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Research paper



Sustained Release of Nanoformulation of Diethyl Carbamazine (Dec) for Filariasis – a Review

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Abstract

Lymphatic filariasis (LF), is a mosquito vector-borne disease and a major public health problem in the tropical countries. The annual mass drug administration (MDA) in India was studied in 1996-97. It was introduced with single dose of Diethylcarbamazine and was investigated as a pilot project covering 41millon population. The study was extended to 77million population by 2002. The MDA is one of the strategies to eliminate LF in India. Liposomes, polymeric and solid lipid nanoparticles are the most promising nanopharmaceuticals which are easy to formulate, cheaper and can bring prolific consequences for filariasis management.

Keywords: *Filariasis, nanopharmaceuticals, Liposomes, Diethylcarbamazine*

1. Introduction

Lymphatic filariasis (LF) is mosquito vector borne disease which are long threadlike adult nematodes namely Wucheria bancrofti, Brugia malayi and Brugia timori are mostly blamed for lymphostatic complaints (lymphodema, elephantiasis and hydrocele) by means of forming "nests" in the human lymphatic system [1]. Different elimination programmes for LF have been launched in India, However the Global Programme for Elimination of Lymphatic Filariasis (GPELF) introducing mass drug administration (MDA) of annual single dose of a combination of Diethyl carbamazine citrate (DEC) (6mg/kg) or Ivermectin and Albendazole (400mg) in the endemic areas [2].

Eradication of LF globally is needed which could be made through developing or designing other effective drugs and drug targets. Further, novel methods for vector control, diagnostic tools and techniques are also needed [2]. Today, a number of Liposomal Amphotericin B formulations (Ambisome, Amhotec) are present in the market for treatment of visceral leishmaniasis [4].

Therefore LF would also definitely benefit from nanopharmaceutical technology to resurrect some of LF drugs or compounds that shown promising antifilarial action against the target parasite species. Sometimes the technology was unfit largely due to poor pharmacokinetics issues and acute toxicity [4]. Nanopharmaceuticals have been targeted to every part of the body and can even permeate the tight epithelial junctions of skin which would minimize first pass-metabolism, target specific for various identified antifilarial drug targets [4]. Therefore liposomes with high potentials that are used for the treatment of LF are promoted and it could provide an improved approach towards antifilariasis chemotherapy. The study will also help to resolve the existing technological lacunae.

2. Liposomes-Nano Carriers

The nanotechnology is an emerging science [5,6] and the nanocarriers have been used for medical applications for a long time [4-13].Liposomes are the first nanocarriers employed for the improvement of antifilarial drugs and that can effectively transport therapeutics to its target sites so as to impart maximum pharmacological effects with minimum adverse reaction in the human body while preventing the degradation/denaturation/inactivation of therapeutic agents [4].

Nano-carriers containing drug have arised an innovative and promising alternative for drug delivery to the targeted site [14]. They also greatly improve free drug safety and drug efficacy [15]. There is a lot of significant proof that nano-carriers are superior in biocompatibility, targeting, and tissue penetration [16]. It is very difficult for an antifilarial drug molecule to reach the target parasites in the complex lymphatic network of host due to many tag limitations. Targeted delivery of antifilarial drugs would assist the drug molecules to reach preferably to the desired site in the lymphatic system and improve the bioavailability of antifilarial agents [4].

Liposomes show various promising features to target lymphatic parasites.

3. Limitations of DEC

Nature - Hydrophilic
Solubility – 63.7mg/mL
Molecular weight – 199.293g/mol
Half life – 2-3hours
Plasma bounding – rarely show plasma bounding
Absorption – readily absorbed from the GIT
Biodistribution – pituitary gland, lymph nodes, adrenal medulla, salivary gland
Dose - 6mg/kg

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Dose frequency – day in 3 divided dose for 3 weeks
Side effects – GIT-nausea,vomiting
CNS-headache,dizziness

