REVIEW ARTICLE

A CONCISE OUTLINE ON INNOVATIVE PERMEATION ENHANCERS IN TRANSDERMAL DRUG DELIVERY APPROACH

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(Received 19 March 2020) (Accepted 12 January 2022)

ABSTRACT

The transdermal drug administration system represents a potent substitute for administering medications orally and is also designed to offer a substitute for hypodermic injections. Presently, three generations of penetration enhancer to permeate through skin are available 1st Generation embraces chemical approaches and pertain to augment the efficacy of the drug transferred across the integral skin, 2nd generation encompasses physical permeation technologies and 3rd generation consists of microneedle and needleless penetration enhancers. There is renewed interest in transdermal drug delivery. This review focuses on some existing novel approaches and the additive upshot of techniques for increasing the permeation of drugs via skin penetration. By using the right methods, drug carriers, or certain chemical agents, it is important to cause the stratum corneum to change physically or biomolecularly.

Keywords: Transdermal, skin, barrier, penetration enhancers, penetration enhancing techniques, generations.

INTRODUCTION

"TRANSDERM-SCOP" was the earliest transdermal patch of an antiemetic medicament, containing scopolamine, which was endorsed by the FDA in 1979. As of now, transdermal medication conveyance is a standout amongst the most encouraging strategies for medication application. The transdermal route offers a few favorable circumstances over customary delivery system, for example, infusions and tablets besides, escaping first-pass digestion. Percutaneous retention includes the entry of medication from surface of the skin to stratum corneum (SC) affected by a fixation slope and its ensuing transport from the SC to the epidermis, dermis and systemic circulation. Further, the skin carries a distinct barrier to puncturing of particles. The SC gives the best protection from entrance and also rate-limiting advance to percutaneous ingestion. Permeation enhancers (PEs) encourage the assimilation of penetrant across the skin by briefly enhancing skin permeation. These materials should, ideally be non-irritating, non-toxic, pharmacologically inert, compatible with medication as well as excipients and possess excellent dissolving qualities. A single PE cannot have all the required properties. This review article endeavors to characterize PE and explain system activity; this will assist in deciding appropriate enhancer(s) intended for transdermal delivery of medications. The review discusses about a couple of vital saturation enhancers utilized in transdermal medication delivery. The transdermal route offers a non-invasive option in contrast to parenteral, subcutaneous, and intramuscular infusions and is appropriate for patients with motion sickness or nausea, etc[1-2]. But there are some limitations in the transdermal route as it causes erythema, tingling and local edema. Moreover, high M.W. drugs (>500Da) are usually difficult to penetrate through SC, while drugs possessing low or higher partition coefficient fail to achieve systemic dissemination. The drug should possess certain attractive physicochemical characteristics for infiltration through SC and the quantity essential for restorative is over 10 mg day^{-1}, else the transdermal delivery will be exceptionally troublesome, even if certainly feasible[3]. The different sites of the skin have variation in absorption efficiency, adherence difficulty in certain types of skin like excessive oily skin and challenges in time duration for which a patch can be applied on any area due to change in permeability (usually not more than 7 to 10 days)[4-10]. The review of various penetration enhancers used in transdermal patch formulation presents how the subject is approached for the development of suitable formulations.

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https://doi.org/10.53879/id.60.08.12392

Table I summarizes the diverse penetration enhancers used in the development of transdermal formulation[11-35].

CHEMICAL ENHANCERS

Chemical penetration enhancers are the 1st generation of penetration enhancers; their purpose is to use methods that maximize medication solubility in the skin or disturb membrane structures to reversibly alter the stratum corneum's barrier properties. Drugs can enter the body through different skin-penetration pathways: non-polar, polar, and non-polar/polar[9]. Causing protein conformational exchange or solvent swelling, changing the rigidity of lipid structure, and fluidizing the crystalline channel are essential for changing polar pathway; increasing the diffusion rate results in changes in non-polar pathway[36-57].

Water, alcohol, glycerol and glycerides

Water serves as the most frequently employed penetration enhancer; permeation of other hydrophilic and lipophilic permeants is increased *via* hydration of the stratum corneum. About 15-25 % of the dry weight of human stratum corneum is made up of water. Improved skin hydration may also cause stratum corneum's dense structure to expand and eventually open, which would augment penetration. However, increased hydration may not always be the cause of the growth in permeation[42-43]. Ethanol enhances diversity of loose sulfhydryl groups of keratins within the stratum corneum protein and functions as a penetration enhancer by removing significant lipid contents from stratum corneum[1]. Normally, ethanol pretreatment of skin will improve permeability of wide range of drugs with varying lipophilicity[58]. Triethanolamine salicylate from a hydrophilic emulsified base and ketoprofen from gel-spray will permeate readily in presence of ethanol[59]. Additionally, efficient permeation promoters include short-chain glycerides, for instance, tricaprylin and ethanol are combined to create a solvent derivative[60]. Papaverine was better distributed across the skins of hairless rats when glyceryl monocaprylate was used[61-62]. Papaverine hydrochloride was able to penetrate the skin more readily due to Sefsol® 318's medium chain glycerides improving the fluidity of stratum corneum's lipoidal membrane[56, 62].

Urea, sulfoxide and similar compounds, and azones

Urea encourages transdermal penetration by hydrating the stratum corneum together with utilizing the development of hydrophilic diffusion modes inside the barrier. When combined with a polar moiety and an extended chain alkyl ester group, cyclic urea permeation enhancers are non-toxic as well as biodegradable[43, 63-64]. Dimethyl sulfoxide (DMSO) can enhance absorption of drug substances by interacting with lipidic contents of stratum corneum and changing the shape of intercellular keratin from α-helical to β-sheet[43,65]. Azones disrupt lipid bilayers, cause lipid solubilization and accelerate fluidization of lipids, all of which contribute to an increase in permeability of diverse drugs, for instance methadone, indomethacin, propranolol hydrochloride and 5-fluorouracil[66-67].

