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Novasome: Advance in Liposome and Niosome

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Abstract
In the aspect of novel drug delivery, day by day new technologies are developed. Attempt was made to modify the liposomal and similar drug delivery and formulation of novasome was done. The two-seven bilayer structure of novasome helps to incorporate both water soluble and insoluble drugs. It helps to overcome stability related problem of liposomes in biological fluid and their targeting efficiency. Its modified entrapment efficiency and encapsulation process gives better dosing frequency and applied in various fields like cosmetics, dermatology, chemical, food, personal care, etc. many researches are going on this technology as an innovation in liposome.

Keywords: Microvesicles**,** encapsulation, dermatology, novasome

Introduction
Novasome is a patented and innovative technology or encapsulation process designed to overcome efficacy as well as efficiency related problem with exiting drug delivery systems. IGI laboratories Inc. take an exclusive ten year renewable license from Novavax regarding most non pharmaceutical application. Novasomes can be defined as the modified form of liposomes which is 0.1-1.0 micron in diameter containing 2-7 bilayer membranes consisting unstructured space which occupies large amorphous core of hydrophilic i.e. water soluble and hydrophobic i.e. water insoluble drug substances [1, 8, 9].

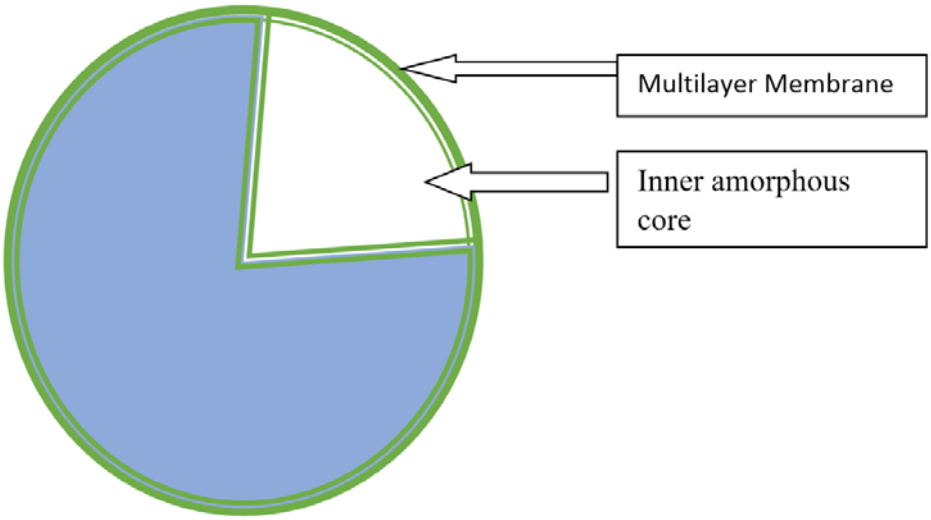


Fig 1: Diagrammatic representation of novasome

Novasome can said be improved structure of liposomes or niosomes. Liposomes are spherical vesicles with a membrane composed of a phospholipid and cholesterol bilayer it can encapsulate a region of aqueous solution inside hydrophobic membrane core and lipid soluble drug can be incorporated in between two lipid layer Niosomes are the non-ionic surfactant vesicles formed in aqueous media with or without the presence of cholesterol or other lipids. It can also entrapped both hydrophilic and hydrophobic drug molecule with better intrinsic activity due to the presence of non-ionic surfactant molecules.

