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ADVANCES IN TRANSDERMAL PATCH FORMULATION FOR CONTROLLED DELIVERY OF PIOGLITAZONE

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ABSTRACT

Diabetes mellitus remains a global health challenge that demands long-term, safe, and patient-centric therapeutic strategies. Pioglitazone, a potent insulin sensitizer belonging to the thiazolidinedione class, plays a significant role in the management of type 2 diabetes mellitus; however, its clinical utility is often compromised by limitations associated with oral administration. Extensive first-pass hepatic metabolism, variable bioavailability, gastrointestinal disturbances, dose-dependent adverse effects, and the requirement for prolonged daily dosing contribute to suboptimal therapeutic outcomes and poor patient compliance. In this context, transdermal drug delivery systems have gained increasing attention as an innovative platform for the controlled and sustained delivery of antidiabetic agents. Transdermal patches offer distinct advantages, including bypassing first-pass metabolism, maintaining steady plasma drug concentrations, minimizing systemic side effects, and enhancing patient adherence during chronic therapy. This review critically examines recent advances in the development of transdermal patch formulations for pioglitazone, emphasizing formulation design strategies that enable controlled drug release and improved skin permeation. Various polymeric matrices, plasticizers, adhesives, and chemical penetration enhancers employed in pioglitazone transdermal patches are discussed, highlighting their influence on mechanical integrity, drug release kinetics, and permeation behavior. In addition, key evaluation parameters such as physicochemical characterization, mechanical strength, in-vitro release, ex-vivo skin permeation, stability, and skin irritation studies are systematically summarized. The review also addresses current formulation challenges and regulatory considerations while exploring future perspectives, including advanced polymer systems and clinically translatable designs. Overall, transdermal patch-based delivery of pioglitazone represents a promising, non-invasive, and patient-friendly approach for improving long-term diabetes management.

KEYWORDS: Pioglitazone; Transdermal patch; Controlled drug delivery; Diabetes mellitus; Polymeric drug delivery systems.

1. INTRODUCTION

Diabetes mellitus is a metabolic long-term disease that is marked by chronic hyperglycemia due to either insulin secretion defects, insulin activity, or both. Diabetes is one of the greatest challenges to the global health issue, given that it has been on the rise in recent decades, and the world is facing it at unprecedented rates.[1] Diabetes mellitus should be managed on a long-term basis with the help of pharmacology that sustains the level of glycemic control and prevents or delays the exertion of severe complications which include cardiovascular disease, neuropathy, nephropathy and retinopathy. As a result, adherence to antidiabetic therapy relies heavily on the regular exposure to the drugs, their adherence by the patients, and the reduction of the adverse effects when using the drugs on the long-term basis.[2]

Pioglitazone is an antidiabetic preparation that belongs to the thiazolidinedione group, which is commonly utilized to treat type 2 diabetes mellitus (DM) as it increases insulin sensitivity in peripheral tissues by activating peroxisome proliferatoractivated receptor gamma (PPAR- -Y). Pioglitazone enhances the process of glycemic control especially in insulin resistant patients by improving glucose uptake and decreasing insulin resistance. Although the use of oral administration of pioglitazone has a proven therapeutic effect, there are also clinical contraindications to its use, which limit the long-term treatment. These encompass, large proportions of first-pass hepatic metabolism, unstable bioavailability and gastrointestinal adverse reactions.[3] Moreover, dose-specific side effects like weight gain, fluid retention and edema could also undermine patient compliance on chronic therapy. Pioglitazone when delivered orally also causes variability in plasma drug concentrations such that the therapeutic results remain inconsistent. Low compliance to daily oral regimens of doses is one of the greatest issues in the treatment of diabetes, especially in patients who are supposed to take medications constantly. All these issues demonstrate the necessity of finding alternative drug delivery methods, which should ensure controlled and prolonged release of drugs and enhance patient comfort and safety.[4]

