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FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES DRUG DELIVERY SYSTEM USING TRAMADOL HYDROCHLORIDE

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ABSTRACT

Transdermal patches of Tramadol hydrochloride were prepared by the synthetic polymers HPMC, PVA, combination of HPMC and PVA. The patches were transparent, smooth andflexible. The preformulation studies involving description, solubility, melting point, partition coefficient of the drug were found to be comparable with the standard. Based on the all the above preformulation studies the drug was suitable for making the transdermal formulation up to 12 hrs when compared to formulations F1 and F2. From the percentage inhibition values obtained from anti-inflammatory studies, the decreasing order for the anti-inflammation can be given as: F3.So it was concluded that the F1 >F2 >F3.

Key words: Transdermal Patches, Tramadol Hydrochloride, Formulation and Evaluation.

INTRODUCTION

The first transdermal system, Transderm SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with travel. Most transdermal patches are designed to release the active ingredient at a zero order rate for a period of several hours to days following application to the skin [1]. This is especially advantageous for prophylactic therapy in chronic conditions. The evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and its metabolites in the urine and through the clinical response of the patient to the administered drug therapy. Both polar and non-polar substances diffuse via transcellular and intercellular routes by different mechanisms. The polar molecules mainly diffuse through the polar pathway consisting of "bound water" within the hydrated stratum corneum whereas the non-polar molecules dissolve and diffuse through the non-aqueous lipid matrix of the stratum corneum. Thus the principal pathway taken by a penetrant is decided mainly by the partition coefficient (log K). Hydrophilic drugs partition preferentially into the intracellular domains, whereas lipophillic permeants (octanol/water log K > 2) traverse the stratum corneum via the intercellular route [2]. Most molecules pass the stratum corneum by both routes. Transdermal permeation is based on passive diffusion. Skin is the most intensive and readily accessible organ of the body as only a fraction of millimeter of tissue separates its surface from the underlying capillary network. And the rate of skin permeation is constant provided the magnitude of C_d remains fairly constant throughout the course of skin permeation. For keeping C_d constant the drug should be released from the device at a rate R_r i.e. either constant or greater than the rate of skin uptake R_a i.e. Since $R_r >> R_a$, the drug concentration on the skin surface C_d is maintained at a level equal to or greater than the equilibrium solubility of the drug in the stratum corneum C_s .i.e. $C_d >> C_s$. The permeation of drug increases ten folds with temperature variation. The diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on the pH and pKa or pKb values. The proportion of unionized drug determines the drug concentration in skin [3]. Heat induced high

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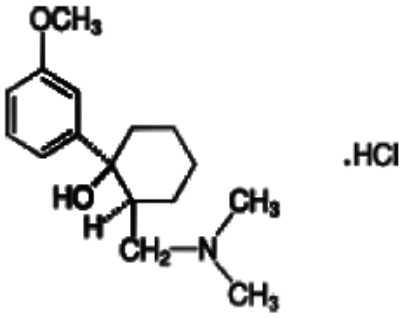
absorption of transdermal delivered drugs. Patient should be advised to avoid exposing the patch application site to external heat source like heated water bags, hot water bottles. Even high body temperature may also increase the transdermally delivered drugs. In this case the patch should be removed immediately [4].

Drug Profile

Tramadol hydrochloride



Structure of Tramadol Hydrochloride

Tramadol hydrochloride is a centrally acting analgesic with weak opoid agonist properties. It is a white, bitter, crystalline and odorless powder. The chemical name for tramadol hydrochloride is (±) cis-2-[(dimethylamino) methyl]-1-(3-methoxyphenyl cyclohexanol hydrochloride.

Molecular formula: $C_{16}H_{25}NO_2$ HCl.

Molecular weight: 299.8

Melting point: 171^0 C

Category: Analgesic and Anti- inflammatory

Dose: 50 to 100 mg every 4 to 6 hrs with a maximum dosage of 400 mg/day

Solubility: Tramadol is readily soluble in water and ethanol, methanol and other organic solvents.

Dissociation constant: pKa value of Tramadol hydrochloride is 9.41 at pH 7.

Pharmacokinetic data

Bio availability: 58-62%

Protein binding: 20%

Metabolism: Hepatic demethylation and Glucuronidation.

Half life: 5-7 hrs.

Route of administration: Oral, IV, IM.

Stability: Tramadol hydrochloride must be protected from light and moisture.

Pharmacodynamics

Tramadol hydrochloride is a centrally acting synthetic analgesic compound. It exists as a racemic mixture of the *Trans* isomer, with important differences in binding, activity, and metabolism associated with the two enantiomers.

Mechanism of action

Tramadol and its O-desmethyl metabolite (M1) are selective, weak OP3-receptor agonists [5]. Opiate receptors are coupled with G-protein receptors and function as both positive and negative regulators of synaptic transmission via G-proteins that activate effector proteins. As the effector system is adenylate cyclase and cAMP located at the inner surface of the plasma membrane, opioids decrease intracellular cAMP by inhibiting adenylate cyclase.

Therapeutic uses

Tramadol hydrochloride is used orally as an analgesic for the relief of moderate to moderately severe pain [6]. Comparative and non comparative clinical studies have shown that tramadol is effective analgesic agent in the treatment of moderately severe acute or chronic pain, including postoperative, gynecologic, and obseric pain, as well as pain of various other origins, including cancer.

Excipient Profile

Hydroxy propyl methyl cellulose

Synonyms: HPMC, Methocel, Methyl cellulose propylene glycol ether, Methyl hydroxyl propyl cellulose, Metolose, Pharmacoat; Cellulose, Hydroxy propyl methyl ether, Culminal MHPC, E464.

