REVIEW ARTICLE

# Deformable Lipid Vesicular Colloidal Carriers: A Paradigm Shift in Vaginal Drug Delivery

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## ABSTRACT

Vaginal drug delivery is a promising route. However, conventional formulations are leaky with low residence time and tissue permeation. Deformable lipid vesicular carriers (DLVC) formulated with lipidic vehicles like phospholipids are a propitious approach. Besides improving drug solubility, stability and encapsulation, DLVC can penetrate deeply into mucosal layers, leading to bioavailability enhancement. Scientific research suggests better penetration of DLVC is due to their elastic and deformable membrane. This review provides an overview on the DLVC with special emphasis on transferosomes. The formulation aspects, advantages, mechanism of penetration, method of preparation and applications have been discussed.

**Keywords:** Deformable lipid vesicular carrier, Tranferosomes, Transethosomes, Ultra-deformable liposomes, Vaginal drug delivery, Penetration, Health, Research.

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## INTRODUCTION

Delivery of drugs through vaginal route has been exploited for a very long time. Its rich blood supply, large surface area, and low enzymatic activity[1] offer diverse advantages. There are several benefits associated with vaginal administration in comparison to oral route. These include reduction in side effects, dose and frequency of administration, and circumventing degradation by liver enzymes. Therefore, it has emerged as an alternative route for both local and systemic delivery of drugs. Traditionally, this route has been explored for the management of the local genital conditions such as vaginitis, bacterial infection, and labor induction. Various reports in the literature indicate vaginal administration of contraceptives, antifungal agents, anti-viral agents, anti-protozoal agents, spermicidal agents, prostaglandins and steroids. Synthetic and herbal drugs are being explored to treat these diseases.[2-4] The most common vaginal diseases include aerobic vaginitis, bacterial vaginosis, candidiasis, atrophic vaginitis, mucoid ectopy, sexually transmitted infections and cervicitis.[5] Now a day's vaginal route is also used for systemic drug delivery, owing to its rich blood supply. Its permeability and enormous surface area have been exploited to deliver a broad range of compounds like peptides and proteins.[6]

The traditional commercial preparations for vaginal drug delivery include creams, tablets, foams, gels, ointments, suppositories and tampons. These have limited applicability because of poor absorption, distribution and retention across the epithelium. The self-cleaning action of the vagina, short residence time and leaky nature of the formulation further accentuate the problem.[7] The bioavailability of drug is also affected by various variables like menstruation cycle, patient age and vaginal anatomy.[8] In light of the above facts, several alternate strategies have been explored for vaginal delivery of drugs and accomplish both patients and clinical needs.[9] Deformable lipid vesicular system has gained significant attention due to their ability to penetrate quickly and deeply into the mucosal layer besides providing the benefits of conventional carriers like improvement in drug solubility, enhancement of bioavailability and high drug entrapment.

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The present review provides an overview of the latest developments and trends in drug delivery through the vaginal route using novel deformable lipid vesicular carriers with special emphasis on transferosomes as deformable carriers with enhanced penetration across the vaginal epithelium. The formulation aspects, advantages, possible obstacles, method of preparation, characterization and salient applications of deformable lipid vesicular carriers have also been discussed.

## Vaginal Physiology and Its Influence on Drug Delivery

Vagina is a fibro-muscular tubular organ of the female reproductive system. It connects the outer vulva to the cervix of the uterus and the organs of the upper reproductive tract. The epithelium cell surface of the vagina has rugae and micro ridges that allow to expansion of vagina. They increase the surface area of the vagina; this allows for greater drug absorption. The vagina has distinctive micro-flora, pH, vaginal secretion and enzymatic activity which influence the performance of a drug delivery system.[10] The vaginal secretions are a combination of fluids from various sources such as Bartholin's ducts, cervical secretions, desquamated vaginal cells, transudations from the blood vessels, leucocytes, and Skene's ducts. Sexual arousal and high estrogen levels influence the production rate of vaginal fluid. These factors affect the absorption and drug release from the formulation by affecting its spreading and retention characteristics.[11]

The pH of vaginal fluid ranges from 3.5 to 4.5 and it is maintained by the presence of Lactobacilli in vagina. *Lactobacillus* metabolizes glycogen to produce lactic acid which acidifies vaginal secretions.[12] The vaginal pH is an important factor that affects formulation design and drug release. However, vaginal dosage forms have been associated with problems such as gender specificity, cultural sensitivity, personal hygiene, low residence time and local irritation. Additionally, variations in the thickness of the vaginal epithelium during the menstruation cycle, menopause and pregnancy might affect the degree and rate of drugs absorption. Conventional vaginal formulations like creams, and tablets tend to be leaky and messy in nature. These drawbacks necessitate the use of novel drug delivery systems.

