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Transdermal Drug Delivery Strategies for Antidiabetic Therapy: Current Progress and Future Perspectives of Dapagliflozin

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Abstract

Diabetes mellitus is a chronic metabolic disorder requiring long-term pharmacotherapy to maintain glycemic control and prevent complications. Conventional oral antidiabetic therapy often faces limitations such as poor patient compliance, gastrointestinal side effects, first-pass metabolism, and fluctuating plasma drug concentrations. Transdermal drug delivery systems (TDDS) have emerged as a promising alternative for the administration of antidiabetic agents due to their ability to provide controlled and sustained drug release, improved bioavailability, reduced dosing frequency, and enhanced patient adherence. This comprehensive review discusses the recent advancements in transdermal delivery of antidiabetic drugs, including insulin, metformin, sulfonylureas, GLP-1 agonists, and SGLT2 inhibitors. Special emphasis is placed on dapagliflozin, a selective sodium-glucose co-transporter-2 (SGLT2) inhibitor widely used in the management of type 2 diabetes mellitus. The review highlights the physicochemical properties of dapagliflozin that make it a potential candidate for transdermal delivery, various formulation approaches such as patches, microneedles, nanoparticles, and permeation enhancers, as well as challenges associated with skin permeation and drug stability. Furthermore, the therapeutic advantages, recent research developments, and future prospects of dapagliflozin-loaded transdermal systems are critically discussed. Overall, transdermal delivery of dapagliflozin represents a novel and patient-friendly strategy that may improve therapeutic outcomes and expand the scope of diabetes management.

Keywords: Diabetes Mellitus, Dapagliflozin, SGLT2 Inhibitors, Transdermal Drug Delivery System, Controlled Release, First-Passmetabolism, Skinpermeation, Permeation Enhancers, Pharmacokinetics, Antidiabetic Therapy, Drug Delivery Optimization

1. Introduction

1.1 Diabetes Mellitus

Diabetes is chronic disease occurred due to increased blood glucose level because of the body cannot produce at all or secrets in sufficient insulin hormone or not use it effectively. Hence, the nonexistence of insulin or the cell is not sensitive to use insulin leads to increased blood glucose level which is the hallmark of diabetes [1]. Diabetes mellitus (DM) affects more than 422 million people around the world. By the year 2040, the number of people with diabetes is expected to rise to 642 million, most of who are going to reside in low- or middle-income countries [2]. Diabetes is a growing public health problem affecting people worldwide, with a rapidly increasing prevalence in both developing and developed countries. Diabetes mellitus (DM) is commonest endocrine disorder that affects more than 100 million people worldwide (6% population) [3]. It is caused by deficiency or ineffective production of insulin by pancreas which results in increase or decrease in concentrations of glucose in the blood. It is found to damage many of body systems particularly blood vessels, eyes, kidneys, heart and nerves [4]. Diabetes mellitus has been classified into two types i.e. insulin dependent diabetes mellitus (IDDM, Type I) and non-insulin dependent diabetes mellitus (NIDDM, Type I□) [5]. Type I diabetes is an autoimmune disease characterized by a local inflammatory reaction in and around islets that is followed by selective destruction of insulin secreting cells whereas Type II diabetes is characterized by peripheral insulin resistance and impaired insulin secretion [6]. The presence of DM shows increased risk of many complications such as cardiovascular diseases, peripheral vascular diseases, stroke, neuropathy, renal failure,

retinopathy, blindness, amputations etc. Drugs are used primarily to save life and alleviate symptoms. Secondary aims are to prevent long-term diabetic complications and, by eliminating various risk factors, to increase longevity [7]. Insulin replacement therapy is the mainstay for patients with type 1 DM while diet and lifestyle modifications are considered the cornerstone for the treatment and management of type 2 DM [8]. Various types of hypoglycemic agents such as biguanides and sulfonylureas are also available for treatment of diabetes. However none of these medications is ideal due to their toxic side effects and diminution of responses is observed sometimes in their prolonged use [9]. The main disadvantage of currently available drugs is that they have to be given throughout the life and produce side effects. Medicinal plants and their bioactive constituents can be used for treatment of DM throughout the world especially in countries where access to the conventional anti-DM agents is inadequate [10]. Various experimental models are also available to screen antidiabetic activity of plant. The present review therefore is an attempt to know more precisely about diabetes mellitus, its clinical presentation, epidemiological data, complications and current available treatment of diabetes [11].

