PDEAS International Journal of Research in Ayurved and Allied Sciences
Volume 4 Issue 1; 28th February 2022 ISSN (online): 2583-2018

PDEAS International Journal of Research in Ayurved and Allied Sciences

Review Article

Hybrid drug delivery system by integrating controlled and targeted drug delivery system: A systematic review

Parijat Suryawanshi[1], Bhavana Sakpal[1], Shubhangi Karkhile[1], Amit Kasabe[2*], Vijaya Barge[3], Ashok Bhosale[3]
P. G. Scholar[1], Associate Professor[2], Professor[3]

PDEA's Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Kharadi, Pune, Maharashtra, India.

Article Received on: 24/11/2021; Accepted on: 09/02/2022
***Corresponding Author:** *Dr. Amit Kasabe*, **E-mail:** amitkasbe@pdeasubpharm.edu.in

ABSTRACT:

Targeted and regulated medication delivery systems are intended to release pharmaceuticals over time and at a specified location. The goal is to achieve a steady (zero-order) rate of medication release over a lengthy period of time. Thus, medicinal effectiveness may be improved while side effects are minimized. Using a unique drug delivery technology, a controlled release of the medication or encapsulated bioactive might be accomplished. The pharmacokinetics and pharmacodynamics of a medicine will improve if the release pattern is optimized. Targeted drug delivery, on the other hand, is a method that introduces the drug moiety directly into the targeted location of the body in order to avoid the particular adverse effects of traditional drug administration and hence reduce the quantity of medication necessary for therapeutic effectiveness. These innovative medication delivery methods have high efficacy and require precise targeting of the target region. Conventional immediate-release dose forms are used to provide the vast majority of medications. They spread throughout the body and accumulate in non-targeted tissues, resulting in unpleasant side effects. A proper carrier system is thus a must in order to minimize these adverse effects and maximize the therapeutic advantages of the drugs. For this objective, innovative carriers have been devised. Hybrid delivery systems are explored in this study in terms of the elements that contribute to their optimal response characteristics and their possible applications.

KEY WORDS: Hybrid drug delivery system, controlled drug delivery system, targeted drug delivery system

INTRODUCTION:

Controlled drug delivery systems are intended to distribute medications gradually over a period of time. The goal is to maintain a steady (zero-order) rate of medication release over an extended period of time. A controlled drug delivery system aims to deliver the proper dosage of a therapy to the intended location and at the right time. A therapeutics effectiveness may be improved while side effects are reduced as a result. It is possible to establish a controlled release of a medicine by adopting innovative drug delivery systems. Drugs with a desired release pattern will have better pharmacokinetics and pharmacodynamics.[1]

Medication moiety is introduced directly into the targeted location of the body to avoid particular adverse effects of traditional administration, and so reduces the quantity of drug that is needed for therapeutic effectiveness by a significant amount.

Because of their efficacy (limited therapeutic window), these recently discovered drug delivery systems must be targeted to specific sites of action. Conventional immediate-release dose forms are used for the majority of medicines. Side effects may occur because they spread throughout the body and accumulate in non-targeted tissues. There should be a proper carrier system in place to carry these drugs to

their target sites in order to minimize adverse effects and maximize therapeutic efficacy. New carriers have been created for this purpose. There follows a short discussion of these and other commonly used drug carriers for the same purpose.[2]

A. Niosomes

Liposomes may be replaced with niosomes, which are non-ionic surfactant-based vesicles that are biodegradable, non-toxic, more stable, and less costly. As a result of their ability to encapsulate both hydrophilic and hydrophobic compounds with equal effectiveness in non-ionic surfactant-based vesicles, which are also known as niosomes, they have garnered considerable interest in the pharmaceutical industry. When non-ionic surfactants of the alkyl or dialkyl polyglycerol ether family are combined with cholesterol, tiny lamellar structures are generated. [3]

