A Novel Approach to Develop Tramadol Hydrochloride Transdermal Films with Complete *In-Vitro* Evaluation

KABITA BANIK[1], DR. NAMRATHA[2], TWILA[3], K HARIKA[4]
[1, 2, 3, 4] *Bharat Institute of Technology, Hyderabad, Telengana.*

Abstract— The oral route is now the most prevalent method of medication administration. While it has the benefit of being simple to administer, it also has substantial disadvantages, including low bioavailability due to hepatic metabolism and the propensity to cause fast blood level spikes, necessitating high and/or frequent doses, which may be expensive and inconvenient. In this study, hydroxypropyl methyl cellulose 6 cps (HPMC 6 cps) and ethyl cellulose are used as release-controlling polymers to create a matrix type transdermal drug delivery system for the analgesic medication tramadol HCl for its systemic delivery. This new drug delivery systems has increased the therapeutic efficacy and safety of pharmaceuticals by allowing for more accurate, site-specific delivery system, it allows temporal placement inside the body, resulting in smaller dosages consumption.

Indexed Terms— Transdermal films, Hydroxypropyl methyl cellulose, Ethylcellulose polymer, Tramadol HCl

I. INTRODUCTION

Transdermal medication delivery refers to the movement of a medicinal substance via the dermis of the skin for later systemic distribution. Therefore, properly speaking, this includes both traditional subcutaneous administrations with a hypodermic needle and syringe as well as the better recognised "patch." By this wide definition, the medication must enter the body through an artificial pathway, which is a feature of all transdermal drug delivery techniques. The key benefit of this method is that the medicine enters the body undisturbed and bypasses the body's different defence mechanisms[1]. The transdermal route of medication administration, while less convenient than oral administration (such as eating a tablet), avoids both drug breakdown in the gastrointestinal system and lower effectiveness due to first-pass metabolism (i.e. in the liver). Additionally, oral-specific adverse effects like liver damage—common with medications like estradiol (oestrogen) or paracetamol—are avoided. [2]

- Conventional patching techniques

Despite the fact that infusion pumps are dependable in providing the desired therapeutic administration profile, using one (such as an insulin pump) is rather difficult, expensive, and necessitates a hypodermic needle-based infusion set [2]. Drug administration using transdermal patches, where the medication diffuses through the skin, is far more practical while still providing the advantages of continuous drug release [3]. Depending on the patch size, the medications now used topically range in molecular weight from 162 Da (for nicotine) to 357 Da (for oxybutynin), with a realistic dosing rate of 4–20 mg/day. The mass of an insulin molecule is 5808 Da, but the molecular weight of contemporary DNA-based vaccines, which are composed of vectors with thousands of base pairs, may range from hundreds to thousands of kilo Daltons (kDa) [4-5].

II. MATERIALS AND METHODS

All the materials used in formulation, evaluation and other experiments are listed below. Distilled water is used in all experiments.

S. No	Use	Materials	Source
1	Drug	Tramadol HCl	Hy-Gro chemicals Pharma Ltd.
2	Polymers	Hydroxy Propyl Methyl Cellulose 6 cps	Dr. Reddy's Laboratories Ltd
		Ethyl cellulose	Dr. Reddy's Laboratories Ltd
3	Plasticizer	Polyethylene glycol 4000	S D Fine Chemicals
		Glycerin	
4	Penetration enhancer	Tween 80	S D Fine Chemicals
5	Solvents	Acetone	S D Fine Chemicals
6	Lubricant	Liquid Paraffin	S D Fine Chemicals

Table 1: List of materials used

S. No	Equipment	Manufacturer
1	UV-Visible Spectrophotometer	Shimadzu-1700, Shimadzu Corporation, Japan
2	Electronic balance	ELB-300, Shimadzu Corporation, Japan
3	Sonicator	Flexit Jour LaboratoriesPvt. Ltd., Mumbai
4	Magnetic stirrer	Remi motors ltd., Hyderabad
5	Fourier transformed infrared spectrophotometer	Shimadzu, Japan, Tokyo
6	Humidity chamber	Sisco 2912,Thane,Maharashtra

Table 2: List of equipments/Instruments used

- PREFORMULATION STUDIES

It is crucial that drug and polymer be chemically and physically defined before formulation of medicinal ingredients into a dosage form. Preformulation studies offer the data required to specify the nature of the drug ingredient and set the stage for the medication's combination with pharmaceutical excipients in the creation of a dosage form [6].

