

NOVASOME: A PIONEERING ADVANCEMENT IN VESICULAR DRUG DELIVERY

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ABSTRACT

Pharmaceutical research has developed various new types of innovative forms of drug delivery. Advancement in current drug delivery methods has led to the development of numerous new revolutionary technologies that support safe and efficient formulations over existing ones. Novasome technology is one of the latest liposome developments that have overcome many of the liposomal drug delivery system-related problems. This provides a seven bilayer membrane which is capable of absorbing water-soluble as well as insoluble drugs. The improved efficiency of entrapping drugs with good encapsulation features enables better frequency of dosing, which can be accomplished through the high shear system. These find their applications in diverse fields such as cosmetics, chemicals, personal care, food, pharmacy, and agrochemicals. Several products have already been launched into the market using this technology with an additional launch plan. Due to its depth of penetration, novasomes have been one of the most popular derma cosmetics. It is being studied continuously to obtain improved release characteristics. The prospect of drug delivery and targeting using novasomes is an important area of research and development. This review pinpoints the various aspect of the novasome and will be a milestone for the researchers in the area of drug delivery.

Keywords: Drug delivery, Novasome, Application, Formulation, Characteristics

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INTRODUCTION

The conception of a drug delivery system (DDS) refers to the process of delivering pharmaceutical compounds such as drugs and macromolecules at a predefined rate to attain a therapeutic effect in animals or humans at a diseased site and, simultaneously, to reduce the drug concentration in surrounding tissues. The localized activity of the drug promotes the potency or efficacy of the drug and decreases the systemic adverse effects on tissues [1]. Over the last few decades, a groundbreaking revolution has been undergone in the area of the drug delivery system (DDS). The main disadvantage of the majority of potential drugs is the failure to attain targeted action. Most of the conventional drugs have poor bioavailability and cause serious systemic toxicity [2]. To avoid such systemic toxicity, novel, sophisticated targeted mechanisms are required for the delivery of drugs. In the present scenario of the drug discovery system, the vesicular drug delivery systems are promising approaches to overcome the limitation of the conventional drug delivery system and enable significant drug bioavailability by controlled deliverance of therapeutic drugs for an extended period. Hence, novasome is an important drug delivery platform for a wide range of medicines [3, 4]. They are paucilamellar vesicles shaped by many biocompatible phospholipids and single-tailed amphiphiles. Therefore, Novasomes can be described as the altered or modified form of liposomes which has a diameter of about 0.1-1.0 micron and containing 2 to 7 bilayer membranes comprising of unstructured space which occupies a huge amorphous nucleus of hydrophobic substances (water-insoluble drug substances) and hydrophilic substances (water-soluble drug substances) [5]. The diagrammatic representation of the novasome is portrayed in fig. 1. Novasome is a licensed invention established by the Novavax IGI laboratories. The 2 to 7 bilayer membrane of novasome aids to integrate both hydrophobic as well as hydrophilic drugs. It also aids to overwhelm the stability associated problems of liposomes in biological fluids as well as their effectiveness in targeting. It's improved encapsulation process and efficiency of entrapment improve the dosage frequency. Hence, it is used in several fields such as dermatology, food, cosmetics, personal care, chemicals, etc. Novasomes may withstand some strain and therefore act accordingly. A lot of research is underway on this technology as an upheaval in liposome [6, 7].

Novasome can be said to have enhanced liposomal or niosome structure [8]. Liposomes are small sac-like structures that contain phospholipids as their monomeric units and they can be found in

series of sizes with either multilamellar or unilamellar construction, and its name refers to its structural building blocks—the phospholipids [9, 10]. They are spherical vesicles with a membrane made up of cholesterol and phospholipid bilayers, which can incorporate a lipid-soluble drug in between two lipid layers and can encapsulate an area of the aqueous solution inside a hydrophobic membrane core [11]. Niosomes are a multilamellar, non-ionic surfactant vesicular structure, similar to liposomes, composed of non-ionic surfactants rather than phospholipids, which are liposomes components. Because of the presence of non-ionic surfactant molecules, it can also entrap both water-soluble and water-insoluble drug molecules with greater intrinsic activity. Niosomes enhance the clinical efficacy of encapsulated drug substances by shielding the drug from extreme biological conditions, resulting in impeded clearance of the drug. Niosomes primarily comprise two categories of ingredients, i.e. additives and non-ionic surfactants. Niosomes have been widely researched in recent years for their ability to assist as a transporter for the transmission of antigens, hormones, drugs, and other bioactive agents. Niosomes have been used to address the issue of toxicity, insolubility, and accelerated product degradation [12].