***Advantages*[4,5]**

1. One of the benefits of niosomes is that they are very stable, cost effective, and simple to create and scale up.
2. Non-ionic surfactants, which are used to produce niosomes, are more stable than lipids in terms of both physical and chemical stability.
3. Third, niosomes may be used for the aim of stabilizing and enhancing therapeutic effectiveness by encapsulating various types of medicines.
4. By allowing M cells from Peyer's patches in the intestinal lymphatic tissues to transcend the anatomical barrier of the gastrointestinal tract, it increases bioavailability.
5. The vesicle's size, lamellarity, and other features may be altered to meet the needs of the experiment.
6. Drugs in the vesicles may be stored and released over time in a regulated manner.
7. Hydrophilic, lipophilic, and amphiphilic drug moieties may all fit into the niosome structure, making them suitable for a wide range of medications.
8. Water-based vesicle suspensions are more patient-friendly than oil-based ones.
9. Their osmotic activity and stability are both excellent.
10. They improve the drug's stability by encasing it in a more durable shell. Skin penetration of medications may be improved.

***Pharmaceutical Application*[6-8]**

1. Many pharmacological agents may benefit from niosomal drug delivery, which might be used to treat a wide range of disorders.
2. To build a unique medication delivery system, it may be employed as the vehicle for poorly absorbed medicines.
3. Antigen-induced immune responses have been studied using niosomes.
4. As a carrier for haemoglobin, niosomes may be used.
5. Furthermore, niosomes offer a number of features that make them a viable choice for a wide range of applications.
6. Sodium stibogluconate, for example, is used to treat dermal and mucocutaneous infections caused by the parasite Leishmania donovani.
7. Hemoglobin Carriers in Niosomes.
8. In addition, it is utilized to deliver Peptide Drugs to patients.
9. The hemoglobin-carrying capacity of niosomes has been shown.
10. It is used in immunological research.
11. Niosome-Based Transdermal Drug Delivery Systems.
12. It is used in the delivery of ophthalmic drugs.
13. As diagnostic agents, the niosomal system may be used.

***Structure*[8]**

An amphiphilic surfactant, such as Span-60, is often used to generate a conventional niosome vesicle, which is then stabilized by the addition of cholesterol and a tiny quantity of anionic surfactant, such as dicetyl phosphate. There is a hydrophilic portion of the nonionic surfactants and a hydrophobic portion of them. Niosomes are made using two primary components:

1. Cholesterol
2. Nonionic surfactant

Cholesterol

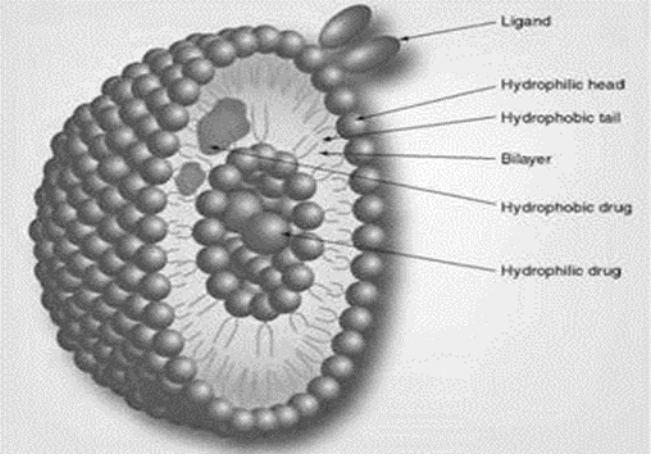
Niosomes are made of cholesterol, a steroid derivative, which is employed to provide them stiffness and the correct shape, conformation.

Nonionic surfactants

The following non-ionic surfactants are generally used for the preparation of niosomes.

e.g. Spans (span 60, 40, 20, 85, 80), Tweens (tween 20, 40, 60, 80), Brijs (brij 30, 35, 52, 58, 72, 76)

Figure No. 1: Niosomes



Types

Based on the vesicle size, niosomes can be divided into three groups.

1. Small unilamellar vesicles (SUV, size=0.025-0.05 µm),
2. Multilamellar vesicles (MLV, size=>0.05 µm)
3. Large unilamellar vesicles (LUV, size=>0.10 µm).

***Methods of Preparation*[9,10]**

These niosomes may be made in a variety ways depending on the size, location, and quantity of double layers of niosomes, as well as their capacity to be trapped and permeable.

