WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 6, 657-671. Research Article ISSN 2277– 7105

# APPROCHES OF ENHANCE TRANSDERMAL DELIVERY OF ROPINIROLE HCL

**G. Koteshwarrao*, Shravan Kumar Dholi[1] and Sridhar Vanga[2]**

*Depatment of Pharmaceutics, Vaageswari College of Pharmacy, Karimnagar, Telanagana, India.

[1]Depatment of Pharmacology, Vaageswari Institute of Pharmaceutical Sciences, Karimnagar, Telanagana, India.

[2]Depatment of Pharmaceutical Chemistry, Vaageswari Institute of Pharmaceutical Sciences, Karimnagar, Telanagana, India.

Article Received on
24 Jan. 2018,
Revised on 14 Feb. 2018,
Accepted on 06 March 2018,
DOI: 10.20959/wjpr20186-11407

***Corresponding Author**
**G. Koteshwarrao**
Depatment of Pharmaceutics, Vaageswari College of Pharmacy, Karimnagar, Telanagana, India.

## ABSTRACT

The present study was to study the approaches to enhance the transdermal delivery of Ropinirole hcl. Chemical approach is one of the approach to increase the permeation of drug. Transdermal patches are prepared with HPMC E-15 with other combination of polymers like Ethyl cellulose, PVA, PVP K-30 and Propylene glycol used as permeation enhancer. The formulation (F11) containing HPMC E15 1500mg, Ethyl cellulose 500mg chooses to study the effect of different types of permeation enhancers(viz. ; Linseed oil, Olive oil, Oleic acid, Urea, Menthol and Camphor) as it shows controlled drug release manner. The in-vitro diffusion studies showed that, compare to other permeation enhancers Menthol and Camphor shows highest drug release 92.13±0.84 %, 94.48±0.68% respectively with 10% concentration. The order of permeation effect of the permeation enhancers in 1% and 5% concentrations is Linseed oil < Olive oil < Oleic acid < Urea < Menthol< Camphor. The ex-vivo studies are conducted to formulation F11 and, the results are 58.28±1.89% and 94.87±1.98% respectively. This study requires further investigations like in-vivo and human trials for therapatic utility.

**KEYWORDS**: Chemical approach, Ropinirole hcl, Fatty oils, Terpenes, Urea.

## INTRODUCTION

The medicaments are applied to skin from ancient days. In India Susruta's Ayurvedic Compendium, dating back to 250 BC, recommends an ointment containing turmeric (medicament) to relieve the effects of poisoned food.[1] The ancient Greeks applied a mixture of water, olive oil and lead oxide as a balm to the skin. Lead oxide has astringent properties, and olive oil may act as an occlusive barrier, moisturising the skin.[2] Parkinson's disease is a degenerative disorder of the central nervous system. The motor symptoms of Parkinson's disease result from the death of dopamine-generating cells in the substantia nigra, which will leads to decreased levels of dopamine in striatum causes muscle tone, rigidity, tremor, nocturnal akinesia. Dopamine agonists have proved to antiparkinsonian activity.[3] Ropinirole Hcl is a potent, non-ergoline dopamine agonist, that bind to dopaminergic post-synaptic receptors and increases the dopamine levels to treat the Parkinson'sdisease. Ropinirole Hclis a $D_2$ agonist[4], plasma half life is 6 hrs., and the time to reach maximum peak plasma concentration is 1.5 hrs., the maximum oral dose is <24mg/day. Ropinirole Hcl having low bioavailability (55%) due to extensive hepatic metabolism, short half life (6 hrs), low molecular weight (260.37), so it is a suitable candidate for transdermal delivery. Patch formulations allowing continues and stable agonist action up to 24hours by controlling drug release, which could allow more effective control of Parkinsonism. In our present study we were prepared transdermal patches using different polymers and detected that Ropinirole Hcl having the low permeability through skin hence permeation enhancers are used in optimised formula for enhancing the permeation of drug through skin, so that we increased the transdermal drug delivery rate.[2-4]

## MATERIALS AND METHODS

Ropinirole Hcl (Gift sample from Hetero Labs, Hyd.), HPMC E15(Central Drug House (P) Ltd, New Delhi), PVP K30(Central Drug House (P) Ltd, New Delhi), PVA(Central Drug House (P) Ltd, New Delhi), Ethyl cellulose (Central Drug House (P) Ltd, New Delhi), Urea (Finar Chemical Ltd., Ahmedabad), Oleic acid(Central Drug House (P) Ltd, New Delhi), Olive oil (Finar Chemical Ltd., Ahmedabad), Linseed oil (Finar Chemical Ltd., Ahmedabad), Menthol (Finar Chemical Ltd., Ahmedabad), Camphor (Finar Chemical Ltd., Ahmedabad).

### Preparation of Transdermal patch

Transdermal patches were prepared by Solvent evaporation method by using different concentrations of polymers. At first, Polymers are soaked in chloroform in closed beaker for

15 mins. Then drug dissolved in little amount of Chloroform and polymeric solution is added to it. Plasticizer (Propylene glycol) is added to the above mixture and stirred for homogenous soft feel solution (In permeation enhancer containing formulations permeation enhancer is dissolved in Propylene glycol). This total mixture is poured into a Petri plate and dried at $37^0$C for 24 hrs by placing an inverted funnel over the Petri plate to control the rate of evaporation and then dried in oven at$50^0$C for 1 hr. for removal of excess moisture. The patches were cut into 2×2 $cm^2$ area and used for further studies.[5]

