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NANOPARTICULATE SYSTEM FOR EFFECTIVE TREATMENT OF TROPICAL DISEASES SUCH AS LEISHMANIASIS AND LYMPHATIC FILARIASIS

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ABSTRACT

Neglected tropical-- diseases (NTD) like lymphatic filariasis and leishmaniasis is a kind of parasitic diseases which affects humans after exposure towards ecosystems where the carriers, vectors and reservoirhost coexists. Lymphatic filariasis (LF) is a type of the neglected tropical disease caused by filarial nematode category parasites, *Brugia timori, Brugia malayi, and Wuchereria bancrofti*. Leishmaniasis is also a non-contagious vector-borne parasitic disease comes from the flagellated protozoans of the genus belongs to *Leishmania* that appear to exert pathological conditions. They often diffuses through the prick of infected sand flies called phlebotomies. The nature and character of these diseases is seeming to be more predominant especially in tropical area (ranging from 23.5^0 north to 23.5^0 south of the equator) and sub-tropical regions (area expands from 23.5^0 to 49^0 north and south result in to humid sub-tropical and dry summer). The disease has high rates of morbidity (rate of disease in population) and mortality (rate of death in population) all over the globe. The conventional drugs therapy are not very much effective due to improper bioavailability and its severe toxicity, hence novel strategy in developments of nanoparticle material have been introduced to accelerate effective and appropriate treatment towards neglected diseases along with lesser risk toxicity, suitable efficacy and enhancement in limited proportion in bioavailability. This review will focus on recent situation of nanoparticulate system in treatment against neglected diseases and also elaborated, how it contributes fundamental character to investigate new perspectives and challenges in approaching the homogenous treatment relevant to particular parasitic diseases.

KEYWORDS: lymphatic filariasis, leishmaniasis, liposomes, nanoparticles, polymeric nanoparticles.

INTRODUCTION

The intention of this study is to imply the basics idea about the parasitic infection and severe illness that are caused by parasites like protozoa, worms together with insects. The parasitic diseases including leishmaniasis and filariasis are extensively scattered in southern Asia, Central and South America followed by Africa. More often, such disease is currently the world's most frequent dangerous infection causing diseases. A parasite is a pretty small tiny micro-organism that exist in a host and consume its nutrients from the host itself. Parasites are capable to cause several variety of disease in human beings. Amongst them, some parasitic diseases treated easily while some are bit complex to be treated or remain untreated, hence control measure of those parasite is important and crucial health concern for the nation. Parasitic infections resultant in accelerating and activating autoimmune mechanisms. Such typical diseases are merged with the development of a various autoantibodies and are affiliated with autoimmune complaints including nephritis, heamolytic anemia, autoimmune hepatitis and other clinical manifestation. In fact, parasitic infections cause a huge burden of disease prevalent in tropical, subtropical followed by more temperate climatic zones. Parasitic underlining diseases including leishmaniasis and filariasis which have been suffered a lot because of lack of attention and so far, called neglected diseases. Generally Low-income countries and several rural areas are being largely affected due to high risk of such infections. These diseases spot the headlines on a constant basis. Leishmaniasis is one individual illness which is bizzare to dispense rigorous awareness and hence stay as neglected class of disease and is the named second most burden parasitic grade disease right after the malaria.

Leishmaniasis

Leishmaniasis is an obligatory intracellular protozoan, capable of infecting humans, animals and sand-flies.[1] Can be lethal if untreated. There are about 20 different Leishmanial species has been yet reported.[2] Amongst, each may is capable of causing a disease based on the specificity to the particular species and the response of host organism.[3] Generally, this organism frequency differs by their geographical distribution. As per Estimation Approximately 70 different species of sand-fly can head to cause and transmit leishmaniasis.[4] Leishmaniasis is circulated to the macrophages of mammalian by the bite of definite breed of tiny female sandfly (2-3mm) over the period of blood suck and accountable

for causing visceral leishmaniasis (VL), cutaneous leishmaniasis (CL) followed by mucocutaneous leishmaniasis (MCL).[2] The organisms are microscopic in size and their dynamic location is accounted for deteriorating the action of therapeutic drugs. The visceral leishmania is Indian Kala-azar also known as Dum-Dum fever is precipitate via parasite which refers to the Leishmania donovani, L.d dum fever archibaldi and L.d infantum in the former world while L.d chagasi in the era of modern world.[5,6] Leishmania donovani, delivered by the prick of sand-fly, at where the infection occurs at the macrophages cell of the liver, spleen, lymph node, and bone marrow followed by the intracellular replication as illustrated in Fig.1.[7] Leishmaniasis is commonly caused by 25 diverse species of parasites usually inherent to the genus *Leishmania*.[3,8] The different species morphologically not easier to distinguish, but can be partially differentiated by molecular methods, isoenzyme analysis, or through monoclonal antibodies [Table 1].

