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REVIEW

Antiviral Drug Delivery System for Enhanced Bioactivity, Better Metabolism and Pharmacokinetic Characteristics

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Abstract: Antiviral drugs (AvDs) are the primary resource in the global battle against viruses, including the recent fight against corona virus disease 2019 (COVID-19). Most AvDs require multiple medications, and their use frequently leads to drug resistance, since they have poor oral bioavailability and low efficacy due to their low solubility/low permeability. Characterizing the in vivo metabolism and pharmacokinetic characteristics of AvDs may help to solve the problems associated with AvDs and enhance their efficacy. In this review of AvDs, we systematically investigated their structure-based metabolic reactions and related enzymes, their cellular pharmacology, and the effects of metabolism on AvD pharmacodynamics and pharmacokinetics. We further assessed how delivery systems achieve better metabolism and pharmacology of AvDs. This review suggests that suitable nanosystems may help to achieve better pharmacological activity and pharmacokinetic behavior of AvDs by altering drug metabolism through the utilization of advanced nanotechnology and appropriate administration routes. Notably, such AvDs as ribavirin, remdesivir, favipiravir, chloroquine, lopinavir and ritonavir have been confirmed to bind to the severe acute respiratory syndrome-like coronavirus (SARS-CoV-2) receptor and thus may represent anti-COVID-19 treatments. Elucidating the metabolic and pharmacokinetic characteristics of AvDs may help pharmacologists to identify new formulations with high bioavailability and efficacy and help physicians to better treat virus-related diseases, including COVID-19.

Keywords: antiviral drug, delivery systems, metabolism, pharmacokinetics, pharmacodynamics

Introduction

Many infectious diseases have rapid propagation and high infection rates with potential for human pandemics. Emerging infectious diseases caused by such viruses as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and Ebola virus, present major threats to public health.[1] The current outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to spread.[2] COVID-19 may cause severe cytokine storm and aggravate immunopathological damage, which make antiviral treatment more complicated. The related cytokines include but not limited to TNF-α, IL-1 and IL-6.[3–5] With the explosive growth of confirmed cases, the World Health Organization (WHO) declared the outbreak to be a public health emergency of international concern on January 30, 2020.[6] At present, COVID-19 has spread to more than 200 countries and regions around the world, and the outbreak of COVID-19 has

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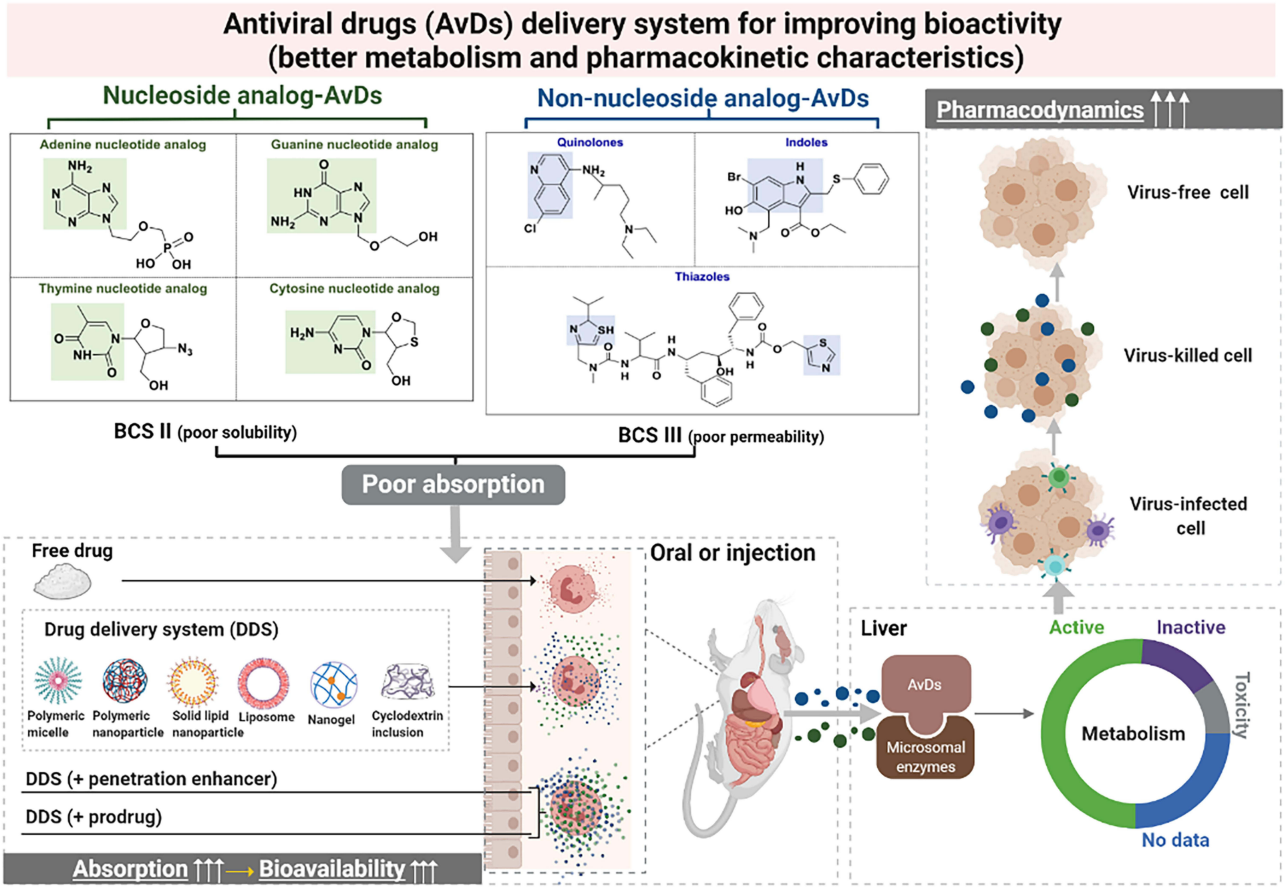
Graphical Abstract



caused serious damage worldwide. As of 14:00 on July 19, 2021, there were a total of 191,229,635 diagnosed cases of COVID-19 diagnosed, and 4,105,799 deaths globally. Compared with SARS and MERS, the spread rate of COVID-19 is more rapid, probably due to the increased globalization and virus adaptability to various environments.[7]

At present, drugs employed to fight viral infections include natural medicines[8–11] (eg, liquorice, *Scutellaria baicalensis* and forsythia), chemical drugs[12] (eg, ribavirin, remdesivir, favipiravir) and biotechnology-derived drugs[3] (eg, IFN-α, IFN-β and peptide). Natural antiviral medicines have multiple targets and moderate effects, and they usually contain complex ingredients but exhibit only limited efficacy.[13] Biotechnology-derived AvDs have high curative effects and induce low drug resistance, but they usually need to be administered by injection due to their poor stability and bioavailability, and they are very easily inactivated in vivo.[14] Chemical AvDs inhibit viruses quickly and strongly, and as most are administered orally, their use and storage are convenient. Chemical AvDs are the main treatment employed in antiviral therapy.[15] The physicochemical properties of these drugs, as well as their metabolism, affect their efficacy to varying degrees.[16–18] To improve the antiviral efficacy of AvDs, we need to comprehensively understand the characteristics of AvDs. In this review, we systematically investigated the structural, physicochemical, metabolic, kinetic and bioactive characteristics and pharmacological effects of popular nucleoside analogs (NA-AvDs) and non-nucleoside analogs of AvDs (NN-AvDs) currently on the market (Figure 1).

The scientific community is urged to explore and develop novel potent antiviral agents. Considering that vaccine development is time-consuming and that viruses mutate quickly, antivirals remain the main treatment for viral infections. To date, there are α-interferon, lopinavir/ritonavir, ribavirin, chloroquine phosphate, and arbidol have been proven to possess effectiveness in the general treatment of COVID-19, and tocilizumab (biological

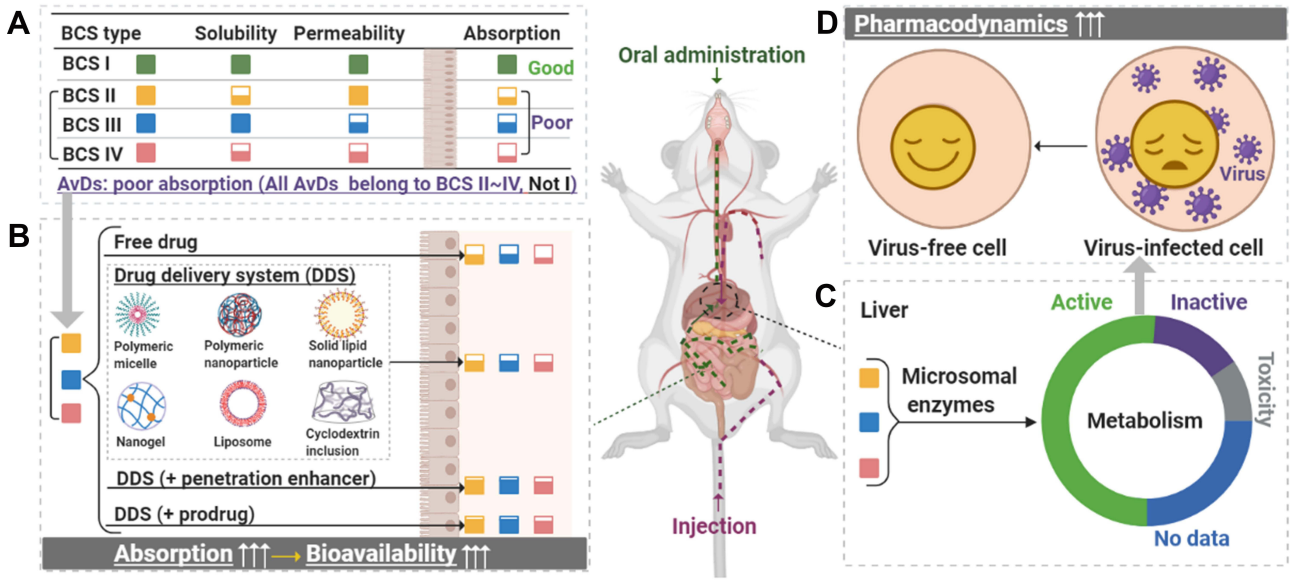


Figure 1 The schematic diagram for antiviral drug delivery systems to improve bioactivity, increase metabolism and pharmacokinetic characteristics. (**A**) AvDs have poor absorption due to low solubility/low permeability. (**B**) drug delivery systems are used to enhance absorption and bioavailability of AvDs. (**C**) AvDs are metabolized by hepatic microsomal enzymes. (**D**) The pharmacodynamics activities of AvDs are enhanced. The upward arrows (↑↑↑): refers to an increase in the absorption/bioavailability of the drug.

