Extended Abstract

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Formulation of the Tazarotene Cutaneous Gel and Its Physicochemical Characteristic

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Abstract

Treatment of psoriasis is divided to three main types: moderate treatment (moisturizers, phototherapy and etc.), low treatment (changing the life style) and high treatment include systemic medications.

Tazaroten is one of the most effective and the most applicable dermal medicine in treatment of two mentioned diseases that available in form of gel, cream and foam. This agent is one component of vitamin A derivatives and it is a selective receptor of acetylene retinoid that binds to beta and gamma retinoid acid receptors.

The purpose of this study is formulation of cutaneous gel of Tazarotene 0.1% that is not available in the internal market of medication in Iran.

So, first the basics of medicine prepared after changing in several stages of amounts and proportions of primary materials and the effective agent added to better formulation after related stability tests. Then the stability of the formula evaluated in terms of clarity, pH, lack of two phases in temperature of 4°C, 25°C and 40°C as well as viscosity, and the best formulation was selected in terms of stability. Then the tests of determination of the effective material amount in wavelength 351 nm was performed by method of spectrophotometer and HPLC, release of medicine in plasmatic membrane and dermal absorption in the medium of acetate ammonium buffer with pH=6.5 and 10% acetonitrile on the final formulation.

The final formulation contained 85% effective material that was in the optimal range in terms of releasing and dermal absorption, while adhere to Higouchi kinetics model.

Keywords: Tazaroten; Gel; Releasing; Formulation

Introduction

Tazarotene is a third-generation retinoid which is effective for topical treatment of psoriasis and acne vulgaris and has cosmetic benefits for photoaging. However, there are adverse effects accompanied with its use where local cutaneous irritation including burning, itching, erythema, peeling or dryness occurs in approximately one-quarter of patients using tazarotene.

Tazarotene (TZR), 6-[2-(4,4-dimethylthiochroman-6-yl) ethynyl] nicotinic acid ethyl ester is a member of a new generation of receptor selective, synthetic retinoids for the topical treatment of mild to moderate plaque psoriasis, acne vulgaris and photoaging. In comparative trials 0.1% tazarotene gel illustrated the highest irritation score followed by tazarotene cream compared to diverse concentration of tretinoin cream. In a later study, tazarotene foam 0.1% was found to be an elective to tazarotene gel with less systemic exposure.

Therefore, the development of new effective topical drug delivery system intended to modulate tazarotene release rate, enhance its localization in the skin and reduce its percutaneous absorption might minimize its adverse effects and could be of particular usefulness. Dermal safety studies also shown that TZR did not show phototoxic or photoallergic potential.

However, mild to direct local cutaneous irritation, with burning, itching, erythema, peeling, and/or dryness, was observed in approximately 25% of treated patients. So, it is necessary to improve the topical delivery and reduce the adverse effects of TZR using a carrier with the ability of skin targeting. A
literature survey revealed a high-performance liquid chromatography method for determination of TZR and its major active metabolite with mass spectroscopy. Isocratic RP-HPLC method with UV detection has been described for quantitative and related substance determination of TZR.12 However, HPLC-based separation methods may not be suitable for the determination of the drug from lipid-based delivery systems such as ME formulations. The formulations contain various lipophilic excipients that are not soluble in commonly used organic solvents used in RP-HPLC methods. Further, extraction of the drug from such lipophilic excipients may not be accomplished easily, and such excipients may get adsorbed on stationary phase. Hence, analysis of TZR, especially from lipid-based delivery systems, would be difficult with respect to identification of suitable solvents and stationary phases. Tazarotene is a retinoid prodrug which is changed over its active form, the cognate carboxylic acid of tazarotene (AGN 190299), by rapid deesterification in animals and man. AGN 190299 (“tazarotenic acid”) binds to all three members of the retinoic acid receptor family:

RARα, RARβ, and RARγ but shows relative selectivity for RARβ, and RARγ and may modify gene expression. The clinical centrality of these findings is unknown. Psoriasis: The mechanism of tazarotene action in psoriasis is not defined. Topical tazarotene blocks induction

of mouse epidermal ornithine decarboxylase (ODC) activity, which is related to cell proliferation and hyperplasia. In cell culture and in vitro models of skin, tazarotene suppresses expression of MRP8, a

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marker of irritation show in the epidermis of psoriasis patients at high levels. In human keratinocyte cultures, it inhibits cornified envelope arrangement, whose build-up is an element of the psoriatic scale. Tazarotene also actuates the expression of a gene which may be a growth suppressor in human keratinocytes and which may inhibit epidermal hyper proliferation in treated plaques. However, the clinical significance of these findings is unknown [6]. Acne: The mechanism of tazarotene activity in acne vulgaris is not defined. However, the premise of tazarotene's therapeutic effect in acne may be due to its anti-hyper proliferative, normalizing-of differentiation and anti-inflammatory effects. Tazarotene repressed corneocyte accumulation in rhino mouse skin and cross-linked envelope formation in cultured human keratinocytes. The clinical significance of these findings is unknown. Following topical application, tazarotene experiences esterase hydrolysis to form its active metabolite, tazarotenic acid. Little parent compound could be recognized in the plasma. Tazarotenic acid was highly bound to plasma proteins (>99%). Tazarotene and tazarotenic acid were metabolized to sulfoxides, sulfones and other polar metabolites which were eliminated through urinary and fecal pathways. The halflife of tazarotenic acid was approximately 18 hours, following topical application of tazarotene to normal, acne or psoriatic skin. The aim of this study was to provide a gel formulation of tazarotene %1.

Discussion and Conclusion

Tazarotene a retinoid drug that is already active form of D-esterification quickly becomes tazarotenic acid (which can be connected to all three of the retinoic acid receptors: RARα, RARβ, RARγ). It also selectively responds binds to the β and γ receptors.

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