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Formulation and Evaluation of Transdermal Patch for Atomoxetine hydrochloride

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ABSTRACT

The aim of this study was to develop transdermal patch of Atomoxetine hydrochloride which has good mechanical properties. The transdermal patches were preapared used solvent casting method. Different groups of films with drug were prepared using different amalgamations of polymers such as HPMC (various grades), Polyox303, Eudragit RL 100.Considering solubility of drug and polymer, the solvent system of water: ethanol was chosen.*In-vitro* release of drug substance was performed using phosphate buffer solution (PBS) pH 7.4. Compatibility of drug with different excipient (drug: excipient in the ratio 1:1) was carried out using Fourier Transform Infra-Red Spectroscopy (FTIR). Evaluation test such as weight variation, content uniformity, drug content, folding endurance, thickness, in-vitro dissolution and in-vitro disintegration were done. The folding endurance of the all batches found less than 500 times.The percentages of drug distribution was found in between 72 to 100%.The formulation F4 containing a combination of HPMC and Eudragit showed maximum drug release of 95.26%. The method employed to prepare patches was capable of producing patches with almost uniform drug distribution. Stability studies were conducted as per ICH guidlines (40±2°C at 75±5% RH) for optimized formulations and was found to be stable.

Keywords: Atomoxetine hydrochloride, Transdermal Patch

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INTRODUCTION

Transdermal drug delivery system (TDDS) is one of the systems lying under the category of controlled drug delivery, in which the aim is to deliver the drug through the skin in a predetermined and controlled rate. TDDS are adhesive drug-containing devices of defined surface area that deliver a predetermined amount of drug to the surface of intact skin at a programmed rate to reach the systemic circulation [1,2].

The novel drug delivery system also be beneficial in the industry for improving the solubility, stability and biological half life of the drugs. The robustness of the strip depends on the type of polymer used in the formulation[3]. Drugs which are prone to considerable first pass metabolism or degraded in acidic environment of stomach are poorly absorbed from the GIT or when the therapy demands rapid onset of action, then transdermal route is used [4].

The precise mechanism by which Atomoxetine produces its therapeutic effects in Attention-Deficit/Hyperactivity Disorder (ADHD) is unknown, but is thought to be related to selective inhibition of the pre-synaptic norepinephrine transporter, as determined in ex vivo uptake and neurotransmitter depletion studies. The drug is used for the treatment of Attention deficit hyperactivity disorder (ADHD) and also in antidepressant. Attention-deficit/hyperactivity disorder (ADHD) is a common psychological diagnosis in children[4].

It Belongs to BCS class 1, and it undergoes first pass metabolism. Atomoxetine HCl appears to have minimal affinity for other noradrenergic receptors. And drug is rapidly absorbed after oral administration, So the drug is used in transdermal formulation[5].

The objective of this work was to prepare transdermal patch of Atomoxetine HCl which has good mechanical properties and evaluate the patch for its appearance, weight uniformity, drug content, drug release, tensile strength, folding endurance, thickness and stability[7].

MATERIAL AND METHODS

Atomoxetine hydrochloride was obtained as gift sample from Mann Medix Pharma ltd, and all the excipients from loba chemicals, Mumbai

Preparation of medicated films:

The polymer was dissolve in 20ml methanol and water solution in beaker A. In B beaker 10ml ethanol, water, polyethylene glycol 400 was dissolve. And in a vial take a

propylene glycol were taken and dissolve the drug by using ultrasonicater. Mix solution A into B. and solution in vial with the help of mechanical stirrer for 2-3 hrs.

Preparation of non-sticky petri plate:

The silicon emulsion was used used to prepare the non-sticky petri plates for casting of plates. Firstly the silicon emulsion was poured and spread with the thumb. The plates were then kept in oven for 12 hours at 120 ^{0}c. The dried plates were used to cast the films. Petri plate had diameter of 9.6 cm.

Casting and drying of films:

Above mixture was poured in petri plates which were pretreated with silicon emulsion. The petri plates were kept in closed box with inverted funnel for the controlled evaporation of organic solvents used. The controlled evaporation is required for uniform drying of films. The drying was carried out at room temperature for at least 24 hours. Then the films were cut into small patches of 2cm ×2cm

Table 1: Formula of medicated patches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
HPMC K15	-	-	-	-	-	-	-	-
HPMC E 50	500mg	-	-	-	400mg	350mg	-	450mg
HPMC E 15	-	-	-	400mg	-	-	400mg	-
Eudragit RL 100	-	500mg	-	50mg	-	-	-	50mg
Polyox 303	-	-	-	-	100mg	50mg	100mg	-
HPMCK 100	-	-	500	-	-	-	-	-
PEG 400	150mg	150mg	150mg	150mg	150mg	150mg	150mg	150mg
Propylene glycol	0.8ml	0.8ml	0.8ml	0.8ml	0.8ml	0.8ml	0.8ml	0.8ml
Atomoxetine HCL	177mg	177mg	177mg	177mg	177mg	177mg	177mg	177mg
Water: ethanol(1:2)	30ml	30ml	30ml	30ml	30ml	30ml	30ml	30ml

Method for Evaluation of Patches

Physicochemical evaluations of oral films

Films were evaluated for their visual inspection or film formation, weight variation, folding endurance, Drug content, thickness test, In-vitro dissolution.

