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A REVIEW ON NOVEL DRUG DELIVERY SYSTEMS ON LINCOSAMIDE ANTIBIOTICS-CLINDAMYCIN A MODEL DRUG

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ABSTRACT

Novel Drug Delivery System refers to the approaches, formulation technologies and systems for transporting a pharmaceutical compound in the body as needed for safety achievement for its desired therapeutic effect. NDDS can be the major advancement for solving the problem related to the release of drugs at a specific site with a specific rate. This article covers the basic information regarding the Novel Drug Delivery System on Lincosamide antibiotics a model drug as Clindamycin. Clindamycin is a derivative of lincosamide which stood the test of time in the treatment of anaerobic infection. It mainly acts by inhibiting protein synthesis by acting on the 50s ribosomal subunit of bacteria. This review describes the recent development of NDDS on lincosamide antibiotic with clindamycin which has been formulated using a particulate vesicle system such as drug carriers for small and large molecules like liposomes, niosomes, solid lipid nanoparticles, microemulsions, etc. These are mainly designed to target the site-specific region to achieve the therapeutic effect by reducing the side effect or the toxic effect. Clindamycin is used with different techniques to give a better formulation for various types of bacterial infection which can be cured by the use of lincosamide antibiotics.

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INTRODUCTION

Novel drug delivery systems are designed to achieve continuous delivery of drugs at predictable and reproducible kinetics over an extended period.[1] It also refers to the approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effects. NDDS is a combination of advance technique and new dosage forms which are far better than conventional dosage forms. The main advantages of the Novel Drug Delivery System are Optimum dose at the right time and right location, Efficient use of expensive drugs, excipients and reduction in production cost, Beneficial to patients, better therapy, improved comfort and standard of living. [2] Novel drug delivery system is mainly based on interdisciplinary approaches that combine polymer science, pharmaceutics, bio conjugate chemistry, and molecular biology which minimizes the drug degradation and loss, to prevent harmful side-effects and also increases the drug bioavailability and the fraction of the drug accumulated in the required zone. To prevent the degradation of drugs carrier-based drug delivery system has been incorporated. The carriers can be made slowly degradable, stimuli-reactive (e.g., pH- or temperature-sensitive), or even targeted (e.g., by conjugating them with specific antibodies against certain characteristic components of the area of interest). Targeting is the ability to direct the drug-loaded system to the site of interest. Two major mechanisms can be distinguished for addressing the desired sites for drug release:

1. Passive targeting and (ii) Active targeting

An example of passive targeting is the preferential accumulation of chemotherapeutic agents in solid tumors as a result of the enhanced vascular permeability of tumor tissues compared with healthy tissue. A strategy that could allow active targeting involves the surface functionalization of drug carriers with ligands that are selectively recognized by receptors on the surface of the cells of interest. Since ligand-receptor interactions can be highly selective, this could allow more precise targeting of the site of interest. [3]

Over the past decades, the treatment of illness has been accomplished by administrating drugs to the human body via various routes namely oral, sublingual, rectal, parental, topical, inhalation, etc.[4] The NDDS has made an integrative approach for delivering the therapeutics to target tissues. By this, the new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs can be generated. [5]

Clindamycin phosphate has been used with different approaches in novel drug delivery system. Clindamycin is a lincosamide antibiotic developed in 1966 by chemically modifying the naturally occurring lincomycin. Its spectrum activity includes staphylococci, streptococci and pneumococci, most anaerobic bacteria (including over 90% of Bacteriodes fragilis), Chlamydia trachomatis and certain protozoa when used in vitro. Clindamycin possesses activity against Staphylococcus aureus. It is used in several types of diseases like Necrotizing Fasciitis, Diabetic foot, Osteomyelitis and septic arthritis, head and neck infection, pneumonia, etc. [6]

2. Physicochemical Properties of Clindamycin phosphate are. [7]

Clindamycin phosphate is a water-soluble semi-synthetic antibiotic. It mainly acts by inhibiting bacterial protein synthesis at the level of the bacterial ribosome. The antibiotic binds preferentially to 50 S ribosomal subunit and affects the process of peptide chain initiation Clindamycin is indicated for the treatment of bacterial vaginosis.

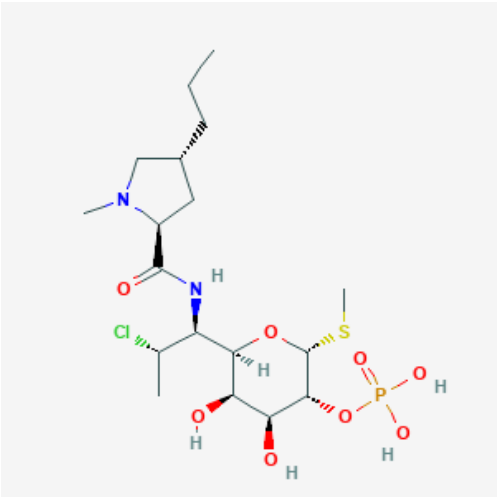

Fig 1: STRUCTURE OF CLINDAMYCIN PHOSPHATE.

Bioavailability of Clindamycin phosphate is more (about 90%) with oral administration, while less (4-5%) with topical administration. The recommended dose of Clindamycin Phosphate is 100 mg per day for 3 consecutive days. Clindamycin preparations for oral administration include capsules. It is also available for topical administration, in gel form and in a foam delivery system (both containing Clindamycin) and a solution in ethanol. Clindamycin is available as a generic drug, for both systemic (oral and intravenous) and topical use.

NOVEL DRUG DELIVERY OF MODEL LINCOSAMIDE ANTIBIOTIC-CLINDAMYCIN

Table no: 1 The different types of Novel Drug delivery systems which incorporated Clindamycin are as follows: [8]

SL.NO	Novel Drug Delivery system	Types
3.1	Colloidal carrier	3.1.1 Microemulsion 3.1.2 Nanoemulsion 3.1.3 Emulgels
3.2	Nanocarriers	3.2.1 Liposomes 3.2.2 Transferosomes 3.2.3 Noisome
3.3	Nanoparticulate carriers	3.3.1 Solid lipid nanoparticles 3.3.2 Nanosponges 3.3.3 Nanogel

Colloidal carriers

Microemulsions :

Colloidal carriers are drug carriers of particle sizes ranging between 25nm to 1 μm in diameter. Microemulsions, micelles, and nanoemulsions are some of the colloidal carriers which have been reported to be used for various delivery systems for antimycotic agents, by the virtue of improving their therapeutic index [8],[9]. Microemulsions are transparent, thermodynamically stable and isotropic liquid dispersions which are one of the most promising colloidal carrier systems for topical drug administration offering several unique advantages which include enhanced drug solubility, high thermodynamic stability, ease of preparation and low costs [10]. The oils and surfactants included in their composition act as drug permeation enhancers across stratum corneum. These formulation components of microemulsions and the internal structure of phases enhance drug diffusion which facilitates drug partitioning to stratum corneum.[11]

Types of microemulsions: Many types of microemulsions are most likely to be formed depending on the composition:

Advantage of Microemulsions: [13]

1. Microemulsions are easily prepared and require no energy contribution during preparation this is due to better thermodynamic stability.
2. The formation of the microemulsion is reversible. They may become unstable at low or high temperature but when the temperature returns to the stability range, the microemulsion forms.
3. Microemulsions are thermodynamically stable systems and allow self-emulsification of the system.
4. Microemulsions have low viscosity compared to emulsions.
5. Microemulsions act as super solvents for the drug can solubilize both hydrophilic and lipophilic drugs including drugs that are insoluble in both aqueous and hydrophobic solvents.
6. Having the ability to carry both lipophilic and hydrophilic drugs.
7. The dispersed phase, lipophilic or hydrophilic (O/W, or W/O microemulsions) can act as a potential reservoir of lipophilic or hydrophilic drugs, respectively.
8. The use of microemulsion as delivery systems can improve the efficacy of a drug, allowing the total dose to be reduced and thus minimizing side effects.

Disadvantages of Microemulsion Systems [14]

1. Having a limited solubilizing capacity for high melting substances.
2. Require a large number of Surfactants for stabilizing droplets.
3. Microemulsion stability is influenced by environmental parameters such as temperature and pH.

