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Nanoparticles: Revolutionizing Antiviral Treatment Strategies

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ABSTRACT:

Virus is a small infectious agent which multiply in living host cells. It is an obligate parasites. There are various pharmacological treatment approved by FDA for the treatment of several viral infection. Due to various drawbacks of these antiviral drugs like they can interact with other drugs and can cause severe adverse effects. There prolong use can cause drug resistance. To overcome these complications there is a need of some advancement in antiviral therapy. Nanoparticles are used for targeted drug delivery in antiviral therapy. These nanoparticles have various advantages due to which they are used recently. They are useful for targeting the drug to a specific site. Nanoparticles are useful in treatment of various enveloped virus like HIV, HSV-1 and HSV-2 These nanoparticles are of various types and transport the drug to the specific site where they show the pharmacological actions. NPs have a limitation that they can accumulate in the body organs and can cause the toxicity. So, we use some strategies and approaches to lower the level of toxicity and produce safe nanoparticles.

Keywords- Virus, Nanoparticles, Targeted drug delivery, Drug resistance, Antiviral therapy, Toxicity.

Introduction :

A virus is a small disease-causing agent that replicate within the living host cells and called as intracellular parasites. Viruses have different sizes and shapes which may be rod shaped or spherical. They have a core of genetic material; it can be either DNA or RNA. This core is coveredby a protective coat of protein known as capsid. Around the capsid there may be a spiky lipid bilayer membrane known as envelope. These spikes are proteins and with the help of these spikes'virus bind to and enter into host cells Due to the lack of ribosomes in viruses, they are not able to make proteins. Due to this they cannot reproduce independently and they are dependent on their host. Virus causes various disease like severe acute respiratory syndrome coronavirus 2 (SARS- Cov-2), causes the disease COVID-19, smallpox, polio, rabies, Ebola, HIV, herpes simplex virus (HSV), dengue fever. There are some useful or friendly bacteria in the intestine which are essentialfor gut health. Human also have useful viruses that help in protection against harmful bacteria, including *Escherichia coli*. When it reproduces inside the host, the particles spread to new hosts. Viruses can spread through touch, direct contact, respiratory droplets, body fluids, insects, contaminated water or food. Virus changes over the time. When they reproduce, copying errors and genetic material, changes occur naturally. Some changes are small and does not cause any major concern but some changes could make a virus transmissible, like in case of B.1.1.7 variant of SARS-Cov-2. Vaccines against some viral infections like Hepatitis A, Hepatitis B and measles lowers the chances of diseases. But, the level of mutation capability in some viruses is more due towhich vaccination can be difficult in some cases (1).

The viral infection easily develop resistance to new drugs, there is a need of permanent improvement in the new antiviral drug development and improvement in the existing drugs formulations. There are some serious factors which affect the rapid development of the new antiviral drugs like virus replication process is different to normal cells. Antiviral drugs have lowsolubility and short half-life period which alter their uses and make it challenging. There are various approaches are done to improve the physicochemical properties of these drugs like controlled-release delivery system like nanoparticle carriers (2).

Nanoparticles have an important characteristic that more than one antiviral drug can be install intoa nanoparticle. They have controllable hydrophobicity and lipophilicity, so they can be used for target drug delivering system. Thus, direct systemic delivery of some antiviral drugs reduces the side effects (3).

Replication Cycle in Virus

Virus life cycle is divided into various steps as shown in fig 1 and fig 2.

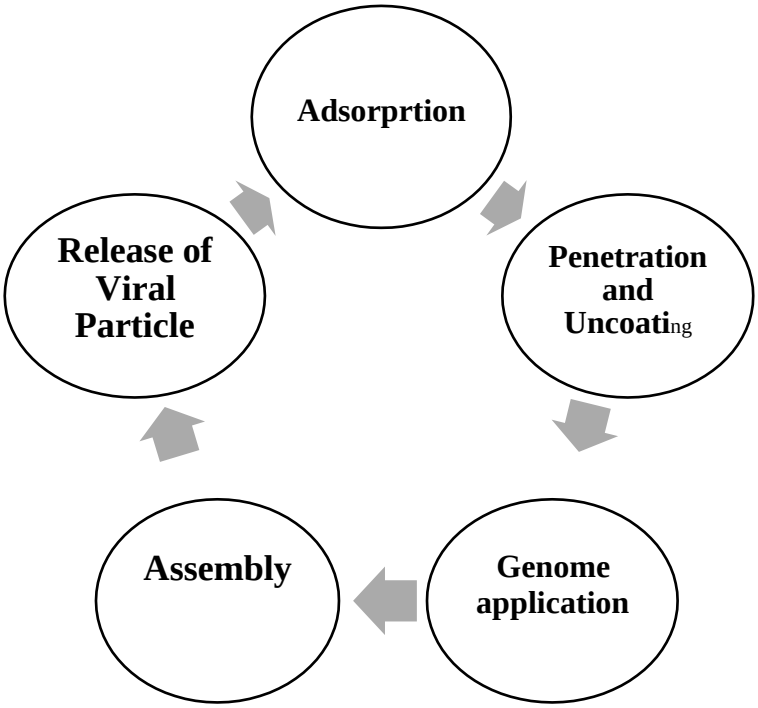

Fig 1: Replication cycle of virus.

