An effective nano-carrier-based archaeosomes for the cell and drug delivery for better pharmacological response: A review

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ABSTRACT

Archaea-specific liposomes called archaeosomes, are unique liposomes. Achaean-type lipids are diether or tetraether archaeols. Traditional methods (hydrated film sonicated, extrusion, and detergent dialysis) can encapsulate thermally stable substances in archaeosomes at physiological temperatures or lower. Many physiological and environmental factors affect its stability. Archaeosomes are utilised to deliver cancer vaccinations, Chagas disease, proteins, peptides, genes, antigens, and natural antioxidants. This study examined how the pharmaceutical business could employ nano-nano-carrier technology.

Keywords: Archaeobacteria, Archaeosomes, Cell Delivery, Drug Delivery, Gene Delivery.

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INTRODUCTION

Archaeosomes are liposomes and vesicles that contain one or more archaea microbial ether lipids. Archaeosome lipid membranes can be bilayers (made exclusively from monopole archaeol lipids or lipid mixtures containing archaeols and non-archaeobacterial monopolar lipids), monolayers (made exclusively from bipolar caldarchaeol lipids), or a combination of

mono and bilayers (made exclusively from bipolar caldarchaeol lipids). Archaeosomes are ether lipid-derived liposomes. Achaean lipids are diether or tetraether archaeols. Archaeosomes can entrap hydrophilic and hydrophobic molecules due to their architecture, which is useful for encapsulation and medication delivery. Synthetic lipids with branching phytanyl chains and ether linkages at sn-2, 3 glycerol carbons are used in archaeosomes. The lipid membrane of archaeosomes can be a bilayer if it is made entirely of monopolar archaeol (diether) lipids, a monolayer if it is made entirely of bipolar caldarchaeol (tetraether) lipids, or a mixture of monolayers and bilayers if it is made entirely of caldarchaeol lipids and standard bilayers. Archaea must modify their essential lipid structures to maintain membrane function in difficult environments [1].

Very stable archaeosomes require a defining feature[2]. Crystallisation is reduced by branching methyl groups, membrane permeability, and steric hindrance of the methyl side groups.The saturated alkyl chains resist oxidative breakdown, while the glycerol backbone's stereochemistry (opposite mesophilic species) resists other organisms' phospholipases.Adding cyclic structures (especially five-membered rings) to the transmembrane region of lipids appears to be a thermo-adaptive response.

Traditional methods (hydrated film sonicated, extrusion, and detergent dialysis) can encapsulate thermally stable substances in archaeosomes (Figure 1) at any temperature in the physiological range or lower. They're stable in air/oxygen. Archaeosomes do not harm animals in vitro or in vivo [3].

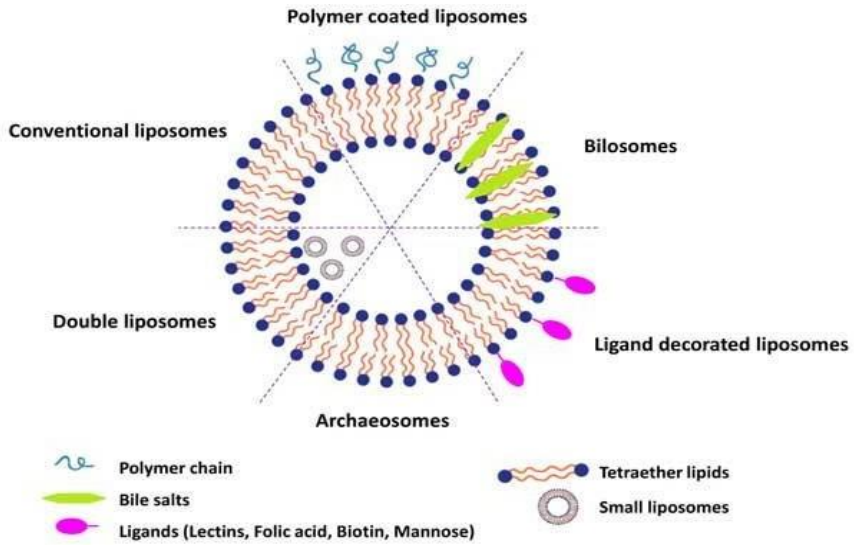

Figure 1. Structure of Archaeosomes.

SOURCE OF ARCHAEA

Three major sources of archaea were found which will be very helpful for the availability of the same [4].

Halophiles:*Halobacterium cutirubrum, Natronobacteriummagadii*.

