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Review Article

Transdermal Spray in Hormone Delivery

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Abstract

This review examines advances in hormone delivery, particularly using transdermal spray. Transdermal gels, emulsions, patches, subcutaneous implants and sprays have been developed for transdermal hormone therapy in recent years. Transdermal sprays, in their general form of metered-dose transdermal spray, possess major advantages such as enhanced passive transdermal drug delivery with little or no skin irritations, improved cosmetic acceptability, dose flexibility, uniform distribution on the application site and ease of manufacture, and have thus assumed significant importance in hormone delivery. Estradiol, nestrone, testosterone and hydrocortisone aceponate are some of the drugs prepared as metered-dose transdermal spray. Results from recent surveys indicate that there is a market for the delivery system and ongoing development of transdermal sprays for hormone delivery.

Keywords: *Transdermal, Delivery systems, Metered dose, Spray, Hormone.*

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INTRODUCTION

Since the introduction of the first estrogen replacement therapy in 1942, hormone therapy has gain importance and new delivery systems have been developed to achieve minimum dose and adverse effects and maximum efficacy as well as patients' compliance [1]. Transdermal dosage forms are one of the best modes for providing foregoing expectations for hormone delivery compared with gels, emulsions, patches, and subcutaneous implants. Among these, patches and gels have been very popular owing to the increasing number of formulations [1,2] which are mostly developed for women. However development of hormone products for men has increased in the last decade [3] of which are several patches and gels of testosterone (TES) have recently become available [4].

Due to the possibility of local skin reactions observed with patches such as redness and irritation, blistering and tattooing, these have been frequently cited as reasons for discontinuation, and as a result, gels have gained importance [5,6]. Implant formulations are developed for efficient delivery of estrogens in particular for women with hysterectomy, libido problems, depression, or severe osteoporosis. However formulation variations which regulate the release rate of the hormone should be followed to improve efficacy of the subcutaneous implants [1]. As a transdermal approach, sprays offer comfort and availability of hormone delivery

[7-17]. In this review transdermal sprays hormone delivery have been examined.

TRANSDERMAL SPRAY

Transdermal sprays have been mostly designed as metered-dose sprays (MDTS) to provide a certain amount of formulation to the skin. MDTS was originally developed at the Victorian College of Pharmacy in Australia and commercialized by Acrux Limited [7,8] which is a topical solution made up of four main contents; drug, solvent systems (volatile:nonvolatile vehicle), polymers and penetration enhancers [8]. Estradiol, nestrone, TES and hydrocortisone aceponate can be exemplified as drugs prepared as MDTS. Generally chloroform, methanol, ethanol, acetone, isopropanol, dichloromethane and ether are used as solvents. Various natural, semi-synthetic, synthetic elastomer and synthetic polymers can be used. Mainly used penetration enhancers are: terpenes, terpenoids or essential oils, pyrrolidones and azones, fatty acids and esters, alcohols, glycols and glycerides, surfactants and phospholipids [7,9,10]. MDTS is used for low-dose delivery of steroids as a result of preliminary experience with estradiol and TES [7,11] and engineered with ACROSS® enhancers (Acrux, Melbourne) to form a depot within the skin (Patchless Patch™ Delivery, Acrux, Melbourne).

A MTDS product, Evamist, was approved by FDA at 2007. This product was developed for estradiol delivery with an 'invisible' skin delivery, and having dose flexibility presents a great level of appeal to users as well as maintaining an efficient concentration level for over 24 h [1,12]. Following application, it forms a fast drying, non-irritating and invisible film onto the skin. MDTS increases in drug diffusivity by stratum corneum lipid fluidization or lipid phase separation [9]. Following a once daily application, a sustained and enhanced penetration of drug across the skin can be achieved from the stratum corneum reservoir [7,10]. The physicochemical properties of non-volatile components have been selected so that they partitions rapidly into the stratum corneum and aid partition of drug into the stratum corneum, as well as serving to disrupt the ordered intercellular lipids and enhance permeation. Thus, this type of delivery system creates an invisible depot of drug and enhancer in the stratum corneum from which the drug can be slowly absorbed into the systemic circulation (Figure 1). This can provide delivery of drug over two to four days following a single application and sustained steady-state serum levels. Clinical experience with estradiol-MDTS to post menopausal women has shown increased higher plasma level of estradiol than the baseline value measured by radioimmunoassay [10]. Drug products using this technology are being developed in a range of therapeutic areas and are typically administered using a Metered-dose Transdermal System, MDTS® [12].

