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Development and Evaluation of Transdermal Patches of Piperine Hydrochloride

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Abstract

The objective of the present study was to develop transdermal matrix patch of Piperine HCl and assess its feasibility for transdermal application. Low dose maintenance therapy of Piperine HCl has the capability to reduce potential side effects and improved patient compliance which are more common with conventional drug delivery.

The results of Piperine HCl transdermal matrix patch showed that the most promising formulation was HE1 (formulation containing Drug: HPMC:EC:Span:PG; **(**1:(2:8)). Thus optimized transdermal matrix patch of Piperine HCl using polymers such as HPMC and EC with Span & PG as permeation enhancers demonstrated their ability to give sustained release, because of excellent release and permeation of drug and its influence on its pharmacological responses. The developed formulation of Piperine HCl is expected to improve the patient compliance, form better dosage regimen and provide maintenance therapy to patients suffering from inflammation and allergy.

These promising results showed the feasibility of delivering Piperine HCl through transdermal matrix patch. The developed transdermal patches of Piperine HCl may prove to be a better alternative to conventional dosage forms in allergy as revealed by the results.

Keywords: Transdermal, Patch, Piperine

Introduction

Piperine, along with its isomer chavicine, is the alkaloid responsible for the pungency of black pepper and long pepper. It has been used in some forms of traditional medicine.

Piperine is a compound belonging to the alkaloids; it is responsible for the pungent taste of various pepper species, and has, in addition to being found in the members of the Piperaceae family, been detected in several other plant species (Rhododendron faurie, Vicoa indica, Anethum sowa, and others). The amount of piperine is highest in Piper nigrum L., and varies from 2% to as high as 9% , depending on environmental factors such as climate and/or place of origin, as well as growing conditions. [1]

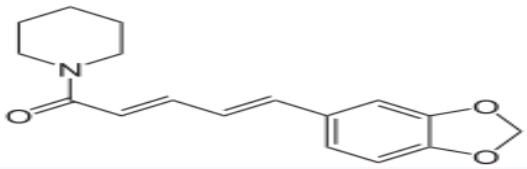

Fig. 1: (2*E*,4*E*)-5-(2*H*-1,3-Benzodioxol-5-yl)-1-(piperidin-1-yl)penta-2,4-dien-1-one

The fundamentals of a successful pharmaceutical formulation depend on the delivery of the medicament to the target site at therapeutically relevant level, with negligible or minimum discomfort and side effects to the patient. In this respect, the route of drug administration has major influence.

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Among all the routes of drug administration, the oral route is the most common form of delivery of drugs because it has advantage of easy administration. But also has potential drawbacks like poor bioavailability due to first pass effect and tendency to produce rapid high and low plasma concentration of drug, due to this, the patient compliance occurs. To overcome the drawbacks of oral route, the continuous intravenous infusion has been recognized to maintain a constant and sustained concentration of drug within therapeutic range for prolonged period of time. But this mode of drug administration also have certain drawbacks like needle pain and accidental needle sticks, therefore necessitates of regular hospitalization during treatment and requires under medical supervision.

The transdermal drug delivery system represents an attractive alternative to oral delivery of drugs and it also provides an alternative to intravenous infusion too. The transdermal drug delivery systems can deliver drug through the skin portal to systemic circulation at a predetermined rate and maintain therapeutically effective concentrations over a prolonged period of time. The transdermal drug delivery system avoids the hazards and discomfort associated with parenteral therapy and improves patient compliance. It is easy to remove patch when need arises. The first pass metabolism of drug by the liver is avoided, thus bioavailability of the drug also increase. Transdermal delivery may also eliminate gastrointestinal side effects of some drugs when presented in conventional dosage forms. At present transdermal delivery system provides the therapy for periods between 1 to 7 days with controlled levels of drug in the plasma thus reducing the repeat dosing intervals. This reduction in dose frequency gives an associated decrease in potential side effects. [2]

Material and Methods

Formulation of Piperine HCl transdermal patches

Matrix patches were casted on a glass mould by solvent casting methods. Seven types of polymer patches were prepared. First three formulation were prepared by using HPMC alone having drug and polymer 1:2, 1:3, 1:4 using distilled water as a solvent and one more formulation is formulated using HPMC with permeation enhancer Span 80 (1%) having drug polymer ratio 1:4. Next two formulations were prepared by using HPMC and EC in combination having drug and polymer in the ratio 1:(2:8), 1:(1:9) using methanol and chloroform as solvent (1:1) ratio and the remaining formulation is formulated with HPMC and EC by using permeation enhancer Span 80 (1%) in ratio of 1:(2:8). Propylene glycol (3%) used as a plasticizer.
[3]

