



A REVIEW: NANOTECHNOLOGY-BASED INTERVENTIONS FOR TREATMENT OF TROPICAL DISEASES

Shaikh T.R.*,

Department of Quality assurance technique

SVPM's College of Pharmacy, Malegaon (Bk) India

Abstract:

Tropical diseases affect the world's poorest countries. The area of the globe between Tropic of Cancer and Tropic of Capricorn is known as the tropical region. Due to geographical and climatic regions such as hot and humid climates and heavy rainfalls, conditions become favourable for vectors and carriers which cause these diseases. Another division of tropical diseases is Neglected tropical diseases (NTD's) because they lack research and development for their eradication. The WHO has recognized 17 diseases as NTD's caused by bacteria, parasites, protozoa, and viruses. Nanocarrier-based novel drug delivery systems (NDDS) or Nano medicine is an emerging field that works on nanosized particles for the treatment of chronic human diseases, diagnosis, and tissue regeneration. Due to limitations of conventional drug therapies like toxicity, unusual pharmacokinetic profiles, there is a need to reformulate available drugs. Importantly, NDDS can boost drug stability and water solubility, increase circulation time, promote drug uptake/entry into target cells or tissues, and decrease enzyme degradation, thus increasing drug safety and efficacy. This review article contains factors prevailing tropical diseases, current drug therapies and challenges associated with them, importance of nanobased therapeutics, types of nanotherapeutics used in treatment of NTD's. This review article also contains overview of different types of nanocarriers used in therapy and nanotechnology based case studies. It is a challenging task to develop new drugs for tropical diseases because a huge investment of time and money is required which is a much risky task.

Keywords: Nanotherapeutics, tropical diseases, neglected tropical diseases, dengue malaria, noisome, dendrimer, liposome, novel drug delivery system.

INTRODUCTION

Tropical diseases affect the world's poorest countries. The area of the globe between Tropic of Cancer and Tropic of Capricorn is known as the tropical region. Due to geographical and climatic regions such as hot and humid climates and heavy rainfalls, conditions become favourable for vectors and carriers which cause these diseases. Another division of tropical diseases is Neglected tropical diseases (NTD's) because they lack research and development for their eradication. The WHO has recognized 17 diseases as NTD's caused by bacteria, parasites, protozoa, and viruses. Conventional drug therapies are available for the treatment of these diseases but some of them like dengue have only supportive therapy. Due to limitations of conventional drug therapies like toxicity, unusual pharmacokinetic profiles, there is a need to reformulate available drugs. Nanotechnology plays a significant role in overcoming the challenges associated with conventional drug therapies. This report emphasizes different nanotechnology-based carriers available for the treatment of NTD's and specific nano therapy based approaches of three diseases namely leishmaniasis, malaria, and dengue.

Nanocarrier-based novel drug delivery systems (NDDS) or nanomedicine is an emerging field that researches the use of nanoparticles in the diagnosis, therapy, and regeneration of human tissue. The combined research works of nanotechnology and pharmaceutical sciences are encouraging and have grown up very rapidly in recent years. As the nanoengineering enabled drug delivery materials intended at the atomic or molecular level, they are usually nanoscale size. In contrast to larger materials or conventional medications, they can therefore freely circulate throughout the entire human body. Additionally, nanoscale-sized particles exhibit unique structural, chemical, mechanical, magnetic, electrical, and biological properties [1]. Importantly, NDDS can enhance circulation time, promote drug uptake/entry, and increase drug stability and water solubility into target cells or tissues, and decrease enzyme degradation, thus increasing drug safety and efficacy.

OVERVIEW OF TROPICAL DISEASES

Those diseases which commonly occur in tropical and subtropical regions of the globe are known as tropical diseases. The area of the globe between the Tropic of Capricorn and Tropic of Cancer is known as the tropical region, because of hot and humid climatic conditions the following diseases prevail in that region [2],

- African trypanosomiasis (sleeping sickness)
- Buruli ulcer
- Dengue fever
- Dracunculiasis
- Echinococcosis
- Human leishmaniasis
- Chagas

- Leprosy
- Malaria
- Lymphatic filariasis (elephantiasis)
- Onchocerciasis (river blindness)
- Rabies
- Schistosomiasis (snail fever)

Global distribution of NTDs

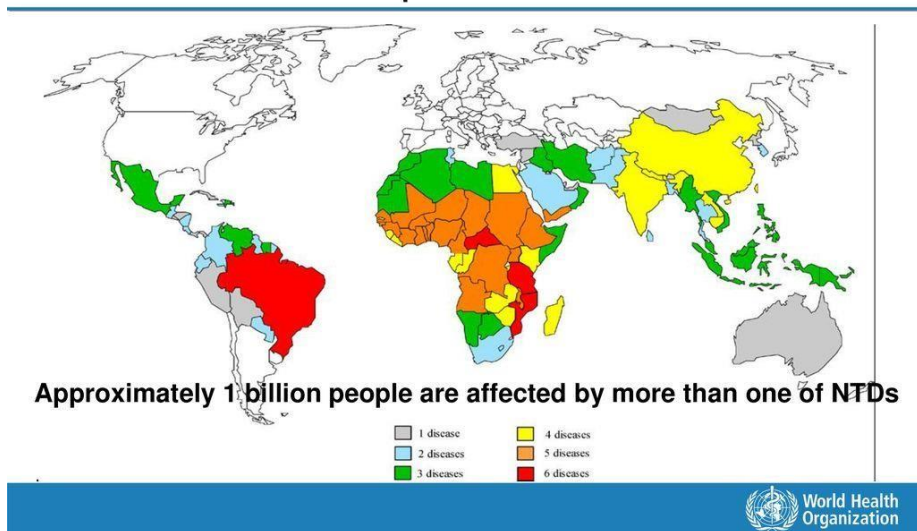


Figure 1. Global distribution of tropical diseases[3]

a) The burden of NTDs in India

India, along with other countries in South Asia, has the highest burden of Neglected tropical disease. South Asian countries account for world 1/4 of soil-transmitted helminths, 1/3 of global deaths from rabies, and 1/2 of the burden of filariasis, visceral leishmaniasis, and leprosy.

b) Visceral Leishmaniasis (VL)

By being bitten by a female sandfly with *Leishmania donovani* infection, *Phlebotomus argentipes*, humans can contract visceral leishmaniasis, also known as kala-azar. Untreated VL results in a very high mortality rate due to the persistent fever, pancytopenia, and enlargement of the spleen and liver. PKDL, also known as post-Kala azar dermal leishmaniasis, is a significant complication. The problem of Post-Kala-Azar-Dermal-Leishmaniasis (PKDL) is also significant. In this condition, numerous parasites are lodged in the lesions in the skin, creating a chronic source for further transmission. VL is also an important opportunistic infection of patients with HIV/AIDS. The people who suffer from VL are mostly poor socioeconomic groups, living in rural areas[4].

c) *Dengue*

There are more than 100 countries in the world where dengue fever is endemic. In India, it is endemic in 35 states /UTs. The highest number of cases were reported from Maharashtra, Odisha, West Bengal, Karnataka, and Gujarat. All the four serotypes i.e., dengue 1,2,3 and 4 are present in India but at present DENV-1 and DENV-2 serotypes are widespread [3]. Recognizing Dengue as a global threat, WHO has launched a global strategy promoting coordination and collaboration among multisectoral partners on integrated vector management, and sustainable control measures at all levels. The goals are to reduce 2020, dengue mortality by at least 50% and dengue morbidity by at least 25% respectively, and to estimate the true burden of disease by 2015.

d) *Malaria*

2020 million people worldwide, or 36% of the world's population, are malaria victims in 107 tropical and subtropical nations and territories. Out of the roughly 1.4 billion people living in 11 countries in the WHO's southeast Asian region, 1.2 billion (85.7%) are at risk of contracting malaria, the majority of whom reside in India. India alone accounts for roughly 70% of the 2.5 million reported cases in South East Asia. At the moment, 80.5% of India's 109 billion people reside in malaria risk areas. 4.2%, 32.5%, and 43.8% of this group reside[5]. Currently, the states of Orissa, Jharkhand, West Bengal, North Eastern States, Chhattisgarh, Madhya Pradesh contribute the bulk of malaria. About 15% of all malaria cases reported in India are from urban areas, which are primarily linked to migrant populations and construction-related activities. Most of the malaria attributable mortality is reported from Orissa and other forested areas occupied by ethnic tribes in the country [5]

FACTORS PREVAILING TROPICAL DISEASES

These diseases are distributed as per geographical basis, mainly concentrated in Tropic Cancer and Tropic of Capricorn. The following are some of the factors contributing to the wide spread of NTD's,

- Geographical and climatic factor- Hot and humid temperatures are favorable for the transmission of diseases and favorable for vectors. High rainfall throughout the year causes water reservoirs and formation of breeding grounds and the largest number of possible insect vectors. e.g., malaria vector female anopheles' mosquito is predominantly found in tropical regions.
- Socio-economic factor- poverty is one of the reasons for this disease as it causes a lack of health facilities, less awareness about health, no reach to medications [6].
- Sanitation and hygiene- This is one of the most important factors because most of the vectors for these diseases are soil born, animal born, and also born from livestock. If water is not properly disposed of then it may give birth to many diseases [6].
- Stigma- Stigma involves negative attitudes or discrimination against someone based on a distinguishing characteristic such as a mental illness, health condition, or disability.