Table 2: Different categories of drugs used in Microemulsion :[15]

Sl.no	Drugs used	Routes	Results
1.	Clindamycin phosphate	Topical gel O/W microemulsion	Increases permeation
2.	Flurbiprofen	Parenterals	Increases the solubility
3.	Piroxicam	Oral	Increases the solubility
4.	Apomorphine HCL	Transdermal	Increased the permeability
5.	Ketoprofen	Transdermal	Enhancement in permeability
6.	Diclofenac	Transdermal	Permeability enhancement
7.	Dexamethasone	Topical Ocular	Enhanced the Bioavailability
8.	Aceclofenac	Dermatological	Increased the solubility
9.	Prilocainne-HCL[27]	Transdermal	Increased the solubility
10.	Chloramphenicol	Ocular	Increased the solubility

Method of preparation of Microemulsions are:

Microemulsions are prepared when interfacial tension at the oil/water is kept at a very low level. The interfacial layer is kept very much flexible and fluid concentration of surfactants should be high enough to give surfactant molecules to stabilize the microemulsion at an extremely low interfacial tension.

There are two methods through which microemulsion are prepared

Phase inversion method

In the phase inversion method phase inversion of microemulsions occurs by the addition of an excess amount of the dispersed phase. During phase inversion, quick physical changes occur including changes in particle size that can affect drug release both in vivo and in vitro. For non-ionic surfactants, this can be completed by changing the temperature, forcing a transition from oil in water microemulsion at low temperatures to water in oil microemulsion at higher temperatures (transitional phase inversion). During cooling, the system crosses a point of zero spontaneous curvature and minimal surface tension, promoting. the formation of finely dispersed oil droplets. This method is also known as the phase inversion temperature (PIT) method. Other than temperature, other parameters such as pH value or salt concentration may be considered more effective instead of the temperature alone. Additionally, a transition in the spontaneous radius of curvature can be obtained by changing the water volume fraction. By successively adding water into the oil, initially, water droplets are formed in a continuous oil phase. By increasing the water volume fraction changes the spontaneous curvature of the surfactant from initially stabilizing a w/o microemulsion to an o/w microemulsions at the inversion point. [16]

Phase Titration Method

Microemulsions are formulated by the spontaneous emulsification method (phase titration method) and can be shown with the help of phase diagrams. A mixture of fatty acid and oil is added to a caustic solution to prepare a microemulsion, then after it is titrated with a cosurfactant, alcohol until the system turned clear. Microemulsions are formed along with various association structures (including emulsion, micelles, lamellar, hexagonal, cubic, and various gels, and oily dispersion) depending on the chemical composition and concentration of each component. It is found that as the chain length of the surfactant increased, microemulsions with significant transmittances by visible spectrum can be formed with oils of longer chain lengths. It is also found that different alcohols affect the formation of microemulsions in different ways. The best results, in terms of the greatest percent transmittance coupled with the widest range of oil (dispersed in water) concentration, are obtained from short or branched alcohols.[17 Enhancement of skin permeation by Clindamycin phosphate as an Aerosol O/T-1 Butanol for microemulsion has been studied in the literature. V.B.Junyaprasert et.al (2014) reported that microemulsion serves efficient promoters for delivering Clindamycin phosphate through human skin. In microemulsion, the efficiency enhances the percutaneous permeation which depends upon the surfactant concentration. They reported that w/o microemulsions showed higher drug permeation.[18]During the last two decades, a lot of research work has been carried out on the microemulsion system for providing novel solutions to overcome the problems of poor aqueous solubility of highly lipophilic drug compounds and provide reproducible bioavailability.[19]

Nanoemulsions

Nano-emulsions consist of fine oil-in-water or water-in-oil dispersions, having droplets covering the size range of 10-600 nm. Nano-emulsion is a group of dispersed particles used for pharmaceuticals and biomedical aids. These vehicles show great promise for the future of cosmetics, diagnostics, drug therapies, and biotechnologies. [19]

The different types of Nanoemulsionsare :

- Oil in water nanoemulsions wherein oil droplets is dispersed in the continuous aqueous phase.
- Water in oil nanoemulsions wherein water droplets are dispersed in the continuous oil phase
- Bi-continuous nanoemulsions wherein microdomains of oil and water are interspersed within the system.

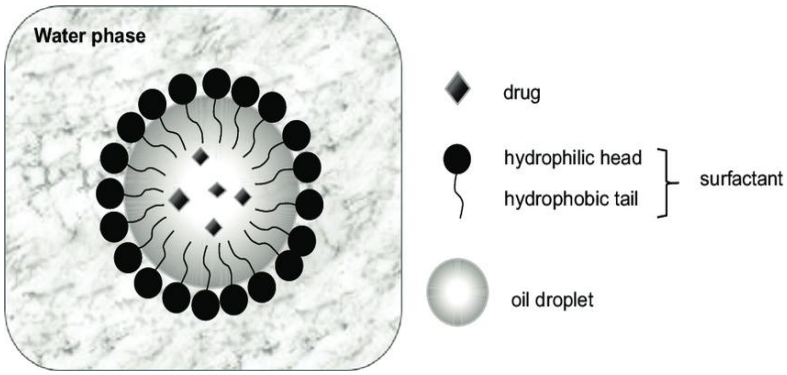

Fig 2: Schematic diagram of O/W Nanoemulsion [21]

Advantages of Nanoemulsions:

1. Increase the rate of absorption.
2. Eliminates variability in absorption.
3. Helpful in taste masking.
4. Less amount of energy requirement.
5. The very small droplet size causes a large reduction in the gravity force and the Brownian motion may be sufficient for overcoming gravity. This means that no creaming or sedimentation occurs on storage.
6. The small droplet size also prevents any flocculation of the droplets. Weak flocculation is prevented and this enables the system to remain dispersed with no separation.
7. The small droplets also prevent their coalescence.
8. Nanoemulsions are thermodynamically stable system and the stability allows self emulsification of the system whose properties are not dependent on the process followed.
9. The same Nanoemulsions can carry both lipophilic and hydrophilic drugs.
10. The use of Nanoemulsion as delivery systems can improve the efficacy of a drug, allowing the total dose to be reduced and thus minimizing side effects.[22]

Disadvantages of Nanoemulsion Based Systems

1. Use of a large concentration of surfactant and co-surfactant necessary for stabilizing the nanodroplets.
2. Limited solubilizing capacity for high-melting substances.
3. The surfactant must be nontoxic for using pharmaceutical applications.
4. Nanoemulsion stability is influenced by environmental parameters such as temperature and pH. These parameters change upon Nanoemulsion delivery to patients.[23]

Different types of drugs used as Nanoemulsions :

1. **Clindamycin phosphate** has been used as a topical gel for the treatment of Acne vulgaris.
2. **Ampicillin** has been used as a nanoemulsion formulation with PEG400 as a carrier with a solid dispersion technique for the delivery of protein drugs inside the phase.
3. **Ramipril** nanoemulsion has been done with capitol as a carrier with the spontaneous emulsification method to enhance the bioavailability of the formulation.
4. **Polyanionic** was used with Poloxamer 188 with high-pressure homogenization and a nanoemulsion was prepared for the treatment of cancer diseases and inflammation caused.
5. **Caffeine** with Caprylo caproyl macrogol -8-glyceride and Tween 80 as the carrier was used with oil phase titration for the preparation of nanoemulsion for the transdermal delivery in cancer treatment.
6. **Positively charged(o/w) nanoemulsions** with carbopol 940 as a carrier was used with high-pressure homogenization a nanoemulsion was formed which increases the skin hydration and elasticity. [24]

Methods for preparation of Nanoemulsions :

There are various methods for the preparation of Nanoemulsion including the high-energy and low-energy emulsification methods with the combined methods. Among the high-energy methods, the emphasis is placed on high-energy stirring, ultrasonic emulsification, high-pressure homogenization including microfluidics and membrane emulsification. Among the low- energy emulsification methods, the methods included are phase inversion temperature method, the emulsion inversion point method and the spontaneous emulsification. The combined method includes the high-energy and low-energy emulsification, it is possible to prepare reverse nano-emulsions in highly viscous systems. [25]

Phase Inversion Method

Fine dispersion is obtained by chemical energy resulting from phase transitions occur through the emulsification method. The adequate phase transitions are produced by changing the composition at a constant temperature or by changing the temperature at constant composition. The phase inversion temperature (PIT) method was introduced based on the principle of changes of solubility of polyoxyethylene type surfactant with temperature. This surfactant becomes lipophilic with an increase in temperature because of the dehydration of the polymer chain. At low temperature the surfactant monolayer has a great positive spontaneous curvature forming oil swollen micellar solution phase.