Oxazolidinones, terpenes, terpenoids, vital oils and surfactants

According to several studies, oxazolidinones localise the transport of various active components in the skin's layers, including retinoic acid and diclofenac sodium[67-68]. Eucalyptol dramatically increases the flow of lipophilic (indomethacin) and hydrophilic (urea) compounds. Terpenes have been used therapeutically for a variety of reasons, including carminative, antispasmodic, aromatic and other properties, but some studies have suggested that they may also increase percutaneous absorption[66]. Ketoprofen's percutaneous penetration through two complexes including d-limonene as well as oleic acid was studied. d-Limonene had a higher rate of percutaneous absorption, but it also led to more skin injury. The increased concentration of d-limonene (20%) in the case of verapamil hydrochloride becomes effective in greatly improving its permeability. A 2 % concentration of the long chain sesquiterpene nerolidol increased enoxaparin sodium permeability by twofold. Using samples of human skin, researchers examined properties of another unsaturated sesquiterpene, α-bisabolol, for improving penetration of model drugs i.e., 5-FU and triamcinolone acetonide[67-70]. Surfactants are amazing transport enhancers due to their ability to denature keratin and solubilize/extract lipids. Non-ionic surfactants are frequently perceived as safe, however anionic and cationic surfactants can damage human skin. Surfactants studied include nonoxynol surfactants as non-ionic, cetyltrimethylammonium bromide as cationic, sodium lauryl sulphate as anionic, and dodecyl betaine as zwitterion[42-43, 67-69, 71].

Miscellaneous

Phosphatidyl glycerol derived compounds amplified bifonazole deposition in the skin along with tenoxicam percutaneous permeation, while phosphatidyl choline variants increased erythromycin percutaneous permeation[54]. Indomethacin has been studied by employing six derivative products of phosphatidyl glycerol i.e. PGE (from egg yolk), PGS (from soyabean),

Table I: Review of various penetration enhancers in transdermal patch formulations[11-35]

Drug	Polymer	Penetration enhancer	Plasticiser
Cissus quadrangularis extract	(HPMC E -15)	DMSO	Dibutyl pthalate[11]
Anti-anxiety drug	Eudragit® RS100, (HPMC E15)	--	Dibutyl pthalate[12]
Desogestrel	Duro-Tak®, Polyisobutylene,	--	Mineral oil[13]
Fenoterol hydrobromide	Duro-Tak, Scotchpak™	Azone	Propylene glycol[14]
Nicotine	Scotchpack™	--	Ethyl dibutyl phthalate glycerine[15]
Ibuprofen	CA/PVP	Azone	Fiber mats[16]
Pregabalin	HPMC, PVA, PVP, Eudragit® RL-100	DMSO	Propylene glycol[17]
Diltiazem hydrochloride	Eudragit® RL 100: Damar Batu gum		Damar Batu gum[18]
Repaglinide	HPMC and PVPK 30		PEG, PG[19]
Anastrozole	Duro-Tak® 87- 4098, ScotchPak®	Isopropyl myristate	Oleic acid[20]
Naproxen	Ethyl vinyl acetate, Eudragit®		Carbon dioxide at 450 psi[21]
Lidocaine hydrochloride	Poly (sodium methacrylate, methylmethacrylate)		PEG 400, glycerine, sorbitol, sodium chloride[22]
Letrozole	Duro-Tak®	Azone, Propylene glycol, Isopropyl myristate[23]	
Meloxicam	Acrylic adhesive (87-900A) Polyoxyethylenecetyl ether	Propylene glycol monolaurate, isopropyl myristate	Co Tran™ [24]
S-Amolidipine	Duro-Tak® 87-2677, 87-4098,87-9301	Isopropyl myristate, *l*-menthol	PEG-400[25]
Ketotifen fumarate	HPMC, Ethyl cellulose	Dimethyl sulfoxide	Di-butyl phthalate in chloroform and menthol[26]
Indapamide	Duro-Tak® 87-2677,87-2852, 87-4098	Isopropyl myristate, *l*-menthol	Polyethylene glycol 400[27]
Gestrodene & ethinylestradiol	Eudragit® RL100, Eudragit® RS 100, Eudragit® E 100	Isopropyl myristate	Polyethylene glycol -400[28]
Glibenclamide	HPMC, PVP, Eudragit® RS100	Dimethyl sulfoxide	Polyethylene glycol[29]
Timolol maleate	Water insoluble but permeable polymer	Sugar fatty acid ester[30]	
Benztropine	Duro-Tak® Scotch Pak® 1022	Isopropyl myristate	PEG -400, propylene glycol (PG), glycerine triacetate[31]
Isosorbide dinitrate & bisoprolol	Acrylic resin composition	Azone, Tween 80	Glycerol[32]
Pinacidil	Eudragit® RL 100, PVP	Dimethyl sulphoxide	Polyethylene glycol[33]
Salbutamol	Eudragit® RL 100, PVP	PEG-400, Tween 60	Propylene glycol[34]
Ibuprofen	Eudragit® E, Eudragit® RL Scotch Pak™		PG[35]