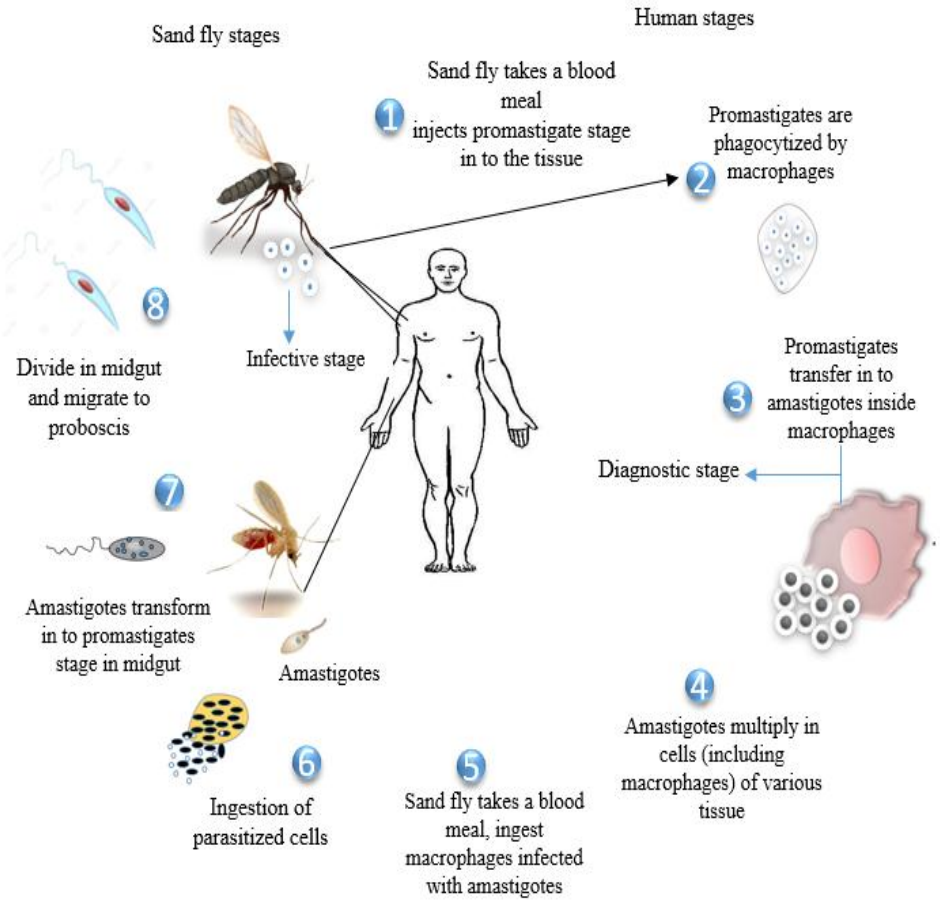

Fig. 1: Life cycle of leishmanial parasites.

Table 1: Distribution of leishmaniasis.

Cutaneous leishmaniasis			
Old world		**New World**	
Leishmanial species	**Infected countries**	**Leishmanial species**	**Infected countries**
Leishmania Donovani	China, India, Bangladesh and Sudan	*L. Maxicana*	North, Central and South America
L. Tropica	China, India, middle East, Mediterranean	*L. donovani chagasi*	Texas, South America, Carribean countries
L. Aethiopica	Ethiopia, Kenya, Namibia	*L. venzuelensis*	Venezuela
L. Major	Middle East, Africa, India and Asia	*L. Peruviana*	Argentina and peruviana
L. Infantum	Asia, Africa and Europe	*L. Panamensis*	Colombia, panama
		L. Brazelliensis	South and Central America
		L. Amazonensis	Central as well as Southern America
Visceral leishmaniasis			
Old world		**New World**	
Leishmanial species	**Infected countries**	**Leishmanial species**	**Infected countries**
L. Infantum	South and North America, Asia	*L. Donovani Chagasi*	Central and south America
L. Donovani	India, Bangladesh, Kenya, Sudan		
L. Tropica	Kenya and Iran		
Mucocutaneous leishmaniasis			
Old world		**New World**	
Leishmanial species	**Infected countries**	**Leishmanial species**	**Infected countries**
L. Aethiopica	Namibia and Kenya	*L. Brazilliensis*	Central and southern Americas
		L. guyanensis	Brazil, Guyana, and Surinam
		L. Mexicana	North, south and central America
		L. Amazonensis	Panama and Brazil
		L. Panamensis	Central and south America

Sand flies contains a leishmaniasis causing species in their body system known as *leishmania* that is more likely to circulate where the population exist in slam areas.[2] The infection chiefly arises to one who is pricked by the sand flies.[9] These species pass through several phases including initially formed flagellate followed by motile promastigotes genesis in alimentary canal through binary fission that remains stay inside the human biological system and are responsible for infecting the healthy humans to greater extent.[5] Multiplication takes

place inside the mid gut and flagellates tend to migrate towards the pharynx followed by buccal cavity of sand-fly.[10]

Leishmaniasis is privilege in nearly more than 70 countries throughout the world, such as North Africa, Southern Europe, South and central America, the Middle East, and the Indian subcontinent.[9,7] It is not that much endemic in South East Asia and Australia with a prevalence of 12 million cases and an approximated incidence of 0.5 million cases of VL and 1.5 million cases of CL.[11]

Filariasis

Lymphatic filariasis is another group of neglected mosquito-borne tropical parasitic diseases.[12,13] It is indigenous in more than 81 countries placing overall 1.3 billion population at endanger zone.[14] With an evaluation over 120 million contaminated peoples and out of that 30% of them are from Africa itself.[15]

The disease is caused by three specific kind of thread-like nematode round worms, known as filariae[16], comprising Brugia timori (fewer body kinks and less dense nuclei in tail), Wuchereria bancrofti (body nuclei are distinct with no nuclei in tail) and Brugia malayi (Dense nuclei with kinked body and two nuclei in tail), respectively called Bancroftian and Brugian filariasis[17]. In fact, *Wuchereria bancrofti*, is the chief parasite responsible for morbidity in 90% of all the cases.[1, 15] In terms of morphology, female worms size ranges from about 8–10 centimetres (80-100 mm) in length whereas Male worms are in between 3–4 centimetres (~ 40mm). These female and male worms combinedly develop “nests” like structure in the area of biological lymphatic system, the vessels and network of nodes that maintain the concentration of fluid balance between blood circulatory system and body tissues as depicted in Fig.2. There are around more than hundred species of filarial, among them only few of them, nearly 8-9 are stated as the main parasite that is responsible for the main cause of filarial.

Over the last past decades, variation in these species have many ecological form that dispute in some feature of their physiology including mosquito transmitter species, host range, periodicity, and morphological arrangement [17]. The genetic variation between those worms is not only crucial from a biological perspective, rather it is important and useful involvement for the Global Program aid to get rid of Lymphatic Filariasis, because they may behave differently towards the diagnostic procedure or medical interventions [18]. Therefore,

appropriate and necessity gathering facts and data on their genetic instability is required.[19] Developed and implemented information on genetic diversity between filaria may lead to increase the probability of successfulness towards lymphatic filariasis elimination.

