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Review

Design and Evaluation of Atomoxetine-Loaded Transdermal Patches for Enhanced Drug Delivery

Amit Kumar Tiwari[1*], Sangamnath B[1], Nile Swati[1], Sneha[1], Vidhya shree[1], Jahagirdar Sohel[1], Shrust[1]

[1]Professor, Aryan college of Pharmacy, Kalaburagi, Karnataka 585102*

[1]B.Pharm Project Student, Aryan college of Pharmacy, Kalaburagi, Karnataka 585102

*Author for Correspondence: Amit Kumar Tiwari
Email: researchterminal3@gmail.com

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Abstract

In present study transdermal drug delivery of Atomoxetine was developed to overcome the first pass metabolism and to reduce frequency of dosing compared to oral route. Oral drug delivery systems have a number of disadvantages, including poor bioavailability because of liver breakdown (first pass) and the propensity to cause fast blood level spikes (both high and low), necessitating high and/or frequent dosage, which can be both expensive and inconvenient. Matrix type of transdermal patches was developed by using polymers HPMC (low viscosity). Transdermal patches were prepared by employing solvent casting method. Ethanol were selected as permeation enhancer and plasticizer. Drug excipient compatibility studies were carried by using FTIR, and it was observed that there were no interactions. Formulations were prepared with varying concentrations polymers ranging from ATF1-ATF9, and all the formulations were evaluated for various physical parameters physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Studies on moisture uptake, moisture content, and swelling as well as in vitro drug release experiments utilising eggs membrane and synthetic membrane all revealed results that were within Pharmacopeial limitations. Among all the 9 formulations ATF9 formulation which contains ethyl cellulose 300mg of HPMC K15 had shown 98.96% cumulative drug release within 24 hours.

Keywords: Atomoxetine, HPMC K15, Ethanol, FTIR

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a chronic neurodevelopmental disorder characterized by persistent patterns of inattention, hyperactivity, and impulsivity that interfere with daily functioning and quality of life.[1] ADHD affects both children and adults worldwide and often requires long-term pharmacotherapy for effective symptom management. Continuous maintenance of therapeutic drug concentrations is essential for optimal clinical outcomes, as fluctuations in plasma levels may lead to reduced efficacy, adverse effects, or poor symptom control.[2] Conventional oral drug delivery systems commonly used in ADHD management are associated with several limitations, including variable gastrointestinal absorption, extensive first-pass hepatic metabolism, short plasma half-life, and the need for frequent dosing, which can negatively impact patient compliance, particularly in pediatric and adolescent populations.[3] These challenges necessitate the development of alternative drug delivery approaches capable of providing sustained and controlled drug release while improving patient adherence.

Atomoxetine is a selective norepinephrine reuptake inhibitor (NRI) approved for the treatment of ADHD and is widely prescribed as a non-stimulant therapeutic option.[4] It exerts its pharmacological action by increasing norepinephrine levels in the prefrontal cortex, thereby enhancing attention and behavioral control without the abuse potential associated with stimulant medications.[5] Despite its clinical advantages, atomoxetine exhibits moderate oral bioavailability due to extensive first-pass metabolism and possesses a relatively short elimination half-life, requiring repeated oral administration to maintain effective plasma concentrations.[6] Additionally, oral atomoxetine therapy may be associated with gastrointestinal side effects, variable pharmacokinetics, and inter-individual differences in drug metabolism, which can compromise treatment efficacy and patient compliance during long-term therapy.[7]

Transdermal drug delivery systems (TDDS) have emerged as a promising alternative to conventional oral dosage forms by providing controlled and sustained drug delivery through the skin into systemic circulation.[8] Transdermal patches offer several advantages, including avoidance of first-pass hepatic metabolism, reduced dosing frequency, maintenance of steady plasma drug levels, improved bioavailability, and enhanced patient convenience.[9] Moreover, TDDS can minimize gastrointestinal side effects and allow for easy termination of therapy in the event of adverse reactions, making them particularly suitable for chronic conditions requiring prolonged treatment.[10]