Nonproprietary names

BP **:** Hypromellose

Ph Eur **:** Methylhydroxypropylcellulosm

USP **:** Hydroxy propyl methyl cellulose

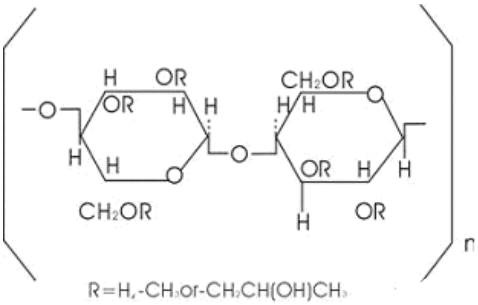
Regulatory status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA. Inactive ingredients guide (ophthalmic preparation, oral capsules, suspensions, syrups, and tablets, topical and vaginal preparations). Included in nonparental medicines licensed in UK.

Chemical name and CAS number: Cellulose, 2-Hydroxypropyl methyl ether [9004-65-3]

Molecular formula: $C_{12}H_{23}O_6$ $(C_{12}H_{22}O_5)$ $nC_{12}H_{23}O_5$ where **n** can vary to provide a wide variety of molecular weights.

Structure formula



Structure of HPMC

Description

Hydroxypropyl methylcellulose is a tasteless and odourless, white to slightly off white, fibrous or granular powder.

Physical properties

- Particle sizes: 100% pass rate in 100 mesh
- Apparent density: 0.25 - 0.70g/ml (usually about 0.5g/ml), specific density- 1.31g/ml
- Color change temperature: 190 - 200°C; carbonization temperature 280 - 300°C
- Surface tension: 42 - 56dyn/cm (2% aqueous solution)
- The higher methoxy content in HPMC, the lower gelation temperature, and the higher solubility in water and surface activity
- Applications: architecture industry, paint industry, printing and ink printing, plastic industry.

Specifications

1) Type: HT-E
2) Methoxy (%): 28.0 - 30.0
3) Hydroxy propyl (%): 7.0 - 12.0
4) Gelatification temperature (°C): 58 - 64
5) Insoluble substances (in water): ≤0.50
6) Loss on drying (wt%): ≤5.0
7) pH: 4.0 - 8.0
8) Viscosity specification (MPoise): 5, 15, 30, 50, 90, 4,000, 8,000, 100,000

Typical Properties

a) Sulphated ash: max 1.0 %
b) Auto ignition temperature: 360°C
c) Density: 0.5-0.7 gm/cm^3 for Methocel
d) Melting point: Browns at 190-200 °C, chars at 225-230 °C. Glass transition temperature: 170-180^{o}C.
e) Solubility: Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%) and ether, but soluble in mixture of ethanol and dichloromethane.
f) Specific gravity: 1.12-1.15 g/cm^3
g) Viscosity: A wide range of viscosity types are available.
h) Solubility and storage condition:

- Solutions are stable between pH: 3-11. Increasing temperature reduces the viscosity of the solutions. HPMC undergoes a reversible sol to gel transformation upon heating and cooling respectively. The gel point is 50-90°C depending upon the grade of material.
- HPMC powder is a stable material although it is hygroscopic after drying.
- HPMC powder should be stored in a well-closed container, in a cool, dry place.
- Aqueous solutions are comparatively enzyme resistant, providing good viscosity stability during long-term storage. However they are prone to microbial spoilage and should be preserved with an antimicrobial preservative.

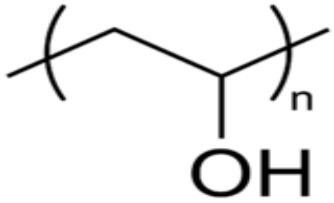
f) Safety: HPMC is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

LD_{50} (mouse, IP) : 5 gm/kg.
LD_{50} (rat, IP) : 5.2 gm/kg.

Functional category

Tablet binder; Coating agent; Flavoring fixative; Tablet filler; Film former; Viscosity-increasing agent; Suspending agent.

Polyvinyl alocohol



Chemical Structure of Poly Vinyl Alcohol

Polyvinyl alcohol has excellent film forming, emulsifying, and adhesive properties. It is also resistant to oil, grease and solvent. It is odorless and nontoxic. It has high tensile strength and flexibility, as well as high oxygen and aroma barrier properties. However these properties are dependent on humidity, in other words, with higher humidity more water is absorbed [7]. The water, which acts as a plasticiser, will then reduce its tensile strength, but increase its elongation and tear strength. PVA is fully degradable and is a quick dissolver. PVA has a melting point of 230°C and 180–190°C for the fully hydrolysed and partially hydrolysed grades. It decomposes rapidly above 200°C as it can undergo pyrolysis at high temperatures. Polyvinyl Alcohol (PVOH, PVAor PVAL) is a water-soluble synthetic polymer.

Chemical Properties of PVA

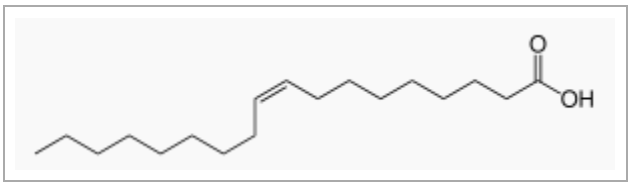
- Good acid and alkali resistance
- Can swell with some detergents although usually very good
- Organic solvents do not, as a rule, affect the sponge unless they are water-miscible and are applied mixed with 30% - 60% water. If so, the sponge will swell and be weakened. Thorough washing in water will return the sponge to its original state
- Incompatible with Nickel Sulphate solutions

Applications

- Medical - wipes, nasal sponges, scalpel cleaning blocks, wound/ burns dressings.
- Electronics - LCD hardware, circuit board wipes
- Glazing industry

OLEIC ACID

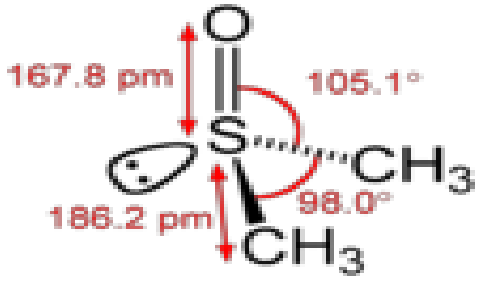
Systematic name: (9Z)-octadec-9-enoic acid;
Other names: (9Z)-Octadecenoic acid; (Z)-Octadec-9-enoic acid; Cis-9-octadecenoic acid; Cis-Δ9-octadecenoic acid; Oleic acid 18:1 cis-9