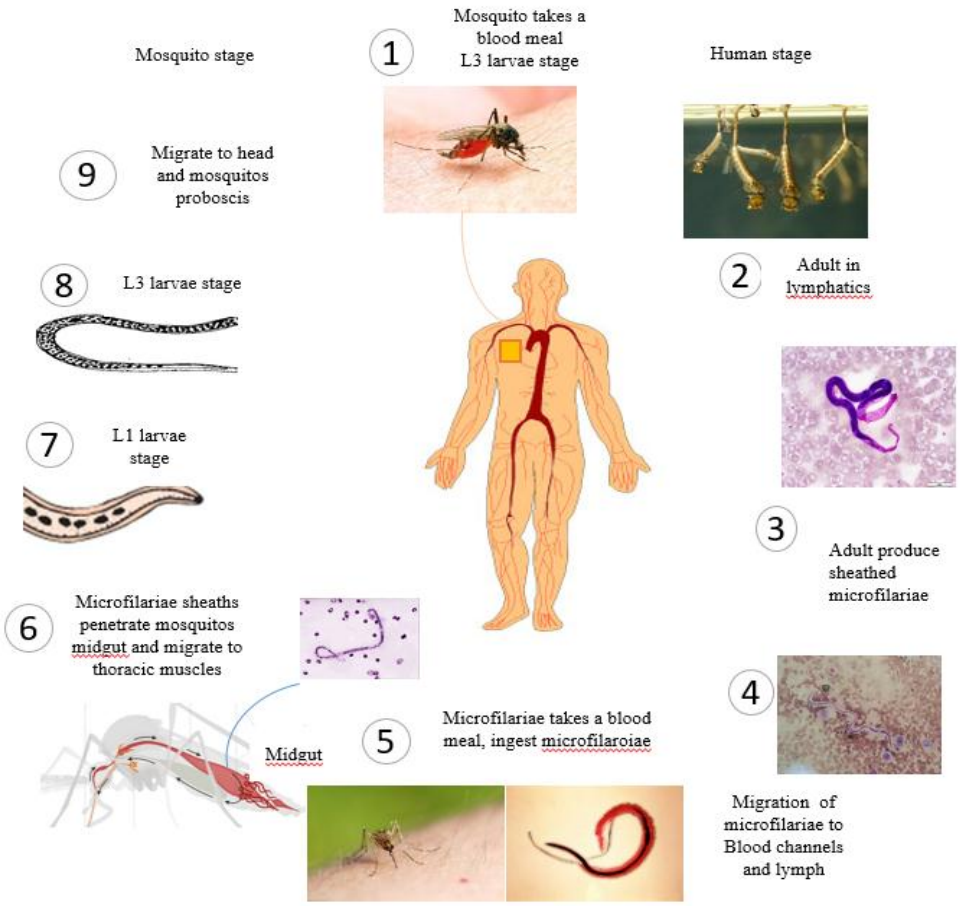

Fig. 2: Life cycle of filarial worm in human lymphatic system.

In fact, India contributes around 41 % of the total global lymphatic filariasis.[20] Due to the psychical myth and social dishonour connected with LF, race carrying such allied disease will have impoverished life and are more often not capable to get a labour job, needed to afford their family members survival or to be counted as active members in area of their municipals and communities [Fig. 3] [Table 2].

The filarial disease is basically characterised in to following groups on the basis of which part of body has been infected:-

- Lymphatic filariasis- In this case, the worms mainly infect the circulatory system of the body
- Sub-cutaneous filariasis - Here, the white part of eyes and the deep bottom layer of skin are infected by the causative worms.

- Serious cavity Filariasis - Generally in this group of filaria, serious cavity of the abdomen is infected by the worms.

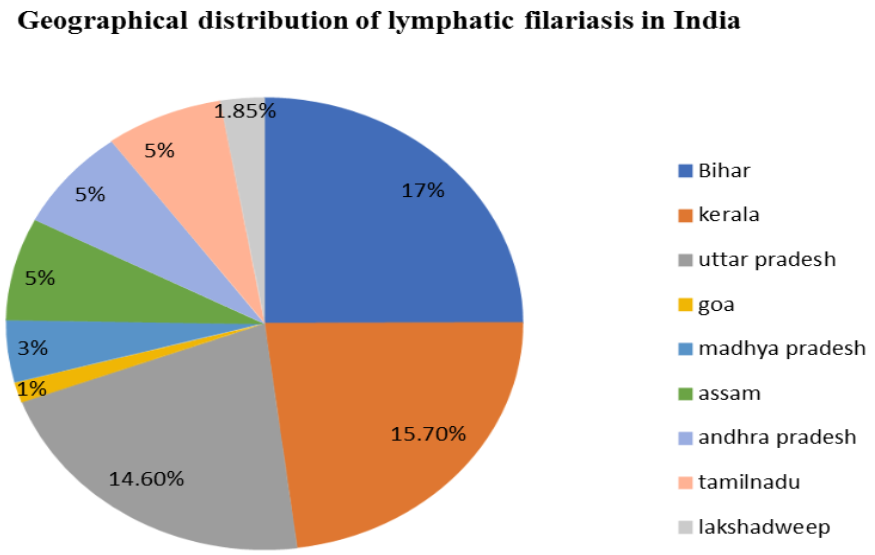

Fig. 3: Geographical distribution of lymphatic filariasis in India.

Table 2: Global and Indian distribution of filariasis.

Particular	Global scenario	Indian scenario
Population at risk	1.2 billion	45.4 c
Number of countries	>80	>16 states & 5 union territory
Number of diseased	44 million	22.5 million
Hydrocele	27 million	12.9 million
Microfilaria carriers	76 million	29.2 million

SYMPTOMS AND TRANSMISSIONS

Leishmaniasis

Visceral leishmaniasis

In India, VL is commonly called "kala-azar," which means "black sickness." Symptoms appear in weeks to several months as soon coming in intercourse with sand fly bite resultant in to Renal failure, bowel and the lung, are affected, weight loss which might be critical harsh, low content of blood cell count (pancytopenia), expansion of the spleen and liver (hepatosplenomegaly) and sometime fever exist.[10]

Cutaneous leishmaniasis

The disease grows slowly may be visible after going through several weeks. Symptoms may involve single lesion, or extreme multiple lesions may occur over the period of time. The skin lesions would be varying in look and may resemble to that of psoriasis, warts and acne. They

look like ulcerated plaques, large scaly, can also form surface ulcerated nodes and swelling. The injury may be moisture less or lachrymose and are not frequently severe unless they furthermore contaminated by bacteria. Sores appearance are more likely to be on the face. Their healing nature is quite bit time consuming taking over a period of months to years, leaving scars behind that often regards to the burns in the past.[21]

Mucocutaneous leishmaniasis

The infection, more often to appear in mouth, nose and larynx. It is generally infrequent as compare to VL and CL. In the beginning, the patient introduced nodules at sand fly bite site with sign consistent with cutaneous leishmaniasis. Generally, mucocutaneous leishmaniasis participation leads to enlargement of the lips and nose, rupture of the nasal baffle, nodules inside the nose. In case involvement of larynx is there, the possible changes of voice can be observed.[22]

Preventive measures

The symptoms can be best prevented through early diagnosis along with effective treatment, controlling of animal reservoir hosts, effective disease surveillance, and vector control and organising a program frequently relevant to Vector borne disease.