Visual inspection and appearance

The films were evaluated visually for its clarity, transparency and stickiness. Films that were satisfactory were evaluated further and if they were unsatisfactory they were discarded.

IR Spectrum [6]

IR absorption spectrum of Atomoxetine HCl was recorded by potassium bromide dispersion technique in which dry samples and potassium bromide were placed in sample holder and infrared spectrum was recorded using FTIR spectrophotometer.

Determination of λ max [6]

10 mg of Atomoxetine HCLwas accurately weighed and was dissolved in 100 ml methanol to get 100 µg/ml solution. UV spectrum was recorded in wavelength range of 200-400nm.

Weight variation [7]

The patches were subjected to weight variation by individually weighing five different randomly selected patches. Such determination was carried out for each formulation.

The test ensures the uniformity of the formed film. From the whole film three small pieces, each of 2×2 cm^2 area and were weighed individually. The standard deviation from the mean value was reported

Water vapour transmission rate: [7]

1 gm. of fused calcium chloride as dessicant was taken in vials and polymeric patch fixed over vial by adhesive tape. Weight the vial and put it in to the humidity chamber at an RH 80% and temp at 30^{0}c. Then the vial for taken out periodically and weighed.

$$\text{Transmission rate} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Time} \times \text{Area}} \times 100$$

Folding endurance [8]

This was determined by repeatedly folding the film at the same place until it broke. The number of times the films could be folded at the same place without breaking/cracking gave the value of folding endurance.

Folding endurance was determined by repeatedly folding a small strip of the film at the same place until it breaks. The number of times the film is folded at specific place without breaking gives the folding endurance.

Thickness of film [8]

Appearances of the films were checked for uniformity and for the presence of air bubbles. Thickness of the randomly selected films was determined using Vernier callipers from every batch and the average values were determined.

The thickness of patches was measured at five different places using a Vernier caliper with least count 0.01mm and mean values were calculated.

Tensile strength [9]

The tensile strength was determined by the tensile strength apparatus and the tensile strength was calculated by using following formula

$$\text{Tensile stress (S)} = \frac{\text{Applied force}}{\text{Cross sectional area}} = \frac{m \times g}{b \times t}$$

where, S = tensile stress in 980 dynes/cm^2
m = mass in grams
g = acceleration due to gravity (980 dynes/cm^2)
b = breadth of strip in centimeters
t = thickness of strip in centimeters

In vitro dissolution [10]

Phosphate buffer pH 7.4 was used as the dissolution medium to determine the in vitro dissolution study. The temperature was maintained at 37±0.5°C with a stirring rate of 100 rpm. Samples were withdrawn at 0, 1, 3, 5, 10 intervals and then replaced by equal volumes of medium. The withdrawn samples were analysed by UV Visible spectrophotometer

Stability study [10]

Stability studies are conducted according to theICH guidelines at 40°C and 75% RH .The samples are analyzed for the drug content.

RESULT AND DISCUSSION

Visual Appearance:

All the formulations were visually transparent, thin and smooth . Some of the polymers are used alone and some of them are used in combinations .The films which are formed with good appearance and smooth are used for further evaluations.

FTIR studies:

The IR spectra of pure Atomoxetine HCl showed peaks at 3195.15, 3395.76,1629.90, 2630.99, 732.97 for C-CH stretch , N-H stretch, N-H stretch (Secondary amine), N-H stretch, C-O stretch.

UV spectroscopic studies:

The UV absorption data at 272.5nm and concentration estimates of pure Atomoxetine HCL showed good linearity (r^2-0.9964) over the concentration range of 1-10 µg/ml. Hence the given sample of pure Atomoxetine HCl was found to obey Beer-Lambert's law over this range.

Thickness of the film:

The thickness of film were found in range of 0.8 to0.25 mm, means uniform thickness was found in all the batches.

Folding endurance:

The folding endurance of the all batches was found to be less than 500 times. Films did not show any cracks even after folding upto 500 times which showed a good flexibility of patches.

Weight Variation:

Uniform weight was found to be in single polymer batches and also in combination batches. The range of weight variation was found in between 45.7 to 71.5 mg, means uniform weight was found.

Drug content:

The result shows that the method employed to prepare patches was capable of producing patches with almost uniform drug distribution. The percentages of drug distribution was found in between 72 to 100%

The water vapour transmission rate:

Water vapour transmission through the different patch formulations prepared by HPMC and Eudragit RL 100 in different ratios. The water vapour transmission rate was found in range of 0.0625 to 2.70gm/cm^2, and this is higher value.

