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Development of Transdermal Patch Loaded with Pitavastatin and Ezetimibe

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Abstract

The present worked aimed at preparing transdermal patches of a combination of Pitavastatin and Ezetimibe to enhance the systemic absorption of both these drugs. Pitavastatin and Ezetimibe transdermal patches formulated with PEG-400 as plasticizer and polymers HPMC and ethyl cellulose by solvent evaporation method are quite stable. The weight variation of the patches was found to be between 1.032±0.092 gm to 0.917±0.085 gm. Thickness of the patches ranged from 0.27±0.04 mm to 0.18±0.05 mm and folding endurance was found between 137±49.10 to 510.25±49.10. The results reflect the ability of patches to withstand rupture satisfactorily. The drug in transdermal patches formulated ranged between 97.15 ± 3.36 to 88.64 ± 3.01% and 98.16 ± 6.95 to 82.49 ± 7.81% for Ezetimibe and Pitavastatin respectively. The low coefficient variation value indicates the uniformity of drug content in all formulations. The combination of HPMC and ethyl cellulose had enhanced diffusion rate.

Keywords

Transdermal, Patch, Pitavastatin, Ezetimibe, lipid lowering

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Introduction

Pitavastatin (Figure 1) is a lipid-lowering drug belonging to the statin class of medications. By inhibiting the endogenous production of cholesterol within the liver, statins lower abnormal cholesterol and lipid levels and ultimately reduce the risk of cardiovascular disease.[1] Ezetimibe (Figure 2) is a therapeutically beneficial drug that works by a unique mechanism and differs from traditional lipid lowering agents. It may be used also or in combination of HMG CoA- reductive inhibitors (Statins).[2]

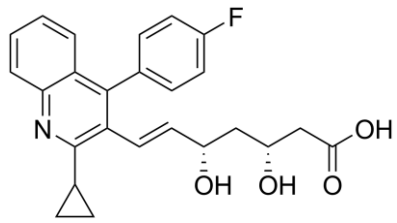

Figure 1 Pitavastatin

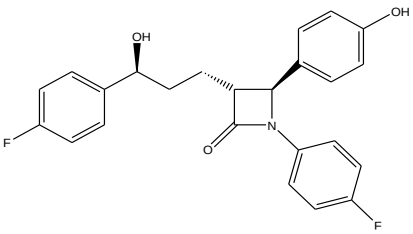

Figure 2 Ezetimibe

In recent years, various drug delivery systems have been developed which provide sustained release therapy via a subdermal insert. Systems have been disclosed which also provide drug delivery systems suitable for transdermal drug administration.[3-8] Many of the statins possess the properties necessary to be effective in a transdermal drug delivery system. The properties include high potency, proper physicochemical characteristics, good dermal penetration and lack of dermal irritation. Literature shows that the combined administration of Pitavastatin and Ezetimibe was not able to contribute significantly to lowering of blood cholesterol due to poor absorption but was able to prevent the kidney damage associated with elevated cholesterol levels.

In the proposed research work, it was therefore hypothesized that by preparing transdermal patches of a combination of Pitavastatin and Ezetimibe the systemic absorption of both these drugs would be increased and the cholesterol levels could be significantly reduced.[9]

Material and Methods

Preformulation Studies

The preformulation studies were carried out in the terms of tests of identification like physical appearance, melting point and λ_{max}. It also includes solubility profile of drug in various solvent systems and determination of partition coefficient.[10]

Preparation of Transdermal Patches

The matrix transdermal patches containing Pitavastatin and Ezetimibe were prepared by solvent evaporation technique using different ratios of HPMC E15 and ethyl cellulose. The backing layer was casted by pouring 4% PVA solution in the petri-plates lined with aluminum foil, followed by drying at 60ºC for 3-4 hrs in hot air oven.

In the process of formulation, initially, the polymer (HPMC K15) was taken in a beaker with a solvent dichloromethane:methanol (2:1) and was allowed to completely swell for a duration of 1 hour. Subsequently, with continuously stirring, ethyl cellulose was added. Afterward, the plasticizer (PEG 400) and permeation enhancer (SLS) were added and mixed uniformly for the few minutes duration. Finally, the drugs were incorporated with continuous stirring to mix well. The resultant homogenous dispersion was spread over a film former with the help of a dragger. Later, the controlled solvent evaporation was achieved by heating and the fabricated dried film was cut into 10 cm^2 dimension. The prepared films were wrapped in aluminum foil and stored in the desiccator for further study. Table 1 describes the composition in formulating the transdermal patches.[11]

