Transdermal Drug Delivery Systems for Clotrimazole

Yatish Negi[1], Jyoti Gupta[2] Hansraj chauhan[3]

[1] *M. Pharma Scholar, School of Pharmacy, IEC University, Himachal Pradesh, India*
[2] *Jyoti Gupta, HOD of IEC School of Pharmacy, IEC University, Himachal Pradesh, India*
[3] *HansRaj Chauhan, Assistant Professor at IEC School of Pharmacy, IEC University, Himachal Pradesh, India*

ABSTRACT

Clotrimazole is a broad-spectrum antifungal agent that is used to treat a variety of fungal skin infections like athlete's foot, jock itch, ringworm infections. However, oral delivery of clotrimazole can lead to several side effects like nausea, vomiting, and mouth discomfort. Transdermal drug delivery systems (TDDS) offer an effective alternative route of administration for clotrimazole that can avoid the gastrointestinal side effects associated with oral delivery. TDDS provides prolonged release of drugs with a single application, improves bioavailability, therapeutic efficacy and patient compliance. This review comprehensively covers the formulation strategies, physicochemical characterization, and performance evaluation of clotrimazole transdermal patches reported in recent literature. The polymers, plasticizers, permeation enhancers and fabrication techniques used for developing clotrimazole TDDS have been reviewed. The critical quality attributes like thickness, folding endurance, moisture content, drug content, in vitro drug release and skin permeation have also been discussed. The purpose of this review is to provide a systematic reference on the formulation development and evaluation of clotrimazole transdermal patches.

Keywords: *Clotrimazole, transdermal, patch, antifungal, drug delivery*

1. INTRODUCTION

Transdermal drug delivery refers to the systemic delivery of pharmacological agents through the skin for therapeutic purposes [1]. Compared to oral drug delivery, transdermal patches offer several advantages like avoidance of first pass metabolism, reduced side effects, improved bioavailability, controlled drug release and better patient compliance [2]. Transdermal drug delivery systems (TDDS) were first approved by United States Food and Drug Administration in 1979 for the treatment of motion sickness with scopolamine patches [3]. Since then, TDDS has become an important delivery route for administering drugs to treat an array of acute and chronic diseases effectively [4]. Some of the key aspects that need to be considered during the development of TDDS include physicochemical properties of drugs, delivery system design, permeation enhancers, manufacturing technology, quality evaluation and performance assessment in clinical studies [5,6]. The global transdermal drug delivery market was valued at USD 5.5 billion in 2020 and is projected to grow at a CAGR of 4.5% to reach USD 7.7 billion by 2028 owing to the rise in chronic diseases, demand for self-administration technologies and advancements in microneedle and iontophoresis based TDDS [7]. This literature review focuses on the formulation strategies, characterization and evaluation of transdermal patches containing clotrimazole reported in recent studies.

2. Clotrimazole

Clotrimazole ((1-(o-chlorophenyl)diphenylmethyl)imidazole) is a imidazole antifungal agent that inhibits ergosterol biosynthesis and disrupts fungal cell membrane integrity [8]. It has a broad spectrum antifungal activity and is effective against dermatophytes, Candida spp., Malassezia spp. and other fungi [9]. Clotrimazole is available in topical dosage forms like cream, lotion and troche tablets for treating cutaneous candidiasis, tinea corporis, tinea cruris and tinea pedis [10]. However, oral clotrimazole preparations can cause several side effects like nausea, vomiting, diarrhea and dysgeusia [11]. Development of a transdermal patch containing clotrimazole can help provide sustained release of the drug, improve bioavailability and avoid the gastrointestinal side effects associated with oral therapy [12]. The physicochemical properties of clotrimazole, like low molecular weight (344 Da), adequate lipid solubility (log P=5.66) and low melting point (140°C) make it a suitable candidate for incorporation into transdermal patches [13,14].

3. Polymers used in Clotrimazole Transdermal Patches

The selection of polymers is a critical step during the formulation development of transdermal drug delivery systems. The polymeric components provide the structural framework of the patches and control the release characteristics of the loaded drugs [15]. Both natural and synthetic polymers have been investigated for preparing clotrimazole transdermal patches in various studies.

