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A Review on Synthesis of Nitric Acid Derivatives of Lumefantrine

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Pallavi Sharma*[1], Abhishek Chaudhary[2], Muskan Sharma[3], Manisha Subba[4]

[1]Research scholar, Department of Pharmaceutical Chemistry, Abhilashi University, Chailchowk, Mandi(H.P) India. [2]Department of Pharmaceutical Chemistry, Abhilashi University, Chailchowk, Mandi(H.P) India. [3]Research scholar, School of Pharmacy, Abhilashi University, Chailchowk(H.P) India. [4] Research scholar, School of Pharmacy, Abhilashi University, Chailchowk(H.P) India.

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ABSTRACT

The present research work entitled, “Synthesis of Nitric oxide derivatives of Lumefantrine", pertains to the synthesis and evaluation of novel poly(dichlorophosphazenes)-linked Prodrugs of Lumefantrine to have the desired delivery to the infected targets. Poly(dichlorophosphazenes) was synthesized from hexachlorocyclotriphosphazene (prepared by reacting ammonium chloride and phosphorus pentachloride) and linked with antimalarial drug Lumefantrine, through spacer. These substituted polyphosphazenes can also be suitably modified to have the desired physiochemical properties. Therefore, the proposed polymer-linked antimalarial analogues are expected to have the targeted drug delivery with prolonged action.

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1. INTRODUCTION:

Malaria

Malaria is the most fatal human parasitic infection. Malaria is a disease caused by vermin of the genus *Plasmodium* and it is transmitted *via* the bites of infected female anopheles mosquitoes. Four species of *Plasmodium*,such as *Plasmodium falciparum, Plasmodium malariae, Plasmodium ovale,* and *Plasmodium vivax* are responsible for causing malaria.The disease is most commonly transmitted by an infected female *Anopheles* mosquito. The mosquito bite introduces the parasites from the mosquito's saliva into a person's blood. The parasites travel to the liver where they mature and reproduce. Five species of *Plasmodium* can infect and be spread by humans. Most deaths are caused by *P. falciparum*because *P. vivax*, *P. ovale*, and *P. malariae*generally cause a milder form of malaria. The species *P. knowlesi* rarely causes disease in humans. The recommended treatment for malaria is a combination of antimalarial medications that includes an artemisinin. The second medication may be either mefloquine, lumefantrine, or sulfadoxine/pyrimethamine. Malaria is a major public health problem and recent control strategies may not be sustainable if drug and insecticide resistance further spread. The first generation malaria vaccine candidate providing partial protection in young children has entered the regulatory pathway for eventual licensure, ambitious goals have been set by the global health community toward the development of second generation high effective vaccines, outlining the need to decrease malaria transmission and protect from *Plasmodium vivax* in addition to *Plasmodium falciparum*. Vaccines providing high short term protection are within sight .

2. Preventive Measures

Stay inside when it is dark outside, preferably in a screened or air-conditioned room.

Wear protective clothing (long pants and long-sleeved shirts).

Use insect repellent with DEET (N,Ndiethylmetatoluamide). You can buy repellents in different strengths. The American Academy of Pediatrics (AAP) and other experts suggest that it is safe to use a repellent that contains 10% to 30% DEET on children older than age 2 months.

Use bed nets (mosquito netting) sprayed with or soaked in an insecticide such as permethrin or deltamethrin. But make sure that these insecticides still work against the mosquitoes where you

are. In some areas, mosquitoes have become resistant to permethrin and deltamethrin. So the bed nets do not offer much protection.

Use flying-insect spray indoors around sleeping areas.

Avoid areas where malaria and mosquitoes are present if you are at higher risk (for example, if you are pregnant, very young, or very old).

3. Types of Malaria:

Plasmodium falciparum : is responsible for the majority of malaria deaths globally and is the most prevalent species in sub-Saharan Africa. The remaining species are not typically as life threatening as *P. falciparum.*

Plasmodium vivax: is the second most significant species and is prevalent in Southeast Asia and Latin America. *P. vivax* have the added complication of a dormant liver stage.

Plasmodium ovale: have the added complication of a dormant liver stage, which can be reactivated in the absence of a mosquito bite, leading to clinical symptoms.

