

Novasome-A Breakthrough in Pharmaceutical Technology a Review Article

Anupama Singh, Rishabha Malviya and Pramod Kumar Sharma

Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology Bypass Road, Baghpat Crossing, NH-58, Meerut-250005, U.P., India

Abstract: Pharmaceutical technology has developed various newer modes of novel drug delivery aspects. Modifications in the previously existing drug delivery methods have led to various newly innovated technologies serving as a safe and effective means of improvement over the existing ones. Novasome technology is one of the new innovations of liposomes which have solved many of the problems related to liposomal drug delivery system. It serves as the encapsulation process for effective delivery of a variety of substances in the field of foods, cosmetics, personal care, chemical, agrochemical and pharmaceuticals.

Key words: Pharmaceutical technology · Non phospholipid · Bilayered · Innovation · Dermatology

INTRODUCTION

Novasome technology is the patented and innovative encapsulation process for effective delivery of a variety of substances. This technology was initially developed by Novavax. IGI laboratories, Inc. owns an exclusive 10-year renewable license from Novavax for the technology regarding most non-pharmaceutical applications. Novasomes are the modified forms of liposomes [1] or a variation of niosomes prepared from the mixture of monoester of polyoxyethylene fatty acids, cholesterol and free fatty acids at 74/22/4 ratio. They may be defined as the non-phospholipid paucilamellar vesicles of 0.1-1.0 microns in diameter. They consist of two to seven bilayered shells that surround an unstructured space occupied by a large amorphous core of hydrophilic or hydrophobic materials as shown in fig. 1 [2].

These molecules have a hydrophilic head group attached to a hydrophobic tail and include long-chain fatty alcohols and derivatives, long-chain acids, long-chain amino and glycerolipids. The bilayered membranes may be formed of many bio-compatible, single tailed amphiphiles as well as phospholipids individually chosen for a particular purpose [2]. The bilayers have the fatty acid tails pointing into the membrane's interior and the polar head groups pointing outward. The polar groups present at one surface of the membrane point towards the interior of the vesicle while those at the other surface point toward their external environment.

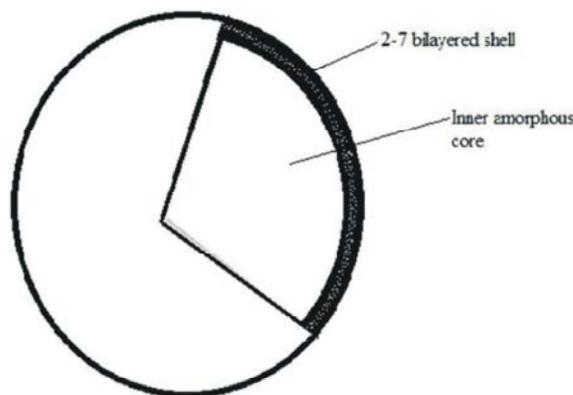


Fig. 1: Diagrammatic representation of novasome showing inner

Any water-soluble molecules that have been mixed to the water at the time of manufacturing process of vesicle, gets incorporated into the aqueous spaces in between the multiple layers of the lipid bilayer membrane. Similarly, any lipid-soluble molecules added at the time of vesicle formation are incorporated inside the vesicles core. The amorphous core accounts for most of the volume of the vesicle, incorporating water soluble, water immiscible (i.e. titanium dioxide, diamonds, insoluble pharmaceuticals) and small solid particles. They have uniformity of size. Their encapsulation efficiency varies from 100% for lipid moieties to 85% for aqueous materials. These microvesicles are stable over a wide pH range of 2-13 and temperature range of liquid nitrogen to above the boiling

point of water [2]. The cost of manufacture of these vesicles is equivalent to that used in making simple emulsions ranging from micro liter to milliliter continuous flow batches.

Characteristics of Novasomes: Novasomes are found to have several characteristics, a few of which mentioned below includes [3]:

- It is a multi bilayered vesicle with a high capacity central core.
- Its surface can be negative, positive or neutral charged.
- The inner amorphous core can be loaded up to 80-85% with a medicated product.
- They can be produced of a specific size range.
- They have the ability to adhere to the skin or hair shaft depending on varying conditions of the vesicle surface charge as well as skin surface.
- They have the advantage of containing more active ingredient in a small volume.
- They show a predictable release of active ingredients thus reducing the frequency of applications.
- They have the ability to carry and release a large volume of water soluble ingredients.

