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Formulation and Evaluation Transdermal Patch of Hesperidin

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ABSTRACT

The aim of the present study is to formulate and evaluate the transdermal patch of Hesperidin. In the present study, transdermal patch of Hesperidin were prepared by using HPMC E 5, Eudragit S 100 as a polymer, Dibutyl phthalate as a plasticizer and glycerin as a lubricant. Nine batches (F1-F9) were prepared by solvent evaporation method using methanol and chloroform in ratio 1:1 as a solvent. The prepared transdermal patches were evaluated on the basis of different parameters like weight, thickness, folding endurance, percent moisture content, drug content , in vitro drug release study. To confirm the optimised batch, the data were computed in design expert software. And it was concluded that the prepared formulation F5 batch showed highest percent of drug release.

Keywords: Transdermal drug delivery, Design expert, HPTLC, Hesperidin.

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INTRODUCTION

Transdermal delivery system allows delivery of drug into the systemic circulation via skin layers at a controlled rate. These systems are easy to apply and remove. This approach of drug delivery is more pertinent in case of chronic disorders which require long-term dosing to maintain therapeutic drug concentration [1-2]. The transdermal route of drug delivery has gained popularity because large number of drugs can be delivered by this route to treat various diseases. Transdermal patches were first developed in the 1970s and the first was approved by the FDA in 1979 for the treatment of motion sickness [3].

Hesperidin is the major flavanone glycoside in sweet orange and lemon obtained as an abundant product of Citrus cultivation. Hesperidin has antioxidant, anti-inflammatory, cholesterol-lowering properties. It is known to reduce permeability and fragility of capillary walls. The bioavailable formulations of this bioflavonoid may prove to be an effective treatment for many blood vessel disorders like haemorrhoid, varicose veins, venous stasis etc. In all these diseases proper therapeutic treatment is not widely available. As a result patient suffers until the disease aggravates to the level of surgery. For improving therapeutic efficacy of hesperidin it is required to identify the problems associated with its bioavailability in order to develop various formulations which can prove to be effective to treat various symptoms of venous diseases at early stage[4-7]. Hesperidin is reported to be unstable at gastric pH where it undergoes hydrolysis into aglycone hesperidin and enzymatic degradation. Hesperidin has a lower bioavailability by its traditional oral route (tablet, film coated tablet) and its gastric absorption is greatly affected by food intake and high acidic pH in the GI track[8]

MATERIAL

Extract of citrus peel, HPMC, Eudragit S 100, Dibutyl phthalate, Glycerin, Potassium dihydrogen orthophosphate, Sodium hydroxide.

METHOD[9-10]

In the present study patch of Hesperidin were prepared by using solvent evaporation technique and evaluated for various parameters. Transdermal patch of hesperidin were prepared by using HPMC E5 and Eudragit as a polymer, Dibutyl phthalate as a plasticizer, glycerin as a lubricant, Chloroform:Methanol as a solvent. Composition of formulation decided as per 3^2 factorial design. Concentrations of HPMC E5 and Eudragit S-100 taken as independent variables at three levels code as (-1,0,+1) respectively (Table 2). Composition of all formulations as per factorial design shown (Table no-3). Polymer HPMC E5 and Eudragit S 100 were mixed in a solvent mixture of

chloroform and methanol (ratio - 1:1) and stirred on magnetic stirrer till a clear liquid solution is obtained. Specified quantity (500mg) of Citrus peel extract is added in this solution and this mixture was stirred again and dibutyl phthalate was added as a plasticizer. This mixture was stirred for 10 mins and then sonicated in bath sonicator for 15 mins. The mixture was poured in to petri plates which is lubricated with glycerin of and mixture were kept for drying at room temperature for 24 hrs.