The microvesicles of Novasome are immanently stable and are designed to be stable at a temperature that varies from liquid nitrogen to temperature above the boiling point of water and pH ranges from 2 to 13. Sustained-release action is offered by novasomes. The Novasome bilayers have no proper array of arrangements. Novasomes can sustain any charge, and can therefore work accordingly. For instance, if the charge on the microvesicle of the novasome is positive, then it can integrate with the hair, mucous membrane, or skin of negative charge. In addition to that, they can also adhere to hair shafts. Novasome improves treatment efficacy and efficiency with virtually no adverse effects. They are natural, and they do not cause cytotoxicity of any kind. Due to the wide range of pH provided by novasomes, they can be used for a broad range of applications. Novasomes can be formulated according to the action and level of absorption desired for release [13].

Novasome molecules have a hydrophilic head group linked to a hydrophobic tail group. These molecules comprise amino acids, glycerol-lipids, a long chain of fatty acids, and alcohol derivatives. They are normally prepared from a combination of free fatty acid, monoester of polyoxyethylene fatty acid, and cholesterol based on concentration. The novasome bilayer membranes are formed by a

wide range of biocompatible, solitary tailed amphiphiles and purposefully selected phospholipids. The tail of fatty acids pointed into the inside of the membrane, whereas the polar head groups pointed outward. During vesicle production, the hydrophilic molecules were admixed with water and placed in aqueous space between multiple layers of a lipid bilayer membrane, while the lipid-

soluble molecules were placed within the core of the vesicle. The bulk of the novosome vesicles are loaded with the amorphous core, which incorporates finely divided insoluble particles such as water-immiscible compounds, diamonds, and titanium dioxide [14]. The diagrammatic representation of the novosome structure is portrayed in fig. 1.

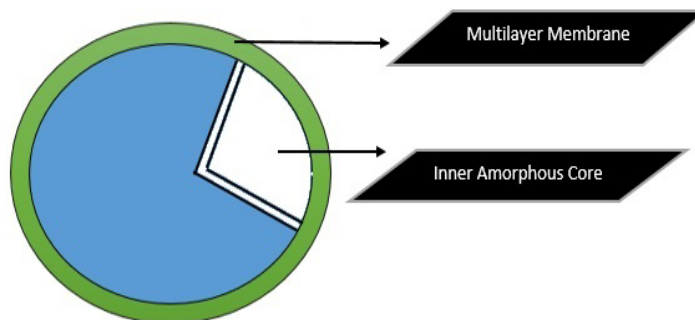


Fig. 1: Diagrammatic representation showing the structure of novosome [15]

Incompatibility issues in the usage of Novosome technologies can be solved by adding different medications within the bilayers. They are organic molecules and do not induce any sort of cytotoxicity. Novasomes may be designed at the optimal degree of release and absorption. Novasomes can be regarded as one of the most successful approaches for treating skin disorders. Novasomes are the altered forms of niosomes or a variation of liposomes that are prepared from the mixture of free fatty acids, cholesterol, and monoester of polyoxyethylene fatty acids at a 4/22/74 ratio. Their efficiency of encapsulation ranges from 85% for aqueous materials to 100% for groups that are present at one surface of the membrane point lipid moieties [16].

Characteristics of novosome

The following are the significant characteristics of novasomes;

- It may be stable over a broad pH range between 2 and 13.
- It is stable at a temperature between 0 and 100 degrees Celsius, i.e. from below the temperature of liquid nitrogen to above the temperature of boiling water.
- They have the benefit of providing more active ingredients in a limited volume.
- They can carry a negative, positive, and neutral charge.
- It ensures a uniform size distribution and therefore a uniform drug or active ingredient content.
- Up to 80-85 percent of the inner amorphous center can be filled with a medicinal drug.
- It provides a large capacity of the central core due to multi-bilayer vesicles [17].
- It prevents the skin from drying away.
- Its surface can be charged negatively, positively, or neutrally.
- It renders targeted and site-specific drug delivery [18].
- They have the potential to hold and release a significant amount of hydrophilic ingredients.
- The release rate is predictable.
- They can adhere to the hair shaft or skin, depending on the different circumstances of the surface load of the vesicle as well as the thickness of the skin [19].

