RESEARCH ARTICLE

Development and characterization of transdermal therapeutics system of tramadol hydrochloride

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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), Eudragit RL-100 and Eudragit RS-100 with triethyl citrate as a plasticizer and dimethyl sulfoxide (DMSO) as a penetration enhancer. Different batches developed using Eudragit RL-100 : HPMC and Eudragit RS-100 : HPMC in ratio of 2 : 8, 4 : 6, 6 : 4, and 8 : 2. Drug - excipients interaction study was further carried out using Fourier transform infrared (FTIR) spectroscopic technique. Physical evaluation was performed such as moisture content, moisture uptake, tensile strength, flatness, and folding endurance. *In vitro* diffusion studies were performed using cellulose acetate membrane (pore size 0.45 μ) in a Franz's diffusion cell. The concentration of diffused drug was measured using UV-visible spectrophotometer (Jasco V-530) at λ_{max} 275 nm. The batch containing Eudragit RL-100 : HPMC (8 : 2) showed 79.65% release within 12 h and batch containing Eudragit RL-100 : HPMC (2 : 8) showed only 58.30% release in 12 h. This is because that the Eudragit produce crystallization free patch.

Key words: *Franz's diffusion cell, tramadol hydrochloride, transdermal patch*

INTRODUCTION

Transdermal drug delivery system attracts many scientists around the world. There has been an increased interest in the drug administration via the skin for both local therapeutic effects on diseased skin (topical delivery) as well as for systemic delivery (transdermal delivery) of drugs. The skin as a route for systemic drug administration has become very attractive since the introduction of transdermal therapeutic systems in the form of patches. There are a number of routes by which a molecule can cross the stratum corneum, these are, intercellular, transcellular, and appendageal but the intercellular route is considered to be the major pathway for permeation of most drugs across the stratum corneum.[1]

The skin as a site of drug delivery has a number of significant advantages over many other routes of drug administration, including the ability to avoid problems of gastric irritation, pH, and emptying rate effects; avoid hepatic first pass metabolism thereby increasing the bioavailability of drug; reduce the risk of systemic side 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;[2] the reduction of fluctuations in plasma levels of drugs[3] and avoids pain associated with injections. 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, since frequent intake of the drug is not necessary.

Transdermal therapy also has some disadvantages, like, higher molecular weight candidates (>500 Dalton) fail to penetrate the stratum corneum without modifying the nature of stratum corneum, drugs with very low or high partition coefficient fail to reach systemic circulation and high melting drugs, due to their low solubility both in water and fat.[4] 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.[5-7] 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

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which increases hydration and diminishes the resistance of the skin.[8,9] 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[10] 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.

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). 3M™ Scotchpack™ 9733 backing membrane and 3M™ Scotchpack™ 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

The pure drug and a mixture of it with the polymers, HPMC and Eudragit were mixed separately with IR grade KBr in the ratio of 100:1 and corresponding pellets were prepared by applying 5.5 metric ton of pressure in a hydraulic press. The pellets were scanned over a wave number range of 4000-400/cm in Jasco FTIR 4100 instrument.[11] The spectra obtained for TH and physical mixtures of TH with polymers were compared.

Preparation of transdermal film

The transdermal patches were prepared by film casting techniques on mercury substrate. The transdermal films were composed of Eudragit RS 100 : HPMC and Eudragit RL 100 : HPMC (in 2:8, 4:6, 6:4 and 8:2 ratios) with 15% wt/wt of TH, 5% wt/wt of penetration enhancer, dimethyl sulfoxide (DMSO) and 5% wt/wt of plasticizer, either polyethylene glycol-400 (PEG-400) or triethyl citrate. Composition of all batches was described in Table 1. Hydrophilic ingredients were dissolved in water and hydrophobic ingredients were dissolve in acetone, then both the solution are mixed and stirred on magnetic stirrer to accomplish homogeneous mixture. The resulting solution was poured in a Petri dish containing mercury. The solvent was allowed to evaporate at 40°C for 24 h to obtain medicated transdermal film. A backing membrane (3M™ Scotchpack™ 9733) and a release liner (3M™ Scotchpack™ 1022) on either side of the film were applied to complete the transdermal therapeutic system for TH. The TH patches were stored in dessicator until further use.