4. Importances of Nanopharmaceuticals-Liposomes

Preparation techniques – mechanical dispersion, solvent dispersion, detergent removal method, freeze thaw method
Ligands for targeting adult worms or Wolbachia in the lymphatic system – antibody sugar residues, apoproteins or hormones Fab9 fragments (immune-liposomes, biotin)
Coating materials for microfilariae clearance – antibodies and hydrophilic polymers
Preferred routes and size range – subcutaneous intraperitoneal 20-70nm
Applications for filariasis – improvement in the MIC activity of antifilarial agents
Disadvantages – instability and dilution, aggregation

5. Drug Assay Standardization

Different aliquots of working standard DEC solution [50µg/mL] ranging from 0.2-20mL was transferred into a series of 10mL flasks and total volume was brought to 2mL with water. To each flask, 3mL of 1:1 Folin-ciocalteu reagent (FC reagent) and 2mL of 20%. Na2CO3 was added. Kept to room temperature for 15mins. The absorbance of each solution was measured at 760nm against a reagent blank.

6. Liposome Synthesis Using Lipid Film Hydration Technique

Liposomes are self-assembling globular vesicles composed of amphiphilic lipid bilayers. It is composed with an inner aqueous core frequently used as platforms in pharmaceuticals and cosmetics for drug release [19-21]. Nanoparticles binding ligands could enhance antiviral activity and improve cytotoxicity, poor water solubility, and rapid phagocytotic character from circulation of the free drug [22].
Dry a chloroform and soya phosphatidyl cholesterol, 1:1 mixture of altered ratio using rotatry vaccum evaporator. At 40°C layer will be formed at the lower round bottom flask.
Then hydrate the resulting lipid film with the distilled water.
For 2 hours at 37°C sonicate the preparation at 4°C in three cycles of 5mins and rest of 5mins between each cycle using probe sonicator.
Homogenize the formulation at 15,000psi pressure in three cycles using high pressure homogenizer to get liposomes.

7. Entrapment Efficiency Analysis

A (A) mixture of 1:1 ratio is prepared using soya lecithin and cholesterol. Condensed in water bath to form thin layer for 15mins 5mL of drug(DEC) is added which is centrifuged at 8000rpm for 5mins. The absorbance is calculated at 700nm and the efficiency of 1:1 mixture entrapment was found to be 97.2%
Optimization of drug entrapment:
A two different altered ratios of mixtures are prepared 2:1(B) and 1:2(C) following the same procedure. The efficiency of 2:1(B) was found to be 97.8%. The efficiency of 1:2(C) mixtures were found to be 97.6%.

8. Drug Release Study (Ex-Vivo)

In Franz-diffusion cell the function of the skin permeation release --study was made. The excised cell was firmly fixed between the compartment of Franz diffusion cell with skin facing the donor compartment which nano formulated drug compound loaded with bilayer patch was placed and clamped in position. The diffusion cell was filled with suitable buffer medium (water or PBS buffer) along with a magnetic pellet and the set was placed over a magnetic stirrer. The readings are tabulated over the interval of everyhalf an hour for the study of drug release profile.

9. Conclusion

Lymphatic filariasis is a tropically ignored disease caused by the accommodation of thread like parasitic worms in the lymphatic system. Compared to a free drug, the advantages of a nano-scale drug delivery system include increasing bioavailability, reduced drug amount and frequency and reduced systemic side effects [17]. In hence, active targeted drug delivery combined nano-technological carrier platforms is a better way to prolong, localize, target with the pathogenic sites and reduction of drug side-effects [18].
Endemic areas has bulk of affected subjects revealing a clinically asymptomatic infection that harbour microfilaria in their peripheral blood. It is important to know that even at this stage of the disease abnormalities of the lymphatic vessels such as dilation appear to be irreversible even after treatment[3]. Over the vast grassland of filariasis explorations, significant advancements have been made to improve antifilarial chemotherapies by means of identifying different drug targets, screening a number of compounds or drugs with promising antifilarial activity, and proposing many potent antifilarial drug combinations. This studies shows that the release of the drug is sustained over the time intervals. Reformulating the existing antifilarial agents would definitely bring prolific improvements in treatment protocols. Liposomes nanoparticles are the most attractive carrier options that possess colossal latent potentials for the cure of this site-specific targeting of antifilarial drugs.

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