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TRANSFEROSOMAL NANOPARTICLES FOR BACTERIAL MENINGITIS - A COMPREHENSIVE REVIEW

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Abstract:

Meningitis is an inflammation of the protective membranes called meninges and fluid adjacent the brain and spinal cord. The inflammatory progression expands all through subarachnoid space of the brain and spinal cord and occupies the ventricles. The pathogens like bacteria, fungi, viruses, or parasites are main sources of infection causing meningitis. Bacterial meningitis is a life-threatening health problem that which needs instantaneous apprehension and treatment. Nesseria meningitidis, Streptococcus pneumoniae, and Haemophilus flu are major widespread factors causing bacterial meningitis. The conventional drug delivery approaches encounter difficulty in crossing this blood-brain barrier (BBB) and therefore are insufficient to elicit the desired pharmacological effect as required for treatment of meningitis. Therefore, application of nanoparticle- based drug delivery systems has become imperative for successful dealing with this deadly disease. The nanoparticles have ability to across BBB via four important transport mechanisms, i.e., paracellular transport, transcellular (transcytosis), endocytosis (adsorptive transcytosis), and receptor-mediated transcytosis. In this review, we reminisce distinctive symptoms of meningitis, and provide an overview of various types of bacterial meningitis, with a focus on its epidemiology, pathogenesis, and pathophysiology. This review describes conventional therapeutic approaches for treatment of meningitis and the problems encountered by them while transmitting across tight junctions of BBB. The nanotechnology approaches like functionalized polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carrier, nanoemulsion, liposomes, transferosomes, and carbon nanotubes which have been recently evaluated for treatment or detection of bacterial meningitis have been focused. This review has also briefly summarized the recent patents and clinical status of therapeutic modalities for meningitis.

Keywords: Transferosome, Nanoparticles, Meningitis, Inflammation

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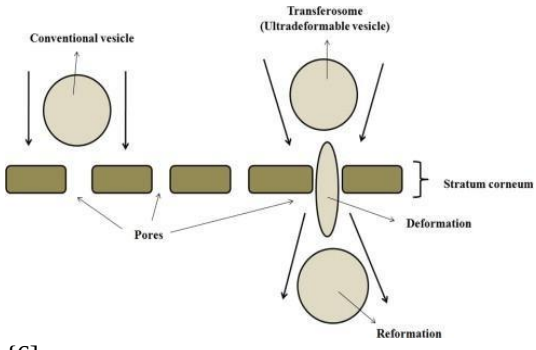
INTRODUCTION:

Transferosomes are vesicular carrier systems that are specially designed to have at least one inner aqueous compartment that is enclosed by a lipid bilayer, together with an edge activator Transferosomes is a term registered as a trademark by the German company IDEA AG, and is used to refer its proprietary drug delivery technology. This concept was introduced in 1991 by Gregor Ceve. The name Transferosomes means "carrying body" and is derived from the Latin word 'transferre' meaning 'to carry across' and the Greek word 'soma', meaning 'a body'. A Transferosome carrier is an artificial vesicle designed to exhibit the characteristics of a cell vesicle or a cell engaged in exocytosis, and thus suitable for controlled and potentially, targeted drug delivery. Transferosomes are complex vesicles that have extremely flexible & self-regulating membranes, which make the vesicle very deformable[1,2].



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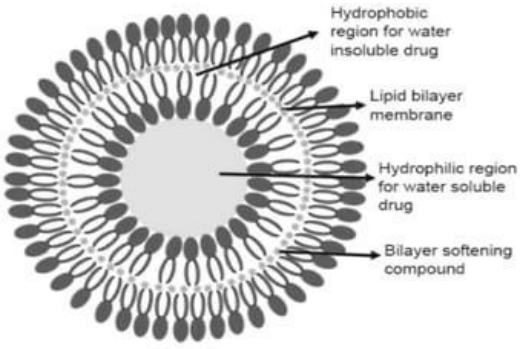
Transferosome vesicle can cross microporous barriers efficiently, even if the porous are much smaller than the vesicles size. Transferosomes are ultra deformable, self optimized aggregates for transdermal application containing a mixture of lipids and biocompatible membrane softeners. Though basic organization is broadly similar to a liposome, the Transferosome differs by its softer, more deformable and better adjustable artificial membrane they posses. Transferosomes are particularly optimized, ultra deformable (ultra flexible) lipid supramolecular aggregates, which are able to penetrate the mammalian skin intact.



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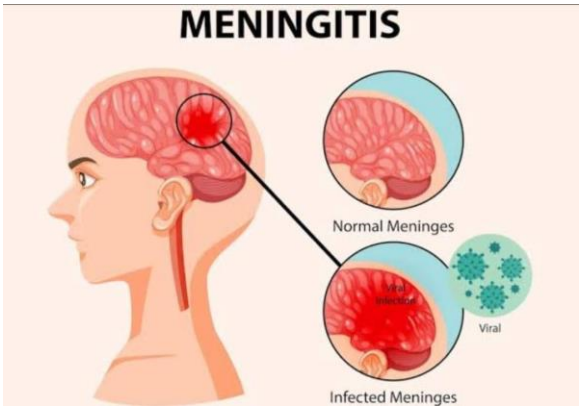
Transferosome is a type of carrier system which is capable of transdermal delivery of low as well as high molecular weight drugs. Transferosomes penetrate through the pores of stratum corneum which are smaller than its size and get into the underlying viable skin in intact form. Acne vulgaris is a disease of the pilosebaceous follicle characterized by non-inflammatory (open and closed comedones) and inflammatory lesions (papules, pustules, and nodules). In such situation transdermal drug delivery remains the most preferential mode of administration. But, stratum corneum forms the most formidable barrier for the penetration of drug through skin. To overcome the stratum corneum barrier, the use of lipid vesicles like transferosomes in delivery systems has involved increasing attention in recent years. The aim of the present study was to statistically optimize the vesicular formulations.

Meningitis is inflammation of the meninges covering the brain. It is a pathological definition. The cerebrospinal fluid (CSF) typically exhibits an elevated number of leucocytes (or a pleocytosis). In adults, >5 leucocytes/μL is defined as elevated. Bacterial or viral meningitis is confirmed by the detection of a pathogen in the CSF. Bacterial meningitis may also be suggested by symptoms of meningism and appropriate bacteria in the blood.