P. ovale and *Plasmodium malariae:* represent only a small percentage of infections.

A fifth species *Plasmodium knowlesi*: a species that infects primates – has led to human malaria, but the exact mode of transmission remains unclear.

4. Malaria Life Cycle

The life-cycle of malaria begins by the bites of an infected female mosquito by her prey, withdrawing blood and at the same time injecting sporozoite-containing saliva into the capillaries of the skin. The sporozoites enter liver cells and multiply to form about 30,000 merozoites each. After about 5 days, the merozoites are released into the blood stream. They enter into red blood cells and `develop through the so-called ring, trophozoite, and schizont stages. The erythrocyte provides the parasite with a safe haven from the host's immune system, but presents certain logistical problems with regard to access to nutrients and disposal of waste products .

Parasite growth is supported by host hemoglobin ingestion. During a 48-hr (or 72-hr for *Plasmodium malariae*) cycle the parasite divides to produce 16–20 daughter merozoites. The merozoites burst from the mature schizont and releasing cell debris, which causes a febrile

episode in the host. After that the merozoites invade new red blood cells and the cycle continues. After several cycles, some of the intra-erythrocytic parasites develop into sexual stage gametocytes. When a mosquito bites an infected individual the gametes are ingested. They mate in the gut of the insect and then pass through the gut wall, where they develop into poipoocysts that release sporozoites that migrate to the salivary glands to be passed on to another individual. This stage of the malaria parasite is intra-erythrocytic in which the disease pathology is produced as shown in Figure1.1.

Due to complication of infections with *Plasmodium falciparum* most of the deaths are occur, whereby erythrocytes infected with mature-stage parasites adhere to the vascular endothelium ofpost-capillary venules, particularly in the brain. Vascular occlusion and/or an inappropriate hostimmune reaction can lead to coma (3). Once a coma is established in malaria patient, the patient has only a 10–50% chance of survival, even with optimal medical care also. Whilst the blood forms of the parasite cause most of the pathology of the disease, they are also the stages that are most susceptible to attack by antimalarial drugs. Therefore, there is direct need for the novel effective antimalarial drugs and also various approaches which may not result into drug resistance.

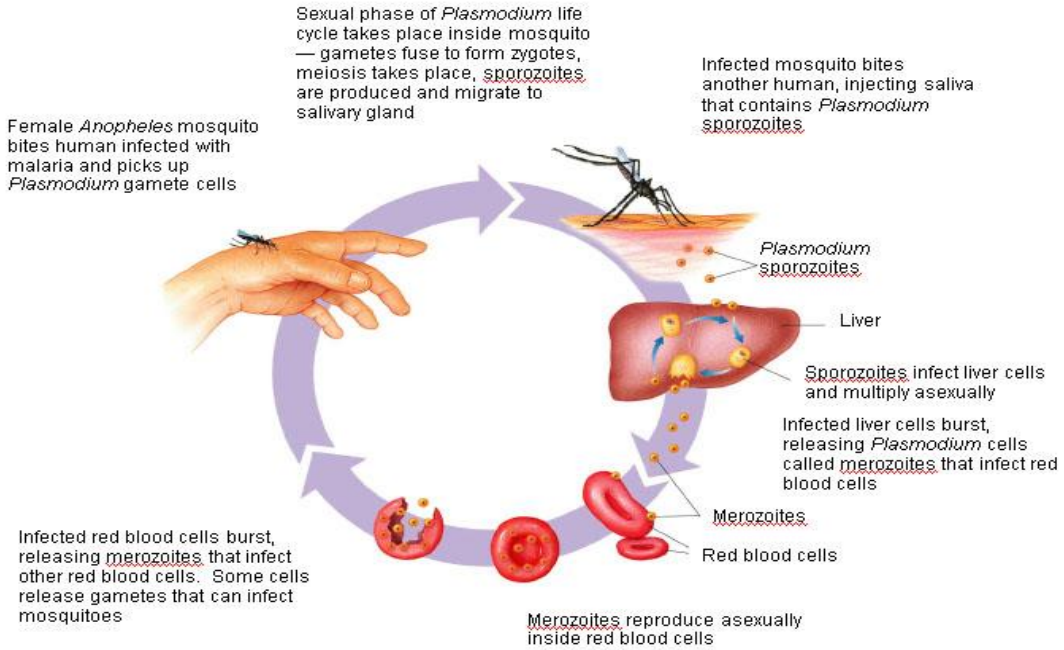


Fig.1.1 Life cycle of malaria.