Table 1: Composition of Transdermal patch formulations

S.No	Formulation	Ratio of polymer (HPMC : EC)	Total wt. of Polymers (mg)	Solvent (DCM: methanol, 2:1) (ml)	Plasticizer (PEG-400) (mg)	Permeation enhancer (SLS) (mg)	Ezetimibe (mg)	Pitavastatin (mg)
1	TDP1	3:1	5000	50	1000	100	15	77.5
2	TDP2	2:1	5000	50	1125	112.5	15	77.5
3	TDP3	3:2	5000	50	1250	125	15	77.5
4	TDP4	2:3	5000	50	1250	125	15	77.5
5	TDP5	1:2	5000	50	1125	112.5	15	77.5
6	TDP6	1:3	5000	50	1000	1000	15	77.5

Evaluation of Transdermal Patches[11]

Uniformity of weight test

The patches were subjected to mass variation by individually weighing randomly selected patches. Such determinations were carried out for each formulation.

Thickness

The thickness of each patch was measured by using screw gauge at different positions of the patch and the average was calculated.

Folding endurance

Folding endurance was determined by repeatedly folding one patch from the same place till it broke. The number of times the film could be folded from the same place without breaking/ cracking gave the value of folding endurance.

Percentage moisture content

The prepared transdermal films were weighed individually and kept in desiccators containing fused calcium chloride at room temperature for the duration of 24 hours. After 24 hours, the films were re-weighed and the percentage moisture content was determined by the formula% $moisture = \frac{initial\ weight - final\ weight}{initial\ weight} \times 100$

Drug content determination

For determining the drug content, an area of 10 cm^2 of the patch was cut and dissolved in 10 ml of phosphate buffer (pH 7.4). After that, 0.1 ml volume was withdrawn from the solution and diluted with the phosphate buffer to 10 ml in a volumetric flask. The absorbances of the solutions were taken at 240 and 255 nm for Ezetimibe and Pitavastatin respectively by using UV spectrophotometer.

***In-Vitro* Permeation Study**

In-vitro permeation studies of the patches were carried out by using Franz diffusion cell with a receptor compartment capacity of 60 ml. The formulated patch of surface area of 0.64 cm^2 was placed in between the dialysis membrane and the donor compartment and then dialysis membrane was mounted between the donor and receptor compartment of diffusion cell. The receptor compartment of diffusion cell was filled with phosphate buffer saline pH 7.4. The whole assembly was fixed on a magnetic stirrer and the solution in the receptor compartment was constantly and continuously stirred magnetic beads at 50 rpm; the temperature was maintained at 37±0.5ºC. The 1 ml aliquots were withdrawal at different time intervals (0, 60, 120, 180, 240, 300 min and 24hrs) and analyzed the drug content by UV at 240 nm and 255 nm. The receptor phase was replenished with an equal volume of phosphate buffer (37ºC) at each sample withdrawal, the cumulative amount of drug permeated per square centimeter of patches were plotted against time.

Results and Discussion

Preformulation Studies

Preformulation studies were carried out for Pitavastatin and Ezetimibe for its physical and chemical properties.

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Table 2: Physical identification tests of Pitavastatin and Ezetimibe

S.No.	Test	Specification	Observation	Specification	Observation
		Pitavastatin		Ezetimibe	
1.	Color	White to off white	White	White	White
2.	Taste	Bitter	Bitter	Bitter	Bitter
3.	Odor	Odorless	Odorless	Odorless	Odorless
4.	State	Solid	Powder	Solid	Crystalline

Table 3: Solubility of Pitavastatin and Ezetimibe

S.No.	Solvent	Solubility	Solvent	Solubility
	Pitavastatin		**Ezetimibe**	
1.	Ethanol	Very slightly soluble	Ethanol	Freely soluble
2.	Chloroform	Freely soluble	Methanol	Freely soluble
3.	Dilute HCl	Freely soluble	Acetone	Freely soluble
4.	Water	Very slightly soluble	Water	Practically insoluble

The partition coefficient study was performed and the log P value was found to be **1.52** and **4.57** for Pitavastatin and Ezetimibe respectively.

Physiochemical Parameters of Transdermal Patches

The evaluation of the patch was performed as per guidelines and the result is reported in table 4.

