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FORMULATION AND EVALUATION OF TRANSDERMAL PATCH OF PREGABALIN

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ABSTRACT

The objective of present study is to determine the permeation of Pregabalin from transdermal patch into microcirculation of skin. Matrix type transdermal drug delivery system (TDDS) of Pregabalin was prepared by the solvent evaporation technique. Several batches were prepared by using combination of HPMC and PVP; PVA and PVP; Eudragit RL-100 and Eudragit RS-100; HPMC and EC in different ratios. Propylene glycol was used as plasticizer and DMSO was incorporated as a permeation enhancer. Formulated transdermal patches were charachterised for their physicochemical parameters like thickness, weight variation, flatness, tensile strength, folding endurance, moisture content, moisture uptake and drug content uniformity. Patches were evaluated for their in-vitro drug release profile and *ex-vivo* skin permeation studies. Patches were also subjected to stability studies and skin irritation studies to determine their compatibility with skin. Formulation P_1 containing HPMC and PVP in the ratio of 3:1 and propylene glycol, 5%w/v and DMSO, 6%w/v was found to be the most optimum formulation. P_1 was also found to exhibit maximum *in -vitro* %drug release of about 81.70%. Result of evaluation studies revealed that Pregabalin can be administered as a controlled drug delivery system to reduce frequency of drug administration. But this hypothesis requires further confirmation via *in-vivo* pharmacodynamic and pharmacokinetic studies in animal and human models.

INTRODUCTION: Pregabalin (PGB) is an anticonvulsant and analgesic drug [1], which is required to be administered three to four times per day for its therapeutic effect by oral route of drug delivery in the treatment of partial seizures. It also finds its use in peripheral diabetic neuropathy, fibromyalgia and post-therapeutic neuralgia.

So, the objective of present work is to develop a controlled release dosage form of Pregabalin other than oral route and injectables. Hence, a non-invasive system in the form of transdermal patch of Pregabalin was thought to be developed and evaluated with the aim of achieving controlled release of Pregabalin over a prolong time period so that frequency of drug administration will be minimised.

Transdermal drug delivery has certain advantages over other systems of drug administration which in turn leads to increase patient compliance. Its non-invasive nature, ease of application and removal, predetermined rate of drug permeation, increased bioavailability of drug and decreased hepatic metabolism; all these factors make this system most suitable for systemic delivery of drug over long time periods of 24hrs.

Therefore, market of transdermal patches has made tremendous growth in recent years [2, 3].

MATERIALS: Pregabalin was obtained as gift sample from Torrent Pharmaceuticals, Ahmedabad. Polymers such as HPMC, PVP, PVA, Eudragit RL-100, Eudragit RS-100 and EC was provided by the institute and other chemicals such as propylene glycol and DMSO and methanol used in the study were of analytical grade.

METHOD:

Technology Employed: Transdermal patch of Pregabalin was prepared by solvent evaporation technology. In this technology, mixture of polymer and drug solution was spread as a film on a suitable support (glass, mercury, aluminium foil etc.) and solvent was allowed to evaporate by keeping the petri dish containing solution for appropriate time period generally at room temperature. After evaporation of solvent, dried residue is the required patch containing drug trapped in the matrix of polymer [4, 5]. The patch thus obtained was then evaluated for various parameters like physicochemical parameters, drug content, drug release profile and for skin irritation studies.

Preparation of different Placebo Polymeric Films: Different placebo patches are prepared by employing hit and trial method on various combinations of different hydrophilic and hydrophobic polymers [6, 7]. From these various placebo patches, the combination having desired properties to support a transdermal drug delivery system is selected for incorporation of drug. Different combinations of polymers are as follows:

1. HPMC and PVP
2. HPMC and EC
3. Eudragit RL-100 and Eudragit RS-100
4. PVA and PVP

Table 1 below shows the composition and characterization of placebo patches prepared by using different polymers in different ratios. From the table 1, it was concluded that most appropriate combination of polymer was that of HPMC and PVP. Different ratios of HPMC and PVP were tried in order to obtain most optimum placebo patch. Composition and flexibility of placebo patch of HPMC and PVP combined in different ratio is shown below in **table 2**.

