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ELASTIC VESICLES IN DERMATOLOGICAL AND TRANSDERMAL DRUG DELIVERY: A COMPREHENSIVE REVIEW ON TRANSFERSOMES

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Abstract

Transferosomes are ultra-deformable vesicular systems designed to enhance the transdermal delivery of therapeutic agents. Characterized by their elastic bilayer structure composed of phospholipids and edge activators, transferosomes can efficiently penetrate the stratum corneum and deliver drugs deep into or across the skin. This study explores the formulation and evaluation of a Gentamicin-loaded transferosomal gel for improved topical drug delivery. Gentamicin, a broad-spectrum aminoglycoside antibiotic, is typically administered parenterally; however, its systemic side effects and poor oral bioavailability warrant alternative delivery approaches. The transferosomal system offers high drug encapsulation efficiency, protection against degradation, and sustained release properties. In this research, transferosomal gels were evaluated for physical appearance, pH, viscosity, spreadability, drug content, in-vitro drug diffusion, and stability. The formulation demonstrated desirable physicochemical characteristics and effective drug release. Transferosomes, as shown by numerous drug applications, provide an advanced platform for delivering a wide range of molecules including peptides, proteins, anti-inflammatory agents, corticosteroids, and vaccines. Their ability to bypass first-pass metabolism, improve bioavailability, and reduce side effects positions them as a promising carrier system in modern pharmaceutics, especially for transdermal and mucosal drug delivery applications.

Keywords: Transferosomes, Transdermal drug delivery, Gentamicin, Transfersomal gel, Vesicular drug delivery, Elastic vesicles, Topical antibiotic, Encapsulation efficiency, Controlled release, Bioavailability enhancement.

Introduction

Transferosomes are ultra-flexible vesicles with a bilayer structure. They can penetrate the skin easily and overcome the barrier function by squeezing through the intracellular lipid of the stratum corneum.8 Transfersomes are considered advantageous in topical and systemic drug delivery for the following distinctive features. On the one hand, transfersomes offer a great encapsulation efficacy up to 90% of drugs with a low or high molecular weight and a large variety in solubility. Moreover, the API is protected from biodegradation and a laggard, incrementally drug release is enabled due to depot function. Regarding production, an easy expansion to large-scale is possible. Despite these benefits, transfersomes still suffer from some shortcomings such as tendency of oxidative degradation, a range in purity of phospholipids from natural origin and an expensive production (Sarmah and Bhupen, 2013).

Transferosomes majorly involve the ingredients like amphipathic ingredients (combination of hydrophilic and lipophilic molecules like soy phosphatidylcholine), surface activators (e.g., surfactants), alcohol, and water. Apart from phospholipids, edge activators such as tween 80 or span 60 are the main constituents in the formulation of transfersomes. This single chain surfactants effect the destabilization of the lipid bilayers leading to an increase in its malleability making them particularly suitable for skin penetration (Sachan *et al*., 2013). The combination of the transferosomal suspension with the gel matrix can lead to formulation of a transferosomal gel, which may prove to be more pertinent for transdermal drug delivery. Gentamicin is a broad-spectrum amino glycoside type antibiotic that is isolated from *Micromonispora purpurea*. Gentamicin kills bacteria by damaging the plasma membrane and binding to the 16s ribosomal RNA, leading to the inhibition of microbial protein synthesis. It is effective against wide spectrum of gram positive and gram-negative bacteria (Laki, 2011). This study is designed to incorporate Gentamicin in the transferosomal gel system for transdermal delivery to avoid problems related with its parenteral delivery, and to improve the drug permeation through the skin and finally increase the bioavailability.

Transdermal drug delivery devices (TDDS) can improve bioavailability and patient compliance by bypassing first-pass metabolism. Because they are designed for controlled, efficient, and targeted drug delivery, vesicular-based TDDS have received a lot of interest in recent years. Transferosomes are advanced drug delivery systems

known as the first generation of elastic liposomes. They combine liposomal phospholipids with edge activators (nonionic surfactants), giving them high deformability. This allows them to penetrate deep skin layers, making them ideal for topical and transdermal drug delivery with improved drug absorption and stability. (Tanwar and Sachdeva, 2016; Wokovich *et al*., 2006).

Transfersomes have been discovered to be one of the most effective drug-delivery methods for topical treatment when compared to conventional topical systems. They have ultraflexible bilayer membranes that allow vesicles to be very elastic and malleable. Under nonocclusive conditions, transfersomes can escape from narrow pores in the stratum corneum (one-tenth their own diameter). Furthermore, transfersomes represent multilateral delivery for improving stability and serving as a medication carrier (Jangme and Chavan, 2013).

These are a complex aggregate that is extremely adaptive and stress resistant. The vesicle is both self-regulating and self-optimizing because of its local composition and bilayer shape independence. This enables transferosomes to efficiently traverse various transport barriers before acting as a drug carrier for non-invasive targeted medication administration and therapeutic agent sustained release (Rajan *et al*., 2011).

