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FORMULATION AND EVALUATION OF TRANSDERMAL PATCH AND GEL OF VENLAFAXINE

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ABSTRACT

This study has been carried out to know the effectiveness of transdermal patch and gel formulations of venlafaxine in the treatment of depression. In this study different formulations of transdermal patches were formed by using various polymers such as hydroxyl-propyl methyl cellulose (HPMC K4M), ethyl cellulose and eudragit S100 in different ratios. Transdermal gel formulations were also prepared by using polymers such as HPMC K4M and carbopol 930P in order to determine which drug delivery system is effective and serve the purpose best. Results obtained from the evaluation studies of each dosage form revealed that topically applied patch drug dosages forms possess immense potential to control the release rate of medicament to improve the bioavaibility as well as patient compliance as compared to their gel counterparts.

KEYWORDS

Transdermal patch, Venlafaxine, Ethyl-cellulose, Eydroxyl-propyl methyl and Cellulose.

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INTRODUCTON

One of the main encumbrances to the use of many hydrophilic macromolecular drugs as potential therapeutic candidates is their inadequate and erratic oral absorption. Once after oral administration many drugs are subjected to presystemic clearance extensive in liver, which often leads to a lack of significant correlation between membrane permeability, absorption, and bioavailability[1]. Difficulties associated with parenteral delivery and poor oral availability provided the impetus for exploring alternative routes for the delivery of such

drugs. These include routes such as pulmonary, ocular, nasal, rectal, buccal, sublingual, vaginal, and transdermal. Among the various routes, transdermal route for delivering drugs has got immense potential to transport drug across the skin membrane while bypassing the first pass effect. Now days this specific route has drawn the attention of scientists worldwide because it can be accepted as an alternative administration path for both oral delivery and intravenous infusion because of its numerous advantages. Continuous intravenous infusion with a pre-programmed rate has been a superior mode of drug delivery since time immemorial not only for bypassing hepatic first pass metabolism but also for maintaining constant drug blood levels for prolonged periods of time to get maximum therapeutic benefits. But one cannot ignore the certain risks associated with this drug delivery which often requires close monitoring and hospitalization of patient. One of the alternative routes which closely duplicate the benefits of continuous intravenous infusion without its possible hazards is continuous transdermal drug administration through intact skin[2,3]. In the present study both transdermal patches and transdermal gels of antidepressant drug venlafaxine were formulated in the quest of therapeutically effective drug delivery system to combat depression. Both these delivery systems are unique of their own as both offers number of advantages over other drug delivery systems[4,5] . Therefore, the main aim of this study is to conclude which out of these systems which would be more therapeutically effective and will serve the purpose best. Venlafaxine HCL was chosen as a model dug which is a selective serotonin and nor epinephrine-reuptake inhibitor (SNRI) antidepressant and anxiolytic agent[6]. The oral bioavailability of venlafaxine is about 45 % because of extensive first pass metabolism in liver and gut wall. It was selected as a model drug for investigation because of its suitable properties like dose strength (25 mg), half-life (5 h) and molecular weight (277.40).Disadvantages of drug delivery by this route are the low permeability of the buccal membrane[7], specifically when compared to the sublingual membrane[8], and a smaller surface area. The total surface area of the membranes of the oral cavity available for drug absorption is 170 cm^2 [9], of which ~50 cm^2 represents non-keratinized tissues, including the buccal membrane. In the present study, the mucoadhesive buccal patches were developed using polymers such as Ethyl cellulose, Eudragit S100 and HPMC K4M at different proportions to get the controlled release rate from the buccal patches.

MATERIAL AND METHODS

Venlafaxine was obtained as a gift sample from Ranbaxy Laboratories, Baddi, India. Hydroxypropyl methylcellulose (HPMC) K4M, Eudragit S100, Ethyl cellulose and Carbopol 930P was provided from S.D Fines chemicals, India. All other reagent and chemicals were of analytical grade.

Drug Polymer Compatibility Studies

Drug polymer compatibility studies were carried out using FTIR spectrophotometer before the formulations of the patch and gel dosage forms. In this study peaks of pure drug were compared with the peaks of drug and polymers used[10].

Preparation of transdermal patch by solvent casting method

Transdermal patches of venlafaxine were prepared by using solvent casting method in the ratio as given in composition table 1.Required quantities of polymers were accurately weighed and dissolved in a mixture of methanol and chloroform in the ratio 1:1 and continuously stirred for 3-4 hours. After this drug was weighed and added to this polymer solution. Required quantity of dibutyl-n-phthalate as plasticizer and DMSO as penetration enhancer were added to the above solution and stirred until clear solution is obtained. The resulted uniform solution was poured carefully within a Petridish. An inverted funnel was placed over the dish to prevent the fast evaporation of the solvent and left for 24 hrs to dry the films. After complete drying for 24hrs the dried patches were carefully recovered from the Petridish and stored in a dessicator for further studies[11].

Melting point

Small amount of drug was taken in a capillary tube closed at one end for the determination of melting point. This tube was then placed in melting point

apparatus and temperature at which the drug melted was noted.

Evaluation of transdermal patches

Physical Appearance

Prepared transdermal patches were inspected visually for clarity, uniformity, colour, flexibility and smoothness[12].

Thickness

The thickness of the drug loaded patch was measured at three different points by using a standard vernier caliper. The average thickness of the patch was determined and reported with appropriate standard deviation[13].

Weight Uniformity Studies

Weight uniformity of patch was determined by taking weight of ten patches of sizes 1 cm^2 diameter from every batch and weigh individually on electronic balance. The average weights were then calculated[14].

Folding endurance

Folding endurance of prepared patches was determined by repeatedly folding a selected patch from the same place until it break. The number of times a film could be folded from the same place without braking gives the value of folding endurance[15].

Flatness

One of the important characteristic of transdermal patch is that it should possess a smooth surface and it should not constrict with time. This characteristic of transdermal patch can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. 0% constriction is equivalent to 100 % flatness[16].

$$\% \text{ Constriction} = \frac{L1-L2}{L1} \times 100$$

L2 = Final length of each strip

L1 = Initial length of each strip

Drug Content uniformity

Drug content study was performed in triplicate for each formulation. Drug content uniformity was determined by dissolving the patch (1 cm^2 in diameter) from each batch by homogenization in 100 ml of an isotonic phosphate buffer (pH 7.4) for 24 h under occasional shaking. The 5 ml solution was taken and diluted with isotonic phosphate buffer pH 7.8 up to 20 ml, and the resulting solution was filtered through a 0.45 mm Whatman filter paper. The drug content was then determined after proper dilution using UV spectrophotometer[17].