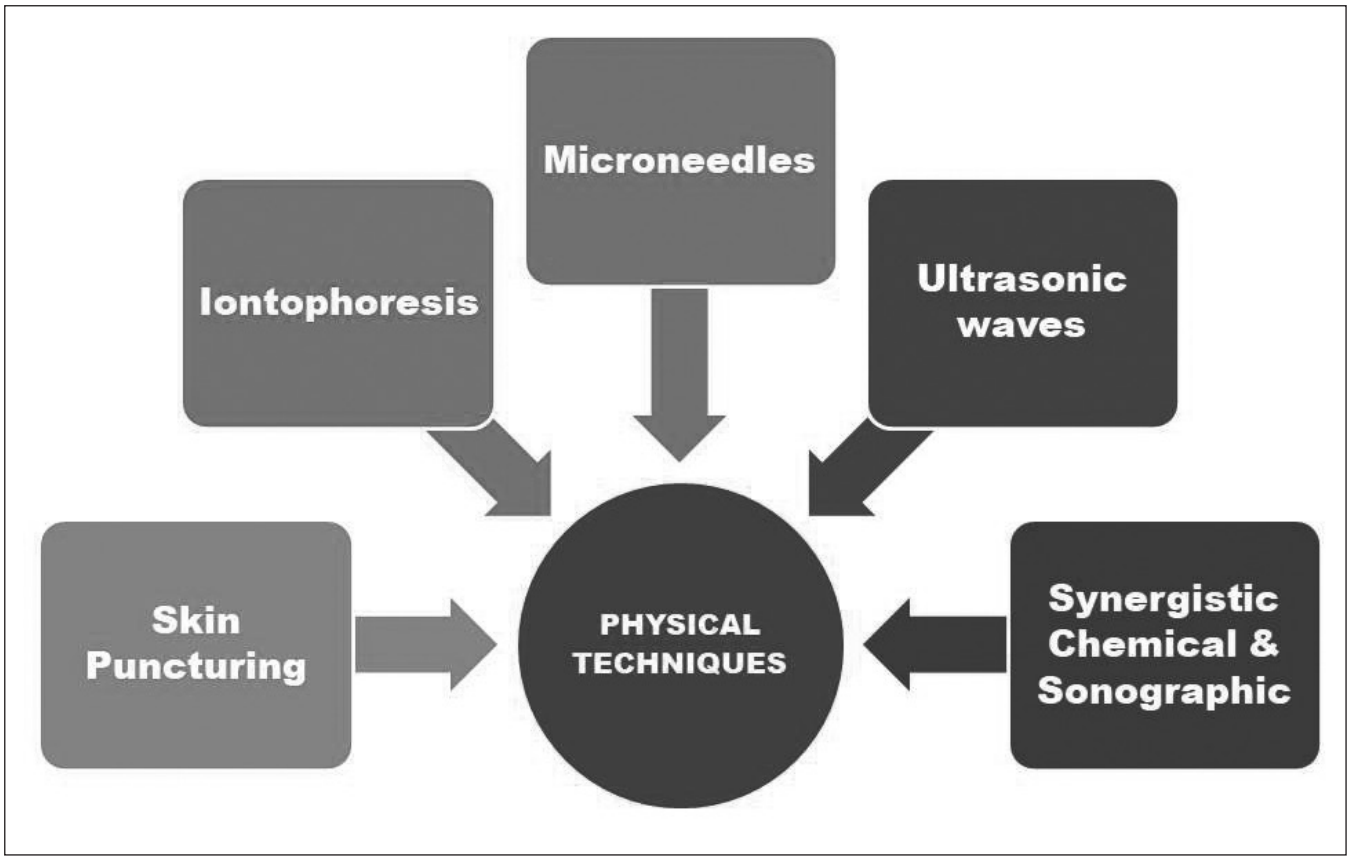

Fig. 1: Various physical techniques describing penetration through skin[56,59,76-77]

dimyristylphosphatidyl glycerol (DMPG), dipalmitylphosphatidylglycerol (DPPG), distearylphosphatidyl glycerol (DSPG) and dioleylphosphatidyl glycerol (DOPG). In addition to this, five derivative products of phosphatidyl choline i.e., PCE (from egg yolk), PCS (from soya-bean), dilinoleoyl PC (DLPC), dioleyl PC (DOPC) and hydrogenated PC (HPC), together with derivatives of phosphatidyl ethanolamine have also been explored for indomethacin[54, 72].

A related composition of clonazepam using methyl-β-cyclodextrin accelerated the drug's release contour through Carbopol hydrogel across cellulose nitrate membrane, and an inclusion complex of piroxicam made with β-cyclodextrin amplified drug flux cases throughout the shaved mouse skin[72-73]. Permeation of hydrocortisone from its suspension was increased by applying *N*-dodecyl-1-amino acid methyl ester and *N*-pentyl-*N*-acetyl prolinate to excised hairless mouse skin 1 h before drug treatment. *N*-pentyl-*N*-acetyl prolinate is significantly safer at low dosages and boosts flux of benzoic acid through the human cadaver skin. Theophylline's transdermal permeation in both oily as well as aqueous conditions was improved by the omega amino acid esters octyl-6-aminohexanoate and decyl-6-aminohexanoate, respectively[49, 74]. Acid phosphatase, phospholipase A2 and triacylglycerol hydrolase (TGH) were three epidermal enzymes that also increased the flux of both mannitol and benzoic acid. Papain pre-treatment of the skin led to reversible changes in the stratum corneum's protein structure that increased the penetration of proteins of diverse molecular weights, with the effect failing with larger molecular weight. Despite the limited efficacy of individual chemical enhancers, combinations of enhancers present new prospects in transdermal formulations[49, 75].

PHYSICAL ENHANCERS

These techniques involve the usage of more recent devices which might be designed to avoid skin barrier for immediately delivering the drug to the dermis by piercing pores and skin mostly under supervision. Iontophoresis, electroporation, ultrasound, microporation, radiofrequency and microneedles are the few techniques of the physical approach as described in Fig. 1[56, 59, 76-77].