Table 51: Formulation of matrix transdermal patches of Piperine HCl

Ingredients	HF1 (1:2)	HF2 (1:3)	HF3 (1:4)	HF4 (1:4)	HE1 (1:(2:8)	HE2 (1:(1:9)	HE3 (1:(2:8)
Drug (Piperine HCl)	525	525	525	525	525	525	525
HPMC	1050	1575	2100	2100	1050	525	1050
EC	-	-	-	-	4200	4725	4200
Span 80 (%)	-	-	-	1	-	-	1
Propylene glycol (%)	3	3	3	3	3	3	3

Note: All the reading is in mg

Evaluation of Piperine HCl patches [4-5]

Physical appearance

All formulated transdermal patches were visually inspected for colour, clarity, entrapment of any air bubble, flexibility and smoothness, which on a large part determines patient acceptability of the patch and also therapeutic efficacy.

Thickness

Thickness of transdermal patch was measured by using digital thickness gauge (Muttato Japan). Thickness of rectangular patch (2x2 cm) was determined with a four different points and average thickness was taken. Same was performed for other patches also.

Weight variation

Weight variation study of transdermal patches was performed by individually weighing 10 randomly selected patches of sizes 4.52 cm2 on digital weighing balance and average weight was calculated. The individual weight of patches should not deviate significantly from the average weight.

Drug content

To determine the drug content of transdermal patch, known amounts of patch was cut from casted film and dissolve in chloroform in 100 ml volumetric flask and placed in shaking incubator for 4 h. The solution was filtered through membrane filter (0.45 µm) and 1 ml solution was taken and diluted with chloroform to 10 ml. The absorbance of solution was measured at 227 nm by using UV/visible spectrophotometer (Model-1700, Shimadzu, Japan). The chloroform was used as a blank. The average reading of three patches was taken as the content of drug in one patch.

Moisture content

To determine moisture contents of transdermal patches, they were weighed individually and kept in a desiccator containing calcium chloride at room temperature for 24 h. The transdermal patches were weighed repeatedly until they showed a constant weight.

Moisture uptake

Transdermal patches were kept in desiccators at room temperature for 24 h with silica gel and weighed (ws) and transfer to other desiccators to expose of 75% RH using a saturated solution of sodium chloride at 25^0C and patches were reweighed again and again, until a constant weight (wm) was obtained.

Flatness

Longitudinal strips from the 5 randomly selected transdermal films of each formulation were cut out. One from the center and one from the other side of patch. The length of each strip was measured and the variation in length because of the non-uniformity of flatness was measured. 0 % constriction was considered to be 100 % flatness.

Folding endurance

The folding endurance of patch was expressed as the number of folds (number of times the patch folded at the same place), either to break the preparation or to develop visible cracks. This test was performed to determine the stability of sample to withstand folding and brittleness. Folding endurance of patches was determined by repeatedly by folding a small strip of patches (approximately 2×2 cm) at the same place till it broke. The number of times patches could be folded at the same place, without breaking gave the value of folding endurance and it was recorded.

Tensile strength

The formulated patches were evaluated for its tensile strength to measure their mechanical properties. The tensile strength of the patches was determined by using a self designed assembly (Department of Pharmacy). Assembly consists of a pan hanged by using a strong thread and the other end of the thread was attached with the centre of the patch. The whole assembly was held like a beam balance and weights were kept on the pan. Weights required to break the patch was noted.

pH Measurement

The pH of the film-forming solutions was determined using a pH meter which was calibrated before use with buffered solutions at pH 4, 7 and 10.[55]

***In Vitro* drug release studies**

The dissolution studies were performed by using dissolution rate test apparatus (USP-II) for the assessment of the release of the drug from the transdermal patches (3.14 cm2). The commercially available water impermeable adhesive backing membrane was placed over the patch and it was further fixed on glass slide (2.3x2.3 cm) using cyanoacrylate adhesive. Then the transdermal patch was covered with a dialysis membrane and placed at the bottom of dissolution vessels with the release surface facing upward. The apparatus was equilibrated to 32 ± 0.50C and the dissolution medium was 0.01 N HCl in PBS pH 7.4. The paddle speed was kept constant at 50 rpm. The samples were withdrawn at appropriate time intervals upto 24 h and analyzed by UV spectrophotometer at 328 nm. After each sampling, an equal volume of fresh dissolution fluid was added to the dissolution vessel to maintain a sink condition. [6-7]

Results and Discussion

The formulated patches were found to be clear, smooth, uniform, flexible in their physical appearance and free from entrapment of air bubble. The moisture content and moisture uptake of various formulations showed that with increasing in concentration of polymer both percentages of moisture content and moisture uptakes were increases. The percentage of moisture contents and moisture uptake were found

in the range from 1.14 ± 0.23 to 5.29 ± 0.97 and 2.10 ± 0.20 to 8.46 ± 0.19 respectively.