Transdermal drug delivery systems (TDDS) have cropped up as an effective non-invasive way of delivering drugs as opposed to the usual oral route. Transdermal patches have a number of benefits such as they bypass first-pass metabolism, provide consistent plasma levels of drugs, lower dosing schedule as well as increased patient adherence. Moreover, the release of drugs through the skin can be controlled and reduce the side effects systemic and enhance general therapeutic effectiveness.[5] The recent years have witnessed increased opportunities of transdermal systems which deliver drugs with appropriate physicochemical properties such as antidiabetic agents like pioglitazone because of advances in the polymer science and formulation technologies.[6]

The purpose of this review is to critically discuss the latest developments in the development of transdermal patches to deliver pioglitazone in a controlled manner. The review dwells on the formulation strategies, choice of polymers and excipients, parameters of evaluation, and challenges that are related to transdermal delivery. Also, the prospects and possible clinical importance of the use of pioglitazone transdermal patches in the long-term management of diabetes are addressed.[7]

2. Literature Search Methodology

The literature search was performed systematically and comprehensively to gather scientific research in the area of creation of transdermal patches formulations used in controlled transfer of pioglitazone. Several electronic databases such as, PubMed, ScienceDirect, Google Scholar and SpringerLink were searched to cover a wide range of peer-

reviewed research articles and review papers. The search had concentrated mainly on the publications in English language.[8]

Appropriate literature was found by using relevant keywords and their combinations such as; pioglitazone, transdermal patch, transdermal drug delivery system, controlled drug delivery, polymeric matrix, permeation enhancers, skin permeation and antidiabetic transdermal system. Words AND and OR were used as Boolean operators that were used to narrow down the search results and make retrieved articles more relevant. Also, reference lists of the chosen publications were filtered manually to retrieve any additional relevant studies that were not picked in the initial search of the database.[9]

The inclusion criteria included original research articles and review articles reporting on the formulation, characterization, evaluation, and performance of the transdermal patches of pioglitazone or the transdermal delivery systems associated with the delivery of the drug. In-vitro and ex-vivo studies and formulation optimization and stability studies were all regarded to give a detailed picture of the topic. Paper that paid special attention to the choice of polymer, the compatibility of drugs and excipients, methods of permeation enhancement, and controlled release behavior were considered.[10]

The review did not cover articles that were not related to transdermal delivery systems, those that did not provide adequate methodological information, and non-scientific reports, as well as articles that were duplicated. The literature review was primarily based on the articles issued between 2000 and 2025 to reflect the oldest and the latest progress in the field of transdermal drug delivery. The literature obtained was critically evaluated, tabulated, and surveyed to elaborate a consistent, current account of developments in the formulation of the transdermal patch of pioglitazone.[11]

3. Drug Profile of Pioglitazone

Pioglitazone is a thiazolidinedione class antidiabetic synthetic agent that is mainly used in the treatment of type 2 diabetes mellitus. Its chemical name is (±)- 5-[[4- [2 -(5-ethyl-2-pyridinyl)ethoxy] phenyl]methyl]-2, 4-thiazolidinedione. Pioglitazone has a molecular structure that is composed of a thiazolidinedione ring that is vital in its pharmacological properties and some aromatic and heterocyclic compounds that make it lipophilic. These structural features are important in its physicochemical behaviors and other drug delivery system suitability.[12]

Pioglitazone has moderate lipophilicity, relatively low aqueous solubility, and a favorable molecular weight, which is a characteristic being sought after in delivering drugs through transdermal means. Transdermal administration drugs should have an optimal lipophilicity to pass through the stratum corneum and at the same time, have a reasonable solubility so that they can be released slowly out of the formulation. Additional evidence supporting the incorporation of the pioglitazone into polymeric transdermal matrices appears in the melting point and partition coefficient, which can be easy to incorporate and allows the control and sustained diffusion of drugs.[13]

