

RECENT ADVANCEMENT IN NANOTECHNOLOGY -BASED DRUG DELIVERY SYSTEM AGAINST VIRAL INFECTIONS: A REVIEW

Vaishnavi Navanath Sarade^{*1}, Meera Deokar^{*2}

^{*1}Student, Late Laxmibai Phadtare College Of Pharmacy, Kalamb, India.

^{*2}Assistant Professor, Late Laxmibai Phadtare College Of Pharmacy, Kalamb, India.

ABSTRACT

In the last few decades the exponential rise in the incidence of viral infections sets a global health emergency across world. Further, inappropriate pharmacodynamic physicochemical and biological parameter such as low aqueous solubility ,poor permeability ,high affinity for plasm proteins, short biological half-lives, and fast elimination from the systemic circulation are the major critical factors that govern the suboptimal drug concentration at the target site that leads to the development of drug resistance. To address this issue nanotechnology-based drug delivery approach is emerged as an altering method to attain the optimal drug concentration at the target site for a prolonged period by integrating the nanoengineering tools inthe synthesis of nanoparticles. However, size, shape, charge, and surface topology of nanoparticles are the greater influential factors that determine target-specific drug delivery, optimum cellular uptake, degree of opsonization by the host immune cells, drug retention time, transcytosis, the extension of biological half-life in vivo stability, and cytotoxicity. The review will enlighten the elaborative role of nanotechnology-based drug delivery and the major challenging aspectof clinical safety and efficacy.

Key Words: antiviral, organic and inorganic nanocarrier system, pharmacokinetics, targeted delivery, therapeutic nanoparticles.

I. INTRODUCTION

In the last few decades, epidemiologic studies reveal the emerging incidences of viral infections have significantly increased worldwide. In the last few decades, epidemiologic studies reveal the emerging incidences of viral infections have significantly increased. lack of antiviral therapies for measles, rubella, chickenpox/shingles, SARS- Co V, MERS-Co V, chikungunya virus, Ebola virus, and Zika virus was successively exemplified in the twenty-first century .[1] The major antiviral drug regimen consists of remdesivir, oseltamivir, zidovudine, zalcitabine, stavudine, abacavir, nelfinavir, ritonavir, efavirenz, etc., which have been used in routine practice for the treatment of various viral infections. However, inappropriate physicochemical and biopharmaceutical parameters like poor aqueous solubility, sub-optimized plasma drug concentration at the target site/low bioavailability, less drug residence time in plasma/shorter half-life, poor permeability, and undesirable side effects restrict their full-fledged clinical utility in the treatment against viral infections. Example [2] Besides, drugs like nevirapine, delavirdine, efavirenz, and etravirine belong to the family of nonnucleoside reverses transcriptase inhibitors (NNRTIs) used in the treatment of HIV which possess poor oral bioavailability that limits their constant therapeutic concentration at the target site.

Adherence to the patient treatment a high dose burden of therapeutics such as fosamprenavir 1400 mg twice daily, nelfinavir 1250 mg twice daily (10 tablets daily), and amprenavir 1200 mg three times daily (16 tablets daily) remain in the routine

practice.[3] Addressing such issues, nanotechnology-based drug delivery is emerging as an alternative approach for improving the therapeutic efficiency by altering the physicochemical properties of the antiviral drugs. Tracking the effectiveness and safety profile, there are still many critical aspects like immunogenicity, target specificity, and compatibility in the biological environment that are

closely associated with the nanotechnology-integrated nanomedicines. In contrast, viruses have been armed with a different strategy to evade humoral and cellular immune responses for about millions of years of evolution [4]Viral physiochemical features that include size, shape, hydrophobicity, and surface charge define many of these stealth activities.

Table .1 - Physicochemical Properties Some of the Antiviral Therapeutic Agents

Sl. no.	Name of the drug	Dose	Aqueous solubility	Half-life	Bioavailability	Reference
	Oseltamivir	75 mg orally once daily	10 mg/ml	6–10 h	4 to 17%	[3]
	Remdesivir	200 mg on day 1	2.17 mg/mL	0.89 h	–	[4]
	Stavudine	40 mg twice daily	83 mg/mL	1.3–1.4 h	68–104%	[5]
	Zalcitabine	0.750 mg every 12 h	2 mg/ml	2 h	70–80%	[6]
	Zidovudine	600 mg/day	28.90 mg/mL	0.5–3 h	64%	[7]
	Abacavir	600 mg daily	77 mg/mL	0.8–1.5 h	83%	[8]
	Nelfinavir	1250 mg orally twice a day	0.00201 mg/mL	3.5–5 h	40–80%	[9]
	Ritonavir	100 mg once daily	0.1 mg/ml	3–5 h	60 to 80%	[10]
	Efavirenz	300 mg orally	less than 10 mg/L	52–76 h	40–45%	[11]
	Delavirdine	400 mg orally 3 times a day	0.086 mg/mL	5.8 h	85%	[12]
	Etravirine	200 mg orally twice a day	0.07 mg / ml	40 h	33–37%	[13]
	Amprenavir	1200 mg twice daily	0.5 mg/ml	7.7 h	> 70%	[14]
	Acyclovir	400 mg every 12 h	1.2 to 1.6 mg/mL	2.9 h	10–20%	[15]
	Ganciclovir	1.25 mg/kg IV day	4.3 mg/mL	2–6 h	8.5%	[16]
	Valganciclovir	900 mg twice daily	70 mg/mL	18 h	60%	[17]
	Lamivudine	300 mg orally once daily	276.08 mg/mL	5–7 h	86%	[18]
	Adefovir	10 mg orally daily	0.4 mg/mL	10.2 h	59%	[19]
	Telbivudine	600 mg orally every 48 h	> 20 mg/mL	14 h	68%	[20]
	Entecavir	0.5 mg orally once daily	2.4 mg/mL	15 h	At least 70%	[21]
	Tenofovir	8 mg/kg orally once a day	13.4 mg/mL	17 h	25%	[22]
Sl. no.	Name of the drug	Dose	Aqueous solubility	Half-life	Bioavailability	Reference
	Emtricitabine	200 mg once daily orally	112 mg/mL	10 h	80%	[23]
	Atazanavir	300 mg once daily orally	4–5 mg/ml	6.74 h	60–68%	[24]
	Lopinavir	400 mg twice daily	~ 5 µg/mL	5–6 h	~ 25%	[25]
	Saquinavir	1000 mg twice daily	2.22 mg/mL	4.3–10.9 h	~ 4%	[26]
	Zanamivir	10 mg inhaled once daily	5 mg/ml	2.5–5.1 h	1–5%	[27]