Preparation of small unilamellar vesicles

a. Sonication

In a scintillation vial, the aqueous phase containing the medication is introduced to the surfactant and cholesterol combination. For three minutes, a sonic probe heated to 60°C homogenises the liquid. These compact, homogeneous vesicles are typical of the genus.

b. Micro fluidization

In the interaction chamber, two fluidized streams go through a carefully defined micro channel and interact at very high velocities. Using a shared gateway, energy may be given to the system while avoiding interference with niosome creation. As a consequence, the product has improved consistency, reduced overall size, and is easier to replicate.

Preparation of multilamellar vesicles

a.* Hand *shaking method (Thin film hydration technique)

Surfactant and cholesterol are dissolved in a volatile organic solvent such as diethyl ether, chloroform, or methanol in a rotary evaporator using the hand shaking technique, leaving a thin coating of solid mixture on the flask wall. Dry layer is hydrated with drug-containing aqueous phase with moderate agitation at room temperature.

b.* Trans-*membrane pH gradient (inside acidic) drug uptake process (remote Loading)

Chloroform is used to dissolve surfactant and cholesterol. Under decreased pressure, the solvent is then evaporated to leave a thin layer on the round-bottom flask's wall. Vortex mixing is used to hydrate the film with 300 mM citric acid (pH 4.0). Sonication of the multilamellar vesicles is performed three times after they have been frozen and thawed. A niosomal suspension containing 10 mg/ml of the medication is added to the aqueous solution and vortexed. Using 1M disodium phosphate, the pH is then increased to 7.0-7.2. The resulting multilamellar vesicles are then heated to 60°C for 10 minutes.

Preparation of large unilamellar vesicles

a. Reverse phase evaporation technique (REV)

Cholesterol and surfactant are dissolved in an ether-chloroform solution in this procedure. Addition of a drug-containing aqueous phase is followed by sonication at 4-5°C of the resultant two phases. After a little quantity of phosphate buffered saline is added to the clear gel, it is sonicated again. At a temperature of 40°C and low pressure, the organic phase is eliminated. To make niosomes, dilute the viscous niosome solution with phosphate-buffered saline and heat it for 10 minutes in a water bath at 60°C.

b. Ether injection method

Slow injection of niosomal components in ether using a 14-gauge needle into a warmed aqueous phase maintained at 60°C is the basis of the ether injection technique. The sluggish vaporization of solvent leads in an ether gradient that extends toward the aqueous/non-aqueous boundary, resulting in bigger unilamellar vesicles. The creation of the bilayer structure may be attributable to the former. The method's drawback is that a trace quantity of ether is typically found in the vesicles suspension, making cleanup a challenge.

B. Ethosomes

To transfer medications to the deeper layers of the epidermis and/or the systemic circulation, ethosomes are soft, flexible vesicles. Ethosomes may be as small as nanometers or as large as microns (μ). "Ethosomes are liposomes containing ethanol." Pharmaceuticals may be delivered using ethosomes, which are noninvasive delivery systems that allow them to penetrate deep into the skin and/or the bloodstream. Active drugs may be delivered more effectively with the use of these soft, flexible vesicles. Ethosomes are liposomes that have been somewhat tweaked. Ethosomes are lipid vesicles that contain phospholipids, high concentrations of alcohol (ethanol and isopropyl alcohol), and water. Polyethylene glycol (PEG) and water are the main components of soft vesicles called ethosomes that are composed of phospholipids and alcohol. Because of their smaller size, ethosomes may pass through the skin layers much more quickly and have a greater transdermal flux. The ethosome size ranges from 10 nanometers (nm) to microns (μ). [11-13]

***Advantages*[12]**

1. Large molecules (peptides and protein molecules) may be delivered.
2. It is made from non-toxic raw materials.
3. For transdermal medication administration, improved drug penetration through the skin is needed.
4. A broad range of pharmaceutical, veterinary, and cosmetic industries may benefit from the Ethosomal drug delivery technology.
5. Ethomal drugs are administered as gel or cream, which means that patients are more likely to comply with their treatment regimens.
6. Iontophoresis, Phonophoresis, and other more sophisticated drug delivery systems pale in contrast to this straightforward approach.
7. As a passive, non-invasive device that is immediately accessible for commercialization, the Ethosomal system has several advantages.