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The inflammatory progression expands all through subarachnoid space of the brain and spinal cord and occupies the ventricles. The pathogens like bacteria, fungi, viruses, or parasites are main sources of infection causing meningitis. Bacterial meningitis is a life-threatening health problem that which needs instantaneous apprehension and treatment. Nesseria meningitidis, Streptococcus pneumoniae, and Haemophilus flu are major widespread factors causing bacterial meningitis. The conventional drug delivery approaches encounter difficulty in crossing this blood-brain barrier (BBB) and therefore are insufficient to elicit

the desired pharmacological effect as required for treatment of meningitis. Therefore, application of nanoparticle-based drug delivery systems has become imperative for successful dealing with this deadly disease. The nanoparticles have ability to across BBB via four important transport mechanisms, i.e., paracellular transport, transcellular (transcytosis), endocytosis (adsorptive transcytosis), and receptor- mediated transcytosis. In this review, we reminisce distinctive symptoms of meningitis, and provide an overview of various types of bacterial meningitis, with a focus on its epidemiology, pathogenesis, and pathophysiology. This review describes conventional therapeutic approaches for treatment of meningitis and the problems encountered by them while transmitting across tight junctions of BBB.The nanotechnology approaches like functionalized polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carrier, nanoemulsion, liposomes, transferosomes, and carbon nanotubes which have been recently evaluated for treatment or detection of bacterial meningitis have been focused. This review has also briefly summarized the recent patents and clinical status of therapeutic modalities for meningitis.[3,4,5]

SALIENT FEATURES OF TRANSFEROSOMES {1,9}

These are made up of natural phospholipids like liposome therefore these are biodegradable and biocompatible.

1. They act as a carrier for low to High molecular weight drugs such as analgesic, corticosteroids, anesthetics, sex hormones, albumins, insulin, anticancer etc.
2. These molecules possess wide range of solubilities as they are made up of hydrophilic and hydrophobic moieties.
3. Transferosomes have high entrapment efficiency, for example for lipophilic drugs the entrapment efficiency is nearly equal to 90%.
4. The transferosome molecules encapsulate the drug and protect it from metabolic degradation. example: proteins and peptides
5. Transferosomes acts as a depot as they release the drug slowly and gradually.
6. Transferosomes are used as topical and as well as for systemic delivery of the drugs.
7. Transferosome preparation involves simple and easy procedures and avoid use of unacceptable pharmaceutical Excipients.
8. The formulation is short, simple, and easy to scale up.
9. Transferosomes possesses high deformability which helps in better penetration of vesicles.
10. They can deform and pass-through narrow constructions (5 to 10 times less diameter of their own size) without any significant loss of the drugs.

RATIONALE OF TRANSFEROSOMES{4,5,10}

The use of the transdermal route has been well established in the past, and because of its inherent advantages, new methods for transdermal delivery are continuously being developed. The introduction of ultra deformable vesicles transferosomes, will thus surely become an important step in relaunching the researches regarding the use of vesicles as transdermal drug delivery systems. In comparison to other transdermal delivery systems, the use of elastic vesicles has certain advantages: They allow enhanced permeation of drug through skin; their composition is safe and the components are approved for pharmaceutical and cosmetic use; they can increase the transdermal flux, prolonging the release and improving the site specificity of bioactive molecules; they can accommodate drug molecules with a wide range of solubility. Hence, enhanced delivery of bioactive molecules through the skin by means of an ultra deformable vesicular carrier opens new challenges and opportunities for the development of novel improved therapies. Thus, it could be concluded that the new ultra flexible drug carrier (transferosome) can overcome all the problems associated with the transdermal delivery as transferosomes itself.

ADVANTAGES{11,12,13]

1. Transferosomes increases the duration of drug in systemic circulation due to its encapsulated form which increases half-lives of the drugs.
2. Both Hydrophilic and hydrophobic moieties can be encapsulated.
3. The vesicles of transferosomes are capable of entrapping hydrophilic, lipophilic, amphiphilic particles.
4. These are nontoxic in nature.
5. These have ability to target the specific organ for drug delivery.
6. Transferosomes avoids first pass metabolism which increase their bioavailability.
7. They have potential to increase transdermal flux and improve site specificity of biologically active agents.
8. These are made up of pharmaceutically acceptable ingredients which are nontoxic and are prepared by using standard methods, optimized on case-by-case basis.
9. They protect the drugs from metabolic degradation by encapsulation and prevent undesirable side effects.
10. Transferosomes are highly recommend for predictable and extended duration of activity, for sustained release of drugs.
11. Transferosomes are used for delivery of numerous active compounds such as insulin, proteins, peptides, corticosteroids, anticancer drugs, analgesics, anesthetics, herbal medicines, and NSAID's.
12. These are made up of natural phospholipids

like liposome hence these are promisingly biocompatible biodegradable.
13. Transferosomes accommodate a variety of agents Independent of their molecular weight, size, structure, polarity.
14. Transferosomes are the versatile and efficient molecules in effective drug delivery.
15. These are ultra-deformable and elastic in nature they squeeze themselves in narrow constructions of skin that are very minute, such as 5 to 10 times less diameter than the vesicle diameter.
16. Transferosomes are the unique drug carrier systems that deliver therapeutic agents with wide range of solubilities as these are composed of hydrophilic and hydrophobic moieties.
17. These can be easily administered in unconscious and comatose patients.
18. These can be used with drugs which have narrow therapeutic index.
19. Equivalent therapeutic effect is achieved in transdermal drug delivery with lower daily dose of a drug than the required dose.
20. Self-administration is possible in this system of drug delivery which is non invasive, painless, and simple application which increases patient compliance.

DISADVANTAGES [12,13,14]

1. Due to their predisposition to oxidative degradation these are chemically unstable.
2. Purity of natural phospholipids is
3. Drug molecules which are used for transferosome delivery must be potent because patch size limits amount that can be delivered.
4. Drugs which require high blood levels cannot be administered.
5. Transferosome molecules permeate the skin slowly as these are hydrophilic in nature.
6. It may cause hypersensitivity reaction in some cases.
7. Transferosomes are chemically unstable because of their susceptibility to oxidative degradation.
8. Transferosomes are not suitable for higher doses of drugs.
9. Along with these limitations the high expense of the product is also a major drawback for the wide acceptance of transferosome.

