



Research Article

## Effects of Transcutol P and Precirol ATO-5 on Percutaneous Absorption of Flutamide from Emulgels

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### Abstract

**Background:** Flutamide is a non-steroidal anti-androgenic agent which is not only used in treating prostate cancer but also can be effective in some disorders such as androgenic alopecia and male pattern baldness. Several serious side effects for systemic administration of flutamide can be overcome by emulgel dosage form. Absorption enhancers can promote permeation of flutamide through skin. Percutaneous absorption of Flutamide emulgels with different concentrations of Transcutol P and Precirol ATO5 was studied.

**Methods:** Various emulgel formulations using different concentrations of Transcutol P and Precirol ATO5 with 0.5 to 5% w/w were prepared. Percutaneous absorption was tested with standard Franz Diffusion Cell equipment using full thickness rat skin. Drug concentrations in the samples were analyzed by High-Performance Liquid Chromatography (HPLC) equipped with UV-Vis detector at 305 nm.

**Results:** The percutaneous absorption of flutamide emulgels formulated with enhancers was higher than control formulations. The enhancement ratio increased from 1.218 to 3.670 and 1.346 to 3.900 for Precirol ATO5 and Transcutol P, respectively. The area under the Curve (AUC) increased by increasing the enhancers' concentration and a significant upsurge was seen in the concentration 1% for both enhancers.

**Conclusion:** The flutamide emulgel containing 1% Transcutol P showed more appropriate percutaneous absorption through the skin compared to others.

### Introduction

Flutamide is a non-steroidal anti-androgenic agent which competitively binds androgen receptors and inhibits testosterone stimulation.<sup>1</sup> It is used to treat advanced prostate cancer as a hormone treatment to slow the growth of the tumor and in some cases, even shrink it.<sup>2</sup> Several unwanted side effects in systemic administration of the drug have been reported.<sup>3,4</sup> Thus, transdermal drug delivery could be an appropriate administration route to deal with systemic side effects. Transdermal drug delivery systems can be used due to some advantages such as bypassing the hepatic first pass metabolism, better patient compliance (non-invasiveness) and less systemic toxicity compared with other administration routes.<sup>5,6</sup> Several anti-cancers and other compounds from different drug classifications such as 5-fluorouracil, methotrexate, mefenamic acid and timolole have been evaluated in order to formulate effective, stable and acceptable transdermal drug delivery system.<sup>7-11</sup> Recent investigations revealed that the topical

dosage forms of flutamide could be effective in the treatment of some disorders such as androgenic alopecia, melasma and male pattern baldness.<sup>12,13</sup>

A wide variation of pharmaceutical vehicles such as solids and liquids have been used for topical treatment purposes, but semisolid preparations attract much interests due to their appropriate consistency with biological membranes.<sup>14</sup> Emulgel as a semi-solid formulation is defined as an emulsion (oil/water or water/oil) which is converted to gelly form by adding appropriate gelling agent(s) to the external phase.<sup>15</sup> This type of formulation exhibits satisfying percutaneous absorption in comparison with other semi-solid dosage forms like ointments, creams and gels and serves several favorable properties.<sup>5,6</sup> The most remarkable point about emulgels compared with simple gels, is their ability to carry both hydrophilic and hydrophobic drugs simultaneously and overcome gel limitations. Several researches have illustrated that the amount of drug absorbed from emulgels is significantly

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higher than simple gels.<sup>16</sup>

Due to physicochemical characteristics of the human skin, it acts as the first barrier against drug permeability.<sup>17,18</sup> Thus, many attempts have been made to circumvent the skin barrier for successful drug permeation. Utilizing skin absorption enhancers is a common approach in topical formulation design to overcome the stratum corneum (SC) as the main barrier of skin. Several groups of compounds such as surfactants, organic solvents, unsaturated fatty acids and some other natural organic materials have been reported to be effective in improving drug permeation through skin.<sup>19,20</sup>

In the current study, the effect of different concentrations of synthetic chemical penetration enhancer Transcutol P (Diethylene glycol monoethyl ether) and Precirol ATO5 (Glyceryl palmitostearate) on flutamide skin permeation were investigated.

## Materials and Methods

### Material

The materials used in this study were: Flutamide (MYC-China- Batch NO. 20150316), sodium dihydrogen phosphate (Merck- Germany), potassium dihydrogen phosphate (AppliChem-USA), sodium hydroxide (Merck-Germany), Carbopol® 934 (B.F. Goodrich-USA), Transcutol® P and Precirol® ATO5 (Gattefosse, France), cetyl alcohol (Merck-Germany), stearyl alcohol (Scharlau-France), isopropyl myristate (Merck-Germany), Tween 80 (Merck- Germany), Span 80 (Merck-Germany), cetyl palmitate (Henkel-Germany) and acetonitrile (Merck-Germany).