Methanogens:*Methanococcusvoltae, Methanococcusjannaschii, Methanosaetaconcilii, Methanosphaerastadtmanae, Methanobacteriumespanolae, Methanospirillumhungatei, Methanosarcinamazei, Methanobrevibactersmithii*.

Thermoacidophiles:*Thermoplasmaacidophilum*

ADVANTAGES OF ARCHAEAL LIPIDS

Archaeal lipids are crucial to pharmaceutical production and stability. The following are some of archaeal lipids' main benefits [5]:Compared to other creatures' phospholipids, archaeal lipids are more stable. The chemically modified archaeal lipid derivative improves hydrolysis stability of other enzymes. Adding cyclic structure to lipids appears to be a thermo-adaptive response that increases membrane packing and decreases membrane fluidity. Saturated alkyl chains enhance oxidative degradation resistance. It doesn't need cholesterol. Species-specific phospholipases cannot penetrate the glycerol backbone's stereochemistry. Targeting organs is possible. Bipolar lipids can be synthesised and kept in air/oxygen without degradation due to their stability. Archaeosome formulations can be autoclaved due to their high thermostability. Archaeal lipids are more thermo-labile. Phagocytic cell absorption is boosted, permitting effective adjuvant activity, and Archaeal lipids operate as self-adjuvant drug delivery mechanisms.

TYPES OF ARCHAEA LIPIDS

Archaea lipids can be classified into three major categories as follows.

Natural lipids

Archaeal lipids are important in pharmaceutical manufacturing and stability. Archaeal lipids' main benefits include the following [5]:Phospholipids in archaea are more stable than those in other species. The chemically modified archaeal lipid derivative improves other enzymes' hydrolysis stability. Adding cyclic structure to lipids increases membrane packing and decreases membrane fluidity, which may be a thermo-adaptive response. Saturated alkyl chains improve stability against oxidative degradation. Cholesterol is not needed. The stereochemistry of the glycerol backbone makes it resistant to other species' phospholipases. It could target certain

organs. Bipolar lipids are stable enough to synthesise and store in air/oxygen. Due to their high thermo-stability, archaeosome formulations can be autoclaved. Archaeal lipids are more thermolabile in the environment.

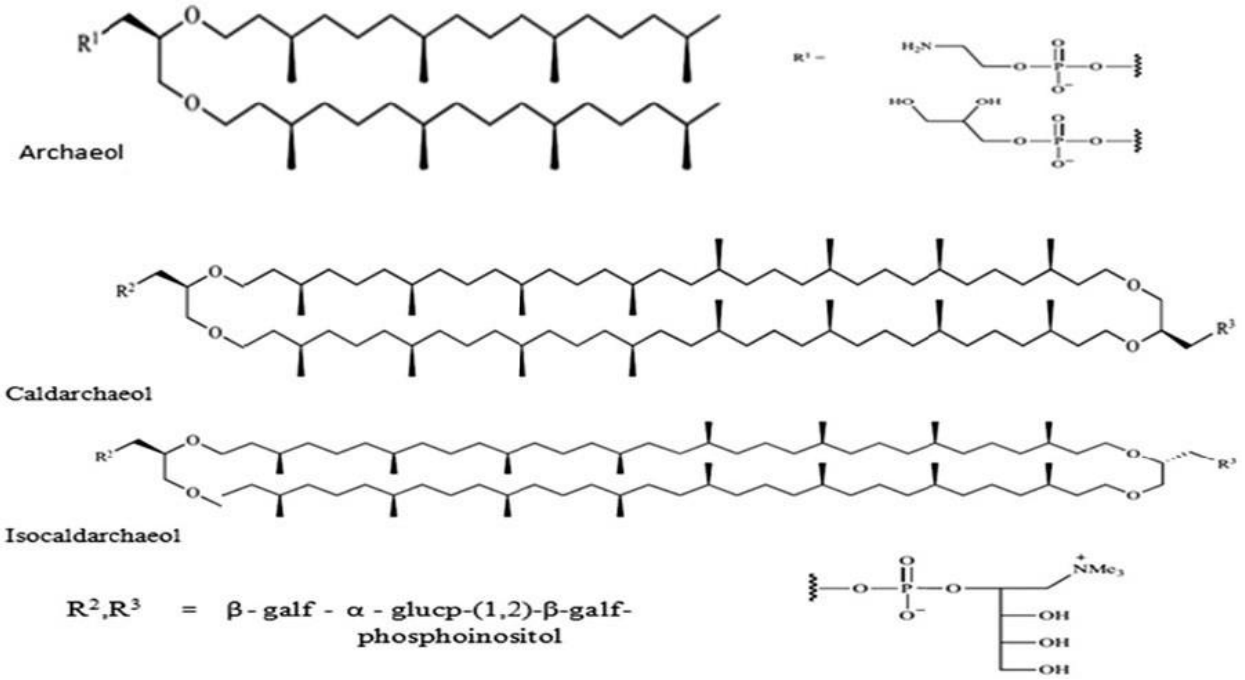

Figure 2. Structures of archaeal lipid.