TRANSFEROSOME VS OTHER CARRIERS SYSTEMS[10,15]

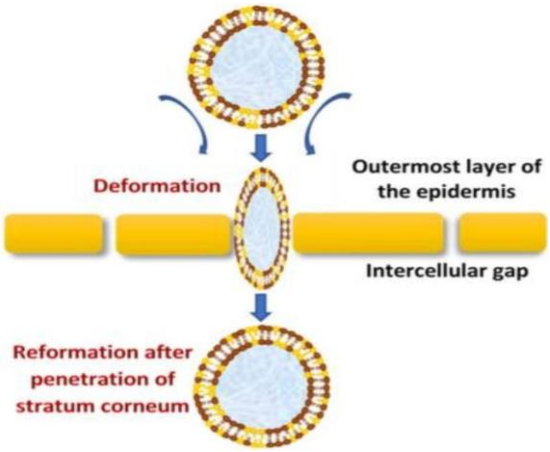
At first glance transferosomes appear to be remotely related to lipid bilayers vesicle liposomes. However in functions appear to be remotely differs widely from commonly used liposomes in that they are much more flexible and adaptable. The extremely high flexibility of their brain permits trance more to squeeze themselves even through pores much smaller than their on diameter.This is due yo high flexibility of the transferosomes membrane and is achieved by judiciously combining at least two lipophilic or amphiphilic components (phospholipids plus biosurfactants with sufficiently different packing characteristics into a single bilayer.

The high resulting aggregate deformability permits transferosomes to penetrate to the skin spontaneously. Thus if the penetration enhancement via the solubilization of the skin lipids was the reason for the superior penetration ability of transferosomes. Transferosomes differ from mixed micelles in at least two basic features. Firstly a transferosome is normally by one to two orders of magnitude (in size) greater than standard lipid micelles. Secondly and more importantly, each vesicular transferosomes contains a water filled core whereas a micelle is just a simple fatty droplet. Transferosome thus carry water as well as fat-soluble agent in comparison to micelles that can only incorporate lipoidal substances.

Method	Advantage	Disadvantage
Liposomes	Phospholipids vesicle, biocompatible, Biodegradable	Less skin penetration less stable
Proliposome	Phospholipid vesicle, more stable than liposomes	Less penetration, cause aggregation and fusion of vesicles
Physical methods e.g. iontophoresis	Increase penetration of intermediate size charged molecule	Only for charged drugs, transfer efficiency is low (less than 10%)
Niosomes	Non-ionic surfactants vesicles	Less skin penetration easy handling But will not reach up to deeper skin layer
Proniosomes	Greater stability, Will convert into noisome in situ, stable	Less skin penetration easy handling But will not reach up to deeper skin layer
Transferosomes and Protransfersomes	More stable, high penetration due to high deformability, biocompatible and biodegradable, suitable for both low and high molecular weight and also for lipophilic as well as hydrophilic drugs and reach	None, but for some limitations

TRANSPORT MECHANISM OF TRANSFEROSOME[17,18,19]

Mechanism behind the penetration of transferosome is the development of osmotic gradient because while lipid suspension applies on skin surface water gets evaporated. Transfersomes have strong bilayer deformability and therefore they have increased affinity to bind and retain water. Dehydration is not happened in case an ultradeformable and highly hydrophilic vesicle; it is not identical to forward osmosis but may involve



in transport process related to forward osmosis. Upon application on skin surface(non-occluded), it penetrates skin barrier and reaches at the deeper strata (water rich portion), where they get hydrated. Then, reach at deeper epidermal layer through dehydration of lipid vesicles within the stratum corneum by natural trans epidermal activity (Fig 2). Therefore, transferosome uptake is a function of hydration gradient that exists across the epidermis, stratum corneum, and ambient atmosphere.

Two mechanisms of action have been proposed:

1) Transferosomes act as drug vectors, remaining intact after entering the skin.
2) Transferosomes act as penetration enhancers, disrupting the highly organized intercellular lipids from stratum corneum, and therefor facilitating the molecule penetration in and across the stratum corneum.

COMPOSITION OF TRANSFEROSOMES [4,10,20]

Transferosomes are the mixed lipid aggregates composed of mainly phospholipids like phosphatidyl choline an amphipathic ingredient and a lipid bilayer softening compound usually known as edge activator which forms the vesicle.

PHOSPHOLIPIDS:

- Vesicles composed of phospholipids as the main ingredient like soya phosphatidylcholine, egg phosphatidylcholine, dipalmitoyl phosphatidylcholine, etc., 10-25% surfactant for providing flexibility, various solvents as ethanol, methanol and hydrating medium consisting of saline phosphate buffer (pH 6.5-7). Dyes like Rhodamine 123, Nile red etc.
- Phosphatidylcholine is a fatty composition which can be obtained from both human and vegetable origin. It is mainly an unsaturated fatty acid. These unsaturated fatty acids are mainly linoleic acid up to 70% of the total fatty acids.
- Foremost reason behind the ability of phospholipids to fluidize the lipid bilayer is soy phosphatidylcholine which has a very low phase-transition temperature of below 0°C in water-containing systems, which can be determined by measuring the increase of the trans epidermal water loss (TEWL) after application for a short period of time. 11.51

2) EDGE ACTIVATORS

- The edge activator is added to increase lipid bilayer flexibility and permeability it is also known as "bilayer softening component", it may be a biocompatible surfactant or an amphiphilic drug.
- An edge activator chiefly consists of single chain surfactant of nonionic nature which causes destabilization of the lipid bilayer Thus by increasing its fluidity and elasticity. Flexibility of the transferosome membrane can be modified by mixing suitable surface-active agents in proper ratios.
- most used edge activators which are biocompatible and increase the vesicle's bilayer flexibility as well as improve the permeability in transferosome preparations are surfactants as sodium cholates, sodium deoxycholate, Tweens and Spans (Tween 20, Tween 60, Tween 80; Span 60, Span 65, and Span 80) and dipotassium glycyrrhizinate.
- Materials which are widely used in the formulation of transferosomes are various phospholipids, surfactants, alcohol, dye, buffering agent etc.

