EFFECT OF PENETRATION ENHANCERS ON THE FORMULATION AND CHARACTERIZATION OF TRANSDERMAL DELIVERY OF OLANZAPINE

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Abstract:
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. 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. The aim of this work was to study the permeation of olanzapine across the skin. The proposed formulations have a number of variables i.e. plasticizers, penetration enhancers, rate controlling process and adhesion on skin. Simple drug-matrix type of transdermal drug delivery system for both type of drugs were designed for prolonged period of maintenance therapy instead of convention oral dosage forms. Moreover, the physicochemical characteristics of olanzapine also comply with the general requirement for designing a TDDS to a good extent. We may be improving the therapeutic effect of drugs via approaches as transdermal patch hold on to part of skin. The power of adhesion of patch creates good penetration ability of TDDs by using arrangement of different penetration enhancers.

Keywords: Penetration Enhancer, Transdermal Patch, Antipsychotic Drug

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Introduction: Oral route is the most preferred route fastens in patient fulfilment; though, oral administration is more prone to hepatic first pass metabolism required higher dose of drug [1]. Additional, gastric irritation is the major restrictions for the presence of surfactants in the lipid based formulations concurrently the distribution of drug throughout the body can lead to obligatory side effects [2]. Psychosis is a psychiatric condition that has significant overlap with neurologic disease. This article is intended to educate the neurologist on the psychiatric manifestations of psychosis and its evaluation, diagnosis, and treatment [3]. Psychosis is commonly a symptom of dementia, and sometimes the psychosis is actually the presenting symptom. It is reported that psychosis has a lifetime risk of 23% and ranks as one of the most common conditions in late life. Delusional disorder is characterized by the presence of one or more delusions. The criteria state that the patient must hold the delusion(s) for at least 1 month and that the delusions cannot be explained by another mental disorder. Classically, the delusions are usually not bizarre in nature (ie, they could happen in real life, such as being loved at a distance by someone famous, being infected with a disease, or being followed) [4]. However, DSM-5 now allows a subtype with bizarre (implausible) delusions. Whatever delusions are held, the patient's functioning is not significantly impacted, and his or her behavior is not usually considered odd or bizarre. The incidence of delusional disorder is 0.2% to 0.3%, making it rare. 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. Major depression with psychosis is different than schizoaffective disorder because the psychosis is only present when the patient is severely depressed [5]. Clozapine has consistently been shown to be more effective than other oral antipsychotics in patients for whom a number of other antipsychotics have failed (ie, treatment-resistant psychosis) and has also been shown to be effective in reducing suicidal behaviors in patients with schizophrenia and schizoaffective disorder. Olanzapine is an antipsychotic drug used in the management of schizophrenia, bipolar 1 disorder, and agitation associated with these disorders. Olanzapine is a thienobenzodiazepine classified as an atypical or second-generation antipsychotic agent.2 The second-generation antipsychotics were introduced in the 90s and quickly gained traction due to their impressive efficacy, reduced risk for extrapyramidal side effects and reduced susceptibility to drug-drug interactions [6]. Olanzapine very closely resembles clozapine and only differs by two additional methyl groups and the absence of a chloride moiety. Olanzapine was initially used orally and intramuscularly for the chronic treatment of schizophrenia in patients over 13 years old and other psychiatric disorders such as bipolar I disorder including mixed or manic episodes. 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. [7] The potential advantages of transdermal /dermal drug delivery (e.g., minimal first-pass metabolism, patient comfort/compliance, local drug delivery to the skin) have various physical and chemical approaches. Such system used to overcome the limiting barrier of drug penetration into the skin [8]. US Food and Drug Administration (FDA) approved first transdermal system containing scopolamine and nicotine patches in the year of 1984. The researchers and FDA approved a number of transdermal patches for pain relief, analgesic activity, contraception, and hormone replacement therapy and the progress in this field continues today [9-10]. The polymer is applied to controls the release of the drug from the device or patches. The polymer has such properties i.e. molecular weight, chemical functionality of the polymer, stable, non-tosic, easily handle, flexible etc for TDDS. The penetration enhancers use to promote skin permeability through skin. These substances can change the skin barrier flux by desired substance. The skin permeability techniques used to increase bioavailability [11-13].