The present study focuses on the design and evaluation of atomoxetine-loaded transdermal patches intended to enhance drug delivery and improve therapeutic performance. Polymeric matrix-type transdermal patches were formulated using suitable film-forming polymers, plasticizers, and permeation enhancers to achieve optimal mechanical strength, flexibility, and controlled drug release.[11] The formulated patches were systematically evaluated for physicochemical characteristics, including thickness, weight uniformity, folding endurance, tensile strength, moisture content, moisture uptake, drug content uniformity, and in vitro drug release. In vitro skin permeation studies were also conducted to assess drug transport across the skin and to elucidate release kinetics and permeation behavior.[12] Stability studies were performed to evaluate formulation integrity and long-term performance. Overall, this study aims to establish a stable and effective transdermal delivery system for atomoxetine that offers sustained drug release, improved bioavailability, enhanced patient compliance, and better therapeutic outcomes in the management of ADHD.[13]

Material:

All the chemicals and reagents used in the present study were of analytical grade. Atomoxetine was procured from MSN Labs, India. Polyvinyl alcohol (PVA), hydroxypropyl methylcellulose (HPMC K5), polyvinylpyrrolidone (PVP), potassium dihydrogen phosphate, sodium hydroxide, methanol, chloroform, ethanol, and distilled water were obtained from S.D. Fine Chemicals, India. All materials were used as received without further purification.

METHODOLOGY

PREPARATION OF BACKING MEMBRANE

The backing membrane was prepared with an aqueous solution of 4 %w/v polyvinyl alcohol (PVA). 4 gm of PVA was added to 100 ml of warm, distilled water and a homogenous solution was made by constant stirring and intermittent heating at 60 °C for a few sec. [14]

Then 15 ml of the homogenous solution was poured into glass Petri dishes of 63.5 cm2 and was allowed to dry in a hot air oven at 60 ° C for 6 h

FORMULATION OF TRANSDERMAL PATCHES

Transdermal patches containing Atomoxetine were cast on a petri dish by a solvent evaporation method using different polymers (HPMC E5:PVP K30 and HPMC E5:Eudragit L 100) [15]. The drug to polymer ratio was fixed as 1:1 and the polymer to polymer ratio was fixed as 1:1, 1:2, and 2:1. Three different concentrations of HPMC E5 were used in all six formulations and another two polymers PVP K 30 and Eudragit L100 were used in every three formulations at varying concentrations. N-dibutyl phthalate and propylene glycol were used as a plasticizer. 1% DMSO was used as a permeation enhancer in all the formulations.

The polymers were accurately weighed and dissolved in 10mL of ethanol and in the case of Eudragit L 100 the chloroform: methanol (1:1) solution was also used and kept aside to form a clear solution. Drug Atomoxetine was dissolved in the above solution and mixed until the formation of clear solution.[16] Then the plasticizer and the permeation enhancers were added to the formulation step by step and mixed uniformly. The resulted uniform solution was cast on the petri dish, which was lubricated with glycerin and dried at room temperature for 24 h. An inverted funnel was placed over the petri dish to prevent fast evaporation of the solvent. After 24 h, the dried patches were taken out and stored in a desiccator for further studies.[17]

EVALUATION OF TRANSDERMAL PATCHES

Folding endurance

A Particular area of the strip (2x2 cm) was cut uniformly and folded over and over until it broke. The value of the folding endurance was determined by the number of times the film was folded at the same location either to break the film or to develop visible cracks.[18]

Tensile strength

The patch's tensile strength was determined using a tensiometer (Erection and instrumentation, Ahmedabad). It is made up of two grips for load cells. The lower one was fixed, while the upper one could be moved. Film strips measuring 2x2 cm were placed between the cell grips, and force was applied progressively until the film broke. The tensile strength was calculated using the dial reading in kilograms.[19]

Percentage elongation break test

The percentage elongation break was calculated by noting the length just before the breaking point and the following formula was used to calculate the percentage elongation.

$$\text{Percentage Elongation} = \frac{\text{Final length of strip} - \text{Intial length of strip}}{\text{Intial length of strip}} \times 100$$

Thickness

The thickness of the transdermal patches was measured using a digital micrometer screw gauge at three different places, and the mean value along with SD was calculated.[20]

Drug content

A 2x2 cm size transdermal patch was dissolved in 100ml methanol and shaken continuously for 24 h. The whole solution was then ultrasonicated for 15 min. After filtration, the drug's content was measured using spectrophotometry at a wavelength of 274 nm.