**Preformulation studies**

**Determination of $\lambda_{max}$ for Ropinirole Hcl**

From the standard stock solution, 1 ml was pippetted into 10 ml volumetric flask. The volume was made up to 10 ml with 7.4 pH phosphate buffer. The resulting solution containing 10 µg/ml was scanned between 200 and 400 nm. The $\lambda_{max}$ was found to be 250 nm.[6]

**Preparation calibration curve for Ropinirole hydrochloride**

Standard graph of Ropinirole hydrochloride was plotted in two different media, in distilled water and 7.4 pH phosphate buffer. 5µg/ml, 10µg/ml, 15 µg/ml, 20 µg/ml, 25 µg/ml, 30 µg/ml, 35 µg/ml and 40 µg/ml were prepared from the stock solution and scanned for absorbance values at 250nm using UV-Visible spectrophotometer. The standard graph is plotted with concentration on X-axis and absorbance on Y-axis.[7]

**Determination of solubility**

The solubility of Ropinirole hydrochloride was determined and found to be 130mg/ml and 128mg/ml in distilled water and 7.4 pH phosphate buffer respectively. The solubility in phosphate buffer found slighltly more than that of distilled water.[8]

**Drug and excipient compatibility**

Drug and excipient compatibility studiese are conducted to Ropinirole hcl pure drug, optimized formula, optimised formula+Camphor, optimised formula+Menthol. The results are showed in figures. In FTIR analysis all the principle peaks shown with Ropinirole Hcl appeaed in transdermal patch suggesting no chemical reactions between drug and excipients.[9-11]

**Evaluation of patches**

**Weight variation Test**

The patch size of 4cm$^2$ area taken and weight is measured by using digital weighing balance. The results of weight variation tests for various transdermal patches are shown in table and results of weight variation test indicated uniformity in weight of patches, as evidenced by SD values, which were less than 4.0 for all patches. Weights of patches almost same with slight variation.[12-15]

**Thickness variation Test**

In thickness variation test, the thickness was founded to be uniform and it is increased with increase in HPMC concentration. The values were in the range of 0.85±0.07 to 1.24±0.12 mm., for all formulations, an indication of more uniform patches with less deviation.[16]

**Folding endurance Test**

The patches prepared with polymer combinations of HPMC E15 and PVA, PVP and PVA have shown higher folding endurance compared to those patches with HPMC and PVP, HPMC and EC. This may be due to high flexibility with PVA. The folding endurance of prepared patches were found to be in the range of 123±2.36 to 83±4.75. The values for all formulations is given in the table. This data revealed the the patches had good strength along with flexibility with HPMC:PVA. HPMC: PVP combinations and HPMC:EC combination patches shown less flexibility.[17]

**Percentage of drug content**

Good uniformity in drug content was observed in all transdermal patches as evidenced by table. The percentage drug content ranged from 97.38±1.097 to 99.14±0.483 mg. These results were better than the weight variation test so far as S.D values were concerned in all formulations. Hence we can proceed for further studies with these patches.[18]

**Percentage moisture absorbance and moisture loss Test**

The moisture absorbance and moisture content studies are conducted. The moisture absorbance test revealed that the combination of both hydrophilic polymers (HPMC, PVA, PVP) containing patches have shown more absorption than patches with hydrophobic polymer(EC). In this the moisture absorption order of polymers is HPMC E15> PVP> PVA>EC. The moisture absorption values are in the range from 18.26±2.75 to 5.12±1.87. The moisture content in the patches is ranged from 6.34±1.57 to 1.43±1.04, the results have

showed that the moisture content values are greater for the hydrophilic polymers and lower for the hydrophobic polymers.[19]

**In-vitro drug release studies using diffusion cell**

The patches were placed on dialysis cell using cellophane membrane in contact with isotonic phosphate buffer pH 7.4 kept at 37 ± 1°C with constant stirring of 50rpm. 1 ml Sample was withdrawn at different time intervals analyzed for drug content spectrophotometrically at 250 nm. The % cumulative drug release was calculated and reported.

Mathematical expressions like first order, zero order, Higuchi and Kosmeyers-Peppas models were applied to drug release studies to analyse the release kinetics.[20-23]

**Release kinetics**

Release kinetics are applied to all the formulations. The optimized formula F12 and F13 showing zero order kinetics and most of the other formulations following peppas kinetics. The formulation F23 which is showing highest drug release kinetic model graphs are shown in figures which are explaining that formulation following zero order based on the $R^2$ value.[24-25]

**ex-vivo drug release studies using rat abdomen skin**

Dialysis membrane is replaced by Rat abdomen skin and drug release studies conducted to optimised formula and formulation with highest drug release using permeation enhancer i.e. F23.[26]