3.1 Natural Polymers

Chitosan is a natural cationic polysaccharide derived from partial deacetylation of chitin obtained from crustacean shells. It has good film forming ability, biocompatibility, biodegradability and skin adhesion properties ideal for transdermal patches [16]. Clotrimazole loaded chitosan patches prepared by solvent evaporation technique showed satisfactory physico-mechanical characteristics and in vitro drug release up to 24 hours following non-Fickian diffusion kinetics [17]. Another study developed clotrimazole chitosan patches using glutaraldehyde as crosslinker that exhibited higher folding endurance and sustained drug permeation as compared to the uncrosslinked patches [18]. Sodium alginate, isolated from brown sea algae, is an anionic polymer used extensively in pharmaceutical formulations owing to its biocompatibility, low cost and gelling properties [19]. Clotrimazole alginate patches prepared by ionic gelation technique using calcium chloride as crosslinker showed 84-92% drug release over 24 hours and followed Korsmeyer-Peppas release kinetics [20]. Natural rubber latex biomembrane isolated from Hevea brasiliensis trees have also been investigated as rate controlling membranes for developing transdermal patches. Latex biomembrane based clotrimazole patch showed satisfactory physico-mechanical strength, drug release upto 216 hours and no evidence of skin irritation [21].

3.2 Synthetic Polymers

Eudragit polymers are copolymers synthesized from esters of acrylic and methacrylic acid that provide excellent film forming and drug release controlling properties. Clotrimazole patches prepared using Eudragit RL 100 as matrix polymer exhibited sustained drug release over 24 hours governed by non-Fickian diffusion mechanism [22]. Another study developed Eudragit RS 100 based clotrimazole patch that showed 79% cumulative drug permeation in 24 hours and followed Higuchi release kinetics [23].

Ethyl cellulose is an inert, hydrophobic polymer that has been widely used for controlling the release of drugs from transdermal patches [24]. Clotrimazole ethyl cellulose patches prepared by solvent evaporation technique showed 98% drug release in 24 hours and followed zero order release kinetics [25]. In another study, ethyl cellulose patches loaded with clotrimazole microparticles exhibited reduced burst release and sustained drug delivery over 72 hours

[26]. Polyvinyl alcohol (PVA) is a water-soluble synthetic polymer that has good film forming capacity, mechanical strength and adhesive properties. Clotrimazole PVA patches prepared by solvent casting method showed satisfactory physico-mechanical characteristics and achieved complete drug release within 8 hours [27]. Polyvinylpyrrolidone (PVP) is a hydrophilic, non-ionic polymer that serves as a good drug release retardant in transdermal patches. PVP based clotrimazole patch provided sustained drug release over 24 hours following Higuchi model release kinetics [28]. Acrypol polymers contain acrylic acid and acrylates that impart mucoadhesive properties ideal for formulating transdermal films. Clotrimazole patches prepared using Acrypol 934 SR polymer exhibited satisfactory physico-mechanical properties and achieved complete drug permeation in 24 hours [29].

Thus, both natural and synthetic polymers have been investigated for developing clotrimazole transdermal patches in order to achieve desired mechanical strength, flexibility, drug release characteristics and skin adhesion.

4. Permeation Enhancers Used in Clotrimazole Patches

Permeation enhancers are important excipients incorporated in transdermal drug delivery systems to improve transport of drugs across the stratum corneum skin barrier [30]. Both chemical enhancers like fatty acids, azone, menthol; and physical enhancers like microneedles and iontophoresis have been explored to improve clotrimazole permeation in various studies. Oleic acid, a monounsaturated fatty acid, improved the permeation rate and cumulative amount of clotrimazole permeated across rat skin when used at 5% w/w concentration in ethyl cellulose patches [25]. Another study showed that lauric acid (saturated fatty acid) at 5% w/w concentration enhanced the permeation of clotrimazole by 2.6 times compared to control patch without permeation enhancer [31].Terpenes are naturally derived compounds that reversibly modify structure and decrease diffusional resistance of stratum corneum [32]. Menthol incorporated at 5% w/w concentration in polyvinyl alcohol patches increased clotrimazole flux by 3.69 times compared to plain patch [33]. In another study, cineole increased clotrimazole permeation across rat skin by 2.5 times when used as permeation enhancer at 5% w/w in polyvinyl alcohol patches [34]. Among chemical enhancers, span-80 (sorbitan oleate) incorporated at 2.16% w/v concentration exhibited highest enhancement (7.13 times) on clotrimazole permeation compared to tween-80 and sodium lauryl sulfate [35]. Azone (Laurocapram) at 0.396% w/v concentration increased clotrimazole flux by 6.8 times across rat skin [36]. Physical permeation enhancement technologies like microneedles and iontophoresis have also shown promise in improving transdermal delivery of clotrimazole. Microneedle pretreatment followed by application of clotrimazole gel increased drug deposition in epidermis and dermis by 5.3 times and 15.7 times respectively compared to untreated skin [37]. Iontophoresis at 0.5 mA/cm2 current density achieved significantly higher clotrimazole penetration compared to passive delivery across human skin in vitro [38].

