INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Paper

Design And Characterization of Controlled Release Transdermal Drug Delivery Systems Containing Sitagliptin Phosphate and Dapagliflozin

Naman Kumar*, Aarti Kori, Shivanand Patil

Veer Madho Singh Bhandari, Uttrakhand Technical University Dehradun.

ARTICLE INFO

Published: 17 Sept 2026
Keywords:
Transdermal drug delivery, Sitagliptin phosphate, Dapagliflozin, Controlled release, Diabetes mellitus, Permeation enhancers
DOI:
10.5281/zenodo.22816027

ABSTRACT

Transdermal drug delivery systems (TDDS) have emerged as an advanced approach for achieving controlled and sustained systemic drug delivery while avoiding gastrointestinal degradation and hepatic first-pass metabolism. Sitagliptin phosphate, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and dapagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, are widely used oral antidiabetic agents for the management of type 2 diabetes mellitus. However, oral administration is associated with fluctuating plasma levels, gastrointestinal side effects, and reduced patient adherence. Controlled release TDDS containing these agents may improve therapeutic efficacy and compliance. This review summarizes formulation strategies, polymers, permeation enhancement methods, evaluation parameters, and recent research advances in the development of transdermal systems for sitagliptin and dapagliflozin

INTRODUCTION

Diabetes mellitus is a chronic and progressive metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The global prevalence of diabetes has risen markedly due to urbanization, sedentary lifestyles, unhealthy dietary patterns, and genetic susceptibility, making it a major public health concern worldwide [1]. Long-term uncontrolled hyperglycemia is strongly associated with severe microvascular and macrovascular complications such as nephropathy, neuropathy, retinopathy, and cardiovascular diseases, thereby increasing morbidity and mortality [2]. Hence, maintaining sustained glycemic control remains the cornerstone of diabetes management.

Conventional oral antidiabetic therapy is widely used for type 2 diabetes mellitus; however, oral drug delivery presents several pharmacokinetic limitations, including variable gastrointestinal absorption, enzymatic degradation, hepatic first-pass metabolism, fluctuating plasma drug levels,

***Corresponding Author:** Naman Kumar
Address: *Veer Madho Singh Bhandari, Uttrakhand Technical University Dehradun.*
Email ✉: namanadvik@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

and the requirement for frequent dosing [3]. These challenges may contribute to suboptimal therapeutic outcomes and poor patient adherence, particularly in long-term multidrug regimens [4]. Additionally, gastrointestinal adverse effects and drug–drug interactions further compromise treatment effectiveness.

Transdermal drug delivery systems (TDDS) have emerged as a promising alternative for chronic disease management because they enable controlled and sustained systemic drug delivery through the skin while bypassing hepatic first-pass metabolism and gastrointestinal degradation [5]. TDDS provide relatively constant plasma drug concentrations, reduced dosing frequency, improved patient compliance, and minimized systemic adverse effects compared with oral therapy [6,7]. Their non-invasive nature, ease of application, and ability to terminate therapy by simple patch removal make them particularly suitable for chronic metabolic disorders such as diabetes [8].

Recent pharmaceutical research has focused on incorporating newer antidiabetic agents—particularly sitagliptin phosphate and dapagliflozin—into controlled release transdermal formulations to enhance therapeutic efficacy and long-term adherence [9,10]. These drugs belong to complementary pharmacological classes and are widely used in modern diabetes therapy, making them attractive candidates for advanced transdermal delivery approaches.

2. Pharmacological Profile of Sitagliptin Phosphate and Dapagliflozin

2.1 Sitagliptin Phosphate

Sitagliptin phosphate is a potent, selective, and orally active inhibitor of dipeptidyl peptidase-4 (DPP-4), the enzyme responsible for rapid degradation of incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Inhibition of DPP-4 prolongs incretin activity, thereby enhancing glucose-dependent insulin secretion from pancreatic β-cells and suppressing glucagon release from α-cells, ultimately improving both fasting and postprandial glycemic control [11,12]. Because this mechanism is glucose dependent, the risk of hypoglycemia is relatively low compared with traditional insulin secretagogues [13].Pharmacokinetic studies indicate that sitagliptin possesses high oral bioavailability (approximately 87%), minimal hepatic metabolism, moderate plasma protein binding, and an elimination half-life supportive of once-daily dosing [14]. Despite these favorable characteristics, oral therapy may still lead to plasma concentration fluctuations and adverse effects such as headache, nasopharyngitis, and mild gastrointestinal discomfort [13]. Sustained and controlled delivery via transdermal systems may therefore improve therapeutic stability and patient adherence [3].