Table 1: Coded factor levels for optimization runs of 3^2 factorial

Formulation Codes	Trial Number	Coded Factor Levels	
		HPMC E5	Eudragit S 100
F1	1	-1	-1
F2	2	-1	0
F3	3	-1	+1
F4	4	0	-1
F5	5	0	0
F6	6	0	+1
F7	7	+1	-1
F8	8	+1	0
F9	9	+1	+1

Table 2: Composition of all formulations as per design of experiments

Formulation	Contents				
	Citrus peel extract (mg)	HPMC E5 (mg)	Eudragit 100 (mg)	Dibutyl phthalate (mg)	Methanol: Chloroform
F1	500	300	300	120	1.1
F2	500	300	400	120	1.1
F3	500	300	500	120	1.1
F4	500	450	300	120	1.1
F5	500	450	400	120	1.1
F6	500	450	500	120	1.1
F7	500	600	300	120	1.1
F8	500	600	400	120	1.1
F9	500	600	500	120	1.1

Evaluation of transdermal patches[11-19]

Weight uniformity

The weight of 1 patch (1 cm^2) from each batch was determined using an electronic balance.

Thickness

The thickness of the formulated patches was measured using by using Vernier Caliper and average thickness was calculated. The average thickness of all prepared transdermal patches ranged from 0.36 to 0.45 mm.

Surface pH

The surface pH of the patch was determined to ensure that it does not cause any irritation to the skin. pH was measured using a pH meter (Deluxe pH meter 101, India). Firstly the surface of the patch moistened and the electrode probe of the pH meter was placed in close contact with the wet surface of the patch and pH was recorded

Surface pH for formulation F1–F9 was found in the range 6.4 to 7.3 which is close to the skin pH (6.5-7.4) shown in (Table 4).

Swelling studies

swelling index study was performed to study the hydration characteristics of the film. 1 cm^2 patches were weighed separately (initial weight= W1) and placed in petri plates containing 6 ml distilled water. The swollen films were weighed individually at regular time intervals up to 25 minutes (Final weight = W2).

Swelling index of each system was calculated using the following formula:

Percentage moisture content = [Finnal weight- Initial weight/ Initial weight] ×100.

Swelling behaviour of patch as a function of time is illustrated in the following figure no-1.

Percent moisture content

The films were kept in desiccator for 24 hours and the moisture content was calculated by the following formula

Percentage moisture content = [Initial weight- Final weight/ Final weight] ×100. The percent moisture content was found to be in range 2.05% - 4.55%. This shows that the moisture content was between the limits.(Table 3).

Folding endurance

The patches were repeatedly folded in the same place 300 times or until they broke, which ever was less, to determine their folding endurance. All formulations shown folding endurance values ranging from 200-300, which indicates the film is highly flexible. (Table 4).

Drug content

The drug content was determined using HPTLC. Patches of 1 cm^2 were cut and placed in test tubes containing 1 ml of DMSO and 9 ml methanol for 24 hrs to extract the drug.

This solution was filtered and further diluted with methanol and analysed by HPTLC at a wavelength of 283 nm. Drug content was calculated using equation obtained from the

standard calibration curve of Hesperidin. The drug content ranged from 97.00 % to 98.63 %.(Table 4).

In-vitro drug release studies

The release pattern of hesperidin from the patches was determined using a Franz diffusion cell and Nylon 66 membrane (pore size 0.45µm), 8.0 ml of phosphate buffer pH 7.4 was placed in the receiver compartment of the Franz diffusion cell. Patches of 1 cm² area were placed on membrane which was positioned between the donor and receiver compartment. The temperature of the system was maintained at 37.0 ± 0.5°C and the buffer was continuously stirred using a magnetic bead for uniform distribution of the diffused drug. 1 ml of sample were withdrawn at 1 hour time intervals up to 6 hours and analysed by HPTLC using mobile phase Ethyl acetate: methanol: water at a wavelength of 283 nm.

F5 batch showed highest diffusion of Hesperidin within 6 hours (Fig 4).