VIRUS: NATURE'S MOST DELICATE NANOPARTICLE

A virus is the microscopic particulate of dimensions ranging from 1 to 100 nm that fuses directly at the plasma membrane followed by various endocytic processes such as clathrin-mediated endocytosis, caveolin-mediated endocytosis, macropinocytosis, and phagocytosis that reach intracellular compartments. After successful internalization of viral components (both enveloped and non-enveloped), it alters the cellular environmental factors, like pH, connection with a target cell, or the activity of proteolytic enzymes, that causes a conformational change in specific proteins that manipulate the host immune responses. The inherent biomimicry tendency of the invading virus inhibits the host cellular immune factors by molecular hijacking or by altering the post-translational modification. Viruses such as mimiviruses with a larger diameter of ~ 760 nm are invaded through phagocytosis by macrophages, whereas smaller viruses tend to be internalized through

clathrin-mediated endocytosis into cells as mentioned in Fig. Fig.1a1a. Although each virus immune evasion mechanism is different, one of the key factors determining the immune evasion ability of viruses may be the size. Literature suggests that the administration of a single hepatitis B virus (HBV) virion is capable of developing hepatocyte infection in chimpanzees. This could be explained by the endogenous stealth characteristic feature of HBV that escaped from RES. For immune escape, surface charge and hydrophobicity of viral particles are also critical. Cells are more likely to uptake non-ionic particles hydrophobic particles than hydrophilic ones. Positively charged particles have longer circulation times than negatively charged particles, as evidence derived from the pattern

virus's circulation life with its surface charge. Virions' surface charge depends on the environment surrounding them. The surface charge of the viral protein varies according to the isoelectric point of the viral protein, which is regulated by the pH of the environment, from negative to positive. In physiological environments, the bulk of viruses exhibit negatively charged surfaces. Opsonization can be avoided by viruses with negatively charged glycans, leading to escape from phagocytosis. Viruses have several methods to escape from the host immune system; alteration surface protein expression is one of the prime suspects. For example, HBV has a polymerized albumin receptor (PAR) in the pre-S2 region. It has been noticed that the phagocytosis of

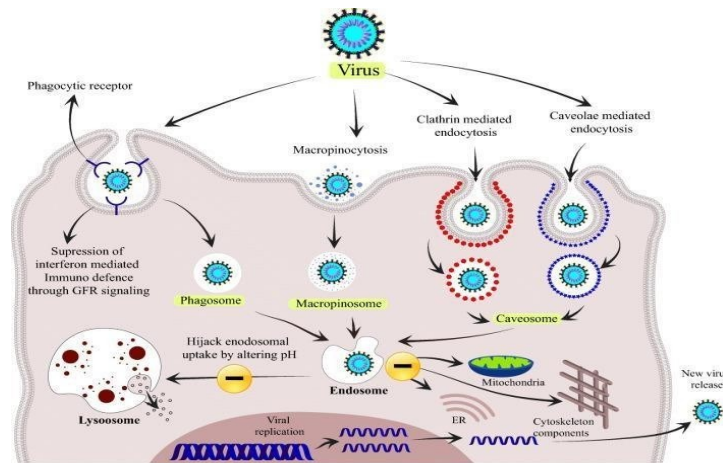


Fig. 1

NPs by Kupffer cells was drastically reduced when NPs were conjugated with peptides containing PAR. Therefore, the recruiting of HSA to the HBV PAR domain (i.e., albumin-coating strategy) could be one of the innovative approaches to encounter the NP clearance, another example citing the surface functionalization of liposome with myristoylated pre-S1(2-47) peptide (for targeting and endosomal escaping activity) and pre-S2(120-129) peptide (for stealth activity) to achieve the efficient in vivo delivery in HBV infection.