Percentage Moisture content

Patches were weighed individually and kept in desiccator that contains fused calcium chloride at room temperature for about 24 hrs. After 24 hrs the patches are reweighed and determine the percentage moisture content by using given formula[13].

$$\text{Percentage moisture content} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} X100$$

Percentage Moisture absorbed:

Patches were weighed individually and kept in desiccators at room temperature for 24 hrs containing saturated solution of potassium chloride in which it maintain 84% RH. After 24 hrs the films are reweighed and calculate the percentage moisture uptake by using given formula[13].

$$\text{PercentageMoistureAbsorbed} = \frac{\text{FinalWeight} - \text{InitialWeight}}{\text{InitialWeight}} X100$$

Tensile strength

A tensile strength study of patch is total weight, which is necessary to break or rupture the dosage form and this was done by a device has rectangular frame with two plates made up of Plexiglas's. The one plate is in front and is movable part of device and can be pulled by loading weights on the string, which is connected to movable part. The 1×1 cm^2 patch equivalent to 2.75 mg drug from each formulation was fixed between the stationary and movable plate. The force needed to fracture the film was determined by measuring the total weight loaded in the string. The weight corresponds to break the patches were taken as tensile strength. The following equation was used to calculate the tensile strength[18].

$$\text{Tensile Strength}\left(\frac{g}{cm^2}\right) = \frac{\text{Force at break(g)}}{\text{Initial Cross sectional area of patch}(cm^2)}$$

Water vapour transmission test (WVTR)

Vapour transmission method was employed for the determination of vapour transmission from the patch. Glass bottle (length = 5 cm, narrow mouth with internal diameter = 0.8 cm) filled with 2 g

anhydrous calcium chloride and an adhesive (Feviquick®) spread across its rim, was used in the study. The patch was fixed over the adhesive and the assembly was placed in a constant humidity chamber, prepared using saturated solution of ammonium chloride and maintained at 37 ± 2°C. The difference in weight after 24 h was calculated. The experiments were carried out in triplicate and vapor transmission rate was obtained by given formula[18].

$$\text{WVTR} = \frac{\text{Amount of moisture transmitted}}{\text{AreaXTime}}$$

***In-vitro* release study**

The *in-vitro* release study for the prepared patches was performed by using the Franz diffusion cell at pH 7.4. The diffusion cell was maintained at 37 ± 0.5°C and 50 rpm. Samples were collected after specific time intervals and subjected for U.V.analysis[19].

***In vitro* drug release kinetics**

Kinetic models are used to describe the drug release from immediate and modified release dosage forms. In order to determine the kinetics and mechanism of drug release from prepared patches of different drug and polymer ratios the release data were examined using various models such as Zero order kinetic, First order kinetic, Higuchi kinetic, Hixon crowell and Korsmeyer-Peppas model[19].

Preparation of Transdermal Gel

Transdermal gel of venlafaxine was prepared by weighing required quantities of either carbopol 934 or HPMC K100. Gel base was prepared by hydration of gelling agent. Accurately weighed venlafaxine was dissolved in ethanol as a co-solvent and the ethanolic solution of drug was added slowly with stirring (400-600 rpm) in the previously prepared gel base. To this solution triethanolamine was added to adjust the pH and Propylene glycol was added with stirring. The final quantity was made up to 100ml with distilled water. The prepared gel was kept for 24h for complete polymer desolvation.

Evaluation of Gel

Physical examination

All the gel formulations were tested for physical parameters such as clarity and appearance by their visual inspection. After the gels have been set in the container they were tested for homogeneity and presence of any aggregates and lumps.

pH determination

The pH of gel formulations was determined by using digital pH meter. 100mg of gel was dissolved in 100 ml of distilled water and stored for 2 hours. The measurement of pH of each formulation was done in triplicate and average values were calculated[20].

Viscosity determination

The measurement of viscosity of the prepared gel was done by using Brookfield Viscometer (DV-E). The viscosity of various gels was determined at different angular velocities 5, 10, 20, 30, 60 and 100 rpm using spindle no.6 at each speed, the corresponding dial reading was noted[20,21].

Spread ability

Concentric circles of different radii were drawn on graph paper and a glass plate was fixed onto it. Gel (5.0 gm) was transferred to the centre of the lower plate and spread over an area of 2 cm diameter. The glass plate of 100±5 gm was placed gently on the gel and the spread diameter was recorded after 1 minute of each addition. Results were presented as the spreading area being a function of the applied mass.

Drug content determination

A specific quantity (1 g) of prepared gel was taken and dissolved in 100 ml of phosphate buffer of pH 7.4. The volumetric flask containing gel solution was shaken for 2 hours on a mechanical shaker in order to get complete solubility of drug. The solution was filtered through whatmann filter paper and appropriately diluted to estimate spectrophotometrically at 260 nm using phosphate buffer (pH 7.4) as blank[22].

***In-vitro* Drug Diffusion Study of transdermal gel**

In-vitro drug release studies were performed by using a Keshary-Chien diffusion cell with a receptor compartment capacity of 25 ml. The gel sample was applied on the membrane and then fixed in between donor and receptor compartment of diffusion cell. The whole assembly was fixed on a magnetic stirrer at 50 rpm; the temperature was maintained at 37 ± 0.50 °C. The samples of 1 ml were withdrawn at

time interval of 15 min, 30 min, 1 hour, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11and 12 hour and analyzed for drug content spectrophotometrically at 260 nm against blank. The receptor phase was replenished with an equal volume of phosphate buffer at each time of sample withdrawal[20,21]. Ultimately the cumulative amounts of drug diffused from gels were plotted against time[23,24].

RESULTS AND DISCUSSION

In the present study an attempt has been made to prepare transdermal drug delivery systems of venlafaxine in the form of patches and gels so that a comparison can be done in-between two different dosage forms to find out the most effective transdermal system for the treatment of depression. Both the patches and gel formulations were prepared using different polymers in different ratios as given in composition Tables No.1 and 2. Formulated patches were evaluated for various evaluation parameters such as thickness, weight uniformity, surface pH, content uniformity, folding endurance, percentage swelling, tensile strength, vapour transmission rate, percentage moisture loss, drug content and *in vitro* diffusion studies. Gel formulations were also evaluated for different parameters such as physical examination, pH, viscosity, spreadibility, drug content and drug release studies. Compatibility studies for both patch and gel delivery systems were conducted using FTIR instrument. The result was based on matching the main peak of pure drug with drug and polymer. No incompatibility was found between drug and polymers.

Results of various parameters for patches and gels are shown in tables 3 and 4.From the given data it can be seen that the thickness of formulated patches ranges from 0.123mm to 0.355mm. Thickness of patches prepared either by using combination of HPMC K4M and ethylcellulose and HPMC K4M and Eudragit S100 increases as the concentration of polymers increases.