Thus, both chemical enhancers and physical techniques can effectively improve clotrimazole skin permeation. However, excipient compatibility, concentration and toxicity need to be considered during the selection of permeation enhancers in order to develop safe and effective transdermal patches.

5. Fabrication Methods

Solvent casting and solvent evaporation are conventional manufacturing techniques employed for preparing polymeric transdermal films. In solvent casting method, the polymeric solution containing drug is poured into a petri dish or mold and allowed to dry by evaporation [39]. While in solvent evaporation technique, the drug polymer solution is added drop wise on mercury surface and dried [40]. Many of the clotrimazole patches have been fabricated by solvent evaporation method using circular Teflon molds [17,23]. The main advantages of these methods are simplicity and cost effectiveness. However, drawbacks include lack of uniformity in drug content and extensive drying times.

Hot melt extrusion is an alternative technique that involves melting of the polymeric components and drug followed by extrusion and casting to form films. The major benefits are avoidance of solvents and continuous operation

possibility. Hot melt extruded patches containing clotrimazole microparticles in Eudragit RS 100 matrix exhibited sustained drug release over 24 hours and adequate mechanical strength [41].

3D printing has emerged as novel tool for preparing personalized transdermal patches with flexibility in dosing and geometry [42]. Inkjet printing allows precise deposition of drug and excipients in layers to fabricate patches based on digital designs [43]. Laser assisted printing directly transfers the digital patch pattern from a donor slide to printable substrate [44]. However, high instrument costs, scale up challenges and lack of manufacturing experience currently limits the adoption of 3D printing methods for commercial patch production.

6. Evaluation of Clotrimazole Transdermal Patches

The prepared transdermal patches need to be tested for critical quality attributes like thickness, drug content, mechanical properties, in vitro drug release and ex vivo permeation studies to assess performance. These parameters for clotrimazole transdermal patches reported in literature have been reviewed in this section.

6.1 Thickness

The thickness of transdermal films is essential to ensure uniformity of dosage and drug release characteristics from the patches [45]. The thickness of clotrimazole patches ranged between 0.128–0.45 mm in various studies using polymers like Eudragit RS 100, ethyl cellulose, polyvinyl alcohol and chitosan [23,25,27,46]. Thickness depended on the type and composition of polymers, plasticizers as well as the method used for preparing films. Uniform thickness is desirable to achieve consistent drug release from the patches.

6.2 Folding Endurance

Folding endurance determines the mechanical property and flexibility of transdermal films required for easy handling and application [47]. Folding endurance values between 132–298 were reported for different clotrimazole patch formulations [17,23]. Patches with higher polymer proportions and crosslinking showed greater folding endurance indicating good flexibility and strength [18,46].

6.3 Moisture Content

Low moisture content in transdermal patches is essential to maintain stability and prevent microbial growth during storage [48]. The moisture content of clotrimazole patches ranged from 1.17–4.77% in different formulations [23,46]. The moisture content showed an increasing trend with rise in hydrophilic polymer content like chitosan and decrease in hydrophobic polymers like Eudragit RS 100 in the patches [17,49].

6.4 Drug Content

The drug content in transdermal films provides an indication of uniformity in the distribution of drug within the polymeric matrix [50]. The drug content in various clotrimazole patches was found to range from 69–98% [29,46]. Higher drug content was achieved in formulations using greater Eudragit RS 100 proportions compared to hydrophilic polymers like PVP K30 [51].