Pioglitazone is pharmacologically an agonist of the peroxisome proliferator-activated receptor gamma (PPAR-) nuclear receptor found mostly in adipose tissue, skeletal muscle and liver. Insulin sensitivity is increased through PPAR-g activation that controls insulin-sensitive genes in glucose and lipid metabolism, resulting in peripheral glucose uptake and decreased insulin resistance. Pioglitazone does not directly trigger insulin release like the insulin secretagogue and thus its use as a monotherapeutic agent does not cause hypoglycemia as frequently.[14]

After orally taking, a pioglitazone is highly absorbed but extensively metabolized in liver tissues leading to a variable systemic bioavailability. It is very protein-bound and it has a fairly long elimination half-life, which facilitates a once-daily dosage, but also leads to prolonged systemic exposure. The oral form of therapy is usually linked to negative consequences like weight gain, fluid retention and gastrointestinal discomfort, especially when the therapy is long term.[15]

In light of these shortcomings, pioglitazone is an appropriate transdermal delivery. Best Transdermal delivery can evade hepatic first-pass metabolism, offer controlled and sustained drug delivery, diminish systemic side effects, and enhance patient compliance. The physicochemical and pharmacokinetic properties of pioglitazone along with the need to administer it orally every day justify the need to look at transdermal patches as an alternative and patient friendly method of controlling diabetes.[16]

Table 1: Physicochemical and pharmacokinetic properties of pioglitazone.[17]

S. No.	Parameter	Description
1	Chemical name	(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione
2	Molecular formula	$C_{19}H_{20}N_2O_3S$
3	Molecular weight	~356.44 g/mol
4	Physical state	White to off-white crystalline powder
5	Melting point	183–184 °C
6	Aqueous solubility	Poorly soluble in water
7	Log P (octanol/water)	~2.3–2.8
8	pKa	~5.6
9	Bioavailability (oral)	Approximately 80%
10	Plasma protein binding	>99%
11	Elimination half-life	3–7 hours (active metabolites: longer)
12	Route of elimination	Primarily hepatic metabolism

4. Rationale for Transdermal Delivery of Pioglitazone

Pharmacotherapy is the most powerful approach that can effectively manage type 2 diabetes mellitus in the long term, but traditional oral drug delivery fails to ensure optimum therapeutic results because of pharmacokinetic and patient-specific constraints. In that regard, transdermal drug delivery system (TDDS) offers an encouraging alternative in enhancing the clinical efficacy of antidiabetic drugs like pioglitazone.[18] Avoidance of first-pass hepatic metabolism is one of the major benefits of transdermal delivery. After orally, the pioglitazone is widely metabolized in the liver, which may result in a fluctuating systemic bioavailability and inter-patient difference in treatment response. Transdermal delivery, where the drug directly enters systemic circulation via the skin, will eliminate the effect of the hepatic first-pass metabolism and increase the delivery efficiency of the drug.[19]

The other important advantage of TDDS is the fact that the plasma levels of drugs can be sustained and controlled. Transdermal patches may be formulated to release a predetermined amount of pioglitazone over a prolonged period at a slow rate to reduce plasma fluctuations that are usually encountered with oral intake. This controlled release profile could be used to improve therapeutic effects and minimize effects of the peaks.[20] Oral pioglitazone therapy has often been linked with nausea and stomach pains as side effects, which may adversely affect the compliance of patients.

Transdermal administration bypasses the gastrointestinal tract, which also lessens gastrointestinal irritation and enhances drug tolerability. Another important justification to transdermal delivery is patient compliance. The non-

invasive characteristic, easy application and decreased dosing schedule of transdermal patches is especially beneficial to patients with a chronic therapy, including diabetes mellitus.[21]

Moreover, the physicochemical properties of the pioglitazone are desirable to transdermal delivery such as moderate lipophilicity, appropriate molecular weight, and strong pharmacological effect at low doses. The properties of these compounds favour their use in polymeric transdermal matrices and explain why they have been chosen as a viable candidate in transdermal drug delivery systems to manage diabetes in a controlled and sustained manner.[22]

