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TRANSDERMAL PATCHES OF KETOPROFEN USING EUDRAGIT POLYMERS: PERMEATION AND SKIN IRRITATION STUDIES

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1. INTRODUCTION

Ketoprofen is a propionic acid anti-inflammatory drug that has been used for pain and inflammation in musculoskeletal disease for several decades [1]. Taken by mouth it works well but carries the usual gastrointestinal burden of the class, and its short half-life means repeated daily dosing. Those two facts explain much of the interest in putting the drug through the skin instead. A patch can hold a defined dose against the painful site, deliver it slowly, and keep systemic exposure modest. Transdermal drug

Abstract

This review examines what the published literature reports on ketoprofen transdermal patches built from Eudragit polymers, with emphasis on skin permeation testing and the assessment of skin irritation, and it presents no new experimental data. It describes why ketoprofen suits transdermal delivery, how different Eudragit grades and plasticisers shape drug release and adhesion, and how in vitro diffusion cells and release kinetics are used to judge performance. Irritation methods, from the classical rabbit scoring system to reconstructed human epidermis models, are compared. Matrix patches generally deliver useful flux, but studies differ widely in membrane choice, vehicle and reporting, and few link in vitro permeation to tolerability or to human exposure.

delivery systems (TDDS) as a whole have been reviewed many times, and their achievements and limits are well documented

[2, 3].

The skin is a hard barrier to cross. Its outer layer, the stratum corneum, restricts most molecules, and the empirical view is that useful passive transport needs a small, moderately lipophilic compound [4, 5]. Ketoprofen sits comfortably inside that window, with a molecular weight near 254 and a lipophilicity that favours partitioning into skin lipids. Studies comparing several non-steroidal drugs through skin have placed it among the more permeable members of the group [6]. Clinical trials of a 100 mg ketoprofen patch in ankle sprain and tendinitis support the idea that a topical dose can be effective [7, 8].

Patch design brings a second set of questions. The polymer matrix controls how fast the drug leaves the system, whether the film stays flexible, and how well it sticks to moving skin. Methacrylate copolymers sold as Eudragit are popular for this role because they form clear films, accept plasticisers and are available in grades that differ in permeability [9, 10]. This review gathers the published evidence on how those polymers behave with ketoprofen, how permeation is measured, and how irritation is judged. Findings are summarised in table 1 and the grouping of evidence is shown in fig. 1.

Because the title of this work reads like a primary study, one clarification is useful. No new patches were prepared and no animals or volunteers were tested for it. Everything below is drawn from the published literature, and the aim is to show where the findings agree, where methods differ enough to prevent direct comparison, and what is still missing before a patch of this kind can be judged against its oral and gel competitors. Where the evidence comes from related drugs rather than ketoprofen, that is stated, because several of the most useful methodological papers on Eudragit patches concern other molecules.

Ketoprofen has an unusual pharmaceutical footprint among topical anti-inflammatory drugs. It is available as gels, plasters and patches in several countries, and its photosensitising behaviour has shaped how those products are labelled and used. That history matters here because any new matrix

patch is judged against products that patients already know, both for pain relief and for the occasional skin reaction. Developers therefore have two jobs, which are to demonstrate adequate delivery and to show that the polymer, plasticiser and adhesive do not add irritation on top of what the drug itself can cause [11]. In practice the two jobs are usually reported in separate papers, often by separate groups, which weakens the case for any single formulation.

Table 1: Published evidence on ketoprofen and related transdermal patch systems

Topic aspect	Reported finding or feature	Ref.
Ketoprofen skin permeability	Ranked among the more permeable NSAIDs through skin in comparative studies.	[4, 6]
Ketoprofen patch ankle sprain	Controlled trial of a 100 mg patch reported benefit over placebo.	[7]
Ketoprofen patch tendinitis	Randomised trial found greater improvement than placebo in tendinitis.	[8]
Eudragit RL and RS permeability	RL films are more permeable than RS owing to higher quaternary ammonium content.	[9, 10]
Plasticiser film properties	Type and level change flexibility, diffusivity and permeability of polymer films.	[12]
PVP-Eudragit matrix dexamethasone	Matrix composition altered skin permeation compared with ethylcellulose blends.	[13]
Franz cell in vitro test	Standard vertical cell; membrane, receptor medium and sink conditions drive results.	[14, 15, 16]
Release kinetics Higuchi, power law	Square-root-of-time and exponent models describe matrix release.	[17, 18, 19]
Enhancers eutectic systems	Eutectic mixtures raised flux of a model NSAID across skin.	[20, 21]
Rabbit scoring Draize	Erythema and oedema scored after patch exposure; subjective and ethically debated.	[22, 23]
Reconstructed epidermis OECD 439	Viability-based classification of irritants in human tissue models.	[24, 25, 26]
Photosensitivity ketoprofen	Photocontact dermatitis with cross-reactivity to benzophenones.	[11]

