EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 5
381-388
Year: 2020

FORMULATION AND CHARACTERIZATION OF MATRIX TYPE TRANSDERMAL PATCH USING AN ANALGESIC DRUG

Mohit Saini[1]*, Sneha Singh[1], Nita Mondal[2] and Amit Kumar[3]

[1]Aroma College Roorkee, Haridwar (UK)-India.
[2]R.V. Northland Institute of Pharmacy, Dadri G B Nagar (UP)-India.
[3]Smt. Manjira Shikshan and Prashikshan Institute Hitanu Dhanari, Uttarkashi, India.

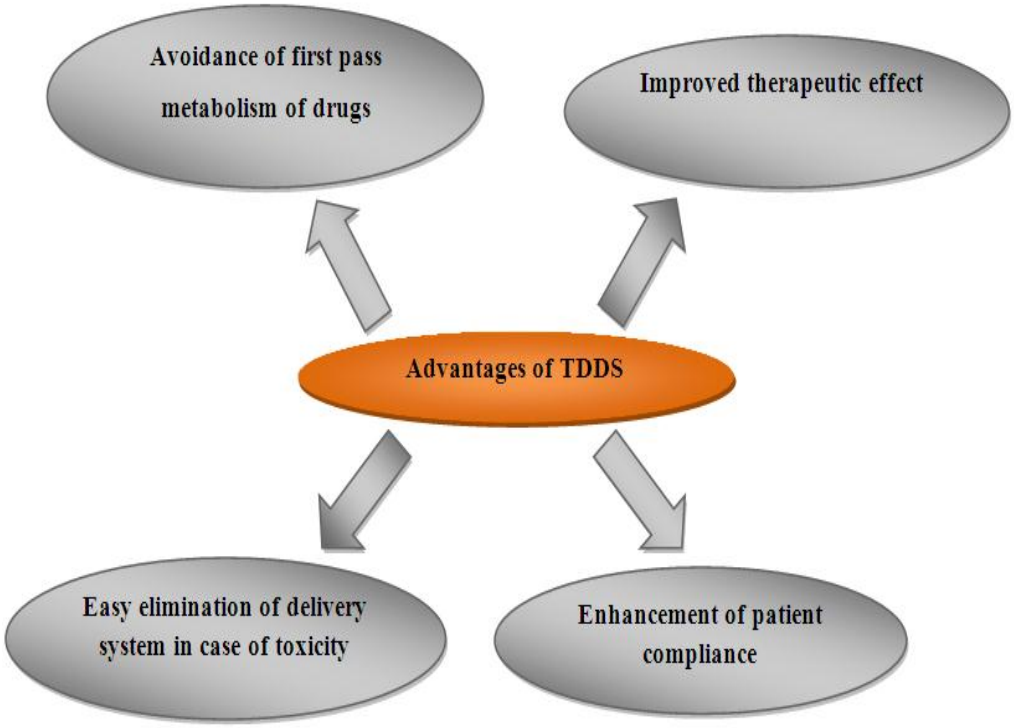
***Corresponding Author: Mohit Saini**
Aroma College Roorkee, Haridwar (UK)-India.

Article Received on 01/03/2020 **Article Revised on 21/03/2020** **Article Accepted on 11/04/2020**

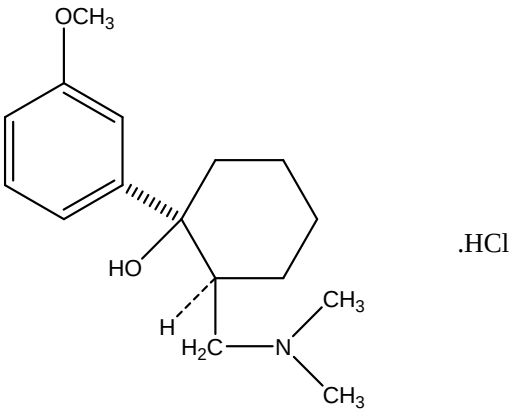
ABSTRACT
Transdermal drug delivery guide direct admittance to the systemic circulation through the skin which bypasses drugs from the hepatic first pass metabolism leading to increase bioavailability. Tramadol HCl has been selected as model analgesic drug. The Tramadol hydrochloride transdermal patches were prepared by solvent casting technique. Formulation of transdermal patches was selected by using different composition of polymers. Physicochemical properties such as thickness, weight uniformity, folding endurance, moisture content, percentage moisture uptake and content uniformity were determined on developed patches. In the present work an attempt was made to formulate the matrix type transdermal patch using Tramadol hydrochloride drug because it has low bioavailability.