Chemically modified natural lipids

Archaea-derived polar lipids frequently have acidic hydrolyzable polar head groups. This chemical method creates matched dihydroxyl archaeal lipid cores. Syrinx Diagnostika patented many T. acidophilum lipid extract-derived archaeal lipid structures. After hydrolysis, oxidation of primary alcohols to carboxylic acids, activation, and coupling with suitable amines produced archaeal lipids containing aminated polar head groups. (**Figure 3**).

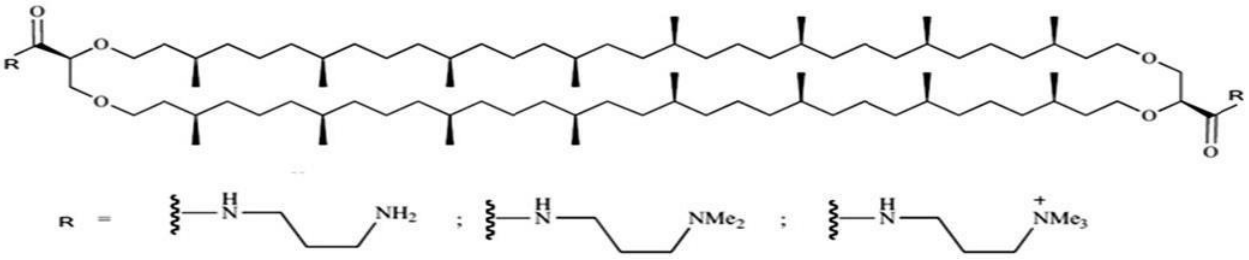

Figure 3. Aminated tetraethers.

Halobacterium salinarum and Tetrabacteriumacidophilum provided the modified diether and tetraether lipid cores. Caldarchaeols were symmetrically or unsymmetrically functionalized with the same polar head groups, while archaeols were sugar or phosphorylated. Phosphoserine, phosphoethanolamine, phosphoinositol, and phosphoglycerol produced phosphorylated groups [7]. Sugars included glucose, trisaccharides, tetrasaccharides, galactose, and mannose. (**Figure 4**).

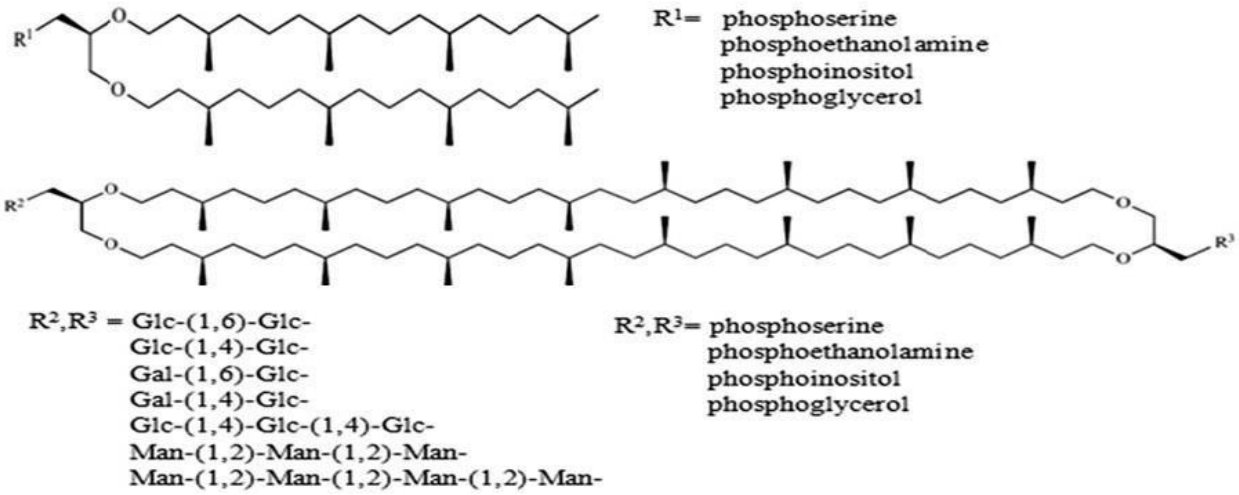

Figure 4. Hemi synthetic diether and tetraether glycolipids.

