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DESIGN AND ASSESSMENT FOR THE PENETRATION ENHANCER WITHIN THE TRANSDERMAL ANTIPSYCHOTIC DRUG PATCH

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Abstract:
Schizophrenia and a mood condition are combined to form schizoaffective disorder. Both conditions are fully present in the same patient and may be diagnosed independently. Crucially, when the mood illness is absent, the psychosis must persist for at least two weeks. It is also necessary for the mood disorder to be diagnostically present during the bulk of the illness's active and residual stages. The Olanzapine transdermal patch is a long-term therapy for schizophrenia that includes a delayed release formulation. Initially, individuals with schizophrenia were treated chronically with oral and intramuscular administration of the intended model medicine, olanzapine. The investigation of olanzapine's skin penetration was the goal of this experiment. There are many factors in the suggested formulations, including plasticizers, penetration enhancers, rate-controlling mechanisms, and skin adherence. Instead of using traditional oral dose forms, a straightforward drug-matrix style transdermal drug delivery system was created for both types of medications to be used for an extended term of maintenance treatment. Furthermore, the physicochemical properties of olanzapine also somewhat abide by the overall need for developing a TDDS. Through techniques like transdermal patches that adhere to a portion of skin, we could be enhancing the therapeutic efficacy of medications. When several penetration enhancers are arranged, the patch's power of adhesion gives TDDs a strong chance of penetrating.

Keywords: Penetration Enhancer, Transdermal Patch, Antipsychotic Drug

Introduction: The oral route is the one that patients choose to use for medication delivery; nevertheless, oral administration is more likely to result in hepatic first-pass metabolism, which calls for a greater dosage of medication [1]. Furthermore, the main barrier to surfactant presence in lipid-based formulations is gastrointestinal irritation. Simultaneously, medication dispersion throughout the body may result in inevitable adverse effects [2]. Neurologic illness and psychosis are mental conditions that are significantly overlapped. The purpose of this paper is to inform neurologists on the assessment, diagnosis, and treatment of psychosis in its psychiatric forms [3]. Dementia often manifests as psychosis, however sometimes psychosis itself is the presenting symptom. According to reports, psychosis is one of the most prevalent illnesses in late age, with a lifetime risk of 23%. A delusional state or states is indicative of delusional illness. According to the requirements, the patient's delusions must be maintained for a minimum of one month and cannot be attributed to any other mental health condition. Traditionally, the illusions are not unusual in the slightest (that is, they may occur in real life, for example, being followed, being ill, or experiencing a celebrity's far affection) [4]. DSM-5, however, now recognises a category

characterised by strange (implausible) delusions. The patient's functioning is not much affected by whatever delusions they may have, and their behaviour is often not seen as strange or abnormal. Delusional disorder is uncommon, with a frequency of 0.2% to 0.3%. A mood disorder and schizophrenia are combined to create schizo affective disorder. Both conditions are fully present in the same patient and may be diagnosed independently. Unlike schizoaffective disease, major depression with psychosis is characterised by the presence of psychosis exclusively in cases of extreme depression [5]. Clozapine has been demonstrated to be more successful than other oral antipsychotics in treating patients with treatment-resistant psychosis, or patients for whom a number of other antipsychotics have failed. It has also been shown to be helpful in lowering suicidal thoughts and behaviours in patients with schizophrenia and schizoaffective disorder. An antipsychotic medication called olanzapine is used to treat schizophrenia, bipolar 1 disorder, and the agitation that goes along with these conditions. A thienobenzodiazepine, olanzapine is categorised as an atypical or second-generation antipsychotic medication.2. When second-generation antipsychotics were first made available in the 1990s, their remarkable effectiveness, lower chance of further pyramidal side effects, and less vulnerability to drug-drug interactions all contributed to their rapid popularity [6]. The main differences between olanzapine and clozapine are the two extra methyl groups and the lack of a chloride moiety. In order to treat schizophrenia in people older than 13 on a long-term basis, olanzapine was first administered orally and intramuscularly. It was also used to treat bipolar I illness, which included mixed or manic episodes. Olanzapine is also recommended for the short-term management of acute manic or mixed episodes linked to bipolar I illness in adults when combined with lithium or valproate. [7] Numerous physical and chemical strategies have been proposed to explain the possible benefits of transdermal/dermal drug administration, such as limited first-pass metabolism, patient comfort and compliance, and local drug distribution to the skin. A technique like this is used to get beyond the obstacle that prevents drugs from penetrating the skin[8].In 1984, the US Food and Drug Administration (FDA) approved the first transdermal system that included nicotine patches and scopolamine. Many transdermal patches for analgesic activities, hormone replacement treatment, contraception, and pain management were authorised by the FDA and researchers, and advancements in this area are still being made today[9–10].The drug's release from the patches or device is regulated by the application of the polymer. For TDDS, the polymer has characteristics such molecular weight, chemical functionality, stability, non-toxicity, ease of handling, flexibility, etc. The purpose of the penetration enhancers is to increase skin permeability. These substances have the ability to alter the target substance's skin barrier flux. The methods of skin permeability that are used to boost bioavailability [11–13].