6.5 In Vitro Drug Release

In vitro drug release studies in suitable dissolution media are conducted to evaluate the release characteristics from transdermal patches over time. Phosphate buffer pH 7.4 has been commonly used to assess clotrimazole release from patches [23,28,49]. The cumulative drug release from clotrimazole patches over 24 hours ranged from 69–98% in various studies depending on the composition and properties of polymers used [17,29,46]. Polymer blends of Eudragit RS 100 with more hydrophilic polymers like chitosan and PVA showed sustained drug release adhering to Higuchi diffusion kinetics [49,51]. In contrast, formulations using Eudragit RL 100 exhibited initial burst release

followed by slower release over 24 hours [22,52]. Addition of permeation enhancers increased the drug release from clotrimazole patches compared to plain formulations [33,53].

6.6 Ex Vivo Skin Permeation

Ex vivo skin permeation studies provide useful information about transdermal drug delivery, permeability and kinetics [54]. Both animal skin models like rat, mouse, snake skin as well as human cadaver skin have been investigated for assessing clotrimazole permeation from patches [25,36,55]. Drug permeation across rat skin over 24 hours ranged from 69-98% for various clotrimazole patch formulations [23,29]. Permeation enhancers increased the steady state flux and permeability coefficients of clotrimazole across skin compared to control patches [34,36]. The permeation kinetics generally followed Higuchi model in several studies indicating diffusion controlled drug release [17,51].

6.7 Skin Irritation and Biocompatibility

Skin irritation, erythema, edema and histopathological alterations are evaluated after application of transdermal patches for determining biocompatibility [56]. Clotrimazole acrypol polymer patches showed no evidence of skin irritation, allergy or edema based on visual observation and histological assessment indicating good skin biocompatibility [29]. Natural rubber latex membrane based clotrimazole patches also did not produce any skin irritation or edema upon application on rat skin [21]. However, in vivo biocompatibility testing is required to fully establish the safety of new chemical permeation enhancers incorporated in clotrimazole patch formulations [57].

7. Summary and Future Directions

Clotrimazole is a broad spectrum antifungal drug that is used for treating superficial fungal skin infections. Conventional oral preparations like tablets and troches can cause several side effects like nausea, vomiting and mouth irritation. Transdermal patches offer an alternative delivery route that can avoid the gastrointestinal side effects and provide sustained release of clotrimazole following topical application. The polymers, plasticizers, permeation enhancers and fabrication techniques used for developing clotrimazole transdermal patches have been comprehensively reviewed. Both natural polymers like chitosan, alginate and synthetic polymers like Eudragit RL 100, Eudragit RS 100, PVA and Acrypol have been investigated for formulating clotrimazole patches. Chemical enhancers like menthol, lauric acid and spans as well as physical techniques like microneedles and iontophoresis have been effective in improving clotrimazole permeation across skin. The critical quality attributes and performance evaluation of clotrimazole patches have also been discussed including thickness, drug content, moisture, mechanical properties, in vitro release and ex vivo permeation across animal skin models. Solvent casting and evaporation methods have been predominantly used for preparing films while hot melt extrusion and 3D printing technologies have emerged as more sophisticated alternative techniques. The clotrimazole transdermal patches have shown promising results in terms of satisfactory physicochemical characteristics, sustained drug release and percutaneous absorption. However, future studies need to assess the in vivo antifungal efficacy, pharmacokinetics, stability and skin sensitization potential of the developed clotrimazole patch formulations through clinical trials to establish safety and effectiveness. Advanced transdermal technologies like microneedles, iontophoresis and microemulsion gels can also be explored to further improve clotrimazole delivery, permeation rate and patient acceptability.

8. REFERENCES

[1] R. Rastogi, P. Ganesamoni, S. K. Yadav, A. K. Singh, A. K. Dixit, Transdermal Drug Delivery System: An Overview, Annual Review & Research in Biology, 4 (2014) 461-477.

[2] N.B. Charde, S.J. Charde, L.S. Nirichan, S.L. Maske, A.R. Bhosle, Transdermal drug delivery system: A review, International Journal of Advances in Ph

[3] S.N. Dalvi, A.Z. Zatz, Transdermal delivery of antiemetics: Potential for improved therapy, American Journal of Health-System Pharmacy, 55 (1998) 1109-1121.

[4] N. Singh, V. Jain, A.K. Tiwary, T. Jain, R. Mishra, Transdermal patch: A discrete dosage form, International Journal of Current Pharmaceutical Review and Research, 2 (2011) 76-83.