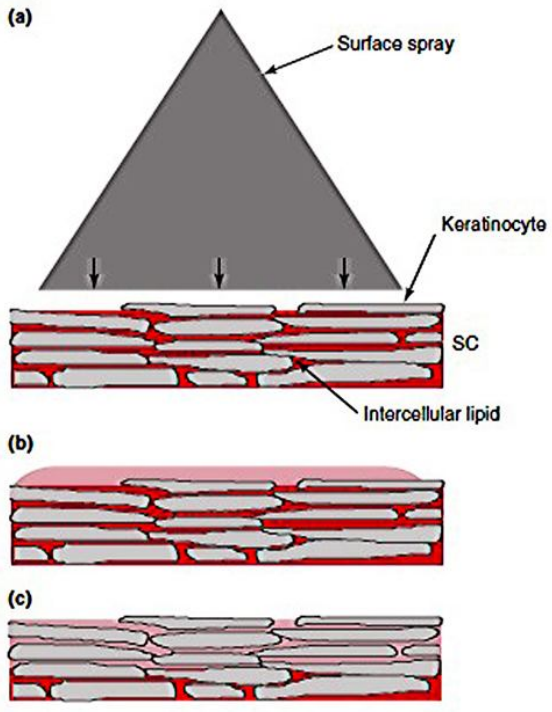

Figure 1: Schematic representation of time course of events with the metered-dose transdermal system (MDTS®; http://www.acrux.com); (a) Surface spray is applied to the stratum corneum (SC), (b) The 'forced partitioning' concept, involving the rapid evaporation of the volatile vehicle and then the partitioning of the drug and enhancer into the SC, (c) The drug and enhancer form a reservoir within the SC that is lipid in character and water resistant [7].

Potential advantages of these systems can be summarized include the following:

- Enhanced passive transdermal drug delivery with little or no skin irritation,
- Nonocclusive nature,
- Skin tolerability of the enhancers,
- Improved cosmetic acceptability,
- Dose flexibility,
- Uniform distribution on the application site,
- Simplicity of manufacture,
- Cost effective,
- Preference by patients against other transdermal deliveries [9-11,15-17].

In a safety announcement, the US Food and Drug Administration (FDA) warned that children who are unintentionally exposed to Evamist that is intended to be sprayed on the forearm between the wrist and elbow may undergo premature puberty. Girls may experience nipple

swelling and breast enlargement; boys also could develop enlarged breasts. Pets exposed to the drug may experience mammary or nipple enlargement and vulvar swelling [18].

Some of the identified sunscreen penetration enhancers such as octisalate (OS) or padimate O (PO) have been shown to enhance the transdermal delivery of various hormonal steroids, both in vitro and in vivo [16,19,20]. However combination of OS and PO with other enhancement strategies has not been extensively investigated and in this respect combining this technology with other methods of enhancement, greater absorption of TES may be possible, resulting in an improved treatment modality for male hypogonadism [21].

Estradiol transdermal spray is a homogeneous liquid solution of 1.7 % estradiol in alcohol and octisalate that is supplied in a glass vial fitted with a metered-dose pump. The pump is encased in a plastic hand-held device that controls the distance, angle and area of application for each metered dose spray. One, two or three sprays are applied daily to nonoverlapping areas of the inner arm for treatment of moderate to severe vasomotor syptoms associated with menopause [22,23].

Transdermal 17 β-estradiol (E2) delivery simulates closely the circulating profiles of E2, estrone, and estrone sulfate normally observed in follicular phase premenopausal women than do oral systems [24,25], in addition problems occurred with patches E2 transdermal spray has been evaluated [24,26]. According to a randomized controlled clinical trial done by Buster *et al* [24], transdermal E2 spray in women with postmenopausal vasomotor symptoms supports the efficacy and safety of the first transdermal E2 spray approved in the United States for the treatment of moderate-to severe vasomotor symptoms in healthy menopausal women [24]. The dose regimen starts with one spray per day and can be increased to a maximum of three sprays per day in women for whom higher E2 levels may be necessary to achieve an acceptable reduction in vasomotor symptom frequency. This E2 “spray-on patch” is a treatment option for women who will benefit from the advantages of transdermal E2 delivery but are intolerant of or are not inclined to use patches, gels or emulsions [24].

Progestins such as, levonorgestrel and its derivatives, and Nestorone® (NES) related to their high progestational potency, pharmaco-kinetic properties, and activities have been successfully used in transdermal sustained release delivery systems. NES applied transdermally is highly active resulting in good systemic bioavailability for this reason transdermal spray is currently in development [27-29]. For consistent ovulation inhibition in normal cycling women, the MDTS containing NES may need to deliver sufficient drug transdermally to achieve average serum concentrations, approximately 250 pmol/L at steady state following daily dosing [28].