Synthetic lipids

Numerous academic and corporate research teams examined the full synthesis of archaeal lipid analogues, even though natural extraction gave enormous volumes of pure molecules with certain challenges. Archaeal lipid analogues are symmetrical 1,3-cyclopentane rings with two alkyl (X=(CH2)2) or alkoxy (X=O) chains connected to two glycerol units. (**Figure 5**).

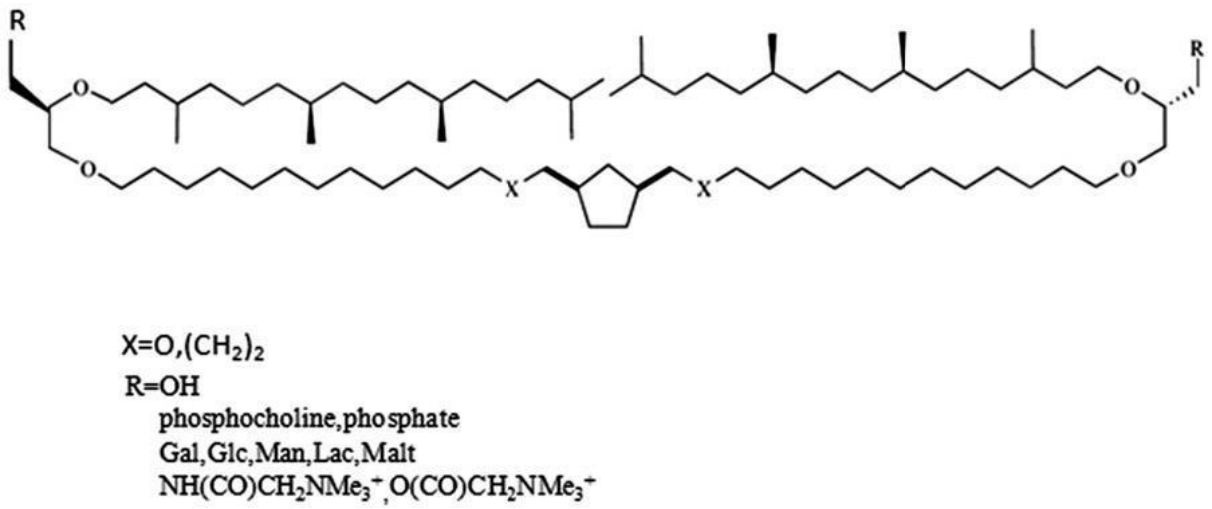

Figure 5. Synthetic archaeal lipid analog.

Each glycerol residue receives a phytanyl arm, creating a quasimacrocyclic tetraether structure. Compared to natural archaeal lipids produced from isocaldarchaeol (parallel glycerol groups), the stereochemistry of the glycerol moieties was preserved. At both terminal ends of the tetraether core, OH, sugars, glycine betaine, phosphorylated groups, PEG chains, and ligands were added. The bridging chain's C-32 chain core has two branching methyl groups. Again, two phytanyl or linear C-16 arms formed quasimacrocyclic backbones. Archaeal lipids share stereochemistry. Caldarchaeol and isocaldarchaeolanalogs were functionalized using PEG chains, aminated groups, and phosphorylated groups. [8] (**Figure 6**).

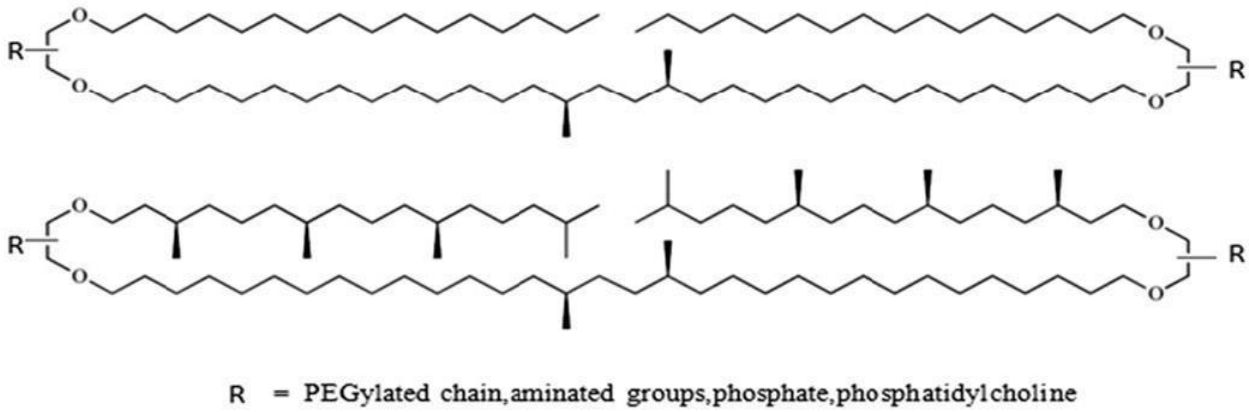

Figure 6. Synthetic archaeal lipid analog.