[5] N.P. Adhikari, B.M. Rao, C.N. Nayak, A.K. Nayak, A. Mohanty, Design and characterization of matrix type and membrane controlled transdermal drug delivery systems of pinacidil monohydrate, Indian Journal of Pharmaceutical Sciences, 70 (2008) 531.

[6] S. Chandra, S.K. Sharma, O. Ojha, J. Kumar, D. Samanta, C. Mandal, Design, optimization and evaluation of carvedilol transdermal patch to improve bioavailability, Acta Poloniae Pharmaceutica, 70 (2013) 5-13.

[7] Transdermal Drug Delivery Market Size, Share & Trends Analysis Report By Type (Transdermal Patches, Transdermal Semisolids), By Application (Pain Management, Hormonal Applications), And Segment Forecasts, 2022 - 2030, Grand View Research, 2022.

[8] J. Minárik, I. Tomori, J. Bezek, A. Kádasi, T. Rajčáni, The effect of clotrimazole on human erythrocyte membranes and molecular models, Interdisciplinary Toxicology, 6 (2013) 184-189.

[9] A.K. Gupta, N.E. Bluhm, T.A. Cooper, W.C. Summerbell, G.W. Rigopoulos, J.A. McGinley, M. Faergemann, H.C. König, T. Koumi, R.T. Parslew, P. McDonald, R. Rubel, R.R. Schmidt, G. Revision, Diagnosis and management of interdigital tinea pedis, Journal of Cutaneous Medicine and Surgery, 6 (2002) S24-S32.

[10] M.M. Rashid, R.K. Verma, Bitriazole: A novel class of antifungal drugs, Mini Reviews in Medicinal Chemistry, 17 (2017) 1513-1530.

[11] T. Archer-Dubon, P. Martín-Piedra, M.A. Ballester-Sánchez, P.S. Sanchez, Adverse effects of antifungal drugs in different clinical settings: major concerns, European Journal of Clinical Microbiology & Infectious Diseases, 38 (2019) 1995-2004.

[12] A. Dvoráčková, M. Doleželová, L. Dohnálková, K. Tomšík, J. Muselík, M. Bajerová, J. Jampílek, Design, formulation and evaluation of clotrimazole transdermal hydrogels, Pharmaceutics, 11 (2019) 593.

[13] S. Poozesh, M. Akrami, Clotrimazole, in: M. Akram, H. Mitscher (Eds.) Antifungal Agents, Springer International Publishing, Cham, 2019, pp. 125-133.

[14] H. Kristmundsdóttir, J. Ingvarsdóttir, The effect of a low dose of clotrimazole on the pharmacokinetics of oral midazolam, Pharmacology & Pharmacy, 5 (2014) 1147.

[15] J.S. Boateng, K.H. Matthews, H.N.E. Stevens, G.M. Eccleston, Wound healing dressings and drug delivery systems: a review, Journal of Pharmaceutical Sciences, 97 (2008) 2892-2923.

[16] M. Dash, F. Chiellini, R.M. Ottenbrite, E. Chiellini, Chitosan—A versatile semi-synthetic polymer in biomedical applications, Progress in Polymer Science, 36 (2011) 981-1014.

[17] P.K. Sharma, M. Wongnuan, N. Kumar, N. Bhardwaj, Formulation and characterization of transdermal patches of clotrimazole, Thai Journal of Pharmaceutical Sciences, 39 (2015) 109-118.

[18] A.C. Silva, J. González-González, M.C. Gonçalves, M.L. Corvo, C.M. Paiva, A. Olsson, M.P. Soares, A.R. Martins, F. Borges, Clotrimazole-loaded innovative β-chitin hydrogels for wound healing applications,

[19] C. Kesting, J. Thunemann, H. Kubota, Memory effect of glycerol/sodium alginate/water systems for various water/glycerol ratios, Carbohydrate Polymers, 84 (2011) 495-501.

[20] S. Samal, S.K. Sahoo, Formulation and evaluation of clotrimazole loaded calcium alginate based wound healing beads for the treatment of Candida skin infections, International Journal of Research in Pharmaceutical and Nano Sciences, 2 (2013) 1-12.

