The possible techniques that used to improve the bioavailablity, pharmacological activity, solubility and permeability of anti-viral drugs: Insight for COVID-19 antiviral drugs

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Abstract:

In early March of 2020, the world was hit by a pandemic caused by the new SARS-COV-2 coronavirus dubbed by the WHO (World health organization) as COVID-19. More than two years later and a series of lockdowns worldwide as a measure to combat the viral spread, had the world facing detrimental effects on health, economic and social fronts. The principal weapon in the worldwide fight against viruses such as corona virus illness in 2019 (COVID-19) is antiviral medicines (AvDs). Because of their low oral bioavailability and limited effectiveness owing to their low solubility/permeability, most AvDs need numerous doses, and their usage commonly results in drug resistance. Solving the issues with AvDs and improving their effectiveness might be aided by a better understanding of their in vivo metabolic and pharmacokinetic properties. In this review the AvDs, were systematically investigated regarding their cellular pharmacology, pharmacokinetics and pharmacodynamics. Additionally, delivery systems used for AvDs to achieve better pharmacology were reviewed. This review assumed that using sophisticated nanotechnology and the right administration routes, together with proper solid dispersion technology and nanosystems, may assist to obtain superior pharmacological activity and pharmacokinetic behavior of AvDs. Antiviral drugs (AvDs) that have been shown to bind to the SARS-CoV-2 receptor are promising candidates for treating COVID-19. These include ribavirin, remdesivir, favipiravir (FAV), chloroquine, lopinavir, and ritonavir.

Key words: Favipravir, Curcumin, Covid-19, Co-amorphous, Solid dispersion

التقنيات الممكنة التي تستخدم لتحسين التوافر البيولوجي والنشاط الدوائي والذوبان والنفاذية للأدوية المضادة للفيروسات نظرة للأدوية المضادة للفيروسات

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الخلاصة:

في أوائل شهر مارس من عام ٢٠٢٠ ، أصيب العالم بجائحة ناجمة عن فيروس كورونا الجديد SARS-COV-2 الذي أطلقت عليه منظمة الصحة العالمية (WHO) اسم COVID-19. بعد أكثر من عامين وبعد سلسلة من عمليات الإغلاق والحجر الصحي في جميع أنحاء العالم كإجراء وقائي لمكافحة انتشار هذا الفيروس ، واجه العالم آثارًا ضارة على الاصعدة الصحية والاقتصادية والاجتماعية. وكان السلاح الرئيسي لمواجهة هذا الفيروس هو الأدوية المضادة للفيروسات (AvDs). نظرًا لضعف قدرة هذه الادوية على الوصول الى داخل جسم الانسان مما يقلل من توافرها الحيوي عند تناولها عن طريق الفم و يقلل من فعاليتها نظرًا لانخفاض قابليتها للذوبان و النفاذية عبر جدار الجهاز الهضمي ، تحتاج معظم

الأدوية المضادة للفيروسات (AvDs) إلى العديد من الجرعات وعادة ما يؤدي استخدامها بشكل مفرط إلى نشوء مقاومة لهذه الأدوية ولكي نتمكن من حل المشكلات المتعلقة بـمضادات الفيروسات ولتحسين فعاليتها فان هذا يتطلب فهما أفضل لخصائصها الأيضية والحركية الدوائية في جسم الانسان. افترضت هذه الدراسة أن استخدام تقنية النانو المتطورة و استخدم طرق تناول الدواء الصحيحة ، جنبًا إلى جنب مع تكنولوجيا التشتت الصلبة المناسبة وأنظمة النانو ، قد تساعد في الحصول على نشاط دوائي متفوق وسلوك حركي دوائي لمضادات الفيروسات. تعتبر الأدوية المضادة للفيروسات التي ثبت ارتباطها بمستقبلات SARS-CoV-2 علاجات واعدة بمواجهة فيروس كورونا المستجد COVID-19. وتشمل هذه المضادات ريبافيرين ، وريمديسفير ، وفافيبيرافير (FAV) ، وكلوروكين ، ولوبينافير ، وريتونافير.

الكلمات المفتاحية: فافيبيرافير, كركمين , كوفيد -١٩ , مشترك غير متبلور, تشتت صلب.

Introduction

In December of 2019, Wuhan, China, had an epidemic of a mysterious sickness that caused severe pneumonia and respiratory distress. It was eventually determined that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was the major cause of the global pandemic that had devastated the globe. Most notably are the effects on the renin-angiotensin-aldosterone system (RAAS) through ACE II (Angiotensin converting enzyme II) which is the way for the viral entry into type 2 pneumocyte [1].