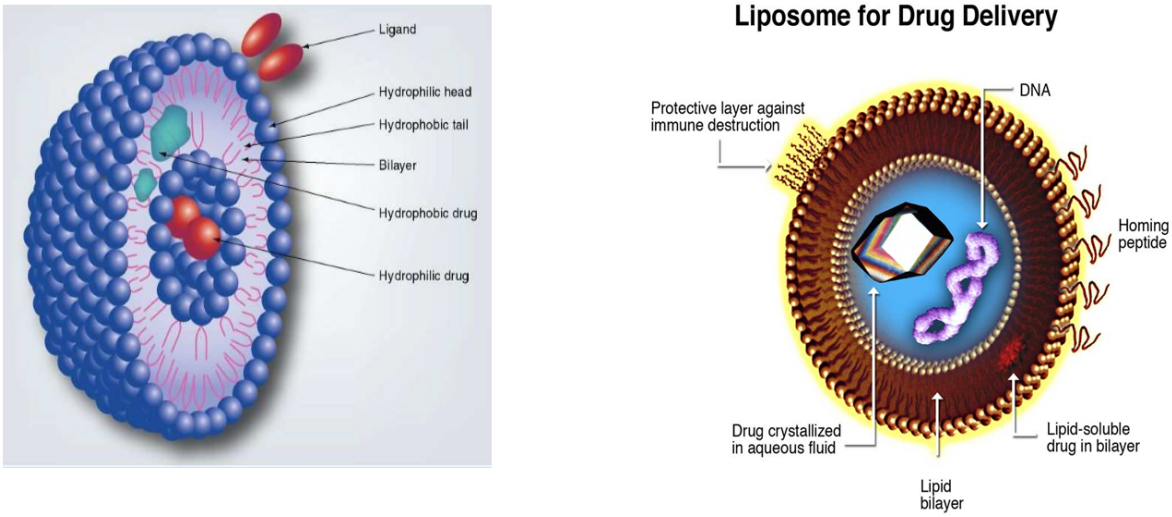


Fig 2: Structure of Niosome and Liposomes

Description of Novasome: In the structure of novasome molecule, there is hydrophilic head group attached to hydrophobic tail including long chain of fatty acid, alcohol derivatives, amino acids and glycerol-lipids. These are generally prepared from concentration based combination of cholesterol, free fatty acid and monoester of polyoxyethylene fatty acid. The bilayer membranes of novasome formed of many bio-compatible, single tailed amphiphiles as well as purposefully selected phospholipid. The fatty acid tails pointed into the membranes interior and the polar head groups pointed outward. During manufacturing of vesicles water soluble molecule mixed with water and placed into aqueous space in between the multiple layers of the lipid bilayer membrane, while lipid soluble molecules placed inside the vesicle core. The larger part of the vesicles is filled by the amorphous core that incorporates finely divided insoluble particles like diamonds, titanium dioxide and water immiscible compound [1-3].

Properties: the following are the important properties of novasome

1. Novasome can be stable over a wide pH range i.e. from 2-13.
2. It is stable at temperature from 0^{o} to 100^{o}c i.e. from lower than the temperature of liquid nitrogen to temperature higher than boiling water.
3. Provide high capacity of central core due to multi-bilayers vesicles.
4. These have ability to carry positive, negative, and neutral charge.
5. Amorphous core of this vesicle can packed up to 80-85% of decided product.
6. It provides uniform size distribution and thus uniform drug or active ingredient content.
7. The most acceptable property is that it can load large amount of drug in small structure.
8. Derived rate of release of drug help to reducing dosing frequency. It provides site specific and targeted drug delivery [1-4].

Advantages: Novasome shows following advantages over other resemble drug delivery;

1. The same formulation contained both hydrophilic and hydrophobic drug molecule.
2. Incompatibility of drugs showing interaction can be prevented as the placement in two different layers.
3. Site specific activity can be achieved due to surface charge activity.
4. As the loading capacity 80% it can delivers large amount of active ingredient and reduces administration frequency.
5. These formulations have ability to adhere skin or hair shaft and widely used in various cosmetic formulation.
6. It reduces product irritation and increases product stability.
7. In the cosmetic preparation rinsing is resisted or reduced as it adheres to skin very well.
8. It is cost effective than liposome and similar preparation [1-4].

Formulation: Basic components used in Novasomes are;

1. Targeting molecule: It is active agent or drug substance.
2. Charge producing agent: these agent help to produce opposite charge in different environment. E.g. Alkylbenzene sulfonate quaternary ammonium compounds, tween.
3. Non-phospholipid surfactant: Polyoxyethylene cetyl ether, Polyoxyethylene lauryl ether, glyceryl monostearate.