Weight uniformity of patches prepared from HPMC K4M and ethyl cellulose ranges from 0.019g to 0.032g and for other combination the range of weight obtained is 0.022g to 0.036g. The data obtained for weight uniformity revealed that with the increase in the amount of polymer the weight of patches increases.

The pH ranges from 6.5±0.15 to 6.8±0.12 which indicates no skin irritation.

For all of the patches formulations except FP1, content uniformity is more than 90% with a maximum of 99.12±1.8% in FP5 and minimum of 89.81±1.3% in FP1. The obtained data for this study showed the uniform dispersion of drug throughout the patches.

Folding endurance which is one of the most important parameter of patch formulation from patch integrity point of view was found to be sufficiently high. The maximum value of folding endurance is 241±1.2 for formulation FP8 and minimum value is145± 2.3 times for FP1 without any sign of rupture and cracks on the surface. From the obtained data which is given in Table No.3, it can be concluded that the formulated patches possess high flexibility and are able to withstand the pressure with general skin folding conditions. This indicates that polymers and plasticizers which are used in the formulation of patches are good enough in providing integrity and flexibility to the patches and the flexibility of patches increases with the increasing amount of polymer.

The fact that swelling of the polymer plays a key role in the release of drug from the dosage form makes this study very important one for the overall success of the drug delivery systems. Swelling studies revealed that maximum swelling is shown by formulations with increasing concentration of hydrophilic polymer.

Tensile strength is one of the important parameter which gives an indication regarding the strength and elasticity of the patches. Obtained data clearly revealed that the tensile strength bears a direct proportionality with the amount of polymer HPMC K4M and increases as the amount of polymer in the patches increases. Tensile strength of formulation FP4 was found to be 188.8±1.6 gram and tensile strength of formulation FP8 was found to be 217.1±1.9g as both the formulations contain highest amount of polymers HPMC K4M.

The result of vapour permeation study showed that all patches were permeable to water vapour and hence the release of drug through the patch takes place by permeation of water.

In-Vitro drug release studies were done by using Franz diffusion cell at pH 7.4. It can be seen from the drug release data for transdermal patches formulations which is given in table 5 that the drug diffusion from the patches decreases and become more controlled as the respective concentration of polymers increases. Formulations FP1 to FP4 were formulated by using combinations of polymers HPMC K4M and ethylcellulose and second batch of formulations which are coded from FP5 to FP8 were formulated by combination of polymers HPMC K4M and eudragit in the ratios given in composition table 1. For formulation FP1 the % cumulative amount of drug release is 97.126±1.31% for 12 hr which respectively decreases with the increase in polymer concentration in further formulation and ultimately get controlled up to 88.993±1.32% for formulation FP4. This decrease in drug release rate with increasing concentration of polymer goes to the fact that with the increase in polymer concentration the barrier properties of the formulated patches and diffusional path length of the drug from the formulated patches increases which ultimately retarded and controlled the release rate of medicament. In second batch, formulation FP5 showed a release of 98.709±1.49% for 12hr with a little decrease and control of drug diffusion in further formulations. Formulation FP8 showed the maximum controlled release of 95.430±1.17% for 12hr. In comparison to batch first which includes formulations FP1-FP4, the rate of drug diffusion in second batch formulations for 12hr period is much less controlled. From the given data in table 5 it can be clearly seen that there is only 3% of drug retardation in second batch formulations from FP5 to FP8 which is much less as compared to almost 10 % of drug release control in formulation FP4 as compared to first formulation FP1. Thus, it can be concluded that not only the polymeric concentration that affect the diffusion of drug from formulation but also the type and nature of polymer which ultimately affect the release rate and play a very significant role in controlling the diffusion of drug from the delivery systems. In order to establish the mechanism of release of the drug from the immediate and modified release dosages forms kinetic models are used. The drug release data were subjected to various mathematical kinetic models like zero order, first order etc. The data were also subjected to Higuchi's model and Korsmeyer model. Korsmeyer model is widely used; when the release mechanism is not well known or when more than one type of release phenomena could be involved. Korsmeyer and Peppas equation: $Mt/M_{\infty} = Kt^n$, where Mt/M_{∞} is the fractional drug release in time't'. K= constant incorporating of structural and geometric characteristics of controlled release device, n = diffusional release exponent indicative of release mechanism. The 'n' value could be used to characterize different release mechanisms as follows $n = 0.5$ means Fickian diffusion, $0.5 < n < 1.0$ non-Fickian diffusion, and $n = 1.0$ case II diffusion[20]. The interpretation of data was based on the value of the resulting regression coefficients.

For all the patches formulations the values of R^2 of zero order, first order and Higuchi are given in Table No.6 and from this table it was clearly observed that for most of the formulations the value of resulting regression coefficient (R^2) is highest for zero order except for formulation FP5 which follows Higuchi model. Experimental results shows that all the formulations predominantly followed zero order kinetics indicating controlled drug diffusion from transdermal patches formulations as expected from system like patches. The corresponding n values of maximum formulation were above 0.5 and less than 1 which indicates that the formulations released the drug through non Fickian diffusion mechanism.

In the same study transdermal gel of venlafaxine was also formulated by using polymers such as carbopol 934P and HPMC K4M in the ratio given in composition Table No.2. All the prepared formulations of gels were successfully evaluated for the various evaluation parameters such as clarity, homogeneity, pH, spreadibility, viscosity, drug content and *in-vitro* diffusion studies. Clarity and homogeneity are the two very important

characteristics of gel dosages form from appearance point of view. These are the parameters which deal with the consumer's acceptance also. Hazy appearance and non homogeneity compromises with the quality of dosage form and gives an alarm of bad quality results in the non acceptance of the dosage form by the patients. Almost all the prepared gel formulations from FG1 TO FG8 showed acceptable clarity and good homogeneity.

pH of all the gel formulations was found in the range of 7.05±0.19 to 7.24±0.06 which is in the normal skin pH range and signifies no irritation to the skin on application.

Spreadibility plays a significant role in gel drug delivery systems. It gives an idea about the ease with which one can apply or spread the gel into the skin with minimum shear stress. The values of spreadibility for the formulated gel were found in the range of 20.6±0.19 gm.cm/sec to 33.5±0.15gm.cm/sec indicating easy spread of all the formulations with little shear stress.

Viscosity of all the gel formulations was found to increase with the increase in the concentration of polymers which can be seen from the given data in Table No.6. Drug content of formulations was found in the range of 90.22 ±0.54% to 98.46±0.36 which is sufficiently high and indicates good content uniformity. All the physical parameters for gel formulations were found in the acceptable range and indicate that the gels are suitable for topical applications.

