REVIEW ARTICLE

Applications of Novel Drug Delivery Systems for Enhancement Bioavailability of Antiretrovirals with Special Focus on Nanotechnology

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Abstract

Antiretroviral (ARV) therapy is a chemotherapeutic approach to treat viral infections such as AIDS. Remarkable therapeutic strategies improved the mortality rate in HIV patients. However, the neurocognitive disorders associated with HIV is not helmed properly due to the tight blood-brain barrier that restricts majority of ARVs to enter the brain parenchyma through the cerebral capillary endothelium. Conventional formulations are not adequate to reach these needs in the ARV therapy. Moreover, careful monitoring of pharmacokinetic parameters of the ARV drugs is important to achieve utmost therapeutic efficiency. However, the majority of the drugs are confronting this issue due to their poor aqueous solubility and inappropriate tissue permeability. Diversified nanotechnological and varied accustomed approaches were impended using novel polymers (both natural and synthetic) to ameliorate these pharmacokinetic constraints. Ample literature is available about the nanotechnological approaches allude to the development in the field for the enhancement of oral bioavailability, potency with less side effects. Nanotechnological cherishment also helps to control drug resistance and drug abuse. Making sub-micron level drug particles of poor water-soluble ARV drugs revamp the oral bioavailability by amplified surface area, improved interfacial tension at drug and solvent interface. The permeability issues are abolished by tailoring physical structure of the drug particle. Stability in the gastric environment, bypassing the early hepatic metabolism of ARV drugs also can be conquered with nanotechnological contrivances. Among all, nanocarrier, nano vesicular drug delivery system are well-crammed techniques. This review enumerates a detailed picture of bioavailability enhancement techniques for ARV drugs through nanotechnological advents.

Keywords: Nanotechnology, Bioavailability enhancement, Nanoparticles, Antiretroviral therapy, AIDS, HIV

INTRODUCTION

Microbial infections are one of the prime concerns in the community health. Among all, treating viral infections is a big challenge to healthcare professionals because of its mutation rate and genetic diversity. The development of antiviral drugs is a complicated task.

From the decades technical and scientific advancements have been contributed to the discovery of around fifty antiviral drugs for human use to combat viruses such as Hepatitis-B and C viruses, Human Immunodeficiency virus, Herpes simplex virus, Influenza virus. However, prolonged utilization of antiviral drugs concentrated the therapeutic effectiveness. Numerous paradigmatic approaches have been attempted to improve the efficacy of the drugs such as nanotechnology.[1]

Drug delivery through the oral route is always the primary choice to the other drug delivery systems. In practice, more than 40 percentage of the new drug candidates conk out in the R and D due to their biopharmaceutical constraints. The drugs with inadequate absorption are

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Received: 09-06-2021
Revised: 02-11-2021
Accepted: 05-12-2021

ineffective to elicit the desired therapeutic potential because of poor bioavailability and cause to sub-optimal drug delivery.[2,3] Poor availability may be due to poor solubility or less permeability through lipid membrane or first pass metabolism or through efflux mechanism or degradation in gut environment.[4] Variousnovel drug delivery systems have been employed to improve bioavailability through oral drug delivery of poor water soluble drugs.[5]

Alteration of poor water soluble drugs at nano level renders the pharmacokinetic benefits.[6] Nanodelivery systems such as liposomes, polymeric-Nanoparticles, solid-lipid Nanoparticles, hybrid-Nanoparticles, dendrimers, nano-emulsions, micellar systems, and self-assembled nanostructures, have been offered for antiviral drugs.[7]