KEYWORDS: TDDS, Matrix type transdermal patch, Tramadol HCl & FT-IR.

INTRODUCTION
The application of medications to the skin to simplicity ailments is a practice that has been utilized by humankind over the millennia and has included the application of poultices, gels, ointments, creams, and pastes. TDDS offer pharmacological compensation over the oral route and improved patient acceptability and compliance.[1] Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. Thus various forms of Novel drug delivery system such as transdermal drug delivery systems, controlled release systems, transmucosal delivery systems etc. emerged. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug.[2] Transdermal therapeutic systems are defined as a self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at control rate to the systemic circulation. Transdermal formulation maintaining drug concentration within the therapeutic window for prolong period of time ensuring that drug levels neither fall below the minimum effective concentration nor exceed the maximum effective concentration. An ideal drug to be formulated as transdermal drug delivery should possess several physico-chemical properties, such as short half-life, small molecular size, low dose, low oral bioavailability, etc.[3]



Analgesic relieves mildmoderate pain. These agents are effective for somatic pain (e.g. musculoskeletal pain in joints, muscle and head ache). They are not effective in reducing discomfort from visceral organ (Heart, liver and lung). All analgesic agents produce their therapeutic effects by inhibiting various prostaglandins substances involved in development of pain as well as regulation of body temperature. Due to extensive use of analgesic agents, the toxicity and untoward effects do occurs many times especially when therapy of pain, inflammation and fevers involves use of higher dose for longer period. The common organs involved are liver, kidney and GIT. It has been estimated that 1 in 5 chronic users (lasting over a long period of time) of NSAIDs will develop gastric damage which can be silent.[4] Tramadol belongs to the anisole. These are organic compounds containing a methoxybenzene or a derivative. Tramadol hydrochloride, (±) cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol Hydrochloride.[5] Tramadol Hydrochloride is a narcotic like analgesic used in severe pain. Tramadol has inhibitory action on 5-HT2C receptor and even though the parent and M1 metabolite of Tramadol binds to μ opioid receptors and results in weak inhibition and reuptake of norepinephrine and serotonin. In several animal tests Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone.[6-7]



Structure of Tramadol HCL.

In the present work an attempt was made to formulate the matrix type transdermal patch using Tramadol hydrochloride drug because it has low bioavailability.

MATERIAL AND METHOD

Drug: Tramadol hydrochloride was obtained as gift sample from Jubilant Chemsys Ltd., Noida.

Polymers: HPMC E15was obtained from Jegchem Universal, Mumbai and Eudragit RS100, Eudragit RL100 and Eudragit RE 100 were obtained from Triown Chemie, Ahmedabad.

Plasticizer: PEG 400 was used.

Solvents: Acetone, phosphate buffer.

Other reagents: Di sodium hydrogen phosphate, sodium hydroxide, potassium di hydrogen orthophosphate.

Drug-excipients interaction by FTIR

Fourier transforms infrared spectroscopy

IR spectroscopy is among the most important analytical techniques to determine the structure of the compound

by predicting the presence of certain functional groups which are observed at a definite frequency and to study the drug-polymer interaction. A peak-by-peak correlation is excellent evidence for identity. The spectra were recorded for Tramadol hydrochloride, Eudragit RS100, Eudragit RL100, HPMC E15 and mixture of Tramadol hydrochloride – Eudragit RS 100 and RL 100 and HPMC E15.

Formulation Development

The tramadol hydrochloride transdermal patches were prepared by solvent casting technique. The polymeric solution was prepared by dissolving Eudragit RS 100, RL100 and Hydroxypropyl methyl cellulose E15 (Eudragit RS100: HPMC E15), (Eudragit RL100: HPMC E15) and (Eudragit RS100: Eudragit RL100) in different ratios, along with drug, in acetone. The solution was poured into a glass ring placed on the surface of backing membrane and aluminum foil kept in a Petri dish. Backing membrane was prepared by the Eudragit E. The patches were kept at room temperature to evaporate the solvent overnight. The patches were cut to desire size and stored in desiccator until use.

