Nat. Volatiles & Essent. Oils, 2021; 8(4): 13737-13764

NVEO
Natural Volatiles & Essential Oils

# Formulation And Characterization Of Multilayered Controlled Release Topical Patch For Cure Of Cardiac Disease

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**Abstract:**

Transdermal drug delivery system (TDDs) is novel specified dosage forms, when drug deliver through the skin at controlled rate to the systemic circulation as applied to the intact skin. The aim of this research was to develop and evaluate a matrix type of multilayered transdermal drug delivery system containing trandolapril and verapamil Hydrochloride. The formulations containing combination of both drugs were formulated by using different polymers like Sodium alginate, Methyl cellulose, Chitosan in different ratios by solvent evaporation technique. Glycerin, PVP (polyvinylpyrrolidone) and polyethylene glycol 400 were used as plasticizers. The prepared formulated multilayered transdermal patches were physically evaluated for thickness, weight variation, drug content, flatness, tensile strength, folding endurance, and water vapour transmission rate. The in-vitro drug release study was carried out by using Franz diffusion cell. The invivo pharmacokinetic sudy animal sudy, skin irritation study and stability study were also developed. The release kinetic study of multilayered transdermal patch confirmed the prepared patch was followed supercase II transport mechanism of diffusion kinetics with sustained release within specific time period and observed deviation from Fickinan mechanism of drug release. The multilayered transdermal patch produced higher bioavailability and was applied on the rat skin, it was found that increased concentration of drug in rat blood plasma was due to the rapid absorption of drug, which was identified by better $C_{max}$ and lower $t_{max}$ values. The pharmacokinetic parameters of prepared multilayered transdermal patch TVP1 was indicated that both drug released and absorbed more than 90 % from 0 to $8^{th}$ h trandolapril. The drug verapamil Hcl was not released during 0 – $6^{th}$ h and was starting to absorb and peak plasma concentration was reached upto $20^{th}$ h. The result of AUC represents the total integrated area under the blood concentration-time profile. It indicated the total amount of drug reaches to the systemic circulation after administration. Thus, it is crucial parameter in identifying the bioavailability of drug from any dosage form. Statistically, $AUC_{0-t}$ of the formulation **TVP1** was significantly higher ($p<0.05$). The $AUC_{0-t}$ values were observed to significantly high and result showed concentration of drug was within therapeutic effective range for a longer period of time for treatment of hypertension. The stability study of prepared multilayered transdermal patch was performed in different

temperature as per guideline of ICH guideline. There was little bit change or degradation of concentration or amount of drug component in formulation.

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**Introduction:** The drug-delivery system should deliver drug at a rate dictated by the needs of the body over a specified period of time. The goal of any drug delivery system is to provide a therapeutic amount of drug to a proper site in the body, so that the desired drug concentration can be achieved promptly and then maintained **[1-3]**. Antianginal drugs are those that prevent or terminate attacks of angina pectoris. Angina pectoris as a pain syndrome due to induction of an adverse oxygen supply situation in a portion of the myocardium **[4]**. A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate- or extended-release characteristics **[5]**. 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. 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. Drugs are administered topically for their action at the site of application, or for systemic effects**.** The topical drug delivery system is normally used where the others system of drug administration not succeed or it is mainly used in fungal infection. Human skin is a large and easily accessible organ offers ideal and multiple sites to administer therapeutic agents for both local and systemic actions**.** It applied locally in mild dermatophyte and cutaneous infections **[6]**. The global market of transdermal drug delivery is estimated to grow and reach approximately $95.57 billion by 2025. The overdosing of drug may be come in force due to fluctuation in peak plasma concentration of drug following oral and parenteral administration, thus create more challenge in monitoring of effective plasma concentration. The TDDS significantly improves systemic bioavailability with reduced risk of side effects associated with concentration of drug substances. This delivery system may improve patient observance because of easy and convenient to apply with a lesser dosing frequency, as the drug is released at a predetermined rate over a prolonged period **[6]**. In the year of 1980s; 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. The multilayer transdermal patches prepare by drug reservoir layer and an adhesive layer for controlled drug release for a period of time. The multilayer system consist temporary protective layer with a permanent backing shield. Multilayer patches mainly used for pain relief medication. The drugs for encourage smoking cessation and hormone therapy and use for prolonged up to seven days **[7]**. The aim of praposed work is to develop a combination of multilayered polymeric transdermal patch for predetermined release of drug

materials for a care of cardiac patients. Trandolapril and Verapamil hydrochloride transdermal patch combines a slow release formulation of a calcium channel blocker, verapamil hydrochloride, and an immediate release formulation of an angiotensin converting enzyme inhibitor, trandolapril. The proposed model drug Trandolapril is the ethyl ester prodrug of a nonsulfhydryl angiotensin converting enzyme (ACE) inhibitor, trandolaprilat. It is a white or almost white powder with a molecular weight of 430.54. It is soluble (>100 mg/mL) in chloroform, dichloromethane, and methanol. Whereas, verapamil have short biological or metabolic half life (1 - 2 hour) with higher dosing, it have high first-pass metabolism, bioavailability is much lower (10–35%). These proposed drug have a wonderful suitable applicant for sustained delivery action as transdermally active system act as calcium channel blockers “class-IV antiarrhythmic agents” for the cure of cardiac disease. The transdermal route for the treatment eliminates major side effects and showed better effect to diseased suffering person. It may relaxes the tone of this smooth muscle, and dilate the blood vessels. It takes 1 to 2 hours to reach peak plasma concentration after oral administration with metabolized in the liver (high first-pass metabolism). So, TDDs worked on management of diseased of cardiac arrhythmias and have short biological half life, low oral bioavailability value, dose, and molecular weight for better bioavailability of drugs. The proposed formulations have a number of variables i.e. plasticizers, penetration enhancers, rate controlling process and adhesion on skin. We may apply biologically active permeation enhancers i.e. Isopropyl myristate, Propylene glycol and Mineral oils etc. We may include any one or combination of permeability enhancement techniques i.e. cyclodextrin inclusion complex, nonoemulsification techniques, chitosan derivatives, self-micro-emulsifying drug delivery system etc. 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.

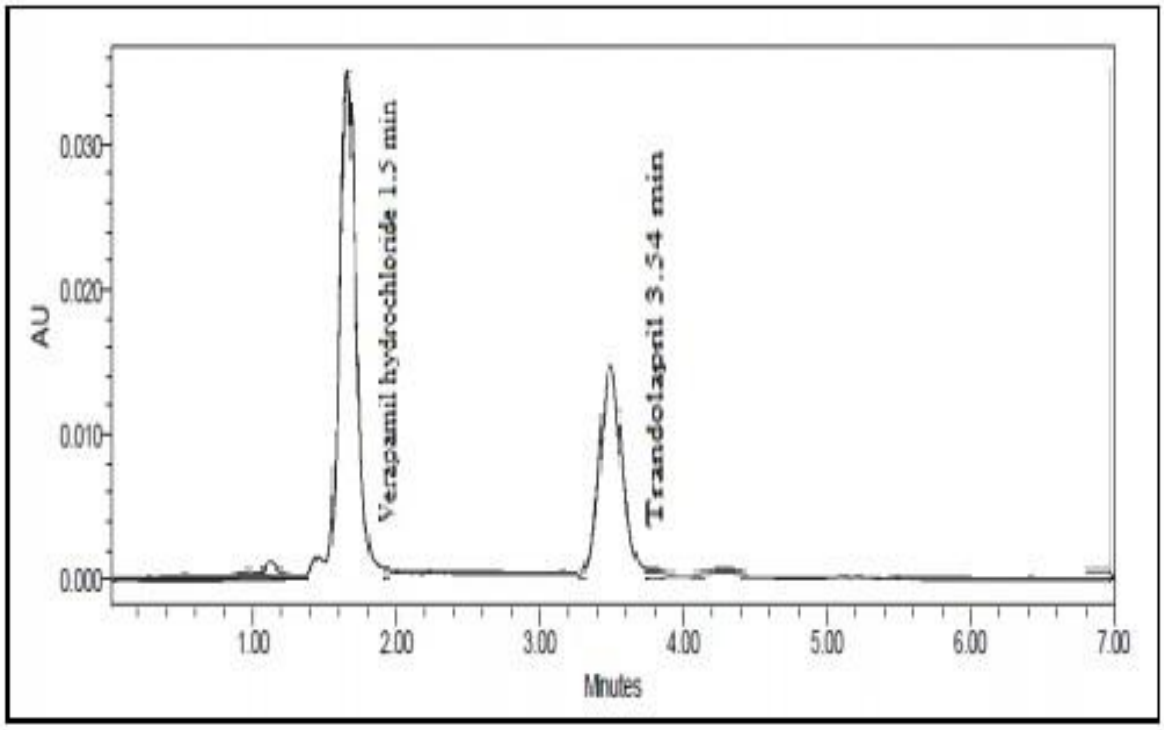
**Materials and Methods:**

**Simultaneous estimation of trandolapril and verapamil Hydrochloride using RP-HPLC Technique:** The estimation of both drug materials in single mixture of blend was studied by using RP-HPLC method as simultaneous estimation study of drug sample. The method was perfomed using Shimadzu HPLC system with a pump (LC-20 AD), a photodiode array detector system (SPD-M 20A) instrument. The instrument having phenomenex RP18 column having length 250 mm and diameter 4.6 mm with particle size of C18 was 5µ. The method was estimated with isocratic mobile phase using ACN (Acetonitrile): phosphate buffer saline (pH 7.4) in the costant ratio of 40: 60 v/v throughout the run. The flow rate was maintained 1.2 mL/min during run of samples. The injected volume of drug sample was 10 µL and sample was filtered with membrane filter prior to injection in to column. The detection wavelength of chromatogram was 216 nm, as both drug showing

highest resolution in this wavelength. The retention time (Rt) of trandolapril (TL) was found 3.45 min and verapamil hydrochloride (VHL) was found to be 1.5 min.The total run time of this method was 7 min, after that column washed with 100 % acetonitrile, after each run column washed with pur acetonitrile for 10 min to wahed out any impurity retained in C18 column.