REASONS FOR POOR BIOAVAILABILITY OF DRUGS

Since gastric environment is aqueous in nature, the drug needs to be soluble and fail to do so will affect the absorption parameters. This is the first check point to be considered for assessing bioavailability of a drug candidate for oral drug delivery.[8] The drug with low partition coefficient will have low permeability across the gastric lining and thus decreases the oral bioavailability. If a drug is metabolized by the liver before entering to the systemic circulation, it is called as hepatic first-pass metabolism. Liver enzymes such as CYP3A type are the enzyme that interacts with most of the drug candidates. First pass metabolism is a significant parameter for oral drug bioavailability than others. Similarly pumping out the drug through efflux mechanism through P-glycoproteins also will reduce the bioavailability.[9] Many retroviral drugs are sensitive to gastric low pH and gut enzymes. Chemical transformations such as hydrolysis, dehydration, isomerization and racemization, elimination and oxidation of the API, or interactions with excipients will reduce the bioavailablity.[10] Enzymes such as peptidase, protease, and esterase may degrade the orally administered drugs. Interaction of the food with drugs through enzymatic or metabolic modification and quick gastric emptying rate also affect the absorption [Figure 1].[11]

Blood-brain barrier (BBB) is a major check point that blocks the majority of the drugs that try to enter the brain through these tight junctions. Various advancements have been adopted to improve the availability of the drugs in the central nervous system (CNS) including non-invasive and invasive methods such as intranasal delivery and direct intra-ventricular or intra-cerebral injection/implantation, infusion respectively; provisional disruption of the BBB is also another technique to improve the bioavailability of the RAVs in the brain.[12]

BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS) CLASSIFICATION

BCS is used for easy classification of drug substance based on their water solubility and gastric permeability to assess the pharmacokinetics. Drugs can be categorized into Class-1 to Class-4 based on their solubility and permeability. The drugs having more solubility and more permeability can be categorized as Class-I; low solubility and more permeability are Class-II; high solubility and low permeability are Class-III; low solubility and low permeability are Class-IV as described in Figure 2.[13]

METHODS FOR THE IMPROVEMENT OF BIOAVAILABILITY

Numerous methods have been adopted to increase the bioavailability of poor water-soluble antiretroviral (ARV) drugs that are described below [Figure 3].

Enhancement of solubility and dissolution rate

Solubility and dissolution rate can be improved by physical methods like size reduction through nanonization and micronization or modifying polymorphism or by making solid dispersion or inclusion complexes. Chemical modifications such as altering the system pH or by converting into suitable salts are also preferred for retroviral drugs.[14,15]

Formulation-based approaches such as co-crystallization techniques were successfully employed for acyclovir to improve the solubility.[16] Co-solvency methods for