Preparation: recently variety of devices can be used for preparation of novasome. This instrument produces high shear mixing. Most popular devices are Microfluidizer^{R} Microfluidics Corp. (Newton Mass) “French” type press other high shear producing devices. For the preparation, all required formulating material was selected, according to targeting active molecule. All the ingredient are mixed, i.e. non-phospholipid surfactant, charge producing agents and targeting molecules, antioxidants if required. This mixture is then heated, blended which turns to confirmed lipophilic phase; which is again blended under shear mixing conditions with an aqueous phase containing an aqueous buffer and an aqueous collagen formulation and subjected to equipment. This equipment consists of a cylindrical mixing house with tangentially arranged for reservoir of lipophilic phase, oil phase or aqueous phase. Pumps are attached to reservoir to formed continuous flow inside the cylindrical chamber. The function of this pumps is to create positive displacement pumping action which helps to moving decided phases in cylindrical housing. With the use of this instrument novasome can be formed with in one second, removed from axially

arranged discharge orifice. E.g. controlled delivery formulation and sustained release fragrant or emollient oils formulation used this technology.

Formulation technologies

Ether injection method: in this method the surfactant is dissolved in Diethyl ether by maintaining temperature at 60ºc. this solution is subjected into an aqueous solution of drug with the help of an injection containing needle of 14 gauze size. After the vaporization of ether single layered vesicles are formed.

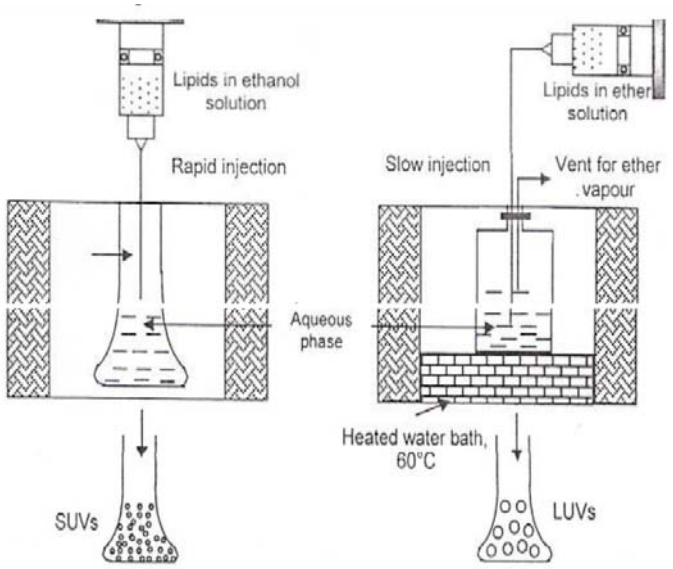


Fig 4: Process of Ether injection method

1. **Micro fluidization method:** Micro fluidization is a recent technique used to prepare unilamellar vesicles of defined size distribution. This method is usually used in the niosomes formulation. This method is based on submerged jet principle in which two fluidized streams interact at ultra-high velocities, in precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheet along a common front is arranged such that the energy supplied to the system remains within the area of targeted molecule formulation. The result is a greater uniformity, smaller size and better reproducibility of Novasomes formed.

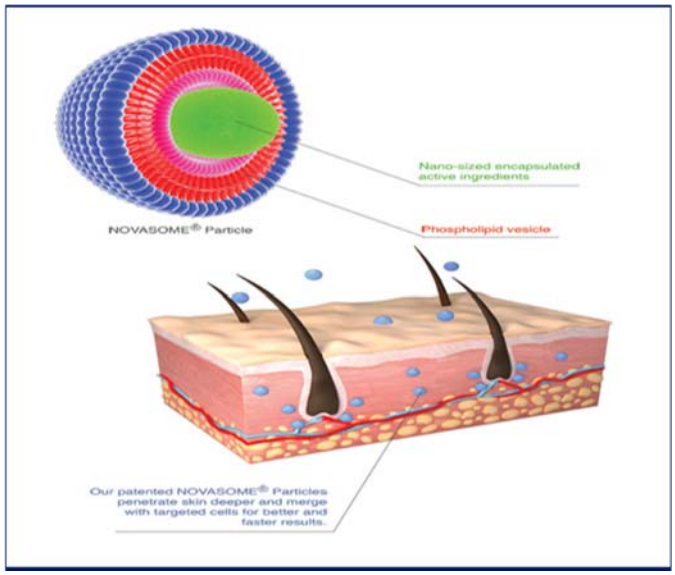
2. **Hand shaking method:** this method also called thin film hydration technique. The mixture of vesicles forming ingredient like surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask. The organic solvent is removed at room temperature (20 ^{o}C) using 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 0º-60 ^{o}C with gentle agitation. This process forms typical multilamellar niosomes.