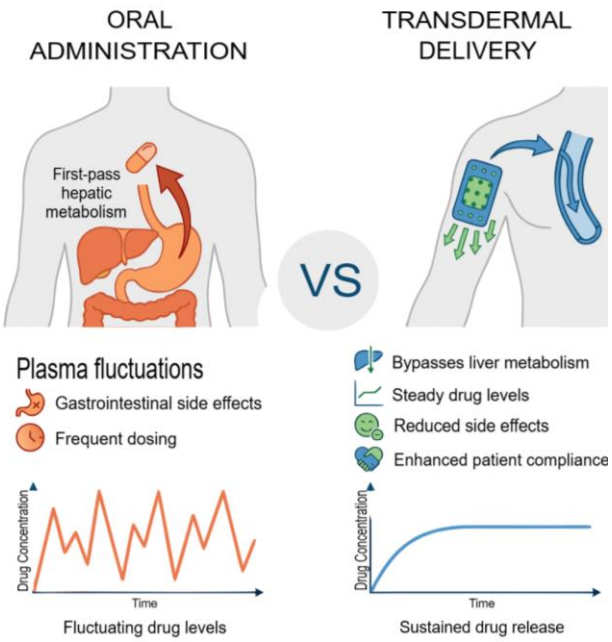

Figure 1: Advantages of transdermal delivery over oral administration of pioglitazone.[23]

5. Formulation Approaches for Pioglitazone Transdermal Patches

The development of the transdermal patches containing pioglitazone involves the prudent choice of patch design, polymer, and excipients to provide the controlled drug release, sufficient penetration into the skin, mechanical stability, and acceptability by the patient. The recent progress in transdermal technology has made possible the formulation of other approaches depending on the physicochemical characteristics of the drug, pioglitazone, and the treatment needs of chronic diabetes management.[24]

5.1 Types of Transdermal Patches

The most commonly studied systems of delivering pioglitazone are matrix-type patches. In such systems, the drug is evenly spread in the polymeric system and the release of the drug is controllable by diffusion as the main mode. The use of matrix patches is desirable because they are simple to design, they can be made easily, their drug distribution is uniform and there is less risk of drug dumping.[25]

The reservoir systems are made up of a drug reservoir that is filled between an impermeable backing layer and a rate limiting membrane. These systems can provide drug at near-zero-order rate but their complicated design and possible leakage have hampered their application in large numbers to deliver pioglitazone.

Drug-in-adhesive systems include drug-in-adhesive layer is built with a direct layer of pioglitazone, so the drug delivery and the adhesive functions are combined into one layer. The systems are better in-patient convenience, patch design slimness, and flexibility; hence they can be used in chronic therapy.[26]

5.2 Polymers Used

Polymers choice is a significant factor that defines the mechanical strength, the drug release, and stability of the pioglitazone transdermal patches. Natural polymers, including chitosan and sodium alginate, have the advantage of biocompatibility and film forming capability, but can be varied and have poor mechanical properties.[27]

The use of synthetic polymers such as hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), ethyl cellulose (EC), and Eudragit grades is quite extensive because they are reproducible, can be easily controlled on their release, and have better mechanical properties. Hydrophilic and hydrophobic polymers are also used to regulate drug delivery and the patching activities.[28]

5.3 Plasticizers and Penetration Enhancers

They are plasticized with the inclusion of polyethylene glycol (PEG), glycerol and dibutyl phthalate that enhance flexibility, greasiness as well as the mechanical integrity of the patch.