CURRENT DRUG THERAPIES AND CHALLENGES ASSOCIATED WITH THEM

a) Dengue Fever

It is an arboviral (Single-stranded RNA virus) infectious disease transmitted by carrier *Aedes aegypti* and to less extent *aedes albopictus* they breed in a tropical climate. Chikungunya and Zika are also transmitted by these vectors. Symptoms of dengue include sudden onset of high fever, retro-orbital pain, headache, myalgia, arthralgia, mild hemorrhage, and maculopapular rash [7].

b) Current therapy for dengue and challenges associated with it

There is no vaccine or appropriate cure for dengue. Early diagnosis of diseases can help to reduce the mortality rate because of early treatment cover-ups the viral infection. Late diagnosis and treatment may increase the mortality rate to 5-10% [8]. Currently, drugs used for dengue therapy are immunomodulators, and antibiotics such as chloroquine, statins, prednisone, favipiravir, celgosivir are mainly used. But their use is limited because of nonspecificity and toxicity [9]. This virus spreads into inaccessible anatomical regions like NS, synovial fluid, and lymphatic system so it is difficult to treat with conventional therapy in emergency cases.

c) Leishmaniasis

The current treatment for leishmaniasis is based on chemotherapy and poses limitations such as toxicity, difficult route of administration, and lack of efficacy on parasitic infections in some endemic areas. Despite considerable efforts to find new drugs against *Leishmania* spp., the treatment of leishmaniasis is still based on the use of the pentavalent antimonials sodium stibogluconate and meglumine antimoniate, developed during the 1920s [9]. These days, both of the aforementioned leishmanial chemotherapy's cornerstones have developed resistance and are no longer working as intended to eradicate the parasite. According to a case report that was just recently published, an unusual instance of amp-B resistance has been reported in India. Amphotericin-B (Amp-B) has been used with caution despite being effective against fungus and leishmaniasis. This is because of the drug's systemic side effects and toxicity. Nephrotoxicity and adverse infusion effects are its main limiting factors. The main causes of pentamidine (PTM) therapy's low adherence and associated lower cure rates are issues like painful necrotic injection site lesions, nephrotoxicity, and hypoglycemia. [9].

d) Malaria

Chloroquine and artemisinin's are widely used drugs for malaria treatment. Major challenges associated with malaria therapy by using these drugs is the development of resistance to available drugs by plasmodium moreover, the toxicity of these drugs is an issue of concern. Chloroquine has a high volume of distribution so it may accumulate in the tissue causing long-term side effects. Also, there is the problem of class resistance among the available drugs of malaria. The following table explains the problems associated

with traditional malaria treatment. In the case of conventional drug therapy of malaria, there is a high chance of relapse as hypnozoites may remain dormant in the liver.

IMPORTANCE OF NANO-BASED THERAPEUTICS?

Nanoparticles have some unique properties such as-

- Small particle size (which may make it easier to deliver drugs to anatomically advantageous sites).
- High surface-to-volume ratios (which allow for the storage of large drug payloads).
- Tunable surface charge (to facilitate cellular entry across the negatively charged cellular barrier membrane).
- It has been shown that nanoparticles can have intrinsic antiviral properties due to their biomimetic characteristics tiny particles, such as silver,
- Additionally, the potential for drug encapsulation can result in functionalization by the creation of stable structures or modifications with polymers like poly (ethylene glycol) (PEG), all of which can improve delivery by enhancing stability and drug retention times and allowing for better drug dosing.
- Drug delivery is thought to be greatly enhanced by creating nanoparticles with targeting moieties that are more specific to desired cell types, target tissues, or subcellular compartments.
- Nano particulate drug carriers can traverse across these membranes and are therefore promising tools for treatment Recent developments in the field of nanotechnology have proven its efficacy in drug delivery applications and overcoming several limitations of conventional drugs [1].
- The carrier/vehicle with nanoengineering capabilities can efficiently deliver the drugs into the infection site and get rid of the parasites, viruses, protozoans, etc.,
- The conventional anti-infective agents/ and drugs have low tolerability, low bioavailability, longer duration of treatment profile, high level of drug resistance against disease-causing parasites, and difficulty to administer, significant advantages have been noted in the development of novel nano-biopharmaceuticals that can cure NTDs [11].
 - The bioavailability of drugs is improved by these nano-engineered particulate systems, which can encapsulate a high density of conventional drug molecules and deliver them directly into target-oriented tissues, cells, or sites that are severely infected. Because of this site-specific drug delivery that can lower drug resistance while also increasing the sensitivity of drugs against disease-causing pathogens by stimulating the immune system [1].
 - Unlike conventional macromolecular drugs, they can freely circulate within the human body. Thirdly, these nanoparticles can be created using a mix of synthetic and natural polymeric materials, allowing for the sustained or controlled release of the therapeutic molecules over a period of days [12].
 - Reducing the toxicity and cost, which had been a major barrier in the current conventional treatment for NTDs, will benefit public health when a lower therapeutic dose of a conventional drug is attached to or

encapsulated in a nanoengineered particulate system.

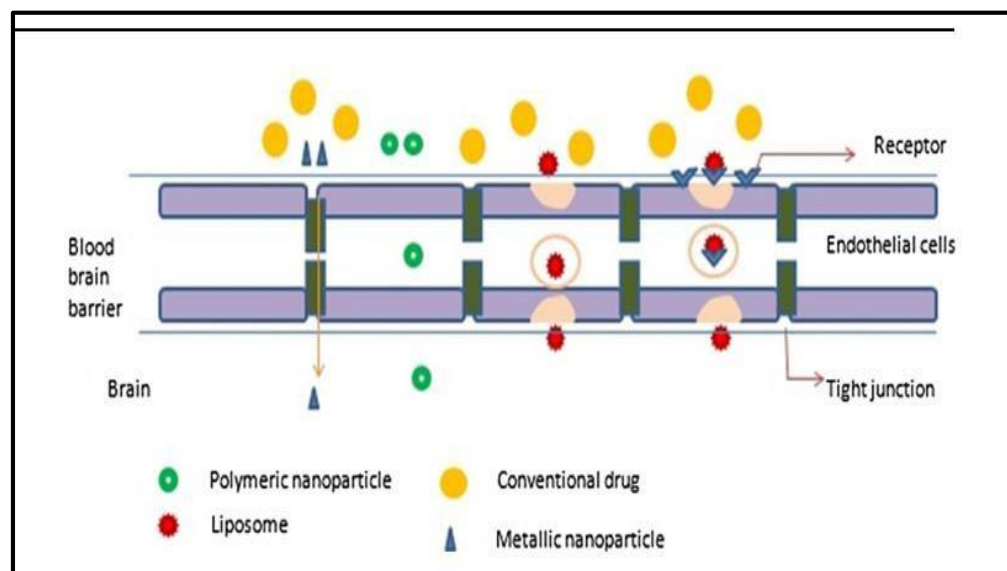


Figure 2. Conventional drugs vs nanotechnology-based drug delivery [13].

TYPES OF NANOTHERAPEUTICS USED IN THE TREATMENT OF NTD’S

The following classification depicts the different types of nanotherapeutics used in NTD’s

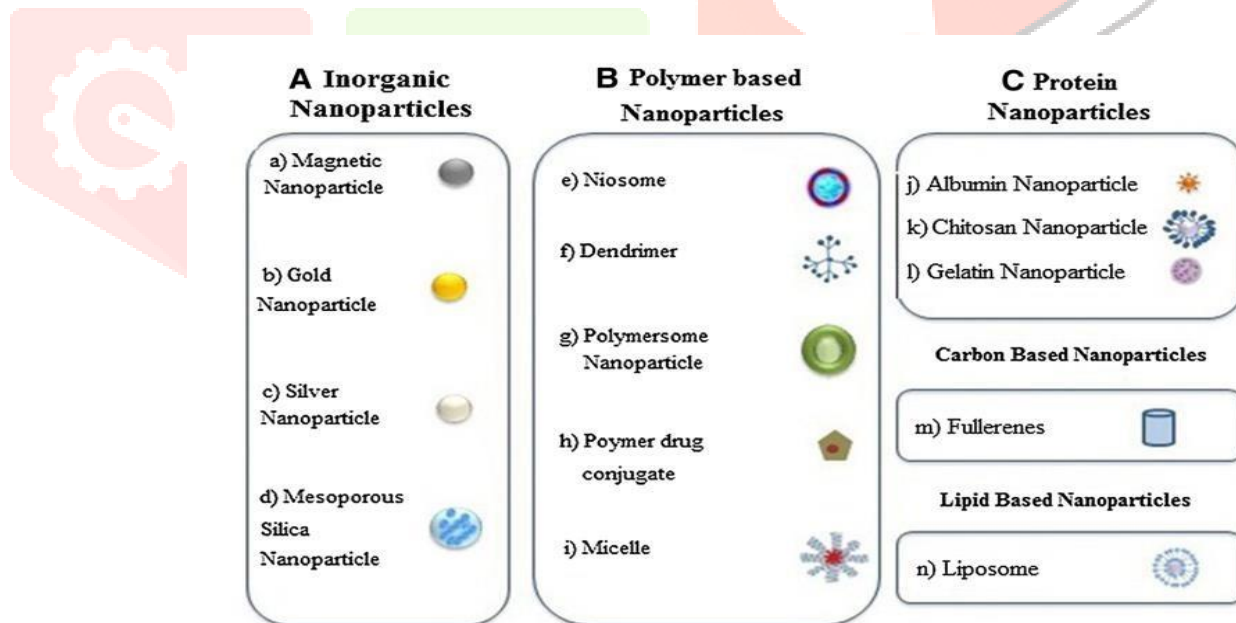


Figure 3. Types of nanocarriers used in therapy of tropical diseases[14]

Tropical disease treatments that use different types of nanocarriers[14]

The best delivery system for molecules in biomedical applications is considered to be nanoparticles with excellent biodegradability and biocompatibility. It is necessary to research the biological and physio-chemical characteristics of the ideal drug delivery system. Drug delivery methods based on nanoparticles, such as solid

lipids, liposomes, dendrimers, noisomes, protein, polymeric, and polysaccharide nanoparticles, are thought to be effective [15]. The two main components of the nanoscale complexes currently under development are the therapeutic drug and the nano vehicle, which serve as the carrier agent. The drug is usually confined within a membrane or a matrix system and can also be absorbed, dissolved, or dispersed from the system. Nanoparticles can be used to provide targeted delivery of drugs at the specific site and thus enhance the uptake of poorly soluble drugs and bioavailability. Drugs are designed with nano-enabled structures to protect them from enzymatic and hydrolytic degradation. They also lengthen the blood residence time and check drugs for first-pass metabolism. The nanoscale allows for efficient tissue penetration and may also cross biological barriers. [1].