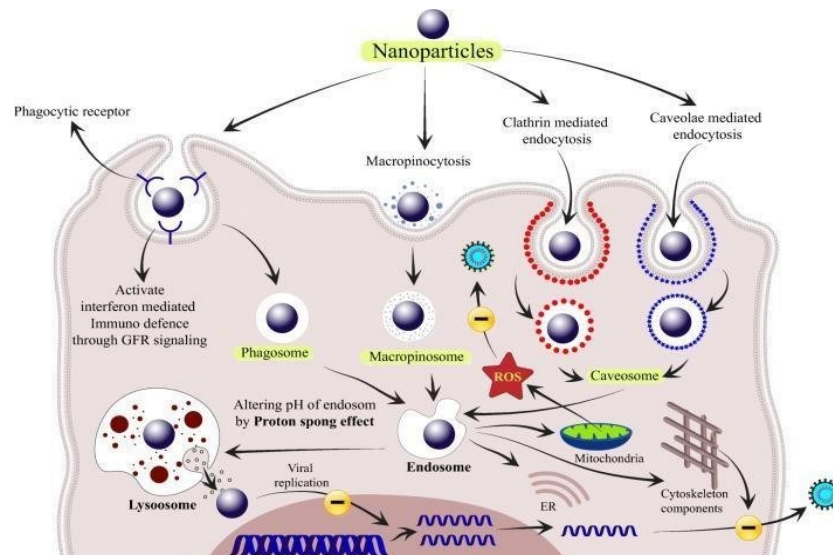


Fig. 2

A Invasion of the virus into the host cell: The various molecular path such as phagocytosis, micropinocytosis, clathrin, and caveola-mediated opt by the virus to enter into the host cell. The bio mimic characteristic feature of the virus enables them to escape from the endosome by altering pH and host cellular immune responses. b Intracellular transport of NPs: NPs opt for a similar mechanism as processed by viral particles. After successive internalization through multiple channel port, NPs are trafficked in the endolysosomal network within the endosomal vesicles triggered by motor proteins and cytoskeleton components. NPs are decorated with stimuli-responsive polymers that modulate the “proton sponge effect” to escape from the endosomal vesicles and safely deliver to the cytoplasmic compartment. The virucidal activity NPs with the free generation of ROS inhibit the DNA/RNA replication

Nanotechnology-Based Drug Delivery System for the Treatment of Viral Infections

As per the Center for Disease Control and Prevention (CDC) guidelines, the appearance of widespread resistance against the strains of influenza A viruses adamantanes (amantadine and rimantadine) a class of antiviral drugs used are not recommended by the physicians in the USA. In addition, antiviral drugs like ganciclovir and valganciclovir (cytomegalovirus), acyclovir (herpes simplex virus), lamivudine, adefovir, telbivudine, entecavir, and tenofovir (hepatitis B virus) show clinical evidence for drug resistance. Nanodimensional configuration with enhanced permeability and retention effect,

increased surface-area-to-volume ratio, ease of surface functionalization for cell targeting, conjugation with biocompatible molecules for prolonged circulation time, etc. are the privileged aspects that make it a promising drug delivery system. Based on the composition, it is broadly divided into organic and inorganic nanocarrier systems (NCs) as described in Fig. 2.