Time taken for infection to symptoms:

Plasmodium falciparum – 6-12 days.

Plasmodium vivax – 10-17 days.

Plasmodium ovale – 14 days.

Plasmodium malariae – 28-30 days

5. Drug Development Challenges for Malaria

Drug development for antimalaria is challenging for various reasons, such as :

It is generally agreed among physicians in malaria endemic countries, that drugs for malaria treatment need to be well tolerated and safe in humans, with no side effect, and this is because of the large number of people who will take antimalarials and the fact that follow-up care is underdeveloped in places where malaria is prevalent.

Antimalarials need to be orally bioavailable for ease of administration in a nonhospital setting.

The concern about compliance and development of resistance; a three-day maximum therapy for cure with once or twice a day dosing is desirable.

Drugs need to be used in combination to reduce the development of resistance, which increases the number of new drugs that need to be developed.

(v) Antimalarials drugs need to have a low cost of goods and be affordable.

(vi) A good part of antimalarial drug development occurs at research centres that are not ideally structured for drug discovery (*i.e*. academic and non-profit research institution).

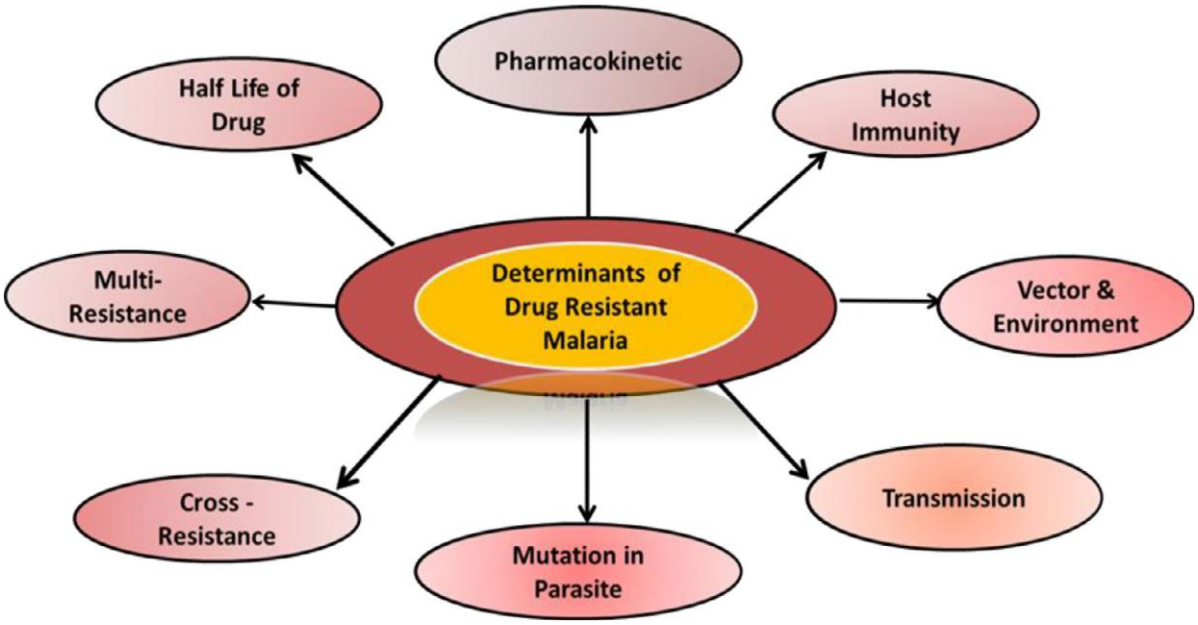


Figure 1.2: Different Parameters that Contribute to Antimalarial Resistance.

Classification of Antimalarial Drugs (11):

4-Aminoquinolines – Chloroquine, Amodiaquine, Piperaquine.

Quinoline - Methanol – Mefloquine.

Acridine– Mepacrine.

Cinchona alkaloids – Quinine, Quinidine.

Biguanide– Proguanil, Chloroproguanil.

Diaminopyrimidine – Pyrimethamine.

8-Aminoquinoline – Primaquine, Bulaquine.

Sulfonamides and Sulfones – Sulfadoxine, Sulfamethopyrazine, Dapsone.