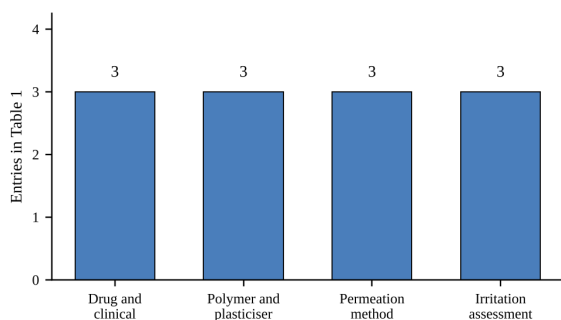


Fig. 1: Number of entries in table 1 by evidence group

2. EUDRAGIT POLYMERS AND PATCH DESIGN

The Eudragit family covers several chemically distinct polymers. Grades RL and RS are copolymers of ethyl acrylate, methyl methacrylate and a small proportion of a quaternary ammonium methacrylate; the higher ammonium content of RL makes its films more permeable and more water-swallowable than RS [10]. Grade E is a cationic copolymer with dimethylaminoethyl groups, and grades L and S are anionic. For a lipophilic, weakly acidic drug such as ketoprofen, RL and RS are the usual choices, often blended to tune the release rate. Reported matrices typically cast the polymer and drug from an organic solvent onto a backing layer and dry them under controlled conditions.

Plasticiser choice is rarely trivial. Unplasticised Eudragit films are brittle and may crack on flexing, so reports add dibutyl phthalate, triethyl citrate, polyethylene glycol or propylene glycol, usually at a modest fraction of polymer weight. The plasticiser changes more than flexibility. It alters free volume in the polymer and therefore the diffusivity of the drug, and in some systems it also acts as a mild permeation enhancer. Work on cellulose acetate films showed the same sensitivity, with permeability moving appreciably as plasticiser type and level changed [12]. A change that improves handling can therefore quietly change release.

Several studies have compared Eudragit with other matrix formers. Patches combining polyvinylpyrrolidone (PVP) with ethylcellulose or with Eudragit have been tested for dexamethasone, with the Eudragit-containing matrices behaving

differently in skin permeation [13]. Diclofenac and glibenclamide patches were developed along similar lines, using polymer blends and enhancers and then confirming activity in animals [27, 28]. These are not ketoprofen studies, but they are often cited as templates because they show the workflow: choose the polymer pair, load the drug, screen plasticisers and enhancers, then test physicochemical properties, permeation and pharmacology in turn.

Adhesion deserves more attention than it normally receives. A matrix that releases drug beautifully in a diffusion cell is of little use if the edges lift after an hour of walking. Poor adhesion lowers the effective contact area, so it reduces dose, and it can also expose a person to skin trauma when the patch is removed [29, 30]. Many Eudragit films are not inherently tacky and need a pressure-sensitive adhesive (PSA) layer or a tackifier, which brings in an additional excipient that must itself be shown to be non-irritating. Reports on drug-in-adhesive and matrix designs seldom quantify peel strength alongside permeation.

Drug loading and casting conditions complete the formulation picture. Ketoprofen is usually dissolved with the polymer in ethanol, acetone or a mixture, poured into a mould or onto a release liner and dried at a modest temperature. Loading is chosen to sit below the saturation limit in the polymer, or deliberately above it to raise thermodynamic activity. The first choice favours stability, while the second favours flux but risks crystallisation on storage. Drying rate affects film density and residual solvent, and a skin layer can form on fast-dried films and slow release. Reports seldom document these variables, even though the excipient literature identifies them as influential for methacrylate films [9, 10].

Characterisation of the finished patch follows a fairly standard list in the diclofenac and glibenclamide literature. Thickness and weight uniformity, folding endurance, moisture uptake and loss, tensile properties and drug content uniformity are the routine measurements, with surface pH and appearance added in some reports [27, 28]. These tests are useful quality checks, yet they

are descriptive. A patch can pass every one of them and still release poorly or stick badly, so they work as release criteria for a batch rather than evidence that a design is good. Content uniformity matters most, since a small area of patch carries a fixed share of the dose [27, 28].

