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Formulation and optimization of desogestrel transdermal contraceptive patch using crystallization studies

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ABSTRACT

Levonorgestrel (LNG) is the most commonly used progestin in contraception. In this study, we report the use of an alternative progestin, desogestrel, for transdermal contraception. The drug was found to be significantly more permeable as compared to LNG ($p < 0.05$). Crystallization studies were used to select the best adhesive among acrylate (Duro-Tak 87-4098 and Duro-Tak 87-202A) and polyisobutylene (PIB, Duro-Tak 87-608A) pressure sensitive adhesives by determining the drug's saturation solubility in them. The use of copovidone and mineral oil as formulation excipients was investigated to increase drug loading in the PIB adhesive. Physical characterization of the patches was performed using *in vitro* drug release, content analysis, patch weight and thickness variations and rolling ball tack and peel adhesion studies. Optimized patches were evaluated for *in vitro* transdermal delivery across hairless rat skin. The saturation solubility of desogestrel was found to be approximately 49.3% (w/w) and 55.6% (w/w) in Duro-Tak 87-4098 and Duro-Tak 87-202A acrylate adhesives, respectively. The saturation solubility of desogestrel was significantly lower (3–4%, w/w) in the PIB adhesive. Mineral oil (10%, w/w) and copovidone (30%, w/w) were found to be optimum for increasing drug loading and patch cosmetics. Results from the physical characterization studies suggest that a uniform and reproducible 7 day drug-in-adhesive patch could be developed.

1. Introduction

Progestogens are one of the most commonly used families of drugs for contraception. These are known to produce their pharmacological effect by suppressing pituitary gonadotropin secretion resulting in follicular development inhibition and ovulation inhibition and also by altering the cervical mucus to inhibit sperm penetration. Progestogens used in the past were useful but in an attempt to develop more potent drugs for improved and safe contraception, scientists synthesized levonorgestrel by chemical modification. However, improvement in progestogenic activity was associated with simultaneous rise in intrinsic androgenic activity. To reduce latter, scientists suggested reduction in progestogenic dose or further chemical modification of the molecule. This led to the development of a new generation of progestogens. Desogestrel was the first of these to be developed for commercial use in Europe in 1981 for oral contraception. In comparison to levonorgestrel, desogestrel showed improved *in vitro* binding affinity to progesterone receptors and greater progestogenic effect on endometrial histology and ovulation inhibition. Further discussion regarding the structural comparison between the two drugs can be found in this publication (Lammers et al., 1998). Currently, several oral combination contraceptive preparations containing desogestrel and ethinyl estradiol are available in the US market. These are marketed under several brands names including Apri®; Azurette™; Caziant®; Cyclessa®; Desogen®; Emoquette™; Kariva®; Mircette®; Ortho-Cept®; Reclipsen® and Velivet™. These oral preparations are available as 21 or 28 tablet packages. The tablets have to be administered at the same time daily and missed tablets have to be followed by specific guidelines to compensate for missed doses (Lexi-Drugs and Online., 2012). Minimum daily dose of desogestrel for a woman with a regular menstrual cycle is 60 μg/day (100 μg/day for levonorgestrel). However, most marketed oral preparations consist of 150 μg drug (2.5 times the required dose), to provide enhanced safety margin. This increased drug loading in tablets has been reasoned as required because the majority of the users have been reported to forget taking one or two pills per cycle. Furthermore, the drug is known to undergo first pass metabolism with oral bioavailability reported to be around 84% and the elimination half life of desogestrel following a single dose is known to be 12.4 ± 1.9 h (Lammers et al., 1998). Thus, despite improved progestogenic activity, desogestrel in the currently available oral dosage forms is associated with the inconvenience of taking one pill daily, risk of pregnancy due to non-compliance

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with required regimen, unnecessary higher systemic drug exposure, high first pass metabolism and short elimination half life. Considering these limitations, delivery of desogestrel from a simple transdermal patch appears to be more reasonable. This is because transdermal delivery systems offer several advantages including reduced systemic drug exposure, bypass of first pass metabolism, suitability for drugs with short half lives, ease of self administration and termination and widespread acceptance of another available weekly patch product for delivery of a different steroid (Banga, 2011; Sitruk-Ware, 1995).

Transdermal patch technology has advanced tremendously since the first scopolamine patch was introduced in the market in 1979. It is due to today's advanced patch making technology that nearly a billion patches are manufactured every year (Prausnitz and Langer, 2008). These transdermal patches are classified into three types: drug in adhesive (consists of drug directly dispersed into adhesive polymer), reservoir (consists of a drug reservoir between a backing membrane and rate controlling membrane with a skin contacting adhesive layer) and matrix (consists of a drug reservoir in the center with a peripheral adhesive ring around the edges) patches (Ghosh et al., 1997; Subedi et al., 2010; Tan and Pfister, 1999). The selection of the most appropriate design of the transdermal system would depend upon several factors such as physicochemical properties of the drug, intended duration of application, drug amount to be delivered, whether or not dose titration will be required and others. Among the three designs mentioned above, the drug in adhesive patches is the simplest and the most commonly used design. In this, the drug is incorporated directly into an adhesive and is layered in between the backing membrane and a release liner (Lipp and Muller-Fahrnow, 1999). These patches offer advantages of being simple and elegant with smaller and thinner dimensions. From the manufacturing point of view, drug-in-adhesive matrix type patches offer advantages such as lack of drug leakage issues and ease of manufacturing over other transdermal systems (Kim and Choi, 2002; Minghetti et al., 2007). It is due to all these reasons why drug in adhesive patches have gained increased popularity among patients in the last two decades (Jain and Banga, 2010; Lipp and Muller-Fahrnow, 1999). Drug release from a drug in adhesive patch depends directly upon the drug concentration in the patch and follows first order kinetics. Upon release from the patch the drug diffuses passively through the skin layers to reach the systemic circulation, to produce the desired therapeutic effect. In order to facilitate this passive diffusion of the drug from the transdermal patches, a supersaturated state would be preferred in these patches (Hadgraft, 1999; Latsch et al., 2004; Lipp, 1998; Tan and Pfister, 1999). Supersaturation refers to a state in which the drug amount solubilized in a given vehicle exceeds its saturation solubility. In such a state, increase in the drug's thermodynamic activity is associated with an increase in drug permeation. However, such systems are metastable (thermodynamically unstable) and there is high probability that the drug will crystallize within such systems during storage (Kim and Choi, 2002; Ma et al., 1996; Minghetti et al., 2007; Variankaval et al., 1999).

