
Modified-Release Drug Delivery Technology

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SupraVail Vaginal Gel

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I. INTRODUCTION

An optimized vaginal delivery system should provide the opportunity for controlled and prolonged release of drugs. It should also be designed to maximize the efficacy of the active drug and minimize the cost. While a number of vaginal drug delivery systems have been developed (e.g., containing permeability/stability-enhancing and bioadhesive agents), phospholipids offer many benefits as a platform for vaginal drug delivery.

II. PHOSPHOLIPIDS

A. Definition

The term “phospholipid” refers to a lipid-containing phosphoric acid as a mono- or diester. Phospholipids comprise a phosphoric head attached to a glycerol backbone, which in turn is linked to the hydrophobic fatty acids. Two types of phospholipids exist—glycerophospholipids (phosphodiglycerides) and sphingophospholipids. The glycerophospholipids are the most abundant and possess a hydrophilic head group containing phosphorus and one other chemical subgroup (e.g., choline, ethanolamine, inositol, or serine).

B. Occurrence and Uses

Phospholipids are a functionally versatile class of compounds that are ubiquitously distributed in human, animal, plant, and microorganism cells. They are important elements in the structure of biological membranes acting essentially

as the "solvent matrix." They have found widespread application within cosmetic, agriculture-food, and pharmaceutical domains. Phospholipids are traditionally used as emulsifiers in many pharmaceutical products and are the key components of liposome formulations.

C. Toxicology

Phospholipids are extremely well tolerated from a physiological standpoint, and their highly favorable toxicity profile has prompted widespread inclusion in many formulations. They are natural substances that occur in foods and are accepted by many regulatory authorities as toxicologically safe. Lecithin (primarily a mixture of phospholipids) is GRAS listed ("generally recognized as safe") by the Food and Drug Administration (FDA) and appears in many drug monographs. Lecithin is also listed in the FDA Inactive Ingredients Guide (inhalations, IM and IV injections, oral capsules, suspensions and tablets, rectal, topical, and vaginal preparations). Phospholipids are included in nonparenteral and parenteral medicines licensed in England and are universally accepted as food additives and cosmetic excipients within the European Community. Furthermore, no apparent adverse side effects arise from phospholipid fractions that have been purified through column chromatography.

III. LIPOSOMES

Phospholipids are the key components of liposomes. Liposomes are vesicular structures that are widely utilized in topical delivery systems and are versatile platforms for drug delivery. They have been used in vaginal therapy with promising results [1–5], although research in this area is fairly limited. Liposomes have the potential to associate amphipathic or lipophilic drugs and can be modified to impart controlled-release properties. However, preformed liposomes are not ideal delivery platforms and have a number of attendant problems. Their major drawbacks are limited drug loading and poor storage stability; it is difficult to attain effective drug loading within the liposomes and drug molecules often leak from the structures. Furthermore, energy-intensive manufacturing techniques such as extrusion, high-pressure homogenization, and solvent evaporation methods are time-consuming and expensive. Not surprisingly, this tends to promote the development of high-cost niche products.

IV. PROLIPOSOMES

The proliposome approach was developed as a straightforward, reproducible, and reliable manufacturing technique for large-scale production of liposome disper-

sions [6,7]. Today, it is one of the most cost-effective and widely used methods for producing commercial liposome products. The technology is based upon the intrinsic property of hydrated membrane lipids to form vesicles on contact with water. A typical formulation consists of suitable fractions of phospholipids with an active component, which may be lipophilic or amphipathic. The formulation does not, however, contain sufficient water to allow liposome formation under storage conditions. Liposomes are formed only when the formulation comes into contact with a moist aqueous environment such as found on the skin or mucosal surfaces. It is designed particularly for the molecular dispersion and delivery of water-insoluble materials where association efficiencies approaching 100% can be achieved. Proliposomes have been employed as a basis for a number of site-specific drug delivery approaches.