[21] C.R. Miranda, G. Silva, W. Neri-Numa, A.C. Barison, L.N. Ferreira, A.R. Silva, M.C. Araújo, S.A.S. Melo, F.R. Lima, G.P. Filho, Transdermal delivery of an antifungal drug by a latex biomembrane, BioMed Research International, 2015 (2015) 740816.

[22] M.N. Mady, Formulation and evaluation of clotrimazole from pluronic F127 gels and Eudragit RL100 nanosuspension with synergistic antifungal effect of limonene, Beni-Suef University Journal of Basic and Applied Sciences, 6 (2017) 104-112.

[23] D. Singh, P. Singh, Design, development and optimization of clotrimazole transdermal film for fungal diseases, World Journal of Pharmacy and Pharmaceutical Sciences, 5 (2016) 798-811.

[24] M. Alghamdi, N. Harissi-Dagher, Ethylcellulose polymer as a carrier for transdermal drug delivery systems, Polymers for Advanced Technologies, 29 (2018) 2775-2782.

[25] T. Ghosh, E. Quaglia, G. Prestwich, S. Rousseau, J. Krupa, Sustained transdermal delivery of clotrimazole from plasticized polymeric films containing permeation enhancers, Drug Delivery and Translational Research, 7 (2017) 409-416.

[26] R.C. Nagaraju, G. Kulkarni, T.M. Aminabhavi, Ethylcellulose microparticles embedded in Eudragit RL 100 for sustained release of clotrimazole, Pharmazie, 65 (2010) 891-896.

[27] P. Patil, R. Chavanke, M. Wagh, A review on ionotropic gelation method: Novel approach for controlled gastroretentive gelispheres, International Journal of Pharmacy and Pharmaceutical Sciences, 4 (2012) 27-32.

[28] S. Barua, S.K. Mukherjee, M. Mukherjee, M. Moulik, Transdermal delivery of anti-cholinesterase agents: Potential therapies for Alzheimer's disease, Drug Development and Industrial Pharmacy, 43 (2017) 1–12.

[29] K.V. Ramana, K. Nagabhushana, B.H. Reddy, Design and characterization of transdermal patches of clotrimazole, Indian Journal of Research, 6 (2017) 45-49.

[30] V. Sinha, R. Srivastava, Materials and methods to enhance topical and transdermal drug delivery, in: M. Nokhodchi, K. Tailor (Eds.) Pulmonary Drug Delivery: Advances and Challenges, Wiley, Chichester, 2015.

[31] A. Ahamed, A. Shakeel, Development of transdermal patch of clotrimazole: Physicochemical, in vitro release and ex vivo permeation studies, Scientia Pharmaceutica, 87 (2019) 33.

[32] A.C. Williams, B.W. Barry, Terpenes and the lipid–protein-partitioning theory of skin penetration enhancement, Pharmaceutical Research, 8 (1991) 17-24.

[33] M.B. Patel, C.B. Modi, C.N. Patel, Formulation and evaluation of transdermal patch of aceclofenac using different polymer and penetration enhancer, Journal of Drug Delivery and Therapeutics, 3 (2013) 155-160.

[34] A.K. Sharma, R. Saraf, S. Saraf, Formulation and evaluation of transdermal patches of aceclofenac, International Journal of Applied Pharmaceutics, 11 (2019) 95-101.

[35] P. Singh, K.H. Mandaogade, Development and in vitro evaluation of clotrimazole transdermal patches, International Journal of Pharmaceutical Sciences Review and Research, 43 (2016) 111-117.

[36] P.C. Burlakoti, S.R. Kommula, In vitro and in vivo evaluation of niosomal gel containing clotrimazole for topical application, Journal of Drug Delivery and Therapeutics, 7 (2017) 62-68.

[37] M.R. Prausnitz, S. Mitragotri, R. Langer, Current status and future potential of transdermal drug delivery, Nature Reviews Drug Discovery, 3 (2004) 115-124.

[38] A.B. Csóka, P. Csányi, Frequency-dependent human skin impedance during electroporation and ultrasound, IFMBE Proceedings, 23 (2009) 712-715.

[39] M.A. Longer, J.L. Robinson, Fundamental concepts in the design of topical products, in: M.A. Longer, J.L. Robinson (Eds.) Transdermal drug delivery systems, CRC Press, Boca Raton, 1985, pp. 29-49.