Chemical Structure of Oleic Acid

Molecular formula: $C_{18}H_{34}O_2$
Molar mass: 282.2559 g/mol
Appearance: Pale yellow or brownish yellow oily liquid with lard-like odour
Properties
Density and phase: 0.895-.947 g/cm³
Solubility in water: Insoluble in water
Solubility in methanol: Soluble
Melting point: 13- 14^0 C (286k)
Boiling point: 300^0 C (633k) (760 mm Hg)

Dimethyl Sulfoxide



Chemical Structure of Dmso

IUPAC name: Dimethyl sulfoxide
Other names: Methyl sulfoxide, methyl sulfonyl methane, DMSO.
Molecular formula: C_2H_6OS
Molar mass: 78.13 g/mol.
Appearance: clear, colorless liquid.
Density: 1.1004 g/cm^3, liquid
Melting point: 18.5^0 C (292 k)
Boiling point: 189^0 C (462 k)
Solubility in water: Miscible

Applications

DMSO is an important polar aprotic solvent. It is less toxic than other members of this class such as dimethyl formamide, dimethylacetamide, N-methyl-2-pyrrolidine, HMPA. Because of its excellent solvating power, DMSO is frequently used as solvent for chemical reactions involving salts [8]. Because DMSO is only weakly acidic, it tolerates relatively strong bases.

MATERIALS AND METHODS

Preformulation studies

It is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included melting point determination, solubility and compatibility studies.

1. Description

Tramadol hydrochloride was physically examined for colour and odour etc.

2. Solubility

Solubility of Tramadol hydrochloride was determined in water, ethanol, methanol, buffer solution and other organic solvents.

3. Melting point

Fine powder of Tramadol hydrochloride was filled in glass capillary tube (previously sealed at one end) and kept in melting point apparatus. The melting point of Tramadol hydrochloride was found.

4. Partition coefficient of the drug

The partition coefficient of the drug was determined by taking equal volumes of 1- octanol and aqueous solution in a separating funnel [9]. 10 mg of drug was dissolved in 10 ml buffer solutions of pH 6.2, 7, 7.4 and 8 separately, to which 10 ml of octanol was added and kept in a separating funnel for 24 hrs. The aqueous layer was collected, and concentration of Tramadol hydrochloride was measured spectrophotometrically at 276 nm using buffer of the respective pH as blank.

5. Compatibility Studies

Compatibility with excipients was conformed by carried out IR studies. The pure drug and its formulations along with excipients were subjected to IR studies. In the present study, the potassium bromide disc (pellet) method was employed.

6. Estimation of Tramadol hydrochloride

A Spectrophotometric method based on the measurement of extinction at 276nm in phosphate buffer of pH 7.4 was used for the estimation of Tramadol hydrochloride.

Phosphate buffer of PH 7.4

Dissolve 2.38gm of disodium hydrogen ortho phosphate, 0.19gm of potassium dihydrogen ortho phosphate and 8gm of sodium chloride in sufficient water to produce 1000ml and adjust the pH if necessary.

Standard solution

An accurately weighed quantity of 100mg of Tramadol hydrochloride was dissolved in 100ml of Methanol. From this, 1ml of Methanolic solution was taken in a 100ml volumetric flask and the solution was made up to 100ml with phosphate buffer of pH 7.4.This solution was used as standard solution.

Procedure

The standard solution of Tramadol hydrochloride was subsequently diluted with phosphate buffer of pH 7.4 to obtain a series of dilutions containing 2, 4, 6, 8 and 10µg of Tramadol hydrochloride per 1ml of solution. The optical densities of the above dilutions were measured in UV spectrophotometer at 276nm using the phosphate buffer of pH 7.4 as blank. The concentrations of Tramadol hydrochloride and corresponding optical densities are given. The optical densities were plotted against concentration of Tramadol hydrochloride as shown in Fig. 1. And this calibration curve was used for estimating the Tramadol hydrochloride in the samples.

Preparation of Transdermal patches

Solvent casting technique

The Transdermal patches prepared are of matrix diffusion controlled systems. Solvent casting technique was used to prepare the transdermal patches.

Procedure

200mg of the polymer (HPMC or PVA or HPMC & PVA) was accurately weighed and soaked in 2.5ml of distilled water in a 50ml beaker for over night. Then 0.25ml of diethyl phthalate and 0.25ml of Oleic acid are added and mixed thoroughly by means of Magnetic stirrer. To the above solution add 100mg of Tramadol hydrochloide dissolved in 2ml of Methanol in a test tube and mixed for 30 minutes. Then the resulting solution was poured in the bangle, which is placed in a Petri dish containing mercury. The whole setup was to be placed in Hot air oven and a funnel is placed to cover the Petri dish so that uniform drying of the patch occurs in the Hot air oven for 24hrs. The Hot air oven is to be maintained at 40^0C through out the process. Formulation 1 (F1) was prepared by using HPMC as a polymer, Formulation 2 (F2) was prepared by using PVA as a polymer and Formulation 3 (F3) was prepared by using the combination of both HPMC and PVA.

Evaluation of Transdermal patches

The prepared Tramadol hydrochloride transdermal patches were evaluated as mentioned below.

1. Weight of the patch
2. Thickness of the patch
3. Moisture content
4. Moisture uptake
5. Drug content
6. *In vitro* drug release studies
7. *In vivo* studies
   a. Skin irritation studies
   b. Anti-inflammatory activity

1. Weight of the patch

Three patches from each batch were taken and weight of each patch was found by using electronic balance. Then average weight of single patch was determined.