Iontophoresis

Iontophoresis is a second-generation electrically assisted technique to supply precise medicine dosage via skin along with control of its desired therapeutic plasma level. Iontophoresis complements transdermal drug delivery by using ion electric discipline interplay, the flow of electric current and electrophoresis. The ionization of the medication is managed by using pH, density, molecular weight, the concentration of drug, physiology and and wavelength. Pilocarpine transport is an FDA-approved application of iontophoresis to treat hyperhidrosis by triggering sweating related to cystic fibrosis diagnostic test[78].

Electroporation

The introduction of bigger macromolecules, including insulin, heparin, DNA, oligonucleotides and microparticles, has also been accomplished using a combination of electroporation and chemical enhancement technique. Electroporation is the development of aqueous pores within the lipid bilayer with the use of short electrical pulses that range in voltage from 100 to 1000 V cm^{-1}. For charged molecules, flux increases up to 10,000-fold have been observed[79]. The number of medications that can be applied transdermally increases when electroporation is employed alone or in conjunction with other enhancing procedures[79-83].

Sonopheoresis / phonophoresis

In sonophoresis, a second-generation permeation enhancer, drug molecules are moved through the skin while being affected by ultrasound, which causes gaseous cavities to form inside the intercellular lipid and causes disruption of the skin[79]. Low-frequency or electricity ultrasound is used for lithotripsy, liposuction, cataract emulsification, dental descaling, ultrasonic scalpels (18-100 kHz) and cancer treatment[84]. High-frequency or diagnostic ultrasound is used in medical facility imaging (3-10MHz); medium-frequency or healing ultrasound is used in bodily remedy (0.7-3.0 MHz); and low-frequency or electricity ultrasound is use in body remedy (18-100 kHz). Also used are shock waves that are not ultrasonic, with stress amplitudes between 300 and 1,000 bar and short duration. Additionally, 1-10 s have been used to improve transdermal medication delivery[85-86].

Microneedles

When microfabricated technology allowed for manufacturing of solid microneedles for skin pretreatment to promote skin permeability, third generation penetration enhancers for microneedles entered the spotlight[87]. Currently, transdermal administration is accomplished via arrays of minuscule needles. These microneedle arrays can improve permeability by orderliness for small medicines, big macromolecules, and nanoparticles by creating a conduit for drug transport across the stratum corneum after being inserted into the skin[88-91]. Proteins and DNA are included in the microneedle-based vaccine delivery system to target Langerhans cells. Silicon needles with a diameter of a few microns are used in microfabricated microneedles technology. This technology enables the delivery of medicinal substances like insulin into the skin. The swellable silk fibroin microneedle for TDDS exhibits minimal distortion and controllable swelling characteristic and can easily puncture porcine skin resulting in strong transdermal drug kinetics and finally accumulating release ratio as compared to non-swelling hydrogel microneedles[41,92-95].

Needleless injection

The third-generation permeation enhancers, known as liquid jet injections, use a high-speed jet to pierce the skin then administer medication exclusive of the usage of a needle or throbbing sensation. The basic way to create pressure is by utilizing either a gas (helium, carbon dioxide or nitrogen). Disposal Cartridge Jet Injectors (DCJIs) and Multi-Use Nozzle Jet Injectors (MUNJIs) are the two primary classes of liquid jet injectors. A needle is put just a few millimeters into skin, and a micro-infusion pump housed inside a sizable “patch” adhered to the skin rashes medication solution into the skin at controlled rates. This method has been used to administer morphine to human test participants[3]. Intra-Ject®, ImplaJect®, mechanical perturbation, jet syringe, Macro Flux™, Crossject, magnetophoresis, mechanical perturbation, and laser ablation are a few of the needle-free injectors currently in use [97-100].

FUTURE ASPECTS AND THE SYNERGISTIC IMPACT OF ENHANCERS

Although each of the above-discuss permeation-enhancement techniques has been proved to improve transdermal medication delivery, their combination is frequently still more efficient[49-50]. Combining several boosters can lessen required “dose” of every single enhancer in addition to enhancing transdermal transport in a potentially synergistic way. Despite the benefits that come from combinations, most commercial efforts have focused on single enhancers, mainly because it is difficult to combine different technologies[99]. Many different compounds, such as polyethylene glycol, linoleic acid, isopropyl myristate and sodium lauryl sulphate have been used to show how chemicals and

ultrasound work in harmony. The goal of this synergy is to boost the enhancer's penetration and dispersion in the stratum corneum because of ultrasound. It has also been shown that ultrasound and ionophores work together synergistically to administer heparin trans-dermally. The substances which are thought to either widen or stabilize pores include urea, polysaccharides (heparin and dextran) and sodium thiosulfate. Iontophoresis and electroporation have been shown to work together for transdermal distribution[59, 66, 100-103]. Chemical enhancers have only limited success; chemical enhancer combinations offer fresh options for transdermal preparations. Transdermal medication delivery is once again receiving attention because of improvements in physical permeation enhancement technologies including microfabrication.

CONCLUSION

The transdermal patch has developed into a trusted technology over the past 20 years which provides many important clinical advantages over alternative dosing modalities. Large drug molecules were difficult to distribute through the skin in the past. To date, numerous chemical and physical techniques have been used to improve the effectiveness of material transfer over intact skin. Transdermal medication delivery is now again gaining popularity because of improvements in physical permeation augmentation technologies.