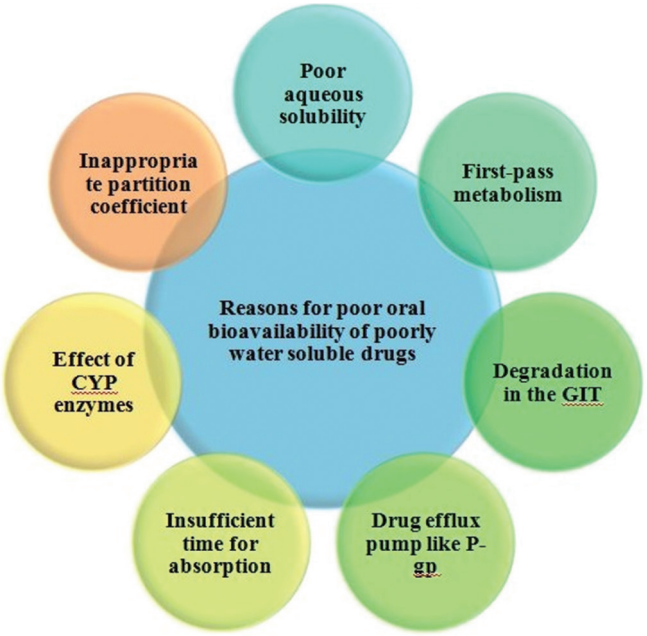

Figure 1: Reasons for poor oral bioavailability of poorly water soluble drugs

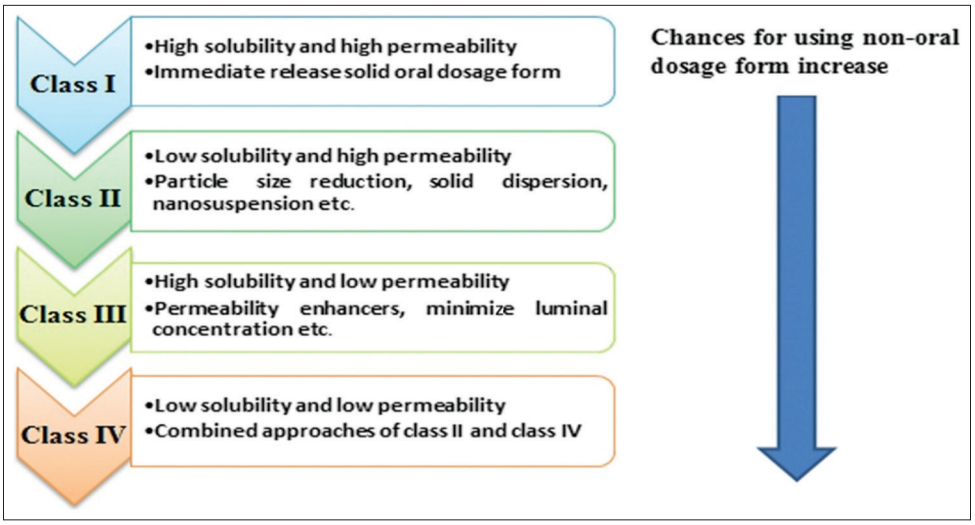

Figure 2: Biopharmaceutical classification system and its application in design of oral dosage forms

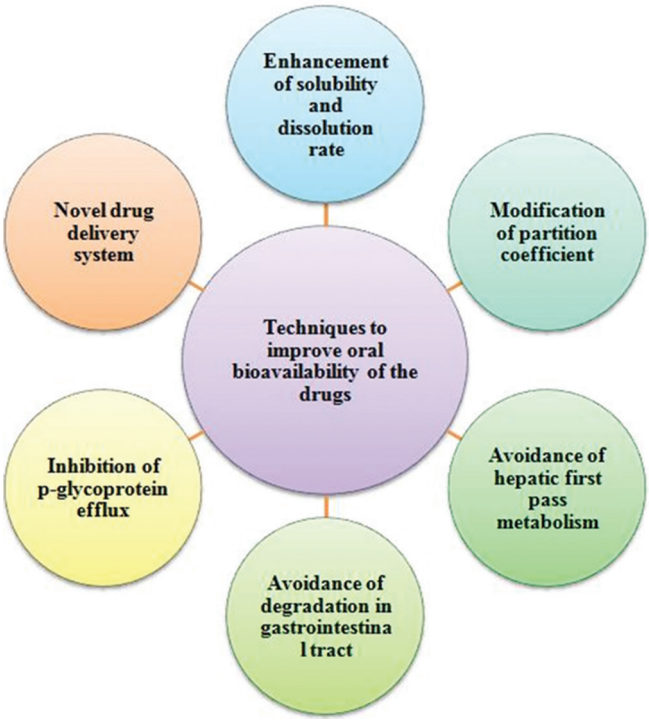

Figure 3: Techniques to improve oral bioavailability of drugs

Efavirenz were developed by Subramaneswari *et al*. and reported to have better dissolution properties.[17] Hydrotropic methods, addition of solubilizing agents and ultra-rapid freeze technology were also reported to show improved bioavailability of the formulations. Porous microparticles technology employed for gold for influenza infections was successfully documented by Kim *et al*.[18]

Alteration of partition coefficient

Partition coefficient is also an important phenomenon for the oral bioavailability. Esterification is one of the ways to improve the oral bioavailability of ARV drugs. Gancyclovir, Cidofovir, Cyclopropavir, Lopinavir, and Amprinavir are few antiviral agents that are successfully modified as prodrugs for better bioavailability through increased partition coefficient.[19-22]

Eschewing of first-pass metabolism

This can be achieved by co-administration of another drug which will inhibit the hepatic enzymes with the original drug. Bioavailability of Ritonavir is increased significantly with a combination of low dose of Lopinavir which is CYP enzyme inhibitor.[23] Making for Valacyclovir and valganciclovir through esterification using valine and tyrosine linked to Cidofovir prodrugs by the National Institute of Health are also a good strategy to improve their oral bioavailability.[24]