PREPARATION TECHNIQUES

Starting lipid extraction from suitable archaebacterial species. TPL and neutral lipids like Squalene and hydrocarbons (TLE) make up the natural archaeal lipid extract. TLE is extracted from freeze-thawed biomass from chosen archaea in chloroform/methanol/water. Acetone precipitates neutral lipids and TPL from TLE. TPL from isoprenoid ether lipids with opposing sn-2,3 stereochemistry can be kept in chloroform or chloroform/methanol (2:1) solutions without special conditions. The vesicle is glycol lipid sulphate and phosphatidyl glycerophosphate. Chromatography—column or preparative thin-layer—can generate pure archaeal lipids. Chemically changing pure archaeal lipids can introduce head groups. Glucopyranose or galactopyranosyl glucopyranose are needed to stabilise the archaeal lipid phosphatidylinositol. Lipids are hard to hydrate. Starting with natural, chemically modified, or synthesised archaeal lipids, it was possible to create archaeosome formulations and encapsulate/associate hydrophilic or hydrophobic compounds using typical liposome procedures [9].

Mechanical dispersion method

This includes all operations that start with a lipid solution in an organic solvent and end with lipid dispersion in water. Mixing components usually involves co-dissolving the lipid in an organic solvent, extracting it, and hydrating the solid–lipid combination with an aqueous buffer. Archaeosomes form when lipids spontaneously expand and hydrate. This level adds further processing aspects to procedures' final features. Vortexing, sonication, freeze-thawing, and high-pressure extrusion post-hydration [10].

Lipid hydration method

Archaea lipid is dissolved in chloroform-methanol (2:1) in a rotary evaporator flask and dried into a thin film. This approach took 15 minutes at 30°C and 60 rpm. This method hydrates the drug/antigen with 5 mL of saline phosphate buffer. A revolving evaporator produced a uniform suspension. Archaeobacterial polar ether lipids can be hydrated at room temperature, thus it was kept there for 2 hours to finish the swelling process. This method can make MLVs. Archaeosomes anneal in subzero temperatures. Thin-lipid film techniques were used to make BMD-loaded archaeosomes and conventional liposomes from Archaea H. salinarum and enhanced soy phosphatidylcholine. Ultra deformable archaeosomes (UDA) are vesicles made of soybean phosphatidylcholine (SPC), sodium cholate (NaChol), and Halorubrumtebenquichense (3:1:3 wt/wt) polar lipids. Topical UDA was made by lipid hydration [11].

Membrane extrusion

At low pressure, gently moving archaeosomes through a membrane filter with a specified pore size reduces their size. To achieve high entrapment, the dispersion medium extrudes the vesicle content as polar phospholipids break and reseal via the polycarbonate membrane. This method produces large unilamellar vesicles through extrusion (LUVETs) archaeosomes with 30% encapsulation at high lipid concentrations. Archaeosomes were made from polar lipid methanol. KPB buffer and 1M MgCl2, pH 7.4, moistened the dry lipid film before vortexing to create multilamellar (ML) vesicles. Extruded through a 400 nm membrane, they become unilamellar (UL) vesicles [12].

Freeze-thaw method

This method freezes the UL dispersion for 15 minutes before melting and sonicating it. Archaeosomes unite and grow significantly. Sonication speeds up packing error removal, reducing archaeosome membrane permeability. Dialysis against hypo-osmolar buffer can substitute sonication to generate 41-μm vesicles. Frozen and thawed SUVs are added to the salt solution. Osmotic lysis causes huge freeze-thawed vesicles to rupture during dialysis. Archaeosomes of polar lipid fraction E (PLFE) and conventional liposomes of EPC/cholesterol (3:2 molar ratio) were freeze-thawed for oral vaccination administration [13].