Adsorption and Attachment:

This is the first step in virus infection in which the virus attaches to its specific receptors presentin the host cell. These receptors are proteins and polysaccharides. A little contact between the hostcell and the virus can lead to a successful infection. For example, HIV binds to CD4 cell receptorof T-lymphocytes. For the attachment to host cell receptors, some virus uses different molecules, called coreceptors.

Penetration and Uncoating

The entry of virus inside the host cell involves two types of mechanism which are, a) transportationof whole virus across the cytoplasmic membrane by endocytosis process) transfer of genome
across the cell membrane c) fusion of viral envelop with cytoplasmic membrane of the host cell. There is a confirmational change in the viral membranes proteins which causes the fusion of hostcell membrane and virus release its nucleocapsid into the host cytoplasm.

Genome replication

After entry of virus into the host cell, the virus gene transcribed to mRNA and translated. Simultaneously viral structural proteins like capsids are also synthesized. The genetic material ofvirus also varies from virus to virus. All the viruses are divided into seven groups by Dr. David Baltimore in 1971. These seven groups are: a) Double stranded DNA, Double Stranded RNA, Single Stranded DNA, Single stranded (+) ve sense RNA, Single stranded (-) ve sense RNA, Singlestranded (+) ve sense RNA with DNA intermediate, Double stranded DNA with RNA intermediate.

Assembly

It involves the collection of all components which are important for the complete formation of a virion and assembled in cellular compartment where the genome replication will take place. Thus,most of the DNA viruses assemble themselves in nucleus whereas the RNA viruses assemble themselves in cytoplasm. For example, pox viruses' assembly occurs in the cytoplasm whereas in adenovirus assembly occurs in nucleus.

2.2 Release of viral particles

After the maturation of virion, it leaves the cell by various mechanism like budding, cell lysis, apoptosis and exocytosis. Viruses containing envelope leave the cell by using budding mechanism.On the other hand, non- envelope virus leaves the cell-by-cell lysis mechanism which will result inthe cell death (4-8).

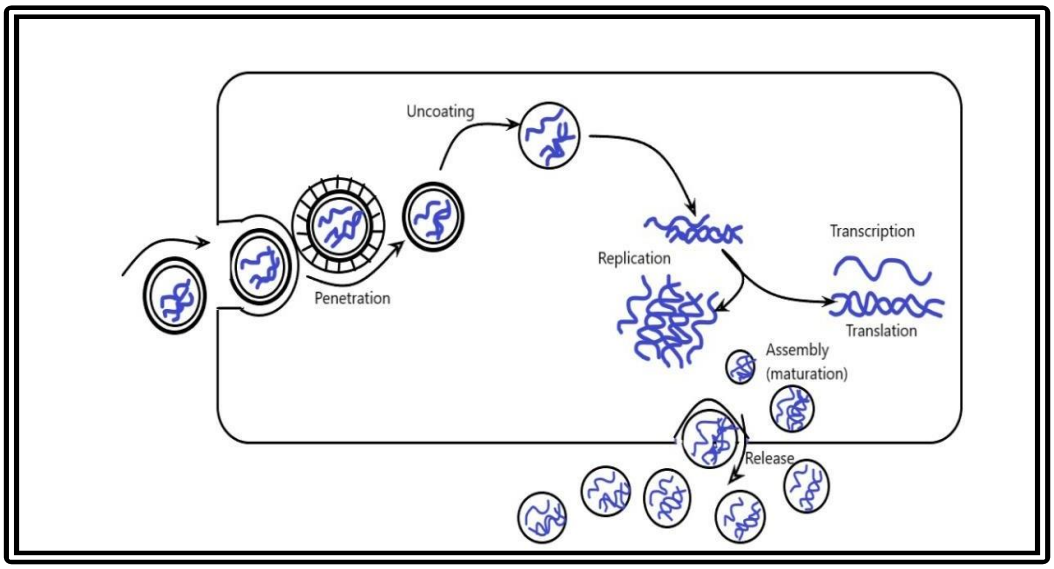

Fig 2: Viral replication cycle

Selected Antiviral Treatment

Table1- List of antiviral treatment

Mechanism of Action	**Drug**	**Used in Virus**	**Route of Administration**
Viral DNA Polymerase inhibition	Acyclovir Cidofovir Ganciclovir Penciclovir	HSV, VZV CMV HSV, VZV, CMVHSV	Oral, topical Intravenous Oral, IntravenousTopical
viral uncoating inhibition	Amantadine Rimantadine	Virus influenza A Virus influenza A	Oral Oral
viral RNA polymerase inhibition	Ribavirin	RSV, HCV	Oral
viral reverse transcriptase inhibition	Stavudine Zidovudine Lamivudine	HIV HIV HIV, HBV	Oral Oral, intravenousOral
viral protease inhibition	Saquinavir Indinavir Ritonavir	HIV HIV HIV	Oral Oral Oral
viral integration inhibition	Raltegravir	HIV	Oral
viral mRNA synthesis inhibition	Interferon alfa-2b	Cytomegalovirus	Eye drops

Challenges of Antiviral Treatment

There are continuous efforts in the field of research to develop some new antiviral treatments whichwill improve the life of patients suffering from viral infections. However, the appearance of new viral infections and their fast resistance to drugs makes it a difficult task to develop new antiviraltherapies.

