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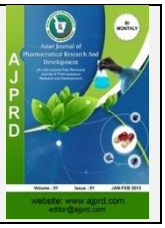

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Research Article

Formulation and evaluation of Transdermal Patch of Antipsychotic Drug to Overcome Nervous Emotional Disease

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A B S T R A C T

The transdermal drug delivery gives several benefits when compared with oral route viz. better adherence of sufferers on durable treatment, plasma drug level maintenance for an extended period of time, bypassing hepatic metabolism with reduced intra-patient variability. The outcomes of the proposed research work intimated that the proposed formulations of quetiapine provide the sustained drug delivery that, results in reduced dosage frequency. Thus, transdermal drug delivery facilitates the patient's adherence to long-term therapy as well as reduces the hurdles of doctors and caregivers regarding the treatment of the patients. Hence, this can be proved to be a propitious opportunity that affords effective treatment of schizophrenia.The present investigation highlights the prospects of alternate route of drug delivery inthe form of transdermal patch for the treatment of schizophrenia. The present research work will be able to develop and optimize transdermal matrix patch of quetiapine.

Keywords: Schizophrenia, TDDS, Antipsychotic Drug, Nervous Emotional Disease, Quetiapine Fumarate, Patch

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INTRODUCTION:

Schizophrenia is one of the most threatening, collateral and fearsome diseases of all mental disorders. Schizophrenia is the disorder that not only arouses anxiety in the patient but also makes the caretakers anxious [1]. Schizophrenia is characterized by the disintegration of thought processes and emotional responsiveness. The prevalence is high due to its chronic nature. Patients with schizophrenia require long-lasting therapy [2]. Early treatment assists to get the symptoms under control before arisen of serious complications and may help to refine the long-term outlook.Human skin contains sweat ducts around 200-250 while hair follicles around 50-80 per centimeter square of human skin which covers tentatively 0.1% of total stratum corneum [3]. Therefore, percutaneous absorption is having very limited scope for the pharmacokinetic parameters of the transdermal preparations. Hence, topical penetration primarily diffused through the stratum corneum and then the interfollicular portion. Traditional drug treatment systems that involve multiple doses have much more troubles [4]. The drug delivery at a controlled rate is a novel perspective to administer medication into the blood at a predestined rate. This would not only bypass biotransformation but should also maintain efficacious and long-lasting therapeutic levels. To achieve this the unimpaired skin acts as a drug reservoir to deliver consistent delivery of a medicament into the blood. Quetiapine is a psychotropic agent used for the management of bipolar disorder, schizophrenia, and major depressive disorder [5].Quetiapine demonstrates a high level of therapeutic efficacy and low risk of adverse effects during long-term treatment. It is well-tolerated and a suitable option for some patients with high sensitivity to other drugs.Quetiapine is used in the symptomatic treatment of schizophrenia [6]. In addition, it may be used for the management of acute manic or mixed episodes in patients with bipolar I disorder, as a monotherapy or combined with other drugs. It may be used to manage depressive episodes in bipolar disorder. In addition to the above indications, quetiapine is used in combination with antidepressant drugs for the treatment of major depression [7].The present investigation highlights the prospects of alternate route of drug delivery in the form of transdermal patch for the treatment of schizophrenia. The prevailing studies were carried out to formulate and optimize the transdermal drug

delivery of antipsychotic drugs quetiapine for improved bioavailability as compared to oral formulation.