Sonication

Sonicating the polar lipid fraction "PLF" of Sulfolobussolfataricus at 60°C produces archaeosomes without lipid replenishment. Sulfolobusacidocaldarius polar lipids formed archaeosomes when sonicated at 0°C. Sonication was used to make BMD-loaded archaeosomes, conventional liposomes, and phosphatidylcholine-enriched Archaea H. salinarum lipids. Sonicating MLV dispersions at 80% amplitude for 4 minutes with a Hielscher UP50H ultrasonic disintegrator formed topical delivery vesicles [14].

French pressure cell extrusion

After setting up the piston, pressure, and power, a liquid sample of prefabricated MLVs is pumped into the sample cavity. MLVs are extruded via a tiny hole and collected in a container at 40°C and 2000 psi. This approach makes uni- or oligo-lamellar archaeosomes. UL vesicles were made from ML vesicles by extrusion 10 times at 65°C (archaeosomes) through two-layered polycarbonate membranes (pore size = 200 nm) under nitrogen gas pressure [15].

Solvent dispersion method

This approach dissolves lipids in an organic solution and mixes them with an aqueous phase containing the components to be entrapped in archaeosomes. The archaeosome bilayer is half lipid monolayer during the organic-aqueous phase transition. Solvent dispersion techniques can be characterised by organic solvent-aqueous solution miscibility. The organic solvent is miscible, excess, and immiscible with the aqueous phase [16].

Reverse phase evaporation

Evaporation removed solvent from the emulsion. Polar lipids are usually dissolved in organic solvents and sonicated in a bath to create an emulsion (w/o), which is dried to a semisolid gel using a rotary evaporator under decreased pressure. Finally, a vortex mixer and severe mechanical shaking can produce LUVs with a given water droplet ratio [17].

Detergent dialysis method

Detergents are used to bring ethereal phospholipids into intimate contact with the aqueous phase. Detergents link with phospholipid molecules, separating the hydrophobic portions from water [18]. Four methods reduce detergent:

Dialysis: Equilibrium or continuous flow dialysis uses dialysis bags wrapped in big detergent-free buffers.

Gel filtration: Size-exclusive chromatography removes detergent. Gel filters can range from Sephadex G-50 to Sephacryl S200–S1000. Archaeosomes cannot enter through column beads' pores.

Bio-beads: Shaking a mixed micelle solution with beaded organic polystyrene absorbers like XAD-2 beads and Bio-beads SM2 adsorbs detergent. Detergent absorbers remove detergents with a low critical micelle concentration that dialysis and gel filtration cannot.

Dilution: When an aqueous mixed micellar solution of detergent and the phospholipids is diluted with buffer, the micellar size and polydispersity increase significantly. As the system is diluted away from the mixed micellar phase boundary, an amorphous change from polydisperse micelles to monodisperse vesicles develops. Due to loaded molecule leakage during dialysis, detergent/dialysis may capture poorly.

HALLMARKS OF AN IDEAL ADJUVANT

- Stability, bioavailability, and cost-effectiveness matter.
- Avoid autoimmune antibodies.
- Non-pathogenic inflammation occurs.

- Promoting innate-acquired immune system communication.
- Increased antibody response to a specific (humoral) antigen.
- Cell-mediated cytotoxic T-cell response.
- T-helper cell activation [19].

APPLICATIONS OF ARCHAEOSOME FORMULATIONS

Cancer vaccine self-adjuvants

Archaeal ether glycolipid vesicles containing soluble antigens induce robust CD4+ and CD8+ CTL responses. Long-term tumour prevention requires host CD8+ CTL responses. Without CD8+ T-cell cytotoxicity, mice develop spontaneous tumours. Patients with advanced cancer benefit from CD8+ CTL responses to tumor-associated antigens. Thus, creating cancer immune treatments has garnered focus. Cancer vaccines need particular antigenic targets and a strong immune response to work. Archaeosomes efficiently carry foreign antigens for humoral and cell-mediated immunity. Since the initiation of CD8+ cytotoxic T cells is important for protective immunisation against malignancies, several archaeosome lipid compositions were tested to elicit a significant CD8+ CTL response to entrapped antigen. When mice were injected with ovalbumin (OVA) entrapped in all archaeosome lipid compositions, a substantial (day 10) splenic CTL response indicated MHC class I presentation. Halophilic archaea polar lipid compositions adjuvanted this early CTL response well. By weeks 6–7, lytic units decreased considerably. Only bipolar membrane-spanning caldarchaeol-rich M. smithii and T. acidophilum evoked memory CTLs at 50 weeks. OVA-entrapped M. smithii, H. salinarum, and T. acidophilum vesicles protected mice from OVA-expressing solid tumours for 6 weeks. Archaeosomes with 3mg OVA inhibited tumour growth. OVA-archaeosomes administered with tumour challenge prevented tumours. Antigen-free T. acidophilumarchaeosomes that captured antigen H. salinarum conferred innate therapeutic protection. Vaccinating archaeosomes with a CTL peptide epitope from the melanoma separation antigen, tyrosinase-related protein-2, produced a protective CD8+ response against B16OVA metastases, suggesting self-tumor antigens can be targeted. Archaea's lipid structural characteristics may affect primary, long-term, and innate immunity, affecting vaccine adjuvant selection [20].