Material and Methods

Maximum absorption wavelength (λmax) and calibration curve of olanzapine: Elanzapine was used as the drug sample, and the absorption maxima were identified by UV scanning the drug solution using an ultraviolet spectrophotometer between 200 and 400 nm in wavelength. Olanzapine's calibration curve was created by precisely weighing the necessary 25 mg of the drug

sample, or olanzapine combined with 25 ml of phosphate buffer pH 7.4 solvent in a volumetric flask. The solutions that were obtained had concentrations of 10 µg/ml, 2µg/ml, 4µg/ml, and up to 10µg/ml, in that order. At 246 nm, the absorbance of each resultant solution was measured separately using phosphate buffer pH 7.4 as a blank. A standard curve was drawn between absorbance and concentration after the absorbance was determined.

Validation of analytical method development: The ability to identify the target analyte when interfering material is present is known as the specificity test for the analytical procedure. By adding known levels of contaminants or contaminating agents to a test together with a known concentration of the target analyte, specificity may be revealed. Precision tests were divided into two categories, namely repeatability tests and intermediate precision tests, in accordance with the ICH criteria. The guidelines also divided the Intermediate Precision Test into two categories: the Intra-day Precision Test and the Inter-day Precision Test. The determination of intra-day precision was conducted by measuring the absorbance of 10 µg/ml of olanzapine in a pH 7.4 phosphate buffer solution, at pre-arranged intervals throughout the day.The determination of the inter-day precision test was conducted on three distinct days by the evaluation of the medication olanzapine's absorbance at 10 µg/ml in a pH 7.4 phosphate buffer solution. The discrepancy between the measured and utilised quantities was defined as the accuracy research test of the analytical procedure.

Pre-formulation studies

Organoleptic Identification: The drug samples were physically identified i.e. Color, odor and taste etc.

Microscopic examination*:* Microscopic examination of the olanzapine sample was done to study the nature / texture of the powder. A pinch of drug powder was spread on a glass slide and observed under phase contrast microscope.

Particle size: The average particle size (d_{avg}) of drug olanzapine was observed by using a phase contrast microscope (66172/Olympus, 100 X, Olympus (India) Pvt. Ltd., New Delhi) fitted with ocular micrometer and stage micrometer.

Flow properties: The flow properties of drug powders olanzapine was characterized in terms of carr's index, hausner's ratio and angle of repose. The Carr's index ((I_C)) and Hausner's ratio (H_R) of drug powders were calculating according to following equation:

- Carr's Index (I_C) = $\rho_{Tapped} - \rho_{Bulk} / \rho_{Tapped}$
- Hausner's ratio (H_R) = $\rho_{Tapped} / \rho_{Bulk}$

The angle of repose (θ) was measured by fixed height method. This was calculated by following equation:

- Angle of repose (θ) = $\tan^{-1} 2\ H / D$

Where H is the surface area of the free standing height of the powder heap and D is diameter of heap that formed after powder flow from the glass funnel.