Percentage moisture content

The prepared transdermal films were individually weighed and stored in a desiccator containing fused calcium chloride at room temperature for 24 h. After 24 h, the films were reweighed and the percentage moisture content was determined from the following formula.

$$\text{Percentage Moisture Content} = \frac{\text{Inital weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Percentage moisture uptake

The prepared transdermal films were individually weighed and stored in a desiccator containing a fused saturated solution of potassium chloride to maintain 84% RH for 24 h at room temperature. After 24 h, the films were reweighed and the percentage moisture uptake was calculated using the following formula.

$$\text{Percentage Moisture Uptake} = \frac{\text{Inital weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Swelling study

The formulated transdermal patches were weighed (W1) individually and incubated at 37±0.5 ° C separately in agar gel (2%) plate. The patches were removed from the petri dish at regular time intervals of every 15 min up to 1 h and the excess water on the surface was removed carefully with filter paper. The swollen patches were reweighed (W2) and the swelling index was calculated by using the formula.

$$\text{Swelling index} = \frac{\text{W2} - \text{W1}}{\text{W1}} \times 100$$

In vitro drug release studies

A Franz diffusion cell with a receptor compartment capacity of 60 ml was used for the in vitro drug release tests. The drug was determined using a cellulose acetate membrane from the prepared transdermal matrix-type patches. The diffusion cell's donor and receptor compartments were separated by a 0.45 µ pore size cellulose acetate membrane. The prepared transdermal patch was and mounted on the cellulose acetate membrane, which was then sealed with aluminum foil. The diffusion cell's receptor compartment was filled with phosphate buffer pH 7.4. The entire assembly was mounted on a hot plate magnetic stirrer, and the solution was constantly and continuously stirred at 50 rpm during the experiments using magnetic beads, as described by Simon et al. in the receptor compartment, while the temperature was maintained at 37±0.5 °C, which corresponds to normal human body temperature. The samples were taken at various intervals and spectrophotometrically analyzed for drug content. During the experiment, the manual sampling requires constant careful attention since air bubbles are easily entered in the receiver compartment when the samples are taken. At each sample removal, the receptor step was replenished with an equal volume of phosphate buffer.

In vitro permeation study

An in vitro permeation study was carried out by using Franz diffusion cell using full-thickness abdominal skin of male Wistar rat weighing 200 to 250 g [26]. Hair was carefully removed from the region of the abdominals with an electrical clipper; the dermal side of the skin was thoroughly cleansed with distilled water to remove any adhesion of tissues or blood vessels. It was equilibrated for an hour in Phosphate buffer saline, pH 7, before beginning the experiment. A thermostatically controlled heater maintained the cell temperature at 37±0.5 °C [27, 28]. The piece of rat skin was mounted between the diffusion cell compartments, and the epidermis faced up into the

donor compartment. At regular intervals, the 1 ml sample volume was removed from the receptor compartment at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24 h, and an equal volume of fresh medium was replaced. The samples have been filtered through the Whatman filter and analyzed in Shimadzu UV 1800 double-beam sodium (Shimadzu, KYOTO/Japan) at 274 nm for Atomoxetine.

Drug release kinetics

The data obtained from in vitro release of drug was plotted in various kinetic models such as zero-order (cumulative amount of drug released vs time), first-order (log cumulative percentage of drug remaining vs time), and Higuchi's model (cumulative percentage of drug released vs square root of time) to know the release kinetic

Stability Study

The stability study for optimized formulation is performed for optimised formulation in compliance with ICH recommendations. The drug content, folding endurance drug diffusion at 12hr was taken as major parameter.

RESULTS & DISCUSSION

DSC (Differential scanning calorimetry):

Differential Scanning Calorimetry excipients are utilised for determination of presence of any interaction between drug & the excipients, as well as any changes in the crystallinity of drug. It measures the enthalpic changes that occur during endothermic or exothermic events. The melting point & heat of fusion is the device which is calibrated through indium (calibration standard, purity > 99.99%). In typical aluminium pans, 5-15 mg of drug sample was obtained for examination. As a guide, the empty pan is used. The heating rate is mostly nitrogen, which was used as a purged gas, and the system was cooled by liquid nitrogen. This was accomplished using a differential thermal analyzer. The peak is observed at 170 °C as referred to the standard.