i. Some drugs interact with other drugs and give rise adverse effects. Also, the long-term use of antiviral leads to other health problems (9).
ii. Due to low bioavailability of these drugs, high dose is required to get the proper pharmacological effect but it can also lead to toxicity (10).
iii. The prolong use of antivirals also causes the drug resistance in some patients (11).
iv. Many antiviral drugs have short half-life due to which patient have to take the medicines for longer duration of time (12).
v. Selectivity of antiviral agents toward the virus and identifying the target which is unique to the virus life cycle is another challenge in the development of antiviral drugs (13).
vi. Every virus has the different structure and different function which makes a difficult task to develop broad- spectrum antivirals (14).
vii. Some viruses like zika virus, HIV, Ebola virus spreads into lymphatic system and synovial fluids and the drug is not able to reach at these sites and show their action (15)

Nanoparticle as Therapeutics

Targeted drug delivery in the treatment of disease is primary strategy because of the directly delivering the drug at the targeted site or the organ where we want to have a therapeutic action ofthe drug. To attain this, development of effective and safer nanoparticles is critical and one of themain goals of the nanomedicines. When the nanoparticles enter into the bloodstream, they aggregate and protein binds to their surface for immune recognition. Due to this, they could be goes out from the circulatory system by the phagocytosis and filtration in spleen, kidney and liver.This rapid clearance of the NPs from the blood stream reduces the retention time of the NPs and lowers the bioavailability. By attaching Polyethylene glycol (PEG), carbohydrates, protein moieties,acetyl groups to the surface of NPs, retention time can be increased (16). Surface charge and the sizeof nanoparticles also have an effective role in targeted therapy. PS smaller than 10nm get easilycleared by filtration through kidney and the NPs having size more than 200nm are cleared by phagocytic cells. Surface modification of the nanoparticles can also increase their therapeutic action at the targeted site and also reduces the chances of their accumulation at non- target site (17-19). 95% of the nanoparticles are ingested by endocytosis via clathrinid- or caveolae-dependent processes (20). when these nanoparticles are ingested by the desired cells, their biodistribution isnecessary. For their distribution nanoparticles' size is also important. In addition, cationic nanoparticles which are rod shape are more favorable to endosomal uptake than cationic nanoparticles in other shapes, indicating that immune system cells may recognize these nanoparticles as rod-shaped microorganisms as depicted in fig 3 (21).

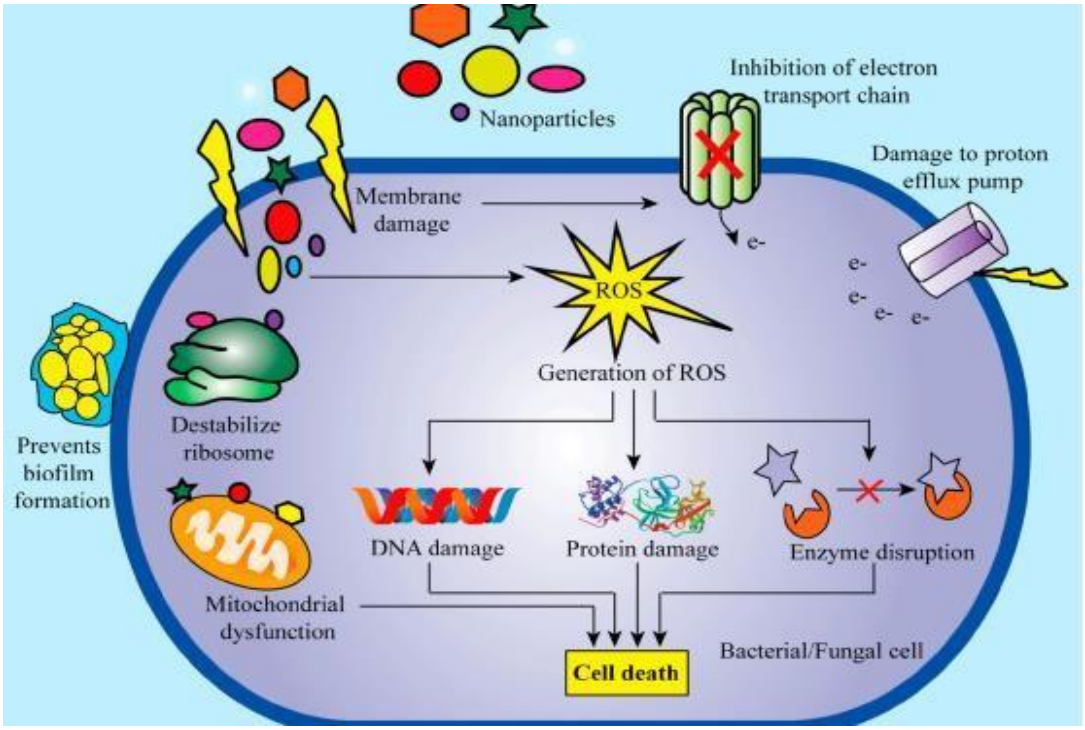

Fig 3: Mechanism of action of nanoparticles in antiviral therapy

Therapeutic nanoparticles surface chare plays a major role in their clearance from the body. In comparison to neutral or negatively charged nanoparticles, positively charged nanoparticlesproduce greater immunological response. Furthermore, it has been established that nanoparticles with a surface potential between 10 and +10 mV are less subject to phagocytosis and unidirectionalinteractions. The composition of the nanoparticles, however, might have an effect

on the optimumrange. Nanoparticle pH sensitivity and surface charge are closely correlated. These nanoparticles could be modified to identify and locate in particular cell compartments (22,23,24).