Physicochemical characterization of patches[8-10]

Thickness uniformity

The thickness of the patches (1 cm^2) were measured at 3 different points using a digital Caliper and average thickness of three reading and standard deviation values were calculated.

Weight determination

The prepared patches are to be dried at 60°C for 4hrs before testing. A specified area of patches (1 cm^2) is cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are calculated from the individual weights.

Folding endurance

A specific area of patch (1 cm^2) is cut and repeatedly folded at the same place till it breaks. The number of times the film could be folded without breaking gave the value of folding endurance.

Percentage moisture content

The prepared patches (1 cm^2) are weighed individually and kept in a desiccator containing fused calcium chloride at room temperature. After 24 hours, the patches are to be reweighed and the percentage moisture content determined by the following formula:

Percentage moisture content (%) = [Initial weight - Final weight / Final weight] ×100

Percentage moisture uptake

The prepared patches (1 cm^2) are weighed individually and kept in a desiccator containing saturated solution of potassium chloride in order to maintain 84% Rhesus factor. After 24 hours, the films are reweighed and the percentage moisture uptake determined by the following formula:

Percentage moisture uptake (%) = (Final weight - Initial weight / initial weight) × 100

Drug content determination

The patches (1 cm^2) was cut and added to a beaker containing 100 ml of phosphate buffered pH 7.4. The medium was stirred (500 rpm) with teflon coated magnetic bead for 5 hours. The contents were filtered using whattman filter paper and the filtrate was analyzed by U.V. Spectrophotometer (UV-1700, Shimadzu) at 271 nm for the drug content against the blank solution.

RESULT AND DISCUSSION

In this study Tramadol hydrochloride loaded transdermal patches were prepared using Eudragit RS 100, Eudragit RL 100 and HPMC E15 in different combination as matrix forming agent and polyethylene glycol 400 (PEG 400) is used as plasticizer. The patches were prepared by varying the ratio of two polymers in each group and also by varying the quantity of plasticizer to understand their impact on the responses. Possibility of drug-excepient interaction was checked by FTIR analysis. The result were tabulated in table 1-5 & Fig.1-5. The result revealed that there was no various of the peak of Tramadol HCL with other polymers as compared with standard spectra thus FTIR analysis revealed that there are no potential chemical interaction between the drug and the polymers. The formulation of patches was carried out in three groups with varying polymers ratio. Composition of different formulation was showed in table 6-8. The developed formulation were characterized for thickness, weight uniformity, folding endurance, moisture content, percentage moisture uptake and drug content uniformity. The thickness of all formulations was found to be at the range 0.23-0.26 mm (table 9). The weight of 1 cm^2 of every patch was in between 33–36 mg, ensuring the uniformity of the weight (table 10). The folding endurance group-1 and group -2 formulations was found to be range between 45-73 and folding endurance of group -3 formulation is increase compare to group-1 and group -2 formulation was found to be range between 79-105 (table 11) which ensure the moisture content of patches were found to be range 2.3-10.2% (table 12) and the moisture absorption study revealed 7.6-16.2% increase in weight at 84% relative humidity (table 13). The drug content study result was tabulated in table14. The drug content analysis revealed the uniformity of drug content in all formulations.

CONCLUSION

The data obtained from the current work propose the possibility of developing the drug into transdermal patch. The transdermal patch can be used a suitable device for long term management of pain. Further studies are needed to *in-vitro* permeation studies, skin sensitivity and pharmacokinetic evaluation which are needed to undertake in future.