Fig 3: Franz Diffusion cell Setup

Optimization

Optimization of the transdermal patches was done using a 3^2 factorial design by taking the concentrations of HPMC E5 and Eudragit S-100 as the independent variables X_1 and X_2 respectively and flux and folding endurance as the responses variables Y_1, Y_2 respectively. (Table 6)

Analysis of experimental results

Analysis of experimental results was done by using the Design of Expert. After filling the data in the design, quadratic model were suggested to run the design. The regression coefficient, standard deviation, F-value and P-value for flux, and folding endurance were obtained from ANOVA.

Effect of formulation variables on flux

The observed flux, from permeation studies, for all the batches was found to be in the range 14.2-19.05 (µg/h/cm²)

The Model F-value of 39.14 implies the model is significant. There is only a 0.62% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case B, A^2, B^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.ve a positive effect on the flux in combined form.

The final equation of flux in terms of coded factors is as follows:

Flux = +15.37-0.1233 A+1.65 B+ -0.0350 AB+ -1.03 A^2B +1.85 AB^2

Effect of formulation variables on folding endurance

Folding endurance is an important property which ensures proper flexibility to the patch and resistance to the external stress and rough handling.

The Model F-value of 29.01 implies the model is significant. There is only a 0.96% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, B, B^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

Validation of optimum design

To obtain an optimum formula and justify the validity of the optimization, design expert is used. The selection criteria used had flux in the range 14-19 µg/hr/cm² , and folding endurance in the range 200 – 300 folds. The predicted and observed values were found to be in good agreement for all the three responses. Formulation F5 had the composition closest to the validation batches (HPMC E5 – 450 mg and Eudragit S100 – 400 mg) was selected as the optimum formulation.

RESULT AND DISCUSSION

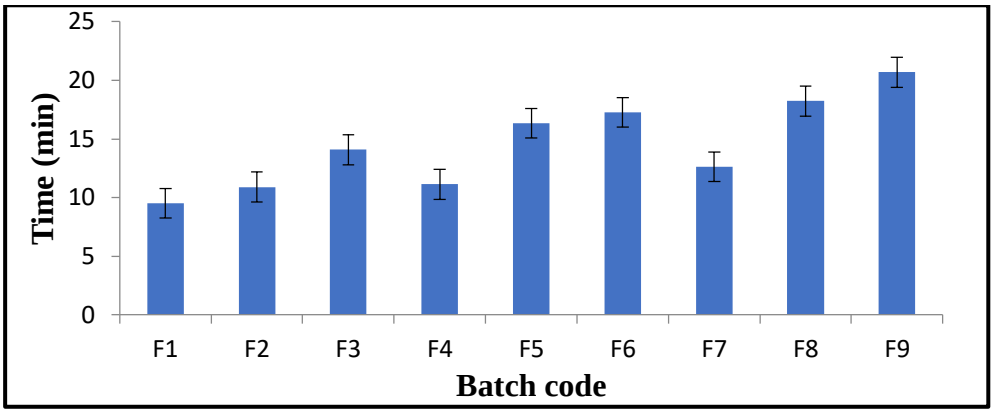

Figure 1:- Swelling Study

Table-3 Percent moisture content

Sr. No.	Formulations	Initial Weight gm	Final weight gm	% Moisture Content
1	F1	0.1805	0.1755	2.84
2	F2	0.2106	0.2054	2.53
3	F3	0.1959	0.1885	3.92
4	F4	0.2010	0.1930	4.14
5	F5	0.2134	0.2079	2.64
6	F6	0.2002	0.1920	4.27
7	F7	0.1994	0.1909	4. 45
8	F8	0.1831	0.1760	4.03
9	F9	0.1934	0.1864	3.75

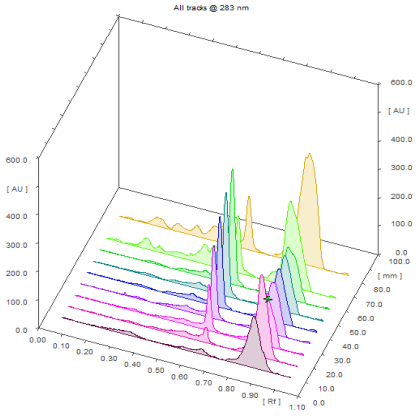

Fig 2:Densitogram for assay of patch

Track 1 Blank, 2-6 Marker linearity 200-1000 ng/band,7-Extract 20000 ng/band, 8 Patch 250 ng/band.