MATERIAL AND METHODS

The objective of pre-formulation study is to develop the elegant, stable, safe and effective dosage form by establishing compatibility with the other ingredients and to establish physicochemical parameters of new drug substance. The preformulation studies were carried out in terms of tests for identification (physical appearance, melting point, IR spectra and UV spectrum), solubility profile, drug excipients interaction [8]. The drug sample of quetiapine Fumarate was obtained as a gift sample from Alembic Pharmaceuticals, Ahmedabad India.Organoleptic parameters of quetiapine Fumarate (QF) were checked by visual inspection.The melting range of quetiapine Fumarate was determined using open capillary method. The drug powder was packed into capillary and melting range was determined by digital melting point apparatus.The solubility of quetiapine fumarate (QF) was tested in various common solvents. A small quantity of drug was dissolved in 5 ml, until the drug was saturated in solvents and kept for 24 h at room temperature [9]. The solution was filtered and solubility was observed by the UV spectroscopyat 252 nm. The partition coefficient of quetiapine Fumarate (QF) was examined in n-octanol: Phosphate buffer pH 7.4 system. It was determined by taking 10mg of drug in separating funnel, containing 10ml of n-octanol and 10ml of Phosphate buffer pH 7.4. The separating funnel was shaken for 1 hour. Two phases were separated and the amount of drug in aqueous phase was analyzedspectrometrically at 252 nm after appropriated dilution. IR spectrum of quetiapine Fumarate (QF) was determined in a FTIR spectroscope (Perkin Elmer-Spectrum RX-I FTIR Spectrophotometer, USA) using KBr pellet. The KBr discs were scanned to obtained FTIR of drug at a resolution of 4 cm-1 , from 4000 to 600 cm-1. Drug-excipients compatibility study was performed to determine any physical change in the drug when kept in contact with various formulation excipients. The drug was mixed with the excipients in 1:1 ratio. The drug- excipients mixture was kept in glass vials properly capped and sealed with aluminium caps. Two vials of each sample were kept at room temperature, in the oven at 40°C/75% RH and in refrigerator for one month period. After every week for one month, the vials were withdrawn and any change in physical appearance as well as color of the contents was observed

Determination of Maximum wavelength (λmax):

Quetiapine Fumarate (QF) was accurately weighed (50 mg) and transferred to a 50 ml volumetric flask. To this, 50 ml Phosphate buffer pH 7.4 was added to dissolve the drug and the volume was made up to 100ml with Phosphate buffer pH 7.4 to prepare a 1000 µg/ml solution. Then 1ml of this stock solution was pipette into a 10ml volumetric flask and volume made up to the mark with Phosphate buffer pH 7.4 to prepare a 100 µg/ml solution. It was scanned on a double- beam UV-visible spectrophotometer (Shimadzu 1800) between wavelength 200-400 nm and UV spectrum was recorded. Wavelength maxima for the drug were found to be 252 nm [10].

Calibration Curve of quetiapine Fumarate (QF) in Phosphate buffer pH 7.4:

Quetiapine Fumarate (QF) was accurately weighed (100mg) and transferred to 100ml volumetric flask. To this 50ml of Phosphate buffer pH 7.4 was added to dissolve the drug and the volume was made up to 100ml with Phosphate buffer pH 7.4 to prepare 1000µg/ml solution. Then 1ml of this stock solution was pipette into a 10ml volumetric flask and volume made up to the mark with Phosphate buffer pH 7.4 to prepare a 100 µg/ml solution. Appropriate dilutions from the stock solution were made in concentration range of 20-100 µg/ml.

Formulation of transdermal patches:

For preparation of quetiapine transdermal patches, the solvent casting technique was used. Quetiapine with the dose of 25 mg per patch in methanol and dichloromethane (0.25:0.75) solvent system was dissolved along with the polymers HPMC K4M and Eudragit RL PO (ERL) mixed in ratio of 0.5:0.5. Furthermore, dibutyl phthalate (15% w/w of dry polymer weight) as plasticizer and isopropyl myristat in amount of 5% w/w with a functional role of enhancement of drug permeation were incorporated in resulting mixture based on dry polymer weight. The resulting solution was cascaded on the laminated aluminium foil placed at the bottom of the cylindrical cup and the solvent was allowed to evaporate at room temperature for 24 h. The patch was cut into small patches containing amounts equivalent to 25 mg of drug [11].