Benefits: It offers several advantages to the owners of the product such as [3, 4]:

- Both hydrophilic as well as hydrophobic products can be incorporated in the same formulation.
- Drugs showing interactions can be incorporated in between bilayers to prevent incompatibility.
- Due to surface charge characteristics, it can be made site specific.
- It can deliver a large volume of active ingredient since it possesses a loading efficiency of 80%, thus also reducing frequency of administration.
- Having the ability to adhere at skin or hair shafts, it offers additional advantage of being used in various cosmetic formulations.

Mechanism of Drug Release: The Novasome bilayers do not show perfect array arrangement. They contain channels (vacancies) that act as a pathway for travel of encapsulated components. Encapsulated components such as active ingredients represented by symbol (A) in fig. 2, in the core travel within and between each bilayer (B) via a series of random jumps which causes lateral movement of the vacancies in the bilayer.

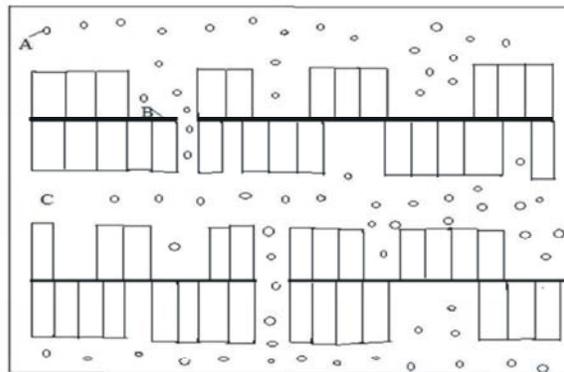


Fig. 2: Mechanism of continuous release of active moieties

This causes the continuous release of active moieties from the bilayers through the aqueous suspension (C) separating the bilayers as shown in fig. 2. The charge on the surface of microvesicles can be net negative, net positive or no net charge which determine their activity. For example, the positively charged microvesicles can combine with the negatively charged skin, mucous membrane or hair. Similarly, a sustained release mechanism is provided by the structure of the Novasome vesicles so a controlled release of the active ingredient can be achieved. Due to the more protected entrapment of the active ingredient within the core prior to use, the storage stability and the stability of the active ingredient is improved. This leads to a more efficient and effective delivery of the active ingredient [4].

Preparation of Novasomes: A variety of devices have been utilized for the preparation of novasomes producing high shear sufficient enough for shear mixing. A few of these devices available in the market include Microfluidizer® made by MicroFluidics Corp. (Newton, Mass.), a "French"-type press, or some other device which provides a high enough shear force and the ability to handle heated, semiviscous lipids. Micro vesicular systems, Inc., have also developed a device which has the property to be particularly useful for making the paucilamellar lipid vesicles. This device consists of a cylindrical mixing chamber with at least one tangentially located inlet orifice. There are one or more orifices which lead to a reservoir containing different phases such as the lipophilic phase, mixture of an oil phase if lipid-core paucilamellar lipid vesicles are to be formed and aqueous phase. These reservoirs are attached to the pumps which intersect in a manner that forms a turbulent flow inside the chamber e.g., positive displacement pumps helps in

driving these phases into the cylindrical chamber. The paucilamellar lipid vesicles (novasomes) formed rapidly in less than 1 second is removed from the chamber through the discharge orifice axially located to the chamber. These lipid vesicles can include non-phospholipid surfactants, charge producing agent and a targeting molecule. Non-phospholipid paucilamellar lipid vesicles (novasomes) made of non-phospholipid surfactant material (polyoxyethylene cetyl ether, polyoxyethylene lauryl ether, glyceryl monostearate and poly oxyethylene glyceryl stearate) and containing an antioxidant, involve formation of a lipophilic phase containing a mixture of several lipophilic components including surfactant material. This mixture is then heated and blended. This resultant lipophilic phase is again blended under shear mixing conditions with an aqueous phase containing an aqueous buffer and an aqueous soluble collagen formulation to form the paucilamellar lipid vesicles [2]. Wallach *et al.*[5] developed a new technology for preparing paucilamellar vesicles or “novasomes” by utilization of N-acyl sarcosinates. This technology can be used for controlled delivery and sustained release of cargo, such as fragrant or emollient oils, which can be effected by varying pH.

Application: Novasomes have extensive utilization in fields of foods, cosmetics, personal care, chemical, agrochemical and pharmaceuticals. The technology enhances absorption rate via topical delivery of pharmaceuticals and cosmeceuticals by utilizing non-phospholipid structures. It offers several advantages such as it aids in formulation, increase delivery to site of action, offers high stability to chemical ingredients in the formulation, low cost and availability in large amounts to all these products. Due to its ability to protect, transport and deliver flavor oils, nutrients and other active ingredients, novasome vesicles can be used for many functions in foods and beverages. It has the ability to provide sustained release of ingredients and to enhance texture, flavor, fragrance, efficacy, safety, stability and various other desirable properties of various materials. Various FDA-regulated products such as human pharmaceuticals and vaccines can be developed using this technology [4, 5]. The summarized advantages of novasome technology are represented below in fig. 3.