3. PERMEATION TESTING AND RELEASE KINETICS

The workhorse for permeation studies is the vertical Franz diffusion cell, in which a membrane separates a donor compartment holding the patch from a stirred receptor medium kept near skin temperature [14]. Flow-through cells offer an alternative that maintains sink conditions more easily and are better suited to continuous sampling [15]. Regulatory guidance describes the core elements of an in vitro skin absorption method, including membrane integrity checks, receptor fluid choice and mass balance [16]. Reports on ketoprofen patches usually follow the Franz format because it is cheap, familiar and sufficiently reproducible for formulation screening.

Membrane selection is the single largest source of disagreement between studies. Human cadaver epidermis is the closest model, yet it is scarce and varies between donors; heat-separated or enzymatically separated sheets of stratum corneum have been in use since the early 1960s [21]. Hairless mouse, rat and pig skin are common substitutes, and pig ear skin is often judged to resemble human skin reasonably well. The substitutes are typically more permeable. Ketoprofen fluxes from the same patch can therefore differ several-fold depending on species and body site, and absolute values cannot be compared across papers without careful reading of methods [31, 32].

Receptor medium and sink conditions matter for a lipophilic acid. Buffered saline at pH 7.4 ionises ketoprofen, which helps solubility, but studies sometimes add ethanol or a surfactant to maintain sink, and these can themselves alter the membrane. Flux is generally derived from the linear part of the cumulative amount curve, and the lag time from its intercept on the time axis. Mathematical treatments of skin transport relate flux to the drug concentration

in the vehicle and a permeability coefficient, a framework that explains why more thermodynamic activity in the matrix tends to raise flux [33]. Ketoprofen studies seldom report activity, only drug loading.

Release from the matrix is usually analysed before permeation. For a thin film in which drug is dispersed in the polymer, the Higuchi model predicts release proportional to the square root of time, and it remains the starting point for many reports [17]. The Korsmeyer–Peppas power law adds an exponent that is read as an indicator of mechanism; values near 0.5 for thin films point to Fickian diffusion, with higher values indicating anomalous transport [18, 19]. Eudragit RL-rich films often show faster, more swelling-assisted release than RS-rich films. Model fitting is a descriptive step, and a good correlation coefficient does not by itself prove a mechanism.

Enhancers are the other lever. Oleic acid, terpenes, fatty-acid esters and glycols are all reported with NSAID patches, and eutectic mixtures have been shown to raise the flux of a model drug of similar lipophilicity [20, 34]. Methods for quantifying passive enhancement in vitro are well established [32], and a broad review of enhancement strategies stresses that increased flux often goes with increased irritation potential [21]. This is where the two halves of the present topic meet. A formulation that gains permeation through disrupted lipids may pay for it with erythema, so permeation and tolerability data belong in the same study.

Interpretation of flux needs a target. The delivery rate of a patch is, to a first approximation, flux multiplied by contact area, so a worker can ask what area would be needed to reach a stated dose per day. Reports often compare their flux values with each other but not with this practical requirement, and not with the flux of marketed products measured in the same system [2, 33]. Steady-state flux, lag time and an enhancement ratio relative to a control are the usual summary numbers. All three depend on the membrane, and none of them says whether the amount delivered would be therapeutically useful in a person [3, 5].

For a topical anti-inflammatory drug, the amount crossing into the receptor is arguably the wrong end point. The target is often muscle, tendon or joint tissue beneath the patch, so what matters is how much drug is retained in and below the skin and for how long. Some papers analyse drug in the skin after the experiment or by tape-stripping, which gives a depth profile in the stratum corneum, but most do not. Ketoprofen's physicochemical properties suggest good local retention, although direct tissue evidence for Eudragit patches is sparse, and the clinical trials of commercial patches offer only indirect support [1, 7, 8, 31].

4. ASSESSMENT OF SKIN IRRITATION

The reference method for decades was the rabbit test of the Draize type, which was compared against human skin response in early work and in which the test material is applied to shaved intact or abraded skin and erythema and oedema are scored at fixed times after exposure [22]. Scores are combined into a primary irritation index. The approach was later formalised in OECD guidance for acute dermal irritation and corrosion [23]. Many patch papers still use a simplified version, applying the placebo patch and the drug patch to rabbits or rats for 24 hours and grading the sites. The method is quick, but it is subjective and ethically contested.