Sonication Method

In this method, the droplet size of conventional emulsion is reduced with the help of the sonication mechanism. Only small batches of nanoemulsion can be prepared by this method.

High-Pressure Homogenizer

This method is performed by applying a high pressure over the system having oil phase, aqueous phase, and surfactant or co-surfactant. The pressure is applied with the help of a homogenizer. Some problems associated with homogenizer are poor productivity, component deterioration due to generation of much heat. With this method, only Oil in water (O/W) liquid nanoemulsion of less than 20% oil phase can be prepared and cream nanoemulsion of high viscosity or hardness with a mean droplet diameter lower than 200 nm cannot be prepared.[26]

Microfluidization

Microfluidization technology makes use of a device called 'MICRO FLUIDIZER". This device uses a high-pressure positive displacement pump (500-200 PSI) which forces the product through the interaction chamber, consisting of small channels called microchannels. The product flows through the microchannels on to an impingement area resulting in very fine particles of submicron range. The two solutions (aqueous phase and oily phase) are combined and processed in an inline homogenizer to yield a coarse emulsion. The coarse emulsion is into a microfluidizer where it is further processed to obtain a stable nanoemulsion.[27]

Production with high amplitude ultrasound

This method is a viable alternative to high-pressure homogenization. Intense shear forces necessary for the nano emulsification are generated by ultrasonic cavitation which produces violently and asymmetrically imploding vacuum bubbles and breaks up particles down to the nanometer scale. This method is successfully used in small scale production of nanoemulsions.[28]

Spontaneous emulsification

Nanoemulsions can be produced by this method at room temperature without the use of any special device. Water is added stepwise into the solution of oil and surfactant at constant temperature and stirred gently to produce o/w nanoemulsions. The spontaneity of the emulsification process depends mainly on: interfacial tension, interfacial and bulk viscosity, phase transition region and surfactant structure and its concentration. [29]

Clindamycin 1% nano-emulsion gel formulation for the treatment of acne vulgaris was studied in the article. B. Bhavasar and his colleagues reported that nanoemulsion formulations are likely to have better stability and longer shelf-life due to their stable thermodynamic properties. Nanoemulsion increases the surface area of the drugs and thereby enhances their solubility as well as permeation through tissue barriers. They also reported that Nanoemulsionsimproves the active ingredients penetration into epidermis, dermis, and pilosebaceous units. They also exert *Invitro* and *Invivo*direct bactericidal effects on several bacterial species including P.acnes. [30]

Emulgels

The presence of a gelling agent in the water phase converts classical emulsion into an emulgel. They provide several advantages over conventional gels for the delivery of hydrophobic drugs, which has consistently been a point of concern. Both waters in oil (w/o) and oil-in-water (o/w) emulsions have been used as a vehicle to deliver drugs. Emulgels have several favorable dermatological properties such as thixotrophicity, non- greasiness, spreadability, removability, emollient, long shelf-life and a pleasing appearance, which has lead to high patient acceptability.[31]

Emulsions are controlled release systems containing two immiscible phases in which one is dispersed (internal or discontinuous phase) into other (external or discontinuous phase), with the use of an emulsifying agent to stabilize the system. an emulsion is of oil-in-water or water-in-oil type, where the drug particle entrapped in the internal phase passes through the external phase and then slowly gets absorbed into the skin to provide the controlled effect.[32]

Advantages of Emulgels:

1. Increased patient acceptability.
2. Provide targeted drug delivery.
3. Easy termination of the therapy.
4. Improve bioavailability and even the low doses can be effective in comparison with another conventional semi-solid preparation.
5. The hydrophobic drug can be incorporated in emulgel using emulsion as the drug carrier that is finely dispersed in the gel.
6. Provide the controlled effect that enhances the prolong the effect of the drug with a short half-life.
7. Easy and cost-effective preparation.
8. Drug loading capacity is better than other novel approaches like noisome and liposomes.

The disadvantage of Emulgels:

1. Poor absorption of macromolecules.
2. Entrapment of bubble during formulation.
3. Hydrophobic drugs are the best choice for such delivery systems [33]

Method of Preparation of Emulgel:

The main aim for the preparation of emulgel is the selection of the oil phase with the emulsifying agent and the gelling agent. The preparation of emulgel is carried out with (O/W or W/O) emulsions. There are different types of oils, emulsifying agents and the gelling agents by which the preparation of emulgel is carried out :

Different types of oils and their concentration used in the dosage form are:

Light Liquid Paraffin - 7.5% is used - Emulsion and Emulgel are the dosage form.
Isopropylmyristate – 7 to 7.5% - Emulsion
Isopropyl stearate - 7 to 7.5% - Emulsion
Isopropyl palmitate - 7to7.5% - Emulsion
Propylene glycol -3 to 5% - Gel form

Types of gelling agent used:

Carbopol-934	0.5%-2%	Emulgel
Carbopol-940	0.5%-2%	Emulgel
HPMC-2910	2.5%	Emulgel
HPMC	3.5%	Gel
Sodium CMC	1%	Gel

Types of penetration enhancers used in the preparation are:

Oleic acid	1%	Gel
Lecithin	5%	Gel
Urea	10%	Gel
Isopropyl myristate	5%	Gel
Linoleic acid	5%	Gel
Clove oil	8%	Emulgel
Menthol	5%	Emulgel
Cinnamon	8%	Emulgel

STEP1: Formulation of Emulsion either O/W or W/O
STEP2: Formulation of the gel base
STEP3: Incorporation of an emulsion into gel base with continuous stirring.

Emulgel was prepared by the method o/w and w/o emulsion with minor modification. The Gel in formulations was prepared by dispersing Carbopol 934 in purified water with constant stirring at a moderate speed and carbopol 940 in purified water with constant stirring at a moderate speed then the pH is adjusted to 6 to 6.5 using triethanolamine (TEA). The oil phase of the emulsion was prepared by dissolving Span 80 in light liquid paraffin having the drug in ethanol solution while the aqueous phase was prepared by dissolving Tween 80 in purified water. Methyl and Propylparaben were dissolved in propylene glycol and was mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70 ° to 80 °C; then the oily phase was added to the aqueous phase with continuous stirring until cooled to room temperature. And add glutaraldehyde in during of mixing of gel and emulsion in ratio 1:1 to obtain the emulgel. [34]

Different categories of drugs used in Emulgel:

- **Clindamycin phosphate** has been used as a topical gel for the treatment of streptococcal gangrene.
- **Amphotericin B** has been used as an emulgel for the alternative treatment of skin leishmaniasis and proved to be the best topical treatment for this disease.
- **Ciprofloxacin** has been used as a Genipin-crosslinked gelatin emulgel which has been prepared for pain relief as emulgel based for topical treatment.
- **Terbinafine hydrochloride** was prepared as a topical emulgel for the treatment of fungal infection.
- **Piroxicam** was loaded into an emulgel formulation for increasing the permeation and absorption of the drug through emulgel for anti-inflammatory activity. [35]

Nanocarriers

Liposomes

Vesicular systems such as liposomes, niosomes, ethosomes, transfersomes, and cubosomes have shown excellent penetration of drugs across stratum corneum for specific dermal targeting. They have numerous advantages such as controlled drug release and localization of topically administered drugs in targeted dermal layers. Besides, the transdermal administration of vesicular systems helps to carry drug molecules into the systemic circulation. [36]

Liposomes are defined as lipidic vesicles composed of phospholipids, with or without cholesterol [37]. Owing to their ability to alter drug biodistribution, they are widely accepted as ideal dermal drug carriers. Various drug penetration enhancing mechanisms like adsorption and deposition of the drug over skin causes localization of dermally administered liposomes in different layers of the skin [38],[39].