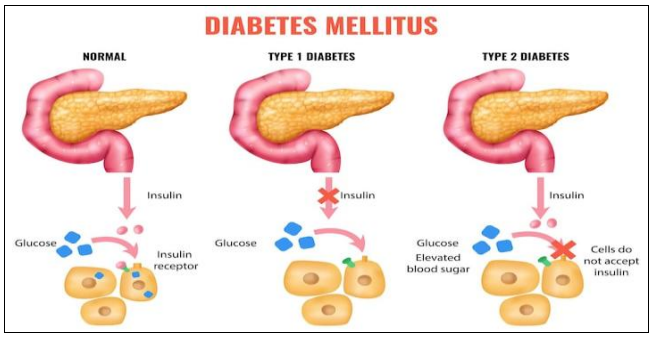


Fig 1.1

2. Diabetesmellitus: An overview

2.1 Types of diabetes

Type1DM: Autoimmune destruction of β-cells leading to absolute insulin deficiency.

Type 2 DM: Characterized by insulin resistance and relative insulin deficiency; accounts for ~90% of cases.

Gestational diabetes: Occurs during pregnancy.

Other specific types: Genetic defects, pancreatic disorders, drug- induced etc [12].

2.2 Pathophysiology

- **Hyperglycemia:** Both types of diabetes result in chronic hyper glycaemia, which disrupts normal carbohydrate, fat, and protein metabolism. This can lead to acute complications like DKA in T1DM and hyperglycaemic hyperosmolar state in T2DM [13].
- **Microvascular and Macrovascular Complications:** Long-Term hyperglycemia associated with various complications, including.
- **Microvascular:** Retinopathy, nephropathy, and neuropathy.
- **Macrovascular:** Increased risk of cardio vascular diseases, stroke, and peripheral vascular disease [14].

2.3 Current treatment limitations

- GI side effects
- Hypoglycemia (sulfonylureas, insulin)
- First-pass metabolism reducing bioavailability
- Frequent dosing
- Patient non-compliance
- Weight gain with some drugs [15]

Due to the challenges, novel drug delivery approaches a required.

3. Dapagliflozin-Ansglt2inhibitor

3.1 Mechanism of action

DapagliflozinselectivelyinhibitstheSodium–GlucoseCotransporter-2(SGLT2) located in the proximal renal tubules, reducing glucose reabsorption and promoting glucosuria. This mechanism is insulin-independent [16].

3.2 Pharmacokinetics

- Oral bioavailability:~78%
- Highly protein-bound
- MetabolisedbyUGT1A9
- Half-life: 12–13 hours
- Excreted mainly via urine

3.3 Advantages

- Low hypoglycemia risk
- Weight reduction
- Improved cardio vascular and renal outcomes
- Reduction in blood pressure

3.4 Limitations of oral dosing

- First-pass metabolism
- Fluctuating plasma levels
- Dose-dependent side effects
- Reduced efficacy in renal impairment [17]

4. Transdermal Drug Delivery Systems (TDDS)

4.1 Concept

A Transdermal Drug Delivery System (TDDS) is a non-invasive method designed to deliver therapeutic agents through the skin and into the systemic circulation in a controlled and sustained manner. Instead of administering medication orally or via injection, the drug is incorporated into a transdermal patch that is applied to the skin. From this patch, the drug gradually permeates through the skin layers and enters the bloodstream, there by producing the desired therapeutic effect [18].