**Preparation of drug solutions for standard curve:** The stock solutions of TL and VHL were prepared separately by dissolving required quantity (50 mg) pure drug sample in 50 ml mixture of acetonitrile: phosphate buffer saline (pH 7.4) solution (1:1 v/v). The resulting solution has concentration 1000 µg/ml. Withrawn 10 ml from the prepared solution diluted with 100 ml of mobile phase mixture has the concentration of 100 µg / ml solution.

**RP-HPLC chromatogram of combination of Trandolapril (TL) and Verapamil hydrochloride (VHL):** The RP-HPLC chromatogram of both drug combination of trandolapril (TL) and verapamil hydrochloride (VHL) having Rt 3.54 min for TL and Rt 1.5 min for VHL **(Figure 1)**.




**Formulation and Evaluation of drug containing films:** The objective of present study was to prepare transdermal film containing trandolapril / verapamil Hcl separately 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 trandolapril quantity 20 mg and verapamil Hcl quantity 480 mg were dissolved in casing solvent before addition of polymeric solution separately as given in **Table 1-2**. The drug polymer mixture was continuously stirred on thermostatic magnetic stirrer at 37±2°C. The plasticizers Glycerin/ PVP/ PEG400 were added with stirring. 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 TL) or 2 $cm^2$ (120 mg drug VHL), wrapped in aluminum foil and stored in air tight polyethylene bags in desiccators.

**Table 1: Preparation of trandolapril containing transdermal film**

| Formulation Code | Polymers (gm) | | | Plasticizers | | |
|---|---|---|---|---|---|---|
| | Sodium alginate | Methyl cellulose | Chitosan | Glycerin (ml) | PVP (gm) | PEG 400 (gm) |
| TTF1 | 2 | - | - | 5 | - | - |
| TTF2 | - | 2 | - | 5 | - | - |
| TTF3 | - | - | 2 | 5 | - | - |
| TTF4 | 2 | - | - | - | 1 | - |
| TTF5 | - | 2 | - | - | 1 | - |
| TTF6 | - | - | 2 | - | 1 | - |
| TTF7 | 2 | - | - | - | - | 1 |
| TTF8 | - | 2 | - | - | - | 1 |
| TTF9 | - | - | 2 | - | - | 1 |

**Table 2: Preparation of verapamil HCl containing transdermal film**

| Formulation Code | Polymers (gm) | | | Plasticizers | | |
|---|---|---|---|---|---|---|
| | Sodium alginate | Methyl cellulose | Chitosan | Glycerin (ml) | PVP (gm) | PEG 400 (gm) |
| VTF1 | 2 | - | - | 5 | - | - |
| VTF2 | - | 2 | - | 5 | - | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| VTF3 | - | - | 2 | 5 | - | - |
| VTF4 | 2 | - | - | - | 1 | - |
| VTF5 | - | 2 | - | - | 1 | - |
| VTF6 | - | - | 2 | - | 1 | - |
| VTF7 | 2 | - | - | - | - | 1 |
| VTF8 | - | 2 | - | - | - | 1 |
| VTF9 | - | - | 2 | - | - | 1 |

**Preparation of the placebo transdermal film:** The transdermal film without addition of API was prepared for the separation of both drugs containing transdermal film in single multilayered transdermal patch. The HPMC polymer 10% and plasticizers PVP 1% solutions were prepared separately by dissolving the required quantities in distilled water with stirring on thermostatic magnetic stirrer at 37±2°C. 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 $cm^2$, wrapped in aluminum foil and stored in air tight polyethylene bags in desiccators.

**Preparation of the backing film:** The backing film was prepared for the provided strength to all transdermal film in single multilayered transdermal patch. The Polyvinyl alcohol (PVA) 1% solutions were prepared separately by dissolving the required quantities in distilled water with stirring on thermostatic magnetic stirrer at 37±2°C. The polymeric 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 $cm^2$, wrapped in aluminum foil and stored in air tight polyethylene bags in desiccators.

**Preparation of the multilayered transdermal patch:** The multilayered transdermal patch was prepared with smooth arrangement of both drug loaded transdermal film, separating layer and backing membrane in single patch **(Table 3)**. Thus, prepared films were stick to adhesive layer of bandage which was purchased from local market. The arrangements of all layers are as follows:

1. The so prepared films were stick to adhesive layer of bandage which was purchased from local market.

2. Backing membrane

3. Layer 2, transdermal film containing verapamil HcL

4. Seperatng layer containing HPMC

5. Layer 1, transdermal film containing trandolapril

6. Liner

* The composite patch was wrapped in aluminum foil and kept in a dessicator until used.

**Table 3: Composition of transdermal patch containing all layers (TVP1)**

| Formulation Code (Patch) | Layer of Patch | Formulation Code of Films | Drug (mg) | Polymers (gm) | | | Plasticizers |
|---|---|---|---|---|---|---|---|
| | | | | Sodium alginate | HPMC | Chitosan | PVP (gm) |
| TVP1 | First Layer | TTF6 | Tandrolapril | - | - | 2 | 1 |
| | Middle layer | TF1 | Placebo | - | 10% | - | 1 |
| | Upper layer | VTF4 | Verapamil Hcl | 2 | - | - | 1 |

**Characterization of multilayered transdermal film / patch:**

**Physical appearance of multilayered transdermal patch:** The parameters of multilayered transdermal patch i.e. “optical checking, smoothness, color, transparency and flexibility” were observed **[9]**.

**Measurement of thickness of multilayered transdermal patch:** Measurement of thickness of multilayered transdermal patch was performed by utilizing a screw gauge (least count of 0.02 mm) **[10]**.

**Measurement of weight variation of multilayered transdermal patch:** Prepared multilayered transdermal patch was 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 multilayered transdermal patch:** The prepared multilayered transdermal patch was 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 multilayered transdermal patch:** The Surface pH of multilayered transdermal patch was determined by using Digital pH meter. 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 multilayered transdermal patch:** Tensile strength of 2 $cm^2$ multilayered transdermal patch 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 **[11-12].**

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

**Evaluation of folding endurance of multilayered transdermal patch:** Folding stamina of prepared multilayered transdermal patch 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 **[13]**.

**Evaluation of moisture content of multilayered transdermal patch:** The prepared multilayered transdermal patch was weigh, dried with current of air at 60ºC and were kept in desiccators having calcium chloride at 40ºC for 24 h. Then dried patch 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 **[10]**.

**Evaluation of swelling ratio of multilayered transdermal patch:** The prepared multilayered transdermal patch was 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 **[14]**.

**SR (%) =** [Mass of patch at time of investigation – Initial mass of patch * 100

Initial mass of patch]

**Evaluation of moisture uptake percentage of multilayered transdermal patch:** Moisture uptake percentage of multilayered transdermal patch was 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 × 100 / Initial mass of Film]

**Evaluation of drug content of multilayered transdermal patch:** 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 and subjected to HPLC method for drug content determination.

**In vitro skin permeation study:** In vitro drug release study of multilayered transdermal patch was performed using phosphate buffered saline (pH 7.4) 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 24 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 and subjected to HPLC method for drug content determination **[15]**.