Evaluation of TH patches

The physical parameters such as thickness, weight variation, folding endurance, tensile strength, moisture content, moisture uptake, and drug content were determined.

Thickness

Patch thickness was measured using digital micrometer screw gauge (Mitutoyo, Japan) at three different places and the mean value was calculated.

Folding endurance

Folding endurance of patches was determined by repeatedly folding a small strip of film (2 cm x 2 cm) at the same place till it broke. The number of time the film could be folded at the same place without breaking was the folding endurance value.

Table 1: Composition of tramadol hydrochloride transdermal films[a]

Code	% wt/wt TH	Ratio of ERS:HPMC	Ratio of ERL:HPMC	% wt/wt Plasticizers	
				PEG-400	Triethyl citrate
F1	15	2:8	-	5	-
F2	15	4:6	-	5	-
F3	15	6:8	-	5	-
F4	15	8:2	-	5	-
F5	15	-	2:8	5	-
F6	15	-	4:6	5	-
F7	15	-	6:8	5	-
F8	15	-	8:2	5	-
F9	15	2:8	-	-	5
F10	15	4:6	-	-	5
F11	15	6:8	-	-	5
F12	15	8:2	-	-	5
F13	15	-	2:8	-	5
F14	15	-	4:6	-	5
F15	15	-	6:8	-	5
F16	15	-	8:2	-	5

[a]All formulation contain 5% wt/wt dimethyl sulfoxide as a penetration enhancer, TH: tramadol hydrochloride, HPMC: hydroxy propyl methyl cellulose, ERL: eudragit RL100, ERS: eudragit RS100, PEG-400: polyethylene glycol-400