Solubility determination: We tested the solubility of both medications (API, olanzapine) in a

range of solvents, including water, 0.1 N Hcl, and phosphate buffer 7.4. Separately, the surplus drug samples (olanzapine) were added to 50 millilitres of medium and continuously stirred at 37±0.5ºC throughout the whole night. Whatmann filter paper with a 0.45µm pore size was used to filter the samples.Using spectrophotometry, the drug's (olanzapine) solubility in various media at 246 nm was assessed.

Partition coefficient: Drug samples' partition coefficient was measured in a 50 ml mixed solvent solution comprising n-octanol and phosphate buffer pH 7.4. Using the following formula, the partition coefficient of API was determined from the ratio of drug concentrations in organic and aqueous quantities.

Log P (oct / pH 7.4) = Log (C_{Oct} / $C_{pH\ 7.4}$) equilibrium

Melting point: The Melting point of drug samples (olanzapine) were obtained by pinch of API sample filled in capillary tube by hand.

Drug Excipients compatibility study of drug samples: Studies on the compatibility and interaction between drugs and certain excipients are carried out in order to determine any potential interactions for the formulation design process. The Shimadzu IR Spectra photometer was used to conduct the drug olanzapine procedure utilising the potassium bromide disc technique. Drug powder combined in a 9:1 ratio with potassium bromide powder. The disc was formed using pressure, then it was put in the FTIR sample holder and scanned.

Preparation of the olanzapine patch: The goal of this research was to create a transdermal patch that would deliver olanzapine in a short amount of time. While the chitosan solution was made by dissolving the polymer in 1% v/v acetic acid solution while stirring at 40 °C, the sodium alginate and methyl cellulose solutions were made independently by dissolving the necessary amounts in distilled water. As shown in Table 1, 10 mg of the API olanzapine were dissolved in the casing solvent prior to the addition of the polymeric solution separately. The drug polymer mixture was constantly agitated at 37±2°C using a thermostatic magnetic stirrer. To maximise the impact of penetration rate through skin, the plasticizers Glycerin were combined with a precise quantity of penetration enhancer oil, such as clove, neem, or linseed oils, and stirred in different proportions. To get rid of the air bubbles, all of the solutions were let to stand for the whole night. Once the stirring process was finished, the mixture was sonicated in an ultrasonic water bath and then transferred onto petri dishes with a mercury base and circular glass bangles that were open on both sides. Aluminium foil was used to cover the bottom of the bangle so that the solvent could evaporate at 35°C (Olven Instruments, India). Solvent casting was the procedure used to prepare the films. After being separated, the dried films were cut into 2 cm2 (4 mg) circular films, covered in aluminium foil, and kept in desiccators in airtight polyethylene bags.

Physical properties of olanzapine containing transdermal patch:

Physical appearance of patch: The parameters i.e. “optical checking, smoothness, color, transparency and flexibility” were observed.

Measurement of polymeric patch thickness: Measurement of polymeric films thickness was performed by utilizing a screw gauge (least count of 0.02 mm).