**Pharmacokinetic Studies:** Male albino rats (wt 250 gm) were used in this study with research Ethical Committee at Oriental University, Indore approved the protocols regarding animal usage in accordance with "IAEC approval no. is IAEC/2019-20/RP-17, Dated 03/03/2020. The in vivo studies were performed on male albino rats nd were divided into two groups (n = 9 for each group). The animals of the first group (oral solution group), while the second group animals have transdermal patch on skin were subjected for the transdermal application of adhesive layer containing the multilayaered patches. To secure the patches on the animals' dorsum during the experiment, simple rat Velcro jackets were designed and made. Prior to the experiment by about 24 h, the hair of dorsal skins was shaved. At the day of experiment, the shaved skin was cleaned carefully with warm water and the patch was applied. The patches were fixed using medical adhesive tape and additionally secured by the designed jackets. The various pharmacokinetic parameters were calculated from the plasma concentrations of the drug at previously decided time profile. The experiment was carried out on the albino rats. The formulations were applied on rats and the blood samples were taken at 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 h after application of prepared patches. The rat tail vein was dilated by topical application of an alcohol swab on the shaved abdominal region. The blood sample was collected with 1 ml syringe fitted with a gauge needle. The needle from upright position was inserted at a 25$^o$

to 30$^{o}$ angle into the tail beside the vein. Blood sample of 0.5 ml were collected at predefined time intervals. The blood samples were transferred to clean 2 ml centrifuge tubes having without anticoagulants. The serum was separated by centrifuged tubes for 10 min and the separated plasma samples were collected in plastic Eppendorff tubes and stored at −20 °C and dilution with dissolution medium "phosphate buffer saline pH 7.4" by micropipette. The tube stored until they were estimated by a simultaneous estimation of both drug using RPHPLC method. The both drug quantity estimated trandolapril and verapamil Hcl API in blood plasma and the peak plasma concentration ($C_{max}$) and time of its occurrence ($t_{max}$) were identified by plasma concentration time profile. Area under concentration time curve ($AUC_{0-t}$) was calculated according to trapezoidal rule.

**Skin Irritation study:** Skin irritation test of prepared multilayered transdermal patch was carried out on healthy albino rats (average wt 250 gm). The dorsal surface (50cm$^2$) of the albino rats was to be cleaned by removing the hair from the dorsal surface by shaving. The rats are divided into 4 groups (n = 6). Group I acted as the normal, Group II applied with transdermal patch without drug and group III, applied with transdermal patch with drug. The application sites of patches are indexed according to a visual scoring scale. The erythema observed has scaled as follows: 0, none; 1, slight; 2, well defined; 3, moderate and 4, severe **[16 - 17]**.

**Pharmacodynamic study (Determination of Antihypertensive Activity of Transdermal Patches in Rats):** The preparared mutilayared transdermal patch was study for determination of antihypertensive activity on healthy albino rats (average wt 250 gm) as pharmacodynamic study. The blood pressure (BP) wass measured with a tail cuff (non-invasive) method by using a digital BP instrument (BIOPAC NIBP 200 A). The albino rats were holded at rat holder and BP was measured by using an digital instrument. The initial BP of rats are found to be normal, dexamethasone (20 µg/kg/day subcutaneously) has been injected for 14 days to induce the hypertension. After two weeks of induction of hypertension in rats with a minimum mean BP of 150 mm Hg were selected. Rats are split into three groups (n = 5). Group I marked as control, group II treated with multilayered transdermal patch **(Table 19-20)**. Blood pressure at different time intervals has been observed (at 2, 4, 8, 12, 24 h) **[18]**.

**Table 19: Treatment schedule of different dosage forms for various groups of animals**

| S. No. | Group | Teeatment | Dose | Route of administration |
|---|---|---|---|---|
| | Toxic | Dexamethasne | 20µg/kg/day | s.c. for 14 days |
| | Contrl group | Normal saline | 2ml/kg | Oral |

| | | | | |
|---|---|---|---|---|
| | Formulation TVP1 | TL and VHL patch | 4 mg+120 mg | Patch |

**Table 20: in-vivo pharmacodynamic study and blood pressure identification of different dosage forms for various groups of animals**

| Groups | Systolic BP (mm Hg) | | | | | | Diastolic BP (mm Hg) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2h | 4h | 6h | 8h | 12h | 24h | 2h | 4h | 6h | 8h | 12h | 24h |
| Control group | 115.12 ± 4.11 | | | | | | 85.76 ± 6.01 | | | | | |
| Formulation TVP1 | 145.32 ± 5.01 | 138.12 ± 4.61 | 128.72 ± 4.11 | 121.11 ± 3.98 | 120.82 ± 3.12 | 117.12 ± 3.51 | 95.32 ± 5.01 | 92.09 ± 4.91 | 89.21 ± 4.11 | 87.02 ± 3.91 | 86.91 ± 2.03 | 85.12 ± 3.33 |

**Stability Studies:** The stability of the prepared multilayered transdermal patch (TVP1) 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 TVP1due to chemical alteration or due to product instability. The prepared multilayered transdermal patche TVP1 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 by using simultaneous method of estimation using RPHPLC method.

The shelf life of the formulations was calculated from the degradation rate constant at 25 ºC ($k_{25}$) by the following formula:

$$t_{10\%} = 0.104 / k_{25}$$

**Drug Release Kinetic Data Analysis**: Several kinetic models have been proposed to describe the release characteristics of a drug from matrix. The following three equations are commonly used, because of their simplicity and applicability. Equation 1, the zero-order model equation (Plotted as cumulative percentage of drug released vs time); Equation 2, Higuchi's square-root equation (Plotted as cumulative percentage of drug released vs square root of time); and Equation 3, the Korsmeyer-Peppa's equation (Plotted as Log cumulative percentage of drug released vs Log time). To study the release kinetics of drug from the microspheres the release data was fitted to these three equations.

**Zero order equation:** When a graph of the cumulative percentage of the drug released from the matrix against time is plotted, zero order release is linear in such a plot, indicating that the release rate is

independent of concentration.

$Qt = k0.t$ …… (1)

Where Qt is the percentage of drug released at time t and k0 is the release rate constant;

**First order equation:**

$In (100-Qt) = In\ 100- kI.t$ …….. (2)

Where kI is the release rate constant;

**Higuchi's equation:**

$Qt = kH.t1/2$ …….. (3)

Where KH is the Higuchi release rate constant

**Korseymeyers-Peppas:** The curves plotted may have different slopes, and hence it becomes difficult to exactly pin-point which curve follows perfect zero order release kinetics. Therefore, to confirm the kinetics of drug release, data were also analyzed using Korsemeyer's equation.

$Qt/Q\infty = kKP.t^n$

Where Qt/ Q∞ is the fraction of drug released at time t, kKP a constant compromising the structural and geometric characteristics of the device and n is the release exponent.

The slope of the linear curve gives the 'n' value . Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. The value of 'n' gives an indication of the release mechanism. When n = 1, the release rate is independent of time (typical zero order release / case II transport); n = 0.5 for Fickian release (diffusion/ case I transport); and when $0.5 < n < 1$, anamalous (non-Fickian or coupled diffusion/ relaxation) are implicated. Lastly, when $n > 1.0$ super case II transport is apparent. 'n' is the slope value of log Mt/M∞ versus log time curve.

**Result and discussion:** The simultaneous estimation of combined drug sample of TL and VHL were performed using Reverse Phase high performance Chromatographic method. Adequate separation and fine peak symmetry was obtained with Phenomenex RP18 column (250 mm X 4.6 mm, 5µ) and mobile phase comprising of ACN (Acetonitrile): phosphate buffer saline (pH 7.4) (40: 60 v/v) at a flow rate of 1.2 ml/min with Injected volume: 10 µL. The retention time of Trandolapril (TL) was found 3.45 min and Verapamil hydrochloride (VHL) was found 1.5 min (**Figure 1**).