Classification of liposomes according to structure

1. Small unilamellar vesicles (SUV): 20–100 nm
2. Large unilamellar vesicles (LUV): > 100 nm
3. Giant unilamellar vesicles (GUV): > 1000 nm
4. Oligolamellar vesicle (OLV): 100–500 nm
5. Multilamellar vesicles (MLV): > 500 nm

Liposomes can be classified in terms of composition and mechanism of intracellular delivery into five types :

1. Conventional liposomes
2. pH-sensitive liposomes
3. Cationic liposomes
4. Immunoliposomes
5. Long-circulating liposomes [40]

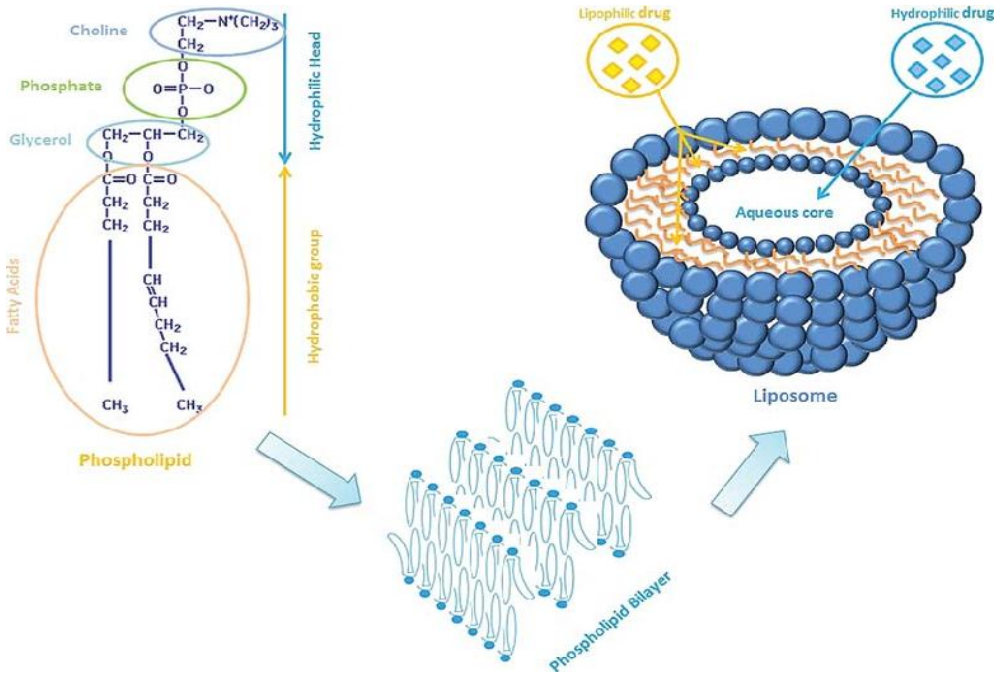

Fig 3: Schematic drawing of liposomes structure and lipophilic or hydrophilic drug entrapment models.[36]

Advantages of liposomes :

1. Stability increased if liposome prepared via encapsulation
2. Liposomes increased efficacy and therapeutic index of the drug (actinomycin-D)
3. Liposomes reduce the toxicity of the encapsulated agent (amphotericin B, Taxol)
4. Liposomes help reduce the exposure of sensitive tissues to toxic drugs
5. Site avoidance effect
6. Liposomes are flexible, non-toxic, biocompatible, completely biodegradable, and non-immunogenic for systemic and non-systemic administrations
7. Flexibility to couple with site-specific ligands to achieve active targeting

Disadvantages of liposomes :

1. Liposomes have a short half-life
2. Low solubility
3. Leakage and fusion of encapsulated drugs
4. Production cost is high
5. Sometimes phospholipids go under oxidation and hydrolysis like reaction. [41]

Different categories of Drugs used in a Liposomes:

- **Lincosamide Antibiotics** as clindamycin phosphate which has been loaded into liposomes topical treatment as a gel and the result was increase the permeability of the formulation.
- **Amphotericin B** has been loaded into liposomes to improves the solubility of lipophilic drugs for better permeation through the topical treatment for Aspergillus fumigates
- **Doxorubicin** loaded liposomes has been used for better-sustained release system of systemically or locally administered product for the treatment of cancer.
- **Insulin** loaded into liposomes has been used to improves the permeability of the drug into the liposomal formulation.

S.Shanmugan and co-workers (2009) employed skin permeation and physicochemical characterization for formulating Clindamycin phosphate into liposomes. They formulated five different liposomes formulation using Phospholipon 85G (PL) and cholesterol (CH) by conventional lipid film hydration technique. The molar ratio of CH to PL was varied in the range of 0.16-1.0. All liposome formulation prepared showed homogeneous size distribution with a mean particle size of about 1micron or less. They reported that among the five formulation prepared liposomes, formulation with the molar ratio of0.5 showed the best result in the physicochemical properties such as polydispersity index, entrapment efficiency, size, evolution, and ability of liposomes.[42]

Method of Preparation of Liposomes: [43]

Handshaking Method:

To produce liposome lipid molecules must be introduced into an aqueous environment. When dry lipid layer film is hydrated the lamellae swell and grow into myelin figures. Only mechanical agitation provided by vortexing, shaking, swearing or pipetting causes myelin figures to break and reseal the exposed hydrophobic edges resulting in the formation of the liposome that can be made by the hand-shaken method.

Freeze Drying:

It is based on the formation of a homogenous dispersion of lipids in water-soluble carrier materials. Liposome forming lipids and water-soluble carrier materials such as sucrose were dissolved in tert-butyl alcohol/water cosolvent systems in appropriate ratio to form a clear isotropic monophase solution. Then the monophase solution was sterilized by filtration and filled into freeze-drying vials. In a recent study, a laboratory freeze drier was used and the freeze-drying process was as follows: freezing at −400C for 8 h; primary drying at 250C for 10 h. The chamber pressure was maintained at 20 Pascal during the drying process. On the addition of water, the lyophilized product spontaneously forms homogenous liposome preparation. After investigation of the various parameters associated with this method, it is found that the lipid/carrier ratio is the key factor affecting the size and the polydispersity of the liposome preparation. [44]

Sonication:

It is the most preferable method for the preparation of SUVs. The MLVs are sonicated either with a bath type or probe-type Sonicator under a passive atmosphere. In that bath Sonicator method liposome dispersion in a tube is placed in Sonicator. Control of the temperature of lipid dispersion is easier in this method than sonication dispersion directly using the tip. Materials that are sonicated can be protected by kept in a sterile container under an inert atmosphere. While in probe sonication the tip of sonicator is directly immersed into the liposome dispersion. The dispersion energy at the tip result in local overheating and therefore the vessel must be immersed into an ice bath. During the sonication in one hour, more than 5% of the lipid can be desertified. The main disadvantages of this method are very low internal volume/encapsulation efficacy, possible degradation of phospholipids and compounds to be encapsulated, elimination of large molecules, metal pollution from the probe tip, and presence of MLV along with SUV.

Ethanol injection method:

In this method, an ethanol solution of lipids is directly injected into an excess of saline rapidly and another aqueous medium through a fine needle. The ethanol is diluted in water and phospholipids molecules are dispersed evenly through the medium. This method yields a high proportion of SUVs ranging from size 70-190nm only. [45]

Ether injection

This method involves injecting the immiscible organic solution very slowly into an aqueous phase through a narrow needle at a temperature of vaporizing of organic solvent. There is less risk of oxidative degradation and forms liposome of size only from 30-110nm[46]

Transferosomes

Transfersomes are called as highly deformable or elastic liposomes. They are composed of phospholipids and a surfactant which gives flexibility to the liposome structure. Transfersomes have been successfully assessed as topical and transdermal carriers for drugs and have also been shown to be effective carriers for genetic material and vaccines. [47] Some researchers showed that transeferosomes showed enhanced permeation through ex vivo permeation characters. Clindamycin phosphate loaded into a transferosomes showed higher entrapment efficiency within about 93.3% 0.8 and uniform particle size. [48]

Transfersomes are complex vesicles that have extremely flexible & self-regulating membranes, which make the vesicle very deformable. Transfersome vesicles can cross microporous barriers efficiently, even if the porous are much smaller than the size of the vesicles.[49]

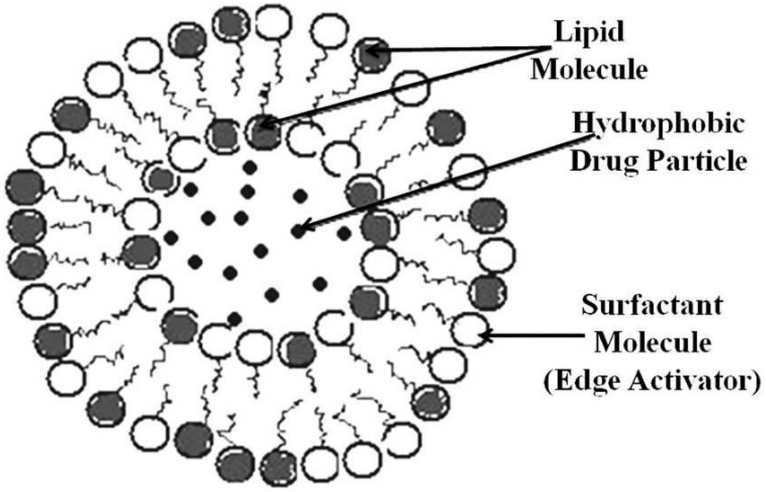

Fig:4 Transferosomes [48]