2.2 Dapagliflozin

Dapagliflozin is a highly selective sodium–glucose cotransporter-2 (SGLT2) inhibitor that reduces renal glucose reabsorption in the proximal convoluted tubules, thereby increasing urinary glucose excretion and lowering plasma glucose levels through an insulin-independent mechanism [15,16]. This mechanism allows dapagliflozin to remain effective even in later stages of type 2 diabetes characterized by β-cell dysfunction. In addition to glycemic control, dapagliflozin therapy is associated with modest body-weight reduction, decreased blood pressure, and cardiovascular as well as renal protective benefits [17].

However, oral administration of dapagliflozin may lead to adverse events such as urinary tract infections, genital mycotic infections, dehydration, and electrolyte imbalance, along with dose-dependent pharmacokinetic variability

[16,18]. Controlled systemic delivery through TDDS may help maintain therapeutic drug concentrations while minimizing peak-related adverse effects and improving overall safety [9].

2.3 Rationale for Transdermal Delivery

Successful transdermal drug delivery depends on physicochemical properties such as molecular weight, lipophilicity, melting point, and required therapeutic dose. Drugs with molecular weight below approximately 500 Da and balanced lipophilicity are generally considered suitable for permeation across the stratum corneum [21,22]. Sitagliptin phosphate and dapagliflozin exhibit physicochemical characteristics that may permit transdermal transport when combined with suitable permeation enhancement strategies [19,20].

Advances in formulation science—including polymeric matrices, chemical permeation enhancers, nanocarriers, microneedles, iontophoresis, and vesicular delivery systems—have significantly expanded the potential of TDDS for systemic delivery of antidiabetic drugs [7,23]. Controlled release transdermal systems containing sitagliptin and dapagliflozin may provide steady-state plasma concentrations, reduced dosing frequency, minimized systemic fluctuations, improved bioavailability, and enhanced long-term patient adherence [9,10]. Furthermore, the complementary mechanisms of DPP-4 inhibition and SGLT2 inhibition make combination transdermal therapy a promising strategy for synergistic glycemic control in type 2 diabetes mellitus [24].

3. Principles of Controlled Release Transdermal Drug Delivery

Controlled release transdermal drug delivery systems (TDDS) are specifically designed to deliver therapeutically effective amounts of drug across the skin into systemic circulation at predetermined and sustained rates over an extended duration. The fundamental objective of controlled release TDDS is to maintain relatively constant plasma drug concentrations within the therapeutic window while minimizing peak-to-trough fluctuations commonly observed with oral dosing [8]. Such systems are particularly advantageous in chronic diseases like diabetes mellitus, where long-term and stable pharmacotherapy is essential for effective disease management.

Drug permeation through the skin primarily occurs via passive diffusion across the stratum corneum, which acts as the principal barrier to transdermal transport. The rate and extent of drug release from TDDS depend on several interrelated factors, including the physicochemical properties of the drug, diffusion characteristics of the polymeric matrix, permeability of biological membranes, degree of skin hydration, and presence of permeation enhancers [6]. Hydration of the stratum corneum increases lipid fluidity and enhances drug diffusion, thereby playing a crucial role in controlled release performance [5].

Different structural designs of TDDS have been developed to regulate drug release kinetics and therapeutic performance. The major types include matrix systems, reservoir systems, drug-in-adhesive systems, and micro-reservoir systems [8].

Matrix systems consist of drug uniformly dispersed within a polymeric matrix that controls diffusion-mediated release.

Reservoir systems contain a drug core enclosed by a rate-controlling membrane, enabling near zero-order release kinetics.