### Preparation of flutamide emulgel

The organic phase was prepared by mixing 5 g cetyl alcohol, 1 g stearyl alcohol, 1 g cetyl palmitate, 15 ml isopropyl myristate, 2 g Tween 80 and 1 g Span 80. The mixture was heated to 60-65°C and 2 g flutamide powder was added while stirring at 500 rpm. The emulsion was formed by adding 60 ml deionized water (60-65°C) to organic phase slowly and stirring continuously. Emulgel formulation was formulated by adding emulsion to aqueous Carbopol solution slowly and then neutralizing by addition of triethanolamin solution (1:2) to pH=5.8. The aqueous Carbopol solution was prepared by dispersing 0.75 g Carbopol® 940 in 20 ml deionized water (3.75% w/w) while continuously stirring and was kept in the refrigerator for 24 h to form the homogenized gelling solution.

### Preparation of flutamide emulgels with enhancers

The emulgels containing Transcutol P and Precirol ATO5 with 0.5, 1, 2 and 5 % w/w were prepared separately. The enhancers were replaced with the same amounts of the organic phase. All formulations were contained 2% w/w of flutamide.

### In vitro permeation studies

Evaluating of drug absorption was done by using

abdominal skin of male Wistar rats, weighing around 150-180 g. The skin hairs was shaved by electronic clipper (Moser- Germany) after anesthetizing/killing animals by pentobarbital injection (500 mg/kg, i.p.). The experiments were performed in accordance with ethical committee of the Tabriz University of Medical Sciences (TBZMED. REC.1394.723).

The abdominal skin was surgically removed then, adhering subcutaneous fat and connective tissues were carefully excised with surgical scissors. To remove extraneous remnant enzymes and skin hydration, the samples were kept in contact with normal saline solution in refrigerator (4 °C) for 2-4 h. The full thickness skin samples were rinsed by fresh normal saline and attached on the Franz Diffusion Cells (FDC) (Erweka HDT6, Germany) with the dorsal side facing the donor compartment. The available diffusion area of each cell was 3.8 cm<sup>2</sup> and the temperature was fixed at 32°C (human skin normal temperature) by water circulation between two layers of cells. The receptor cell volume was 26 cm<sup>3</sup> which was fully filled by phosphate buffer (pH= 7.4) and was stirred continuously using a magnetic bar which stirs at 500 rpm. In all experiments, 1 g of the emulgel was placed on the skin surface in the donor compartment. In order to avoid any leaking from the cells, two compartments of FDC were sealed by silicon grease before clamping and the top of the cells was covered by parafilm to prevent evaporating of the donor phase. Sampling was performed by removing 500 µl of the receptor solution by a micropipette (Transferpette-Germany) at 0, 15, 30, 60, 120 and 240 min and this volume was replaced with the same volume of phosphate buffer solution at 37°C.

### Analytical procedure

The amount of flutamide in the receptor phase was assayed with HPLC (KNAUER- Germany) apparatus equipped by UV-Vis detector. A Eurospher100-5 C18 (250×4.6 mm) (KNAUER- Germany) HPLC column was used and the loop volume was 20 µl. The mobile phase consisted of water/ acetonitrile (70:30) mixture and eluted at the flow rate of 1 ml/min. Detection was performed at 305 nm and run time was 10 min. In each sampling time, 30 µl of the sample solution was injected to the column. The retention time of flutamide at this HPLC condition was 4.417 min. Calibration curve with standard concentrations ranging from 0.3125 to 5 µg/ml of flutamide were prepared using a stock solution (200 µg/ml). Water/ acetonitrile (70:30) and phosphate buffer (pH=7.4) were used for preparing stock and standard solutions, respectively.

### Analytical method validation

In order to validate the analytical method, parameters like specificity, linearity, accuracy, precision, limit of detection (LOD) and limit of quantitation (LOQ) were assessed. Also, based on USP instructions, capacity factor (K'), number of theoretical plates (N) and tailing factor (T<sub>r</sub>) were also calculated.