In-Vitro drug release studies for transdermal gels were also done by using Franz diffusion cell at pH 7.4. Experimental results of the study are given in table 8. Formulations FG1 to FG4 were formulated by using polymer Cabopol 934 and polymer HPMC K4M was used for the formulations of second batch of gel formulations from FG5 to FG8. From the obtained drug release data which is given in table 8 it can be clearly seen that the gel formulations which were formulated by using carbopol 934 were found better in controlling the drug release from the gel as compared to formulations belongs to second batch. FG1 showed highest drug release of 98.195±1.18% for 12hr which slowed and controlled gradually in further formulations and FG4 showed a release of 90.857±1.43% for 12 hr. The decrease of drug release was also found in formulations FG5 to FG8 with the increase in polymer concentration. Thus it can be concluded that the release rate of drug from the various gel formulations decreases with the increase in concentration of polymer. Second batch of formulations were found to control the medicament for lesser extent as compared to first batch formulations (FG1-FG4). This thing clearly revealed the fact that out of the two polymers which were used for the gel formulations, carbopol 934 was found to control the drug release for longer period of time. To know the exact release order and behavior of gel drug delivery system the data obtained from release studies was subjected to kinetic modelling and from the results obtained which are shown in Table No.9 it can be clearly seen that most of the gel formulations obey Higuchi Kinetic model except few which obey zero order kinetics. Ultimately from the results obtained for various dosages forms from the entire study it can be concluded that the transdermal patch formulations possess immense potential to be used as a successful controlled release drug delivery systems and falls ahead in the effective treatment of depression.

Table No.1: Formulation composition of transdermal patches

S.No	Ingredients	FP1	FP2	FP3	FP4	FP5	FP6	FP7	FP8
1	Drug (mg)	100	100	100	100	100	100	100	100
2	HPMC K4M (mg)	150	200	250	275	150	200	250	275
3	Ethylcellulose (mg)	150	100	50	25	-	-	-	-
4	Eudragit S100 (mg)	-	-	-	-	150	100	50	25
5	Propylene Glycol (%w/v)	40	40	40	40	-	-	-	-
6	Dibutylpthalate (%w/v)	-	-	-	-	40	40	40	40
7	Methanol: Chloroform	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1

FP = Formulation patch, HPMC = Hydroxypropyl methylcellulose

Table No.2: Composition of transdermal Gel containing Carbopol 934 and HPMC K100M

S.No	Ingredients	FG1	FG2	FG3	FG4	FG5	FG6	FG7	FG8
1	Drug (mg)	100	100	100	100	100	100	100	100
2	Carbopol 934 (mg)	100	150	200	250	-	-	-	-
3	HPMC K4M (mg)	-	-	-	-	100	150	200	250
4	Triethanolamine (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
5	Ethanol (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
6	Propylene glycol (%v/w)	40	40	40	40	40	40	40	40
7	Distilled Water (ml)	100	100	100	100	100	100	100	100

Table No.3: Peak table of FTIR spectra of pure drug and drug with selected polymers

Peaks	Sample			
	venlafaxine	venlafaxine+ Ethyl Cellulose	venlafaxine+ HPMCK4M	venlafaxine+ Eudragit S 100
1	3350.60	3473.91	3352.18	3350.05
2	3369.57	3352.15	3069.57	3000.00
3	3008.70	3060.87	3013.04	2944.27
4	2937.62	2934.99	2936.86	2860.87
5	2861.54	2869.57	2862.14	2586.96
6	2580.44	2665.22	2666.10	2513.04
7	2514.42	2581.11	2581.86	2469.57
8	1613.04	1604.35	1617.39	1504.35
9	1036.49	1142.98	1037.14	1043.48
10	921.74	921.74	921.74	930.43
11	834.78	839.13	843.48	834.78
12	528.61	582.61	582.61	591.30

Table No.4: Evaluation of Transdermal patches

Formulation code	Thickness* (mm)	Wt.uniformity* (g)	pH*	Content uniformity* (%)	Folding endurance*
FP1	0.123±0.005	0.019±0.002	6.5±0.15	89.81±1.3	145± 2.3
FP2	0.182±0.005	0.023±0.001	6.4±0.17	92.61±2.1	160 ±1.4
FP3	0.221±0.007	0.027±0.001	6.5±0.2	95.88±3.1	180±1.2
FP4	0.310±0.006	0.032±0.002	6.4±0.18	98.42±1.3	226±1.3
FP5	0.292±0.008	0.022±0.003	6.4±0.1	99.12±1.8	214±1.0
FP6	0.319±0.005	0.029±0.002	6.5±0.15	95.32±2.5	219±2.1
FP7	0.329±0.006	0.034 ±0.001	6.7±0.2	98.19 ±3.1	225 ±1.7
FP8	0.355±0.008	0.036±0.001	6.8±0.12	92.32±1.8	241 ±1.2

Mean ± SD (n=3)

Table No.5: Evaluation of Transdermal patches

Formulation code	Percentage swelling* (%)	Tensile strength* (g)	Vapour transmission rate* (%)	Percentage moisture loss* (%)
FP1	54.52±2.5	142.5±1.1	7.18 ±0.9	7.21 ±1.9
FP2	66.44±2.4	157.7±2.3	6.93 ±0.12	5.88 ±2.0
FP3	71.71±3.1	169.5±2.5	6.66 ±0.42	8.44±1.7
FP4	84.29±3.2	188.8±1.6	5.22±0.7	4.76±1.9
FP5	56.81±3.5	157.7 ±2.3	5.45±0.56	8.55±2.7
FP6	76.19 ±2.5	132.6±2.6	6.24 ±0.9	6.42±1.2
FP7	85.67 ±4.0	198.7 ±1.6	5.55±0.32	4.75 ±1.6
FP8	89.45±3.7	217.1±1.9	7.13±0.47	9.88 ±2.7

Mean ± SD (n=3)

Table No.6: *In-Vitro* drug release profile of transdermal Patches formulations FP1-FP8