Advantages of Transferosmes :

1. They have high entrapment efficiency, in case of lipophilic drug near to 90%
2. This high deformability gives better penetration of intact vesicles.
3. They can act as a carrier for low as well as high molecular weight drugs e.g. analgesic, anesthetic, corticosteroids, sex hormone, anticancer, insulin, gap junction protein, and albumin.
4. Transferosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result, can accommodate drug molecules with a wide range of solubility.
5. They act as a depot, releasing their contents slowly and gradually.
6. They can be used for both systemic as well as topical delivery of the drug.
7. They are biocompatible and biodegradable as they are made from natural phospholipids similar to liposomes.
8. They protect the encapsulated drug from metabolic degradation. [50]

Disadvantages of Transferosomes :

1. Chemically unstable, highly susceptible to oxidative degradation.
2. Formulations are expensive [51]

Transferosomes penetrates 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 nodule). Thakur. et al. investigation that for enhanced skin delivery of model drug Clindamycin phosphate. [52]

Different categories of drugs loaded into transeferosomes:

- **Clindamycin** used for the topical treatment for the inflammatory lesions on the skin in the form of transeferosomes and the result claimed that transeferosomes loaded with clindamycin increases the permeability formulation through transdermal route.
- **Meloxicam** loaded cationic transfersomes as skin delivery carriers which resulted in greater skin permeation through the stratum corneum and worked to reduce inflammation on the skin.
- **Curcumin** loaded into transfersomes were prepared by modified handshaking method using a surfactant such as a tween 80 and span 80 in various concentration and the result observed was increased in the permeability of the formulation for topical treatment.
- **Hydrocortisone** as transfersomes act as a biologically active dose and several times lowers currently used formulation.
- **Insulin** acts as a high encapsulation efficiency when loaded into transferosomes which can transfer across the skin with an efficiency of >50% and provide noninvasive means of therapeutic use. [53]

Methods of preparation of Transferosomes:

Thin-film hydration technique

It is employed for the preparation of transfersomes which comprised of three steps

1. A thin film is prepared from the mixture of vesicles forming ingredients that are phospholipids and surfactants by dissolving in a volatile organic solvent (chloroform-methanol). The organic solvent is then evaporated above the lipid transition temperature (room temp. for pure PC vesicles, or 50°C for dipalmitoylphosphatidylcholine) using a rotary evaporator. Final traces of solvent were removed under vacuum overnight.
2. A prepared thin film is hydrated with buffer (pH 6.5) by rotation at 60 rpm for 1 hr at the corresponding temperature. The resulting vesicles were swollen for 2 hr at room temperature.
3. To prepare small vesicles, resulting vesicles were sonicated at room temperature or 50°C for 30 min. using a bath sonicator or probe sonicated at 4°C for 30 min. The sonicated vesicles were homogenized by manual extrusion 10 times through a sandwich of 200 and 100 nm polycarbonate membranes. [54]

Modified handshaking, lipid film hydration technique

It is also found for the preparation of transfersomes which comprised the following steps

1. The drug, lecithin (PC) and edge activator were dissolved in ethanol: chloroform (1:1) mixture. The organic solvent was removed by evaporation while handshaking above the lipid transition temperature (43°C). A thin lipid film was formed inside the flask wall with rotation. The thin film was kept overnight for complete evaporation of the solvent.
2. The film was then hydrated with phosphate buffer (pH 7.4) with gentle shaking for 15 minutes at a corresponding temperature. The transfersome suspension further hydrated up to 1 hour at 2-8°C. [55]

Niosomes

Niosomes are lipidic vesicles prepared with non- ionic surfactants which have advantages of being economical and chemically stable, establishing themselves as potential drug delivery carriers for cosmetics.[56] Dermal penetration of niosomes depends on the potential penetration-enhancing activity of surfactants in its content, penetration, and accumulation of the vesicle to stratum corneum and/or increasing thermodynamic activity of a drug on the skin surface. These mechanisms depend on the physicochemical properties of drugs, vesicle and the lipids used.[57]

Noisome are non-ionic surfactant vesicles obtained by a hydrating mixture of cholesterol and nonionic surfactants. It can be used as carriers of an amphiphilic and lipophilic drug. In the niosomes drug delivery system, the medication is encapsulated in a vesicle. Niosomes are biodegradable, biocompatible non-immunogenic and exhibit flexibility in their structural characterization. [58]

Advantages of Niosomes:

1. The characteristics such as size, lamellarity, etc. of the vesicle can be varied depending on the requirement.
2. The vesicles can act as a depot to release the drug slowly and offer a controlled release.
3. Since the structure of the niosomes offers a place to accommodate hydrophilic, lipophilic as well as amphiphilic drug moieties, they can be used for a variety of drugs.
4. The vesicle suspension being water-based offers greater patient compliance over oil-based systems
5. They are osmotically active and stable
6. They increase the stability of the entrapped drug
7. It can enhance the skin penetration of drugs. [59]

Disadvantage of Niosomes:

1. Aggregation is the main problem
2. Leakage of entrapped drugs.
3. Physical instability
4. Time-consuming

Types of Niosomes :

- Multi lamellar vesicles (MLV) vesicle size greater than 0.05µm
- Large unilamellar vesicles (LUV) vesicle Size 0.025 – 0.05µm
- Small unilamellar vesicles (SUV) vesicle Size Greater than 0.10µm [60]

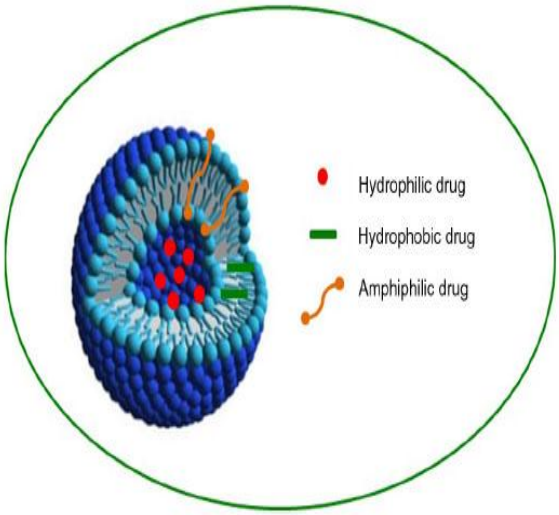

Fig 5: Structure of niosomes [61]

Different categories of drugs used in Niosomes:

- **Ciprofloxacin** used as inhalers in the form of niosomes from the lipid hydration method with the surfactant used as tween 60 and was proved to be a better formulation for pulmonary delivery.
- **N-acetyl glucosamine** was loaded into niosomes which were prepared by using Span 60 as a surfactant with lipid layer hydration method and results in the best topical treatment for protein delivery.
- **Clindamycin phosphate** was used in topical treatment was the niosomes were prepared by using non-ionic surfactant sorbitan and the cholesterol by a reverse-phase evaporation method using span 60 as polymer and got effective results as the formulation increases the permeability.
- **Cisplatin** used for topical treatment in cancer chemotherapy were cisplatin was loaded into a niosomes with lipid layer hydration method were span 60 was used as a surfactant and a niosomes were prepared for cancer chemotherapy.
- **Bovine serum albumin** loaded niosomes were prepared for topical vaccines by reverse-phase evaporation method and mainly effective for vaccine and antigen drug delivery. [62]

Method of preparation of Niosomes:

Multiple membrane extrusion method

The mixture of surfactant, cholesterol, and diacetyl phosphate in chloroform is made into a thin film by evaporation. The film is hydrated with aqueous drug solution and the resultant suspension extruded through polycarbonate membranes, which are placed in series for up to 8 passages. It is a good method for controlling noisome size. [63]

Sonication

A typical method of production of vesicles is by sonication as described by cable. In this method, an aliquot of drug solution in the buffer is added to the surfactant/cholesterol mixture in a 10ml glass vial. The mixture is probe sonicated at 60oC for 3 minutes using a sonicator with a titanium probe to yield niosomes.[64] [65]