OVERVIEW ON DIFFERENT TYPES OF NANOPARICLES USED IN THERAPY

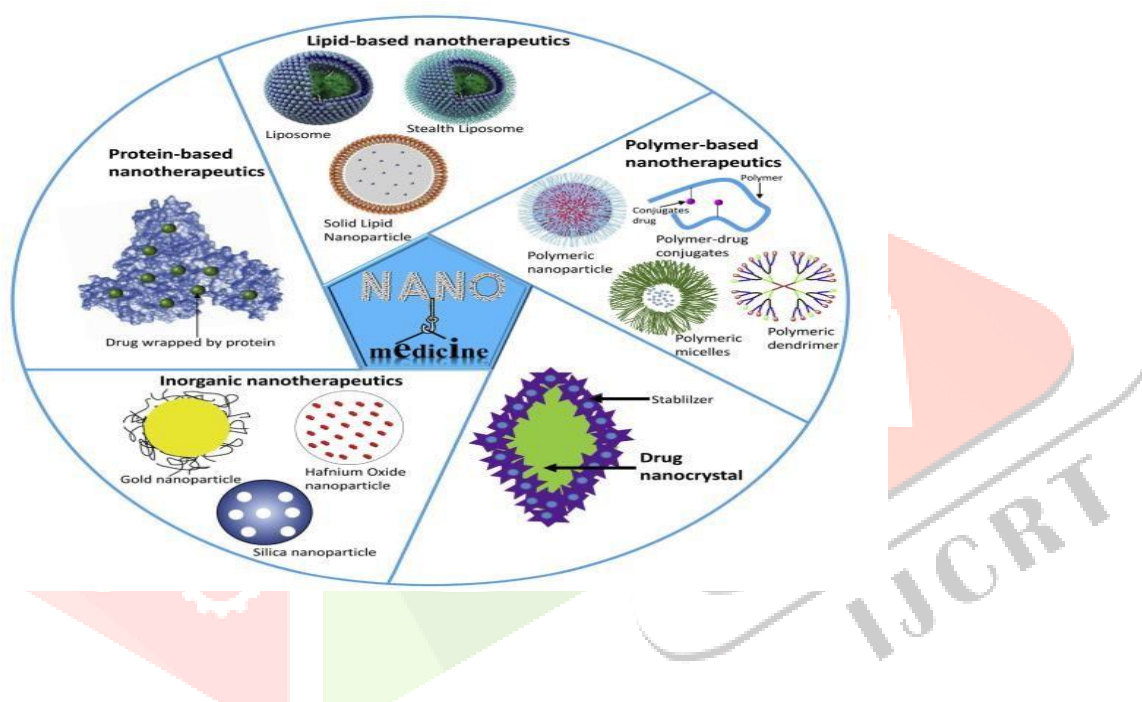


Figure 4. Types of nanocarrier systems used in the treatment of tropical diseases[16]

a) Inorganic nanoparticles

Inorganic nanoparticles such as magnetic nanoparticles (iron oxide), gold, platinum, chromium, manganese, zinc, selenium, titanium, molybdenum, palladium, silica, copper, cerium oxide, and silver nanoparticles, bimetallic, nano shells, and nanocages have been continuously used and modified to enable their use as a therapeutic and diagnostic agent. Depending on size and shape, an inorganic nanoparticle can be used for a variety of purposes, including catalysis, sense, optics, antibacterial activity, cytotoxicity, and data storage.

b) Gold Nanoparticles (AuNPs)

It is the most attractive microelement that plays a significant role in the field of bionanotechnology. WHO also recommended gold as a food additive in 1983 [1]. Colloidal gold has been used as a medicinal agent for treating rheumatoid arthritis, alcoholism, tuberculosis, and neoplastic disorder. Scientists are currently interested in metal nanoparticles, particularly gold nanoparticles (AuNPs), due to their stability, oxidation

resistance, and biocompatibility. AuNPs offer numerous beneficial properties for the development of drug delivery systems. The core materials of gold are chemically static and non-cytotoxic. The unique nanometric dimension of AuNPs provides a large surface area readily available for modification with loading targeting molecules or specific biomarkers for drug delivery systems. It can be utilized as a potential vehicle to deliver macromolecules such as proteins, DNA, or RNA. It also enables ease of drug attachment through ionic or covalent bonds or adhesion. Like many nanodrugs, PEG can be used as an attachment biomaterial on the surface of metallic nanoparticles to increase stability and circulation time, in addition to other targeting agents, it has been investigated that AuNPs with a diameter of 50 nm can cross the BBB. Moreover, PEGylated AuNPs conjugated with TNF (tumour necrosis factor) can extravasate through tumour cells due to their leaky vasculature[1].

c) Silver Nanoparticles (AuNPs)

Several types of research have conceded that AgNPs are widely known for their antimicrobial and anticancer activity [12]. The use of silver in nanoparticle form has reduced cellular toxicity but not antibacterial efficacy as compared to its ionic form. AgNPs are a popular choice in disease management because of their specific interaction with and disruption of the mitochondrial respiratory chain. AgNPs disrupt mitochondrial function by inducing the generation of ROS and suppressing ATP synthesis, which leads to DNA damage.

d) Magnetic nanoparticles

For biomedical applications, such particles with superparamagnetism at room temperature are typically chosen. Owing to its high field irreversibility, high saturation field, superparamagnetism, and extra anisotropy, magnetic nanoparticles cover a broad spectrum of biomedical applications. These characteristics result from the surface effects and limited and finite-size effects that determine the magnetic behaviour of specific nanoparticles[17]. Such particles with superparamagnetism at room temperature are usually selected for biomedical applications. Owing to its high field irreversibility, high saturation field, superparamagnetism, and extra anisotropy, magnetic nanoparticles cover a broad the spectrum of biomedical applications. These traits are due to the narrow and finite-size effects and surface effects that define the magnetic behavior of individual nanoparticles. Magnetic nanoparticles enable the systematic administration of the drug to an exact target site in the human body while remaining eventually localized, due to applied magnetic field. The basic idea is that therapeutic agents are either attached to or encapsulated in, magnetic micro or nanoparticles. The polymers or metal/nonmetal coating acts as a support for the delivery of therapeutic drugs or nucleic acid. These particles are made of porous polymers with magnetic nanoparticle precipitates inside the pores and have magnetic cores enclosed by polymer or metal coatings. By functionalizing the polymer or metal coating, cytotoxic drugs or therapeutic DNA for targeted chemotherapy is attached to address the genetic flaw. Magnetic nanoparticle technology thus offers the potential for selective and competent delivery of therapeutic genes or drugs due to external magnetic fields [17].

e) Polymer Based nanoparticles

Polymeric nanoparticles are submicron colloidal solid particles ranging approximately from 10 to 1000 nm is increasingly gaining popularity owing to their better stability and higher encapsulation efficiency for delivery of drugs to tumor cells. The drug is either loaded inside a polymer or conjugated on the surface of polymeric nanoparticles. The polymeric coating enhances the solubility of the hydrophobic drugs, provides stability from the extracellular environment, and lowers the toxicity of drugs with a high therapeutic ratio. These particles also permit controlled and persistent release of drugs to the specific target sites. These particles also permit controlled and persistent release of drugs to the specific target. One of the polymers found to be highly effective as a coating material for nanoparticles in degenerative diseases is polyethylene glycol (PEG). It is either used for encapsulation or surface modification owing to its targeting capabilities and avoiding uptake by the reticuloendothelial system. Biodegradable polymers such as chitosan and collagen or non-biodegradable polymers such as polyvinyl alcohol (PVA), PEG, monomethoxy poly-(ethylene glycol) (MPEG), polysorbate are some of the blood compatible polymers that have been used for the development [12].

f) Niosomes

Niosomes are nanometric-scale classes of vesicular drug delivery systems with a bilayer membrane as well as hollow space. In niosomes, medication is encapsulated in vesicles and it is composed of bilayer-hydrated non-ionic surface-active agents such as cholesterol or its derivatives and hence the name niosomes. Certainly, the formation of vesicles by surfactants is not a coincidence. The creation of thermodynamically stable niosomes requires a specific ratio of surfactants and additives. Mechanical energy, chemical potential excess energy, and surface energy are three types of interaction energies that provide the energy needed for the formation of niosomes. The aggregation of nonionic surfactant monomers and the formation of niosomes is the result of two opposing forces: first, a high interfacial tension between lipophilic groups and water that causes these groups to associate, and second, repulsive forces between head groups (the steric and hydrophilic repulsion). Niosomes in the range of 1–10 μm have been found to bear more stability than those in the submicron size. Bigger niosomes tend to segregate more than smaller ones to increase the excess free energy because they have lower surface free energy from a thermodynamic perspective [16]. Niosomes are stable and osmotically active. Additionally, compared to liposomes, the drug has much higher stability over extended periods of storage. Since the nonionic surfactants that are frequently used are biocompatible, biodegradable, and non-immunogenic, niosomes are highly compatible with biological systems and have low toxicity. Niosomes are administered via a variety of different pathways. The niosomes can trap a wide range of drugs, including hydrophilic and lipophilic ones with various solubilities.