4.2 Advantages

- Avoid first- pass metabolism
- Maintain steady plasma drug levels
- Enhanced patient compliance
- Reduced systemic side effects

4.3 Skin structure in drug delivery-

- Stratum corneum (main barrier)
- Epidermis Dermis
- Subcutaneous tissue

4.4 Drug permeation depends upon:

- Molecular weight(<500Da ideal)
- Lipophilicity (logP1–3optimal)
- Skin hydration
- Enhancers and polymer choice [19]

TDDS Approach for Diabetes

Transdermal Drug Delivery System (TDDS) for diabetes is an advanced drug delivery approach in which anti-diabetic drugs are administered through the skin in the form of a patch to achieve controlled and sustained release into systemic circulation. This method helps overcome limitations of oral and injectable therapies such as frequent dosing, gastrointestinal side effects, and poor patient compliance [20]. In diabetes management, TDDS is mainly explored for drugs like insulin and certain oral hypoglycemics, where maintaining stable blood glucose levels is important. Since the skin acts as a strong barrier, various enhancement techniques such as chemical permeation enhancers, microneedles, iontophoresis, and nanoparticle based systems are used to improve drug penetration [21]. TDDS offers advantages like improved patient adherence, reduced fluctuations in blood glucose, and avoidance of injections, making therapy more comfortable. However, its use is still largely in the research and development stage due to challenges in drug permeability and formulation stability [22].

Transdermal Drug Delivery System (TDDS) for diabetes is a novel and promising approach in which anti-diabetic drugs are delivered through the skin using a patch, allowing controlled and sustained release into systemic circulation. This system is designed to improve the limitations of conventional oral and injectable therapies, such as frequent dosing, poor patient compliance, first-pass metabolism, and gastrointestinal side effects. In diabetes management, TDDS is mainly explored for drugs like insulin and some oral hypoglycemic agents, where maintaining a steady blood glucose level is very important [23]. However, due to the strong barrier function of the stratum corneum, drug permeation is challenging, and therefore various enhancement techniques such as chemical permeation enhancers, microneedles, iontophoresis, sonophoresis, and nanoparticle-based carriers are used to improve drug absorption. TDDS provides several advantages including better patient adherence, painless administration, reduced fluctuation in plasma drug levels, and improved therapeutic efficiency. Despite these benefits, its application in diabetes is still mostly in the experimental and research phase because of issues like limited drug permeability, formulation instability, and high development cost [24].

5. Drug Profile

- **Name of drug:** Dapagliflozin
- **Molecular formula:** C21H2sC1O%
- **IUPAC name:** (2S,3R,4R,5S,6R)-2-{4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl}-6-(hydroxymethyl) oxane-3,4,5-triol
- **Molecular weight:** 408.87 g/mol
- **Melting Point:** 75°C-78°C
- **Solubility:** Freely soluble in: Methanol, ethanol, DMSO Slightly to moderately soluble in: Water Practically insoluble in: Non-polar solvents like hexane
- **Toxicity:** Increased urination, Mild dehydration, Hypotension
- **Mechanism of action:** Dapagliflozin works by selectively inhibiting the sodium-glucose co-transporter-2 (SGLT2) in the proximal renal tubules of the kidneys. This blocks glucose reabsorption, increases urinary glucose excretion, and there by lowers blood glucose levels [25].

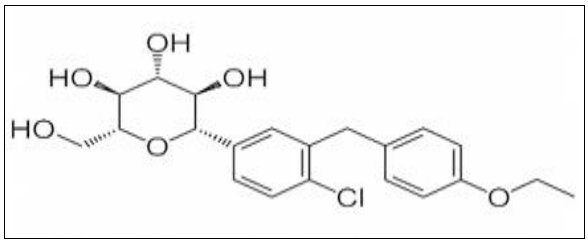


Fig 5.1: Dapagliflozin

6. Pre-Formulation

1. Organoleptic Test:

- **Colour:** White to off-white crystalline powder
- **Odour:** Odourless
- **Taste:** Slightly bitter
- **Appearance:** Fine crystalline solid
- **Physical state:** Solid at room temperature

Interpretation: The Organoleptic characteristics observed were consistent with the reported standard properties of dapagliflozin, indicating the purity and stability of the drug for formulation development [26].

