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DEVELOPMENT AND *IN-VITRO* EVALUATION OF TRAMADOL HYDROCHLORIDE TRANSDERMAL FILMS

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ABSTRACT

The present work was designed to develop suitable transdermal matrix patches of tramadol hydrochloride, a non-steroidal anti-inflammatory drug, using hydroxy propyl methyl cellulose (HPMC), Ethyl cellulose (EC) with glycerine as a plasticizer. The TDDS was prepared by film casting technique. Drug - excipients interaction study was further carried out using Fourier transform infrared (FTIR) spectroscopic technique. Physical evaluation was performed. *In vitro* diffusion studies were performed in a Franz's diffusion cell. The F5 batch showed highest drug release within 12 h.

INTRODUCTION

Transdermal drug delivery systems (TDDS) (patches) are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin also defined as medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the blood stream [1]. Actually, transdermal drug delivery is a transport process of drugs through a multi-laminar structure, from the patch to stratum corneum then to the viable epidermis, then dermis and hypodermis, and finally penetrating into the blood. The skin as a site of drug delivery has a number of significant advantages over many other routes of drug effects by minimizing plasma concentrations compared to oral therapy; provide a sustained release of drug at the site of application; rapid termination of therapy by removal of the device or formulation; the reduction of fluctuations in plasma levels of drugs and avoids pain associated with injections [2]. The transdermal delivery can also eliminate pulsed entry into the systemic circulation, which might often cause undesirable side effects. Transdermal therapeutic systems may produce

sustained, constant and controlled levels of drug in the plasma, thereby improving patient compliance [3], since frequent intake of the drug is not necessary. The effective barrier properties of the skin may prevent the entry of drug molecules from the external environment. Molecules may activate allergic responses and the drug may be metabolized by mircoflora on the surface of skin or by enzymes in the skin. An ideal penetration enhancer reversibly reduces the barrier resistance of the stratum corneum without damaging the skin. The safest and most widely used penetration enhancer is water administration, including the ability to avoid problems of gastric irritation, pH, and emptying rate effects; avoid hepatic first pass metabolism [4,5] thereby increasing the bioavailability of drug; reduce the risk of systemic side which increases hydration and diminishes the resistance of the skin. In this study, dimethyl sulfoxide was used as a penetration enhancer. Tramadol hydrochloride (TH) is used in the treatment of osteoarthritis. It has a molecular weight 299.8, melting point is 179°-180°C and an octanol water partition coefficient 1.35 at pH 7, so it is suitable to administer through transdermal route. In this study, we observed the effect of different types of plasticizers on the physical strength as well as on the release of drug from the prepared transdermal patches. Formulated Tramadol HCl transdermal films are to be ensure satisfactory drug release with the help of polymers and thereby avoid first pass metabolism, avoiding side effects and prolong duration of action.

MATERIALS AND METHODS

MATERIALS: Tramadol hydrochloride was a gift sample from Rantus pharma Pvt Ltd. (Hyderabad, India). Eudragit RL-100 and Eudragit RS-100 were obtained from Degussa India Pvt. Ltd. (Mumbai, India). HPMC obtained from Colorcon Asia Pvt. Ltd. (Goa, India). 3MTM ScotchpackTM 9733 backing membrane and 3MTM ScotchpackTM 1022 release liner were obtained from 3M (USA). Cellulose acetate membrane was purchased from Sartorious Biotech GmbH (Germany). All other ingredients used were of pharmaceutical grade.

METHODS

Drug polymer interaction

FTIR study: Infrared spectrum of drug and excipients were determined on Fourier Transform Infrared spectrophotometer (8400 S Shimadzu) using KBr dispersion method.

Solubility: An excess amount of drug was taken and dissolved in a measured volume of Phosphate buffer pH 7.4 in a glass vial to get a saturated solution. The solution was sonicated and kept at room temperature for the attainment of equilibrium. The concentration of Tramadol HCl in the filtrate was determined spectrophotometrically by measuring absorbance at 271 nm after 12 hrs

Calibration curve: The standard solution was prepared by dissolving 10 mg of Tramadol HCl in 10 ml of phosphate buffer pH 7.4 and the volume was made up to 100 ml using phosphate buffer pH 7.4. From this standard solution, a series of dilutions containing 0.1, 0.2, 0.4, 0.6, 0.8, 1,1.2, 1.4, and 1.6, ml were pipetted out and subsequently diluted to10 ml with phosphate buffer pH 7.4 to give 1, 2, 4, 6, 8, 10, 12, 14, 16 μg/ml respectively. The absorbances of these dilutions were measured using UV spectrophotometer at 271nm using phosphate buffer pH 7.4 as blank solution.

