CHAPTER 2

Micellar Nanoparticles: Applications for Topical and Passive Transdermal Drug Delivery

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2.1 INTRODUCTION

Nanotechnology has evolved to be an integral part of the twenty-first century. Nanotech-enabled products find applicability in almost everything we touch on a day-to-day basis, such as medicine, pharmaceuticals, chemicals, biologics, and information technology. In particular, the pharmaceutical industry has been energized with breakthroughs in nano-engineering, especially in the fields of drug delivery and formulation development. Over the last few decades, there has been an explosion of research – at both academic and industrial levels – pertaining to nano-formulations: liposomes

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(El Maghraby et al., 2006; Kazakov and Levon, 2006; Mainardes et al., 2006; Minko et al., 2006; Sharma et al., 2006; Torchilin, 2006; Tyagi et al., 2006; Weissig et al., 2006; Dutta, 2007; Elsayed et al., 2007; Karanth and Murthy, 2007; Koning and Krijger, 2007; Letchford and Burt, 2007; Malik et al., 2007; Vyas and Khatri, 2007), nanoparticles (Asghar and Chandran, 2006; Conti et al., 2006; Mainardes et al., 2006; Singhvi, 2006; Caruthers et al., 2007; Emerich and Thanos, 2007; Garg and Saraf, 2007; Goldberg et al., 2007; Illum, 2007; Kohane, 2007; Koning and Krijger, 2007; Navalakhe and Nandedkar, 2007; Patel and Vavia, 2007; Silva, 2007; Torchilin, 2007; Wang et al., 2007), nanoemulsions (Sarker, 2005; Pattani et al., 2006; Saupe et al., 2006; Tiwari and Amiji, 2006; Date and Nagarsenker, 2007; de Araujo et al., 2007; Fatouros et al., 2007; Khandavilli and Panchagnula, 2007; Schaffazick et al., 2007), dendrimers (Duncan and Izzo, 2005; Kitchens et al., 2005; Koo et al., 2005; Bai et al., 2006; Gupta et al., 2006; Najlah and D'Emanuele, 2006; Qiu and Bae, 2006; Reddy et al., 2006; Yang and Kao, 2006), supramolecular assemblies (Giraud-Guille et al., 2003; Lukin and Vogtle, 2005; Hamacek et al., 2006; Perez-Garcia and Amabilino, 2007), and surface nano-engineered products, to name a few.

Transdermal delivery involves application of a pharmacologically active compound on to the skin to achieve therapeutic blood levels in order to treat diseases remote from the site of application. Ever since the approval of Transderm-Scop®, the first transdermal drug delivery system (TDDS) in 1981, there has been explosive research in the field of transdermal therapeutics for treatment of a variety of clinical conditions (Gordon and Peterson, 2003). Unmatched clinical benefits (Gordon and Peterson, 2003), profound industry interest, existence of strong and *niche* markets, and regulatory precedence show why the TDDS has become a flourishing and viable dosage form. The current transdermal therapeutics market is segmented into traditional formulations (gels), advanced delivery systems (patches), and novel physical technologies (microporation, iontophoresis, and sonophoresis). Transdermal delivery is particularly advantageous for those drugs having significant hepatic first-pass metabolism or degradation in the gastrointestinal tract. Over the years, the US Food and Drug Administration (FDA) has approved more than 40 transdermal products, spanning about 15 molecules with sales of nearly $2.5 billion.

Micellar nanoparticle (MNP) technology was invented in the mid-1990s (Wright, 1997; Simon, 2006; Singhvi, 2006). Scientists at Novavax developed and patented MNP technology and subsequently rolled out the first nano-engineered transdermal lotion product (Estrasorb™) in 2003. Estrasorb is commercially manufactured on a kiloton scale and the manufacturing

process is economical. The ingredients used in Estrasorb are all generally recognized as safe (GRAS).

MNP is a nanotechnology-based formulation that has achieved a breakthrough in transdermal therapeutics. The formulation represents a robust and versatile delivery system that can accommodate a range of therapeutic compounds having varying physicochemical properties. MNP-based emulsions (lotions) are attractive alternatives for systemic drug delivery via topical application. The technology allows high concentrations of drug to penetrate the skin and functionally create a drug depot in the stratum corneum and epidermis. This route of delivery provides similar advantages of patch technology in avoiding both contact with the gastrointestinal tract and hepatic first-pass effects, and is cosmetically more acceptable to many patients. MNP drug delivery offers a potentially fast and inexpensive pharmaceutical development model by using drugs already proven safe and effective to create new proprietary formulations.

2.1.1 MNP composition and structures

In broad terms, MNP is a multiphasic nanoemulsion. MNP technology presents the active pharmaceutical ingredient (API) in a more readily bioavailable form. There are five basic components of an MNP system: (i) one or more APIs; (ii) solvent; (iii) stabilizer; (iv) oil; and (v) aqueous medium. When these components are mixed together and subjected to a milling process (assisted by high-shear or high-pressure mixing), the API presents in one or more composite fractions (Figure 2.1):

- Solid particulates (micro/nanoparticles)
- Micelle-associated
- Oil-associated
- Solubilized (in aqueous and/or solvent medium).

MNPs can accommodate both water-soluble and poorly water-soluble APIs. While the technology can accommodate more traditional crystalline compounds, surprisingly it can also be used with amorphous drugs. Depending upon the physicochemical properties of the API and the dose requirements, drug loading up to 20% (w/w) can be achieved. The range of APIs that can be formulated in MNP technology is quite broad – from physicochemical and therapeutic perspectives. This aspect will be elaborated upon in the following sections.