**Data treatment**

The Fick's second law is used to determine the total amount of drug ( $Q_t$ ) appearing in the receptor solution in time ( $t$ ) as following Equation 1:

$$Q_t = AKLC_0 \left[ \left( \frac{D_t}{L^2} \right) - \left( \frac{1}{6} \right) - \left( \frac{2}{\pi^2} \right) \sum \frac{(-1)^n}{\pi^2} \right] \exp\left( \frac{D^n 2\pi^2 t}{L^2} \right) \quad \text{Eq. (1)}$$

Where  $A$ , is the effective diffusion area,  $C_0$ , represents the drug concentration which remains constant in the vehicle,  $D$  is the diffusion coefficient,  $L$  denotes the thickness of the membrane and  $K$  is the partition coefficient of the drug between membrane and vehicle. At steady state, it is expressed as follows:

$$\frac{Q_t}{A} = KLC_0 \left[ \left( \frac{D_t}{L^2} \right) - \left( \frac{1}{6} \right) \right] \quad \text{Eq. (2)}$$

The flux ( $J$ ) was obtained from the slope of the steady-state portion of the amount of drug permeated divided by  $A$  versus time. The lag time value is determined from the x-intercept of the slope at steady-state. The flux is expressed as:

$$J = \frac{C_0 KD}{L} = C_0 K_p \quad \text{Eq. (3)}$$

Where,  $K_p$  is the permeability coefficient.

The Enhancement Ratio ( $ER_s$ ) for each formulation has been calculated by the following equation in order to present the effect of different concentrations of absorption enhancers on drug permeation:

$$ER_s = \frac{Kp(\text{with pretreatment})}{Kp(\text{without pretreatment})} \quad \text{Eq. (4)}$$

The area under curve (AUC) of permeated drug per unit area per unit time is known as absorption efficacy which was obtained using each formulation chromatogram and

used to calculate  $E_fR$  (Efficacy Ratio) from the following equation:

$$E_fR = \frac{\text{AUC (with penetration enhancer)}}{\text{AUC (without penetration enhancer)}} \quad \text{Eq. (5)}$$

All absorption parameters of formulations were evaluated in 3 different times and the average of data was used for calculations.

**Results**

HPLC is a versatile technique to evaluate the drug concentration after in transdermal preparations.<sup>21-23</sup> A previously validated HPLC method was used for quantitation analyses.<sup>12</sup> To revalidate the method, specificity and linearity parameters were calculated in the same condition as analyzed samples. In addition accuracy, precision, regression coefficient, LOD, LOQ and system suitability parameters are shown were all in the acceptable range and confirmed the validity of the analytical method. Flutamide LOD and LOQ were as 0.024 and 0.028  $\mu\text{g/ml}$  respectively.

Figure 1 illustrates the permeation profile of 2% flutamide emulgel without any absorption enhancer (control formulation). Similar concentrations of flutamide in transdermal delivery systems have been used in previous studies.<sup>12,24</sup> It is clear that the drug permeation diagram follows the classic pattern profile with single steady state portion. Flux is defined as the permeated drug through the skin per unit time and can be obtained from the slope of the linear portion of the graph. The flux of flutamide from emulgel was calculate as 1.035 and the AUC of the control formulation was 7.795.

The amount of permeated flutamide versus time for formulations with different concentration of Transcutol P are shown in Figure 2. Although the formulation with 0.5 and 1% w/w of Transcutol P showed the classic absorption pattern for lipophilic compounds, emulgels contained 2 and 5 % w/w Transcutol P indicated two-compartment

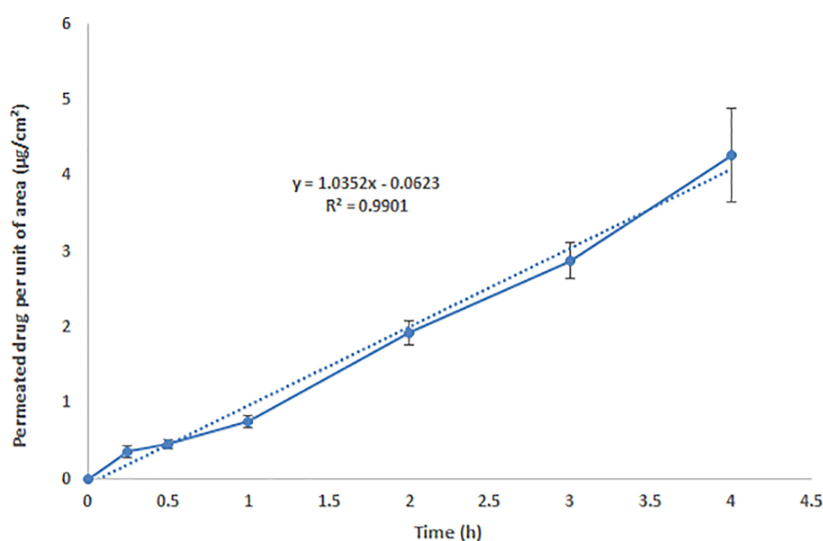
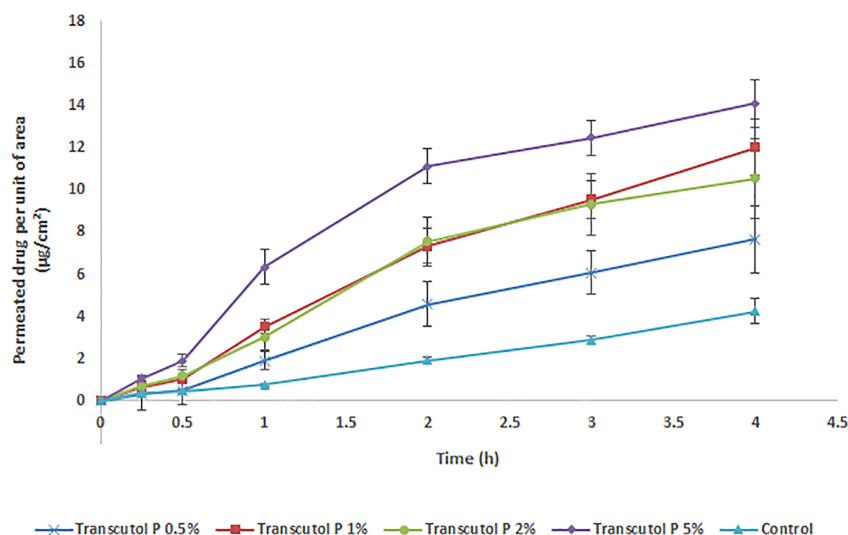


