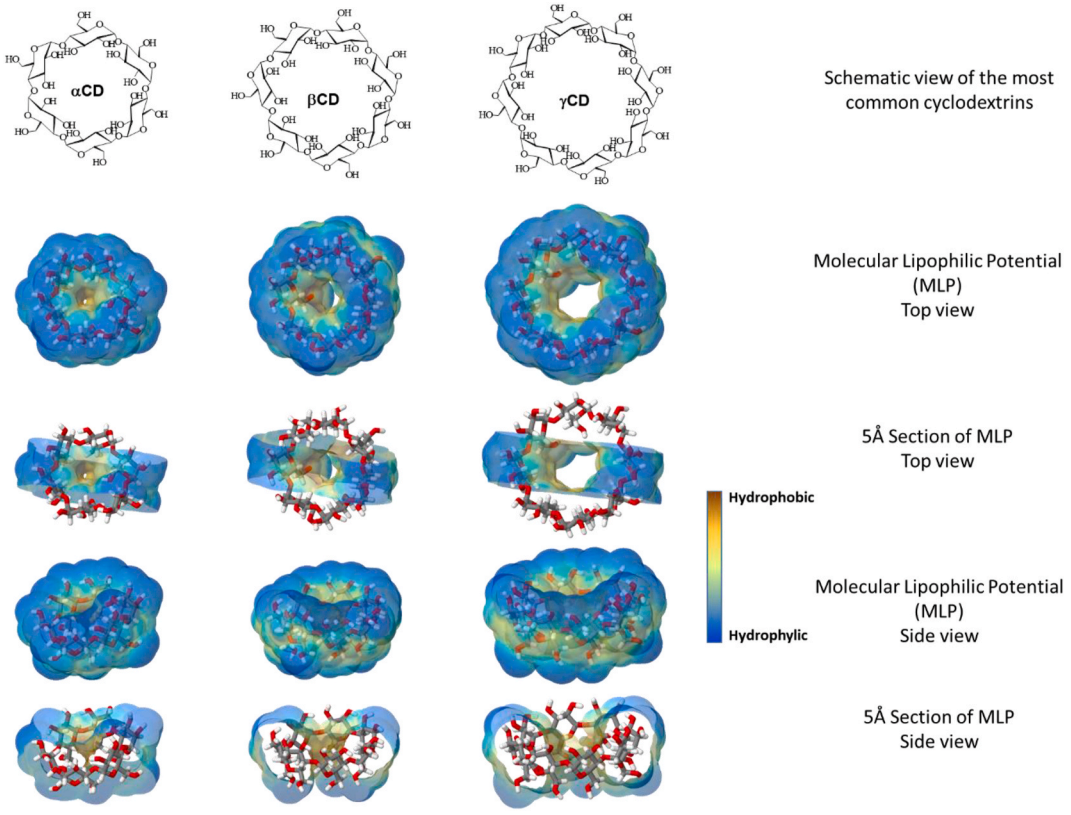


Fig. 1. Structural characteristic of α-, β-, and γ-cyclodextrins. Molecular Lipophilicity Potentials (MLPs) were created with JMol v14.31.2 (Jmol: an open-source Java viewer for chemical structures in 3D. http://www.jmol.org).

mentioned here superficially only.

During the review process of this manuscript, some excellent reviews have appeared on pharmaceuticals [23], particularly on the nano-encapsulation of antiviral drugs [24] and cyclodextrins [25]. The most common antiviral drugs and CDs discussed in detail in the publication of Braga et al. [25], which also includes some patented new approaches, and provides additional information to this review.

2. Cyclodextrins in drug delivery

Although the number of CD derivatives is continuously increasing, the number of pharmacologically accepted molecules, either as active components or excipients, has not changed much in the past decades. The presence of CDs in the GRAS list shows a similar trend. A specially designed curare-type antagonist Sugammadex, (octakis(6-deoxy-6-S-(2-carboxy)ethylsulfanyl)-γ-cyclodextrin, Bridion®), and (2-hydroxy)propyl-β- and -γCD (HPβCD and with restrictions HPγCD), and (4-sulfobutyl-βCD) are approved derivatives for parenteral administration so far. The SB- and HP-CD derivatives are randomly (statistically) substituted derivatives, i. e., not only the degree of substitution (DS, number of substituents/CD ring) is an average value, but the numerous regioisomers are also present in the accepted derivatives. This kind of structural diversity has posed grave challenges to drug authorities and makes it difficult to register a new and more effective CD derivative. The glucopyranoside units have three, somehow different reactive hydroxyl groups. In CDs, the most reactive hydroxyl group is C(2)-OH. Although it is also true that the C(3)-OH groups are practically as reactive as the C (2)-OH groups, owing to the truncated cone average shape of the most common CDs, the C(3)-OHs sterically hindered that reduces their reactivity, particularly in cases of bulkier reagents. In general, the sterically crowded, bulk reagents prefer the primary hydroxyls. However, it is also true that as the molecular complexity or symmetry increases, whether it is a cyclodextrin derivative with a well-defined structure or another good solubility enhancing property, the production costs increase significantly.

While the formation of an inclusion complex may not only affect the distribution of drug molecules, the interaction of HPβCD, unlike the SBβCD, with cellular components may even be detrimental. In some cases, however, this effect may be beneficial. Parenteral administration of this drug additive can successfully cure some rare diseases [26] and atherosclerosis, although the mechanism is still the subject of dispute [27,28].

The methylated cyclodextrins are among the best solubilizing CD derivatives, but their high affinity to cholesterol causes hemolysis, at least *in vitro*. Until now, this critical drawback has prevented the approval of methylated CDs in pharmaceutical compositions. A methylated βCD of fewer methyl substituents (DS is 4–6), CRYSMEB, shows less hemolytic activity and higher biotolerability than RAMEB. Currently, it is near to the approval in dermal formulations only.

The application of Sugammadex in the after-surgery recovery processes is hopeful, but numerous medical publications have been still continuously finding contraindications for its applications [29]. The acetylcholinesterase enzyme regenerative capacity of pyridinium aldoximes can also be improved with the appropriate cyclodextrin derivatives [30]. These regioselective cyclodextrin derivatives have appeared to be promising in reducing the biological effects of certain neurotoxins. Studies on the development and biological efficacy of this type of drug-targeted CD derivatives have so far been less popular, or at least less public. EMA published an excellent summary of currently approved CDs [3] on their physicochemical, physiological, and pharmacokinetic properties. In a recent review, Chakravarty [31] outlined potential targets for the development of antimicrobial therapy. A better aspect of CD derivatives in specific applications is well-discussed in various recent reviews, too [32–35].

2.1. Non-parenteral use of cyclodextrins

Many excellent reviews have been dealing with the CD application in various drug deliveries. Here this general topic is touched superficially only. For oral delivery, by taking care of the GRAS list recommended maximal CD intake, practically all the natural CDs and some derivatives are available. Table 1 shows the currently used CDs in various drug delivery systems.

EMA just recently approved a vaginal formulation of saquinavir and HPβCD for prevention purposes only [36]. The main direction of vaginal drug developments is usually targeted at antibiotics and antifungals, and

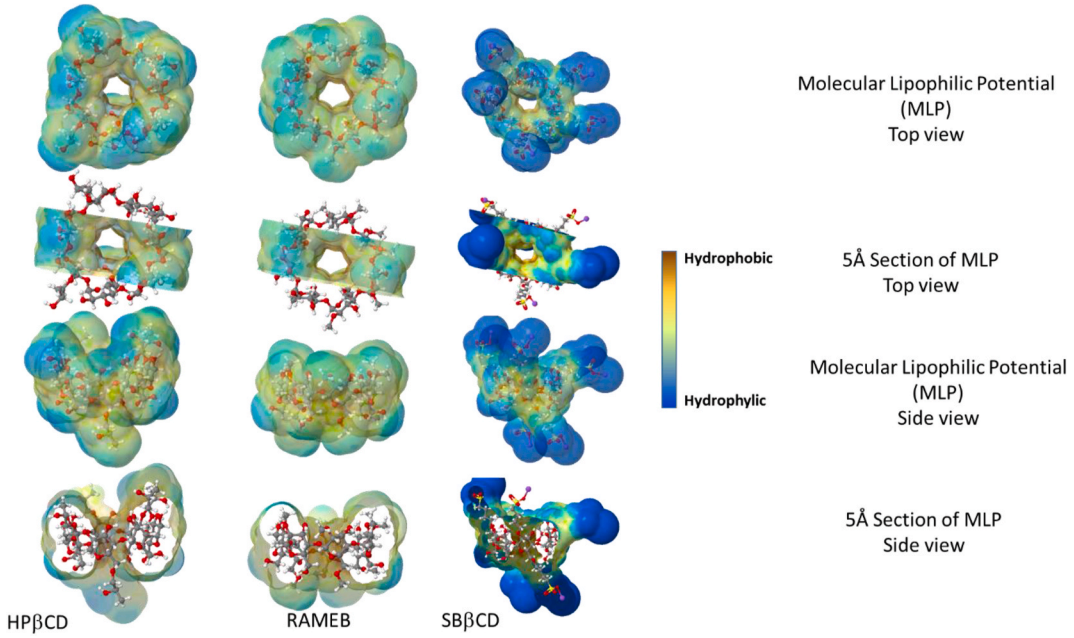


Fig. 2. MLP characteristic of the most common CD derivatives, (2-hydroxy)propylated βCD (DS = 5, HPβCD), randomly methylated βCD (DS = 12, RAMEB), and sulfobutylated βCD (DS = 7 as Na salt, SBβCD). Molecular Lipophilicity Potentials (MLPs) were created with JMol v14.31.2 (Jmol: an open-source Java viewer for chemical structures in 3D. http://www.jmol.org).

