

DESIGN AND STANDARDIZATION OF TRANSDERMAL PATCHES USING OPIATE ANALGESIC DRUG

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Article Received on 28/05/2020

Article Revised on 18/06/2020

Article Accepted on 08/07/2020

ABSTRACT

The aim of the current study was to design a transdermal patch of opiate analgesic drug. It is a painkiller belonging to the class of opioids that act on the central nervous system. It can be defined as the passage of a medicament from the outside of the skin through its various layers into the bloodstream. Transdermal patches of Tramadol HCl were designed by solvent mercury casting method using different polymers i.e. HPMC, PVA, mixture of HPMC & PVA. The prepared formulations were standardized for drug content uniformity, *in vitro* diffusion study, thickness, tensile strength, moisture content, folding endurances etc. Amongst all formulations, formulation F3 had more desirable characteristic & shows longer duration of time. The Transdermal patch formulated from F1, F2 and F3 showed satisfactory physicochemical properties. The ratios of hydrophilic polymers F1, F2 and F3 formulations good moisture content property, good tensile strength, folding endurances and *in-vitro* drug release. So, it can be concluded that transdermal patches of F1, F2 and F3 could be a good carrier in transdermal delivery of Tramadol HCl. FTIR studies showed there were no incompatibilities between drug and other excipients.

KEYWORDS: Opiate analgesic, Transdermal, Tramadol, Standardization, excipients etc.

INTRODUCTION

New drug delivery research continues to identify the new therapies for the prevention and treatment of current and new diseases. It shows major role is played by drug delivery system by providing standardized products for existing drugs in terms of either enhanced or improved presentation of drug to the systemic circulation.^[1] 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.^[2]

Tramadol is a synthetic opioid analgesic and is chemically trans-2-(dimethylaminomethyl)-1-(m-methoxyphenyl)cyclohexanol hydrochloride. It is a centrally active analgesic, which is used orally and parenterally for their relief of moderate to moderately severe acute or chronic pain, including postoperative, gynecologic and obstetric pain, as well as pain of various other organs, including cancer.^[3] Tramadol binds weakly to μ - and δ - opioid receptors and inhibits the reuptake of serotonin and nor epinephrine. A major metabolite of tramadol, O-desmethyl tramadol, has an approximately 200fold higher affinity for opioid receptors than the parent compound. Tramadol is indicated in the treatment of moderate to severe pain. It is suitable for those who are prone to constipation or respiratory depression.^[4]

Tramadol is used to treat postoperative, dental, cancer and acute musculoskeletal pain and as an adjuvant to nonsteroidal anti-inflammatory drug (NSAID) therapy in patients with osteoarthritis. Also, it is recommended in postsurgical pain when patient is hospitalized. In such conditions of pain, orally disintegrating dosage form will be preferred by patient over conventional solid dosage

forms.^[5] Development of controlled release transdermal dosage form is a complex process involving extensive efforts. This review article describes the methods of preparation of different types of transdermal patches viz., matrix patches, reservoir type, membrane matrix hybrid patches, drug-inadhesive patches and micro reservoir patches. In addition, the various methods of evaluation of transdermal dosage form have also been reviewed.^[6]

MATERIAL AND METHODS

Materials: Tramadol hydrochloride was obtained as a gift sample from S.K. Parenterals Pvt Ltd, Tanuku, Hydroxy Propyl Methyl Cellulose obtained as a sample from Sisco research laboratories, Mumbai. Oleic acid obtained from SD Fine chemical Ltd, Mumbai. Carbinol obtained from Finar chemical Pvt. Ltd, Ahmadabad. Poly vinyl alcohol LR obtained from SD Fine chemical Ltd, Mumbai. Dimethyl Sulfoxide obtained from SD Fine chemical Ltd, Mumbai. Methanol obtained from SD Fine chemical Ltd, Mumbai. Calcium chloride obtained from Karnataka fine chemicals, Bangalore. Sodium chloride obtained from Fine chem. Industries, Chennai. Potassium chloride obtained from SD Fine chemical Ltd, Mumbai. All the chemicals used were of analytical grade.