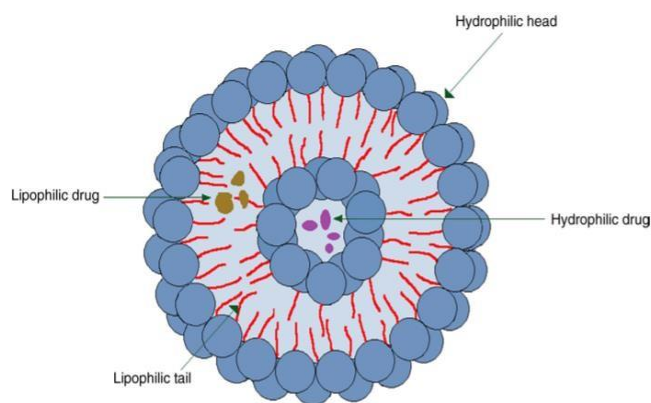


Figure 5. Noisome as nanocarrier [18]

g) Dendrimers

Dendrimers are novel three-dimensional, hyperbranched globular nano polymeric architectures. The term dendrimer is derived from a Greek term dendron that means —tree, which is logical given their typical structure with several branching units [19]. Dendrimers are defined as synthetic macromolecules characterized by high branching points, threedimensional globular shapes, monodispersity, and nanometric size range. They are globular, nano-sized (1-100 nm) macromolecules with a particular architecture constituted of three distinct domains: i) a dendrimer's core, which is composed of an atom or molecule with at least two chemical functions that are identical; ii) branches that branch out from the core are made up of repeat units with have at least one branch junction, whose repetition is organized in a geometrical progression that results in a series of radially concentric layers called —generation [19].

Types of dendrimers

- Polypropylene imine (PPI) dendrimers
- Polyamidoamine (PAMAM) dendrimers
- Core-shell dendrimer
- Chiral dendrimers
- Polyester dendrimers
- Peptide dendrimers [20]

Dendrimers have a distinct 3D structure and a number of surface functional groups, which allow them to act by encapsulating drugs within the dendritic structure or by forming electrostatic or covalent bonds between drugs and dendrimers' terminal functional groups as a means of drug delivery. The first mechanism is owed to *in vivo* cleavage of covalent bonds between drug and dendrimer in the existence of enzymes or an environment required for bond breaking. The second mode of drug release is the alteration in physical conditions temperature and pH which are not dependent on external factors [20].

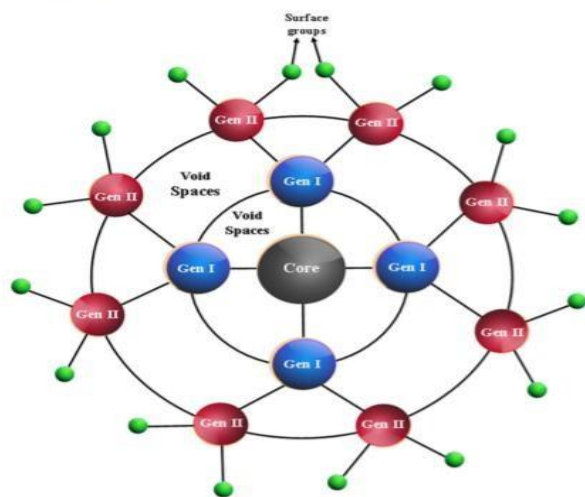


Figure 6. Dendrimer

h) Liposomes

Hollow spherical structures called liposomes and vesicle-like nanocarriers are created by the self-assembly of surfactants and natural and/or synthetic lipids or block copolymers in an aqueous solution. Liposomes are suitable soft nanocarriers for a variety of therapeutic applications because of their high loading capacity, excellent biocompatibility, and ease of incorporation of tissue-recognition ligands. The self-association of phospholipids to form nanocarriers is a flexible prototype for drug delivery applications[21]. Block copolymer vesicles, phospholipids, and surfactants make up liposomes, which are a versatile platform for the creation of improved drug delivery therapies in a variety of biomedical applications. [22]. Deoxyribonucleic acids (DNA), proteins, or imaging agents can all be enclosed by liposomal systems due to their capacity to entrap both lipophilic and hydrophilic compounds[21].

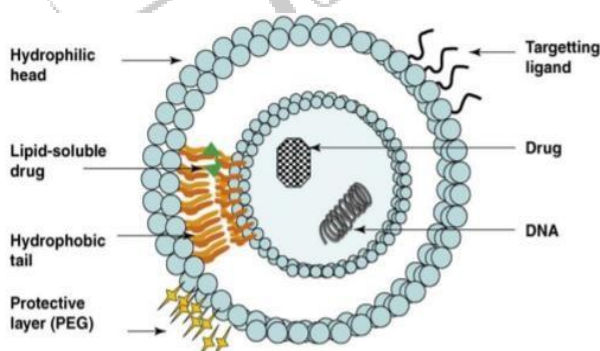


Figure 7 Liposomes as nanocarrier [22]

Drug loading into liposomes can be achieved through (i) liposome formation in an aqueous solution saturated with soluble drug; (ii) the use of organic solvents and solvent exchange mechanisms; (iii) the use of lipophilic drugs; and (iv) pH gradient methods [23]. Liposome and lipid nanoparticle-based therapeutic drugs approved for humans typically contain phosphatidylcholine (PC; neutral charge) as a major membrane building block, with fatty acyl chains of varying lengths and saturation. In some cases, cholesterol (~30 mol % of total lipid)

is included to increase rigidity and reduce serum-induced membrane instability because of serum protein binding [20].

i) Albumin based nanocarriers

Albumin, a versatile protein carrier for drug delivery, is non-toxic, non-immunogenic, biocompatible, and biodegradable. Therefore, it is an ideal material to fabricate nanoparticles for drug delivery [24]. It is easy to purify and is soluble in the water allowing better delivery by injection and thus a perfect candidate for nanoparticles preparation. Therefore, it is a perfect material to fabricate nanoparticles for drug delivery [1]. Albumin nanoparticles have gained considerable attention owing to their high binding capacity of various drugs and being well tolerated without any serious side effects. It holds bioactive molecules and has shown improved pharmacokinetic properties by providing longer circulation time and more disease-specific accumulation, and they are emerging as a capable theranostic agent.

Types of albumin nanoparticles

- Ovalbumin
- Bovine serum albumin
- Human serum albumin

Covalent derivatization of albumin nanoparticles with drug targeting ligands is possible, due to the presence of functional groups (i.e. amino and carboxylic groups) on the nanoparticle surfaces [24]. Also, they are expected to be well tolerated, which is supported by clinical studies with registered HSA-based particle formulations such as Alunex™ and Abraxane™ [24].

NANOTECHNOLOGY BASED CASE STUDIES FOR THE TREATMENT OF TROPICAL DISEASES

Leishmaniasis

a) Polymeric nanoparticle

Polymeric nanoparticles such as nanocapsules and nanospheres have been introduced to be used as passive drug delivery systems because they have a long circulation time and are rapid.

Additionally, the bioavailability of medications is enhanced by nanoencapsulating antileishmanial agents.