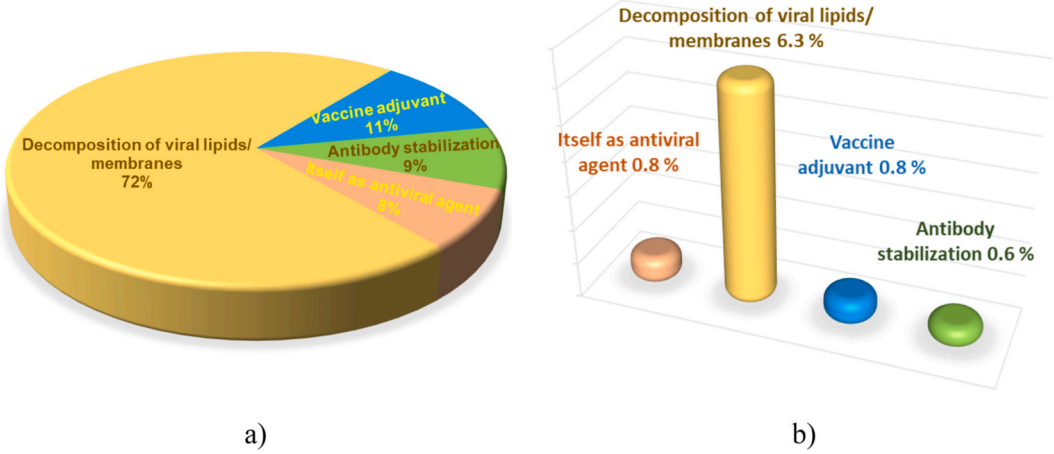


Fig. 3. Relative distribution of the publications: a) direct antiviral effects of the CDs are discussed, b) without analytical applications of CDs and patents.

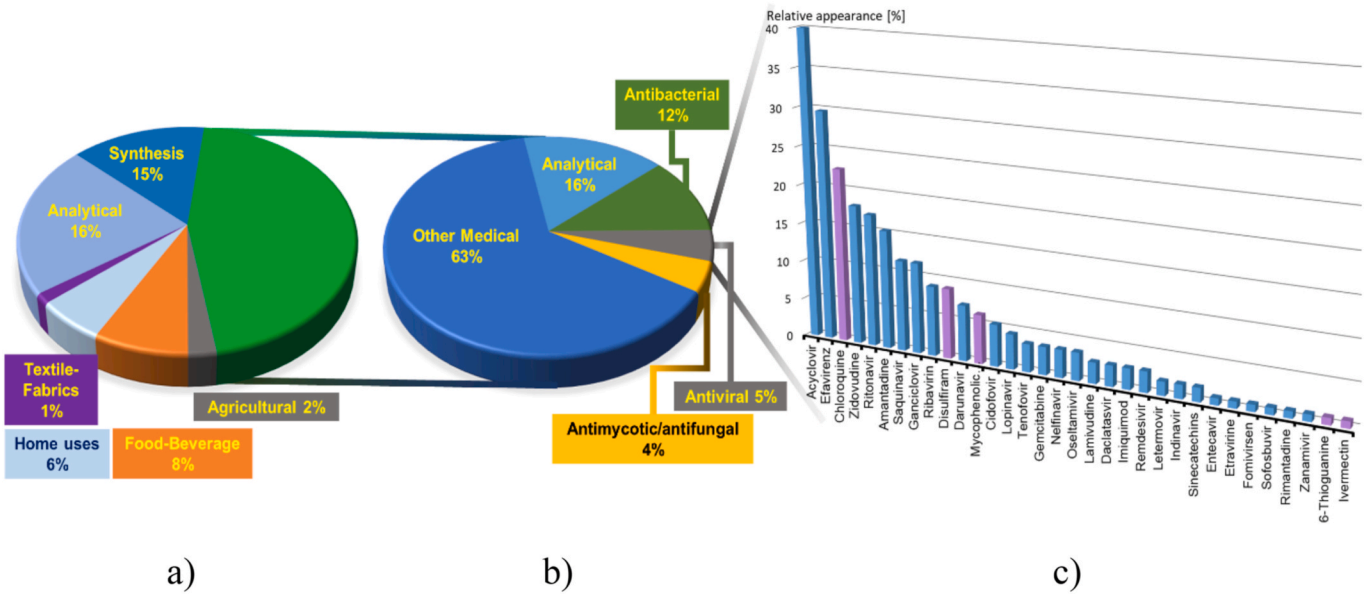


Fig. 4. Relative distribution of CD-related publications (without patents). a) distribution of CD publications within the complete set, b) the CD share in treatments of various infections, c) the relative distribution of the antiviral drug/CD publications. Purple bars represent non-antiviral compounds recommended for testing in Covid-19 treatments. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Use of cyclodextrins as drug delivery aid, based on EMA/CHMP/333892/2013 (Cyclodextrins used as excipients) guideline, as of October 9, 2017 [3].

Oral	βCD, γCD, HPβCD, SBβCD, RAMEB
Parenteral	αCD, HPβCD, SBβCD
Topical	
Dermal	βCD, γCD, HPβCD
Ocular	βCD, HPβCD, RAMEB
Nasal	RAMEB
Rectal	βCD, HPβCD
Vaginal[a]	HPβCD

[a] with restrictions.

antiviral drugs are only sporadically involved in these studies, despite the much higher risk of some viral infections [6].

2.2. Parenteral use of cyclodextrins

Since among the most common non-derivatized CDs, only the αCD is approved, with restrictions, for parenteral use, the number of generally useable CD excipients is small, actually only two: HPβCD and SBβCD.

While, due to dominantly patent reasons, only one type of SBβCD (DS: 6–7, with a tight distribution of differently sulfobutylated βCDs) is suitable as a parenteral additive, the HPβCD has a little higher variability. The most common feature of both derivatized βCDs is that the substituents are predominantly pending on the secondary (C(2/3)) oxygen, thus widening and lengthening the less hydrophilic cavity [37,38]. The hydrophobic butyl chain and the very hydrophilic sulfonate end-group make the sulfobutyl substitution amphiphilic. The (2-hydroxy)propyl group is less amphiphilic because, in the HP moiety, the hydroxyl group locates in the middle of this short pendant group that results in a characteristically less hydrophilic property. Additionally, the number of free hydroxyl groups in the HPβCDs is identical to the parent

CD. Besides the higher variability in the number of substituents, this higher hydrophilicity also makes the HP-CDs better libraries for drug molecules.

However, it is worth mentioning that Sugammadex plays just the opposite role to the traditional meaning of usual drug delivery. While the CDs are working as a drug delivery vehicle from outside into the body, the Sugammadex pulls/washes out the commonly used curare-type aminosteroid non-depolarizing neuromuscular-blocking agents from the targeted cells [39,40].

3. Cyclodextrins in drug analysis

About 15–20% of CD technical papers deal with the analytical application of CDs. The vast majority of these publications concern drug analysis, especially chiral separations. CDs are not only excellent chiral selectors but also have successful positional isomer-selector properties [41–43]. Due to its low reagent requirements, flexibility, and sensitivity, capillary electrophoresis (CE) is increasingly paving the way for analytical applications of CDs in pharmaceutical analyses. The CE method is currently not the most widely accepted pharmacopoeial method yet, but it is exactly the method that perfectly exploits the complexation properties of CDs. Pharmaceutical analysis is on the top priorities of medical developments, and, of course, the number of drug analysis publications is much more than the use of CDs in pharmaceutical formulations.