Reconstructed human epidermis models offer a replacement. Commercial tissues such as EpiSkin, SkinEthic and EpiDerm reproduce a differentiated stratified epithelium with a functional barrier, and they have been compared for irritancy, corrosivity and substance transport [26]. A test guideline adopted in 2010 uses tissue viability measured by reduction of a tetrazolium dye (MTT) after exposure, classifying a substance as an irritant when viability falls below a defined threshold [24]. Reviews of in vitro irritation emphasise that the tests predict hazard well for chemicals but need adaptation for solid, adhesive devices such as patches [25].

Patches pose a particular challenge for these models. Occlusion raises skin hydration and temperature, and the adhesive can pull on the

tissue at removal, so a test that exposes cells to a liquid extract is not the same as wearing a patch. Studies have used extracts, direct contact of cut discs with tissue, or both. Each captures a different part of the risk. Chemical irritation from polymer residues, plasticiser or enhancer is best probed by extraction; mechanical and occlusive effects need either direct contact or a human patch test. Few ketoprofen publications state which of these problems their chosen method can actually answer.

Ketoprofen itself adds a specific hazard that standard irritation tests do not capture. Photoallergic and phototoxic contact dermatitis after topical ketoprofen is well described, with cross-reactivity to benzophenone-containing sunscreens and to fenofibrate in some patients [11]. A reconstructed epidermis irritation assay run in the dark would miss it entirely. Developers therefore need to treat irritation and photosensitivity as separate endpoints, and patch instructions should keep skin covered from sunlight for a period after removal. Eudragit polymers have not generally been implicated, but the question is rarely tested directly. A sensible precaution in any development programme is to include a photopatch assessment before wider clinical use.

Understanding why a patch irritates helps in choosing tests. Occlusion alone swells the stratum corneum, raises temperature and prolongs contact between skin and every excipient. The adhesive can bond to corneocytes, and its removal strips layers away. Ketoprofen is a carboxylic acid, so the local microenvironment may shift towards acidity, and penetration enhancers disturb lipids by design. Keratinocytes respond to such insults by releasing inflammatory mediators, which is the biological signal that reconstructed tissue assays read out in different ways [5, 25, 26, 29]. A single patch can therefore combine several mild stressors, which is why a whole-device test is wanted.

Human exposure data complete the picture. In the controlled trials of the commercial ketoprofen patch, local skin reactions were among the reported adverse events and were generally described as mild, although the

trials were not designed to define irritation potential [7, 8]. Formal human repeat-insult and cumulative irritation patch tests exist for that purpose and are usually applied by dermatologically trained staff to small panels. They are costly, which is why early development relies on animal or tissue models, but animal scores that look acceptable should still be treated as provisional [22, 23].

5. LIMITATIONS AND FUTURE DIRECTIONS

Taken at face value, the literature suggests that Eudragit matrices can deliver clinically relevant amounts of ketoprofen across skin in vitro. The difficulty is translating those numbers. In vitro flux across animal skin overestimates human delivery, the receptor conditions are artificial, and nearly all reports measure the amount reaching the receptor rather than the concentration in underlying tissue, which is where an anti-inflammatory is meant to act [3, 14]. Clinical patch trials show benefit, but they used specific commercial formulations and do not validate any particular experimental Eudragit matrix [7, 8].

Reporting is the second limitation. Papers differ in drug loading, polymer ratio, membrane, receptor medium, surface area and sampling schedule, so pooled comparison is close to impossible. Many give only cumulative permeation at a single time. Few include a marketed comparator, long-term stability, adhesion data, or irritation methods applied under conditions that mimic wear. Standardised reporting, similar in spirit to guidance already available for in vitro absorption studies, would make results from different laboratories far easier to weigh [16]. Even simple measures, such as stating the membrane thickness and the number of donors, would remove much of the current ambiguity [14, 31].

Future work could usefully pair permeation and tolerability in a single study, using human skin or well-characterised epidermis models, a marketed comparator and defined sink conditions. Skin imaging, microdialysis or tape-stripping would show how much drug reaches the target layer rather than the receptor. Photosafety testing of ketoprofen

systems should be routine. Finally, adhesion and wear testing should move from an afterthought to a design criterion, since a patch that does not stay in contact cannot deliver its dose, whatever its permeation profile looks like in a diffusion cell [29, 30].