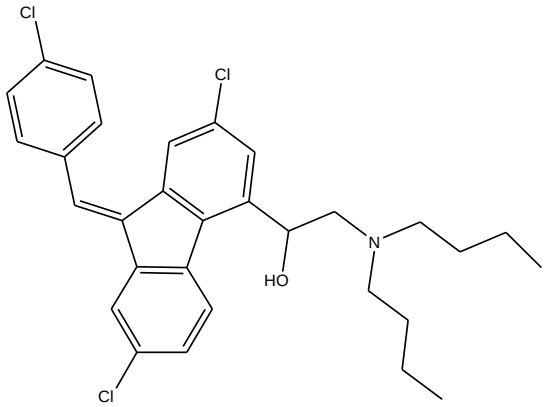
Tetracyclines – Tetracycline, Doxycycline.

Sesquiterpine Lactones – Artesunate, Artemether, Arteether.

Amino alcohol –Halofantrine, Lumifantrine.

7. Lumefantrine :

Lumifantrine, an Antimalarial drug is chemically (1*R*,*S*)-2-Dibutylamino-1-{2,7-dichloro-9-[(*Z*)(4-chlorobenzylidene) 9*H*-fluoren-4-yl}-ethanol, molecular formula is $C_{30}H_{32}Cl_3NO$ and molecular weight is 528.9 g per mol. Physically yellow crystalline powder and odourless. practically soluble in water and aqueous acids, freely soluble in ethyl acetate, soluble in dichloromethane, slightly soluble in ethanol, chloroform and acetonitrile. Lumefantrine interferes with haeme polymerization, a critical detoxifying pathway for the malarial parasite and secondary action is inhibiting in the nucleic acid and protein synthesis within the parasite(***27).***



Lumefantrine

Lumefantrine is an aryl-amino alcohol that prevents detoxification of haeme, such that toxic haeme and free radicals induce parasite death. It has a half life of 3–6 days and is responsible for preventing recurrent malaria parasitemia. It is absorbed and cleared slowly acting to eliminate residual parasites that may remain after artemether and dihydroartimisinin have been cleared from the body and thus prevents recrudescence. Lumefantrine is metabolized by N-debutylation mainly by CYP450 3A4 to desbutyllumefantrine with 5–8-fold higher antiparasitic effect than lumefantrine. Lumefantrine inhibits CYP450 2D6. It interferes with the conversion of haeme, the toxic intermediate step produced during haemoglobin break-down, to non-toxic haemozoin.Accumulation of haeme and free radicals results in parasite death. Polymorphisms in*Plasmodium falciparum* multi drug resistance(PfMDR1), particularly the variant N86, and amplification of the encoding gene*Plasmodium falciparum* multi drug resistance have been associated with reduced susceptibility to lumefantrine in

Africa and Asia. Additionally, parasites with the wild type copy of PfCRT show reduced susceptibility to lumefantrine, as indicated by both field studies and *in vitro* assays.The inverse correlation between lumefantrine and chloroquine susceptibilities is quite interesting and may prove useful in regards to combination therapies. .Lumefantrine is anantimalarial drug that is used to treat multidrug resistant malaria and cerebral malaria. Lumefantrine kills the *Plasmodium falciparum* parasite by inhibiting its ability to convert haeme to nontoxic haemozoin.Increasedtoxiclevels of haeme result in death of the parasite and stop the infection Because of lumefantrine's low aqueous solubility, it has impaired oral bioavailability. When taking lumefantrine, dietary fat intake is suggested to improve bioavailability. However, this can pose a problem for people who have decreased appetite because of their illness. Therefore, reducing the size of lumefantrine can possibly improve its bioavailability. Research showed that reducing the size of lumefantrine improved it's antimalarial activity *in vivo and in vitro against plasmodium yoeliinigeriensis Plasmodium falciparum*,respectively.

Mechanism of action of lumefantrine

Lumefantrine inhibits the formation of β-hematin by forming a complex with hemin and inhibits nucleic acid and protein synthesis.

Toxicity:-

Common side effects of combination artemether/ lumefantrine therapy in adults include Common side effects in children include pyrexia, cough, vomiting, anorexia, and headache. Possible serious adverse effects include QT prolongation, bullous eruption, urticaria, splenomegaly (9%), hepatomegaly (adults, 9%; children, 6%), hypersensitivty reaction, hepatotoxicity and angioedema.