% Cumulative Amount of Drug release (n=3) mean ± SD								
Time (hr)	**FP1**	**FP2**	**FP3**	**FP4**	**FP5**	**FP6**	**FP7**	**FP8**
0	0	0	0	0	0	0	0	0
1	24.314±1.23	21.822±1.12	17.837±1.87	11.151±1.12	28.796±1.32	25.576±1.23	18.126±1.51	13.662±1.23
2	29.512±1.14	27.151±1.66	19.797±1.53	14.414±1.03	31.977±1.57	29.314±1.54	19.512±1.80	18.892±1.94
3	31.623±1.01	29.779±1.70	27.408±1.20	22.966±1.93	37.054±1.93	31.849±1.11	28.635±1.33	25.958±0.98
4	41.901±1.98	40.329±1.26	35.111±1.88	29.867±1.44	46.382±0.75	44.089±1.05	37.431±1.49	32.874±1.57
5	49.142±1.32	46.296±1.39	45.825±1.93	36.982±1.56	59.651±1.03	48.838±0.48	44.252±1.61	43.032±1.32
6	58.351±1.44	55.774±1.40	48.281±1.18	39.416±1.74	70.199±1.19	58.997±1.84	56.619±1.09	54.355±1.15
7	64.871±0.99	61.502±1.58	57.364±1.79	51.533±1.73	73.592±1.17	69.006±1.09	67.418±1.62	66.676±1.75
8	70.862±1.08	67.511±1.69	63.246±1.62	58.326±1.39	75.432±1.06	74.951±1.73	69.543±1.36	68.132±1.69
9	77.213±1.29	69.342±0.98	68.918±1.18	67.932±1.72	78.154±0.85	78.349±1.36	74.241±1.55	70.045±1.81
10	79.531±1.87	77.460±1.91	75.463±1.63	72.723±1.07	89.220±0.73	88.223±1.88	82.311±0.77	81.335±1.94
11	84.291±1.53	81.751±1.11	79.273±1.39	79.482±1.37	89.967±1.18	95.609±1.79	92.219±1.88	86.708±1.48
12	97.126±1.31	91.319±1.36	90.494±1.72	88.993±1.32	98.709±1.49	98.655±1.66	96.732±1.09	95.430±1.17

Table No.7: Result of correlation coefficients of release data by curve fitting method on zero order, first order, higuchi kinetic, hixon crowell model and there diffusion exponent (n):s for transdermal patches

Formulation code	Zero order	First order	Higuchi kinetics	n*	Best fit model	Mechanism of release
FP1	0.971	0.805	0.968	0.589	Zero order	Non Fickian diffusion
FP2	0.975	0.920	0.969	0.610	Zero order	Non Fickian diffusion
FP3	0.988	0.911	0.952	0.708	Zero order	Non Fickian diffusion
FP4	0.995	0.903	0.914	0.885	Zero order	Non Fickian diffusion
FP5	0.944	0.805	0.977	0.556	Higuchi kinetics	Non Fickian diffusion
FP6	0.978	0.817	0.960	0.610	Zero order	Non Fickian diffusion
FP7	0.987	0.856	0.945	0.757	Zero order	Non Fickian diffusion
FP8	0.987	0.870	0.937	0.834	Zero order	Non Fickian diffusion

Table No.8: Physical Evaluation of gel

Formulation code	Clarity	Homogeneity	*pH (±SD)	*Spreadability (gm.cm/sec)±SD	*Drug Content % (±SD)	*Viscosity Cps (±SD)
FG1	+++	Good	7.12±0.18	23.7±0.15	90.22 ±0.54	31570 ±0.52
FG2	+++	Good	7.14±0.08	22.5±0.19	94.24 ±0.55	3640 ±0.023
FG3	++	Good	7.23±0.06	31.9±0.15	97.45 ±0.29	4220 ±0.460
FG4	+++	Good	7.15±0.16	24.2±0.15	96.34±0.32	4650 ±0.350
FG5	+++	Good	7.24±0.16	24.2±0.09	95.34 ±0.34	32450 ±0.53
FG6	+++	Good	7.14±0.03	20.6±0.19	92.69 ±0.55	3840 ±0.830
FG7	++	Good	7.12±0.05	33.5±0.15	97.9 ±0.12	4224 ±0.940
FG8	+++	Good	7.05±0.19	22.4±0.14	98.46±0.36	4691 ±0.210

Mean ± SD (n=3)

Table No.9: *In-Vitro* drug release profile of transdermal Gel formulations FG1-FG8

% Cumulative Amount of Drug release (n=3) mean ± SD								
Time (hr)	**FG1**	**FG2**	**FG3**	**FG4**	**FG5**	**FG6**	**FG7**	**FG8**
0	0	0	0	0	0	0	0	0
1	29.194±1.19	23.232±1.78	21.559±1.63	20.733±1.23	32.132±1.57	28.327±1.66	26.593±1.79	24.138±1.05
2	31.195±1.13	29.542±1.67	29.803±1.13	24.504±1.56	45.109±1.11	39.599±1.23	33.512±1.02	29.857±0.33
3	38.678±1.98	36.901±1.54	33.591±1.40	29.881±1.75	49.112±1.79	41.925±1.27	39.635±1.43	35.146±1.26
4	46.919±1.72	43.178±1.33	39.153±1.47	36.912±1.32	53.217±1.07	49.783±1.74	45.431±1.58	39.992±1.49
5	54.167±1.56	49.961±1.79	48.597±1.79	42.893±1.77	59.993±1.88	56.445±1.93	52.252±1.09	48.881v1.83
6	59.489±1.92	56.981±1.84	53.347±1.11	49.581±0.75	73.542±1.19	62.521±1.05	57.619±0.94	55.805±1.21
7	68.902±1.03	64.731±1.72	59.895±1.97	56.437±0.38	78.687±1.43	70.932±1.66	68.418±1.72	63.734±1.87
8	75.921±0.92	69.430±1.19	65.239±1.36	62.193±1.02	82.445±1.54	78.918±1.14	74.543±1.88	71.119±1.93
9	79.127±1.38	76.198±1.49	69.173±1.52	67.281±1.22	87.109±1.29	83.298±1.44	79.241±±0.95	76.052±1.34
10	83.509±1.78	84.225±1.03	78.581±1.04	75.559±1.37	92.118±1.03	91.117±1.38	87.311±1.22	83.649±1.06
11	89.127±1.90	87.269±1.93	83.552±0.98	81.613±1.72	95.309±1.16	93.291±1.91	91.219±1.06	88.708±1.55
12	98.195±1.18	92.815±1.62	91.091±1.99	90.857±1.43	99.134±1.79	97.326±1.14	95.732±1.53	94.430±1.32

Table No.10: Result of correlation coefficients of release data by curve fitting method on zero order, first order, Higuchi kinetic , Hixon crowell model and there diffusion exponent (n):s

