Advances in Bioresearch
Adv. Biores., Vol 15 (4) July 2024:67-71

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.15.4.6771

Advances in Bioresearch

ORIGINAL ARTICLE

Effect of Plasticizer and Polymeric Combination for Optimization of Penetration Rate of Antipsychotic Transdermal Patch

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ABSTRACT
Transdermal patches are a non-invasive method of drug administration. It is an adhesive patch designed to deliver a specific dose of medication through the skin and into the bloodstream throughout the body. Transdermal drug delivery has several advantages over other routes of administration, for instance, it is less invasive, patient-friendly, and has the ability to bypass first-pass metabolism and the destructive acidic environment of the stomach that occurs upon the oral ingestion of drugs. The proposed work formulated and evaluated transdermal patche of olanzapine using adhesive polymers for produces muco-adhesives in combination. They concluded that by their experiment that an ideal combination of adhesives can act as best choice for fabrication of patches, for its sustained effect with better improvement in permeation characteristics and robustness.
Keywords: *Plasticizer, Polymeric Combination, Optimization, Penetration Rate, Antipsychotic Drug, Transdermal Patch.*

Received 26.03.2024 Revised 14.04.2024 Accepted 18.06.2024

How to cite this article:
Rohit S P, Shweta S, Rakesh P. Effect of Plasticizer and Polymeric Combination for Optimization of Penetration Rate of Antipsychotic Transdermal Patch. Adv. Biores. Vol 15 [4] July 2024. 67-71

INTRODUCTION

Schizoaffective disorder is a combination of schizophrenia and a mood disorder. Both disorders could be diagnosed separately and are present in full in the same patient. Critically, the psychosis must be present for at least 2 weeks when the mood disorder is not present. Additionally, the mood disorder must be diagnostically present during a majority of the active and residual phases of the illness.3 In other words, more than 50% of the time either depression or bipolar disorder must be evident. Major depression with psychosis is different than schizoaffective disorder because the psychosis is only present when the patient is severely depressed. Mental illness has always been a part of human experience and so is the quest to understand and treat it. Mental illness, psychosis in particular, is a chronic and brain disabling disease.[1] Typical and atypical antipsychotics have transformed the lives of many psychotic patients by abolishing troublesome symptoms and permitting their return to more normal behavior.[2] The efficacy of oral olanzapine in treatment of psychosis is well known. Olanzapine, a newer atypical antipsychotic, is better tolerated, more potent, and causes lesser side effects than typical antipsychotics. [3,4] Currently, olanzapine is administered orally or through parenteral route. It is usually administered as one or two daily doses, with an overall dosage of 5–20mg/day. Olanzapine is eliminated extensively by first-pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation Although olanzapine is an effective antipsychotic agent, noncompliance is a serious problem for patients and it is believed to account for high short-stay hospital costs.[5] Since the treatment duration of olanzapine is quite prolonged, the formulations of olanzapine that deliver controlled amount of drug is worth experimenting as it may improve compliance and offer efficacy and safety benefits in long-term management of patients. It has been observed that patients suffering from anxiety, depression, psychosis, and mania are noncompliant, and transdermal drug delivery is useful in achieving patient compliance.[6] Thus, transdermal delivery offers convenience and a simple dosing regimen can aid in patient adherence