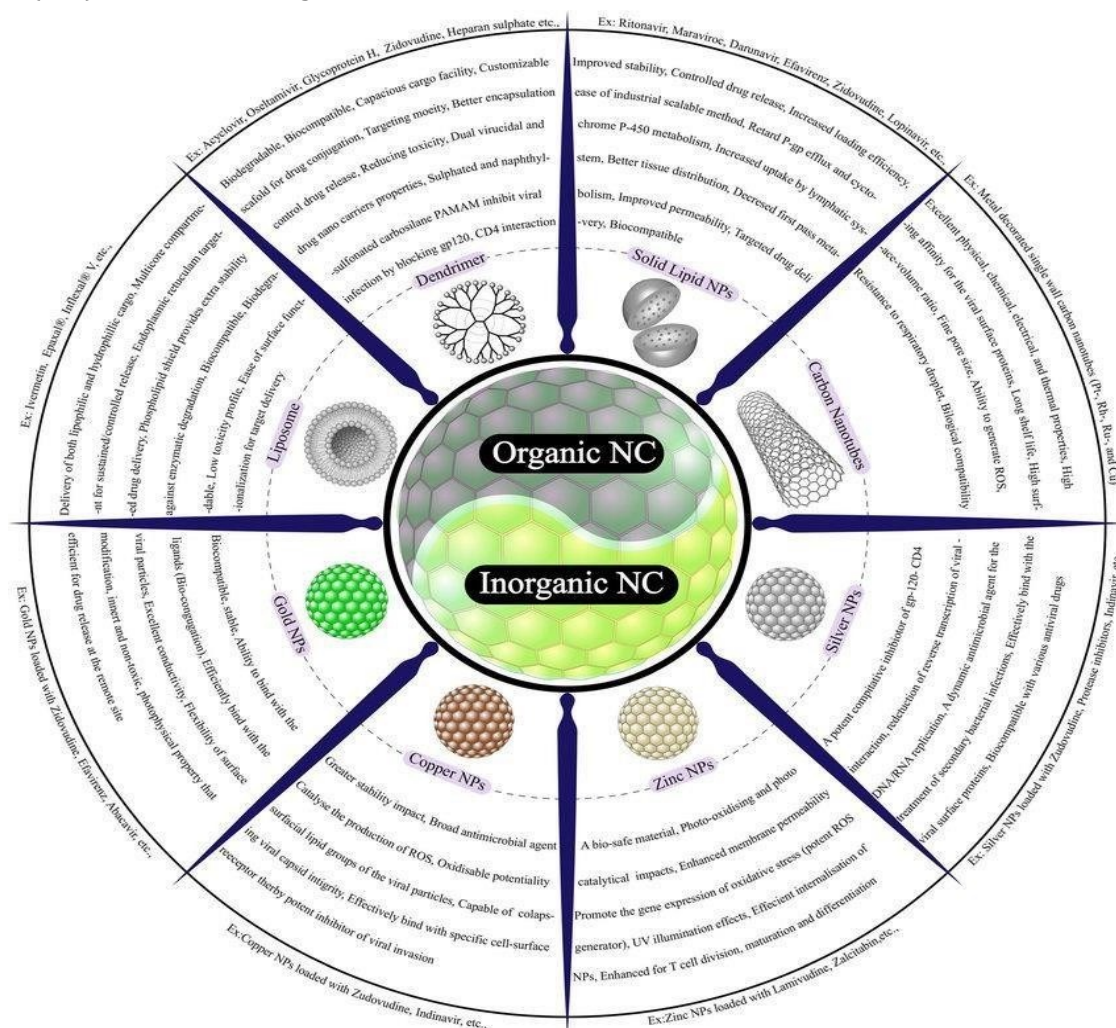


Fig. 3- A schematic diagram elaborate the diversified nanocarrier system in the improvement of physicochemical properties of the antiviral therapeutic agents

Organic NCs consist of liposomes, dendrimers, carbon nanotubes, micelles, microemulsion, polymeric nanoparticles, etc., which are extensively used to improve drug solubility, permeability, and bioavailability of the antiviral drugs as mentioned in Table II.

Further, altering the surface charge and conjugating with the target ligands assist in the cell-targeted drug delivery.

The inorganic NCs include superparamagnetic nanoparticles (iron oxide nanoparticles), quantum dots, and plasmonic nanoparticles (gold and silver nanoparticles) with an average dimension less than organic NCs, i.e., 1–100 nm. Inorganic NCs are widely used to improve the therapeutic efficiency, biodistribution, and pharmacokinetic profiles of the antiviral drugs as mentioned in Table III.

Table 2

Alteration of Physicochemical Parameters of the Antiviral Drugs Formulated with Organic NCs

Drug	Virus type	Nanoplatfor m type	Nanoplatfor m characteristics	Model	Outcomes	Reference
Liposome						
GCV	HSV	PC/CH/NaDC dissolved in chloroform/ diethyl	- Reverse phase evaporation - Sephadex G-	Male and female albino rabbits (2 to ~ 2.5 kg)	-Shows 3.9-fold higher transcorneal permeability than that of the solution	[43]
			50, CH			
					- AUC	
			- Spherical liposomes;		profile shows a 1.7-fold higher concentration time	
					of GAN	
			Sizes (210 ± 17nm)		liposomes compared with the observed	
					solution.	
PIs	HIV	Pegylated	- HSPC, CH, mPEG- DSPE	Human T cell lines HUT78	- Antiviral effect of the F105-LPI1	[44]
				and PM1	is about 20fold	
			- Mean diameter of 100 nm		higher than that of free drug	
Indinavir	HIV	Immunoliposomes	- DPPC, DPPG, DSPE-PEG-MAL, 14C-DPPC - Averaged diameter	- Female C3H mice (18–20 g) and adult male Sprague-Dawley rats (200–250 g)	Drug accumulation (15 days) ↑ up to 126 times in lymph nodes No	[45]
					damage to liver	
			(100 and 120 nm)		and spleen	

Solid lipid nanoparticle						
GCV	CMV	Borneol	- Microemulsion method	Kunming strain mice (17–22 g)	- GAN-SLN enhance drugs to the CNS.	[46]
Drug	Virus type	Nanoplatform type	Nanoplatform characteristics	Model	Outcomes	Reference
			- Particle size (113 and 142 nm) - ζ -potential (– 15.1 and – 18.3 Mv)		- The cumulative % of GAN released from SLNs can be up to 80% in 12 h.	
ATV, PI	HIV	Stearic acid + Poloxamer 188		Immortalized human brain microvessel endothelial cellline (hCMEC/D3)	Initial burst release of drug of approximately 17% by 1 h with a gradual release up to 46% after 24 h	[47]
			- Thin-film hydration technique			
			- Spherical			
			SLNs with a mean diameter of 167 nm, ζ -potential around – 18 mV		- Successive delivery of drug in vitro to human brain endothelial cells	
Penciclovir	HSV, CMV	Lyophilization	- Emulsion technique	Male Wistar rats (200 ± 20 g)	- Amount of penciclovir penetrated into the dermis from SLNs increased by 130%	[48]
			- Poloxamer 188 and Brij 78, EPC, GMS, dichloromethane, Tween 80, and Tween 20		- SLN-based drug was more than 2-fold that of the commercial cream at 12 h.	
Dendrimer						
ACV or TFV	HSV-2	Polyanionic carbosilane	- G1-C8, G1-S4, G3-S16, G2-NF16, G2-S16,	Female BALB/c mice 6–	- ↓DNA polymerase	[49]
		dendrimers	G2STE16, G2-CTE16, and G2-S24P	8 weeks old (20 ± 2 g)	- G1-S4 or G2S16 on topical vaginal or rectal	

