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PREPARATION AND EVALUATION OF TAPENTADOL HYDROCHLORIDE TRANSDERMAL PATCHES

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Abstract:

The objective of present study was to develop matrix type transdermal therapeutic systems of Tapentadol Hydrochloride using various such as HPMC and Sodium alginate 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 F4 formulation showed maximum release in 8 hrs. Formulation F8was 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 patch of Tapentadol Hydrochloride has been developed. F4 formulation showed highest cumulative percentage drug release of 96.89 % were obtained during in vitro drug release studies after 8hrs. 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.

Key words: *Tapentadol Hydrochloride, HPMC, Sodium alginate, solvent casting technique, in vitro drug release studies.*

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INTRODUCTION:

Transdermal drug delivery system is a therapeutic system of defined surface area that delivers a predetermined amount of drug to the surface of intact skin at a preprogrammed rate. [1]These systems systemically provide drug at a predictable rate and maintain the rate for extended period of time, thus eliminating numerous problems associated with oral products such as, unpredictable or reduced bioavailability, enhanced first pass hepatic metabolism, relatively short residence time, dose dumping and dose inflexibility [2]. Also, transdermal drug delivery system provides continuous percutaneous administration of a drug at controlled rate which permits elimination of pulse entry into the systemic circulation, a phenomenon often associated with side effects. It also allows the option of rapidly terminating absorption of medication therapy, which needs to be interrupted [3]. Hence these systems can be designed to put in drugs, through intact skin at appropriate rates to maintain suitable plasma drug levels for therapeutic efficacy, without periodic fluctuations into plasma concentrations that would accompany toxicity or lack of efficacy. [4] Transdermal drug delivery is a potential alternative to the conventional therapy. Transdermal is a viable administration route for potent, low molecular weight therapeutic agents which cannot withstand the hostile environment of the gastrointestinal tract and are subject to considerable first-pass metabolism by the liver[5]. The choice of therapeutic agent is determined by a number of factors including the physicochemical properties of the drug, its interaction with the membrane and its pharmacokinetic properties. [6] The objective of present study was to develop matrix type transdermal therapeutic systems of Tapentadol hydrochloride using various Sodium alginate and HPMC polymers as matrix formers.

Drug excipient compatibility studies [7]

In the formulation of Tapentadol Hydrochloride 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 Tapentadol Hydrochloride and the selected polymers. The pure drug and drug with excipients were scanned separately.

MATERIALS AND METHODS:

Tapentadol was collected as a gift sample from Aurobindo ltd,Hyderabad and various excipients and polymers were purchased from Synpharma Research Labs, HYD

METHODOLOGY:

Formulation development:

Preparation of transdermal patches:

Transdermal patches containing Tapentadol Hydrochloride were prepared by the solvent casting evaporation technique. The drug Tapentadol Hydrochloride was dissolved in suitable solvent. Polymers HPMCK 4M, Sodium alginate were taken in a boiling tube, to this add Tapentadol Hydrochloride drug which was previously dissolved in methanol. PEG was taken as a plasticizer, and DMSO as a permeation enhancer 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. [8,9]

Table-1: Formulation Design of Tapentadol Hydrochloride Transdermal Patches

F. code	Drug (mg)	Sodium alginate	HPMC K4M(mg)	PEG (ml)	DMSO (ml)
F1	20	100	-	1	0.1
F2	20	200	-	1	0.1
F3	20	-	100	1	0.1
F4	20	-	200	1	0.1

Evaluation of transdermal formulation [10,11,12]:

Physical appearance:

All the prepared transdermal patches 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 patch was measured by using screw gauze. The thickness was measured at three different places on each patch and the average thickness of the patch was taken as the thickness of the patch.

Weight uniformity:
The prepared patches are to be dried at 60^0C 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 patches 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 patch from each was taken and assayed for content of drug.

Moisture absorption studies:
The patches were weighed accurately and placed in a desiccator containing aluminium chloride to maintain 79.50% RH. After 3 days, the patches 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 37^0C 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 Drug release studies:
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.