TABLE 1: COMPOSITION AND CHARACTERIZATION OF PLACEBO PATCHES

POLYMERS	RATIO	PHYSICAL APPEARANCE
HPMC: EC	1:2	Non-uniform film
EC: HPMC	2:4	Non-uniform film
PVA: PVP	1:3	Tough and hard film
PVP: PVA	1:2	Tough and hard film
Eudragit RL100: EudragitRS100	3:1	Brittle and non-flexible film
HPMC: PVP	1:3	Smooth, transparent, uniform and flexible film
PVP: HPMC	1:1	Smooth, transparent and flexible film

TABLE 2: COMPOSITION OF PLACEBO PATCH OF HPMC AND PVP IN DIFFERENT RATIOS

FORMULATION CODE	HPMC:PVP RATIO	Conc$^{n.}$ OF DMSO	Conc$^{n.}$ OF PROPYLENE GLYCOL	FLEXIBILITY OF PATCH
P_1	3:1	6%	5%	Very flexible
P_2	1:3	4%	6%	Moderately flexible
P_3	3:5	2%	3%	Least flexible
P_4	5:3	1%	2%	Least flexible
P_5	1:1	3%	4%	Fairly flexible
P_6	1:1	6%	5%	Moderately flexible
P_7	1:1	5%	6%	Moderately flexible

Fabrication of Medicated Patch of HPMC and PVP: Appropriate amount of hydroxypropylmethylcellulose and polyvinylpyrrolidone were weighed as per the ratio. These polymers were then dissolved in solvent system containing water: methanol (3:1). Drug solution containing plasticizer and penetration enhancer in appropriate concentration was added to the polymer solution. The polymer solution thus obtained was spread in petri dish previously coated with a lubricant (castor oil). This petri dish was placed in tray dryer

maintained at temperature not more than 30^{o}C for about 6hrs. After 6hrs petri dish was taken out of tray dryer and patch was removed and observed for its physical appearance and for various other parameters. Such patches were found to be uniform, smooth and flexible. Composition of medicated patches of HPMC and PVP is shown in **table 3**.

TABLE 3: COMPOSITION OF MEDICATED HPMC: PVP PATCHES

Name of Ingredients	FORMULATION CODE						
	P_1	P_2	P_3	P_4	P_5	P_6	P_7
Drug (gm)	0.075	0.075	0.075	0.075	0.075	0.075	0.075
HPMC (gm)	1.5	0.5	1.5	2.5	0.5	1.5	2.5
PVP (gm)	0.5	1.5	2.5	1.5	0.5	1.5	2.5
Propylene Glycol (%)	5%	5%	5%	5%	5%	5%	5%
DMSO (%)	6%	6%	6%	6%	6%	6%	6%
Solvent (water: methanol)	3:1	3:1	3:1	3:1	3:1	3:1	3:1

Evaluation of Drug Loaded Patches of HPMC and PVP

Physicochemical Evaluation:

Physical Appearance: Formulated patches were evaluated for their physical appearance, uniformity, entrapment of any air bubble or precipitation of drug, which on a large part determines patient acceptability of the patch and also therapeutic efficacy [8].

Thickness: Thickness of Transdermal patch was measured by using Mitutoyo Digimatic Micrometer. Thickness of rectangular patch (2x2cms) was determined at three different points and average thickness was calculated. Same was performed for other patches also. Thickness of each individual patch should not deviate significantly from each other [8].

Weight Variation: Weight variation was studied by individually weighing 10 randomly selected patches and average weight was calculated. The individual weight should not deviate significantly from the average weight [8, 9].

Folding Endurance: Evaluation of folding endurance involves determining the folding capacity of the patches. Folding endurance is determined by repeatedly folding the patch at the same place until it break [10]. The number of times the patch could be folded at the same place without breaking is folding endurance value.