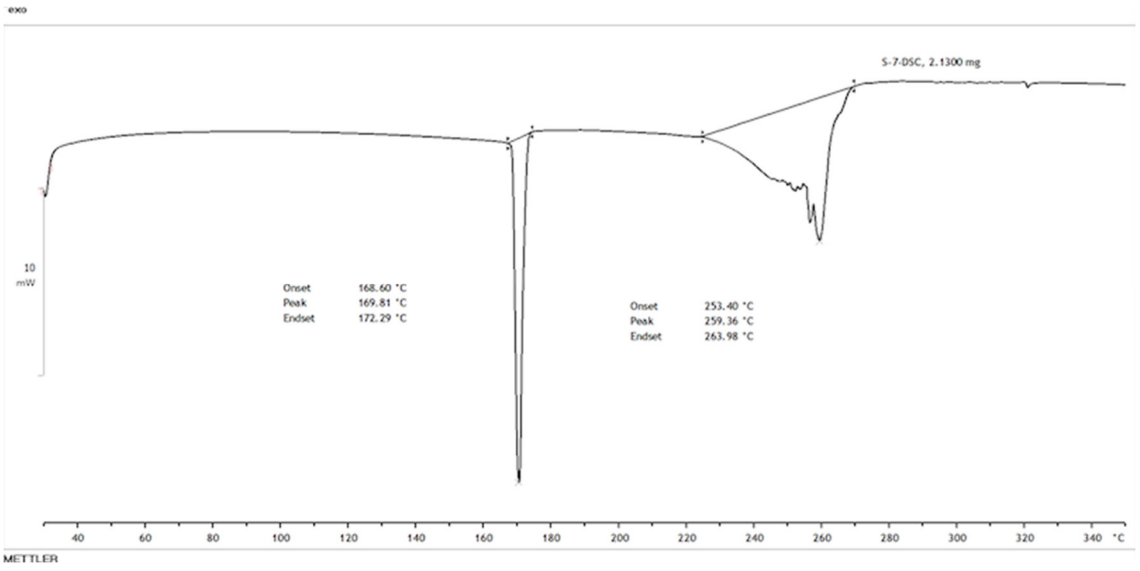

Figure 1: DSC of Pure Drug

FTIR

Pure Atomoxetine IR spectra are displayed in Figure 5. Atomoxetine's spectra exhibit peaks at 1755.28 C=O cm 1 for NH- stretching, 1618.33 cm 1 for C=C stretching, 1276.92 cm 1 for C-N amine bond, 516.94 cm 1 for halogen compound (C-Cl) link, 2997.48

(alkane compound), 2947.33, 2883.68 with O-H bond, and 1188.19 with C-N bond. Atomoxetine-formulated NLC spectra exhibit a shift in the pure drug's spectral peaks, proving the presence of drug in these formulations.