Class	Example	Uses
Phospholipids	Soya phosphatidyl choline Dipalmitoyl phosphatidyl choline Distearoyl phoshatidyl choline	Vesicles forming component
Surfactant	Sod. cholate Sod.deoxycholate tween-80 Span-80	For providing flexibility
Alcohol	Sod. cholate Sod.deoxycholate tween-80 Span-80	As a solvent
Dye	Rhodamine-123 Rhodamine-DHPE Fluorescein-DHPE Nile-red	For CSLM study
Buffering agent	Saline phosphate buffer (pH 6.4)	As a hydrating medium

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METHODS OF PREPARATION OF TRANSFEROSOMES{20,22,23}

1. THIN FILM HYDRATION TECHNIQUE

Also known as ROTARY EVAPORATION SONICATION METHOD. The phospholipids and edge activator (vesicle-forming ingredients) are dissolved in a round-bottom flask using a volatile organic solvent mixture (example: chloroform and methanol in a suitable (v/v) ratio). The lipophilic drug can be incorporated in this step. In order to form a thin film, the organic solvent is evaporated above the lipid transition temperature under reduced pressure using a rotary vacuum evaporator. Keep it under vacuum to remove the final traces of the solvent. The deposited thin film is then hydrated using a buffer solution with the appropriate pH (example: pH 7.4) by rotation for a respective time at the corresponding temperature. The hydrophilic drug incorporation can be done in this stage. The resulting vesicles are swollen at room temperature and sonicated in a bath or probe sonicator to obtain small vesicles. The sonicated vesicles are homogenized by extrusion through a sandwich of 200 nm to 100 nm polycarbonate membranes.

2. VORTEXING-SONICATION METHOD

The phospholipids, edge activator and the drug are mixed in a phosphate buffer. The mixture is then vortexed until a milky transfersomal suspension is obtained. It is then sonicated, using a bath sonicator, for a respective time at room temperature and then extruded through polycarbonate membranes (example: 450 and 220 nm)

3. MODIFIED HANDSHAKING PROCESS

The modified handshaking method has the same basic principle as the rotary evaporation-sonication method. In the modified handshaking process, the organic solvent, the lipophilic drug, the phospholipids and edge activator are added in a round-bottom flask. All the excipients should completely dissolve in the solvent and obtain a clear transparent solution. Then, the organic solvent is removed by evaporation while handshaking instead of using the rotary vacuum evaporator. In the meantime, the round-bottom flask is partially immersed in the water bath maintained at a high temperature (example: 40-60 °C). A thin lipid film is then formed inside the flask wall. The flask is kept overnight for complete evaporation of the solvent. The formed film is then hydrated with the appropriate buffer solution with gentle shaking at a temperature above its phase transition temperature. The hydrophilic drug incorporation can be done in this stage.

4. SUSPENSION HOMOGENIZATION METHOD

Transfersomes are prepared by mixing an ethanolic phospholipid solution with an appropriate amount of edge activator. The prepared suspension is subsequently mixed with buffer to yield a total lipid concentration. The resulting formulation is then sonicated, frozen and thawed respectively two to three times.

5. CENTRIFUGATION PROCESS

The phospholipids, edge activator and the lipophilic drug are dissolved in the organic solvent. The solvent is then removed using a rotary evaporator under reduced pressure at the respective temperature. The remaining traces of solvent are removed under vacuum. The deposited lipid film is hydrated with the appropriate buffer solution by centrifuging at room temperature. The hydrophilic drug incorporation can be done in this stage. The resulting vesicles are swollen at room temperature.

The obtained multilamellar lipid vesicles are further sonicated at room temperature.

6. REVERSE PHASE EVAPORATION METHOD

The phospholipids and edge activator are added to a round-bottom flask and dissolved in the organic solvent mixture (example: diethyl ether and chloroform). The lipophilic drug can be incorporated in this step. Then, the solvent is evaporated using rotary evaporator to obtain the lipid films. The lipid films are redissolved in the organic phase mostly composed of isopropyl ether and/or diethyl ether. Subsequently, the aqueous phase is added to the organic phase, leading to a two-phase system. The hydrophilic drug incorporation can be done in this stage. This system is then subjected to sonication using a bath sonicator until a homogeneous w/o (water in oil) emulsion is formed. The organic solvent is slowly evaporated using rotary evaporator to form a viscous gel, which then becomes a vesicular suspension.

7. HIGH PRESSURE HOMOGENIZATION TECHNIQUE

The phospholipids, edge activator and the drug are uniformly dispersed in PBS or distilled water containing alcohol and followed by ultrasonic shaking and stirred simultaneously. The mixture is then subjected to intermittent ultrasonic shaking. The resulting mixture is then homogenized using a high-pressure homogenizer. Finally, the transfersomes are stored in appropriate conditions.

8. ETHANOL INJECTION METHOD

The organic phase is produced by dissolving the phospholipid, edge activator and the lipophilic drug in ethanol with magnetic stirring for the respective time, until a clear solution is obtained. The aqueous phase is produced by dissolving the water-soluble substances in the phosphate buffer. The hydrophilic drug incorporation can be done in this stage. Both solutions are heated up to 45-50 °C. Afterwards, the ethanolic phospholipid solution is injected dropwise into the aqueous solution with continuous stirring for the respective time. Ethanol removal is done by transferring the resultant dispersion into a vacuum evaporator and then sonicating for particle size reduction

FACTORS AFFECTING PROPERTIES OF TRANSFEROSOMES {4,10,22}

In the process of obtaining an optimized formulation of Transfersomes, there are number of process variables that could affect the properties of the Transfersomes. These variables basically involve the manufacturing of Transfersomal formulations, which are identified as follows:

1. EFFECT OF PHOSPHOLIPIDS: EDGE ACTIVATOR RATIO

The phospholipid: Edge activator (lecithin:surfactant) should be an optimized ratio due to the fact that this greatly affects the entrapment efficiency, vesicle size and permeation ability. In general, it has been reported that the EE could be reduced due to the presence of a higher surfactant concentration. This may be due to the result of increased vesicles membrane permeability because of the arrangement of surfactant molecules within the vesicular lipid bilayer structure, which could generate pores within the vesicular membrane and lead to an increased fluidity and prompt the leakage of the entrapped drug. A further increase in the edge activator content may lead to pore formation in the bilayer and a reduced permeation ability of the vesicles, whereas the incorporation of low concentrations of surfactants may result in growth of the vesicle size. In addition, the decrease in vesicles size at high phospholipid concentrations has been reported in various studies.