Drug-in-adhesive patches incorporate the drug directly into the pressure-sensitive adhesive layer, simplifying design and improving patient comfort.

Micro-reservoir systems combine characteristics of matrix and reservoir systems, where drug-

loaded microscopic reservoirs are dispersed within a polymeric matrix to achieve controlled release behavior.

Selection of an appropriate TDDS design depends on drug properties, required release profile, stability considerations, and therapeutic objectives.

4. Formulation Strategies for Sitagliptin and Dapagliflozin TDDS

Development of controlled release TDDS containing sitagliptin phosphate and dapagliflozin requires careful optimization of formulation components to achieve desirable mechanical strength, adhesion, permeation, and sustained drug release. Modern formulation strategies integrate polymer science, permeation enhancement, and nanotechnology-based delivery approaches to improve therapeutic outcomes.

4.1 Selection of Polymers

Polymers constitute the backbone of transdermal patches and play a decisive role in regulating drug release kinetics, structural integrity, flexibility, and adhesion to the skin surface. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and chitosan facilitate drug diffusion by swelling in the presence of moisture and forming gel-like networks that enable controlled release [25]. In contrast, hydrophobic polymers such as ethyl cellulose and Eudragit reduce rapid drug diffusion and provide prolonged release due to their water-insoluble nature [26].

Blending hydrophilic and hydrophobic polymers is a widely adopted strategy for achieving balanced mechanical properties and optimized diffusion control. Polymer combinations improve tensile strength, flexibility, folding endurance, and sustained drug permeation across the skin [27]. Proper polymer selection is therefore essential for designing effective TDDS of sitagliptin and dapagliflozin.

For the sustained-release objective of the present transdermal system, a 1:3 drug-to-polymer coating/matrix ratio may be considered the optimized formulation ratio. The higher proportion of polymer is expected to form a denser diffusion barrier, reduce the initial burst release, and prolong drug release by providing sustained diffusion of the incorporated drugs. Therefore, the 1:3 ratio should be highlighted as the preferred ratio when presenting the formulation and release profile, provided that the experimental results confirm superior sustained-release performance [27].

4.2 Plasticizers

Plasticizers are incorporated into polymeric films to enhance flexibility, reduce brittleness, and improve mechanical stability of transdermal patches. Commonly used plasticizers include polyethylene glycol-400 (PEG-400), glycerol, and dibutyl phthalate, which function by reducing intermolecular forces between polymer chains and increasing chain mobility [28].

In addition to improving film handling characteristics, plasticizers may also influence drug diffusion and release rate by modifying polymer free volume and permeability. Optimal plasticizer concentration is therefore critical, as excessive amounts may weaken mechanical strength or cause rapid drug release.

4.3 Permeation Enhancers

The stratum corneum presents the greatest barrier to transdermal drug transport; therefore, permeation enhancers are frequently employed to improve drug flux across the skin. Chemical permeation enhancers act by disrupting lipid organization, altering protein conformation, or increasing drug partitioning into the skin [22]. Common examples include oleic acid, dimethyl

sulfoxide (DMSO), propylene glycol, and naturally derived terpenes, all of which enhance drug diffusion through different molecular mechanisms.

In addition to chemical enhancers, **physical enhancement techniques** such as microneedles, iontophoresis, and sonophoresis have gained considerable attention. These approaches transiently disrupt the stratum corneum or apply external energy to facilitate deeper drug penetration and improved systemic absorption [21,23]. Such techniques may be particularly valuable for relatively hydrophilic antidiabetic drugs like sitagliptin phosphate.

4.4 Novel Nanocarrier Approaches

Recent advances in nanotechnology have significantly expanded the potential of TDDS for systemic delivery of poorly permeable drugs. Nanocarrier-based systems—including nanoemulsions, liposomes, solid lipid nanoparticles, and ultra-deformable vesicles such as transfersomes—enhance drug solubility, stability, and penetration through the skin barrier [29].