Figure 1. The drug permeation profile for the control formulation.



**Figure 2.** Permeation profile of flutamide from emulgel formulations containing different concentration of Transcutol P as absorption enhancer

model. Therefore, for first two concentrations (0.5 and 1% w/w) a single flux was defined whereas for the last two fluxes were calculated. In two-compartment model, the first fluxes were greater than second ones and were used in our evaluations. Comparative absorption parameters including flux values, lag time ( $t_L$ ), AUC, ER and,  $E_rR$  are reported in Table 1.

Flutamide transdermal permeation from emulgels containing various concentration of Precirol ATO5 are presented in Figure 3. These diagrams have classic pattern with one steady state zone similar to the control. Permeation kinetic parameters such as AUC and flux reveal that the increase in the enhancer concentration can lead to higher rate and amount of permeability through the skin (Table 1).

Increasing the enhancers' concentrations lead to elevated AUC values, significantly. Meanwhile, in all concentration the higher AUC values resulted from Transcutol P compared to the control.

As results demonstrate both enhancers can be effective in

improving the skin permeability at this concentration but emulgel base with Transcutol P is capable of transporting more flutamide through the skin.

### Discussion

Flutamide is categorized as a lipophilic compound (Log P = 3.35) thus, it is expected to be highly soluble in organic phase and slightly soluble in water.<sup>25</sup> Therefore, the hydrogel formulation cannot be an appropriate vehicle for the drug whilst, the emulgels could be a suitable dosage form for transdermal delivery purposes.<sup>26-28</sup> Furthermore, several previous studies have revealed that emulgels indicate not only higher flux and permeation of drug compared with gels but they also offer more skin compatible formulations because they are alcohol free and have biphasic (aqueous and organic phases) structure, which allow the incorporation several permeation enhancers.<sup>9,21,29</sup>

Intact stratum corneum (SC) or horny layer is the major barrier against skin permeation that can significantly affect drug absorption thus drug diffusion through skin is

**Table 1.** Absorption parameters for formulations contained different ratio of Transcutol P.

|               | Conc. <sup>1</sup> (% w/w) | Flux (µg/cm <sup>2</sup> /min) | ER <sup>2</sup> | $t_L$ <sup>3</sup> (h) | AUC <sup>4</sup> | $E_rR$ <sup>5</sup> |
|---------------|----------------------------|--------------------------------|-----------------|------------------------|------------------|---------------------|
| Transcutol P  | 0                          | 1.035                          | -               | 0.206                  | 7.795            | -                   |
|               | 0.5                        | 2.024                          | 1.975           | 0.208                  | 16.299           | 2.091               |
|               | 1                          | 3.132                          | 3.026           | 0.207                  | 26.154           | 3.355               |
|               | 2                          | 3.826                          | 3.696           | 0.159                  | 25.085           | 3.218               |
|               | 5                          | 5.799                          | 5.601           | 0.073                  | 36.450           | 4.676               |
| Precirol ATO5 | 0                          | 1.035                          | -               | 0.206                  | 7.795            | -                   |
|               | 0.5                        | 1.261                          | 1.218           | 0.421                  | 10.635           | 1.364               |
|               | 1                          | 2.647                          | 2.557           | 0.815                  | 20.174           | 2.588               |
|               | 2                          | 2.756                          | 2.662           | 0.050                  | 23.178           | 2.973               |
|               | 5                          | 3.799                          | 3.670           | 0.073                  | 30.403           | 3.900               |