Fig 6.1: Dapagliflozin drug

2. Solubility Studies:

The solubility of Dapagliflozin was determined in various solvents including distilled water, phosphate buffer (pH 6.8 and 7.4), methanol, and ethanol. The vials were shaken using a mechanical shaker for 24 hours at room temperature to attain equilibrium. The filtrate was suitably diluted and analyzed using UV spectrophotometry at the max of Dapagliflozin.

Interpretaion: The solubility study indicates that Dapagliflozin shows low solubility in distilled water and aqueous buffer solutions, while exhibiting comparatively higher solubility inorganic solvent such as methanol and ethanol. This confirms its hydrophobic nature [27].

Fig 6.2: Solubility Test

3. Ph determination:

Interpretation: The pH of the Dapagliflozin solution was found to be in the range of **6.0to** 7.0, depending on the solvent system and drug concentration used. This suggests that the drug exhibits a **near-neutral Ph profile** in solution, which is favorable for transdermal formulation, as it minimizes the risk of skin irritation during prolonged application.

Despite its high **pKa(~12.6)** indicating weak acidity, the observed pH of the prepared solution remains with in the physiological range. This makes Dapagliflozin compatible with various polymers and excipients used in patch formulation, without causing chemical instability or degradation due to pH mismatch [28].

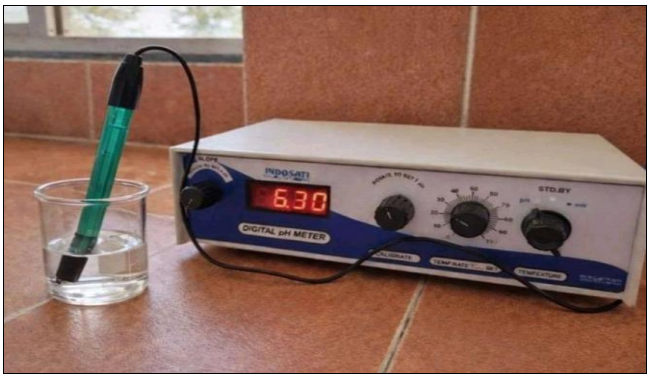


Fig 6.3: ph determination

4. FT-IR: The FT-IR spectrum of Dapagliflozin showed characteristics absorption peaks at 3400-3500cm-1correspondingto0-Hstretchingvibrations, 2920-2850cm-1due to C-H stretching, and 1100-1200 cm-1indicating C-0stretching. The presence of these peaks confirms the functional groups present in the drug molecule and verifies its identity [29].

Interpretation: The FT-IR spectrum of Dapagliflozin exhibited characteristic absorption peaks corresponding to its functional groups. A broad peak observed around 3400-3500 cm-1 confirms the presence of hydroxyl (-OH) groups. Peaks in the region of2920-2850 cm-1 indicate C-H stretching of alkyl groups, while the absorptionaround1600-1650 cm-1 corresponds to aromatic C=C stretching vibrations. The peak observed in the range of 1100- 1200 cm-1confirmsC-0stretchingof ether linkages. The presence of the characteristics peaks confirms the structural integrity and purity of the drug. No unexpected peaks were observed, indicating the absence of impurities [30].

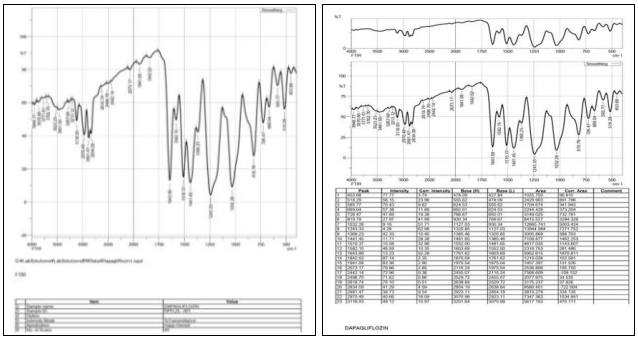


Fig 6.4: ft-ir

5. UV Spectro-photometric Analysis

UV-Visible spectro-photometry is a widely used analytical technique in pharmaceutical analysis for the quantitative estimation of drugs. It is based on the principle that molecules absorb ultra violet or visible light at specific wavelengths, and the amount of light absorbed is directly proportional to the concentration of the substance present in the solution [43]. This relationship is explained by Beer-Lambert's Law, which states that absorbance is directly proportional to the concentration of the absorbing species and the path length of the cuvette [31].