2. EFFECT OF VARIOUS SOLVENTS

Various solvents such as ethanol or methanol are used. Selection of the appropriate solvent depends on the solubility of all the formulation ingredients in the solvent and their compatibility with the solvent. Preferably, all the excipients, including the drug, should completely dissolve in the solvent and should obtain a clear transparent solution to produce a better film-forming ability and good stability after hydration. Solvents used in the formulation can also exert their function as penetration enhancers that improve drug flus through the membrane. According to Williams and Barry (2004), ethanol was used in various studies to enhance the flux of hydrocortisone, 5-fluorouracil, estradiol and levonorgestrel through rat skin. For an example, ethanol increases the permeation through different mechanisms, such as increasing the drug solubility in vesicles by acting as a solvent, moreover permeating into the stratum corneum and altering the solubility properties of the respective tissue and, consequently, improving the drug partitioning into the membrane.

3. EFFECT OF VARIOUS EDGE ACTIVATORS (SURFACTANTS)

Deformability, as well as the entrapment efficiency of transferosome vesicles, are affected by the type of edge activators used in their formulations. This could be due to the difference in the chemical structure of the EA. Generally, the vesicle size decreases by increasing the surfactant concentration, the hydrophilicity of the surfactant head group, carbon chain length and the hydrophilic lipophilic balance (HLB). The three surfactants, including tween 80, span 80 and sodium deoxycholate, were used to prepare the transfersomes, and a reduction of the vesicle size was found when the higher surfactant concentration used. This might be due to the fact that the high surfactant concentrations (more than 15%) induce micelle formation rather than vesicle formation. A small polydispersity index (PDI) was reported with

the higher surfactant concentration. A small PDI is responsible for consistent size distribution, which is thought to be an important factor for the reduction of interfacial tension and provides a homogeneous formulation. Additionally, an increased surfactant concentration may lead to an increase in charge of the vesicles, which results in a reduction of vesicle aggregation and enhances the stability of the system. In addition, surfactant properties are one of the properties that are responsible for the entrapment efficiency of the vesicles, as, for an example, the entrapment of a lipophilic drug would be enhanced with the use of a surfactant with a low HLB value.

4. EFFECT OF THE HYDRATION MEDIUM

The hydrating medium may consist of either water or saline phosphate buffer (pH 6.5-7). The pH level of the formulation should be suitable to achieve a balance between both the formulation properties and biological applications, as well as the route of administration. The lipid bilayer of transfersomes mimics the phospholipid layer of the cell membrane, and only unionized drugs remain membrane-bound to the phospholipid bilayer and penetrate through the intracellular route. It is important to use the suitable pH of the hydration medium, which keeps the drug unionized to increase the entrapment and permeation of the drug.

EQUIPMENTS USED IN PREPARATION OF TRANSFEROSOMES AND THEIR WORKING PRINCIPLE {10,15,17,20]

1. ROTARY VACCUM EVAPORATOR

Rotary evaporator is the most effective and important apparatus for Research and development, educational purpose and Pilot testing in Biological, biochemical, pharmaceutical, chemical, food and fragrance industry. Rotary evaporators work on the principle that solvents have a range of boiling points, which decrease under reduced pressure. The evaporation flask rotates at a specified speed forcing the materials to form a large area of thin film on the inner wall of the flask.

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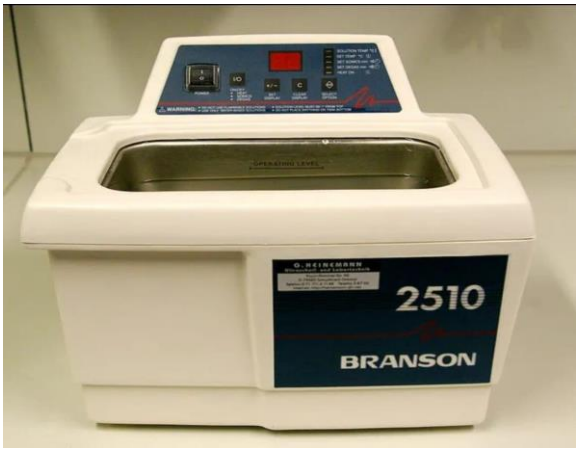
The flask is heated evenly, and materials with a lower boiling point rapidly evaporate. Recycling of the solvent stream occurs in the receiving flask, following cooling by the glass condenser. Users can carry out solvent removal faster and more efficiently than evaporation under atmospheric pressure, thus saving time and increasing productivity in the laboratory. In part, this accelerated evaporation is due to the film's formation on the flask's inner surface, which increases evaporation significantly. It is there for relatively quick to achieve solvent removal (depending on volume and solvent). Rotary evaporators are simple to use and are commonly found in laboratories.

2. SONICATOR

There are different types of Sonicators. They are BATH SONICATOR and PROBE SONICATOR

A) BATH SONICATOR

Bath sonicator is the equipment used in indirect sonication, in which a water bath is involved to provide energy to the sample. A probe sonicator makes direct contact with the sample. This can be an advantage since a more concentrated energy can be added to the sample. The disadvantage of probe sonicators is the potential for sample cross- contamination and contamination by erosion of the probe tip.



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Bath sonication is an indirect sonication method in which a water bath is used. In bath sonication, ultrasonic energy is transmitted to a water bath and then into a vessel or multiple sample tubes. This method is most effective for very small samples. Bath sonicator separates samples from the energy source. Therefore, bath sonication requires significantly more energy input to energize whole water bath, unlike probe sonication. Moreover, bath sonicator eliminates the need for a probe to come into contact with the sample. Hence, the sample cross- contamination and contamination by

the erosion of the probe tip can be prevented by bath sonicator. In addition to the agitation of particles in a sample or cell breaking, bath sonication is useful when cleaning objects such as spectacles and jewellery.

B) PROBE SONICATOR

The principle behind probe sonicator is high frequency vibrations are produced by velocity horn-generally made out of SS material, when is immersed in the liquid to be processed. These vibrations produce millions of microscopic vacuum bubbles, which form and implode at a very high rate. The normal frequency is twenty-five thousand cycles per second. This phenomenon is known as CAVITATION, Cavitation gives rise to intense focal pressure waves and micro streaming of the liquid around the point of collapse. This is turn leads to highshear gradients that are responsible for the chemical process such as Homogenization, Disintegration and Emulsification etc.