Translation into practice raises a final set of questions. A transdermal product is a drug-device combination in the minds of many regulators, so quality attributes such as adhesion, residual solvent, content uniformity and stability sit beside efficacy and safety [29, 30, 35]. Patients bring their own variables, including hairy or sweaty skin, movement over joints and showering, none of which a diffusion cell sees. Pharmacists advising on topical NSAIDs also need to remember that low systemic exposure does not remove interactions or precautions in people with a history of asthma, ulcer or renal impairment, so clear labelling remains part of the safety package [1].

6. CONCLUSION

The published evidence indicates that ketoprofen is a sensible candidate for transdermal delivery and that Eudragit RL and RS matrices, adjusted with plasticisers and sometimes enhancers, can release it at rates that translate into measurable skin permeation in vitro [4, 6, 9, 10]. Clinical trials of commercial ketoprofen patches show analgesic benefit in sprains and tendinitis, which supports the concept though not any specific experimental matrix [7, 8]. Choice of membrane, receptor medium and model remains the largest influence on reported numbers [14, 16, 31]. Release is usually well described by Higuchi or power-law equations, although these describe the data rather than explain the mechanism [17, 18, 19, 36].

Irritation is where the evidence is thinnest. Classical rabbit scoring is giving way to reconstructed epidermis tests, but neither addresses ketoprofen photosensitivity and neither fully reflects occlusion and adhesive removal [11, 22, 24, 25]. Progress will depend on studies that measure permeation, adhesion, stability and tolerability together, with marketed comparators and transparent reporting, so that a laboratory formulation can be judged on grounds that matter to patients.

Pharmacists and formulators reading this literature should therefore treat single-laboratory permeation values as hypotheses rather than proof. Until then, claims of superiority over marketed ketoprofen products rest on thin ground [29, 35].

7. ABBREVIATIONS

NSAID-Non-steroidal anti-inflammatory drug, RL-Eudragit RL (higher permeability ammonio methacrylate copolymer), RS-Eudragit RS (lower permeability ammonio methacrylate copolymer), PVP-Polyvinylpyrrolidone, OECD-Organisation for Economic Co-operation and Development, ICH-International Council for Harmonisation, PSA-Pressure-sensitive adhesive, MTT-3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, TDDS-Transdermal drug delivery system

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9. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

10. CONFLICT OF INTERESTS

Declared none

11. REFERENCES

- Kantor TG. Ketoprofen: a review of its pharmacologic and clinical properties. *Pharmacotherapy* 1986;6:93–103.
- Guy RH. Current status and future prospects of transdermal drug delivery. *Pharm Res* 1996;13:1765–9.
- Prausnitz MR, Mitragotri S, Langer R. Current status and future potential of transdermal drug delivery. *Nat Rev Drug Discov* 2004;3:115–124.
- Magnusson BM, Anissimov YG, Cross SE, Roberts MS. Molecular size as the main determinant of solute maximum flux across the skin. *J Invest Dermatol* 2004;122:993–999.
- Barry BW. Novel mechanisms and devices to enable successful transdermal drug delivery. *Eur J Pharm Sci* 2001;14:101–114.
- Cordero JA, Alarcon L, Escribano E, Obach R, Domenech J. A comparative study of the transdermal penetration of a series of nonsteroidal antiinflammatory drugs. *J Pharm Sci* 1997;86:503–508.
- Mazières B, Rouanet S, Velicy J, Scarsi C, Reiner V. Topical ketoprofen patch (100 mg) for the treatment of ankle sprain: a randomized, double-blind, placebo-controlled study. *Am J Sports Med* 2005;33:515–523.
- Mazières B, Rouanet S, Guillon Y, Scarsi C, Reiner V. Topical ketoprofen patch in the treatment of tendinitis: a randomized, double blind, placebo controlled study. *J Rheumatol* 2005;32:1563–1570.
- Lin SY, Lee CJ, Lin YY. The effect of plasticizers on compatibility, mechanical properties, and adhesion strength of drug-free Eudragit E, L, and S films. *Pharm Res* 1991;8:1137–43.
- Lehmann KO. Chemistry and application properties of polymethacrylate coating systems. In: McGinity JW, editor. *Aqueous polymeric coatings for pharmaceutical dosage forms*. New York: Marcel Dekker; 1989. p. 153–245.
- Le Coz CJ, Bottlaender A, Scrivener JN, *et al*. Photocontact dermatitis from ketoprofen and tiaprofenic acid: cross-reactivity study in 12 consecutive patients. *Contact Dermatitis* 1998;38:245–252.
- Rao PR, Diwan PV. Permeability studies of cellulose acetate free films for transdermal use: influence of plasticizers. *Pharm Acta Helv* 1997;72:47–51.
- Mukherjee B, Mahapatra S, Gupta R, Patra B, Tiwari A, Arora P. A comparison between povidone-ethylcellulose and povidone-eudragit transdermal dexamethasone matrix patches based on in vitro skin permeation. *Eur J Pharm Biopharm* 2005;59:475–483.
- Ng SF, Rouse JJ, Sanderson FD, Meidan V, Eccleston GM. Validation of a static Franz diffusion cell system for in vitro permeation studies. *AAPS PharmSciTech* 2010;11:1432–1441.
- Bronaugh RL, Stewart RF. Methods for in vitro percutaneous absorption studies IV: the flow-through diffusion cell. *J Pharm Sci* 1985;74:64–67.
- OECD. Test No. 428: skin absorption: in vitro method. Paris: OECD Publishing; 2004.
- Roseman TJ, Higuchi WI. Release of medroxyprogesterone acetate from a silicone polymer. *J Pharm Sci* 1970;59:353–7.
- Costa FO, Sousa JJS, Pais AACC, Formosinho SJ. Comparison of dissolution profiles of ibuprofen pellets. *J Control*