					avoid HSV-2	
					transmission	
AZT	HIV	PETIM dendrimer	Methanol, acetonitrile	Albino rats (100–200 g in weight),	- ↓ Hemolytic toxicity	[50]
				Sprague-Dawley strain, 6 to 8 weeks old	- Sustained drug release from dendrimer 6.5 ± 0.3% and 95.8 ± 4.1% is the control drug solution.	
					Application	
					of	
					AZT-dendrimer	
Drug	Virus type	Nanoplatform type	Nanoplatform characteristics	Model	Outcomes	Reference
					shows 4-fold higher after 6 h and 18-fold higher after 12 h.	
Oseltamivir	IV	Carbosilane	Sialyl lactose,	Mardin-Darby	- Shows	
		dendrimers with	dichlorodimethylsilane,	canine kidney	effectiveness	
		hemagglutinin	trichlorosilane,	(MDCK) cell	against human virus	
		binding peptide	dicyclohexylborane		A/PR/8/34 (H1N1)	
					and	
					A/Aichi/2/68	
					(H3N2) with	
					IC50 values of	
					0.60 µm	

Table 3

Size-Dependent Antiviral Activity of Inorganic NCs

Name of nanoparticle	Size (nm)	Virus	Cell line/model	IC50/Expt Conc	Target site for virus inhibition	Reference
Ag NPs	30– 50	HIV-1	HeLa cell	0.44 µg/mL (IC50)	Prevent virus entry	[56]
Ag NPs	10	Feline calicivirus	CRFK cells	50 and 100 µg/mL achieved 5.7 and 6.5 log10 TCID50.	Viral inactivation	[57]

Ag NPs	8–12	Respiratory syncytial virus	A549 epithelial cell	1 mg/mL (Expt. Conc.)	Binding to the surface of the glycoprotein of the virus over the respiratory epithelium	[58]
Ag NPs	25	Monkeypox virus	Vero cells	25 µg/mL	Inhibit early steps of binding and penetration by blocking virus-host cell	[59]
AgNPs-MHC	30	Bacteriophage φX174, murine norovirus, and	MS2, RAW 264.7 cells, A549 cells	2log10 after exposure to 4.6×10^9	Damaging the viral coat protein	[60]
Name of nanoparticle	Size (nm)	Virus	Cell line model	IC₅₀/Expt Conc	Target site for virus inhibition	Reference
		adenovirus serotype 2				
Au NPs using garlic extract	6	Measles virus	Vero cells	EC ₅₀ = 8.8 µg/ml	Inhibit viral infection by blocking viral particles directly	[61]
Au NPs	30	Influenza virus	MDCK cell lines	–	Interact with virus capsid	[62]
Au NPs	10	HIV-1	HeLa-CD4-LTR-B-gal cell	57 to 78 µg/mL	Inhibit HIV-1 fusion	[63]
Au NPs	8–17	Peptide-food-and-mouth disease virus	BALB/c mice	–	Immunogenic property	[64]
ZnO NPs	20–50	H1N1 influenza virus	MDCK-SIAT ₁ cell	Viability ≥ 90% @ 75 µg/mL	Inhibit progeny release	[65]
CuI NPs	160	Influenza A virus	MDCK cells	50% reduction of virus titer @ 17 µg/ml	Inactivation of viral protein	[66]
CuO NPs	40	Herpes simplex 1	Vero cell	83% of viral load	Interfere with the viral replication	[

Organic Nanocarriers

Liposomes

Liposomes are the self-assembled spherical vesicle with a diameter range from 10 to 1000 nm enclosed by a phospholipid bilayer with a central aqueous core. Depending upon the number of a phospholipid bilayer (lamellar), liposomes further divided into small unilamellar (20–100 nm), large unilamellar (100–500 nm), and multilamellar (500–5000 nm). Different types of lipids such as phosphatidylcholine, phosphatidylserine, dioleoyl dimethyl ammonium bromide/chloride (DODAB/C), dioleoyl trimethylammonium propane (DOTAP), 1-

stearoyl-2-linoleoyl-sn-glycerol-3-[phospho-L-serine] (sodium salt), and cholesterol are extensively used in the synthesis of various functional liposomes

Dendrimer

Dendrimers are the symmetrically multibranched arranged core-shell structures. The nanometric dimension, monodispersed, void-assisted cargo facility, controllable release potency, and improved translocation across epithelial and endothelial barriers make them a suitable carrier system for delivery of antiviral therapeutic.

Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are nano-lipid structures with an average diameter of 10–1000 nm considered an alternative colloidal carrier system parallel to liposomes and lipid shell-based nanoparticles. The characteristics of SLNs include high physical strength; excellent biocompatibility; good tolerability; and improved stability, control, and target drug delivery, and safety, and availability decreased toxicity with better drug release profiles for lipophilic and hydrophilic drugs, making the nanocarrier a unique one.

Inorganic Nanocarriers

Silver Nanoparticles

Silver nanoparticles (AgNPs) are known for their broad-spectrum antimicrobial activity against a variety of microorganisms including fungus, bacteria (gram positive and gram negative), and viruses (respiratory syncytial virus, hepatitis B, simplex virus, HIV-1, and retrovirus). The antimicrobial potential of AgNPs is related to their ability to attract an electron from the surrounding; as a result, silver interacts with a wide variety of biomolecules including respiratory enzymes, RNA and DNA, and viral protein which leads to cellular dysfunction and eventually causes microbial death.