Types of Therapeutic Nanoparticles

There are various nanoparticles are produced which are used as carrier for antiviral agents. The drug is installed in these NPs and administered into the body. After that NPs shows its affect at targeted site in the body. Few most commonly known NPs are mentioned in fig 4.

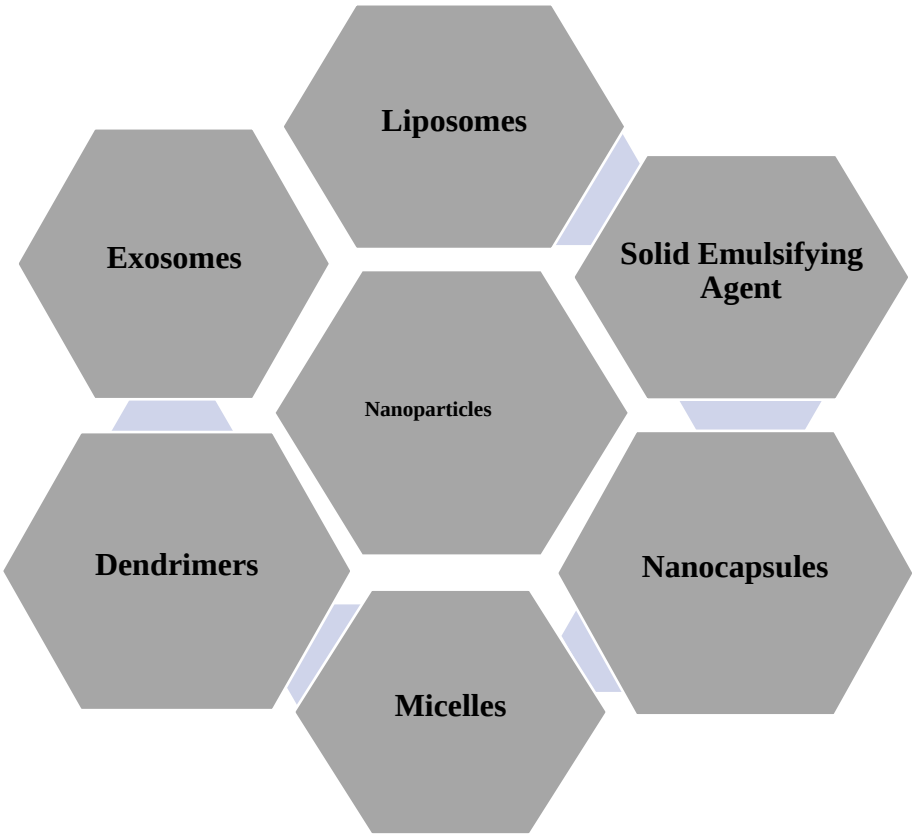

Fig 4: Types of therapeutic nanoparticles

A number of lipids have been used as a carrier for antiviral agents. Lipids are biocompatible, biodegradable, non- toxic, easily available and inert. Lipids have some special characterization like they have high drug loading capacity, small size, larger surface area, controlled release and hence they increase the performance of the drug they deliver [25]. Some of the examples of lipidsthat are used are bees wax, lecithin and they are mixed with surfactants and co-solvents to increasethe solubility of the drug (26).

Liposomes

Liposomes are small artificial vesicle having size between 40 – 80nm. They are one of the most frequently used drug delivery system described in 1965. They contain phospholipid bilayer and acholesterol layer which trap an aqueous core in which the drug is inserted. Liposomes has an advantage that they directly fused with cell membrane and releases the drug into cytoplasm whichmake them perfect carrier for target drug delivery (27). These structural properties of these liposomes allow them to transport both hydrophobic and hydrophilic molecules. Hydrophilic molecules can be transported in the aqueous medium of liposomes, whereas hydrophobic molecules can dissolve in the lipid membrane. In addition, different types of drugs can be loaded into 2 compartments (like water and lipid) or into various aqueous layers of multilamellar liposomes. It provides sequential release of several drug molecules separated layer by layer from the outer shell to the inner core (28) Small neutral or positively charged liposomes have longer circulation times compared to large unmodified liposomes. Additionally, surface modification can
be achieved by coating with functionalized polymers or PEG chains, which improves targeting and increases cycle time in biological systems. Liposomes are being studied for a variety of therapeutic applications, including cancer diagnosis and treatment, vaccines, drug delivery to the brain, and antibacterial therapy (29)

Dendrimers

Dendrimers are three-dimensional, synthetic nano-architectures with an exterior shell that serves a variety of purposes. They are 2- to 10-nm in diameter, highly branching, well-defined, homogeneous, and have a centralized core made up of repeating units of the building blocks (30).While the functional groups on the surfaces of dendrimers either actively involve with the desirablebiological targets or transport pharmaceuticals via chemical or electrostatic conjugation, their gapsand flexible spaces make it simpler for host molecules to get lodged inside of them. Dendrimers have better cell absorption, longer circulation times, enhanced solubility and stability, and specificdispersion when used as theranostics (31). Commercially, dendrimers such poly-propylene, polyamidoamine (PAMAM), and others are easily accessible. Dendrimer surface modification often involves the use of peptides, anionic groups, and carbohydrates. Amazingly, certain dendrimers already are bactericidal or virucidal (32).