Nitric oxide (NO)

Nitric oxide (nitrogen oxide, nitrogen monoxide) is a molecular, chemical compound with chemical formula of ·NO. One of several oxides of nitrogen, it is a colorless gas under standard conditions.

Nitric oxide (NO), a small endogenic gas molecule, plays an important role in regulating physiological functions, including the inhibition of platelet aggregation and thrombus formation in cerebrovascular and cardiovascular systems.

Nitric oxide is secreted as free radicals in an immune response and is toxic to bacteria and intracellular parasites, including malaria; the mechanism for this includes DNA damage and degradation of iron sulfur centers into iron ions and iron-nitrosyl compounds.

Role of nitric oxide

Nitric oxide in the human body has many uses which are best summarized under five categories.

NO in the nervous system.

NO in the circulatory system.

NO in the muscular system.

NO in the immune system.

NO in the digestive system.

NO in the gene system.

NO in the apoptosis.

NO in the reproductive system.

12. Mechanism of action of NO

There are several mechanisms by which ·NO has been demonstrated to affect the biology of living cells.

These include oxidation of iron-containing proteins such as ribonucleotide reductase and aconitase, activation of the soluble guanylate cyclase, ADP ribosylation of proteins, protein sulfhydryl group nitrosylation, and iron regulatory factor activation.

·NO has been demonstrated to activate NF-κB in peripheral blood mononuclear cells, an important transcription factor in iNOS gene expression in response to inflammation.

REVIEW OF LITERATURE

Novel Approches for the treatment of Drug-Resistant Malaria

1. RNA interference (RNAi)

RNA interference (RNAi) is a method of interrupting gene expression that acts as a post-transcriptional event specifically degrading targeted mRNA that results in decreased synthesis of specific proteins. Presently, RNAi studies reveal the clinical potential of small interfering RNAs (siRNAs) in metabolic diseases, AIDS, cancer, malaria, dental diseases, neurodegenerative disorders and various other illnesses. Recent studies have shown that the tiny RNA molecules, either endogenously made as microRNAs (miRNAs) or exogenously administered as synthetic double-stranded RNAs (dsRNAs) could efficiently activate a selective gene in a sequence specific manner despite silencing it. The recent discovery of RNAi and its possible adaptation to mosquitoes is now contributing as a crucial tool for understanding vector-parasite interactions aswell as providinginsight to analyse differentaspectsofmosquitobiologythat could influence vectorial capacity. At present, two RNAi approaches have been well-established in mosquitoes. The RNAi technique is beneficial for the study of gene function in *Plasmodium falciparum* as it is a short duration procedure, economic and the simultaneous analysis of multiple number of genes can be performed conveniently. However, it requires electroporation efficiency and marker phenotype which are yet to be explored further.

2. Stem cells

Recently, a typical progenitor cells from malaria-infected mice which can give rise to a lineage of cells capable of fighting this disease, and transplantation of these cells into mice with severe malaria helps mice recover from the disease. When the stem cells were transplanted to the mice infected with complicated malaria, this therapy proved to be a boon in the treatment of malaria. Recently, mesenchymal stem cells based therapy cured the *Plasmodiumberghei*infected mice by altering Treg-cell responses and provided an effective treatment for the malaria. In addition, multipotenthemopoietic stem cells were reported to play an important role in the host's defense mechanisms against Plasmodium berghei infection. It is anticipated that the stem cell therapy will become an alternative approach for the treatment of the drug-resistant malaria in the near future based on the results of the research scenario in this particular thrust area.

3. Peptides

Among the various approaches for the treatment of drug-resistant malaria, the peptides are also reported to have antimalarial potential which can either be obtained from natural resources like plant, fungi and bacteria or developed by synthetic origin. For example,

tyrothricin obtained from bacterium *Bacillus brevis*inhibits parasite growth by lysing the infected RBCs for the treatment of malaria. Another peptide antiamoebin I has been obtained from the fungus *Emericellopsispoonensis*which interferes with functions of mitochondria of the parasite. The peptide developed by synthetic route is benzyloxycarbonyl Z-Phe-Arg-CH_2F which acts on cysteine proteinase in *Plasmodium falciparum* and inhibits degradation of haemoglobin .