- Release 2003;89:199–212.
19. Kanjickal DG, Lopina ST. Modeling of drug release from polymeric delivery systems: a review. *Crit Rev Ther Drug Carrier Syst* 2004;21:345–86.
20. Stott PW, Williams AC, Barry BW. Transdermal delivery from eutectic systems: enhanced permeation of a model drug, ibuprofen. *J Control Release* 1998;50:297–308.
21. Benson HAE. Transdermal drug delivery: penetration enhancement techniques. *Curr Drug Deliv* 2005;2:23–33.
22. Phillips L, Steinberg M, Maibach HI, Akers WA. A comparison of rabbit and human skin response to certain irritants. *Toxicol Appl Pharmacol* 1972;21:369–382.
23. OECD. Test No. 404: acute dermal irritation/corrosion. Paris: OECD Publishing; 2002.
24. OECD. Test No. 439: in vitro skin irritation: reconstructed human epidermis test method. Paris: OECD Publishing; 2010.
25. Welss T, Basketter DA, Schröder KR. In vitro skin irritation: facts and future. State of the art review of mechanisms and models. *Toxicol In Vitro* 2004;18:231–243.
26. Netzlaff F, Lehr CM, Wertz PW, Schaefer UF. The human epidermis models EpiSkin, SkinEthic and EpiDerm: an evaluation of morphology and their suitability for testing phototoxicity, irritancy, corrosivity, and substance transport. *Eur J Pharm Biopharm* 2005;60:167–178.
27. Arora P, Mukherjee B. Design, development, physicochemical, and in vitro and in vivo evaluation of transdermal patches containing diclofenac diethylammonium salt. *J Pharm Sci* 2002;91:2076–2089.
28. Mutalik S, Udupa N. Glibenclamide transdermal patches: physicochemical, pharmacodynamic, and pharmacokinetic evaluations. *J Pharm Sci* 2004;93:1577–1594.
29. Wokovich AM, Prodduturi S, Doub WH, Hussain AS, Buhse LF. Transdermal drug delivery system (TDDS) adhesion as a critical safety, efficacy and quality attribute. *Eur J Pharm Biopharm* 2006;64:1–8.
30. Tan HS, Pfister WR. Pressure-sensitive adhesives for transdermal drug delivery systems. *Pharm Sci Technol Today* 1999;2:60–69.
31. Hadgraft J. Skin, the final frontier. *Int J Pharm* 2001;224:1–18.
32. Moser K, Kriwet K, Naik A, Kalia YN, Guy RH. Passive skin penetration enhancement and its quantification in vitro. *Eur J Pharm Biopharm* 2001;52:103–112.
33. Kalia YN, Guy RH. Modeling transdermal drug release. *Adv Drug Deliv Rev* 2001;48:159–172.
34. Williams AC, Barry BW. Penetration enhancers. *Adv Drug Deliv Rev* 2004;56:603–618.
35. European Medicines Agency. Guideline on quality of transdermal patches. London: EMA; 2014.
36. Ramteke KH, Dighe PA, Kharat AR, Patil SV. Mathematical models of drug dissolution: a review. *Sch Acad J Pharm* 2014;3:388–96.