Preparation of Transdermal patches

Transdermal patches containing Tramadol HCl were prepared by solvent casting method using varying ratios of different grades of polymers and plasticizers in different concentrations as shown in the table 1.

Procedure for patch preparation

The Matrix type Transdermal patches of Tramadol Hydrochloride were prepared by the Solvent casting method. Briefly, Solution I was prepared by dissolving polymers F1, F2 and F3 in different ratios in water and was allowed to stir for 2 hours and kept for overnight swelling. Solution II was prepared by dissolving the

accurately weighed quantity of Tramadol Hydrochloride in methanol. Then the drug solution added slowly to the polymer solution and stirred on a magnetic stirrer to obtain uniform solution. Propylene glycol was used as a plasticizer. Then the solution was poured on the Petri dish having the area of 18.8cm² and dried at room temperature. Then the patches were cut into 2X1cm² patches. Drug incorporated for each patch was 100 mg. The dried patches were wrapped in butter paper and stored in a closed container away from light and in cool place.^[7]

Formulation design

Tab 1: Formula for Tramadol HCl Transdermal patch.

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

RESULTS AND DISCUSSION

Compatibility studies by FTIR: The drug and excipient compatibility studies were carried out by FTIR study.^[8] The study showed peaks for the corresponding functional groups in Tramadol HCl. When the study was carried out with the combination of Tramadol HCl and polymers, there was no major change in the peaks. Hence there was no interaction with the polymers. The results were shown below.

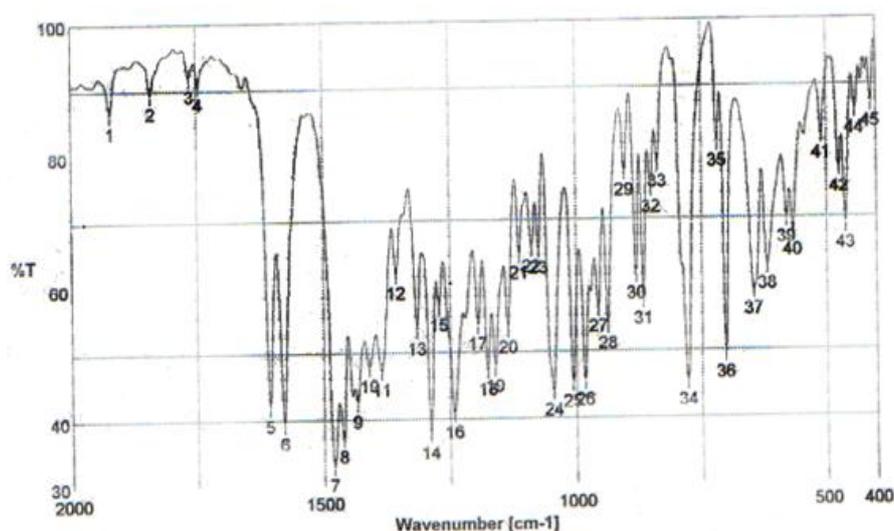


Fig. 1: IR Spectrum of Tramadol HCl.

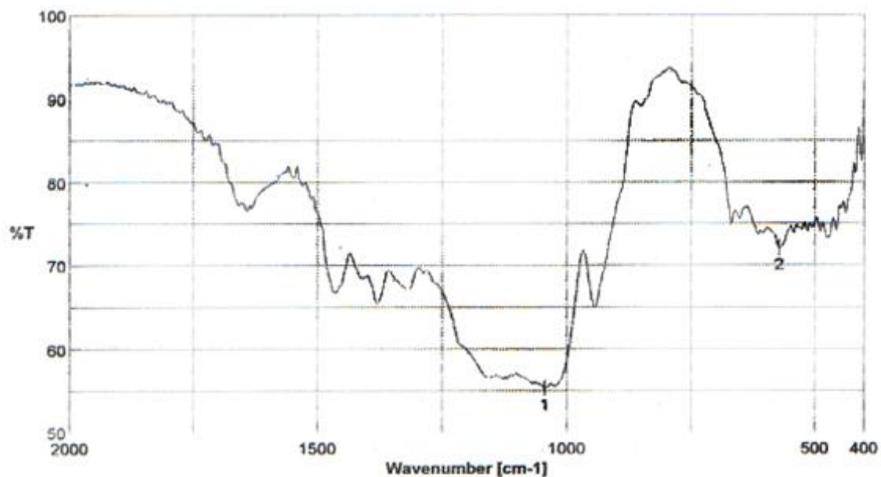


Fig. 2: IR spectrum of HPMC.