In 2020, everybody could learn the importance of various tests in the fight against microbial infections. Unlike conventional analytical applications, these methods use CD to remove interfering components from samples instead of separating similar molecules. In a fast test of a common bacterial infection, βCD with activated carbon can increase the polymerase chain reaction (PCR) test sensitivity (≈3 CFU/g) by removing lipids and shorten the test period in food samples [44]. Until now, no publication has appeared on similar studies in the antiviral PCR tests. Another fast post-Covid-19 testing technology, the micro-chromatography of immunoglobulins (Igs), uses blood droplets or intravenous blood samples. This test methodology, because of the not 100% sensitivity and selectivity, many times provides a false negative result. The essay utilizes the different chromatographic mobilities of IgG and IgM, and the used microliter volume of blood sample needs a special in situ sample preparation. A recent publication reports the interaction between IgG and HPβCD, which may provide information for a possible development [44].

4. Cyclodextrins and antiviral pharmacons

Among the near one hundred common antiviral agents [45–47], less than 40 have some connection to cyclodextrin, as seen in Fig. 4c, and only 10 have more than 5% mention together with CDs. In Fig. 5, the most mentioned antiviral drugs and their appearance are seen [48].

4.1. Small organic molecules

Due to the aqueous solubility of the small organic antiviral molecules, the CDs, particularly the polymeric CDs, are suitable for the controlled release of drugs [49–51]. Although numerous articles are published on this topic, the potentially acceptable formulations are difficult to find [52].

4.1.1. Orally administered antiviral drugs

The most common orally administered antiviral drugs are oseltamivir (influenza), acyclovir and famciclovir (herpes simplex and zooster), entecavir, tenofovir, adefovir, lamivudine, and telbivudine (chronic hepatitis B).

CDs have a minimum molecular weight (MW) of 973 Da (αCD) that is 3–4 fold larger than small antiviral molecules, whereas the MW of most common CDs, the βCD (MW = 1135) and its derivatives, is even higher than αCD that further worsen the drug:CD weight ratio. The molecular weight of oral drugs is generally in the range of 225–350 Da, which would result in large tablets, even with a complex of 1: 1 M ratio. Besides the drug:CD ratio, the relatively high doses further limit the use of CDs. Generally, the absorption of the active ingredients is faster from CD complexes, i.e., the complexation can usually increase the solubility and improve the bioavailability, too.

As a new combination, graphene oxide functionalized βCD/curcumin complex successfully inhibited *in vitro* the respiratory syncytial virus [53], but difficult to see the presence and future of such composites in therapy.

4.1.2. Topical antiviral drugs

Skin formulations dominate the topical applications, though the

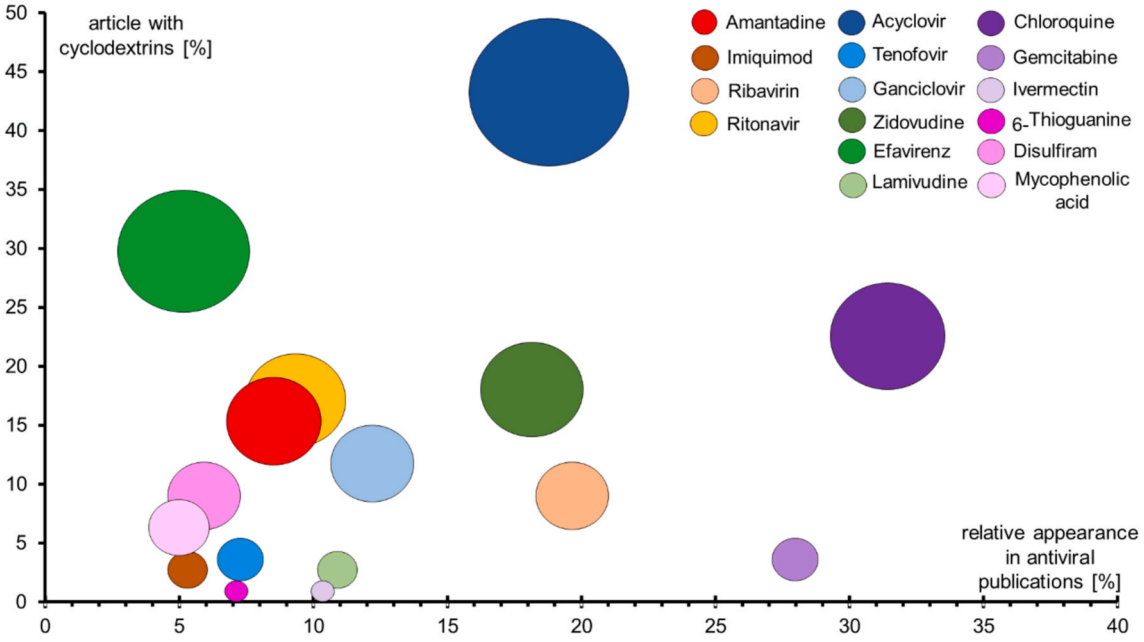


Fig. 5. Relative distribution of articles on antiviral drugs with cyclodextrins (without analytical papers).

number of studies on transmucosal delivery is increasing. A recent publication summarizes [54] the CD uses in skin formulations, so this topic is touched superficially only. Due to the limited transfer of CDs through the skin, these formulations require fewer pharmaceutical considerations, which widen the potential CDs in those applications.

The eye, nasal, or pulmonary formulations represent different targets for drug delivery, and the CD absorption from these formulations is not completely clear. In those formulations, the CDs generally are for enhancing the aqueous solubility of drugs. Because hydrophilic antiviral agents are usually well-soluble in water, the CDs are, obviously, not the first-choice additive. A good example is the ribavirin (against hepatitis C and viral hemorrhagic fevers). The CD complexes of this compound are effective against the measles virus, but they are used in parenteral formulations only, and for pulmonary delivery, a liposomal aerosol in combination with other antiviral agents was chosen instead [55].

CD-based polymers, either the CD-polymers, nanosponges, or CD-combinations with other polymers, can play an increasing role in topical applications, particularly in the mucosal and transdermal administrations [54,56–58]. The controlled release of acyclovir in ocular and subcutaneous administrations from a (hydroxy)propyl methylcellulose/cellulose acetate phthalate sandwiched acyclovir-βCD complex was successful [49], but the composition is still far from an everyday application.

4.2. Complex molecules, proteins, nucleic acids

The gastrointestinal tract, which is targeted by oral administration, rarely transfers macromolecules. The majority of the CD derivatives are poorly penetrating through the biological membranes, too. Although potential CD derivatives show more variability in topical administrations, attempts to formulate these drugs use only the most common CDs. Parenteral macromolecular formulations rarely contain CDs, as currently approved CD derivatives do not provide additional benefits in these formulations. The CDs in the local administrations have another advantage, besides the (potentially) controlled drug release as the complexation properties after the drug release can be further exploited. Destruction of the cell walls, eventually, the virus structures, or selective removal of potentially toxic components can accelerate the healing of wounds or skin infections [59–62].

Carbohydrate groups are usually unsuitable guests for CDs. Consequently, oligo- and polysaccharides can only interact through hydrogen bridges O···H···O. This weak connection rarely has enough power for targeted drug delivery and can significantly limit the CD-virus interactions as it leaves the carbohydrate moieties of viruses intact [16,63,64]. When the lipid envelope is enriched in cholesterol, successful microbicidal effects are found [65].

Because of their molecular dimensions, macrocycles are generally less suitable guest molecules, but the substituents attached to them can interact with CDs. In such cases, CD-macrocycle complexes of various compositions may be formed, as is the case, e.g., among the taxane derivatives [66]. However, a new, more effective formulation is rarely attractive for the profit-oriented pharmaceutical industry because a new composition does not always bring quick benefits and may discard earlier investments into the formulation developments.

The lipid fraction of a cell is usually the perfect guest for CDs, and changes in membrane structure often cause cell death. Although this may be useful in antibacterial agents, it is less prevalent in antiviral therapy because, unfortunately, viruses do not have a cell wall, which reduces the direct virus-killing potential of CDs. Advantageously, when the lipid envelope has a high cholesterol content, an antiviral effect is reported.

Although cyclodextrin-protein interaction can modify the secondary and tertiary structures [67], these effects do not always lead to denaturation. Due to the dynamic equilibrium, the regeneration of tertiary/quaternary protein structures is generally possible, as only a few amino acids have an appropriate moiety for a stable inclusion [68]. Since the high affinity of sulfur-containing molecules to CD [69–71], through the complexation of the cysteine sulfhydryl group(s), the CD can protect the thiol moieties, thus prevents the irreversible oxidative denaturation of proteins. This can even increase the stability/shelf-life of conventional vaccines [72,73]. The most recently approved, one-dose vaccine [74] is formulated with ≈5% HPβCD [75], but further details are not available until now.

Reports on the gene and oligonucleotide drugs are summarized in the book chapter of Mohammed [14]. Nucleosides and nucleotides can generally form loose complexes with native CDs. From a geometric point of view, an intact DNA cannot fit properly into the CD cavity. A DNA fragment can form a rotaxane-like molecular association with CDs which can be exploited in DNA sequencing [76,77] but less suitable for the entire DNA delivery. Amphiphilic CDs both as neutral and cationic versions have been found appropriate for antiviral oligonucleotide delivery [14,78–84], but their complex synthesis and structure have placed them only onto the shelf of promise so far. It seems possible that cyclodextrin-containing macromolecules are suitable for intracellular delivery of shorter oligonucleotides or siRNAs, though the exploitation of these associations is currently in an experimental phase only [80,83,85].

