Formulation and evaluation of metoprolol tartrate transdermal drug patches

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Abstract
The objective of present study was to develop matrix type transdermal therapeutic systems of Metoprolol tartrate using various such as Sodium alginate and HPMC polymers as matrix formers. Results revealed that prepared patches showed good physical characteristics and no drug-polymer interaction was observed. The in vitro release study revealed that F3 formulation showed maximum release in 8 hrs. Formulation F3 was subjected for accelerated stability studies. The F3 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 patch of Metoprolol tartrate has been developed. F3 formulation showed highest cumulative percentage drug release of 93.97 % were obtained during in vitro drug release studies after 8 hrs. 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 F3 formulation was concluded as optimized formulation.

Keywords: Metoprolol tartrate, Sodium alginate and HPMC, solvent casting technique, in vitro drug release studies

Introduction
Transdermal drug delivery system (TDDS) is a widely accepted means of drug delivery, and transdermal patches are devised to treat various diseases [1]. TDDS are extended release dosage forms that can offer a stable systemic drug concentration and avoid first pass metabolism. They can even avoid gastrointestinal problems associated with drugs and low absorption [2]. These therapeutic advantages reflect the higher marketing potential of TDDS [3]. Transdermal drug delivery system is a self-contained delivery use for topical application in the form of multilaminated adhesive patch which gives a specific dose of drug at a predetermined rate and controlled the rate of drug release through skin [4] Metoprolol tartrate, a beta adrenoreceptor-blocking agent used in the treatment of cardiovascular disorders. The drug has a short half-life due to extensive first pass metabolism [5]. The Transdermal drug delivery system designed by various methods such as transdermal patches includes matrix, micro reservoir, reservoir, adhesive, and membrane matrix hybrid. Matrix type transdermal patches are most popular as they are easy to construct [6]. The Metoprolol tartrate transdermal patch in this paper also developed by using the Matrix type of transdermal drug delivery system [7].

Materials
Metoprolol tartrate was obtained from Hetero Labs, HYD. HPMC and Eudragit were procured from Synpharma Research Labs, Hyderabad, and other chemicals the reagents used were of analytical grade.

Methodology
Compatibility studies of drug and polymers [8]
In the formulation of Metoprolol tartrate patch formation, API and Excipient may interact as they are in close communication

with each other, which could lead to the instability of drug. FT-IR spectroscopy was employed to ascertain the compatibility between Metoprolol tartrate and the selected polymers. The pure drug and drug with excipients were scanned separately.

Formulation design [9]

Preparation of transdermal patches

Transdermal patches containing Metoprolol tartrate were prepared by the solvent casting evaporation technique. The drug Metoprolol tartrate was dissolved in suitable solvent. Polymers HPMCK 4M, Eudragit RL 100 were taken in a boiling tube, to this add Metoprolol tartrate drug which was previously dissolved in methanol. PEG was taken as a plasticizer, 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 petri plate (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 Metoprolol tartrate Transdermal Patches

Formulation Code	DRUG (MG)	HPMC K4M	EUDRAGIT RL100	PEG	DMSO
F1	50	100	-	1ml	0.1ml
F2	50	200	-	1ml	0.1ml
F3	50	-	100	1ml	0.1ml
F4	50	-	200	1ml	0.1ml

Evaluation of transdermal formulation [10, 11, 12]

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 Patch

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 weight.

Drug content

The formulated transdermal patch were assayed for drug content in each case. Three patches from each formulation were assayed for content of drug. Each formulation was casted in triplicate and one film from each was taken and assayed for content of drug.

Moisture absorption studies

The patches 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 patches were weighed individually and kept in a desiccator containing calcium chloride at 37^{0}C 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* drug release studies [13]**

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. 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 [14]

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 1 month 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.

Results and Discussion

FT-IR Spectrum of Metoprolol tartrate

FT-IR Spectra of Metoprolol tartrate and polymers were recorded. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Metoprolol tartrate and polymers. It also confirmed that the stability of drug during process.