A solvent is generally used to assist solubilization of the API during processing – though it is not a prerequisite. The typical solvent used in MNP

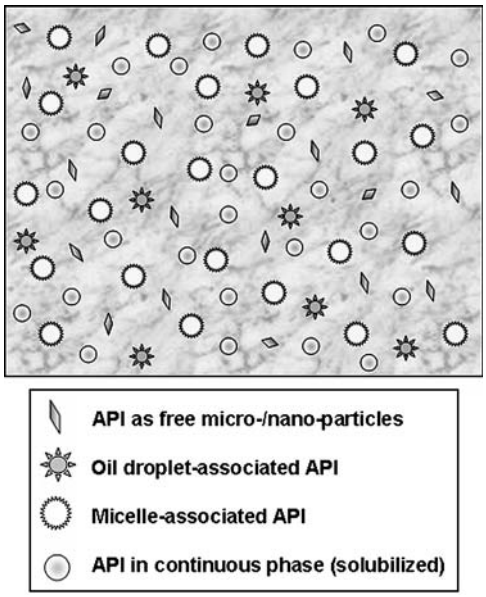

Figure 2.1 Schematic representation of the micro/nanostructures within an MNP formulation showing the different API components.

preparation is ethanol. In addition, stable MNPs can be obtained using other solvents such as propylene glycol, low-molecular-weight polyethylene glycols, triacetin, and *N*-methylpyrrolidinone. The solvent plays an important role in controlling the solubilized fraction of the drug, which is a key facilitator for rapid transmembrane permeation of the API.

The stabilizers used are generally non-ionic surfactants. Stable MNP preparations have been prepared using both hydrophilic and lipophilic stabilizers that encompass a wide hydrophilic–lipophilic balance (HLB) range. The surfactants include such classes as sorbitan esters, glycerol esters, block copolymers, polyethylene glycol esters, and ethoxylated fatty esters. The surfactant helps to sterically stabilize the micro/nanoparticles and the oil droplets, besides contributing to formation of the micellar phase.

The oil forms the internal phase of the emulsion. Depending upon the properties of the drug, the oil phase can accommodate an API fraction in soluble form. Some of the oils used are mineral oil, vegetable oils (soybean, corn, etc.), medium-chain triglycerides, and squalane. The aqueous medium used is generally purified water. A buffering agent may be included to maintain the pH and maximize stability of the API. The product-specific composition of the MNP formulation is dependent on the physicochemical

properties of the API, the therapeutic need, intended site of action (local or systemic), and target product profile.

For topical or transdermal administration, MNPs can be classified as a type of microreservoir-dissolution-controlled system that can be tailored to deliver drugs topically (skin being the site of action) or transdermally (systemic availability). The physicochemical properties of MNP formulations can be tailored for a given route of administration. This may encompass adjusting the viscosity appropriately for topical or transdermal formulations, incorporating a mucoadhesive for vaginal or rectal administration, changing the particle/droplet size, tuning the formulation composition and components, adjusting the zeta potential, or tailoring the fraction of drug in solution versus in suspension. In a highly fragmented transdermal drug delivery market, MNP is the only passive, nanotechnology-enabled, cosmetically appealing, lotion-like topical dosage form offering a tunable delivery profile for a wide range of APIs. Figure 2.2 depicts a model for deposition of the MNP formulation within skin layers. The composite structures within the MNP preparation are complementary to the skin architecture and we hypothesize that this facilitates stratified positioning of the API within different skin layers.

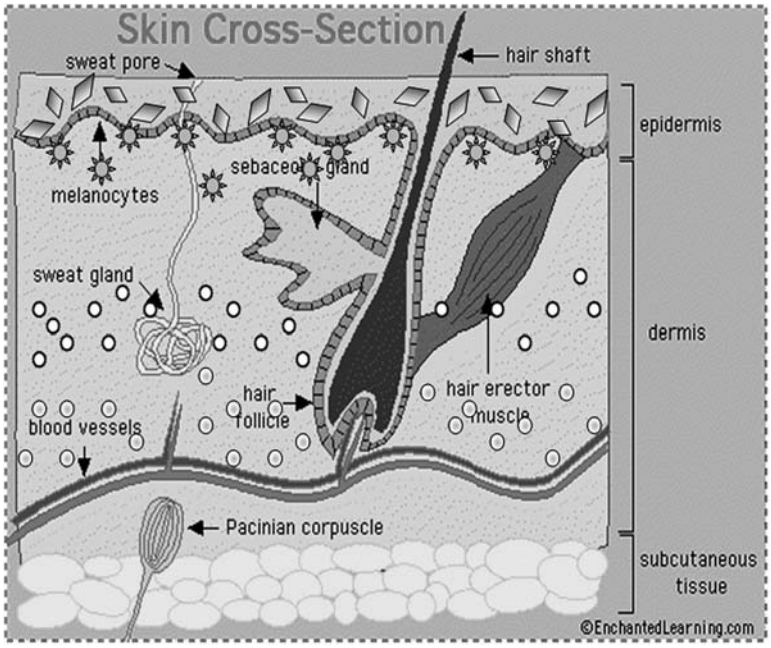

Figure 2.2 Schematic representation (hypothesis) of deposition and disposition of MNP structures within skin layers showing stratification of API.