drugs) is used in severe/critical immunotherapy in accordance with the guidelines of the Chinese Diagnosis and Treatment Protocol on the government website (Trial Version 7) (https://china.huanqiu.com/article/9CaKrnKpIEe. Available on October 19, 2020). Most AvDs currently on the market are oral tablets. Poor pharmacokinetic profiles and high resistance are already known to the main disadvantages of these AvDs. Therefore, loading antiviral drugs into advanced delivery systems, such as lipid-based, macromolecule-based, and nanoparticle-based systems, may conducive to overcoming the abovementioned disadvantages. In this review, 16 typical AvDs currently on the market are investigated by retrieving their data from available databases (Table 1).

Solubility, Permeability and Structural Properties of AvDs

Solubility and Permeability Limits of AvDs

The dose number (D_0) and oil-water partition coefficient (log P) were employed to estimate the biopharmaceutics classification system (BCS) for AvDs. The D_0 value > 1 is the defining criterion of low solubility and log $P \leq 1.632$ is the defining criterion of low permeability.[23] According to the solubility and permeability, the AvDs are classified into 3 groups (Figure 2). Among these drugs, 50% belong to BCS II with low solubility, 44% belong to BCS III with low permeability, 6% belong to BCS IV with low solubility and low permeability. These parameters illustrate the low absorption of AvDs in vivo.

Structural Characteristics of AvDs

According to molecular structure, AvDs are divided into 2 types (Figure 3). (1) NA-AvD, which are modified nucleosides with a structure that mimics the structure of natural nucleosides. NA-AvDs are recognized by cellular or viral enzymes and lead to disruption/termination of replication or other biological processes due to incorrect structural modifications.[24] NA-AvDs are further classified into 3 subtypes: (i) purine NA-AvDs (eg, adefovir, entecavir and acyclovir), (ii) pyrimidine NA-AvDs (eg, zidovudine and lamivudine), and (iii) other NA-AvDs (eg, ribavirin, remdesivir and favipiravir). (2) NN-AvDs, include 4 subtypes: (i) quinolines, such as chloroquine phosphate, (ii) amides, such as lopinavir, oseltamivir (neuraminidase inhibitor: cyclohexene derivative) and palamivir (neuraminidase inhibitor: cyclopentane derivative), (iii) indoles, such as abidol, (iv) thiazoles (ritonavir), and (v) others (baloxavir marboxil and letermovir).

Relationship Between Structure and Solubility/Permeability of AvDs

Seventy-five percent of the abovementioned NA-AvDs (such as ribavirin, adefovir, entecavir, acyclovir, zidovudine, lamivudine) and approximately 12% of the NN-AvDs (such as

Table 1 Solubility and Permeability of AvDs

Structure	AvD	Antiviral Spectrum	Solubility	Permeability	BCS	Structure	AvD	Antiviral Spectrum	Solubility	Permeability	BCS
			D_0	*LogP*					D_0	*LogP*	
Nucleoside Analogs						**Non-Nucleoside Analogs**					
	Ribavirin	Broad-spectrum	0.12	−1.85[19]	III	Quinolines	Chloroquine	Broad-spectrum	37.66	4.69	II
	Remdesivir	Broad-spectrum	1.18	2.10	II	Amides	Lopinavir	Anti-CoV	0.21E+06	3.69	II
	Favipiravir	Broad-spectrum	8.21	0.83	IV		Oseltamivir	Anti-influenza	0.44	0.36[20]	III
	Zidovudine	Anti-HIV	0.15	0.05	III	Indoles	Arbidol	Broad-spectrum	0.42E+03	4.64	II
	Lamivudine	Anti-HBV, HIV	0.15	−1.40	III	Thiazoles	Ritonavir	Anti-CoV	0.16E+03	3.10[21]	II
	Adefovir	Anti-HBV	9.44E-04	−2.06	III	Cyclopen tane	Peramivir	Anti-influenza	2.36	3.12	II
	Entecavir	Anti-HBV	3.03E-04	−0.96[22]	III	–	Baloxavir Marboxil	Anti-influenza	1.60	2.24	II
	Aciclovir	Anti-HSV	8.00E-04	−1.56	III	–	Letermovir	Anti-CMV	1.92	3.47	II

Abbreviation: AvD, antiviral drug.

oseltamivir) had low permeability, probably due to the hydroxyl groups in their molecular structures, which increase their polarity. Also, 25% of NA-AvDs (such as remdesivir, favipiravir) and 88% of NN-AvDs (such as chloroquine, lopinavir, arbidol, ritonavir, peramivir, baloxavir marboxil and letermovir) had low solubility due to their hydrophobic macromolecular structures.

Pharmaceutical Technology to Improve Solubility and Permeability

Oral drugs require sufficient solubility and intestinal absorption to enable drug molecules to reach action sites and exert therapeutic effects.[25] Solubility is a prerequisite to confirm drug absorption and clinical response for drugs given orally.[23] Permeability represents the speed and extent of oral drug diffusion through the mucus layer and then through the submucosa and epithelial cell barriers into the blood or lymphatic circulation.[26] Currently, numerous advanced pharmaceutical technologies have been applied to increase the solubility and permeability of AvDs, including adding auxiliary ingredients (such as latent solvents and penetration enhancers) and applying cutting-edge preparation methods (such as inclusion technology, solid dispersion technology and micronization technology and nanotechnology).

Pharmaceutical Technology to Increase Both Solubility and Permeability

Adding Auxiliary Ingredients

Lopinavir solid dispersions were developed by using Soluplus as a polymeric solubilizer.[27] An in vitro characterization study showed that Soluplus solubilized lopinavir in water almost linearly as a function of concentration by creating H-bonds of water with the drug carbonyl group and forming micelles in water. A Caco-2 cell transport study demonstrated that Soluplus significantly enhanced the permeability of lopinavir through the rat intestine via H-bond or micelle formation and P-glycoprotein (P-gp) inhibition. The bioavailability of lopinavir in Soluplus matrixed extrudate was 3.70-fold that of lopinavir crystal. Soluplus (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol grafted copolymer) is a new amphiphilic nonionic medicinal polymer material that not only changes the interface state of the solution system but also increases the solubility of poorly soluble drugs.[28]

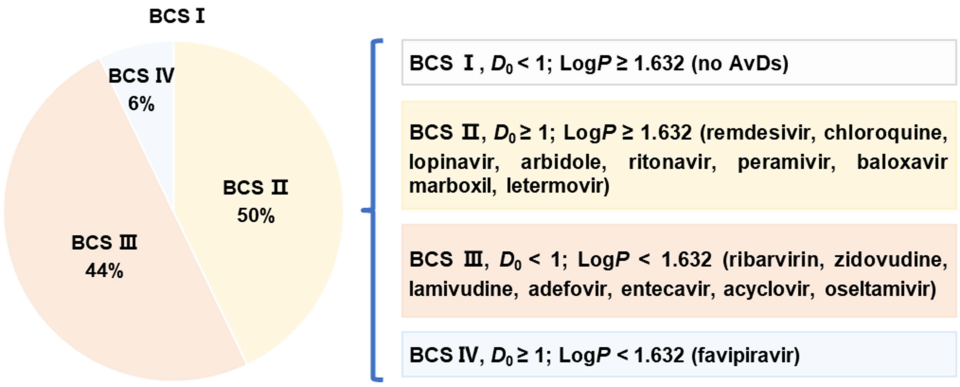


Figure 2 The classification ratio of antiviral drugs (AvDs) according to the biopharmaceutics classification system (BCS) criteria.