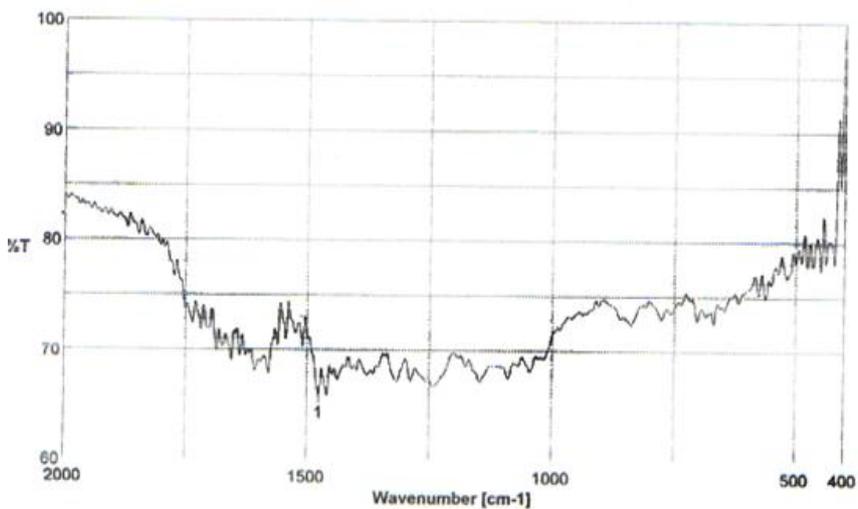


Fig. 3: IR Spectrum of PVA.

SHIMADZU

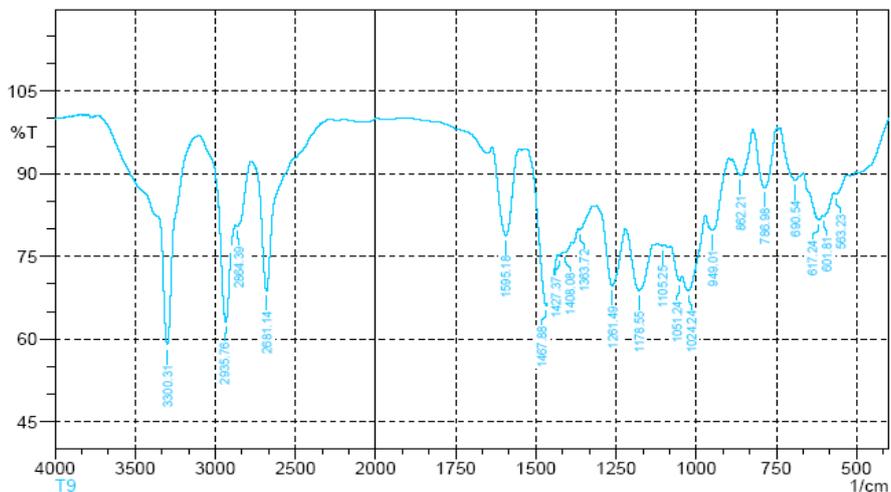


Fig. 4: IR Spectrum of Physical Mixture of Tramadol Hcl And HPMC.

