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Formulation and Evaluation of Lisuride Transdermal Patches Using Various Polymers and Permeation Enhancers

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ABSTRACT

The present study aimed to formulate and evaluate Lisuride transdermal patches using hydrophilic and hydrophobic polymers to overcome hepatic first-pass metabolism and provide sustained drug release. Patches were prepared by the solvent casting method using combinations of Eudragit L-100, HPMC K4M, and HPMC K15M, with propylene glycol and Tween-80 serving as permeation enhancers and plasticizers. The formulations were evaluated for physicochemical parameters and in-vitro drug release. Among the formulations, F6 demonstrated optimal physicochemical properties and maximum cumulative drug release of 94.7% in 12 hours, suggesting the effectiveness of HPMC K4M in sustained release.

Keywords: Drug, Eudragit, Formulations, Lisuride, Patches, Polymers

1. INTRODUCTION

Oral drug delivery remains the most widely used route of administration due to its simplicity, patient compliance, and cost-effectiveness. However, this method is not without limitations. A major drawback is the first-pass hepatic metabolism, which significantly reduces the bioavailability of certain drugs, thereby requiring higher doses to achieve therapeutic efficacy. Additionally, fluctuations in plasma drug concentrations are commonly observed with oral administration, often leading to sub-therapeutic levels or dose-related side effects. These challenges are particularly pronounced in drugs with narrow therapeutic windows or short biological half-lives.

In contrast, Transdermal Drug Delivery Systems (TDDS) have emerged as a promising alternative that can overcome many of the limitations associated with oral delivery. TDDS offers controlled and sustained drug release, allowing for consistent plasma levels over extended periods. This mode of delivery bypasses the gastrointestinal tract and hepatic first-pass metabolism, thereby improving systemic bioavailability. Furthermore, TDDS can reduce dosing frequency, enhance patient adherence, and minimize drug-related side effects by avoiding peak-trough fluctuations.

Lisuride, a semi-synthetic ergot derivative and potent dopamine receptor agonist, is commonly used in the treatment of Parkinson's disease, migraine, and hyperprolactinemia. Despite its therapeutic benefits, Lisuride suffers from low oral bioavailability (~10%) due to extensive first-pass metabolism and has a short plasma half-life (approximately 2 hours), necessitating frequent dosing. These pharmacokinetic limitations make Lisuride an ideal candidate for transdermal delivery, where bypassing hepatic metabolism and maintaining steady drug levels could substantially enhance therapeutic efficacy and patient compliance.

Given these considerations, the present study is aimed at the formulation and evaluation of transdermal patches of Lisuride using matrix-type systems. The goal is to achieve sustained drug release over an extended period through the skin, thereby enhancing its pharmacokinetic profile and reducing the limitations associated with oral administration. The study involves the use of various polymers and permeation enhancers to optimize drug release, mechanical properties, and skin permeability of the patches, thus contributing to the advancement of Lisuride transdermal therapy.

2. MATERIALS AND METHODS

2.1 Materials

Drug: Lisuride maleate

Polymers: Eudragit L-100, HPMC K4M, HPMC K15M

Plasticizer: Propylene glycol

Permeation Enhancer: Tween-80

Solvents: Dichloromethane and Ethanol

2.2 Preparation of Standard Graph of Lisuride

Lisuride was analyzed using a UV-spectrophotometer at 266 nm in PBS pH 7.4. The standard curve is shown in Figure 1.

2.3 Formulation of Transdermal Patches: The patches were prepared using the solvent casting method. Formulations (F1-F10) were varied based on the polymer type and concentration as shown in Table 1.

Table 1: Formulation Composition of Lisuride Transdermal Patches

Formulation	Lisuride (mg)	Eudragit L-100 (mg)	HPMC K4M (mg)	HPMC K15M (mg)	Dichloromethane (ml)	Ethanol (ml)	Propylene Glycol (ml)	Tween-80 (ml)
F1	15	200	–	–	8	8	0.3	0.3
F2	15	250	–	–	8	8	0.3	0.3
F3	15	300	–	–	8	8	0.3	0.3
F4	15	–	200	–	8	8	0.3	0.3
F5	15	–	250	–	8	8	0.3	0.3
F6	15	60	300	–	8	8	0.3	0.3
F7	15	–	–	200	8	8	0.3	0.3
F8	15	–	–	250	8	8	0.3	0.3
F9	15	–	–	300	8	8	0.3	0.3
F10	15	150	150	–	8	8	0.3	0.3