These nanoscale carriers improve drug partitioning into the stratum corneum, provide sustained release, and may enable targeted or stimulus-responsive delivery. Incorporation of sitagliptin and dapagliflozin into nanocarrier-loaded transdermal patches has shown promising results in terms of enhanced permeation, prolonged drug release, and improved bioavailability in recent experimental studies. Consequently, nanotechnology-assisted TDDS represent a rapidly evolving and highly promising strategy for advanced diabetes therapy.

5. Methods of Patch Preparation

The successful development of controlled release transdermal drug delivery systems depends greatly on the selection of an appropriate fabrication technique, as the preparation method directly influences drug distribution, mechanical strength, adhesion, and release kinetics of the final patch. Several preparation approaches have been explored for formulating transdermal patches containing antidiabetic agents such as sitagliptin phosphate and dapagliflozin.

The **solvent casting method** is the most widely employed technique due to its simplicity, cost-effectiveness, and ability to produce uniform films with controlled thickness. In this method, polymers are dissolved in a suitable volatile solvent system followed by incorporation of the drug, plasticizer, and permeation enhancer. The homogeneous solution is then poured into a casting mold or petri plate and allowed to dry under controlled temperature conditions to form a thin polymeric film [30]. This method enables uniform drug dispersion and predictable diffusion-controlled release, making it particularly suitable for matrix-type TDDS.

Hot-melt extrusion represents a solvent-free alternative in which the drug and polymer are blended and processed at elevated temperatures to form a homogeneous molten mass that is subsequently shaped into films or patches. This technique minimizes residual solvent toxicity and improves drug–polymer interaction; however, it may not be appropriate for thermolabile drugs due to potential degradation during heating.

Direct compression is another approach primarily used for reservoir or multilayer patch systems. In this method, drug-polymer blends are compressed into thin discs or layers using specialized dies. Although the technique is simple and avoids solvents, achieving uniform drug distribution and adequate mechanical flexibility can be challenging.

More recently, **electrospinning** has emerged as an advanced fabrication technology for producing **nanofibrous transdermal patches** with

extremely high surface area, porosity, and controlled drug release characteristics. Electrospun nanofibers enable rapid hydration, improved skin contact, and enhanced permeation of incorporated drugs [31]. This technique is gaining significant attention for next-generation TDDS, particularly when combined with nanocarrier-based drug loading.

Overall, the choice of preparation method depends on drug stability, desired release profile, polymer compatibility, scalability, and regulatory considerations.

6. Characterization and Evaluation of Transdermal Patches

Comprehensive characterization of transdermal patches is essential to ensure **quality, safety, efficacy, and reproducibility** of the developed formulation. Evaluation parameters generally include physicochemical properties, mechanical strength, drug release behavior, skin permeation performance, and stability under storage conditions.

6.1 Physicochemical Evaluation

Physicochemical characterization provides preliminary information regarding **uniformity, integrity, and suitability** of the prepared patches.

Thickness measurement ensures uniform drug distribution and consistent diffusion path length, typically determined using a digital micrometer at multiple points across the patch surface.

Weight variation analysis confirms batch-to-batch uniformity and proper mixing of formulation components.

Folding endurance reflects the flexibility and mechanical resistance of the film by counting the number of times a patch can be folded at the same position without breaking.

Surface pH determination is particularly important to avoid skin irritation; ideally, the patch pH should remain close to physiological skin pH.

Drug content uniformity ensures accurate dosing and homogeneous drug dispersion within the polymeric matrix, usually quantified using validated spectrophotometric or chromatographic methods [32].

6.2 Mechanical Properties

Mechanical evaluation determines the **strength, elasticity, and adhesive performance** required for proper skin application and patient comfort.

Tensile strength measures the maximum stress the patch can withstand before breaking, indicating structural robustness.

Percentage elongation evaluates elasticity and flexibility, which are critical for maintaining adhesion during skin movement.

Adhesion properties, including peel strength and tack, ensure that the patch remains attached to the skin for the intended duration without causing discomfort or residue formation. These mechanical parameters are fundamental for designing clinically acceptable TDDS [33].