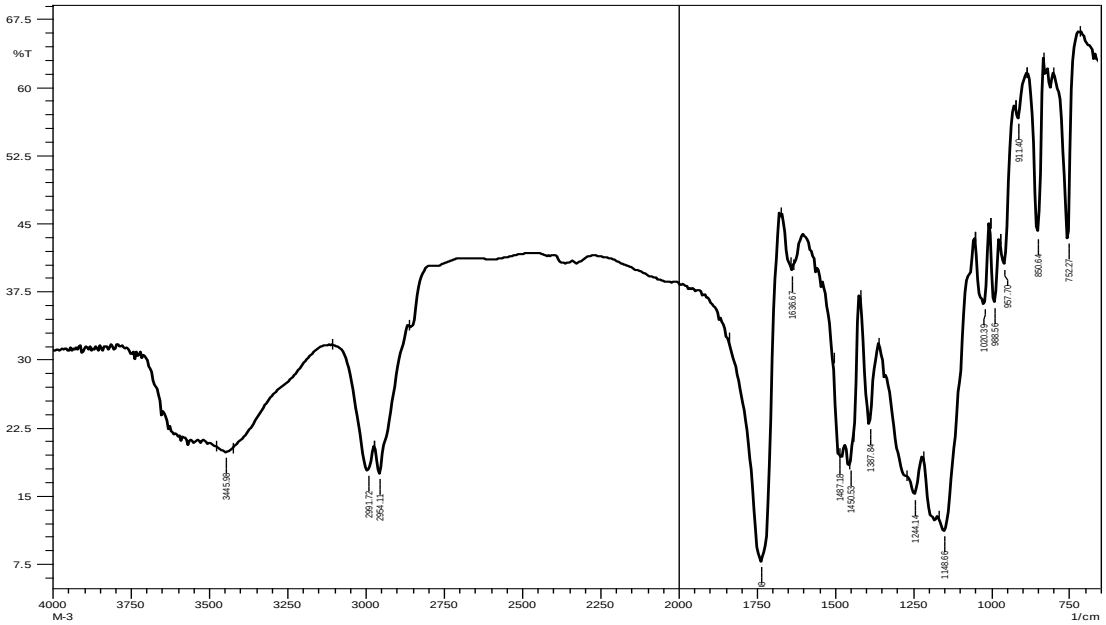


Figure 1: FT-IR spectra of TH Eudragit RS100 & RL100 and HPMC E15.

Table 1: Peaks of combination of tramadol hydrochloride, Eudragit RS100 & RL100 and HPMC E15.

PEAKS RANGE (cm^{-1})	FUNCTIONAL GROUPS
2991.72	Miscellaneous chromophoric groups, alcohol and phenols O-H stretching vibration (chelate compound)
02954.11	Hydrocarbon chromophore C-H stretching, alkane.
1750.74	Carbonyl chromophore, ketone stretching vibration, saturated, acyclic 5-membered ring.
1387.84	C-H bending, alkane pentbutyle.
752.77	Halogen compounds, C-X stretching vibration.
983.56	C-H bending, alkene, monosubstituted (vinyl)