Tensile Strength: Mechanical properties of the polymeric patches were conveniently determined by measuring their tensile strength [11, 12]. The tensile strength of the patches was determined by using an assembly designed to measure the tensile strength of the patch. Assembly consist of a pan hanged by using a strong thread and the other end of the thread was attached with the centre of the patch. The whole assembly was held like a beam balance and weights were kept on the pan. Weights required to break the patch was noted. Tensile strength was then calculated using the following formula:

$$\text{Tensile Strength} = \text{Break Force} / a.b(1 + \Delta L/L)$$

Where; a = width of the patch, b = thickness of the patch, L = length of the patch, ΔL = elongation of patch at break point, Break Force= weight required to break the patch (Kg).

Moisture Uptake: Patch was kept in a desiccator at room temperature for 24hrs. The patch was then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. The % moisture uptake was calculated by using following formula.

$$\% \text{ Moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture Content: The prepared patches were weighed individually and kept in a desiccator containing calcium chloride at room temperature for 24hrs. The patches were weighed again after a specified interval until they show a constant weight. The percent moisture content was calculated using following formula.

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Drug Content Uniformity: Amount of drug entrapped in a patch was determined by completely dissolving a patch of size 2x2 cm^2 in 100ml phosphate buffer solution (pH 7.4). Complete dissolution was achieved by placing the solution containing patch on shaker for about 24 hrs. Solution was then filtered and drug content was estimated spectrophotometrically at 210nm after suitable dilution.

***In-Vitro* Permeation Studies:** Permeation studies are carried out in order to determine transition of drug from patch to skin microcirculation. In this study, synthetic membrane like cellulose nitrate was placed between the donor and receptor compartment of Franz diffusion cell [12, 13]. Receptor compartment was filled with phosphate buffer of pH 7.4. Transdermal patch was placed upon the cellulose nitrate membrane facing towards the donor compartment. The other side of cellulose nitrate membrane was towards the receptor compartment having phosphate buffer.

The receiver compartment was maintained at room temperature and was continuously stirred with the help of magnetic stirrer. Samples were withdrawn at specific time interval and equal amount of phosphate buffer was replaced each time to maintain volume of receptor compartment at a constant level. Samples withdrawn were then analysed for their absorbance and concentration was then calculated. **Table 4** below shows the *in-vitro* permeation profile of drug from each batch. Graph was then plotted between % drug release and time interval which compares % drug release from different batches.

TABLE 4: DETERMINATION OF PHYSICOCHEMICAL PARAMETERS AND IN-VITRO DRUG RELEASE OF EACH FORMULATION

Formulation code/ Physical parameters	P_1 (3:1)	P_2 (1:3)	P_3 (3:5)	P_4 (5:3)	P_5 (1:1)	P_6 (1:1)	P_7 (1:1)
Appearance	Smooth, uniform and flexible	Smooth, uniform and tough	Rough, non-uniform and tough	Rough, non-uniform and tough	Smooth, uniform and flexible	Smooth, uniform and flexible	Smooth, uniform and flexible
Thickness (mm)	0.2795±0.3	0.288±0.28	0.1765±0.3	0.198±0.2	0.278±0.2	0.274±0.3	0.288±0.3
%Flatness	100	100	100	100	100	100	100
Weight Variation (gm)	2.754±1.5	2.761±1.7	4.758±1.5	4.754±2.0	1.711±1.8	3.751±2.0	5.798±1.5
Folding Endurance	90±1	91±1	88±1	87±2	90±1	90±1	91±2
Tensile Strength	3.20±0.3	3.11±0.3	2.99±0.2	3.12±0.2	3.20±0.2	2.99±0.3	3.12±0.2
%Moisture Content	10.67±0.01	10.80±0.05	11.99±0.10	11.01±0.01	13.98±0.03	13.11±0.03	15.56±0.05
%Moisture Uptake	22.50±0.15	22.80±0.17	22.99±0.13	22.89±0.09	23.87±0.13	23.93±0.09	24.76±0.09
%Drug Content	99.99± 0.8	99.95±0.8	86.84± 0.7	88.80±0.8	99.86±0.7	99.85±0.7	99.88±0.7
In-vitro Drug Release (%)	81.70	76.22	74.32	66.52	67.11	78.46	72.02