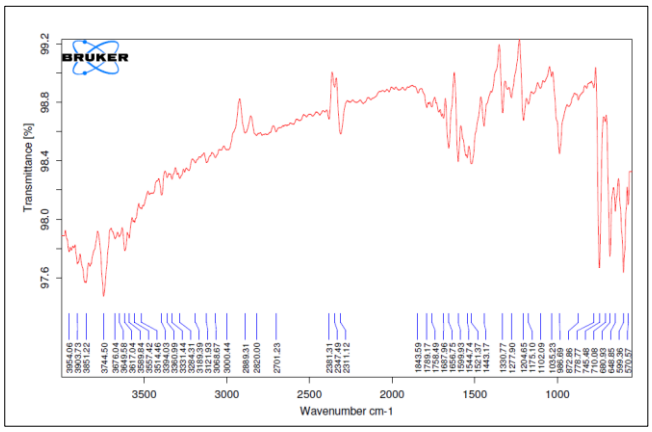

Fig 1: FTIR Studies of Metoprolol tartrate

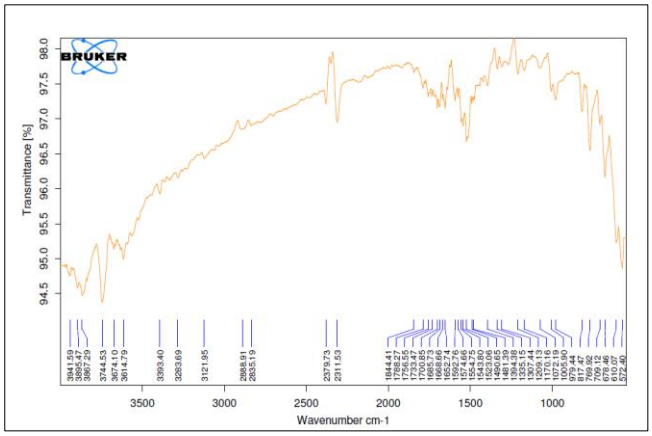

Fig 2: FTIR Studies of Physical mixture of drug and excipients

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 Metoprolol tartrate patches are 183 – 190. 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 Eudragit content. These results indicated that the patches would not break and maintain their integrity with general skin folding when applied.

Thickness of the patch

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 weights are in the range of 230.8-246.2. The F3 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 89 – 100%. So the method employed i.e. solvent evaporation method is satisfactory for the preparation of Metoprolol tartrate transdermal patches.

Table 3: Physicochemical evaluation of Metoprolol tartrate patches

Formulation code	Weight (mg)	Thickness (mm)	Folding endurance	Drug content (%)	% moisture loss	% moisture absorption
F1	246.2	0.90	188	90.13	7.96	8.32
F2	230.8	0.89	189	92.58	7.85	8.16
F3	239.1	0.91	190	95.14	7.51	8.20
F4	242.9	0.88	183	93.18	7.32	8.15

In vitro release study

Phosphate buffer pH 7.4 containing 0.5% SLS was used as medium for the release studies and good linearity was observed in the plotted standard graph with a correlation coefficient of 0.998. The drug release profiles of Metoprolol tartrate patches containing different ratios of polymers sodium alginate and HPMC. It was cleared from the release profiles of formulations, that the drug release was governed by polymer nature and content.

Table 4: *In vitro* drug release profiles of Metoprolol tartrate transdermal patch (F1-F4)

Time	F1	F2	F3	F4
0	0	0	0	0
1	12.58	13.49	13.86	14.13
2	24.59	24.59	25.89	25.92
3	35.83	38.36	32.41	37.57
4	40.92	50.28	45.63	47.18
5	53.48	55.19	52.94	57.83
6	66.92	68.17	63.58	70.16
7	73.86	81.46	82.90	82.42
8	91.59	92.90	93.97	90.12

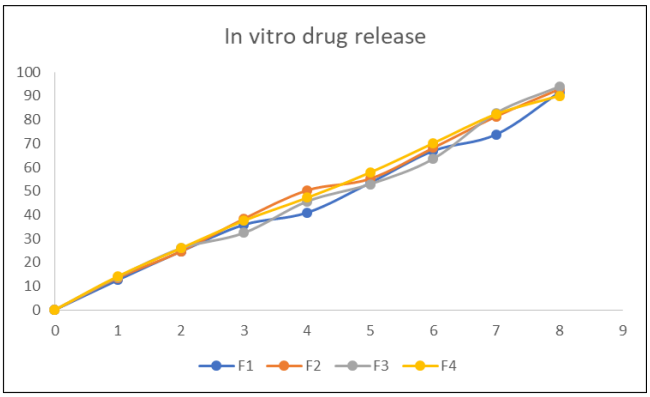

Fig 3: Drug release for all formulations

Stability studies

Optimized formulations F3 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	95.14	190	No change in color	93.97
90	95.02	190	Slight yellowish color	93.10

Conclusion

The objective of the present study was to develop a transdermal matrix patch of Metoprolol tartrate and assess its feasibility for transdermal application. Low dose maintenance therapy of Metoprolol tartrate can reduce potential side effects and improved patient compliance which are more common with conventional drug delivery. Transdermal patches of Metoprolol tartrate were formulated by solvent casting technique. The I.R spectra let out that, there was no interaction between polymers and drug. All the polymers used were compatible with the drug. Characterization parameters like thickness, tensile strength, folding endurance, percentage moisture loss indicates that films were mechanically stable. Percentage weight variation and content uniformity were found to be uniform in all the films. Among all the formulations, the formulated patch F_3 showed 93.97 % of release. Throughout the *in-vitro* release studies, the films remained intact without any disintegration. All the patches were found to be stable over the storage period and conditions tested. Overall study suggests that among the films prepared F_3 was found to show the best results. Hence it was considered as optimized formulation. Thus, optimized transdermal matrix patch of Metoprolol tartrate using polymers such as HPMC as permeation enhancers demonstrated their ability to give sustained release, because of excellent release and permeation of drug and its influence on calcium channel blocker. These promising results showed the feasibility of delivering Metoprolol tartrate through transdermal matrix patch. The developed transdermal patches of Metoprolol tartrate may prove to be a better alternative to conventional dosage forms in Hypertension.

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