Tensile strength:

Tensile strength ranging from 2.4 to 5.9 dynes/cm^2,as the polymer concentration increase slightly increase in tensile strength.

Drug release of medicated films:

Average cumulative present release from (F1,F2,F3,F4, F5,F6,F7,F8) containing mg polymer concentration was different from each other. They give the 72.42%, 57.46%, 78.49%, 95.26%, 93.06%, 86.36%, 69.29% and 94.01% release.

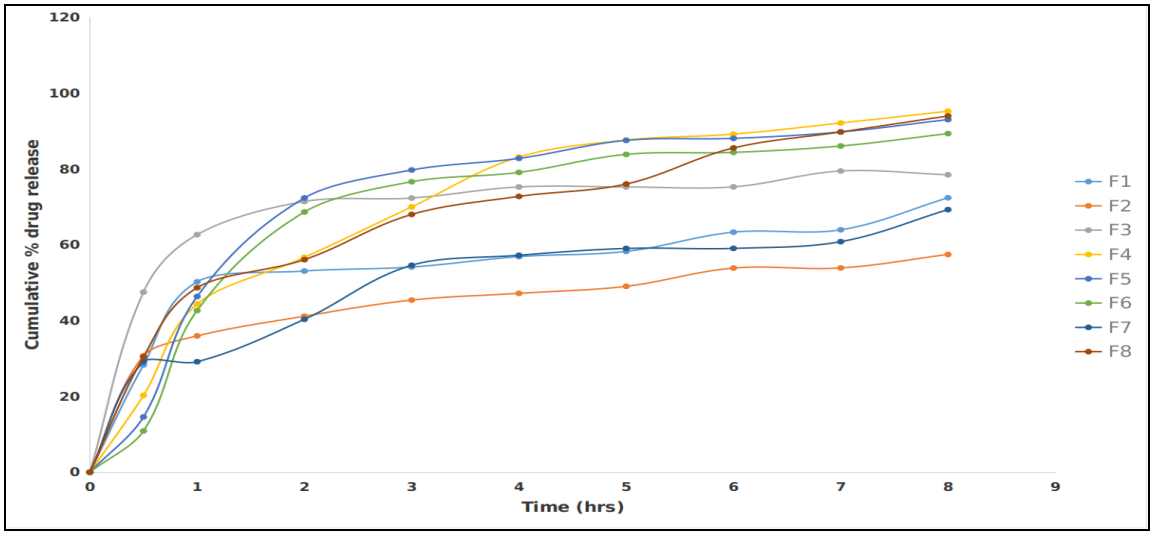

Figure 1: Average cumulative present release from (F1,F2,F3,F4,F5,F6,F7,F8)

Stability study:

Stability study where performed on film obtained with formulation F4 and F8 for 2 months at different storages conditionas per ICH guidelines.From the result it was found that no major changes in values of drug content and drug diffusion. It means that formulations are stable in different temp.

Table 2: Evaluation of drug loaded patch Evaluation of drug loaded patch [Thickness, Folding Endurance, Water vapour transmission rate, Tensile strength]

FC	Thickness	Folding endurance	Weight variation(mg)	Water vapour transmission rate (gm/cm²)	Tensile strength (dynes/cm²)	% Drug release
F1	0.08mm	438	58.4	0.135	3.4	72.42±1.99%
F2	0.12mm	480	45.7	0.142	4.5	87.46±1.44%
F3	0.12mm	390	47.9	0.114	2.4	78.49±0.56%
F4	0.12mm	487	47.4	0.197	3.4	95.26±2.10%
F5	0.16mm	388	49.1	0.201	3.8	93.06±0.38%
F6	0.16mm	470	48.3	0.132	3.4	86.36±0.46%
F7	0.08mm	370	72.6	1.140	3.9	69.29±0.84%
F8	0.13mm	388	64.5	0.112	4.5	94.01±0.55%

FC: Formulation Code

CONCLUSION

Atomoxetine HCl was successfully formulated as transdermal patch. Drug excipient compatibility concluded that the drug and excipient were compatible with each other. Transdermal patches were prepared by using polymers like HPMC E 50, HPMC K 15M HPMC K 100,HPMC E 15, chitosan, and various combinations of HPMC E 50, Polyox 303 ,Eudragit RL 100. Considering solubility of drug and polymer, the solvent system of water: ethanol was chosen. Polyethylene glycol 400(PEG 400) was used as a plasticizer.

All the films were evaluated for physical and mechanical properties like thickness, weight variation, moisture uptake, tensile strength, and evaluations like drug content, weight variation and in vitro drug release and the values were found to be within the acceptable limits. The formulation F4 containing HMPC E15 and Eudragit showed a good mechanical and physicochemical properties was selected as a suitable formulation for further studies.

The method employed to prepare transdermal patches was capable of producing patches with almost uniform drug distribution. The optimized formulations were found to be stable as per ICH guidelines. However Pharmacokinetic studies are needed to be performed to confirm the results of this study.

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