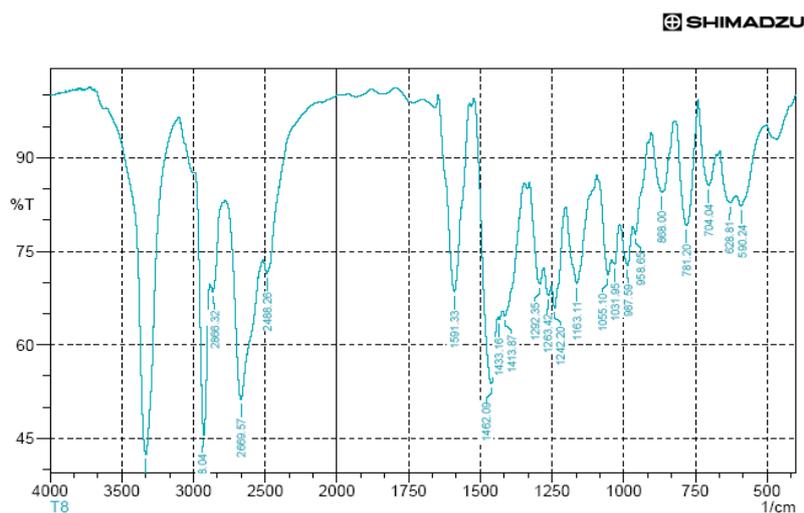


Fig. 5: IR Spectrum of physical mixture of Tramadol HCl and PVA.

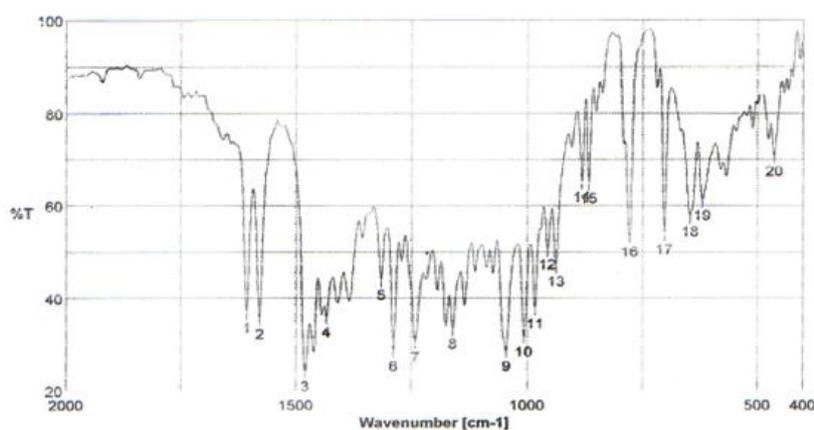


Fig. 6: IR Spectrum of physical mixture of Tramadol HCl, HPMC and PVA.

Spectra of optimised formulation: The FTIR studies of pure drug and the optimised formulation were performed as shown in figure 1. The results were found to be there are no interaction with the pure drug and other excipients and shown compatibility with each other.

EVALUATION STUDIES

Physical appearance

All the Transdermal patches were visually inspected for colour, clarity, flexibility. It is white amorphous powder and odourless.

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. 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.^{[9],[10]}

Thickness of the patch

The thickness of the patch was assessed by using thickness gauge (screw gauge) 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. 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.^[11]

Moisture content

The patches ($n=3$) were weighed individually and kept in a desiccator containing calcium chloride at 37°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. Moisture content in F1, F2 and F3 were found to be $21 \pm 0.957\%$, $9 \pm 0.957\%$, $4 \pm 0.645\%$ respectively.^[12]

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. 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.^[13]

Drug content determination

The patches at 1Cm² 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. Drug content in F1, F2 and F3 were found to be 97.5%, 98%, 97% respectively.^[14]

In-vitro drug release studies

The drug release profiles of Transdermal patches of Tramadol HCl and their release data was shown in table no 3 & 4. The drug release was governed by the amount of matrix forming polymer. An increase in polymer concentration causes an increase in the viscosity of the gel as well as for mation of a gel layer with a longer diffusion path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore a reduction in the drug release rate however, the difference is insignificant among the formulations. The maximum cumulative % drug release for formulation F1 was found to be 81.22%, for F2 was 67.89% and for F3 was 57.12% at 12 hrs. Data of the in vitro diffusion release was fit into different equations and kinetic models to explain the release kinetics of Tramadol HCl from transdermal patches. The kinetic models used were zeroorder equation, first-order equation, and Korsmeyer Peppas models.