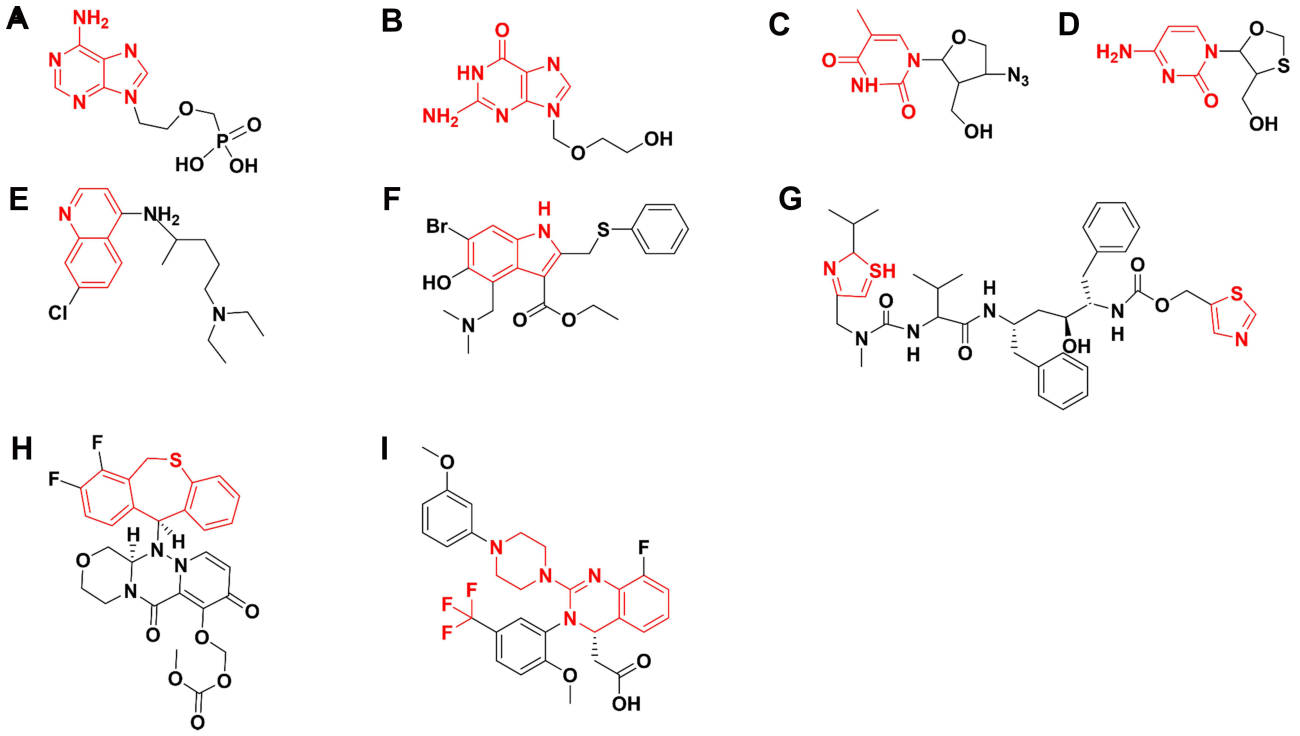


Figure 3 Structures of AvDs. Basic structures of (**A**) adenine nucleotide analog, (**B**) guanine nucleotide analog, (**C**) thymine nucleotide analog, (**D**) cytosine, (**E**) quinolones, (**F**) indoles, (**G**) thiazoles nucleotide analog; (**H**) baloxavir marboxil; (**I**) letermovir.

Preparing Polymeric Micelles

The polymeric micelles enhanced the solubility and permeability of acyclovir.[29] The apparent solubility value (1.39 mg/mL) of acyclovir polymeric micelles was 1.36-fold that of acyclovir. The amount of acyclovir in the polymeric micelles that passed through the cornea in 6 h was approximately 10 times greater and the lag time was apparently shorter than that of aqueous solution. Polymeric micelles are colloidal structures of block copolymers: hydrophobic fragments form the spherical inner core, encapsulating poorly water-soluble drugs, while hydrophilic fragments form the outer shell.[30]

Preparing Solid Dispersion

A lyophilized milk-based solid dispersion was developed to enhance the solubility and permeability of ritonavir.[31] Ritonavir was dispersed in an amorphous polymer matrix and existed primarily in a molecularly dispersed state.[32] This formulation (drug:carrier mass ratio of 1:4) exhibited higher dissolution efficiency (~55.26 ± 1.29%, representing a 10-fold increase compared to pure ritonavir). Ex vivo

permeation research indicated that the permeation extent of ritonavir formulation (33~75% w/w) was ~1.5~3.7-fold greater than that of pure ritonavir (~20%).

Pharmaceutical Technology to Increase Solubility Alone

Preparing Cyclodextrin Inclusion

The use of γ-cyclodextrin (a cyclodextrin derivatization) resulted in an 87-fold increase in lopinavir solubilization.[33] Cyclodextrin is a class of cyclic oligosaccharides of α (1→4) glucopyranosides, having a hydrophilic outer surface and a considerably less hydrophilic central cavity that enable it to form complexes with drug molecules, thereby enhancing the aqueous solubility and bioavailability of the drug.[34]

Preparing Nanosuspension

The use of ritonavir nanosuspension increased up the dissolution rate of ritonavir. The area under the plasma concentration-time curve (AUC) values of ritonavir nanosuspension were 1.40-, 6.16- and 12.40-fold higher, and the maximum plasma concentration (C_{max}) values were 1.90-, 3.23- and 8.91-fold higher, than those of the commercial product, physical mixture and coarse powder of ritonavir, respectively.[35] Nanosuspensions containing surfactants or polymers as stabilizers may be employed to address drug delivery issues.[36]

Preparing a self-microemulsifying drug delivery system (SMEDDS). The solid SMEDDS tablets (completely dissolved in 60 min) markedly enhanced the drug dissolution rate (30%), C_{max} (160.63%) and oral bioavailability (196.46%) compared to free ritonavir.[37] SMEDDS is a promising approach to deliver lipophilic drugs due to their self-dispersion characteristics. The small droplet sizes observed upon dispersion have shown that drug absorption benefited from the large interfacial area.[38]

Pharmaceutical Technology to Increase Permeability Alone

Adding Penetration Enhancer

Caco-2 cell permeation studies showed that the permeability of acyclovir increases by 30 to 40 times in the presence of chitosan.[39] Chitosan is an unbranched binary heteropolysaccharide consisting of the two units N-acetyl-d-glucosamine and d-glucosamine, which can increase or accelerate drug penetration.[17,40]

Adding an Absorption Enhancer

Gelucire 44/14 (at a concentration of 0.05% or 0.1% w/v) is able to increase the apparent permeability coefficient (P_{app}) by 6.47-fold and promote ocular bioavailability by 5.40-fold compared to free ribavirin.[41] Gelucires are a series of amphiphilic pharmaceutical excipients that are widely used as powerful solubilization agents and bioavailability enhancers via oral and topical routes.

Preparing Prodrugs

Oseltamivir carboxylate formed a valyl amino acid prodrug via an isopropyl-methylenedioxy linker. This oseltamivir prodrug had a 9-fold enhanced P_{app} value in Caco-2 cells compared to that of the parent drug.[42] The ethanol and butanol prodrugs of lamivudine increased permeability 2- and 10-fold, respectively.[43]

Metabolic Enzyme, Reaction and Metabolite of AvDs

AvDs are converted into active ingredients or metabolites with high polarity and high-water solubility, mainly in the liver and intestine. Phase I biotransformation involves oxidation, reduction or hydrolysis reaction of the functional group of drug molecules. Phase II biotransformation (combination reaction) combines the polar groups produced by phase I with endogenous components in the body through covalent bonds.[23,44] The produced combination, possessing high polarity, is easy to dissolve in water and discharge from the body. Renal clearance is mainly controlled by membrane transport proteins and is an important elimination pathway for antiviral agents.

Enzymatic System Related to Metabolism of AvDs

The main metabolic enzymes of AvDs are microsomal enzymes existing in the liver, lung, kidney, small intestine, placenta and skin, mainly in intestinal epithelial cells and hepatocytes. Cytochrome P450 enzyme system (CYP450) mainly exists on the smooth endoplasmic reticulum and mitochondria of hepatocytes and in the small intestinal epithelia or the proximal tubules of the kidneys to a lesser extent. CYP450 is mainly involved in phase I reactions of AvDs.[45] Approximately 40–70% of all clinical drugs are subjected to glucuronidation reactions metabolized by uridine diphosphate-glucuronosyl transferases (UGTs) in humans.[46] UGTs are a superfamily of membrane-bound enzymes that catalyze the formation of

a chemical bond between a nucleophilic O-, N-, S-, or C atom and uridine-5'-diphosphate-α-D-glucuronic acid (UDPGA).[47]

Metabolic Reaction and Metabolite in the Liver and Intestine

Metabolic Reaction of NA-AvDs

NA-AvDs enter cells through specific plasma membrane nucleoside transporters, such as the *SLC22, SLC15, SLC28* and *SLC29* gene family.[48] After entering the cells, NA-AvDs are phosphorylated by cellular nucleoside kinase to form nucleoside monophosphate, diphosphate and triphosphate. Nucleoside triphosphates are the active form of NA-AvDs, which work by inhibiting cellular or viral enzymes (such as DNA/RNA polymerase).[49] Most NA-AvDs are activated in vivo through 5'-phosphorylation. NA-AvDs are subjected to phosphorylation (7/8, ie, 7 of a total of 8), glucuronidation (1/8), oxidation (1/8), and reduction (1/8) (Table 2).