- Measuring the drug's solubility

Tramadol HCl's solubility was assessed using the procedure developed by Krishniah ltd. To create a saturated solution, an excess of the medication was obtained and dissolved in a predetermined volume of phosphate buffer pH 7.4 in a glass container[7]. To achieve equilibrium, the solution was sonicated and held at room temperature. After 12 hours, the absorbance at 271 nm was measured in order to spectrophotometrically estimate the quantity of tramadol HCl in the filtrate.

pH	Volume of 0.2M NaOH (ml)	pH	Volume of 0.2M NaOH (ml)
5.8	3.6	7.0	29.1
6.0	5.6	7.2	34.7
6.2	8.1	7.4	39.1
6.4	11.6	7.6	42.4
6.6	16.4	7.8	44.5
6.8	22.4	8.0	46.1

Table 3: Volume of 0.2M NaOH to be added for the preparation of buffers of various pH

- Preparation of the standard solution

The standard solution was created by combining 10 mg of tramadol HCl with 10 ml of phosphate buffer pH 7.4, and then increasing the amount to 100 ml.

In order to get 1, 2, 4, 6, 8, 10, 12, and 16 g/ml of the standard solution, a series of dilutions including 0.1, 0.2, 0.4, 0.6, 0.8, 1, 1.2, 1.4, and 1.6 ml were pipetted out and then diluted to 10 ml with phosphate buffer pH 7.4.

When using phosphate buffer pH 7.4 as a blank solution, the absorbances of these dilutions were determined using a UV spectrophotometer at 271nm.

- Construction of Standard Graph: The calibration curve, absorbance v/s concentration was constructed and slope was calculated.

- FORMULATION OF TRANSDERMAL FILMS

Liquid paraffin was used as lubricant to prepare the TDDS utilising the film casting procedure. One by one, each polymer was dissolved in a solvent solution in a boiling tube. After ultrasonication, which helps to eliminate the air bubbles, the resultant homogeneous solution was left to stand for roughly 6 hours [8].

The medicine was then gradually added to the solution in little amounts while being stirred consistently. After completing the ultrasonication, plasticizer and penetration enhancer were added and the mixture was again put aside for roughly 2 hours. The result was poured onto a petridish that had been greased with liquid paraffin[9].At room temperature, the solvent was left to evaporate.

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Tramadol HCl (mg/2X2cm²)	100	100	100	100	100	100	100	100	100	100
HPMC 6 cps (mg)	100	200	300	400	500	100	200	300	400	500
EC (mg)	50	50	50	50	50	100	100	100	100	100
PEG 4000 (mg)	100	200	100	200	100	-	-	-	-	-
Glycerine (ml)	-	-	-	-	-	8	8	8	8	8
Tween 80 (ml)	3	3	3	3	3	3	3	3	3	3
Acetone (ml)	7	7	7	7	7	7	7	7	7	7
Water (ml)	5	5	5	5	5	5	5	5	5	5

Table 4: Composition of Formulations

- ASSESSMENT OF TRANSDERMAL FILIMS

Transdermal dosage form development is a challenging procedure that requires substantial investigation. Transdermal patches, which provide a reduced dose of the medicine at a predefined pace, have been created to increase clinical effectiveness of the treatment and patient compliance. In order to

assure their expected performance and repeatability within the required environmental circumstances, evaluation studies are now even more crucial[10].

- *In-vitro* drug permeation

The amount of medication released from the polymeric transdermal films has a significant impact on how much is accessible for absorption into the systemic pool. The medication enters the skin surface and then travels through the epidermis and between the epidermis cells through skin appendages to the dermal microcirculation[11].

The constructed transdermal patch with rat skin or a synthetic membrane is often placed between the donor and receptor compartments in a vertical diffusion cell, such as a Franz diffusion cell or a Keshary-Chien diffusion cell, to conduct permeation tests [12]. The lipophilic side of the membrane is in touch with the buffer as the transdermal system is installed in the diffusion cell with the hydrophilic side of the membrane. Throughout the experiment, magnetic beads are used to mix the solution in the receiver compartment while the entire system is kept on a magnetic stirrer[13].