The most widely used polymers are

- Polylactide (PLA),
- Polylactide–polyglycolide copolymers (PLGA),
- Polycaprolactones (PCL),
- Polyacrylates (PCA)

- Polyalkylcyanoacrylates (PACA)

Gaspar *et al.*, evaluated the potential of primaquine-loaded poly-alkyl cyanoacrylate (PACA) nanoparticles against *Leishmania donovani* in macrophages. The primaquine loaded on the nanoparticles was reported to be 21 times more efficient than the free form of primaquine in reducing the parasite burden in macrophages. Among the polymeric carrier systems, PLGA is widely used in the passive and active delivery of drugs. Carvalho *et al.*, developed deoxycholate amphotericin B in PLGA nanoparticles and dimercaptosuccinic acid (DMSA) nanoparticles. They evaluated the efficacy of a new nano-drug delivery system in the treatment of cutaneous leishmaniasis and it appeared significantly more effective in reducing parasite number and cell viability compared with the free form of amphotericin B [25]. Moreover, reduced dose frequency requirement and increased dosing interval to achieve the same therapeutic level of free amphotericin B was resulted by using this nano amphotericin B delivery system [26].

b) Metal Oxide nanoparticle

Metal oxide nanoparticles are particularly proposed as an alternative approach to current antibiotics in the treatment of bacterial infections because they have major efficacy mechanisms such as developing multi-complexes against bacteria. Their ultra-small size and large surface areas interact with DNA and enzymes and disrupt vital activity and structures of the infectious agents. As an example, metallic compounds and metal oxide nanoparticles are effective in inhibiting the enzyme of trypanothione metabolism that is vital in the survival of *Leishmania* parasites. Silver doped titanium dioxide (TiAg) nanoparticles have been demonstrated as promising antimicrobial agents because they inhibit several types of bacteria. Also, there is information regarding the antibacterial effects of TiAg nanoparticles on resistant and drug-sensitive bacteria [26].

c). Liposomes

Drugs that are liposomally encapsulated can be targeted to the intracellular *Leishmania* amastigotes for antileishmanial therapy. By phagocytosis, the drug-containing liposomes naturally enter the macrophages and passively deliver the drugs to the phagolysosome, where they can act on the parasites directly [24]. AmB deoxycholate's effectiveness as an antileishmanial agent has been constrained by severe acute and long-term side effects. When compared to AmB deoxycholate (Fungizone), the commercial liposomal AmB, Ambisome, produced by Gilead Sciences, showed low toxicity and a high cure rate (above 90%). It is the only medication that has been approved by the FDA since 1997 for the treatment of VL brought on by *L. donovani* in India. AmB liposomal formulation, there are currently other formulations of this medication on the market: the colloidal formulation Amphocyl in Europe (also known as Amphotec in the USA), the injectable suspension Abelcet in the USA, Fungisome in India, and the emulsion Amphomul in India. However, problems with administration and toxicity still exist in each of these therapeutic options. There are not many studies in experimental models examining the use of liposomes containing antimonials for the treatment of leishmaniasis, despite the urgent need to improve antimonial chemotherapy. [27]. L-AMB pharmacokinetic studies were carried out on immunocompromised patients who had fungus infections. It has never been examined on leishmaniasis patients. Paromomycin (PRM) delivered by liposomes showed preferential targeting of the antibiotic to the spleen, lungs, and liver when compared to free PRM [14].

d)Solid Lipid Nanoparticles

Lipid colloidal drug carriers such as nanoemulsion (NE), solid lipid nanoparticles (SLN), and nanostructured lipid carriers (NLC) have been of great interest to drug delivery scientists mainly due to their versatile nature and interesting advantages as administration of the very poorly water-soluble drugs. SLNs are prepared by using physiologically tolerated solid lipid components and are applied for the administration of the lipophilic drug. Paromomycin has been the most intensively studied compound for the potential topical treatment for leishmaniasis. Conventional topical dosage forms are already available and have promising results but the efficacy of these dosage forms is not satisfactory. This is because of the physiochemical properties of paromomycin. Studies show that SLN improves the interaction of the drug with the stratum corneum and improves its penetration[14].

e)Nanotechnology-based case studies for the treatment of leishmaniasis

Amphotericin B (Amp-B) is the second-line treatment for the treatment of Leishmaniasis but it is associated with nephrotoxicity which limits its use in therapy. A study was performed by Mussadara Saquib et,al 2020 in which A nanosized formulation of Amp-B was formulated using biopolymer polycaprolactone (PCL) and optimized.The nanosized formulation was studied for *in vitro* dissolution, particle size, pharmacological efficacy, rate of drug release. The main objective of this study is to develop the polymeric nanoparticles by high-pressure homogenization (HPH). These formulations are desirable to reduce the side effects associated with oral and IV routes. Size distribution and particle morphology studies were carried out by zeta sizer and scanning electron microscopy respectively. The average size of formulation was 183 nm and the particle morphology was spherical. The following figure 8 represents pharmacological evaluation of the anti-leishmanial activities of the polymeric nanoparticles, which are also compared with Amp B and AmBisome at different concentrations (1–0.004 $\mu\text{g/mL}$ Amp B) as prepared by serial dilution. It was obvious that the prepared emulsion loaded with Amp B significantly improved its anti-leishmanial activity.

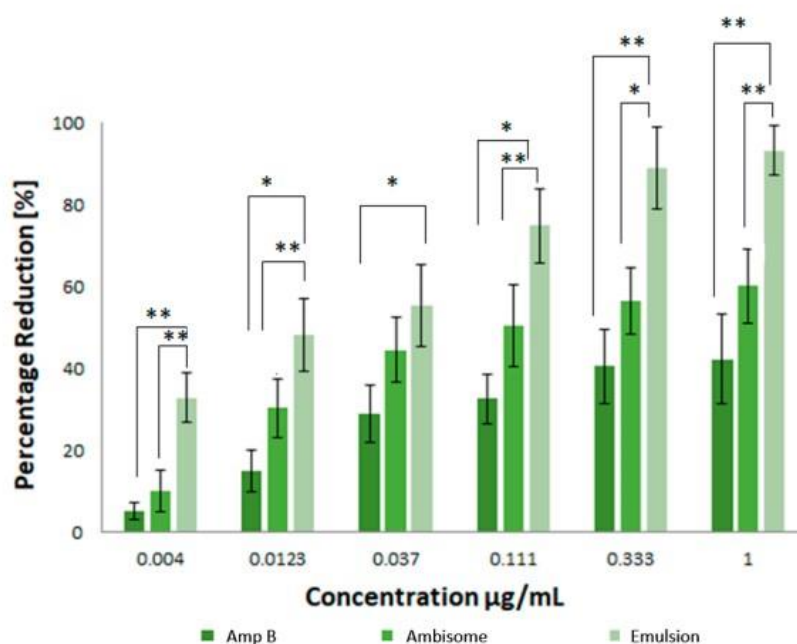


Figure 8. Amphotericin loaded nanoparticles vs Ambisome vs amphotericin B [28]

The parasites were exposed to Amp B, AmBisome, and the emulsion to show that each of the prepared samples had the ability to stop parasite growth. Amp B, AmBisome, and emulsion all had measured half-maximum inhibitory concentrations (IC₅₀) of 0.289 0.07, 0.21 0.05, and 0.023 0.007 g/mL, respectively. By comparing IC₅₀ value it can be concluded that Amp B loaded nanoemulsion has greater efficiency in inhibition of *L. donovani*.

Case study-Paromomycin was loaded in PLGA polymer and coated with mannothiosylated chitosan (MTC) and its efficiency against leishmaniasis was compared by Iqra Afzal *et al*. PLGA is a synthetic, non-toxic, biocompatible, and biodegradable polymer used for loading hydrophilic drugs but it lacks the properties of mucoadhesion and enzyme inhibition. So, to overcome this mannosylated chitosan was prepared and coated with a thiolated polymer which results in excellent mucoadhesion, enhanced permeability, and P-gp inhibition. These properties are based on the ability of thiomers to develop disulfide bonds with cysteine-rich subunits of proteins. Later on, the prepared MTC-PLGA-PM (Mannosylated thiolated paromomycin loaded PLGA) were evaluated for physicochemical properties and *in vitro* and *in vivo* efficacy average particle size of MTC-PLGA-PM was found to be 391nm. *In vivo* anti Leishmanial efficiency of MTC-PLGA-PM was compared against free drug. Paromomycin (PM), PLGA-PM, CS-PLGA-PM (chitosan-PLGA-Paromomycin), TCS-PLGA-PM and blank sample. This was performed by loading drugs against *Leishmania donovani* burden in the liver and a graph of *L. Donovanii* units survived vs the formulation used was plotted as below:

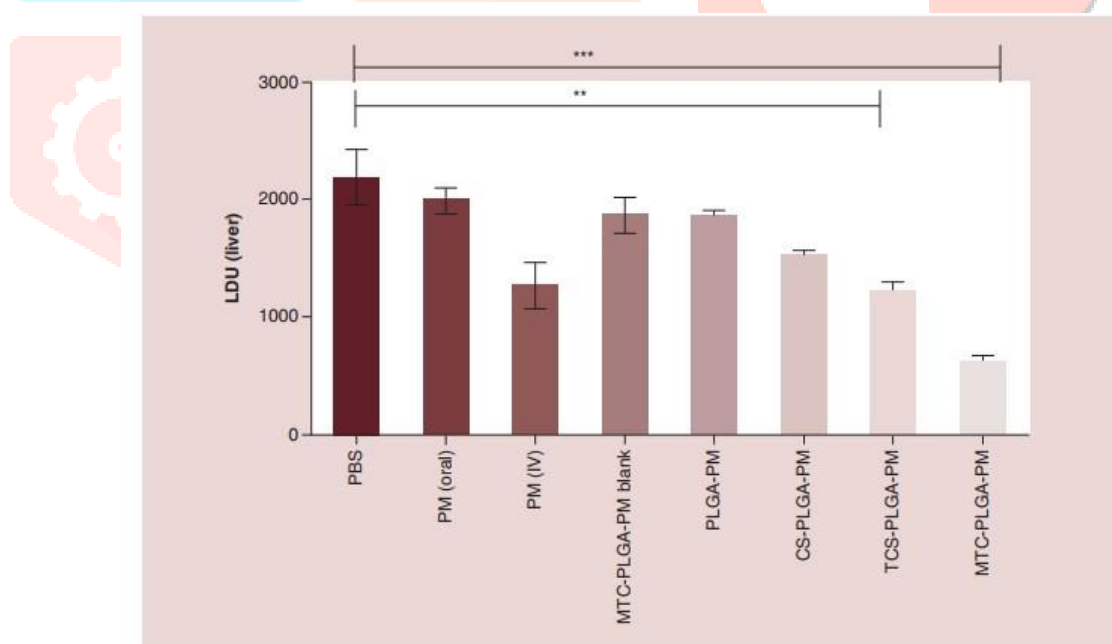


Figure 9. *In vivo* antileishmanial activity of MTC-PLGA-PM vs other preparations[29]

From the graph, it can be concluded that the *L. donovani* units (LDU) in the liver after treatment with MTC-PLGA-PM had the least count that meant the inhibition efficiency of MTC-PLGAPM was the maximum of all which were used in the experiment [30].

