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FORMULATION, DEVELOPMENT OF TRANSDERMAL PATCHES OF ANTIDIABETIC DRUG FOR MANAGEMENT OF TYPE 2 DIABETES

Gayatri Dahariya*
B. Pharmacy College Rampura (Kakanpur), Gujarat

***Correspondence Info:**
Gayatri Dahariya
B. Pharmacy College Rampura (Kakanpur), Gujarat
Email:
gayatridahariya123@gmail.com

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ABSTRACT

The present study focuses on the formulation and evaluation of transdermal patches containing Saxagliptin, an antidiabetic agent, for the effective management of type 2 diabetes mellitus. The patches were developed using various polymers, including Eudragit L-100, Ethyl Cellulose, and HPMC, through the solvent casting method. Propylene glycol was used as a plasticizer and permeation enhancer. The prepared patches were evaluated for physicochemical parameters such as thickness, moisture uptake, folding endurance, and drug content, all of which were found within acceptable limits. The optimized formulation (F4) exhibited desirable mechanical properties and sustained drug release up to 12 hours, reaching 98.98% cumulative release. The drug release followed zero-order kinetics and fitted well into the Korsmeyer-Peppas model, indicating non-Fickian diffusion. The findings suggest that Saxagliptin transdermal patches offer a promising alternative for controlled and sustained drug delivery in the treatment of type 2 diabetes, improving patient compliance and therapeutic efficacy.

Keywords: Transdermal patch, Saxagliptin, Type 2 diabetes, Controlled release, Solvent casting, Eudragit, Drug kinetics, HPMC, Zero-order release, Non-Fickian diffusion.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and impaired insulin secretion, leading to persistent hyperglycemia. It is one of the most prevalent endocrine disorders globally, affecting over 460 million people and projected to rise to 700 million by 2045 according to the International Diabetes Federation (IDF, 2020). Conventional oral antidiabetic therapies, while effective, are often associated with several limitations including first-pass metabolism, gastrointestinal irritation, frequent dosing, and poor patient compliance (Patel *et al.*, 2009; Desai *et al.*, 2014). To overcome these challenges, transdermal drug delivery systems (TDDS) have emerged as a promising alternative for the management of T2DM. Transdermal patches deliver the drug directly through the skin into systemic circulation, thereby bypassing hepatic first-pass metabolism, providing controlled and sustained drug release, reducing dosing frequency, and improving patient compliance (Prausnitz and Langer, 2008). Moreover, TDDS can maintain steady plasma drug concentrations, thus minimizing the risk of hypoglycemia and enhancing therapeutic outcomes (Mutalik and Udupa, 2005).

Recent research has explored various polymers such as HPMC, Eudragit, and PVA, along with permeation enhancers, to formulate stable and efficient transdermal

patches of antidiabetic drugs like metformin, glibenclamide, and pioglitazone (Ahad *et al.*, 2010; Basha *et al.*, 2013). These systems have shown promising results in terms of drug release, skin permeability, and pharmacokinetic profiles, indicating their potential for effective diabetes management.

Therefore, the present study aims to formulate and evaluate transdermal patches of a selected antidiabetic drug to improve therapeutic efficacy and patient adherence in T2DM treatment.

MATERIALS AND METHODS

Materials

Saxagliptin, an antidiabetic drug belonging to the DPP-4 inhibitor class, was used as the active pharmaceutical ingredient. It was obtained as a gift sample from Aurobindo Pharmaceuticals for the formulation of transdermal patches. Eudragit L-100, Ethyl Cellulose, and Hydroxypropyl Methylcellulose (HPMC) were selected as film-forming polymers. These were procured from Loba Chemie Pvt. Ltd., Mumbai, and chosen for their biocompatibility and sustained-release properties. Propylene glycol 400, from Thomas Baker, served dual roles as a plasticizer to enhance film flexibility and as a permeation enhancer to improve drug delivery through the skin. Analytical-grade solvents such as methanol, ethanol, and chloroform, along with disodium hydrogen phosphate and hydrochloric acid for buffer preparation and pH adjustment, were sourced from S. D. Fine Chem. Ltd., Mumbai.

Methods

Preparation of matrix type transdermal patches

Saxagliptin containing transdermal patch was prepared utilizing method given by (Touitou *et al.*, 2000) with slight modification. The casting solution was prepared by dissolving weighed quantities of HPMC (350, 400 and 450mg) and ethyl cellulose, Eudragit L-100 (50, 100 and 150mg) in 10 mL of methanol and dichloromethane mixture in ratio 1:2. To the resulting solution, 0.5% w/w of propylene glycol as plastisizer and 10% w/w penetration enhancer was added in this solution. Then drug (60mg) was added and mixed thoroughly to form a homogeneous mixture. The casting solution was then poured into glass mould/Petri dish specially designed to seize the contents. The glass mould containing the casting solution was dried at room temperature for 24 hours in vacuum oven. The patch was removed by peeling and cut into round shape of 1 cm^2. These patches were kept in desiccators for 2 days for further drying and enclose in aluminum foil and then packed in self-sealing cover.