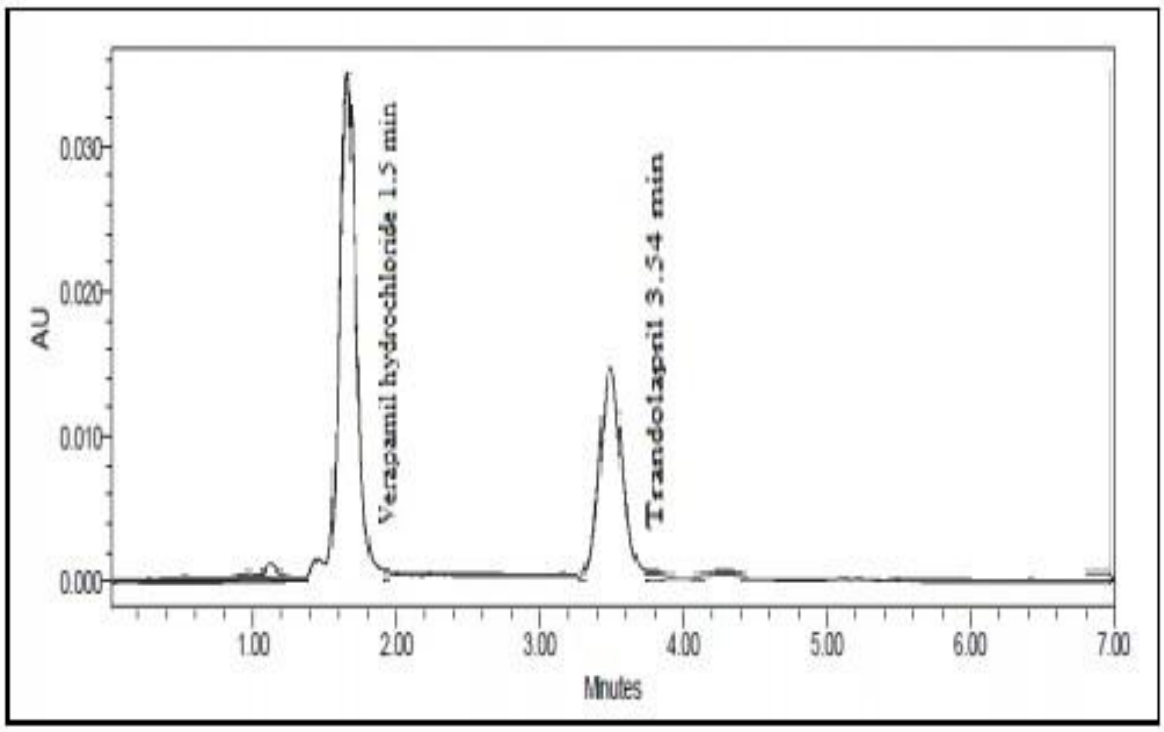



**Figure 1: RP-HPLC chromatogram of combination of Trandolapril (TL) Verapamil hydrochloride (VHL)**

The characterization of transdermal film containing trandolapril films were (TTF1 – TTF9) flexible, smooth, opaque and non sticky in nature. The prepared Trandolapril 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 (58.34 – 95.37 %), that polymers chitosan have hydrophilic nature and able to enhanced spreadability and dispersibility of the water soluble trandolapril **(Table 4 – 6)**. The hydrophilic polymer layer produces a water-permeable with more hydrated film. Such hydration allows losing the polymer matrix and consequently enhanced drug release more than 95.5% within a 6 - 7 h as needed for immediate release. The all evaluation parameters and in-vitro drug release study was using for selection of best polymeric film prepared with chitosan and PVP as plasticizer for the preparation of multilayered transdermal patch as first immediate release layer. The polymeric films (TTF6) 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 diffusion kinetics with immediate release within specific time period.

**Table 4: Physical appearance of films of trandolapril containing transdermal film**

| Formulation code | Flexibility | Smoothness | Transparency | Stickness |
|---|---|---|---|---|
| TTF1 | Flexible | Smooth | Opaque | Non sticky |
| TTF2 | Flexible | Smooth | Opaque | Non sticky |
| TTF3 | Flexible | Smooth | Opaque | Non sticky |
| TTF4 | Flexible | Smooth | Opaque | Non sticky |
| TTF5 | Flexible | Smooth | Opaque | Non sticky |
| TTF6 | Flexible | Smooth | Opaque | Non sticky |
| TTF7 | Flexible | Smooth | Opaque | Non sticky |
| TTF8 | Flexible | Smooth | Opaque | Non sticky |
| TTF9 | Flexible | Smooth | Opaque | Non sticky |

**Table 5: Characterization of trandolapril containing transdermal film**

| Formulation code | Thickness (mm) | Average weight (mg) | Folding endurance | Percentage Elongation |
|---|---|---|---|---|
| TTF1 | 0.29±0.03 | 111.32.±1.154 | 75-80 | 93.74±0.15 |
| TTF2 | 0.26±0.02 | 110.33±1.156 | 79-80 | 94.81± 0.02 |
| TTF3 | 0.25±0.03 | 112.60±0.144 | 86-91 | 101.42± 0.09 |
| TTF4 | 0.24±0.02 | 119.23±1.154 | 92-95 | 116.52± 0.02 |
| TTF5 | 0.23±0.01 | 118.33±1.155 | 93-97 | 118.12± 0.03 |
| TTF6 | 0.22±0.01 | 114.66±1.165 | 91-94 | 119.11±0.02 |
| TTF7 | 0.23±0.03 | 116.37±1.154 | 90-93 | 95.91±0.15 |
| TTF8 | 0.25±0.03 | 113.78±0.111 | 94-98 | 104.72±0.15 |
| TTF9 | 0.26±0.02 | 112.43±1.152 | 99-101 | 102.72±0.15 |
| Mean ± SD; n = 3 | | | | |

**Table 6: Characterization of trandolapril containing transdermal film**

| Formulation code | Tensile Strength $N/mm^2$ | Swelling ratio (%) | Surface pH | Drug content of films (%) |
|---|---|---|---|---|
| TTF1 | 3.66±1.18 | 23.97± 0.43 | 5.5 ± 0.14 | 93.99±0.8 |
| TTF2 | 6.69±0.23 | 22.32 ± 0.39 | 5.6 ± 0.14 | 94.95±0.9 |
| TTF3 | 5.93±0.13 | 22.18 ± 0.58 | 5.7 ± 0.12 | 95.79±0.10 |

| | | | | |
|---|---|---|---|---|
| TTF4 | 6.79±0.23 | 21.43 ± 0.49 | 5.8± 0.12 | 99.59±0.11 |
| TTF5 | 5.86±1.18 | 19.42 ± 0.57 | 5.5 ± 0.13 | 98.07±0.12 |
| TTF6 | 6.13±0.13 | 16.63 ± 0.54 | 5.5 ± 0.14 | 99.85±0.13 |
| TTF7 | 5.76±1.18 | 20.13 ± 0.55 | 5.6 ± 0.14 | 97.55±0.14 |
| TTF8 | 5.59±0.23 | 22.87 ± 0.46 | 5.7 ± 0.14 | 99.74±0.15 |
| TTF9 | 4.63 ±0.13 | 25.48 ± 0.45 | 5.6 ± 0.12 | 97.99±0.16 |
| Mean ± SD; n = 3 | | | | |

The characterization of transdermal film containing **Verapamil HCl film** were (VTF1 – VTF9) were flexible, smooth-rough, transparent-opaque and some sticky and some were non sticky in nature. The result of drug content varied from 94.01 – 99.48 % of VTF1 – VTF9. The prepared verapamil Hcl 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 (77.11 – 95.23 %), that polymers sodium alginate have swelling character and able to enhanced drug retarding characteristics of drug verapamil Hcl **(Table 7 – 9)**. The alginate polymer with PVP plasticizer polymer produces a water impermeable layer with more swelling index. The matrix layer of polymer allows creating the pores during the time span within the pH of skin layer and consequently enhanced drug retardation more than 75% after 12 h as needed for sustained release. The all evaluation parameters and in-vitro drug release study was using for selection of best polymeric film prepared with sodium alginate and PVP as plasticizer use for the preparation of multilayered transdermal patch as sustained release layer for further study. The polymeric films (VTF4) 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.

**Table 7: Physical characterization of verapamil HCl containing transdermal film**

| Formulation code | Flexibility | Smoothness | Transparency | Stickness |
|---|---|---|---|---|
| VTF1 | Flexible | Smooth - Rough | Opaque | Non sticky |
| VTF2 | Flexible | Smooth - Rough | Opaque | Sticky |
| VTF3 | Flexible | Smooth | Transparent | Non sticky |

| | | | | |
|---|---|---|---|---|
| VTF4 | Flexible | Smooth | Transparent | Non sticky |
| VTF5 | Flexible | Smooth | Transparent | Non sticky |
| VTF6 | Flexible | Smooth | Transparent | Son sticky |
| VTF7 | Flexible | Smooth - Rough | Opaque | Non sticky |
| VTF8 | Flexible | Smooth | Opaque | Son sticky |
| VTF9 | Flexible | Smooth - Rough | Opaque | Non sticky |

**Table 8: Characterization of verapamil HCl containing transdermal film**

| Formulation code | Thickness (mm) | Average weight (mg) | Folding endurance | Percentage Elongation |
|---|---|---|---|---|
| VTF1 | 0.129±0.031 | 551.31.±1.112 | 55-60 | 83.22±0.25 |
| VTF2 | 0.124±0.022 | 510.23±1.121 | 59-61 | 84.14± 0.11 |
| VTF3 | 0.128±0.011 | 548.50±0.124 | 66-71 | 98.92± 0.21 |
| VTF4 | 0.122±0.014 | 525.13±1.104 | 68-72 | 99.01± 0.27 |
| VTF5 | 0.123±0.015 | 513.23±1.105 | 66-77 | 98.19± 0.16 |
| VTF6 | 0.127±0.012 | 514.41±1.121 | 57-64 | 79.18±0.21 |
| VTF7 | 0.126±0.021 | 516.17±1.124 | 69-73 | 91.01±0.18 |
| VTF8 | 0.125±0.026 | 513.18±0.981 | 54-68 | 99.16±0.12 |
| VTF9 | 0.124±0.025 | 512.23±1.132 | 59-61 | 98.12±0.11 |
| Mean ± SD; n = 3 | | | | |