Benefits of novosome over other vesicular drug delivery system

The following are the significant benefits of novasomes over other vesicular drug delivery system;

- To avoid incompatibility, drugs displaying interactions can be integrated in between bilayers of the novosome molecules.
- Both hydrophobic as well as hydrophilic ingredients can be introduced in the same formulation [20].
- Because of the characteristics of the surface charge, it can be made site-specific.
- It can adhere to the hair shaft or skin, depending on the various circumstances.
- It decreases product irritation and enhances product stability.
- It is cost-effective in contrast to liposomes and similar preparations.
- Residues are not left on the surface of the skin, and over a prolonged period of time, they are rehydrated.
- They have the ability to deliver a high amount of active ingredient because it possesses a loading efficiency of 80 %, thereby decreasing drug administration frequency also [21].

Mechanism of action of novosome

The bilayers of the novosome will not give an optimal array layout. It comprises channels (vacancies) that serve as a mechanism for transporting encapsulated constituents (fig. 2). Encapsulated constituents like active compounds (A) in the central core transit inside as well as between the individual bilayers (B) through a sequence of arbitrary leaps which allows the bilayer vacancies to move laterally. This enables the active substituents to be released continuously from the lipid bilayers via a watery suspension (C) dividing the membrane bilayers. The microvesicle layer can have a net charge of negative, positive, or neutral which regulates its function. The microvesicles having a positive charge, for example, can be combined with skin, mucous membranes, or hair charged negatively. Likewise, the arrangement of the vesicles of the novosome provides a continuous release system so that the active substance is released in a controlled manner [22].

Formulation of novasomes

A powerful shear system that yields greater shear rates is necessary for the preparation of novasomes. Micro fluidizers and French pressure cells are the systems used to formulate Novasomes. Other systems that achieve large shear levels and have the capacity to handle heated and semi-viscous lipids can also be utilized. Nowadays an innovative technology is used in novosome production. It contains a cylindrical blending compartment with a tangentially positioned inlet orifice [24]. All the other openings result in a storage tank that includes various phases. These comprise of the lipophilic and aqueous phase. When the storage tank is

attached to the pumps, a turbulent motion is generated inside the compartment.

Normally, the mix used here is a non-phospholipid surface-active, charge generating agent, an antioxidant, and a target molecule. The same mix is heated initially and then combined. This blend is once again mixed with an aqueous phase comprising an aqueous buffer and water-soluble collagen. The small vesicles are produced within

seconds and it is withdrawn from the compartment's axially positioned release orifice. An innovative technology for preparing the novasomes with N-acyl sarcosinates has now been developed. This technique has been employed for the distribution of emollients or aromatic oils in a regulated and sustainable manner [25, 26].

There are various techniques used in the formulation of novasome which are discussed below.

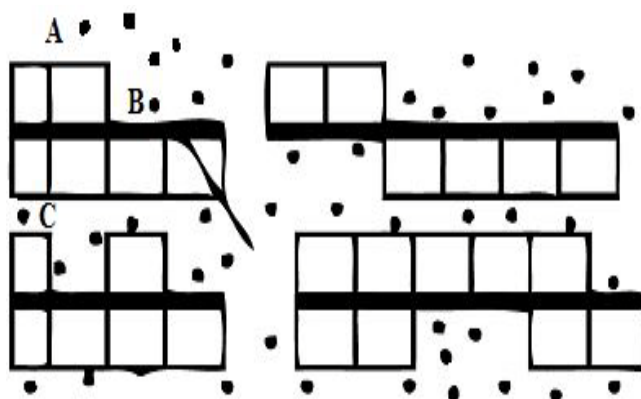


Fig. 2: Mechanism of continuous release of active moieties from novasome [23]

Ether injection method

Here Diethyl ether is mixed with the surface active agent by keeping a temperature of 60 °C. The said formulation is exposed to an aqueous drug solution with the aid of a 14-gauge needle injection. After ether vaporization vesicles having a single layer is obtained.

Micro fluidization method

This is the latest approach designed for the production of unilamellar vesicles with specified size allocation. This process is commonly employed in the formulation of niosomes. This process is concentrated on the theory of submerged jet principle, where two fluidized streams combine at high speeds, in clearly specified microchannels inside the compartment of interaction. Micro fluidization method results in the formation of uniform, reproducible and smaller Sized novasomes.