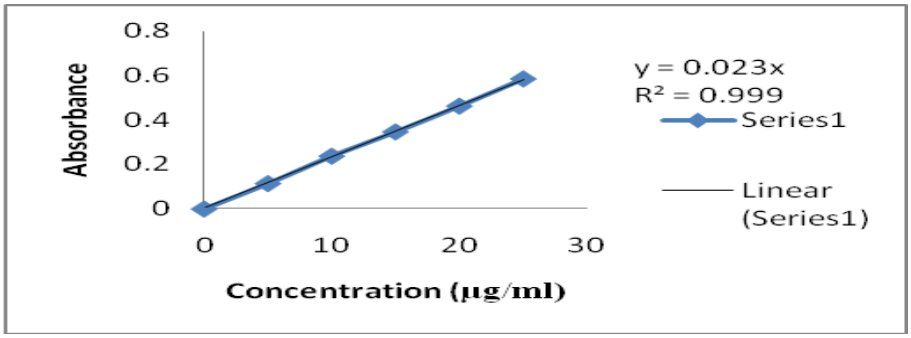
## RESULTS AND DISCUSSIONS

**Preformulation studies**

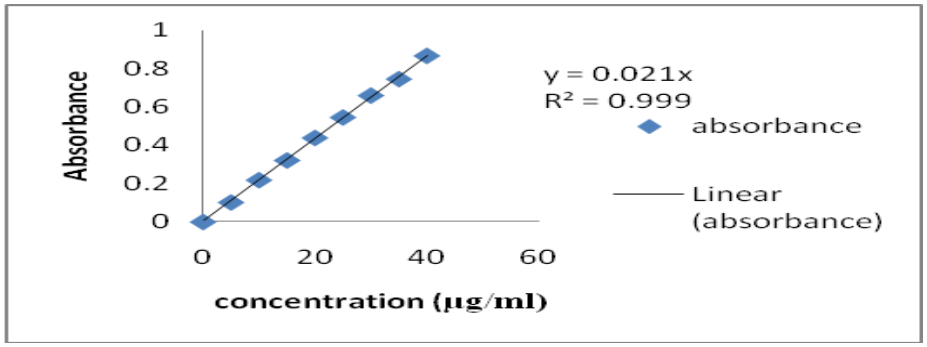
**Analytical method**

**Preparation calibration curve for Ropinirole hydrochloride**

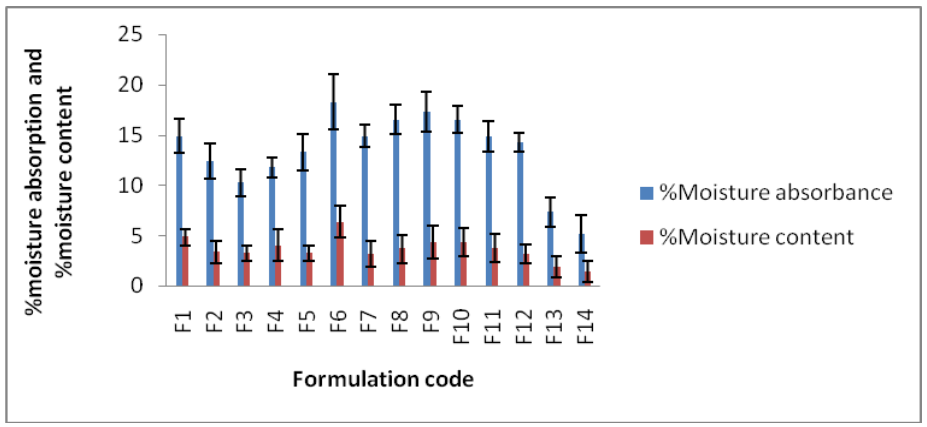
Standard graph of Ropinirole hydrochloride was plotted in two different media, in distilled water and 7.4 pH phosphate buffer. 5µg/ml, 10 µg/ml, 15 µg/ml, 20 µg/ml, 25 µg/ml, 30 µg/ml, 35 µg/ml and 40 µg/ml were prepared from the stock solution and scanned for absorbance values at 250nm using UV-Visible spectrophotometer. The standard graph plotted with concentration on X-axis and absorbance on Y-axis.