2. Thickness of the patch

The thickness of the patch was assessed by using thickness gauze (screw gauze) at different points of the patch. From each formulation three randomly selected patches were used. The average value for thickness of a single patch was determined.

3. Moisture content

The patches (n =3) were weighed individually and kept in a desiccator containing calcium chloride at 37^0 c for 24 hrs. The final weight was noted when there was no change in the weight of individual patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight.

4. Moisture uptake

The patches (n=3) were weighed accurately and placed in a desiccator where a humidity condition of 75% RH was maintained by using saturated solution of sodium chloride. After three days, the patches were taken out and weighed. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

5. Drug content determination

The patches at $1Cm^2$ were cut and added to a beaker containing 100ml of Phosphate buffered solution of pH 7.4. The medium was stirred with a Teflon coated magnetic bead for 5hrs. The solution was later filtered and analyzed for drug content with proper dilution at 276nm spectrophotometrically.

6. In-vitro drug release studies

a) Preparation of rat Abdominal Skin

The male rat was sacrificed by excess Diethyl ether inhalation and hair on the abdominal skin was removed with a razor taking extreme precaution not to damage skin. The shaved skin was excised from the animal and kept in the beaker containing distilled water covered with Aluminum foil.

b) In-vitro Drug Release

The fabricated film was placed on the rat skin and attached to the diffusion cell such that the cell's drug releasing surface towards the receptor compartment which was filled with phosphate buffer solution of pH 7.4 at 37 ± 1^0C. The elution medium was stirred magnetically. The aliquots (5ml) were withdrawn at predetermined time intervals and replaced with same volume of phosphate buffer of pH 7.4. The samples were analysed for drug content using UV spectrophotometer at 276nm.

c. Kinetics of drug release

To examine the drug release kinetics and mechanism, the cumulative release data [10] were fitted to models representing zero order (Q v/s t), first order [Log(Q_0-Q) v/s t], Higuchi's square root of time (Q v/s $t^{1/2}$) and Korsemeyer Peppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug

released at time t and (Q_0-Q) is the cumulative percentage of drug remaining after time t.

***In-vivo* studies**

a. Skin irritation studies

Skin irritation studies were carried out on six healthy rats. The dorsal surface of the rat was cleared and the hair was removed by shaving. The skin was cleared with rectified spirit. The patches were (F1, F2, F3) were placed over the skin with the help of adhesive tape. The patches were removed after 24 hrs. And the skin was examined for any untoward reaction.

b. Anti inflammatory studies

The animals are divided into two groups. Acute inflammation was produced by sub planter injection 0.1ml of 1%solution of carrageenan in normal saline, in the right hind paw of the rats; one hour after application of patch. The paw volume was measured by using plethysmometer at regular periods of time interval after the injection of carrageenan. The difference between the two readings was taken as the volume of the edema and the percentage anti-inflammatory activity was calculated by using the following formula.

% Inhibition = $(V_T - V_O)_{CONTROL} - (V_T - V_O)_{TREATED} / (V_T - V_0)_{CONTROL}$

RESULTS AND DISCUSSION

Preformulation Studies

1. Description

Tramadol hydrochloride was physically examined for colour and odor etc. It is white amorphous powder and odourless.

2. Solubility

Tramadol hydrochloride was freely soluble in water, ethanol, methanol, buffer solutions and other organic solvents.

3. Melting point

The melting point of Tramadol hydrochloride was found be 171^0C.

4. Partition coefficient of the drug

Partition coefficient of drug was found to be 9.41 at pH 7.

5. Compatibility Studies

The results of compatibility studies are studied.

6. Preparation of standard calibration curve of Tramadol hydrochloride

The standard calibration curve of Tramadol hydrochloride was shown.

Evaluation of Transdermal patches

1. Weight of the patch

The Transdermal patches of F1, F2 and F3 exhibited weights were found to be 372 ± 3.6055 mg, 232.3 ± 2.51 mg, 452.6 ± 3.055 mg. respectively.

2. Thickness of the patch

Thickness of Transdermal patches of F1, F2 and F3 were found to be 0.124 ± 0.032 mm, 0.16 ± 0.013 mm and 0.19 ± 0.036 mm respectively.

3. Moisture content

Moisture content in F1, F2 and F3 were found to be 21±0.957 %, 9±0.957 %, 4±0.645 % respectively.

4. Moisture uptake

Moisture uptake of F1 was found to be 16.6%, 56.6%, 103.3% per day1, day2, and day3 respectively. Moisture uptake of F2 was found to be 23.3%, 41.6%, 73.3% per day1, day2, and day3 respectively. Moisture uptake of F3 was found to be 13.0%, 26.6%, 36.0% per day1, day2, and day3 respectively.

5. Drug content determination

Drug content in F1, F2 and F3 were found to be 97.5%, 98%, 97% respectively

6. In vitro drug release studies

The maximum cumulative % drug release for formulation F1 was found to be 81.22%, for F2 67.89% and for F3 57.12% at 12 hrs. *In vitro* release profiles are shown (Fig. 5.8). The data obtained were fitted to zero order, first order, Higuchi's square root of time and Korsemeyer-Peppas equations to understand the mechanism of drug release from the Tramadol HCl Transdermal patches. The slopes and the regression co-efficient of determinations (R^2) are listed. The co-efficient of determination indicated that the release data was best fitted with zero order kinetics. Higuchi equation explains the diffusion controlled release mechanism.

Additional evidence for the diffusion controlled mechanism was obtained by fitting the Korsemeyer-Peppas equation to the release data. The diffusion exponent 'n' value was found to be in between 0.5-1, for different drug polymer compositions, indicating non-fickian diffusion of drug through transdermal patches. Thus, all patches showed initial burst release followed by non-fickian diffusion.