Self-emulsifying drug delivery systems

Self-emulsifying drug delivery systems (SNEDDS) are formed by the spontaneous emulsificationof oils or lipids with water using surfactants, co-surfactants, solvents and co-solvents. They are another type of lipid-based monotropic system (33). Hydrophobic active ingredients dissolve in theoil phase. These are thermostable and nano-sized oil droplets that provide better penetration and bioavailability. A variety of antiretroviral drugs with different lipids are prescribed, such as Lauroglycol 90, Labafril, and Capmul MCM. Nevirapine from SNEDDS using Captex 200 as lipid (34).

Exosomes

Exosomes are produced and secreted by a variety of cell types naturally. They typically exist in bodily fluids like saliva, blood, urine, and breast milk and range in size from 30 to 150 nm [35]. Exosomes are lipid bilayer vesicles that resemble cell membranes and contain a variety of substances, such as RNA, Chromatin, lipopeptides, and proteins. By transporting various molecules in physiological functions like immune response, neuronal connection, and antigen presentation in disorders like cancer, atherosclerosis, diabetes, and inflammation, exosomes play a significant role in intracellular communication [36]. Multipotent nanoparticles have an edge overimmune system in that they can be easily isolated from a patient's bodily fluids, protecting the cargo from quick clearance and enhancing medicine delivery to specific areas. Exosomes may therefore be employed as medication delivery systems for cancer and autoimmune illnesses, as cancer diagnostic biomarkers, or even for tissue regeneration, according to research that are now being done (37).

Nano capsules

Nanoparticles structures (50–300 nm) with a core and a shell make up a nano capsule. The polymeric shell is contained within the inner core, which alone contains the medication. The advantages of nano capsules include high drug loading, controlled release, and targeted drug delivery (38). They are typically made using layer-by-layer technique, nanoprecipitation,
emulsion-diffusion, emulsion-coacervation, emulsion-evaporation, and double emulsification. In a study, nano capsules made of poly (iso-butyl cyanoacrylate), the core of which contains azidothymidine-triphosphate (AZT-TP), and polyethyleneimine, the shell, were developed to deliver (AZT-TP) directly into the cytoplasm (39).

Nanocarriers in the Treatment of Enveloped Viruses

Human Immunodeficiency Virus (HIV)

Human Immunodeficiency Virus-1 infects different cells like T lymphocytes, Langerhans cells, monocytes. But damage of CD4- T lymphocytes cause major effect on HIV infection. These CD4- T Lymphocytes plays an important role in the activation of the immune system against various infectious diseases.
There are some antiviral drugs which have low efficacy and safety. To defeat this problem, varioustypes of NPs have been synthesized in some years and used as protective agents in HIV treatment.The production of silver nanoparticles with the ability to stop HIV infection represented the first approach to use nanomaterials in antiviral therapy. Around 1 and 10 nm in size, silver nanoparticlesinteract with HIV. HIV cannot attach to or fuse with cell membranes due to interactions between silver nanoparticles and the glycolipids of the HIV envelope. This is one of a number of additionalways that nanomaterials work. Nanomaterials coated with poly(N-vinyl-2-pyrrolidone) bind to residues of the gp120 glycoprotein and hinder interaction with host cells since the antiviral activityof AgNPs only appears at very high doses.
The gold nanoparticles coated with oligomannose can prevent HIV trans infection of human T lymphocytes. Carbon nanotubes cross the cell membrane and deliver the various therapeutics incells. Carboxyl group present in nanotubes allows the prolongation in therapeutic actions of the drug (40).

Herpes Simplex Virus

Herpes simplex virus is an envelope virus having a central core which contain double- stranded DNA. It is of two types; HSV-1 and HSV-2. HSV- 1 causes the infection of CNS and face. On theother hand, HSV-2 causes the infection in genital area. There are various recent approaches for thetreatment of Herpes Simplex Virus like gold and silver nanoparticles. These both types of nanoparticles have sulfonate function which inhibit the entry of virus in the host cell and further stops it from spreading. Gold nanoparticles containing mercaptoethane-sulfonate have heparan sulfate and hence block HSV-1 attachment and inhibit the entry of viral. Microemulsions containing acyclovir is most effective treatment used as topical preparation (41).

A Major Drawback of Nanoparticles

Like other drugs, NPs can also accumulate in the body organ which leads to toxicity. Route of NPsadministration influence the actions of the nanoparticles. Unintentional exposure of NPs at the siteif manufacturing can lead to toxicity. Exposure of NPs through lungs leads to inflammatory responses and death of tissues in lungs. Some exposures are done intentionally like applying the products to the skin and route of administration also effects the level of toxicity (42).

After reaching to the systemic circulation, NPs will distribute to the body organs and theprobability of their accumulation in various organs like liver, spleen, lungs and kidneys is also there (43). Due to their smaller size, they can also cross the blood brain barrier and accumulate inthe brain. Due to the leaky blood vessels of organs NPs accumulation chances are higher. Surfacearea and the charge ratio on nanoparticles define their distribution behavior. There are still not proper evidences regarding the toxicity mechanism of NPs. So, we need a high-level study on pharmacokinetic properties of NPs (44). The mechanism of NPs causing toxicity includes the DNA damage, production of reactive oxygenspecies. They inhibit the action of antioxidants by generating free radicals which damage DNA and mitochondrial dysfunctioning which ultimately leads to cell death. Some NPs like titanium dioxide starts inflammation pathway and release cytokines and they get accumulated in body organs which leads to toxicity (45).