Table-4 Evaluation results of F1-F9 batches

Batch	F1	F2	F3	F4	F5	F6	F7	F8	F9
Swelling index	9.52 ±0.14	10.9 ±0.08	14.09 ±0.06	11.13 ±0.07	16.33 ±0.0.04	17.27 ±0.02	12.62 ±0.06	18.24 ±0.06	20.69 ±0.02
Thickness (mm)	0.41 ±0.02	0.39 ±0.01	0.36 ±0.06	0.40 ±0.06	0.38 ±0.04	0.40 ±0.02	0.42 ±0.04	0.41 ±0.02	0.44 ±0.05
Weight (mg)	0.18 ±0.04	0.19 ±0.03	0.20 ±0.05	0.21 ±0.03	0.21 ±0.02	0.20 ±0.06	0.19 ±0.04	0.18 ±0.03	0.19 ±0.02
Surface pH	6.56 ± 0.24	6.59 ± 0.52	6.57 ± 0.08	6.58 ± 0.06	7.0 ± 0.05	6.52 ± 0.13	6.55 ± 0.31	6.59 ± 0.61	6.54 ± 0.05
Folding Endurance	244 ± 4	233 ± 5	210 ± 6	229 ± 11	275 ± 3	249 ± 3	254 ± 4	237 ± 7	268 ± 2
Drug content (%)	97.63 ± 8.29	97.96 ± 5.70	96.41 ± 4.28	90.64 ± 9.11	98.01 ± 7.49	96.82 ± 9.50	95.03 ± 8.72	96.21 ± 4.61	95.81 ± 4.37
Moisture content (%)	2.84 ± 0.5	2.53 ± 0.5	3.92 ± 0.5	4.14 ± 0.5	2.64 ± 0.5	4.27 ± 0.5	4.45 ± 0.5	4.03 ± 0.5	3.75 ± 0.5

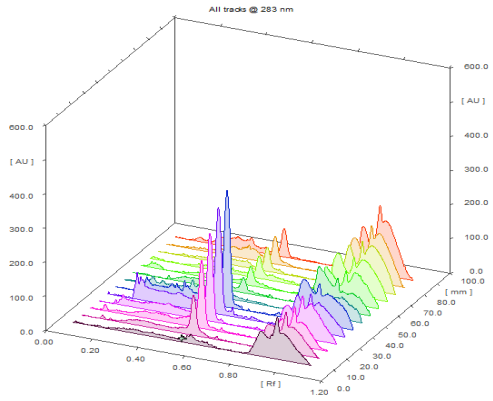

Fig 4: Densitogram for % drug release (F5 batch)

Table 5: % drug release data for F5 batch

Time (hrs)	Area	Concentration	Amount release	% Amoumt release
0	0	0	0	0
1	1005.5	1.75	0.14	1.80
2	1155.0	24.39	1.95	25.02
3	1299.5	46.12	3.69	47.31
4	1395.2	60.61	4.85	62.17
5	1489.9	74.86	5.99	76.79
6	1598.9	91.32	7.31	93.66