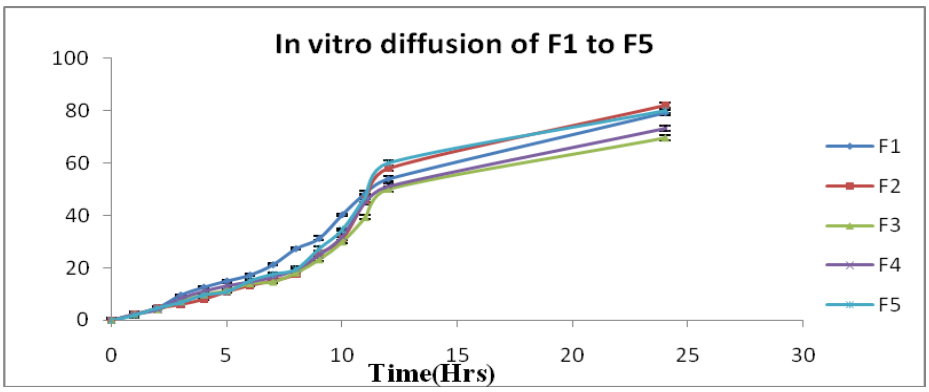

**Calibration curve of Ropinirole hcl in 7.4 Phosphate buffer**



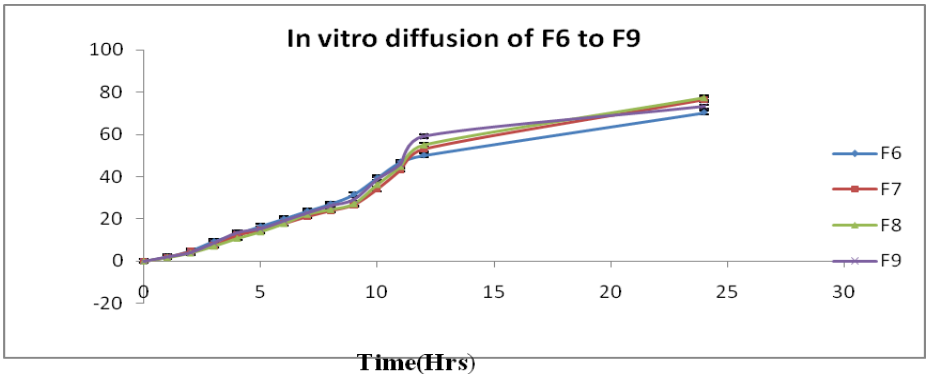

**Calibration curve of Ropinirole hcl in distilled water**



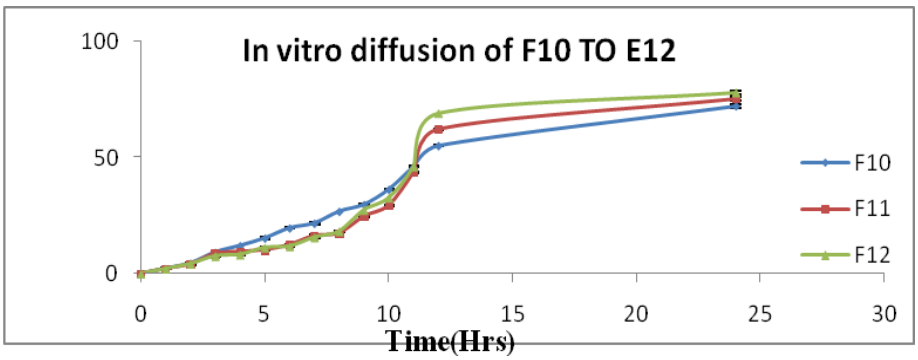

**Moisture absorption and moisture content of Ropinirole hcl Transdermal patches.**



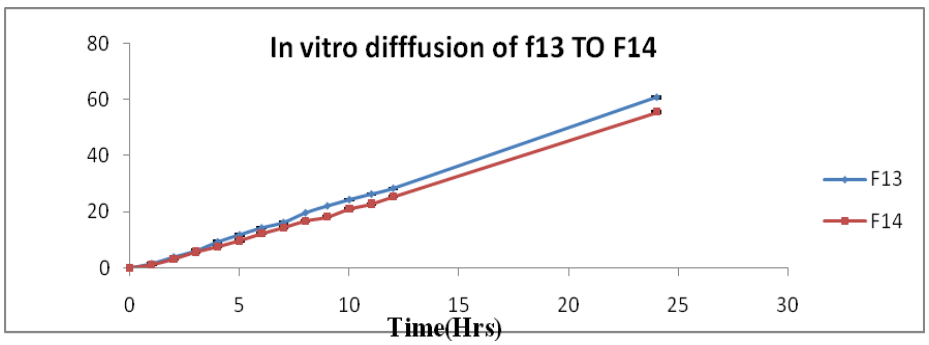

**Release of Ropinirole hcl from Transedermal patches (PVA:PVP combinations).**



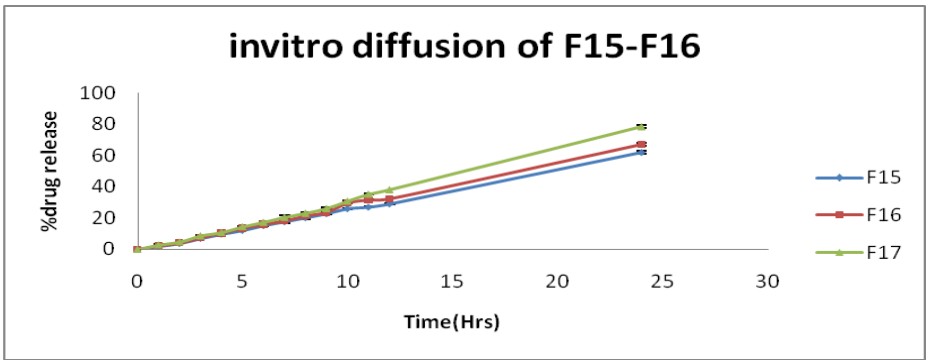

**Release of Ropinirole hcl from Transdermal patches (HPMC E15: PVA combinations).**



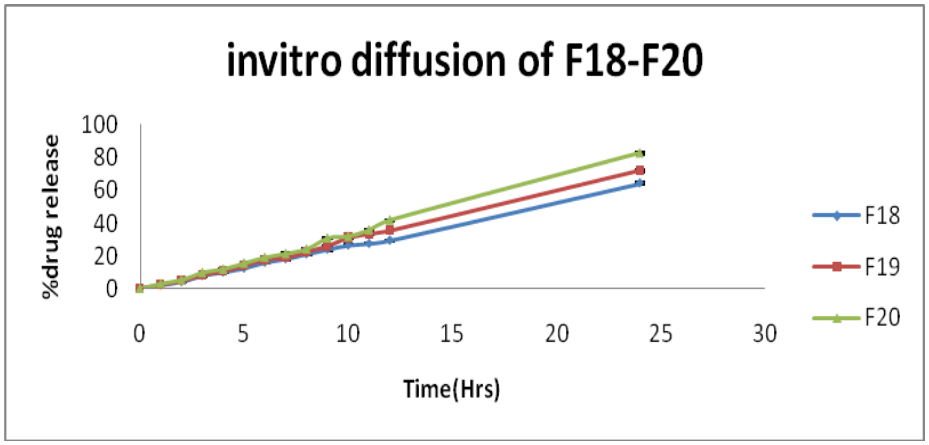

**Release of Ropinirole hcl from Transdermal patches (F10-F12: HPMC E15-PVP combinations).**



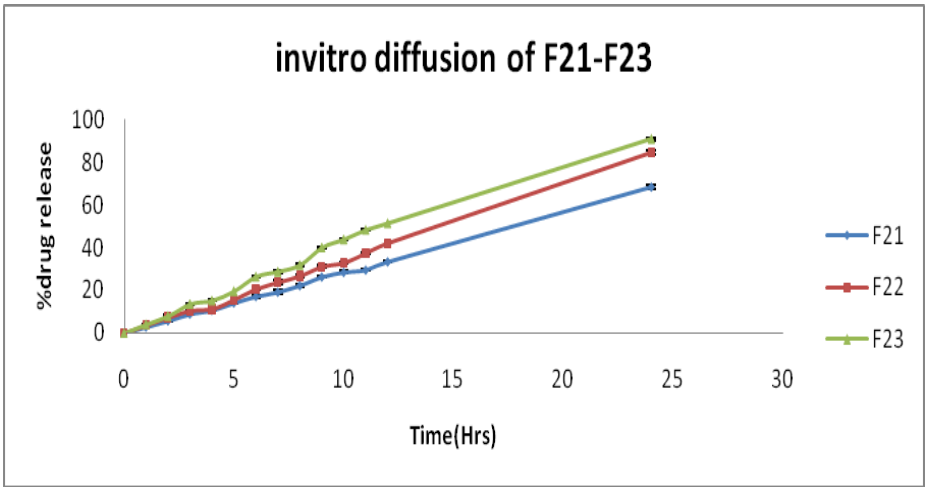

**Release of Ropinirole hcl from Transdermal patches HPMC E15-EC combinations).**



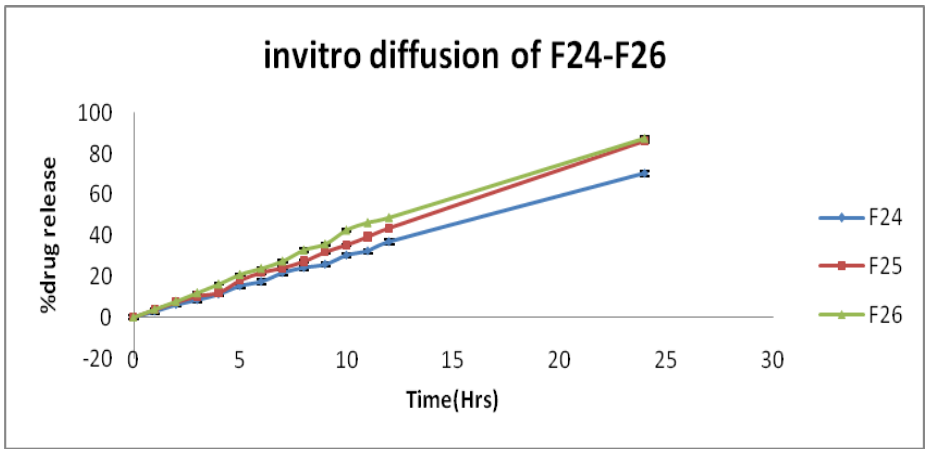

**With HPMC E15:EC(1500:500).**



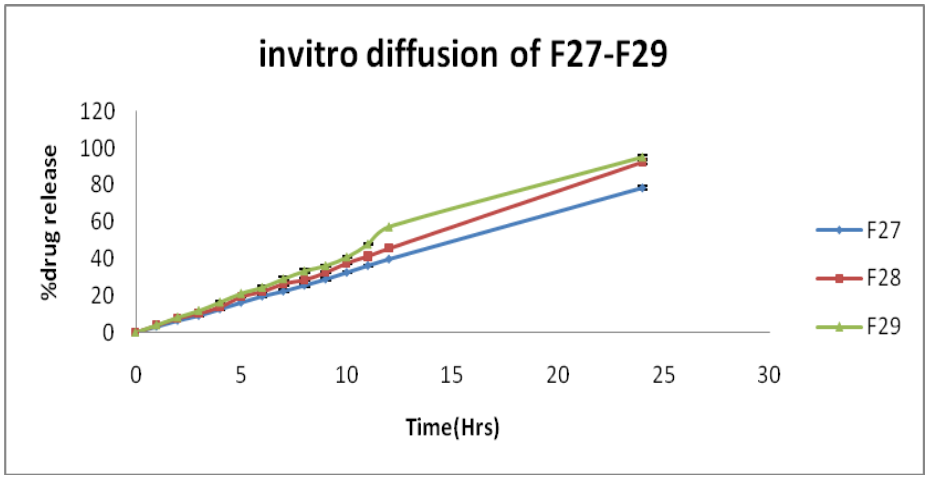

**Effect of Olive oil on permeation of Ropinirole hcl from Transdermal patch with HPMC E15:EC(1500:500).**



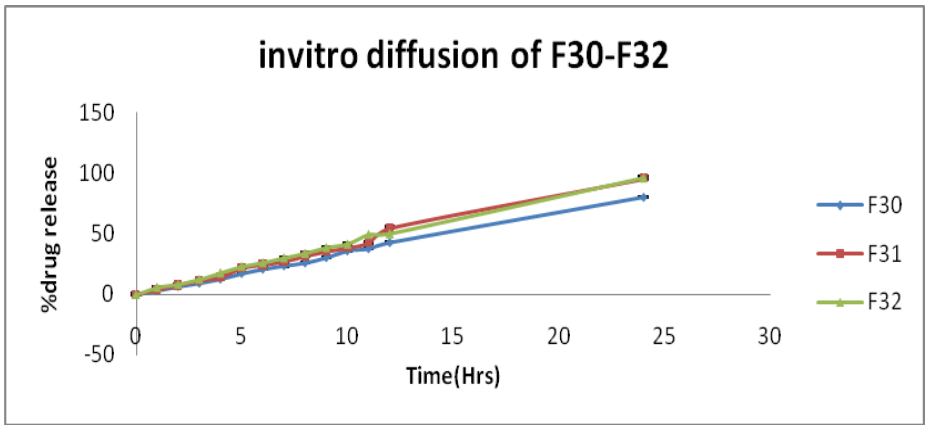

**Effect of Oleic oil on permeation of Ropinirole hcl from Transdermal patch with HPMC E15:EC(1500:500).**




**Effect of Urea on permeation of Ropinirole hcl from Transdermal patch with HPMC E15:EC(1500:500).**




**Effect of Menthol on permeation of Ropinirole hcl from Transdermal patch with HPMC E15:EC(1500:500).**




**Effect of Camphor on permeation of Ropinirole hcl from Transdermal patch with HPMC E15:EC(1500:500).