Advantages

Transferosomes are highly advanced drug delivery systems uniquely composed of both hydrophilic and hydrophobic components. This dual nature enables them to encapsulate and deliver a broad range of therapeutic agents, regardless of their solubility profiles. A significant advantage of transferosomes lies in their exceptional deformability and elasticity, which allows them to navigate through narrow pores and skin barrier constrictions that are often 5 to 10 times smaller than the vesicle diameter. This property not only enhances skin penetration but also ensures minimal loss of vesicles during transit, thereby making transferosomes effective for both topical and systemic drug delivery.

These vesicular systems are remarkably versatile, capable of carrying molecules of varying sizes, shapes, molecular weights, and polarities. Constructed using natural phospholipids and edge activators, transferosomes are biodegradable and biocompatible, making them safe and sustainable options for clinical use. Their structural flexibility and biocompatibility support the delivery of diverse active

pharmaceutical ingredients including proteins, peptides, insulin, corticosteroids, interferons, anesthetics, NSAIDs, anticancer drugs, and herbal extracts.

One of the primary benefits of transferosomes is their ability to provide sustained drug release, offering prolonged therapeutic effects and improved site-specific drug delivery. They enhance transdermal drug flux while ensuring that the bioactive agents reach the intended target efficiently. Moreover, the fabrication process of transferosomes is relatively simple and scalable, allowing for easy transition from laboratory research to industrial production.

Importantly, transferosomes bypass the first-pass hepatic metabolism, a significant limitation associated with conventional oral drug delivery systems. This results in enhanced bioavailability of the administered drug. Additionally, their entrapment efficiency for hydrophilic drugs is notably high, sometimes reaching up to 90%, further underscoring their utility in modern pharmaceutics as an effective and reliable drug delivery platform.

Transfersomes gel evaluations

Physical appearance

All prepared gel formulations have been observed for their visual appearance, such as transparency, colour, texture, grittiness, greasiness, stickiness, smoothness, stiffness and tackiness. The prepared gels were also evaluated for the presence of any particles. Smears of gels were prepared on glass slide and observed under the microscope for the presence of particles or grittiness.

pH of formulation

pH measurement of the gel was measured by using a digital pH meter, dipping the glass electrode completely into the gel system, taken in a 10ml beaker. The observed pH values were recorded for all formulations (F1-F6) (Nimker *et al*., 2017).

Determination of viscosity

Viscosities of the gels were determined by using Brookfield Viscometer. Spindle type, RV-7 at 100 rpm. 100gm of the gel was taken in a beaker and the spindle was dipped in it and rotated for about 5 minutes and then reading was taken.

Spreadability

For the determination of spreadability, excess of sample was applied in between two glass slides and was compressed to uniform thickness by placing 1kg weight for 5 min.

weight (50 g) was added to the pan. The time in which the upper glass slide moves over to the lower plate was taken as measure of spread ability (Mishra and Biswal, 2012).

Drug content

1 gm. of the prepared gel was mixed with 100 ml. of water aliquots of different concentrations were prepared by suitable dilutions after filtering the stock solution and the absorbance was measured at 205 nm. drug content was calculated by linear regression analysis of the calibration curve (Jivrani and Patel, 2014).

In-vitro diffusion study

An in-vitro drug release study was performed using modified franz diffusion cell. Dialysis membrane, was placed between receptor and donor compartments. transferosomal gel was placed in the donor compartment and the receptor compartment was filled with phosphate buffer, ph 6.8 (24 ml). The diffusion cells were maintained at 37±0.5°c with stirring at 50 rpm throughout the experiment at different time interval, 5 ml of aliquots were withdrawn from receiver compartment through side tube and analyzed for drug content by UV visible spectrophotometer and analyzed spectrophotometrically at 205 nm using phosphate buffer pH 6.8 as blank (Mishra and Biswal, 2012).

Stability studies

The stability study of the Transfersomal gels was performed as per ICH guidelines. Freshly prepared formulations were divided into groups and kept at specified storage conditions as per ICH guidelines. The sample was withdrawn periodically and tested for various evaluation parameters.

Applications

Transferosomes have emerged as a highly promising carrier system with diverse applications across various therapeutic areas. One of their significant uses lies in the treatment of dermal cancer, where their unique ability to penetrate deep skin layers enables effective localized drug delivery. Their ultra-deformable nature allows them to traverse the tight junctions of mucosal layers, facilitating the delivery of high molecular weight drugs that typically struggle to cross biological membranes. This makes transferosomes a valuable tool in the administration of biologically active drugs and even genetic material such as DNA, through lipid vesicle-based systems.

Moreover, transferosomes provide a strategic advantage in delivering drugs that are associated with gastrointestinal side effects when administered orally. For instance,

non-steroidal anti-inflammatory drugs (NSAIDs), known for their GI irritation potential, can be effectively delivered transdermally using transferosomes, minimizing systemic side effects. These vesicular carriers are also widely employed in the administration of corticosteroids, offering improved drug targeting and reduced systemic exposure.