Crystallization generally initiates with the formation of an embryo by collision of single drug molecules. The continuation of such collisions between the molecules results in an increase in the critical radius of the embryo that does not re-dissolve easily, resulting in the formation of a drug crystal. The crystal growth then continues until a state of saturation is achieved (Lipp, 1998). The development of crystals in transdermal patches is undesirable because it makes them unstable, could allow dangerous amounts of drug to be delivered, influences skin permeation negatively and reduces the esthetic appeal of the product leading to reduced patient product acceptability (Kim and Choi, 2002; Ma et al., 1996). Crystallization of sex steroids in drug-in-adhesive patches has occurred in the past and has been reported in the literature (Lipp, 1998; Lipp and Muller-Fahrnow, 1999; Ma et al., 1996; Yu et al., 1991). Most recently, the rotigotine patch (Neupro®) was recalled from the market in 2008 due to drug crystallization issues, as snowflake like crystals were detected on the patch surface (Chaudhuri, 2008). Thus, investigation into the crystallization potential of a drug in a specific formulation and the use of alternate approaches to prevent it are essential for the development of an acceptable and efficient transdermal product. A number of different approaches have been reported by which crystallization in a patch can be eliminated. These include reducing drug loading below the saturation solubility, pro-drug usage where the pro-drug has higher solubility in the formulation, use of co-solvents to increase solubility, adhesive modification to increase solubility of the drug in the adhesive, and crystallization inhibitors (Lipp, 1998). Among these the use of additives such as crystallization inhibitors and/or solublizers has been reported widely in the literature (Cilurzo et al., 2005; Jain and Banga, 2010; Kim and Choi, 2002; Kotiyan and Vavia, 2001; Lipp, 1998; Ma et al., 1996; Schulz et al., 2011). These additives include polyvinylpyrrolidone (PVP) and its derivatives, copovidone, crospovidone, dextrin derivatives, mannitol, polyethylene glycol, polypropylene glycol, poloxamer, Tween 80®, Labrasol® and glycerin (Jain and Banga, 2010; Kim and Choi, 2002; Lipp, 1998; Ma et al., 1996; Schulz et al., 2011). A number of mechanisms have been proposed in the literature by which these additives might prevent crystallization. These include additives getting adsorbed on the crystal surfaces, preventing the crystal nucleation process, and co-precipitate formation between the drug and the additives to form amorphous solids, *i.e.*, forming a solid "solution", which is a more plausible explanation of this phenomenon. Incorporation of these additives in the patch formulation helps in maintaining higher amounts of drug in the patch and in achieving higher drug flux across the skin for a longer time period. The hypothesis of crystallization inhibition is not well established; for example it was recently shown that PVP acts as a solubilizing agent for levonorgestrel and not as a crystallization inhibitor (Jain and Banga, 2010).

In this study, a 7 day transdermal drug in adhesive contraceptive patch using desogestrel was prepared, optimized and evaluated. For this, both slide and patch crystallization studies were performed to determine the saturation solubility of the drug in the patch components. The use of two acrylate adhesives and one polyisobutylene (PIB) adhesive was investigated. In order to increase drug loading in the PIB adhesive without causing crystallization, the use of two additives – copovidone (Plasdone® S-630) and mineral oil were also investigated. *In vitro* skin permeation studies were then performed using optimized patches. Physical characterization of these patches was also performed using drug release studies, patch content analysis, patch thickness and weight variation studies, rolling ball tack test and peel adhesion test.

2. Materials and methods

2.1. Materials

Desogestrel, copovidone (Plasdone® S-630), backing membrane (2 mil polyester with an ethylene vinyl acetate copolymer, Scotchpak™ 9732 from 3M) and release liner (3 mil fluoropolymer-coated polyester film, Scotchpak™ 9744 from 3M) were provided by Agile Therapeutics, Inc. (Princeton, NJ, USA). Mineral oil was obtained from Sigma–Aldrich (St. Louis, MO, USA). Acrylate PSA adhesives (Duro-Tak 87-4098 and Duro-Tak 87-202A) and a polyisobutylene (PIB) adhesive (Duro-Tak 87-608A) were obtained as gift samples from Henkel Corporation (Dusseldorf, Germany). PEG-400, gentamycin sulfate, tetra hydrogen furan (THF), and HPLC