Patch weight variation measurement: Carefully prepared polymeric films were weighed three times, and the mean was determined. Each movie's weight should fall within the allowed maximum and the average weight of all the movies.
Patch homogeneity or texture: The produced films were cut into strips. Two films were cut from the opposite sides, and one film was cut from the middle. Use a scale to measure the length of the film strips once they have been cut. Films shouldn't include any restrictions.
Patch's surface pH: A digital pH metre was used to ascertain the pH of the produced films' surface. The prepared film piece was cut, stored in 0.5 millilitres of double-distilled water, and given a full hour to swell.
Tensile strength of patch: A manufactured tensile strength equipment was used to test the tensile strength of a 2 cm2 film. The films were put in the film holder after being taped. An adhesive tape hole was formed, and a hook was placed into it. This hook has a thread fastened to it. To hold the weights, a tiny pin was fastened to the other end of this hook, which was passed across the pulley. The thread that passes across the graph paper fastened to the base plate has a tiny pointer connected to it. Until the film breaks, continue adding weights from the beginning low mass to the more. The following calculations were used to compute the tensile strength and break force, which indicated the weight needed to break the film.
Tensile strength (N / mm^2) = Breaking force (N) / Cross sectional area of sample (mm^2)
Folding endurance: By manually cutting a section of the film, the prepared film's folding endurance was determined. The film segment that was eliminated was folded in the same spot. The process of folding was carried out many times till the film broke. The film's folding durability was determined by taking the mean number of folds at the same location without breaking.
Moisture content: The films were weighed, air-dried at 60 degrees Celsius, and then preserved for 24 hours at 40 degrees Celsius in desiccators filled with calcium chloride. Following that, the dried films were stored at room temperature and 75 ± 0.5%. Relative humidity (75% humidity maintained throughout storage until equilibrium by a saturated sodium chloride solution), weighed films, and computed the weight percent increase.
Swelling Ratio: Films were weighed at predetermined intervals and kept in a petri dish with distilled water until they reached a consistent weight. The following formula was used to determine the degree of swelling (SR%).

$$\textbf{SR (\%)} = \frac{[\text{Mass of films at time of investigation} - \text{Initial mass of films}] * 100}{\text{Initial mass of films}}$$

Moisture uptake percentage: Moisture uptake percentage determined by weighted the piece of film which was carefully cut by knife. It was placed in desiccators for 24h at temperature 25-30°C ; 75% Relative humidity, then weighed and calculated moisture uptake property using the below equation.
Moisture uptake percentage of patch = [Final mass of patch - Initial mass of patch /Initial mass of patch] × 100
Drug content: Square piece of prepared patch (2^2 cm) placed in of dissolution medium (100 ml),

stirred constantly for 24 hour. The resulting mixture was ultra sonicated for 15 min, filtered. Filtrate was diluted with same dissolution medium at 246 nm for olanzapine by UV spectrophotometer for drug content determination.

***In vitro* skin permeation study:** Utilising distilled water in a glass Franz-diffusion cell constructed in a lab, an in vitro drug release investigation was carried out. The 2cm2 prepared formulation films were sliced, evenly distributed, and securely kept in place by springs between the donor and receptor compartments of the diffusion cell's cellophane membrane. Whereas the receptor compartment had 75 millilitres of phosphate buffered saline (pH 7.4), the donor compartment was empty. The temperature was maintained at 37±5ºC and the magnetic stirrer was set at 100 rpm. Five millilitre aliquots of the medication were removed at various times up to a 12-hour period in order to measure the quantity released. An equivalent amount of fresh, pre-warmed (37±5ºC) phosphate buffered saline (pH 7.4) was used to replace the volume removed. After 15 minutes of ultrasonication, the resultant aliquates were filtered. To determine the drug content, the filtrate was diluted using the same dissolving media for olanzapine at a wavelength of 246 nm using a UV spectrophotometer.

Results and Discussion

In a phosphate buffer pH 7.4 solution, the medication olanzapine has an absorption maximum (λ-max) of 246 nm. The specificity tests for the two medications individually shown that none of the formulations' components interfered with the drug content research, proving the specificity of the technique for determining drug quantity in phosphate buffer pH 7.4 solution. Every validation study result, including the intra- and inter-day precision tests, was accompanied by a repeatability pass in the real parameters.