Gold Nanoparticles

Gold nanoparticles (AuNPs) owing to their distinct structural and functional properties offer a multiplex platform for the antimicrobial application. With excellent characteristics such as electrical, optical, mechanical, and biological properties, gold nanoparticles (AuNPs) attracted significant interest in the pharmaceutical industries.

Literature evidence reveals AuNPs exhibit broad-spectrum antimicrobial performance against a wide variety of microorganisms including both gram-positive and gram-negative bacteria and viruses such as HIV-1, influenza virus, hepatitis B virus, and herpes simplex virus.

Copper Nanoparticles

Copper nanoparticles (CuO NPs) are a well-known catalytic nature, which has been extensively used to reduce the bacterial and virus population. Literature suggests that increased oxidative stress of Cu²⁺ ion resulted in antiviral potential against all types of the virus such as HIV-1, influenza, and herpes simplex.

Zinc Oxide Nanoparticles

Zinc oxide nanoparticles (ZnO NPs) show strong reducing ability and excellent biocompatibility that have been extensively investigated for different medical conditions especially in the field of antimicrobial, cancer, and anti-inflammatory.

Challenges of NPs/NCs as Nanomedicines

Nanotechnology-based drug delivery system offers improved physicochemical properties of the antiviral drugs with ameliorating the therapeutic responses incorporated with nanotoxicity, instability, and complexity in the scaling-up nanoformulations as mentioned in Fig. 3.

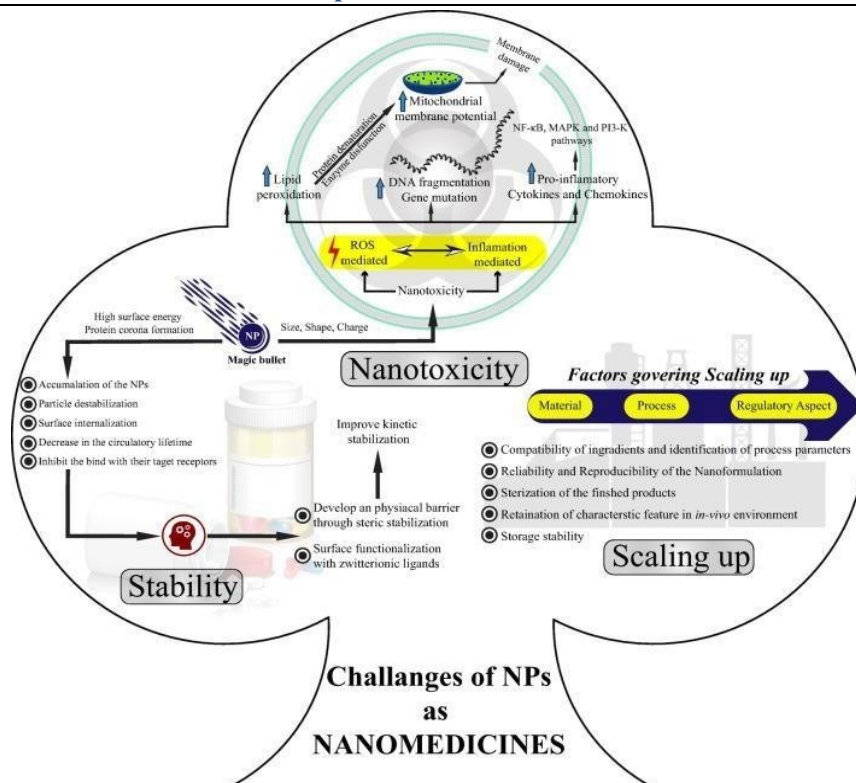


Fig. 4

A diagrammatic overlay on major key challenges in front of nanocarriers/nanoparticles to come out as nanomedicines.

II. CONCLUSION

Recent developments in nanomedicine design and engineering have provided many privileges over the traditional approach of drug administration for the prevention and treatment of viral infections. An ongoing research is rooted against many life-threatening virus infections, and various nanotechnology-enriched NPs such as nanotraps, nanodiamonds, and nanofibers have found their way and can be further applied to other viral infections. The challenges involved in their manufacture and characterization and their large scale processing are among the few obstacles to the production of these advanced types of nanomaterials. In the design of nanomaterials, the question of long-term toxicity and in vivo stability should be given paramount importance. Besides, nanoengineered NPs offer tremendous antiviral therapeutic potential by overwhelming the challenges of therapy resistance, low solubility, and drug bioavailability, erratic drug release, and short retention time of drugs in the plasma, etc. Further research is aimed at achieving a programmable multifunctional NPs of biocompatible and biodegradable nanomaterials to achieve site-specific, simultaneous delivery of multiple drugs and “multiplexing” in a heterogeneous population to enable the treatment of a wide spectrum of viral diseases and related comorbidities.