Chagas vaccine immunoadjuvant

American trypanosomiasis (Chagas sickness) is a neglected tropical disease caused by the protozoan parasite Trypanosoma cruzi. The WHO estimates 15 million cases. 50,000 children

and adults die annually from T. cruzi-induced cardiac disease due to a lack of therapy. Large-scale migrations have spread the disease to non-endemic areas of the Americas and Europe. Chagas disease prevention and control must be innovated. T. cruzi has no vaccines or immunotherapies. In the hunt for T. cruzi vaccine candidates, several adjuvants have failed to induce protective immunity. Archaeosomes have strong adjuvant effects (ARC). Traditional liposomes are better absorbed by macrophages and antigen-presenting cells in vitro and in vivo. Unlike liposomes, immune modulators aren't needed to promote adjuvancy beyond the depot effect, enabling larger production scale. T. cruzi antigens can be integrated into ARC, creating an immunogen that protects mice from intracellular parasites after sc injection. ARCs may be a safe and effective nano-nano-carrier adjuvant for future vaccines against this disease [21].

New gene delivery systems

Archaeobacterial cationic or co-lipids can promote gene transfection in vitro. Combining bilayer-forming and monolayer-forming lipids can modify CL–DNA complex membrane characteristics. Novel archaeoplexes for in vivo gene transfection into the airway epithelium via nasal instillation or aerosolization for cystic fibrosis lung-directed gene therapy. Protein/peptide oral delivery systems The unfavourable GI environment makes oral peptide and protein treatments difficult to take. Lipid-based administration preserves peptides and proteins. Archaeosomes, lipid-based oral drug delivery systems from S. acidocaldarius PLFE, are unique. Archaeosomes stabilised in simulated GI fluids, allowing fluorescently labelled peptides to stay in the GI tract longer after oral delivery. In vivo, archaeosomes containing insulin lowered blood glucose levels more than liposomes, even though they had little effect on insulin transport through Caco-2 cell monolayers. In vitro, PLFE-produced archaeosomes were stable and let fluorescently tagged peptides move slowly through the GI tract. In diabetic rats, oral insulin nano-nano-carrier archaeosomes reduced blood glucose better than liposomes. The formulation's restricted intestinal epithelial permeability after oral therapy may have caused slight hypoglycemia **[22].**

As novel antigen delivery systems

Encapsulating bovine serum albumin in 200-nm-diameter archaeal lipid vesicles (archaeosomes) raised antibody titers in mice vaccinated intraperitoneally to levels comparable to Freund's adjuvant. Archaeosomes potentiated immune responses better than three regular liposome formulations. Archaeosomes made from polar lipids from M. smithii, a human colon microbe, required only two injections to reach the maximum antibody titer. M. smithiiarchaeosomes were

found when mice's immune systems responded to the more immunogenic cholera B component protein. For full humoral reaction, the antigen must reside in archaeosomes [23].

Drug delivery systems for natural antioxidant compounds

Archaeal polar lipid-based multilamellar (MLVs) and unilamellar (SUVs) liposomes distribute natural antioxidant chemicals from olive mill waste topically. Throughout the stability experiment, SUVs were smaller than MLVs at less than 200 nm. Transmission electron microscopy showed that archaeosomes had uneven membranes while standard liposomes were spherical. Both formulations had comparable vesicle encapsulation efficiency, which provided high antioxidant action. One month following formulation, stability testing showed no change in the suspensions' early characteristics. Liposomal suspensions in Carbopol-940 and Pluronic-127 were also tested for topical delivery. Vertical diffusion Franz cells were used to test the release behaviour of the systems developed. Vesicles emerged from gels after 24 hours. Archaeosome gels produced the same phenolic chemicals regardless of excipient. Due to their stability, entrapment efficiency, and antioxidant activity, archaeosomes were a promising nano-nano-carrier for topical administration of antioxidant phenolic chemicals, similar to those produced with traditional phosphatidylcholine liposomes. Archaeosomes were also more gel-inclusion-flexible than liposomes. Thus, archaeosomes release carbopol or pluronic similarly, allowing both excipients to be used interchangeably, whereas conventional liposomes do not, so the choice of excipient depends on the desired impact [24].