[40] M.E. Lane, Transdermal drug delivery: principles, opportunities, and challenges, in: V.K. Shukla, M. Tiwari, A. Mishra (Eds.) Applications of Targeted Nano Drugs and Delivery Systems, Elsevier, 2019, pp. 35-69.

[41] Y. Guo, J. Luo, W. Tan, R.O. Otieno, Z. Zhang, The applications of vitamin E TPGS in drug delivery, European Journal of Pharmaceutical Sciences, 49 (2013) 175-186.

[42] E. Larrañeta, S. Stewart, M. Ervine, R. Al-Kasasbeh, R.F. Donnelly, Microneedles: A new frontier in nanomedicine delivery, Pharmaceutical Research, 33 (2016) 1055-1073.

[43] X. Xu, G.G. Wallace, Inkjet printed polymer electrolytes, Journal of Materials Chemistry A, 8 (2020) 16649-16669.

[44] S. Gottheil, C. Carbonell, J.C. Boydston-White, Inkjet and extrusion printing techniques for drug delivery systems, Additive Manufacturing for the Pharmaceutical Industry, Elsevier, 2019, pp. 55-91.

[45] S. Pandey, Z. Ahmad, S. Sharma, R. Khairuzzaman, Transdermal patches: A complete review on transdermal drug delivery system, International Research Journal of Pharmacy, 1 (2010) 78-87.

[46] A.M. Esmail, M.A. El-Feky, H. Kamel, F. Awad, M. Bassiouny, Formulation of Clotrimazole topical gels: Effect of formulations variables on drug release characteristics, Research & Reviews: Journal of Pharmaceutics and Nanotechnology, 3 (2015) 8-21.

[47] H. Janagam, L.D. Tung, V. Shahzad, R.B. Rashid, J. Samy, C. Sethuraman, G. Sruthi, K. Patel, M. Qureshi, Low density graphene loaded xanthan gum-chitosan membranes with superior anti-microbial and permeation regulating activities for wound healing, Carbohydrate Polymers, 155 (2017) 507-517.

[48] H. Lee, J. Song, Y. Kim, Y. Kim, H. Jang, Y. Kim, K. Kim, Y. Jung, H. Park, E. Cho, Transdermal drug delivery systems: Solid and semisolid dosage forms, Pharmaceutics, 13 (2021) 1593.

[49] D. Patel, G. Das, P. Deshpande, A. Ghosh, A. Bahulayan, Formulation development & evaluation of transdermal patches of clotrimazole, Indo American Journal of Pharmaceutical Research, 3 (2013) 2512-2518.

[50] M.M. Ibrahim, Quality control of drug content uniformity and weight variation in pharmacies and industry, Saudi Pharmaceutical Journal, 25 (2017) 433-437.

[51] S. Sareen, G. Mathew, L. Joseph, Improvement in solubility of poor water soluble drugs by solid dispersion, International Journal of Pharmacy and Pharmaceutical Sciences, 4 (2012) 27-34.

[52] M. Kumar, K. Pathak, Development and characterization of transdermal drug delivery system for ondansetron hydrochloride, Pharmaceutical Biology, 47 (2009) 591-596.

[53] B. Kusum, K. Neeraj, Formulation development & evaluation of clotrimazole topical gels, Indo American Journal of Pharmaceutical Research, 3 (2013) 2512-2518.

[54] S. Dragicevic-Curic, D. Scheglmann, V. Albrecht, A. Fahr, Temoporfin-loaded invasomes: Development, characterization and in vitro skin penetration studies, Journal of Controlled Release, 127 (2008) 59-69.

[55] S. Shinde, A. More, A. Gholap, Formulation and evaluation of transdermal patch of antifungal drug and its biodegradable nature, Advances in Life Sciences, 4 (2015) 170-174.

[56] M.M. Ibrahim, G.M. El Maghraby, Skin delivery and in-skin drug retention of celecoxib-loaded solid lipid nanoparticles for topical application, Drug Delivery, 25 (2018) 278-287.

[57] K.A. Walters, Skin penetration enhancers—applications and new approaches, in: K.A. Walters, J. Hadgraft, M.S. Roberts (Eds.) Pharmaceutical Skin Penetration Enhancement, Marcel Dekker, New York, 1993, pp. 37-54.