The clinical picture produced by SARS-Cov-2 is broad, ranging from asymptomatic to fatal infection. Sadly, treatment is still mainly supportive with no cure for the infection yet [2]. This puts an emphasis on early diagnosis due to the finite availability of mechanical ventilators or critical care units worldwide. This puts an emphasis on determining Covid-19 through observing the picture associated with the diseases and its outcomes [3]. Hypoxemia, pneumonia, high fever characterized the second phase of infection with Covid-19 regardless of the considerable viral load reduction, here cytokines may be a contributor. According to meta-analysis and systemic reviews, the most frequently encountered symptoms are fever, fatigue and cough, this was similar to what general viral infection and pneumonia produce [4].

Supportive care and symptom management are the mainstays of therapy for Covid-19 [5]. The first assessment of patients in the emergency room is based on how serious their symptoms seem to be. The majority of patients only complain of moderate symptoms, such as a high temperature, a persistent dry cough, general aches and pains, and sometimes shortness of breath [6]. In addition, some individuals may show up with sepsis or multi-organ failure on top of acute respiratory failure or acute respiratory distress syndrome. Several antivirals were involved in the treatment of Covid-19 but the major problem that faced the scientists is to formulate a soluble dosage form that provide an acceptable bioavailability given that the majority of these antivirals have low solubility and permeability [7].

Medicines used to combat viral infections now include natural drugs (eg, forsythia [8], Scutellaria liquorice [9], and baicalensis [10]), chemical drugs (such as favipiravir, remdesivir, and ribavirin) [11] in addition to the biotechnology-derived medications (for example: IFN-α, IFN-β and peptide) [12]. The antiviral effects of natural remedies are often mild, and their complicated chemical profiles and wide range of targets may explain why they are not as effective as synthetic drugs [13]. Due to their weak stability and bioavailability, Antiviral drugs (AvDs) generated from biotechnology are readily inactivated in vivo, despite their strong curative benefits and little induction of drug resistance [14].

Since most chemical AvDs are orally delivered, they are easy to use and store, and they suppress viruses rapidly and effectively. They made from chemicals are the mainstay of treatment [15]. Each drug's effectiveness is influenced by a unique combination of physicochemical features and metabolic processes [16,17,18].

Enhancing the effectiveness of AvDs against viruses requires a thorough understanding of their properties. Oral tablets make up the vast majority of available AvDs (Table 1). Two major drawbacks of these AvDs are their high rate of resistance in addition to poor pharmacokinetic profiles. Therefore, it may be helpful to overcome the above-mentioned drawbacks by using novel methods for the delivery of antiviral drugs by using nanotechnology or loading them into macromolecule and lipid - based systems[19].

This review was aimed to summarizes the possible techniques that used to improve the bioavailablity, pharmaological activity, solubility and permeability of anti-viral drugs that used in the treatment of COVID-19

Table (1): Antiviral spectrum, solubility, permeability and Biopharmaceutics classification system category of some Antiviral drugs [19]

Structure	The Spectrum	Name of the Antivirals	Permeability	Solubility	*BCS
			LogP	D_0	
Nucleoside Analogs					
	Broad-spectrum	Ribavirin	−1.85	0.12	3
	Broad-spectrum	Favipiravir	0.83	8.21	4
	Anti-HIV	Zidovudine	0.05	0.15	3
	Broad-spectrum	Remdesivir	2.10	1.18	2
	Anti-HBV, HIV	Lamivudine	−1.40	0.15	3
	Anti-HBV	Adefovir	−2.06	9.44×10^{-4}	3
	Anti-HBV	Entecavir	−0.96	3.03×10^{-4}	3
	Anti-HSV	Aciclovir	−1.56	8.00×10^{-4}	3
Non-Nucleoside Analogs					
Indoles	Broad-spectrum	Arbidol	4.64	0.42×10^{3}	2
Amides	Anti-influenza	Oseltamivir	0.36	0.44	3
	Anti-CoV	Lopinavir	3.69	0.21×10^{6}	2
Quinolines	Broad-spectrum	Chloroquine	4.69	37.66	2
Thiazoles	Anti-CoV	Ritonavir	3.1021	0.16×10^{3}	2
Cyclopentane	Anti-influenza	Peramivir	3.12	2.36	2
–	Anti-influenza	Baloxavir Marboxil	2.24	1.60	2
–	Anti-CMV	Letermovir	3.47	1.92	2

* Biopharmaceutics classification system (BCS)

Structural Properties, Solubility and Permeability of AvDs

The Limits of the Solubility and Permeability in AvDs

According to the dosage number (D_o) and the oil-water partition coefficient (log P) The AvDs' biopharmaceutics classification system (BCS) were estimated. Low solubility is defined by a D_o value > 1, and low permeability is defined by a log P value ≤ 1.632 [20]. The AvDs are divided into three categories based on their solubility and permeability (Figure 1). Half of these medications are classified as BCS II, which has poor solubility; 44% as BCS III, which has poor permeability; and 6% as BCS IV, which has poor solubility and poor permeability. These values demonstrate the poor in vivo uptake of AvDs [19].