6.3 In-Vitro Drug Release Studies

In-vitro release studies are conducted to understand **drug diffusion kinetics and release mechanisms** from the transdermal matrix. These studies are commonly performed using **Franz diffusion cells**, where the patch is placed between donor and receptor compartments separated by synthetic membranes or biological skin models. The receptor medium is sampled at predetermined intervals and analyzed for drug content to construct release profiles and determine kinetic models such as zero-order, first-order, Higuchi, or Korsmeyer–Peppas equations [34]. Such analysis helps predict in-vivo performance and optimize formulation variables.

6.4 Skin Permeation Studies

Ex-vivo permeation studies evaluate the ability of the drug to cross biological skin barriers and reach systemic circulation. These experiments typically employ excised **rat abdominal skin or human cadaver skin** mounted on diffusion cells. Key permeation parameters include **steady-state flux, permeability coefficient, diffusion coefficient, and lag time**, which collectively describe transdermal transport efficiency [35]. These studies are crucial for assessing the effectiveness of permeation enhancers and nanocarrier systems incorporated into sitagliptin and dapagliflozin TDDS.

6.5 Stability Studies

Stability testing determines the **shelf life, physical integrity, and chemical stability** of transdermal patches under various environmental conditions. Studies are conducted according to **International Council for Harmonisation (ICH) guidelines**, typically involving storage at controlled temperature and humidity conditions such as accelerated and long-term stability chambers [36]. Periodic evaluation of drug content, mechanical properties, appearance, and release profile ensures formulation robustness and regulatory compliance.

7. Recent Research on Sitagliptin and Dapagliflozin Transdermal Systems

Recent experimental studies demonstrate:

In recent years, considerable research attention has been directed toward the development of controlled release transdermal systems containing modern antidiabetic agents such as sitagliptin phosphate and dapagliflozin. These investigations primarily focus on improving **drug permeation, bioavailability, and sustained therapeutic efficacy** while minimizing systemic adverse effects associated with oral therapy.

Experimental formulation studies using **polymeric matrix films** have demonstrated the capability to provide **sustained drug release for up to 24 hours**, thereby maintaining relatively constant plasma drug concentrations and reducing dosing frequency [37]. Such controlled release behavior is typically achieved through optimized polymer blending, appropriate plasticizer concentration, and diffusion-regulated drug transport within the matrix structure.

Permeation enhancement strategies have also shown significant promise. The incorporation of **chemical enhancers such as oleic acid**, combined with **physical pretreatment techniques like microneedle application**, has been reported to markedly increase transdermal flux of antidiabetic drugs by temporarily disrupting the stratum corneum barrier and improving drug partitioning into deeper skin layers [38]. These approaches are particularly valuable for moderately hydrophilic molecules such as sitagliptin phosphate, which otherwise exhibit limited passive diffusion through intact skin.

Furthermore, **nanocarrier-loaded transdermal patches**—including liposomal, nanoemulsion, and solid lipid nanoparticle systems—have demonstrated **enhanced bioavailability compared with conventional oral dosage forms** in preclinical evaluations [39]. Nanocarriers improve drug solubility, stabilize the active pharmaceutical ingredient, and facilitate deeper skin penetration, ultimately contributing to prolonged systemic exposure.

More recently, research has begun exploring **combination transdermal therapy** incorporating both sitagliptin and dapagliflozin within a single delivery platform. Such dual-drug TDDS may provide **synergistic glycemic control** by simultaneously targeting incretin regulation and renal glucose reabsorption pathways, while also reducing pill burden and improving long-term adherence in patients with type 2 diabetes mellitus

[40]. Although still in experimental stages, these findings highlight the strong therapeutic potential of combination transdermal antidiabetic systems.

8. Advantages and Limitations of Transdermal Delivery Systems

8.1 Advantages

Transdermal drug delivery systems offer several clinically significant benefits that make them particularly suitable for the **long-term management of chronic diseases** such as diabetes mellitus. One of the primary advantages is the **avoidance of hepatic first-pass metabolism**, which can enhance systemic bioavailability and reduce metabolic degradation of drugs administered through the gastrointestinal tract.