In the present experiment, Dapagliflozin was analyzed using a UV spectrophotometer in order to establish its calibration curve and determine the relationship between concentration and absorbance. A series of standard solutions of dapagliflozin were prepared with different concentrations ranging from4 µg/mL to 20 µg/mL. These solutions were scanned at the selected wave length using a UV spectrophotometer, and the absorbance values were recorded [32].

Table 6.1: UVSpectrophotometric

Reading	Concentration(µg/mL)	Absorbance
Dilution1	4µg/mL	0.242
Dilution2	8µg/mL	0.458
Dilution3	12µg/mL	0.728
Dilution4	16µg/mL	0.972
Dilution 5	20µg/mL	1.215

The recorded absorbance values show edagradual increase with increasing concentration of the drug. For example, at4µg/mL concentration, the absorbance was 0.242, where as at20 µg/mL concentration, the absorbance increased to 1.215. Similarly, intermediate concentrations such as 8 µg/mL, 12 µg/mL, and 16 µg/mL showed absorbance values of 0.485, 0.728, and 0.972 respectively. These values clearly indicate that the absorbance increases proportionally with the increase in concentration [33].

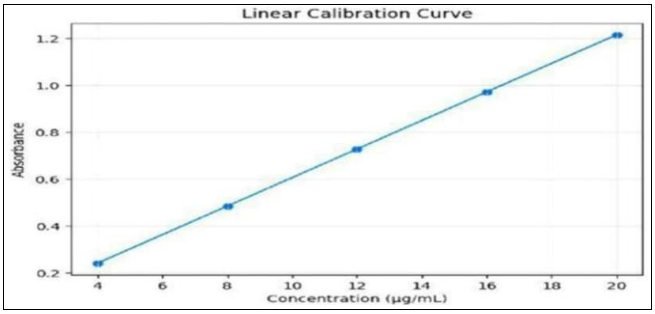


Fig 6.5: Calibration curve of Dapagliflozin obtained by UV spectrophotometric method

The obtained data was further used to plot a calibration curve by taking concentration on the X-axis and absorbance on the Y-axis. The plotted graph showed a straight line, indicating a linear relationship between concentration and absorbance. This confirms that dapagliflozin follows Beer-Lambert's law within the selected concentration range.

The linear calibration curve demonstrates that the UV spectro-photometric method used in this experiments reliable and suitable for the quantitative determination of dapagliflozin. The straight-line relationship also confirms

the accuracy and precision of the prepared standard solutions and the analytical procedure [34].

7. Preparation of Dapagliflozin Transdermal Patch

7.1 Materials

Formulation of the antidiabetic transdermal patch of Dapagliflozin was prepared using all excipients. The formulation components, quantities and their roles are listed below.

Table 7.1: Ingredients of formulations

S. No	Ingredient	Role	Quantity (Per 100ml)
1.	Dapagliflozin	API / Drug	0.03gm
2.	HPMC	Film Former	0.02gm
3.	Polyvinyl pyrrolidine	Film Enhancer	0.02gm
4.	Propylene Glycol	Plasticizer	1.2ml
5.	Sodium Lauryl Sulphate	Permeation Enhancer	1.2ml
6.	Chloroform: Methanol	Solvent System	1:4

7.2 Method of Preparation-

1. The HPMC and polyvinyl pyrrolidine were accurately weighed and dissolved in mixture of Methanol: Water (solvent).
2. The drug was then dispersed in the polymeric solution and plasticizer of propylene glycol and permeation enhancer of sodium lauryl sulphate was added with continuous stirring using a magnetic stirrer to obtain homogeneous mixture.
3. Glycerine was spread into petridish and then resulting mass was poured into the petridish.
4. The petridish was left undisturbed at room temperature for 24 hours.
5. This pertidish was obtained inact by slowly lifting from the petridish and transdermal patch were cut into radius of 2cm sq.