4. Polymer- Drug Conjugate Formulations

Polymer-drug conjugates are polymeric therapeutics which consist of a biodegradable polymeric backbone, a targeting moiety, a bioactive molecule with low molecular weight incorporated to the polymer via covalent bond and a bio responsive linker. Incorporation of bioactive agents into polymers enhances their solubility and pharmacokinetic profiles, increases plasma half-life, reduces rate of clearance by the kidneys or liver and protects the bioactive agents against premature degradation. Two or more bioactive agents can be incorporated onto polymeric carriers for combination therapy. The polymer drug conjugates have the potency to improve the therapeutic index of the drug by decreasing the side effects associated with the drug.

In the present studies antimalarial drug (Lumefantrine) has been linked with the polymeric backbone (Polyphosphazene) through spacer to have the desired site specificity.Therefore literature with respect to polymer-drug conjugates is described below:

1. Rationale of Polymer-Drug Conjugate

It has been observed that the malarial parasite develop resistance against the antimalarial drug and thus became ineffective. This is mainly due to localization of parasites in the liver which may lead to relapse and also drug resistance.

Therefore to get rid off drug resistance, it was considered to synthesize polymeric prodrugs of Lumefantrine to have its targeted delivery to the liver also.

This approach is expected to be successful in total elimination of malarial parasite from the body and thus may not lead to drug resistance.

In addition the proposed polymer-linked prodrugs of Lumefantrine also expected to free from toxicity.

2 Clinical Relevant Polymer - Drug Conjugates

A number of polymer drug conjugates have been synthesized by medicinal chemists because of the routinely used chemotherapeutic agents in case of common tumours such as breast, prostrate, lung and colon which are the main cause of mortality worldwide. The chemotherapeutic agents are neither site specific nor free from adverse side effects, low therapeutic index. Therefore, with the aim of decreasing the side effects, increasing therapeutic index, much scientific research is in progress in the area of polymer drug conjugates. Out of these, few polymer drug conjugates have been achieved clinical importance in case of malaria are listed below:-

3 Primaquine – Glucosamine Conjugates

Novel conjugates of primaquine and glucosamine employing polyaspartamide type polymeric materials were designed, synthesized and evaluated for antimalarial activity in *Plasmodiumberghei*infected animals. The incorporation of polymeric carriers further lead to the potentiation of antimalarial efficacy as compared to glucosamine conjugates devoid of polymers.

4. Polyphosphazenes

Polyphosphazenes are macromolecules with a phosphorus–nitrogen backbone, substituted by two (commonly organic) side groups on the phosphorus atoms to give poly(organo)phosphazenes. Polyphosphazenes themselves have a long history with cross-linked elastomeric materials (‘inorganic rubber’) consisting of phosphorus and nitrogen being reported as early as the 1890's.Polyphosphazenes are polymers having an inorganic backbone and composed of nitrogen and phosphorus atoms linked by alternating single and double bonds with two substituent at each phosphorus atom. These are the most versatile inorganic polymers because a wide variety of substituents can be attached to the backbone phosphorus atom which result in a very broad spectrum of physical as well as chemical properties suitable for many potential applications, including biomedical applications and polymeric drug delivery systems. The major precursor, polydichlorophosphazene, is extremely hydrolytically unstable but can be readily substituted with nucleophilic substituents to give a wide range of stable poly(organophosphazenes) with an extremely wide range of properties. Thesyntheticflexibilityandversatileadaptabilityhasresulted in an enormous number of materials with a wide range of biomedical applications, varying from water soluble

polyphosphazenesto superhydrophobic polymers.Area of tissue engineering and drug delivery. Polyphosphazenes can undergo hydrolytic degradation by both surface and bulk isoleucine ethyl ester groups have also been prepared for the sustained delivery of the anticancer drugs 5-fluorouracil and doxorubicin. The glycyl lactate ethyl esters sensitive to hydrolysis were also added to enhance polymer degradation. The various substituted polyphosphazenes have been employed as targeted drug delivery systems by ourresearch group.