Another MDTS as a contraceptive method is in its development stages for delivery of NES and an estrogen prepared as a fast drying liquid formulation is used in a nonocclusive spray that can deliver NES through the skin surface. The serum levels of NES achieved with this system was found to be within the range of 285 – 290 pmol/L, which is sufficient to block ovulation and hence provide effective contraception [30]. Initial pharmacokinetic studies of spray formulation incorporating both NES and an estrogen [(E2) or 17-ethinylestradiol (EE)] [31] as Phase 1 study was designed to explore the possibility that the progestogen NES could be delivered once daily by the MDTS at an adequate dose to achieve serum levels capable of suppressing ovulation [30].

Transdermal delivery of TES from a spray was studied by Leichtnam *et al* [32]. Isopropyl-myristate (IPM) was found to be the most efficient excipient amongst the tried, as it was increasing TES transport by more than a factor of 5. The enhancing ability of IPM was also apparent when the drug was formulated in 3:1 ethanol/propylene glycol, a more compatible vehicle for use in a spray. IPM was incorporated into formulation directly over a range of concentrations from 10 – 25 %v/v and TES transport was evaluated when delivered from either a solution, or from a mechanical spray, or from an aerosol (which also contained 50 %v/v propellant) (Figure 2). At the highest level of enhancer, the flux was improved 2.5-fold from both the spray and the aerosol, relative to a control. However, these formulations were far from optimally conceived, in that the amount of drug which eventually contacted the skin represented only ~10% of the pulverized quantity from the spray, and ~40 % of that from the aerosol. Repeated application, especially from the aerosol, improved matters somewhat, but further work is clearly required before the concept can be developed for practical application [32].

TES transport from a series of ethanol/propylene glycol (PG)/water formulations was assessed in vitro across hairless rat skin, and the optimal

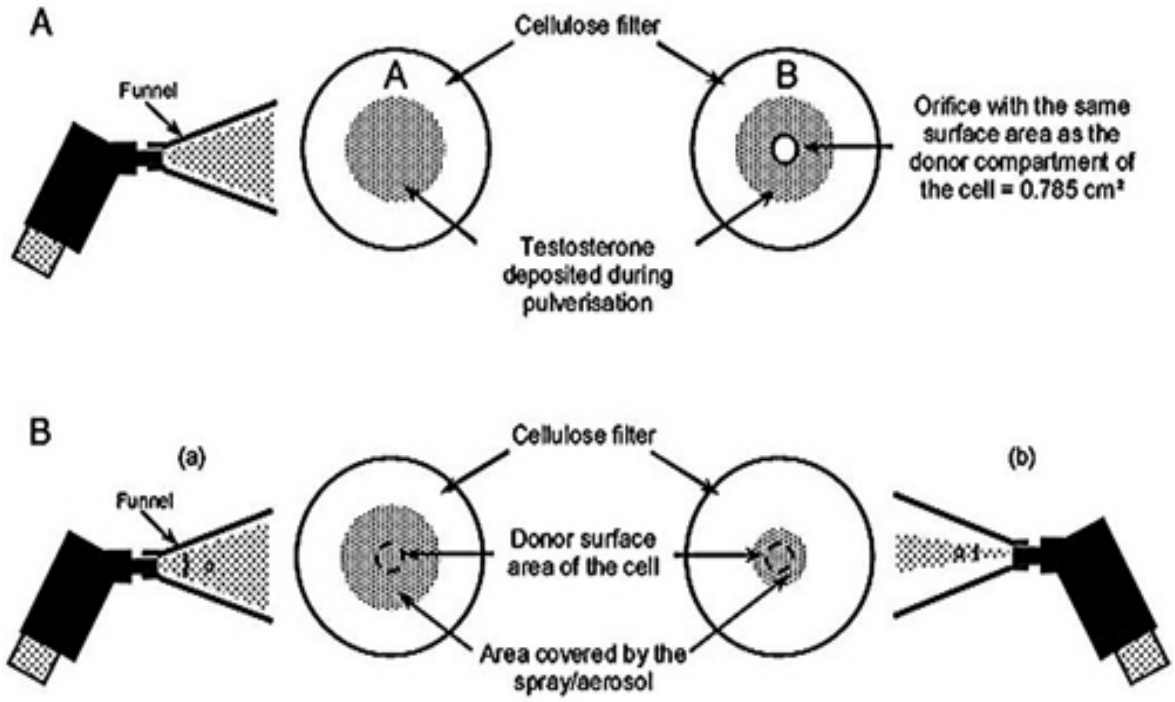

Figure 2: A. Evaluation of the amount of drug deposited on the skin. B. Schematic illustration of an experiment characterizing the deposition patterns of a formulation delivered from either (a) a mechanical spray, or (b) an aerosol. α is the so-called pulverization angle [35].