III. REFERENCES

- [1] Kubin CJ, Hammer SM. Antiretroviral agents. Infectious Diseases [Internet]. Elsevier; 2010 [cited 2020 Dec 2]. p. 1434–53. Available from: <https://linkinghub.elsevier.com/retrieve/pii/B9780323045797001453>
- [2] Best BM, Goicoechea M. Efavirenz--still first-line king? Expert Opin Drug Metab Toxicol. 2008;4:965–72. [PMC free article] [PubMed]
- [3] Usach I, Melis V, Peris J-E. Non-nucleoside reverse transcriptase inhibitors: a review on pharmacokinetics, pharmacodynamics, safety and tolerability. J Int AIDS Soc. 2013;16:1–14. doi: 10.7448/IAS.16.1.18567. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [4] Viani RM. Role of etravirine in the management of treatment-experienced patients with human immunodeficiency virus type 1. HIV AIDS (Auckl). 2010;2: 141–9. [PMC free article] [PubMed]

- [5] Nadler JP, Gathe JC, Pollard RB, Richmond GJ, Liao Q, Griffith S, et al. Twice-daily amprenavir 1200 mg versus amprenavir 600 mg/ritonavir 100 mg, in combination with at least 2 other antiretroviral drugs, in HIV-1-infected patients. *BMC Infect Dis.* 2003;3:10. doi: 10.1186/1471-2334-3-10. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [6] Palma-Aguirre JA, Absalo n-Reyes JA, Novoa-Heckel G, de Lago A, Oliva I, Rodríguez Z, et al. Bioavailability of two oral suspension and two oral tablet formulations of acyclovir 400 mg: two single-dose, open-label, randomized, two-period crossover comparisons in healthy Mexican adult subjects. *Clin Ther.* 2007;29:1146–52. [PubMed]
- [7] Colson P, Raoult D. Fighting viruses with antibiotics: an overlooked path. *Int J Antimicrob Agents.* 2016;48:349–352. doi: 10.1016/j.ijantimicag.2016.07.004. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [8] Zhang Y, Xu C, Zhang H, Liu GD, Xue C, Cao Y. Targeting Hemagglutinin: approaches for broad protection against the influenza A virus. *Viruses.* 2019;11. [PMC free article] [PubMed]
- [9] Schloer S, Goretzko J, Pleschka S, Ludwig S, Rescher U. Combinatory treatment with oseltamivir and itraconazole targeting both virus and host factors in influenza A virus infection. *Viruses.* 2020;12. [PMC free article] [PubMed]
- [10] Tempestilli M, Caputi P, Avataneo V, Notari S, Forini O, Scorzolini L, et al. Pharmacokinetics of remdesivir and GS-441524 in two critically ill patients who recovered from COVID-19. *J Antimicrob Chemother.* 2020;75:2977–80. [PMC free article] [PubMed]
- [11] Rosenbach KA, Allison R, Nadler JP. Daily dosing of highly active antiretroviral therapy. *Clin Infect Dis.* 2002;34:686–692. doi: 10.1086/338255. [PubMed] [CrossRef] [Google Scholar]
- [12] Chaudhary B, Verma S. Preparation and evaluation of novel in situ gels containing acyclovir for the treatment of oral herpes simplex virus infections. *Sci World J.* 2014;2014:1–7. doi: 10.1155/2014/280928. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [13] Vossen MTM, Westerhout EM, So derberg-Naucle r C, Wiertz EJHJ. Viral immune evasion: a masterpiece of evolution. *Immunogenetics.* 2002;54:527– 542. doi: 10.1007/s00251-002-0493-1. [PubMed] [CrossRef] [Google Scholar]
- [14] Buzea C, Pacheco II, Robbie K. Nanomaterials and nanoparticles: sources and toxicity. *Biointerphases.* 2007;2:MR17–MR71. doi: 10.1116/1.2815690. [PubMed] [CrossRef] [Google Scholar]
- [15] Ghigo E, Kartenbeck J, Lien P, Pelkmans L, Capo C, Mege J-L, et al. Ameobal pathogen mimivirus infects macrophages through phagocytosis. Farzan M, editor. *PLoS Pathog.* 2008; 4:e1000087. [PMC free article] [PubMed]
- [16] Tan A, Koh S, Bertoletti A. Immune response in hepatitis B virus infection. *Cold Spring Harb Perspect Med.* 2015;5:a021428. doi: 10.1101/cshperspect.a021428. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [17] Hagbom M, Nordgren J, Nybom R, Hedlund K-O, Wigzell H, Svensson L. Ionizing air affects influenza virus infectivity and prevents airborne transmission. *Sci Rep.* 2015;5:11431. doi: 10.1038/srep11431. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [18] Mele ndez-Villanueva MA, Mora n-Santibañ ez K, Martí nez-Sanmiguel JJ, Rangel López R, Garza-Navarro MA, Rodríguez-Padilla C, et al. Virucidal activity of gold nanoparticles synthesized by green chemistry using garlic extract. *Viruses.* 2019;11:1111. [PMC free article] [PubMed]
- [19] Lozovski V, Lysenko V, Piatnytsia V, Scherbakov O, Zholobak N, Spivak M. Physical point of view for antiviral effect caused by the interaction between the viruses and nanoparticles. *J Nanosci.* 2012; 6:109–112.
- [20] Vijayakumar S, Ganesan S. Gold nanoparticles as an HIV entry inhibitor. *CHR.* 2012;10:643–646. doi: 10.2174/157016212803901383. [PubMed] [CrossRef] [Google Scholar] Chen Y-S, Hung Y-C, Lin W-H, Huang GS. Assessment of gold nanoparticles as a size-dependent vaccine carrier for enhancing the antibody response against synthetic foot-and-mouth disease virus peptide. *Nanotechnology.* 2010;21:195101. doi: 10.1088/0957-4484/21/19/195101. [PubMed] [CrossRef] [Google Scholar]