Malaria

The aim of nanotechnology-based therapy in malaria is to protect the drug from extracellular degradation, improve the selectivity of drugs to target molecules, and reduce the dosing frequency of drugs. In general, long-circulating nanoparticles can improve the AUC. The ability of a nanocarrier to stay in the bloodstream for an extended period of time is crucial for improving the interaction with infected red blood cells (RBCs) and the parasite membrane in the context of malaria[31]. Passive drug targeting using hydrophilic surface-modified Nanocarriers. Nanocarriers' surfaces can be modified with hydrophilic polymers like poly (ethylene glycol) (PEG) to delay phagocytosis, lengthen the drug's half-life in the blood, and alter the drug's biodistribution and pharmacokinetic profile. Passive targeting of the Mononuclear phagocytic System (MPS) can be done by, longcirculating nanocarriers. Also, the reduced by drug-loaded nanocarriers which results in reduced toxicity.

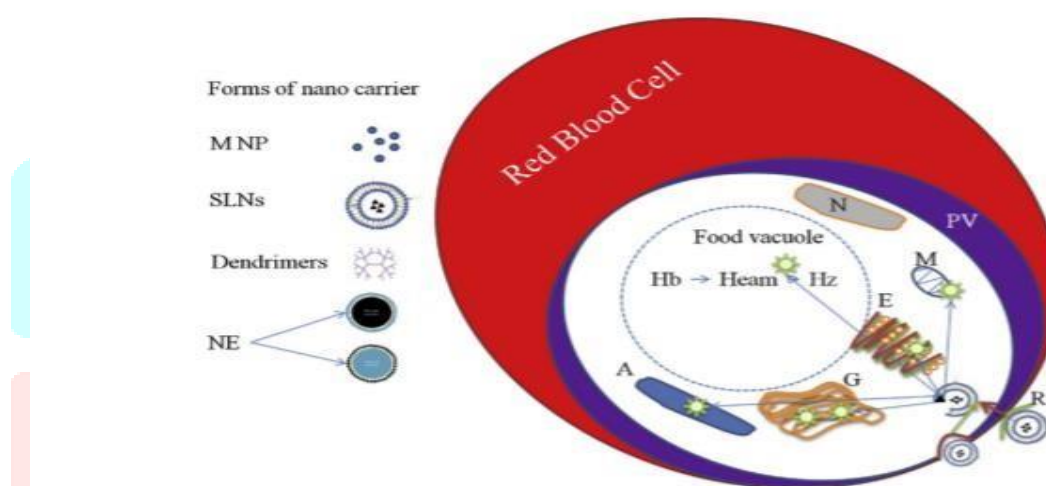


Figure 10. Nanocarriers used in malaria [32]

a) Solid lipid nanoparticles for loading antimalarials

Colloidal carriers known as solid lipid nanoparticles (SLNs) are made of complex acylglycerol mixtures, waxes, and para-acrylarenes, which are stabilised by surfactants. In addition, the SLNs have the ability to sustain the controlled drug targeting and delivery, have less toxicity due to the physiological biocompatibility, prevent the photochemical degradation during the drug immobilization, reduce drug leakage [34] Transferrin (Tf) coupled solid lipid nanoparticles SLN were investigated for their ability to target quinine hydrochloride to the brain in management of cerebral malaria. *In vitro* fluorescence studies were performed and levels of quinine loaded on transferrin vs plasma levels of conventional quinine drug were compared and it showed that the SLN loaded with quinine show enhanced uptake in the treatment of cerebral malaria.

Case study- Another study was performed by Kanan *et.al.* on artemisinin (AM) which has low oral bioavailability of about 40% [35]. It has poor aqueous solubility and degrades in the acidic environment of stomach. To overcome this nanostructured SLN were investigated recently. Amphotericin-loaded SLN known as *Nanoject* with a particle size of 60 nm were formulated using the microemulsion template technique. Antimalarial activity of *Nanoject* and conventional Artemesin (*Larither*®) was evaluated and compared. The

project showed significant antimalarial activity [36]. Nisha *et al.*, also reported the synthesis of the Artemether SLNs (ART-SLNs) using the hot homogenization method by mixing the drug with tripalmitin (organic phase) and Cremaphor® (aqueous surfactant) solution. The ART-SLNs showed lesser hemolysis and improved *in vivo* antiplasmodial (70% chemosuppression) activities in *P. berghei* when compared with the free artemether treatment [32].

b) Nano and microemulsions

Nano and microemulsion (o/w) with a mean diameter less than 500 nm were investigated as antimalarial carriers. It showed two important advantages over colloidal carriers i.e., low cost and availability as the oral dosage form. In this primaquine, PQ was encapsulated in nanoemulsion with Chylomicron proposed for targeting hepatocytes [10]. Recently, an O/W NE made with Miglyol® was reported to be used to encapsulate PQ for oral delivery. Nanoemulsion PQ's antimalarial activity was improved at a lower dose than that of PQ in solution form. Furthermore, NE PQ levels in the liver were substantially higher following oral administration, confirming the drug's improved antimalarial efficacy.

c) Dendrimers

Dendrimers were used to solubilize artemether, a powerful and extremely hydrophobic antimalarial drug. PEG-lysine type dendrimer and chondroitin sulfate A (CSA) were used to create a drug delivery system that was both sustained and regulated and administered through the intravenous route. This system entrapped 10-18 molecules of Artemisinin's. The *in vivo* studies revealed that both CSA-coated and uncoated CSAs released AM for a longer period. Dendrimer system with no coating lasted up to 13 hours. The Mean residence time (MRT) of was discovered to have grown between 2- and 4-fold respectively from those coated to uncoated dendrimer as compared to injected AM solution as antimalarial nanocarriers that release antimalarials over time [25].

d) Nanotechnology-based case studies for the treatment of malaria

Another study was performed by Warner *et al.* Two formulations were designed for intravenous administration: (i) conventional poly (lactic acid)-NC without surface modification (ii) PLA-PEG NC. Despite the different biodistribution profiles of unloaded Nanocarrier only a slight difference in PK profile was observed in halofantrine-loaded nanocarrier. As senescent and parasitized RBC are removed by the liver and spleen in infected mice, this process may saturate the MPS, which would then affect NC pharmacokinetics and lessen the difference between conventional PLA-NC and long-circulating PLA-PEG NC. This example demonstrated that, even in mice with unmodified PLA nanocapsules, passive targeting was likely accomplished [28]. Furthermore, conventional neutral multilamellar liposomes prepared with egg phosphatidylcholine (EPC) and cholesterol (CHOL) were the first proposed nanocarriers followed by long-circulating and targeted liposomes for carrying drugs. Artemether (AM), an antimalarial drug introduced in 1988, was encapsulated in neutral multilamellar liposomal formulations to be used by the oral route. Evidence was found that the type of the phospholipid, as well as the incorporation of cholesterol in the liposomal bilayer, altered the AM entrapment efficiency, the size of the liposomes, and the drug release rate. Multilamellar liposomes prepared with dibehenoylphosphatidylcholine (DBPC), CHOL and AM (1:1:2 molar ratio)

presented a mean size of $3.20 \pm 1.03 \mu\text{m}$ and a drug entrapment of 82.3%. The AM release rate from liposomes prepared with mixtures of DBPC and dipalmitoylphosphatidylcholine (DPPC) (1:1 molar ratio) was 0.818%/day, while it was only 0.783%/day when CHOL was added to DBPC in a ratio of 1:1 (low CHOL) and 0.616% when CHOL was used in a ratio of 1:2 (high CHOL). These findings showed that the increase in the length of the acyl chain of the phospholipids as well as the addition of CHOL led to a decrease in the AM release rate. Recently AM was encapsulated in neutral liposomes and its therapeutic efficacy was evaluated in mice infected with *P. chabaudi*. Encapsulation efficiency of about 100% was achieved and formulations maintained their stability for 3 months at 4 °C. A 100% cure of *P. chabaudi*-infected mice was observed after 22 days of infection [33].

Case study-Deepika Kanana et.al. antimalarial efficacy of iron oxide nanoparticle fortified artesunate was evaluated in wild-type artemisinin resistant *P.falciparum*. The IONPs were synthesized by aqueous co-precipitation of iron salts in an alkaline medium. The average size of prepared nanoparticles by SEM (scanning electron microscopy) was found to be 10 nm. To evaluate the efficiency of iron oxide nanoparticles, synchronized late-stage rings were treated with increasing concentrations of artesunate along with 100 $\mu\text{g/mL}$ ATA-IONPs. A cycle of GIA was carried out for 48 hours, and the parasitemia was determined by scoring the Giemsa-stained slides. *In vivo*, the drug gets metabolized immediately upon administration, resulting in an outburst of its activity with a high plasma level. This can be overcome by slow release of the catalyst Fe^{2+} within the cells thereby activating artesunate (ART) in a sustainable manner. Upon administration, the pro-drug artesunate gets activated in the presence of Fe^{2+} within the cells. Iron-mediated cleavage of the endoperoxide bridge, which results in the formation of toxic free radicals, catalyses this drug's abrupt activation. Such non-specific activation can be avoided by providing a controlled and targeted release of the catalyst (Fe^{2+}). From the below graph, it can be concluded that the iron oxide-loaded nanoparticles fortified artesunate gives more inhibition of *P.falciparum* as compared to free artesunate.

