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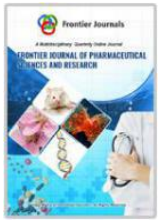

Original Research Paper

FORMULATION AND EVALUATION OF METFORMIN TRANSDERMAL PATCHES

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ABSTRACT

The objective of present study was to develop matrix type transdermal therapeutic systems of Metformin using various hydrophilic and hydrophobic polymers as matrix formers. Results revealed that prepared patches showed good physical characteristics, no drug-polymer interaction and no skin irritation was observed. The in vitro release study revealed that F4 formulation showed maximum release in 12 hrs. Formulation F4 was subjected for accelerated stability studies. The F4 formulation was found to be stable as there was no drastic change in the Physico-chemical properties of the patches, which was also confirmed by FTIR. Thus conclusion can be made that stable transdermal patches of Metformin has been developed. F1, F2, F3, F4 formulations showed highest cumulative percentage drug release of 92.63%, 89.35%, 88.98%, 96.28% were obtained during in vitro drug release studies after 12 hrs. The release of Metformin appears to be dependent on lipophilicity of the matrix. Moderately lipophillic matrices showed best release. The predominant release mechanism of drug through the fabricated matrices was believed to be by diffusion mechanism. Based upon the in vitro dissolution data the F4 formulation was concluded as optimized formulation.

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1. INTRODUCTION :

Transdermal drug delivery system (TDDS) is topically administered medicaments in the form of patches or semisolids (gels) that deliver drugs for the systemic effects at a predetermined & controlled rate. [1,2] Transdermal drug delivery system has many advantages over conventional modes of drug administration, it provides a controlled rate release of medicaments, it avoids hepatic metabolism, ease of termination and long duration of action. Metformin hydrochloride, an oral anti-diabetic drug frequently used as 1st line drug of choice in treatment of type 2 diabetes, particularly in overweight and obese people and those with normal kidney function.[3,4] Metformin is anti-hyperglycaemic and it does not cause insulin release in the pancreas. Metformin reduces glucose levels primarily by decreasing hepatic glucose production and by increasing insulin action in muscle and fat. Metformin is absorbed mainly from the small intestine and does not bind to plasma proteins. Obstacle to more successful use of metformin HCl therapy

is the high incidence of gastro-intestinal side effects and rapid first pass metabolism.[5] These problems can be overcome by the preparation of transdermal patches of Metformin Hydrochloride.

2. METHODOLOGY

Materials

Metformin was collected as a gift sample from Hetero labs, Hyderabad and various excipients like sodium alginate, ethylcellulose and hydroxyl propyl methyl ellulose were purchased from AR chemicals, Hyderabed.

Methods

Formulation design

Preparation of transdermal patches:

Transdermal patches containing metformin were prepared by the solvent evaporation technique. The drug metformin was dissolved insuitable solvent . Polymers HPMC k 15 M, Ethylcellulose and sodium alginate were taken. These polymeric solution kept under magnetic stirrer after 1 hr get viscous solution. After that drug add into the polymeric solution. Sufficient care was taken to prevent the formation of lumps. Glycerine was taken as a plasticizer and permeation enhancer like DMSO, and added to the mixture and mixed well. It was set aside for 2 hours to exclude any entrapped air and was then transferred into a previously cleaned petriplate (40cm^2), drying of patches was carried out in vacuum oven at room temperature. Dried patches were packed in aluminium foil and stored in a desiccator for further evaluation

Table-1: Formulation Design of Metformin Transdermal Patches

S. No	F. no	Ingredients (gms)			
		Drug (mg)	HPMC k5 M	Ethyl cellulose	Sodium alginate
1	F1	100	1000	-	-
2	F2	100	-	1000	-
3	F3	100	-	-	1000
4	F4	100	500	500	-
5	F5	100	-	500	500
6	F6	100	500		500

Fig-1:Metformin transdermal patch

Evaluation of transdermal formulation[9,10]

Physico- chemical evaluation:

Physical appearance:

All the prepared transdermal films were observed for color, clarity, flexibility, and smoothness.

Folding endurance:

Folding endurance of the patches was determined by repeatedly folding at the same place till it broke. The number of times the patch could be folded at the same place without breaking is the folding endurance. This was repeated on all the patches for three times and the mean values plus standard deviation was calculated.

Thickness of the film:

The thickness of each film was measured by using screw gauze. The thickness was measured at three different places on each film and the average thickness of the film was taken as the thickness of the film.

Weight uniformity:

The prepared patches are to be dried at 60^{0}C for 4hrs before testing. A specified area of 4.52 cm^2 of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Drug content:

The transdermal films (4.52 cm^2) were added to conical flask containing 100 ml of phosphate buffer pH 7.4. This was then stirred with magnetic bead at 400 rpm for 2 hrs. The contents were filtered and the filtrate was analysed spectrophotometrically for drug content at 235 nm. Similarly a blank was prepared from transdermal films without drug.

Moisture absorption studies:

The films were weighed accurately and placed in a desiccators containing aluminium chloride to maintain 79.50% RH. After 3 days, the films were taken out and weighed. The percentage of moisture uptake was calculated using the following formula.

$$\text{Perentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture loss studies:

Three films were weighed individually and kept in a desiccator containing calcium chloride at 37^0C for 24 hrs. Then the final weight was noted when there was no further change in the weight of the patch. The percentage of moisture loss was calculated using the following formula.