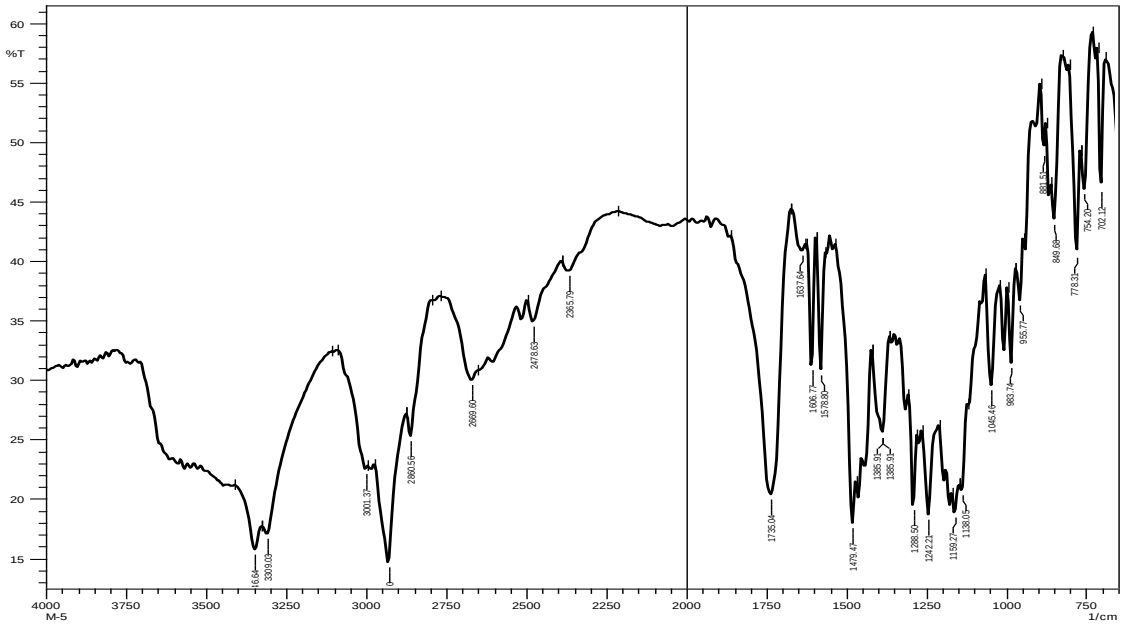


Figure 2 – FTIR-Spectra of Eudragit RS100.

Table 2: Peaks of Eudragit RS100.

PEAKS RANGE (cm^{-1})	FUNCTIONAL GROUPS
1725.04	Aldehydes (carbonyl stretching vibrations saturated aliphatic)
1637.84	Unsaturated nitrogen compounds C-NO, nitrous compounds
849.88	(C-H bending two adjacent hydrogen atoms
754.20	(C-H bending) Aromatic, substitution type

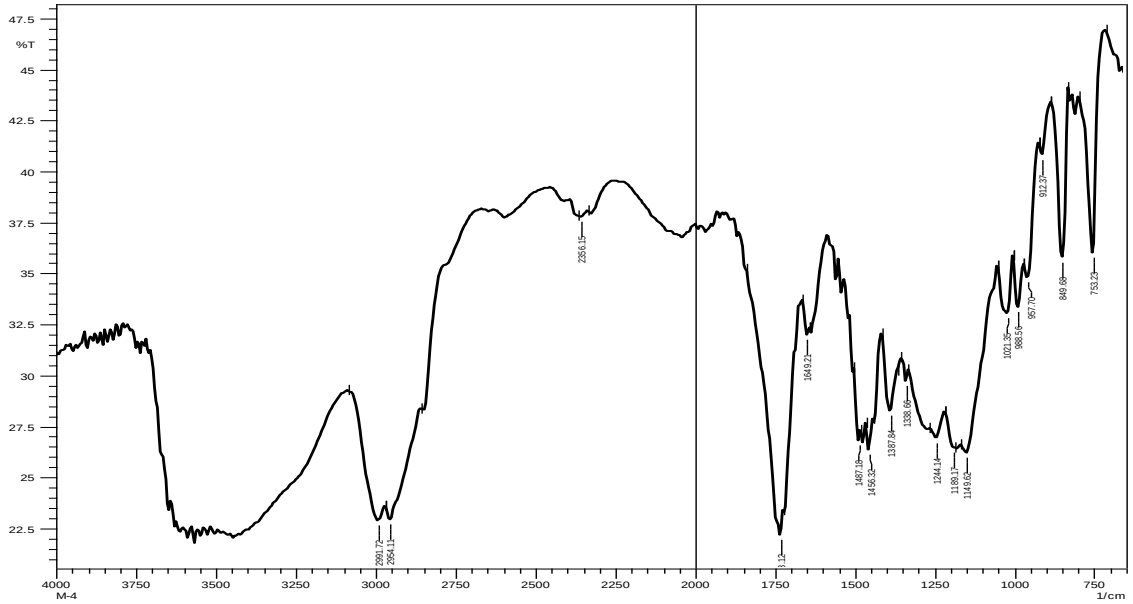


Figure 3: FTIR Spectra of Eudragit RL100.

Table 3: Peaks of Eudragit RL100.

PEAKS RANGE (cm^{-1})	FUNCTIONAL GROUPS
2991.72	Miscellaneous chromophoric groups, alcohol and phenols, O-H stretching vibrations (chelate compound)
1487.18	C-C multiple bonds stretching, aromatic.
983.58	C-H bending, alkane monosubstituted (vinyl)
849.69	C-H bending, alkane, trisubstituted.
753.23	C-H bending, aromatic substitution type, pour adjacent hydrogen atoms.