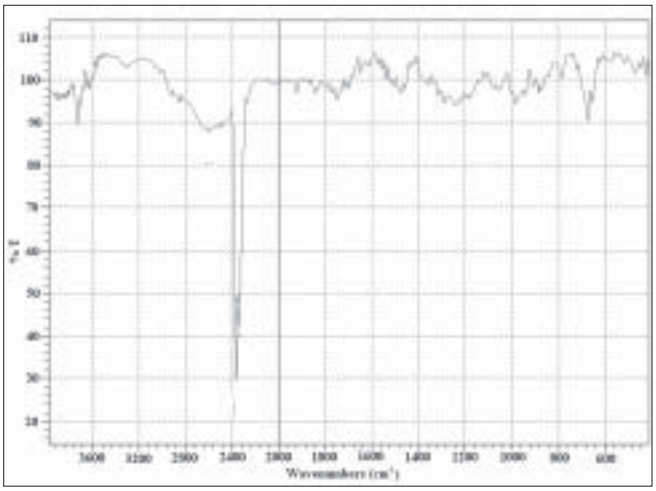

Figure 1: IR spectra of pure drug, tramadol hydrochloride

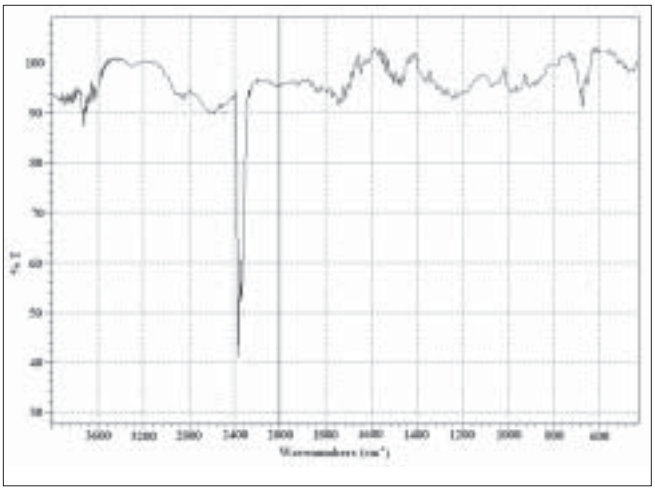

Figure 2: IR spectra of drug, HPMC and Eudragit RS 100

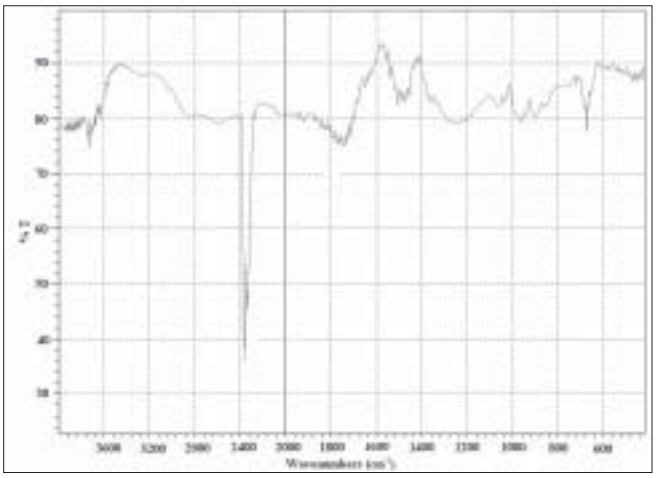

Figure 3: IR spectra of drug, HPMC and Eudragit RL 100

Tensile strength

The tensile strength was determined by using a modified pulley system. Weight was gradually increased so as to increase the pulling force till the patch broke. The force required to break the film was consider as a tensile strength and it was calculated as kg/cm^2.

Weight variation

Weight variation was studied by individually weighing 10 randomly selected patches. Such determination was performed for each formulation.

Drug content

A 5 cm^2 film was cut into small pieces, put into a 100 ml buffer (pH 7.4), and shaken continuously for 24 h. Then the whole solution was ultrasonicated for 15 min. After filtration, the drug was estimated spectrometrically at wavelength of 272 nm and the drug content was determined.

Flatness

Three longitudinal strips were cut out from each film: one from the center, one from the left side, and one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.[12]

Percentage of moisture content

The films were weighed individually and kept in a desiccator containing activated silica at room temperature for 24 hours. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.[13]

Percentage of moisture uptake

A weighed film kept in a desiccator at room temperature for 24 h was taken out and exposed to 84% relative humidity (a saturated solution of aluminum chloride) in a desiccator until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.[14]

In vitro diffusion studies

In vitro diffusion studies were performed by using a Franz diffusion cell with a receptor compartment capacity of 20 ml. The cellulose acetate membrane (pore size 0.45 μ) was mounted between the donor and receptor compartment of the diffusion cell. The TH film was placed on the cellulose acetate membrane and covered with aluminum foil. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a hot plate magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads and the temperature was maintained at 32 ± 0.5°C. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.

Table 2: Evaluation of transdermal patches of tramadol hydrochloride[b]