2.1.2 Physicochemical characterization

The composite and multiphasic nature of the MNP formulation makes it difficult to capture the complete picture with a single characterization tool. Being the first of its kind, Estrasorb underwent tight scrutiny by the US FDA during the approval process, which led to state-of-the-art quality control test procedures (including particle sizing, crystal quantity, crystal number, *in vitro* release test).

The physical appearance of MNPs has been captured using transmission electron microscopy (TEM; negative staining with phosphotungstic acid – Figure 2.3) as well as freeze-fracture electron microscopy (FFEM – Figure 2.4). The TEM image captures the internal emulsion droplets, while FFEM shows oil droplets as well as micelles (tiny nubbles spread throughout the image – approximate size 8 nm). Particle size analysis (using dynamic light scattering) confirms the coexistence of micelles and oil-in-water (o/w) emulsion droplets (Figure 2.5). It is worth noting that particles fall into two fairly tight peaks of uniform size, with a peak at 8 nm representing the micelles and the second peak at 110 nm representing the oil droplets. Furthermore, particle size can be modulated via alterations to the manufacturing process or the formulation.

The amount of drug present as solid particulates varies and correlates with drug loading and the solubility of the API. Typically, the particle size of a poorly water-soluble API (i.e. acyclovir) can be effectively reduced to less

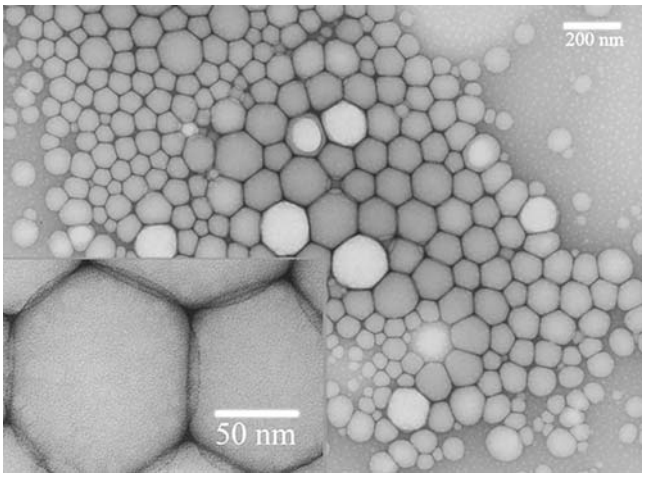

Figure 2.3 Transmission electron microscopic (TEM) image of a representative MNP formulation manufactured using a high-pressure process.

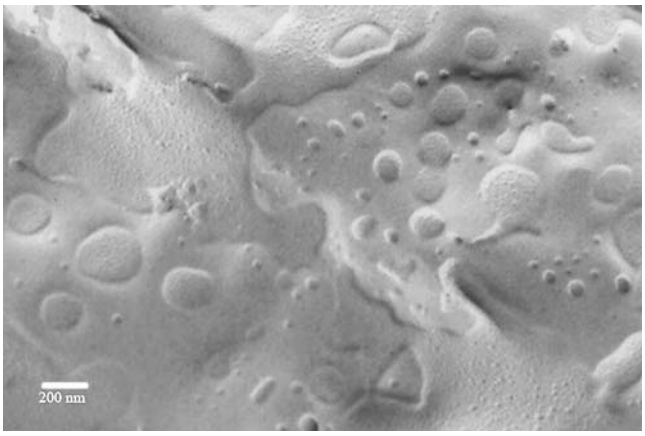

Figure 2.4 Freeze-fracture electron microscopic (FFEM) image of a representative MNP formulation manufactured using a high-pressure process.

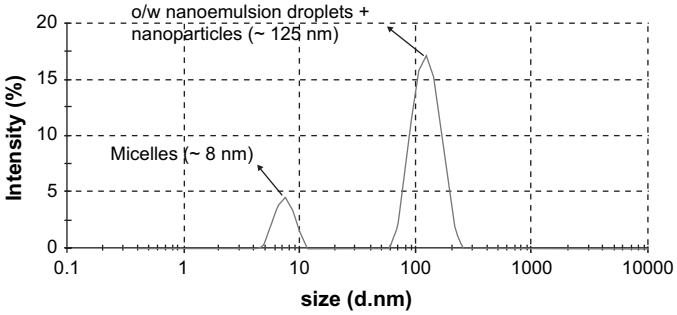

Figure 2.5 Particle size data for a representative MNP formulation showing co-existence of o/w emulsion droplets and micelles.

than 3 μm in the MNP formulation. Figure 2.6a shows the particle size of the API (raw material – before incorporation into MNP formulation) and Figure 2.6b shows the size of the o/w emulsion (approximately 200 nm) and the solid particulate drug upon formulating into the MNP product. The particle size of the droplet and particulates can be tailored by choosing the appropriate manufacturing technique (high-shear or high-pressure).

The viscosity of the MNP formulation can be tuned depending upon the intended application. For a lotion-like appearance, a viscosity of about 80–350 mPa s can be achieved. A stiffer preparation (like a semisolid) can be obtained by incorporating a suitable thickening agent (i.e. carbopol, xanthan gum, stearyl alcohol). The nature and amount of oil and stabilizer also play a role in modulating the viscosity of the final product.