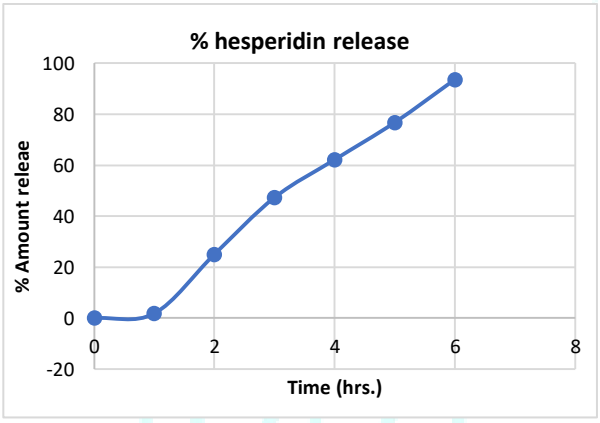

Fig-5: % Drug release graph of F5 batch

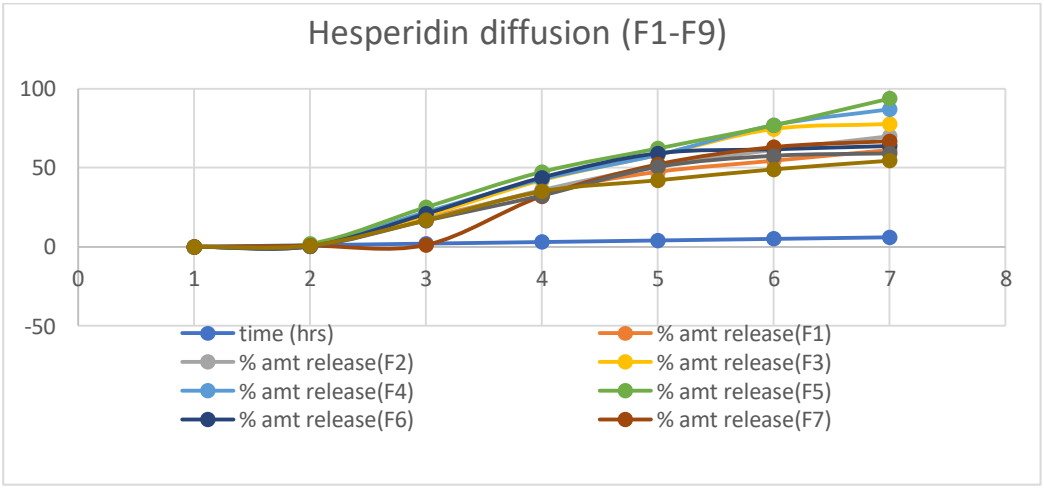

Fig-6: Hesperidin diffusion from all batches.

Table 6: Flux and folding endurance of optimised batch

Batch no.	Variable levels in coded form		Responses	
			Flux (µg/h/cm²)	Folding Endurance
	X_1	X_2	Y_1	Y_3
F1	-1	-1	14.2	244
F2	-1	0	17.5	233
F3	-1	+1	18.0	210
F4	0	-1	14.6	229
F5	0	0	19.05	275
F6	0	+1	14.23	249
F7	+1	-1	15.52	254
F8	+1	0	14.87	237
F9	+1	+1	15.23	268