5. Cyclodextrins and virucidal pharmacons

5.1. Virucidal small organic molecules

Among the antiviral agents, some simple molecules have been on the playground for many years. Although some new molecules have been found, the research is dominantly based on the decoration of old structures, as seen in Scheme 1 .

Although numerous publications are dealing with the effects of various CDs in antiviral drug deliveries, only a few of them can go closer to the accepted status. Antiviral/CD compositions in topical deliveries [86] can be a better playground, though this kind of application is restricted only for some - but important - viral infections. The various nanosuspensions can also be good candidates for these non-parenteral purposes [87,88].

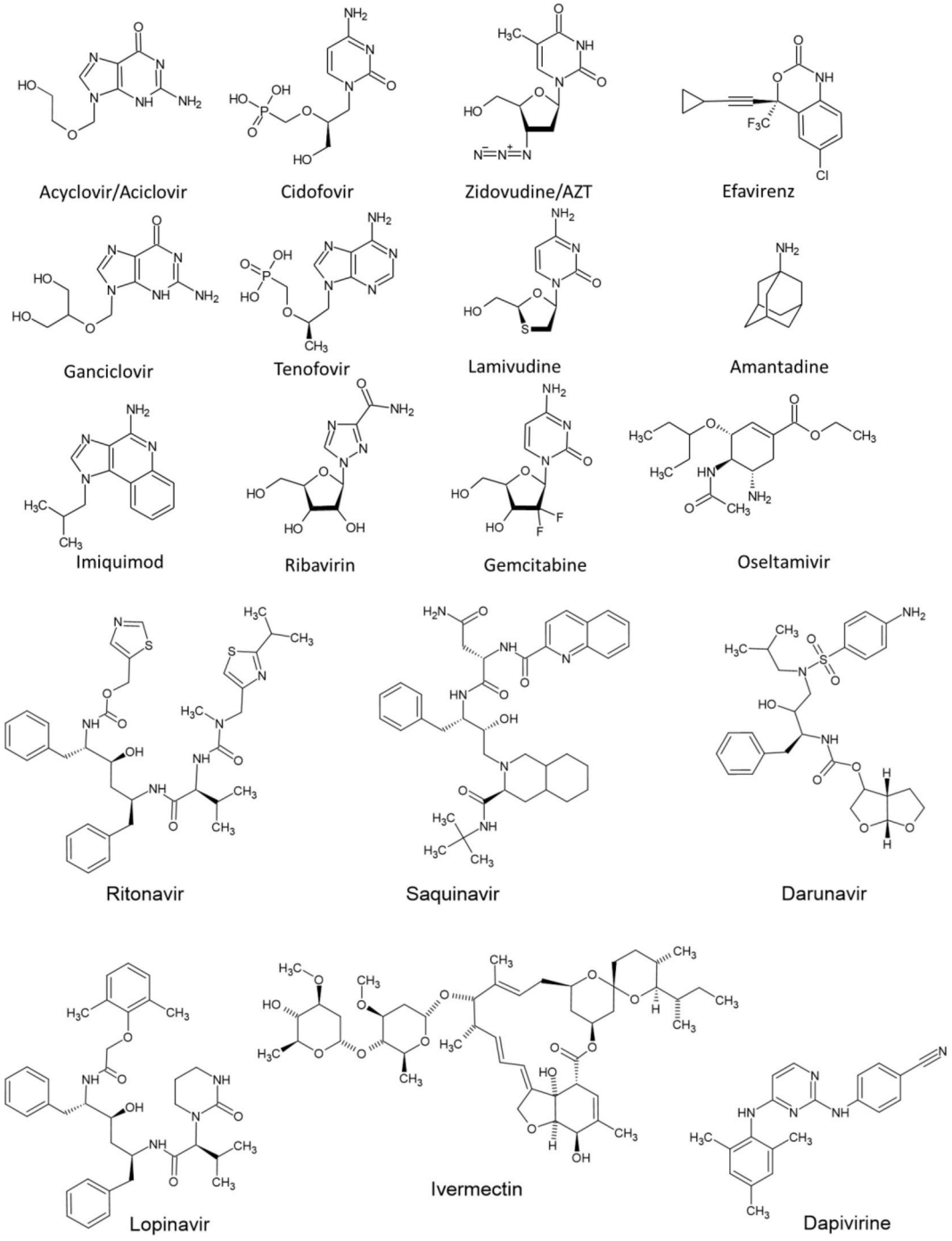
5.1.1. Acyclovir/aciclovir

Acyclovir (aciclovir), is one of the oldest nucleoside analog antiviral drugs. Oral, mucosal, and transdermal absorption are weak, and only 10–20% absorb from oral formulations. Although it can be administered internally, the dominant application is a topical formulation despite the low absorption rate. Aqueous solubility is moderate, and though conversion to the sodium salt may increase it, the bioavailability of the ionized form remains low [89].

The cyclodextrin complexation can considerably increase the solubility (1.3–2.7-fold) and oral bioavailability (≈1.6-fold) [86,90,91], but more expressed in transmucosal processes where the HPβCD complexes are the most effective [86,92–94]. The HP group not only extends the CD cavity but can form hydrogen bonds with a nucleoside. The limited absorption of the CDs potentially allows the use of unsubstituted CDs, too, and the higher nonaqueous solubility and random structure of HPβCD provide the adequate complexing ability for many active ingredients [86].

Amphiphilic CDs containing ester moieties can increase both the bioavailability and antiviral effect as concluded from the membrane penetration studies [51]. Polymeric CD composites work as smart components in drug delivery, though owing to their generally undefined structures, they are more suitable for topical application [52,95,96]. Although transdermal drug delivery is also the primary target of various polymeric CDs [97,98], no information is available in real applications. Dominantly the orally approved CDs and derivatives are still recommended for skin formulations [3].

Although some antiviral molecules, including aciclovir, can be conjugated to ferrocenyl-CD complexes [99], their pharmacological use is



Scheme 1. Most cited antiviral compounds together with cyclodextrins.

expected only in the distant future.

5.1.2. Cidofovir, ganciclovir, imiquimod, ribavirin, tenofovir

These molecules have been developed against various viruses, basically cytomegalovirus, HIV and hepatitis viruses, and cancer. They have numerous side effects and drug interactions. Reliable data about their aqueous solubilities are hard to find in online databanks, which often contain very diverse, many times estimated data only. Characteristic examples are ribavirin [100], which has 14.2%, >10%, 0.33%, and imiquimod [101] with ≈2.5%, ≈0.6% on the homepage of a known chemical database. In technical papers, 7.9% for ribavirin [102] and 0.24% for imiquimod [56] are reported.

Today, cidofovir treatment uses intravenous administration only. A cell-targeted polyethyleneimine-modified βCD-nanotube combination vector is reported to increase cellular internalization and reduce the dose and side effects [103].

Ganciclovir has been approved for medical use more than 30 years ago and administered both oral and intravenous ways. The oral absorption is low, and some topical applications are also known. The aqueous solubility is in the range of ≈0.4–0.9% range. CD complexation can increase not only its solubility but the bioavailability, as well. Interaction with natural CDs has been tested, and β- and γCD showed some significant improvements in the physiological properties by decreasing the LD50 value. The βCD can form a complex with ganciclovir only [104]. Since the symmetrically methylated βCD, DIMEB (heptakis(2,6-di-O-methyl)- βCD) can enhance transepithelial

permeability, increase bioavailability, but this βCD derivative is actually out of play due to the limited availability of isomeric pure DIMEB and price. The fine-chemical version of DIMEB is much more a high DS (≈14) RAMEB due to its low isomeric purity (≈35–50%) and with which commercial RAMEB (DS ≈ 12) has almost the same advantageous properties.

Imiquimod has been introduced into anti-cancer and immunomodulatory therapy for more than 20 years. Aqueous solubility is very low (≈0.02%) and is used primarily in topical medications as a cream. Mannosylated βCD, HPβCD, carboxymethylated βCD, and βCD-based nanosponges can improve both aqueous solubility and bioavailability [56,105].

Ribavirin is a guanosine analog wide-spectrum antiviral molecule with noticeable aqueous solubility. Although it has some teratogenic effects, it has been used as a medicine for almost 40 years in oral and inhalation formulations. Complexation with native α-, β- and γCDs increased the antiviral activity [106–110]. It is suspected that αCD and HPβCD increase the transfer through the brain-blood barrier and improve the antiviral efficacy in virus encephalitis by suppressing the virus replication [110,111].