Filariasis

Filariasis can be characterised by the painful and chronic disease in which the symptoms may appears by the accumulation of body fluids, swelling of the skin layer basically sub-cutaneous layer which gather fats and many connective tissues.[23] In most severe form, the skin surface and underlying cells, Tissues of the lower part of legs and scrotum gets bulky and dense and limbs become heavy. symptoms may also include blockage in the lymphatic system which leads to edema, swelling, redness and pain in the arms and legs followed by the accumulation of pus in cells.[24,25] These symptoms appear in gradual manner, sometimes takes years. Infected person does not indicate any external mark until the disease penetrate to the late phase, at this extreme level affected persons are now immediately recognised and distinguish because of their crudely visible balloon legs, arms, chest or genitals with cracked, thickened skin that is bumpy, stiff and hardened.[26] LF can also have the damage effect over the vital body organs like kidneys and the entire lymphatic system. Filarial parasites disease transmitted by black flies and mosquito. Firstly, a mosquito bites an infected individual with larvae.[23] This mosquito injects their larvae in to the blood of healthy person and consume the necessity for the larva to grow, all these processes are taking place in the lymphatic

system.[27] Now, the adult and mature filarial worm starts to secrete smaller worms called microfilariae that is further again enters in the mosquito along with the host blood and this way the cycle repeats itself.[19]

These infections giving parasites are thin, round and worms-like structure and appear in whitish colour, the life span of filariae is around in between 5- years.[23] During this period, they produce millions of larvae which are creamy in colour and the size length of female larvae ranges from 2-5-cm while the size of male filaria larvae is doubled of the size of that female larvae.[28]

Preventive measures

It may include avoiding the accumulation of the stagnant water near your windows and doors, practice applying the protective stuff such as of mosquito mats, coils, net screen and maintenance of hygienic environment around the home can be helpful, also using of any perfumes and colognes especially during night times should be strictly prohibited, wearing long length sleeves clothes to prevent the mosquito's bites., avoid dark coloured clothing, mattress and curtains as they attract mosquitos, initially applying insect repellents over the skin surface including odomos may work.

Therapeutic approaches

Conventional drug delivery system for

1. **Visceral leishmaniasis**

- Oral Miltefosine
- I.V pentavalent antimony or i.v amphotericin B
- I.V Paromycin

2. **Cutaneous leishmaniasis**

Complicated

- Oral azoles or Miltefosine
- I.V pentavalent antimony or amphotericin B
- I.V pentamidine

Uncomplicated

- Paromycin ointment
- Intralesional pentavalent antimony

- Cryotherapy and thermotherapy

a. Limitations of conventional drug delivery employed in leishmaniasis and filariasis

Since long back, many times an approach towards efficient therapy to gain access in targeting parasitic family diseases becomes the crucial drug delivery problems in association with its several challenging drawbacks including low uptake of drug absorption in the gastrointestinal tract, faster clearance of drug by phagocytic and immune cells that can result in to insufficiency of drug in the human blood circulatory system [Fig. 4] [Table 3]. During the period of therapy, the limited plasma half-life of drug along with severe toxicity evidence has been observed and reported that leads to an inappropriate bioavailability followed by the failure of cure.