Micro-fluidization

This is a recent technique to prepare small multilamellar vesicles. A microfluidizer is used to pump the fluid at very high pressure (10,000 psi) through a 5 pm screen. Thereafter; it is forced along defined microchannels, which direct two streams of fluid to collide together at right angles, thereby affecting a very efficient transfer of energy. The lipid can be introduced into the fluidizer. The fluid collected can be recycled through the pump until vesicles of spherical dimensions are obtained. This method resulted in niosomes with greater uniformity and small size which shows better reproducibility. [66]

Thin-film hydration technique/Handshaking method

The mixture of vesicles forming ingredients like surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask. The organic solvent is removed at room temperature (20oC) using a rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 0-60oC with gentle agitation. This process forms a typical Multi lamellar noisome film of lipid on the wall of the rotary flash evaporator. The aqueous phase containing drug was added slowly with intermittent shaking of the flask at room temperature followed by sonication. [67]

Ether injection method

This method provides a means of making niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether into warm water maintained at 60oC. The surfactant mixture in ether is injected through a 14-gauge needle into an aqueous solution of material. Vaporization of ether leads to the formation of single-layered vesicles. Depending upon the conditions used the diameter of the vesicle range from 50 to 1000 nm. [68]

Ethanol injection method

This method has been reported as one of the alternatives used for the preparation of small unilamellar vesicles (SUVs) without sonication. In this method, an ethanol solution of surfactant is injected rapidly through a fine needle into an excess of saline or other aqueous media. Vaporization of ethanol leads to the formation of vesicles. [69]

Bubble method

It is a novel technique for one-step preparation of liposomes and niosomes without the use of organic solvents. The bubbling unit consists of the round-bottomed flask with three necks positioned in a water bath to control the temperature. Water-cooled reflux and thermometer are positioned in the first and second neck and nitrogen is supplied through the third neck. Researchers dispersed cholesterol and surfactants together in a buffer (pH 7.4) at 70oC, the dispersion is mixed for 15 seconds with a high shear homogenizer and immediately afterward "bubbled" at 70oC using nitrogen gas. [70]

Investigator investigated that the niosomes drug delivery system for clindamycin phosphate increases the effectiveness of the formulation by increasing penetration through the skin and reduces the side effect Sorbitan ester which is nonionic surfactant was used as the key ingredient which forms vesicles upon hydration with aqueous media. Cholesterol was used to make vesicles stable and right. Clindamycin phosphate as well as for the enhanced delivery through the skin by variation in cholesterol level. Niosomes were prepared by a reverse-phase evaporation method using span 60 as polymer.[71]

Nanoparticulate Carrier

Solid lipid Nanoparticles:

Solid lipid nanoparticles are one of the novel potential colloidal carrier systems as alternative materials to polymers which is identical to oil in water emulsion for parenteral nutrition, but the liquid lipid of the emulsion has been replaced by a solid lipid shown on Fig.6. They have many advantages such as good biocompatibility, low toxicity, and lipophilic drugs are better delivered by solid lipid nanoparticles and the system is physically stable. [72]

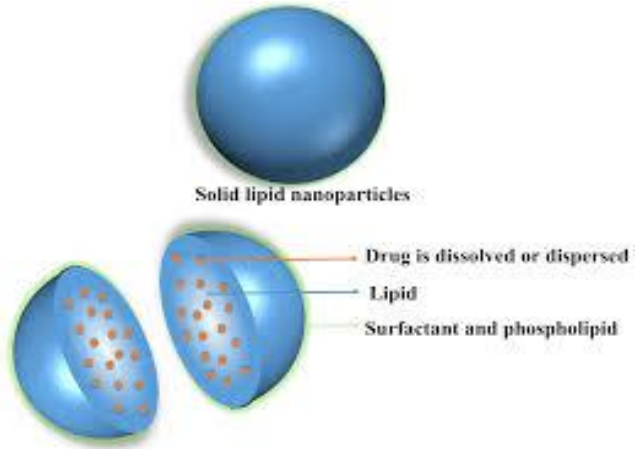

Fig 6: General structure of solid lipid nanoparticle (SLN) loaded with drug [73]

Advantage of Solid lipid Nanoparticles:

1. Very high long-term stability
2. It is easy to manufacture than biopolymeric nanoparticles.
3. Better control over release kinetics of encapsulated compound.
4. SLNs can be enhancing the bioavailability of entrapped bioactive.
5. Chemical protection of labile incorporated compound.
6. The raw material which is required is the same as that of emulsion.
7. Large scale production is possible.
8. The high concentration of functional compounds can be achieved.
9. Lyophilization is possible.[74]

Disadvantages of Solid lipid Nanoparticles:

1. Poor drug loading capacity is observed.
2. Drug expulsion after the polymeric transition occurs during storage.
3. Relatively high-water content of the dispersions (70-99.9%) observed.
4. The low capacity to load hydrophilic drugs due to partitioning effects during the production process. [75]

The main reason for using Solid Lipid Nanoparticle are:

- Lipids enhance oral bioavailability and reduce plasma profile variability.
- Better characterization of lipid excipients.
- An improved ability to address the key issues of technology transfer and manufacture scale-up.

Different categories of drugs used in Solid Lipid Nanoparticles:

- **Clindamycin phosphate** as Solid lipid Nanoparticles was prepared by the solvent evaporation method with the incorporation of anionic polymers increases the drug loading of SLNs and addition of sodium alginate gives a sustained release of topical treatment.
- **Diclofenac sodium** has been used as SLNs with hot homogenization techniques using high-pressure homogenizer with phospholipid 90G as a lipid and tween 80 as a surfactant which used as oral dosage form with sustained release of the drug.
- **Tobramycin** was loaded into a solid lipid nanoparticle with lipids as stearic acid and surfactant as epicurean 200 by warm o/w microemulsions method which increases the permeability of the drug formulation.
- **Chloramphenicol** SLNs were formulated with glyceryl monostearate and poloxamer 188 with melt-emulsion, ultrasonication, and low-temperature solidification techniques that enhance the solubility of the formulation.
- **Indomethacin** was loaded into solid lipid nanoparticles with compritol 888ATO/poloxamer 188 and or tween 80 with hot homogenization method and increases permeability. [76]

Methods of preparation of Solid lipid Nanoparticles:

The different types of methods of preparation of SLN are

High-Pressure Homogenization (HPH):

In this method, lipids are pushed with 100 - 200 bars high pressure through a narrow gap of few microns ranges. Disruption of particles to submicron ranges occurs because of the shear stress and cavitations force (due to sudden changes in pressure). Lipid content in the range 5 - 10% normally. This technique is used for nanoemulsion and PTN. There are 2 basic production methods by high-pressure homogenization: Hot homogenization and cold Homogenization. In these both techniques, the drug is dispersed or solubilized in the lipids above their melting points. [77]

Hot Homogenization:

Lipid components are the first melted by heating above the melting point. Therefore it can be regarded as a homogenization of an emulsion. The drug is either dispersed or dissolved in molten lipids. Then aqueous surfactant is added at the same temperature. This pre-emulsion of the drug-loaded lipid melt and aqueous surfactant phase is obtained with a high shearing device such as ultra turrax. High-pressure homogenization of pre-emulsion is taken at the temperature higher than the melting point of lipid. While increasing temperature heat accelerated drug degradation occurs. The process is continued until the desired particle size. 3 - 5 homogenization cycle is sufficient for requisite particle size. After homogenization, the nanoemulsion is formed due to the liquid nature of lipid. This on cooling gives rise to solid lipid Nanoparticles. This technique is an advantage for suitable for scale-up.