Table 1: Preparation of transdermal patch (QTP1 – QTP9)

Formulation Code	Amount (g)				Amount (ml)			Amount (g)
	Drug	Polymers			Penetration enhancers			Plasticizer
	(g)	Sodium alginate	Methyl cellulose	Chitosan	Isopropyl myristate	Mineral oil	Propylene glycol	PVP
QTP1	0.500	3	-	-	0.500			1
QTP2	0.500	3	-	-		0.500		1
QTP3	0.500	3	-	-			0.500	1
QTP4	0.500	-	3	-	0.500			1
QTP5	0.500	-	3	-		0.500		1
QTP6	0.500	-	3	-			0.500	1
QTP7	0.500	-	-	3	0.500			1
QTP8	0.500	-	-	3		0.500		1
QTP9	0.500	-	-	3			0.500	1

Characterization of transdermal patches

Uniformity of weight:

The formulated films having 25 mg (4 cm2) dose were checked for uniformity of weight using an electronic balance (Scientech, Boulder, USA).

Thickness of patch:

Thickness of the patch was evaluated by a digital caliper (Mitutoyo, Japan) at random points.

Weight variation of transdermal patch:

The weight of identified films was weighed very carefully. The average weight of transdermal patch was calculated.

Surface pH of the transdermal patch:

The surface pH of the patches was determined by placing the probe of the pH meter in close contact with the wetted surface of the patch [12].

Tensile strength and percentage elongation of transdermal patch:

Tensile strength and percent elongation of the patches were determined on tensile strength testing apparatus. Tensile strength of 2 cm^2 diameter film was measured by using fabricated tensile strength apparatus. The films were fixed between bonding agent 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. The evaluated polymeric films were trailed by dragging system. Now add the weights from initial low mass to the more until the film was broken [13]. 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)

The Percentage elongation: Length before the break point / Original length of each step * 100

Folding endurance of transdermal patch:

The folding acceptance power of prepared film was measured manually. A piece of film was cut with the help of knife. Strip repeatedly folded at the same place till it broke. The number of times the film was folded at the same place without breaking gave the value of the folding endurance.

Swelling Ratio of transdermal patch:

The effect of polymers combination was identified by swellability effect of the film. The prepared film was kept in double distilled water in a petri dish. The swelling nature of film was observed when in contact with water for specified time. The increase in weight of the each film at specific time intervals was determined. Films were kept in water upto constant weight of film was observed.The degree of swelling (SR %) was calculated using the following formula

$$\text{SR (\%)} = \frac{\text{The weight of the swollen film at different time intervals}}{\text{The weight of dry film}} \times 100$$

Moisture uptake percentage of transdermal patch:

A piece of transdermal patch (RTP) was cut with the help of knife. The piece so cut of film was weighed at initial level. After weighing the mass of film, it was kept in desiccators having Saturated Potassium Chloride Solution at 25-30°C, 75% RH for 24h. The films were sweeping out from desiccators and reweighed the upgraded mass. The Moisture uptake property of prepared films was calculated using the following formulae.

Moisture uptake (%)

$$= \frac{\text{Final weight of Film - Initial weight of Film}}{\text{Initial weight of Film}} \times 100$$

Drug content: Drug content was quantified by dissolving the patch of size 2 cm2 in 100 mL of methanol, which was then analyzed spectrophotometrically at a wavelength of 252 nm. [14]

In vitro Release Study:

The in vitro characterization of transdermal formulations was determined using Franz diffusion cell. The receptor compartment of the diffusion cell was filled with 30.0 ml of phosphate buffered saline (pH 7.4), and in vitro drug release studies were carried out using synthetic cellophane membrane. The prepared formulations 2cm2 were cut and fixed on to the membrane in the donor compartment and were uniformly spread onto the cellophane membrane. The assembly was constantly maintained at 37.0 ± 2.0 °C at 50 rpm. Samples (1.0 ml aliquots) were then withdrawn at suitable time intervals (0, 1, 2, 3, 4, 5, 6, 7, 8 and 24 h) and replenished with an equal amount of medium to maintain the receptor phase volume to 30 ml. The samples were suitably diluted analyzed by spectrophotometric method at 252 λmax [15].