## Deformable Lipid Vesicular Carriers

Lipid vesicular carriers are a promising vehicle to effectively transport drugs and overcome the problems associated with conventional vaginal formulations. These include niosomes, ethosomes, spingosomes and liposomes.[13] Out of these liposomes are the most commonly used lipid vesicular carrier. The major benefit of these carriers is the targeted delivery of drugs in the body.[14] Additionally, these are biodegradable, non-toxic and biocompatible.[15] Nonetheless, conventional liposomes lack the ability to penetrate deeper tissue layers and reach blood circulation.[16] Also, they have drawbacks including short half-life and drug leakage from vesicles because of an unstable membrane.[17]

Deformable lipid vesicular carriers (DLVC) are a novel and potential effective vaginal drug delivery approach. DLVC, offers the advantage of being non-toxic and thermodynamically stable formulations. DLVC are nearly 100 nm in diameter. DLVC have a bilayer structure similar to liposomes that facilitate the entrapment of hydrophilic, hydrophobic, or amphiphilic drugs, with the difference that they exhibit better penetration through narrow tissue pores than conventional liposomes. Their ultra-deformable membrane, adaptable and softer nature are its distinctive features.[18] Currently, there are various types of deformable lipid vesicular carriers that have been successfully developed particularly transferosomes, transethosomes and ultra-deformable liposomes.

## Transferosomes as Deformable Lipid Vesicular Carriers for Vaginal Drug Delivery

Transferosomes belong to the first generation of elastic vesicles, a modified liposome carrier system. Cevc and Blume first proposed transferosomes in the early 1990s.[19] The name transferosome has its root in Latin namely "Transfer," that is "to carry across," and "Soma" means "body".[20] They have a phospholipid bilayer with one aqueous interior compartment and an edge activator (Figure 1). Transferosomes was made of phospholipids and edge activators (EAs). Lipid bilayer of transferosomes is comprised of phospholipids (e.g., soya phosphatidylcholine, egg phosphatidylcholine) and an edge activator/surfactant (e.g., sodium cholate, sodium deoxycholate, Tweens, Spans). Transferosomes are highly ultra-deformable carriers that have self-regulating and self-optimizing potential.

Edge activators are usually single-chain surfactants capable of imparting high mobility and have a large curvature radius. The edge activators are function as membrane destabilizing agents and make vesicle membrane more deformable. They disrupt the intercellular lipid membrane of the skin, enabling the drug molecules to pass through the tissues.[21] Transferosomes squeeze and deform themselves as whole vesicles via small pores or tissue constrictions without significant loss.[22] According to literature reports, they can squeeze or deform themselves and pass-through constrictions of the tissues that are 5 to 10 times smaller than the vesicle diameter. The deformability and flexibility of transferosomes is achieved by using phospholipid and edge activators in an appropriate ratio. A change in the ratio of both ingredients results in change in flexibility and hence permeability of the formulation. The edge activators could also improve the solubilization of lipophilic drugs in transferosomal formulation, enhancing the efficacy of drugs.

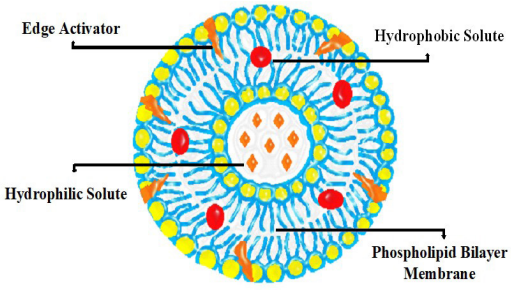


**Figure 1:** Structure of transferosomes

Transferosomes can deliver the low and high molecular weight drug molecules and transport the hydrophobic and hydrophilic molecules across the tissues with a ~≥50% efficiency.[23] Several transferosomal formulations are in various phases of clinical testing. For instance, a phase III clinical trial study was conducted to determine the effectiveness and safety of ketoprofen loaded transferosomes (Diractin®) for osteoarthritis treatment. Over a six-week treatment period, it was found that the drug encapsulated in transferosomal vesicle carriers exhibited greater therapeutic potency in reducing the knee pain associated with osteoarthritis as compared to a placebo and has fewer adverse effects.[24]