The medication samples' sensory attributes include olanzapine's white colour, odorlessness, and mildly bitter taste. Olanzapine was discovered to be crystalline in form. A tapped density device was used to measure the tapped density. Olanzapine was to be supplied in bulk and tapped densities of 0.618 and 0.676 gm/cm3, respectively.Particle size of olanzapine averaged 82 μm.The unmilled olanzapine exhibited exceptional flow characteristics as shown by its Carr's index (%) of 8.57±0.038, Hausner's ratio of 1.09±0.012, and angle of repose of θ24.5±0.111. Olanzapine's pH solubility profile is as follows: 0.821±0.822 for phosphate buffer pH 4.5, 3.122±0.2016 for phosphate buffer pH 6.8, and 1.061±1.063 for phosphate buffer pH 7.4. The drug samples have a partition coefficient of 1.39±0.021 and are hydrophillic in nature, with a melting point of 123 ± 0.115 °C. "Optical checking, smoothness colour, transparency and flexibility, thickness of polymeric films, mass deviation of films, uniformity or texture of films, surface pH of films, tensile strength of films, cracking acceptance power of films, water ingestion amount of films, swelling ratio of films, wetness of films" were among the optimised parameters that were used to characterise the prepared olanzapine films. The results of the investigation showed that sodium alginate polymers had swelling properties and may improve the drug-retarding properties of olanzapine. This was determined by an in-vitro drug release research.

A water-impermeable layer with an excellent swelling index is produced by the chitosan polymer

and glycerin plasticizer. Because the polymer matrix layer permits the creation of pores over time as a result of the employment of a penetration enhancer inside the skin layer's pH, drug retardation is improved by more than 75% after 12 hours is required for sustained release. The physical characteristics, tensile strength, percentage elongation, folding endurance, swelling ratio, moisture content, moisture absorption type, drug content, and in-vitro drug release research factors were taken into consideration while choosing the polymeric films (TPOZ6). The produced film was verified by the release kinetic investigation to have adhered to the supercase II transport mechanism of diffusion kinetics with sustained release within the designated time frame.

Table 1: Preparation of olanzapine containing transdermalpatch

Form. Code	Polymers (gm)	Plasticizers (ml)	Penetration enhancer		
	Chitosan	Glycerin	Clove oil (ml)	Neem oil (ml)	Linseed oil (ml)
TPOZ1	2	5	5	-	-
TPOZ2	2	5	5	-	-
TPOZ3	2	5	-	-	-
TPOZ4	2	5	-	5	-
TPOZ5	2	5	-	5	-
TPOZ6	2	5	-	5	-
TPOZ7	2	5	5	-	5
TPOZ8	2	5	-	-	5
TPOZ9	2	5	-5	-	5

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

Formulation code	Thickness (mm)	Average weight (mg)	Folding endurance	Percentage Elongation	Tensile Strength N/mm^2	Swelling ratio (%)	Surface pH	Drug content of patch
TPOZ1	0.129±0.03	111.32.±1.154	75-80	93.74±0.15	3.46±1.18	38.97 ± 0.43	5.5 ± 0.14	93.99±0.8
TPOZ2	0.126±0.02	110.33±1.156	79-80	94.81± 0.02	6.69±0.23	35.32 ± 0.39	5.6 ± 0.14	94.95±0.9
TPOZ3	0.125±0.03	112.60±0.144	86-91	9.42± 0.09	5.93±0.13	42.18 ± 0.58	5.7 ± 0.52	95.89±0.10
TPOZ4	0.124±0.02	119.23±1.154	92-95	96.52± 0.02	6.89±0.23	41.43 ± 0.49	5.8± 0.12	99.59±0.11

TPOZ5	0.123±0.01	118.33±1.155	93-97	97.12±0.03	5.76±1.18	39.42 ± 0.57	5.5 ± 0.43	98.27±0.12
TPOZ6	0.122±0.01	114.66±1.165	91-94	99.11±0.02	6.23±0.13	36.63 ± 0.54	5.5 ± 0.14	99.25±0.13
TPOZ7	0.124±0.03	116.37±1.154	90-93	95.91±0.15	5.46±1.18	40.13 ± 0.55	5.6 ± 0.24	97.15±0.14
TPOZ8	0.125±0.03	113.78±0.111	94-98	94.72±0.15	5.29±0.23	42.87 ± 0.46	5.7 ± 0.34	99.84±0.15
TPOZ9	0.126±0.02	112.43±1.152	99-101	92.72±0.15	4.43 ±0.13	39.48 ± 0.45	5.6 ± 0.72	97.49±0.16