to drug therapy. It can be used as an alternative route of administration to accommodate patients who cannot tolerate oral dosage forms.[7] On the basis of this hypothesis, it was envisaged to develop transdermal drug delivery system (TDDS) of olanzapine that delivers optimum amount of the drug Research Article Formulation, in vitro, and in vivo evaluation of matrix-type transdermal patches containing olanzapine Geeta Aggarwal1 , Sanju Dhawan2 , and S. L. Harikumar1 1 Rayat and Bahra Institute of Pharmacy, Sahauran, Mohali, Punjab, India and 2 Panjab University, UIPS, Chandigarh, India Abstract Transdermal patches of olanzapine were aimed to be prepared to overcome the side effects by oral application. The strategy was formulation of eudragit-based polymeric films to prepare transdermal patches by using nonionic (span-20), anionic (sodium lauryl sulfate), cationic surfactant (benzalkonium chloride), and vegetable oil (olive oil) as permeation enhancers. The patches were subjected to physicochemical, in vitro release and ex vivo permeation studies. On the basis of in vitro release performance, ERL 100: ERS 100 in the ratio of 3:2 was selected for incorporation of permeation enhancers. The permeation studies showed that formulation containing 10% span 20 (OD3) exhibited greatest cumulative amount of drug permeated (19.02±0.21mg) in 72h, so OD3 was concluded as optimized formulation and assessed for pharmacokinetic, pharmacodynamic, and skin irritation potential. In vivo studies of optimized olanzapine patch in rabbit model revealed prolongation of action with Frel 116.09% during 72-h study period. Neuroleptic efficacy of transdermal patch was comparable to oral formulation during rotarod and grip test in Wistar albino rats with no skin irritation. Thus, developed formulation of olanzapine is expected to improve the patient compliance, form better dosage regimen, and provide maintenance therapy to psychotic patients. Formulation and evaluation of TDDS of olanzapine to control the disease condition and minimize the side effects. The successful development of the transdermal therapeutic system depends on a pondered choice of drug. The drug should neither be irritant nor produce allergic reaction when applied in this delivery system. It should permeate the skin in adequate amounts to produce the desired therapeutic effect. Previous studies reported the formulation of drug in adhesive-type transdermal therapeutic system of olanzapine. [8] This investigation, therefore, aims at exploiting the potential of eudragit-based TDDS for sustained release of olanzapine to optimize drug therapy in psychotic patients. For development of TDDS, permeation enhancers like solvents, azones, pyrrolidones, and surfactants are generally used to enhance permeability of drug through skin. These permeation enhancers have some challenges as solvents may cause reversible denaturation of keratin and azones being less effective on human skin.[10] Other synthetic permeation enhancers like surfactants increase the permeability of drugs but rate of permeation depends on their physicochemical properties. Natural permeation enhancers like vegetable oils are easily available and are metabolized in body.[11] Olanzapine transdermal patch combines a slow release formulation of a chronic treatment of schizophrenia in patients.The proposed model drug olanzapine was initially used orally and intramuscularly for the chronic treatment of schizophrenia in patients. Olanzapine is also indicated, in combination with lithium or valproate for the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder in adults. The aim of present work is to develop a polymeric transdermal patch for predetermined release of drug materials for a care of cardiac patients. In vitro and in vivo studies were also conducted to explore the potential of prepared transdermal patches for sustained release of olanzapine.

MATERIAL AND METHODS

Formulation of transdermal patches: Transdermal patches of olanzapine were prepared by solvent casting technique in a glass mould fabricated locally. The formulations were formulated to determine the optimum combination of polymers, plasticizer, and solvent. The polymers sodium alginate / Chitosan were mixed in different ratios to a total weight of 500mg and dissolved in 10mL of ethanol solvent system using magnetic stirrer.Drug (10 mg) was added slowly to the polymer solution and mixed thoroughly to obtain a homogenous solution. Different permeation enhancers (clove oil / neem oil) were added in three different concentrations, i.e. 5%, w/w of polymer weight for skin irritant at higher concentrations. The resulting polymeric solution was poured in circular aluminum foil cups placed in circular glass mould (internal diameter 3.57cm and thickness 1 cm) and dried at 35°C in dust-free environment. After 24h, the films were collected and peeled off. A circular adhesive tape of internal diameter 5cm was attached on the patch. A backing film made up of aluminum was applied with the help of adhesive and a release liner (wax paper) was applied on other side of the film to complete the TDDS. The composition of optimized transdermal formulations is given in Table 1.

Table 1: Various combination of transdermal patches

Formulation Code	Polymers (gm)		Plasticizers		Penetration enhancer	
	Sodium alginate	Chitosan	Glycerin (ml)	PVP (gm)	Clove oil (ml)	Neem oil (ml)
OZTP1	2	-	5	-	5	-
OZTP2	-	2	5	-	5	-
OZTP3	1	1	5	-	5	-
OZTP4	2	-	-	5	-	5
OZTP5	-	2	-	5	-	5
OZTP6	1	1	-	5	-	5

Evaluation of transdermal patch:

Physical characterization: The prepared transdermal films were evaluated for weight variation by individually weighing 10 randomly selected patches. Thickness was measured by micrometer at random points on the films of every batch. Folding endurance was determined by repeatedly folding the film at the same place until it breaks and flatness was measured by determining percent constriction. Tensile strength was determined by weight pulley method, and for moisture content and uptake, prepared films were weighed individually, kept in desiccators containing activated calcium chloride and saturated solutions of potassium chloride, respectively, at room temperature for 24h and percentage of moisture content and uptake was calculated.