### Advantages of Transferosomes

Transferosomal carriers are efficient and versatile in incorporating a variety of agents irrespective of their morphology, size, polarity and molecular weight for both topical and systemic drug delivery. Their unique structure made of hydrophilic and hydrophobic moieties enables them to incorporate drug substances with varied solubility characteristics. Lipophilic drugs are reported to have an entrapment efficiency of about 90% in transferosomes. They are biodegradable and biocompatible in nature. They can capable of avoiding the liver first-pass effect; a common problem associated with oral delivery. Encapsulation of drug in such carriers shields the drug, prevents its metabolic degradation, and reduces the undesirable side effects. Transferosomes can be used to achieve a sustained or controlled delivery of therapeutic agents and improve their site specificity. They have good patient compliance and are also suitable for unconscious patients.[25-27]

### Mechanism of Transferosomal Penetration

The transferosomes penetration is a result of its moisture-seeking tendency from the deeper tissue layers, also known as xerophobia.[23] The moisture loss/dehydration from the transferosomal formulation upon tissue application and subsequent deformation causes this moisture-seeking behavior (non-occlusive state).[28] The flexible nature of vesicles reduces the likelihood of complete rupture. It also helps the vesicles to follow the aqueous gradient prevalent across the layers of non-occlusive tissue[29] (Figure 2). The flexibility and deformability of the transferosomes depends on vesicle composition, particularly ratio of phospholipid and surfactant. This influences the penetration ability of the vesicles.[30] Additionally, the flexibility of transferosomes is responsible for locally changing their bilayer composition. This reversible phenomenon occurs when transferosomes are pressed against or made to pass through a narrow pore.[20]

### Formulation Aspects of Transferosomes

The type and concentration of each component affects the properties and performance of the transferosomal formulation. Some of the factors are discussed in subsequent sections.

### Effect of Formulation Variables on Entrapment Efficiency

The concentration of phospholipid and edge activator have significant impact on the entrapment efficiency of drug in transferosomal formulation. The most commonly used edge activators are surfactants but other edge activators like bile salts have also been reported in literature.[31] The addition of a higher surfactant concentration has been reported to minimize the entrapment efficiency. This may be because, at higher concentrations, the molecules of surfactant arrange themselves in such a way so as to create pores within the vesicular membrane which causes higher fluidity and permeability within the lipid bilayer, resulting in leakage of the entrapped drug.[25] Balata *et al*., 2020 reported that a greater number of vesicles will form as the concentration of surfactant increases. This leads to a higher volume of the lipophilic bilayer domain that can be used for the encapsulation of lipophilic drugs. The authors also reported that vesicular bilayer membrane was disrupted at very high drug concentrations due to exhaustion of vesicular loading capacity. This leads to drug leakage, decreased entrapment efficiency and penetrability.[32]

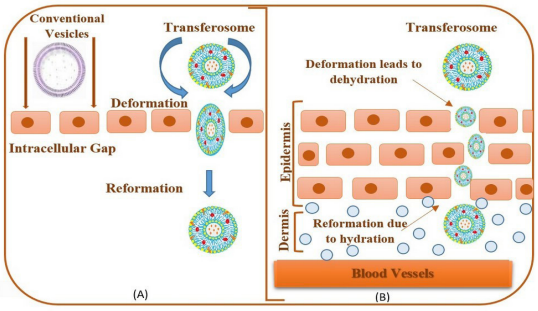


**Figure 2:** Mechanism of transfersomal penetration: (a) Deformation and reformation during penetration (b) Moisture seeking tendency that drives transferosomal permeation.

### Effect of Formulation Variables on Vesicle Size

The concentration of surfactants used in formulation influences the vesicle size of transferosomes. An increase in surfactant concentration, the hydrophilicity of the surfactant head group, the hydrophilic-lipophilic balance and carbon chain length leads to decrease in the vesicle size. In a study by Jain *et al*., 2003 different edge activators/surfactants, including sodium deoxycholate, tween 80, and span 80 were used to develop the transferosomes formulation. It was found that the vesicle size reduced as the concentration of surfactant increased. The higher surfactant concentration (>15%) induced micelle formation instead of vesicle formation. In addition, an increased surfactant concentration resulted in an increase in vesicle charge, which reduced the vesicle agglomeration and improved the stability of transferosomes.[32,33]