Approaches for Production of Safer Nanoparticles

Defining the risk of Various Nanoparticles

NPs should be classified on the basis of their potency and their action. This approach is beneficialin determine the potency of chemical assays that are also used for degradable NPs having less retention time in the body. By using this chemical assay procedure, NPs toxic responses and theirbiodegradation can also measure (46). There are many toxicological assays which cannot predict the actual reason of toxicity so we need to find out the adverse effects. NPs pharmacokinetic profileand mechanism of toxicity must be top priority for the production of nanoparticles which will be safe and effective (47).

Approach to Produce Non-Cytotoxic nanoparticles

The first step to produce safe NPs is to use next generation lipids which are biodegradable in nature as they easily got eliminated from the body and reduces the chances of toxicity (48). Modifications in the NPs structure can also helpful in development of safer nanoparticles.Polymers like Polyethylene glycol, Polyvinylpyrrolidone (PVP), Polyvinyl alcohol, Zwitter ions polymers and polysaccharides can be used as a surface coating agents as they provide better compatibility and also influence the absorption and distribution of NPs in the body (49).

Doping is used at high level for the production of inorganic nanoparticles. This method adds impurities by altering the crystal structure of the substance to enhance physical and chemical properties (50-52). Various dopants are incorporated into the nanoparticles like aluminum and titanium. By doping technique, the use of inorganic nanoparticle is increased. Doping increases theantiviral action of silver nanoparticles by adding titanium oxide as doping agent (53-54).

Safe nanoparticles in Clinics

Due to low safety of NPs, many of them got rejected in the clinical trials. For human use, they should be safe and non-toxic. This is attained by various pre-clinical trials and then by the approvalof various regulatory agencies like Food and Drug Administration (FDA) (55). Cancer therapy is the main target of NPs. Various kind of new NPs are under clinical trials specially lipid based. Various steps are taken for producing safe and effective NPs by adding one or two layers of polymers. This is a fact that not all NPs can be 100% safe but it can be increased to a great level by applying various strategies (56).

Conclusion :

Nanotechnology is spreading rapidly in last 10 years. There is a development of nanoparticles carriers which play an effective role in targeted drug delivery system. Nanoparticles can cross thelipid membrane and can deliver the drug at specific targeted site and shows effective therapeutic effects. They have several advantages which make them perfect carriers for drug like they are biocompatible, small in size, have large surface area and immunogenic and has less chances of toxicity. We can also modify the nanocarrier structure by adding some polymer which further increases the activity of these nanoparticles. Different types of NPs are used in viral treatment. These nanoparticles can enhance the effect of antiviral drugs and lowers the adverse effects of thedrugs. Nanoparticles carriers reduce the treatment time with antiviral drugs to a greater extent

Different technologies are ongoing in nanoparticles development field like nanotubes, nanofiberswhich are effective against HIV-1 virus. It is very necessary to find out the perfect way of preparingor developing the nanocarriers having high safety profile and very low toxic profile. With the useof these nanocarriers there is a hope that various types of virous which are spreading nowadays canbe controlled to a larger extent in upcoming years.

REFERENCES :

1. Albertini, A.A., Rui grok, R.W., & Blondel, D. (2011). Rabies virus transcription and replication. *Advances in Virus Research*, 79, 1–22.
2. Arpino, C., Curatolo, P., & Rezza, G. (2009). Chikungunya and the nervous system: what we do and do not know. *Reviews in Medical Virology*, 19, 121–129.