***In-Vitro* Skin Permeation Studies:** *In-vitro* skin permeation studies were carried out using rat's skin. Rat was sacrificed and skin was removed from abdominal portion [12]. Appropriate size of sin was shaved using depilatory cream and this skin was then used as a barrier between donor and receptor compartment of Franz diffusion cell. Transdermal patch (P_1) was placed upon it (facing towards stratum corneum of the skin). Receptor compartment was filled with Phosphate buffer (pH 7.4) and magnetic bead was placed inside the receptor compartment. Franz diffusion cell was placed upon magnetic stirrer and temperature was maintained at about 37±0.5°C. Samples were withdrawn at different time interval and equal amount of phosphate buffer was then added to the receptor compartment in order to maintain volume of the receptor compartment constant. Samples thus withdrawn were analysed by means of U.V Spectrophotometer in order to estimate amount of drug present in the sample.

Formulation P_1 was initially found to exhibit maximum *in-vitro* drug release profile (**table 5**) where drug was permeated through cellulose nitrate membrane; moreover formulation P_1 was found to possess other parameters also at a significantly optimum level; that's why P_1 formulation was selected for drug permeation study across rat's skin. Data obtained from drug permeation study across rat's skin for the formulation P_1 is shown below in **table 6**.

TABLE 5: *IN-VITRO* PERMEATION RATE PROFILE OF BATCH P_1

Time (min.)	Absorbance	Conc^n (µg/ml)	Drug Amount (mg/5ml)	Cumulative amount of drug release	Drug Amount (mg/15ml)	Total Drug release	% Drug Release
0	0.000	0.000	0.000	0.000	0.000	0.000	0.00
60	0.02	15.7	0.0789	0.000	2.355	2.355	3.14
120	0.04	32.3	0.1615	0.0789	4.845	4.9239	6.56
180	0.08	62.2	0.311	0.2404	9.330	9.5704	12.76
240	0.103	79.5	0.3975	0.5514	11.92	12.4714	16.62
360	0.143	110.6	0.553	0.9489	16.59	17.5389	23.38
480	0.293	225.4	1.127	1.5019	33.81	35.3119	47.08
600	0.424	326.4	1.632	2.6289	48.96	51.5889	68.77
720	0.455	350.0	1.75	4.3789	52.50	56.8789	75.8
1440	0.478	367.69	1.838	6.1289	55.15	61.2789	81.70

TABLE 6: *IN-VITRO* DRUG RELEASE PROFILE OF MOST OPTIMISED FORMULATION P_1 ACROSS RAT'S SKIN

Time (min)	Abs.	Dilution factor	Conc^n. (µg/ml)	Drug Amount (mg/5ml)	Cumulative Drug Release	Drug Amount (mg/15ml)	Total Drug Release	% Drug Release
0	0	0	0	0	0	0	0	0
60	0.015	1	12.0	0.006	0	1.80	1.8	2.4
120	0.037	1	29.0	0.145	0.006	4.35	4.356	5.80
180	0.076	1	59.5	0.297	0.151	8.92	9.071	12.09
240	0.104	1	80.1	0.400	0.448	12.01	12.458	16.61
360	0.149	1	115.3	0.576	0.848	17.29	18.138	24.18
480	0.286	1	220.6	1.103	1.424	33.09	34.514	46.01
600	0.422	1	325.3	1.626	2.527	48.79	51.322	68.42
720	0.455	1	350.3	1.7515	4.153	52.54	56.693	75.59
1440	0.478	1	368.2	1.841	5.9045	55.23	61.134	81.51