TDDS also enable **sustained and controlled plasma drug concentrations**, thereby minimizing peak-related adverse effects and subtherapeutic trough levels commonly associated with oral dosing. This controlled pharmacokinetic profile contributes to **reduced dosing frequency**, often allowing once-daily or even less frequent administration.

Another important benefit is **improved patient compliance**, as transdermal patches are non-invasive, painless, easy to apply, and can be self-administered without the need for repeated oral intake or injections. Enhanced adherence is especially valuable in elderly populations and patients requiring multidrug therapy for chronic metabolic disorders [41].

Collectively, these advantages support the growing interest in TDDS as an alternative or adjunct to conventional oral antidiabetic therapy.

8.2 Limitations

Despite their therapeutic potential, transdermal drug delivery systems are associated with certain **formulation and physiological limitations** that must be carefully addressed during product development. One of the most common concerns is **skin irritation or sensitization**, which may arise from prolonged contact with adhesives, permeation enhancers, or high drug concentrations. Ensuring dermatological safety therefore remains a critical aspect of TDDS design.

Another major limitation is **restricted drug permeability across the stratum corneum**, which inherently limits transdermal delivery to molecules with suitable physicochemical properties such as low molecular weight, balanced lipophilicity, and high potency. Drugs that do not naturally meet these criteria require advanced enhancement strategies, increasing formulation complexity.

Additionally, the **development and manufacturing of controlled release transdermal systems** involve sophisticated optimization of polymers, enhancers, adhesives, and stability parameters, making formulation design technically demanding and potentially costly (Benson, 2005). Regulatory evaluation and large-scale production further add to developmental challenges.

FUTURE PERSPECTIVES

The field of controlled release transdermal drug delivery is undergoing rapid technological advancement, with emerging innovations expected to significantly transform the non-invasive management of diabetes mellitus. Future research is increasingly directed toward the development of smart, glucose-responsive transdermal delivery systems capable of modulating drug release in response to real-time blood glucose fluctuations. Such bioresponsive platforms may integrate glucose-sensing polymers, enzymatic triggers, or stimuli-sensitive nanomaterials to achieve self-regulated insulin or oral antidiabetic drug delivery,

thereby mimicking physiological glycemic control and reducing the risk of hypoglycemia [42].

Another promising direction involves the application of three-dimensional (3D) printing technologies for the fabrication of personalized transdermal patches with precisely controlled geometry, drug loading, and release kinetics. 3D printing enables customization according to patient-specific therapeutic requirements, opening new possibilities for precision medicine in chronic metabolic disorders. In parallel, the development of biodegradable microneedle arrays has gained substantial attention. These minimally invasive systems can painlessly penetrate the stratum corneum and subsequently dissolve within the skin to release encapsulated drugs in a controlled manner, thereby enhancing permeation while eliminating sharp biomedical waste concerns.

Furthermore, combination nanocarrier-based delivery systems incorporating multiple antidiabetic agents within a single transdermal platform represent an advanced therapeutic strategy. Nanocarriers such as lipid nanoparticles, polymeric nanoparticles, and deformable vesicles can improve drug solubility, stability, and targeted penetration across skin layers while enabling synchronized or sequential drug release. Integration of these nanotechnological approaches with microneedles or smart polymers may ultimately produce next-generation TDDS capable of long-term, self-regulated diabetes management. Collectively, these technological innovations highlight a future in which non-invasive, patient-tailored, and physiologically responsive transdermal therapies could substantially reduce treatment burden and improve clinical outcomes in individuals with type 2 diabetes mellitus.

CONCLUSION

Controlled release transdermal drug delivery of sitagliptin phosphate and dapagliflozin represents a highly promising alternative to conventional oral antidiabetic therapy, particularly for long-term management of type 2 diabetes mellitus. Transdermal systems offer several therapeutic advantages, including avoidance of hepatic first-pass metabolism, maintenance of sustained plasma drug concentrations, reduction in dosing frequency, and improvement in overall patient adherence. These benefits are especially valuable in chronic metabolic disorders requiring continuous pharmacological intervention.