Fig 1: Franz diffusion cell

The optimal pH setting for the dissolving media is pH 7.4, which corresponds to physiological skin conditions. The test temperature is commonly set at 32°C for the same reason (even though the temperature may be higher when skin is covered).

PhEur permits testing an aliquot patch piece and views 100 rpm as a normal agitation rate. Both the temperature and agitation rate are maintained constant. If the release mechanism is confirmed to be unaffected by cutting a section of the patch, then this could be a suitable method of achieving sink conditions[14].

At regular intervals, samples are taken, and an identical volume of new receptor fluid is replenished. After properly diluting the samples, the absorbance is calculated spectrophotometrically. The release of the medicine can be impacted by a number of factors, including system design, patch size, skin surface area, thickness, temperature, and others.

III. RESULTS AND DISCUSSION

The results are arranged in the order of the experimental methods performed.

Preformulation studies

The following Preformulation study was performed for Tramadol HCl.

Determination of drug solubility

Melting point	**179-180**
pH	**3.82**
Solubility	**42.98 µg/ml**

Table 5: Preformulation study

The active concentration at which a medicine may be applied to the skin's surface depends on how well it dissolves in a particular carrier. Tramadol HCl is soluble in chloroform, dichloromethane, and methanol as well as phosphate buffer at pH 7.4 (be 42.98 g/ml).

ii) Measuring the melting point

Tramadol HCl was discovered to have a melting point of 179–180°C. This value is the same as the citation value for the literature. The reciprocal of melting points and log flux have a linear relationship, meaning that the lower the melting point, the better the penetration.

COMPATABILITY STUDY BY FT-IR

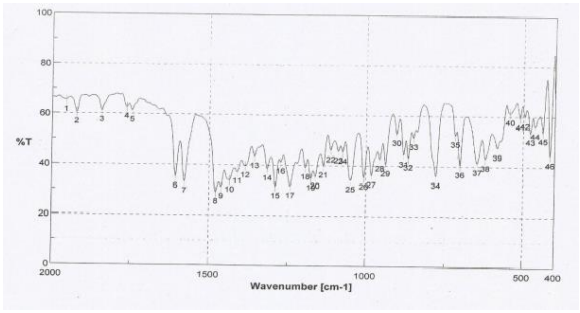

Fig. 2: FT-IR Spectra of Pure drug Tramadol HCl

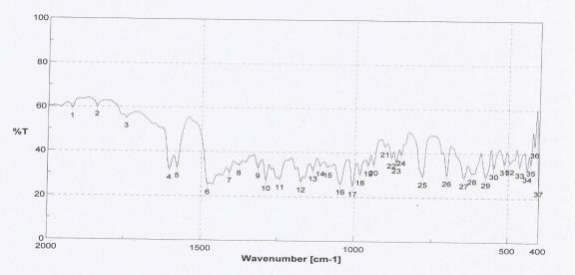

Fig. 3: FT-IR Spectra of Tramadol HCl with polymers (F10)

DETERMINATION OF λmax

Determination of λmax of Tramadol HCl in pH 7.4 phosphate buffer solution is 271nm

Construction of Calibration Curve for drug Tramadol HCl at λ_{max}271nm

The absorbance were measured by taking 1 µg/ml, 2 µg/ml, 4 µg/ml, 6 µg/ml, 8µg/ml,10 µg/ml, and 12 µg/ml, as the serial concentrations spectrometrically at 271nm.

S.No	Concentration (µg/ml)	Absorbance
1	0	0.000
2	1	0.076
3	2	0.159
4	4	0.323
5	6	0.477
6	8	0.640
7	10	0.779
8	12	0.914

Table 6: Spectrophotometric data for the estimation of Tramadol HCl

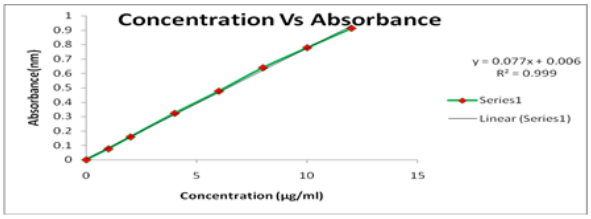

Figure 4: Calibration curve for the estimation of Tramadol HCl

Formulation of transdermal films

The matrix-type transdermal films ofTramadol HCl were prepared by solvent-evaporation technique using combination of HPMC 6 cps, EC in different ratios.

