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Formulation and Evaluation of Transdermal patches of Ropinirole HCl

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ABSTRACT

The conventional multidose antiparkinsons therapy leads to re-emergence of Parkinson's symptoms, due to fluctuations in serum levels of drug. The rational strategy to overcome this drawback is to minimize the fluctuations by fabricating sustained release formulations. Ropinirole HCl is a drug used to treat Parkinson's disorder and it is suitable drug candidate for transdermal delivery due to its small molecular size, optimum log P and low oral bioavailability due to first pass metabolism. Hence the present study was aimed at development of transdermal patch of Ropinirole HCl to show its prolonged release. The combination of HPMC K15 and Eudragit RL100 was tried as a porous matrix to control the release of Ropinirole HCl up to 12 hrs. The transdermal patches were prepared by solvent casting method. All the patches were evaluated for the permeation along with physical studies including appearance, thickness, folding endurance, drug content, percentage of moisture content and percentage of moisture uptake. The results of physical parameters ensured integrity, stability and applicability of the patches. The results of permeation studies clearly indicated that the release pattern of Ropinirole HCl can be controlled by maintaining appropriate proportion of HPMC K15 and Eudragit RL 100 in the matrix. No erythma was found within 12 hr after application of optimized transdermal patch when compared with standard irritant. Thus this formulation was suitable for transdermal application.

Keywords: Ropinirole HCl, Transdermal patch, DMSO, penetration enhancer.

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INTRODUCTION

Parkinson's disease is neurological, chronic and progressive disorder that affects extrapyrimidal system of brain. Ropinirole HCl (4-[2-dipropylamino)ethyl]-1,3-dihydro-2-H-indol-2-one-hydrochloride) is a new nonergoline dopamine agonist recently introduced into Parkinson's disease therapy. The conventional oral antiparkinsons therapy related motor manifestations described as "On-Off" phenomena leads to re-emergence of Parkinson's symptoms during 'off' state period. In such cases physicians constantly need to adjust the dose and dosing frequency of the medications to maximize the period of 'on' state and minimize the period of 'off' state and dyskinesia. The rational strategy to bypass this phenomenon is to minimize the periods the fluctuations in plasma levels of drug. This can be attained by incorporating the drug into transdermal patch and controlling its permeation from the matrix. This study was aimed at development of transdermal patch for delivery of Ropinirole HCl as it is better accepted and convenient than transdermal gels and ensures prolonged release of drug [1].

The term "Transdermal Drug Delivery System" (TDDS) essentially means any formulation containing substances that allows the drug to transit from the outside of the skin through various skin layers and finally into the circulatory system to produce a pharmacological action. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a particular tissue [2]. Transdermal drug delivery system can deliver medicines via the skin portal to systemic circulation at a predetermined rate and maintain clinically effective concentrations over a prolonged period of time [3].

The short elimination half life of 4-6hrs of Ropinirole HCl, its low oral bioavailability(35%) due to its extensive first pass metabolism, along with disadvantage of its conventional therapy reported as "off phenomenon" demands better alternative for its delivery. Though TDDS is the dosage form of choice for very few drugs, Ropinirole would be a right candidate ,due to its low molecular weight (260.37 D) and optimum log P value(2.3) [4]. Hence, in the present study, Transdermal patch for Ropinirole HCl was designed and developed to achieve sustained release of Ropinirole HCl.

In spite of many advantages of transdermal delivery system over oral delivery only limited numbers of drugs have been used to develop the system due to excellent barrier function of the skin [5]. Inclusion of penetration enhancer is one of the technique to overcome this drawback and hence dimethyl sulphoxide was selected in the present study as a penetration enhancer. Transdermal drug delivery systems also contain many other components than penetration enhancer including those which control the release rate of drug from matrix. Since the present study was aimed at prolonged release of Ropinirole HCl, a combination of Eudragit RL 100 and HPMC K15 were used in formulation. The permeation from the optimized batch was found to be of zero order.