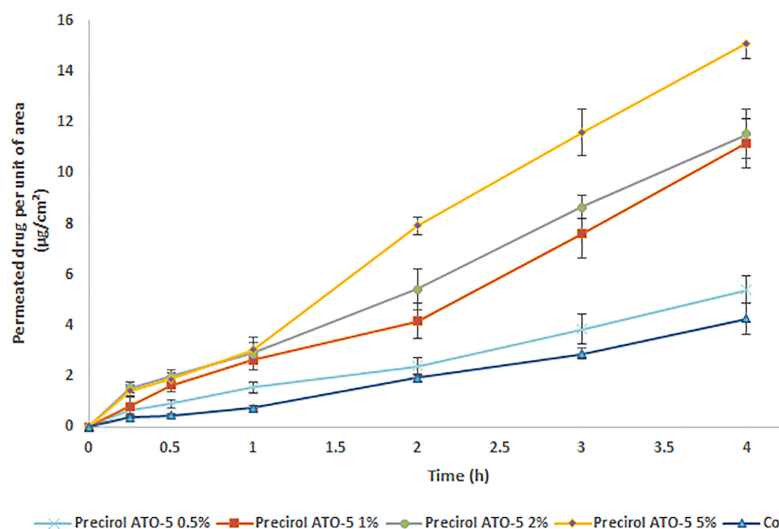
<sup>1</sup>Conc: Concentration

<sup>2</sup>ER: Enhancement Ratio

<sup>3</sup> $t_L$ : Lag time

<sup>4</sup>AUC: Area under Curve

<sup>5</sup> $E_rR$ : Efficacy Ratio



**Figure 3.** Flutamide skin penetration from emulgels containing different concentration of Precirol ATO5 as absorption enhancer.

assumed as a rate-limiting step.<sup>30,31</sup> The rate of absorption is another important parameter for topical vehicles, especially for aqueous formulations such as solutions, lotions and gels as their fewer resistance time on the skin.<sup>22</sup> Therefore, flux and lag time are two important absorption parameters in transdermal delivery evaluations to ensure that the formulation has acceptable properties in transmitting adequate amount of drug through the skin. To clarify, an appropriate topical preparation need to have a good flux value and an acceptable lag time, simultaneously. Therefore, there is a great interest to develop enhancers to improve percutaneous absorption of therapeutic agents. These chemicals in topical vehicles could change flux, lag time and total amount of the permeated drug. Enhancers can increase skin permeability by different mechanisms like temporary destruction or changing in physicochemical characteristics of the SC to decrease its resistance.<sup>32,33</sup>

Transcutol P is used in topical products as a powerful solubilizing agent and penetration enhancer.<sup>34</sup> The results of this study shows that Transcutol P in all concentrations (0.5 to 5% w/w) increase flutamide permeation rate (flux) compared with the simple emulgel. The permeation profiles of formulations with 0.5 and 1 % w/w Transcutol P follow the classic permeation pattern but, their flux (2.02 and 3.13  $\mu\text{g}/\text{cm}^2/\text{h}$  for 0.5 and 1 % respectively) are higher than the simple emulgel (1.035  $\mu\text{g}/\text{cm}^2/\text{min}$ ). Meanwhile, two-compartment model of absorption profile of emulgels containing 2 and 5 % w/w of Transcutol P, indicate fluxes almost 4 to 5 times greater than the blank emulgel. The similar observations have been reported by previous investigations about Transcutol P effects on drugs transdermal permeation.<sup>34-36</sup> Additionally, ERs are getting higher in consequence of increasing the enhancer concentration (1.975 and 5.601 for 0.5 and 5 % w/w respectively). Also according to the results, the increase in enhancer concentration lead to greater  $E_rR$  values (2.091 and 4.676 for 0.5 and 5 % w/w respectively). Consequently, according to the results, any increase in the enhancer

concentration leads to improve all absorption parameters compared with the blank emulgel. This issue can be attributed to Transcutol P promoting role in the flutamide solubility in emulgel biphasic base with limited organic phase that could provide higher driving force to move drug molecules through the skin with higher rate of diffusion. Transcutol P capability to solve lipophilic compounds could alter the skin double layers lipid structure. Due to its physicochemical properties, Transcutol P could penetrate into skin rapidly which leads to co-transportation of the significant amounts of the drug through the sample. The high concentration of Transcutol P as a solvent could cause irreversible destructive changes in skin structure which can be harmful, so low concentration may be a preferable formulation. Furthermore, almost in all parameters the significant surge in the presence of 1 % of the enhancer can be seen without any major difference ( $P$  value > 0.05). Additionally, the formulation showed fewer Lag time in comparison with simple emulgel in an acceptable range. Thus, emulgel with 1 % w/w Transcutol P has been selected as the most appropriate one due to less skin destruction probability.