Averting of degradation by gut environment

Enteric coating is a renowned strategy to avoid degradation in the stomach. Similarly, gastro-retentive drug delivery systems such as magnetic field aided system, swelling system (plug type), mucoadhesion method, floating system with or without effervescence were developed by increasing the gastric residence time to prevent the degradation in the intestine.[25-27] In case colon targeted drug delivery, pH, pressure, bacterial, and time-based approaches were adopted.[28]

Inhibition of P-glycoprotein efflux

P-gp inhibitors and surfactants like Kolliphor TPGS and Soluplus are reported to increase the intestinal absorption of Darunavir and enhanced bioavailability through solid dispersion method.[29-31]

Novel drug delivery system

Nanosuspensions[33]

Particles in nano size (<200 nm) are having more surface area that is responsible for high dissolution rate and subsequently improve the bioavailability.[31] If nanoparticles are prepared from suspension they are known as nanosuspensions. Methods such as top-down, bottom-up, or combinative techniques were developed to prepare nanosuspensions [Table 1]. High shear forces will be applied to generate nano size particles in top-down method using ball mill, stirred media mill, and high-pressure homogenizer are widely used in the top-down technique. Whereas the liquid anti-solvent precipitation technique is an easy method in bottom-up technique. Few modifications are made by replacing the solvents with supercritical fluids. In case of low melting point compounds, melt emulsification is a better choice. A blend of both the top-down and bottom-up techniques is called the combination method.[32]

Microemulsion

These are bicontinuous systems having water and oil interfaced by a surfactant that are thermodynamically stable. Microemulsions can be prepared by phase inversion method and phase titration method [Table 2]. By the addition excess dispersed phase one can change the particle size of the emulsion. In case of non-ionic surfactants, thermal differences are generally applied to make the phase inversion. Similarly, sudden shift of pH or salt concentration also used for making phase inversion to create microemulsion. In phase titration method one of the phase will be added to dilute the emulsion and for the subsequent formation of microemulsion. Ternary phase diagrams are used to assess the formation.[36]

Nanoemulsion

Nanoemulsions are nano sized (50–1000 nm) particles, formed by dispersing the phases with the help of shear forces and surfactants. Comparatively, nanoemulsions are stable than microemulsions. They are extensively used for lipophillic drug molecules, which are solubilized in the oil phase of the emulsion. High and low energy methods are used to produce nanoemulsions. Preparation of nanoemulsions is comparatively easy and convenient. Detailed methods are described in [Table 3].[39]

Nanocrystals

These are pure drug particles that are dispersed as a colloidal system in nanoscale level with the help of surfactants. Nanocrystals are also prepared similar to nanosuspension methods such as top-down, bottom-up, and combination

Table 1: Methods of preparation for Nanosuspensions

Method	Techniques	Advantages	Disadvantages	Examples
A. Top-down	Highpressure homogenization Nanoedge Nanopure Nanojet Mediamilling (Nanocrystals) Dry-co-grinding	• Cost-effective • Simple • Exhibits better reproducibility • Increased dissolution rate and saturation solubility forhydrophobic drugs	• Physical stability is less • Sedimentation and compaction rate is high • Dosage issues	• Rilpivirine • Atazanavir • Ritonavir • Efavirenz[34,35]
B. Bottom-up	Precipitation Supercritical fluid process Emulsification-solvent Solvent evaporation Meltemulsification method Lipid emulsion/microemulsion template			
Combination method	Combination of A and B			

Table 2: Methods of preparation of Microemulsions

Method	Advantages	Disadvantages	Examples
A. Phase inversion B. Phase titration	• Thermodynamically stable • Act as super solvents • Reservoir for both hydrophilic and lipophilic type drugs • Can follow pseudo-zero-order kinetics • Easy to prepare • Improve the efficacy • Reversible	• Practically huge concentration of surfactant and co-surfactant are needed • Restricted solubillity for high-melting substances • Influenced by pH and temperature	• Penciclovir • Acyclovir[37,38]