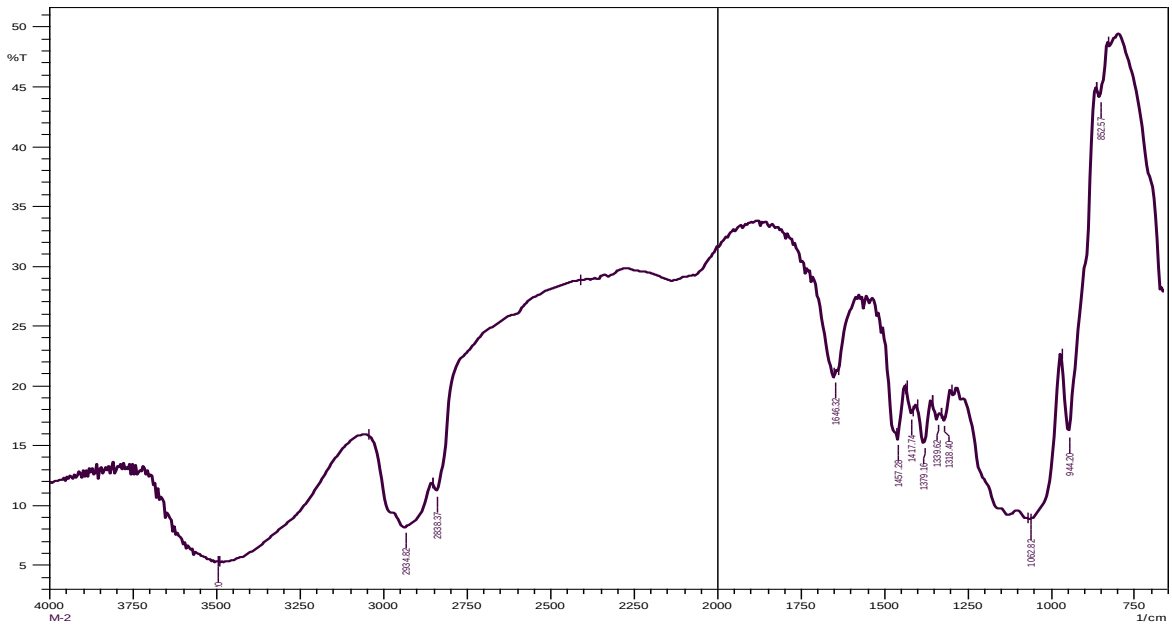


Figure 4: FTIR Spectra of HPMC E15.

Table 4: Peaks of HPMC 15.

PEAKS RANGE (cm^{-1})	FUNCTIONAL GROUPS
1646.32	(N-H bending vibrations)
1614.31	(N-H bending vibrations) primary amides, dilute solutions
3416.66	(N-H stretching vibrations) secondary free one bond
1339.82	(C-N vibrations) aromatic primary

