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FORMULATION, DEVELOPMENT AND EVALUATION OF TRANSDERMAL PATCH OF LIPID-LOWERING DRUG

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ABSTRACT

This research focused on the formulation, development, and evaluation of transdermal patches for the lipid-lowering drug Pitavastatin. Pitavastatin, a poorly water-soluble drug, poses challenges in achieving consistent bioavailability. The study aimed to enhance the solubility of Pitavastatin and provide sustained release through the application of solid dispersion techniques. Various formulations were prepared, incorporating polymers such as HPMC, Ethyl Cellulose, Eudragit RLPO, and Eudragit RSPO. The transdermal patches were evaluated for thickness, folding endurance, moisture content, moisture uptake, tensile strength, drug content, and in-vitro drug release. The optimized formulation (F4) exhibited promising characteristics with sustained release properties.

Keywords: Transdermal patches, Pitavastatin, Formulation, Drug delivery, Sustained release.

INTRODUCTION

Cardiovascular diseases, particularly those associated with dyslipidemia, remain a leading cause of morbidity and mortality globally. Hyperlipidemia, characterized by elevated levels of cholesterol and triglycerides, contributes significantly to the progression of atherosclerosis and cardiovascular events. Statins, a class of lipid-lowering drugs, have been instrumental in managing hyperlipidemia by inhibiting the enzyme HMG-CoA reductase, a key player in cholesterol biosynthesis.

Pitavastatin, a member of the statin class, exhibits potent cholesterol-lowering effects and has gained prominence for its efficacy in managing dyslipidemia and preventing cardiovascular events (Momose et al., 2009). However, like other statins, pitavastatin's oral administration is associated with challenges such as first-pass metabolism and systemic side effects (Duggan; 2014). To address these issues and enhance patient compliance, alternative drug delivery systems are being explored.

Transdermal drug delivery systems offer several advantages, including bypassing first-pass metabolism, providing controlled release, and minimizing systemic side effects (Prausnitz and Langer; 2008). The use of transdermal patches for delivering lipid-lowering drugs, including statins, presents an attractive approach to optimize therapeutic outcomes.

This study aims to formulate, develop, and evaluate a transdermal patch for pitavastatin, emphasizing the enhancement of solubility and controlled release. Solid dispersion, utilizing polyvinylpyrrolidone (PVP K30) as a carrier, is explored to improve the solubility of pitavastatin. The developed transdermal patch is expected to provide sustained and

controlled drug release, contributing to improved patient adherence and therapeutic efficacy.

MATERIALS AND METHODS

Formulation of transdermal patch

Transdermal patches were formulated using a combination of polymers, including HPMC, Ethyl Cellulose, Eudragit RLPO, and Eudragit RSPO. The polymers, along with a plasticizer, were dissolved in chloroform and methanol (Mamatha *et al.,* 2010). The resulting solution was poured into a glass Petri dish containing glycerin. The solvent was allowed to evaporate over 24 hours at room temperature. For the matrix type patches, 500 mg of polymers and 20 mg of the drug were weighed, dissolved in a solution of chloroform, methanol, and PEG 400, and poured onto glycerin in a glass Petri dish. The mixture was then dried at room temperature for 24 hours. This multistep process aimed to develop effective transdermal patches for the controlled release of Pitavastatin, utilizing various polymers and membranes to optimize drug delivery characteristics.

Evaluation parameters

The prepared transdermal patches were evaluated for the following parameters:

Thickness

The thickness of patches was measured by Vernier calipers.The thickness of patches were measured at three different places and average of three readings was taken with standard deviation (Sridevi *et al.,* 2000).

Folding endurance

This was determined by repeatedly folding one patch at the same place until it broken. The number of times the patch could be folded at the same place without breaking / cracking gave the value of folding endurance (Sankar *et al.,* 2003).

Tensile strength

Cut the patch at the centre having 2cm length and 2cm breadth. Patch was hanged on top and lower side of instrument, then start the switch and note the reading on screen (Ryan *et al.,* 2006). The thickness and breadth of strips were noted at three sites and average value was taken for calculation.

$$\text{Tensile stress (S)} = \frac{\text{Applied force}}{\text{Cross sectional area}} = \frac{m \times g}{b \times t}$$

Where, S = tensile stress in 980 dynes/cm^2

m = mass in grams

g = acceleration due to gravity (980 dynes/cm^2)

b = breadth of strip in centimeters

t = thickness of strip in centimetres

Percentage of moisture content

The prepared patches were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual patches were weighed. The percentage of moisture content was calculated as the difference between final and initial weight with respect to initial weight (Hemangi *et al.,* 2009).

Percentage of moisture uptake

Firstly weighed the patches and then kept in a desiccators at room temperature for 24 hrs and then it's exposed to 84% RH (A saturated solution of potassium chloride) in a desiccators. The % of moisture uptake was calculated by difference between final and initial weight with respect to initial weight (Rani *et al.,* 2011).