In the case of Precirol ATO5 as a lipid matrix, it is detectable that all permeation profiles follow the classic pattern of lipophilic compounds. A direct relationship was observed between the total amount of flutamide penetrated through the skin (AUC) and the concentrations of the enhancer. Therefore,  $E_rR$  values gradually increased when higher concentration of Precirol ATO5 used in the formulations. Generally, different concentration of the enhancer show greater flux than the simple emulgel ( $ER > 1$ ) but not in the same way as Transcutol P does. The highest ERs (2.662 and 3.670) are devoted to emulgels with 2 and 5 % w/w Precirol ATO5, respectively. Precirol ATO5 (glyceryl palmitostearate) has lipophilic innate and is highly soluble in organic phases. Moreover, the similarity between Precirol ATO5 chemical structure and ceramides is remarkable. Ceramides are one of the essential



compounds of epidermis layer of skin. They exhibit the excessive molecular variation with lipophilic nature such as sphingoid and fatty acid compositions.<sup>37,38</sup> Thus, Precirol ATO5 can be easily solved in epidermis lipophilic base and penetrate through the skin and facilitate the drug permeation. It seems that in initial time the skin was saturated and afterward drug permeation reaches steady state with a constant diffusion rate. Although lag time for emulgels with Precirol ATO5 were acceptable, the enhancer addition up to 1 % illustrated greater lag time compared with enhancer free emulgel. A significant lag time decrease for emulgels containing 2 and 5 % w/w of the enhancer were observed that could be caused by enhancer effects on skin barriers function. The selection of an optimum enhancer percentage should be based not only on its efficacy in improvement of skin permeation but also on its compatibility with skin and possible side effects.<sup>39,40</sup> Hence, whilst, emulgel with 5% w/w Precirol ATO5 proves better kinetic permeation parameters over other concentrations and the base emulgel, it seems as a consequence of higher damage on the skin structure. Although the stability of the formulations kept in the refrigerator during the study period (2 months) was acceptable, detailed stability evaluation should be assessed in the future studies.

As there was no difference between the high and low enhancer concentrations, thus the formulation containing Precirol ATO5 in a 1% concentration is introduced as the optimum formulation.

### Conclusion

According to the findings, the optimum concentration of both enhancers were found to be 1 percent. The enhancers were capable of transferring flutamide more efficiently through the rat skin compared to the blank emulgel. Based on the absorption parameters, Transcutol P was a better enhancer for flutamide emulgel preparation compared to Precirol ATO5. The results of this study reveal that the enhancer type and concentration can significantly affect the kinetic of the drug permeation through the skin, and need to be considered and optimized as essential formulation variables.

### Ethical Issues

The experiments were performed in accordance with ethical committee of the Tabriz University of Medical Sciences (TBZMED.REC.1394.723).

### Author Contributions

PK: Data analysis, drafting and editing the manuscript, SA: Data acquisition, drafting the work, JS: Skin studies and formulation design, data interpretation, FM: Main idea, study design, data interpretation, editing the manuscript, All authors have read and agreed to the published version of the manuscript.

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### Conflict of Interest

The authors report no conflicts of interest.