Tab 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	

Tab 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	

Tab. 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	

Tab. 5: Moisture uptake of Tramadol HCl Transdermal patches for F1, F2 and F3.

S.No.	Forml ⁿ	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	23.3	41.6	73.3
		2	255	255	265	295	20	35	60			
		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			

Tab. 6: Drug content of Tramadol HCl 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

Tab 7: Data for the Calibration curve of tramadol hydrochloride 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

Tab 8: In-vitro drug release profile of Tramadol HCl transdermal patch F1, F2 and F3.

Formulation	Time (hrs)	√T	Log T	Cumulative % of drug released	Log cumulative % of drug released	Cumulative % of drug remained	Log cumulative % of drug remained
F1	12.00	3.464	1.079	81.225	1.909	18.775	1.273
F2	12.00	3.464	1.079	67.89	1.831	32.11	1.506
F3	12.00	3.464	1.079	57.123	1.756	42.877	1.632

Tab 9: 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

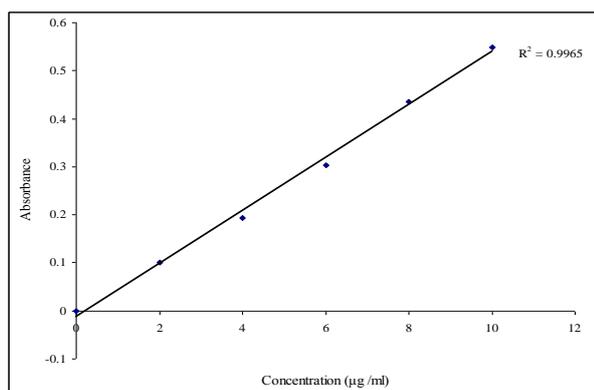


Fig. 7: Standard calibration curve of Tramadol HCl in phosphate buffer pH 7.4 at 276nm.

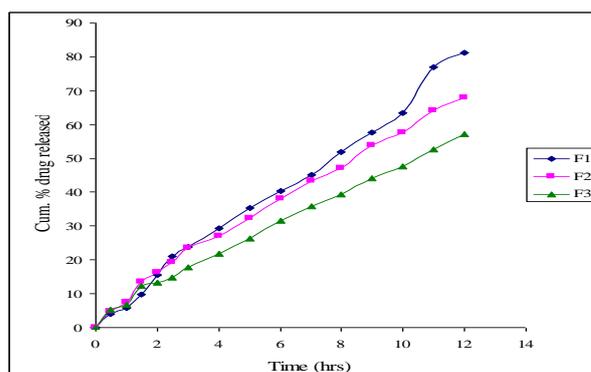


Fig. 8: In-vitro release profile of Tramadol HCl transdermal patches.

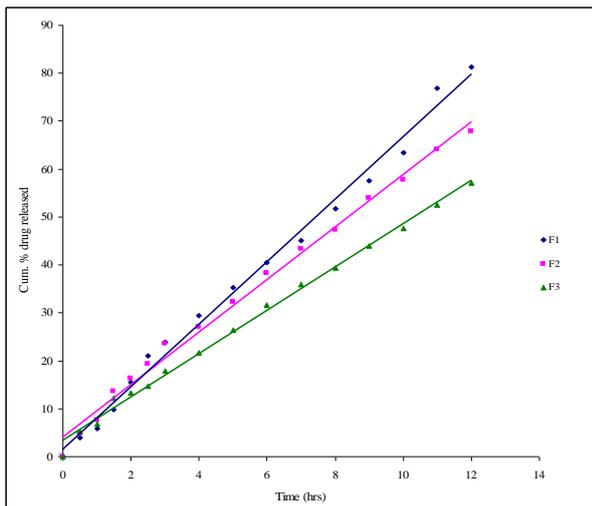


Fig. 9: Zero order release kinetic profile of Tramadol HCl transdermal patches.