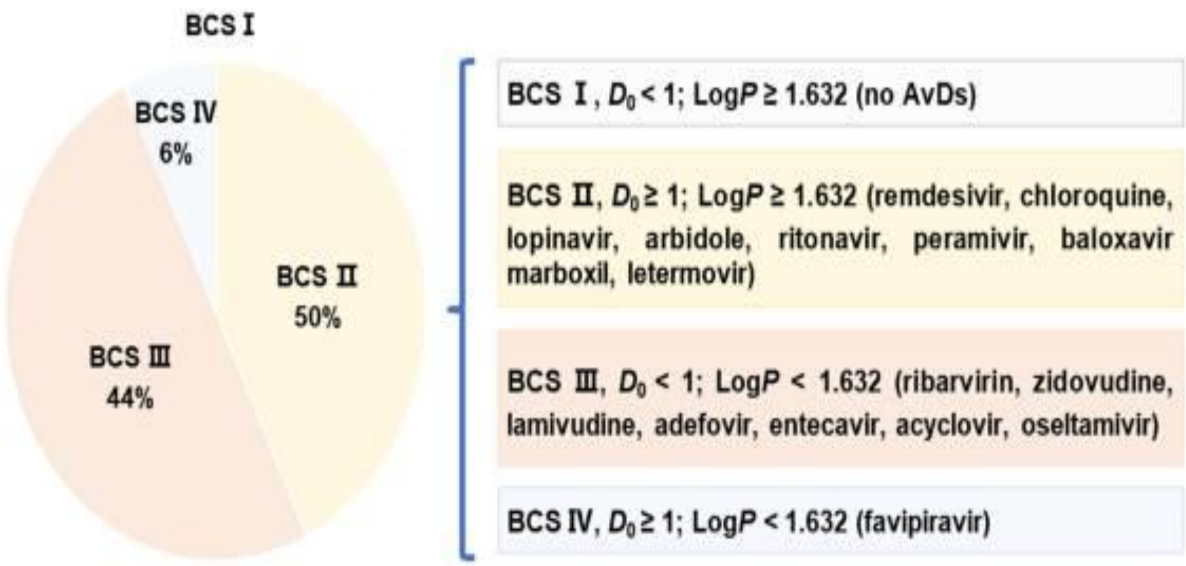

Figure (1): Biopharmaceutical classification system (BCS) criteria used in the categorization of antiviral medicines (AvDs) [19].

Structural Characteristics of AvDs

Two distinct classes of AvDs may be distinguished by analyzing their molecular structures (Figure 2).

(1) Nucleoside analogs of AvDs (NA-AvD) are synthetic antivirals that showed a similarity in their structures to nucleosides that found naturally in the viruses. Since NA-AvDs have undergone inappropriate structural alterations, they are identified by viral or cellular enzymes and cause termination / disruption of replication or other biological processes [21]. NA-AvDs are further classified into 3 subtypes:

a) Pyrimidine NA-AvDs (eg, lamivudine and zidovudine) [22]
b) Purine NA-AvDs (eg, acyclovir [23], entecavir [24] and adefovir [25])
c) Other NA-AvDs (eg, favipiravir[٢٦], remdesivir[٢٧] and ribavirin [٢٨]).

(2) Non-nucleoside analogs of AvDs (NN-AvDs), is an antiviral agent which are not based on nucleosides at all which formulated to overcome the antiviral resistance towards nucleoside-based antiviral agents as well as provide more potent and pharmacokinetically attractive agents and they are divided into 4 types [16]:

a) Quinolines, such as chloroquine phosphate,
b) Indoles, such as abidol,
c) Amides, such as palamivir (derivative of cyclopentane and inhibitor of neuraminidase), lopinavir, and oseltamivir (derivative of cyclohexene; inhibitor of neuraminidase) and
d) Thiazoles (ritonavir).
e) Others (letermovir and baloxavir marboxil) [19].

Relationship Between Structure and Solubility/Permeability of AvDs

It was observed that about 75% of NA-AvDs showed low permeability (e.g., lamivudine, adefovir, ribavirin, acyclovir, entecavir and zidovudine) and about 12% of the NN-AvDs (e.g., oseltamivir), most likely because of their high polarity that owned to the presence of OH groups in their molecular structures. In addition, the hydrophobic macromolecular structures of 88% of NN-AvDs (like arbidol, peramivir, ritonavir, lopinavir, baloxavir marboxil, letermovir, and chloroquine) and 25% of NA-AvDs (like favipiravir and remdesivir) led to poor solubility [29].