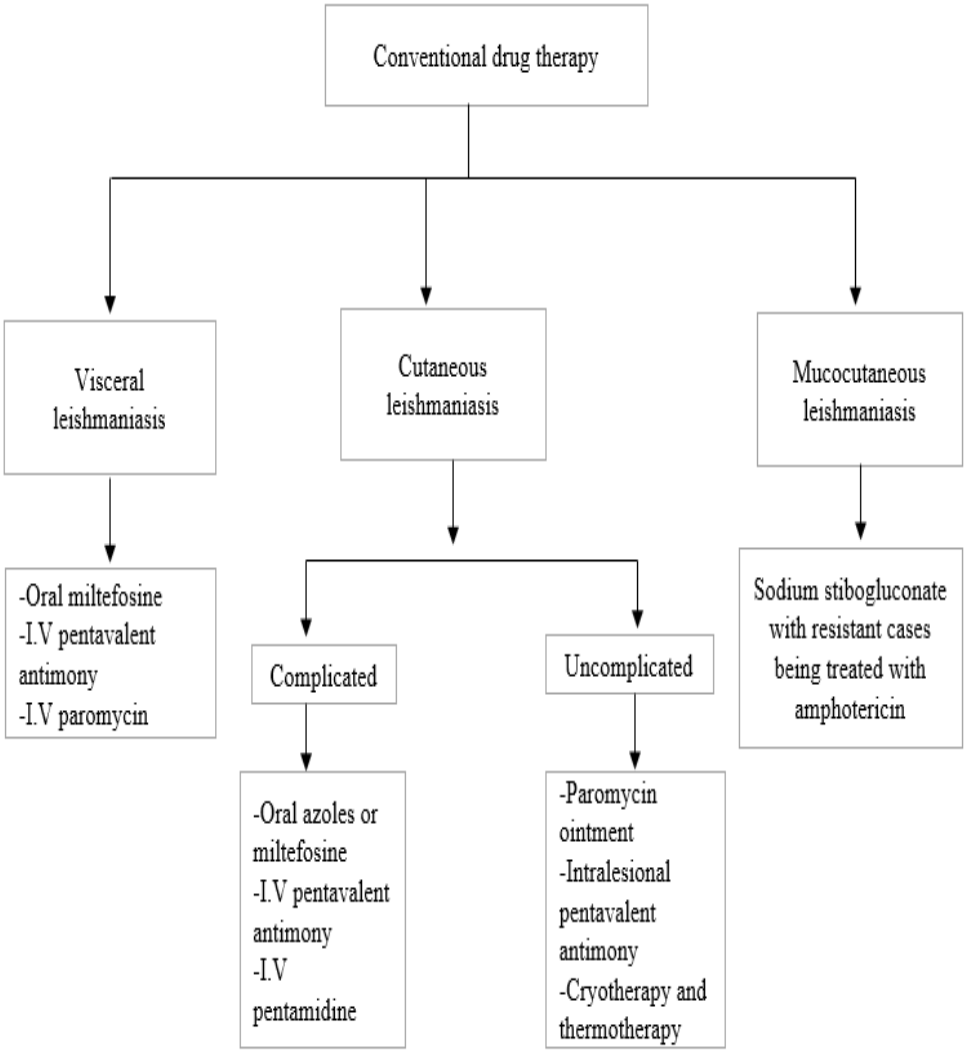

Fig. 4: Conventional drug therapy for leishmaniasis.

Table 3: Currently used anti-leishmanial drugs.

Drugs	Preffered route	Indication	Comments
Pentavalent antimonials (sodium stibogluconate)	Intravenous	cutaneous leishmaniasis	Available through CDC under an IND, not available in USA
AmB, (AmBisome)	Intravenous	Visceral, mucocutaneous	Effective against pentavalent antimony resistant MC, VL
Miltefosine deoxycholate	Oral	Visceral, cutaneous	Approved by FDA in march, 2014 for VL
Sitamaquine	Oral	Visceral leishmaniasis	Undergoing clinical trial 3
Paromycin	Topical	cutaneous leishmaniasis	Shown to be effective against CL
Meglumine antimonate	Intramuscular	Cutaneous leishmaniasis	Similar to pentavalent antimony
Pentamidine	Intramuscular	Visceral leishmaniasis	Effective against VL, cause diabetes mellitus

b. Novel drug delivery system

Drug delivery system for targeting filariasis and leishmaniasis

In spite of large number of issues ahead to leishmaniasis and filariasis merit consideration: resistance occurs, ultimately the possibility of suitable cure to conventional drug treatment, a further development is necessary to replace the first line drugs; a quality stress on effective and less invading protocol for the diagnosis purpose need to be initiated utilizing some advance medical devices.

In the aspect of current scenario, the drug and its respective cure should be more prominent in killing the parasite rather than showing any unintended, unwanted effect. In case the drug is causing severe abnormal responses beside of their significant effect the whole treatment is useless and continuing those therapeutic agents as anti-parasitic agents is worthless. For these drugs the cost is much more important and key factor to be considered because they are more likely to be commercialised in the use of economical population where money is the major problems. As stated earlier, leishmaniasis is more likely to be prevalent especially in the territory where development problems are frequent with poor families. Hence, the high-priced treatment agent AmBisome are tolerated by the person living in those populations.

Since last two decades on, in pharmaceutical current research strategy has been investigated employing colloidal based drug delivery system to attain effective procurement.

In general, nanoparticulate [Fig. 5] technologies provides significant benefits covers solubilisation of many hydrophobic moieties, enhancement in potentiating the drugs

bioavailability, potentiate or modify pharmacokinetics pattern of active therapeutic moieties, also aids in stabilization of API from chemical, physical and biological deterioration.

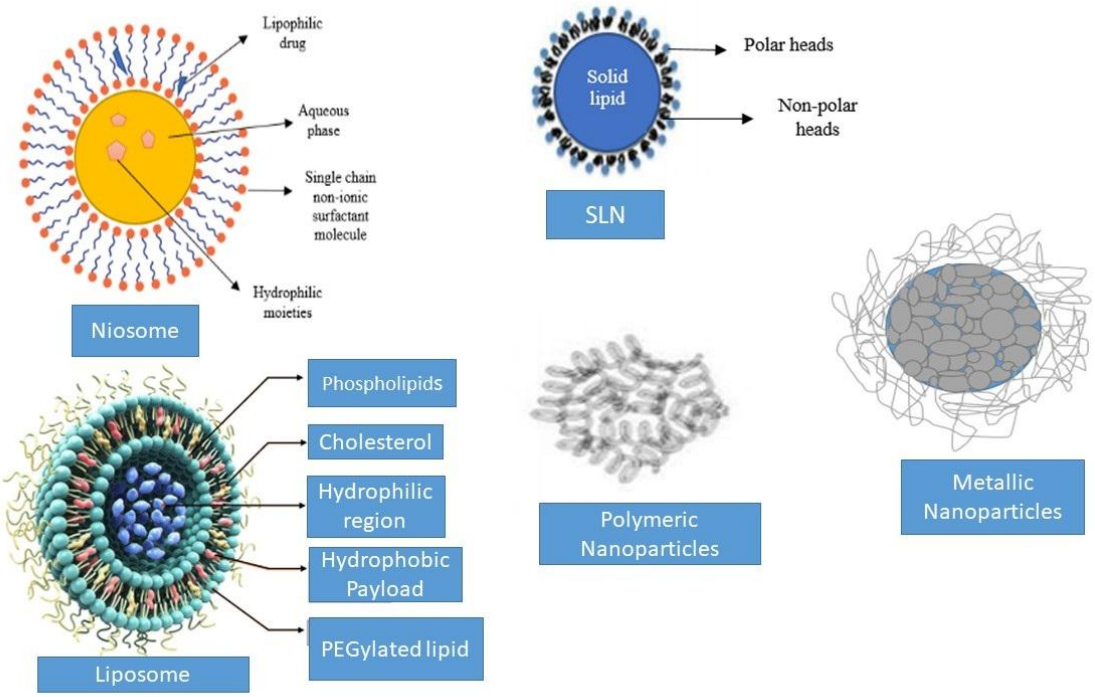

Fig. 5: Illustration of different nanoparticles drug delivery systems

Fig. 5: Illustration of different nanoparticles drug delivery systems.