Table 7: Response for flux

Response	F-value	P-value	SD	R^2
Folding endurance	29.01	0.0500	4.66	0.9797

Table 8: Response for folding endurance

Response	F-value	P-value	SD	R^2
Flux	39.14	0.0500	0.361	0.9849

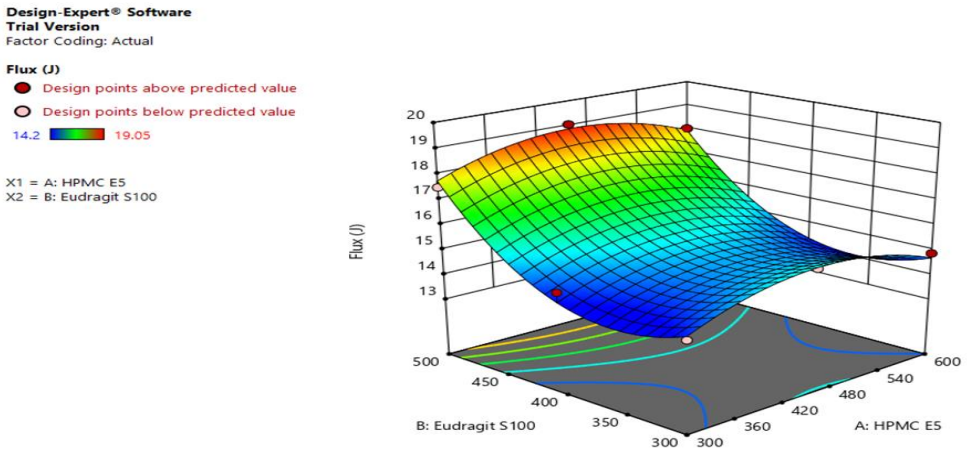

Fig 7: Plot for Flux.

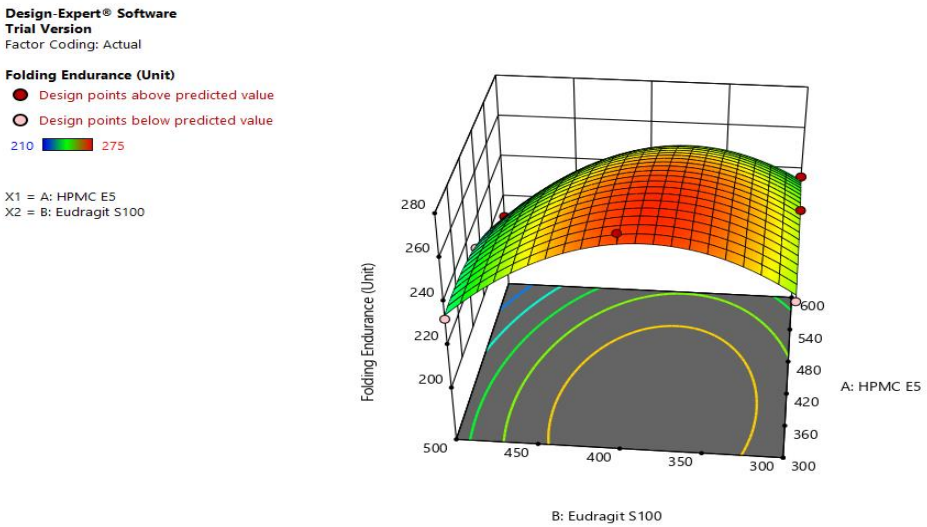

Fig 8: Plot for Folding Endurance

CONCLUSION

The objective of the study was to formulate and evaluate transdermal patches of Hesperidin. Transdermal patches were formulated using a combination of two polymers, HPMC E5 and Eudragit S 100 by solvent evaporation method. Optimization was done using a 3^2 factorial design taking concentrations of HPMC E5 and Eudragit S-100 as independent variables at three levels code as (-1,0,+1) respectively. Formulated patches were subjected to evaluation tests such as measurement of thickness, surface pH, swelling index, drug content, folding endurance,% drug release. Results showed that patches were prepared with uniform thickness which ensured uniformity of content. Surface pH of all patches was in the range 6.5 to 7.4 which is close to skin pH, hence, no skin irritation was expected. Drug content was found to be in the range 97.00%-98.63 %. In-vitro drug release studies were performed using Nylon 66 mebrane by Franz diffusion cell . Flux for all patches was calculated from the results of In-vitro drug release studies. Effect of formulation variables on the two response variables was studied. Flux and Folding Endurance were chosen as the response variables. The data obtained by experimental design was evaluated using Design expert. 3D response surfaces curves were constructed to study the effect of two independent variables. Batch F5 showed high folding endurance value (275) while others had not less than 200 which indicate that they have good flexibility. It also showed the high % drug release.

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