Cold homogenization:

This method has been developed to overcome the problems that occur in hot homogenization.

a. Drug distribution into aqueous phase during homogenization.

b. Temperature-induced drug degradation.

c. The complexity of the crystallization step of nanoemulsion leading to several alterations and/or supercooled melts. [78] [79]

Table no: 3 Steps of the hot and cold method of homogenization shown in Table 3:

Steps	Cold Homogenization Technique	Hot Homogenization Technique
1.	Melting of lipid 5 - 10 ºC above the melting point	
2.	Dissolve / Disperse drug in melted lipid.	
3.	Rapidly cooled to solidify the drug-loaded lipid in liquid nitrogen or dry ice	Dispersing drug-loaded lipid in aqueous surfactant solution
4.	Solid lipid drug milled to micron size (50 -100 µ)	High-speed stirrer used to premix and pre-emulsion formed
5.	Dispersed the milled powder in aqueous surfactant solution to form a premix.	High-pressure homogenization at a temperature above lipid melting point
6.	High-Pressure homogenization in room temperature or below room temperature	Hot o/w nanoemulsion. Recrystallization of nanoemulsion by cooling to room temperature

Solvent evaporation:

LNs can also be prepared by a solvent evaporation method. The lipophilic material is dissolved in a water-immiscible organic solvent (e.g. cyclohexane) that is emulsified in an aqueous phase. Upon evaporation of the solvent, nanoparticles dispersion is formed by the precipitation of the lipid in the aqueous medium by giving the nanoparticles of 25 nm mean size. The solution was emulsified in an aqueous phase by high-pressure homogenization. The organic solvent was removed from the emulsion by evaporation under reduced pressure (40–60 bar). Effect of anionic polymers on drug loading and release from Clindamycin phosphate as Solid lipid Nanoparticles has been investigated by Abbaspour.M et al (2013) researched that incorporation of anionic polymers increases drug loading of the SLNs. Dextran sulfate has a greater effect on drug loading, increases in from 1.32 to 18.19%, compared to the 6.73 % achieved using sodium alginate. They also reported that dextran sulfate reduced the drug release rate by half compared with sodium alginate, probably due to higher charge density, lower molecular weight and lower branching density of the ionic polymer. [80]

Nanosponges :

Nanosponges are porous polymeric delivery systems consisting of a network of interconnecting voids within a collapsible structure with a large porous surface. These are used for the passive targeting of cosmetic agents to the skin, thereby achieving major benefits such as reduction of the total dose, avoidance of systemic absorption and retention of dosage form on the skin. [81]

Nanosponges are made up of microscopic particles with few nanometers wide cavities, in which a large variety of substances can be encapsulated. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly water-soluble molecules. Nanosponges are encapsulating the type of nanoparticles that encapsulates the drug molecules within its core. As compared to other nanoparticles, nanosponges are insoluble in water and organic solvents, porous, non-toxic and stable at high temperatures up to 300^0 C. [82]

Advantage of Nanosponges

1. Increase aqueous solubility of the poorly water-soluble drug.
2. Nanosponges can predictably release drug molecules.
3. Because of their tiny pore size (0.25 µm), bacteria cannot penetrate the nanosponges and they act like a self-sterilizer.
4. Nanosponges drug delivery system are non-irritating, non-mutagenic and non-toxic.
5. Nanosponges help to remove the toxic and venom substance from the body.
6. Nanosponges drug delivery system minimize side effects.
7. Increase formulation stability and enhance the flexibility of the formulation.
8. Reduce dosing frequency.
9. Better patient compliance.
10. Nanosponges complexes are stable over a wide range of pH (i.e. 1-11) and a temperature of 130 °C. [83] [84]

Disadvantage of Nanosponges

1. Nanosponges have the capacity of encapsulating small molecules, not suitable for larger molecules.
2. Dose dumping may occur at times [85]

Table No: 4 Materials used in the preparation of Nanosponges:[86] [87]

Polymers	Copolymer	Crosslinker
Hyper cross-linked polystyrenes, cyclodextrin and its derivatives like methyl β-cyclodextrin, 2-hydroxypropyl β-cyclodextrin	Ethylcellulose (EC), polyvinyl alcohol (PVA),	Di-phenyl carbonate (DPC), diaryl carbonate, diisocyanates, pyromellitic anhydride, carbonyl diimidazole, 22-bis (acrylamide) acidic acid and dichloromethane.

Nanosponges are tiny sponges having a size of about a virus and can be filled with a variety of drugs. These sponges can circulate the body until they interact with a specific target site and stick on the surface and start releasing the drug in a controlled manner. Some cyclodextrin based nanosponges proposed nano delivery system and form porous insoluble nanoparticles having crystalline and amorphous nature. [88]

Different categories of drugs used as Nanosponges:

- **Tamoxifen** loaded into a Nanosponges with vehicles used as β-cyclodextrin for the treatment of breast cancer and the survey was carried out for the cytotoxicity study.
- **Dexamethasone was** loaded into a nanosponge with β-cyclodextrin which was used in the treatment of brain tumors and the study was carried out which checked the drug release performance from a Nanosponges and works as a sustained release and was used as the oral dosage form.
- **Econazole nitrate** loaded into nanosponges with ethyl cellulose and polyvinyl alcohol as a vehicle for the treatment of fungal infection and the study was carried out for the irritation study.
- **Itraconazole** loaded into nanosponges with β-cyclodextrin and copolyvidonum was used for the treatment of fungal infections enhanced the solubility the routes were oral and topical.
- **Clindamycin phosphate** loaded into nanosponges was used in a topical treatment for enhanced permeability of topical treatment of acne vulgaris. [89]

Methods of Preparation of Nanosponges:

Emulsion solvent diffusion method:

In this method, the two phases used are organic and aqueous. The aqueous phase consists of polyvinyl alcohol and organic phase include drug and polymer. After dissolving drug and polymer to suitable organic solvent, this phase is added slowly to the aqueous phase and stirred for two or more hours and then nanosponges are collected by filtration, washed and then dried in air at room temperature or in vacuum oven 40 0C for 24 hrs.[90]

Quasi-emulsion solvent diffusion:

The nanosponges can also be prepared by the quasi-emulsion solvent diffusion method using the different polymer amounts. To prepare the inner phase, eudragit RS100 was dissolved in a suitable solvent. Then, the drug can be added to the solution and dissolved under ultrasonication at 350C. The inner phase was poured into the polyvinyl alcohol solution in water (outer phase). Following 60minutes of stirring, the mixture is filtered to separate the nanosponges. The nanosponges are dried in an air-heated oven at 400C for 12 hrs.[91][92]

Solvent method:

Mix the polymer with a suitable solvent, in particular, polar aprotic solvent such as dimethylformamide, dimethyl sulfoxide. Then add this mixture to excess quantity of the cross-linker, preferably in crosslinker/polymer molar ratio of 4 to 16. Carry out the reaction at a temperature ranging from 10°C to the reflux temperature of the solvent, for a time ranging from 1 to 48h. Preferred crosslinkers are carbonyl compounds (Dimethyl carbonate and Carbonyl di imidazole). [93] After completion of the reaction, allow the solution to cool at room temperature, then add the product to a large excess of bi distilled water and recover the product by filtration under vacuum and subsequently purify by prolonged soxhlet extraction with ethanol. Dry the product under vacuum and grind in a mechanical mill to obtain a homogeneous powder. [94]

Nanogel

Nanogels are three-dimensional hydrogel materials in the nanoscale size range formed by crosslinked swellable polymer networks with a high capacity to hold water, without actually dissolving into the aqueous medium. Nanogels can be composed of a variety of naturally occurring polymers, synthetic polymers or a combination thereof. Their characteristics such as size, charge, porosity, amphiphilicity, softness, and degradability can be fine-tuned by varying the chemical composition of the nanogels.[95] It can be composed of a variety of natural polymers, synthetic polymers or a combination thereof, chemically (covalent) cross-linked or physically crosslinked with non-covalent bonds by hydrogen bonds, electrostatic and hydrophobic interactions.[96]

Classification of Nanogel :

Nanogel is more commonly classified into two major ways. The first classification is based on their responsive behavior, which can be either stimuli-responsive or non-responsive. In the case of non-responsive microgels, they simply swell as a result of absorbing water.

1. Stimuli-responsive nanogels swell or de swell upon exposure to environmental changes such as temperature, pH, magnetic field, and ionic strength.
2. Multi-responsive nanogels are responsive to more than one environmental stimulus. The second classification is based on the type of linkages present in the network chains of gel structure, polymeric gels (including nanogel) are subdivided into two main categories.[97]

Classification of Nanogel According to Structure:

Nanogel is also characterized according to its structure. There are different types of nanogels which have been discussed in Table no:5 [98]

Table no:5 Nanogel according to their structure which has been used for drug loading of lincosamide antibiotics:

Sl.No	Types of Nanogel	Network Structure	Examples
1.	Simple Nanogel	a) Cross-linked b) Semi-interpenetrating polymer(semi-IPN) c) Self-assembled	Artificial chaperone, cholesterol-bearing pullulan (CHP) nanogelQuantum dot nanogel. Artificial chaperone cholesterol enzymatically synthesized glycogen (CHSEG) nanogel.
2.	Hollow Nanogel	Interpenetrating polymer	Stimuli sensitive/responsive nanogel
3.	Core-Shell Nanogel	Cross-linked	Stimuli sensitive/responsive nanogel
4.	Hairy Nanogel	Cross-linked	Stimuli-responsive nanogel
5.	Multilayer Nanogel	Cross-linked	Stimuli sensitive/responsive nanogel
6.	Functionalized Nanogel	Cross-linked	Polyethyleneglycol-b-poly (methacrylic acid) [PEGb-PMA] with PEG terminal aldehyde functionality.