**

**In-vitro drug release studies**

The release profiles of Ropinirole hcl transdermal patches were shown in tables. Formulation F2 have shown highest drug release(82.25±0.52) which is having PVA:PVP in 500:1500 ratios, after this formulation the single polymer containing transdermal patches shown the more drug release than combinations of polymers containing transdermal patches. The lowest drug release (55.53±0.33) observed in formulation F14 as it contains the maximum content of hydrophobic polymer (EC).

The transdermal patches containing hydrophilic polymers have shown the more drug release than hydrophobic polymer containing patches. As the hydrophilic content increased transdermal drug release increased substantially, the addition of hydrophobic polymer is retarding the drug release.

In order to understand the mechanism of release from the patches, different kinetics (zero order, first order, Higuchi and Peppas models) were applied to interpret the release rate from matrices, in-vitro release data were treated to the models, linearity and highest $R^2$ values were observed with respect to Peppas model kinetics and zero order. Peppas model explains the diffusion mechanism of drug release and zero order kinetics followed by the F13 formulation(HPMC:EC polymers with 1500:500 ratio). F13 formulation chooses as optimized formula for further studies of effect of permeation enhancer on the transdermal permeation of Ropinirole hcl, as the formulation F13 follows the zero order drug release.

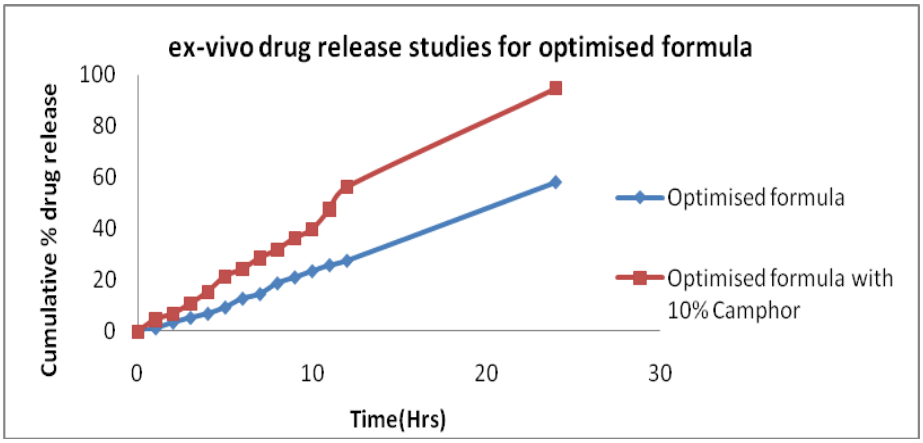
**Effect of permeation enhancers on the transdermal delivery of Ropinirole hcl from transdermal patch**

Effect of permeation enhancers on the transdermal delivery of Ropinirole hcl have been studied by using different permeation enhancers. The permeation enhancers chooses for the study are Linseed oil, olive oil, oleic acid, urea, menthol, camphor. These are used in different concentrations in optimized formula (F13). The permeation enhancer with 1%, 5%, 10% have been studied. The highest drug permeation (96.32±0.74) effect showed by the 10% camphor and lowest drug permeation (61.72±0.4) effect showed by the 1% Linseed oil.

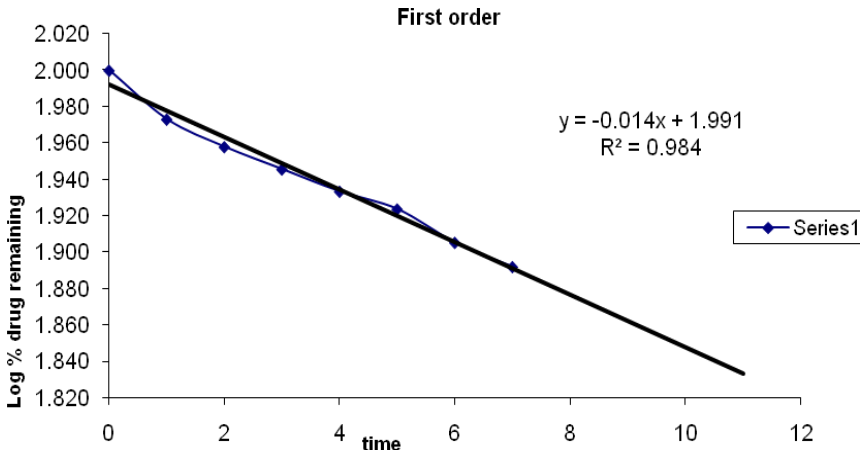
The order of permeation effect of the permeation enhancers with 1% and 5% is Linseed oil < Olive oil < Oleic acid < Urea < Menthol< Camphor, but the order of permeation effect of permeation enhancers with 10% is Linseed oil < Olive oil < Urea < Oleic acid < Menthol < Camphor.[12,27,9] These results showed that the fatty oils showed the lower drug release as they moisturize the skin. When compared both Oleic acid and Urea, Oleic acid in low (1%, 5% ) concentrations showed less drug release than urea but in higher concentration (10%) oleic acid exhibits higher drug release than Urea. Terpenes (Menthol and Camphor) showed the more permeation effect even in low concentrations than the other permeation enhancers (Linseed oil. Olive oil, Oleic acid, Urea) with higher concentrations.