**Table 9: Characterization of verapamil HCl containing transdermal film**

| Formulation code | Tensile Strength $N/mm^2$ | Swelling ratio (%) | Surface pH | Drug content of films (%) |
|---|---|---|---|---|
| VTF1 | 4.61±1.02 | 24.01± 0.23 | 5.1 ± 0.04 | 94.91±0.15 |
| VTF2 | 5.29±0.14 | 38.02 ± 0.19 | 5.2 ± 0.04 | 96.05±0.85 |
| VTF3 | 6.08±0.14 | 49.01 ± 0.18 | 5.5 ± 0.02 | 97.19±0.24 |
| VTF4 | 6.19±0.15 | 43.01 ± 0.51 | 5.6± 0.02 | 98.19±0.19 |
| VTF5 | 6.01±1.11 | 32.01 ± 0.27 | 5.6 ± 0.03 | 99.03±0.18 |
| VTF6 | 5.11±0.11 | 31.03 ± 0.34 | 5.2 ± 0.02 | 94.01±0.17 |
| VTF7 | 5.01±1.01 | 41.03 ± 0.15 | 5.4 ± 0.04 | 99.48±0.19 |
| VTF8 | 5.21±0.91 | 42.01 ± 0.16 | 5.5 ± 0.02 | 97.71±0.41 |

| | | | | |
|---|---|---|---|---|
| VTF9 | 4.27 ±0.18 | 45.01 ± 0.25 | 5.5 ± 0.02 | 98.91±0.22 |
| Mean ± SD; n = 3 | | | | |

The prepared multilayered transdermal patch were flexible, smooth, opaque and non sticky in nature **(Table 10)**.

**Table 10: Physical appearance of multilayered transdermal patch**

| Formulation code | Flexibility | Smoothness | Transparency | Stickness |
|---|---|---|---|---|
| TVP1 | Flexible | Rough | Opaque | Non sticky |

The result of thickness, mass deviation, cracking acceptance power, percentage elongation, tensile strength, swelling ratio, surface pH, drug content of TVP1 were shown in **Table (11 – 12)**.

**Table 11: Characterization of verapamil HCl containing transdermal film**

| Formulation code | Thickness (mm) | Average weight (mg) | Folding endurance | Percentage Elongation |
|---|---|---|---|---|
| TVP1 | 0.316±0.24 | 824.13±2.023 | 21-34 | 31.01±1.21 |

**Table 12: Characterization of verapamil HCl containing transdermal film**

| Formulation code | Tensile Strength $N/mm^2$ | Swelling ratio (%) | Surface pH | Drug content of films (%) | |
|---|---|---|---|---|---|
| | | | | TL | VHL |
| TVP1 | 6.13±0.13 | 128.63 ± 1.14 | 5.6 ± 0.04 | 98.24 | 99.54 |

The values obtained from first layer of trandolapril were examined by in-vitro drug release study and more than 85 % drug was completely release within 8 h. The drug was released through polymers chitosan have matrix, which is hydrophilic nature and able to enhanced spreadability and dispersibility of the water soluble trandolapril as needed for immediate release. The all evaluation parameters in-vitro drug release study was using for selection of best polymeric film prepared with chitosan and PVP as plasticizer for the preparation of multilayered transdermal patch as first immediate release layer. The HPMC separating layer was also start to dissolve after completely dissolvation of first layer. The next layer or film containing verapamil Hcl start to dissolve and swell alginate polymer and create water impermeable layer with more swelling index. The matrix layer of polymer allows creating the pores and enhance time span within the pH of skin layer and

consequently enhanced drug retardation more than 95% start to release from 8 h upto 24 h as needed for sustained release **(Table 13)**.

**Table 13: In-vitro drug release study of multilayered transdermal patch**

| Time (h) | TVP1 | |
|---|---|---|
| | TL | VHL |
| 0 | 0 | 0 |
| 2 | 8.65 | 0 |
| 4 | 25.67 | 0 |
| 6 | 62.21 | 0 |
| 8 | 84.78 | 1.01 |
| 10 | 98.23 | 5.23 |
| 12 | 99.01 | 14.87 |
| 14 | 99.12 | 28.23 |
| 16 | 99.23 | 55.78 |
| 18 | 99.56 | 74.32 |
| 20 | 99.75 | 85.23 |
| 22 | 99.81 | 90.13 |
| 24 | 99.98 | 95.23 |

The release kinetic study confirmed the prepared patch was followed supercase II transport mechanism of diffusion kinetics **(Table 14 – 15 and Figure 2 – 5)** 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.

**Table 14: in-vitro drug kinetic profile of multilayered transdermal patch (TVP1)**

| Formulation Code | Zero Order | | | | First Order | | | |
|---|---|---|---|---|---|---|---|---|
| | TL | | VHL | | TL | | VHL | |
| | $r^2$ | $K_0$ | $r^2$ | $K_0$ | $r^2$ | k-1 | $r^2$ | k-1 |
| TVP1 | 0.702 | 4.104 | 0.793 | 4.368 | 0.946 | 0.148 | 0.783 | 0.051 |

**Table 15: in-vitro drug kinetic profile of multilayered transdermal patch (TVP1)**

| Formulation Code | Higuchi Equation | | | | Korsmeyer Peppas Equation | | | |
|---|---|---|---|---|---|---|---|---|
| | TL | | VHL | | TL | | VHL | |
| | $r^2$ | $K_H$ | $r^2$ | $K_H$ | $r^2$ | n | $r^2$ | n |
| TVP1 | 0.84 | 24.52 | 0.676 | 22.69 | 0.674 | 2.358 | 0.816 | 2.68 |