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

Where, Dt = Total amount of the drug in the patch
Da = The amount of drug released

Stability studies:
Optimized medicated patches were subjected to short term stability testing. The transdermal patches 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 patches were investigated after storage at the end of every week. [13]

RESULTS & DISCUSSION:

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

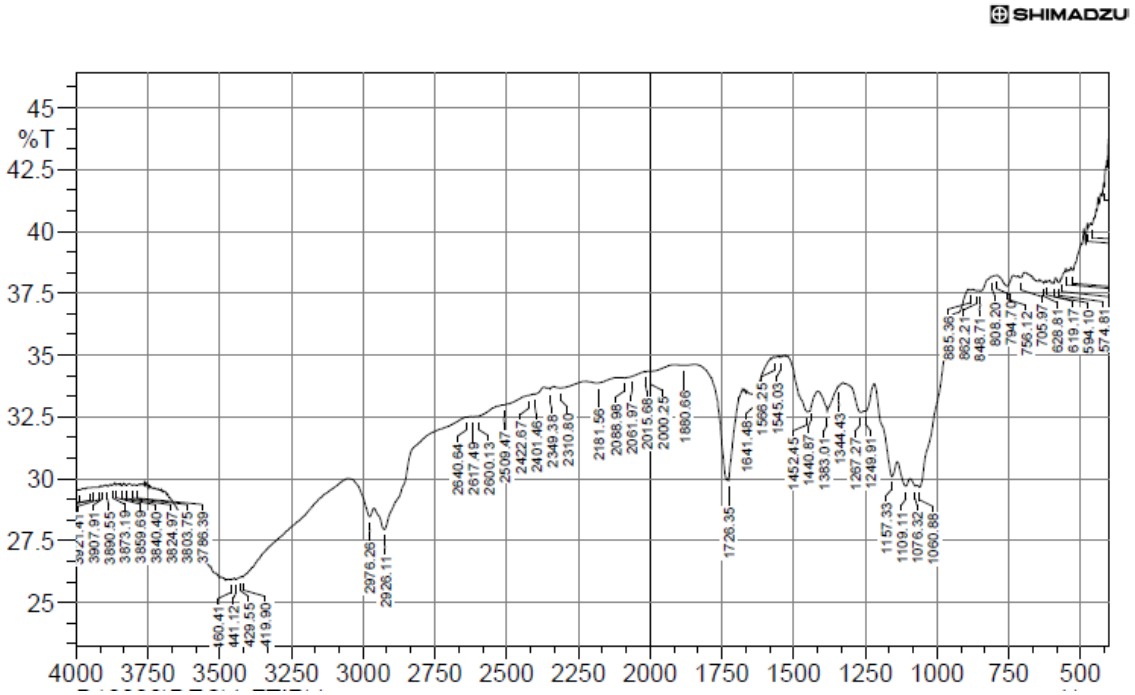

Fig-1: FTIR spectra of Tapentadol hydrochloride

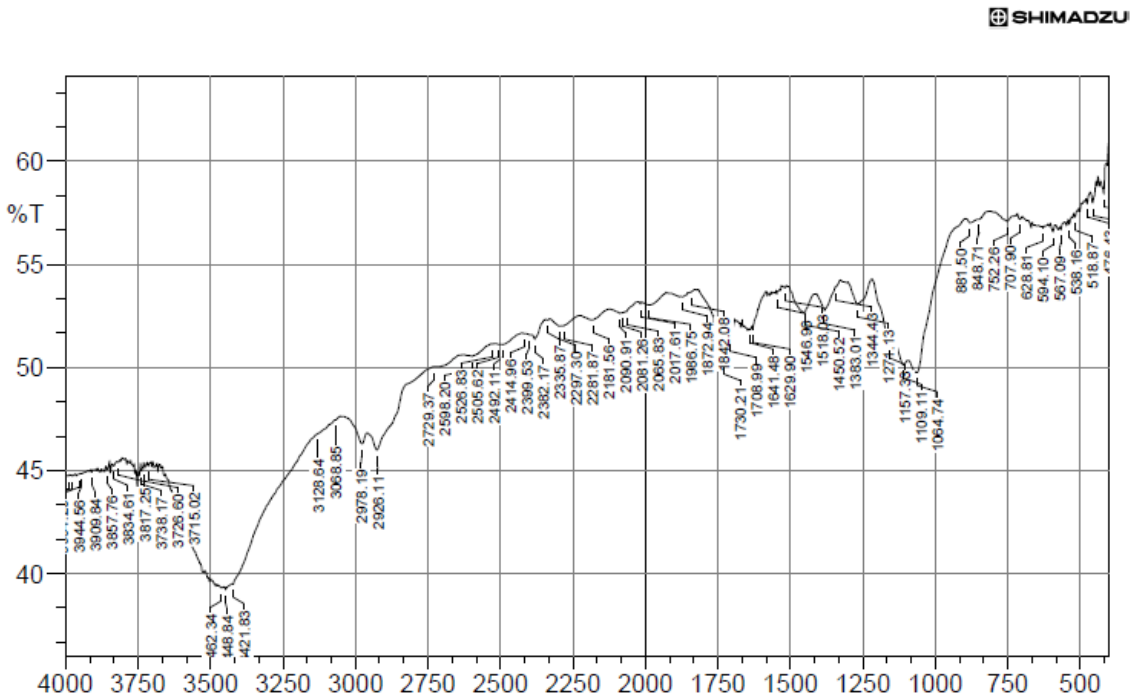

Fig-2: FTIR Spectra of physical mixture of drug and excipients

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of Pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks were obtained as above and as they were in official limits (±100 cm^{-1}) the drug is compatible with 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 Tapentadol hydrochloride patches are 178 – 190. The folding endurance number gives the mechanical property of the patches, high folding endurance number indicate that has high mechanical property. 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 158-165. The F4 formulation patches showed maximum weight.