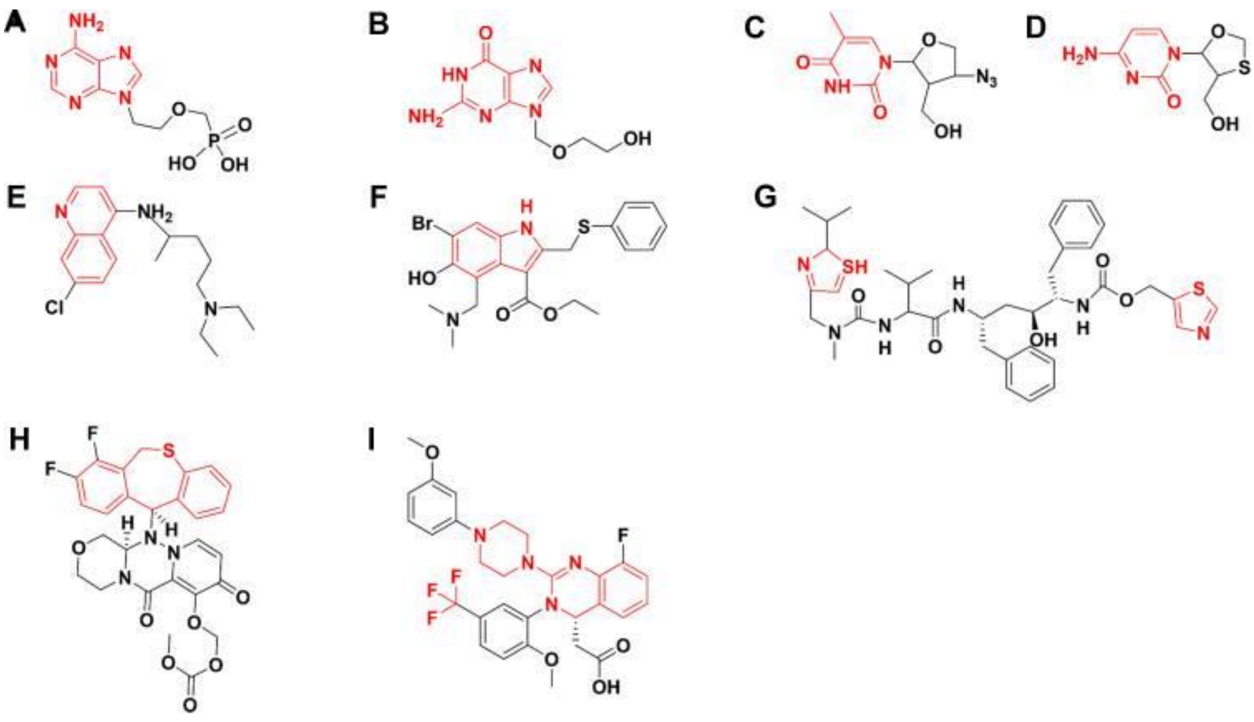

Figure (2): Structures of AvDs. I) Nucleoside analogs of AvDs including: (A) analog to adenine nucleotide, (B) analog to guanine nucleotide, (C) analog to thymine nucleotide, (D) cytosine. II) Non-nucleoside analogs of AvDs including (A) quinolones, (B) indoles, (C) analog to thiazoles nucleotide; (D) baloxavir marboxil; (E) letermovir

Solubility and Permeability Enhancing Pharmaceutical Technology

In order for drug molecules to reach the sites of action and produce therapeutic actions when taken orally, there must be enough solubility and intestinal absorption of the medication [30]. Adequate medication solubility is necessary for verifying oral drug absorption and clinical response [20]. In terms of oral medication absorption, permeability is the rate and degree to which the drug diffuses past the layers of mucosa and sub-mucosa in addition to the epithelial cell barriers to reach the lymphatic / blood circulation [31]. A variety of advanced pharmaceutical technologies, including the addition of some additives (like latent solvents [32] and penetration enhancers) and the application of innovative preparation methods (like inclusion technology, solid dispersion technology, micronization technology, and nanotechnology), have been used to improve AvDs' solubility and permeability properties in recent years [31].

Pharmaceutical Technology to Increase Solubility

Preparing Cyclodextrin Inclusion

Cyclodextrin is a family of cyclic oligosaccharides of α (1→4) glucopyranosides. An 87-fold improvement in lopinavir solubilization was achieved by using -cyclodextrin (a cyclodextrin derivatization). Drug molecules complexes with cyclodextrin were obtained as a result of the hydrophilic outer surface of cyclodextrin and the much less hydrophilic interior cavity that allow for the formation of such complex leading to an increase in the water solubility and bioavailability[33].