Advantages of Nanogel

1. Highly biocompatible (due to high water content and hence behave like natural tissue) and therefore immunological responses
2. Biodegradable, that makes these nanocarriers nontoxic
3. High drug loading capacity
4. Easily escape entrapment by the reticuloendothelial system
5. By tuning crosslinking densities drug release can be regulated [99]

Disadvantages of Nanogel:

1. It is the expensive techniques which require to completely remove the solvent and surfactant at the end of the technique.
2. Sometimes the traces of surfactant causes toxicity.

Method of Preparation of Nanogel:

The different method for preparation of Nanogel is as follows:

Photolithographic Technique

Photolithographic techniques, the photochemical reaction for activation and subsequent reaction have been explored in the strive of producing 3D hydrogel particles and nanogels for drug delivery. In this method, stamps or replica molds are treated to give the surface-specific properties that allow the molded gels to release the incorporated agents. [101] Microfabrication of such gels follows the general strategy where poly (dimethylsiloxane) (PDMS) stamps are utilized to mold, release, and stack gels into 3-dimensional structures. Surface modification enhances the release or adhesion of molded gels to a substrate. The most known techniques to modify PDMS stamps are usually achieved by Hexa (ethylene glycol)-terminated self-assembled monolayers (SAMs), or by adsorbed monolayers of bovine serum albumin. [102]

Micromolding Method:

Water-in-oil (W/O) heterogeneous emulsion methods:

W/O emulsion methods involve generally two steps: emulsification of aqueous droplets of water-soluble biopolymers in continuous oil phase with an aid of oil-soluble surfactants and cross-linking of biopolymers with water-soluble crosslinkers.

Inverse (mini) emulsion method

A W/O emulsion is formed from a mixture consisting of aqueous biopolymer droplets and a continuous oil phase using either a homogenizer or a high-speed mechanical stirrer. Resulting aqueous droplets of biopolymers are then crosslinked with appropriate crosslinking agents. then crosslinked microgel particles are prepared as a dispersion in organic solvents purified by precipitation, centrifugation, washing with organic solvents such as isopropanol, and lyophilization. the size of the prepared microgel particles can be controlled by the number of surfactants and crosslinking agents as well as stirring speed during the formation of an inverse emulsion. [103]

Reverse Micellar Method

Similar to the inverse (mini) emulsion method, the reverse micellar method also involves a W/O dispersion, however, a relatively large amount of oil-soluble surfactants is used to form a thermodynamically stable micellar solution consisting of aqueous droplets dispersed in the continuous oil phase. The resulting micellar droplets have a submicron size ranged from tens to hundreds of nanometers in diameter. Tumor targeted Chitosan-based nanogels were prepared by inverse microemulsion of hexane containing Aerosol OT as a stabilizer in the presence of doxorubicin (Dox)-modified Dex. Aqueous glutaraldehyde was used to crosslink CS. The resulting doc-encapsulating CS-based Nanogels have a diameter of around100nm. [104]

Modified pullulan technique

The example that can be given for this category is selfassembled hydrophobized pullulan nanogel. The pullulans are modified into stages; initially, methacrylates are used, then with hydrophobic 1-hexadecane thiol. The end product is an amphiphilic material that upon the addition of water starts to assemble itself by hydrophobic interaction among alkyl chains.

Another example is Cholesterol based pullulan nanogel. Here, pullulan was substituted with 1.4 cholesterol and the nanogel is fabricated by simply reacting cholesterol isocyanate in dimethyl sulfoxide and pyridine. This mixture was freeze-dried and in the aqueous phase, it formed nanogel which further formed a complex with W-9 peptide, a TNF-alpha and RANKL antagonist for delivery of osteological disorder. [105]

Different categories of drugs used as a Nanogel :

- **Clindamycin phosphate** loaded with aloe-vera as a gelling agent with the other excipient as polymer acryl 940 an emulsifier and the penetration enhancer for transdermal delivery as a topical treatment and showed that the better permeability and the sustained release of drugs.
- **Timolol maleate** was prepared as a diamond nanogel with spontaneous cluster formation and the compositions used were a Nanodiamond, chitosan, poly(hydroxyl ethyl methacrylate) matrix and results as lysozyme mediated sustained release Enhanced retention in the eye localized delivery to treat glaucoma and used in ophthalmic treatment.
- **Dexamethasone** loaded into nanogel was prepared by the Emulsion-solvent Evaporation method for enhanced ocular bioavailability and extended drug retention at eye surface with the composition of cyclodextrin.
- **Bupivacaine** was prepared as a ph sensitive nanogel with the composition of methacrylic acid–ethyl acrylate cross-linked with diallyl phthalate with emulsion polymerization techniques results in enhanced ph dependent anesthetic effects.
- **Cisplatin** loaded as ligand-gated polyelectrolyte NG with the composition of Folic acid conjugated poly(ethylene oxide)-b-poly(methacrylic acid) and was prepared by Cross-linking method and results In vivo anticancer effect strengthens their use for the treatment of ovarian cancer. [100]

Diseases and Infections Cured by Clindamycin as Lincosamide Antibiotics. [5]

Table no:6 List of Diseases Cured by Licosamide Antibiotic as Clindamycin which are:

SL.no	Diseases Caused	Causative organism	Drugs used
1.	Skin and soft tissue infection consist of two types of diseases a) Necrotizing fasciitis b) Diabetic foot	Staphylococcus aureus, streptococci and anaerobes.	Clindamycin is used which decreases the toxin production in necrotizing fasciitis caused by invasive group A streptococci and used as a quinolone antibiotic for the diabetic foot.
2.	Osteomyelitis	S aureus and anaerobes	Lincosamide antibiotic has been claimed for the effective treatment for many organisms that cause osteomyelitis.
3.	Septic arthritis	S aureus and anaerobes	Clindamycin combined with Penicillin has been claimed for the treatment of septic arthritis
4.	Head and neck infection	Mainly caused by aerobic or facultatively anaerobic respiratory flora such as S pneumoniae, S aureus, Haemophilus influenza or group A streptococci bacteria.	Clindamycin is an alternative treatment for several head and neck infections. Which includes dental infections, recurrent pharyngitis, and chronic sinusitis.
5.	Preoperative prophylaxis	Caused by mixed aerobic and anaerobic bacteria.	Clindamycin phosphate has been used in reducing the rate of postoperative infection
6.	Pneumonia	Aerobic Gram-negative organism	clindamycin is probably the therapy of choice for anaerobic necrotizing pneumonia and aspiration pneumonia
7.	Gynecological infection	Neisseria gonorrhoeae,	Clindamycin, in an oral dose or as a vaginal gel, is effective for the treatment of bacterial vaginosis in both pregnant and non-pregnant patients.

CONCLUSION

Evolution of an existing drug molecule from a conventional form to a novel drug delivery system which significantly improves the performance in terms of patient compliance, safety, and efficacy. In the form of the Novel, Drug Delivery System is an existing drug molecule that can get a new life. Clindamycin,7(s)-chloro-7-deoxy derivative of lincosamide has stood the test of time in the treatment of anaerobic infection. It mainly acts by inhibiting protein synthesis by acting on the 50s ribosomal subunit of bacteria. The pursuit of this review is to concisely describe the recent development of NDDS on lincosamide antibiotic as clindamycin which has been formulated using a particulate vesicle system such as drug carriers for small and large molecules like liposomes, neosomes, solid lipid nanoparticles, microemulsions, etc. These are mainly designed to target the site-specific region to achieve the therapeutic effect by reducing the side effect or the toxic effect. Clindamycin is used with different techniques to give a better formulation for various types of bacterial infection which can be cured by the use of lincosamide antibiotics.

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