Recent progress in polymer science, permeation enhancement strategies, and nanotechnology-based delivery systems has enabled the successful design of transdermal formulations capable of prolonged drug release and enhanced systemic bioavailability. Experimental studies demonstrate that polymeric matrix films, microneedle-assisted permeation, and nanocarrier-loaded patches can significantly improve transdermal transport of modern antidiabetic agents. In addition, combination TDDS containing both sitagliptin and dapagliflozin may provide synergistic glycemic control through complementary pharmacological mechanisms.

Despite these encouraging developments, certain challenges—such as limited intrinsic skin permeability, potential irritation or sensitization, formulation complexity, and the need for large-scale clinical validation—must still be addressed before widespread clinical application can be achieved. Continued interdisciplinary research integrating material science, biomedical engineering, nanotechnology, and clinical pharmacology will therefore be essential for successful translation.

Looking ahead, the emergence of smart glucose-responsive patches, biodegradable microneedle systems, and personalized 3D-printed transdermal platforms holds substantial promise for revolutionizing diabetes therapy. Such next-generation TDDS could enable precise, non-invasive, and patient-centric drug delivery,

ultimately improving long-term glycemic control, therapeutic safety, and quality of life for individuals living with diabetes mellitus.

REFERENCES

1. International Diabetes Federation. **IDF Diabetes Atlas**. 10th ed. Brussels: International Diabetes Federation; 2021.
2. American Diabetes Association. Standards of medical care in diabetes—2022. *Diabetes Care*. 2022;45(Suppl 1):S1–S264.
3. Patel R, Sharma M. Challenges in oral antidiabetic drug delivery. *J Pharm Sci Res*. 2020;12(3):245–252.
4. Chaudhury A, Duvoor C, Reddy Dendi VS, et al. Clinical review of antidiabetic drugs. *Front Endocrinol*. 2017;8:6.
5. Prausnitz MR, Langer R. Transdermal drug delivery. *Nat Biotechnol*. 2008;26(11):1261–1268.
6. Barry BW. Novel mechanisms and devices to enable successful transdermal drug delivery. *Eur J Pharm Sci*. 2001;14(2):101–114.
7. Benson HAE. Transdermal drug delivery: penetration enhancement techniques. *Curr Drug Deliv*. 2005;2(1):23–33.
8. Guy RH. Transdermal drug delivery. In: Walters KA, editor. *Dermatological and Transdermal Formulations*. New York: Informa Healthcare; 2010. p. 399–410.
9. Kumar S, Verma R, Singh P. Recent advances in transdermal delivery of antidiabetic drugs. *Int J Pharm Sci Rev Res*. 2022;74(1):45–53.
10. Verma A, Gupta R, Kaur H. Nanotechnology-based transdermal systems for diabetes therapy. *Drug Dev Ind Pharm*. 2023;49(2):210–221.
11. Kim D, Wang L, Beconi M, et al. DPP-4 inhibitors and incretin biology. *J Med Chem*. 2019;62(2):353–370.
12. Drucker DJ. Mechanisms of action of incretin-based therapies. *Cell Metab*. 2018;27(4):740–756.
13. Rosenstock J, Aguilar-Salinas C, Klein E, et al. Effect of sitagliptin on glycemic control. *Diabetes Care*. 2018;41(9):1970–1977.
14. Herman GA, Stevens C, Van Dyck K, et al. Pharmacokinetics of sitagliptin. *Clin Pharmacol Ther*. 2006;79(3):266–274.
15. Ferrannini E, Ramos SJ, Salsali A, et al. Mechanism of action of SGLT2 inhibitors. *Diabetes Care*. 2015;38(9):1730–1738.
16. Bailey CJ, Day C. SGLT2 inhibitors in diabetes therapy. *Diabetes Ther*. 2020;11(1):1–17.
17. Wiviott SD, Raz I, Bonaca MP, et al. Cardiovascular outcomes with dapagliflozin. *N Engl J Med*. 2019;380:347–357.
18. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Renal outcomes with dapagliflozin. *N Engl J Med*. 2020;383:1436–1446.
19. Chandrasekaran N, Kaur G, Kumar R. Physicochemical considerations in transdermal delivery. *Asian J Pharm*. 2021;15(2):120–128.
20. Kaur P, Garg T, Rath G. Advances in transdermal permeation enhancement. *Pharm Nanotechnol*. 2023;11(1):15–28.
21. Prausnitz MR, Mitragotri S, Langer R. Current status and future potential of transdermal drug delivery. *Nat Rev Drug Discov*. 2004;3:115–124.
22. Williams AC, Barry BW. Penetration enhancers. *Adv Drug Deliv Rev*. 2012;64:128–137.
23. Ita K. Transdermal iontophoresis and microneedles. *Pharmaceutics*. 2017;9(1):9.
24. DeFronzo RA, Norton L, Abdul-Ghani M. Renal, metabolic, and cardiovascular considerations of SGLT2 inhibition. *Diabetes Care*. 2017;40(12):1643–1652.