3. Akhtar, J., & Shukla, D. (2009). Viral entry mechanisms: cellular and viral mediators of herpes simplex virus entry. *FEBS Journal*, 276, 7228–7236.
4. Ryu, W.S. (2017). Virus Life Cycle. *Molecular Virology of Human Pathogenic Viruses*, 31–45. doi: 10.1016/B978-0-12-800838-6.00003-5. Epub 2016 May 6. PMCID: PMC7158286.
5. Akhtar, J., & Shukla, D. (2009). Viral entry mechanisms: cellular and viral mediators of herpes simplex virus entry. *FEBS Journal*, 276, 7228–7236.
6. Antoine, T.E., Mishra, Y.K., Trigilio, J., Tiwari, V., Adelung, R., & Shukla, D. (2012). Prophylactic, therapeutic, and neutralizing effects of zinc oxide tetrapod structures against herpes simplex virus type-2 infection. *Antiviral Research*, 96, 363–375.
7. Ryu, W.S. (2017). Virus Life Cycle. *Molecular Virology of Human Pathogenic Viruses*, 31–45. doi: 10.1016/B978-0-12-800838-6.00003-5. Epub 2016 May 6. PMCID: PMC7158286.
8. Akhtar, J., & Shukla, D. (2009). Viral entry mechanisms: cellular and viral mediators of herpes simplex virus entry. *FEBS Journal*, 276, 7228–7236.
9. Oshikoya, K.A., Ogunleye, O., Lawal, S., Senbanjo, I., & Oreagba, I. (2013). Clinically significant interactions between antiretroviral and co-prescribed drugs for HIV-infected children: profiling and comparison of two drug databases. *Therapeutics and Clinical Risk Management*, 9, 215.
10. Singh, R., & Lilliard, J.W. Jr. (2009). Nanoparticle-based targeted drug delivery. *Experimental and Molecular Pathology*, 86, 215–223.
11. Strasfeld, L., & Chou, S. (2010). Antiviral drug resistance: mechanisms and clinical implications. *Infectious Disease Clinics of North America*, 24, 413–437.
12. Gerber, J.G. (2000). Using pharmacokinetics to optimize antiretroviral drug-drug interactions in the treatment of human immunodeficiency virus infection. *Clinical Infectious Diseases*, 30, S123–S129.
13. Bule, M., Khan, F., & Niaz, K. (2019). Antivirals: past, present and future. In Recent Advances in Animal Virology (pp. 425–446). Singapore: Springer.
14. Adalja, A., & Inglesby, T. (2019). Broad-spectrum antiviral agents: a crucial pandemic tool. *Expert Review of Anti-infective Therapy*, 17, 467–470.
15. Vyas, S.P., Subhedar, R., & Jain, S. (2006). Development and characterization of emulsomes for sustained and targeted delivery of an antiviral agent to liver. *Journal of Drug Delivery*, 321.
16. Shreffler, J.W., Pullan, J.E., Dailey, K.M., Mallik, S., & Brooks, A.E. (2019). Overcoming hurdles in nanoparticle clinical translation: the influence of experimental design and surface modification. *International Journal of Molecular Sciences*, 20, 6056.
17. Ernsting, M.J., Murakami, M., Roy, A., & Li, S.D. (2013). Factors controlling the pharmacokinetics, biodistribution, and intratumoral penetration of nanoparticles. *Journal of Controlled Release*, 172, 782–794.
18. Wu, W., Luo, L., Wang, Y., Wu, Q., Dai, H.B., Li, J.S., Durkan, C., Wang, N., & Wang, G.X. (2018). Endogenous pH-responsive nanoparticles with programmable size changes for targeted tumor therapy and imaging applications. *Theranostics*, 8, 3038–3058.
19. Bhatia, S. (2016). Nanoparticles types, classification, characterization, fabrication methods, and drug delivery applications. In Natural Polymer Drug Delivery Systems: Nanoparticles, Plants, and Algae (pp. 33–93). Cham, Switzerland: Springer International Publishing.
20. Zhang, S., Li, J., Lykotrafitis, G., Bao, G., & Suresh, S. (2009). Size-dependent endocytosis of nanoparticles. *Advanced Materials*, 21, 419–424.
21. Gratton, S.E., Ropp, P.A., Pohlhaus, P.D., Luft, J.C., Madden, V.J., Napier, M.E., & DeSimone, J.M. (2008). The effect of particle design on cellular internalization pathways. *Proceedings of the National Academy of Sciences of the USA*, 105, 11613–11618.
22. Ernsting, M.J., Murakami, M., Roy, A., & Li, S.D. (2013). Factors controlling the pharmacokinetics, biodistribution, and intratumoral penetration of nanoparticles. *Journal of Controlled Release*, 172, 782–794.
23. Wu, W., Luo, L., Wang, Y., Wu, Q., Dai, H.B., Li, J.S., Durkan, C., Wang, N., & Wang, G.X. (2018). Endogenous pH-responsive nanoparticles with programmable size changes for targeted tumor therapy and imaging applications. *Theranostics*, 8, 3038–3058.
24. Bhatia, S. (2016). Nanoparticles types, classification, characterization, fabrication methods, and drug delivery applications. In Natural Polymer Drug Delivery Systems: Nanoparticles, Plants, and Algae (pp. 33–93). Cham, Switzerland: Springer International Publishing.
25. Puri, A., Loomis, K., Smith, B., Lee, J.H., Yavlovich, A., Heldman, E., et al. (2010). Lipid-based nanoparticles. *Nature Reviews Drug Discovery*, 523–580.
26. Mukherjee, S., Ray, S., & Thakur, R. (2009). Solid lipid nanoparticles: a modern formulation approach in drug delivery system. *Indian Journal of Pharmaceutical Sciences*, 71, 349.
27. Li, T., Cipolla, D., Rades, T., & Boyd, B.J. (2018). Drug nanocrystallization within liposomes. *Journal of Controlled Release*, 288, 96–110.
28. Liposomes for oral drug delivery. *Acta Pharmaceutica Sinica B*.
29. Huang, Z., Li, X., Zhang, T., Song, Y., She, Z., Li, J., et al. (2014). Progress involving new techniques for liposome preparation. *Asian Journal of Pharmaceutical Sciences*, 9, 176–182.
30. Tomalia, D.A. (2005). The dendritic state. *Materials Today*, 8, 34–46.
31. Tripathy, S., & Das, M.K. (2013). Dendrimers and their applications as novel drug delivery carriers. *Journal of Applied Pharmaceutical Science*, 3, 142–149.
32. Šebestík, J., Reiniš, M., & Ježek, J. (2012). Synthesis of dendrimers: convergent and divergent approaches. In *Biomed Appl Pept GlycoGlycopeptide Dendrimers, Analog Dendrimeric Struct* (pp. 55–81). Vienna: Springer Vienna.
33. M, U.S., Lobo, F.J.R., & Uppuluri, K.B. (2013). Self nano emulsifying drug delivery systems for oral delivery of hydrophobic drugs. *Biomed Pharmacology Journal*, 6, 355–362.