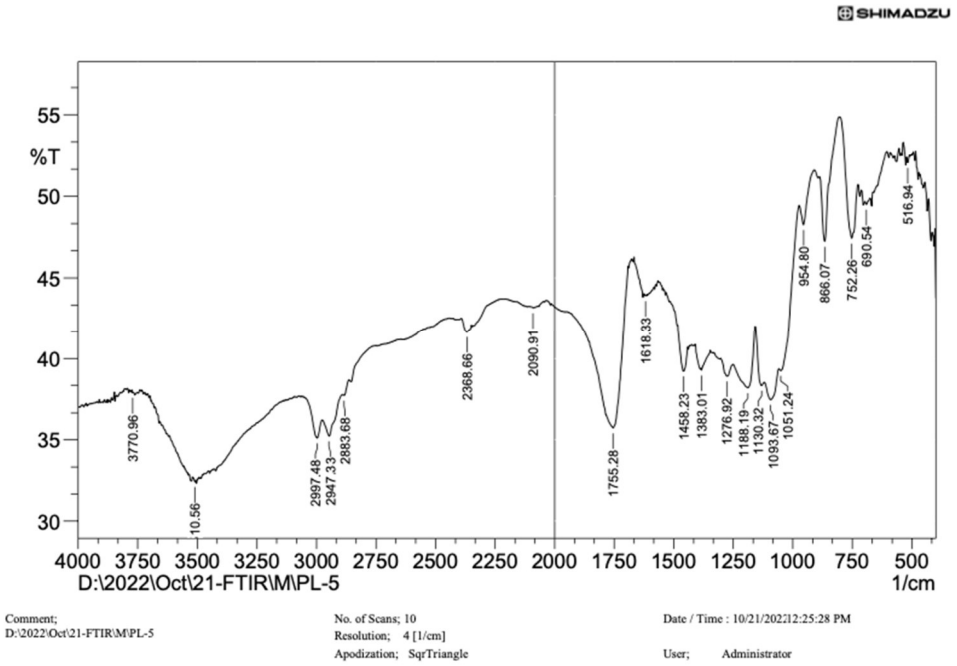

Figure 2: FTIR of Pure Drug

Table 1- Formulation Table for Atomoxetine Transdermal Patch

Formulation code	Drug API(mg)	HPMC K 15	Plasticizer(PEG)	chloroform	Methanol	Ethanol
ATF1	10mg	200mg	0.2ml	5ml	5ml	0.5ml
ATF2	10mg	250mg	0.4ml	5ml	5ml	0.5ml
ATF3	10mg	300mg	0.6ml	5ml	5ml	0.5ml
ATF4	10mg	200mg	0.4ml	5ml	5ml	0.5ml
ATF5	10mg	250mg	0.6ml	5ml	5ml	0.5ml
ATF6	10mg	300mg	0.4ml	5ml	5ml	0.5ml
ATF7	10mg	200mg	0.6ml	5ml	5ml	0.5ml
ATF8	10mg	250mg	0.2ml	5ml	5ml	0.5ml
ATF9	10mg	300mg	0.4ml	5ml	5ml	0.5ml

ATF: ATOMOXETINE TRANSDERMAL PATCH

EVALUATION OF ATOMOXETINE TRANSDERMAL PATCH

Table 2: Evaluation of transdermal patch by physical methods(n=3)

Formulation	Thickness(mm)	Folding endurance	Drug content(%)	Moisture uptake(%)	Moisture content(%)
ATF1	0.281	308	91	7.79	4.79
ATF2	0.272	317	93	8.41	8.41
ATF3	0.2872	373	92	7.18	6.18
ATF4	0.2798	348	94	8.68	7.68
ATF5	0.2862	403	93	7.89	8.89
ATF6	0.2819	399	93	8.69	9.69
ATF7	0.288	342	94	9.45	8.45
ATF8	0.2839	490	96	8.74	9.74
ATF9	0.2805	500	98	5.64	10.64