RESULTS AND DISCUSSION:

Preformulation studies are the first step for the rational development of dosage forms of model drug substances. It is an investigation of physical and chemical properties of drug substances alone and in combination with excipients in research. The overall objective of preformulation studies is to produce information constructive to the formulator in development of stable and bioavailable dosage forms. Quetiapine Fumarate (QF) was found to be offwhite, practically faint order, Bitter tastein nature. The microscopic examination of the drug sample was crystalline powder. The melting point of drug was 278°C. The solubility of drug was very soluble in all dissolution media and the result of drug is shown in Table 6.3. The partition coefficient of drug was found to be 1.1 and the value of partition coefficient of drug showed that the drug was hydrophillic in nature. The Infrared spectra were obtained using an FTIR spectrometer.The drug was estimated in-vitro by reported UV spectrophotometric methods. The reported UV spectrophotometric methods were slightly modified and optimized according to the existing laboratory conditions. The drugs were estimated in the dissolution medium pH 7.4 phosphate buffer. The calibration curves in the dissolution medium i.e. pH 7.4 phosphate buffer prepared with drug solutions of known concentrations. The absorbance of each solution was measured separately at 252 nm for quetiapine fumarate (QF). The absorbance was measured and standard curve was plotted between absorbance

vs. concentration. The result of linearity is as shown in Table 6.7 and Figure 6.2 to 6.3. The calibration curves show excellent linearity of data as evidenced by the values of correlation coefficients that were found to be greater than 0.99. The curves were found to be recti-linear in the concentration range 5 µg / ml to 20 µg / ml for the drug.The result of drug content of prepared patch varied from 93.12-99.59 %. The prepared polymeric base films were characterized a number of optimized parameters i.e. "optical checking, smoothness color, transparency and flexibility, Thickness of polymeric films, Weight Variation of films, Surface pH of films, Tensile strength of films, Percentage elongation, Folding endurance Swelling Ratio of films, Moisture Content and Moisture uptake Percentage. The values obtained after the examination identified, that polymers have hydrophilic nature and able to enhanced spreadability and dispersibility of the drug combination for all the monolithic films. The hydrophilic polymer layer produces a water-permeable with more hydrated film. Such hydration allows losing the polymer matrix and consequently enhanced drug release.The effect of penetration enhancers also examined after selecting a best formulation from base medicated films i.e. QTP2, QTP5 and QTP3. All formulation showed very good result and can reproduce after each interval. The in vitro studies were performed using Franz diffusion cell with the help of synthetic cellophane membrane. The drug release rate for all formulations QTP1-QTP9. The drug release rate was found maximum for formulation QTP2 and QTP3 i.e 98.03 and 97.01 percent. Both formulations were formulated with polymer sodium alginate dissolved in ethanol and water in ratio (1:2) having PVP as plasticizers. Mineral oil act as penetration enhancer. The cumulative percent drug released from formulations of QTP1 – QTP3 were released drug 44.37%, 38.98% and 38.54% respectively in 8th hr, which was increases up to 24th h and drug release after 24th h were 97.04%, 98.03% and 97.01%.The cumulative percent drug released from formulations of QTP4 – QTP6 were released drug 40.42%, 43.32% and 41.39% respectively in 8^{h} h, which was increased up to 24th h and drug release after 24th h was 96.56%, 98.43% and 96.07%. The cumulative percent drug released from formulations of QTP7 – QTP9 were released drug 43.67%, 46.98% and 48.98% respectively in 8th h, which were increased up to 24th h and drug release after 24th h was 97.23%, 98.05% and 99.45%. It was observed that the combination of mineral oils in different polymeric system increases the drug perfusion rate and enhancing the property of drug combination through the membrane.The coefficient of regression and release rate constant values for Zero-order kinetics, First order kinetics, Korsmeyer-peppas plot and Higuchi's square root kinetics for QTP1 – QTP9. The Zero-order plots of different formulations were found to be linear, as indicated by their high regression values. Hence to confirm the exact mechanism of drug release from the formulations, the data was computed and graphed according to Korsmeyer-peppas plot. 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 1.023 to 1.176. For all of the batches the value of release exponent "n"was< 1.0 indicating Super-case II transport mechanism.