Tenofovir is an oral antiretroviral drug from the beginning of the XXI century, and many times it is combined with other antiviral compounds. It has a high aqueous solubility (≈1.5%), particularly its phosphate ester or salt forms. The combination with HPβCD considerably increases its antiviral effect and accumulation in various tissues [112], despite that in a hydrogel formulation HPβCD, HPγCD, and SBβCD showed no solubility enhancement [113].

5.1.3. Azidothymidine (AZT, zidovudine), lamivudine, gemcitabine

AZT is among the first approved anti-HIV drugs, both as treatment and prevention. More recently, its combination with lamivudine or acabavir-lamividune can leave the HIV exclusivity. While the combination of zidovudine with other virucidals is relatively new, lamivudine occurs in several formulations, but the stand-alone application is less common. These antiviral compounds are highly soluble in water, and although typically oral formulations use lamivudine, AZT is also administered in infusions.

A study on the glycosidic bond scission in nucleosides suggests a beneficial effect of CDs (native CDs, HP-, and methylated βCDs) on the chemical stabilities [114]. An increase of the low aqueous solubility of AZT by various CDs reported (from <0.01 mg/ml up to ≈0.05 mg/ml), although much higher solubilities of pure AZT can be found in various databases (10–50 mg/ml) [115]. In parenteral formulations, the HPβCD enhanced permeation across the blood-brain barrier and successfully substituted the co-solubilizer DMSO in various formulations, particularly in the high-dose treatments [116]. The less stable polymeric version of the CD-based polymers, the nanosponges, showed noticeable complexation abilities toward AZT and demonstrated extended chemical stability. Anionic CDs (sulfated CDs) showed synergistic effects with AZT [117]. The SBβCD combination with zidovudine-lamivudine showed a sustained release behavior, reducing the daily drug administration frequency [118].

Recently, many researchers study metal-organic networks (MOFs) [119] in drug delivery systems that can be suitable in antiviral drug formulations. The complexation can extend their applicability in various pharmaceutical compositions, whether in monomeric or polymeric forms of CDs this field is, for the time being, still of more scientific interest. A new excipient can further prolong the life-cycle of AZT-like virucidals.

Gemcitabine is a fluoro-cytidine analog with primarily antitumor activity and is administered intravenously [120]. Although its hydrochloride salt is well soluble in water (≈4%), its chemical stability in aqueous solutions is far from optimal [121]. Various CD derivatives, namely SBβCD [122], and positively charged CD derivatives (guanidino and aminoalkyl CDs) [123,124] can successfully increase its activity, but among these derivatives, only the SBβCD has perspectives as an accepted parenteral drug additive. The antitumor effect can be even more effective in combination with the HPγCD/curcumin complex. In the last years discovered its broad-spectrum virucidal properties against human enteroviruses [125,126]. While the antitumor therapy usually needs parenteral administration, an intranasal formulation has shown a broad spectrum of antiviral activity [125–128].

The aqueous solubility of gemcitabine is good (≈4%), and CD complexation can influence its releasing and absorption properties. Several positively charged CD derivatives have been synthesized [123], but actually, HPγCD [129] is the only suitable candidate for gemcitabine.

5.1.4. Efavirenz

Efavirenz is an oral antiretroviral drug that is often administered in combination with other antiviral molecules, like emtricitabine and tenofovir. Although it has numerous side effects and restrictions as not recommended in pregnancy, it is on the WHO list of essential medicines and is accepted worldwide as an antiviral pharmacon [130].

Efavirenz has low aqueous solubility (<1 mg/100 ml) and is usually administered orally once a day. Despite the high dose, the plasma concentration slowly reaches a maximum only, making it a suitable candidate to improve both properties in a host-guest complex [131]. Due to its structural properties, this molecule appears to be less appropriate for strong interaction with most CDs. The use of βCD nanosuspension [132], γCD [133], HPβCD [133,134] and -γCD [133], or RAMEB [135] could improve its physicochemical (≈10-80-fold solubility enhancements) and pharmacokinetic properties (≈3-fold dissolution rate). Those compositions required a third component to achieve the desired effects. Among the tested CDs, HPβCD with arginine significantly increased the aqueous solubility (≈60-80-fold) and bioavailability [134]. Although the three-component system was found better than the binary complexes, the calculated apparent stability constant of the complex, nearly 1000 M^{-1}, appears to be exaggerating, which is a general deficiency of apparent complex stability constants calculated from solubility isotherms.

5.1.5. Oseltamivir

Oseltamivir was developed to treat common influenza viruses (A and B) in patients with high-risk complications that showed moderate resistance to H1N1 (swine flu), H3N2, and H5N1 (bird flu) viruses. It is moderately soluble in water (≈0.2%) and has a good bioavailability (>80%), is therefore usually administered orally. Oseltamivir metabolizes fast, and the urine eliminates it and its metabolites almost quantitatively.

Complexation with βCD primarily targets to mask the bitter taste of its phosphate [136]. The formulation has not been approved by any authority so far.

5.1.6. Darunavir, lopinavir, ritonavir, saquinavir, dapivirine

High molecular weights of this group of antiviral molecules can result in a high drug/CD weight in formulations. Darunavir is one of the latest antiretroviral oral drugs. It is commonly used with ritonavir because, despite its moderate aqueous solubility (≈0.7%), the relatively high absorption rate increases bioavailability and can reduce its amount to a single dose. The two aromatic groups, especially the *p*-aminobenzenesulfonic group, are suitable for complexation with natural hosts. A combination of a βCD complex and hydroxyethylcellulose was developed almost immediately after its appearance for topical treatments [113]. The HPβCD complex increases darunavir aqueous solubility (≈14-fold), while the effect of HPγCD and SBβCD was similar, but somehow smaller (HPγCD ≈6-8-fold SBβCD ≈11-12-fold), though no solubility enhancements for tenofovir were observed. The HPβCD complex also increased the bioavailability of darunavir [113,137].

AIDS medications have been using lopinavir for more than 20 years. Although 1,2-propylene glycol dramatically increases its aqueous solubility (<0.001% => ≈0.1%), applied alone poorly absorbs from the oral

formulations, while the combination with ritonavir can improve both the solubility and bioavailability.

Despite the many suitable aromatic moieties, only HPβCD and RAMEB resulted in moderate solubility enhancement (≈10-fold) of lopinavir [138]. An *in-silico* designed HPγCD of high DS could further improve its physicochemical and physiological properties [139].

Ritonavir has been used in antiretroviral therapy since 1996, administered orally, more recently in combination with other antiviral drugs as mentioned above. Although its aqueous solubility on its own is low (<0.04%), the combination of other antiviral components generally increases the solubility of all molecules. Despite that this compound contains numerous suitable substituents for the complexation, only βCD [140] and HPβCD [141] could moderately improve the aqueous solubility.

Saquinavir, as its mesylate, has moderate aqueous solubility (≈0.2%) but low oral bioavailability. The combination in oral formulation with other antiviral molecules in AIDS medication, as lopinavir and/or ritonavir, is more common than the administration on its own. HPβCD, together with hydroxyethyl cellulose in hydrogels [113] or polyethylene glycol matrix [142], can increase its bioavailability in vaginal formulations. Increased aqueous solubility of saquinavir in RAMEB (=> ≈1%) [143] and HPβCD(=> ≈1–1.5%) [144] complexes that improved the absorption properties through the gastrointestinal tract, as well.

Dapivirine is an almost insoluble in water (<0.002%) anti-HIV drug molecule which is dominantly intended to use for transmucosal formulation application, and oral or parenteral administration against hepatitis E and influenza viruses is pending [144]. As a vaginal preventive formulation has been approved in the mid of 2020 [36]. Complexation increases the aqueous solubility, until now HPβCD (≈3-4-fold), HPγCD (≈2-3-fold), and SBβCD (≈20-fold [145] or ≈60-fold [113]) have been used in a combination with hydroxyethyl and hydroxypropylmethyl celluloses, although in the accepted formulation none of the applicable CDs are used.

5.1.7. Amantadine

Amantadine has been used selectively as an oral prophylactic agent against the influenza A virus since the early 1960s. However, since the early 1980s, when the first publication appeared about drug resistance, the incidence of resistance has been steadily increasing. Although its importance as an antiviral agent is gradually diminishing, it is early to bury it because it inhibits the virus's genetic material release. In combination with other virucidals, it can control the spreading of similar viruses.

As a salt, it is highly soluble in water and forms a stable complex with βCD, which has apparent complex stability constant in the range of 10^4 M^{-1} [146]. Later various CD derivatives, namely SBβCD [147], carboxymethylated βCD [93], and heptacarboxyl-βCD [148] were also tested., but the last one is not a cyclic glucuronic acid variant of βCD, but a 1H-1,2,3-triazole-4-carboxylic acid substituted βCD. The excellent guest properties of adamantyl derivatives have led to the study of various biopolymers in controlled release experiments. A common feature of these attempts is the loose connection to the antiviral properties of amantadine.