Material and Methods

Maximum absorption wavelength (λmax) and calibration curve of olanzapine: The identification of absorption maxima was determined by UV scanning of drug solution under ultraviolet spectrophotometer between 200 to 400 nm wavelengths offer drug sample i.e olanzapine.

The calibration curve of olanzapine was prepared by accurately weighed required quantity 25 mg of drug sample i.e. olanzapine mixed in volumetric flask containing 25 ml of phosphate buffer pH 7.4 solvent. The concentration of resulting solutions were 10 µg / ml, 2 µg / ml, 4 µg / ml, upto 10 µg / ml respectively. The absorbance of all resulting solution was calculated individually at 246 nm with phosphate buffer pH 7.4 as a blank. The

absorbance was measured and standard curve was plotted between absorbance vs. concentration.

Validation of analytical method development: The specificity test for the analytical method is defined as the capability to notice the analyte of attention in the occurrence of interfering material. Specificity is exposed by spiking recognized stage of impurities or corrupting agents in to a test with a known quantity of the analyte of concentration. As per the ICH guidelines precision test was classified in to two parameters i.e.; repeatability test and intermediate precision test. As per guidelines Intermediate precision test was also classified in to two parameters i.e.; Intra-day precision test and Inter-day precision precision test. Intra-day precision was determined at predetermined time interval within a day by assessment of the absorbance of 10 µg / ml drug olanzapine in phosphate buffer pH 7.4 solution. Inter-day precision test was determined on three different days by by assessment of the absorbance of 10 µg / ml drug olanzapine in phosphate buffer pH 7.4 solution. The test of accuracy study of analytical method was specified as the difference between the measured quantity and the used quantity.

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: The solubility of both drugs API (olanzapine) was determined in various solvents (Water, 0.1 N Hcl, and phosphate buffer 7.4. The excess amount of drug samples (olanzapine) seperately was further to 50 ml of medium and stirred constantly overnight at 37±0.5ºC. The samples were filtered by using whatmann filter paper (0.45µm pore size). The solubility assessment of drug (olanzapine) in 246 nm in different medium was determined spectrophotometrically.

Partition coefficient: The partition coefficient of drug samples was observed in mixed solvent of 50 ml containing n-octanol: phosphate buffer pH 7.4 solution. The partition coefficient of API was calculated from the proportion between the concentrations of drug in organic and aqueous quantity using following equation.

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: Drug-excipients interaction/ compatibility studies are performed to ascertain any interaction between drug and selected excipients for formulation design. It was carried out using potassium bromide disc method for drug olanzapine by Shimadzu IR Spectra photometer. Drug powder mixed with potassium bromide powder in 9:1 ratio. Disc was prepared by using pressure then placed in sample holder of FTIR and scanned.

Preparation of the olanzapine patch: The objective of present study was to prepare transdermal patch containing olanzapine able to release drug within short time interval. The sodium alginate and methyl cellulose solutions were prepared separately by dissolving the required quantities in distilled water, whereas chitosan solution was prepared by dissolving the polymer in 1 % v/v acetic acid solution with stirring at 40 °C. The API olanzapine quantity 10 mg were dissolved in casing solvent before addition of polymeric solution separately as given in **Table 1**. The drug polymer mixture was

continuously stirred on thermostatic magnetic stirrer at 37±2°C. The plasticizers Glycerin with the addition of accurate amount of penetration enhancer oil i.e. clove oil / neem oil / linseed oil were added with stirring in various concentrations for optimized the effect of penetration rate through skin. All the solutions were allowed to stand overnight to remove the air bubbles. After stirring completion, it was sonicated in ultrasonic water bath and poured in petri dishes containing mercury base having circular glass bangles with open at both sides. The bottom of the bangle was wrapped with aluminum foil to allow solvent evaporation at 35°C (Olven Instruments, India). The films were prepared by solvent casting method. The dried films were separated, cut into circular films of 2 cm^2 (4 mg drug), wrapped in aluminum foil and stored in air tight polyethylene bags in desiccators.

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).

Measurement of patch weight variation: Prepared polymeric films were weighed cautiously in triplicate manner and calculated the mean. The weight of individual films should be within permitted limit the mean weight of films.