Nanomedicines incorporation in nanoparticulate drug delivery systems based on either liposome, solid lipid nanoparticles, or polymeric nanoparticles and others as well. These Nano based carriers increase effectiveness of many drugs followed by hindering drug toxicity by improving pharmacodynamic and pharmacokinetic profile.

c. Nanoparticulate drug delivery system

Nanocarrier delivery system are widely being examine as the current drug delivery approach in the pharmaceutical area of formulation and research development. In general, nanoparticulate applied science provides significant impact on solubilisation of lipid soluble moieties, improvement in approaching appropriate availability of drug in circulatory system, alter pharmacokinetics profile of therapeutic agents, prevention of active moieties degradation from several environmental factors.[29] Moreover, the nanosized of these systems offers to gain access for efficient penetration of different types of barriers exist inside the biological system, mitigate in tissue tolerance, improved transport and cellular engulf thereby enabling sufficient delivery of the loaded therapeutic agents over the target sites like brain,

liver and solid tumour. Moreover, by modifying the properties related to surface activity, in such cases, the desired and suitable release of the therapeutic agent and its biodistribution can be attained. Apart from several utility discussed earlier, one of the chief advantages linked with nano based particulate systems is their capability to withstand along the side of better biological stability, physiological stress and this way the possible opportunities arise for oral administration which makes it efficient drug delivery.[30]

The mechanism involved with these nanoparticles (NP) are either the entrapment of therapeutic moieties that is incorporated until it dissolved, encapsulated or entrapped, or assimilate onto the matrix surface formed by the predetermined polymer (e.g., nanosphere based matrix type systems where the drug dispersion is done throughout the network of particles); they are Nano capsules (vesicular based reservoir type systems in which the drug is strictly restricted to an aqueous or oily phase cavity bounded by a single polymeric ground membrane). Several kind of polymers used for such purpose is polylactide, poly(lactic-co-glycolic acid), chitosan, polyglycolide, polycaprolactone, poly(d,l-lactide) have been expand for attaining passive as well as ligand-targeted delivery of therapeutic agents.

The second most important and popular nanocarrier system applied in curing the Leishmaniasis is polymer based on nanoparticles, which accounts for the overcoming possible limitations of liposomes. The significant effect of polymeric nanoparticles is the lower extent of toxicity, the possibility to aid in developing biodegradable systems, the cost-effectiveness, smaller size particle, possibility to modify the surface functionalization property and co-administration with incorporation of large number of drugs. Among the wide range of polymers, such as poly D,L-lactide-co-glycolide (PLGA) which is versatile in nature and frequently preferred to used due to its biodegradable as well as biocompatible property. Polysaccharides such as chitosan are also employed. By conversion in the polymer, physicochemical property associated with the nanoparticulate system, such as zeta potential activity responsible for the stability of suspension can be possibly modulated. As polymeric nanoparticles along with liposomes are usually internalized via macrophages present inside the biological system which itself dominate greater surface area that can be largely accessible for functionalization, compatible with the biological system as well as promote the development to improve drug targeting followed by optimum stability.

Advantages of Nanoparticle system in NTD

- Minimise first pass effect
- Enhance bioavailability and stability
- Reduce toxicity
- Minimise drug degradation, protein plasma interactions, and preserve its structure
- Target specificity
- Reduce dosage and dosage frequency
- Improve solubility, plasma half-life, overall pharmacokinetics.

Disadvantages of Nanoparticle system in NTD

- Polymeric nanoparticles possess limited drug loading capacity
- Sometime the polymeric nanoparticles are relatively slowly biodegradable which might cause toxicity
- Degradation of the carriers
- Chances of agglomeration after exposure to plasma and may lead to decreased the activity

i. Polymeric nanoparticles

Polymeric nanoparticles are one of the attention grabbing colloidal particles, ranging in size between 1 to 1000 nm.[31] They comprise of various types of available biodegradable and biocompatible polymeric matrices at where drug compound can be entrapped, adsorbed or bonded covalently.[29] In the past few years, polymer-based DDSs widely been applied for treating parasitic diseases along with site-specific targeting of medical diagnostic agents to the lymphatic system site. These type of characteristics of these colloidal carriers are largely required for targeting leishmaniasis and antifilarials [Table 4].

Generally synthetic biodegradable and biocompatible polymers such as, polyalkylcyanoacrylates (PACA), PLGA are suitable and employed for attaining nanoparticles.[3] polysaccharides like bigger molecules like chitosan, gelatine and albumin has been offered suitability of nanoparticles fabrication.[29] Owing to their particulate existing nature, these polymeric nanoparticles are quickly cleared off by the cells of Mononuclear phagocyte system after administrating it through IV injection. Moreover, similar to liposomes, size, composition, surface properties, concentration and hydrophobicity or hydrophilicity of nanoparticles play a key role in vivo performance. For example, polyethylene glycol (PEG), PLGA, polysaccharide based, and amino acid based polymers.[16]

Table 4: Lipid based and Polymer based system for neglected disease.

Lipid based nanoparticulate system for neglected disease			
Carriers	Encapsulated drug	Indication	Significant effect
Liposome	Amphotericin B	Leishmaniasis	Reduction in toxicity
	Diethylcarbamazine citrate	Filariasis	eliminating systemic filarial parasites
Lipid, NPs Abelcet, Amphocil	Amphotericin B, oryzalin	Leishmaniasis	Potentiate bioavailability of drug compare to that of free drug
Polymer based nanoparticulate system for neglected disease			
Polymer/carriers	Encapsulated drug	Mechanism	Disease
Chitosan (polysaccharide)	Amphotericin B	Effective in lowering the infection in animal model	Leishmaniasis
Gelatine NPs	Amphotericin B	Increase accumulation in spleen and liver	Leishmaniasis
PLGA NPs PLGA-PEG	B-aescin AmB	Reduce cytotoxicity Increase efficacy	Leishmaniasis
	Ivermectin	gain microfilaricidal effect	Filariasis

Polymeric nanoparticles are currently been brought as a drug delivery for the treatment of leishmaniasis. While designing nanoparticles for treatment of leishmaniasis, selection of appropriate is majorly concerned, as variety of polymers choice is available to fabricate nanoparticles system. Moreover, the right choice of hydrophobic polymer is critical parameters that is responsible for regulating the intensity of drug uptake by microphages which is account for the chief site of leishmaniasis [Table 5]. Illustration in between nanoparticles developed from polyalkyl cyanoacrylate and poly methylacrylate. NPs prepared by the incorporation of polymethyl methacrylate appears to be well suited towards microphages site in comparison to the previously used polymer called polyalkyl cyanoacrylate. Nanoparticle charged with primaquine were observed to be 21 times more efficient towards leishmanial parasites than that of free primaquine. Afterwards primaquine encapsulated with polylactic acid raises potential and desirable efficacy done in infected mice. They were stated to be 3 times more dynamic in hindering the parasitic load as comparison to former used drug. Moreover, blank nanoparticles did not show any activity against Leishmania thus indicating the importance of polymer matrix in the efficacy of nanoparticles.