5.1.8. Antiviral drugs with minimal cyclodextrin literature impact

Dolutegravir sodium (DTG) loaded nanoparticles HPβCD-based nanosponges successfully enhanced the CNS uptake by intranasal administration [149].

The aqueous solubility of rilpivirine could be increased around 4-fold using βCD and HPβCD [150], while βCD nanosponges somehow increased the oral bioavailability, too [151,152].

5.2. Small antiviral organic molecules with potential anti-SARS-Cov2 property

Compounds (Scheme 2) in this section have just recently been placed in the repurposing category because anti-coronavirus effects have been found and assumed to be effective against SARS-Cov2, as well [45].

5.2.1. Disulfiram

Disulfiram inhibits the acetaldehyde dehydrogenase enzyme, and this property allows its use in the treatment of chronic alcoholism. Recently some antiviral effects against SARS and MERS viruses have been reported [153]. Its aqueous solubility is low (<0.02%)

The rich sulfur content is suitable for CD complexation, and the use of HPβCD increased in topical administration not only its aqueous solubility (up to near 1%) but bioavailability (≈3-fold), too [71].

5.2.2. 6-Thioguanine

Thioguanine is developed as an antimetabolite administered in oral formulations against various leukemias and has many side effects [154]. Its aqueous solubility near-neutral pH is low (<0.1%), but alkaline solutions can ionize it, and the solubility increases dramatically.

The antiviral properties of 6-thioguanine against rotaviruses have recently been discovered [155]. Its protease inhibitory properties may allow inhibition of SARS-Cov2 replication [156].

A non-analytical application of the 6-thioguanine/CD complex uses gold nanoparticles for drug delivery [70].

5.2.3. Mycophenolic acid

Mycophenolic acid was discovered more than a hundred years ago [157], and its long journey from antibiotic to a virucidal molecule is an instructive story as summarized in an excellent review. Its principal physiologic effect is immunosuppression. Its protonated form is poorly soluble in water (<0.04%) around the neutral pH, but 1 M NaOH increases it dramatically.

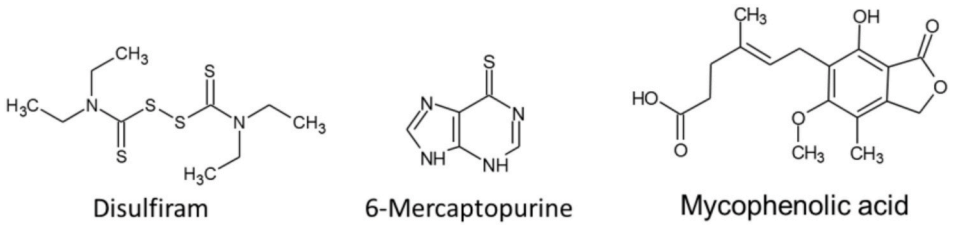
Succinyl(2-amidoethyl)[1] βCD-based [158,159] liposomal polymeric gels can form a complex of native mycophenolic acid.

N-Morpholinoethyl ester of mycophenolic acid was successfully complexed by βCD [160] in topical [161] and controlled release formulations [162].

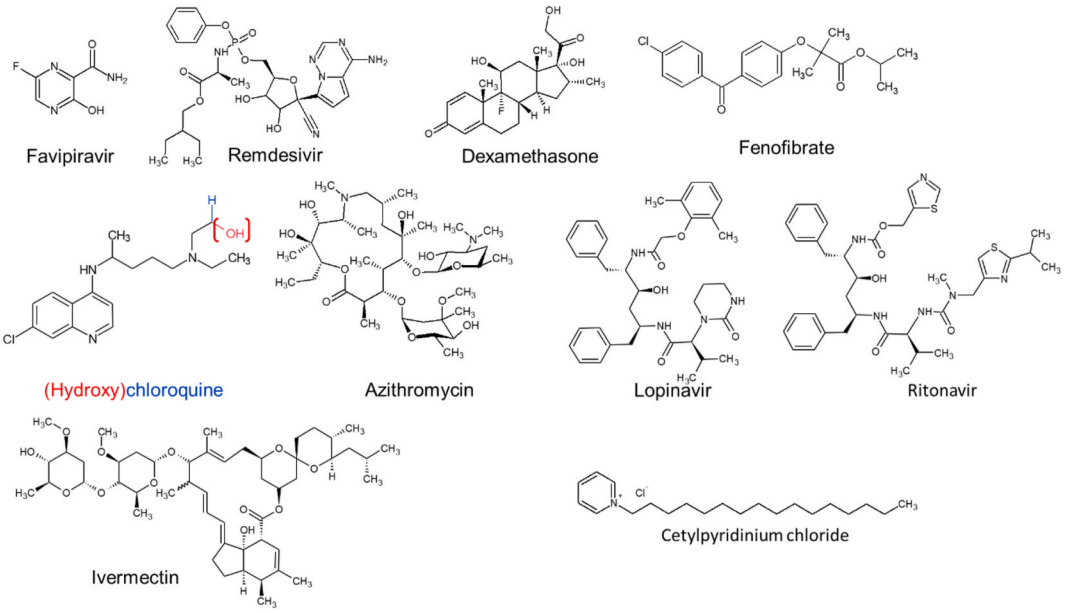
6. Cyclodextrins and potential anti-SARS-Cov2 molecules

Although there are huge expectations worldwide for the development and rapid production of a safe, general Covid-19 vaccine for everybody, researchers are still looking for a well-known traditional drug to reduce the symptoms of SARS-Cov2. Dozens of clinical trials have been launched to test a variety of known molecules that can directly or indirectly inhibit the spread of the virus or, in more severe cases, increase survival. More than a year after the outbreak, we still do not know enough about the virus, its behavior, and how to effectively treat the disease. The scientists started to find the most effective compounds, obviously, among the already known drugs based on the mechanism of action and infection analogies. Many medicines and therapies have already been named miracle cures, which were then, even the following week, pushed into the background due to ineffectiveness or even adverse effects. It is equally valid for HCQ, an otherwise effectively used drug in the cure of malaria and autoimmune diseases, the antiviral favipiravir, or fenofibrate (Scheme 3), which reduces blood cholesterol [163]. Last spring, one major cyclodextrin manufacturer announced its recommendation of βCD derivatives [164] as host molecules for some supposedly effective anti-Covid-19 pharmacon [165], as solubilizers of remdesivir (SBβCD) [166] and lopinavir-ritonavir combination (HPβCD), and as a taste masker for oseltamivir (βCD) [136]. The first enthusiasm against Covid-19 already envisioned the protecting

[1] The authors' best knowledge suggests that despite the incorrect starting βCD structure shown – because the commercially available succinyl βCD has different structure – in the publication of Park et al. ([159]), the synthesized compound structure might be correct.



Scheme 2. Small antiviral molecules are supposed to have anti-SARS-Cov2 properties.



Scheme 3. Recommended virucidal drugs for testing against Covid-19.

properties of βCD-chlorhexidine containing mouthwashes [167]. As in many other cases, a few months later, it was the authors who refuted the anti-SARS-Cov2 effect of many types of mouthwashes [168].

6.1. Cetylpryridinium chloride

Cetylpyridinium chloride is an amphiphilic compound that has been widely used for decades in personal care products such as mouthwashes, throat sprays, breathable sprays, and the like. This compound has antiseptic properties, effectively kills bacteria and fungi [169], disrupts the lipid layer of membranes [170], reduces the expression of viral genes [171], and is popular in antimicrobial products due to its relatively low toxicity. Recently, a beneficial effect has been observed in the prevention of SARS-Cov2 infection [172–174] that has generated more detailed studies on the antimicrobial mechanism.

Although the aqueous solubility is high (≈5%), both the aromatic moiety and the hydrophobic long alkyl-chain can form complexes with CDs. The CD complexes are suitable for controlled release [175].

6.2. Favipiravir

Generic favipiravir is an RNA polymerase inhibitor used mainly in Asian countries to treat more severe flu cases. One publication discussed in detail the mechanism of its effect, finding lethal mutagenesis of SARS-Cov2, though the published results did not yet provide convincing evidence for efficacy, primarily due to inadequately followed study protocols. However, favipiravir was more effective against Covid-19 than the combination of lopinavir and ritonavir [176,177].

Favipiravir is poorly soluble in PBS (≈0.01%), and its effective dose is relatively high (600–1600 mg/day). A serious drawback, in the best case, the 1:1 complexation of βCD would require a minimum of ≈4.3–13.5 g/day βCD orally. Although large tablets could resolve these amounts only, the βCD intake would be well above the EMA recommendation of ≈0.5–1 g/day. The more tolerated other CDs oral intake can be higher, 1–10 g per day, but their molecular weights are even higher than the βCD. So far, no favipiravir/CD complexes are reported in the literature, although the molecular structure suggests only low stability constant or little improvement in aqueous solubility.