Disadvantages [14]

1. Fast bolus-type drug intake is not the goal of ethosomal administration; rather, it is intended to provide delayed, sustained drug delivery.
2. Enough lipid and water solubility for the medication to penetrate the dermal microcirculation and enter systemic circulation.

3. The drug's molecular size must be appropriate in order for it to be absorbed via the skin.
4. Some kinds of skin may not be well-suited for adhesive application.
5. There may not be a financial benefit to this.
6. Poor return on investment.
7. Excipients and enhancers in medication delivery systems may cause dermatitis or irritation of the skin.
8. It is possible that the ethosomes will consolidate and subsequently disintegrate if the shell locking mechanism is not functional.
9. When moving from organic to water medium, there is a loss of product.
10. The main advantage of ethosomes over liposomes is that the drug is more easily absorbed.

Applications of Ethosomes

1. Delivery of Anti-Viral Drugs
2. Topical Delivery of DNA
3. Transdermal Delivery of Hormones
4. Delivery of anti-parkinsonism agent
5. Transcellular Delivery
6. Delivery of Anti-Arthritis Drug
3. Delivery of Antibiotics

Composition [12]

A high quantity of ethanol and water are found in ethosomes, which are mostly constituted of phospholipids (phosphatidylcholine, phosphatidylserine, and phosphatitidic acid). Between 22 and 70% of the mixture is in the nonaqueous phase. Ethanol or isopropyl alcohol are both acceptable choices for the alcohol. Incorporating large levels of ethanol into a vesicle membrane allows the ethosomes to enter the stratum corneum, which is known to disrupt the skin's lipid bilayer architecture. Stratum corneum lipids benefit from a more pliable lipid membrane structure due to the higher ethanol content, which also makes them less densely packed than traditional vesicles.

Methods of preparation of Ethosomes[14-16]

Ethosomes can be prepared by two very simple and convenient methods that is;

a. Cold method

b. Hot method

a. Cold Method

For the production of ethosomal formulation, this is the most usual procedure. Phospholipid, medication, and other lipid components are mixed with ethanol at room temperature in a closed container and mixed vigorously with a mixer in this procedure. While the mixture is being stirred, a polyol such as propylene glycol or another is added. It is heated in a water bath to 30^0C. For 5 minutes, the mixture is agitated in a covered jar with 30^0C water heated in a separate pot. Sonication or extrusion may be used to reduce the ethosomal formulation's vesicle size to the desired extent. Finally, the mixture is kept in the refrigerator.

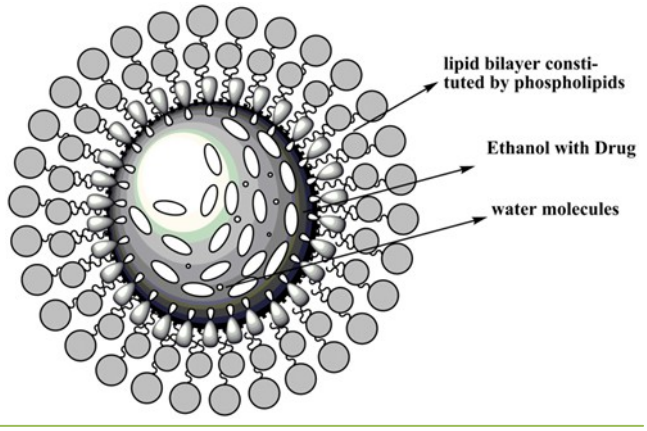
b. Hot Method

By heating the water bath to 40^0°C, phospholipids are dispersed into a colloidal solution. Ethanol and propylene glycol are combined in a separate vessel and heated to 400°C. At 400 degrees Celsius, the aqueous and organic phases are combined. According to the hydrophilic/hydrophobic qualities of the medication, it is dissolved in water or ethanol. Probe sonication or extrusion may be used to reduce the size of ethosomal formulation vesicles.