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MATERIALS AND METHODS

Materials

Ropinirole Hydrochloride was received as a gift sample from Wockhardt Ltd (Aurangabad, India), Eudragit RL 100 and HPMC K15 were obtained from Colorcon Asia Pvt Ltd. All other ingredients used were of pharmaceutical grade.

Methods

Preparation of preliminary transdermal patches

Table 1 Compositions of Preliminary formulations

Formulations	Drug(mg)	Ratios of HPMCK15+Eudragit RL100*	Methanol:water (9:1)	PEG400(ml)
F1	100	8:2	10 ml	0.1
F2	100	6:4	10 ml	0.1
F3	100	4:6	10 ml	0.1
F4	100	2:8	10 ml	0.1

*The amount of polymer mixture used was 300 mg.

Transdermal patches composed of different ratios of HPMC K15, Eudragit RL 100, PEG 400 were prepared by solvent casting method. The drug and polymers were weighed in requisite ratio and they were then dissolved in 10 ml of Methanol: water (9:1) mixture. PEG400 was incorporated as a plasticizer. The resultant solutions were poured into a Petri dish and were dried overnight. The Ropinirole HCl patches were then stored in dessicator [6]. The compositions of preliminary patches are reported in table number 1.

In Vitro skin permeation study

In vitro skin permeation study for all preliminary patches were performed using a vertical Franz diffusion cell whose diffusion area was 1.59 cm^2 , and hairless rat skin as a permeation membrane. The skin was excised and subcutaneous fat and other extraneous tissue were trimmed. The skin was mounted on the Franz diffusion cells with the stratum corneum (SC) facing the donor compartment. The receptor compartment was 7 ml in volume, and filled with pH 7.4 phosphate buffer solution (PBS) whose temperature was maintained as 32^0 C. sampling was done after every 1 hr till 12 hrs.

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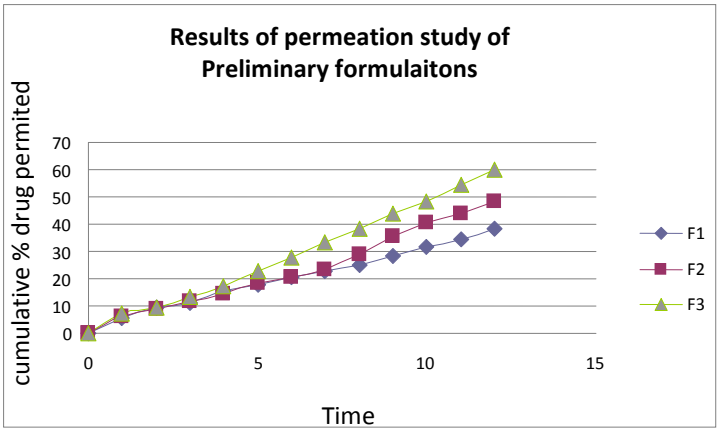

Figure 1 Results of permeation studies for formulations F1-F3

The collected samples were subjected to UV analysis to determine the content of Ropinirole HCl in PBS [7]. The results are reported in figure number 1. The conducted study in present work was approved by IAEC CPCSEA/311/18/2009-10.

Compositions of formulations to study the effect of penetration enhancer on permeation of Ropinirole HCl

Table 2 Compositions of formulations contain penetration enhancer

Formulations	Drug(mg)	Ratios of HPMCK15+ Eudragit RL 100*	Methanol: water (9:1)	PEG400 (ml)	Penetration enhancer
F5	100	4:6	10 ml	0.1	DMSO(5%)
F6	100	4:6	10 ml	0.1	Ethanol(5%)
F7	100	4:6	10 ml	0.1	SLS(5%)

*The amount of polymer mixture used was 300 mg.

The results of permeation study of formulations F1-F4 clearly indicated optimum permeation of Ropinirole HCl from formulation F3. Therefore this formulation was selected for further studies to study the effect of penetration enhancer on permeation of Ropinirole HCl**.** The permeation enhancers selected were DMSO, Ethanol and sodium lauryl sulphate (SLS). The compositions of formulations are reported table number 2. The method of preparation of patch was same as reported earlier. The penetration enhancer was dissolved at the end in the concentration of 5% or 10% w/w of total weight of polymer.