The results indicated that the hydrophilicity of the polymers is directly proportional to the percent of moisture contents and moisture uptake. The low percentage of moisture content in formulations could help them to remain stable and prevents them from being completely dried. Also, low moisture uptake protects the material from microbial contamination and bulkiness of the patch.

Table 2: Physiochemical evaluation of Piperine HCl transdermal Patches

FC	Thickness (mm)	Weight Variation (mg)	Drug Content (%)	Flatness	Folding Endurance	Tensile Strength (kg/mm2)	pH
HF1	0.251 ± 0.017	168.61 ± 2.33	94.03 ± 1.56	100	42±2.43	0.351 ± 0.03	5.9
HF2	0.25 ± 0.011	163.40 ± 1.89	95.20 ± 1.11	100	41±4.82	0.400 ± 0.03	6.2
HF3	0.262 ± 0.014	168.61 ± 2.33	95.20 ± 0.61	100	45±2.29	0.342 ± 0.03	5.9
HF4	0.257 ± 0.012	164.20 ± 2.08	96.64 ± 1.04	100	44±4.85	0.344 ± 0.05	6.0
HE1	0.232± 0.17	163.07±1.18	97.12±0.94	100	34±3.17	0.371±0.04	6.1
HE2	0.236 ± 0.027	165.76± 2.76	96.64 ± 1.04	100	36±4.73	0.360 ± 0.07	5.4
HE3	0.238 ± 0.031	171.01 ± 2.77	95.20 ± 0.61	100	37±4.23	0.312 ± 0.03	5.8

The dissolution studies of transdermal patches are very crucial to ensure sustained release pattern. One need to maintain concentration of drug on the stratum corneum surface consistently and subsequently morrmke than concentration of drug in the plasma to obtain a constant permeation drug release rate. The modified paddle over disc assembly using 20% methanol in PBS pH 7.4 as a dissolution medium at 32 ± 0.50C was used to conduct dissolution studies. The result of *in vitro* dissolution studies of prepared transdermal patches are presented in Table 3 and Figure 2.

Table 3: *In vitro* dissolution profile of Piperine HCl transdermal patches

Time (h)	Cummulative % of drug release						
	HF1	HF2	HF3	HF4	HE1	HE2	HE3
0	0	0	0	0	0	0	0
1	2.10	2.71	3.18	3.16	4.62	4.32	3.78
4	6.28	7.29	8.38	8.22	11.78	10.90	9.29
8	8.38	9.51	12.29	13.83	16.77	15.48	14.22
12	9.29	11.77	20.76	27.49	36.28	35.83	29.41
16	12.18	14.42	23.72	31.54	49.62	43.61	36.26
20	18.29	21.39	31.65	35.65	51.66	49.36	39.75
24	32.38	38.61	41.29	46.83	56.39	55.26	48.61
28	41.29	47.39	51.52	55.62	61.48	58.81	56.66
32	61.28	65.39	68.81	71.44	78.38	74.33	72.38
36	73.10	74.41	75.77	76.34	83.83	80.43	78.48

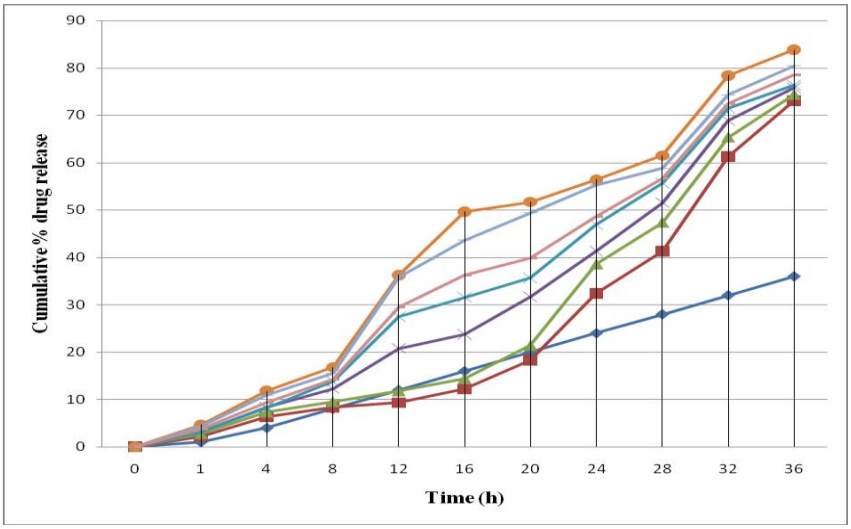

Fig. 2: Cumulative % drug release

Conclusion

These promising results showed the feasibility of delivering Piperine HCl through transdermal matrix patch. The developed transdermal patches of Piperine HCl may prove to be a better alternative to conventional dosage forms in allergy as revealed by the results.

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