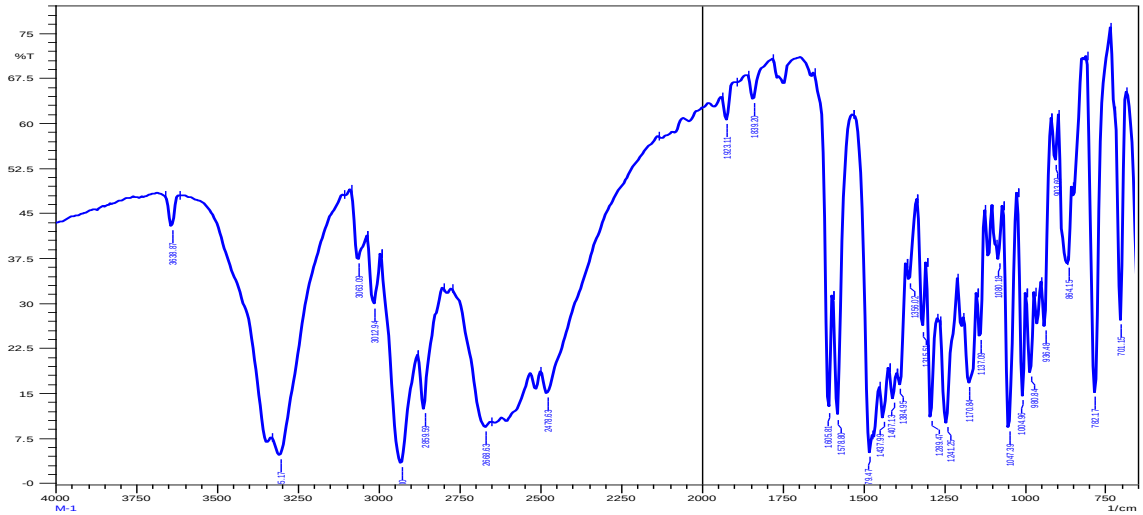


Figure 5: FTIR Spectra of tramadol hydrochloride.

Table 5: Peaks of tramadol hydrochloride.

PEAKS RANGE (cm^{-1})	FUNCTIONAL GROUPS
3638	Miscellaneous chromophoric groups, alcohol and phenols, O-H stretching vibrations, free O-H
2889.59	Aldehydes, carbonyl stretching, C-H stretching, vibration two bonds.
1605.81	C-C multiple bonds stretching.
1578.80	N-H binding vibration, amines.
1283.47	C-N vibration, aromatic secondary, amines.
1047.39	Miscellaneous chromophoric group, alcohol and O-H bending, C-O stretching vibration, primary alcohols.
782.17	Halogens compounds, C-X stretching vibration.

Composition of different formulation

Table 6: Different formulation of group – 1.

S.NO.	FORMULATION CODE	RATIO OF POLYMER	EUDRAGIT RS100 (mg)	HPMC E15 (mg)	DRUG (mg)	PLASTICIZER (ml)
1.	F1	2:1	240	120	360	0.2
2.	F2	1:1	180	180	360	0.2
3.	F3	1:2	120	240	360	0.2
4.	F4	2:1	320	160	240	0.2
5.	F5	1:1	240	240	240	0.2
6.	F6	1:2	160	320	240	0.2

Table 7: Different formulation of group – 2.

S.NO.	FORMULATION CODE	RATIO OF POLYMER	EUDRAGIT RL100 (mg)	HPMC E15 (mg)	DRUG (mg)	PLASTICIZER (ml)
1.	F1	2:1	240	120	360	0.2
2.	F2	1:1	180	180	360	0.2
3.	F3	1:2	120	240	360	0.2
4.	F4	2:1	320	160	240	0.2
5.	F5	1:1	240	240	240	0.2
6.	F6	1:2	160	320	240	0.2

Table 8: Different formulation of group- 3.

S.NO.	FORMULATION CODE	RATIO OF POLYMER	EUDRAGIT RS100 (mg)	EUDRAGIT RL100 (mg)	DRUG (mg)	PLASTICIZER (ml)
1.	F1	2:1	240	120	360	0.5
2.	F22	1:1	180	180	360	0.5
3.	F3	1:2	120	240	360	0.5
4.	F4	2:1	320	160	240	0.5
5.	F5	1:1	240	240	240	0.5
6.	F6	1:2	160	320	240	0.5

Table 9: Thickness of transdermal patches.

Thickness (mm)			
Formulation Code	**Group-1**	**Group-2**	**Group-3**
F1	0.25±0.01	0.25±0.02	0.26±0.02
F2	0.25±0.03	0.23±0.03	0.25±0.01
F3	0.24±0.02	0.24±0.02	0.23±0.03
F4	0.25±0.01	0.25±0.02	0.25±0.01
F5	0.23±0.03	0.25±0.03	0.25±0.03
F6	0.26±0.01	0.24±0.01	0.26±0.01

Table 10: Uniformity of weight at different area of patches.

Weight (mg/cm^2)			
Formulation Code	**Group-1**	**Group-2**	**Group-3**
F1	35±1.4	35±2.3	34±2.5
F2	36±2.4	35±1.4	36±1.4
F3	34±4.3	36±1.2	34±3.6
F4	35±2.5	34±3.6	35±2.5
F5	35±2.2	35±3.4	35±3.2
F6	33±4.3	36±2.3	34±4.4

Table 11: Folding endurance of transdermal patches.