V. SUPRAVAIL MUCOCUTANEOUS DELIVERY

A. Background

SupraVail™ is the name given to the platform technology for delivering poorly water soluble drugs as molecular associates to maximize bioavailability. These associates are formed from lipid complexes, which may be liquids, semisolids, or solids. The complexes can be incorporated into various dosage forms for different routes of administration. SupraVail dosage forms have the intrinsic capacity to form lipid aggregates where the drug is in molecular association. Depending upon the type of phospholipids selected, these structures may be vesicles, micelles, or mixed micelles. The SupraVail technology designed for topical and mucosal applications, including intravaginal drug delivery, is a semisolid proliposome gel.

The formulations utilize fractionated phospholipids to form vesicular structures *in vivo*, triggered by the aqueous environment found on mucosal surfaces. These have a high potential to associate with both lipophilic and hydrophilic compounds. The type of phospholipid fraction used for mucocutaneous application will depend on the physicochemical properties of the drug and also on the required characteristics for the formulation. The key to SupraVail delivery is, first, to disperse the drug in a monomolecular state within phospholipid bilayers. Second, in the presence of excess water the bilayers readily convert into discrete vesicular structures. The important feature in this process is that the drug should remain associated with the vesicles even after conversion. While the phospholipid and drug form the basis of the formulation, a number of excipients can be readily incorporated to optimize the product characteristics.

B. SupraVail Vaginal Gels

A gel presentation is particularly suitable for vaginal administration. It is non-greasy, aesthetically appealing, and offers the potential for improved drug reten-

tion. In SupraVail gels, the phospholipid adopts a liquid crystalline matrix and forms a bilayered translucent gel. Lipophilic drugs readily associate with the phospholipid molecules. The SupraVail gel is particularly suitable for incorporation of lipophilic drugs and thus acts an excellent carrier for antifungal and steroid compounds. On contact with the mucosal surface, the bilayered gel formulation converts readily *in vivo* to vesicular structures.

A typical SupraVail formulation consists of three essential components; phospholipids, hydrophilic media, and active compound. Other excipients, such as polymers to improve bioadhesion and stabilizers (e.g., buffers and antioxidants), may also be added if necessary. Figure 1 shows a freeze fracture of a bilayered gel and Figure 2 shows a freeze fracture of a liposome dispersion formed from a proliposome gel after contact with water.



Figure 1 Freeze fracture of a bilayered gel.

isoconazole, and miconazole) and nystatin. The poor aqueous solubility of the antifungal agents in these conventional formulations means that they are not in molecular dispersion and consequently have reduced drug concentration at the active sites. However, the poor aqueous solubility of antifungal drugs such as amphotericin, miconazole, clotrimazole, and nystatin makes them ideal candidates for SupraVail technology.

VI. DEVELOPMENT OF A SUPRAVAIL AMPHOTERICIN B GEL

A. Development

A SupraVail gel can be employed in topical drug delivery for treating mucosal fungal infections. While preliminary studies have centered on amphotericin B, it also presents as an ideal formulation for antifungal agents such as miconazole, clotrimazole, and nystatin. It consists of selected fractions of phospholipid dispersed in an anhydrous hydrophilic medium, wherein the drug is partitioned between the hydrophobic membrane lipid bilayer formed in the gel and the hydrophilic solvent phase. It confers many unique features for drug delivery to mucosal surfaces, notably:

It is a highly efficient lipophilic carrier, utilizing natural lipid to molecularly disperse the drug. Phospholipids have natural affinity for biological membranes and are generally nontoxic and nonirritant.

The drug is in molecular dispersion in the bilayers offering improved drug activity.

The vehicle is nontoxic and contains pharmaceutically acceptable excipients.

Difficulties associated with liposomal preparations, e.g., stability and loading, are circumvented because the proliposomes only convert to vesicular structures (liposomes) *in vivo*, i.e., on the mucosa.