Purine NA-AvDs: (1) Phosphorylation. Adefovir with hydroxyl groups was phosphorylated to the diphosphate compound, which competes with deoxyadenosine triphosphate kinase for incorporation by HBV reverse transcriptase to exert its antiviral effect.[55] Entecavir undergoes intracellular phosphorylation to form di- and triphosphate metabolites by the natural substrate deoxyguanosine triphosphate and is then incorporated into HBV DNA polymerase to inhibit replication.[56] (2) Oxidation. Acyclovir with the primary hydroxyl group in the side chain underwent oxidation, resulting in the formation of active carboxy-acyclovir.[62]

Pyrimidine NA-AvDs: (1) Phosphorylation. Zidovudine undergoes intracellular phosphorylation to form monophosphate, diphosphate and active triphosphate compounds by thymidine, thymidylate kinase and nucleoside diphosphate kinase, respectively.[53] Lamivudine formed monophosphate, diphosphate and active 5'-triphosphate by deoxycytidine kinase, deoxycytidylate kinase and nucleoside diphosphate kinase, in turn.[54] (2) Glucuronidation. Zidovudine underwent glucuronidation by UGT2B7 to form inactive metabolites excreted in urine.[53] (3) Reduction. CYP450s and CYP450 reductase have been applied in the reduction of the azido moiety of zidovudine. The metabolite 30-amino-3'-deoxythymidine of zidovudine has been shown to be approximately 5- to 7-fold more toxic to human hematopoietic progenitor cells.[53]

Other NA-AvDs: Phosphorylation. Favipiravir first forms ribonucleoside 5'-monophosphate and then forms ribonucleosides 5'-diphosphate and 5'-triphosphate under the action of guanine phosphoribosyltransferase. In addition, another active metabolite, nicotinamide adenosine favipiravir, was formed by nicotinamide mononucleotide adenylyltransferase.[52] Remdesivir is metabolized through the following 3 pathways: forming nucleoside triphosphate by phosphorylation, forming alanine metabolite by dephenylization, and forming nucleoside monophosphate by deamination.[51] Ribavirin forms 5'-phosphorylation compounds by adenosine kinase catalysis.[63] Phosphorylated ribavirin metabolites have exhibited broad antiviral activity.[50]

Metabolic Reaction of NN-AvDs

The whole 8 NN-AvDs investigated in this article are subjected to oxidation (3/8), reduction (2/8), hydrolysis (1/8) and conjugation (1/8).

Oxidation: Lopinavir is mainly catalyzed by CYP3A to undergo oxidative metabolism. The predominant metabolic site was carbon-4 of the cyclic urea moiety, with subsequent secondary metabolism occurring on the diphenyl core moiety.[58] Arbidol contains sulfide, which forms sulfinylarbidol by sulfoxidation. The oxidation was catalyzed by flavin-containing monooxygenases.[60] Ritonavir undergoes several oxidations, including hydroxylation at the isopropyl group by CYP2D6 to form the major metabolite and the oxidation of the thiazole rings on the eastern and western side of the molecule catalyzed by CYP2J2.[61] CYP3A4 was the major isoform involved in arbidol metabolism in the liver and intestines.[60]

Reduction: Chloroquine was rapidly dealkylated into the pharmacologically active desethylchloroquine, bisdesethylchloroquine and 7-chloro-4-aminoquinoline. The main metabolic enzymes were two major isoforms, CYP3As and CYP2D6.[57] Ritonavir underwent dealkylation by CYP3A4 to form demethylation metabolites.[61]

Hydrolysis: Oseltamivir was metabolized to GS4071, (3R,4R,5S)-3-(1-ethylpropyloxy)-4-acetamido-5-amino-cyclohexene-1-carboxylate (an active neuraminidase inhibitor) through ester hydrolysis.[59]

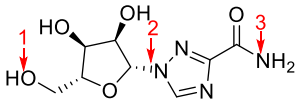
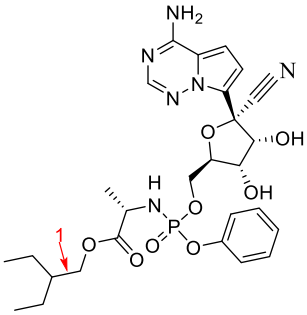
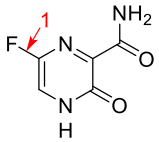
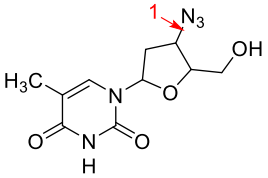
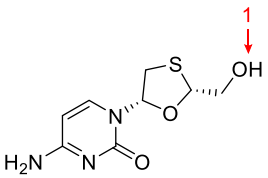
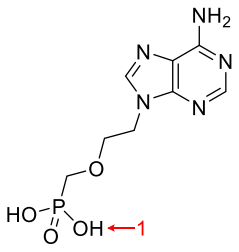
Conjugation: Arbidol was conjugated with glucuronide and sulfate via free hydroxyl groups on the indole ring by UGT1A9.[64] The obtained conjugates were major metabolites in human urine.

Pharmacological Activity of AvDs and Their Delivery Systems

Pharmacological Activity of AvDs

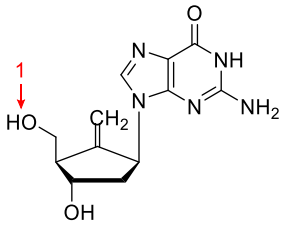
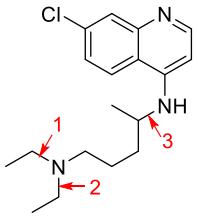
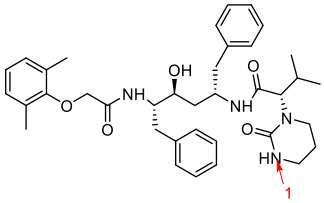
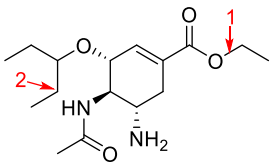
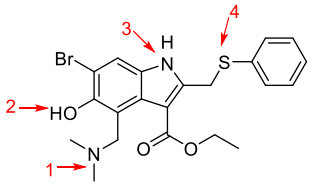
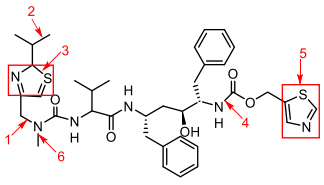
AvDs usually reduce viral synthesis by interfering with the synthesis cycle of viral RNA (Figure 4). Among all 14

Table 2 Main Metabolic Pathway of AvDs in Liver and Intestine

AvD	Structure	Phase I Reaction			Phase II Reaction	Ref.
		Oxidation	Reduction	Hydrolysis	Binding	
Ribavirin		–	Deribosylation at 2: —N—C→—N—H	Amide hydrolysis at 3: —NH2→—COOH	Phosphorylation at 1: —OH→—OPO_3→—$O(PO_3)_2$→—$O(PO_3)_3$	[50]
Remdesivir		–	–	–	Phosphorylation at 1: —OH→—OPO_3→—$O(PO_3)_2$→—$O(PO_3)_3$	[51]
Favipiravir		–	–	–	Phosphorylation at 1: —OH→—OPO_3→—$O(PO_3)_2$→—$O(PO_3)_3$ Glucuronidation at 1: —C—F→—C—ADP	[52]
Zidovudine		–	CYP-450/P450 reduction at 2: —N—N_2→—N—H_2	–	Phosphorylation at 1: —OH→—OPO_3→—$O(PO_3)_2$→—$O(PO_3)_3$ Glucuronidation at 1: —OH+;Glucuronic acid →Glucuronides	[53]
Lamivudine		–	–	–	Phosphorylation at 1: —OH→—OPO_3→—$O(PO_3)_2$→—$O(PO_3)_3$	[54]
Adefovir		–	–	–	Phosphorylation at 1: —OPO_3→—$O(PO_3)_2$→—$O(PO_3)_3$	[55]

(*Continued*)

Table 2 (Continued).

AvD	Structure	Phase I Reaction			Phase II Reaction	Ref.
		Oxidation	Reduction	Hydrolysis	Binding	
Entecavir		–	–	–	Phosphorylation at 1: —OPO_3→—O (PO_3)$_2$→ —O(PO_3)$_3$	[56]
Chloroquine		–	Dealkylate at 1,2,3: —N—C→—N—H	–	–	[57]
Lopinavir		Hydroxylation at 1: —NH→—C—OH→—C—O=O	–	–	–	[58]
Oseltamivir		Hydroxylation at 2: —C—H→C—OH Carbonylation: —C—H→—C=O	–	Hydrolysis at 1: —O—C→—O—H	–	[59]
Arbidol		S-Oxidation at 4; Hydroxylation at 5: —C—H→—C—OH	N-demethylation,di-N-demethylation at 1: —N—C→—N—H; N-demethylation at 3: —N—C→—N—H	–	O-Glucuronide conjugation, O-Sulfate conjugation at 2,5.	[60]
Ritonavir		Hydroxylation at 2: —C—H→—C—OH; S-oxide,N-oxide, epoxide at 3,5	Dealkylation at 1,4,6: —N—C→—N—H	–	–	[61]

AvDs, 5 AvDs are broad-spectrum AvDs, 3 AvDs are mainly for HBV, 2 are mainly for HIV, 2 are mainly for CoV, 2 are mainly for influenza and 1 is for HSV (Table 3). In particular, half of the abovementioned AvDs, including ribavirin,[65] remdesivir,[66] favipiravir,[67] chloroquine,[68] lopinavir, ritonavir[69] and arbidol,[12]