### Effect of Formulation Variables on Permeability

The vesicle membrane permeability depends on the surfactant's carbon chain length and transition temperature. The density of phospholipid used in a formulation and the surfactant-phospholipid interaction determines the amount of surfactant required to develop deformable lipid vesicles.[34] A high concentration surfactant concentration may result in the formation of pores in the lipid bilayer and decrease the penetration ability of the vesicles across membrane.[25]

### Effect of Various Solvents and Hydrating Medium

Solvents are utilized such as ethanol, methanol and chloroform are used in transferosomes preparation for the solubilization of components. The selection of a specific solvent is based primarily on the compatibility and solubility of different excipients and active ingredients in a particular solvent. For uniform film formation and good stability after hydration, the drug and excipients must completely dissolve in the solvent and form a translucent solution. In a study by Shamma *et al*., 2013 ethanol was used as a solvent for transferosomal preparation. Ethanol improved drug partitioning into membrane through a three-fold mechanism. It enhanced the solubility of drugs in vesicles through its solvent action and improved permeation into tissues.[20]

The hydration medium's characteristics determine the drug's ionization state incorporated in transferosomes. Only unionized drugs are membrane-bound in lipid bilayer and can penetrate across tissues. This is because of the fact that the transferosomal lipid bilayer mimics the phospholipid layer of the biological cell membrane. The formulation pH level affects the ionization state and hence should be appropriate for achieving a balance between the formulation characteristics and its biological application through the intended route of administration.

### Ultradeformable Liposomes as Deformable Lipid Vesicular Carriers

The concept of deformable liposomes was first introduced in 1992 by Cevc and collaborators.[19] The significance of vesicle morphology in effective delivery of drug has long been emphasized. The rigidity and micron size range of conventional liposomes can obstruct tissue permeation. To overcome these problems, deformable liposomes were introduced, which significantly enhanced the drug delivery, by improving vesicle penetration. However, they are unable to permeate the innermost layers of stratum corenum. Therefore, the concept of ultra-deformable liposomes was introduced to further improve the degree of elasticity.[35]

Ultra-deformable liposomes are referred as first generation of elastic liposomes. In contrast to conventional and deformable liposomes, they have the ability to penetrate intact tissue when applied in non-occlusive conditions. These ultra-deformable liposomes contain an additional ingredient, glycol (e.g., propylene glycol), besides the conventional ingredients of elastic liposomes like phospholipids and edge activators.[35] The presence of glycols is responsible for the additional increase in elasticity of these vesicles as compared to the elastic liposomes.

Ultra-deformable liposomes consist of a phospholipid bilayer which surrounds an inner aqueous compartment. Elmoslemany *et al*., 2012 prepared propylene glycol containing liposomes of miconazole nitrate. They were shown to significantly increase the delivery of drugs. They also improved the stability of vesicles, enhanced tissue deposition and penetration of miconazole nitrate. The authors used a different preparation method for vesicles that excluded the use of any hazardous solvents. A one-step process was followed. The phospholipid was dissolved in a liquid additive (propylene glycol). This was followed by gradual addition of the aqueous phase. The authors emphasized the use of optimum quantity of liquid additive, as an excessive amount of additive can interfere with vesicle formation.[36]

### Transethosomes as Deformable Lipid Vesicular Carriers

Transethosomes are another deformable lipid-based vesicular system that were introduced by Song *et al*., 2012.[37] They are composed of phospholipids, a substantial amount of ethanol (30–40%) and edge activators. Alcohol is primary component of the transethosomal formulation system. Apart from providing flexibility to transethosomes, alcohol deforms the skin layer and fluidizes the membranes allowing penetration of tranethosomes via small pores. Transethosomes may show both the advantages of transferosomes and ethosomes. Transethsomes have been explored for both topical and systemic administration. The advantages of transethosomes include enhanced drug permeability through tissues. They have better stability as compared to conventional vesicles. They have been administered as a semisolid form and therefore has better patient compliance. Avoidance of first pass metabolism. They are non-toxic, biocompatible and biodegradable. Some of the disadvantages are associated with transethosomes include skin inflammation or irritation and allergic reactions in certain patients.[38]