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Ultrasonic Processor-Sonicator, consists of two parts;

1. Ultrasonic Generator - This unit produces high frequency - 20 +/-3 KHz, Ultrasonic Power and the power is fed to the Velocity Horn.
2. Velocity Horn This is generally constructed out of SS 316 material of required dimension and contains transducer. These transducers use PZT crystals in sandwich form to convert the Electrical Power into Vibrations leading to Cavitation. This titanium horn is used for the processing by dipping in the solutions.

3. HIGH PRESSURE HOMOGENIZER

The principle behind high-pressure homogenization is the sudden formation of turbulence, shear stress, and cavitation, caused by the mechanically induced movements of the algal cell suspension being forced to pass through a small-sized orifice. The cell disruption efficiency of high-pressure homogenization is a function of a number of factors including the system design, the range of applied pressure, and the microalgal cell dry weight.

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High-pressure homogenization was capable of simultaneously disrupting microalgal cell structure and releasing intra-molecules (eg, protein) from microalgae However, the formation of large concentrations of fine cell debris also appeared, therefore, further downstream processing was required for the high- pressure homogenization method. The requirement for downstream processing, the high energy input and expensive facility remain as significant challenges for the industrialization of high-pressure homogenization approach

4. CENTRIFUGE

A centrifuge is a mechanical or electromechanical device used to separate various components of a liquid. It achieves that by simulating a very high gravity environment inside the tubes by producing centrifugal forces by spinning very fast. The centrifuge works on the principle of centrifugation. Centrifugation is the process of sedimentation of the particles (materials) present within the container (test tube, buckets, etc.) using the angular motion. So, it helps in the separation of particles having different sizes and shapes.

[28}

When the particle is moving with a certain angular velocity, the particle will experience a centripetal force towards the center of rotation. In our case, the centripetal force is due to the upthrust of the fluid media and the electrostatic repulsion due to

the charged particles present on the surfaces of the sample particles. To balance the inward centripetal force, the pseudo force (known as the centrifugal force) acts away from the center. During this process, the particle begins to move away from the center. This is due to the inertia of the particles. Different particles can have different sedimentation rates. A higher sedimentation rate means that the particle will quickly settle at the base. Thus this helps to separate the particles. The RPM of the centrifuge can range from around 300- 1,50,000.

EVALUATION OF TRANSFEROSOME [13,18,19]

1. VESICLE SIZE DISTRIBUTION AND ZETA POTENTIAL

Vesicle size, size distribution and zeta potential were determined by Dynamic Light Scattering system by Malvern Zeta sizer.

2. VESICLE MORPHOLOGY

Vesicle diameter can be determined using photon correlation spectroscopy or dynamic light scattering (DLS) method. Samples were prepared in distilled water, filtered through a 0.2 mm membrane filter and diluted with filtered saline and then size measurement done by using photon correlation spectroscopy or dynamic light scattering (DLS) measurements. Transferosomes vesicles can be visualized by TEM, phase contrast microscopy, etc The stability of vesicle can be determined by assessing the size and structure of vesicles over time. Mean size is measured by DLS and structural changes are observed by TEM.

3. NO. OF VESICLES PER CUBIC MM

This is an important parameter for optimizing the composition and other process variables. Non sonicated Transferosome formulations are diluted five times with 0.9% sodium chloride solution Hemocytometer and optical microscope can then be used for further study. The Transferosomes in 80 small squares are counted and calculated using the following formula: Total number of Transfersomes per cubic mm (Total number of Transferosomes counted dilution factor 4000)/Total number of squares counted.

4. ENTRAPMENT EFFICIENCY

The entrapment efficiency is expressed as the percentage entrapment of the drug added. Entrapment efficiency was determined by first separation of the un- entrapped drag by use of mini-column centrifugation method. After centrifugation, the vesicles were disrupted using 0.1% Triton X-100 or 50% n- propanol). The entrapment efficiency is expressed as: Entrapment efficiency (Amount entrapped/Total amount added) ×100

5. DRUG CONTENT

The drug content can be determined using one of the instrumental analytical methods such as modified high performance liquid chromatography method (HPLC) method using a UV detector, column oven, auto sample, pump and computerized analysis program depending upon the analytical method of the pharmacopoeial drug

6. TURBIDITY MEASUREMENT

Turbidity of drug in aqueous solution can be measured using nephelometer

DEGREE MEASUREMENT OF DEFORMABILITY OR PERMEABILITY

In the case of transferosomes, the permeability study is one of the important and unique parameter for characterization. The deformability study is done against the pure water as standard. Transferosomes preparation is passed through a large number of pores of known size (through a sandwich of different micro porous filters, with pore diameter between 50 nm and 400 nm, depending on the starting transferosomes suspension). Particle size and size distributions are noted after each pass by dynamic light scattering (DLS) measurements.

7. PENETRATION ABILITY

Penetration ability of Transferosomes can be evaluated using fluorescence microscopy.

8. OCCLUSION EFFECT

Occlusion of skin is considered to be helpful for permeation of drug in case of traditional topical preparations. But the same proves to be detrimental for elastic vesicles. Hydrotaxis (movement in the direction) of water is the major driving force for permeation of vesicles through the skin, from its relatively dry surface to water rich deeper regions. Occlusion affects hydration forces as it prevents evaporation of water from skin.

9. SURFACE CHARGE AND CHARGE DENSITY

Surface charge and charge density of Transferosomes can be determined using zeta sizer.

10. IN-VITRO DRUG RELEASE

In vitro drug release study is performed for determining the permeation rate. Time needed to attain steady state permeation and the permeation flux at steady state and the information from in vitro studies are used to optimize the formulation before more expensive in vivo studies are performed. For determining drug release, transferosomes suspension is incubated at 320C and samples are taken at different times and the free drug is separated by mini column centrifugation. The amount of drug released is then calculated indirectly from the amount of drug entrapped at zero times as the initial amount (100% entrapped and 0% released).

11. IN-VITRO SKIN PERMEATION STUDIES

Modified Franz diffusion cell with a receiver compartment volume of 50ml and effective diffusion area of 2.50 cm2 was used for this study. In vitro drug study was performed by using goat

skin in phosphate buffer solution (pH 7.4). Fresh Abdominal skin of goat were collected from slaughterhouse and used in the permeation experiments. Abdominal skin hairs were removed and the skin was hydrated in normal saline solution. The adipose tissue layer of the skin was removed by rubbing with a cotton swab. Skin was kept in isopropyl alcohol solution and stored at 0-40°C. To perform skin permeation study, treated skin was mounted horizontally on the receptor compartment with the stratum corneum side facing upwards towards the donor compartment of Franz diffusion cell. The effective permeation area of donor compartment exposed to receptor compartment was 2.50cm2 and capacity of receptor compartment was 50ml. The receptor compartment was filled with 50ml of phosphate buffer (pH 7.4) saline maintained at 37±0.5°C and stirred by a magnetic bar at 100RPM. Formulation (equivalent to 10mg drug) was placed on the skin and the top of the diffusion cell was covered.