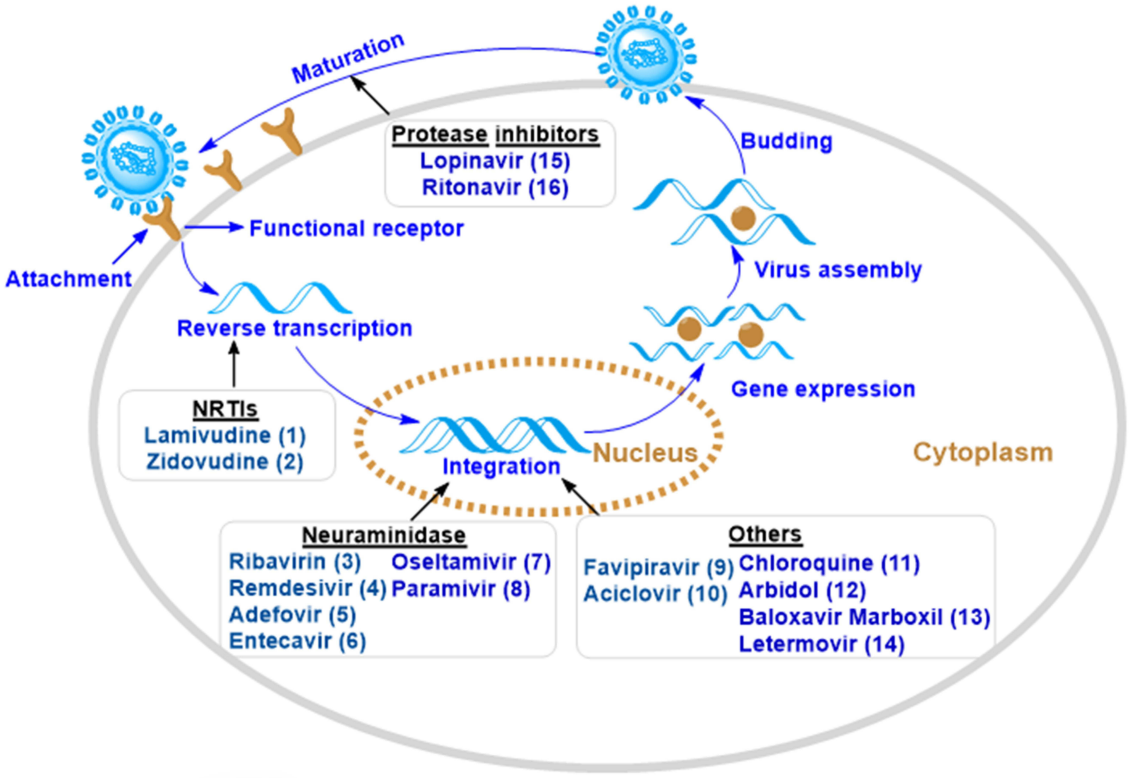


Figure 4 The antiviral mechanisms of AvDs include reverse transcription inhibition, integration inhibition, maturation interference. NRTIs refer to nucleoside reverse transcriptase. (1)-(6), (9), (10) belong to nucleoside analogues antiviral drugs (NA-AvDs) written in the color ■; (7), (8), (11)-(16) belong to non-nucleoside analogues antiviral drugs (NN-AvDs) written in the color ■.

exhibited potential efficacy for COVID-19 treatment. Ribavirin interfered with the replication of DNA and RNA viruses and boosted the antiviral Th1 arm of the immune system to regulate T cells. In addition, ribavirin was proven to be effective for COVID-19 in several clinical trials.[70] Recently, remdesivir in the triphosphate form was found to compete with the natural counterpart ATP and cause SARS-CoV RNA synthesis arrest at a specific position; thus, remdesivir might resist COVID-19.[71] Favipiravir was effective in reducing the SARS-CoV-2 infection in vitro.[12] Favipiravir stopped the disease progression of COVID-19 by inhibiting and clearing SARS-CoV-2 virus to achieve good treatment outcomes in COVID-19 patients.[72] Chloroquine was a potential drug for COVID-19, since it altered the crosstalk of SARS-CoV-2 molecules with target cells because the inhibition capability of p38 mitogen-activated protein kinase (MAPK) interfered with proteolytic processing of the M protein and altered virion assembly and budding.[73] Both lopinavir and ritonavir bound well to the SARS-CoV 3C-like protease.[74] The combination of lopinavir and ritonavir represent a potential treatment for COVID-19. Arbidol effectively acted against SARS-CoV-2 in vivo and in vitro study.[75]

(1) Five AvDs exhibited broad-spectrum antiviral effects. Three NA-AvDs (ribavirin,[99] remdesivir[100] and favipiravir[101]) are inhibitors of RNA-dependent RNA polymerase. NN-AvD chloroquine[69] inhibited phosphorylation of MAPK in THP-1 (a human monocytic leukemia) cells, as well as caspase-1, and then blocked the virus replication cycle.[102] The NN-AvD arbidol[103] had broad-spectrum activity, since it interacted with both membranes and with viral/cellular proteins.[104]

(2) Three AvDs exhibited anti-HBV effects. Three NA-AvDs (lamivudine,[85] adefovir,[86] entecavir[87]) effectively inhibited the replication of HBV virus. Lamivudine also reduced viral load and reversed fibrosis, and entecavir was also a highly selective inhibitor of HBV DNA polymerase.[105]

(3) Two AvDs exhibited anti-HIV effects. Two NA-AvDs (zidovudine[106] and lamivudine[107] are inhibitors of reverse transcriptase enzymes. Zidovudine also inhibited

Table 3 Pharmacological Activities of AvDs

AvD	Anti-Virus Type	Mechanism	Cell	Parameter				Ref.
				EC_{50} (μM)	CC_{50} (μM)	IC_{50} (μM)	SI	
Ribavirin	Anti COVID-19	Prevented viral replication by inhibiting viral DNA polymerase, inhibited viral penetration and viral protein synthesis	Vero E6	105.90	>400.00	–	>3.65	[12]
	Anti influenza virus	Acted by GTP depletion via inosine monophosphate dehydrogenase (IMPDH) inhibition.	Canine Kidney (MDCK) epithelial	0.34E-02	–	–	–	[76]
	Anti influenza virus	Acted by GTP depletion via IMPDH inhibition.	MDCK epithelial	0.37E-02	–	–	–	[76]
	Anti-HCV	Inhibited IMPDH	HuH6	87.00	>135.00	–	>1.55	[77]
	Anti-RSV	Inhibited virus replication	HEp2	11.00	42.00	–	3.82	[78]
	Anti Lassa virus	(1) Limited the infectivity of new virions; (2) Reduced viremia by impairing viral production; (3) Modulated cell damage, and (4) Enhanced antiviral immunity.	Vero E6	–	–	26.00	–	[79]
	Anti CCHF virus	Inhibited virus replication	Vero E6	–	–	2.80μg/mL	–	[80]
	Anti Chikungunya virus	Reduced viral burden	HUH-7	2.58 μg/mL	11.95 μg/mL	–	4.63	[81]
Remdesivir	Anti COVID-19	Incorporated into nascent viral RNA chains and results in premature termination	Vero E6	0.77	>100.00	–	>129.87	[12]
	Anti Ebola virus	Acted as an alternative substrate and RNA-chain terminator	Primary macrophages	0.09	–	–	–	[51]
	Anti MERS	Reduced viral loads and improves pulmonary function	Calu-3	0.09	>10.00	–	>100.00	[82]
	Anti SARS	Inhibits virus replication	HAE	0.07	>10.00	–	>142.86	[83]
Favipiravir	Anti COVID-19	Reduced viral infection	Vero E6	61.88	> 400.00	–	6.46	[12]
	Anti Lassa virus	Disrupted viral replication	Vero E6	–	–	29.00	–	[79]
	Anti CCHF virus	Suppressed virus replication	Vero E6	–	–	1.10 μg/mL	–	[80]
	Anti Chikungunya virus	Reduced viral burden	HUV-7	20.00 μg/mL	>1000.00 μg/mL	–	>50.00	[81]
Zidovudine	Anti-HIV	Nucleoside reverse transcriptase inhibitor	CEM-GFP	–	>1000.00	0.52	–	[84]

(*Continued*)

Table 3 (Continued).

AvD	Anti-Virus Type	Mechanism	Cell	Parameter				Ref.
				EC_{50} (μM)	CC_{50} (μM)	IC_{50} (μM)	SI	
Lamivudine	Anti-HIV	Inhibited HIV-1 reverse transcriptase via DNA chain termination	MDCK	–	>1000.00	0.04	–	[84]
	Anti-HBV	Terminated DNA chain	Hep-G2	0.45	>1000.00	–	–	[85]
Adefovir	Anti-HBV	Prevented viral replication by inhibiting viral DNA polymerase	Hep-G2	0.96	471.10	–	490.73	[86]
Entecavir	Anti-HBV	Inhibited the replication of HBV virus and exhibit a highly selective inhibitor of HBV DNA polymerase.	Hep-G2	3.75E-03	30.00	–	8000	[87]
Aciclovir	Anti-HSV-1	Activated by the viral thymidine-kinase (TK), preventing viral genome replication.	WI 38	0.80 μg/mL	> 200.00 μg/mL	–	> 250.00	[88]
	Anti-HSV-2	Activated by the viral thymidine-kinase (TK), preventing viral genome replication.	WI 38	1.38 μg/mL	> 200.00 μg/mL	–	> 145.00	[88]
Chloroquine	Anti COVID-19	Function at both entries, and at post-entry stages of the COVID-19 infection, immune-modulating activity.	Vero E6	1.13	> 100.00	–	> 100.00	[12]
	Anti SARS-CoV	Increased endosomal pH is required for virus/cell fusion as well as interfering with the glycosylation of cellular receptors of SARS-CoV.	Vero	4.10	>128.00	–	>31.00	[89]
	Anti MERS-CoV	Inhibited the replication of virus	Vero	3.00	58.10	–	19.40	[90]
	Anti HCoV-229E-GFP	Inhibited the replication of virus	Vero	3.30	>50.00	–	>15.00	[90]
	Anti Zika virus	(1) Inhibited endosomal disassembly of the internalized virus and reducing the release of viral RNA to the cytoplasm for replication; (2) inhibited ZIKV RNA replication through blocking ZIKV induced autophagy.	Vero	9.82	134.54	–	13.70	[91]

(*Continued*)

Table 3 (Continued).