Preparing Nanosuspension

Using a ritonavir nanosuspension improved the drug's solubility. Maximum plasma concentration (Cmax) values for ritonavir anosuspension were greater by 1.90-, 3.23-, and 8.91-fold in a comparison with commercial product, physical mixture (Sodium dodecyl sulfate (SDS), hydroxypropyl methyl cellulose (HPMC) and Ritonavir) and coarse powder, respectively [34]. Surfactants and polymers may be used as stabilizers in nanosuspensions for medication delivery [35].

Self-microemulsifying drug delivery system (SMEDDS) preparation

When compared to free ritonavir, the solid SMEDDS tablets significantly improved drug dissolution rate (30%), Cmax (160.63%), and oral bioavailability (196.46%) [36]. Due to the self-dispersion properties of lipophilic medicines, SMEDDS is a viable method for delivering these medications. The large interfacial area was beneficial to drug absorption due to the tiny droplet sizes seen during dispersion [37].

Pharmaceutical Technology to Increase Permeability

Adding Penetration and Absorption Enhancer

Studies on the permeability of acyclovir via Caco-2 cells suggest that its permeability rises by a factor of 30–40 in the presence of chitosan [38]. Increased or accelerated drug penetration may be achieved using binary heteropolysaccharide in an unbranched form such as chitosan which is composed of d-glucosamine and N-acetyl-d-glucosamine [17,39].

Amphiphilic pharmaceutical excipients known as gelucires are utilized extensively as potent solubilization agents and bioavailability enhancers in both oral and topical formulations [40]. Increases in apparent permeability coefficient (Papp) of 6.47-fold and ocular bioavailability of 5.40-fold in a comparison with ribavirin in its freeform which were achieved when Gelucire 44/14 was used (at concentrations of 0.05% or 0.1% w/v).

Prodrugs preparation

A valyl amino acid prodrug was synthesized from oseltamivir carboxylate by use of an isopropyl-methylenedioxy linker. In Caco-2 cells, the Papp value of this oseltamivir prodrug was 9 times higher than that of the parent drug [41]. Lamivudine's prodrugs with butanol and ethanol, respectively, yielded 10- and 2-fold improvements in permeability [42].

Pharmaceutical Technology to Increase Both Solubility and Permeability

Adding Auxiliary Ingredients

Soluplus®, a polymeric solubilizer, was used in the preparation of solid dispersions of lopinavir [43]. In vitro characterization studies showed that Soluplus® solubilized lopinavir in water almost linearly as a function of its concentrations by creating H-bond with the carbonyl group of the drug and forming micelle in water at the equilibrium state. It was shown that Soluplus® cause a dramatical increase in the lopinavir's permeability through the gut of rat by forming hydogin bonds or micelles and inhibiting P-glycoprotein (P-gp). Soluplus® matrixed extrudate increased lopinavir bioavailability 3.70-fold compared to lopinavir crystal. As a novel amphiphilic nonionic medicinal polymer material, Soluplus® (polyvinyl caprolactam-polyvinyl acetate-poly-ethylene glycol grafted copolymer) not only alters the interface state of the solution system but also improves the bioavailability of poorly soluble pharmaceuticals [44].

Preparing Polymeric Micelles

Acyclovir was made more soluble and permeable by the polymeric micelles by using Soluplus and Solutolas that considered as amphiphilic block copolymers. Acyclovir polymeric micelles had a solubility value 1.39 times higher than acyclovir (1 mg/mL). Polymeric micelles contained around 10 times more acyclovir than aqueous solution, and the lag period was reportedly shorter (just 6 hours vs. 24 hours) [45]. Hydrophobic small molecules by using polymeric micelles could be encapsulated in amphiphilic block copolymers which have both hydrophilic and hydrophobic blocks. Amphiphilic block copolymers self-assemble in aqueous media to form micelles that have hydrophilic shells and hydrophobic cores [46].

Preparing Solid Dispersion

To improve ritonavir 's solubility and permeability, a lyophilized milk-based solid dispersion was prepared [47]. Ritonavir was mostly present in a molecularly dispersed form while scattered in an amorphous polymer matrix [48]. Dissolution efficiency was improved by using a formulation of a carrier to drug of 4:1 mass ratio compared to pure ritonavir (55.26 1.29%). It has been shown via ex vivo permeation studies that ritonavir formulations (33–75% w/w) have a penetration extent 1.5–3.7 times larger than pure ritonavir (20%). Using amorphous solid dispersion technology, ritonavir was developed as a solid oral dose form. Due to its anti-HIV activity, ritonavir was developed; however, it is no longer the sole protease inhibitor utilized in antiretroviral therapy. In contrast, ritonavir has shown to be an essential pharmacokinetic enhancer in the treatment of patients with and without prior treatment experience. The inhibition of cytochrome P-450 (CYP) metabolic pathways could account for the observed improvement [49].