Oleic acid, dimethyl sulfoxide (DMSO), ethanol, and other solvents are chemical permeation facilitators that can temporarily destabilize the stratum corneum stratum and thus increase skin permeation of pioglitazone and enhancement of transdermal flux without inflicting permanent skin damage.[29]

Table 2: Polymers and excipients used in pioglitazone transdermal patch formulations.[30]

S. No.	Category	Material	Functional role in formulation
1	Synthetic polymer	Hydroxypropyl methylcellulose (HPMC)	Film formation and controlled drug release
2	Synthetic polymer	Polyvinyl alcohol (PVA)	Mechanical strength and flexibility
3	Synthetic polymer	Ethyl cellulose (EC)	Hydrophobic matrix for sustained release
4	Synthetic polymer	Eudragit (RL/RS grades)	Rate-controlling polymer
5	Natural polymer	Chitosan	Biocompatibility and film-forming agent
6	Natural polymer	Sodium alginate	Swelling and drug diffusion control
7	Plasticizer	Polyethylene glycol (PEG)	Improves flexibility and reduces brittleness
8	Plasticizer	Glycerol	Enhances elasticity and film uniformity
9	Plasticizer	Dibutyl phthalate	Increases tensile strength and softness
10	Permeation enhancer	Oleic acid	Disrupts lipid structure of stratum corneum
11	Permeation enhancer	Dimethyl sulfoxide (DMSO)	Enhances drug permeation through skin
12	Permeation enhancer	Ethanol	Solvent and skin permeation enhancer

6. Evaluation Parameters of Transdermal Patches

Transdermal patches need to be evaluated in detail to guarantee quality, performance, safety and therapeutic efficacy. The Pioglitazone transdermal patches are evaluated based on a combination of physicochemical, mechanical, in-vitro, and ex-vivo assessment parameters that determine their aptitude as controlled drug delivery method using the skin.[31]

6.1 Physicochemical Evaluation

Physicochemical analysis is a preliminary information of the uniformity and stability of transdermal patches. To determine the uniformity of the formation of films and even distribution of drugs, the patch thickness is measured at several points with the help of a micrometer or a digital vernier caliper. We conduct weight variation studies in order to determine the consistency of drug content in various patches and that is important in the accuracy of the dose.[32]

Folding endurance, which is measured by continually folding the patch at the same point until the point fails, is a measure of the flexibility and mechanical resistance of the formulation. The more the folding endurance value, the better the flexibility and durability. The moisture take-up studies and moisture content studies are conducted to determine the stability of patches in various moisture levels. These parameters determine patch integrity, stability of the drugs and the growth of bacteria.[33]

6.2 Mechanical Properties

Mechanical strength is an important parameter that is required to ensure integrity of the patch during manipulation and application. The tensile strength is a measure of the force to be broken in order to open the patch which is used as an indication of its mechanical strength. Percent elongation is the elasticity of the patch and capability to stretch without rupture, which is crucial to the comfort of patients and the success of their skin gluing.[34]

6.3 In-vitro Drug Release Studies

The release profile of the pioglitazone in the transdermal patch is usually studied in-vitro by the use of a Franz diffusion cell. Drug release is measured by appropriate dissolution media and sample is taken at specific intervals. To gain insight into the mechanism of drug release, the release data are studied by kinetic models which include, zero-order, first-order, Higuchi, and Korsmeyer-Peppas models.[35]

6.4 Ex-vivo Skin Permeation Studies

Ex-vivo permeation experiments are conducted on either an animal skin or human cadaver skin on a Franz diffusion cell to determine the capability of pioglitazone to penetrate through the skin. In the process of assessing the effectiveness of permeation enhancers in enhancing the drug delivery through the skin, parameters like permeation flux and enhancement ratio were determined to gauge the competence of the formulation and performance of the permeation enhancers.[36]