Preparation of transdermal patch [6]

The TDDS was prepared by film casting technique using liquid Paraffin as lubricant (Table 1). All the polymers were dissolved in solvent system one by one in a boiling tube. The resulting homogenous solution was set aside for about 6hrs allowing the polymers to swell after ultra-sonication which aids to remove the air bubbles. Then the drug was slowly added to the solution in little quantities by uniform stirring. Finally, plasticizer and penetration enhancer were added and again set aside for about 2hrs after subjecting to ultra-sonication. The resulting solution was poured in a petri dish lubricated with liquid paraffin. The solvent was allowed to evaporate at ambient conditions of room temperature and humidity for 24 hours to obtain medicated

polymer matrix. The patches were stored in desiccators for further evaluation.

Evaluation of transdermal films: development of controlled release transdermal dosage form is a complex process involving extensive research. Transdermal patches have been developed.

Physical Appearance: All the transdermal systems were visually inspected for colour, transparency, clarity,
flexibility and smoothness.

Weight uniformity: Weight variation is studied by individually weighing randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

Thickness uniformity: The thickness of transdermal film is determined by screw gauge at 5 different points of the film. The average of the five observations was calculated.

Drug content uniformity[7] An accurately weighed portion of film (about 100 mg) is dissolved in 100 mL of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution.

Water vapour transmission (WVT) studies: For the determination of WVT weighed one gram of calcium chloride and placed it in previously dried empty vials having equal diameter. The polymer films were pasted over the brim with the help of adhesive like silicon adhesive grease and the adhesive was allowed to set for 5 minutes. Then, the vials were accurately weighed and placed in humidity chamber maintained at 68 % RH. The vials were again weighed at the end of every 1st hr, 2nd hr, 3rd hr up to a period of 24 hrs and an increase in weight was considered as a quantitative measure of moisture transmitted through the patch.

$WVT = W/ ST$

Where W is the increase in weight in 24 h, S is area of film exposed (cm^2), T is exposure time

Folding Endurance: Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value. This is important to check the ability of sample to withstand folding. This also gives an indication
of brittleness.

***In-vitro* drug permeation [8,9]:** The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophillic side in contact with receptor fluid i.e., buffer. The whole assembly is kept on magnetic stirrer and solution in the receiver compartment is constantly and continuously stirred throughout the experiment using magnetic beads. The pH of the dissolution medium ideally should be adjusted to pH 7.4, reflecting physiological skin conditions. For the same reason, the test temperature is typically set at 32°C.

Stability study: Accelerated stability studies The optimized formulation (F5) was subjected to accelerated stability studies as per ICH guidelines by storing the transdermal patches at 40±0.5°C and 75±5% RH for 3 months using programmable environmental test chamber (Remi, India). Physical parameters before and after accelerated stability study of optimized F-5 patches were observed [10].

RESULTS AND DISCUSSION

Preliminary solubility of Tramadol HCl: The solubility of Tramadol HCl was studied in phosphate buffer pH 7.4 at 37 ± 0.5^0C. The result of solubility of Tramadol HCl was found to be 42.98 µg/ml.

Analytical methods for the estimation of Tramadol HCl: For *in vitro* estimation of Tramadol HCl during drug content study and dissolution studies, calibration curve of pure drug was obtained in phosphate buffer pH 7.4. The values of absorbance to corresponding concentration in different buffer for Tramadol HCl obtained. The analytical parameters for UV-Visible spectroscopic method were presented in Table 2.