AvD	Anti-Virus Type	Mechanism	Cell	Parameter				Ref.
				EC_{50} (μM)	CC_{50} (μM)	IC_{50} (μM)	SI	
Lopinavir	Anti MERS-CoV	Inhibited CoV-virus replication	Vero	8.00	24.40	–	3.10	[90]
	Anti SARS-CoV	Inhibited CoV-virus replication	Vero	17.10	>32.00	–	>2.00	[90]
	Anti HCoV-229E-GFP	Inhibited CoV-virus reolication	Vero	6.60	37.60	–	5.70	[90]
Oseltamivir	Anti-H1N1	Prevented viral replication by inhibiting viral DNA polymerase; binding to specific cell-surface receptors and inhibiting viral penetration or uncoating; inhibiting viral protein synthesis; or blocking late stages of virus assembly.	MDCK	90.60	>900.00	–	>9.90	[92]
	Anti-H3N2	Prevented viral replication by inhibiting viral DNA polymerase; binding to specific cell-surface receptors and inhibiting viral penetration or uncoating; inhibiting viral protein synthesis; or blocking late stages of virus assembly.	MDCK	0.10	>900.00	–	>9000	[92]
Arbidol	Ant-COVID-19	Against SARS-CoV-2	Vero E6	4.11	31.79	–	7.73	[75]
	Anti-HSV-2	Viral entry inhibitors	Hep-2	-	-	5.05 μg/mL	6.46	[93]
	Anti-H1N1	Blocked the fusion between the viral envelope and the endosomal membrane; modulating virus-induced inflammatory cytokines, including	MDCK	4.40	59.39	–	13.40	[94]
	Anti-H3N2	Blocked the fusion between the viral envelope and the endosomal membrane; modulating virus-induced inflammatory cytokines, including	MDCK	11.80	59.39	–	5.10	[94]

(*Continued*)

Table 3 (Continued).

AvD	Anti-Virus Type	Mechanism	Cell	Parameter				Ref.
				EC_{50} (μM)	CC_{50} (μM)	IC_{50} (μM)	SI	
	Anti-H9N2	Blocked the fusion between the viral envelope and the endosomal membrane; modulating virus-induced inflammatory cytokines, including	MDCK	6.50	59.39	–	9.10	[94]
	Anti Ebola virus	Inhibited virus entry and replication	HepG2	2.70	24.40	–	9.00	[95]
	Anti poliovirus type 3	Inhibited virus entry and replication	HepG2	4.10	28.60	–	7.70	[95]
	Anti-HBV	Inhibited virus entry and replication	HepG2	17.90	>188.00	–	>11.00	[95]
	Anti arenavirus	Inhibited virus entry and replication	HepG2	5.80	31.00	–	6.20	[95]
	Anti human herpesvirus 8	Inhibited virus entry and replication	HepG2	1.60	>60.00	–	>37.00	[95]
Ritonavir	Anti MERS-CoV	HIV-1 protease inhibitor	Calu-3	24.90	>50.00	–	>2.00	[82]
Peramivir	Anti-H1N1	Neuraminidase inhibitor	MDCK	643.00nM	>E+05nM	0.48nM	>155.52	[96]
Baloxavir Marboxil	Anti-H1N1	Polymerase acidic protein inhibitor inhibited cap-dependent endonuclease, inhibited viral mRNA synthesis	MDCK	1.2±0.83 nM	–	–	2500	[97]
Letermovir	Anti-CMV	Inhibited viral replication	HELF	5.0E-03	64.00	–	12,903	[98]

Abbreviations: Calu-3 cell, cultured human airway epithelial cell; CC_{50}, half-cytotoxic concentration; CCHF, crimean-congo hemorrhagic fever virus; CMV, cytomegalovirus; CoV, coronavirus; COVID-19, coronavirus disease 2019; EC_{50}, half-maximal effective concentration; HBV, hepatitis C virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HELF, human embryonic lung fibroblast cells; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IFN, interferon; MDCK, Madin Darby canine kidney cell; MERS, Middle East respiratory syndrome; RSV, respiratory syncytial virus; SI, selectivity index; Vero E6 cell, monkey kidney cell line; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

viral replication by interfering with chain elongation of the viral DNA.[108] Lamivudine also exerted antiviral effects by acting as a DNA chain terminator.[107]

(4) Two AvDs exhibited anti-CoV effects. Two NN-AvDs (lopinavir[109] and ritonavir[82]) were combined to treat coronavirus infections. Lopinavir was a protease inhibitor which mainly inhibited the 3C-like protease of CoV-virus and modulated apoptosis in human cells.[110] While ritonavir inhibited the CYP3A mediated metabolism of lopinavir and thereby potentiated the serum level of lopinavir.[111]

(5) Two AvDs exhibited anti-influenza effects. Two NN-AvDs contained oseltamivir[112] and peramivir[96]). The former mainly targeted a glycoprotein neuraminidase on the surface of influenza virus.[113] Peramivir is an efficacious nucleoside analog inhibitor to treat influenza.[96]

(6) 1 AvDs exhibited anti-HSV effects. NA-AvD acyclovir[88] was activated by viral thymidine kinase and then di- and tri-phosphorylated by cellular kinases. The active tri-phosphorylated forms of acyclovir specifically interfered with viral DNA polymerase and caused chain termination.[88]

Effect of Metabolism on Pharmacological Activity

The in vivo metabolization of AvDs had a large influence on viral replication processes and pharmacological function.

Table 4 Main Pharmacokinetic Properties of AvDs via Oral Administration

AvD	Formulation	Dosage (mg/kg)	Subject (Number)	Pharmacokinetics Parameters						Ref.
				AUC (μg·h·mL^{-1})	T_{max} (h)					
	C_{max} (μg·mL^{-1})	$t_{1/2}$ (h)	*MRT* (h)	*Cl* (L/h)						
Ribavirin	Solution	30	SD rats (3)	3.04	1.00	0.43	8.10	–	10.20	[131]
Favipiravir	Suspension	100	Hamsters (53)	8.02E-05	0.29	25.60	0.55E-01	0.34	–	[132]
Zidovudine	Solution	10	Wistar rats (3)	6.35E+01	1.00	37.67	1.76	–	–	[133]
	Lactoferrin nanoparticles	10	Wistar rats (3)	2.52E+02	2.00	49.20	3.07	–	–	[133]
Lamivudine	Solution	10	Wistar rats (4)	1.87±0.39	1.75±0.43	0.46±0.10	2.02±0.83	3.04±0.11	–	[134]
Adefovir	Suspension	1.30	Swiss albino mice (16)	1.64±0.17	1.00	0.14±0.01ng/g	7.75±0.10	11.68±0.41	–	[135]
	Nanosuspension	1.30	Swiss albino mice (16)	2.51±0.21	1.00	0.25±0.02ng/g	6.50±0.11	9.75±0.33	–	[135]
	Solid lipid nanoparticles	1.30	Swiss albino mice (16)	3.75±0.33	4.00	0.18±0.01ng/g	11.43±0.42	17.67±0.62	–	[135]
Entecavir	Suspension	1.54E-02	Beagle dogs (6)	0.03±0.01	0.24	0.015.4	4.09±1.99	–	–	[136]
Acyclovir	Suspension	5	Wistar rats (6)	0.58±0.24	0.43±0.09	0.29±0.09	1.55±0.88	2.29±0.62	–	[137]
	Semisolid self-microemulsifying	5	Wistar rats (6)	0.92±0.26	0.23±0.18	0.92±0.21	0.73±0.20	1.46±0.53	–	[137]
Lopinavir	Suspension	20	Wistar rats (5)	1.65±0.05	0.85	0.65± 0.09	–	5.09±0.25	–	[138]
	Pullulan acetate nanoparticles	20	Wistar rats (5)	8.40±0.10	1.40	1.69±0.16	–	8.57±0.52	–	[138]
	Suspension	10	Wistar rats (5)	1.60±0.22	0.14±0.02	–	8.45	–	–	[139]
	PLGA nanoparticles	10	Wistar rats (5)	22.34±2.31	0.83±0.09	–	17.93	–	–	[139]
	Suspension	52	SD rats (3)	5.04±0.18	6.00±0.00	0.52±0.05	5.81±1.28	6.30± 0.10	–	[140]
	Kaletra (marketed liquid formulation)	52	SD rats (3)	15.86±0.68	3.00±0.00	1.77 ± 0.20	6.53± 1.45	6.70± 0.31	–	[140]
	Zein-Whey protein isolate nanoparticles	52	SD rats (3)	23.63±2.21	6.00±0.00	1.29 ± 0.05	11.72±3.30	16.97±3.51	–	[140]
	Powder	10	SD rats (6)	0.75±0.12	2.00±0.63	0.16±0.02	–	–	–	[27]
	Extrudate (LPV-VA64-SBM-CLSF =1:4:0.4:0.6, w/w)	10	SD rats (6)	1.34±0.35	1.50±0.55	0.35±0.08	–	–	–	[27]
	Extrudate (LPV-Soluplus-SBM-CLSF=1:4:0.4:0.6, w/w)	10	SD rats (6)	2.79±0.44	1.83±0.41	0.57±0.10	–	–	–	[27]

(*Continued*)

https://doi.org/10.2147/IJN.S315705

Table 4 (Continued).