Another solid oral dosage form that formulated by an amorphous solid dispersion technology is Kaletra®. Soft-gelatin capsules (SGCs) were the first solid oral formulation of Kaletra®. They included 133.3 mg of lopinavir (an HIV protease inhibitor) and 33.3 mg of ritonavir, the latter of which increased the bioavailability of the former. Lopinavir in the SGC dosage form had to be refrigerated for optimal absorption. To improve dosing and delivery, Kaletra® has been reformulated as an amorphous solid dispersion using hot-melt extrusion (HME) technology. A tablet formulation of 200/50 mg lopinavir/ritonavir was developed, decreasing the number of dosage units and doing away with the requirement for refrigeration [50].

Pharmacological Activity of AvDs and Their Delivery Systems

Pharmacological Activity of AvDs

It is common for AvDs to inhibit viral production by disrupting the RNA replication cycle. Five of the 14 AvDs are broad-spectrum, two are specific to HBV, two to HIV, two to CoV, two to influenza, and one is specific to herpes simplex virus (Table 3).

More specifically, ribavirin [51], remdesivir [52], favipiravir [53], chloroquine [54], lopinavir, ritonavir [55] and arbidol [11] (half of the aforementioned AvDs) showed promise as COVID-19 treatments. Ribavirin inhibited DNA and RNA virus replication and stimulated the antiviral T helper 1 (Th1) immune response. Additionally, ribavirin's efficacy against COVID-19 has been shown in a number of clinical studies [56]. The triphosphate form of remdesivir was recently discovered to compete with the natural homologue ATP and induce SARS-CoV RNA synthesis arrest at a particular location, suggesting that remdesivir may be resistant to COVID-19 [57]. It was shown that favipiravir inhibited SARS-CoV-2 infection in vitro [11].

Patients with COVID-19 who took favipiravir had successful results due to the drug's ability to halt disease development by suppressing and eliminating SARS-CoV- 2 virus [58]. Chloroquine was considered a promising COVID-19 treatment due to its ability to inhibit p38 mitogen-activated protein kinase (MAPK), which in turn altered M protein's proteolytic processing and influenced virion budding and assembly [59]. Both ritonavir and lopinavir bind competitively to the SARS-CoV 3C-like protease [60]. Lopinavir and ritonavir in combination provide a promising new therapeutic option for COVID-19. previous studies found that arbidol was effective against SARS-CoV-2 both in vitro and in vivo [61].

Five AvDs were shown to have broad-spectrum antiviral properties. Inhibitors of RNA-dependent RNA polymerase were found in three different NA-AvDs (ribavirin [62], remdesivir [63] and favipiravir [64]). In THP-1 (human monocytic leukemia) cells, NN-AvD chloroquine prevented the viral replication cycle by inhibiting activation of MAPK and caspase-1 [65]. Since the NN-AvD arbidol [66] interacted with both membranes and cellular / viral proteins, it had broad-spectrum action [67].

An anti-HBV impact was seen for three AvDs. The replication of HBV virus was successfully reduced by three different NA-AvDs (lamivudine [68], adefovir [69], entecavir [70]). Entecavir was a very specific inhibitor of HBV DNA polymerase and lamivudine was similarly effective in lowering viral load and reversing [71].

Specifically, two AvDs were shown to have anti-HIV properties. The reverse transcriptase enzymes are inhibited by two of the NA-AvDs (zidovudine [72] and lamivudine [73]). Zidovudine's ability to block viral replication was based on its ability to prevent the synthesis of new viral DNA [74]. Lamivudine acted as a DNA chain terminator, which contributed to its antiviral activities [73].

The anti-CoV effects were seen in two AvDs. To combat coronavirus infections, researchers combined two NN- AvDs (lopinavir [75] and ritonavir [76]) Protease inhibitor lopinavir altered apoptosis in human cells by blocking the 3C-like protease of the CoV-virus [77]. While ritonavir increased the blood level of lopinavir by blocking its metabolism by CYP3A [78].

There were two AvDs that were effective against the influenza. Two of the NN-AvDs had the antiviral drugs (oseltamivir [79] and peramivir [80]). The former mostly targeted focused an outer membrane glycoprotein called neuraminidase on Influenza Virus [81]. The nucleoside analog inhibitor peramivir is very effective against influenza [80].

There was evidence that AvDs might inhibit the spread of HSV. The viral thymidine kinase activated NA-AvD acyclovir, which was subsequently phosphorylated twice more by cellular kinases. acyclovir in its Tri-phosphorylated forms which considered as the active forms inhibit viral DNA polymerase, leading to chain termination [82].