The product has a low initial microbiological burden and does not encourage microbial growth (it is preservative-free).

SupraVail formulations can be produced on a large scale economically and reliably.

The product is economically viable (i.e., in similar price range as current topical antifungal therapies).

B. Formulation Issues and Product Stability

A satisfactory proliposome amphotericin B gel suitable for direct application to the vaginal mucosa should take into consideration the following key factors:



Figure 2 Freeze fracture of a liposome dispersion formed from a proliposome gel after contact with water.

C. Applications of SupraVail Vaginal Gels

Vaginal delivery systems are frequently required to treat local fungal infections, particularly candidiasis. The term “candidiasis” refers to the most common fungal infection affecting humans, and was originally ascribed to infections due to a single yeast species; *Candida albicans*. It has now been expanded to encompass a range of yeast species of the genus *Candida*. While systemic *Candida* occur, the most common *Candida* infections are superficial lesions especially of the mucous surfaces of the vagina or mouth.

Vaginal candidiasis is primarily treated with antifungal cream or pessaries inserted high into the vagina (including during menstruation). Vulvitis and superficial sites of infection can be readily treated with appropriate creams. The drugs of choice include the imidazole drugs (clotrimazole, econazole, fenticonazole,

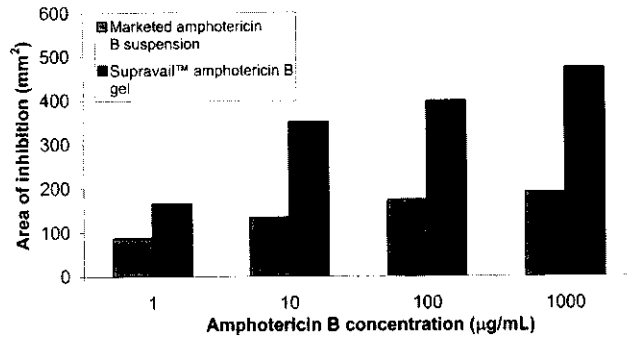


Figure 3 Comparison of antifungal activity of amphotericin B in SupraVail against commercially marketed suspension.

ure 3. The data show that higher antifungal properties were obtained with the phospholipid preparation.

6. Release Profile

The release of the drug can be controlled by altering the composition of the formulations. The release of three amphotericin B gels was determined at 37°C. It can be seen from Figure 4 that the amphotericin B can either be released immediately or more gradually, where about 40% diffuses out after 2 h.

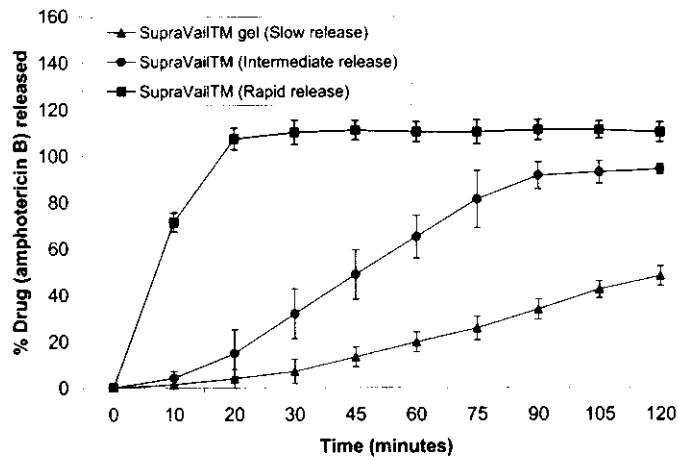


Figure 4 Release profile of amphotericin B from three SupraVail gel formulations.

Stability and packaging
Drug concentration
Manufacturing method
Excipients
Antifungal activity
Release profile

1. Stability and Packaging

The stability of the drug and phospholipid components can be maximized through the selection of an appropriate hydrophilic base. Accelerated stability studies were undertaken in a variety of tube and pump packs. Accelerated stability data predicted a shelf life of 24 months at 25°C/60% relative humidity.