6.3. Remdesivir

Remdesivir targets the inhibition of an enzyme that is necessary for the genetic material copy of a virus, and it was among the first targets of drug reconsiderations against the symptoms of Covid-19. Remdesivir is still the subject of studies to assess its effectiveness [178–182]. Although it is allowed to use in Japan, and both FDA and EMA have also permitted its therapeutic use within the USA and EU in less severe infections, some conditions of use and biological effects are still unclear.

Low aqueous solubility at neutral or slightly acidic pHs is its serious drawback of parenterally administered remdesivir. To increase the solubility, SBβCD is used, which, while having much worse complexing properties than HPβCD, makes its anionic property suitable for the solubility enhancement of an ionizable molecule at a tolerable pH. SBβCD has fewer side effects than HPβCD, though the drug/CD weight ratio is worse. The current formulation contains, in the dissolvable powder contains near 3% remdesivir, and about half of this in the liquid infusion formulation [183]. Increasing the drug/CD ratio is more than a wish. In some formulations, using organic co-solvents and/or ultrasound-assisted

dissolution can result in better solubilization of remdesivir by SBβCD [184]. The sulfobutyl group is a relatively strong acid, almost entirely neutralized by sodium ions in the commercial product. The solubility enhancement of this CD derivative is more related to some non-ionized sulfobutyl groups than to the formation of inclusion complexes. These protonated sulfonic acid groups provide a strongly acidic microenvironment for remdesivir. The substituents mainly locate on the secondary hydroxyl edge of βCD, which not only widens the cavity but may promote the ionization of remdesivir due to the high density of negatively charged groups. A recent publication that appeared during the revision process made attempts to demonstrate some lipophilic interaction between remdesivir both the cyclodextrin and the sulfobutyl side chain, furthermore, NMR and molecular modeling make the interaction of ionizable groups also possible [185]. The NMR studies suggest a more realistic ensemble of the guest than as figured on a drug development forum in the mid of 2020 [186].

Although the salt formation can be more expressed than inclusion formation, finally, it is entirely irrelevant for the current formulation. A significantly increased drug content and enhanced efficacy in patients in the early stages of Covid-19 may accelerate recovery from the disease, decrease the side effects of high SBβCD dose, reduce the hospital burden and patient suffering.

6.4. Dexamethasone

Dexamethasone is a corticosteroid immunomodulator introduced to medical treatments in the early 1960s. Many ways, including oral formulations, are available to treat the patients. This drug is on the NIH recommendation list [187] after it was found effective in reducing mortality rates in critical stages in Covid-19. Although its wide application in antiviral therapy is still under study, the available data suggest its beneficial effect on infected patients [188,189]. Currently, a single daily dose of medication appears to be sufficient, as it successfully increases patient survival in either injectable or tablet form, and this long-lived molecule is one of the inexpensive treatments.

Although the aqueous solubility is low (<0.01%), its bioavailability is over 80%. From the beginning of its life-cycle, numerous reviews deal with its interactions with various CDs and CD derivatives [190–192].

The CDs can increase the aqueous solubility of dexamethasone and the residence time in the body. Many times topical applications can provide faster absorption and better bioavailability, too [193–197].

6.5. (Hydroxy)chloroquine

Hydroxychloroquine and chloroquine are oral anti-malarial drugs worldwide that have also been used since the middle of the last century and to treat rheumatoid arthritis and porphyria, as well. Its use in Covid-19 treatments [198,199] resulted in the most controversial compound due to the extensive political tailwind [200]. In some cases, it has had a beneficial effect on patients infected with SARS-Cov2 [201], but in addition to serious side effects, more questions have raised than answered [202,203].

Although chloroquine (CQ) and hydroxychloroquine (HCQ) are hydrophilic drugs (CQ: <0.01%, diphosphate> 5%, HCQ <0.03%,> 22%), their solubility and bioavailability can be further improved by βCD complexation [204]. Besides, the reduction in some side effects has also been reported. HCQ also forms a complex with both α- and βCD [205, 206], which can be exploited in pharmaceutical compositions within its accepted scope.

CQ and HCQ also have adverse systemic effects that can be life-threatening, especially at high doses. Unfortunately, an attempt to combine antiviral azithromycin with HCQ neither had any positive effects [207].

Although βCD may improve the solubility of both CQs, this is still of little importance for the treatment of Covid-19 in comparison with the reported side -effects [208].

6.6. Ivermectin

Although ivermectin is principally intended for use in animals, there are also some human formulations [209,210]. Although the replication of SARS-Cov2 was successfully inhibited *in vitro* [211], after a short period of study, NIH does not recommend it against SARS-Cov2. The high dose and many side effects have put it into a non-recommended status [212].

This macrocyclic compound, despite the conjugated 2,6-dideoxy-4-O-(2,6-dideoxy-3-O-methyl-alpha-L-arabino-hexopyranosyl)-3-O-methyl-alpha-L-arabino-hexopyranoside moiety, practically insoluble in water (<0.04%). Contrary to low aqueous solubility and bioavailability, it is used in oral formulations [213].

The ivermectin/βCD complex has a large apparent stability constant (1700 M^{-1}), though the aqueous solubility of the complex is still low: in the preparation of the complex nanoprecipitation forms. Although an agricultural formulation mentions the ivermectin/RAMEB complex [214], detailed information is not available.

After the submission of the first version of this manuscript, the FDA and EMA withdrew ivermectin from the 'recommended for testing' list [215,216].

6.7. Fenofibrate

Fenofibrate is used to lower blood lipids, but since this type of statins has shown a less significant reduction in the risk of heart disease or death, its popularity has dropped. Its prolonged use causes some hepatotoxic effects, too. The mechanism of action of SARS-Cov2 suggests that Covid-19 leads to lipid deposits in the lung. This effect increases the severity of the infection. Although this drug is safe, further comprehensive studies are needed to prove its effectiveness against the new coronavirus, as there is currently no direct evidence that Covid-19 is beneficial for patients [232].

The aqueous solubility (<0.01%) and oral bioavailability of fenofibrate are very low, but some nanoparticle formulations can improve these properties [254].

As an old drug, numerous attempts have tried to increase the aqueous solubility by complexation. HPβCD could increase the fenofibrate concentration in water (up to ~1%) and improve its absorption [255]. The solubilizing power of βCD could not outperform the results of HPβCD [256]. Attempts with βCD in the presence of hydroxypropyl methylcellulose improved the redissolution properties of fenofibrate [254,257].

6.8. Lopinavir and ritonavir

Antiretroviral drugs, as lopinavir and ritonavir, are commonly used together to treat HIV-infected people, and the recently found some anti-SARS-Cov2 effects [177] has put lopinavir/ritonavir combination to the NIH recommended-to-try list. Later, NIH withdrew this recommendation because the clinical trials have not demonstrated the benefits of protease inhibitors in Covid-19 [217]. The discussion of these virucidals is in a previous section.

6.9. SNG001 (Interferon-β)

Interferon-β is used to treat chronic obstructive pulmonary disease, and this product can reduce the amount of MERS-COV virus. Although inhalation of interferon-β, SNG001 has also shown positive results in ongoing Phase II SARS-Cov2 studies, detailed information is not yet available, and independent researchers have not confirmed it so far [218].

Methylated cyclodextrins can positively influence the interferon-β secretion by the RAMEB-cholesterol interaction in cell membranes [219], but this connection to SARS-Cov2 viral infection is still unclear.

During the preparation of the manuscript, a new molecule was

approved for preclinical studies for Covid-19 treatment after ptilidepsin showed greater efficacy than remdesivir [220]. Two other new drug candidates (bepridil and thapsigargin) also showed beneficial properties against SARS-Cov2, although the results have not been confirmed yet. These structures are shown in Scheme 4. The previously mentioned compounds are more or less synthetic organic substances, while glycyrrhizin is a natural molecule widely used in various food products. This compound has been studied with varying degrees of success against different viruses [221–223].

6.10. Glycyrrhizin

A principal component of licorice (liquorice, liquirizia) is glycyrrhizin. Last year periodically appeared several communications on glycyrrhizin-containing products in the prophylaxis of SARS-Cov2 spreading [224] or even patient treatment [223,225]. Up to now, the scientific community has not yet clearly confirmed the preventive properties of these products. FDA has put some warning messages [226, 227] about fake natural products, scientific papers report its efficacy against Covid-19. Glycyrrhizin is a saponin, a glycosylated plant steroid analog. After hydrolysis by gastrointestinal bacteria, aglycone is completely absorbed and then metabolized in the bloodstream. CD complexation can improve the chemical stability of the aglycone, The chemical stability of aglycone can be improved by CD complexation, which in some cases can reduce the adverse effects of other drugs [229, 230]. Glycyrrhetinic acid conjugation to CD showed visible antiviral activity against influenza A (H1N1) in some cases [231].