***7. In vivo* studies**

a. Skin Irritation studies

No signs of edema, erythmea, ulceration were observed.

b. Anti inflammatory studies

The anti inflammatory activity of F1, F2 and F3 are shown. The comparison of anti inflammatory activity of F1, F2 and F3 are shown**.**

Table 1. Formula for Tramadol HCL Transdermal Patch F1

S. No	Name of the Ingredient	Quantity for 1 Patch		
		F1	F2	F3
1	Tramadol hydrochloride	100mg	100mg	100mg

2	HPMC	200mg	-	100mg
3	PVA	-	200mg	100mg
4	Dimethyl Sulfoxide	0.25ml	0.25ml	0.25ml
5	Oleic acid	0.25ml	0.25ml	0.25ml
6	Water	2.5ml	2.5ml	2.5ml
7	Methanol	2.5ml	2.5ml	2.5ml

Table 2. Weight of Tramadol HCL Transdermal Patches

S. No	Formulation	Weight of the patch (mg)	Average weight (mg)
1	F1	373	372.0±3.605
		375	
		368	
2	F2	230	232.3±2.510
		235	
		232	
3	F3	450	452.6±3.055
		456	
		452	

Table 3. Thickness of Tramadol HCL Transdermal Patches

S.No.	Formulation	Patch no.	Thickness of the patch (mm)	Mean Thickness (mm)
1	F_1	1	0.272	0.241±0.032
		2	0.244	
		3	0.208	
2	F_2	1	0.152	0.160±0.013
		2	0.152	
		3	0.176	
3	F_3	1	0.230	0.190±0.036
		2	0.176	
		3	0.160	

Table 4. Moisture Content of Tramadol HCL Transdermal Patches For F1, F2 and F3

S.No.	Formulation	Initial weight (mg)	Final weight (mg)	Difference in weight (mg)	Moisture %
1	F_1	373	353	20	21 ± 0.957
		375	354	21	
		368	346	22	
2	F_2	230	220	10	9 ± 0.957
		235	226	9	
		232	224	8	
3	F_3	450	447	3	4 ± 0.645
		456	449	7	
		452	450	2	

Table 5. Moisture Uptake of Tramadol HCL Transdermal Patches For F1, F2 and F3

S.No.	Formulation	Patch no.	Initial weight (mg)	Final weight (mg)			Difference			Moisture %		
				1 Day	2 Day	3 Day	1 Day	2 Day	3 Day	1 Day	2 Day	3 Day
1	F_1	1	373	383	403	453	10	30	80	16.6	56.6	103.3
		2	375	395	435	495	20	60	120			
		3	368	388	448	478	20	80	110			
2	F_2	1	260	260	290	310	30	60	80			

		2	255	255	265	295	20	35	60	23.3	41.6	73.3
		3	252	252	262	312	20	30	80			
3	F_3	1	450	459	469	478	9	19	28	13.0	26.3	36.0
		2	456	466	486	496	10	30	40			
		3	472	472	482	492	20	30	40			

Table 6. Drug Content of Tramadol HCL Transdermal Patches In Phosphate Buffer PH 7.4 at 276 nm

S.No.	Formulation	Drug content (%)
1	F_1	97.5
2	F_2	98
3	F_3	97

Table 7. Data for the Calibration Curve of Tramadol HCL in Phosphate Buffer PH 7.4 at 276nm

S.No.	Tramadol hydrochloride concentration (µg /ml)	Absorbance
1	2	0.101
2	4	0.194
3	6	0.303
4	8	0.436
5	10	0.549

Table 8. *In-Vitro* Drug Release Profile of Tramadol HCL

S.No.	Time (hrs)	√T	Log T	Cumulative % of drug released	Log cumulative % of drug released	Cumulative % of drug remained	Log cumulative % of drug remained
1	0.50	0.907	-0.301	3.947	0.596	96.053	1.982
2	1.00	1.000	0.000	5.834	0.765	94.166	1.973
3	1.50	1.224	0.176	9.849	0.993	90.151	1.954
4	2.00	1.414	0.301	15.502	1.190	84.498	1.926
5	2.50	1.581	0.397	21.028	1.322	78.972	1.897
6	3.00	1.732	0.477	23.916	1.378	76.084	1.881
7	4.00	2.000	0.602	29.395	1.468	70.605	1.848
8	5.00	2.236	0.698	35.287	1.547	64.713	.810
9	6.00	2.449	0.778	40.440	1.606	59.560	1.774
10	7.00	2.645	0.845	45.074	1.653	54.926	1.739
11	8.00	2.828	0.903	51.788	1.714	48.212	1.683
12	9.00	3.000	0.954	57.604	1.760	36.396	1.627
13	10.00	3.162	1.000	63.484	1.802	23.516	1.562
14	11.00	3.316	1.041	76.947	1.886	23.053	1.362
15	12.00	3.464	1.079	81.225	1.909	18.775	1.273

Table 9. *In-Vitro* Drug Release Profile of Tramadol hcl Transdermal Patch (F2*)*

S.No.	Time (hrs)	√T	Log T	Cumulative % of drug released	Log cumulative % of drug released	Cumulative % of drug remained	Log cumulative% of drug remained
1	0.50	0.907	-0.301	4.763	0.677	95.237	1.978
2	1.00	1.000	0.000	7.555	0.878	92.445	1.965
3	1.50	1.224	0.176	13.525	1.131	86.475	1.936
4	2.00	1.414	0.301	16.305	1.212	83.695	1.922
5	2.50	1.581	0.397	19.292	1.285	80.708	1.906
6	3.00	1.732	0.477	23.57	1.372	76.430	1.883
7	4.00	2.000	0.602	27.012	1.431	72.988	1.863
8	5.00	2.236	0.698	32.269	1.508	67.731	1.830
9	6.00	2.449	0.778	38.216	1.582	61.784	1.790
10	7.00	2.645	0.845	43.268	1.636	56.732	1.753

11	8.00	2.828	0.903	47.215	1.674	52.785	1.722
12	9.00	3.000	0.954	53.89	1.731	46.110	1.663
13	10.00	3.162	1.000	57.77	1.761	42.230	1.625
14	11.00	3.316	1.041	64.07	1.806	35.930	1.555
15	12.00	3.464	1.079	67.89	1.831	32.11	1.506