Another notable application includes the delivery of interferons, where transferosomes enhance therapeutic efficacy by improving skin permeability and protecting the bioactive molecules. Furthermore, they are particularly suitable for the transdermal transport of peptides and proteins, which are otherwise challenging to administer due to their instability and large molecular size. Transferosomes have also been successfully utilized in vaccine delivery, with promising results demonstrated in transcutaneous immunization strategies, such as improved immune response in hepatitis B vaccination. These versatile applications underscore the immense potential of transferosomes as a modern and efficient drug delivery platform.

Preparation of Transferosomal Gel

Taking a one-unit equivalent dose of transfersomes and integrating them into a suitable gel basis or vehicle can produce the gel. If the amount of unentrapped medication is greater than 10%, it can be removed before turning in the gel by centrifuging the transferosomes at 6000 rpm for 15-30 minutes and discarding the supernatant. Mechanical stirring at 25 rpm for five minutes is used to incorporate transfersosomes into gel (Malakar *et al*., 2012).

67Table: Summary of drugs formulated as transfersomal gels with their applications

S. No.	Drug	Formulation	Application/Use	Reference
1	Clindamycin Phosphate	Transfersomal gel	Antibacterial agent for acne and skin infections	Neha et al., (2018)
2	Methotrexate	Transfersomal gel	Treatment of psoriasis, rheumatoid arthritis (enhanced dermal delivery)	Chetna and Praful, (2023)
3	Famciclovir	Transfersomal gel	Antiviral drug for herpes infections (improved skin penetration)	Sayani et al., (2024)
4	Chrysin	Transfersomal gel	Flavonoid with antioxidant and anti-inflammatory activity	Madhulika and Manish, (2023)

5	Gentamicin	Transfersomal gel	Topical antibiotic with enhanced penetration and reduced systemic side effects	Arjumand et al., (2023)
6	Etodolac	Transfersomal gel	NSAID for local pain relief and reduced GI side effects	Bachhav et al., (2024)
7	Berberine Chloride	Transfersomal gel	Herbal antimicrobial agent with improved dermal delivery	Silvia et al., (2022)
8	Metronidazole	Transfersomal gel	Antiprotozoal/antibacterial agent for topical infections	Shukla et al., (2019)
9	Isotretinoin	Transfersomal gel	Topical acne treatment with reduced irritation	Deepak et al., (2014)
10	Insulin	Transfersomal gel	Non-invasive systemic delivery for diabetes treatment	Padma et al., (2023)
11	Tinidazole	Transfersomal gel	Antiprotozoal drug for skin infections	Supriya et al., (2021)
12	Silymarin	Transfersomal gel	Hepatoprotective and antioxidant flavonoid	Abdallah et al., (2022)
13	Fusidic Acid	Transfersomal gel	Topical antibiotic with enhanced skin retention	Sushma and Annammadevi, (2024)
14	Amphotericin B	Transfersomal gel	Antifungal agent with improved transdermal delivery	Verma et al., (2019)
15	Fluconazole	Transfersomal gel	Broad-spectrum antifungal drug	Cheng et al., (2024)
16	Baclofen	Transfersomal gel	Muscle relaxant with localized action	Fatima et al., (2023)
17	Febuxostat	Transfersomal gel	Used in gout treatment; enhanced transdermal delivery	Kedar et al., (2023)
18	Lidocaine	Transfersomal gel	Local anesthetic for pain relief	Mahmoud et al., (2019)
19	Clotrimazole	Transfersomal gel	Antifungal agent for dermal fungal infections	Kalim and Upadhyay, (2021)
20	Lornoxicam	Transfersomal gel	NSAID for pain and inflammation with enhanced topical action	Hesham et al., (2020)

Conclusion

Transfersomes represent a highly promising and innovative vesicular drug delivery system due to their exceptional deformability, biocompatibility, and ability to traverse even the narrowest pores in the skin. Their unique structure composed of phospholipids and edge activators allows for the encapsulation and delivery of both hydrophilic and lipophilic drugs, enhancing drug permeation, retention, and therapeutic efficacy while minimizing systemic side effects. These ultra-deformable carriers overcome limitations associated with conventional transdermal systems by providing controlled and sustained release, improving bioavailability, and bypassing hepatic first-pass metabolism.

The wide range of applications from anti-inflammatory and antifungal agents to peptides, proteins, and even vaccines demonstrates the versatility of transfersomal systems. Numerous studies have validated their potential in enhancing dermal and transdermal drug delivery, particularly for drugs with poor skin permeability or systemic side effects. The scalability, ease of preparation, and high entrapment efficiency further highlight their utility in both pharmaceutical and cosmeceutical fields. Transfersomes offer a powerful platform for future advancements in non-invasive drug delivery systems. Ongoing research and development in this domain are likely to unlock new therapeutic opportunities and improve patient compliance, especially in the management of chronic and localized conditions.

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