3. **Reverse Phase Evaporation Technique (REV):** This method involved the creation of cholesterol and surfactant (1:1 ratio) in a mixture of ether and chloroform. An aqueous phase containing the drug to be loaded as added to this, and the resulting two phases are sonicated at 4-5^{0} C. a clear gel is formed which is further sonicated after the addition of phosphate buffered saline (PBS). After this the temperature is raised to 40 ^{0}C and pressure is reduced to remove the organic phase. This result in a viscous niosome suspension which can be diluted with PBS and heated on a water bath at 60c for 10 min. to yield niosomes.

4. **Multiple membrane extrusion method:** Mixture of surfactant cholesterol and dicetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug polycarbonate membranes, solution and resultant suspension extruded through which are placed in series for upto 8 passages. It is good method for controlling size of formed particles.

5. **Sonication Method:** It is atypical method of vesicles production. In this method, an aliquot of drug solution in buffer is added to the surfactant or cholesterol mixture in a 10 ml glass vial. The mixture is probe sonicated at 60c for 3 minutes using a sonicator with a titanium probe to yield product [5, 6].

Drug Release Mechanism: Novasome contain channels of lipoprotein which acts as a pathway for discharge of targeting molecule. Active molecule or targeting moiety passes within and between each bilayer throughout the series jumps result in lateral movement of voids of channels in the bilayer. This tends to continuous release of active molecule from the bilayer through the aqueous solution separating bilayer. The activity of active molecule determined by ne charge present on surface of micro vesicles either it is positive, negative or neutral. For example, the micro vesicles of positively charged get combine with negatively charged skin, mucous membrane or hair. Similarly, the active drug achieved. Due to its structural arrangement problems related to stability of active ingredient and stability during storage could be avoided [7-9].



Application

The described technology has wide uses in the following field;

1. Nano particle drug delivery.
2. High cargo capacity than liposome.
3. Enhance product stability.
4. Extend product performance.
5. Various cosmetics.
6. In agro chemical [1-4].

It helps to increase the rate of absorption through topical delivery of pharmaceuticals and cosmetics products by using non-phospholipid materials. It helps to increase formulation efficiency, enhance site specific delivery of drug, achieves more stability of active in the formulation. More availability and less cost of formulating agent. Novasome vesicles possess the ability to protect, transport and deliver the various nutrients, flavors and oil like active substance can be used as foods and beverages. It can increase the effect of properties like texture, flavors, fragrance, efficacy, safety, stability and other desirable properties of essential materials like oils, flavors, fragrances, etc. some examples novasome product given as; [1-5].

Formulation	Ingredient	Action
MPA Hydra-Pearls	Novasome micro vesicles	Humectant
MPA Benzoyl plus	2.5 % Benzoyl peroxide Novasome Microvesicles.	Keratolytic, Antibacterial, Degreasing, Follicular, Flushing, Humectant.
MPA Dermal- soothe	Pramoxine HCL, Colloidal Oatmeal skin Respiratory Factor Novasome Microvesicles.	Antipruritic, Cellular Repair, Humectant.
MPA Miconazole Shampoo	1 % Miconazole Nitrate Novasome Microvesicles.	Antifungal, Humectant.
MPA Seba-Hex	2 % Chlorhexidine Gluconate, Sulfur, Salicylic Acid Novasome Microvesicles.	Antibacterial, Antifungal, Keratoplastic, Keratolytic, Humectant.
MPA Dermal-soothe Cream Rinse	Pramoxine HCL Skin Respiratory Factor Novasome Microvesicles.	Antipruritic, Cellular Repair, Humectant.
MPA Dermal-Soothe Spray	Pramoxine HCL Novasome Microvesicles.	Antipruritic, Cellular Repair, Humectant.
Novasome^{R}	Vaccine	Small Pox
Novasome I	a-Interferon cyclosporine	Novasome I showed great
Acne Worx^{R}	2 % Salicylic Acid.	Reduced acne blemishes, prevent new pimples before appearing.
Nova Pearls ^{TM}	Slow release power moisturizers.	Deodorant for pet skin care

Recent Advances in Novasome Technology

Although the technology of Novasome was evaluated for flavor encapsulation and as adjuvants in the vaccine preparation but now it is the most advanced derma cosmetic technology which expands limits of dermatology.