Structure

Phospholipid-based Ethosomes are made up of numerous concentric layers of flexible phospholipids that contain 20 to 45 percent alcohol, glycols, and water. By ^{31}P-NMR, EM, and DSC, it has been shown that their general structure is correct.

Figure No. 2: Ethosomes



C. Transfersomes

It is a vesicular carrier system containing at least one inner aqueous compartment that is encompassed by a lipid bilayer, along with an edge activator. Transfersome is a complex aggregation that is extremely flexible and sensitive to stress. As an ultra-deformable vesicle, it's ideal for transporting water and lipid bilayers. Local composition and the form of the bilayer are interdependent, which makes the vesicle self-regulating and self-optimizing at the same time. This makes it possible for the Transfersome to easily traverse a variety of transport obstacles and operate as a Drug carrier for non-invasive targeted drug administration and sustained release of therapeutics.[17]

Advantages[18,19]

a. Hydrophilic and hydrophobic moieties combine in the transfersomes carriers to provide an innovative drug delivery system capable of delivering therapeutic drugs with a broad range of solubility.
b. Due to their ultra-deformability and elastic qualities, transfersomes may squeeze themselves through skin barrier constrictions that are as small as 5 to 10 times the vesicle width.
c. When medications are transported through skin without any loss in intact vesicles, they may be employed for both topical and systemic therapy.
d. A wide range of agents, practically regardless of their size, structure, molecular weight or polarity may be accommodated by transfersomes carriers.
e. Biocompatible and biodegradable due to their inherent phospholipid and EA composition.
f. Proteins and peptides, insulin, corticosteroids and interferons, as well as NSAIDs, anticancer drugs and herbal medicines can all be delivered via transfersomes.
g. When it comes to creating long-acting drug delivery systems, transfersomes are the logical option.
h. They may enhance bioactive agent site selectivity and transdermal flow by up to eightfold.
i. Optimized bioavailability of the medicine by eliminating the first-pass metabolism, which is a key disadvantage of oral drug delivery.
j. In addition, the use of medications with short half-lives may help reduce unwanted side effects and keep the drug safe from metabolism.

Disadvantages[18]

1. Due to their oxidative breakdown, transfersomes are considered chemically unstable. Using nitrogen and argon as inert gases, degassing and purging aqueous media may considerably reduce the oxidation of transfersomes. Oxidation may be minimized by low-temperature storage and light protection. Transfersomes' storage stability may be improved by post-preparation processing such as freeze-drying or spray-drying.
2. A second problem with using transfersomes as a medication delivery mechanism is that natural phospholipids are difficult to purify. Alternatives to natural phospholipids include synthetic versions.
3. Transfersomal formulations are costly because of the raw ingredients used in lipid excipients and the expensive equipment required to expand manufacture. As a result, phosphatidylcholine is the most often utilized lipid component due to its inexpensive cost.

Composition [17-19]

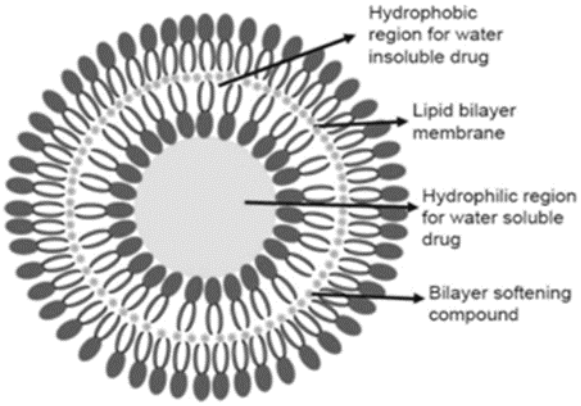
The transfersome is composed of two main aggregates namely,

1. Phosphatidylcholine, for example, is an amphipathic component that, when mixed with water, forms the bilayer of the simple lipid vesicle.
2. Lipid bilayer flexibility and permeability are considerably improved by adding a bilayer softening component (such as a biocompatible surfactant or an amphiphile medication).

Transfersome vesicles are consequently able to quickly and readily alter their form to the environment by modifying the concentration of each bilayer component in response to local

stress. As a result, the Transfersomes "softer," more malleable, and better modifiable artificial membrane sets it apart from more traditional vesicles.