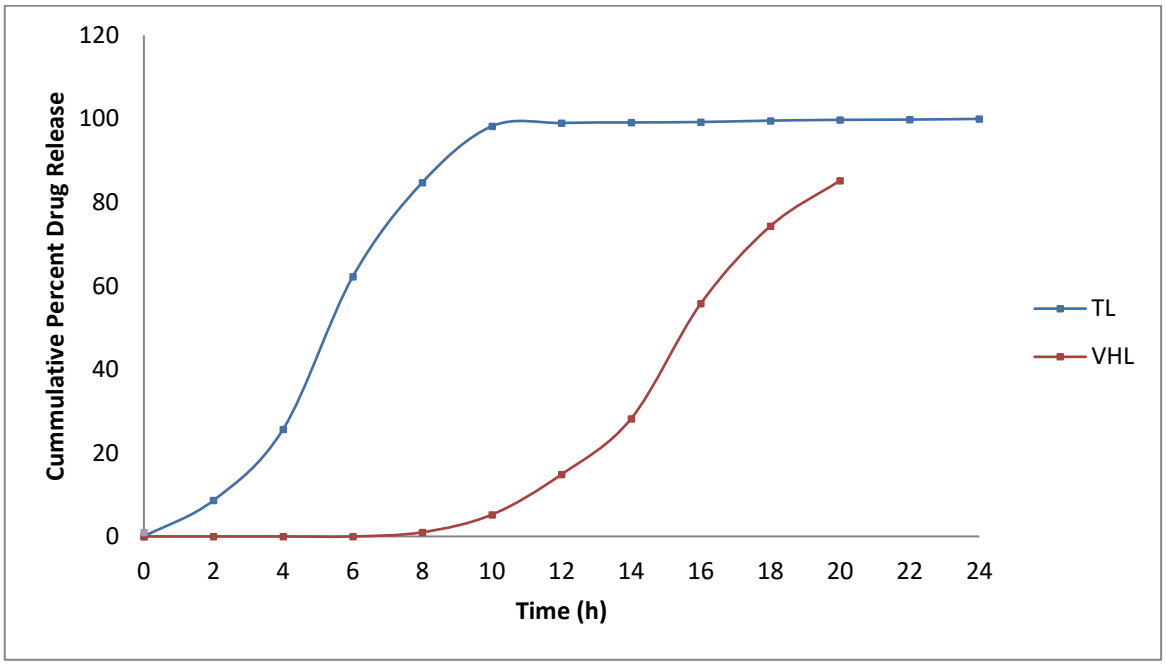



**Figure 2: In vitro drug release profile (Zero-order) of multilayered transdermal patch (TVP1)**

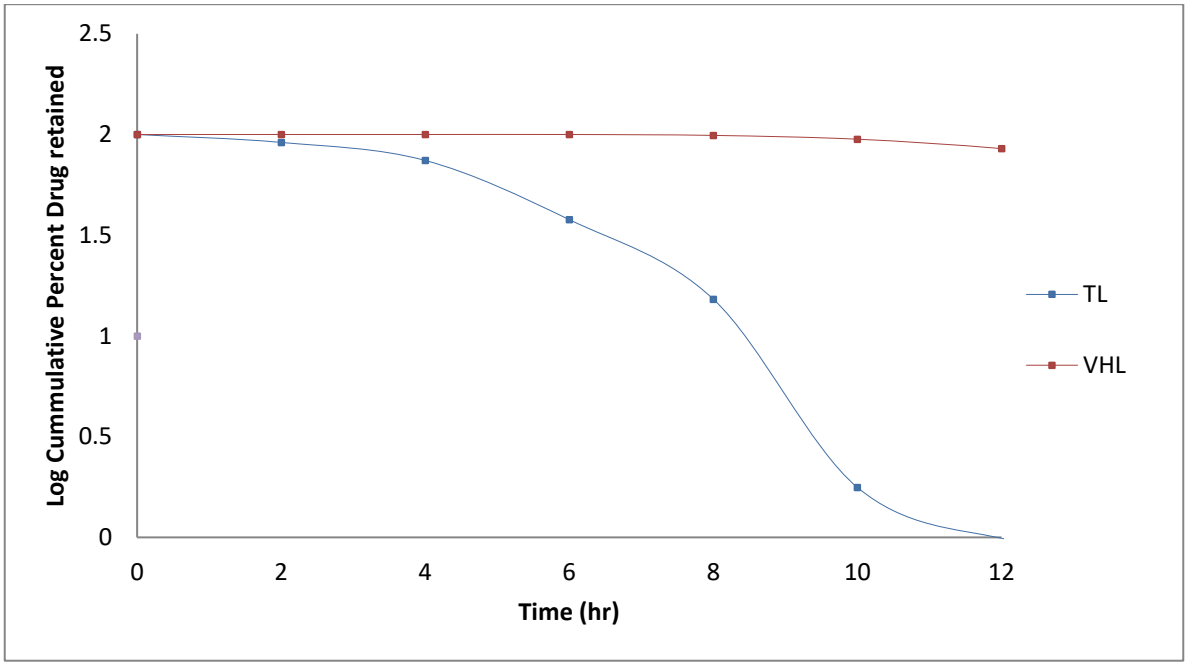



**Figure 3: In vitro drug release profile (First-order) of multilayered transdermal patch (TVP1)**

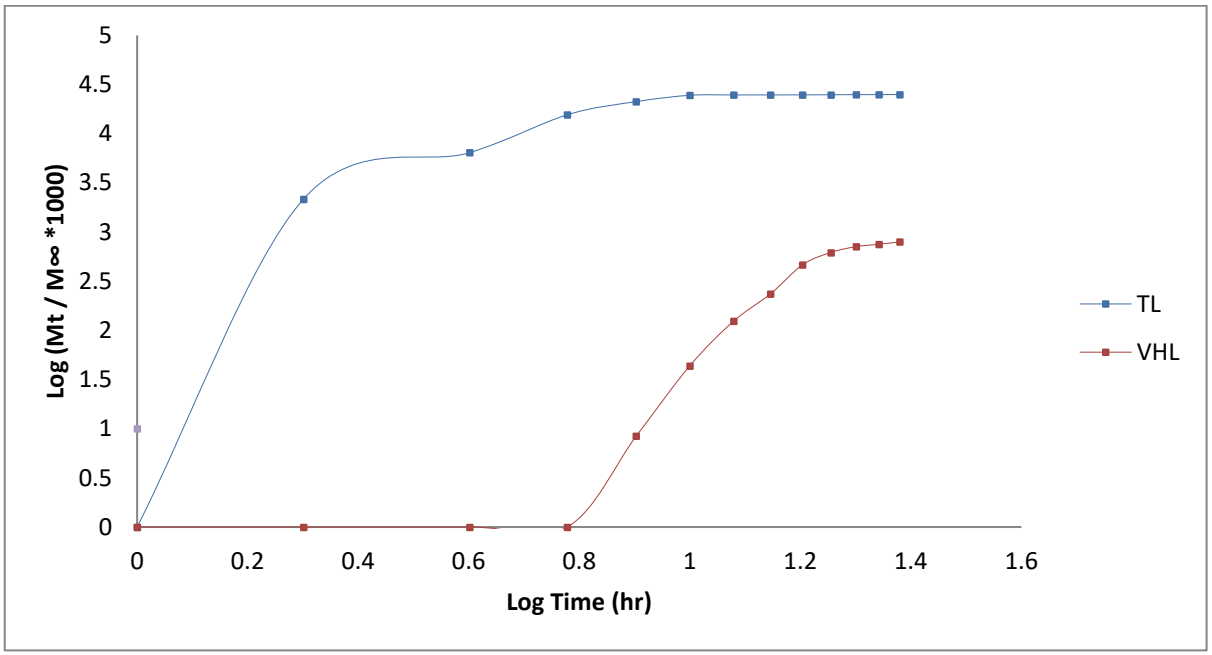



**Figure 4: In vitro drug release profile (Korsmeyer-peppas) of multilayered transdermal patch (TVP1)**

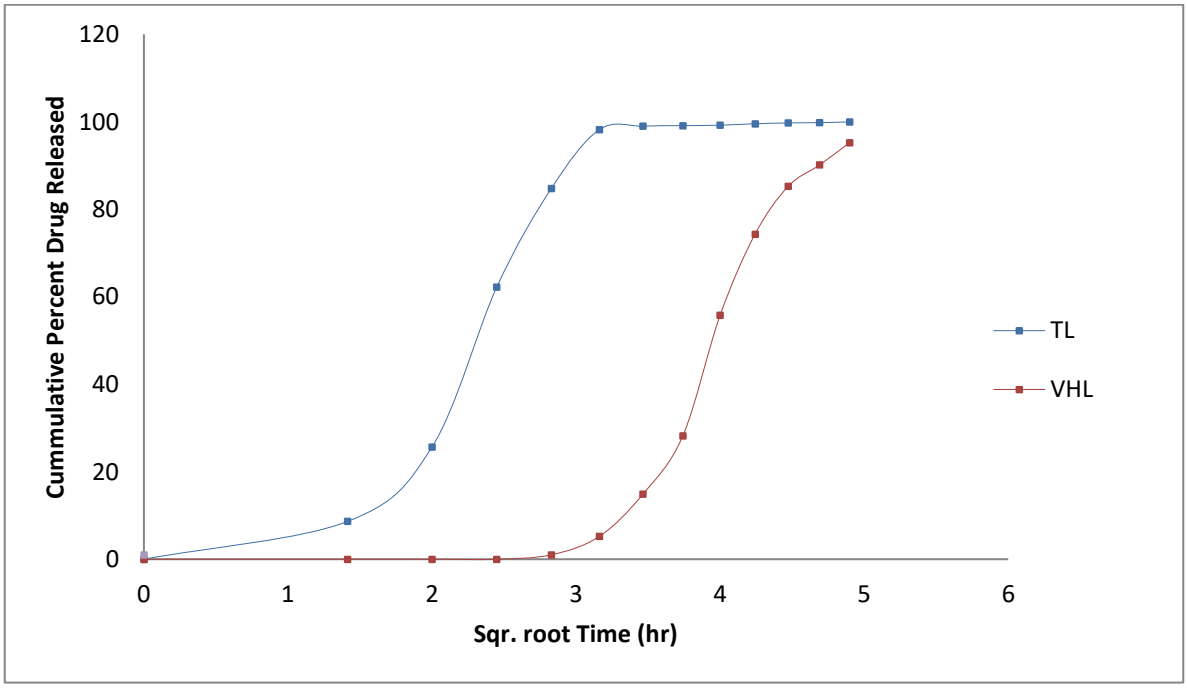



**Figure 5: In vitro drug release profile (Higuchi-plot) of multilayered transdermal patch (TVP1)**

The multilayered transdermal patch **TVP1** produced higher bioavailability and were applied on the rat skin, it was found that increased concentration of drug in rat blood plasma was due to the rapid absorption of drug, which was identified by better $C_{max}$ and lower $t_{max}$ values. The pharmacokinetic parameters were shown in

**Table 16 - 17**.

**Table 16: Pharmacokinetic Studies of multilayered transdermal patch (TVP1)**

| Time (h) | TVP1 (ng/ml) | |
|---|---|---|
| | TL | VHL |
| 0 | 0 | **0** |
| 2 | 1.25±0.0987 | 0 |
| 4 | 18.74±1.045 | 0 |
| 6 | 51.78±1.874 | 0 |
| 8 | 91.87±2.012 | 1.01±0.012 |
| 10 | 11.78±0.987 | 5.23±0.874 |
| 12 | 1.14±0.146 | 14.87±1.012 |
| 14 | 0.147±0.004 | 28.23±1.132 |
| 16 | 0 | 51.23±1.745 |
| 18 | 0 | 82.54±2.124 |
| 20 | 0 | 99.74±2.147 |
| 22 | 0 | 2.01±0.021 |
| 24 | 0 | 1.04±0.0014 |

**Table 17: Pharmacokinetic Studies of multilayered transdermal patch (TVP1) of multilayered transdermal patch (TVP1)**

| S. No | Parameters | TVP1 | |
|---|---|---|---|
| | | TL | VHL |
| 1 | $C_{max}$ (µg/ml) | 91.87±2.012 | 99.74±2.147 |
| 2 | $AUC_{0-t}$ (µg h/ml) | 176.707±3.144 | 285.9.78 ± 5.077 |
| 3 | $T_{max}$ (h) | 8.0± 0.02 | 20.0 ± 0.11 |
| 4 | $t_{1/2}$ (h) | 2.31 ± 0.014 | 2.45 ± 0.05 |
| Mean ± SD, n = 3 | | | |

The plasma drug concentration peak obtained from prepared multilayered transdermal patch TVP1 was indicated that both drug released and absorbed more than 90 % from 0 to 8$^{th}$ h trandolapril. The drug verapamil Hcl was not released during 0 – 6$^{th}$ h and was start to absorb and peak plasma concentration was reached upto 20$^{th}$ h **(Figure 6)**.