Table 5: Important nanoparticulate system for lymphatic filariasis

Nanoparticle	Coating material	Application	Preferred DD Route	Size ranges
Liposome	Antibodies, Hydrophilic polymers	Improve ant filarial activity	Sub-cutaneous	20-70nm
Polymeric NPs	PEG & copolymers	Site specific delivery of anti-filarial	Subcutaneous	20-70nm
Nano emulsion, Nano capsule	PEG	Good carrier for lymphatic agents	Intramuscular, Intraperitoneal	10-100nm
SLN	Polaxamine	Highly controlled release kinetics and avoid hepatic first pass effect	Subcutaneous	10-200nm

In leishmaniasis, parasites more inhabitat in macrophages of the cell and hence these macrophages can be considered as promising targeting sites for anti-leishmanial drugs. Nanoparticles prepared by incorporating polymethyl methacrylate polymer shows better macrophage targeting than of polyalkylcyanoacrylate. Thus, depending upon the location of parasites existence, election of appropriate polymer is a crucial factor because error while selecting the improper polymer would lead to rise several unwanted effects. In the same manner, for targeting the therapy in filarial parasites patient the polymer should be in such a way that there must be remarkable enhancement in lymphatic uptake, important polymers employed for the those drugs utilised in treating lymphatic filariasis include poly(L-lactic acid), polyhexylcyanoacrylate, poly(lactide-co-glycolide), as well as polymethylmethacrylate.

ii. Liposomes

Liposomes are widely investigated amongst several available colloidal carriers. They are made up of few spheres of phospholipid containing bilayers and are microscopic vesicles separated by compartments between buffer and aqueous.[29,32] Liposomes are spherical in shape ranging of diameter from 80 nm to 100 μm.[33]

In modern era, they have seen to be successfully progressed surpassing conventional established vesicles form to ‘next generation liposomes. They are modulated by the varying the concentration and composition of lipids, charge attributes of the vesicle followed by functionalized lipid molecules (glycolipids, sialic acid). Liposomes are well targeted through intracellular based delivery systems for endogenous molecules, proteins, DNA, peptides followed by ribosomes. Perhaps the most crucial and important desirable purpose of liposomes is to support targeting of better cell site associated with particular diseased.

Liposomal category drugs has shown to reduced toxicities to the greater extent while retaining required efficacy.[16]

Liposomes are accounted for the most extensively recognised nanocarrier for their application in the treatment of Leishmaniasis. Both hydrophilic and lipophilic carrying feature drugs are suitable to incorporate in this formulation which makes this system more popular and effective, the probability of surface modifications, and the fortune of liposomes is the macrophage where the parasite exists.[34] In particular, liposome formulation offers possibility to modify their structural activities that is more likely to improve delivery system better drug targeting, since macrophages exhibit different types of receptors. The current literature stated that the incorporation of sugar molecule in liposomal formulation significantly improves macrophage targeting in parasitic disease as it constitutes receptor that specifically recognise the sugar molecule to attain greater functionalization property. Similarly, liposomes preparation containing anionic charge are quickly internalized via macrophages as a result of their ionic interacting correlation with cationic charged macrophage membrane.[6] However, liposomes exhibit few limitations such as instability that induces certain toxicity as a result escaping of the drug out of the nanocarrier has been reported.[35] Nanoemulsions drug delivery systems is emerging formulation along with high feasibility properties includes scale-up, ease of preparation, ability to solubilize hydrophobic drugs as well as physicochemical stability. The significant minimization of potential toxicity for the drugs that is formulated by the cooperation of hydrophobic and hydrophilic drugs makes it popular in the research of drug delivery. Earlier the research data was investigated for liposomes was suitable only for the therapy in parasitic diseases but soon after development in technology and research the application of liposomes distributed taking consideration for all the diseases. Liposomes are rapidly cleared off by the phagocytic cells of liver and spleen (larger concentration of microphages) through passive diffusion later on the exposure towards their application for targeting intracellular parasitic infections which exist intracellularly.[36] Previously, the most prominent use of liposomal formulation was targeting the macrophages in leishmanial infections. Currently with the development in in liposomal research, number of plans were concerned to modify the increase chance of success of liposomes in order to procure various other class of parasitic infections followed by improved drug targeting. Liposomes efficacy generally interfered by composition of lipids, surface charge, melting phase transition temperature of phospholipid. Followed by size and charge of the surface.

iii. Metallic nanoparticles

Metallic nanoparticles along with carbon-based nanomaterials have been developed as versatile nanocarriers in the treatment of Leishmaniasis and lymphatic filariasis.[37] In a similar manner, dendrimers are nanocarriers with great potential to carry and delivery ant leishmanial drugs due to their ability to load with amounts of the drug on their branched surface, improving the drug bioavailability, although the recent advantages on the development of efficient anti leishmanial releasing nanocarriers, there are requirement of some challenges to be overcome.[38] For example, the development of efficient oral Nano formulations for the treatment of Leishmaniasis, with low costs. In comparison with conventional available pharmaceutical drugs, the nanostructure formulations have higher costs. However, it should be noted below that traditional drugs often need substitutions treatment due to lack of efficiency and undesired side effects, which can in turn result in further economic burden in investments.[37]

iv. Niosomes

Niosomes are morphologically similar to liposomes comprises of lipid content cholesterol and surfactants (non-ionic).[36] Like liposomes, Niosomes offers in extending the distribution of captured drugs to modify distributions towards organ and potential metabolic stability like liposomes.[39] These preparation does not require any special critical attention conditions like constant low temperature, vacuum feed, inert nitrogen fused surrounding atmosphere for manufacturing, production and storage because there is rare chance of phospholipids to go under oxidation degradation.[35,40]