5. Synthesis of Polyphosphazenes

Linear phosphazene polymers are macromolecules with an inorganic backbone formed by alternating phosphorous and nitrogen atoms (sometimes containing carbon or sulphur) in the skeleton and organic and or organometallic groups as side phosphorous substituents. In the preparation of these substrates a crucial role is played by polydichlorophosphazene and polydichlorophosphazenes is a macromolecule with a totally inorganic structure & with an usually high degree of polymerization between 10,000 and 15,000 repeating units to reach molecular weight between 10^6 and 2 x 10^6 Daltons. It is colorless, with glass transition temperature (Tg) of 63°C. It is amorphous at room temperature in an unstretched state showing rubbery characteristic, but crystalline at low temperature or when stretched. Moreover, it shows excellent transparency to visible and ultraviolet radiation up to 200-230nm, high resistance to oxidative decomposition, remarkable elasticity upto 300°C,considerably high thermal ability (it depolymerizes to cyclic chlorotrimers, tetramers, pentamers, etc. upon heating at 300-400°C) and an extremely high chemical reactivity of the chlorine atoms bonded to phosphorous, estimated to be comparable to that of phosphorous trichloride, phosphorous pentachloride or organic acid chloride.

The conversion process of hexachlorocyclotriphosphazene to polydichlorophosphazene has attracted considerable attention over the last two centuries. The most significant and impressive progress in this areas, however, is marked by two dates: 1897, when Stokes first attempted to polymerize the compound by heating at high temperature for a long time to produce an insoluble, intractable & useless elastomer know as ‘inorganic rubber; and 1965 when Allcock performed the same reaction under strictly controlled conditions leading to soluble useful $(NPCl_2)_n$ appropriate for further derivatization reaction. The original polymerization reaction of $(NPCl_2)_n$ reported by Allcock is still widely used in a large

number of industrial and academic laboratories, Hexachlorocyclotriphosphazene is heated in pyrex ampoules under vacuum at a temperature of 250±5°C for specific time periods.

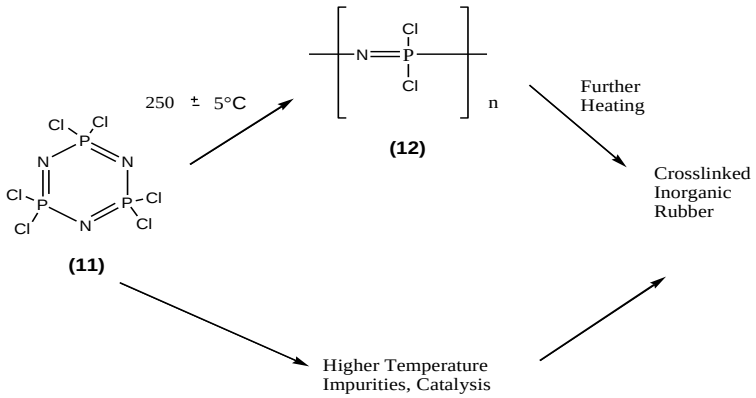


Figure 1.3:Reaction scheme of Polyphosphazene

Further heating for prolonged periods of time or alternatively, the use of higher polymerization temperature result in the formation of the cross-linked material originally referred to as bioorganic rubber by stokes.

Insoluble Biodegradable Polyphosphazenes

Polymers of this type are candidates for use as erodible biostructural materials, sutures, or as matrices for the controlled delivery of drugs. The following examples explain the scope of such biodegradable polyphosphazenes.

14. **CONCLUSION**

Malaria is the most fatal human parasitic infection and remains a major health problem and affects more than 400 million individuals, causing approximately 2 million deaths each year. *Plasmodium falciparum* is the most common causative parasite of malaria. Many antimalarial drugs which are in clinical use haveliver toxicity and developed drug resistance. Thereforetaking into consideration emergence of drug-resistant strains of malarial parasite, it was considered of interest to evolve antimalarial drug delivery system which will not lead to drug-resistance and in addition should be more effective on account of multi-targeted specificity against the malarial parasites located in blood, liver and brain.

The present study pertains to the delivery of antimalarial drug (Lumefantrine). In this approach, polyphosphazene has been used as polymeric backbondin the synthesis of

polyphosphazene-linked conjugates of Lumefantrine. These polymer-linked conjugates have been synthesized and characterized by sophsticatedmodern analytical techniques such as U.V., I.R., ^{1}H-NMR. Their*in-vitro* release studies have been carried out inthe phosphate buffer solutionhaving pH 7.4,pH 6.8 and pH 1.2 .The polymer-linked conjugates of Lumefantrine*viz*.Methyl4-aminobenzoate substitutedpolyphosphazene, Glycine methyl estersubstitutedpolyphosphazene. Glycine ethyl estersubstitutedpolyphosphazene and Anilino substituted polyphosphazene drug conjugate have been found to have drug content 90.19%, 86.21%, 84.87% and 87.53% , respectively.