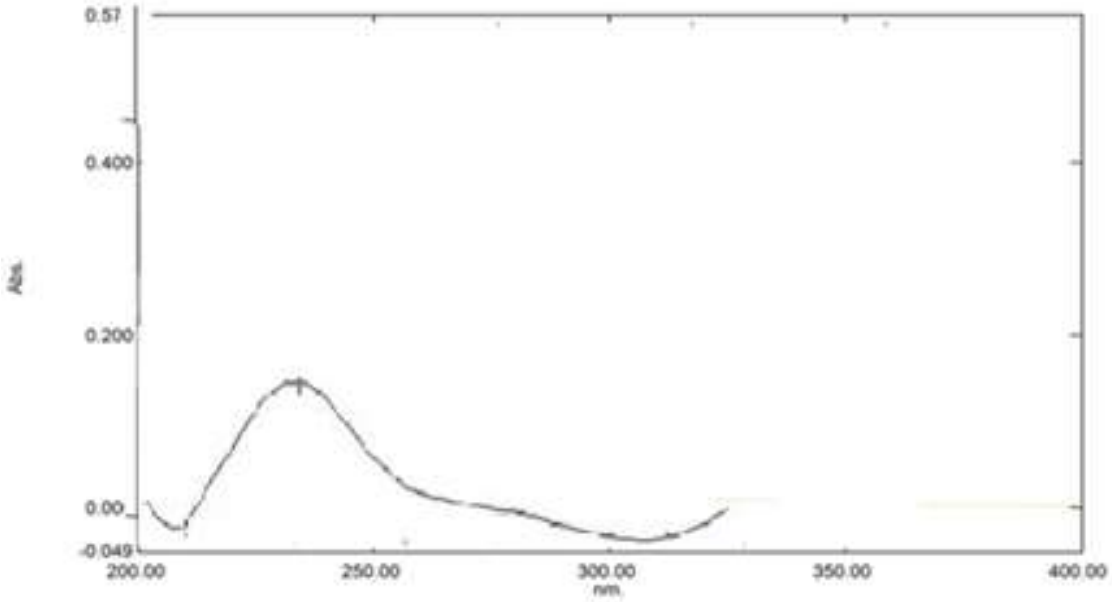

Figure 1: Absorption maxima (λ-max) of olanzapine in phosphate buffer pH 7.4 solution (10 µg/ml)