Table 10. *In-Vitro* Drug Release Profile of Tramadol HCL Transdermal Patch (F3)

S.No.	Time (hrs)	√T	Log T	Cumulative % of drug released	Log cumulative % of drug released	Cumulative % of drug remained	Log cumulative % of drug remained
1	0.50	0.907	-0.301	5.221	0.717	94.779	1.976
2	1.00	1.000	0.000	6.754	0.829	93.240	1.969
3	1.50	1.224	0.176	12.242	1.087	87.758	1.943
4	2.00	1.414	0.301	13.235	1.121	86.765	1.938
5	2.50	1.581	0.397	14.782	1.169	85.218	1.930
6	3.00	1.732	0.477	17.924	1.253	82.076	1.914
7	4.00	2.000	0.602	21.737	1.337	78.263	1.893
8	5.00	2.236	0.698	26.353	1.420	73.647	1.867
9	6.00	2.449	0.778	31.582	1.449	68.418	1.835
10	7.00	2.645	0.845	35.848	1.554	64.152	1.807
11	8.00	2.828	0.903	39.432	1.595	60.568	1.782
12	9.00	3.000	0.954	44.041	1.643	55.959	1.747
13	10.00	3.162	1.000	47.556	1.677	52.444	1.719
14	11.00	3.316	1.041	52.591	1.720	47.409	1.675
15	12.00	3.464	1.079	57.123	1.756	42.877	1.632

Table 11. Regression Co-Efficient (R2) Values, Diffusion Exponent (N) Of Peppas Model of Tramadol HCL Transdermal Patches According to Different Kinetic Models

Formulation	Zero order	First order	Higuchi matrix	Peppas kinetics	'n'values for Peppas
F1	0.9925	0.9287	0.9361	0.9888	0.9652
F2	0.9930	0.9877	0.9620	0.9947	0.8371
F3	0.9953	0.9915	0.9578	0.9889	0.7721

Table 12. Anti Inflammatory Studies of Tramadol HCL Transdermal Patch (F3)

S.No.	Treatment	Paw volume (ml) as measured by mercury displacement at									
		0hrs	2hrs	4hrs	5hrs	6hrs	7hrs	8hrs	10hr	11hr	12hr
1	Control	0.7	0.9	1.12	1.13	1.5	1.6	1.8	2.0	2.2	1.5
2	Control	0.6	0.8	0.90	1.1	1.3	1.5	1.7	1.8	2.0	1.4
3	Control	0.8	1.1	1.2	1.3	1.4	1.6	1.8	1.9	2.1	1.5
4	Control	0.8	1.06	1.1	1.2	1.3	1.5	1.6	1.7	1.9	1.4
Mean		0.725	0.96	1.08	1.22	1.37	1.55	1.72	1.85	2.05	1.45
1	Tramadol HCl	0.7	0.9	1.0	1.1	1.2	1.3	1.4	1.5	1.5	1.1
2	Tramadol HCl	0.7	1.0	1.1	1.2	1.3	1.4	1.5	1.5	1.6	1.2
3	Tramadol HCl	0.8	1.1	1.2	1.3	1.4	1.5	1.5	1.6	1.6	1.2
4	Tramadol HCl	0.6	0.7	0.8	0.9	1.0	1.1	1.2	1.2	1.3	0.9
Mean		0.7	0.92	1.02	1.12	1.22	1.32	1.4	1.45	1.5	1.1

Table 7.15 Comparision of % Inhibition of Edema By Tramadol HCL Transdermal Patches

S.No.	Formulation	% Inhibition of edema at									
		0hrs	2hrs	4hrs	5hrs	6hrs	7hrs	8hrs	10hrs	11hrs	12hrs
1	F1	3.7	8.4	18.1	25	29.7	33.1	37.5	35.8	32.7	29.6
2	F2	7.6	17.6	23	25	26.3	31.8	34.6	32.6	30.6	29.3
3	F3	6.25	8.45	15	19.2	24.2	30	33.3	39.6	44.8	42.5