Handshaking method

It is also known as the thin-film hydration technique. Here the combination of vesicle-generating ingredients such as surfactant and cholesterol are incorporated in a round bottom flask of volatile organic solvents like diethyl ether, methanol, or chloroform. At room temperature (20 °C), the organic solvent is extracted by the means of a rotary evaporator that leaves a small film of the solid blend on the flask's wall. The extracted film of the surfactant is rehydratable and finally, it produces the characteristic multilamellar niosomes [27].

Multiple membrane extrusion methods

The combination of surface-active agent cholesterol and diacetyl phosphate in chloroform is transformed into a thin layer by evaporation. The thin layer is hydrated using a solution of aqueous drugs. The resulting suspension is now extruded via polycarbonate membranes. This is an excellent method to manage niosomal size.

Reverse phase evaporation technique (REV)

In REV, a combination of ether and chloroform dissolves the cholesterol and surface active agent. To this mixture an aqueous phase comprising the drug molecules are added and sonicate the following phases at 4-5 °C. Upon the introduction of a small quantity of phosphate-buffered saline, the transparent gel produced is again sonicated. Under low pressure, the organic phase is separated at 40 °C. Then the viscous suspension of the niosome developed is mixed with saline buffered with phosphate and heated at 60 °C in a water bath for 10 min to produce niosome.

Sonication method

Here the surfactant-cholesterol combination is initially dispersed in the aqueous phase. This mix is then sonicated at 60 °C for 10 min. It contributes to multilamellar vesicle (MLV) production. MLVs are further ultrasonicated by either a probe or a bath sonicator, this results in the production of unilamellar vesicles [28, 29].

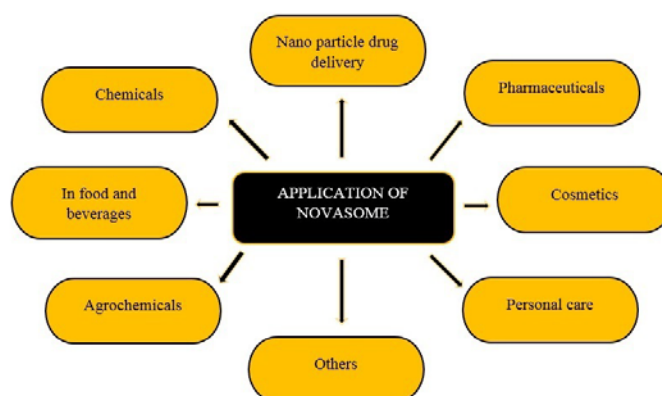


Fig. 3: Applications of novasomes [30]

Applications of novasomes

Novasomes are commonly used in the food, cosmetics, personal care, chemical, agrochemical, and pharmaceutical industries. The applications of the novasome are illustrated in fig. 3.

Through using non-phospholipid materials, novasomes aid in the increase of absorption rate over the topical application of cosmetics as well as pharmaceuticals. This benefits to maximize the potency of the formulation increases the site distribution of the medication, enhances the safety of the lively ingredient in the preparation. Novasome vesicles possess the capacity to preserve, carry, and distribute a range of nutrients, flavors, and oils such as active compounds that can castoff food and beverages. It can intensify properties such as consistency, flavoring, aroma, potency, protection, firmness, and other needed possessions of essential materials such as oils, flavorings, fragrances, etc. This technology can be used to produce diverse FDA-regulated products like human pharmaceuticals as well as vaccines. Drug delivery mechanisms use niosomes via transdermal, parenteral, and ophthalmic pathways are well studied. Niosomal transmission through transdermal routes is capable of overcoming the sluggish penetration rate of traditional transdermal approaches.

Marketed novasome formulation: Nonphospholipid paucilamellar lipid vesicles are marketed in the trade name Novasome (IGI Inc., Buena, N. J.). There are many novasome formulations on the market (e. g. Novasome A, Novasome D, Novasome Day Cream) containing skin-protective agents, oil, moisturizers, and skin-cleaners [31, 32].