These vesicles not only penetrate the deepest layers of skin easily but they also incorporate into the targeted cells as preprogrammed. A Cornell university 2 Novasome based dermatological products were examined, the first study was done to evaluate the efficacy of novasome based and non-encapsulated emollients in the treatment of winter time dry skin in dogs. After it was concluded that the novasome based emollients was the superior agent in 80% of the dogs. This study proved that novasome can serve as potent humectants. In the second study evaluation of novasome and non-novasome based shampoos was done which contained Benzoyl peroxide. The test result showed that novasome based shampoo have the better efficacy for the treatment of scaling (70%) while another was minimum (20%) [12].

Novasome based sustained release veterinary products are now available to pets for long lasting skin hydration and delivery of anti-pyretic agent. Sustained release technology uses novasome Microvesicles to encapsulate moisture within skin treatment, shampoo and sprays to get hydrating effect.

Novasome technology for the delivery of *Mahonia aquifolium* extract patented by mills et.al. Which is used in the treatment of psoriasis, eczema and other skin disease. From the study it was concluded that the 5-20% of *Mahonia aquifolium* extract along with other excipients can be effectively used as lotion or cream in topical application to the affected area.

Novasome technology now can extensively use for the preparation of vaccines. Small pox vaccine has been developed and other novasome based vaccines under development. Immunization can be done using novasome based vaccines against Rheovirus and new castle disease virus. The novasome composed of cholesterol, oleic acid and dioxyethylene cetyl ether when evaluated with Diphtheria toxoid and tetanus toxoid, it was found that novasome can be used as a potent adjuvant for the human vaccines containing aluminum phosphate.

When single dose of formalin inactivated BCG mixed with Novasome^{TM} and administered to Guinea pigs as single subcutaneous inoculation, treated subject get protected from lethal tuberculosis. Gram negative bacterial infection can be prevented by using oral vaccines of novasome- WFI diluents in the preparation of oral vaccine the novasome lipid vesicles are diluted with WFI in a ratio 1:32(v/v) to maintain 99.2 % of water. Novasome Microvesicles can be used as an adjuvants for influenza virus particle to treat the infection Avian Influenza [9].

There was marked improvement in lesions caused because of psoriasis with the treatment of parathyroid hormone analog PTH (1-34) when encapsulated in Novasome^{R} cream. This type of encapsulation process for peptide drug was done successfully for the treatment of skin disease, to increase the absorption of peptide drug into human skin [14, 16].

An attempt was made that, the use of Novasome Microvesicles and organic acid or base e.g. lactic acid to increased hydrophilic nature of Minoxidil to enhance the topical drug delivery and penetration power.

When Vandegriff et.al examined the encapsulation efficiency of hemoglobin in non-phospholipid liposomes by rapidly mixing hemoglobin with lipids heated above their solid liquid phase transition temperature. It was found that the percent encapsulation varied from 13-30%, with the greatest efficiency, i.e., at a 4:1 hydration ratio of hemoglobin: lipid at 5.6 mM hemoglobin [13].

One of the inventions involved patented lipid Novasome^{R} vesicles containing water and/ or water soluble fuel additives and liquid energy sources comprising liquid fuels which result in enhanced performance characteristics compared to conventional fuels such as gasoline, diesel and other liquid fuels. Moreover under normal storage conditions and at a fairly wide temperature range, these formulations are more stable than emulsion already used in the past to incorporate water into petroleum fuels [8-11].

Conclusion

From various studies it was concluded that novasome technology proved to have more product stability, extend shelf life from weeks to sometimes years, prevent oxidation and emulsification, and also permits isolating antagonistic ingredient with in the formulation until use. Some patented information shows its wide range of application in the field of pharmaceutical, foods, agrochemical, etc. many dermatological preparation have marked a new improvement in their efficacy by utilizing novasome technology. The incremental cost of manufacturing products using Novasomes is minimal. Continuous advances are being made in novasome technology. Many Novasome based products are under developed to be launched into market.

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