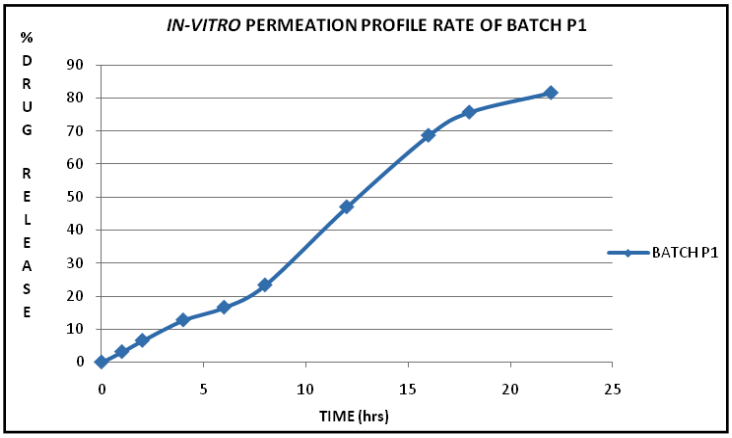

FIGURE 1: *IN-VITRO* PERMEATION RATE PROFILE OF BATCH P_1

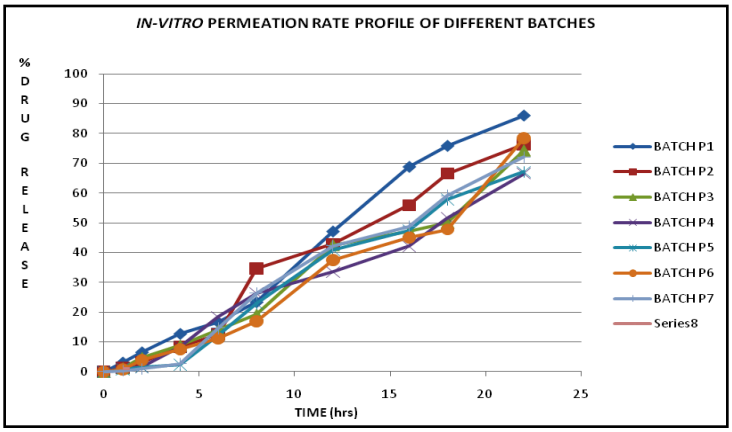

FIGURE 2: COMPARISON OF *IN-VITRO* PERMEATION RATE PROFILE OF DIFFERENT BATCHES OF TRANSDERMAL PATCH CONTAINING PREGABALIN