AvD	Formulation	Dosage (mg/kg)	Subject (Number)	Pharmacokinetics Parameters						Ref.
				AUC (μg·h·mL^{-1})	T_{max} (h)					
	C_{max} (μg·mL^{-1})	$t_{1/2}$ (h)	*MRT* (h)	*Cl* (L/h)						
Oseltamivir	Solution (solvent:100 mg/mL distilled water)	10	BALA/c mice (5)	9.80±3.00	0.80±0.30	4.10±1.20	3.80±0.80	–	–	[92]
	Phosphate solution (solvent:100 mg/mL distilled water)	10	BALA/c mice (5)	9.40±5.10	0.80±0.30	3.30±1.30	2.80±0.70	–	–	[92]
Arbidol	Suspension	1.30	Swiss albino mice (16)	0.81±0.02	1.00	0.14±0.01	7.75±0.10	11.68±0.41		[135]
	Nanosuspension	1.30	Swiss albino mice (16)	1.66±0.33	1.00	0.25±0.02	6.50±0.11	9.75±0.33		[135]
	Solid lipid nanoparticles	1.30	Swiss albino mice (16)	2.77±0.20	4.00	0.18±0.01	11.43±0.42	17.67±0.62		[135]
	Arbidol hydrochloride monohydrate powders	60	SD rats (6)	1.37±0.11	0.25±0.04	1.30±0.24	2.97±0.46	–	–	[22]
	Arbidol mesylate powders	65	SD rats (6)	2.73±0.09	0.25±0.03	1.46± 0.17	4.04±0.88	–	–	[22]
Ritonavir	Powder	10	Wistar rats (6)	0.23±0.10	0.88±0.31	0.09±0.04	4.71±2.69	–	–	[35]
	Physical mixture	10	Wistar rats (6)	0.35±0.11	0.92±0.20	0.09±0.03	7.91±9.20	–	–	[35]
	Lyophilized nanosuspension	10	Wistar rats (6)	0.80±0.27	1.17±0.41	0.15±0.04	5.87±1.71	–	–	[35]
Peramivir	Solution	10	SD rats (6)	1.73±0.21	1.50±0.30	0.38±0.13	5.60±0.60	–	–	[141]
Baloxavir Marboxil	Tablet	1.00	Adults patients (446)	6.48E-03	–	9.82E-05	–	–	–	[142]
Letermovir	Solution	120	Healthy volunteer (8)	11.41	1.50	2.61	16.21	–	11.25	[143]

Abbreviations: p.o, oral administration; SD, to sprague-dawley rat.

(1) Generation of active metabolites. Eight inactive or low-activity AvDs were transformed into active or high-activity forms through metabolism in the body.

Typically, NA-AvDs are prodrugs that must be converted to nucleotide triphosphate metabolites to exert antiviral activity. Ribavirin was phosphorylated to form monophosphate by adenosine kinase and triphosphate by nucleoside mono- and diphosphate kinases.[114] The triphosphate metabolite of remdesivir markedly increased the plasma half-life time ($t_{1/2}$) value (14 h versus 0.39 h for remdesivir) and antiviral activity (> 40 times) compared to the free drug.[115] Favipiravir showed no inhibitory effect on influenza, whereas its active metabolite (favipiravir triphosphate) strongly inhibited influenza virus RNA polymerase.[116] Zidovudine was phosphorylated at the intracellular site, and zidovudine triphosphate was the inhibitor of reverse transcriptase activity required for viral replication.[117] Lamivudine was phosphorylated to lamivudine triphosphate, which was able to inhibit viral reverse transcriptase and terminate proviral DNA chain extension due to the lack of the 3'-hydroxyl group required for nucleic acid replication.[118] Entecavir-formed triphosphate inside cells inhibited replication of the hepatitis B virus.[119]

In the case of NN-AvDs, desethylchloroquine was an active metabolite of chloroquine. Both chloroquine and its metabolite acted against Zika virus at low concentrations (ie, at the micromolar level).[120] Oseltamivir was converted into oseltamivir carboxylate (a potent neuraminidase inhibitor).[121] The active metabolites of arbidol, sulfinylarbidol and sulfonylarbidol, increased the $t_{1/2}$ values (25 h, 26 h versus 15.7 h for arbidol) and peak time (T_{max}) values (13 h, 19 h versus 1.38 h), respectively.[122]

(2) Generation of inactive/low-active metabolites. Zidovudine was metabolized quickly to the inactive form glucuronide with a $t_{1/2}$ value of 1 h.[123] Lopinavir was primarily mediated by CYP3A enzymes and yielded metabolites that were less potent as protease inhibitors.[124]

(3) Generation of toxic metabolites. Zidovudine's metabolite (30-amino-3'-deoxythymidine) was approximately 5- to 7-fold more toxic to human hematopoietic progenitor cells.[53]

Delivery System to Improve Pharmacological Activity of AvDs

Most AvDs had poor solubility/permeability and low oral bioavailability. Appropriate drug delivery systems might be able to overcome the shortcomings of AvDs and improve pharmacological activity.

(1) Preparing nanocarriers to lessen the side effects of AvDs. Ribavirin caused hemolytic anemia due to the accumulation inside red blood cells. Poly(glycerol-adipate) nanoparticles (NPs) delivered ribavirin to the targeted liver and subsequently decreased the red blood cell uptake rate, which overcame the side effects of ribavirin (hemolytic anemia caused by ribavirin due to its accumulation inside red blood cells).[125] Lamivudine has low bioavailability in the brain (0.05–1.14%) and cannot kill viruses completely. Mannosylated polymeric NPs improved brain bioavailability and targeted mannose receptors on the macrophage surface to improve the therapeutic outcome and reduce toxicity.[126] Oseltamivir loaded into the surface of selenium NPs improved antiviral activity and increased the viability of cells infected with a virus to 83.2%.[127]

(2) Preparing nanocarriers to extend the dose interval of AvDs. Zidovudine had low bioavailability and biological $t_{1/2}$ value that led to dose-dependent anemia and first-pass metabolism. Amide-functionalized alginate NPs were used to encapsulate zidovudine to realize slow and sustained drug release.[123]

(3) Other delivery systems to improve pharmacological activity of AvDs. Acyclovir was loaded onto activated carbon particles. The highly porous carbon structures trapped virions, blocked infection and thus improved efficacy with acyclovir.[128] Ribavirin was coupled to macromolecular carriers and delivered the drug to the targeted site liver, which may reduce systemic complications. Hemoglobin-ribavirin conjugates had greater antiviral activity on both isolated hepatocytes and macrophages, and they significantly reduced viral replication at 1 μM, while free ribavirin was ineffective at the same concentration.[129]

Pharmacokinetic Characteristics of AvDs and Their Delivery System

Pharmacokinetic Behavior of AvDs

Most AvDs belong to BCS II, III or IV types with low solubility/permeability. Therefore, their *AUC*, C_{max}, t_{max}, $t_{1/2}$ or mean retention time (MRT) values are low (Table 4). These adverse pharmacokinetic behaviors are often unfavorable to the pharmacological action of AvDs. The bioavailabilities of orally administered adefovir were 1% in monkeys and 8–11% in rats. The low bioavailability was mainly attributed to the low passive permeability

across the intestinal membrane.[130] It is crucial to apply appropriate drug delivery systems to improve the bioavailability and enhance the pharmacological effects of AvDs.

Nanotechnology to Improve Pharmacokinetics of AvDs

Delivery System to Improve Pharmacokinetics

Iron-catechol-based nanoscale coordination polymers with antiretroviral ligand functionalization served as a promising strategy for the bioavailability enhancement of zidovudine. These polymers offered long-lasting drug release and improved colloidal stabilities, as well as enhanced cellular uptake (ie, an increase of up to 50-fold).[144]

The proliposomes increased the MRT of adefovir dipivoxil in the liver by approximately 3-fold compared with the adefovir suspension.[145]

The poly (lactic acid)-poly (ethylene glycol)-ligand NPs targeted the intestinal transporter PepT1 and increased permeability by 2.7-fold compared with free acyclovir.[146]

The triglyceride-mimetic superficially modified mesoporous silica NPs increased the *AUC,* C_{max} and *MRT* values of lopinavir by 9.65-, 3.87- and 2.70-fold, respectively. The NPs improved poor solubility and avoided the first-pass metabolism of oral lopinavir to achieve high oral bioavailability with no side effects.[147] The lopinavir-loaded bioadhesive protein NPs increased the oral bioavailability by 4- and 1.5-fold compared to the free lopinavir suspension and lopinavir/ritonavir formulations, respectively.[140] The poly (lactic-co-glycolic acid) NPs increased the permeability and oral bioavailability of lopinavir by 3.04- and 13.9-fold in rats.[139] The lopinavir in hydrophobically modified pullulan NPs was metabolized to a lesser extent in the gut. The NPs increased the bioavailability twofold.[148]

Effect of Prodrugs on Pharmacokinetics of AvDs

Prodrugs usually offer a versatile strategy to overcome the flaws of antiviral drugs. The prodrugs strategy improved the pharmacokinetic properties, efficacy and safety profile of many viable drugs.[149] Effective prodrug strategies include ester prodrugs, targeted delivery prodrugs, macromolecular prodrugs and nucleoside conjugates.[16] Zidovudine prodrug (the ester conjugation of zidovudine with ursodeoxycholic acid) permeated considerably more efficiently, and remained in murine macrophages longer, than the parent drug. The *MRTs* for zidovudine and its prodrug were 6.5 min and 19.6 min, respectively.[150] Entecavir ester prodrugs prolonged the therapeutic period. After subcutaneous injection of the entecavir prodrug in beagle dogs, the plasma drug concentration was markedly protracted ($T_{1/2}$ is 129.3 h) with a lower maximum plasma concentration (C_{max} is 4.7 ng/mL) compared to entecavir (oral administration, $T_{1/2}$ is 4.09 h and C_{max} is 15.4 ng/mL).[136] The chloroquine prodrug hydroxychloroquine had higher accumulation in cells and a longer elimination half-life, resulting in a more effect against SARS-CoV-2 infection.[151]

Effect of Administration Route on Pharmacokinetics of AvDs

The current primary administration route for AvDs is oral administration, which has the advantages of convenience, safety and cost-effectiveness. However, the oral bioavailability of most AvDs was not satisfactory due to poor solubility and permeability. Therefore, it was very important to choose the appropriate administration route[152] according to the treatment needs and safety assessment to maximize the efficacy of AvDs (Table 5).