The drug transport mechanism via transethosomes has been explored by Shaji *et al*., 2018 and Mishra *et al*., 2019. Ethanol comes in contact with tissue layers, disrupting the phospholipids and fluidizing the lipid layer. Both transethosomes and tranferosomes penetrate deeper tissue layers by fluidization of the membrane and the vesicle flexibility inherited in both vesicles. In transethosomes the penetration is further accentuated by the presence of ethanol in the formulation. The rearrangements of the lipid bilayer make the vesicles more flexible, allowing the vesicles to penetrate into deeper layers of tissues.[39,38]

### Applications of Deformable Lipid Vesicular Carriers for Vaginal Drug Delivery

DLVC are a step ahead from the normal lipidic vesicles. They are a promising carrier for drug delivery with limitations like low solubility, low permeability and limited bioavailability. These carriers can effectively transport substances like antibodies, vitamins, nucleic acid, enzymes, polypeptides, and other synthetic drugs.[40]

### Delivery of Antimicrobial Agents

Hady *et al*., 2022 developed nystatin transferosomes using thin film hydration method for treatment of vulvovaginal candidiasis. The transferosomal formulation was optimized by full factorial design to estimate the effect of different independent variables on dependent variables. Results demonstrated that nystatin has high entrapment efficiency of 97.35 ± 0.03 to 98.01 ± 0.20%. The *in-vitro* and *in-vivo* studies showed significant antifungal activity and eradication of *Candida* infection compared to control, demonstrating the

transferosomal preparation to be a potential delivery system for improving antifungal activity of nystatin.[41]

Singh *et al*., 2017 developed formulation of ketoconazole transferosomal gel for treatment of vaginal candidiasis. Solvent evaporation method was used for the preparation of ketoconazole transferosomes. Drug release studies over a period of 72 hours showed 74 and 97% release from drug suspension gel and transferosomal gel, respectively. The flux of ketoconazole transferosomal gel was three times more than that of ketoconazole suspension gel. The prepared transferosomal gel exhibit an improved antimicrobial effect against *Candida albicans* with a minimal inhibitory concentration of 4.57 to 4.6 µg/mL. An effective zone of inhibition as compared to control was also observed for the transferosomal gel.[42]

Vanic *et al*., 2013 prepared metronidazole or clotrimazole-loaded deformable propylene glycol liposome for treatment of microbial infections of vagina. The ethanol injection method is used for preparation of deformable propylene glycol liposomes. Results demonstrate that the deformable propylene glycol-containing liposomes hydrogel penetrated quickly as compared to conventional liposomes. *In-vitro* release studies showed sustained drug release from the developed gel formulation. The rheological and textural characterization of deformable propylene glycol-in-hydrogels showed that the mechanical properties of hydrogels did not vary significantly as compared to conventional liposomes. Deformable propylene glycol liposomes-in-hydrogels proved be a potential delivery system for vaginal delivery of antimicrobial drugs.[35]

### Delivery of Hormonal Agents

Salem *et al*., 2019 developed progesterone-loaded nanovesicle transethosomal mucoadhesive gel for vaginal delivery of progesterone as potential luteal-phase support. The mucoadhesive gel was optimized through full factorial design. Progesterone-loaded nanovesicle transethosomes were developed by injection sonication technique. Findings suggested that the drug release varied from 50.9 ± 2.75 to 90.69 ± 2.07% whereas the transvaginal flux was found to be in range of 0.274 ± 0.03 mg/cm$^2$/h to 0.531 ± 0.04 mg/cm$^2$/h. The gel was clinically tested on human volunteers with PCOS, demonstrating augmented echogenicity degree and endometrial thickness. An increase in pregnancy rate was also observed. Overall, progesterone nanovesicle transethosomes vaginal gel formulation exhibited improved pregnancy rate in anovulatory polycystic ovary syndrome and provided luteal phase support.

## CONCLUSION

Deformable lipid vesicular carriers are a promising strategy for both pharmaceuticals and cosmeceuticals. DLVC particularly, transferosomes, transethosomes and ultra-deformable liposomes are explored for various routes, especially vaginal routes of administration. These vesicular systems improve drug delivery owing to their better penetration efficiency across the tissue as compared to the conventional liposomes. Their higher permeation efficiency is due to their moisture-seeking tendency, which drives the vesicles to penetrate deeper tissue layers. DLVC, have been developed for a wide variety of agents, including anti-bacterial, antifungal and hormonal agents. They are adaptable and efficient for both topical and systemic drug delivery. Overall, DLVC are a potential and efficient vehicle to deliver drugs through vaginal route.

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