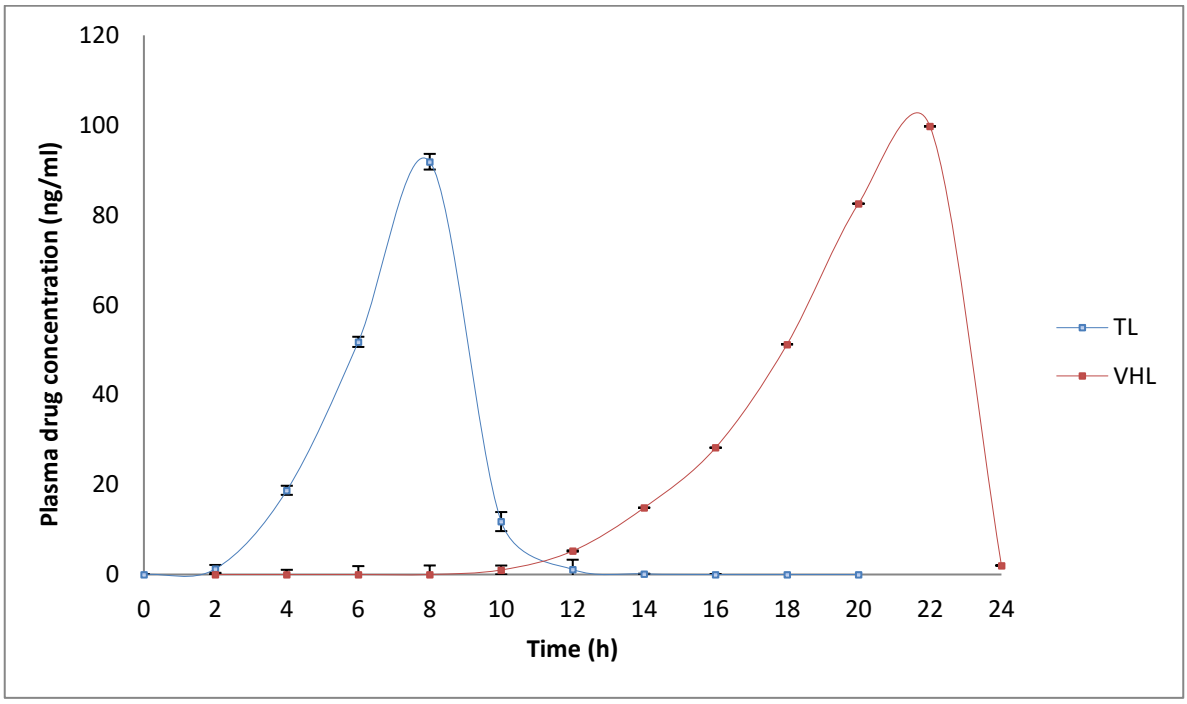



**Figure 6: in-vivo animal pharmacokinetic analytical study**

The result of AUC represents the total integrated area under the blood concentration-time profile. It indicated the total amount of drug reaches to the systemic circulation after administration. Thus, it is crucial parameter in identifying the bioavailability of drug from any dosage form. Statistically, $AUC_{0-t}$ of the formulation **TVP1** was significantly higher ($p<0.05$). The $AUC_{0-t}$ values were observed to significantly high and result showed concentration of drug was within therapeutic effective range for a longer period of time for treatment of hypertension. The primary skin irritation study was carried out on albino rats for formulation TVP1 indicates that there is score calculated (erythema and edema) of less than two **(Table 18)** as compared with control patch. The result indicated skin acceptability of praposed formulation for topical application and may be allowed for commercialization in futue. The formulation showing scores of two or less are considered negative (no skin irritation), on that basis it was decided that the developed transdermal patches are free of any skin irritation.

**Table 18: Results of skin irritation studies multilayered transdermal patch (TVP1)**

| S. No | Formulation | Visual observation | |
|---|---|---|---|
| | | Erythmea | Edema |
| 1 | Normal | 0.0±0.00 | 0.0±0.00 |
| 2 | Blank | 1.21±0.14 | 1.11 ± 0.07 |

| | | | |
|---|---|---|---|
| 3 | Multilayered transdermal patch (TVP1) | 1.32± 0.02 | 1.53 ± 0.11 |

The treatment schedule for determination the blood pressure as pharmacodynamic study was shown in **Table 19**. The results indicate that significant hypertension can be induced after administration of dexamethasone. The hypertension is initially controlled by oral administration, with the maximum effect observed at 2 hours, but latter on approximately after 2-4 hours the BP started gradually decrease with effects for longer duration as compare to oral administration. The patches maintain the continuous plasma level from the first two hour and the effect maintained continued for 24 h and prolonged control of hypertension uto 24 hours **(Table 19-20)**.

**Table 19: Treatment schedule of different dosage forms for various groups of animals**

| S. No. | Group | Teeatment | Dose | Route of administration |
|---|---|---|---|---|
| | Toxic | Dexamethasne | 20µg/kg/day | s.c. for 14 days |
| | Contrl group | Normal saline | 2ml/kg | Oral |
| | Formulation TVP1 | TL and VHL patch | 4 mg+120 mg | Patch |

**Table 20: in-vivo pharmacodynamic study and blood pressure identification of different dosage forms for various groups of animals**

| Groups | Systolic BP (mm Hg) | | | | | | Diastolic BP (mm Hg) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2h | 4h | 6h | 8h | 12h | 24h | 2h | 4h | 6h | 8h | 12h | 24h |
| Control group | 115.12 ± 4.11 | | | | | | 85.76 ± 6.01 | | | | | |
| Formulation TVP1 | 145.32 ± 5.01 | 138.12 ± 4.61 | 128.72 ± 4.11 | 121.11 ± 3.98 | 120.82 ± 3.12 | 117.12 ± 3.51 | 95.32 ± 5.01 | 92.09 ± 4.91 | 89.21 ± 4.11 | 87.02 ± 3.91 | 86.91 ± 2.03 | 85.12 ± 3.33 |

The stability study of prepared multilayered transdermal patch was performed in different temperature as per guideline of ICH guideline. The result was showed on **Table 21 – 23 and Figure 7 – 9**. There was little bit change or degradation of concentration or amount of drug component in formulation.

**Table 21: Stability Studies of multilayered transdermal patch (TVP1) at 2ºC ± 0.5ºC**

| S. No | Time Interval (days) | Percent Drug Content | |
|---|---|---|---|
| | | TL | VHL |
| 1 | 0 | 99.85±0.13 | 98.19±0.19 |
| 2 | 30 | 99.72±0.11 | 98.01±0.11 |
| 3 | 60 | 99.66±0.17 | 97.97±0.18 |
| 4 | 90 | 99.31±0.18 | 97.72±0.12 |
| 5 | 180 | 98.27±0.13 | 97.66±0.17 |

**Table 22: Stability Studies of multilayered transdermal patch (TVP1) at 25°C± 2ºc/60% ± 5% RH**

| S. No | Time Interval (days) | Percent Drug Content | |
|---|---|---|---|
| | | TL | VHL |
| 1 | 0 | 99.85±0.13 | 98.19±0.12 |
| 2 | 30 | 99.12±0.12 | 97.81±0.13 |
| 3 | 60 | 98.86±0.07 | 97.07±0.11 |
| 4 | 90 | 98.11±0.11 | 96.52±0.14 |
| 5 | 180 | 97.27±0.09 | 96.06±0.11 |

**Table 23: Stability Studies of multilayered transdermal patch (TVP1) at 40ºC ± 2ºC/75% ± 5% RH**

| S. No | Time Interval (days) | Percent Drug Content | |
|---|---|---|---|
| | | TL | VHL |
| 1 | 0 | 99.85±0.18 | 98.19±0.12 |
| 2 | 30 | 98.42±0.11 | 97.01±0.11 |
| 3 | 60 | 97.06±0.17 | 96.17±0.09 |
| 4 | 90 | 96.21±0.01 | 95.82±0.11 |
| 5 | 180 | 95.01±0.11 | 95.01±0.13 |