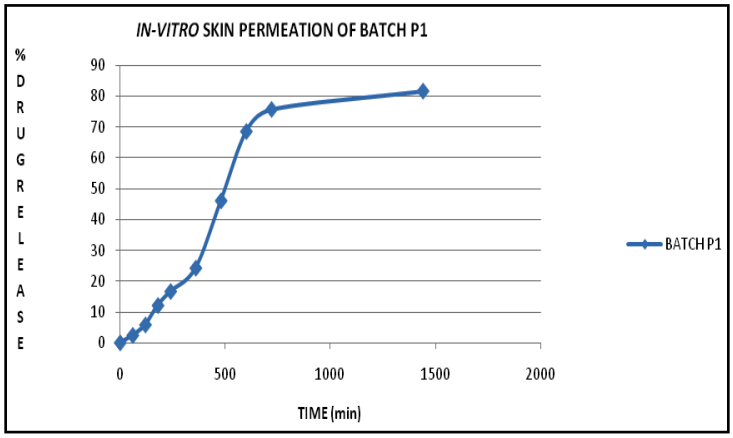

FIGURE 3: *IN-VITRO* DRUG RELEASE PROFILE OF BATCH P_1 ACROSS RAT'S SKIN

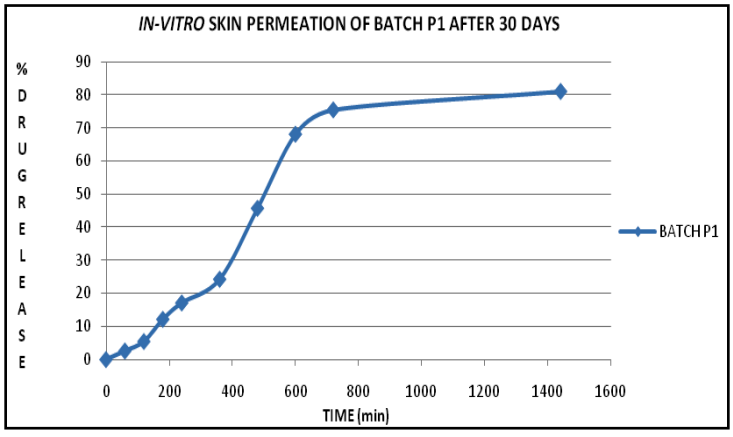

FIGURE 4: *IN-VITRO* DRUG RELEASE PROFILE OF BATCH P_1 AFTER 30 DAYS

Stability Studies: Stability of a TDDS is a very important factor to be considered while formulating such system because it affects therapeutic efficacy of the system as well as patient compliance. Here, formulated patches were wrapped in aluminium foil and kept at room temperature for a period of 30 days.

After completion of 30 days, patches were analysed for their drug release profile across rat's skin. Formulation P_1 was selected for this study as this formulation seemed quite promising throughout all evaluation studies performed previously on this formulation.

Formulation was also characterised for other parameters like physical appearance and physical parameters and drug content uniformity.

Procedure adopted for evaluation of formulation after 30 days was same as used earlier that is by using Franz diffusion cell containing phosphate buffer of pH 7.4. Samples withdrawn at different time intervals were analysed by U.V spectrophotometer to determine their concentration. **Table 7** shows the drug release profile data after 30 days.

TABLE 7: *IN-VITRO* DRUG RELEASE PROFILE OF FORMULATION P_1 AFTER 30 DAYS

Time (min)	Abs.	Dil. factor	Conc^n. (µg/ml)	Drug amount (mg/5ml)	Cumulative drug release	Drug amount (mg/15ml)	Total drug release	% drug release
0	0	0	0	0	0	0	0	0
60	0.0169	1	13.0	0.065	0	1.95	1.95	2.6
120	0.0351	1	27.0	0.135	0.0650	4.05	4.115	5.48
180	0.0773	1	59.5	0.2975	0.2000	8.925	9.125	12.166
240	0.1069	1	82.3	0.4115	0.4975	12.345	12.842	17.122
360	0.1498	1	115.3	0.576	0.9090	17.295	18.204	24.272
480	0.2841	1	218.6	1.093	1.485	32.79	34.275	45.70
600	0.4202	1	323.3	1.616	2.578	48.495	51.073	68.093
720	0.4540	1	349.3	1.746	4.194	52.395	56.589	75.452
1440	0.4751	1	365.5	1.827	5.940	54.825	60.765	81.02

Skin Irritation Studies: Skin irritation studies were carried out in order to detect irritation and sensitization under conditions of maximal stress which may occur over a prolong contact with the skin surface. For this study rat was used as an animal model. Patch (P_1) (2x2 cm^2) was applied to the shaved skin of the rat on one side of the back and secured using adhesive tape. On other back side of the rat, control patch (without drug) was placed in a similar manner. Animal was then kept under observation for a period of 48hrs to detect any sign of erythma, redness, sensitization or any other allergic reaction.

RESULT AND DISCUSSION: Result of physicochemical parameters and *in-vitro* drug release profile is shown in Table 4. Result of *in-vitro* drug release across rat's skin is shown in **Table 5**. Stability studies indicate that drug release rate of transdermal patch does not reveal significant variation. It was found to be 81.02% for most optimised formulation P_1, after keeping it for 30 days at room temperature and humidity. Skin irritation studies show no sign of erythma or any other skin irritation reaction, so it can be concluded that neither the drug nor any polymer or excipient was found to cause adverse effects on skin, hence, patch was found to be compatible with skin. Result of all evaluation parameters was found to be satisfactory within permissible limits.

CONCLUSION: From the present work it can be concluded that Pregabalin can be administered via matrix type transdermal drug delivery system, which provides controlled release which ultimately reduces the frequency of administration of drug in patients suffering from epilepsy and fibromyalgia. Hence this non-invasive, compatible patch with ease of application and removal may find increase patient compliance but present work required to be supported by further studies involving in-vivo pharmacodynamic and pharmacokinetic studies in animal and human models.

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