Fig. 1. IR Spectrum of Physical Mixture of Tramadol HCL and HPMC

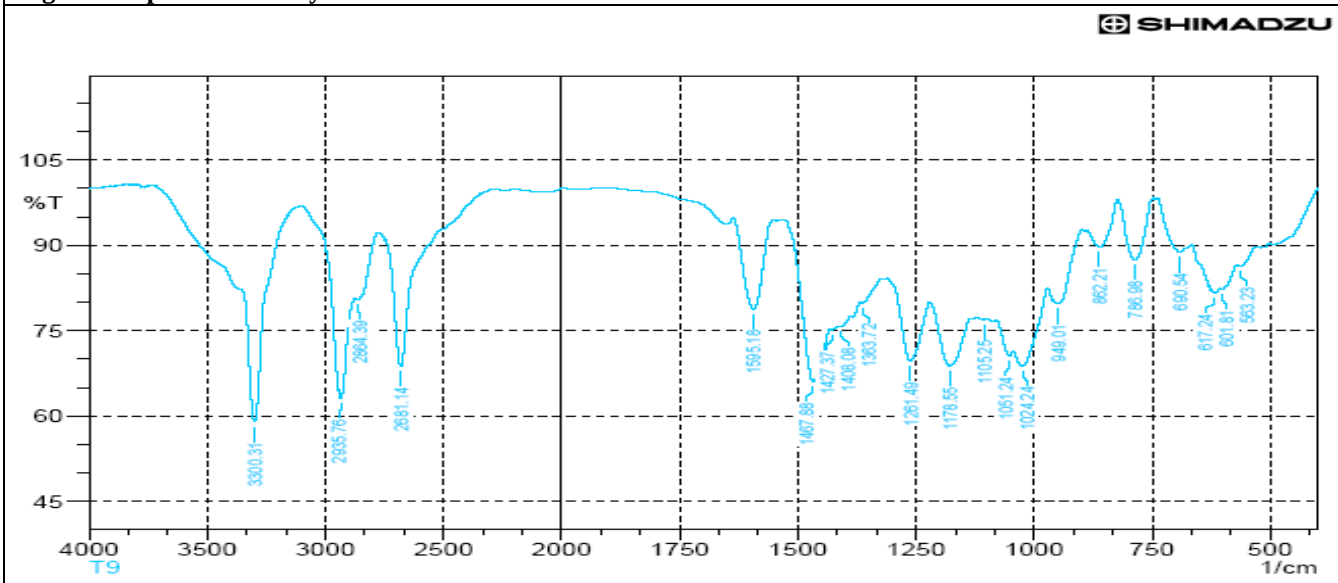


Fig. 2. IR Spectrum of Physical Mixture of Tramadol HCL and PVA

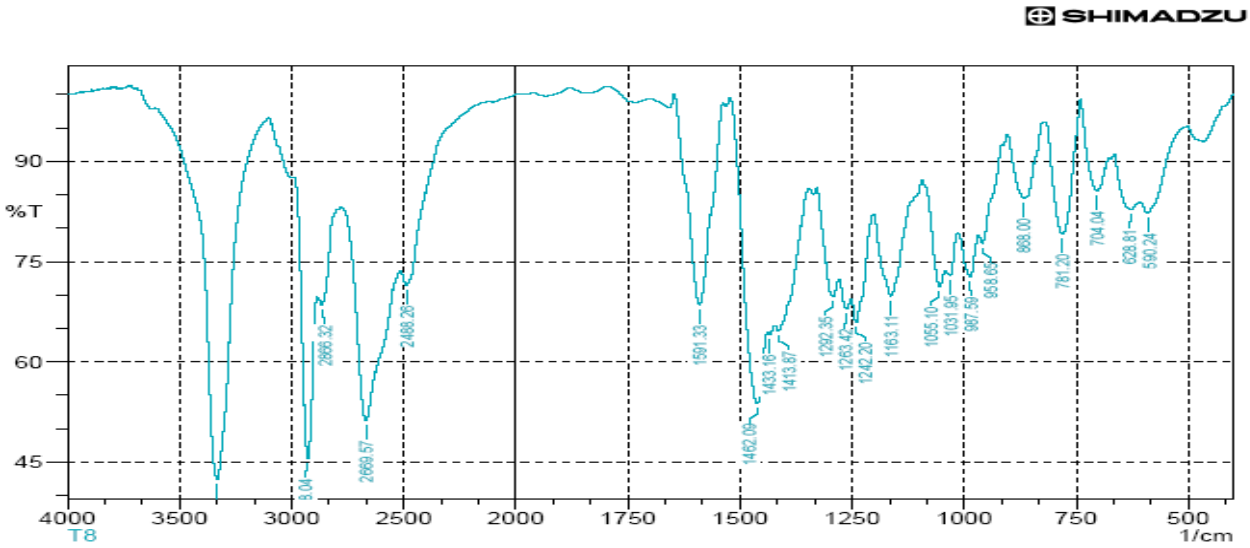


Fig. 3. Standard Calibration Curve of Tramadol HCL in Phosphate Buffer PH 7.4 At 276nm