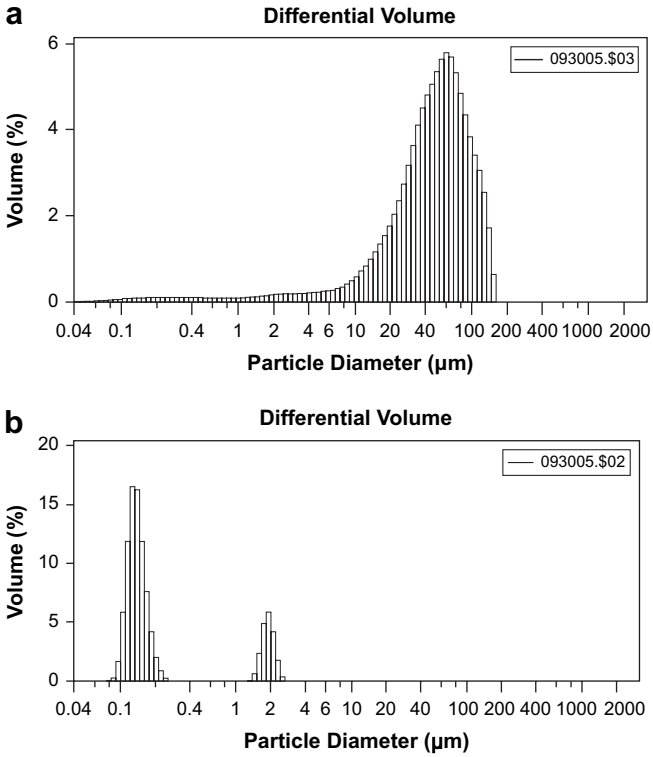

Figure 2.6 Particle size data for acyclovir. (a) Raw material. (b) Upon formulating as MNP product.

Optimized MNPs are highly stable products. The validated shelf-life claim for the commercial product based on MNP technology (Estrasorb™) is 3 years at room temperature with excursions allowed to 40°C. It has been demonstrated that there is no Oswald ripening phenomenon occurring in the MNP product, and that both the number of crystals per unit volume and crystal quantity of the API (estradiol) remain stable during room temperature and accelerated stability storage conditions. The MNP vehicle composition can be altered to offer enhanced thermal stability and some preparations can withstand a standard terminal heat sterilization cycle (i.e. 120°C for 25 min at 15 psi).

2.1.3 Antimicrobial properties

The MNP composition is inherently antimicrobial. Figure 2.7 depicts the results of the United States Pharmacopeia (USP) antimicrobial effectiveness test (AET) for a representative placebo MNP formulation. The results indicate that the MNPs are not only microbistatic, but are essentially

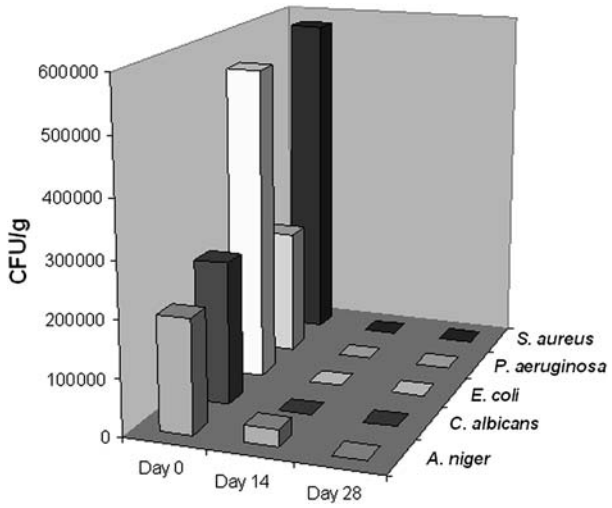

Figure 2.7 Antimicrobial effectiveness testing (USP) data for a representative placebo MNP preparation.

microbicidal. This can be attributed to the nano-size of the preparation and the nature of the composition (i.e. the high concentration of non-ionic surfactant). However, MNPs exhibit good safety profiles and they are relatively non-irritating dermally. This property offers commercial benefits such as the possible elimination of an antimicrobial preservative (especially for product filled in a multi-dose container), or the possible synergy of the microbicidal effect of an MNP preparation when formulated with an antibacterial, antifungal, and/or antiviral API.

2.2 TRANSDERMAL DRUG DELIVERY APPLICATIONS OF MNP TECHNOLOGY

2.2.1 Estrasorb™ – commercial validation of MNP technology

MNP technology was originally developed for transdermal delivery of APIs. MNP technology has been applied for estrogen replacement therapy with 17β-estradiol in Estrasorb (Estrasorb Package Insert, http://www.estrasorb.com/EstrasorbBrief.pdf) – Novavax's first internally developed FDA-approved product and the only emulsion-based formulation in the topical estrogen replacement market (primary indication being moderate-to-severe vasomotor symptoms associated with menopause). Estrasorb is the world's first nano-engineered topical dosage form that is approved by the US FDA for hormone replacement therapy, and represents commercial validation of the MNP technology.

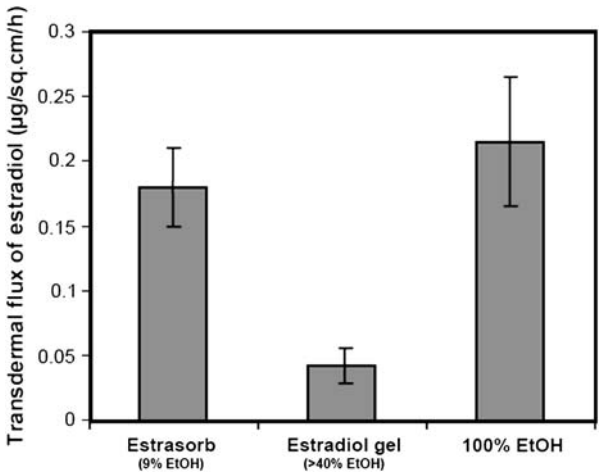

Figure 2.8 *In vitro* (Franz cell–cadaver skin assembly) data comparing transdermal flux rates for estradiol preparations.