These formulations were critically evaluated for evaluated for in vitro flux (Jss) and permeability coefficient (Kp). The in vitro flux(J_{ss}) was determined by Fick's law of diffusion, considering the transport of drugs across the skin barrier as a process of passive diffusion. The skin flux(µg/cm^2/h),was determined from the slope of linear portion of the cumulative amount

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permeated per unit area versus the time plot. The permeability coefficient (K_p) (cm/h), was determined from the equation number 1:

$$Kp = J_{ss} / C_0 \text{ - - - - - - - - - - - - - - - Eq.(1)}$$

Where C_0 is the concentrationof drug in donor compartment [8].

Table 4 Compositions of Formulations containing various concentrations of DMSO

Formulations	Drug(mg)	HPMCK15+ Eudragit RL 100*	Methanol: water (9:1)	PEG400(ml)	Penetration enhancer
F8	100	4.5:5.5	10 ml	0.1	_
F9	100	4.5:5.5	10 ml	0.1	5%
F10	100	4.5:5.5	10 ml	0.1	10%
F11	100	4:6	10 ml	0.1	10%
F12	100	3.5:6.5	10 ml	0.1	_
F13	100	3.5:6.5	10 ml	0.1	5%
F14	100	3.5:6.5	10 ml	0.1	10%

*The amount of polymer mixture used was 300 mg.

The results of these permeation parameters for formulations F5-F7 are reported in table number 4.

Optimization of Composition of transdermal patch of Ropinirole HCl

Table 3 Results of Flux,permeability coefficient

Formulation code	Flux (µg/cm^2/hr)	Permeability coefficient(cm^2/hr)
F5	194	0.0388
F6	170	0.034
F7	178	0.0356

Table 5. Evaluation of Transdermal patches

Code	Drug content (mg/cm^2)	Folding Endurance	Wt variation mg	%moisture content	%moisture uptake	Thickness (mm)	Cumulative % Drug diffuse in 12 h	Flux (µg/cm^2/hr)	Permeability coefficient (cm^2/hr)
F8	1.59±0.02	>100	25±1	2.77±0.2	1.12±0.2	0.5	52.33±0.2	134	0.0268
F9	1.6±0.01	>100	26±1	2.29±0.1	2.48±0.1	0.6	63.65±0.5	254	0.0338
F10	1.59±0.02	>100	25±2	1.48±0.1	2.56±0.2	0.7	74.27±0.7	204	0.041
F3	1.6±0.01	>100	26±1	1.75±0.2	2.43±0.3	0.6	60.75±0.6	156	
F4	1.59±0.02	>100	25±2	1.85±0.2	2.64±0.2	0.7	70.24±0.3	194	0.0388
F11	1.61±0.01	>100	25±1	2.93±0.2	1.92±0.1	0.6	85.38±0.1	223	0.0446
F12	1.6±0.01	>100	26±1	1.58±0.1	1.12±0.1	0.7	72.83±0.3	174	0.0348
F13	1.59±0.01	>100	26±2	2.17±0.1	2.97±0.2	0.7	81.77±1.2	204	0.041
F14	1.6±0.01	>100	25±1	2.38±0.2	2.29±0.1	0.6	96.27±0.9	264	0.0528