**Ex-vivo drug release studies for optimized formula**

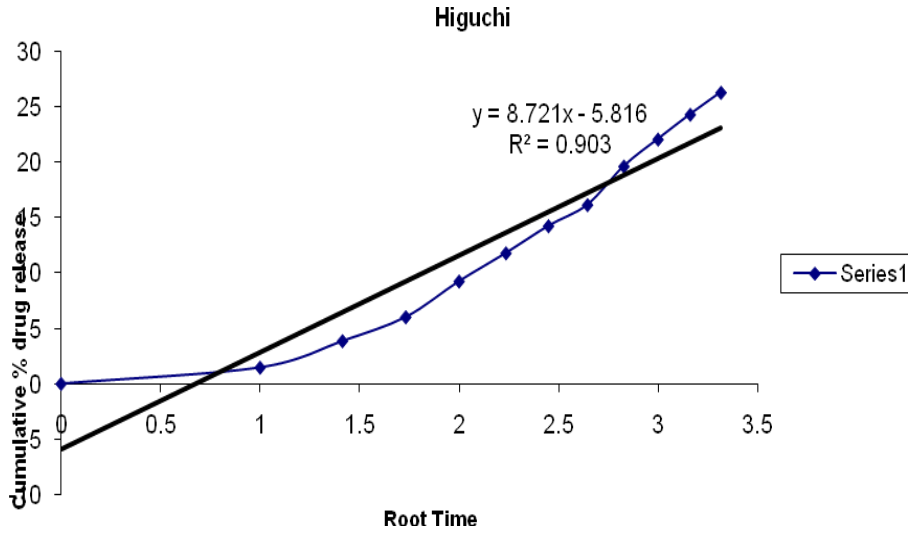
The ex-vivo studies are conducted for optimized formulae F13 and F32 using rat abdominal skin. The drug release from the Ropinirole hcl transdermal patches had shown in table. The optimized formula showing 58.28% drug release and the optimized formula with 10% Camphor showed 94.87% drug release with tremendous increase in flux and the enhancement ratio is 1.627. Hence camphor with 10% concentration showing the best results as permeation enhancer even in ex-vivo studies.



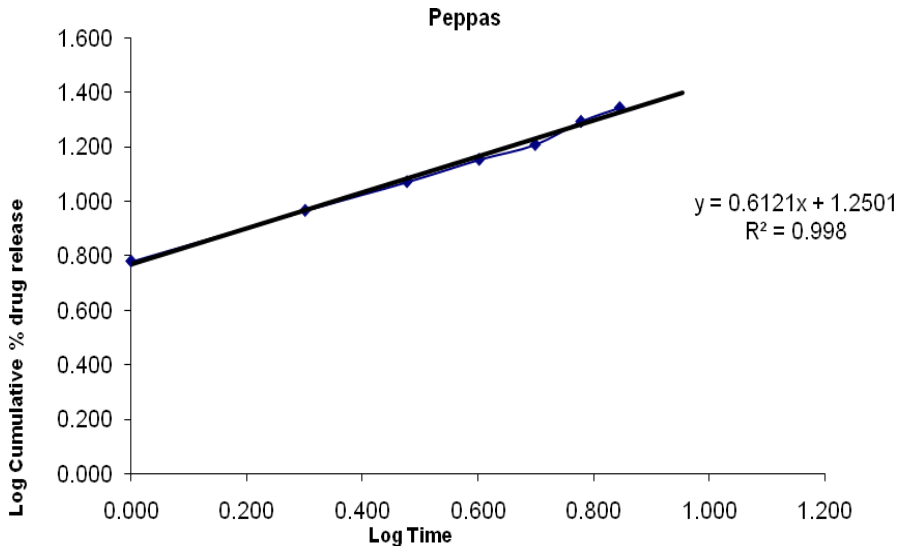

**Ex-vivo drug release studies for optimized formula.**




**First order release kinetic for optimized formula.**




**Higuchi release kinetic for optimized formula.**




**Peppas release kinetics for optimized formula.**


**Zero order release kinetics for optimized formula.**

## CONCLUSION

The transdermal patches of Ropinirole hcl are prepared with different amounts of polymers and different concentrations of various permeation enhancers. Formulation F32 (HPMC 1500mg and Ethyl cellulose 500mg containing 10% Camphor as a permeation enhancer) showed better penetrating activity to other permeation enhancers(Menthol, Urea, Oleic acid, Olive oil, Linseed oil) and targeted flux too achieved, thus providing a better way of preventing first pass metabolism and obtaining a controlled release effect for treatment of Parkinson's disease. The f32 formulation showed better drug release properties both in in-vivo and ex-vivo studies.

The effect of permeation enhanceres on transdermal delivery of Ropinirole Hcl has been studied. Based on the drug diffusion studies effect of the permeation enhancers detected. The order of permeation effect of permeation enhancers is Linseed oil < Olive oil < Oleic acid < Urea < Menthol < Camphor. This variation in their effect of penetration may be because of their permeation mechanisms. Linseed oil and Olive oil increases the penetration by moisturizing the skin so that the cells become loosen, Urea increasing penetration by increasing the fluidity of stratum corneum and partition in aqueous regions, Oleic acid, Menthol and Camphor enhances permeation by lipid disruption mechanism. The release kinetic studies showing that the optimized formulations are following zero order.