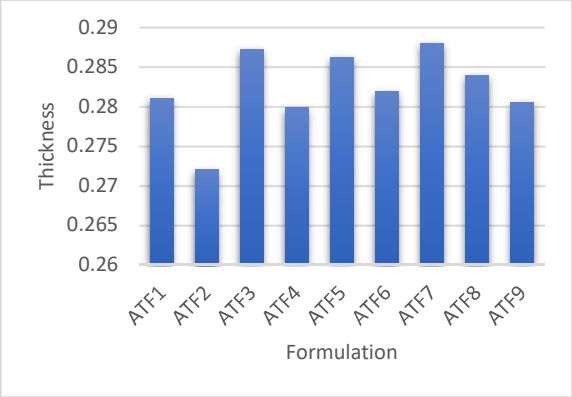

Figure 3.1: Thickness of Atomoxetine Patches

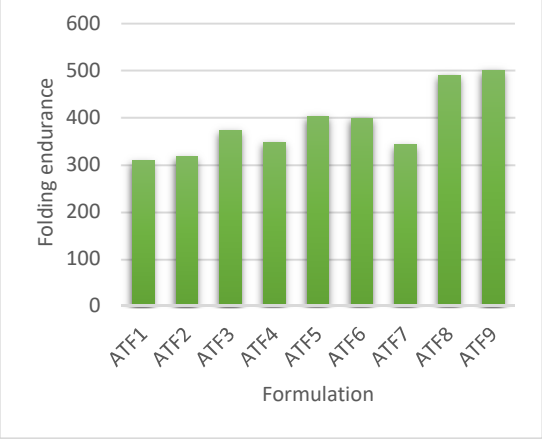

Figure 3.2: Folding endurance of Atomoxetine Patches

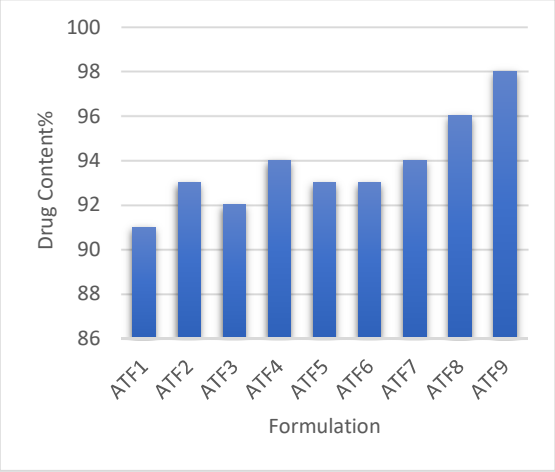

Figure 3.3: Drug content% of Atomoxetine Patches

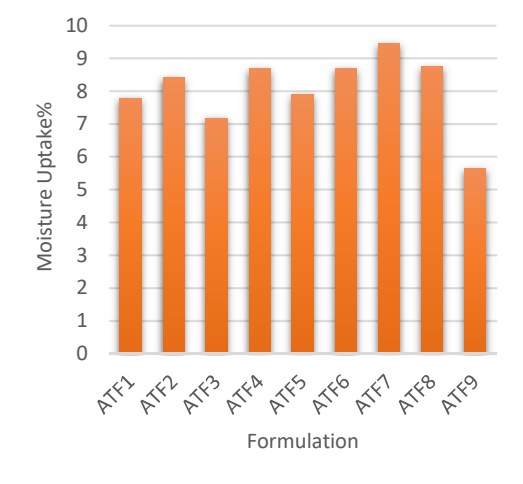

Figure 3.4: Moisture uptake % of Atomoxetine Patches

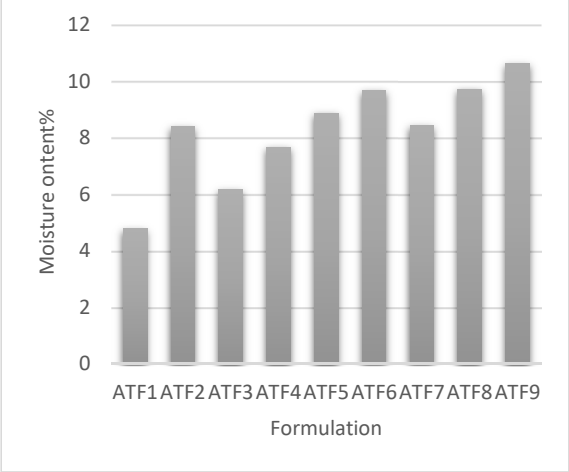

Figure 3.5: Moisture content % of Atomoxetine Patches

Table 3: In-vitro diffusion study (ATF1 to ATF5)

Time (Hours)	ATF1	ATF2	ATF3	ATF4	ATF5
0	0	0	0	0	0
1	22.52	12.97	7.57	12.77	7.02
2	34.85	25.98	15.8	21.59	16.4
4	66.48	35.36	22.85	38.01	24.82
8	79.46	51.85	37.13	46.56	37.49
12	81.8	67.81	51.84	83.81	61.12
24	89.84	85.11	83.68	90.52	95.15

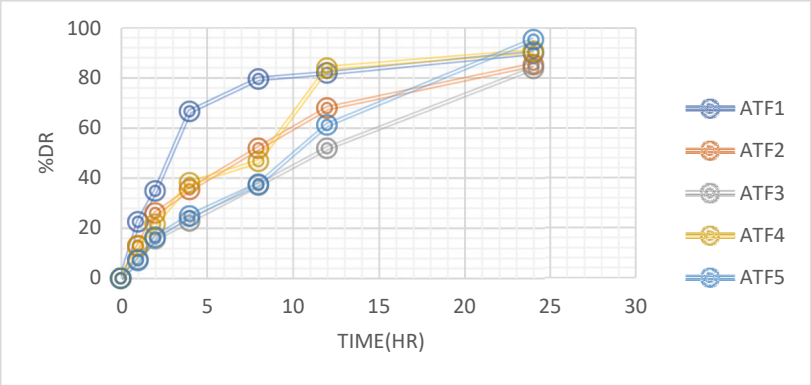

Figure 4: In-vitro diffusion study% of Atomoxetine Patches

Table 4: In-vitro diffusion study (ATF6 to ATF9)

Time (Hours)	ATF6	ATF7	ATF8	ATF9
0	0	0	0	0
1	6.46	5.13	0.65	14.77
2	16.63	11.1	7.54	28.59
4	25.15	19.66	15.8	38.01
8	37.63	37.68	32.41	53.56
12	62.15	62.33	50.48	73.81
24	94.07	87.84	79.67	98.96