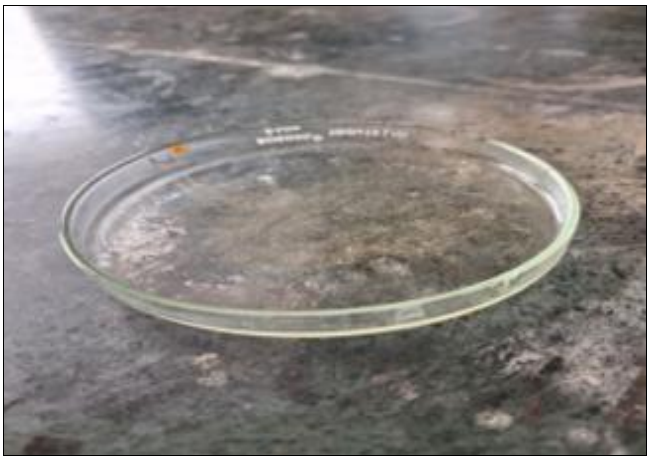
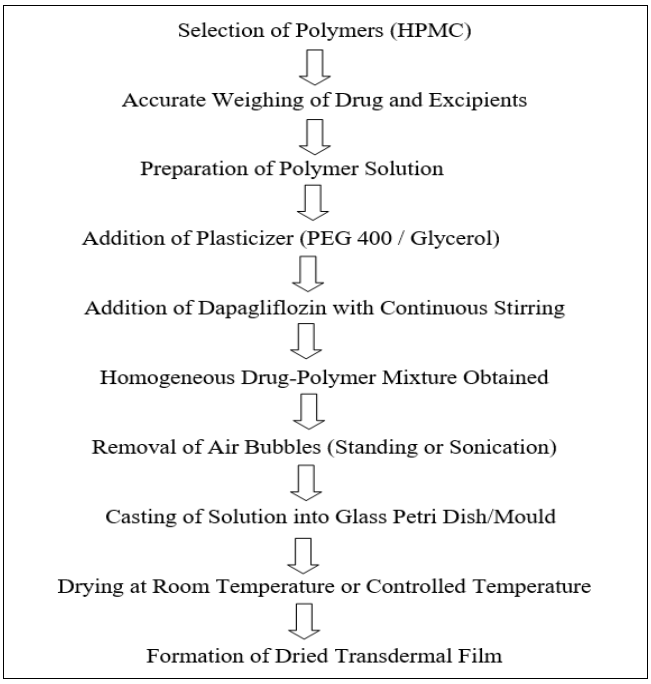


Fig 7.1: Preparation of patch

➢ Flow Chart



8. Evaluation Test-

- **Physical Appearance-**

The prepared patches were visually inspected for color, transparency, smoothness, flexibility, and absence of air bubbles or cracks.

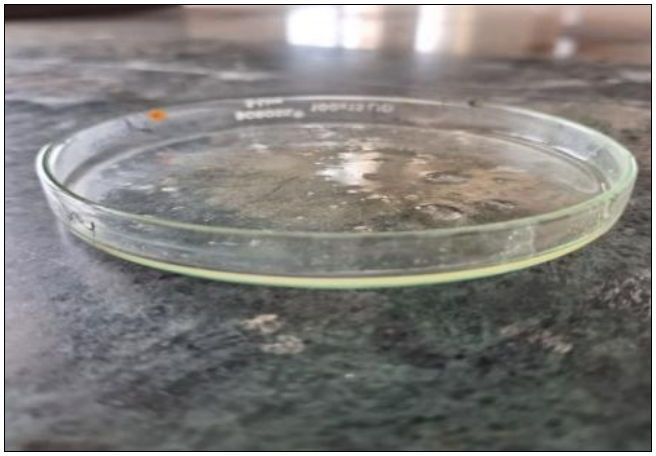


Fig 8.1

- **Thickness-**

The thickness of patches was measured at different points using a vernier caliper, and the average value was calculated.