Table 3: Nanoemulsions method of preparations

Method		Advantages	Disadvantages	Examples
A. High energy methods	High-pressure homogenization Microfluidization Ultrasonication	• Suitable for dissolving lipophilic drugs • Optically transparent • Stable than microemulsions • Efficient perrmeability	• Practically huge concentration of surfactant and co-surfactant are needed • restricted solubillity for high-melting substances • Influenced by pH and temperature	• Indinavir • Lamivudine • Saquinavir • Acyclovir[40]
B. Low energy methods	Phase inversion emulsification method • Transitional phase inversion - Phase inversion temperature - Phase inversion composition • Catastrophic phase inversion - Emulsion inversion point			
	The self-nanoemulsification method			

technologies. Bottom-up method is comparatively low energy consuming technique and also suitable for the majority of the poor water-soluble drugs. Large surface area, increased saturation solubility, increased cellular adhesion, and improved dissolution rate will enhance the bioavailability of the oral drugs. The drug properties also can be tailored to escape the degradation in gastric environment.[41] Cabotegravir, dolutegravir, 5-Chloro-3-phenylsulfonylindole-2-carboxamide.[42,43]

Mesoporous silica nanoparticles (MSNs)

MSNs are the recent advancement in the new drug delivery approaches. They absorb the drug molecules into their honey-like pores and capable of loading relatively high amount of drug with heat resistance and release control. Since silica is the chief component of the MSNs, they are having less bio-incompatibility issues.[44] Ritonavir MSNs is an example for the enhancement of bioavailablity through improved dissolution rate.[45]

Self micro emulsifying drug delivery system

These are O/W type emulsions that are formulated as an anhydrous mixture of oil, surfactant, and drug which will convert into nanoemulsion after introduced into the digestive tract (aqueous phase). The emulsion is formed not with the chemical techniques but with mechanical means (peristaltic movements). This is an in-situ preparation method that provides more cell permeability, stability, and enhanced oral bioavailability.[46] Self-micro emulsifying drug delivery system was successfully applied for Ritonavir, Saquinavir, Darunavir for better oral bioavailability.[47,48]

Nano carrier system

Solid lipid nanoparticles

Solid lipid nanoparticles are spherical colloidal carriers (10–1000 nm) that are produced by dispersing lipid materials (mostly physiological lipids such as glycerides) into the aqueous phase with the help of a surfactant. They are the manipulated nano-structured lipid carriers. They are extensively useful for water-insoluble drugs with controlled and targeted drug delivery. Solid lipid nanoparticles are practically safe, more drug loading capacity, physical and thermal stability. The preparation techniques are near to the nanosuspensions with slight modifications.[49] Tenofovir, Ritonavir, Darunavir, Efavirenz, and Nevirapine were modified into solid lipid nanoparticles with increased bioavailability for better ARV therapy.[50-53]

Polymeric nanoparticles

These are the nanoscale colloidal preparations that are adsorbed or encapsulated within a polymer substance that is widely used in the nanotechnology-based drug delivery. Polymeric nanoparticles can be prepared by broadly two methods namely, polymerization (of monomer) based method and preformed polymers. The method of preparations can be selected based on the physical and chemical parameters of the drug and can be achieved either through one-step process where emulsification is skipped and two-step process where the emulsification and subsequent nanoparticles formation.[54] Efavirenz, lopinavir, Lamivudine, Saquinavir, Stavudine, delavirdine, Indinavir, Zidovudine, and azidothymidine (AZT) modified polymeric nanoparticles for ARV therapy for targeted and sustained release. These modifications gave a better efficacy, potency, with less drug resistance, toxicity, and unwanted effects.[55]

Dendrimers

Dendrimers are the monodispersed three dimensional polymeric nano-carrier (1–100 nm) systems that are having well-defined geometric definitions. It is a well-tailored arrangement of the polymer not a compound. It is composed of a core, inner and outer shell which gives an encapsulating property. Dendrimers will enhance the half life. Unimolecular micellar nature of Dendrimeric conjugated drugs will have more aqueous solubility and increased oral bioavailability. They are synthesized by a structure controlled divergent or convergent methods.[56] Dendritic modifications of Efavirenz, Saquinavir, and tenofovir are reported to have increased water solubility and improved oral bioavailability.[57,58]