- [21] Ghaffari H, Tavakoli A, Moradi A, Tabarraei A, Bokharaei-Salim F, Zahmatkeshan M, et al. Inhibition of H1N1 influenza virus infection by zinc oxide nanoparticles: another emerging application of nanomedicine. *J Biomed Sci.* 2019;26:70. [PMC free article] [PubMed]
- [22] Fujimori Y, Sato T, Hayata T, Nagao T, Nakayama M, Nakayama T, et al. Novel antiviral characteristics of nanosized copper(I) iodide particles showing inactivation activity against 2009 pandemic H1N1 influenza virus. *Appl Environ Microbiol.* 2012;78:951–5. [PMC free article] [PubMed]
- [23] Drouet C. Nanotechnologies: a key role in virus fight. *BJSTR [Internet].* 2020 [cited 2020 Sep 30];27. Available from: <https://biomedres.us/fulltexts/BJSTR.MS.ID.004500.php>
- [24] Al-Halifa S, Gauthier L, Arpin D, Bourgault S, Archambault D. Nanoparticle-based vaccines against respiratory viruses. *Front Immunol.* 2019;10:22. doi: 10.3389/fimmu.2019.00022. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [25] Zhang L, Liu Y. Potential interventions for novel coronavirus in China: a systematic review. *J Med Virol.* 2020;92:479–490. doi: 10.1002/jmv.25707. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [26] Xiang D, Zheng C, Zheng Y, Li X, Yin J, O'Conner M, et al. Inhibition of A/human/Hubei/3/2005 (H3N2) influenza virus infection by silver nanoparticles in vitro and in vivo. *IJN.* 2013; 4103. [PMC free article] [PubMed]
- [27] Kuo Y, Su F. Transport of stavudine, delavirdine, and saquinavir across the blood–brain barrier by polybutylcyanoacrylate, methylmethacrylate-sulfopropylmethacrylate, and solid lipid nanoparticles. *Int J Pharm.* 2007;340:143–152. doi: 10.1016/j.ijpharm.2007.03.012. [PubMed] [CrossRef] [Google Scholar]
- [28] Khan S, Baboota S, Ali J, Khan S, Narang R, Narang J. Nanostructured lipid carriers: An emerging platform for improving oral bioavailability of lipophilic drugs. *Int J Pharma Investig.* 2015;5:182. doi: 10.4103/2230-973X.167661. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [29] Aji Alex MR, Chacko AJ, Jose S, Souto EB. Lopinavir loaded solid lipid nanoparticles (SLN) for intestinal lymphatic targeting. *Eur J Pharm Sci.* 2011;42:11–18. doi: 10.1016/j.ejps.2010.10.002. [PubMed] [CrossRef] [Google Scholar]
- [30] Darwis Y, Ali Khan A, Mudassir J, Mohtar N. Advanced drug delivery to the lymphatic system: lipid-based nanoformulations. *IJN.* 2013;2733. [PMC free article] [PubMed]
- [31] Kerry RG, Malik S, Redda YT, Sahoo S, Patra JK, Majhi S. Nano-based approach to combat emerging viral (NIPAH virus) infection. *Nanomedicine.* 2019;18:196–220. doi: 10.1016/j.nano.2019.03.004. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [32] Narayanan KB, Sakthivel N. Biological synthesis of metal nanoparticles by microbes. *Adv Colloid Interf Sci.* 2010;156:1–13. doi: 10.1016/j.cis.2010.02.001. [PubMed] [CrossRef] [Google Scholar]
- [33] Elechiguerra J, Burt JL, Morones JR, Camacho-Bragado A, Gao X, Lara HH, et al. Interaction of silver nanoparticles with HIV-1. *J Nanobiotechnol.* 2005;3:6. [PMC free article] [PubMed]
- [34] Reina G, Peng S, Jacquemin L, Andrade AF, Bianco A. Hard nanomaterials in time of viral pandemics. *ACS Nano.* 2020;14:9364–9388. doi: 10.1021/acsnano.0c04117. [PubMed] [CrossRef] [Google Scholar]
- [35] Chen Y-N, Hsueh Y-H, Hsieh C-T, Tzou D-Y, Chang P-L. Antiviral activity of graphene–silver nanocomposites against non-enveloped and enveloped viruses. *IJERPH.* 2016;13:430. doi: 10.3390/ijerph13040430. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [36] Lee S, Jun B-H. Silver nanoparticles: synthesis and application for nanomedicine. *IJMS.* 2019;20:865. doi: 10.3390/ijms20040865. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [37] Szyman ska E, Orłowski P, Winnicka K, Tomaszewska E, Baska P, Celichowski G, et al. Multifunctional tannic acid/silver nanoparticle-based mucoadhesive hydrogel for improved local treatment of HSV infection: in vitro and in vivo studies. *IJMS.* 2018;19:387. [PMC free article] [PubMed]
- [38] Yang XX, Li CM, Huang CZ. Curcumin modified silver nanoparticles for highly efficient inhibition of respiratory syncytial virus infection. *Nanoscale.* 2016;8:3040–3048. doi: 10.1039/C5NR07918G. [PubMed] [CrossRef] [Google Scholar]