New Paclitaxel nano-carrier for breast cancer.

Paclitaxel-loaded archaeosomes increase side effects and therapeutic index. Nano-nano-carriers have advanced in treating many diseases. Lipid nano-nano-carriers vary greatly. Lipid nano-nano-carriers like archaeosomes are crucial. Paclitaxel, a breast cancer treatment, has side effects. Archaeosomes were synthesised in PBS with a precise Paclitaxel ratio from methanogenic archi bacteria. Paclitaxel archaeosomes released most pharmaceuticals in the first three hours over 26 hours. Archaeosomes Paclitaxel showed more cytotoxicity than regular Paclitaxel on a breast cancer cell line in the MTT test. Archaeosome-based medication delivery has increased paclitaxel's therapeutic index [25].

A nano-nano-carrier for topical delivery of BMD

BMD-loaded archaeosomes and conventional liposomes using Archaea H. salinarum lipids and phosphatidylcholine. In vitro drug permeation experiments through full-thickness pig skin using

Franz diffusion vertical cells examined the effects of archaeal and liposomal dispersions on (trans) cutaneous medication delivery. Archaeosomes penetrated and accumulated drugs in the skin layer and epidermis best. Archaeosomes have great delivery potential. Incorporating archaeosomes into an anti-inflammatory drug's efficacy for local skin diseases may be a novel and promising approach [26].

In vitro epithelial cells receive various payloads from archaeosomes.

Polar lipids from archaeobacteria generate archaeosomes. These have special structural features that promote lipid bilayer stability in high temperatures, low or high pH, phospholipases, and bile salts. They're ideal for developing novel medication, gene, and vaccine delivery systems. Aeropyrumpernix K1 produced large UL archaeosomes (400 nm) that might be used to build a universal method for treating epithelial cells. These archaeosomes can transport calcein, 60-kD proteins like listeriolysin, big protein aggregates like keratin 14, and plasmid DNA to epithelial cells produced in vitro. Small molecules deliver 40% at this early level of development. Keratinocytes are unharmed by 500 μg/mL UL archaeosomes [27].

UDA as topical adjuvant

Parenteral immunisation only reaches the skin's strong antigen-presenting cells (APC) via a challenging intradermal pathway. Topical APC application is preferable since it allows closer skin contact. Topical vaccination has higher patient compliance, less chance of reinfection from contaminated material, and less need for highly trained staff, sterilised equipment, and cold chain management than injectable vaccination. Dose flexibility and the need for powerful immunomodulators such bacterial ADP-ribosylating exotoxins (cholera toxin, Escherichia coli, and their variants) negate these advantages. SPC, NaCl, and H. tebenquichense polar lipids (3:1:3 w/w) form UDA vesicles. UDL (SPC and NaChol in a 6:1 w/w ratio) and UDA were not caught or cytotoxic to keratinocytes, however macrophages captured UDA, which could be decreased by 25–60% by 0.4–1.6 mg/mL phospholipids. UDL was scarce and harmless. Balb/C mice immunised with four doses of Ovalbumin (OVA)-loaded UDA at 75 μg OVA/600 g phospholipids (125 nm mean size and 42 mV zeta potential) have ten-fold to 100-fold greater IgG titers than those infected with UDL at the same dose. Due to UDA's topical adjutancy and higher phagocytic absorption due to its glycolipid content, both matrices penetrate almost 10 m after 1 hr on human skin. Traditional liposomes mix and don't penetrate mice's healthy skin beyond 1 mm. UDL's lipid matrix delivers aqueous content to the living epidermis by penetrating

SC. Due to its ultra-deformability, UDL outperforms regular liposomes as topical adjuvants. After SC penetration, live skin cells absorbed UDL lipids. Archaeosomes induce Th1, Th2, and CD8+ T cell responses to entrapped soluble Ag in mice after s.c. injection [28].

CONCLUSION

Finally, the nano-nano-nano-carrier system described above has great potential for developing novel, low-dose, and effective disease treatments. The amount of archaeosome and lipid-based clinical trials is encouraging. Several companies are heavily investing in archaeosome product development and testing for a variety of ailments. Archaeosomes transport medicines, DNA, and cells efficiently. They are promising and may be researched.

CONFLICTS OF INTEREST

No conflict of interest is declared.

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