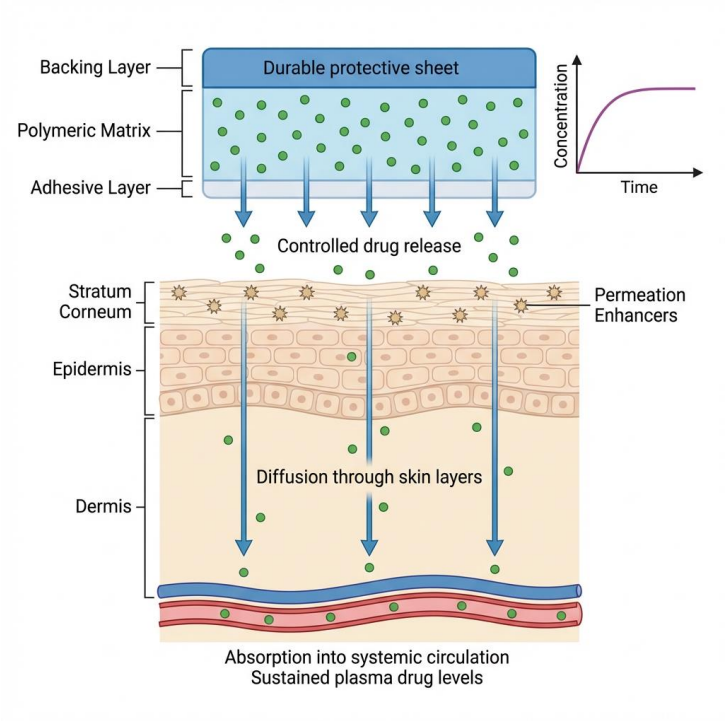

Figure 2: Schematic representation of drug release and skin permeation from pioglitazone transdermal patch.[37]

7. Controlled Drug Release Mechanism

Controlled drug release is a very important feature of transdermal patch systems, as it provides a long-term effect of therapeutic drugs and reduces the frequency of dosage and side effects. The release characteristics in a transdermal patch of pioglitazone are dominated by the polymeric matrix, drug-polymer interactions, as well as the physicochemical characteristics of the drug.[38]

The most common mechanism in matrix type transdermal patches is diffusion-controlled release. Under this system, the diffusion of the polymeric matrix is through diffusion of the pioglitazone into the skin through a concentration gradient. Diffusion rate depends on the solubility of drug in the polymer, permeability of matrix and porosity of the matrix. A properly crafted diffusion-controlled system will allow controlled release of the drug over a prolonged time, which adds to the constant plasma drug concentrations.[39]

Swelling and erosion of polymer also contribute significantly in the regulation of drug release especially in formulations that contain hydrophilic polymers. When hydrophilic polymers are in contact with water in the form of skin moisture or dissolution media, they take on water and expand forming channels in which the drug may be diffused. In other instances, slow erosion of the polymer also helps in release of drugs by increasing surfaces area and by reducing diffusion path length. Swelling, erosion, and diffusion balance define the total profile of release of the pioglitazone.[40]

Polymers composition and ratio in the patch also have a significant impact on the release kinetics. Mixed hydrophilic and hydrophobic polymers are normally employed to control the release of drugs through fine-tuning of the hydration of the matrix and diffusion impairment. Hydrophobic polymers will slow the diffusion of drugs, and hydrophilic polymers will accelerate the diffusion of drugs, which enables the formulation scientists to obtain the required controlled-release profile.[41]

In order to quantitatively characterize the release mechanism, mathematical kinetic models are used to in-vitro release data. Zero-order kinetics is used to describe a constant rate of release that is not dependent on the drug concentration and Higuchi model is used to explain diffusion-controlled release through a matrix system. The combined effects of diffusion and polymer relaxation processes are commonly referred to as the KorsmeyerPeppas model and it can be used to give insight into the overriding release characteristics of pioglitazone transdermal patches.[42]

8. Safety, Stability, and Skin Irritation Studies

The concept of safety and stability evaluation is one of the most important factors in creating the pioglitazone transdermal patches because these factors directly affect the levels of patient acceptability, therapeutic reliability, and the regulatory approval. Transdermal systems are supposed to be in contact with the skin a long period of time, so an extensive assessment of skin compatibility and formulation stability is necessary.[43]

The dermal safety studies of transdermal patches are conducted to demonstrate skin irritation and sensitization. Such studies are usually done with animal models or proven in-vitro techniques to evaluate the indications of erythema, edema or allergy after patch application. The formulation is said to be safe when it causes little or no irritation and on repeated exposures it does not cause sensitization. Effective choice of polymers, adhesives and permeation enhancers is crucial in ensuring that skin irritation is reduced and the drug permeation is effective.[44]