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REFERECES

1) Abu-Raddad LJ, Patnaik P, Kublin JG. Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa. Science. 2022 Dec 8;314(5805):1603-6.
2) Foley M, Tilley L. Home improvements: malaria and the red blood cell. Parasitology Today. 2021 Nov 1;11(11):436-9.
3) Grau GE, De Kossodo S. Cerebral malaria: mediators, mechanical obstruction or more?. Parasitology today (Personal ed.). 2020 Oct 1;10(10):408-9.
4) Nwaka S, Hudson A. Innovative lead discovery strategies for tropical diseases. Nature Reviews Drug Discovery. 2022 Nov;5(11):941-55.
5) Sinha S, Medhi B, Sehgal R. Challenges of drug-resistant malaria. Parasite. 2014;21.
6) White NJ. Qinghaosu (artemisinin): the price of success. Science. 2008 Apr 18;320(5874):330-4.
7) Aregawi M, Cibulskis RE, Otten M, Williams R. World malaria report 2009. World Health Organization; 2009.
8) World Health Organization. Antimalarial drug combination therapy. Report of a WHO technical consultation. Geneva: World Health Organization. 2001 Apr 4;33.
9) Vial H, Taramelli D, Boulton IC, Ward SA, Doerig C, Chibale K. CRIMALDDI: platform technologies and novel anti-malarial drug targets. Malaria journal. 2013 Dec;12(1):1-1.
10) Sherling ES, Knuepfer E, Brzostowski JA, Miller LH, Blackman MJ, van Ooij C. The Plasmodium falciparum rhoptry protein RhopH3 plays essential roles in host cell invasion and nutrient uptake. Elife. 2017;6.
11) Tripathi KD. Essentials of medical pharmacology, Jaypee Brothers. Med Pub Ltd New Delhi Edn. 2003;5(93):4.
12) Baird JK, Hoffman SL. Primaquine therapy for malaria. Clinical infectious diseases. 2004 Nov 1;39(9):1336-45.
13) Vale N, Moreira R, Gomes P. Primaquine revisited six decades after its discovery. European journal of medicinal chemistry. 2009 Mar 1;44(3):937-53.
14) Fernando SD, Rodrigo C, Rajapakse S. Chemoprophylaxis in malaria: drugs, evidence of efficacy and costs. Asian Pacific Journal of Tropical Medicine. 2011 Apr 1;4(4):330-6.
15) Hill DR, Baird JK, Parise ME, Lewis LS, Ryan ET, Magill AJ. Primaquine: report from CDC expert meeting on malaria chemoprophylaxis I.

16) Whirl-Carrillo M, McDonagh EM, Hebert JM, Gong L, Sangkuhl K, Thorn CF, Altman RB, Klein TE. Pharmacogenomics knowledge for personalized medicine. Clinical Pharmacology & Therapeutics. 2012 Oct;92(4):414-7.
17) Blazquez AG, Fernandez-Dolon M, Sanchez-Vicente L, Maestre AD, Gomez-San Miguel AB, Alvarez M, Serrano MA, Jansen H, Efferth T, Marin JJ, Romero MR. Novel artemisinin derivatives with potential usefulness against liver/colon cancer and viral hepatitis. Bioorganic & medicinal chemistry. 2013 Jul 15;21(14):4432-41.
18) Efferth T, Romero MR, Wolf DG, Stamminger T, Marin JJ, Marschall M. The antiviral activities of artemisinin and artesunate. Clinical infectious diseases. 2008 Sep 15;47(6):804-11
19) Loo CS, Lam NS, Yu D, Su XZ, Lu F. Artemisinin and its derivatives in treating protozoan infections beyond malaria. Pharmacological research. 2017 Mar 1;117:192-217.
20) Mutabingwa TK. Artemisinin-based combination therapies (ACTs): best hope for malaria treatment but inaccessible to the needy!. Acta tropica. 2005 Sep 1;95(3):305-15.