Drug content analysis

The patches (n = 3) of specified area (6.16cm^2) were taken into a 10 ml volumetric flask and dissolved in methanol (10ml) with

the help of shaker (Parthasarathy *et al.,* 2011). After the vortex the solution was filtered and prepared subsequent dilutions and analyzed by UV spectrophotometer at 282nm.

***In vitro* skin permeation study**

The in vitro skin permeation study was done by using a Franz diffusion cell (receptor compartment capacity: 80 ml: surface area: 3.14 cm^2. The egg membrane was separated and used for in vitro study (Prabhu *et al.,* 2010). 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. The whole assembly was kept on a magnetic stirrer with suitable rpm throughout the experiment using magnetic beads. The temperature of receptor compartment was maintained at 37± 0.5ºC. The samples were withdrawn at different time intervals up to 10 hrs and analyzed for drug content. Receptor phase was replaced with an equal volume of buffer solution at each time interval.

RESULTS AND DISCUSSION

The thickness and folding endurance data in Table 2 demonstrate variations among different formulations, with F4 having a thickness of 97±4 µm and a folding endurance of 285±6. These variations could influence the patch's flexibility and adherence to the skin.

In Table 3, % moisture content, moisture uptake, tensile strength, and % drug content are reported. F4 exhibits favorable characteristics, such as low moisture content (2.85%), high tensile strength (0.969 kg/cm2), and a high % drug content (99.45±0.36), indicating its potential as an optimized formulation.

The in-vitro drug release data in Table 4 for F4 over time reveal a sustained release profile. The regression analysis in Table 4 provides R^2 values for zero and first-order kinetics. A high R^2 value for zero order (0.987) suggests that drug release is predominantly based on time, indicating a sustained and controlled release pattern. However, the first-order kinetics (R^2 = 0.700) indicates a deviation from linearity. Formulation F4 shows promising characteristics, making it a potential candidate for further development as a Pitavastatin transdermal patch. The sustained drug release profile aligns with desired therapeutic outcomes.

Table 1: Preparation of matrix type transdermal patches

Formulation Code	Drug (mg)	HPMC (mg)	RLPO (mg)	RSPO (mg)	Ethyl cellulose (mg)	Total polymer weight (mg)	Plasticizer % w/w of total polymer PEG 600 ml	Permeation Enhancer % w/w of total polymer (Methanol, chloroform) ml
F1	24	800	50	-	50	900	0.5	10
F2	24	700	100	-	100	900	0.5	10
F3	24	600	150	-	150	900	0.5	10
F4	24	800	-	50	50	900	0.5	10
F5	24	700	-	100	100	900	0.5	10
F6	24	600	-	150	150	900	0.5	10

Table 2: Thicknesses and folding endurance of different formulations of transdermal patch

S. No.	Formulation Code	Thickness (µm)*	Folding Endurance*
1.	**F1**	98±5	235±7
2.	**F2**	95±3	248±3
3.	**F3**	93±2	256±5
4.	**F4**	97±4	285±6
5.	**F5**	95±5	236±4
6.	**F6**	90±6	224±2

Table 3: % Moisture content, moisture uptake, tensile strength, % drug content of different formulations of transdermal patches

S. No.	Formulation Code	% Moisture Content	% Moisture Uptake	Tensile Strength (kg/cm^2)	% Drug Content
1.	**F1**	3.45	7.12	0.891	95.65±0.35
2.	**F2**	3.15	6.32	0.865	98.85±0.25
3.	**F3**	3.29	7.45	0.845	96.65±0.15
4.	**F4**	2.85	5.32	0.969	99.45±0.36
5.	**F5**	3.83	8.15	0.945	95.45±0.24
6.	**F6**	3.19	6.74	0.995	96.85±0.18

Table 4: *In-vitro* drug release data for optimized formulation F4

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	16.65	1.221	83.35	1.921
1	1.000	0.000	20.14	1.304	79.86	1.902
2	1.414	0.301	31.45	1.498	68.55	1.836
4	2.000	0.602	43.12	1.635	56.88	1.755
6	2.449	0.778	53.65	1.730	46.35	1.666
8	2.828	0.903	62.25	1.794	37.75	1.577
10	3.162	1.000	78.89	1.897	21.11	1.324
12	3.464	1.079	98.65	1.994	1.35	0.130

Table 5: Regression analysis data of Pitavastatin Transdermal patches

Batch	Zero Order	First Order
	R^2	R^2
F4	0.987	0.700

CONCLUSION

The development and evaluation of Pitavastatin transdermal patches, particularly formulation F4, exhibit promising characteristics. The optimized formulation (F4) demonstrates favorable properties, including appropriate thickness, high folding endurance, low moisture content, excellent tensile strength, and a high percentage of drug content. Moreover, the in-vitro drug release profile of F4 follows a sustained and controlled pattern, as evidenced by the regression analysis with a high R^2 value for zero-order kinetics. These findings suggest that F4 has the potential for providing a sustained release of Pitavastatin, which is crucial for achieving therapeutic efficacy in lipid-lowering applications. The sustained release profile is essential for maintaining a consistent drug concentration, ensuring prolonged therapeutic effects, and potentially improving patient compliance.

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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