In vitro release studies: The in vitro drug release studies were performed by using a modified USP type II dissolution apparatus using 900mL of PBS 7.4 as dissolution medium. A circular patch with an internal diameter of 4 cm^2 was used for this study and a stainless-steel ring was employed to sink the patch at bottom of dissolution apparatus. All dissolution studies were performed at 37±0.5° C at 50 rpm. Samples were withdrawn at different time intervals and analyzed spectrophotometrically at 246nm.

In vitro permeation studies: The in vitro permeation studies were carried out in vertical Franz diffusion cell with a capacity of 35mL, using cellophone membrane as skin after removing. The patch was placed on the skin with the drug matrix side toward the donor side and backing membrane on the upper side. Receptor fluid was kept same as dissolution media and agitated at 50rpm by magnetic stirrer and temperature was maintained at 37±0.5° C at 50 rpm. The samples were withdrawn at different time intervals and replaced with equal amounts of dissolution media. Samples were analyzed for its drug content spectrophotometrically at 246nm.. The drug permeated per cm2 of patch was calculated and plotted against time and the flux was calculated as drug permeated per cm^2 per hour.

Stability Studies: The stability of the prepared transdermal patch (OZTP6) patches was evaluated as per the ICH guidelines. The shelf life of both API drugs was identified for drug decomposition during storage at different storage conditions at different temperatures. The degradation may result in environmental changes during storage of drug amount at **OZTP6**due to chemical alteration or due to product instability. The prepared transdermal patch OZTP6 were stored at three different temperature and relative humidity conditions in covered polythyne bags and aluminium paper. The samples were stored at 2ºC ± 0.5ºC, 25°C/60% RH and 40°C/75% RH for 180 days in stability chambers. These samples were analyzed for drug content study was done.

RESULTS AND DISCUSSION

Evaluation of transdermal patches smooth and transparent films were obtained by using mixture of sodium alginate and chitosan. The films prepared without plasticizer were brittle compared with the plasticized films, which showed good elasticity and flexibility. It was observed that upon increasing the permeation enhancer concentration, there is an increase in the weight and thickness of patches. Uniformity of drug content ranged between 91% and 97%. It is concluded that all films had the same strip length before and after their cuts, indicating 100% flatness. No constrictions were observed indicating all patches had a smooth and flat surface. The films maintained their integrity with general skin folding. The results indicating physicochemical characteristics of TDDS are given in Table 2-3. Moisture content and moisture uptake were determined for batch OZTP to find the effect of bioadhesive polymers in transdermal patches. The cumulative % drug release from mixed polymers without permeation enhancer (OZTP) was found to effective. It was observed that initial release was fast in formulation containing sopdium alginate / chitosan with glycerol / PVP or clove oil and neem oil. The decrease in drug release rate with increase in concentration of neem oil may be due to formation of micelles. These micelles could be difficult to diffuse out of matrix patches, so it could decrease the release rate. Results showed that

release rate increased with increase in concentration of oil. Release was also found to increase with increase in concentration of natural oil, i.e. neem oil, which may be attributed to presence of arachdioniuc content. The mechanism of penetration enhancement of surfactants is primarily believed to be due to the promotion of membrane-vehicle partitioning tendency of the drug. The polymeric films (OTP14) were selected on the basis of its physical appearance, tensile strength, percentage elongation, folding endurance, swelling ratio, moisture content, moisture uptake nature, drug content and in-vitro drug release study parameters. The release kinetic study confirmed the prepared film was followed super case II transport mechanism of diffusion kinetics with sustained release within specific time period.