composition determined. The formulation was then modified for delivery from a mechanical spray, and from an aerosol containing a high percentage of propellant. Drug transport was greatest from a saturated solution in 1:1:1 ethanol/PG/water, however, formulation as an aerosol produced primarily unstable vehicles due to phase separation and crystallization (except 3:1 ethanol/PG combination) (Figure 3).

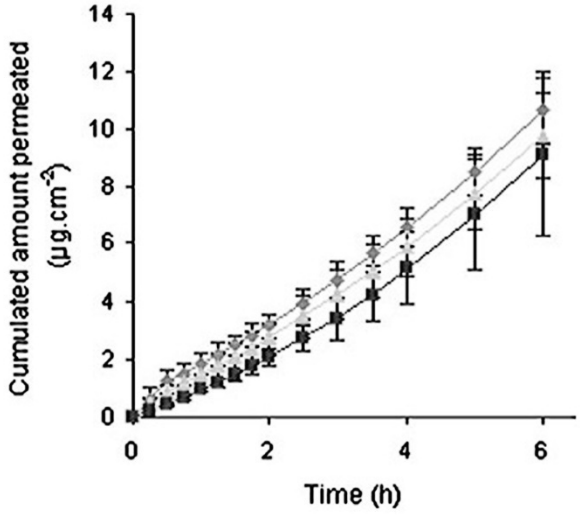

Figure 3: *In vitro* TES permeation from an ethanol/PG (3:1) saturated formulation delivered as either a spray (◊), an aerosol (Δ) or a solution (□). Data are mean ± SD (n = 4) [36].

Eliminating water to improve sprayability identified 1:1 ethanol/PG as a vehicle, which might allow transient supersaturation (and improved delivery). However, this effect was not improved by using a pressurized aerosol due to instability. Finally, TES fluxes were 5- to 10-fold lower than those required for useful transdermal therapy [33].

In a pilot study done by Davison *et al* showed that, TES therapy improved cognitive performance in the areas of visual and verbal learning and memory in healthy postmenopausal women stabilized on estrogen, over 26 weeks. When the treatment group was compared to a nonintervention group of women the significant effect of TES treatment was on the cognitive domain of verbal learning and memory. TES improved cognitive performance in the domain of verbal learning and memory in a pilot study of healthy postmenopausal women and is worthy of further exploration in a randomized placebo controlled study [34].

In the study of Morton *et al*, steady-state pharmacokinetics of estradiol and its metabolites, estrone and estrone sulfate, following application of a novel estradiol transdermal spray to healthy postmenopausal women was evaluated [35]. Participants were randomly assigned in parallel to receive 1-, 2-, or 3-spray doses (24 participants/dose level) of a 1.7 % estradiol metered-dose transdermal spray (1.53 mg/spray)

once daily for 14 days. It was shown that, estradiol MDTS delivers drug at therapeutic levels and produces low serum estrone concentrations [35].

A case of hyperpigmentation due to application of estradiol spray was reported by Diven and Crawford. A 48 year old postmenopausal female noted hyperpigmentation of the left areola 3 months after beginning estradiol spray to her left forearm. She then applied the spray to the right forearm instead until the areolae were the same color again and then applied 1 spray to each forearm thereafter [36].

Questions regarding the benefit–risk profile of hormone therapy have prompted some women to seek alternative therapies. Compounded bioidentical hormone therapy has been promoted as a potentially safer option than conventional hormone therapy. However, there are lacks of sufficient data from well-designed comparative trials to support the safety or efficacy of this approach. Compounded bioidentical hormone formulations may be associated with additional risks for variability in quality, purity, and batch-to-batch consistency. There remains a need for studies of compounded bioidentical hormones and combination formulations, conducted according to clinical evidence-based guidelines, to provide support for their usage [37].

CONCLUSION

Transdermal spray in hormone therapy is a fast-growing and promising approach, especially for post-menapausal hormone therapy. Advances in transdermal spray have increasingly brought about rate-controlled delivery with fewer side effects as well as increased efficacy and steady drug delivery.

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