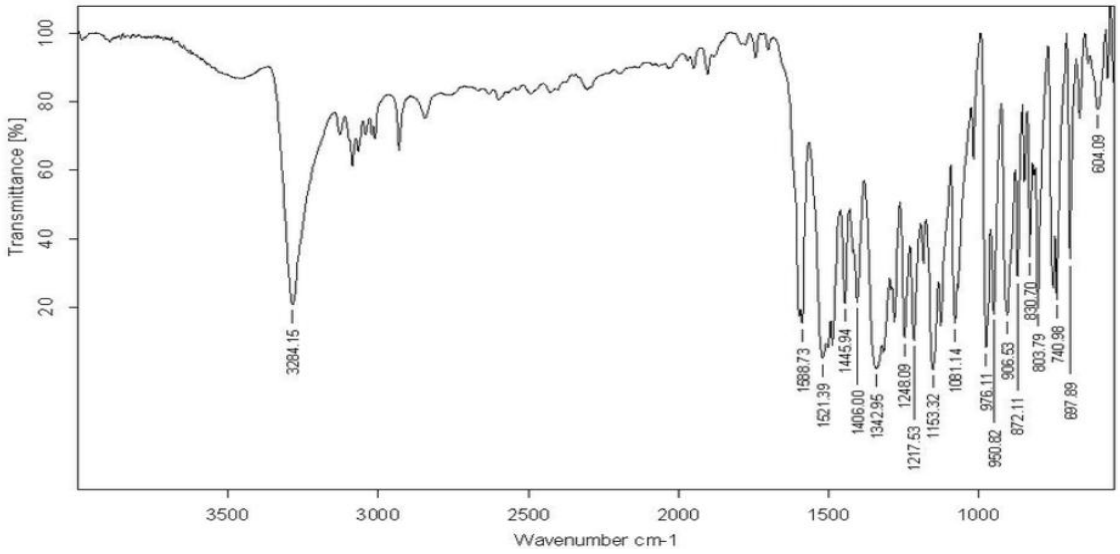

Figure 1: IR Spectrum of quetiapine fumarate (QF)drug sample

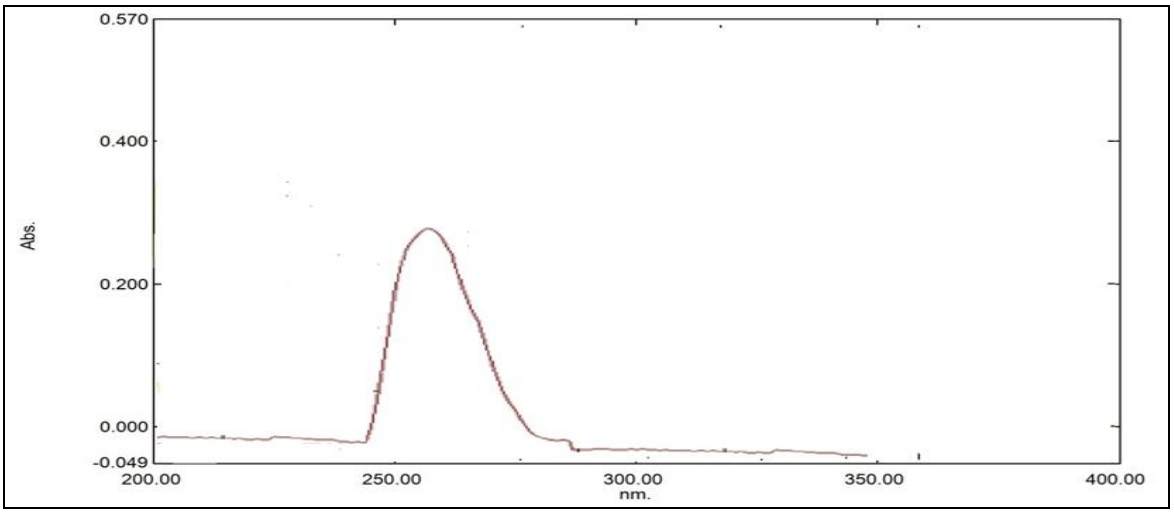

Figure 2: UV spectrum of Quetiapine fumarate (QF)