Stability tests are conducted as per the International Council for harmonisation (ICH) guidelines to ascertain the physical, chemical as well as the mechanical stability of the transdermal patches during storage. The formulations are kept at various temperatures and humidity conditions e.g. accelerated and long-term stability conditions and analyzed at regular intervals with regard to changes in drug content, appearance, flexibility, mechanical strength and drug release behavior. The stability information is what guarantees the formulation that it does not change, lose its quality, efficacy and safety during its shelf lives.[45]

Patient safety and patch adhesion matters are of equal importance in achieving therapeutic effect. Good adhesion has to ensure consistent skin contact and even distribution of the drug during the period of intended use whereas excessive adhesion can result in discomfort or skin damage during the removal of the patch. As such, the adhesion system should offer the best strike between the adhesion and removal. Furthermore, the patient safety factors of convenience to use, comfort in their use, and little interference with the daily activities are also a key to successful clinical acceptance of the pioglitazone transdermal patches.[46]

Table 3: Summary of reported studies on pioglitazone transdermal patches.[47]

S. No.	Study type	Formulation / approach	Key findings	Outcome
1	In-vitro release study	Matrix-type patch (HPMC)	Sustained drug release up to 24 h	Controlled release achieved
2	In-vitro release study	EC-based patch	Slower release due to hydrophobic matrix	Prolonged drug release
3	Ex-vivo permeation	Patch with oleic acid	Enhanced skin permeation	Increased permeation flux
4	Ex-vivo permeation	Patch with DMSO	Significant enhancement of drug transport	Improved transdermal delivery
5	Polymer comparison study	HPMC:PVA blend	Improved mechanical strength and release control	Optimized formulation
6	Plasticizer optimization	PEG-plasticized patch	Improved flexibility and uniformity	Enhanced patch integrity
7	Kinetic modeling study	Matrix diffusion system	Higuchi model best fitted	Diffusion-controlled release
8	Stability study	Optimized patch formulation	No significant changes under ICH conditions	Stable formulation
9	Skin irritation study	Patch with ethanol enhancer	No erythema or edema observed	Dermally safe
10	Adhesion study	Drug-in-adhesive patch	Adequate adhesion without discomfort	Patient-acceptable adhesion
11	Mechanical evaluation	PVA-based patch	High tensile strength and elongation	Good mechanical performance
12	Comparative delivery study	Oral vs transdermal pioglitazone	Reduced plasma fluctuation	Improved delivery profile

9. Challenges and Limitations

Although the use of transdermal patches has great potential in the delivery of pioglitazone in a controlled fashion, a number of challenges and limitations have to be overcome to enable the effective development of the formulation and its translation into the clinical process. The skin barrier resistance, which was dominated by stratum corneum, is one of the most prominent hindrances in the process of transdermal drug delivery. This is the skin layer that is the most effective and limits the penetration of most drug molecules. Despite the fact that chemical permeation enhancers and optimized polymeric systems can work to enhance the transport of drugs, a consistent and adequate amount of transdermal flux of pioglitazone has posed a serious challenge.[48]

Dose loading capacity is another significant limitation. Transdermal systems tend to be applicable in those drugs that need small doses on a daily basis because very little drug can be added to the patch without interfering with its mechanical strength and adhesive characteristics. Pioglitazone is powerful but it still needs to be optimized properly to achieve a satisfactory drug loading with a controlled release and stable patches.[49]

The problem of long-term adhesion is also a practical issue, especially concerning chronic cases like diabetes mellitus that need constant medication. Weak adhesion can lead to patch removal and unequal drug delivery and a strong adhesion can cause pain, irritation, or injury on the skin, when removed. To ensure long-term use, the strength of adhesion and comfort of the patient must be kept at an optimal level.[50]