REFERENCES

1. Alkilani A. Z., McCrudden M. T. and Donnelly R. F.: Transdermal drug delivery: Innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum, **Pharmaceutics**, 2015, 7(4), 438-470.
2. Sashikant D. and Mrugendra B.: Formulation of transdermal patch of carvedilol by using novel polymers, **Der Pharmacia Sinica**, 2011, 2 (2), 185-189.
3. Kumar R. and Philip A.: Modified transdermal technologies: Breaking the barriers of drug permeation via the skin, **Trop. J. Pharm. Res**., 2007, 6(1), 633-644.
4. Patel H. J., Trivedi D. G., Bhandari A. K. and Shah D. A.: Penetration enhancers for transdermal drug delivery system: A review, **IJPI's J. Pharmaceut. Cosmetol**., 2011, 1(2), 67-80.
5. Rao R., Mahant S., Chhabra L. and Nanda S.: Transdermal innovations in diabetes management, **Curr. Diabetes Rev.**, 2014, 10(6), 343-359.
6. Benson H. A.: Transdermal drug delivery: penetration enhancement techniques, **Curr. Drug Deliv.**, 2005, 2(1), 23-33.
7. Barry B. W.: Novel mechanisms and devices to enable successful transdermal drug delivery, **Eur. J. Pharm. Sci.**, 2001, 14(2), 101-114.
8. Rajadhyaksha V. J.: Penetration enhancers for transdermal drug delivery of systemic agents. **US Patent 4405616A,** 1983.
9. Prakash K. and Soni D.: Current trends and recent development of transdermal drug delivery system TDDS, **Asian J. Pharm. Res. Dev**., 2023, 11(3), 181-189.
10. Herman A. and Herman A. P.: Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review, **J. Pharm. Pharmacol**., 2015, 67(4), 473-485.
11. Das R., Kolhe S., Patil A., Wadher K. and Umekar M.: Development and evaluation of transdermal patches with *Cissus quadrangularis* plant extract, **Int. J. Life Sci.,** 2018, 8(2), 29-34.
12. Peddapalli H., Ganta R. P. and Boggula N.: Formulation and evaluation of transdermal patches for antianxiety drug, **Asian J. Pharm. Sci.**, 2018, 12(2), 127-137.
13. Jain P. and Banga A. K.: Inhibition of crystallization in drug-in-adhesive-type transdermal patches, **Int. J. Pharmaceut**., 2010, 394(1-2), 68-74.
14. Elshafeey A. H., Hamza Y. E., Amin S. Y. and Zia H.: *In vitro* transdermal permeation of fenoterol hydrobromide, **J. Adv. Res.**, 2012, 3(2), 125-132.
15. Pichayakorn W., Suksaeree J., Boonme P., Amnuaikit T., Taweepreda W. and Ritthidej G. C.: Nicotine transdermal patches using polymeric natural rubber as the matrix controlling system: effect of polymer and plasticizer blends, **J. Membrane Sci.,** 2012, 411, 81-90.
16. Shi Y., Xu S., Dong A. and Zhang J.: Design and *in vitro* evaluation of transdermal patches based on ibuprofen-loaded electrospun fiber mats, **J. Mater. Sci.: Mater. Med.,** 2013, 24(2), 333-341.
17. Bhatia C., Sachdeva M. and Bajpai M.: Formulation and evaluation of transdermal patch of pregabalin, **Int. J. Pharm. Sci.**, 2012, 3(2), 569-575.
18. Mundada A. and Avari J.: Novel biomaterial for transdermal application: *In vitro* and *in vivo* characterization, **Drug Deliv.,** 2011, 18(6), 424-431.
19. Prajapati S. T., Patel C. G. and Patel C. N.: Formulation and evaluation of transdermal patch of repaglinide, **ISRN Pharm.,** 2011, v2011, 651909. doi: 10.5402/2011/651909
20. Xi H., Yang Y., Zhao D., Fang L., Sun L., Mu L. and He Z.: Transdermal patches for site-specific delivery of anastrozole: *In vitro* and local tissue disposition evaluation, **Int. J. Pharm.**, 2010, 391(1-2), 73-78.
21. Argemí A., Ellis J. L., Saurina J. and Tomasko D. L.: Development of a polymeric patch impregnated with naproxen as a model of transdermal sustained release system, **J. Pharm. Sci.**, 2011, 100(3), 992-1000.
22. Cilurzo F., Minghetti P., Gennari C. G., Casiraghi A. and Montanari L.: A novel polymethylmethacrylate hydrophilic adhesive matrix intended for transdermal patch formulations, **Drug Deliv.**, 2010, 17(3), 171-177.
23. Li L., Xu X., Fang L., LiuY., Sun Y., Wang M., Zhao N. and He Z.: The transdermal patches for site-specific delivery of letrozole: a new option for breast cancer therapy, **AAPS Pharm Sci. Tech.,** 2010,11(3), 1054-1057.
24. Ah Y. C., Choi J. K., Choi Y. K., Ki H. M. and Bae J. H.: A novel transdermal patch incorporating meloxicam: *In vitro* and *in vivo* characterization, **Int. J. Pharm.,** 2010, 385(1-2), 12-19.
25. Sun Y., Fang L., Zhu M., LiW., Meng P., Li L. and He Z.: A drug-in-adhesive transdermal patch for S-amlodipine free base: *In vitro* and *in vivo* characterization, **Int. J. Pharm**., 382(1-2), 165-171.
26. Manvi F., Gadad A., Mastiholimath V. and Jagadeesh T.: Formulation of a transdermal drug delivery system of ketotifen fumarate, **Indian J. Pharm. Sci.**, 2003, 65(3), 239-243.
27. Ren C., Fang L., Ling L., Wang Q., Liu S., Zhao L. and He Z.: Design and *in vivo* evaluation of an indapamide transdermal patch, **Int. J. Pharm.**, 370(1-2), 129-135.