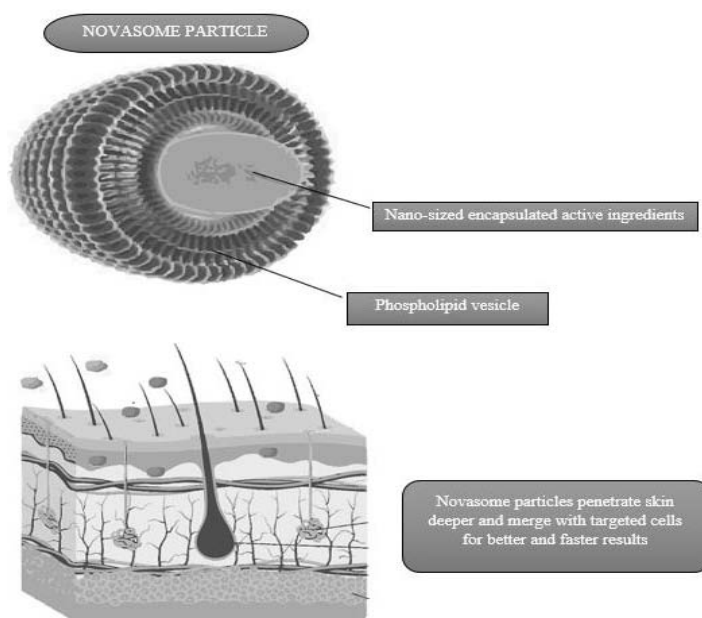


Fig. 4: Novasome penetration to the deepest layers of skin [39]

Novasome dermatological preparations developed at Cornell University have been tested in 2 usual clinical contexts. The initial research investigated the effectiveness of novasomes for cold, dog skin during winter based on and non-encapsulated emollients, where twenty dogs were administered two types of medication. Those outcomes revealed in 80 percent of the Dogs, the Emollient related Novasome was the top agent. Those research had shown that Novasome can act as potent Humectants. The later research analyzed shampoos based on Novasome and Non-Novasome containing benzoyl peroxide. Test effects revealed that novasome-built shampoos diminished scaling by 70 percent while Non-Novasome-built diminished scaling by just 20 percent [40].

Novasome-related extended-release veterinary medicines are also licensed for extended skin hydration and antipyretic agent transfer to pets. Continued discharge processing uses innovative

Some of the novasomal formulations, its ingredients, and its action are illustrated below:

- MPA Hydra-pearls (Novasome Microvesicles)-Humectant [33].
- Pramoxine HCl Novasome Microvesicles which is incorporated in MPA Dermal-Soothe Spray is intended for cell repair, antipruritic, humectant.
- 2.5% Benzoyl Peroxide; Novasome Microvesicles embodied as MPA Benzoyl-Plus are beneficial for keratolysis, bacterial infection, humectant, follicular flushing [34].
- Nova Pearls that are slow-release power moisturizers are geared towards deodorizer for maintenance of pets skin [35].
- Acne Worx that contains 2% salicylic acid is helpful to reduce acne blemishes and to avoid fresh pimples beforehand.
- MPA Miconazole Shampoo which consists of 1% Miconazole Nitrate, a Novasome Microvesicles are aimed at fungal infection, Antibacterial, Keratolytic, Keratoplastic [36, 37].

Recent advances in novasome technology

Recent developments in innovative skills allowed novasome to be tested for encapsulation, flavor, and as adjuvants in vaccine research, and in the sophisticated derma cosmetic technology that extends the dermatology boundaries and is clearly depicted in fig. 4. Not only can novasome vesicles quickly pierce the innermost layers of the skin, but also penetrate as pre-programmed into the desired cell [38].

microvesicles to condense moisture to achieve hydrating results when applying the skin, shampoo, and sprays. These non-ionic vesicles of glyceryl dilaurate using polyoxyethylene-10-stearyl ether as well as cholesterol are identified to spread larger quantities of cyclosporine in as well as over the mouse skin than vesicles based on ceramide or phosphatidylcholine [41, 42]. As a lotion or cream, it has been found to be beneficial for topical delivery into the damaged area. Studies displayed novasome skill has the better quality for the localized transport of H₂ antagonists for the treatment of parodontal ailment because of augmented local absorption of H₂ antagonists and increased action of drug [43]. This will also be utilized in treating inflammatory skin and other conditions.