Pharmacological Activity of AvDs enhancement by drug Delivery System

The solubility/permeability and oral bioavailability of the majority of the AvDs were rather poor. Some of AvDs' drawbacks may be addressed and pharmacological efficacy enhanced by using suitable drug delivery devices.

1) Developing nanocarriers in order to reduce AvDs' unwanted side effects. The accumulation of ribavirin inside red blood cells led to hemolytic anemia. Overcoming ribavirin's negative effects required targeting the liver using poly(glycerol-adipate) nanoparticles (NPs), which transported the drug directly to the organ and lowered the uptake rate at which it was taken up by red blood cells [83]. Lamivudine showed poor brain bioavailability (0.05–1.14%) and cannot eradicate viruses entirely. By targeting

mannose receptors on the surface of macrophages, mannosylated polymeric NPs increased bioavailability in the brain and decreased toxicity [84]. The antiviral activity of oseltamivir was enhanced when it was loaded onto the surface of selenium NPs, and the survival rate of virus-infected cells was boosted to 83.2% [85].

(2) In order to lengthen the time between AvDs doses, preparations are being made using nanocarriers. Dose-dependent anemia and first-pass metabolism resulted in zidovudine's limited bioavailability and biological $t_{1/2}$ value. Zidovudine was encapsulated in amine-functionalized alginate NPs for controlled release over a long period of time [86]. So, pharmacologically this formulation prolongs the $t_{1/2}$ by reducing the first-pass metabolism and reduces the dose-dependent anemia that considered as a zidovudine's side effect.

(3) Alternative delivery strategies to enhance AvDs' pharmacological efficacy. Placing acyclovir onto activated carbon particles improve its effectiveness by entrapping viruses in extremely porous carbon frameworks and so blocking infection. [87]. Coupling ribavirin to macromolecular carriers allowed the medicine to reach the liver, where it is needed, potentially lowering the risk of systemic side effects. Compared to free ribavirin, hemoglobin-ribavirin conjugates dramatically inhibited viral replication at 1 μM in both isolated hepatocytes and macrophages, whereas free ribavirin had no impact at this concentration [88].

(4) Several studies have attempted to find a solution to the solubility issue of favipiravir (FAV), with some success; one such study used an ionic liquid (IL)-based formulation of FAV as a possible method of drug delivery. Because of its superior physicochemical and biological qualities compared to crystalline or other solid forms of medicines, ILs have been widely employed in medication formulations [89,90,91]. Polymorphism is a different medical issue that IL-based API formulations may assist with [90,92]. Conventional medications may be converted to an IL form (APIILs)[82] by combining weakly water-soluble crystalline APIs with a suitable IL-forming counterion [93]. This method may lessen drug polymorphism and crystallinity, two factors that negatively impact medications' water solubility, therapeutic efficacy, and thermal stability [94].

5) Two salts of FAV have been found to boost its solubility, suggesting that this may be another method for increasing FAV's solubility. However, the tabletability (the capacity of a powdered material to be transformed into a tablet of specified strength under the effect of compaction pressure [95]) and permeability of FAV are still low. In FAV, hydrogen-bonding acceptors and donors are available and have the ability to create multicomponent crystals with appropriate co-formers through hydrogen bonds. In prior work, four co-formers (theophylline, piperazine, saccharin, and 5-fluorouracil) were chosen to synthesize novel multicomponent species of FAV; three co-crystals and one salt of FAV have been produced, which display an increased permeability and tabletability. Similar to FAV, the FAV theophylline (FAV -TP) co-crystal has solubility, permeability, and tabletability. When compared to FAV, the permeability and tabletability of the FAV -piperazine (FAV -PP) salt, FAV -saccharin (FAV-SAC), and FAV -5-fluorouracil (FAV -5FU) co-crystals are markedly improved [96].

Pharmacokinetic Characteristics of AvDs and Their Delivery System

Pharmacokinetic Behavior of AvDs

The BCS II, III, and IV classes account for the vast majority of AvDs, and all of them have poor solubility or permeability or both. As a result, they have poor values for AUC, Cmax, tmax, $t_{1/2}$, and mean retention time (MRT). These undesirable pharmacokinetic tendencies often interfere with the pharmacological effect of AvDs.

Adefovir has a bioavailability of 1% when given orally to monkeys and 8-11% when given to rats. To a large extent, the limited passive permeability across the membrane of intestine was responsible for the poor bioavailability [97]. Enhancing the bioavailability and pharmacological effects of AvDs requires the use of suitable drug delivery methods.

Improving the Pharmacokinetics of AvDs by Nanotechnology

Improving zidovudine's bioavailability through the development of polymers coordinated nanoscale that based on catechol and iron that are functionalized with antiretroviral ligands is an exciting new direction. These polymers not only improved colloidal stability and sustained drug release, but also increased cellular absorption (by as much as 50-fold) [98].