Code	Thickness (mm)	Drug content (mg/cm²)	Folding endurance	Tensile strength (kg /cm²)	% Moisture content	% Moisture uptake	Flatness (%)	% Drug diffuse in 12 h
F1	0.14 ± 0.03	0.32 ± 0.01	98 ± 2.03	0.327 ± 0.10	6.93 ± 0.29	4.03 ± 0.98	100.01 ± 0.04	64.55 ± 0.03
F2	0.17 ± 0.01	0.32 ± 0.02	103 ± 1.51	0.223 ± 0.27	5.5 ± 0.71	5.98 ± 1.94	99.82 ± 0.02	68.92 ± 0.05
F3	0.146 ± 0.08	0.31 ± 0.01	88 ± 2.43	0.428 ± 0.14	5.22 ± 1.34	6.96 ± 0.32	100.12 ± 0.03	71.40 ± 0.02
F4	0.182 ± 0.07	0.34 ± 0.01	75 ± 2.83	0.342 ± 0.25	4.87 ± 1.46	6.34 ± 2.19	99.23 ± 0.05	73.32 ± 0.05
F5	0.155 ± 0.02	0.33 ± 0.02	99 ± 1.11	0.552 ± 0.31	5.29 ± 0.86	6.24 ± 1.43	100.02 ± 0.01	61.12 ± 0.09
F6	0.158 ± 0.05	0.32 ± 0.01	92 ± 2.53	0.643 ± 0.12	4.77 ± 1.02	5.85 ± 0.94	100.01 ± 0.03	63.74 ± 0.01
F7	0.149 ± 0.01	0.34 ± 0.03	77 ± 2.95	0.513 ± 0.35	3.67 ± 0.51	4.23 ± 1.37	99.92 ± 0.03	68.07 ± 0.03
F8	0.192 ± 0.01	0.32 ± 0.02	84 ± 2.12	0.294 ± 0.30	3.23 ± 0.91	4.94 ± .2.15	99.13 ± 0.02	72.93 ± 0.07
F9	0.148 ± 0.81	0.32 ± 0.01	114 ± 5.03	0.538 ± 0.45	7.21 ± 0.26	7.84 ± 2.52	100.34 ± 0.01	58.30 ± 0.07
F10	0.178 ± 0.04	0.33 ± 0.02	147 ± 2.71	0.739 ± 0.28	5.28 ± 0.79	6.23 ± 1.86	100.03 ± 0.05	60.10 ± 0.04
F11	0.159 ± 0.02	0.32 ± 0.02	166 ± 3.14	0.693 ± 0.17	4.99 ± 1.96	5.39 ± 1.94	100.01 ± 0.04	66.43 ± 0.05
F12	0.181 ± 0.04	0.32 ± 0.05	135 ± 1.21	0.846 ± 0.36	3.38 ± 2.53	6.34 ± 1.54	100.23 ± 0.01	70.09 ± 0.04
F13	0.177 ± 0.01	0.33 ± 0.03	138 ± 3.93	0.736 ± 0.19	6.29 ± 2.11	5.58 ± 1.03	100.42 ± 0.01	62.58 ± 0.01
F14	0.183 ± 0.03	0.31 ± 0.03	188 ± 2.41	0.981 ± 0.35	5.58 ± 1.64	6.18 ± 0.95	100.41 ± 0.01	66.25 ± 0.09
F15	0.175 ± 0.02	0.32 ± 0.04	154 ± 2.31	0.922 ± 0.29	5.02 ± 1.31	7.12 ± 2.17	100.03 ± 0.02	70.00 ± 0.05
F16	0.17 ± 0.09	0.32 ± 0.03	142 ± 1.46	0.864 ± 0.31	4.26 ± 0.94	6.04 ± 1.41	100.83 ± 0.03	79.65 ± 0.02

[b]All values are expressed as mean ± SD (n = 3)

RESULTS

The infrared (IR) spectra of pure drug and with polymers showed in Figures 1-3. The results of the characterization of the patches are shown in Table 2. The weights ranged between 128.45 mg and 131.28 mg observed for all prepared transdermal films. The folding endurance and tensile strength were lies in between 77 and 188 and 0.223 and 0.9817; the difference depended on the composition of polymer used and type of plasticizer incorporated in film. The result revealed that the flatness of transdermal film is very close to 100%. The drug diffusion profiles were showed in Figures 4-7. The diffusion studies reveled that as the concentration of Eudragits increases the rate of drug diffusion also increases.

DISCUSSION

From the IR spectrum of drug with polymer showed negligible or no interaction of drug with polymers. The thicknesses of all the batches are nearly similar which indicates physical uniformity of the prepared patches. Folding endurance test results indicated that the patches would not break and would maintain their integrity with general skin folding when used. The folding endurance of the patches contains are higher as compared to the PEG-400 as a plasticizer. Tensile strength test results showed that the patch contains triethyl citrate are more strengthen than the patch contains PEG-400. Results of folding endurance and tensile strength indicate that the triethyl citrate is more beneficial than the PEG-400 as a plasticizer. The flatness study showed that all the formulations had the same strip length before and after their cuts, indicating nearly 100% flatness. It indicates that all the patches had a smooth and flat surface. Moisture content and moisture uptake studies indicated that the increase in the concentration of hydrophilic polymer was directly proportional to the increase in moisture content and moisture uptake of the patches. The moisture content of the prepared transdermal film was low, which could help the formulations remain stable and reduce brittleness during storage. The moisture uptake of the transdermal formulations was also low, which could protect the formulations from microbial contamination and also reduce bulkiness of films.