This knowledge is widely utilized in vaccine grounding [44, 45]. A smallpox vaccine centered on Novasome had been established. The new novasome-centered vaccine is also in advancement. For the

control of the Avian Rheovirus and New Castle Disease virus species, novasome-centric vaccines were cast-off. Novasome microvesicles deactivate viruses like coronaviruses, orthomyxoviruses, retroviruses, and paramyxoviruses by mixing them immediately after union with the enclosed virus and the nucleic acid virus. The novasomes can be transmitted as an adjuvant in vaccines. Novasomes were recognized to be a powerful adjuvant for human vaccines (aluminum phosphate) when Gupta *et al.* [46] tested Novasome made from oleic acid, cholesterol, and dioxyethylene cetyl ether with tetanus toxoid and diphtheria toxoid. Chambers *et al.* [47] established that they were secured from fatal tuberculosis by a single dose of formalin impaired BCG assorted with Novasome when directed to guinea pigs as a single subcutaneous injection. Another method patented included the preparation of the surfactant-containing novasome (NONOXYNOL-9) which are latex compliant and for inactivation of enveloped viruses and spermatozoa in touch. Usage of Wright [48] oral vaccines to prevent gram-negative bacterial infections by novasome-WFI diluents (paucilamellar, non-phospholipid encapsulated cherry oil). Novasome lipid vesicles are combined with WFI in the preparation for an oral vaccine in a ratio of Novasome: WFI 1:32(v/v) to conserve 99.2 percent of water.

Pushko *et al.* have utilized the Novasome microvesicles as a candidate for avian influenza as an adjuvant of the influenza virus, including particulates [49]. Holick *et al.* successfully encapsulated the Parathyroid hormone analog PTH (1-34) in Novasome cream, improved the absorption of this peptide product into the human skin. The erythema and scaling of the psoriatic lesions, with the usage of PTH (1-34) disclosed clear expansion. There was major progress in erythema and scaling of the psoriatic lesions treated with PTH (1-34) [50]. This was the first proof that a peptide drug was successfully formulated to treat skin diseases [51]. Minoxidil's topical formulation has been improved by creating it further hydrophilic by using novasome microvesicle as well as organic acid, or a base like lactic acid. Fuels combined with patented lipid vesicles, dispersion-assistant molecules have been used to transport water as well as water-soluble fuel additives in fuels and have improved performance characteristics compared to traditional fuels [52]. Novasomes indicate higher tolerance to acidity, alkalinity, and temperature. Often, goods could be combined effortlessly by using those tools. Some of the currently available marketed products of novasome are listed below in table 1.

Table 1: Currently available marketed products of novasome

S. No.	Marketed formulation	Manufacturing company	Applications	References
1.	Novasomes	Neutrogena, Estee Lauder, Pierre Fab	It is used in cosmetics.	[53]
2.	Moisturizing cream and gel in its popular Water Bank products line	Amore Pacific	It is used for body skin.	[53]
3.	Acne-worx	Dermworx	It is used in adult acne product.	[54]
4.	Retinoid products	Johnson and Johnson	It is mainly used for skin care.	[55]
5.	Icy Hot cream, patches and lotions	Chattem Pharmaceuticals	It is used as a line of over the counter pain therapy.	[56]
6.	Skincare products	Dermatology Associates of Georgia	It is used for care.	[57]
7.	MIAJ anti-wrinkle cosmetics	IGI	It is used in cosmetics.	[58]
8.	Pharmaceuticals, grooming and vaccines	Vetoquinol USA	It is used for animal care.	[58]
9.	Relieva cream, shampoo and lotions	Apollo Pharmaceuticals	It is mainly used for the treatment of psoriasis.	[59, 60]

CONCLUSION

Various studies have concluded that novel technology has shown more product strength, the half-life rises from weeks to years at times, prevents oxidation and emulsification, and also license the shielding of antagonistic components in the formulation till usage. Besides, novasomes allow the regulation of the release of lively elements overpressure, heat, and/or time. Time-release is exclusively advantageous as it has been revealed to be highly effective and slightly a few harmful effects than medicines which at one time dump a full dose on the skin. Trapping efficacy has been shown. The marginal cost of fabricating goods using novasomes is negligible. Any proprietary evidence shows its widespread use in pharmaceuticals, milk, agrochemicals, and so on. Through the use of advanced technology, numerous dermatological therapies have exposed new progress in their efficiency. Continuous progress is being made in the innovative technology market. A variety of novasome-based products are in development for market access.

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CONFLICT OF INTERESTS

There is no conflict of interest.

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