Polymeric micells

As the name indicates, they are amphiphillic polymers that are self dispersed into spherical carriers in the aqueous phase. propylene oxide and ethylene oxide are the block copolymers

used along with Polaxamers to enhance the aqueous solubility. They are prepared by direct dissolution method and precipitation method. In the first method, suitable solvent is taken and the polymer is solubilized followed by dialysis. In the second method, a solvent is selected in such a way that it will precipitate on the block polymer. Finally, it leads to the formation of a micelle with hydrophobic core that is to attract the lipophilic drug and hydrophilic surface.[59] Efavirenz and darunavir are the ARV drugs for HIV treatment that are having more circulation half life, increased oral bioavailability, and cellular uptake.[60]

Carbon nanotubes

They are the most useful nanotechnological advancement that are having diversified applications. They are made up of grapheme sheets with excellent surface area, chemical stability which can be the carriers (<2 mn in core diameter) to various drug categories with improved pharmacokinetics. These carbon nanotubes are produced by Arc-Discharge method, Laser Ablation method, and Chemical Vapor Deposition method followed by the purification process.[61]

Nanoparticles composed of chitosan and chitosan derivatives are proved to open the tight junctions temporarily that allows the drug to enter the brain parenchyma especially in the nose to brain nanoformulations; Quetiapine chitosan nanoparticle system is a good example. Poly l-Lactide-co-Glycolide (PLGA) Nanoparticles are a biodegradable polymer that is also having similar advantages such as chitosan-based nanoparticles.[62]

Vesicular delivery systems

Liposomes[63]

They are spherical, colloidal vesicles made up of one or more phospholipid bilayers surrounded to aqueous core. Based on the size of the vesicles and number of phospholipid bilayers, this can be classified Multilamellar and Unilamellar. Giant unilamellar, Medium-sized Unilamellar vesicles, Small Unilamellar, Unilamellar, Oligolamellar, and Multilamellar large vesicles. The sizes and types of liposomes are described in [Table 4].

Table 4: Classification of liposomes according to size

Type	Specification
MLV	Multilamellar large vesicles- >0.5 μm
OLV	Oligolamellar vesicles- 0.1–1 μm
UV	Unilamellar vesicles 1 μm
SUV	Small Unilamellar vesicles- 20–100 nm
MUV	Medium sized Unilamellar vesicles
LUV	Large Unilamellar vesicles- >100
GUV	Giant Unilamellar vesicles- >1 μm
MV	Multivesicular vesicles- 1 μm

The principle of enhancing the bioavailability through liposomes was proven with the ARV candidate AZT. The average oral capsule bioavailability of AZT is 65% due to the extensive first-pass metabolism. Larger doses 200 mg are required to maintain therapeutic concentration. Such, larger doses of blood levels exceed toxic levels, decreases granulocytes and anemia. But AZT liposomes formulated by solvent evaporation method enhance the area under the curve (AUC) from 0.62 ng.h/ml to 14.52 ng.h./ml by parenteral route as it is increasing their half life and eliminate the adverse effects.[64]

Niosomes

Niosomes are synthetic non-ionic surfactant vesicles that are extensively used to maintain desired concentration at the target for longer duration. Similar to liposomes niosomes are also formed by self assembly of monomeric polymer substances. However, niosomes are comparatively more flexible chemical and physical characters. Method of preparations is also non-expensive and convenient.[65] Zidovudine Nevirapine is the antiviral drugs that are modified as niosomes for better bioavailability.[66-67]

Pro-vesicular drug delivery

To improve the stability problems in the vesicular drug delivery system, few modifications are made as Proliposomes and proniosomes with comparatively better stability and drug loading capacity. Tenofovir is an example of enhanced therapeutic effect in anti-HIV therapy.[68-69]

NANO APPROACHES FOR NEURO HIV PATHOGENESIS[70]