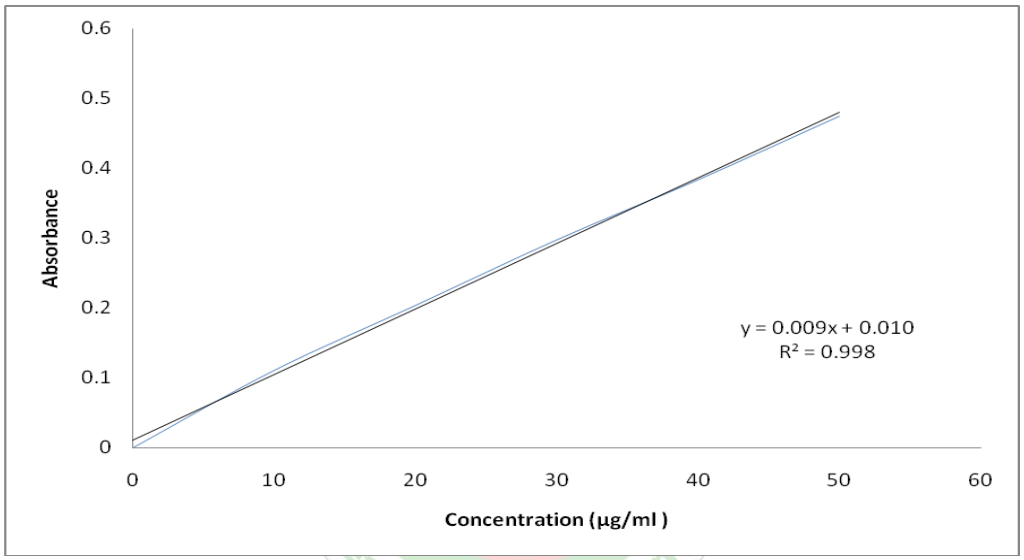

Figure 3: Calibration curve of Quetiapine fumarate (QF)in phosphate buffer pH 7.4

Table 2: Physical characterization of transdermal patch

Formulation code	Flexibility	Smoothness	Transparency	Thickness (mm)	Average weight (mg)
QTP1	Hard	Smooth	Transparent	0.21±0.01	31.32.±1.121
QTP2	Flexible	Smooth	Opaque	0.24±0.02	34.21±1.131
QTP3	Flexible	Smooth	Opaque	0.22±0.01	36.37±1.134
QTP4	Flexible	Smooth	Transparent	0.26±0.02	37.22±1.116
QTP5	Soft	Smooth	Transparent	0.24±0.02	38.33±1.135
QTP6	Hard	Rough	Opaque	0.22±0.01	34.41±0.111
QTP7	Hard	Rough	Transparent	0.21±0.02	36.20±0.124
QTP8	Soft	Smooth	Translucent	0.26±0.03	34.22±1.115
QTP9	Hard	Rough	Opaque	0.21±0.02	33.23±1.112

Formulation code	Surface pH	Percentage Elongation	Tensile Strength N/mm^2	Folding endurance	Swelling ratio (%)	Moisture Content (%)	Moisture Uptake (%)	Drug content of films (%)
QTP1	4.4 ± 0.13	93.74±0.02	4.66±1.08	95-90	48.17± 0.13	3.12± 0.13	3.65± 0.23	98.99±0.8
QTP2	4.7± 0.11	98.12± 0.02	5.79±0.23	89-97	42.13 ± 0.21	4.19 ± 0.07	4.93 ± 0.23	94.85±0.7