The principal driving force behind transdermal flux is the concentration gradient. An *in vitro* Franz cell study was conducted using human cadaver skin to compare the relative flux rates obtained for Estrasorb (containing about 9% w/w ethanol), a commercial estradiol gel (containing about 40% w/w ethanol), and a 100% ethanolic solution of estradiol (Figure 2.8). The three formulations were applied on the skin at equivalent estradiol concentrations and the concentration of drug that permeated across the skin into the donor compartment was measured as a function of time. The results indicated that there was no significant difference between the 100% ethanolic solution and Estrasorb – while the gel exhibited one-fourth the rate of drug transfer of Estrasorb. This supports the claim that the composition of the MNP formulation promotes improved product–skin interactions and drives the API more efficiently across the skin – in a comparable fashion to a pure drug solution.

MNPs behave like a pseudo-patch or patchless-patch. The data from human clinical trials are shown in Figure 2.9 (once-daily application of 3.45 g of Estrasorb containing 0.25% w/w estradiol in 100 patients). It took approximately 2 weeks to attain steady-state plasma levels. A constant and controlled infusion of the drug from the topically applied estradiol emulsion maintained the drug at therapeutic levels for prolonged periods of time. Such a "depot effect" can be attributed to the multiphasic composition of the MNP preparation and stratified skin deposition upon dermal application, which results in establishment and maintenance of a concentration gradient across the skin. As the API from deeper skin layers becomes

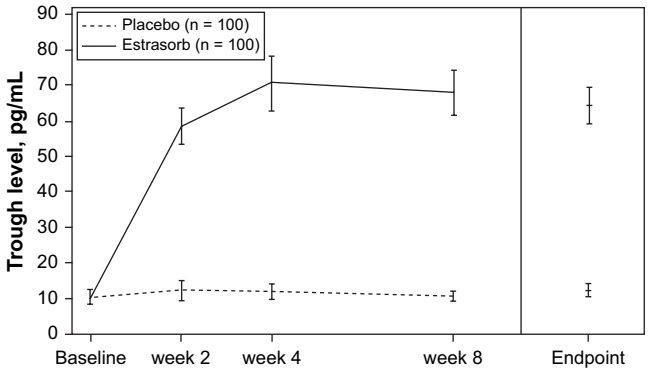

Figure 2.9 Mean trough serum estradiol concentrations following daily topical application of 3.45 g of Estrasorb™ containing 2.5 mg/g estradiol for 12 weeks.

depleted (through absorption into systemic circulation), more API dissolves from the solid particulate drug reservoir (deposited in superficial skin layers), maintaining a steady drug infusion. The effective plasma half-life for estradiol in Estrasorb (57.6 h) is significantly higher as compared to the commercial estradiol gel (36 h) or oral tablet (16.5 h). This provides strong evidence of the patch-like delivery profile for the MNPs.

Several small-molecular-weight compounds have been evaluated to prove the versatility and expandability of the MNP technology. A testosterone MNP formulation (Androsorb™) has completed phase I clinical evaluation for two indications: hormone replacement therapy in hypogonadal males, and to treat sexual dysfunction in females. A brief list of APIs that have been successfully formulated as MNP products and have completed key proof-of-concept (PoC) investigation has been compiled in Table 2.1.

Two case studies are presented, which will help define the MNP technology in terms of delivering a nontraditional transdermal API (raloxifene), or tuning the delivery profile for a classical transdermal candidate (nicotine).

2.2.2 Raloxifene MNP product

Raloxifene is a selective estrogen receptor modulator that belongs to the benzothiophene class of compounds. It is commercially available in tablet form. Approximately 60% of the oral dose is absorbed, but extensive hepatic conjugation to a number of inactive glucuronides results in an absolute bioavailability of 2%. The rationale for developing a transdermal delivery system for raloxifene was based on two considerations: (i) if therapeutic concentrations of raloxifene could be delivered to the systemic circulation transdermally, high hepatic concentrations would be avoided – thereby

Table 2.1 Proof-of-concept studies for various APIs formulated using MNP technology

API and indication	PoC investigation model	Key outcomes
Traditional transdermal APIs		
Testosterone (hormone replacement therapy in males or female sexual dysfunction)	• Phase I completed for both indications	• Pharmacokinetic end-points have been met in phase I • Dose-dependent blood levels seen in males and females • Same strength formulation can be used for both indications – simply by varying the amount applied
Nicotine (smoking cessation)	• *In vitro* Franz cell–cadaver skin study for formulation screening • Preclinical pharmacokinetic evaluation in rabbits	• Not a replacement product for patch • Product ideally suited for intermediate duration of action (3–6 h) to address withdrawal symptoms • Delivery profile can be tuned to fit quick onset of action (to address craving)
Oxybutynin (urinary incontinence)	• Preclinical pharmacokinetic evaluation in rabbits	• Data showed clinically exploitable transdermal delivery profile • Ideal formulation for treating urinary incontinence considering the drawbacks of the commercial patch • Can be tuned to create once-a-day application product
Fentanyl (severe pain)	• Preclinical pharmacokinetic evaluation in rabbits	• Data demonstrate a product with a rapid onset of action (and pain relief) • Opportunity to create an abuse-resistant product through formulation engineering
Clonidine (hypertension)	• Preclinical pharmacokinetic evaluation in rabbits	• Data showed clinically exploitable transdermal delivery profile • Can be tuned to create once-a-day application product