Uniformity or texture of patch: The prepared films were cut as strips. One film cut from centre and two were cut from other sides. After cutting the strips of films, measure the length by using scale. There should not be any constriction in films.

Surface pH of patch: Digital pH meter was used to determine the pH of surface of prepared films. The prepared film piece was cut and kept in 0.5 ml double distilled water and allowed to swell for 1 h.

Tensile strength of patch: Tensile strength of 2 cm^2 film was measured by using fabricated tensile strength apparatus. The films were fixed by tapes and placed in the film holder. A small hole was made in the adhesive tape in which a hook was inserted. A thread was tied to this hook. This hook was passed over the pulley and a small pin attached to the other end to the hold the weights. A small pointer was attached to the thread, which travels over the graph paper affixed on the base plate. Now add the weights from initial low mass to the more until the film was broken. The weight required to break the film was noted as break force and tensile strength calculated by the following formulae**.**

Tensile strength (N / mm^2) = Breaking force (N) / Cross sectional area of sample (mm^2)

Folding endurance: Folding stamina of prepared film was ascertained by manual method as cutting a portion of film. The cut piece or portion of film was folded at the same place. The folding procedure was performed repeatedly till the film broke. Folding endurance were calculated mean of the number of times the film was folded at the same place without breaking **(Murthy et al., 2008)**.

Moisture content: The films were weigh, dried with current of air at 60ºC and were kept in desiccators having calcium chloride at 40ºC for 24 h. Then dried films were kept at room temperature and temperature 75 ± 0.5% Relative humidity (75% humidity maintained by saturated solution of sodium chloride during storage till equilibrium, weighed films, calculated the increase in weight percent.

Swelling Ratio: Films were placed in petri dish having distilled water till film achieved constant weight, which as ascertained by weighed the film at a certain time interval. Degree of swelling (SR %) was calculated using the below equation.

SR (%) = [Mass of films at time of investigation – Initial mass of films * 100
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 24 h 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 ultrasonicated 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:** In vitro drug release study was performed using distilled water in a glass Franz-diffusion cell composed in laboratory. The prepared formulations films 2 cm^2 were cut and were uniformly spread onto the cellophane membrane in between donor and receptor compartments of the diffusion cell and were held tightly by springs. The donor compartment was empty, whereas the receptor compartment was filled with 75 ml of phosphate buffered saline (pH 7.4). The magnetic stirrer was set at 100 rpm and the temperature was maintained at 37±5ºC. The amount of drug released was determined by withdrawing 5 ml aliquots at different time intervals upto 12 h. The volume withdrawn was replaced with an equal volume of fresh, prewarmed (37±5ºC) phosphate buffered saline (pH 7.4). The resulting aliquates was ultrasonicated for 15 min, filtered. Filtrate was diluted with same dissolution medium at 246 nm for olanzapine by UV spectrophotometer for drug content determination.

Results and Discussion

The absorption maxima (λ-max) of olanzapine drug in phosphate buffer pH 7.4 solution are 246 nm. The results of specificity tests for individual both drugs were showed that there is no interference of the all component of the formulations for the drug content study and thus prove that the method is specific for determination of drug amount in phosphate buffer pH 7.4 solution. All the results of validation study as inter-day, intra-day precision test was followed with repeatability pass in actual parameters.

The sensory characteristics of drug samples olanzapine white in color, odorless, slightly bitter in taste. olanzapine was found to be crystalline in nature, The tapped density was determined using tapped density apparatus. Bulk and tapped densities of olanzapine were to be 0.618 gm / cm^3 and 0.676 gm / cm^3. Olanzapine mean particle size was found 82 μm. The flow properties of unmilled olanzapine in terms of Carr's index (%) 8.57±0.038, Hausner's ratio 1.09±0.012 and Angle of repose θ 24.5±0.111 and followed excellent flow characterstics. The pH solubility profile of olanzapine in terms of Phosphate buffer pH 4.5 is 0.821±0.822, Phosphate buffer pH 6.8 is 3.122±0.2016 and Phosphate buffer pH 7.4 is 1.061±1.063. The partition coefficient of drug samples is 1.39±0.021 and followed as hydrophiullic in nature with melting point is 123 ± 0.115 °C temperatures. The prepared olanzapine films were characterized a number of optimized parameters i.e. "optical checking, smoothness color, 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". The values obtained after the examination identified by in-vitro drug release study, that polymers sodium alginate have swelling character and able to enhanced drug retarding characteristics of drug olanzapine**.**