Ribavirin nasal spray consisting of spray-dried excipient particles was suitable for nasal deposition. This method provided effective mucosal adhesion and penetration enhancement. In vivo results confirmed that the agglutination rate was nearly 6 times higher than conventional intravenous administration, suggesting that the preparation has the potential to deliver a highly brain-targeted antiviral from the nose to the brain.[160] Adefovir suspension after intravenous administration increased the *AUC* 5.45-fold compared with oral administration.[135] After subcutaneous injection of entecavir in beagle dogs, the C_{max} (4.70 ng/mL) was protracted, and the $t_{1/2}$ value was lengthened (129.30 h) compared to oral administration (15.40ng/mL, 4.1 h).[136]

After intravenous administration of acyclovir solution, there was 90-fold higher C_{max} (~26.23 μg/mL) and considerably shorter T_{max} (~8.00 min) compared to that of acyclovir suspension by oral administration (C_{max} was ~0.29 μg/mL and T_{max} was ~26.00 min).[137] After intravenous administration of oseltamivir solution[92] or peramivir solution,[141] there were 1.50- and 2.26-fold *AUC* increases compared to oral administration.

Table 5 Main Pharmacokinetic Properties of AvDs via Intravenous Administration

AvD	Formulation	Administration	Dosage (mg/kg)	Subject (Number)	Pharmacokinetics Parameters						Ref.
					AUC (μg·h·mL^{-1})	T_{max} (h)	C_{max} (μg/mL)	$t_{1/2}$ (h)	*MRT* (h)	*Cl* (L/h/kg)	
Ribavirin	Injection	i.v.	30.00	SD rats (3)	11.20	–	20.50	9.90	–	2.60	[131]
Zidovudine	Sterile saline solution	i.v.	8.46	SD rats (3)	5.14±0.48	–	–	1.3±0.09	0.35±0.02	0.47±0.04	[153]
	Solution of dextrin-AZT conjugate	i.v.	8.46	SD rats (3)	6.09±0.09	–	–	19.34±4.93	23.63±3.04	0.39±0.01	[153]
	Cholesteryl-ε-polylysine nanogels	i.v.	0.25	Balb/c mice (3)	212.98±1.60	–	–	115.00± 0.18	–	1.92±0.14	[154]
	Suspension	i.v.	10~15	SD rats (3)	2.00±0.02	–	–	1.15±0.04	1.26±0.08	2.99±0.04	[155]
	Lipid-based nanocarrier (fatty acid combination)	i.v.	10~15	SD rats (3)	5.41±0.15	–	–	9.71±0.21	6.43±0.28	1.10±0.03	[155]
	Lipid-based nanocarrier (soya lecithin combination)	i.v.	10~15	SD rats (3)	5.11±0.15	–	–	7.64±0.08	4.09±0.24	1.17±0.03	[155]
Lamivudine	Solution	i.v.	10.00	SD rats (6)	1.24±0.19	–	7.02±2.37	0.46±0.04	0.38±0.07	8.21±1.29	[156]
Adefovir	Sulotion (solvent: PEG 400)	i.m.	60.00	Albino rats (6)	667.55 ± 10.54	1.00	7.45±1.98	62.16± 3.52	96.55±4.36	–	[157]
	PLGA microspheres	i.m.	60.00	Albino rats (6)	81,915.36±207.36	12.00	7.40±1.88	8.62E+03	1.21E+04	–	[157]
Entecavir	Suspension	s.c.	0.43	Beagle dogs (6)	1.19±0.28	216.00	0.005 ± 0.002	129.30± 46.60	–	–	[136]
	Suspension	i.m.	2.59	Beagle dogs (3)	4.32±1.27	96.00	0.02±0.01	75.90± 38.40	–	–	[136]
	PLGA microspheres	i.m.	0.25	SD rats (6)	1.74E+04	96.00	0.03±0.003	28.38± 8.66	562.56 ±99.84	–	[158]
Acyclovir	Solution (solvent: water)	i.v.	5.00	Wistar rats (6)	15.47±3.65	0.33±0.05	–	0.75±0.21	0.70±0.26	0.34±0.06	[137]
Lopinavir	Suspension	i.v.	25.00	Macaques (10)	150.00	0.80	48.00	16.00	4.90	–	[159]

(*Continued*)

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Table 5 (Continued).

AvD	Formulation	Administration	Dosage (mg/kg)	Subject (Number)	Pharmacokinetics Parameters						Ref.
					AUC (μg h mL^{-1})	T_{max} (h)	C_{max} (μg/mL)	$t_{1/2}$ (h)	*MRT* (h)	*Cl* (L/h/kg)	
Oseltamivir	Solution (solvent: 100mg/mL distilled water)	i.v.	5	BALA/c mice (5)	14.70± 4.20	–	–	3.20± 0.50	–	–	[92]
	Phosphate solution (solvent:100 mg/mL distilled water)	i.v.	5	BALA/c mice (5)	10.00±3.30	–	–	1.90± 1.30	–	–	[92]
Arbidol	Suspension	i.v.	1.30	Swiss albino mice (16)	4.79±0.10	–	–	2.50±0.25	0.01± 0.00	–	[135]
Ritonavir	Suspension	i.v.	7.20	Macaques (10)	18.00	0.80	16.00	14.00	1.90	–	[159]
Peramivir	Solution	i.v.	1	SD rats (6)	3.91±0.35	–	–	5.70±0.50	–	–	[141]

Abbreviations: i.m., intramuscular injection; i.v., intravenous injection; PEG, polyethylene glycol; PLGA, poly-d,l-lactic-co-glycolic acid; s.c, subcutaneous injection.

Conclusion and Prospects

As the main resource in the effort to treat viruses, AvDs have advantages such as convenient use, accurate dosage, clear targets and strong antiviral efficacy. However, insufficient solubility/permeability of AvDs (most belong to BCS II and III), has a great impact on their oral absorption and results in lower oral bioavailability and requires multiple medications. A better understanding of the in vivo metabolism and pharmacokinetic process of AvDs may help researchers to develop new formulations to overcome these problems. In this review, we investigated the structure-based metabolic reactions of AvDs mainly in the liver and intestine. Phosphorylation (one conjugation reaction) is the most common reaction of NA-AvDs; other reactions, such as oxidation and reduction, also occur, but no hydrolysis occurs. For NN-AvDs, in addition to oxidation, reduction and conjugation reactions, hydrolysis also occurs. Enzymatic systems (CYPs and phosphokinase) are mainly produced by epithelial cells. Most AvDs are activated, and a small number are inactivated or maintain activity through metabolic reactions. The pharmacological activity and pharmacokinetics of AvDs are improved by loading into suitable delivery systems with nanotechnology, prodrug strategy and administration route consideration. The mechanisms of action of AvDs are generally to inhibit the key enzymes (such as RNA-dependent RNA polymerase, reverse transcriptase and nucleoside reverse transcriptase) of virus synthesis and consequently block viral synthesis.

Notably, some AvDs (such as ribavirin, remdesivir, favipiravir, chloroquine, lopinavir and ritonavir) exhibit potential as treatments for COVID-19. Several new antiviral drugs have been approved for marketing, such as bictegravir sodium, emtricitabine and tenofovir alafenamide fumarate tablets (Biktarvy®, a nucleotide reverse transcriptase inhibitor); baloxavir marboxil tablets (Xofluza®, a polymerase acidic endonuclease inhibitor) and letermovir injections (Prevymis®, viral terminase inhibitor) have been developed rapidly, and several antiviral drugs that are undergoing clinical trials may also contribute to the global management of antiviral infections (such as albuvirtide and elsulfavirine). In addition, Regeneron's REGN-COV2 antibody cocktail and Eli Lilly's LY-CoV555 are being used in the treatment of the president of the US, and their clinical trials have proven that the drugs have anti-COVID-19 efficacy. In the future, new antiviral drugs in suitable delivery systems are expected to perform better than old ones.

Abbreviations

AvD, antiviral drug; BCS, biopharmaceutical classification system; COVID-19, coronavirus disease 2019; CYP450, cytochrome P450 enzyme system; dATP, deoxyadenosine triphosphate; D_0, dose number; log *P*, oil-water partition coefficient; MAPK, p38 mitogen-activated protein kinase; MERS, Middle East respiratory syndrome; NA-AvD, nucleoside analog of antiviral drug; NN-AvD, non-nucleoside analog of antiviral drug; NP, nanoparticle; SARS, severe acute respiratory syndrome; SMEDDS, semisolid self-microemulsifying drug delivery system; P_{app}, apparent permeability coefficient; P-gp, P-glycoprotein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; T_{max}, peak time; $t_{1/2}$, plasma half-life time; UDPGA, uridine-5'-diphosphate-α-D-glucuronic acid; UGT, uridine diphosphate-glucuronosyl transferase; WHO, world health organization.

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