Table 2: Physical properties of patch of olanzapine containing transdermal patch

Formulation code	Flexibility	Smoothness	Transparency	Stickness
OZTP1	Flexible	Smooth	Transparent	Non sticky
OZTP2	Flexible	Smooth	Transparent	Non sticky
OZTP3	Flexible	Smooth	Transparent	Non sticky
OZTP4	Flexible	Smooth	Transparent	Son sticky
OZTP5	Flexible	Smooth - Rough	Opaque	Non sticky
OZTP6	Flexible	Smooth	Opaque	Son sticky

Table 3: Physical properties of patch of olanzapine containing transdermal patch

Formulation code	Thickness (mm)	Average weight (mg)	Folding endurance	Percentage Elongation	Tensile Strength N/mm²	Swelling ratio (%)	Surface pH	Drug content of patch
OZTP1	0.128±0.011	148.50±0.124	66-71	98.92± 0.21	6.08±0.14	49.01 ± 0.18	5.5 ± 0.02	97.19±0.24
OZTP2	0.122±0.014	125.13±1.104	68-72	99.01± 0.27	6.19±0.15	43.01 ± 0.51	5.6± 0.02	98.19±0.19
OZTP3	0.123±0.015	113.23±1.105	66-77	98.19± 0.16	6.01±1.11	32.01 ± 0.27	5.6 ± 0.03	99.03±0.18
OZTP4	0.127±0.012	114.41±1.121	57-64	79.18±0.21	5.11±0.11	31.03 ± 0.34	5.2 ± 0.02	94.01±0.17
OZTP5	0.126±0.021	116.17±1.124	69-73	91.01±0.18	5.01±1.01	41.03 ± 0.15	5.4 ± 0.04	99.48±0.19
OZTP6	0.125±0.026	113.18±0.981	54-68	99.16±0.12	5.21±0.91	42.01 ± 0.16	5.5 ± 0.02	97.71±0.41

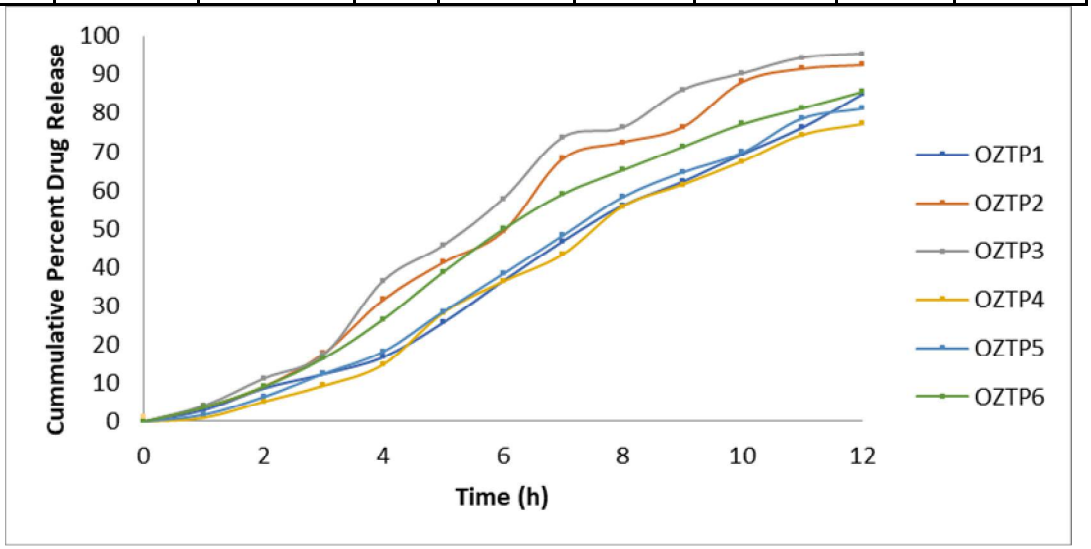

Figure1: Zero-order kinetics plotof olanzapine containing transdermal patch(OZTP1-OZTP6)

CONCLUSIONS

The TDDS have a number of variables i.e. plasticizers, penetration enhancers, rate controlling process and adhesion on skin, which will improve the therapeutic effect of drugs. The proposed approaches as transdermal patch have power of adhesion, which creates good penetration ability through the skin with controlled manner. The prepared proposed transdermal patch were flexible, smooth, opaque and non sticky in nature. The result of thickness, mass deviation, cracking acceptance power, percentage elongation, tensile strength, swelling ratio, surface pH, drug content with better values other the formulations. The release kinetic study confirmed the prepared patch was followed supercase II transport

mechanism of diffusion kinetics with sustained release within specific time period. Regression analysis was performed and the r^2 values suggested that the curves were fairly linear and slope values were computed from the graph. The release exponent "n" values were in the range of 1.033 to 1.169. The release exponent "n" was > 1.0 indicating Super-case II transport mechanism and observed deviation from Fickinan mechanism of drug release.

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