The chitosan polymer with glycerin plasticizer produces a water impermeable layer with good swelling index. The matrix layer of polymer allows creating the pores during the time span due to use of penetration enhancer within the pH of skin layer and consequently enhanced drug retardation more than 75% after 12 has needed for sustained release. The polymeric films (TPOZ6) 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 supercase II transport mechanism of diffusion kinetics with sustained release within specific time period.

Summary And 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 of TPOZ6 were shown better values other the formulations. The drug was released through polymers chitosan have matrix, which is hydrophilic nature and able to enhanced spreadability and dispersibility of the water soluble olanzapine as needed for immediate release. The release exponent "n" was > 1.0 indicating Super-case II transport mechanism and

observed deviation from Fickinan mechanism of drug release.

Table 1: Preparation of olanzapine containing transdermal patch

Formulation 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	5	-	-
TPOZ4	2	5	-	5	-
TPOZ5	2	5	-	5	-
TPOZ6	2	5	-	5	-
TPOZ7	2	5	-	-	5
TPOZ8	2	5	-	-	5
TPOZ9	2	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	3.66±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 ± 0.12	95.79±0.10
TPOZ4	0.124±0.02	119.23±1.154	92-95	96.52± 0.02	6.79±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	98.12± 0.03	5.86±1.18	39.42 ± 0.57	5.5 ± 0.13	98.07±0.12
TPOZ6	0.122±0.01	114.66±1.165	91-94	99.11±0.02	6.13±0.13	36.63 ± 0.54	5.5 ± 0.14	99.85±0.13
TPOZ7	0.123±0.03	116.37±1.154	90-93	95.91±0.15	5.76±1.18	40.13 ± 0.55	5.6 ± 0.14	97.55±0.14
TPOZ8	0.125±0.03	113.78±0.111	94-98	94.72±0.15	5.59±0.23	42.87 ± 0.46	5.7 ± 0.14	99.74±0.15
TPOZ9	0.126±0.02	112.43±1.152	99-101	92.72±0.15	4.63 ±0.13	39.48 ± 0.45	5.6 ± 0.12	97.99±0.16