When compared to adefovir suspension, the proliposomes raised the MRT of adefovir dipivoxil in the liver by almost threefold.[99].

Targeting the intestinal transporter PepT1, the poly (lactic acid)-poly (ethylene glycol)-ligand NPs improved intestinal permeability by a factor of 2.7 compared to free acyclovir [100].

Surface-modified mesoporous silica NPs mimicking triglycerides improved lopinavir's AUC, Cmax, and MRT by a factor of 9.65, 3.87, and 2.70, respectively. High oral bioavailability of lopinavir was achieved without any adverse effects attributed to the NPs, which ameliorated the drug's low solubility and prevented it from being metabolized in the body's first pass metabolism [101]. In a comparison with the lopinavir/ritonavir formulations and free lopinavir solution, the oral bioavailability was improved 4- and 1.5-fold by the lopinavir-loaded bioadhesive protein NPs, respectively. Proteins used in lopinavir-loaded bioadhesive protein NPs are zein (Z), a hydrophobic corn protein as the core and whey protein (WP) as the shell [102]. Compared to untreated rats, poly (lactic-co-glycolic acid) NPs improved lopinavir oral bioavailability and permeability by 3.04- and 13.9-fold, respectively [103]. Hydrophobically modified pullulan NPs contained lopinavir, which was partially protected from gut metabolism. Bioavailability was improved by a factor of two owing to the NPs [104].

Prodrugs Effect on AvDs Pharmacokinetics

Prodrugs are an adaptable method for addressing the limitations of antiviral medications. Many effective medications had their pharmacokinetic characteristics, effectiveness, and safety profile enhanced by the prodrug's method [105]. Macromolecular prodrugs, ester prodrugs, nucleoside conjugates, and targeted delivery prodrugs are all examples of useful prodrug techniques [106]. The formulation of zidovudine in an ester conjugation with ursodeoxycholic acid creates a prodrug that is much more permeable and bioavailable than the parent drug when used on murine macrophages. Zidovudine and its prodrug had MRT of 6.5 and 19.6 minutes, respectively [107]. The therapeutic range was expanded with entecavir ester prodrugs. Compared to entecavir (oral administration, Cmax is 15.4 ng/mL and $T_{1/2}$ is 4.09), the plasma drug concentration of the entecavir prodrug after subcutaneous injection in beagle dogs was much prolonged ($T_{1/2}$ of 129.3 hr.) and had a lower maximum plasma concentration (Cmax is 4.7 ng/mL) [108]. Hydroxychloroquine, a prodrug of chloroquine, was shown to be more effective against SARS-CoV-2 infection due to its increased concentration in cells and prolonged elimination $t_{1/2}$ [109].

Changes in AvD Pharmacokinetics Due to Administration Route

Oral administration is now the preferred method of administering AvDs since it is convenient, safe, and economical. Due to their weak solubility and permeability, the oral bioavailability of the majority of AvDs was, nevertheless, unsatisfactory. To enhance the effectiveness of AvDs, it was crucial to choose the proper administration route in accordance with the therapeutic requirements and safety evaluation [110].

Spray-dried excipient particles in ribavirin nasal spray were appropriate for nasal deposition. This technique effectively improved mucosal adherence and penetration. The formulation may be able to use nasal passages as a means of transporting a brain-specific antiviral drug, according to in vivo data that showed the rate of agglutination was greater by approximately of six times than with traditional intravenous delivery [111]. In comparison to oral treatment, intravenous delivery of a suspension of adefovir raised the AUC by 5.45-fold as obtained by Dodiya et al [63]. Entecavir was administered subcutaneously to beagle dogs, and this prolonged the Cmax (4.70 ng/ mL) and extended the $t_{1/2}$ value (129.30 h) in comparison to oral administration (15.40 ng/ mL, 4.1) [108].

When acyclovir solution was administered intravenously, the Cmax was 90 times greater (26.23 g/mL) and the Tmax was much shorter (only 8.00 min) than when acyclovir suspension was administered orally (Cmax was 0.29 g/mL and Tmax was 26.00 min) [112]. There were 1.50- and 2.26-fold AUC increases after intravenous administration of oseltamivir solution [113] or peramivir solution compared to oral treatment [114].

Conclusion

The most important challenge that faced the researchers in their attempts to develop an effective treatment is the solubility that affect the bioavailability and also affect drug activity especially for drugs intended to be administered orally which should be absorbed efficiently and for that issue several approaches were used to improve drug solubility. To improve the solubility of medications that are weakly water-soluble, there are several solubility improvement techniques. We discuss a number of techniques in this overview, each having advantages and disadvantages. Here, we have simply provided a basic explanation of the procedures; further investigation of each method is necessary.

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