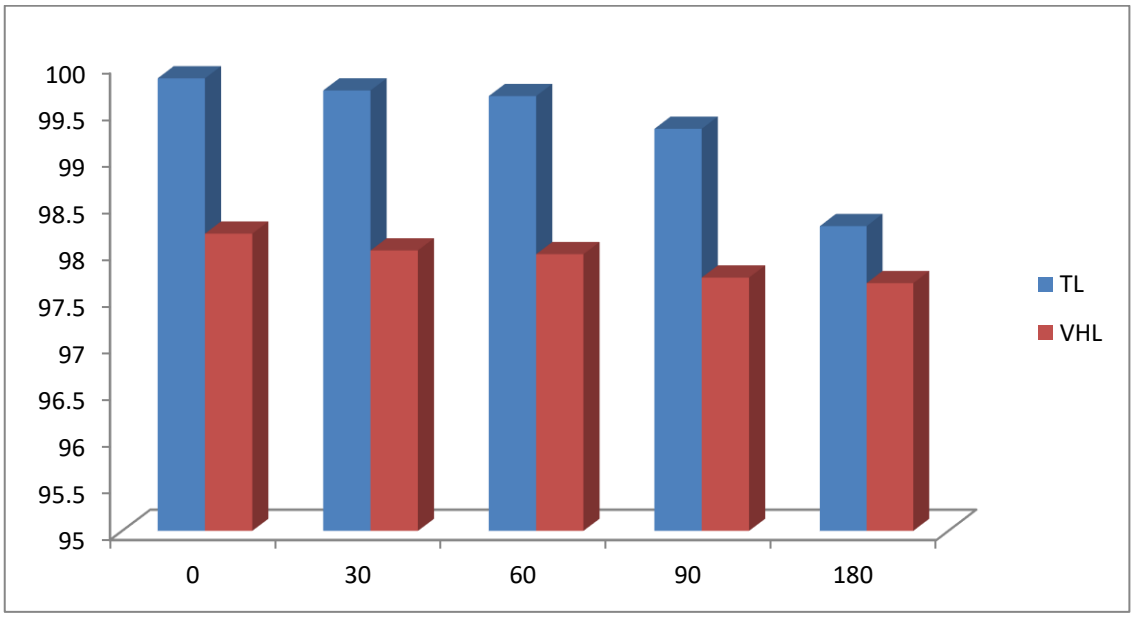



**Figure 7: Stability Studies of multilayered transdermal patch (TVP1) graphical representation showing residual drug content (%) at 2ºC ± 0.5ºC**

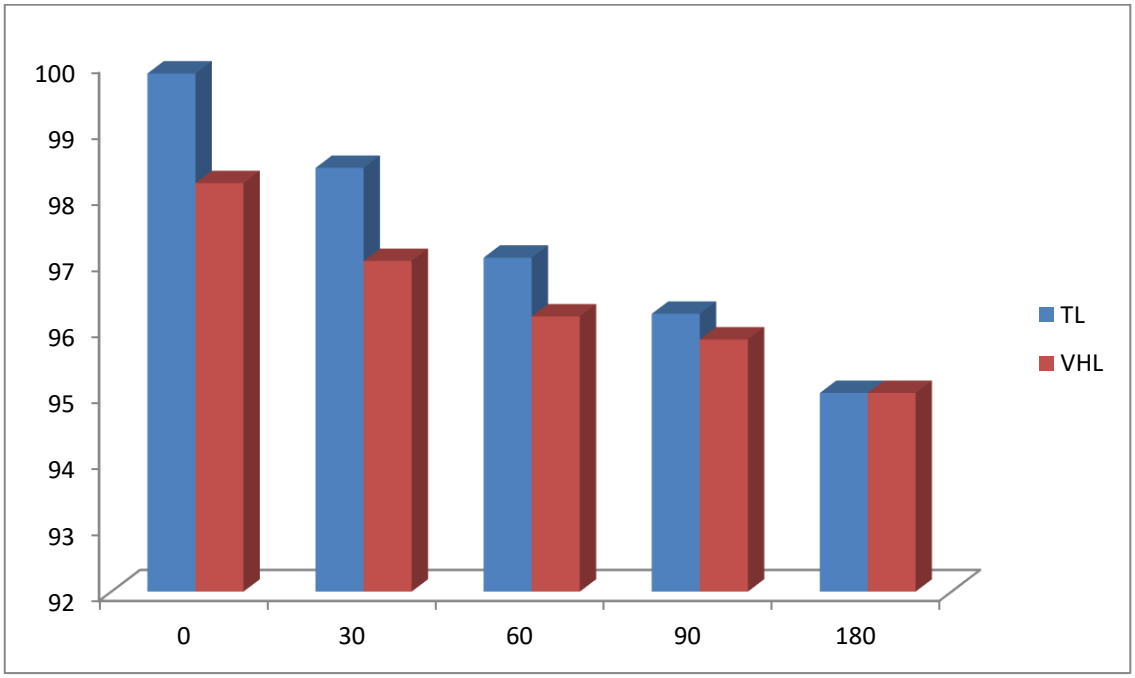



**Figure 8: Stability Studies of multilayered transdermal patch (TVP1) graphical representation showing residual drug content (%) at 25°C± 2ºc/60% ± 5% RH**

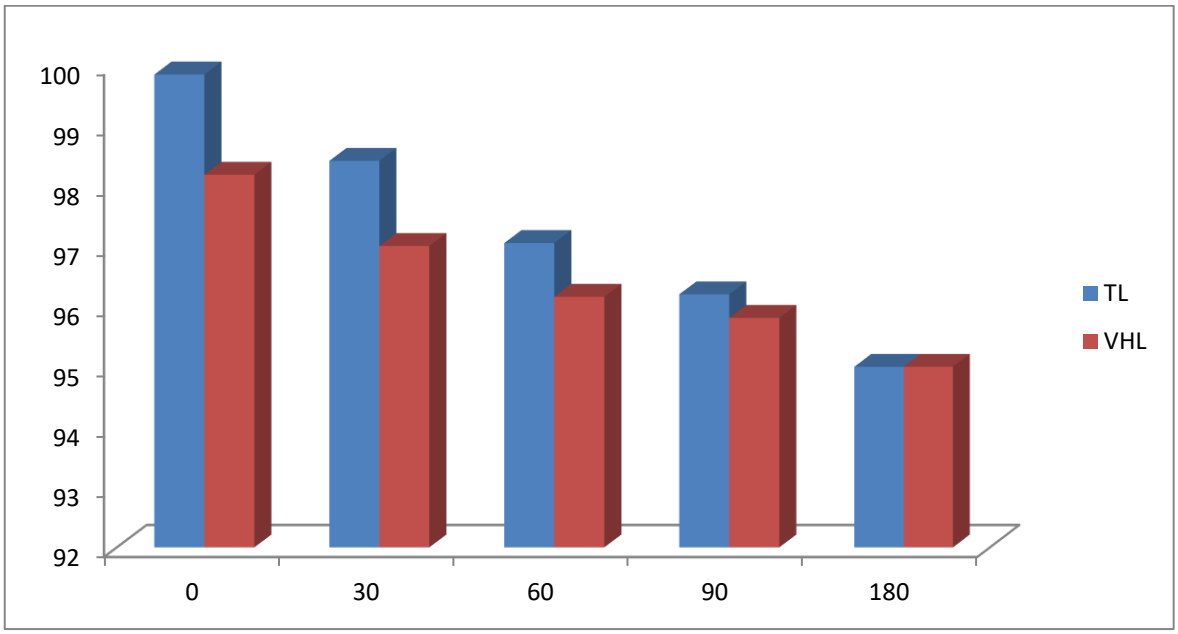



**Figure 9: Stability Studies of multilayered transdermal patch (TVP1) graphical representation showing residual drug content (%) at 40ºC ± 2ºC/75% ± 5% RH**

**Summary and Conclusion:** The proposed model drug trandolapril is the ethyl ester prodrug of a nonsulfhydryl angiotensin converting enzyme (ACE) inhibitor, trandolaprilat. The verapamil have short biological or metabolic half life (1 - 2 hour) with higher dosing, it have high first-pass metabolism, bioavailability is much lower (10–35%). These proposed TDDs worked on management of diseased of cardiac arrhythmias and have short biological half life, low oral bioavailability value, dose, and molecular weight for better bioavailability of drugs. The proposed transdermal patch combines a slow release formulation of a calcium channel blocker, verapamil hydrochloride, and an immediate release formulation of an angiotensin converting enzyme inhibitor, trandolapril. The prepared multilayered 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 examined by in-vitro drug release study and more than 85 % drug was completely release within 8 h. The HPMC separating layer was also start to dissolve after completely dissolvation of first layer. The next layer or film containing verapamil Hcl start to dissolve and swell alginate polymer and create water impermeable layer with more swelling index and consequently enhanced drug retardation more than 95% start to release from 8 h upto 24 h as needed for sustained release. 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 pharmacodynamic study confirmed patches maintain the continuous plasma level from

the first two hour and the effect regularly maintained continued for 24 h, thus produced prolonged control of hypertension uto 24 hours

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