2. Drug Concentration

The amphotericin B concentration was 1% w/w. Greater than 95% of the drug resides in the lipid bilayers, effectively protecting the drug from degradation during storage, compared to the unprotected form.

3. Manufacturing Method

The pilot manufacturing method for producing 5 kg of the gels utilized a conventional high-shear mixer. The process may be readily scaled up for larger production batches.

4. Excipients

A number of studies were performed to assess the effects of modifying the standard proliposome gel. These included addition of antibacterial agents, antioxidants, chelating agents, and complexing agents. None of these agents (in the concentrations used) were found to alter the degradation or encapsulation profiles for the drug in the proliposome gel. The gel passes a British Pharmacopoeia (BP) microbial challenge test and was deemed to have sufficient antimicrobial activity without need for preservatives.

5. Antifungal Activity

The proliposomal amphotericin B gels demonstrated a superior antifungal activity over equivalent concentrations of drug in aqueous suspension. These findings were substantiated by growth inhibition both in solid media (cup-plate diffusion assay) and in liquid media. A comparison of the activity of amphotericin B in a SupraVail formulation against a commercially marketed product is shown in Fig-

Table 1 Association of Drug After Conversion

Formulation	% association after conversion
1% amphotericin B	99.2
1% miconazole	97.7
1% clotrimazole	97.3

VII. DEVELOPMENT OF ALTERNATIVE ANTIFUNGAL DRUGS IN A SUPRAVAIL GEL

While amphotericin B was selected as a test model drug, development programs have also been instigated for a number of other drugs, namely clotrimazole, miconazole, and nystatin. In addition to excellent association (Table 1) and stability profiles (6 months accelerated stability data), these prototype formulations have supporting microbiological efficacy data.

VIII. REGULATORY ISSUES

While the SupraVail gel must comply with the normal demands for a standard mucocutaneous gel preparation, no specific regulatory issues arise. It should be stressed that the phospholipids used for the SupraVail gels are of exceptionally high specification and exceed the general pharmacopoeial requirements for lecithin. Certificates of analysis are issued for each of the phospholipid fractions employed, and Drug Master Files (DMFs) are available for selected fractions. Lecithin is GRAS status and would present a low toxicological challenge. While it may be necessary to perform a tolerability study for the final product (active in association with all excipients), it is believed that there would be no requirement to undertake extensive toxicological profiling of the individual formulation components.

IX. COMPETITIVE ADVANTAGE

The formulation components are readily available in bulk quantities at competitive prices and would readily lend themselves to mass marketing of competitively priced products. In addition, the manufacturing process involves standard mixing equipment and facilitates production of large-scale batches economically and reliably.

There is a potential to reduce drug dosage in these formulations. Enhanced

bioavailability and drug activity have been demonstrated by presenting the drug to membranes in molecular dispersion. These formulations are also nontoxic and nonirritant and do not require the inclusion of preservatives. The gel formulations can be packaged in a number of presentations (e.g., pumps, tubes, jars).

The SupraVail gel is highly versatile and is suitable for inclusion of a number of drug compounds. While initial research has focused on the hydrophobic antifungal agents, it could be readily adapted for delivery of other actives (e.g., steroids, peptides, vaccines, and antimicrobial agents).

X. FUTURE DIRECTIONS

There is considerable promise for development and expansion of the innovative SupraVail platform technology. While vaginal delivery systems have traditionally focused on local treatment of infective and inflammatory conditions, interest has been directed on the suitability of this route for systemic delivery (e.g., peptides, vaccines, microcides, etc.). The dual-vector nature of phospholipids facilitates incorporation of both hydrophobic and hydrophilic drugs. Gels, foams, and creams can be developed and individually tailored for specific actives. The phospholipid(s) can be carefully selected and blended with actives/excipients to confer superior stability, efficacy, and patient acceptability profiles.

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