QTP3	4.5 ± 0.13	92.62±0.14	4.76±1.11	95-97	30.13 ± 0.15	4.11 ± 0.05	3.94 ± 0.25	96.99±0.10
QTP4	4.5 ± 0.13	94.13± 0.02	5.19±0.23	96-98	41.82 ± 0.19	3.44 ± 0.01	3.70 ± 0.29	98.89±0.11
QTP5	4.4 ± 0.12	98.12± 0.03	4.16±1.12	90-93	39.02 ± 0.17	3.86± 0.11	5.61± 0.111	99.57±0.14
QTP6	4.6 ± 0.13	99.12±0.15	5.19±0.03	99-100	38.17 ± 0.26	3.02 ± 0.02	3.81 ± 0.22	98.55±0.14
QTP7	4.6 ± 0.11	93.01± 0.100	6.03±0.03	94-99	38.08 ± 0.38	3.08 ± 0.12	3.90 ± 0.11	98.99±0.17
QTP8	4.4 ± 0.13	95.13±0.02	4.33±0.11	97-98	33.13 ± 0.34	3.12± 0.12	4.81 ± 0.54	98.12±0.8
QTP9	4.5 ± 0.11	98.71±0.05	5.63 ±0.11	92-99	32.18 ± 0.15	3.19 ± 0.10	4.88 ± 0.24	98.82±0.12

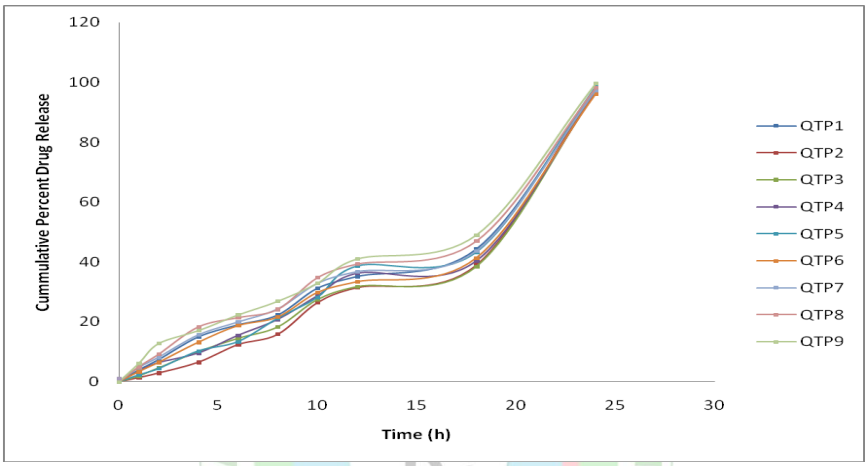

Figure 4: Zero-order kinetic plot of Quetiapine fumarate (QF) transdermal patch

SUMMARY AND CONCLUSION:

The proposed drug is suitable for sustained action as transdermally active system for the management and inhibits polysynaptic reflexes and reduces muscle tone, muscle spasms without reducing muscle strength. Quetiapine Fumarate is a well-used Clonidine congener, active against α2-adrenergic receptor. The transdermal route delivery system will able to management dementia in people with muscular pain disease for better administration of drugs via transdermal route. The formulation develops a controlled release polymeric transdermal patch of quetiapine fumarate for improving the therapeutic effect of drugs via approaches as transdermal patch hold on to part of skin. All the evaluation data of patch QTP was concluded that polymers have hydrophilic nature and able to enhanced spreadability and dispersibility of the water-soluble drug combination for all the monolithic films. The hydrophilic polymer layer produces a water-permeable with more hydrated film. Such hydration allows losing the polymer matrix and consequently enhanced drug release. The effect of penetration enhancers also examined with physical observations and other characterization parameters specifically in-vitro drug release data QTP2, QTP5 and QTP3 were suggested very good result and can reproduce after each interval. The in-vitro value of release exponent "n" was < 1.0 indicating Super-case II transport mechanism. The formulations behaviour based on penetration enhancers i.e. mineral oil and plasticizer as PVP with combination of sodium alginate as ood supporting polymer for best perfusion release of drug at desired time intervals.

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