### References

1. Malešević N, Bokan G, Đajić V. Flutamide induced liver injury in female patients. *Euro J of Med Health Sci.* 2020;2(5):1-3. doi:10.24018/ejmed.2020.2.5.476
2. Yang C, Dai Y, Pang S, Guo X. Efficacy of abiraterone combined with flutamide on prostate cancer patients and its effect on serum mir-493-5p and mir-195-5p. *Oncol Lett.* 2020;20(2):1922-30. doi:10.3892/ol.2020.11719
3. Leroy D, Domp Martin A, Szczurko C. Flutamide photosensitivity. *Photodermatol Photoimmunol Photomed.* 1996;12(5):216-8. doi:10.1111/j.1600-0781.1996.tb00203.x
4. Wysowski DK, Fourcroy JL. Flutamide hepatotoxicity. *J Urol.* 1996;155(1):209-12. doi: 10.1016/s0022-5347(01)66600-x
5. Panwar A, Upadhyay N, Bairagi M, Gujar S, Darwhekar G, Jain D. Emulgel: A review. *Asian J Pharm Life Sci.* 2011;2231:4423.
6. Schoellhammer CM, Blankschtein D, Langer R. Skin permeabilization for transdermal drug delivery: Recent advances and future prospects. *Expert Opin Drug Deliv.* 2014;11(3):393-407. doi:10.1517/17425247.2014.875528
7. Cramptom HJ. A comparison of the relative clinical efficacy of a single dose of ketotifen fumarate 0.025% ophthalmic solution versus placebo in inhibiting the signs and symptoms of allergic rhinoconjunctivitis as induced by the conjunctival allergen challenge model. *Clin Ther.* 2002;24(11):1800-8. doi:10.1016/s0149-2918(03)80199-6.
8. Kass MA, Gordon M, Morley RE, Meltzer DW, Goldberg JJ. Compliance with topical timolol treatment. *Am J Ophthalmol.* 1987;103(2):188-93. doi:10.1016/s0002-9394(14)74225-4
9. Khullar R, Kumar D, Seth N, Saini S. Formulation and evaluation of mefenamic acid emulgel for topical delivery. *Saudi Pharm J.* 2012;20(1):63-7. doi:10.1016/j.jsps.2011.08.001
10. ElMeshad AN, Tadros MI. Transdermal delivery of an anti-cancer drug via w/o emulsions based on alkyl polyglycosides and lecithin: Design, characterization, and in vivo evaluation of the possible irritation potential in rats. *AAPS PharmSciTech.* 2011;12(1):1-9. doi:10.1208/s12249-010-9557-y.
11. Alvarez-Figueroa M, Blanco-Mendez J. Transdermal delivery of methotrexate: Iontophoretic delivery from hydrogels and passive delivery from microemulsions. *Int J Pharm.* 2001;215(1-2):57-65. doi:10.1016/s0378-