Figure No. 3: Transfersome



Applications

1. As a transporter for proteins and peptides, transfersomes have been employed extensively.
2. Transferosomes are a non-invasive method of using big molecular weight medicines on the skin for medicinal purposes.
3. A naturally occurring protein called leukocytic derived interferone- (INF-) has antiviral, antiproliferative, and immunomodulatory properties, and has been employed as a transferosome carrier.
4. Corticosteroids have also been delivered via transferosomes.
5. Under the right circumstances, anesthetics suspended in highly deformable vesicles, such as transferosomes, may produce topical anesthesia in less than 10 minutes.
6. Transdermal administration of anti-cancer medications like methotrexate has been attempted via transfersome technology. The outcomes were positive. This was a novel method to skin cancer therapy, in particular.

D. Virosomes

An unilamellar membrane phospholipid vesicle (either mono- or bi-layer) containing virus-derived proteins is a virosome, which is a medication or vaccine delivery method.

Flu virus fusion proteins are embedded in lipid membranes of virosomes, which are tiny spherical vesicles. The size of the particle is in the 120-180 nm region. Reconstituted influenza virus virosomes lack the nucleocapsid, which contains the original virus's genetic material, and are so called "virosomes." Virosomes are fusion-active vesicles that cannot be replicated. Natural phospholipids (PL) and phosphatidylcholine (PC) are the primary components of immunostimulating reconstituted influenza virosomes (IRIVs) (PC). About 70% of the virosomal structure is made up of phosphatidylcholine. In addition to the neuraminidase (NA) and haemagglutinin (HA) glycoproteins, the influenza virus's envelope phospholipids account for the remaining 30% of the membrane components. [20]

Advantages[21,23]

a. This technology has been authorized by the FDA and has a high level of safety for use in people.
b. Virosomes, on the other hand, are non-toxic, biocompatible, and degradable.
c. There is no danger of disease transmission.
d. no autoimmunity or anaphylaxis are present.
e. widely applicable to practically all of the most essential pharmaceuticals (anticancer drugs, proteins, peptides, nucleic acids, antibiotics, fungicides).
f. the target cell's cytoplasm, allowing for medication administration to occur.
g. According to FDA approval and a strong safety profile of Virosomal technology, it can be used in people.
h. Prevents the deterioration of medicines.
i. I Delivery of antigens to particular locations inside the body and amplification of the immune system.
j. Enhance endosomal fusion activity.
k. Virosome allows for a modular vaccination schedule tailored to each patient.

Application

1. To reach their target cells, virosomes transport antigens and therapeutic substances.
2. As immunopotentiating agents, virosomes may also be used to deliver drugs to specific locations.
3. Virosomes, as immunopotentiating substances, trigger both cell-mediated and humoral immune responses.

4. IV, Oral, intramuscular, and topical modes of administration are used to give saline buffered virosomes.
5. Tissue-associated antigen peptides have also been employed in the cancer field using Virosome carriers (TAA).

Properties of Virosomes [22]

Virosomes are non-toxic, biodegradable, and biocompatible. It is possible for an antigen to be cross-linked to lipid moieties and then integrated into the virosome membrane through hydrophobic domains or lipid moieties. Vaccine studies on HIV-1 may also use them. Virosomes used as a medication delivery system for cancer treatment trials.

Structure

Unilamellar virosomes have a diameter of around 150 nm and are round, spherical vesicles. For the creation of virosomes, influenza virus is the most usually utilized. Virosomes are fusion-active vesicles that cannot be replicated. Influenza hemagglutinin (HA) and neuraminidase (NA) are intercalated inside the phospholipid bilayer membrane of virosomes, unlike liposomes. The choice of bilayer components has a significant impact on the further features of virosomes. A variety of membrane lipids may be utilized to optimise virosomes for maximum medication integration or the optimum physiological benefit. In fact, carriers for antisense oligonucleotides and other genetic molecules may be generated depending on whether the membrane incorporates positively or negatively loaded phospholipids. An array of molecules, including monoclonal antibodies (MAbs), may be integrated into the virosomal surface and exhibited on the virosomal surface. For targeted delivery, virosomes may also be used to join tumor-specific monoclonal antibody fragments (Fab). [21-23]