6.11. Plitidepsin (Dehydrodidemnin B, Aplidin)

Plitidepsin is a cyclic oligopeptide, possesses antitumor, antiviral, and immunosuppressive activities, isolated from a marine species (Aplidium albicans, an ascidian). In Australia, it has limited clinical approval in a dexamethasone combination against relapsed and refractory multiple myeloma. In the drug repurposing screening, the preclinical efficacy against SARS-CoV-2 is found by inhibiting the translation mechanism in the virus [232]. Plitidepsin has been shown to induce apoptosis and was accepted as an orphan drug in 2003. Some results suggest its mechanism of action is related to the cholesterol content of the SARS-Cov2 lipid shell [233]. Although it contains a suitable methoxybenzyl group for CD complexation, no CD complexes have been described so far.

6.12. Bepridil and thapsigargin

Bepridil is an old calcium channel blocker to treat angina and atrial fibrillation but is supposed to cause ventricular arrhythmia. A combination with amiodarone successfully inhibited the Anthrax lethal toxin entry into host cells [234], founded its presence in an antiviral drug repurposing study, and showed a 100% survival rate of ebola infected mice was published [235]. The two phenyl moieties can form CD complexes, although this property is exploited in analytical applications only.

Thapsigargin is a sesquiterpene lactone inhibition effect against coronavirus, respiratory syncytial virus, and influenza A virus [236]. This inhibition could be extremely useful in the prophylaxis of viral infection. The principal mechanism of inhibition is blocking the Ca^{2+} ATPase pump. Although its structure is weakly suitable for the complex formation with CDs, together with RAMEB, it may increase the efficacy as reported in an *in vitro* study [237].

A recent publication set the focus of the IgG-HPβCD interaction which can be utilized in the Ig-based therapy of various cancers and autoimmune diseases [44] and although the utilization potential of this interaction in oral or intranasal vaccinations has not been studied [238].

7. Pharmaceutically active cyclodextrins

Nowadays, more and more facts show that CDs are not as inert molecules as believed for many decades [239]. Of course, the pharmacological activities are about their complex formation abilities.

Completely reverse action is when a specifically derivatized CD is the guest molecule for pore-forming proteins. Although some symmetrically substituted aminocyclodextrins have adjuvant effects, particularly in anthrax treatments [240] or C. perfringens infection [241], their physiological properties are still not entirely studied.

Although there are attempts to use CD derivatives as antiviral agents, a real therapeutic utilization is far below the horizon. It is much more due to their complicated and expensive synthesis [242], industrial production difficulties, and eventually their inadequate *in vivo* properties. Among the authorized CD derivatives, the anti-HIV properties of HPβCD had been a promising candidate in contagion prevention but the initial enthusiasm soon was followed by a long silence [65,243].

Some CD derivatives have antiviral properties on their own, but confirmation of these findings is still in the research phase [244]. In a recent report, per-6-thioalkylsulfonic acid βCDs against HIV, HIV, ebola, and zika viruses were effective. These amphiphilic CD derivatives have excellent antiviral activity at the tens of μg/ml level [6].

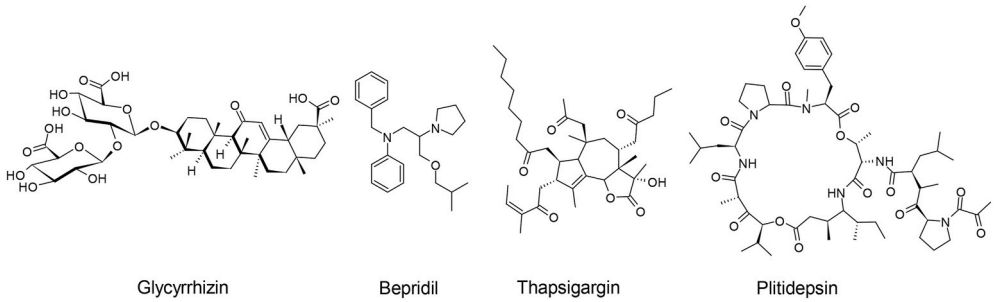
Anti-HIV agents showed synergistic interaction with many sulfated oligo- and polysaccharides or sulfated CDs. However, cross-resistance of sulfated βCD with JM3100-resistant virus also suggests that CDs may not only have beneficial effects in antiviral therapies [245].

8. Toxicologic considerations

The literature on CD toxicology is continuously increasing. Many reviews summarize this aspect of CD applications, and here only some most important points are mentioned [190,246–249].

The CDs practically do not absorb through the gastrointestinal tract, which allows a better variety of applicable CDs in oral and topical formulations to enhance aqueous solubilities and bioavailabilities. The topical formulations are in an even better situation because insoluble CD-based polymers can further widen the potentially applicable CDs.

In general, in parenteral formulations, the statistically substituted CDs are most suitable, as the random arrangement of substituents rarely



Scheme 4. Some new candidates in Covid-19 treatment.

leads to poorly soluble complexes. Random substitution has another advantage as it has non-uniform substitution: due to the mixture of CDs substituted in different ways, this type of derivatives can serve as a library for a wide variety of guest molecules. Some organ damage phenomena are associated with the low solubility of crystalline CD complexes. The high affinity to cholesterol is at least as crucial as that seen for many neutral βCD derivatives. The complexation of cholesterol, this principal component of cell membranes, can destroy the cell membrane and lead to cell death. This principally characterizes methylated CDs, but many neutral, less hydrophilic CD derivatives have affinities to cholesterol, too. In the case of HPβCD, it is DS-dependent, and attaching an ionizable substituent to RAMEB, this property can be reduced, as in the case of succinylated RAMEB. The beneficial effect of endosomal cholesterol removal in Nieman-Pick disease type C treatment [250] also brings a new complication as the HPβCD accumulates cholesterol in the lungs [251].

9. Conclusion

This review has attempted to summarize the current knowledge on the interaction between different virucides and CDs. The Covid-19 pandemic has caused a boom in publications on viruses and resulted in a constant and rapid change in the information available, with often contradictory results week after week, even in peer-reviewed journals.

Bioavailability improvements of drugs are the principal purpose of CD complexations, and these property improvements often reduce side effects, too. Less than half of the just over 100 approved antiviral molecules have been tested with cyclodextrins. Not all virucides are appropriate to interact with native CDs, but the substitution of the CD hydroxyls can expand the CD cavity, converting them into suitable hosts. The statistically derived CDs, HP- and SBβCD, are the most commonly used host molecules, as they are also parenteral drug carriers. While oral and topical formulations can use both native and methylated CDs, CD polymers and nanosponges are mainly suitable for topical applications.

Due to the Covid-19 pandemic, many old drugs have been repurposed, and most of them have no CD history. The new antiviral molecules usually have a high MW, which provides a favorable host-to-guest mass ratio, while their complex structures often contain a suitable moiety to interact with CDs.

The interaction of CDs with peptides, proteins, and nucleotides makes CDs suitable adjuvants for vaccines or drug vectors, opening new research directions in antiviral therapy.

Declaration of competing interest

The authors declare that they have no known conflict of interest.

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Abbreviations

AIDS	Acquired immunodeficiency syndrome
AZT	Azidothymidine, zidovudine
CD	Cyclodextrin
αCD, βCD, and γCD	α-, β-, and γ-cyclodextrin, respectively
CE	Capillary electrophoresis
CNS	Central nervous system
Covid-19	Coronavirus disease 2019
CRYSMEB	Crystalline methylated β-cyclodextrin (DS ≈ 4–6)
CQ	Chloroquine
DIMEB	Heptakis(2,6-di-O-methyl)-β-cyclodextrin
DMSO	Dimethyl sulfoxide
DS	Degree of Substitution, number of substituents in a cyclodextrin ring
EMA	European Medical Agency
FDA	Food and Drug Administration (USA)
GRAS	Generally accepted as safe
Glc*p*:	Glucopyranose
HCQ	Hydroxychloroquine
HIV	Human immunodeficiency viruses
HPCD	Randomly substituted (2-hydroxy)propyl cyclodextrin
LD	Lethal dose
M	Mol
MERS	Middle East respiratory syndrome
MLP	Molecular Lipophilicity Potential
MW	Molecular weight
NIH	National Institute of Health (USA)
NaOH	Sodium hydroxide
PBS	Physiologically buffered saline
PCR	Polymerase chain reaction
RAMEB	Randomly methylated β-cyclodextrin, DS ≈ 12
SBβCD/SBECD	4-Sulfobutylated β-cyclodextrin sodium salt (DS ≈ 6–7)
SARS	Severe acute respiratory syndrome
SARS-Cov2	Severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization

Authors' contribution

All authors equally contributed in the preparation of the manuscript.

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