34. Selvam, R.P., & Kulkarni, P.K. (2014). Design and evaluation of self nanoemulsifying systems for poorly water-soluble HIV drug. *Journal of Pharma SciTech*, 4, 23–28.
35. He, C., Zheng, S., Luo, Y., & Wang, B. (2018). Exosome theranostics: Biology and translational medicine. *Theranostics*, 8, 237–255.
36. Shimasaki, T., Yamamoto, S., & Arisawa, T. (2018). Exosome research and co-culture study. *Biological & Pharmaceutical Bulletin*, 41, 1311–1321.
37. Yamashita, T., Takahashi, Y., & Takakura, Y. (2018). Possibility of exosome-based therapeutics and challenges in production of exosomes eligible for therapeutic application. *Biological & Pharmaceutical Bulletin*, 41, 835–842.
38. Mayer, C. (2005). Nanocapsules as drug delivery systems. *International Journal of Artificial Organs*, 28, 1163–1171.
39. Parboosing, R., Maguire, G.E.M., Govender, P., Kruger, H.G., & Alber, I.C. (2012). Nanotechnology and the treatment of HIV infection. *Viruses*, 4(4), 488–520.
40. Akhtar, J., & Shukla, D. (2009). Viral entry mechanisms: cellular and viral mediators of herpes simplex virus entry. *FEBS Journal*, 276, 7228–7236.
41. Antoine, T.E., Mishra, Y.K., Trigilio, J., Tiwari, V., Adelung, R., & Shukla, D. (2012). Prophylactic, therapeutic, and neutralizing effects of zinc oxide tetrapod structures against herpes simplex virus type-2 infection. *Antiviral Research*, 96, 363–375.
42. Sukhanova, A., Bozrova, S., Sokolov, P., Berestovoy, M., Karaulov, A., & Nabiev, I. (2018). Dependence of nanoparticle toxicity on their physical and chemical properties. *Nanoscale Research Letters*, 13, 44.
43. Fu, P.P., Xia, Q., Hwang, H.M., Ray, P.C., & Yu, H. (2014). Mechanisms of nanotoxicity: generation of reactive oxygen species. *Journal of Food and Drug Analysis*, 22, 64–75.
44. Sereemaspun, A., Rojanathanes, R., & Wiwanitkit, V. (2008). Effect of gold nanoparticle on renal cell: an implication for exposure risk. *Renal Failure*, 30, 323–325.
45. Antony, J.J., & Sivalingam, P.C.B. (2015). Toxicological effects of silver nanoparticles. *Environmental Toxicology and Pharmacology*, 40, 729–732.
46. Wu, T., & Tang, M. (2018). Review of the effects of manufactured nanoparticles on mammalian target organs. *Journal of Applied Toxicology*, 38, 25–40.
47. Liu, J., Feng, X., Wei, L., Chen, L., Song, B., & Shao, L. (2016). The toxicology of ion-shedding zinc oxide nanoparticles. *Critical Reviews in Toxicology*, 46, 348–384.
48. Maier, M.A., Jayaraman, M., Matsuda, S., Liu, J., Barros, S., Querbes, W., Tam, Y.K., Ansell, S.M., Kumar, V., Qin, J., et al. (2013). Biodegradable lipids enabling rapidly eliminated lipid nanoparticles for systemic delivery of RNAi therapeutics. *Molecular Therapy*, 21, 1570–1578.
49. Schubert, J., & Chanana, M. (2018). Coating matters: Review on colloidal stability of nanoparticles with biocompatible coatings in biological media, living cells and organisms. *Current Medical Chemistry*, 25, 4553–4586.
50. Rao, G.T., Babu, B., Stella, R.J., Manjari, V.P., & Ravikumar, R.V. (2015). Spectral investigations on undoped and Cu(2+) doped ZnO-CdS composite nanopowders. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 139, 86–93.
51. Adeleye, A.S., Pokhrel, S., Madler, L., & Keller, A.A. (2018). Influence of nanoparticle doping on the colloidal stability and toxicity of copper oxide nanoparticles in synthetic and natural waters. *Water Research*, 132, 12–22.
52. Ahmad, J., Siddiqui, M.A., Akhtar, M.J., Alhadlaq, H.A., Alshamsan, A., Khan, S.T., Wahab, R., Al-Khedhairy, A.A., Al-Salim, A., Musarrat, J., et al. (2018). Copper doping enhanced the oxidative stress-mediated cytotoxicity of TiO2 nanoparticles in A549 cells. *Human & Experimental Toxicology*, 37, 496–507.
53. Missaoui, W.N., Arnold, R.D., & Cummings, B.S. (2018). Toxicological status of nanoparticles: What we know and what we don't know. *Chemico-Biological Interactions*, 295, 1–12.
54. Yang, G., Phua, S.Z.F., Bindra, A.K., & Zhao, Y. (2019). Degradability and clearance of inorganic nanoparticles for biomedical applications. *Advanced Materials*, 31, e1805730.
55. Schütz, C.A., Juillerat-Jeanneret, L., Mueller, H., Lynch, I., & Riediker, M. (2013). Therapeutic nanoparticles in clinics and under clinical evaluation. *Nanomedicine (Lond)*, 8, 449–467.
56. Anselmo, A.C., & Mitragotri, S. (2019). Nanoparticles in the clinic: An update. *Bioengineering & Translational Medicine*, 4, e10143.