Apart from these merits, the necessity to used essential material to formulate this system is quite lower in cost which develop the probability of this novel system to commercialise in poor population communities where parasitic disease are more privilege.[41] These facts of niosome are quite interesting and attractive in comparisons to the liposomes for manufacturing at the industrial level. Liposomes and niosome incorporated with sodium stibogluconate (NI-SSG) effective given by the intravenous routes of administration but earlier formulation was not fully capable of eliminating the parasites present in liver but also those exist inside the bone marrow and spleen, during experimental of visceral leishmaniasis. Since only few smaller particles are capable of reaching the reticuloendothelial system inner of the bone marrow cavities. Later, it was established that a single dose of NI-SSG was

significantly eliminating the presence of pathological parasites in mononuclear phagocyte system to similar extent resembling to AmBisome formulation.

v. Solid lipid nanoparticles

The solid lipid nanoparticle (SLNs) are nanoparticulate colloidal carrier novel in comparison to the more conventional ones, such as liposomes, lipid emulsions and polymeric nanoparticles. SLNs generally possess acceptable tolerability and safety profile.[42] SLNs almost beneficial for solving delivery problems with antigens derived by biotechnology with different level of solubilities. The suitability of these NPs has been proven because previously, they have been successfully investigated in clinical trial phases of human studies (e.g., cyclosporine-loaded SLNs) and will be commercialized in the market in upcoming future. In SLN the drug formulation carried out by former technology can also be applicable to incorporate them in colloidal based drug delivery systems like polymeric nanoparticles, emulsion and liposomes as novel techniques, but at the meantime avoidance or minimization of the variety of drawbacks is required. SLN have been developed successfully in approaching the skilled delivery of number of therapeutic drugs delivered through various routes.[43]

SLN are often solid, microscopic size particulate carriers system ranging from 1 to 1000 nm and collection of physiological, biodegradable and biocompatible lipids, appropriate for the inclusion of hydrophilic and lipophilic drugs inner section of the core of lipid matrix in considerable quantity.[29] In general, lipids that could be act as matrix forming constituent for SLN are waxes, highly purified triglycerides and mixtures of glyceride.[44] However, recently, SLN based on mixture of solid lipid and liquid lipids so, called nanostructured lipid carries or Nano liquid carriers, amphiphilic cyclodextrins, excess content of lecithin have been investigated.[42]

The amalgamation of the drug candidate in SLN can be best defined by three specific group of models stated as:[45]-

- Homogenous type matrix model - drug is either molecularly dispersed or remain as in the form of amorphous clusters inside the lipid matrix.
- Drug-enriched shell type model -outer lipid shell containing drug along with lipid core.
- Drug-enriched core type model - drug core is surrounded by dispersion of lipid layer or reservoir type system.

SLN carriers offers several interesting features offering improved tolerance of body tissue due to capable of entrapping lipophilic moieties followed by hydrophilic drugs by going through different approaches of fabrication., accounts for lesser biotoxicity related carrier, providing Protection and stabilization of labile drugs against chemical degradation, based on the prepared SLN-type, modification in releasing the desirable drug is possible depending upon the necessity, SLN loaded with a drug-enriched shell provides features of burst release and SLN loaded with a drug-enriched core offers sustained release [Table 6].

Table 6: Anti-leishmanial nanoparticulate drug delivery system for parenteral administration.

Drug delivery	Incorporated drug	Leishmanial species	Preferred route	Animal model
Niosome	AmB	L. donavani	I.V	Mice
Emulsion	AmB	Leishmaniasis	I.P	Mice
Polymeric NPs	AmB	L. Infantum	I.V	Hamster
Conjugation polymer	AmB	Leishmaniasis	I.V, I.P	Mice

CHALLENGES AND FUTURE PERSPECTIVE

Since the treatment strategy and delivery approaches over the parasitic diseases are not much effective with that of previously and commercially available applied drugs due to their several chief drawbacks like safety, efficacy and relatively their limited bioavailability followed by high toxicity. In such scenario, nanoparticulate colloidal based drug carrier system can be demonstrated as prominent role in delivering current and emerging therapeutic agents by modifying the formulation pattern that helps in providing suitable specificity for the parasites along with lesser extent toxicity, enhanced efficacy, rectify bioavailability issues and prolongation of drug release at lower doses. In future, this will leave high impact on the treatment of neglected diseases.

CONCLUSION

Over the past decades Tropical neglected disease including leishmaniasis and filariasis being a parasitic disease are life threatening and full of challenging to treat because of large number of factors related to the delivery system, parasitic resistance to older drugs, and risk of relapse as well as the dynamic location of parasites to these diseases. This category of diseases may be lethal if not treated efficiently and even responsible for causing high rate of morbidity and mortality in the poor population. The conventional therapeutic agent used earlier during the treatment was not optimum as they were leading to cause unintended effects, lower

concentration of drug moieties delivery in the circulatory system resulted in to limited bioavailability, high rate of toxicity, expensive, non-efficacious followed by the necessity of higher dose. Our sound literature strongly suggests that nanoparticulate system is the most promising approaches in coating these existing issues due to their particulate nature. Particularly the development of novel nano based formulation which is going to be future trend for developing more efficient drug delivery system for parasitic diseases. Colloidal drug carriers and lipid-based system have been emerging and effective alternative to the conventional drug delivery system as it exhibits all the potential quality aspects which is more likely to overcome above mentioned limitations which chiefly appears in parasitic infection.

AUTHOR'S CONTRIBUTIONS

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Concept and collection of data - Ms. Priyanka Gresess Anand, Moazzam Ahmad and Chetan Rajak. Writing the article and critical review of article - Ms. Priyanka Gresess Anand and Dr. Satya Prakash Singh.

Conflict of interest

The authors declare that they have no conflict of interest.

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