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

***In vitro* release study:**

The *in-vitro* study of drug permeation through the Dialysis membrane was performed using a modified Franz type glass diffusion cell. The modified cell having higher capacity is (10 ml) is used to maintain sink condition. The samples were analyzed for drug content spectrophotometrically at 235 nm. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.

Percentage of drug release was determined using the following formula.

$$\text{Perentage drug release} = \frac{\text{Da}}{\text{Dt}} \times 100$$

Where, Dt = Total amount of the drug in the patch

Da = The amount of drug released

Stability studies:

Optimized medicated films were subjected to short term stability testing. The transdermal films were sealed in aluminium foils and kept in a humidity chamber maintained at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months as per ICH guidelines. Changes in the appearance and drug content of the stored films were investigated after storage at the end of every week.

3. RESULTS AND DISCUSSION

Evaluation of Transdermal formulation

Physical appearance:

The prepared patches were found to be uniform, smooth, flexible and homogenous.

Folding endurance:

The folding endurance numbers of all the Metformin patches are 287- 292. The folding endurance number gives the mechanical property of the patches, high folding endurance number indicate that has high mechanical property. The folding endurance number was increased with increasing the HPMC content. These results indicated that the patches would not break and maintain their integrity with general skin folding when applied.

Thickness of the film:

Thickness was changed from batch to batch in individual strips of medicated patch carry uniform thickness, which indicates that total medicated patch carry uniform thickness.

Weight uniformity:

The mean weights of all the prepared patches. The F4 formulation patches showed maximum weight.

Drug content:

The drug content analysis of the prepared formulations have shown that the process employed to prepare the patches was capable of giving uniform drug content with minimum batch variability. All the patches were found to have drug content in the range of 90 - 101%. So the method employed i.e. solvent evaporation method is satisfactory for the preparation of Metformin transdermal patches.

Table-2: Physicochemical evaluation of patch

Formulation code	Weight (mg)	Thickness (µm)	Folding endurance	Drug content (%)
F1	251	200	292	101
F2	245	213	290	97.39
F3	265	214	288	92.45
F4	312	219	287	98.86

***In vitro* release study:**

Phosphate buffer pH 7.4 was used as medium for the release studies. The drug release profiles of Metformin patches containing different ratios of polymers HPMC, Ethyl cellulose and sodium alginate. It was cleared from the release profiles of formulations, that the drug release was governed by polymer nature and content. The release was decreased as the concentration of hydrophobic polymer increase.

Table-3: *In vitro* drug release profiles of Metformin transdermal patch (F1-F4)

Time (hrs)	% Cumulative drug released			
	F1	F2	F3	F4
0	0	0	0	0
1	13.56	10.65	13.48	11.79
2	22.72	19.27	26.50	24.67
3	34.94	25.4	31.71	26.627
4	41.16	30.28	34.36	30.18
5	47.88	33.63	40.25	36.71
6	51.33	37.46	41.07	39.20
7	53.46	41.60	45.53	43.76
8	62.87	49.35	52.15	50.92
9	69.01	53.61	60.71	55.08
10	76.93	63.49	70.30	69.48
11	88.98	71.26	79.96	82.59
12	92.63	89.35	88.98	96.28

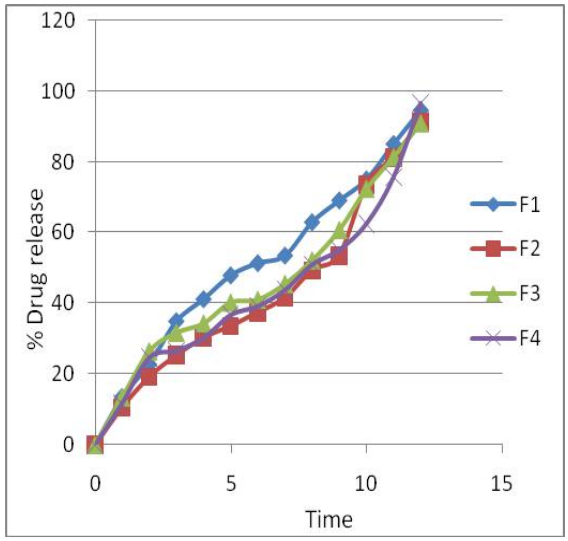

Fig-2: Drug release formulations

Stability studies:

Optimized formulations F4 was selected for accelerated stability studies as per ICH guidelines. The patches were observed for color, appearance and flexibility for a period of three months. The folding endurance, weight, drug content, % cumulative drug release of the formulation was found to be decreasing. This decrease may be attributed to the harsh environment (40^0C) maintained during the studies.

Table-4: Stability studies of optimized formulations at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months

Time in days	Drug content (%)	Folding endurance	Physical appearance	% Cumulative drug release
0	98.86	285	No change in color	96.28
30	98.78	281	Slight yellowish color	96.12

4. CONCLUSION

Results revealed that prepared patches showed good physical characteristics, no drug-polymer interaction and no skin irritation was observed. The F4 formulation was found to be stable as there was no drastic change in the Physico-chemical properties of the patches, which was

also confirmed by FTIR. Thus conclusion can be made that stable transdermal patches of Metformin has been developed. F1, F2, F3, F4 formulations showed highest cumulative percentage drug release of 92.63%, 89.35%, 88.98%, 96.28% were obtained during *in vitro* drug release studies after 12 hrs. The release of Metformin appears to be dependent on lipophilicity of the matrix. Moderately lipophillic matrices showed best release. The predominant release mechanism of drug through the fabricated matrices was believed to be by diffusion mechanism. Based upon the *in vitro* dissolution data the F4 formulation was concluded as optimized formulation.

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