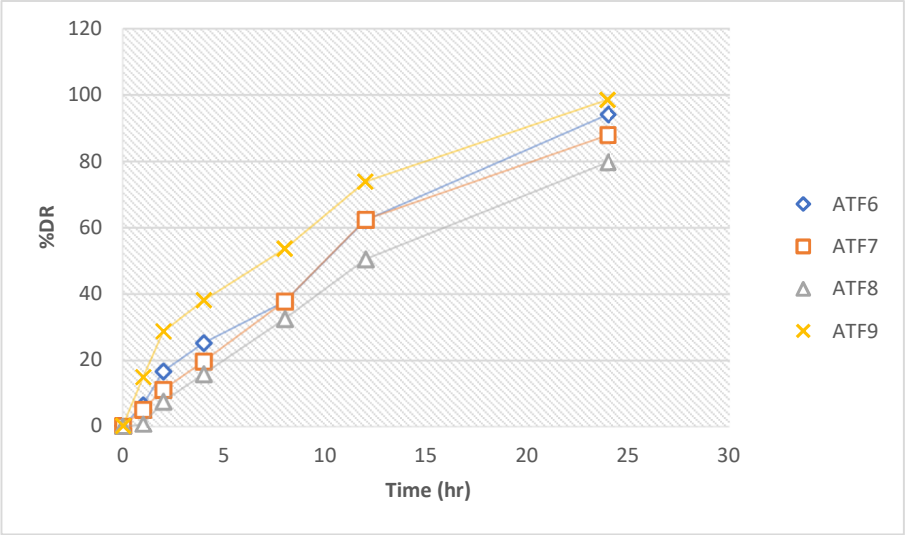

Figure 5: In-vitro diffusion study % of Atomoxetine Patches

Table5: Release kinetics of Patch

Formulationcode	r^2			
	Zero	First	Higuchi	Korsmeyer& Peppas
ATF1	0.99	0.89	0.91	0.96
ATF2	0.93	0.92	0.98	0.99
ATF3	0.98	0.92	0.92	0.99
ATF4	0.98	0.94	0.95	0.99
ATF5	0.98	0.76	0.95	0.99
ATF6	0.98	0.87	0.95	0.99
ATF7	0.99	0.94	0.95	0.99
ATF8	0.98	0.99	0.96	0.99
ATF9	0.99	0.97	0.95	0.98

Table 6: Stability Results

Parameters observed during stability study	0 month	After 3 month	After 6 month
Drug Content % mean±SD (n=3)	99.11	99.08	98.88
Folding Endurance mean±SD (n=3)	500	500	499
Drug diffusion at 12 hr	98	98	97.08

SUMMARY & CONCLUSION

In the present study, a transdermal drug delivery system of atomoxetine was developed with the aim of overcoming extensive first-pass hepatic metabolism and reducing dosing frequency compared to conventional oral administration. Oral drug delivery systems are often associated with several limitations, including reduced bioavailability due to first-pass metabolism and rapid fluctuations in plasma drug concentrations, leading to frequent or higher dosing requirements that may increase cost, inconvenience, and the risk of adverse effects. To address these drawbacks, matrix-type transdermal patches were formulated using low-viscosity polymers, primarily hydroxypropyl methylcellulose (HPMC).

The transdermal patches were prepared by the solvent casting method, employing ethanol as both a permeation enhancer and plasticizer to improve drug permeation and patch flexibility. Drug–excipient compatibility studies were conducted using Fourier Transform Infrared (FT-IR) spectroscopy, which confirmed the absence of any significant interactions between atomoxetine and the selected excipients. A total of nine formulations (ATF1–ATF9) were prepared using varying concentrations of polymers and were systematically evaluated for physical and physicochemical parameters, including physical appearance, flatness, weight variation, thickness, folding endurance, drug content uniformity, moisture uptake, moisture content, swelling behavior, and in vitro drug release.

In vitro drug release studies were carried out using egg membrane and synthetic membrane diffusion models, and all formulations demonstrated results within acceptable pharmacopeial limits. Among the nine formulations, ATF9—containing ethyl cellulose and 300 mg of HPMC K15—exhibited the highest cumulative drug release of 98.96% within 24 hours, indicating effective sustained drug delivery. Based on the overall evaluation, ATF9 was identified as the optimized formulation, demonstrating superior release characteristics and suitability for transdermal delivery of atomoxetine.

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