28. Gao Y., Liang J., Liu J. and Xiao Y.: Double-layer weekly sustained release transdermal patch containing gestodene and ethinylestradiol, **Int. J. Pharm.,** 2009, 377(1-2), 128-134.
29. Gupta J., Irchhiaya R., Garud N., Tripathi P., Dubey P. and Patel J.: Formulation and evaluation of matrix type transdermal patches of glibenclamide, **Int. J. Pharm. Sci. Drug Res.,** 2009, 1(1), 46-50.
30. El-Laithy H. M.: Novel transdermal delivery of Timolol maleate using sugar esters: preclinical and clinical studies, **Eur. J. Pharm. Sci.**, 2009, 72(1), 239-245.
31. Hai N. T., Kim J., Park E. S. and Chi S. C.: Formulation and biopharmaceutical evaluation of transdermal patch containing benztropine, **Int. J. Pharm.,** 2008, 357(1-2), 55-60.
32. Zhao J. H., Fu J. H., Wang S. M., Su C. H., Shan Y., Kong S. J., Wang Y., Lu W. L., Zhang H., Zhang S. and Li L.: A novel transdermal patch incorporating isosorbide dinitrate with bisoprolol: *in vitro* and *in vivo* characterization, **Int. J. Pharm.**, 337(1-2), 88-101.
33. Aqil M., Ali A., Sultana Y., Dubey K., Najmi A. K., and Pillai K. K.: *In vivo* characterization of monolithic matrix type transdermal drug delivery systems of pinacidil monohydrate: A technical note., **AAPS Pharm. Sci. Tech.**, 2006, 7(1), E38-E42.
34. Tanwar Y.: Formulation and evaluation of transdermal films of salbutamol sulphate, **Dhaka Univ. J. Pharm. Sci.,** 2005, 4, 93-97.
35. Cilurzo F., Minghetti P., Casiraghi A., Tosi L., Pagani S. and Montanari L.: Polymethacrylates as crystallization inhibitors in monolayer transdermal patches containing ibuprofen, **Eur. J. Pharm. Biopharm.**, 2005, 60(1), 61-66.
36. Lane M. E.: Skin penetration enhancers, **Int. J. Pharm.,** 2013, 447(1-2), 12-21.
37. Williams A. C. and Barry B. W.: Penetration enhancers, **Adv. Drug Deliv. Rev.**, 2012, 64, 128-137.
38. Nair S. S.: Strategies to improve the potential of transdermal devices by enhancing the skin permeation of therapeutic entities, **J. Drug Deliv. Ther.**, 2019, 9, 972-976.
39. Jain N. K.: Controlled and novel drug delivery, CBS Publishers & Distributors, New Delhi 1997, pp. 100-110.
40. Barel A. O., Paye M. and Maibach H. I.: Handbook of Cosmetic Science and Technology, CRC Press, Boca Raton 2014, pp. 300-383.
41. Marwah H., Garg T., Goyal A. K. and Rath G.: Permeation enhancer strategies in transdermal drug delivery, **Drug Deliv.,** 2016, 23(2), 564-578.
42. Kamboj S., Jhawat V., Saini V. and Bala S.: Recent advances in permeation enhancement techniques for transdermal drug delivery systems: A review, **Curr. Drug Deliv.,** 2013, 8(3),181-188.
43. Pathan I. B. and Setty C. M.: Chemical penetration enhancers for transdermal drug delivery systems, **Trop. J. Pharm. Res.,** 2009, 8(2), 173-179.
44. Jouyban A., Fakhree M. A. and Shayanfar A.: Review of pharmaceutical applications of *N*-methyl-2-pyrrolidone, **J. Pharm. Pharm. Sci.,** 2010, 13(4), 524-535.
45. Aqil M., Ahad A., Sultana Y. and Ali A.: Status of terpenes as skin penetration enhancers, **Drug Discov. Today,** 2007, 12(23-24),1061-1067.
46. Babu R. J., Chen. L. and Kanikkannan N.: Fatty alcohols, fatty acids, and fatty acid esters as penetration enhancers, percutaneous penetration enhancers chemical methods in penetration enhancement, Springer, 2015. pp. 133-150.
47. Mittal A., Sara U., Ali A. and Aqil M.: Status of fatty acids as skin penetration enhancers-a review, **Curr. Drug Deliv.,** 2009, 6(3), 274-279.