Lastly, absence of widespread clinical validation is also a significant limitation. Although several in-vitro and ex-vivo investigations have been conducted to establish the viability of pioglitazone transdermal patches, clinical trials should be developed to determine their safety, efficacy and therapeutic advantage over the traditional oral preparations. To effectively transfer the concept of translating pioglitazone transdermal patches into the normal process of managing diabetes, it is important to address these barriers using superior formulation strategy and clinical research.[51]

10. Future Perspectives

In the creation of transdermal patches used to control the delivery of pioglitazone, it is a growing area, and some new technologies have the potential to improve on the current shortcomings and improve the performance of the therapy. New strategies of formulation, novel materials and translation techniques that can be used to enhance permeation of the drug, safety and compliance of the patient are likely to be the subject of future research.[52]

The application of advanced polymers and nanocomposites patch systems is also a major direction in the future. Addition of nanomaterials like polymeric nanoparticles, lipid-based carriers or nano-fillers into the transdermal matrices can increase efficiency of drug loading, mechanical strength and controlled drug release. Polymer-drug interactions can be further controlled in nanocomposite systems to allow release kinetics and skin permeation of pioglitazone to be more controlled.[53]

Transdermal penetration systems based on microneedle-assisted delivery are becoming popular as a method of minimal skin barrier that bypasses the skin barrier. Microneedles form microscopic holes in the stratum corneum, which enable greater availability of drugs without producing pain and bleeding. Combining the arrays of microneedles with the patches loaded with pioglitazone would considerably enhance the transdermal flux, and increase the opportunities of transdermal therapy to the medications that have low skin permeability.[54]

Another promising opportunity is the creation of smart and stimuli-reactive transdermal patches. These types of systems react to external or physiological changes (temperature, pH or glucose) to release drugs on demand and in a controlled manner. These smart delivery systems have the potential to deliver personalized and responsive diabetes care with the release schedule of pioglitazone being modulated based on patient requirements.[55]

Lastly, it is important to note that in the future the success of clinically translated and considered forms of pioglitazone transdermal patches is also subject to clinical translation and regulatory considerations. To guarantee safety, efficacy and market approval it is important to conduct rigorous clinical trials, standardized manufacturing procedures and

follow regulatory demands. By covering these areas, the way to the incorporation of advanced transdermal systems into clinical practice will be opened.[56]

11. CONCLUSION

The advancements in transdermal patch technology have opened new avenues for the controlled and patient-friendly delivery of antidiabetic drugs. This review highlights the significant progress made in the formulation of pioglitazone transdermal patches, emphasizing innovative polymeric matrices, optimized use of plasticizers and permeation enhancers, and robust evaluation strategies to achieve sustained and reliable drug delivery. Such formulation advances have enabled better control over drug release kinetics while ensuring mechanical integrity, stability, and dermal safety of the patches.

Controlled transdermal delivery of pioglitazone demonstrates clear therapeutic advantages over conventional oral administration. By bypassing first-pass hepatic metabolism, transdermal patches help maintain steady plasma drug concentrations, thereby minimizing fluctuations associated with oral dosing. This sustained delivery approach has the potential to reduce gastrointestinal discomfort and dose-related adverse effects, ultimately enhancing the overall safety profile of pioglitazone therapy.

Transdermal drug delivery systems represent a promising platform for improving long-term diabetes management. Their non-invasive nature, ease of application, and reduced dosing frequency can significantly enhance patient adherence, a critical factor in chronic disease management. Moreover, the ability to design controlled-release systems tailored to individual therapeutic needs positions TDDS as a valuable alternative in modern diabetes care. Despite encouraging preclinical outcomes, further efforts are required to translate these formulations into clinical practice. Comprehensive clinical studies, along with regulatory validation and large-scale manufacturing optimization, are essential to confirm the efficacy and safety of pioglitazone transdermal patches. Continued research in this direction may ultimately lead to the development of clinically viable, transdermal therapies that offer improved quality of life for patients with diabetes mellitus.

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Conflict of Interest: Nil

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