Recent Advancements in Novasome Technology: Novasomes are non phospholipid vesicles tested originally for flavor encapsulation as well as vaccine adjuvants. These nonionic vesicles composed of glyceryl

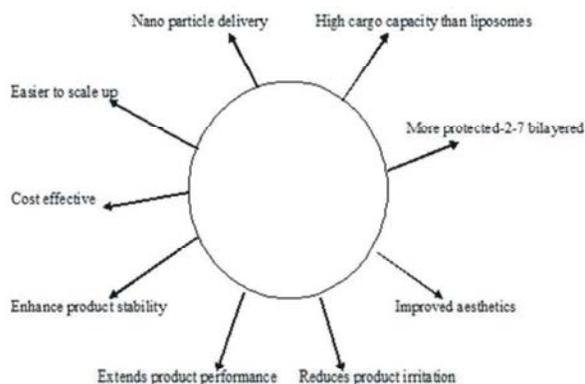


Fig. 3: Advantages of novasome technology

dilaurate (or glyceryl distearate) with cholesterol and polyoxyethylene-10-stearyl ether have been known to deliver greater amounts of cyclosporine into and through hairless mouse skin than phosphatidyl choline or ceramide based vesicles [6]. Among various liposomal formulations, novasomes appeared more effective when delivered under non-occluded conditions from a finite dose [6]. Various vaccines based on novasomes have been licensed for the immunization of fowl against Newcastle disease virus and avian rheovirus [7]. Some of the novasome- based vaccines against bacterial and viral infections have been developed such as small pox vaccine while still many are under development [8]. These paucilamellar lipid vesicles (novasomes) inactivate viruses such as orthomyxoviruses, paramyxoviruses, coronaviruses and retroviruses, etc., by fusing with enveloped virus and that the nucleic acid of the virus denatures shortly after the fusion. For example, Newcastle disease vaccine developed by Immunogenetics, Inc [9]. These novasomes also offers adjuvant properties for the delivery of vaccines. Gupta *et al.* [10] evaluated novasomes composed of dioxyethylene cetyl ether, cholesterol and oleic acid with human vaccine antigens, tetanus toxoid (TT) and diphtheria toxoid (DT), in mice and rabbits. It was found that novasomes act as potent adjuvants to the currently employed adjuvant for human vaccines (aluminum phosphate) and a benchmark adjuvant for experimental immunology (Freund's adjuvant). Chambers *et al.* [11] found that a single dose of formalin-inactivated BCG mixed with non-phospholipid liposome adjuvants (Novasomes™) when administered to guinea pigs as a single subcutaneous inoculation protects them from lethal tuberculosis. Pushko *et al.* [12] developed safe and effective vaccines through novasome adjuvant for avian influenza H9N2 virus with pandemic potential. Norton *et al.* [13] tested the agglutinating

activity of the S19 mAb in a formulation designed for vaginal use. The study involved the binding of S19 mAb to the surface of Novasomes, a multilamellar liposome delivery vehicle. The results showed that S19-Novasome formulations agglutinated human spermatozoa and were as effective as unbound S19 mAb, indicating the feasibility of spermistatic contraceptives targeted to the male reproductive tract specific carbohydrate epitope. Studies have shown that this technology have improved localized delivery of H2 antagonists for the treatment and/or prevention of periodontal diseases due to increased local absorption of the H2 antagonist and enhanced drug action. In an experimental study done on rabbit periodontitis model, it was also found by the inventors that the topical application of the novasomal preparation of H2 antagonist (Cimetidine), prevented gingival inflammation as well as bone destruction in the model. It also finds applications in the management of inflammatory skin and other disorders [14]. This approach can also be used in the delivery of proteins and peptides therapeutics. Holick *et al.* [15] developed the first successful formulation of topical peptide viz. the parathyroid hormone analog PTH (1-34) encapsulated in Novasome(R) A cream. It was found from the study that topical PTH (1-34) encapsulated in Novasome(R) A cream proved to be a novel, safe and effective therapy for the treatment of psoriasis as this approach enhanced the absorption of PTH (1-34) into human skin. Thus, novasome technology is considered to pave new ways in the treatment of several dermatological disorders.