A blend of varied combinations of techniques has been adopted to suppress all types of viral replications. To conquer the obstacles in CNS delivery, much advancements have been implemented successfully to reach the desired bioavailability in the brain. Few strategies have been listed below that improve drug delivery to the brain. Although some of approaches were developed toward this anatomical site through penetrating across the BBB such as the ATP-binding cassette transporters blocking approach, The BBB opening approach for navigation of drug to the brain and Prodrug based approaches. However, the problems encountered with this technique is toxicity, low efficacy, seizures, neurological abnormalities, and entry of peripheral viral particles into the brain through BBB. However, few nano technology-based approaches shows promising and efficacious. They are all as follows:

Magnetic nanoformulations for neuroAIDS treatment

Super-paramagnetic property of these magnetic nanoformulations can have extended speed and control

over site of delivery through invasive magnetic force. The ARVs can be attached to magnetic nanoparticles for better bioavailability.

Polymeric NCs for ARV delivery

Polymer based nanocarrier system is a renowned strategy in the nanotechnology-based ARV delivery. Zidovudine, Lamivudine, and stavudine nanoparticles were developed using polymers such as Poly (butyl cyanoacrylate) and methylmethacrylate-sulfopropylmethacrylate with improved permeability more than 10 folds through BBB. Similarly, stavudine, delavirdine, and saquinavir solid lipid nanoparticles were prepared using cocoa butter and tripalmitin to increase the permeability across BBB. Recently, zidovudine, lamivudine nanoformulations were developed using PLGA and polylactide that enhanced the bioavailability by more than 1.2 times intranasally.

Dendrimer based BBB ARV delivery

Mannose-capped poly (propyleneimine) and polyamidoamine dendrimers loaded with lamivudine were the successful candidates to increase the cellular uptake by more than 20 times. Tuftsin is a natural polymer that is used to conjugate efavirenz to increase the efficiency and selectivity of the drug.

Micelle-based NCs and ARV delivery

Pluronic micelles (ex. Pluronic P85) are successful micelle-based nanocarriers with increased BBB permeability. ARVs such as zidovudine, nelfinavir, and lamivudine are reported to increase the permeability through tight junctions of BBB by the *In vitro* and *In vivo* experiments. However, low drug dissociation rate limits its application clinically.

Lipid-based NCs for the brain delivery

Cationic, anionic, sterically stabilized and immune-liposomes are widely studies for their applications in ARV therapy. ARVs such as 2′,3′-dideoxycytidine-5′-triphosphate, zidovudine, didanosine, and zalcitabine can be successfully adopted to nanotechnology-based formulations using suitable polymers.

Polymers play a key role in the improving bioavailability of the drugs, especially in ARVs. Natural polymers such as Chitosan, alginate, squalene, carrageenan, pullulan, cellulose, pectin, collagen, starch, and dextran are the few polysaccharide-based natural polymers whereas silk, casein, gliadin are the protein-based natural polymers that are successfully adopted to nanotechnological formulations.[71] They are having advantages such as target specificity, stability, and biocompatibility which make them renowned in the nanoformulations.

Synthetic polymers such as PLGA, PHIC, Eudragit RL 100, PHCA, PMAA, poloxamer 388, and PCL; tuftsindendrimers and mannosylated dendrimer; cyclodextrins were used for the improvement of bioavailability of ARVs in ARV therapy.[72]

CONCLUSION

It is well known that, treating viral infections is always a challenge owing to their tricky methods of infection. This review summarized various aspects of reasons for the poor oral bioavailability and methods for subduing these hassles. Majority of the drug candidates generated with the help of combinatorial chemistry, high throughput screening, and other drug discovery approaches are facing solubility issues leading to poor bioavailability. This is the major hurdle for any drug candidate, to elicit desired therapeutic effect. This review also illustrates various nanotechnological approaches and conventional modification techniques currently in the practice for the enhancement of oral bioavailability, with special emphasis on ARV drugs. In the way of developing various methods, flaws that are identified in one technique is modified and advanced for the development of another novel technique. In the future, much more advancements are anticipated for enhancing oral bioavailability, especially for ARVs.

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Source of Support: Nil. **Conflicts of Interest:** None declared.