Evaluation

i) Physicochemical evaluation

Formulation Code	Physical appearance
F1	Transparent, flexible
F2	Smooth, uniform, soft
F3	Smooth, uniform, tough
F4	Smooth, uniform, soft
F5	Smooth, uniform, flexible
F6	Uniform, brittle
F7	Smooth, uniform, flexible
F8	Smooth, uniform, tough
F9	Transparent, flexible
F10	Smooth, uniform, soft

Table 7: Physical appearance of films

The results of remaining physico-chemical evaluations are tabulated as follows

FC	Weight uniformity (mg)	Thickness uniformity (mm)	Drug content uniformity (%)	WVT (gcm/cm²·24h)	Folding Endurance
F1	102±1.79	0.17±0.0020	97.86±4.2	5.91±0.059	270±4.32
F2	105.6±1.75	0.20±0.0035	97.91±1.7	6.70±0.052	261±3.00
F3	110.2±2.35	0.25±0.0060	97.1±2.5	6.65±0.030	250±5.21
F4	108.5±2.51	0.2±0.0025	98.95±4.1	6.45±0.026	249±3.87
F5	100±1.31	0.4±0.0024	98.4±3.4	6.25±0.029	246±4.60
F6	100±1.91	0.2±0.0041	96.85±3.5	5.99±0.038	316±4.15
F7	105±2.39	0.17±0.0032	97.5±4.9	5.93±0.023	309±3.89
F8	111.5±2.15	0.22±0.0023	98.65±2.5	5.57±0.049	297±5.10
F9	116.8±1.85	0.1±0.0042	98.79±1.7	5.19±0.035	293±5.15
F10	117.2±1.20	0.31±0.0035	98.65±2.6	4.90±0.05	290±4.72

Table 8: Data obtained from physico-chemical evaluation

All the values are represented as Mean ± SD (n=3) except WVT as Mean ± SD (n=3)

I. Outward appearance

All formulations had thin, clear, flexible, smooth, and homogeneous transdermal films. PEG 4000 was added, and the result was flexible, smooth patches.

II. Weight uniformity

As may be seen from their low SD values, all transdermal films were determined to have consistent weights.

III. Consistency of thickness

Low SD values in the measurements of film thickness guaranteed thickness homogeneity throughout each formulation.

IV. Uniformity of drug composition

One crucial aspect of a transdermal film that promotes the consistent, repeatable, continuous release of the medication from the patch is homogeneous homogenous drug distribution. The low values of the SD, which were used to estimate the drug

concentration, showed that the medication is evenly distributed throughout the patches.

V. Water vapour transmission

Because it is thought that it impacts drug release from controlled release matrix, the research of the hydration of polymers employed in sustained release applications has garnered interest. As a result of water absorption, the film may develop empty gaps that might weaken the structure's resistance to mechanical pressures.

Both the crosslink density and polymer concentration have an impact on the rate of WVT of films. WVT decreased as film thickness and crosslink density rose, which may be related to the lengthened diffusional pathway and heightened film stiffness at higher crosslink densities.

VI. Folding Stamina

A film's resistance to rupturing is measured by its folding endurance. It was judged sufficient.

The results demonstrated that, when used, the films would maintain their integrity despite regular skin folding and would not tear.

VII. Drug permeation in vitro

The degree to which a drug can pass through the patch depends on both the patch crosslink density and polymer concentration. How soon a drug is released from transdermal films depends on the chemical properties of the drug, its delivery method, and the physicochemical properties of the dialysis membrane. In the majority of controlled release devices, diffusion regulates the process of drug release, and the three-dimensional network of polymer chains in the polymer matrix significantly affects diffusivity.

The order in which the medication releases from its transdermal film formulations is as follows:

F10 > F1 > F6 > F3 > F7 > F10 > F2 > F4 > F8 > F9 > F5

where, after 12 hours, the levels of the drug released were, in order, 94.19%, 89.43%, 82.39%, 79.46%, 78.3%, 72.8%, 71.45%, 69.7%, 61.7%, and 51.59%. The inclusion of EC and HPMC may be the cause of the highest percentage release from the F10 formulation.