Method of Preparations[24]

a. Selection of virus for virosomes

It is possible for virosomes to be generated from a variety of viruses. Influenza virus envelope is the most common source of virosome, although other viruses, including as Sendai, Epstein-burr, HIV, sindbis, semliki-forest, friend murine leukaemia, herpes simplex, and Newcastle disease, may also provide virosome.

b. Selection of antigen for virosomes

Antigens are chosen in accordance with our specifications. Antigens include parasites, cancerous cells, bacteria, and entire cells. DNA, RNA, and plasmids are examples of cell components that may be utilized as antigens. Virosomes may be loaded with these antigens since lipid anchors have been attached to them.

c. Reconstitution of virosome

Detergents octaglucoside, triton X-100, and nonidert p-40 were used to dissolve the virosome. Internal viral proteins and genetic material are dissolved in detergent, and then the detergent is extracted from the supernatant using dialysis and hydrophobic resins. The viral matrix protein and nucleiocapsid are then extracted by an ultracentrifugation procedure. Supernatant contains 82 percent of the viral phospholipids and viral protein. Only the viral envelope protein is found in the protein isolated from the supernatant. An already-coupled antigen is combined with polymer or surfactant solution and the resulting virosome carrier solution is processed to produce an antigen-bound virosome.

Characterization of Virosomes

a. Protein detection

SDS-PAGE can validate the presence of hemagglutinin (HA) protein in virosomes because of the typically homogeneous protein-to-lipid ratio produced during the virosome preparation process.

b. Structure and size

Virosome structure and size may be determined using electron microscopy using negative staining. To minimize acid-induced conformational changes in hemagglutinin, neutral pH staining solutions should be used (HA).

c. Fusion activity

The pH-dependent membrane fusion activity of virosomes is identical to that of natural influenza viruses. A fluorescence resonance energy transfer test is used to detect the fusion of virosomal membranes with either biological or artificial target membranes (RET). An excimer test utilizing pyrene-labeled lipids may be used to measure fusion in vitro, and a drop in surface density of the pyrene-phosphatidylcholine-label on fusing with an unlabeled membrane correlates to a reduction in excimer fluorescence.

CONCLUSION:

Procedures to enable may be delivered over time and at a specific location using drug delivery systems. Because of their tremendous effectiveness, these new techniques of administering medicine need precise localization. The overwhelming majority of drugs are delivered in conventional, immediate-release dosage forms. Unpleasant side effects are the outcome of their widespread distribution and accumulation in tissues other than the ones intended for their intended use. To reduce these side effects and optimise the therapeutic benefits of the medications, a good carrier system is essential. Various aspects that contribute to the best response qualities and potential uses of hybrid delivery systems are examined.

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

REFERENCES:

[1] Kazi, K. M., Mandal, A. S., Biswas, N., Guha, A., Chatterjee, S., Behera, M., & Kuotsu, K. (2010). Niosome: a future of targeted drug delivery systems. Journal of advanced pharmaceutical technology & research, 1(4), 374.

[2] Khar, R. K. (2013). Lachman/Liebermans: The theory and practice of industrial pharmacy. CBS Publishers &Distributor, Mumbai.

[3] Ge, X., Wei, M., He, S., & Yuan, W. E. (2019). Advances of non-ionic surfactant vesicles (niosomes) and their application in drug delivery. Pharmaceutics, 11(2), 55.

[4] Sharma, D., Ali, A. A. E., &Aate, J. R. (2018). Niosomes as novel drug delivery system. PharmaTutor, 6(3), 58-65.

[5] Arunachalam, A., Jeganath, S., Yamini, K., &Tharangini, K. (2012). Niosomes: a novel drug delivery system. International journal of novel trends in pharmaceutical sciences, 2(1), 25-31.

[6] Lohumi, A. (2012). A novel drug delivery system: niosomes review. Journal of drug delivery and therapeutics, 2(5).