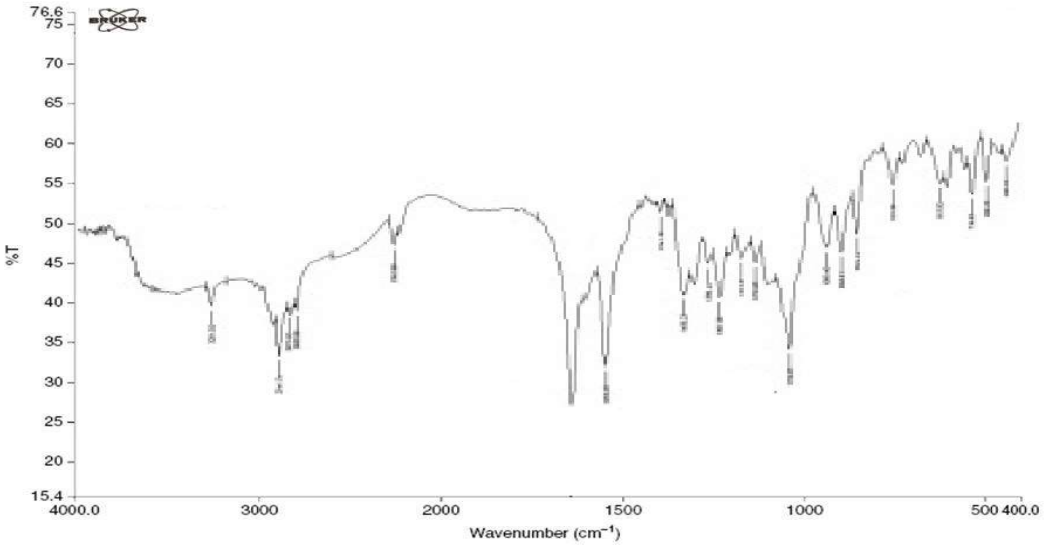

Figure 2: The I. R. Spectrum of olanzapine drug and all excipients

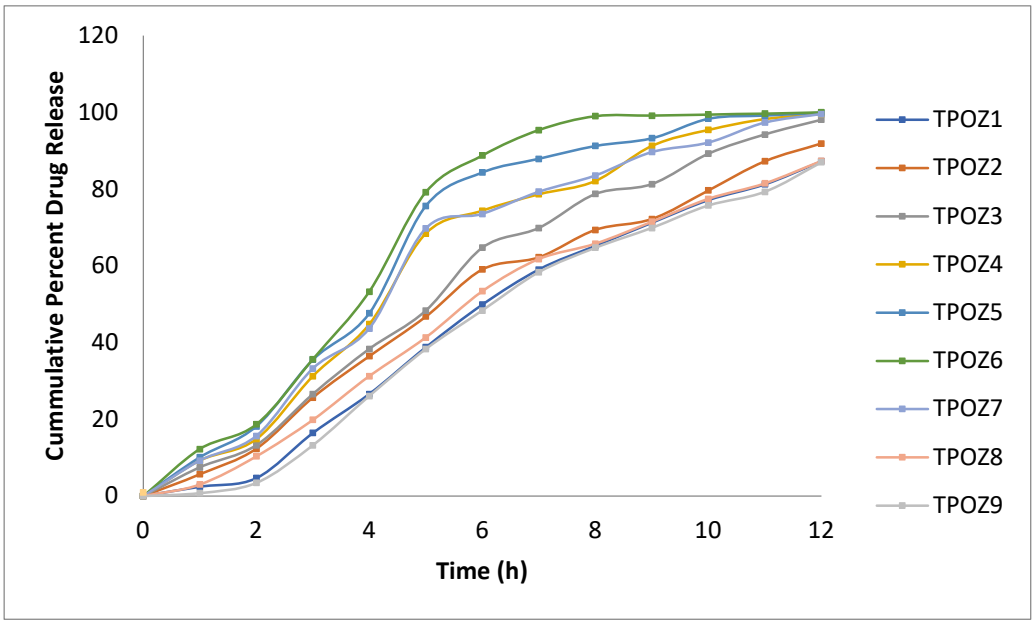

Figure3: In-vitro drug release study (zero-order kinetics) of olanzapine containing transdermal patch (TPOZ1-TPOZ9)

Summary and Conclusions

The therapeutic efficacy of pharmaceuticals may be enhanced by a variety of factors found in TDDS, such as plasticizers, penetration enhancers, rate regulating processes, and skin adherence. The transdermal patches that are being suggested have a strong adhesive strength that allows for regulated skin penetration. The transdermal patch that was produced and suggested was smooth, flexible, opaque, and non-stick. Thickness, mass deviation, % elongation, cracking acceptance power, tensile strength, swelling ratio, surface pH, and TPOZ6 drug content results were all better than those of the other formulations. The medicine was released using a hydrophilic polymer

matrix made of chitosan, which improved the water soluble olanzapine's spreadability and dispersibility when it was required for instant release. The observed divergence from the Fickinan mechanism of drug release was indicated by the release exponent "n" of > 1.0, which indicates the Super-case II transport mechanism.

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