- 5173(00)00674-8
12. Hamishehkar H, Ghanbarzadeh S, Sepehran S, Javadzadeh Y, Adib ZM, Kouhsoltani M. Histological assessment of follicular delivery of flutamide by solid lipid nanoparticles: Potential tool for the treatment of androgenic alopecia. *Drug Dev Ind Pharm.* 2016;42(6):846-53.
  13. Sintov A, Serafimovich S, Gilhar A. New topical antiandrogenic formulations can stimulate hair growth in human bald scalp grafted onto mice. *Int J Pharm.* 2000;194(1):125-34. doi:10.1016/s0378-5173(99)00359-2
  14. Lippacher A, Müller R, Mäder K. Preparation of semisolid drug carriers for topical application based on solid lipid nanoparticles. *Int J Pharm.* 2001;214(1-2):9-12. doi:10.1016/s0378-5173(00)00623-2
  15. Haneefa KM, Easo S, Hafsa P, Mohanta GP, Nayar C. Emulgel: An advanced review. *J Pharm Sci Res.* 2013;5(12):254.
  16. Singla V, Saini S, Joshi B, Rana A. Emulgel: A new platform for topical drug delivery. *Int J Pharma Bio Sci.* 2012;3(1):485-98.
  17. Harding CR. The stratum corneum: Structure and function in health and disease. *Dermatol Ther.* 2004;17:6-15. doi:10.1111/j.1396-0296.2004.04s1001.x
  18. Caliskan UK, Karakus MM. Essential oils as skin permeation boosters and their predicted effect mechanisms. *J Dermatol Skin Sci.* 2020;2(3):24-30.
  19. Pandey A, Mittal A, Chauhan N, Alam S. Role of surfactants as penetration enhancer in transdermal drug delivery system. *J Mol Pharm Org Process Res.* 2014;2(113):2-7. doi:10.4172/2329-9053.1000113
  20. Patel D, Chaudhary SA, Parmar B, Bhura N. Transdermal drug delivery system: A review. *Pharma Innov.* 2012;1(4):66-75.
  21. Shokri J, Azarmi S, Fasihi Z, Hallaj-Nezhadi S, Nokhodchi A, Javadzadeh Y. Effects of various penetration enhancers on percutaneous absorption of piroxicam from emulgels. *Res Pharm Sci.* 2012;7(4):225-34.
  22. Javadzadeh Y, Shokri J, Hallaj-Nezhadi S, Hamishehkar H, Nokhodchi A. Enhancement of percutaneous absorption of finasteride by cosolvents, cosurfactant and surfactants. *Pharm Dev Technol.* 2010;15(6):619-25. doi: 10.3109/10837450903397610.
  23. Tazesh S, Tamizi E, Shadbad MS, Mostaghimi N, Monajjemzadeh F. Comparative stability of two anti-hyperpigmentation agents: Kojic acid as a natural metabolite and its di-palmitate ester, under oxidative stress; application to pharmaceutical formulation design. *Adv Pharm Bull.* 2021. doi:10.34172/apb.2022.031
  24. Sallam MA, Elzoghby AO. Flutamide-loaded zein nanocapsule hydrogel, a promising dermal delivery system for pilosebaceous unit disorders. *AAPS PharmSciTech.* 2018;19(5):2370-82. doi:10.1208/s12249-018-1087-z
  25. Jeevana JB, Sreelakshmi K. Design and evaluation of self-nanoemulsifying drug delivery system of flutamide. *J Young Pharm.* 2011;3(1):4. doi:10.4103/0975-1483.76413.
  26. Khan Q, Shah SNH, Arshad MS, Usman F, Khalil R, Ul-Haq Z, et al. Formulation and optimization of dimenhydrinate emulgels for topical delivery using response surface methodology. *Pak J Pharm Sci.* 2021;34(1):245-55. doi:10.36721/PJPS.2021.34.1.SUP.245-255.1
  27. Sri BU, Arjun G. Formulation and evaluation of naproxen emulgels topical drug delivery systems. *Am J PharmTech Res.* 2019;9(05):65-75.
  28. Sainy J, Atneriya U, Kori JL, Maheshwari R. Development of an *Aloe vera*-based Emulgel for the topical delivery of desoximetasone. *Turk J Pharm Sci.* 2021;18(4):465-75.
  29. Effionora A, Ramadon D. Formulation and evaluation of gel and emulgel of chili extract (*Capsicum frutescens* L.) as topical dosage forms. *Int J Pharm Pharm Sci.* 2014;6(Supplement 3):13-6.
  30. Allen L, Ansel HC. Ansel's pharmaceutical dosage forms and drug delivery systems. Philadelphia: Lippincott Williams & Wilkins; 2013.
  31. Singh BN, Singh RB, Singh J. Effects of ionization and penetration enhancers on the transdermal delivery of 5-fluorouracil through excised human stratum corneum. *Int J Pharm.* 2005;298(1):98-107. doi:10.1016/j.ijpharm.2005.04.004.
  32. Marwah H, Garg T, Goyal AK, Rath G. Permeation enhancer strategies in transdermal drug delivery. *Drug Deliv.* 2016;23(2):564-78. doi: 10.3109/10717544.2014.935532.
  33. Mitragotri S. Synergistic effect of enhancers for transdermal drug delivery. *Pharm Res.* 2000;17(11):1354-9. doi:10.1023/A:1007522114438
  34. Lee SG, Kang JB, Kim SR, Kim CJ, Yeom DW, Yoon HY, et al. Enhanced topical delivery of tacrolimus by a carbomer hydrogel formulation with transcutool p. *Drug Dev Ind Pharm.* 2016;42(10):1636-42. doi:10.3109/03639045.2016.1160107
  35. Censi R, Martena V, Hoti E, Malaj L, Di Martino P. Permeation and skin retention of quercetin from microemulsions containing transcutool® P. *Drug Dev Ind Pharm.* 2012;38(9):1128-33. doi:10.3109/03639045.2011.641564.
  36. Liu Z, Nie S, Guo H, Pan W, Li J. Effects of transcutool p on the corneal permeability of drugs and evaluation of its ocular irritation of rabbit eyes. *J Pharm Pharmacol.* 2006;58(1):45-50. doi:10.1211/jpp.58.1.0006
  37. Goldstein AM, Abramovits W. Ceramides and the stratum corneum: Structure, function, and new methods to promote repair. *Int J Dermatol* 2003;42(4):256-9. doi: 10.1046/j.1365-4362.2003.01507.x
  38. Mizutani Y, Mitsutake S, Tsuji K, Kihara A, Igarashi Y. Ceramide biosynthesis in keratinocyte and its role in skin function. *Biochimie.* 2009;91(6):784-90.

39. Nokhodchi A, Shokri J, Dashbolaghi A, Hassan-Zadeh D, Ghafourian T, Barzegar-Jalali M. The enhancement effect of surfactants on the penetration of lorazepam through rat skin. *Int J Pharm.* 2003;250(2):359-69. doi:10.1016/s0378-5173(02)00554-9
40. Shokri J, Nokhodchi A, Dashbolaghi A, Hassan-Zadeh D, Ghafourian T, Barzgar Jalali M. The effect of surfactants on the skin penetration of diazepam. *Int J Pharm.* 2001;228(1-2):99-107. doi:10.1016/s0378-5173(01)00805-5