48. Patil U.K. and Saraogi R.: Natural products as potential drug permeation enhancer in transdermal drug delivery system, **Arch. Dermatol. Res.,** 2014, 306(5), 419-426.
49. Sinha V. and Kaur M. P.: Permeation enhancers for transdermal drug delivery, **Drug Dev. Ind. Pharm.,** 2000, 26(11), 1131-1140.
50. Zhang H., Wang Z. and Liu O.: Development and validation of a GC–FID method for quantitative analysis of oleic acid and related fatty acids, **J. Pharm. Anal.**, 2015, 5(4), 223-230.
51. Dragicevic N., Atkinson J. P. and Maibach H. I.: Chemical penetration enhancers: classification and mode of action, Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement, Springer, 2015, pp. 11-27.
52. Atta N. F. and Ekram H.: Nanosensors Based on Surfactant Modified Electrodes. Nanosensors: Materials and Technologies, IFSA publishing Atla N. F., Ed - 2014, pp. 143-150.
53. Saikumar Y., Saikishore V., Pavani K., Sairam D. and Sindhura A.: Role of penetration enhancers in transdermal drug delivery system, **Res. J. Pharm. Technol.**, 2012, 4(6), 300-308.
54. Gupta M., Singh S., Jindal R. and Patidar S.: Penetration enhancers: Role in transdermal drug delivery system, **Pharmacie Globale.**, 2012, 3(9), 1-8.
55. Brychtova K., Dittrichova S., Slaba B., Placek L., Opatrilova R., Jampilek J. and Csollei J.: Synthesis of esters of 6-(2, 5-Dioxopyrrolidin-1-yl)-2-(morpholin-4-yl) hexanoic acid as potential transdermal penetration enhancers. In : Proceedings of the 13th International Electronic Conference on Synthetic Organic Chemistry (ECSOC13), November 1–30 (400). Basel: MDPI.
56. Hussain A., Wahab G.M.K.A., Rahman M.A.S., Altaf H., Akhtar N. and Qayyum M. I.: Potential enhancers for transdermal drug delivery: A review, **Int. J. Basic Appl. Med. Sci.,** 2014, 4(1), 19-24.
57. Roberts M.S., Cross S.E. and Pellett M.A.: Skin transport in, Dermatological and Transdermal Formulations, CRC Press, Boca Raton**,** Walters K. A., Ed 2002, pp. 107-214.
58. Lee C. K., Uchida T., Kitagawa K., Yagi A., Kim N. S. and Goto S.: Skin permeability of various drugs with different lipophilicity, **J. Pharm. Sci.**, 1994, 83(4), 562-565.
59. Mathur V., Satrawala Y. and Rajput M. S.: Physical and chemical penetration enhancers in transdermal drug delivery system, **Asian J. Pharm.,** 2014, 4(3), 173-183.
60. Walters K. A. and Hadgraft J.: Pharmaceutical skin penetration enhancement, Informa Health Care, London 1993, pp. 260-270.
61. Okumura M., Nakamori Y., Yoshida Y., Niwa H., Sugibayashi K. and Morimoto Y.: Effect of monoglycerides on the percutaneous absorption of papaverine hydrochloride, **Drug Des. Deliv.,** 1990, 6(2), 137-148.
62. Goswami D. S., Uppal N., Goyal S., Mehta N. and Gupta A. K.: Permeation enhancer for TDDS from natural and synthetic sources: a review, **J. Biomed. Pharm. Res.,** 2013, 2(1), 19-29.
63. Purdon C. H., Azzi C. G., Zhang J., Smith E. W. and Maibach H. I.: Penetration enhancement of transdermal delivery—current permutations and limitations, **Crit. Rev. Ther. Drug,** 2004, 21(2), 97-132.
64. Prakash D., Singh A. P., Katiyar N. S., Pathak K. and Pathak D.: Penetration enhancers: adjuvants in transdermal drug delivery system, **World J. Pharm. Pharm. Sci.,** 2016, 5(5), 353-376.
65. Marren K.: Dimethyl sulfoxide: an effective penetration enhancer for topical administration of NSAIDs, **Phys. Sportsmed**., 2011, 39(3), 75-82.
66. Dragicevic N. and Maibach H.I.: Percutaneous penetration enhancers chemical methods in penetration enhancement, Springer, 2016, 121-132.