Characterization of transdermal patches

The prepared transdermal patches were evaluated for the following parameters:

Microscopic pictures of transdermal patches

Microscopic pictures of all the formulations were observed using an electronic microscope with digital camera to determine the surface of the films formed and uniform dispersion of drug and polymer. In addition to microscopic study, transdermal patches were evaluated for their physicochemical characteristics (Kumar *et al.*, 2013).

Thickness

Patch thickness was measured using digital micrometer screw gauge at three different places, and the mean value was calculated (Santosh *et al.*, 2003).

Percent moisture content

Weighed individually the films (1cm^2) and kept them in desiccators containing calcium chloride at room temperature for at least 24 hrs. Film was weighed again; the difference in weight (initial and final weight) gives moisture content (Murthy *et al.,* 2001; Saxena *et al.,* 2006).

$$\%\ Moisture\ \ content = \frac{Intial\ \ weight - final\ \ weight}{\text{Intial weight}} \times 100$$

Percent moisture uptake

Weighed individually the films and kept them in desiccator containing calcium chloride at room temperature for at least 24 hrs. remove the films from desiccators and exposed to 4% relative humidity using saturated solution of potassium chloride in a another desiccator until a constant weight is achieved (Mali *et al.,* 2015; Darwhekar *et al.,* 2011).

$$\%\ Moisture\ \ content = \frac{Final\ \ weight - Intial\ \ weight}{final\ \ weight} \times 100$$

Folding endurance

This was determined by repeatedly folding one film at the same place until it broken. The number of times the film could be folded at the same place without breaking / cracking gave the value of folding endurance (Prabhakar *et al.,* 2011).

Tensile Strength

The tensile strength of the patch was evaluated by using the tensiometer. It consists of two load cell grips. The lower one was fixed and upper one was movable. Film strips with dimensions of 2×2cm were fixed between these cell grips, and force was gradually applied till the film broke. The tensile strength was taken directly from the dial reading in kg.

$$Tensile\ \ Strength\ \ (s) = \frac{Applied\ \ force\ \ (m \times g)}{Cross\ \ sectional\ \ area(b \times t)}$$

Where, S = tensile stress

m = mass in grams

g = acceleration due to gravity

b = breadth of strip in centimeters

t = thickness of strip in centimeters

Drug Content

The patches (2.5*2.5 cm (Equivalent to 25 mg of drug) were taken into a three separate 10 ml volumetric flask and dissolved in methanol (10ml) with the help of shaker. The solution was centrifuged to separate out any particulate matter. 1mL of sample was withdrawn and transferred in volumetric flask (10 mL of capacity). The sample was dilute upto the mark with methanol and dilute suitably and analyzed by UV spectrophotometer at 210.0 nm (Jadhav *et al.,* 2009).

***In-vitro* skin permeation study**

The *in-vitro* skin permeation study was carried out by using a Franz diffusion cell (receptor compartment capacity: 80 ml: area: 2.5*2.5 cm (Equivalent to 5 mg of drug). The egg membrane was separated and used for in vitro study. The receiver compartment was filled with 40 ml of phosphate buffer, pH 7.4. The Transdermal patch was firmly pressed onto the centre of the egg membrane and then the membrane was mounted on the donor compartment. The donor compartment was then placed in position such that the surface of membrane just touches the receptor fluid surface. Heat is provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by Teflon coated magnetic bead which is placed in the diffusion cell. The temperature of receptor compartment was maintained at 37±0.5ºC.

The samples were withdrawn at different time intervals and analyzed for drug content. At the same time receptor phase was replaced with an equal volume of buffer solution at each time interval (Prajapati *et al.,* 2011).

RESULTS AND DISCUSSION

The prepared transdermal patches of Saxagliptin were evaluated for key physicochemical parameters, including thickness, moisture uptake, folding endurance, and drug content. The thickness of the patches ranged from 26.65 ± 0.45 mm to 32.25 ± 0.58 mm, with formulation F4 exhibiting the highest thickness. This increase in thickness may be attributed to the optimized concentration of polymers, particularly Eudragit L-100 and HPMC, which are known to enhance film-forming capacity. The uniform thickness across all formulations indicates consistent casting and solvent evaporation during preparation.