Because of the high permeability of the polymer matrix in HPMC, the cumulative percent drug penetration was greater. ii) *In-vitro* drug permeation

The release of Tramadol HCl through the dialysis membrane from its various transdermal film formulations are represented as following.

Time in hours	FORMULATION CODE									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0		0	0	0	0	0	0	0	0
1	9.25	0	6.8	2.53	1.73	9.15	9.23	5.63	3.45	11.52
2	24.19	5.29	17.5	5.78	4.98	36.45	21.45	13.70	7.23	27.8
4	33.56	19.68	24.93	12.30	7.25	40.93	32.32	27.82	15.57	40.1
6	45.30	30.19	39.20	15.6	11.23	50.85	45.8	38.5	43.24	45.26
8	51.93	45.99	45.79	19.23	13.76	60.87	55.10	49.26	50.10	55.93
10	63.5	56.90	68.23	25.63	25.3	70.37	68.57	59.50	55.23	63.89
12	89.43	65.20	79.46	71.45	51.59	83.29	78.52	69.71	61.7	94.19

Table 9: Cumulative % drug release of all the formulations

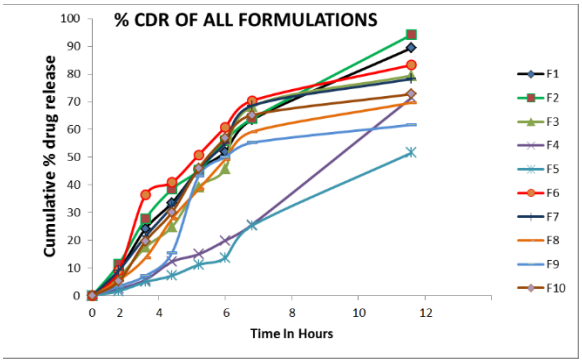

Fig 5: Plot of Cumulative % drug release of all the formulations

The release of the drug from its transdermal film formulations can be ranked in the following descending order:

F10 > F1 > F6 > F3 > F7 > F2 > F10 > F4 > F8 > F9 > F5

SUMMARY

- Numerous factors must be taken into account for successful transdermal medication administration. Given that the skin's primary purposes are containment and protection, it would appear incredibly challenging to administer drugs directly to the skin. However, more and more brand-new medication formulations are being created for transdermal distribution as a result of our improved understanding of the structure and function of the skin and how to change these characteristics. For safe and efficient drug distribution, it is crucial to consider the features of the medication, the transdermal device, the choice of the in-vivo model, and the condition of the patient's skin.
- Tramadol HCl is currently a recognised pharmacological substance because to its excellent therapeutic potential.
- In the current work, efforts were undertaken to use HPMC 6 cps and EC to make and assess transdermal films containing the analgesic medication tramadol HCl.
- Solubility, partition coefficient, and melting point were assessed in the pre-formulation tests to evaluate its suitability for transdermal distribution.
- The transdermal films were assessed for their appearance, homogeneity of weight and thickness, ability to transmit water vapour, and uniformity of medication content. All of the patches were homogeneous in terms of drug concentration, weight, and thickness, with low SD values. They were also thin, smooth, and flexible.
- The transdermal drug delivery system of tramadol HCl may be created, and it gives greater compliance than traditional drug delivery system, according to assessment tests of the transdermal films. The form of the permeation profiles over the dialysis membrane demonstrates how the films function as a matrix regulating drug delivery. It has been demonstrated that altering the kind or quantity of components can modify the drug's ability to pass through the barrier. The content of the film-forming polymer was more significant than its molecular weight, which had little bearing on the drug release.

CONCLUSION

Tramadol HCl transdermal films were created, evaluated physicochemically, and studied in vitro. All formulations had good physicochemical characteristics. Depending on the thickness and crosslink density, the produced patches were permeable to water vapour. According to the dissolution profile, the F10 formulation was the best one.

The transdermal formulation can be an inventive and promising method of delivering Tramadol HCl for the treatment of mild to severe pain, both acute and chronic. This is the conclusion of the current investigation.

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