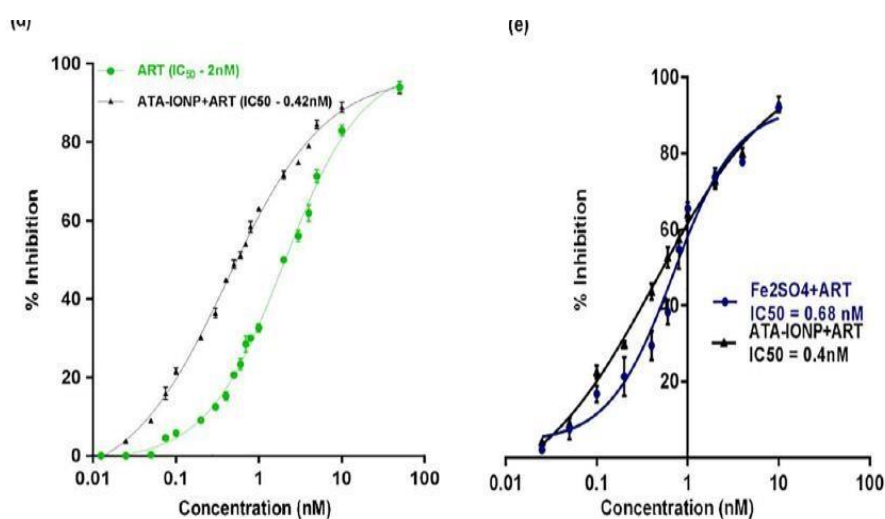


Figure 11. Inhibition efficiency of artesunate vs IONP artesunate

Dengue

Currently, no effective treatment is available on dengue. Only supportive and symptomatic treatments are available. However, lots of work is going on the development of nano-based formulations of currently available drugs.

a) Nanotechnology-based case studies for the treatment of dengue

Carica papaya leaf extract silver synthesized is known for its medicinal value. This is because of its anti-inflammatory, anti-microbial, and antioxidant properties. The *in vitro* anti-dengue effect was evaluated using a focus reduction neutralization test on kidney Vero E2 cell lines. In the study conducted by A.Winkdkouni *et al.*, the AgNPs were synthesized using aqueous and methanol extracts of *C. papaya*. Initially, the formation of AgNPs was confirmed by observing the colour change of the reaction mixture. Through scanning electron microscopy, the synthesized nanoparticles showed particle sizes ranging from 10 and 35 nm, which may confer the ability to penetrate the cells. This is in agreement with previous studies by Bangla *et al.*, who reported average nanoparticle sizes between 5 and 40 nm, with a spherical morphology. *C.papaya* extract loaded Methanol AgNP showed better efficiency for inhibiting the DENV 2 virus *in-vitro*.

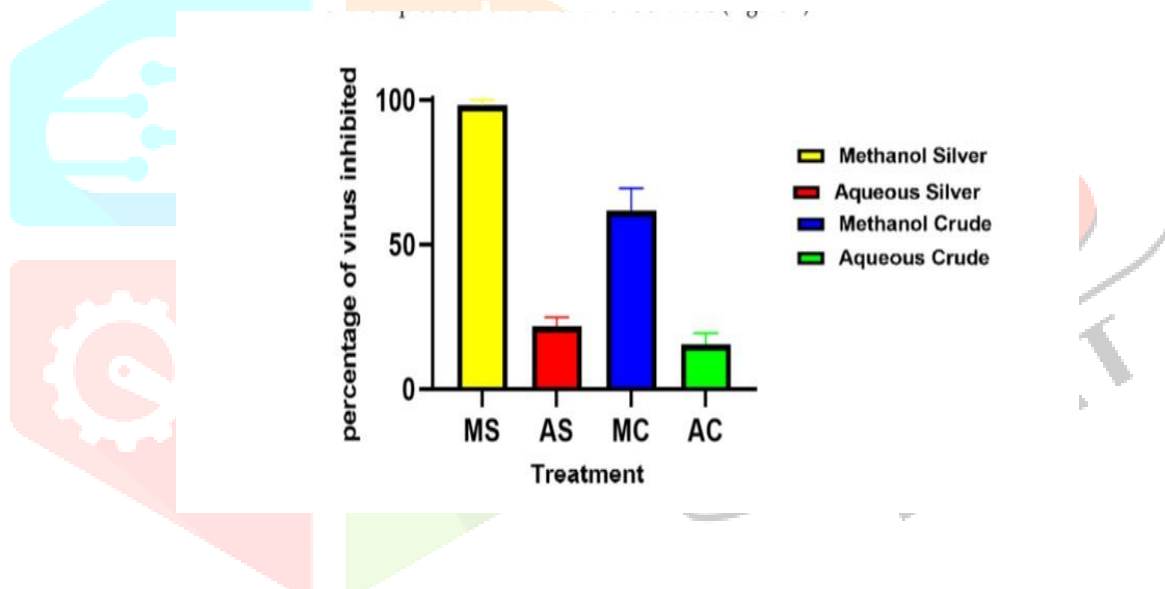


Figure 12. Efficiency of silver coated nanoparticles against DENV2 virus[16]

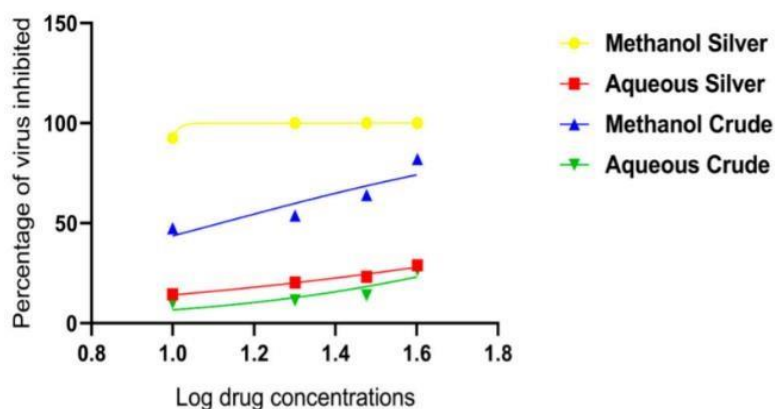


Figure 13. Log drug concentration of *C.papaya* AgNP vs inhibition of DENV2

CONCLUSION AND FUTURE PERSPECTIVE-

It is a challenging task to develop new drugs for tropical diseases because a huge investment of time and money is required which is a much risky task. Moreover, resistance has emerged to available drugs so the role of nanotechnology comes here. This is because nanotechnology has the potential to improve the pharmacokinetic properties, therapeutic efficiency, and safety of available drugs. Recent advances in nanomedicine like the drug can be incorporated with surface modifications, targeted drug delivery, biocompatibility, and sustained release. These modifications help to overcome the limitations of conventional therapies of tropical diseases. It can be also concluded that more research is needed on Nano formulations for therapy of dengue. There are still many issues with toxicity, targeted delivery, and selective binding that need to be solved. Lack of information regarding the toxicity of nanoparticles is a serious concern that should unquestionably receive more attention.

In upcoming times, the research should be focused on toxicity profiling of nanomaterials. Reducing the cost of Nano formulations to make them available for everyone. There is much to explore in the field of nanomedicines. Also, in the future it is needed to emphasize regulatory aspects of nano-based therapies. The lack of regulation and standards for nanotherapeutics in manufacturing practices, quality control, safety, and efficacy evaluation is a barrier to the development of nanotherapeutics. There are no global regulatory requirements for the clinical translation of nanotherapeutics at this time. Only initial guidance documents for nanotechnology products have been issued by regulatory authorities such as the FDA and European Medicines Agency (EMA) to provide guidance[25].

REFERENCES :

- [1] A. Chowdhury, S. Kunjiappan, T. Panneerselvam, B. Somasundaram, C. Bhattacharjee, Nanotechnology and nanocarrier-based approaches on treatment of degenerative diseases, *Int Nano Lett.* 7 (2017) 91–122. <https://doi.org/10.1007/s40089-017-0208-0>.
- [2] M. Booth, Chapter Three - Climate Change and the Neglected Tropical Diseases, in: D. Rollinson, J.R. Stothard (Eds.), *Advances in Parasitology*, Academic Press, 2018: pp. 39– 126. <https://doi.org/10.1016/bs.apar.2018.02.001>.
- [3] World Health Organization, Ending the neglect to attain the sustainable development goals: a global strategy on water, sanitation and hygiene to combat neglected tropical diseases, 2021–2030, World Health Organization, Geneva, 2021. <https://apps.who.int/iris/handle/10665/340240> (accessed November 29, 2021).
- [4] A.S. Acharya, R. Kaur, A.D. Goel, Neglected tropical diseases—Challenges and opportunities in India, *Indian Journal of Medical Specialities.* 8 (2017) 102–108. <https://doi.org/10.1016/j.injms.2017.07.006>.
- [5] A.P. Dash, N. Valecha, A.R. Anvikar, A. Kumar, Malaria in India: Challenges and opportunities, *J Biosci.* 33 (2008) 583–592. <https://doi.org/10.1007/s12038-008-0076-x>.
- [6] N. Sun, J.J. Amon, Addressing Inequity: Neglected Tropical Diseases and Human Rights, *Health Hum Rights.* 20 (2018) 11–25.
- [7] R. Hassan, M.M. Rahman, M. Moniruzzaman, A. Rahim, S. Barua, R. Biswas, P. Biswas, S.G.M. Mowla, M.J. Chowdhury, Chikungunya – an emerging infection in Bangladesh: a case series, *J Med Case Rep.* 8 (2014) 67. <https://doi.org/10.1186/1752-1947-8-67>.
- [8] J.G. Rigau-Pérez, Severe dengue: the need for new case definitions, *The Lancet Infectious Diseases.* 6 (2006) 297–302. [https://doi.org/10.1016/S1473-3099\(06\)70465-](https://doi.org/10.1016/S1473-3099(06)70465-)

0.