Drug content:
The drug content analysis of the prepared formulations has 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 83.12 – 90.55%. So, the method employed i.e. solvent evaporation method is satisfactory for the preparation of Tapentadol hydrochloride transdermal patches.

Table 2: Physicochemical evaluation of Tapentadol hydrochloride patches

Formulation code	Weight (mg)	Thickness (mm)	Folding endurance	Drug content (%)	% Moisture loss	% Moisture absorption
F1	162	0.75	178	85.36	7.8	8.3
F2	158	0.80	183	83.12	7.6	8.1
F3	165	0.79	190	89.66	7.3	8.5
F4	159	0.77	182	90.55	7.9	8.4

***In vitro* release study:**
Phosphate buffer pH 7.4 was used as medium for the release studies and good linearity was observed in the plotted standard graph with a correlation coefficient of 0.996. The drug release profiles of Tapentadol hydrochloride patches containing different ratios of polymers HPMC, Sodium alginate. It was cleared from the release profiles of formulations, that the drug release was governed by polymer nature and content.

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

Time (hrs.)	F_1	F_2	F_3	F_4
0	0	0	0	0
1	29.12	28.20	27.11	28.09
2	32.45	35.30	33.11	31.45
3	42.80	45.32	43.76	49.90
4	52.63	54.65	53.23	59.70
5	68.21	69.28	62.11	65.16
6	73.35	78.55	75.22	71.22
7	88.26	83.10	85.16	80.26
8	94.25	92.99	96.89	92.50

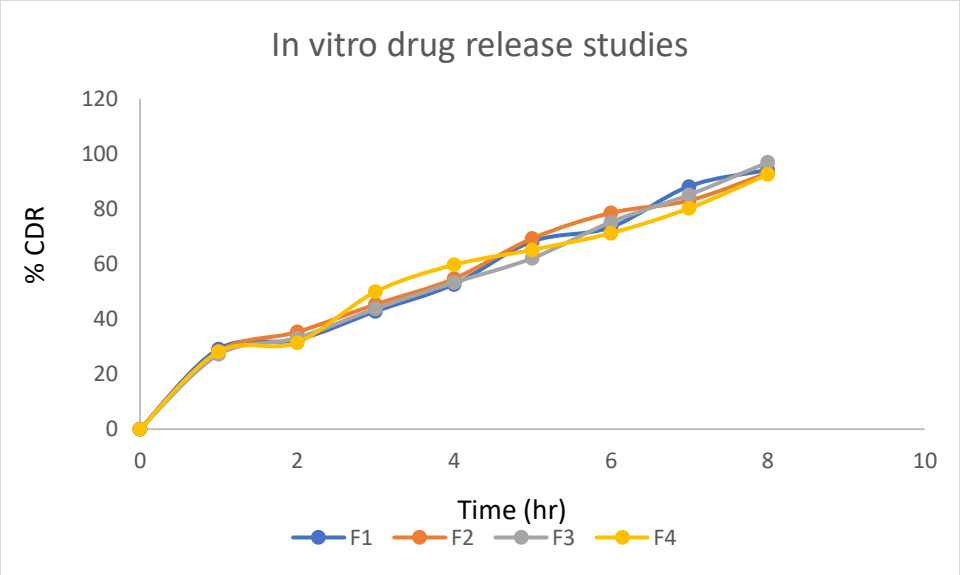

Fig-3: Drug release for all formulations

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	90.55	190	No change in color	96.89
90	89.69	189	Slight yellowish color	95.82

CONCLUSION:

The objective of the present study was to develop transdermal matrix patch of Tapentadol hydrochloride and assess its feasibility for transdermal application. Low dose maintenance therapy of Tapentadol hydrochloride has the capability to reduce potential side effects and improved patient compliance which are more common with conventional drug delivery. Transdermal patches of Tapentadol hydrochloride 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 patches were mechanically stable. Percentage weight variation and content uniformity were found to be uniform in all the patches. Among all the formulations, the formulated patch F4 showed 96.89 % of release. All the patches were found to be stable over the storage period and conditions tested. Overall study suggests that among the films prepared F4 was found to show the best results. Hence it was considered as optimized formulation. These promising results showed the feasibility of delivering Tapentadol hydrochloride through transdermal matrix patch.

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