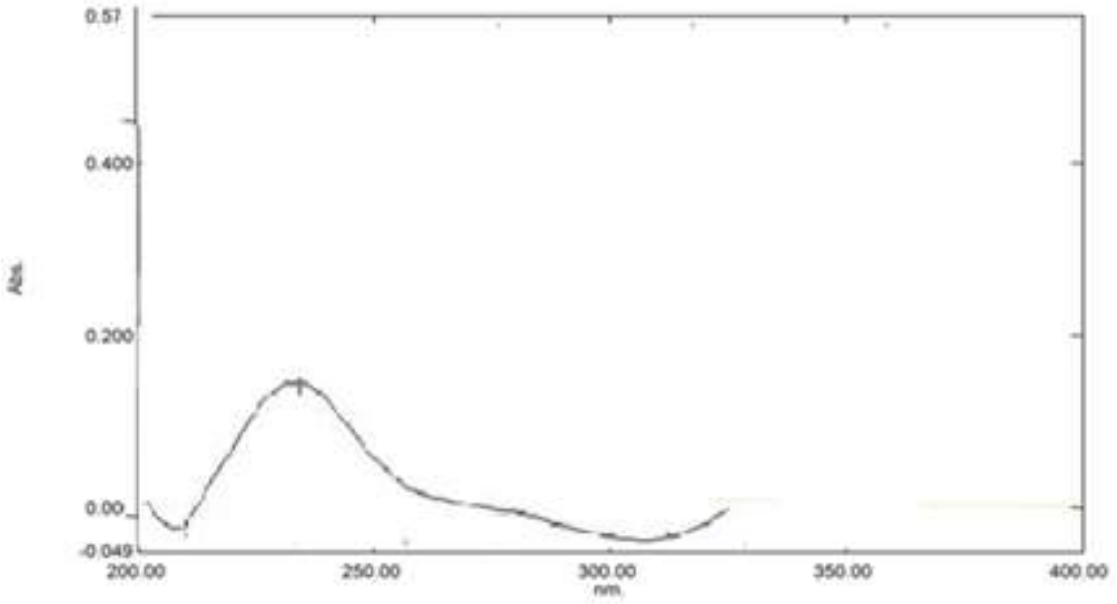

Figure 1: Absorption maxima (λ-max) of olanzapine in phosphate buffer pH 7.4 solution (10 µg/ml)