- [9] J.G.H. Low, E.E. Ooi, S.G. Vasudevan, Current Status of Dengue Therapeutics Research and Development, *J Infect Dis.* 215 (2017) S96–S102. <https://doi.org/10.1093/infdis/jiw423>.
- [10] L. Singh, H.G. Kruger, G.E.M. Maguire, T. Govender, R. Parboosing, The role of nanotechnology in the treatment of viral infections, *Therapeutic Advances in Infection.* 4 (2017) 105–131. <https://doi.org/10.1177/2049936117713593>.
- [11] P. Subhaswaraj, A. Syed, B. Siddhardha, Novel Nanotherapeutics as Next-generation Anti-infective Agents: Current Trends and Future Prospectives, *Curr Drug Discov Technol.* 17 (2020) 457–468. <https://doi.org/10.2174/1570163816666190715120708>.
- [12] S.R.K. Pandian, T. Panneerselvam, P. Pavadai, S. Govindaraj, V. Ravishankar, P. Palanisamy, M. Sampath, M. Sankaranarayanan, S. Kunjiappan, Nano Based Approach for the Treatment of Neglected Tropical Diseases, *Frontiers in Nanotechnology.* 3 (2021) 49. <https://doi.org/10.3389/fnano.2021.665274>.
- [13] S. Zaidi, L. Misba, A.U. Khan, Nano-therapeutics: A revolution in infection control in post antibiotic era, *Nanomedicine: Nanotechnology, Biology and Medicine.* 13 (2017) 2281–2301. <https://doi.org/10.1016/j.nano.2017.06.015>.
- [14] Y. Duan, A. Dhar, C. Patel, M. Khimani, S. Neogi, P. Sharma, N. Siva Kumar, R.L. Vekariya, A brief review on solid lipid nanoparticles: part and parcel of contemporary drug delivery systems, *RSC Adv.* 10 (2020) 26777–26791. <https://doi.org/10.1039/D0RA03491F>.
- [15] C. Zhang, L. Yan, X. Wang, S. Zhu, C. Chen, Z. Gu, Y. Zhao, Progress, challenges, and future of nanomedicine, *Nano Today.* 35 (2020) 101008. <https://doi.org/10.1016/j.nantod.2020.101008>.
- [16] S.G. Grancharov, H. Zeng, S. Sun, S.X. Wang, S. O'Brien, C.B. Murray, J.R. Kirtley, G.A. Held, Bio-functionalization of monodisperse magnetic nanoparticles and their use as biomolecular labels in a magnetic tunnel junction based sensor, *J Phys Chem B.* 109 (2005) 13030–13035. <https://doi.org/10.1021/jp051098c>.
- [17] S. Khoee, M. Yaghoobian, Niosomes: a novel approach in modern drug delivery systems, in: *Nanostructures for Drug Delivery*, Elsevier, 2017: pp. 207–237. <https://doi.org/10.1016/B978-0-323-46143-6.00006-3>.
- [18] P. Kesharwani, K. Jain, N.K. Jain, Dendrimer as nanocarrier for drug delivery, *Progress in Polymer Science.* 39 (2014) 268–307. <https://doi.org/10.1016/j.progpolymsci.2013.07.005>.
- [19] A.P. Sherje, M. Jadhav, B.R. Dravyakar, D. Kadam, Dendrimers: A versatile nanocarrier for drug delivery and targeting, *International Journal of Pharmaceutics.* 548 (2018) 707–720. <https://doi.org/10.1016/j.ijpharm.2018.07.030>.
- [20] D. Lombardo, P. Calandra, D. Barreca, S. Magazù, M. Kiselev, Soft Interaction in Liposome Nanocarriers for Therapeutic Drug Delivery, *Nanomaterials.* 6 (2016) 125. <https://doi.org/10.3390/nano6070125>.
- [21] Y. Malam, M. Loizidou, A.M. Seifalian, Liposomes and nanoparticles: nanosized vehicles for drug delivery in cancer, *Trends in Pharmacological Sciences.* 30 (2009) 592–599. <https://doi.org/10.1016/j.tips.2009.08.004>.
- [22] L. Qiu, N. Jing, Y. Jin, Preparation and in vitro evaluation of liposomal chloroquine diphosphate loaded by a transmembrane pH-gradient method, *International Journal of Pharmaceutics.* 361 (2008) 56–63. <https://doi.org/10.1016/j.ijpharm.2008.05.010>.
- [23] A.O. Elzoghby, W.M. Samy, N.A. Elgindy, Albumin-based nanoparticles as potential controlled release drug delivery systems, *Journal of Controlled Release.* 157 (2012) 168–182. <https://doi.org/10.1016/j.jconrel.2011.07.031>.
- [24] L. De Almeida, A.T. Fujimura, M.L.D. Cistia, B. Fonseca-Santos, K.B. Imamura, Paul A.M. Michels, M. Chorilli, Márcia A.S. Graminha, Nanotechnological Strategies for Treatment of Leishmaniasis—A Review, *J Biomed Nanotechnol.* 13 (2017) 117–133. <https://doi.org/10.1166/jbn.2017.2349>.
- [25] M. Akbari, A. Oryan, G. Hatam, Application of nanotechnology in treatment of leishmaniasis: A Review, *Acta Tropica.* 172 (2017) 86–90. <https://doi.org/10.1016/j.actatropica.2017.04.029>.
- [26] R.R. Ribeiro, E.P. Moura, V.M. Pimentel, W.M. Sampaio, S.M. Silva, D.A. Schettini, C.F. Alves, F.A. Melo, W.L. Tafuri, C. Demicheli, M.N. Melo, F. Frézard, M.S.M. Michalick, Reduced tissue parasitic load and

infectivity to sand flies in dogs naturally infected by *Leishmania* (*Leishmania*) *chagasi* following treatment with a liposome formulation of meglumine antimoniate, *Antimicrob Agents Chemother.* 52 (2008) 2564–2572. <https://doi.org/10.1128/AAC.00223-08>.

- [27] N.S. Santos-Magalhães, V.C.F. Mosqueira, Nanotechnology applied to the treatment of malaria, *Advanced Drug Delivery Reviews.* 62 (2010) 560–575. <https://doi.org/10.1016/j.addr.2009.11.024>.
- [28] I. Afzal, H.S. Sarwar, M.F. Sohail, S. Varikuti, S. Jahan, S. Akhtar, M. Yasinzai, A.R. Satoskar, G. Shahnaz, Mannosylated thiolated paromomycin-loaded PLGA nanoparticles for the oral therapy of visceral leishmaniasis, *Nanomedicine.* 14 (2019) 387–406. <https://doi.org/10.2217/nmm-2018-0038>.
- [29] I. Afzal, H.S. Sarwar, M.F. Sohail, S. Varikuti, S. Jahan, S. Akhtar, M. Yasinzai, A.R. Satoskar, G. Shahnaz, Mannosylated thiolated paromomycin-loaded PLGA nanoparticles for the oral therapy of visceral leishmaniasis, *Nanomedicine.* 14 (2019) 387–406. <https://doi.org/10.2217/nmm-2018-0038>.
- [30] N.S. Santos-Magalhães, V.C.F. Mosqueira, Nanotechnology applied to the treatment of malaria, *Advanced Drug Delivery Reviews.* 62 (2010) 560–575. <https://doi.org/10.1016/j.addr.2009.11.024>.
- [31] M. Gnanadesigan, V. Nandagopalan, G. Kapildev, M. Gundappa, Nano Drugs for Curing Malaria, in: *Applications of Targeted Nano Drugs and Delivery Systems*, Elsevier, 2019: pp. 451–467. <https://doi.org/10.1016/B978-0-12-814029-1.00016-8>.
- [32] H. Rashidzadeh, S.J. Tabatabaei Rezaei, S.M. Adyani, M. Abazari, S. Rahamooz Haghighi, H. Abdollahi, A. Ramazani, Recent advances in targeting malaria with nanotechnology based drug carriers, *Pharmaceutical Development and Technology.* 26 (2021) 807–823. <https://doi.org/10.1080/10837450.2021.1948568>.
- [33] M. Gnanadesigan, V. Nandagopalan, G. Kapildev, M. Gundappa, Nano Drugs for Curing Malaria, in: *Applications of Targeted Nano Drugs and Delivery Systems*, Elsevier, 2019: pp. 451–467. <https://doi.org/10.1016/B978-0-12-814029-1.00016-8>.
- [34] M. Thakkar, B. S., Combating malaria with nanotechnology-based targeted and combinatorial drug delivery strategies, *Drug Deliv. and Transl. Res.* (2016). <https://doi.org/10.1007/s13346-016-0290-2>.