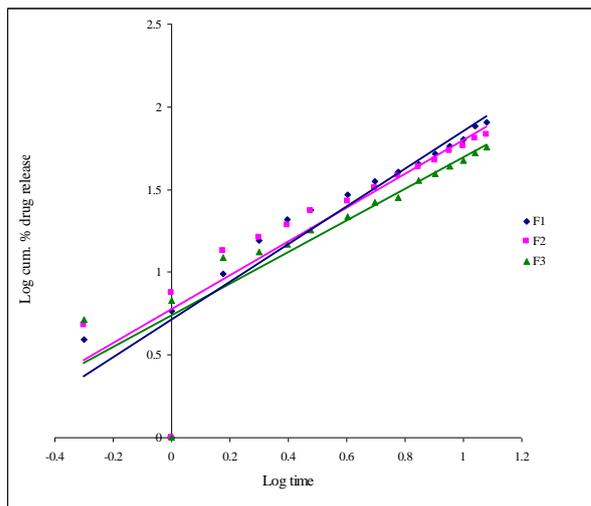


Fig. 12: Peppas release kinetic profile of Tramadol HCl transdermal patches.

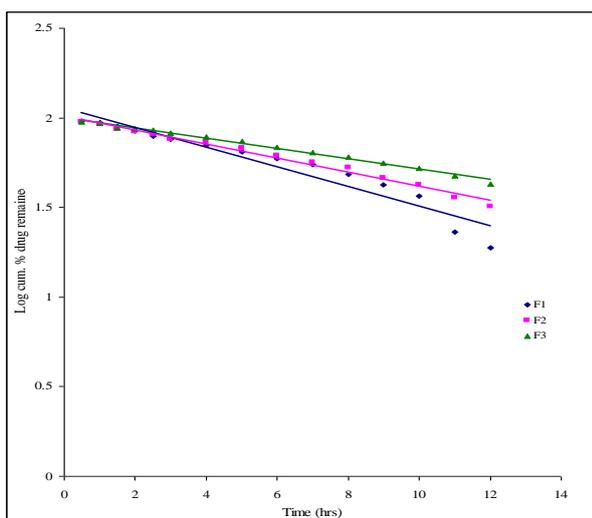


Fig. 10: First order release kinetic profile of Tramadol HCl transdermal patches.

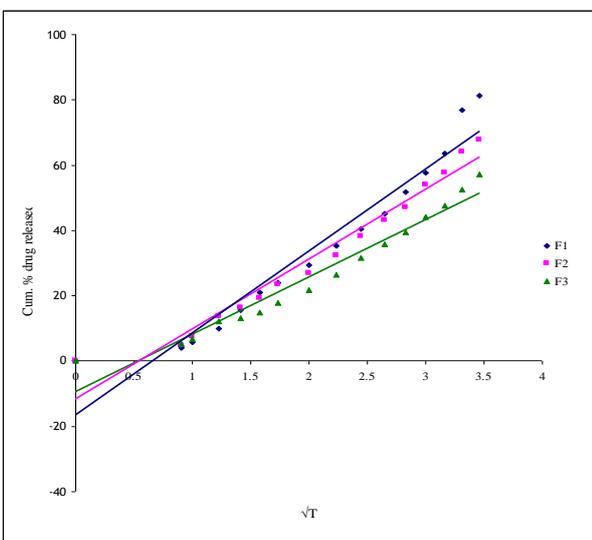


Fig. 11: Higuchi release kinetic profile of Tramadol HCl transdermal patches.

CONCLUSION

The current study was observed that optimum correlation was observed between drug release and drug permeation study in-vitro. It can be concluded that patches of F1, F2 and F3 could be a good carrier in transdermal delivery of Tramadol HCl. It may also concluded that adhesion of transdermal drug delivery device to skin membrane leads to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systemically delivered drug. All the formulated Transdermal patches were visually observed for color, clarity, flexibility, checked for physical parameters such as Physical appearance, Weight variation, Thickness, Drug content, Moisture uptake, Moisture content and all the results were found to be within the pharmacoepial limits.