Nontraditional transdermal APIs		
Raloxifene (osteoporosis in postmenopausal women)	• *In vitro* Franz cell–cadaver skin study for formulation screening	• Data showed clinically exploitable transdermal delivery profile – unlike the hydro-alcoholic gel (50% ethanol), which showed zero transdermal delivery
Alprostadil (erectile dysfunction)	• Preclinical pharmacodynamic evaluation in rabbits (vasodilatation in ears)	• Positive data showed improved efficacy over pure ethanolic solution • Significant degree (visual scoring) and extent (vein diameter) of vasodilatation suggest an increased probability of success for use as localized treatment for erectile dysfunction
Cetirizine (antihistaminic)	• Preclinical pharmacokinetic evaluation in rabbits	• Data showed clinically exploitable transdermal delivery profile • In addition, the product is likely to offer significant benefits at the site of action (i.e. local inflammation)
Naltrexone (narcotic antagonist)	• Preclinical pharmacokinetic evaluation in rabbits • *In vitro* Franz cell–cadaver skin study for formulation screening	• Data showed clinically exploitable transdermal delivery profile
Cyclobenzaprine (antispasmodic)	• Preclinical pharmacokinetic evaluation in rabbits	• Data showed clinically exploitable local and transdermal drug delivery profile

reducing or avoiding adverse effects on coagulation factors and the consequent risk of thromboembolism; and (ii) by avoiding extensive first-pass metabolism to inactive metabolites, the total amount of raloxifene required to achieve therapeutic concentrations is reduced – with an expected result of a reduction in the adverse effects of metabolites. The physicochemical properties of raloxifene (molecular weight 473, melting point 145°C, log *P* 5.7, water solubility 0.25 mg/L) make it challenging to formulate using conventional transdermal technologies, and difficult to create an elegant topical formulation.

An MNP-based raloxifene formulation was prepared at 3% w/w of raloxifene base. The inactive ingredients were ethanol, benzyl alcohol, soybean oil, poloxamer 188, and water. A control formulation was prepared at the same drug loading using 50% w/w ethanol in 4% w/w hydroxypropylmethylcellulose (HPMC) aqueous gel. The rate and extent of drug transportation across human cadaver skin was evaluated *in vitro* using a Franz cell assembly. A known quantity (20 or 80 mg) of each test article was applied per cell (area of exposure = 0.64 cm^2) and the quantity of raloxifene diffusing across the skin into the receptor medium (phosphate-buffered saline (PBS), pH 7.4–ethanol, 60:40 v/v) was measured as a function of time.

The results are summarized in Figure 2.10. There was no recorded transdermal drug transportation across the skin with the control formulation (gel) up through 48 h – even though the formulation contained 50% w/w ethanol. The MNP formulation produced significant passive transdermal

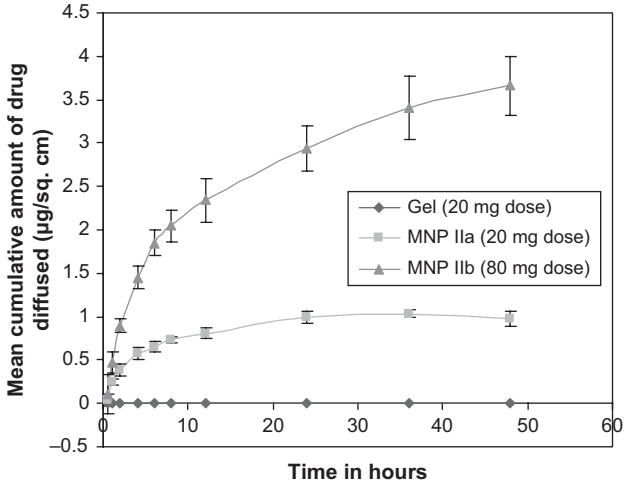

Figure 2.10 *In vitro* (Franz cell–cadaver skin assembly) data comparing transdermal flux rates for MNP compared to gel raloxifene preparations.

drug flux and showed a linear dose–response (MNP IIa and IIb) relationship at two doses – a fourfold increase in the amount of raloxifene applied resulted in a corresponding fourfold increase in transdermal drug flux. Based on these data, 2 g of 3% w/w MNP product (60 mg raloxifene) applied on two thighs (~375 cm^2 each) could provide the targeted 1.2 mg/day dose (equivalent to a single oral dose of 60 mg).

It is evident from this study that the MNP technology can facilitate transdermal transportation of APIs that may not be considered as the ideal candidates for transdermal delivery, or that cannot be formulated using conventional dosage forms.

2.2.3 Nicotine MNP product

Nicotine is an alkaloid found in the nightshade family of plants, predominantly in tobacco. It functions as an antiherbivore chemical, being a potent neurotoxin with particular specificity to insects. In low concentrations (an average cigarette yields about 1 mg of absorbed nicotine), the substance acts as a stimulant in mammals and is one of the main factors responsible for the dependence-forming properties of tobacco smoking. The pharmacologic and behavioral characteristics that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine.

Current nicotine products include chewing gum, oral lozenge, nasal spray, oral inhalant, and transdermal patch. The objective of the nicotine MNP product is to provide controlled and continuous delivery of nicotine through the skin. The MNP formulation can be customized with respect to onset and duration of action. Based on *in vitro* data (given below), it is expected that the MNP product will have an intermediate pharmacokinetic profile falling between that of a gum and a patch.