Formulation code	Zero order	First order	Higuchi kinetics	n*	Best fit model	Mechanism of release
FG1	0.961	0.804	0.980	0.532	Higuchi kinetics	Non Fickian diffusion
FG2	0.974	0.938	0.980	0.587	Higuchi kinetics	Non Fickian diffusion
FG3	0.976	0.918	0.972	0.588	Zero order	Non Fickian diffusion
FG4	0.985	0.886	0.954	0.626	Zero order	Non Fickian diffusion
FG5	0.912	0.922	0.991	0.463	Higuchi kinetics	Fickian diffusion
FG6	0.950	0.908	0.987	0.515	Higuchi kinetics	Non Fickian diffusion
FG7	0.966	0.911	0.980	0.547	Higuchi kinetics	Non Fickian diffusion
FG8	0.978	0.910	0.969	0.588	Zero order	Non Fickian diffusion

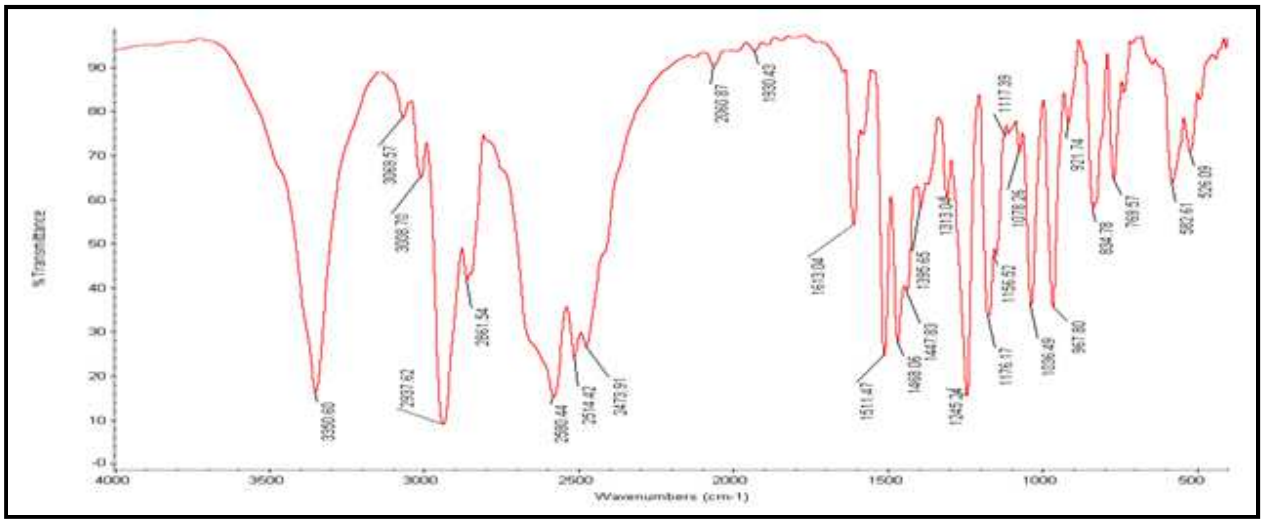

Figure No.1: Spectrum of Pure drug Venlafaxine

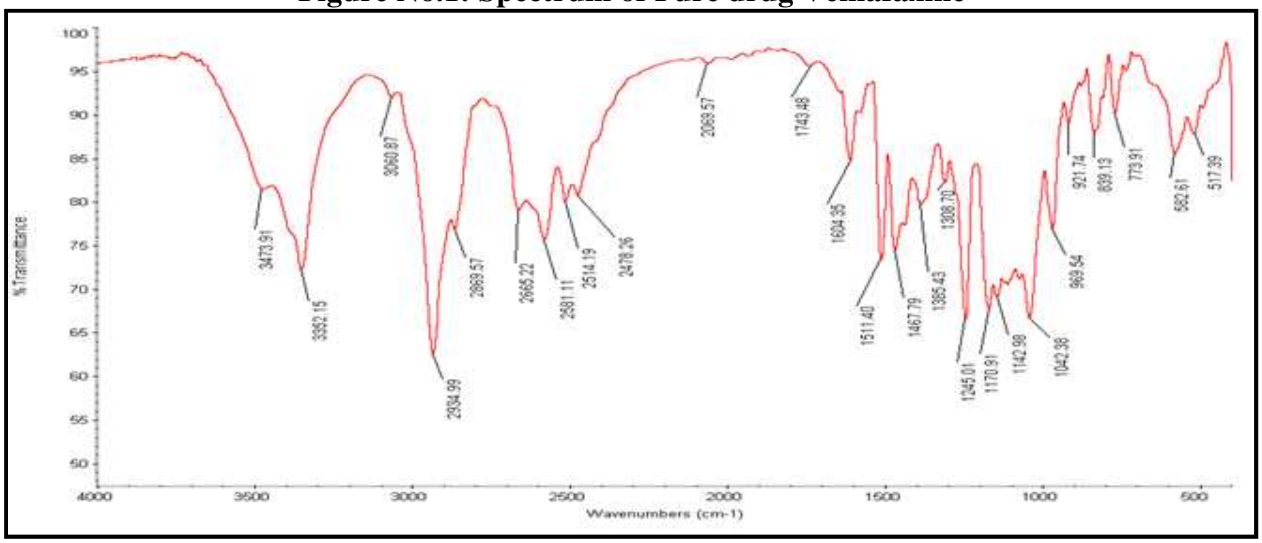

Figure No.2: Spectrum graph of venlafaxine +Ethylcellulose

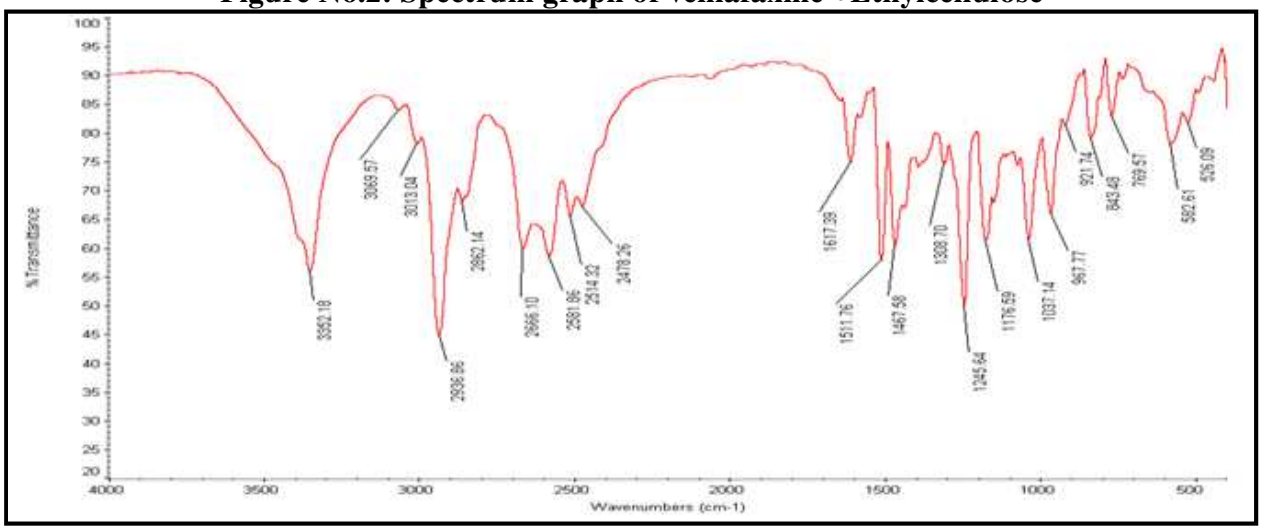

Figure No.3: Spectrum graph of venlafaxine +HPMCK4M

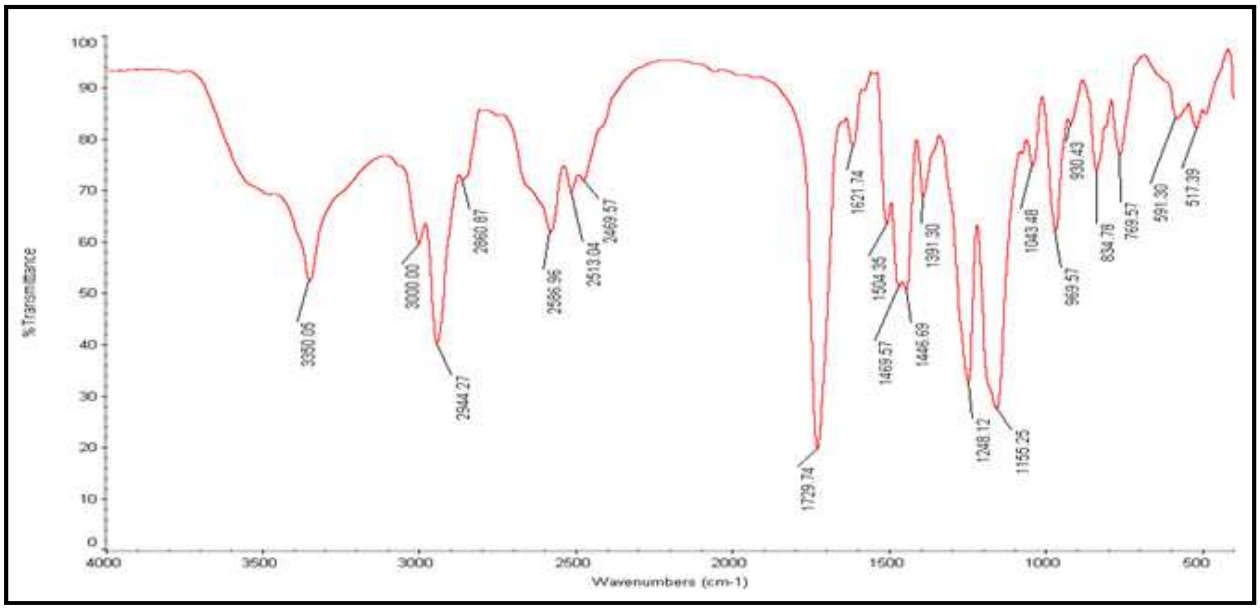

Figure No.4: Spectrum graph of venlafaxine +EudragitS100

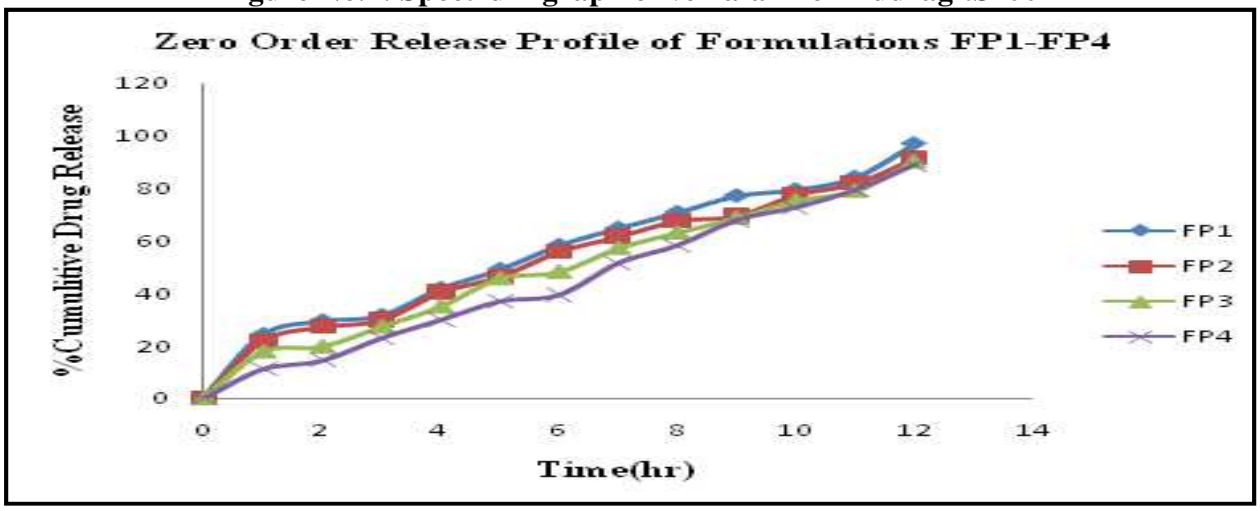

Figure No.5: Plot of %CR vs. time of various formulations for zero order kinetics

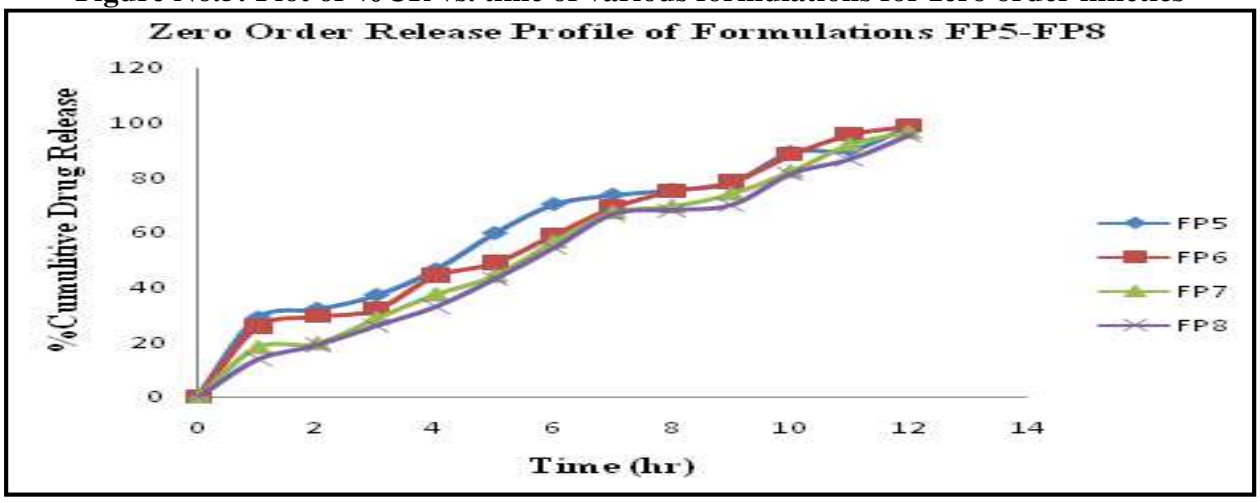

Figure No.6: Plot of %CR vs. time of various formulations for zero order kinetics