3. EVALUATION OF TRANSDERMAL PATCHES

3.1 Physicochemical Parameters

Formulation	Weight (mg)	Thickness (mm)	Folding Endurance	Drug Content (%)	Moisture Uptake (%)	Moisture Content (%)
F1	140.2	0.3569	20	45	7.98	3.77
F2	48.3	0.3520	25	65	25.05	9.2
F3	85.5	0.3470	27	57.5	13.09	5.16
F4	78.3	0.3496	24	60	15.63	5.66
F5	94.6	0.3460	30	67.5	11.73	4.87
F6	63.1	0.3517	32	92.5	19.65	12.67
F7	129.5	0.3478	40	101.7	9.42	3.43
F8	113.1	0.3437	37	85	10.87	4.72
F9	82.1	0.3503	34	55	16.44	6.62
F10	92.5	0.3532	29	62.5	13.08	6.17

All formulations exhibited satisfactory physical characteristics within pharmacopeial limits.

3.2 In-vitro Drug Release

In vitro permeation of Lisuride from Transdermal patches through dialysis membrane (Hi-Media) with molecular weight cut off of 12000 was studied. The membrane was mounted over a Franz diffusion cell and a Transdermal patch. The receiver compartment of the diffusion cell was filled with 15.0 ml of PBS pH 7.4 and the setup was placed over a magnetic stirrer with temperature maintained at 370C. Samples of 3 ml were withdrawn and replenished immediately from the receiver compartment at 1, 2, 3, 4, 6 and 12h. They were stored in refrigerated condition till the analysis was performed. The content of Lisuride in the samples was analyzed by UV-Visible spectrophotometer. The concentrations of drug were determined at 266 nm.

4. RESULTS AND DISCUSSION

A standard curve was constructed for Lisuride by plotting the absorbance values at 5 different known concentrations (5, 10, 15, 20, and 25 µg/ml) against their respective UV absorbance values measured in nanometers (nm). The standard curve of Lisuride demonstrates a strong linear relationship between absorbance and concentration in the 5–25 µg/ml range. This validates the UV spectrophotometric method as accurate, precise, and suitable for the routine quantitative analysis of Lisuride in pharmaceutical formulations and results were mentioned in table 4.1.

Table 4.1: Standard Curve of Lisuride

Concentration (µg/ml)	Absorbance (nm)
5	0.123
10	0.210
15	0.320
20	0.411
25	0.501

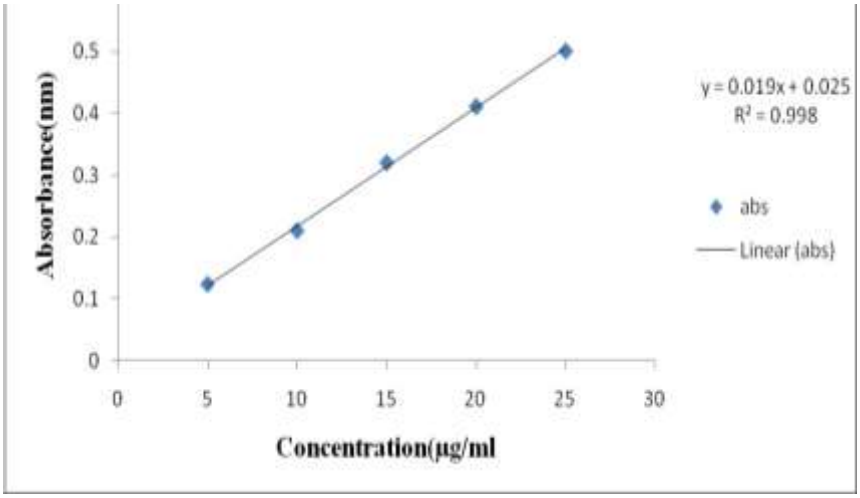


Figure 4.1: Standard curve of Lisuride

4.2. Evaluation of Lisuride Transdermal patches:

Physical appearance: All the Transdermal patches were visually inspected for colour, clarity, flexibility.

Flatness: All the Transdermal patches was found to be flat without any foams.