12. PHYSICAL STABILITY

The initial percentage of the drug entrapped in the formulation was determined and were stored in sealed glass ampoules. The ampoules were placed at 420C months. Samples from each ampoule were analyzed after 30 days to determine drug leakage. Percent drug lose was calculated by keeping the initial entrapment of drug as 100%.

PATHOPHYSIOLOGY OF MENINGITIS[29]

Meningitis typically occurs through two routes of inoculation:

Hematogenous seeding

Bacteria colonize the nasopharynx and enter the bloodstream after mucosal invasion. Upon making their way to the subarachnoid space, the bacteria cross the blood-brain barrier, causing a direct inflammatory and immune-mediated reaction.

Direct contiguous spread

Organisms can enter the cerebrospinal fluid (CSF) via neighboring anatomic structures (otitis media, sinusitis), foreign objects (medical devices, penetrating trauma), or during operative procedures.

Viruses can penetrate the central nervous system (CNS) via retrograde transmission along neuronal pathways or by hematogenous seeding.

CAUSES OF MENINGITIS[30}

Viral infections are the most common cause of meningitis. That's followed by bacterial infections and, rarely, fungal and parasitic infections. Because bacterial infections can lead to death, learning the cause is essential.

Bacterial meningitis

Bacteria that enter the bloodstream and travel to the brain and spinal cord cause bacterial meningitis. But bacterial meningitis also can occur when bacteria directly invade the meninges. This may be caused by an ear or sinus infection, a skull fracture, or rarely some surgeries.

Several strains of bacteria can cause bacterial meningitis, most commonly

Streptococcus pneumoniae. This bacterium is the most common cause of bacterial meningitis in infants, young children and adults in the United States. It more commonly causes pneumonia or ear or sinus infections. A vaccine can help prevent this infection.

Neisseria meningitidis. This bacterium causes a bacterial meningitis called meningococcal meningitis. These bacteria commonly cause an upper respiratory infection but can cause meningococcal meningitis when they enter the bloodstream. This is a highly contagious infection that affects mainly teenagers and young adults. It may cause local epidemics in college dormitories, boarding schools and military bases. A vaccine can help prevent infection. Even if vaccinated, anybody who has been in close contact with a person with meningococcal meningitis should receive an oral antibiotic to prevent the disease.

Haemophilus influenzae. Haemophilus influenzae type b (Hib) bacterium was once the leading cause of bacterial meningitis in children. But new Hib vaccines have greatly reduced the number of cases of this type of meningitis.

Listeria monocytogenes. These bacteria can be found in unpasteurized cheeses, hot dogs and lunchmeats. People who are pregnant, newborns, older adults and people with weakened immune systems are most susceptible. During pregnancy, listeria can cross the placenta. Infections in late pregnancy may be fatal to the baby.

Viral meningitis

Viral meningitis is usually mild and often clears on its own. Most cases in the United States are caused by a group of viruses known as enteroviruses. They're most common in late summer and early fall. Viruses such as herpes simplex virus, HIV, mumps virus, West Nile virus and others also can cause viral meningitis.

Chronic meningitis

Chronic meningitis — one that's long-lasting — can be caused by slow-growing organisms such as fungi and Mycobacterium tuberculosis. They invade the membranes and fluid surrounding the brain. Chronic meningitis develops over two weeks

or more. Symptoms are similar to acute meningitis, which is a sudden, new case. They include headache, fever, vomiting and mental cloudiness.

Fungal meningitis

Fungal meningitis isn't common in the United States. It may mimic acute bacterial meningitis. It's often contracted by breathing in fungal spores that may be found in soil, decaying wood and bird droppings.

Fungal meningitis isn't spread from person to person. Cryptococcal meningitis is a common fungal form of the disease. It affects people with weakened immune systems, such as from AIDS. It can cause death if not treated with an antifungal medicine. Even with treatment, fungal meningitis may come back.

Parasitic meningitis

Parasites can cause a rare type of meningitis called eosinophilic meningitis. Parasitic meningitis also can be caused by a tapeworm infection in the brain or cerebral malaria. Amoebic meningitis is a rare type that is sometimes contracted through swimming in fresh water and can quickly become life-threatening.

The main parasites that cause meningitis typically infect animals. People are usually infected by eating foods contaminated with these parasites. Parasitic meningitis isn't spread between people.

Other meningitis causes

Meningitis also can result from noninfectious causes. They include chemical reactions, drug allergies, some types of cancer and inflammatory diseases such as sarcoidosis.

NANOPARTICLES AS AN ALTERNATIVE FOR TREATMENT OF MENINGITIS [31]

The prevailing treatment methods for meningitis tend to be successful but hold many difficulties like increased systemic toxicity, antibiotic resistance, and poor penetration into the CSF compared to nanoparticles, reduced half-life of the drug particles, and instigating impairment to the normal healthy tissues. All of these downsides can be disregarded with emergence of nanoparticles which can act as a carrier that convey the drug substances into the desired target.

CONCLUSION AND FUTURE PERSPECTIVES[32,33]

NPs can undergo transport to across BBB via paracellular transport by opening TJs between endothelial cells leading to localised permeabilization of the BBB which allocates drug penetration from conjugated NPs; transcellular transport by crossing through endothelial cells; endocytosis via transport across endothelial cells; or receptor-mediated transcytosis to target several receptors like transferrin and low-density lipoprotein receptors. NPs like polymeric nanoparticles, liposomes, transferosomes, solid lipid nanoparticles, nanostructured lipid carrier, functionalized polymeric nanoparticles and carbon nanotubes have capability to be remodelled in requisites of their size, shape, hydrophobicity, surface charge, coating and chemistry. The functionalized NPs surface coated with specific ligands like peptides, proteins, and antibodies either chemically or physically could be successfully used for brain targeting to achieve improved treatment of bacterial meningitis. Therefore, due to wonderful physical, chemical, and biological characteristics of NPs, they could be considered as revitalizing optimistic systems for targeted drug delivery CNS and are complementary for the diagnosis and alleviation of brain disorders like bacterial meningitis

REFERENCES:

1 Opatha SA, Titapiwatanakun V, Chutoprapat R. Transfersomes: A promising nanoencapsulation technique for transdermal drug delivery. Pharmaceutics. 2020 Sep;12(9):855.