The physicochemical properties of nicotine (molecular weight 162.26, melting point −79°C, log *P* 1.305, oily liquid but miscible in water) make it an ideal fit for transdermal therapeutics – this fact is evident through the multitude of transdermal formulations commercially available. However, for a nonpolymer-based topical lotion technology like MNP, the challenge is to deliver the drug upon dermal application over longer periods of time. The objective of the *in vitro* proof-of-concept study (Franz cell–cadaver skin assembly) was to demonstrate the capability of the MNP technology to modulate the rate and extent of nicotine delivery through variations in the formulation.

Four different MNP formulations were prepared with different excipients and at different drug-loading levels. Nicoderm® patch was used as the standard, and a hydro-alcoholic gel (HPMC based) as the control (Table 2.2). The first-generation MNPs were prepared using essentially the same components and process as used in Estrasorb, while the second-generation MNPs used different components and a different manufacturing process. In addition to the formulation variables given in Table 2.2, the nicotine MNPs were further optimized with varying quantities of inactive ingredients and pH (data not presented).

Forty milligrams of each test article (or a single Nicoderm patch per cell) were applied to the cadaver skin (donor side of the Franz cell) with 0.64 cm^2 area of exposure. The quantity of nicotine diffusing across the skin into the receptor medium (PBS, pH 7.4–ethanol 90:10 v/v) was measured as a function of time (Figure 2.11).

The Nicoderm patch exhibited a greater rate (flux) of drug transfer across the skin (refer to Table 2.2 for flux rates; graph for Nicoderm not shown due to significant difference in scale). The drug–polymer matrix within the patch not only ensured a continual concentration gradient, but a larger one when

Table 2.2 Formulation, dose, and flux data (*in vitro*) for nicotine MNP products

Formulation	Transdermal flux (mg/15 cm^2/24 h)
Nicoderm patch (78 mg/patch)	42.03
Nicotine gel (14 mg/g) (ethanol, HPMC, citric acid, water)	6.95
Nicotine MNP, first gen. (30 mg/g) (ethanol, soybean oil, polysorbate 80, citric acid, water)	4.67
Nicotine MNP, second gen. I (14 mg/g) (ethanol, squalane, poloxamer 188, citric acid, water)	7.82
Nicotine MNP, second gen. II (14 mg/g) (squalane, poloxamer 188, citric acid, water)	1.22
Nicotine MNP, second gen. III (50 mg/g) (ethanol, soybean oil, poloxamer 188, tartaric acid, water)	13.49

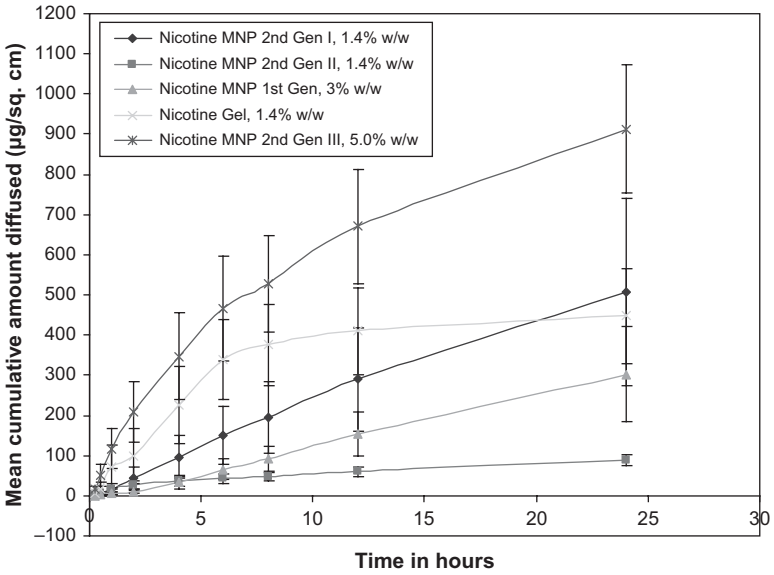

Figure 2.11 *In vitro* (Franz cell–cadaver skin assembly) data comparing transdermal flux rates for MNP compared to gel nicotine preparations.

compared to the MNPs or gel (0.64 cm^2 of patch contained approximately 3.33 mg nicotine vs. 0.56, 1.2, and 2.0 mg of nicotine for 14, 30, and 50 mg/g strengths respectively). The nicotine gel had no effective control over drug disposition as it followed a first-order release during the initial 8-h release phase and reached a plateau within about 8 h. The two second-generation MNP formulations (I and II) containing the same loading of nicotine as the gel (14 mg/g) not only exhibited prominent control over drug transportation rates (zero-order release), but also a significant difference in the rate or drug transport (sixfold difference in flux). This was essentially because of the difference in the composition of the two MNPs, which were tailored to release the drug at faster or slower rates. In spite of having higher drug loading (30 mg/g), the first-generation MNP showed a lower drug transportation pattern than the second-generation MNP I, which can be attributed to the difference in formulation components.