Folding endurance			
Formulation Code	**Group-1**	**Group-2**	**Group-3**
F1	56	60	90
F2	49	53	98
F3	62	49	105
F4	73	58	86
F5	65	65	79
F6	45	58	102

Table 12: Percentage moisture content of transdermal patches.

Percentage moisture content			
Formulation Code	**Group-1**	**Group-2**	**Group-3**
F1	7.3	5.3	2.3
F2	3.5	3.6	6.8
F3	6.2	8.9	7.3
F4	5.6	5.6	8.8
F5	8.4	9.2	7.4
F6	10.2	4.4	9.6

Table 13: Percentage moisture uptake of transdermal patches.

Percentage moisture uptake			
Formulation Code	**Group-1**	**Group-2**	**Group-3**
F1	11.2	7.6	15.4
F2	15.4	13.3	13.8
F3	10.0	10.9	16.2
F4	9.6	9.9	10.5
F5	12.3	11.5	8.2
F6	8.5	13.8	14.4

Table 14: Drug content of transdermal patches.

Drug content (%)			
Formulation Code	**Group-1**	**Group-2**	**Group-3**
F1	90.25±2.56	96.25±1.64	86.95±3.66
F2	88.38±4.23	92.02±2.36	95.43±1.56
F3	93.05±2.02	91.55±3.33	92.48±2.85
F4	92.68±3.49	87.45±4.12	92.86±1.02
F5	91.35±1.96	90.12±2.45	90.55±2.53
F6	85.54±4.22	89.63±1.78	82.16±4.59

REFERENCES

1. Lyn Margetts FRCA & Richard Sawyer FRCA FIPP. Transdermal drug delivery: principles and opioid therapy. *Continuing Education in Anaesthesia, Critical Care & Pain j*., 2007. 7; 5: 171.
2. Allen, L.V. and H.C. Ansel, Pharmaceutical dosage forms and drug delivery systems: 8th Edition., Wolter Kluwer Publishers, New Delhi, 2005; 298-299.
3. Gannu, R., et al., Development of nitrendipine transdermal patches: in vitro and ex vivo characterization. Current Drug Delivery, 2007; 4(1): 69-76.
4. Meingassner, J.G., et al., A novel anti-inflammatory drug, SDZ ASM 981, for the topical and oral treatment of skin diseases: in vivo pharmacology. British Journal of Dermatology, 1997; 137(4): 568-576.
5. Budavari, S., Eds., In; The Merck Index, 13th Edn., Merck & Co., Inc., Whitehouse Station, NJ, 2001; 958, 1163, 1809.
6. Kathleen P., Eds., In; Martindale The Complete Drug Reference 32nd Edn., Pharmaceutical Press, London, 1999; 622,623,630.
7. Kumar Amit *et al*. Formulation and evaluation of fast dissolving uncoated tablets of Drotaverine HCl, World Journal of Pharmaceutical Research, Jan 2020; 9(1): 1716-1727.
8. Suneetha Cherukuri *etal*. Formulation and evaluation of transdermal drug delivery of topiramate. *Int J Pharm Investig*, 2017; 7(1): 10–17.
9. Malik Jitender, Process Evaluation and In-vitro drug release study of fast dissolving uncoated tablets of Drotaverine HCl., European Journal of Scientific Exploration, 2019; 2(6): 1-8.
10. Shivaraj, A., et al., Design and evaluation of transdermal drug delivery of ketotifenfumarate. Int. J. Pharm. Biomed. Res., 1(2): 42-47.
11. Ramkanth, S., et al., Design and characterization of matrix type transdermal drug delivery system using metoprololtartarate. International Journal of Advances in Pharmaceutical Research, 1(1): 1-5.
12. Amit K, Preformulation Studies of Drotaverine HCl: An Integral Part of Formulation Design, European Journal of Biomedical and Pharmaceutical sciences, 2019; 6(13): 304-307.
13. Bose A, Development and Optimization of fixed dose Antihypertensive combination drugs using double layer sustained release Microsphere Technology. *Asian Journal of Chemistry*, 2011; 23(9): 3883-3886.