2 Sharma N, Zahoor I, Sachdeva M, Subramaniyan V, Fuloria S, Fuloria NK, Naved T, Bhatia S, Al-Harrasi A, Aleya L, Bungau S. Deciphering the role of nanoparticles for management of bacterial meningitis: an update on recent studies. Environmental Science and Pollution Research. 2021 Nov 1:1-8.

3 Griffiths MJ, McGill F, Solomon T. Management of acute meningitis. Clinical Medicine. 2018 Apr 1;18(2):164-9.

4 Sachan R., Parashar T, Vishal Singh S., Singh G., Tyagi S., Pateal C., Gupta A., "Transfersomes: A Novel Tool For Transdermal Drug Delivery System" International Journal of research and Development in Pharmacy and Life Sciences, 2013; 2(2): 309-316.

5 Chaurasiya P., Ganju E., Upmanyu N., Ray S.K., Jain P. Transfersomes: A novel technique for transdermal drug delivery. J. Drug Deliv. Ther. 2019;9:279-285. doi: 10.22270/jddt.v9i1.2198.

6 Malakar J, Sen SO, Nayak AK, Sen KK. Formulation, optimization and evaluation of transferosomal gel for transdermal insulin delivery. Saudi pharmaceutical journal. 2012 Oct 1;20(4):355-63.

7 Priyanka K, Singh S. A review on skin targeted delivery of bioactives as ultradeformable vesicles: Overcoming the penetration problem. Current drug targets. 2014 Feb 1;15(2):184-98.

8 World Health Organization. Investing to defeat meningitis and beyond. World Health Organization; 2024 Apr 24.
9 Anusha V. Transferosomes-A Novel Vesicular System. Research Journal of Pharmaceutical Dosage Forms and Technology. 2014;6(4):286-91.
10 Pharmaceutical product development, N K Jain; page no:237, 451-452.
11 Rajkumar J, Lakshmi RS, Vineesha S. A New Approach to Transdermal Drug Delivery Using Transfersomes-Based Nanoencapsulation: A Research Update. Asian Journal of Pharmaceutical Research and Development. 2022 Feb 15;10(1):64-70.
12 Kumar R, Philip A. Modified Transdermal Technologies: Breaking the barriers of drug permeation via skin. Trop J Pharm Res 2007;6:633-44.
13 Patel SN, Patel N, Patel K.R., Patel N.M. "A Vesicular Transdermal Delivery System For enhance Drug Permeation-Ethosomes and Transfeosomed" Inter-national Pharmaceutical Sciencia, 2012; 2(2).
14 Das B, Nayak AK, Mallick S. Transferosomes: a novel nanovesicular approach for drug delivery. InSystems of nanovesicular drug delivery 2022 Jan 1 (pp. 103-114). Academic Press.1
15 Reshmy Rajan, Shoma Jose, and Deepa T. Vasudevan. Transferosomes - A ve- sicular transdermal delivery system for enhanced drug permeation Journal of Advanced Pharmaceutical Technology & Research. 2011; 138-14311
16 Reddy YD, Sravani AB, Ravisankar V, Prakash PR, Reddy YS, Bhaskar NV. Transferosomes a novel vesicular carrier for transdermal drug delivery system.J. Innov. Pharm. Biol. Sci. 2015;2(2):193-208.
17 Jain S, Umamaheshwari RB, Bhadra D, Jain NK. Ethosomes: A novel vesicular carrier for enhanced transdermal delivery of an anti-HIV agent. Indian J Pharm Sci 2004;66:72-81.
18 Dave V., Kumar D., Lewis S., Paliwal S., "Ethosome for Enhanced Transdermal Drug Delivery of Aceclofenac" International Journal of Drug Delivery, 2010; 2: 81-92,
19 Patel R., Singh S.K., Singh. S, Sheth N.R., Gendle R. "Development and Characterization of Curcumim Loaded Transfersome for Transdermal Deliv- ery" journal of pharmaceutical research and science, 2009; 1(4): 71-80.
20 Vyas SP, Khar RK. Targeted and controlled drug delivery. 1st Ed Delhi: CBS Publishers; 2002. p. 219-43.
21 Gavali SM, Pacharane SS, Jadhav KR, Kadam VJ. Clinical P transfersome: a new technique for transdermal drug delivery. International Journal of Research in Pharmacy and Chemistry. 2011;1(3):735-40.
22 Chien YW. Logics of transdermal controlled drug administration. Drug Dev Ind Pharm 1983;9:497-520.
23 Modi CD and Bharadia PD. Transfersomes: New Dominants for Trans- dermal Drug Delivery. Am J PharmTech Res. 2012; 2(3): 71-91. 2
24 https://www.asynt.com/blog/what-is-a-rotary-evaporator/
25 https://www.differencebetween.com/difference-between-probe-sonicator- and-bath-sonicator/amp/
26 https://m.indiamart.com/proddetail/probe-sonicator-q500-4923288862.html
27 https://images.app.goo.gl/CqC4EybAsdRFQLZE6
28 https://en.m.wikipedia.org/wiki/Centrifuge#/media/File%3ATabletop_centrifu ge.jpg
29 https://www.ncbi.nlm.nih.gov/books/NBK459360/
30 https://www.mayoclinic.org/diseases-conditions/meningitis/symptoms- causes/syc-20350508
31 Joseph SK, Arya MA, Thomas S, Nair SC. Nanomedicine as a future therapeutic approach for treating meningitis. Journal of Drug Delivery Science and Technology. 2022 Jan 1;67:102968.
32 Emad NA, Ahmed B, Alhalmi A, Alzobaidi N, Al-Kubati SS. Recent progress in nanocarriers for direct nose to brain drug delivery. Journal of Drug Delivery Science and Technology. 2021 Aug 1;64:102642.
33 Schaad UB. Treatment of bacterial meningitis. European Journal of Clinical Microbiology. 1986 Oct;5:492-7.