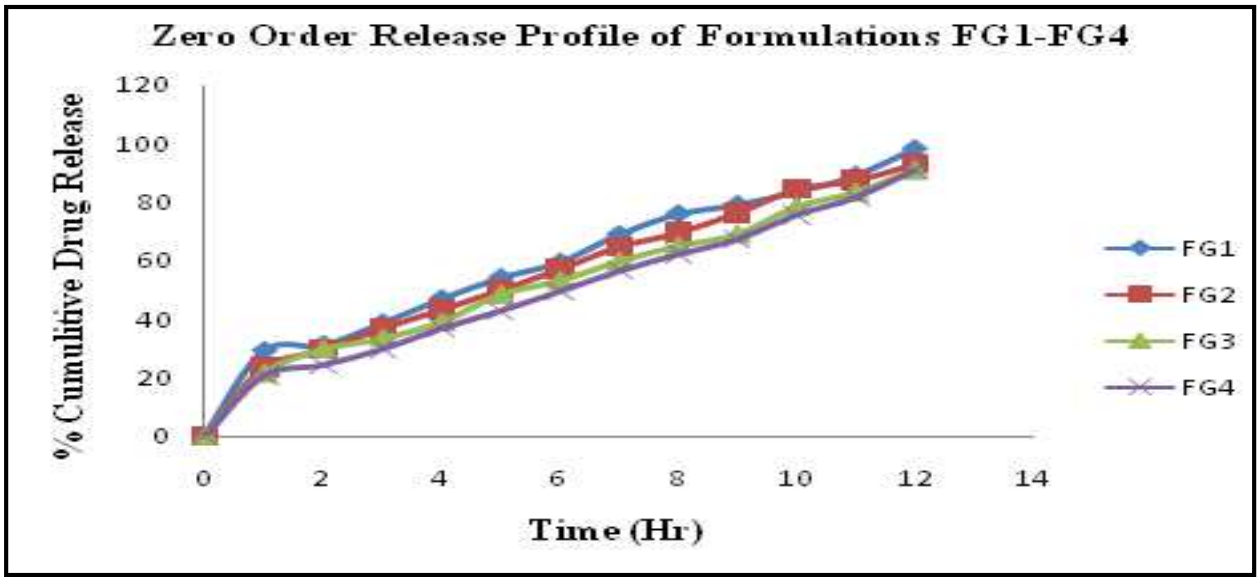

Figure No.7: Plot of %CR vs. time of various formulations for zero order kinetics

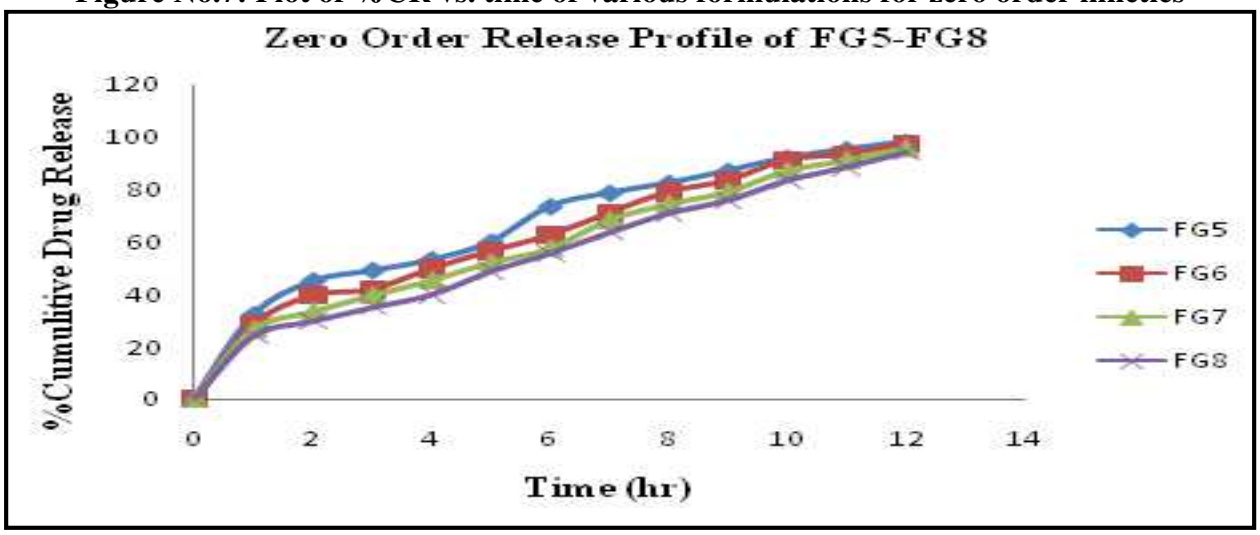

Figure No.8: Plot of %CR vs. time of various formulations for zero order kinetics

CONCLUSION

In the quest of effective transdermal drug delivery system which can meet the demand of depression, transdermal patches as well as transdermal gels of venlafaxine were formulated and successfully evaluated for various evaluation parameters. Data obtained for various evaluation parameters for patches clearly revealed that the selected polymers such as HPMC K4M, ethylcellulose and eudragit S 100 in different combination ratios were found suitable for the formulation and plays a significant role in controlling the release rate of medicament from the patches and increases the effectiveness of transdermal patches as a controlled release drug delivery system. Patches formulated using HPMC K4M and ethylcellulose were found to control the drug release for prolonged periods as compared to patches formulated by using combination of HPMC K4M and eudragit S 100. Transdermal gels were also formulated by using polymers such as carbopol 934 and HPMC K4M in different proportions and evaluated for different evaluation parameters. Results obtained from various studies indicated that patches showed better control release than transdermal gels and are more effective in combating depression.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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