Mills *et al.* [4] also patented novasome technology for the delivery of *Mahonia aquifolium* extract in the treatment of psoriasis. The preparation containing 5-20% w/w of *Mahonia aquifolium* extract along with other excipients is used in a liposomal (novasome) delivery system. From the study, it was found to be effectively utilized as lotion or cream in topical application to the affected area.

An invention to develop a novel approach and delivery system for therapeutic weak acid or base materials has been developed. This system meant for topical delivery of minoxidil, utilizes a therapeutic material modified to make it more hydrophilic and encapsulated in a lipid vesicle, preferably a non-phospholipid lipid vesicle (novasome) particularly those having glycerol dilaurate as the primary lipid in the wall material. In this system the materials are made more hydrophilic by reacting them with an acid or base, e.g., an organic acid or base such as lactic acid, which further improves the penetration power [16].

Another patented formulation involved preparation of novasome containing surfactants (NONOXYNOL-9) which are latex compatible and designed to inactivate enveloped viruses and spermatozoa on contact [17]. Wright [17] has also formulated oral vaccine utilizing Novasome-WFI diluents for prevention against gram negative bacterial infections. These Novasome-WFI diluent are characterized to be paucilamellar, non-phospholipid liposomes encapsulating cherry-flavored oil for the enhancement of palatability of the *E. coli* 0157:H7 vaccine. The Novasome lipid vesicles prepared are diluted with WFI in a ratio of Novasomes:WFI of 1:32 (v/v) to

Table 1: Some marketed formulations of novasomes with different pharmacological actions

Formulation	Ingredients	Action	Reference
MPA Hydra-Pearls	Novasome Microvesicles	Humectant	[2, 22]
MPA Benzoyl-Plus	2.5% Benzoyl Peroxide Novasome Microvesicles	Keratolytic, Antibacterial, Degreasing, Follicular Flushing, Humectant	[2, 21]
MPA Dermal-Soothe	Pramoxine HCl, Colloidal Oatmeal Skin Respiratory Factor Novasome Microvesicles	Antipruritic, Cellular Repair, Humectant	[2]
MPA Miconazole Shampoo	1% Miconazole Nitrate Novasome Microvesicles	Antifungal, Humectant	[2]
MPA Seba-Hex	2% Chlorhexidine Gluconate, Sulfur, Salicylic Acid Novasome Microvesicles	Antibacterial, Antifungal, Keratolytic, Keratoplastic, Humectant	[2]
MPA Dermal-Soothe Cream Rinse	Pramoxine HCl Skin Respiratory Factor Novasome Microvesicles	Antipruritic, Cellular Repair, Humectant	[21]
MPA Dermal-Soothe Spray	Pramoxine HCl Novasome Microvesicles	Antipruritic, Cellular Repair, Humectant	[22]
Novasome®	Vaccine	Small pox	[23]
Novasome I	a-interferon, cyclosporin	Novasome I showed great levels of drug compared with liposomes	[24]
AcneWorx®	2% salicylic acid	Reduce acne blemishes, prevent new pimples before appearing	[2]
Nova Pearls™	Slow-release power moisturizers	Deodorant for pet skin care	[25]

maintain 99.2% of water in final formulation. This sterile suspension of resultant Novasome-WFI diluents in water is used for injection in a single use vial [18]. Vandegriff *et al.* [19] 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.*, 30%, at a 4:1 hydration ratio of hemoglobin: lipid at 5.6 mM hemoglobin. One of the inventions involves 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 emulsions already used in the past to incorporate water into petroleum fuels [20].

Marketed formulation of novasomes: Non-phospholipid paucilamellar lipid vesicles are sold under the trade name Novasome® (IGI Inc., Buena, N.J.). Several Novasome® formulations exist (e.g., Novasome® A, Novasome® D, Novasome® Day Cream) in the market which involves skin-protective agents, oil, moisturizers and skin cleansers [2, 21] as shown in table 1.

Due to the resistance of cosmetic formulations to variations of alkalinity, acidity and temperature, novasome technology enables the product to be easily integrated into the formulation process of cosmetic products. This also enables sustained release and delivery of these substances and enhances the effectiveness and texture of these cosmetics [2, 22].

CONCLUSION

It was concluded from various studies that non phospholipid vesicles (novasome technology) proved to have more encapsulation efficiency and shows better targeting and sustained release of active ingredients. Several patented information shows its wide range of applications in the field of pharmaceuticals, foods, agrochemicals, etc. Recently, many dermatological preparations have marked a new improvement in their treatment efficacy by utilizing novasome technology.

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