Table No. 4.2 : Evaluation of Transdermal patch by physical methods

Formulation	Weight variation(mg)	Thickness (mm)	Folding endurance	Drug content (%)	Moisture uptake (%)	Moisture content (%)
F1	140.2	0.3569	20	45	7.98	3.77
F2	48.3	0.3520	25	65	25.05	9.2
F3	85.5	0.3470	27	57.5	13.09	5.16
F4	78.3	0.3496	24	60	15.63	5.66
F5	94.6	0.3460	30	67.5	11.73	4.87

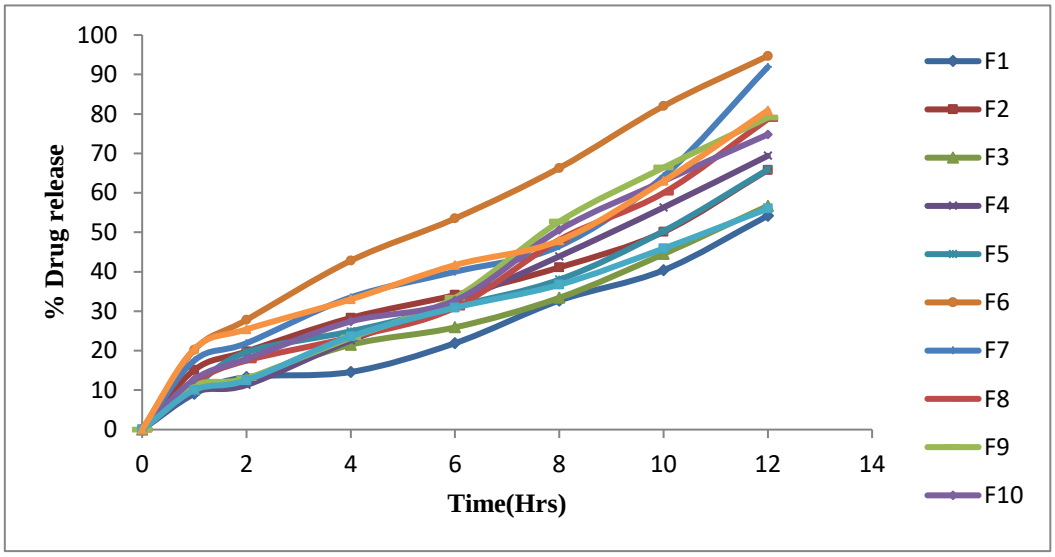
F6	63.1	0.3517	32	92.5	19.65	12.67
F7	129.5	0.3478	40	101.7	9.42	3.43
F8	113.1	0.3437	37	85	10.87	4.72
F9	82.1	0.3503	34	55	16.44	6.62
F10	92.5	0.3532	29	62.5	13.08	6.17

The prepared Lisuride Transdermal patches were evaluated by physical methods such as Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake and Moisture content and all the results were found to be with in the pharmacopeial limits.

Table No. 4.3: Evaluation of Trandermal patch by In-vitro permeation studies using dialysis membrane

Time (hrs)	**% Drug release**									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
1	9.05	15.1	10.1	9.49	10.9	20.2	17.5	12.0	11.1	12.7
2	13.3	19.8	12.8	11.3	19.6	27.8	21.9	17.5	13.0	17.9
4	14.6	28.3	21.5	22.6	24.9	42.8	33.5	23.4	23.3	27.4
6	21.9	34.1	25.9	32.3	31.2	53.5	40.0	30.9	33.4	32.7
8	32.7	41.1	33.4	43.9	38.0	66.3	46.5	48.1	52.7	50.6
10	40.4	50.1	44.5	56.3	50.3	82.0	64.2	60.0	66.4	63.0
12	54.2	65.8	56.7	69.4	65.9	94.7	91.9	78.7	79.1	74.8

Fig No. 4.3: Release profile of In-vitro permeation studies using dialysis membrane



The prepared Lisuride Transdermal patches were evaluated for In-vitro permeation studies using dialysis membrane, Among all the 10 formulations F6 formulation which contain HPMC K4M 300mg and Eudragit L-100 60mg had shown 94% cumulative drug release within 12 hours and compared to HPMC K15M, HPMC K4M showed better drug release profile.

5. CONCLUSION

In present study transdermal drug delivery of Lisuride was developed to overcome the first pass metabolism and to reduce frequency of dosing compared to oral route. Oral drug delivery system has various drawbacks like poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient. Matrix type of transdermal patches was developed by using polymers Eudragit-L100, HPMCk4M and HPMCk15M. Transdermal patches were prepared by employing solvent casting method. Propylene glycol and Tween80 were selected as permeation enhancer and plasticizer. Formulations were prepared with the varying concentrations polymers ranging from F1-F10, and all the formulations were evaluated for various physical parameters Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake, Moisture content and Swelling study and all the results were found to be were found to be with in the pharmacopeial limits, invitro drug release studies by using dialysis membrane. Among all the 10 formulations F6 formulation which contain HPMC K4M 300mg and Eudragit L-100 60mg had shown 94% cumulative drug release within 12 hours and compared to HPMC K15M, HPMC K4M showed better drug release profile.

6. Conflict of Interest: None

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