[7] Sharma, R., Dua, J. S., Prasad, D. N., & Hira, S. (2019). Advancement in novel drug delivery system: niosomes. Journal of Drug Delivery and Therapeutics, 9(3-s), 995-1001.

[8] Shaji, J., & Shah, A. (2015). Niosomes: A novel drug delivery system. World J Pharm Res, 4(06), 853-76.

[9] Rajera, R., Nagpal, K., Singh, S. K., & Mishra, D. N. (2011). Niosomes: a controlled and novel drug delivery system. Biological and Pharmaceutical Bulletin, 34(7), 945-953.

[10] Nasir, A., Harikumar, S. L., &Amanpreet, K. (2012). Niosomes: an excellent tool for drug delivery. international journal of research in pharmacy and chemistry, 2(2), 479-487.

[11] Jain, H., Patel, J., Joshi, K., Patel, P., &Upadhyay, U. M. (2011). Ethosomes: A novel drug carrier. International Journal of Clinical Practice, 7(1), 1-4.

[12] Patrekar, P. V., Inamdar, S. J., Mali, S. S., Mujib, M. T., Ahir, A. A., &Hosmani, A. H. (2015). Ethosomes as novel drug delivery system: A review. The Pharma Innovation, 4(9, Part A), 10.

[13] Shabreen, M. R., &Sangeetha, S. (2020). Ethosomes: A novel drug delivery system and their therapeutic applications-A review. Research Journal of Pharmacy and Technology, 13(4), 1970-1978.

[14] Das, S. K., Chakraborty, S., Roy, C., Rajabalaya, R., Mohaimin, A. W., Khanam, J., & David, S. R. (2018). Ethosomes as novel vesicular carrier: An overview of the principle, preparation and its applications. Current drug delivery, 15(6), 795-817.

[15] Kumar, N., Dubey, A., Mishra, A., & Tiwari, P. (2020). Ethosomes: A Novel Approach in Transdermal Drug Delivery System. International Journal of Pharmacy & Life Sciences, 11(5).

[16] Aggarwal, D., &Nautiyal, U. (2016). Ethosomes: A review. Int J pharm med res, 4(4), 354-63.

[17] Benson, H. A. (2006). Transfersomes for transdermal drug delivery. Expert opinion on drug delivery, 3(6), 727-737.

[18]Jain, S., Jain, P., Umamaheshwari, R. B., & Jain, N. K. (2003). Transfersomes—a novel vesicular carrier for enhanced transdermal delivery: development, characterization, and performance evaluation. Drug development and industrial pharmacy, 29(9), 1013-1026.

[19]Walve, J. R., Bakliwal, S. R., Rane, B. R., & Pawar, S. P. (2011). Transfersomes: A surrogated carrier for transdermal drug delivery system.

[20]Kaneda, Y. (2000). Virosomes: evolution of the liposome as a targeted drug delivery system. Advanced drug delivery reviews, 43(2-3), 197-205.

[21]Singh, N., Gautam, S. P., Kumari, N., Kaur, R., & Kaur, M. (2017). Virosomes as novel drug delivery system: an overview. PharmaTutor, 5(9), 47-55.

[22]Kalra, N., Dhanya, V., Saini, V., &Jeyabalan, G. (2013). Virosomes: as a drug delivery carrier. American Journal of Advanced Drug Delivery, 1(1), 29-35.

[23]Babar, M. M., Najam-us-Sahar Sadaf Zaidi, A., Kazi, G., &Rehman, A. (2013). Virosomes-Hybrid drug delivery systems. Liposome & Nanotechnology, 415.

[24]Sen, R., Gupta, R., Singh, S., Mantry, S., & Das, S. (2017). A Review on Cubosome and Virosome: the novel drug delivery system. UJPSR, 3(1), 24-33.

Cite this article as:

Parijat Suryawanshi, Bhavana Sakpal, Shubhangi Karkhile, Amit Kasabe, Vijaya Barge, Ashok Bhosale, Hybrid drug delivery system by integrating controlled and targeted drug delivery system: A systematic review, PDEAS Int. J. R. Ayu. & A. Sc., 4(1); Feb 2022, p. 18-27.