The results of *in vitro* diffusion study shows that the diffusion of drug increases as the concentration of the Eudragits increase. This is because that the Eudragits produce crystallization free polymeric films leading to higher drug release from the film. The patches containing the higher amount of Eudragits shows more release of drug than the other formulations, the drug release profile observed in the Figures 4-7. The formulation F16 shows 79.65 % release in 12 h, that is the maximum concentration of drug release as compared to other formulations and the formulation F9 shows 58.30% release in 12 h, this is may be because of the least amount of Eudragit present in the formulation. From the drug release profile, it is observed that the significant improvement of the release

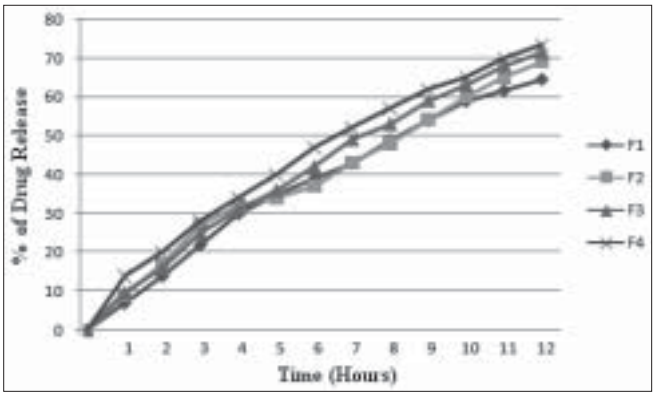

Figure 4: Drug diffusion profile of formulations F1, F2, F3, and F4

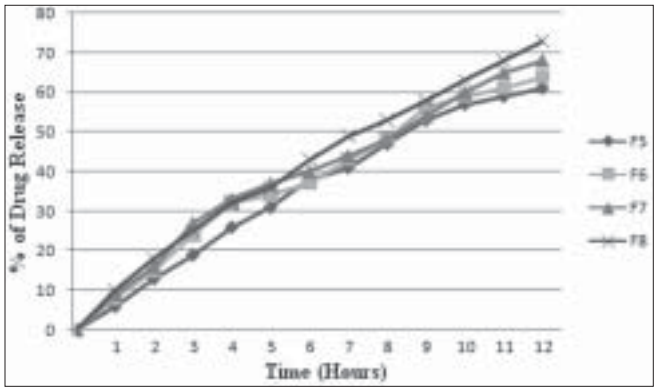

Figure 5: Drug diffusion profile of formulations F5, F6, F7, and F8

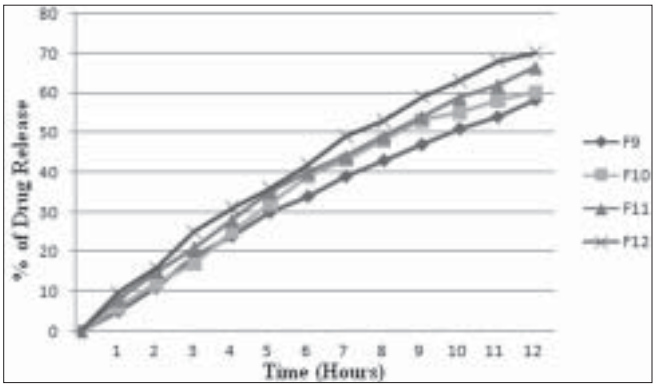

Figure 6: Drug diffusion profile of formulations F9, F10, F11, and F12

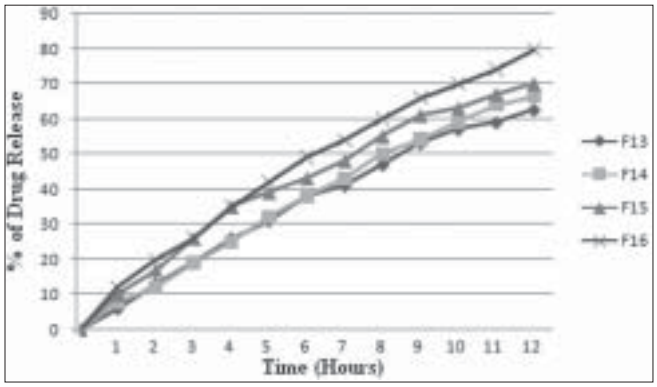

Figure 7: Drug diffusion profile of formulations F13, F14, F15, and F16

observed in formulations containing triethyl citrate.

Formulation F14 containing triethyl citrate had highest tensile strength as well as folding endurance. The result obtained from the present work revealed that the triethyl citrate was better plasticizer as compared to the PEG-400. From the drug release profile it is concluded that the concentration of the Eudragit increases in the formulation with increase in the release of drug from the patch.

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