Fig 8.2: Thickness of patch

- **Weight Variation-**

Individual patches of specified dimensions were weighed separately, and the average weight was determined to ensure uniformity.

- **pH-**

The patch was allowed to swell in distilled water for a specified period, and the pH was measured using a pH meter.

Fig 8.3: ph of transdermal patch

Viscosity Test:

The viscosity of the polymeric solution was determined using a Brookfield viscometer at room temperature.

Fig 8.4: viscosity of patch

Irritation test - The dapagliflozin transdermal patch was applied to the shaved dorsal skin of rabbit for 24 hours. No signs of erythema or edema were observed during the 72-hour observation period.

Stability test at room temperature:

The dapagliflozin transdermal patch remained stable at room temperature throughout the study period. No significant changes were observed in its physical appearance, pH, or viscosity, indicating good formulation stability. The patch maintained its desired characteristics under room-temperature storage conditions.

Outcomes

The development of a transdermal dapagliflozin patch has demonstrated promising outcomes in preclinical studies, showing effective permeation of the drug through the skin and sustained systemic delivery. In animal models, the transdermal therapeutic system achieved prolonged plasma drug concentrations, with peak levels observed several days after application, indicating controlled and continuous drug release. Dapagliflozin delivered via the patch was distributed to major organs, including the kidneys, liver, heart, and skeletal muscle, and retained its pharmacological activity as evidenced by increased urinary glucose excretion. Additionally, the formulation exhibited a skin depot effect, allowing gradual drug release and potentially reducing dosing frequency. These findings suggest that transdermal delivery of dapagliflozin may offer advantages such as improved patient compliance, stable plasma concentrations, and reduced peak–trough fluctuations compared with conventional oral administration. However, further clinical studies are required to establish its safety, efficacy, and long-term therapeutic benefits in humans.

Future Prospect

The future prospects of a transdermal patch for Dapagliflozin are promising because it could provide sustained drug release, improve patient adherence, avoid gastrointestinal absorption issues, and maintain more stable blood drug concentrations compared with oral tablets. Dapagliflozin possesses physicochemical properties that make it a potential candidate for transdermal delivery, and recent preclinical studies have demonstrated successful systemic absorption and pharmacological activity from patch formulations.

Advances in technologies such as microneedles, nanocarriers, and permeation enhancers are expected to further improve skin penetration and drug delivery efficiency. However, challenges including achieving adequate drug flux through human skin, preventing skin irritation, ensuring formulation stability, scaling up manufacturing, and obtaining regulatory approval must be overcome before commercialization.

The potential to become a convenient and effective long-acting alternative to oral therapy for diabetes, heart failure, and chronic kidney disease management.

9. Conclusion

The development of a transdermal patch of dapagliflozin represents a promising and innovative strategy for achieving controlled and sustained drug delivery in the management of diabetes mellitus. Compared to conventional oral therapy, this system can provide several advantages such as avoiding first-pass metabolism, reducing gastrointestinal side effects, and maintaining more stable plasma drug concentrations over an extended period. This leads to improved therapeutic

efficiency and better patient compliance, especially in long-term treatments where regular dosing can be challenging.

In addition, the transdermal route offers a non-invasive and convenient mode of administration, which may enhance patient acceptance and adherence to therapy. Proper selection of polymers, permeation enhancers, and formulation techniques plays a crucial role in ensuring effective drug release and adequate skin permeation of dapagliflozin. Evaluation studies such as drug release profile, skin irritation tests, and stability analysis further support the potential of this system.

Overall, the transdermal patch of dapagliflozin provides a novel and patient-friendly alternative to oral dosage forms, with the potential to improve glycemic control and quality of life in diabetic patients.

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