Table 1: Composition of Formulations

Formulation Code	F1	F2	F3	F4	F5
Tramadol HCl (mg/2X2cm^2)	100	100	100	100	100
HPMC 6 cps	100	200	300	400	500
EC (mg)	100	100	100	100	100
Glycerine (ml)	8	8	8	8	8
Tween 80 (ml)	3	3	3	3	3
Acetone (ml)	7	7	7	7	7
Water (ml)	5	5	5	5	5

Table 2: Analytical parameters of Tramadol HCl for the development of UV method

Parameters	Values for phosphate buffer pH 7.4
λmax (nm)	271
Beer's law limit (µg/ml)	0-12
Regression equation	Y = 0.0771X+0.0065
Slope	0.0771
Intercept	0.0065
Correlation coefficient (R)	0.999

Table 3: Physical appearance of films

Formulation Codes	Physical appearance
F1	Uniform, brittle
F2	Smooth, uniform, flexible
F3	Smooth, uniform, tough
F4	Transparent, flexible
F5	Smooth, uniform, soft

Table 4: Data obtained from physico-chemical evaluation

FC	Weight uniformity (mg)	Thickness uniformity (mm)	Drug content (%)	WVT (gcm/cm^2.24h)	Folding Endurance
F1	100±1.91	0.2±0.0041	96.85±3.5	5.99±0.038	316±4.15
F2	105±2.39	0.17±0.0032	97.5±4.9	5.93±0.023	309±3.89
F3	111.5±2.15	0.22±0.0023	98.65±2.5	5.57±0.049	297±5.10
F4	116.8±1.85	0.1±0.0042	98.79±1.7	5.19±0.035	293±5.15
F5	117.2±1.20	0.31±0.0035	98.65±2.6	4.90±0.05	290±4.72

N.B. All the values are represented as Mean ± SD (n=3)

Table 5: Cumulative % drug release of all the formulations

Time (h)	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	9.15	9.23	5.63	3.45	11.52
2	36.45	21.45	13.70	7.23	27.8
4	40.93	32.32	27.82	15.57	40.1
6	50.85	45.8	38.5	43.24	45.26
8	60.87	55.10	49.26	50.10	55.93
10	70.37	68.57	59.50	55.23	63.89
12	83.29	78.52	69.71	61.7	94.19

The calibration curve of pure drug was dissolved in phosphate buffer pH 7.4 for *in vitro* estimation of Tramadol HCl during drug content study and dissolution studies. The estimated λmax for standard concentration of Tramadol HCl in phosphate buffer pH 7.4 was found to be 271. The stock solutions were prepared with proper dilutions and absorbance of different aliquots was taken with suitable dilutions. The processes were carried out thrice to get good precession in results. The regression values (R^2) of calibration curve for phosphate buffer pH 7.4 was found 0.999 that indicates the linearity of the curve. The equations for straight line obtained from calibration curves were used for *in vitro* dissolution studies and drug content uniformity.

Formulation of transdermal films: The matrix-type transdermal films of Tramadol HCl were prepared by solvent evaporation technique using combination of HPMC 6 cps, Ethyl Cellulose (EC) in different ratios.

Fourier Transform Infrared Spectroscopy (FTIR) Study: FTIR is used to know characteristics peaks indicating compatibility between drug and excipients. In order to know compatibilities between drug and excipients various FTIR spectra are observed. drug-excipient mixture reveals that here is no incompatibility was observed between Tramadol HCl.

Physical appearance: The physical appearances of all the formulations were observed visually and the results are tabulated in Table 3 and Table 4.

***In-vitro* drug permeation:** The drug permeability depends on the polymer concentration and the crosslink density of patches. Release of the drug from transdermal films is controlled by the chemical properties of the drug and delivery form, as well as physicochemical properties of the dialysis membrane. The process of drug release in most controlled release devices is governed by diffusion and the polymer matrix has strong influence on the diffusivity as the motion of a small molecule is restricted by the three-dimensional network of polymer chains. The F5 formulation showed maximum permeation at the end of 12 hrs. Cumulative % drug release of all the formulations is shown in Table 5.

Stability studies: The different physiochemical parameters those were measured at different time intervals during stressed conditions for the formulations of Tramadol HCl patches. It was observed that there was no significant change in drug content, *in vitro* drug permeation etc.

CONCLUSSION

The transdermal films of Tramadol HCl were prepared and subjected to physicochemical evaluation and *in vitro* study. The physicochemical properties shown by all formulations were satisfactory. The prepared patches were permeable to water vapour depending upon the thickness and crosslink density. F5 formulation was the best formulation as per the dissolution profile. In the present work, it can be concluded that the transdermal formulation can be an innovative and promising approach for the delivery of Tramadol HCl for the treatment of mild-severe pain, both acute and chronic.

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