Moisture uptake values varied between 0.89 ± 0.65% and 1.85 ± 0.25%. Notably, formulation F4 showed the lowest moisture uptake, suggesting better moisture resistance. Low moisture absorption is beneficial as it prevents microbial growth, patch degradation, and changes in drug release behavior during storage. The folding endurance test, which evaluates mechanical strength and flexibility, showed values from 125 ± 4 to 156 ± 4 folds, with F4 having the highest value. This indicates that the patch can withstand repeated bending without breaking, an essential quality for patient compliance and handling.

The drug content among all formulations was within acceptable limits, ranging from 98.69 ± 0.56% to 99.65 ± 0.45%. Formulation F4 demonstrated the highest drug content uniformity, confirming the effective dispersion of Saxagliptin in the polymer matrix. This ensures accurate and reproducible dosing, which is critical for chronic conditions such as diabetes.

In vitro drug release studies for the optimized batch F4 showed a sustained and controlled release pattern. The cumulative percentage drug release increased steadily over time, reaching 98.98 ± 0.78% at the end of 12 hours. This indicates that the patch formulation successfully provides prolonged drug delivery, which is desirable for maintaining steady blood glucose levels in patients with type 2 diabetes. The early moderate release followed by sustained diffusion supports the use of the patch for once-daily application.

Kinetic modeling of drug release data showed that the release followed zero-order kinetics with a correlation coefficient (R^2) of 0.985, indicating a constant drug release rate independent of drug concentration. This is ideal for transdermal patches, as it ensures a steady-state plasma level of the drug. The Korsmeyer-Peppas model also fit well (R^2 = 0.983), suggesting that the drug release mechanism was governed by a combination of diffusion and polymer relaxation (non-Fickian transport). In contrast, the first-order model showed a poor fit (R^2 = 0.708), confirming that the release was not concentration-dependent.

Table 1: Different Formulation used for Optimization TDDS

Formulation Code	Drug (mg)	HPMC (mg)	Eudragit L-100 (mg)	Ethyl cellulose (mg)	Total polymer weight (mg)	Propylene glycol (Plasticizer) % w/w	Permeation Enhancer % w/w
F1	60	450	-	50	500	0.5	10
F2	60	425	-	75	500	0.5	10
F3	60	400	-	100	500	0.5	10
F4	60	450	50	-	500	0.5	10
F5	60	425	75	-	500	0.5	10
F6	60	400	100	-	500	0.5	10

Dose calculations

- Width of the plate (mould) = 5 cm
- Length of the plate (mould) = 12 cm
- No. of 2.5 x 2.5 cm patch present whole(mould) = 12
- Each film contains 5 mg of drug.
- 12 no. of films contains mg of drug = 5×12 = 60mg
- The amount of drug added in each plate was approximately equal to 60 mg.

Table 2: Results of Thickness

S. No.	Formulation Code	Thickness* (mm)	% Moisture Uptake	Folding Endurance (Number of fold)	% Drug Content
1.	**F1**	26.65±0.45	1.85±0.25	125±4	98.85±0.65
2.	**F2**	29.98±0.32	1.23±0.36	135±3	98.69±0.56
3.	**F3**	30.25±0.65	1.65±0.45	135±5	99.12±0.21
4.	**F4**	32.25±0.58	0.89±0.65	156±4	99.65±0.45
5.	**F5**	32.14±0.41	1.32±0.32	125±7	98.98±078
6.	**F6**	30.65±0.27	1.45±0.47	130±4	98.74±041

(Mean± SD, n=3)

Table 3: *In Vitro* cumulative % drug release from optimized batch of transdermal patches F4

S. No.	Time (Hrs.)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release ± SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	0.5	0.707	-0.301	15.56±0.85	1.192	84.44	1.927
2	1	1	0	23.32±0.32	1.368	76.68	1.885
3	2	1.414	0.301	36.65±0.45	1.564	63.35	1.802
4	4	2	0.602	42.25±0.65	1.626	57.75	1.762
5	6	2.449	0.778	56.65±058	1.753	43.35	1.637
6	8	2.828	0.903	69.98±0.42	1.845	30.02	1.477
7	10	3.162	1	79.85±0.15	1.902	20.15	1.304
8	12	3.464	1.079	98.98±0.78	1.996	1.02	0.009

Values are represented as mean ±SD (n=3)

Table 4: Regression Analysis Data of Formulation F4

Formulation	Zero order	First order	Pappas plot
F4	$R^2 = 0.985$	$R^2 = 0.708$	$R^2 = 0.983$

CONCLUSION

The results confirm that formulation F4 exhibits excellent physical characteristics and provides a sustained and controlled release of Saxagliptin, which is suitable for the transdermal management of Type 2 diabetes. The optimized patch demonstrates strong mechanical integrity, consistent drug content, and zero-order drug release kinetics, ensuring prolonged therapeutic efficacy with minimal dosing frequency.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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