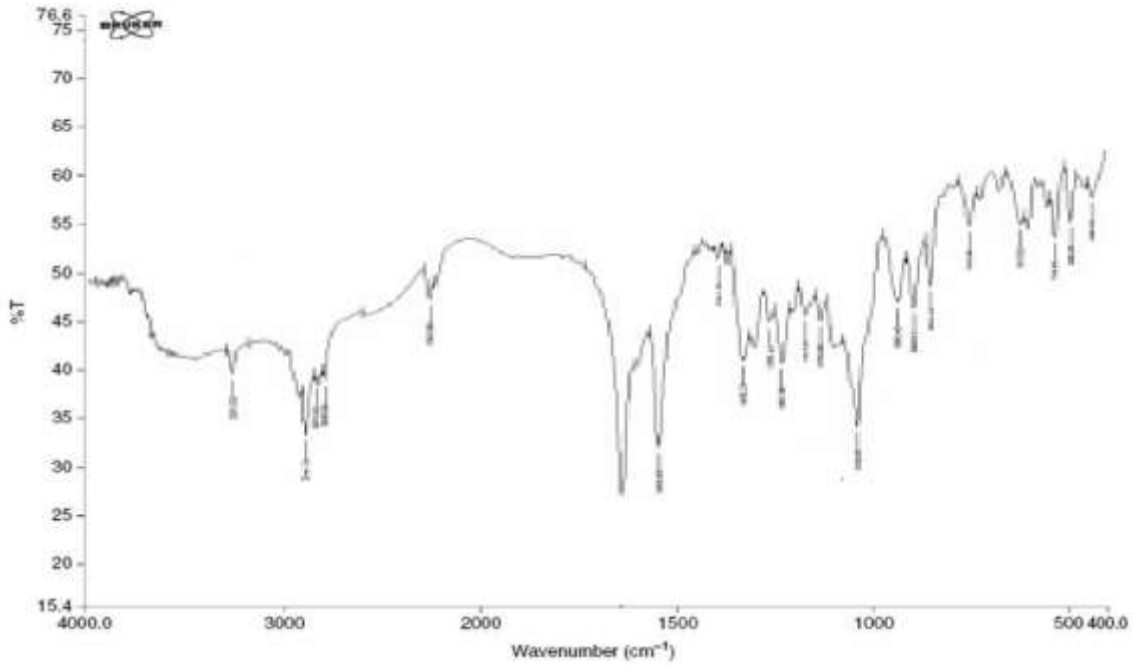

Figure 2: The I. R. Spectrum of olanzapine drug and all excipients

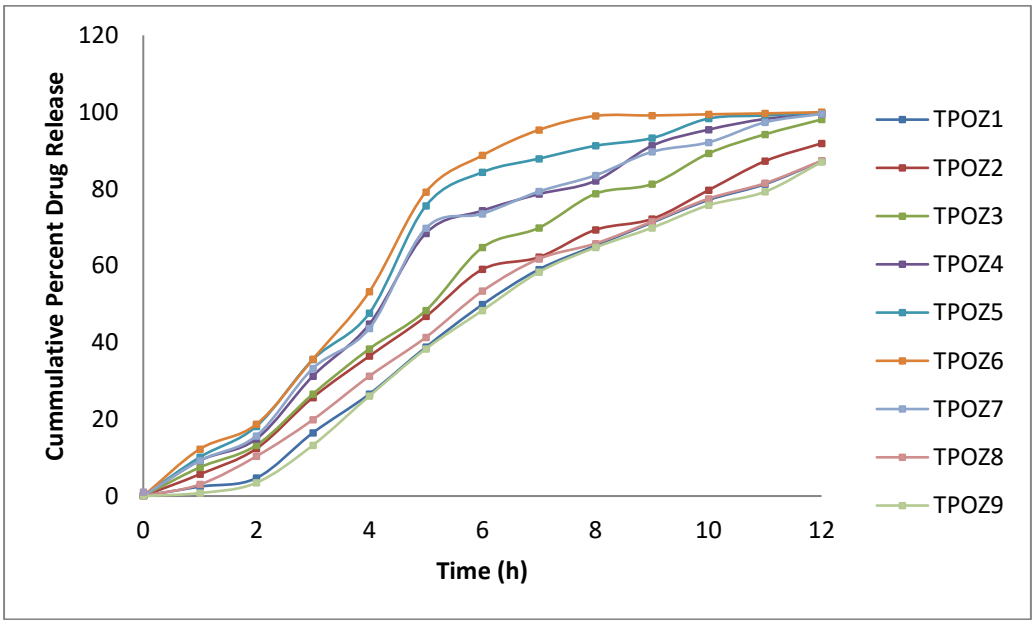

Figure 3: In-vitro drug release study (zero-order kinetics) of olanzapine containing transdermal patch (TPOZ1-TPOZ9)

References:

1. Ding, X., Alani, A.W. (2005) Robinson JR. Extended-Release and Targeted Drug Delivery Systems. In: Bringer, P., Gupta, P.K., Felton, K.L., editors. Remington: The Science And Practice of Pharmacy. 21st edition. Baltimore: Lippincott Williams & Wilkins, USA;. 1, P. 939
2. Ansel, H.C. (1990) Pharmaceutical Dosage Forms and Drug Delivery Systems. 5th edition. London: Lea & Febiger, Philadelphia, UK; P. 69.
3. Farrelly, S., Lester, H. (2014) Therapeutic relationships between mental health service users with psychotic disorders and their clinicians: a critical interpretive synthesis. *Health Soc Care Community*, 22(5):449–460.
4. Cynthia, L.S., John, T.S., Robert, L., (2012) Reservoir-based drug delivery systems utilizing microtechnology; *Advanced Drug Delivery Reviews*; 64, 14, 1590–1602.
5. Sachdev, P. (1998) Schizophrenia-like psychosis and epilepsy: the status of the

association. *Am J Psychiatry* 155(3):325–336.
6. Fathima, S.A., Begum, S., Fatima, S.S. (2017) Transdermal drug delivery system; *International Journal of Pharmaceutical and Clinical Research*; 9, 1, 35-43.
7. Green, M.F. (2016) Impact of cognitive and social cognitive impairment on functional outcomes in patients with schizophrenia. *J Clin Psychiatry*. 77(suppl 2):8–11.
8. Shargel, L., Pong, S.W., Yu, A.B. (2005) Applied Biopharmaceutics & Pharmacokinetics. 5th edition. New York: McGraw Hill companies, Inc., USA; P. 470-472.
9. Kotta, S., Khan, A.W., Ansari, S.H., Sharma, R.K., Ali, J. (2014) Anti HIV nanoemulsion formulation: Optimization and in vitro-in vivo evaluation, *Int. J. Pharm*., 462, 129–134.
10. Moser, K., Kriwet, K., Naik, A., Kalia, Y.N., Guy, R.H. (2001) Passive skin penetration enhancement and its quantification in vitro, *Eur J Pharm Biopharm*, 52, 103–112.
11. Roderick, B., Walker, Eric, Smith, W. (1996) The role of percutaneous penetration enhancers, *Advanced Drug Delivery Reviews* 18; 295-301.
12. Prausnitz, M.R. (2004) Microneedles for transdermal drug delivery. *Adv Drug Deliv Rev* 56: 581–587.
13. Ramoller, I.K., Tekko, I.A., McCarthy, H.O., Donnelly, R.F. (2019) Rapidly dissolving bilayer microneedle arrays – A minimally invasive transdermal drug delivery system for vitamin B12; *International Journal of Pharmaceutics*, 566, 299-306.