2.3 TOPICAL DRUG DELIVERY APPLICATIONS OF MNP TECHNOLOGY

Although the transdermal drug delivery field has enjoyed a significant amount of research effort and technological breakthrough, there has not been much corresponding innovation taking place in the field of topical drug delivery. The majority of the dosage forms are limited to traditional

creams, ointments, and gels. Some of the new additions have been sprays, foams, and patches. MNP technology can be exploited to design improved topical dosage forms that deliver the API locally (at site of application) in an efficient and effective manner. It is possible to tailor drug deposition, disposition, and permeation kinetics through formulation engineering (altered composition, drug loading, droplet size, etc.). This concept has been demonstrated using acyclovir as the model drug. Commercially, a topical acyclovir product is available (Zovirax®) and is indicated for the treatment of recurrent herpes labialis (cold sores), for genital herpes, and in limited nonlife-threatening mucocutaneous herpes simplex viral infections in immunocompromised patients. The product needs to be applied topically five to seven times a day for 4–7 days. A comparative investigation (*in vitro* using Franz cell–cadaver skin assembly) was carried out with two MNP formulations (designed to differentiate topical and transdermal delivery) and Zovirax cream. All the formulations had a drug loading of 5% w/w. The product was applied to the skin (donor compartment), and drug that permeated across the skin as well as that retained within skin layers was estimated. The results are captured in Figure 2.12a and b. MNP I was designed to retain the API preferentially in the skin layers, while MNP II was engineered to facilitate transdermal permeation of the same drug. It is clear from the data that the transdermal flux rate for MNP I was comparable to that for Zovirax – but the amount of drug retained within skin was about twofold higher for the former. If this effect can be translated into clinical use (or *in vivo* systems), one can expect to witness:

- Increased rate of skin permeation, resulting in faster onset of action
- Greater degree of skin deposition, leading to higher local drug concentrations
- Skin depot effects, leading to longer drug residence time
- Potential reductions of total dose, frequency of application, or both.

In addition, the inherent antimicrobial nature of the MNP vehicle would be beneficial from a therapeutic and packaging perspective. Based on these benefits, the MNP technology could offer a novel perspective to the field of topical drug delivery – especially for nonsteroidal anti-inflammatory drugs (NSAIDs), antifungals, antibacterials, antivirals, antispasmodics, and vasodilatory drugs.

2.4 CONCLUSION

Transdermal drug delivery is not suited or clinically justified for all drugs, yet it is viewed to be much more limited than is warranted. MNP technology helps to incorporate and deliver many therapeutic compounds

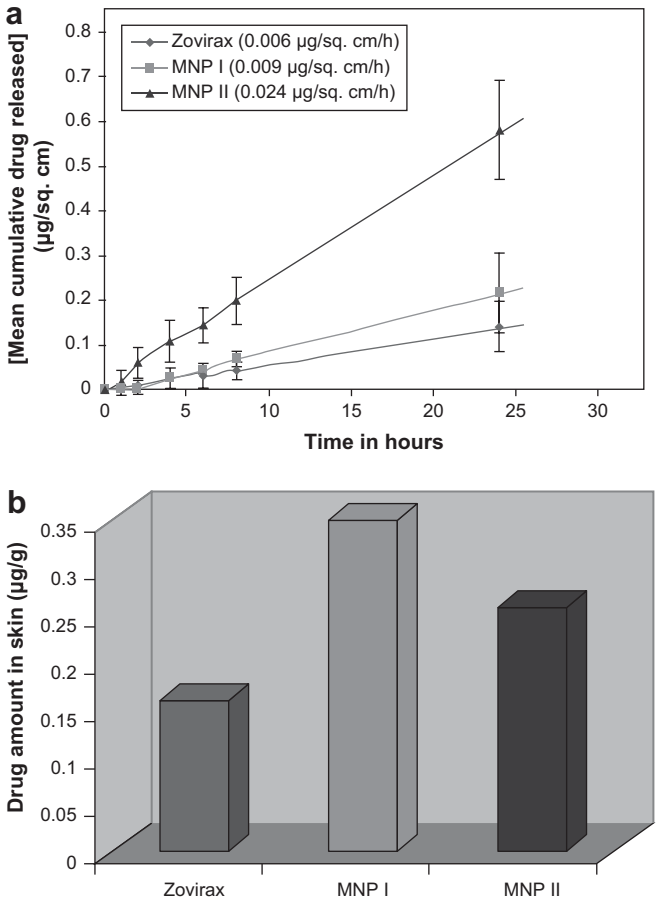

Figure 2.12 *In vitro* (Franz cell–cadaver skin assembly) data comparing acyclovir preparations. (a) Transdermal flux rates. (b) Amount retained within skin layers after 23 h.

that are otherwise viewed as unsuitable for transdermal delivery. MNP technology allows fast, low-cost product development compared with the typical development of new chemical entities. From proof of principle in a validated preclinical model through beginning a phase I study in humans requires approximately 12 months to complete. The data from the preclinical studies described here show a high probability of clinical success within a shorter development time frame, and a lower cost than a typical NDA (New Drug Application).

Research to date has shown the MNP drug delivery platform to be a versatile technology for multiple routes of administration (data not presented for ophthalmic, vaginal, and oral routes). Understanding the basic

physicochemical properties of MNPs has enabled a degree of control over pharmacokinetic parameters that may provide an attractive option for pharmaceutical formulators. The technology is validated for transdermal delivery and a commercial MNP product, Estrasorb, is manufactured on a kiloton scale. The Estrasorb ingredients are GRAS and the manufacturing process is attractive from a cost of goods perspective. The heterogeneous, multiphasic nanoemulsion that comprises the MNPs is surprisingly stable and, in some cases, amenable to terminal heat sterilization. Experiments have shown the potential for MNPs to be used for intranasal, vaginal, rectal, and parenteral routes of administration – for poorly water-soluble drugs in particular. Better commercial exploitation of the MNP technology, to its fullest potential, is expected in coming years.

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