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.

ACKNOWLEDGMENT

I would like thank my college management for providing excellent facilities to carry out this research work. I am also grateful to my colleagues and non-teaching staff for their support during my work.

REFERENCES

1. Rajesh A. Keraliya, Chirag Patel, Pranav Patel, Vipul Keraliya, Tejal G. Soni, Rajnikant C. Patel, and M. M. Patel, Osmotic Drug Delivery System as a Part of Modified Release Dosage Form, *ISRN Pharmaceutics*; 2012; 2012: 1-9.
2. Anil J Shinde, Kevin C Garala, Harinath N More, Development and characterization of transdermal therapeutics system of tramadol hydrochloride, *Asian Journal of Pharmaceutics*, 2008; 265-269.
3. Upadhyay DK, S.Palaian, P.V.Kishore, R.Paudel, M.Prabhu, P.R.Shankar, P.Mishra, Tramadol, *Journal of Institute of Medicine*, 2006; 28(3): 57-61.
4. Nagarajan G, Shaik Mohammad Abdulla, Raja Amaranth P, Venu Madhav K, Jona Methusala R, Ramana B.V, Formulation and evaluation of tramadol HCl oral fast dissolving films, *World Journal of Pharmaceutical Sciences*, 2015; 3(2): 337-346.
5. Harsha Kathpalia, Bhairavi Sule, Aasavari Gupte, Development and Evaluation of Orally Disintegrating Film of Tramadol Hydrochloride, *Asian Journal of Biomedical and Pharmaceutical Sciences*; 2013; 3(2): 27-32.
6. Beedha. Saraswathi, Dr. T. Satyanarayana, K. Mounika, G. Swathi, K. Sravika, M. Mohan Krishna, Formulation and Characterization of Tramadol HCl Transdermal Patch, *Asian Journal of Pharmacy and Technology*. 2018; 8(1): 23-28.
7. Liao CJ, Chen CF, Chen JH, Chiang SF, Lin YJ, Chang KY, "Fabrication of porous biodegradable polymer scaffolds using a solvent merging/particulate leaching method". *Journal of Biomedical Materials Research*. 2002; 59(4): 676-81.
8. Newa M., Bhandari K.H., Xun Li D. et al., Preparation, characterization and in vivo evaluation of ibuprofen binary solid dispersions with poloxamer 188, *Int. J.Pharm.* 2007; 343: 1-2, 228-237.
9. Sadhana P. Gupta, Jain SK. Effective and controlled Transdermal delivery of Metoprolol tartarate. *Indian J Pharm Sci.*, 2005; 67(3): 346-50.
10. Dinda SC, Vijay Ratna J. Enhancement of the skin permeation of Ibuprofen from ointments and gels by sesame oil, sunflower oil, and oleic acid. *Indian J Pharm Sci.* 2006; 68(3): 313-22.
11. Pankaj Dayal, Narayanasamy Kanikkannan, Amarjit Singh, Mandip Singh. Comparision of the Transdermal absorption of Nimesulide from the commercially available gel formulations. *Drug Dev Ind Pharm*, 2002; 28(3): 297-304.
12. Kusum Devi V, Saisivam S, Maria GR, Deepthi PU. Design and evaluation of matrix diffusion controlled Transdermal patches of Verapamil hydrochloride. *Drug Dev Industrial Pharm.* 2003; 29(5): 495-503.
13. Pavan Shah, Viral Jogani, Pushpa Mishra, Anil Kumar Mishra, Tamishraha Bagchi Ambikanandan Misra. *In vitro* assessment of Acyclovir permeation across cell monolayer in the presence of absorption enhancers. *Drug Dev Ind Pharm.*, 2008; 34: 279-88.
14. Gye Ju Rhee, Jong Soo Woo, Sung-Joo Hwang, Young Wook Lee, Chang Hyun Lee. Topical oleo-hydrogel preparation of Ketoprofen with enhanced skin permeability. *Drug Dev Ind Pharm.* 1999; 25(6): 717-26.