Table 4: Physiochemical Parameters of Transdermal Patches

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Formulation	Weight Variation (Mean±S.D.)	Thickness (Mean±S.D.)	Folding Endurance (Mean±S.D.)	% Drug Content (Mean±S.D.) Ezetimibe	% Drug Content (Mean±S.D.) Pitavastatin	% Moisture content
TDP1	1.032±0.092	0.27±0.04	127±56.12	91.21±1.27	87±4.65	3.17
TDP2	1.027±0.061	0.23±0.03	137±49.10	97.15±3.36	93.05±3.47	2.45
TDP3	0.917±0.085	0.18±0.05	102±72.73		98.16±6.95	2.01
TDP4	0.962±0.043	0.22±0.02	120±78.98	89.77±6.45	84.33±8.58	1.97
TDP5	0.987±0.036	0.25±0.05	131±58.08	93.39±7.12	82.49±7.81	2.15
TDP6	1.015±0.087	0.23±0.03	109±36.50	88.64±3.01	89.38±4.15	1.89

				92.85±8.18		

***In vitro* permeation study**

Release studies are required for predicting the reproducibility of rate and duration of drug release. The importance of polymer dissolution on drug release from matrices has been known for ensuring the sustained release performance. The diffusion kinetics of the drug was analyzed by graphical method for Zero order, First order, Higuchi and Peppas equation. The R^2value (Table 5) of fitting model indicates that the drug release kinetics of formulations.

Table 5: *In vitro* drug release of formulations

Formulation	Time	Actual cumulative amt. of drug permeated	Quantity /cm² (µg/cm²)	% Drug Permeated	% Drug remaining	Log % drug remaining
TDP1	1 hrs	159.64	249.44	10.50	89.49	1.95
	2 hrs	361.86	565.41	23.80	76.19	1.88
	3 hrs	673.83	1052.86	44.33	55.66	1.74
	4 hrs	778.04	1215.70	51.18	48.81	1.68
	5 hrs	883.81	1380.95	58.14	41.85	1.62
	24 hrs	1004.43	1569.42	66.08	33.91	1.53

TDP2	1 hrs	186.25	291.02	11.19	88.80	1.94
	2 hrs	399.62	624.41	24.01	75.98	1.88
	3 hrs	448.78	701.219	26.96	73.03	1.86
	4 hrs	615.74	962.09	37.00	62.99	1.79
	5 hrs	802.21	1253.46	48.21	51.78	1.71
	24 hrs	1077.60	1683.75	64.75	35.24	1.54
TDP3	1 hrs	212.86	332.59	18.68	81.31	1.91
	2 hrs	376.05	587.58	33.01	66.99	1.82
	3 hrs	541.90	846.72	47.57	52.43	1.72
	4 hrs	630.59	985.31	55.35	44.64	1.65
	5 hrs	787.13	1229.90	69.09	30.90	1.49
	24 hrs	1039.24	1623.82	91.23	8.77	0.94
TDP4	1 hrs	252.77	394.95	21.06	78.93	1.89
	2 hrs	350.11	547.04	29.17	70.82	1.85
	3 hrs	542.12	847.07	45.17	54.82	1.73
	4 hrs	697.33	1089.59	58.11	41.88	1.62
	5 hrs	761.86	1190.41	63.48	36.51	1.56
	24 hrs	1093.34	1708.356	91.11	8.88	0.94
TDP5	1 hrs	252.77	394.95	21.06	78.93	1.89
	2 hrs	350.11	547.04	29.17	70.82	1.85

	3 hrs	542.12	847.07	45.17	54.82	1.73
	4 hrs	697.33	1089.59	58.11	41.88	1.62
	5 hrs	761.86	1190.41	63.48	36.51	1.56
	24 hrs	1093.34	1708.356	91.11	8.88	0.94
TDP6	1 hrs	252.77	394.95	21.06	78.93	1.89
	2 hrs	350.11	547.04	29.17	70.82	1.85
	3 hrs	542.12	847.07	45.17	54.82	1.73
	4 hrs	697.33	1089.59	58.11	41.88	1.62
	5 hrs	761.86	1190.41	63.48	36.51	1.56
	24 hrs	1093.34	1708.356	91.11	8.88	0.94

Table 6: Drug released kinetic model report

Formulation Code	Zero order R^2	First order R^2	Higuchi's model R^2	Peppas model R^2
TDP1	0.715	0.817	0.790	0.722
TDP2	0.657	0.913	0.768	0.698
TDP3	0.453	0.567	0.608	0.883
TDP4	0.724	0.830	0.844	0.961

TDP5	0.697	0.929	0.828	0.959
TDP6	0.740	0.952	0.828	0.948

From the above table it can be concluded that the formulations are following mixed order kinetics.

Conclusion

Pitavastatin and Ezetimibe transdermal patches formulated with PEG-400 as plasticizer and polymers HPMC and ethyl cellulose by solvent evaporation method are quite stable, there is no interaction between drug and formulation component on the basis of physical appearance and FTIR data. The low coefficient variation value indicates the uniformity of drug content in all formulations. The combination of HPMC and ethyl cellulose had enhanced diffusion rate. The kinetic study and mechanism for diffusion of the patches reflects that the patches obey mixed order kinetics.

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