67. Vikas S., Seema S., Gurpreet S., Rana A. and Baibhav J.: Penetration enhancers: a novel strategy for enhancing transdermal drug delivery, **Int. Res. J. Pharm.**, 2011, 2, 32-36.
68. Malvey S., Rao J. V. and Arumugam K. M.: Transdermal drug delivery system: A mini review, **Pharm. Innovation,** 2019, 8(1), 181-197.
69. Chen J., Jiang Q. D., Chai Y. P., Zhang H., Peng P. and Yang X. X.: Natural terpenes as penetration enhancers for transdermal drug delivery, **Molecules**, 2016, 21(12), 1709-1731.
70. Babaie S., Bakhshayesh A. R., Ha J. W., Hamishehkar H. and Kim K. H.: Invasome: A novel nanocarrier for transdermal drug delivery, **Nanomaterials,** 2020, 10(2), 341-353.
71. Ghafourian T., Nokhodchi A. and Kaialy W.: Surfactants as penetration enhancers for dermal and transdermal drug delivery, In: Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement: Springer, Berlin Heidelberg 2015, pp. 207-230.
72. Paudel K. S., Milewski M., Swadley C. L., Brogden N. K., Ghosh P. and Stinchcomb A. L.: Challenges and opportunities in dermal/ transdermal delivery, **Ther. Deliv.**, 2010, 1(1), 109-131.
73. Muankaew C. and Loftsson T.: Cyclodextrin based formulations: A non-invasive platform for targeted drug delivery, **Basic Clin. Pharmacol. Toxicol.,** 2018, 122(1), 46-55.
74. Rambharose S., Kalhapure R. S., Jadhav M. and Govender T.: Exploring unsaturated fatty acid cholesteryl esters as transdermal permeation enhancers, **Drug Deliv. Transl. Res.**, 2017, 7(2), 333-345.
75. Asbill C. S. and Michniak B. B.: Percutaneous penetration enhancers: local versus transdermal activity, **Pharmaceut. Sci. Tech. Today**, 2000, 3(1), 36-41.
76. Bavaskar K., Jain A., Patil M. and Kalamkar R.: The impact of penetration enhancers on transdermal drug delivery system: physical and chemical approach, **Int. J. Phar. Res. Rev**., 2015, 4(7), 14-24.
77. Cross S. and Roberts M.: Physical enhancement of transdermal drug application: Is delivery technology keeping up with pharmaceutical development? **Curr. Drug Deliv.,** 2004, 1(1), 81-92.
78. Fatima T., Ajjarapu S., Shankar V. K., Rangappa S., Shivakumar H. N., Biswas S. K., Hoque M. and Murthy S. N.: Topical pilocarpine formulation for diagnosis of cystic fibrosis., **J. Pharm. Sci.**, 2020, 109(5), 1747-1751.
79. Denet A. R., Vanbever R. and Préat V.: Skin electroporation for transdermal and topical delivery, **Adv. Drug Deliv. Rev.,** 2004, 56(5), 659-674.
80. Vanbever R. and Preat V.: *In vivo* efficacy and safety of skin electroporation, **Adv. Drug Deliv. Rev.,** 1999, 35(1), 77-88.
81. Badkar A. V. and Banga A. K.: Electrically enhanced transdermal delivery of a macromolecule. **J. Pharm. Pharmacol.**, 2002, 54(7), 907-912.
82. Wallace M. S., Ridgeway B., Jun E., Schulteis G., Rabussay D. and Zhang L.: Topical delivery of lidocaine in healthy volunteers by electroporation, electroincorporation, or iontophoresis: an evaluation of skin anesthesia, **Reg. Anesth. Pain Med.,** 2001, 26(3), 229-238.
83. Charoo N.A., Rahman Z., Repka M.A. and Murthy S.N.: Electroporation: an avenue for transdermal drug delivery, **Curr. Drug Deliv.,** 2010, 7(2), 125-136.
84. Oberli M. A., Schoellhammer C. M., Langer R. and Blankschtein D.: Ultrasound-enhanced transdermal delivery: recent advances and future challenges, **Ter. Deliv.,** 2014, 5(7), 843-857.
85. Serikov N.: Efficacy of ibuprofen (nurofen gel) ultraphonophoresis for pain relief in osteoarthrosis, **Ter. Arkh.**, 2007, 79(5), 79-81.
86. Park E. J., Dodds J. and Smith B. N.: Dose comparison of ultrasonic transdermal insulin delivery to subcutaneous insulin injection, **Int. J. Nanomedicine**, 2008, 3(3), 335-341.
87. Amjadi M., Mostaghaci B. and Sitti M.: Recent advances in skin penetration enhancers for transdermal gene and drug delivery, **Curr. Gene Ter.**, 2017, 17(2), 139-146.
88. Prausnitz M. R.: Microneedles for transdermal drug delivery, **Adv. Drug Deliv. Rev.**, 2004, 56(5), 581-587.
89. Lee J. W., Park J. H. and Prausnitz M. R.: Dissolving microneedles for transdermal drug delivery, **Biomaterials**, 2008, 29(13), 2113-2124.
90. Bariya S. H., Gohel M. C., Mehta T. A. and Sharma O. P.: Microneedles: an emerging transdermal drug delivery system, **J. Pharm. Pharmacol.**, 2012, 64(1), 11-29.
91. Escobar Chavez J. J., Bonilla Martínez D., Angelica M., Molina Trinidad E., Casas Alancaster N. and Revilla Vazquez A. L.: Microneedles: a valuable physical enhancer to increase transdermal drug delivery,**J. Clin. Pharmacol.**, 2011, 51(7), 964-977.
92. Han T. and Das D. B.: Potential of combined ultrasound and microneedles for enhanced transdermal drug permeation: a review, **Eur. J. Pharm. Biopharm.**, 2015, 89, 312-328.
93. Yin Z., Kuang D., Wang S., Zheng Z., Yadavalli V. K. and Lu S.: Swellable silk fibroin microneedles for transdermal drug delivery,**Int. J. Biol. Macromol.**, 2018, 106, 48-56.
94. Gao Y., Hou M., Yang R., Zhang L., Xu Z.,Kang Y. and Xue P.: Highly porous silk fibroin scaffold packed in PEGDA/sucrose microneedles for controllable transdermal drug delivery, **Biomacromolecules,** 2019, 20(3), 1334-1345.
95. Indermun S., Luttge R., Choonara Y. E., Kumar P., Du Toit L. C.,Modi G. and Pillay V.: Current advances in the fabrication of microneedles for transdermal delivery, **J. Control. Release,** 2014, 185, 130-138.
96. Patel M., Bharadia P. and Patel M.: Skin penetration enhancement techniques–physical approaches, **Int. Res. J. Pharm. Appl. Sci.,** 2010,12(13),62-72.
97. Sammeta S. M., Repka M. A., Murthy S. N.: Magnetophoresis in combination with chemical enhancers for transdermal drug delivery, **Drug Dev. Ind. Pharm.,** 2011, 37(9), 1076-1082.
98. Murthy S. N.: Magnetophoresis: an approach to enhance transdermal drug diffusion. **Pharmazie**, 1999, 54(5), 377-379.
99. Johnson M. E., Mitragotri S., Patel A., Blankschtein D. and Langer R.: Synergistic effects of chemical enhancers and therapeutic ultrasound on transdermal drug delivery, **J. Pharm. Sci.**, 1996, 85(7), 670-679.
100. Mitragotri S.: Synergistic effect of enhancers for transdermal drug delivery, **Pharm. Res.,** 2000, 17(11), 1354-1359.
101. Mitragotri S., Ray D., Farrell J., Tang H., Yu B., Kost J., Blankschtein D. and Langer R.: Synergistic effect of low frequency ultrasound and sodium lauryl sulfate on transdermal transport**, J. Pharm. Sci**., 2000, 89(7), 892-900.
102. Schafer N., Balwierz R., Biernat P., Ochędzan-Siodłak W. and Lipok J.: Natural ingredients of transdermal drug delivery systems as permeation enhancers of active substances through the stratum corneum, **Mol. Pharm.**, 2023, 20, 3278-3297.
103. Bhardwaj K., Sharma P. K., Sachdeva M., Budhlakoti P. and Ghosh N. C.: Effective topical psoralen herbal hydrogel expending capsaicin as a penetration enhancer, **Curr. Drug Ther**., 2023, 18(1), 33-48.