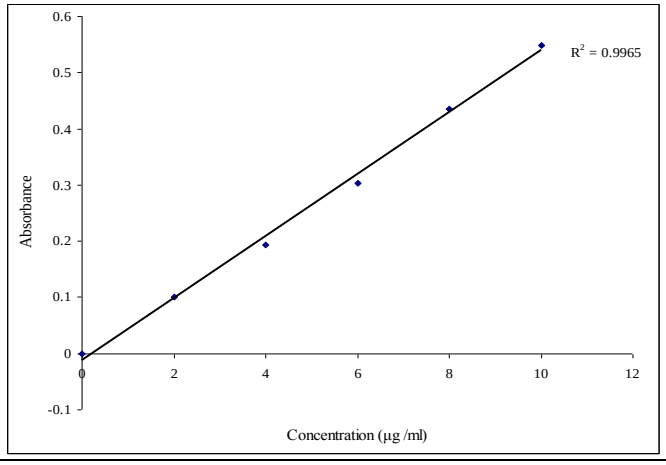


Fig. 4. *In-Vitro* Release Profile of Tramadol HCL Transdermal Patches

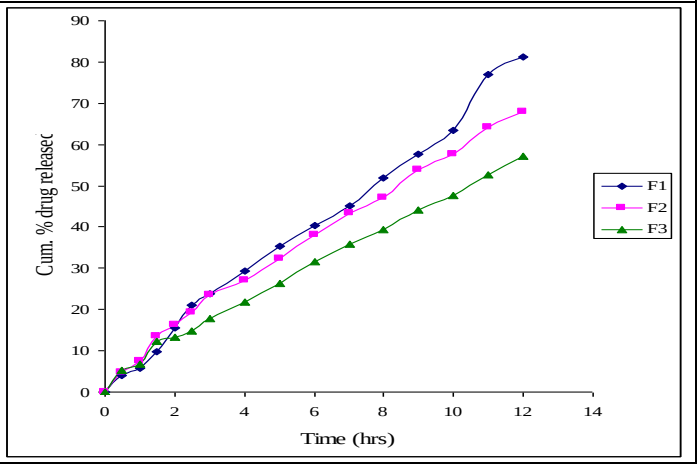


Fig. 5. Zero Order Release Kinetic Profile of Tramadol HCL Transdermal Patches

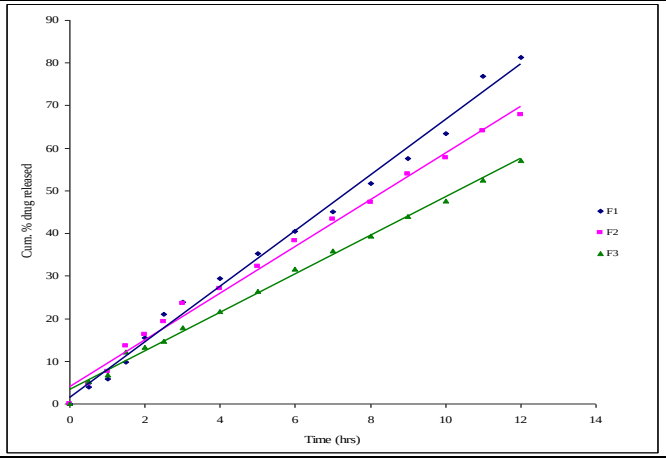
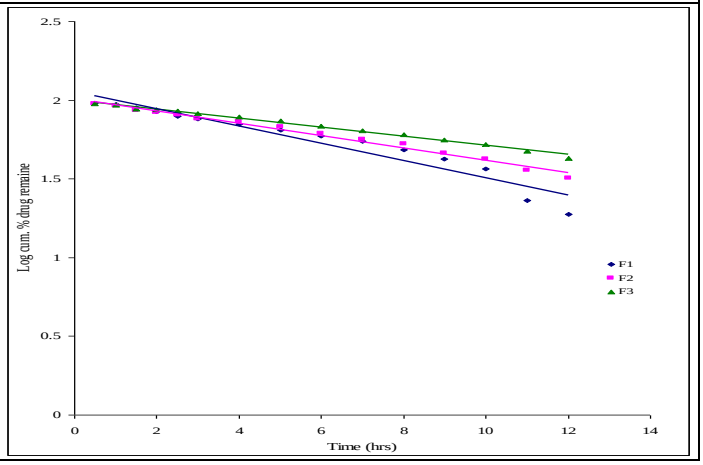


Fig. 6. First Order Release Kinetic Profile of Tramadol HCL Transdermal Patches



Transdermal patches of Tramadol hydrochloride were prepared by the synthetic polymers HPMC, PVA, combination of HPMC and PVA. The patches were transparent, smooth and flexible. The results of weight variation, thickness, moisture content, moisture uptake and drug content are shown

The patches F_1, F_2, F_3 exhibited uniform weight ranging from 232.3 ± 2.51 to 452.6 ± 3.055. And thickness of F_1, F_2, F_3 are ranging from 0.124± 0.032 to 0.19±0.036. Among the various batches, the uniformity weight and thickness indicates that the polymeric solution of the drug is well dispersed in the patches. All the formulations exhibited fairly uniform drug content ranging from F_1, F_2, F_3 are 97 to 98% (respectively). The moisture uptake and content was found to be low in formulation containing combination of HPMC and PVA.

However the moisture absorbed the patch did not affect adversely the patch strength and integrity. The small moisture content helps them to remain stable and from being a completely dried and brittle patches.

The *in vitro* permeation studies of patches using rat skin as membrane barrier was carried out. The results of *in vitro* permeation studies cross the rat skin are shown

The maximum cumulative percentages of drug permeation from the various formulations are 90.2%, 71.8%, and 57.12% for F_1, F_2, and F_3 formulations respectively. The cumulative percentage of drug permeated from different formulations is given in the following order F_1> F2> F3.

The drug release from all the patches was rapid in the initial hours, which could be due to the presence of drug on the surface of the patch. Later drug was released slowly from the patches. From the graph it is evident that drug release is decreased with the incorporation PVA .The slow release mechanism for incorporation PVA can be explained by comparative increase in the hydrophobicity of the polymer. With incorporation of PVA the matrix water porosity for diffusion of drug get decreased.

The release kinetics was evaluated by making by use of zero order, first order, Higuchi's diffusion and Korsemeyer - Peppas equation. The drug release through the transdermal patches of tramadol hydrochloride following zero order kinetics. And the release kinetics following diffusion controlled mechanism. By fitting in the Korsemeyer -Peppas equation the release kinetics following non-fickian kinetics. The range of 'n' value for Korsemeyer – Peppas equation -1 to 1. If the 'n' values of Korsemeyer – Peppas equation is below 0.5, which indicates fickian kinetics. If the 'n' value of Korsemeyer – Peppas equation is in between 0.5 to 1, this indicates non-fickian kinetics. Here the patches of tramadol hydrochloride release kinetics fitted in Korsemeyer – Peppas equation 'n' values showing in between 0.5 to 1, that's why it is following diffusion controlled, non- fickian kinetics.

The male albino rats are used for the study of anti-inflammatory activity. From the percentage inhibition of edema values obtained from anti-inflammatory studies which shows the order of the inflammation can be given as $F_1 > F_2 > F_3$.

CONCLUSION

The preformulation studies involving description, solubility, melting point, partition coefficient of the drug were found to be comparable with the standard. Based on the all the above preformulation studies the drug was suitable for making the transdermal formulation.

Based on all these factors the transdermal drug delivery system F1 is having more drug release. Formulation F2 having less drug release capacity than F1 and more than F3. The formulation F3 shows better extended release up to 12 hrs when compared to formulations F1 and F2. From the percentage inhibition values obtained from anti-inflammatory studies, the decreasing order for the anti-inflammation can be given as:

$$F_1 > F_2 > F_3.$$

So it was concluded that the formulation F3 prepared by the mixture of polymers HPMC and PVA is the

better formulation for control release of drug up to 12 hrs of time. The *in vitro* drug release of the best formulation F3 follows zero order kinetics and the mechanism of diffusion is Non- Fickian type.

From the above studies, it is revealed that the present work was a satisfactory preliminary study of improving bioavailability of Tramadol HCl by using HPMC and PVA transderml patches. Further detailed investigations and elaborate *in-vivo* targeting studies need to be carried out and an *in vitro – in vivo* correlation need to be established to guarantee the efficiency and bioavailability of the formulation. Further studies on improving bioavailability have to be carried out with different polymers.

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