The Transdermal patches of Ropinirole hcl with required flux could be prepared with suitable physical properties, and permeation effect of different permeation enhancers studied, further studies are recommended to conduct in-vivo studies and to find therapeutic utility in humans by pharmacokinetic and pharmacodynamic studies.

**REFERENCES**

1. Sahdeo Prasad and Bharat B. Aggarwal, Herbal Medicine: Biomolecular and Clinical Aspects. 2nd edition, Turmeric, the Golden Spice.
2. D.I.J. Morrow, P.A. McCarron, A.D. Woolfson and R.F. Donnelly, Innovative Strategies for Enhancing Topical and Transdermal Drug Delivery, The Open Drug Delivery Journal, 2007; 1: 36-59.
3. Uitti RJ, Ahlskog JE. Comparative review of dopamine receptor agonists in Parkinson's disease. CNS Drugs, 1996; 5: 369–88.
4. D.J. Brooks, J Neurol Neurosurg Psychiatry, 2000; 68: 685–690.
5. Patel, Anil, International application published under The Patent Cooperation Treaty, PCT/EP96/02435, Dec 12, 1996.
6. R.F. Donnelly, D.I.J. Morrow, P.A. McCarron, A.D. Woolfson, Innovative Strategies for Enhancing Topical and Transdermal Drug Delivery, *The Open Drug Delivery Journal*, 2007; 1: 36-59.
7. Oya kerimo lu, Ebru keskin, Betul dortunc and Sela anah, Matrix type Transdermal therapeutic system containing Captopril: formulation optimization, *in-vitro* and *ex-vivo* characterization, Acta Poloniae Pharmaceutica and Drug Research, 2013; 70(2): 291-300.

8. Rizwan. M, Aqil. M, Talegaonkar. S, Azeem. A, Sultana. Y, Ali. A, Enhanced transdermal drug delivery techniques: an extensive review of patents. Recent Patents on Drug Delivery & Formulations, 2009; 3(2): 105-24.
9. S. Lakshmana prabu, A.A Shirwaikar, Annie Shirwaikar, Aravind kumar, Abraham jacob, Design and Evaluation of Matrix Diffusion Controlled Transdermal Patches of Diltiazem Hydrochloride, Ars Pharm., 2008; 49(3): 211-227.
10. Shuming Wang, Hulyong Xue, Li wang, Enhong zang, Hongjun Lian, Xiaoyan shi, Guohua Chi, Yucheng Lu, Xiquang Liu, Li song, Xuying zhong, Hongguang Du, Composition containing Rotigotine and use there of and Transdermal Patch containing the composition, PCT/CN08/01267, Jun 14 2010.
11. Thomas BJ, Finnin BC. The transdermal revolution. Drug Discovery Today, 2004; 9: 697-703.
12. Tsung-Min Hsu, Eric C Jacobson, Rose C.Lobello, Eric C. Luo, Dual Enhancer Composition for Topical and Transdermal Drug Delivery, Patent No. US 6,835,392 B2, Dec 28 2004.
13. V. R. Sinha and Maninder Pal Kaur, Permeation Enhancers for Transdermal Drug Delivery, Drug Development and Industrial Pharmacy, 2000; 26(11): 1131–1140.
14. Jialiang Lin, Jinmai Xiao, Jie Deng, Transdermal Patch containing Rasagiline for treatment or prophylaxis of nervous system disease and its preparation process, PCT/CN07/00713, Sep 05 2008.
15. Ji-Hua Fu, Qiang Zhang, Ji-Hui Zhao, Shu-Ming Wang, Chang-Hai Su, Ying Shan, Shu-Jia Kong, Yuan Wang, Wan-Liang Lu, Hua Zhan, Shuang Zhang, Lin Li, En-Hong Zhang, Li Wang, Qiu-Ling Pei, Jian-Cheng Wang, Xuan Zhang, A novel transdermal patch incorporating isosorbide dinitrate with bisoprolol: In-vitro and in vivo characterization, International Journal of Pharmaceutics, 2007; 337: 88–101.
16. Dennis Lee Schmirler, Edward Malcolm Portman, Michael S. Christensen, compositions, methods and devices for the transdermal delivery of drugs, Patent no.US 6214374 B1, April 10, 2001.
17. Bharti Sap ra, Subheet Jain, and A. K. Tiwary, Percutaneous Permeation Enhancement by Terpenes: Mechanistic View, The AAPS Journal, 2008; 10: 120-132.
18. Bhosale Nilesh R, Hardikar Sharwaree R, Bhosale Ashok V, Formulation and Evaluation of Transdermal patches of Ropinirole HCl, Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2011; 2(1): 138-148.

19. Heather A.E. Benson, Transdermal Drug Delivery: Penetration Enhancement Techniques, Current Drug Delivery, 2005; 2: 23-33.
20. Sravanthi Anampally, Santhosh kumar Mankala, Praveen kumar Gogu, Jithan Aukunuru, Development of Ropinirole (free base) Transdermal Patch using blends of Hydroxypropyl methylcellulose/Eudragits and it's in-vitro/ in vivo characterization, Asian Journal of Pharmaceutical Research and Health care, 2012; 3(4): 89-98.
21. http://triggeryourprime.com/?page_id=29.
22. http://www.drugbank.ca/drugs/DB00268.
23. http://www.drugs.com/monograph/ropinirole-hydrochloride.html.
24. http://www.ncbi.nlm.nih.gov/books/NBK92752/.
25. http://www.rxlist.com/requip-drug.htm.