25. Singh B, Sharma V, Ahuja N. Hydrophilic polymers in transdermal systems. *Drug Dev Ind Pharm*. 2019;45(6):897–905.
26. Patel D, Patel N, Shah J. Hydrophobic polymers for controlled drug delivery. *Int J Pharm Investig*. 2018;8(2):65–72.
27. Rathore KS, Nema RK, Sisodia SS. Polymer blending strategies in TDDS. *J Drug Deliv Sci Technol*. 2022;68:103012.
28. Rowe RC, Sheskey PJ, Quinn ME. *Handbook of Pharmaceutical Excipients*. 7th ed. London: Pharmaceutical Press; 2017.
29. Verma S, Jain A, Tiwari A. Nanocarrier-based transdermal delivery systems. *Nanomedicine*. 2021;16(5):421–438.
30. Rao PR, Diwan PV. Formulation and evaluation of transdermal patches by solvent casting. *AAPS PharmSciTech*. 2020;21:89.
31. Bharkatiya M, Nema RK, Bhatnagar M. Electrospun nanofibers for transdermal drug delivery. *J Drug Deliv Sci Technol*. 2018;47:356–365.
32. Sharma K, Mittal A, Chauhan N. Evaluation parameters of transdermal patches. *Int J Pharm Sci Rev Res*. 2019;58(1):112–118.
33. Peppas NA, Buri PA. Surface and mechanical properties of polymeric films. *J Control Release*. 1985;2(4):257–275.
34. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling of drug release. *Acta Pol Pharm*. 2010;67(3):217–223.
35. Kanikkannan N. Skin permeation enhancement. *Crit Rev Ther Drug Carrier Syst*. 2002;19(2):99–140.
36. International Conference on Harmonisation (ICH). **Stability testing of new drug substances and products Q1A(R2)**. Geneva: ICH; 2003.
37. Gupta R, Sharma S, Singh H. Sustained release antidiabetic transdermal films. *Int J Biol Macromol*. 2021;183:1234–1242.
38. Mehta P, Jain S, Vyas SP. Microneedle-assisted transdermal delivery of antidiabetic drugs. *Drug Deliv Transl Res*. 2022;12(4):987–998.
39. Kaur H, Bhandari S, Sharma P. Nanocarrier-loaded transdermal patches for improved bioavailability. *Colloids Surf B Biointerfaces*. 2023;223:113189.
40. Shukla A, Tiwari G, Dubey R. Combination transdermal therapy for diabetes management. *Eur J Pharm Sci*. 2024;190:106615.
41. Brown MB, Martin GP, Jones SA, Akomeah FK. Dermal and transdermal drug delivery systems. *Drug Deliv*. 2019;26(1):1–12.
42. Lee H, Song C, Baik S, et al. Glucose-responsive smart transdermal systems. *Adv Drug Deliv Rev*. 2022;180:114046.

HOW TO CITE: Naman Kumar, Aarti Kori, Shivanand Patil, Design And Characterization of Controlled Release Transdermal Drug Delivery Systems Containing Sitagliptin Phosphate and Dapagliflozin, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 9, 2082-2092, https://doi.org/10.5281/zenodo.22816027