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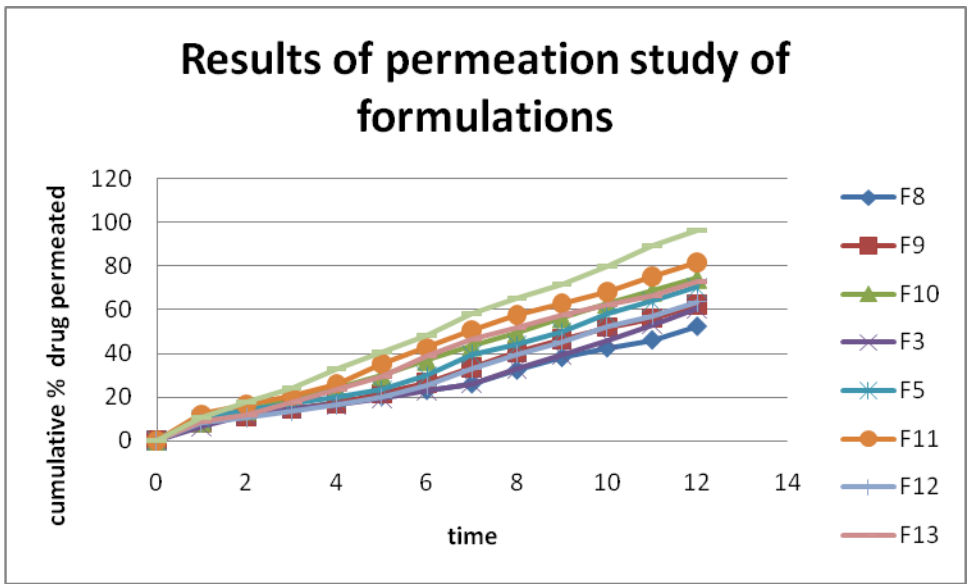

Figure 3. Results of permeation study for F3,F5 and F8-F14

In the present study DMSO was proved to be most efficient as a penetration enhancer than ethanol and SLS. It was also observed that optimum release of drug was there when the proportion of Eudragit RL 100 was greater than HPMCK15. Since both these factors influenced the permeation pattern of drug; different formulations (F8-F14) were designed using different concentrations of DMSO and polymer mixtures. The compositions of formulations are reported in table number 3. All the formulations were evaluated for various permeation parameters and the results are reported in table number 5 and figure number 3.

Evaluation of Transdermal patches [9]

Formulations F8- F14 were evaluated for physical appearance, weight uniformity, thickness, folding endurance, percent moisture content, percent moisture uptake, drug content uniformity and permeation studies. The results are reported in table number 5.

Physical appearance

All the transdermal patches (F8-F14) were visually inspected for color, clarity, flexibility and smoothness.

Weight uniformity

The dried patches were weighed on digital balance. Averages of five observations were taken.

Thickness

Patch thickness was measured using micrometer screw gauge at three different places of each patch and the mean value was calculated and reported.

Folding endurance

Folding endurance of each patch was determined by repeatedly folding a small strip of patch at same place till it broke. The number of times the patch could be folded at the same place without breaking was reported as the folding endurance value.

Percentage of moisture content

The patches were weighed individually and kept in a desiccators containing activated silica at room temperature until they lost all the moisture and was confirmed by their constant weight. The percentage of moisture content was calculated from the difference between initial and final weight of the patch.

Percentage of moisture uptake

A weighed patch kept in a desiccator at room temperature for 24 hrs was taken out and exposed to 84% relative humidity (a saturated solution of aluminium chloride) in a desiccator until a constant weight for the patch was obtained. The percentage of moisture uptake was calculated from the difference between final and initial weight of the patch.

Drug content uniformity

Transdermal patch of 1 sq.cm area was cut into small pieces and transferred into 100 ml volumetric flask. 25 ml of methanol was added and shaken for 4 hrs to extract the drug. Finally suitable dilutions were made using phosphate buffer pH 7.4 and absorbance was measured at 249 nm.

Skin irritation study [10, 11]

The albino Wistar rats were housed in polypropylene cages, with free access to standard laboratory diet and water. Animal were acclimatized for at least 7 days before experimentation. The dorsal abdominal skin of rats was shaved 24 h before study. Transdermal patch (F14) was applied and side of application was occluded with gauze and covered with a nonsensitizing microporous tapes. A 0.8 %v/v aqueous solution of formalin was applied as standard skin irritant. The formulation was removed after 24 h and score of erythema was recorded and compared with standard. Score of erythema is read and recorded as: Score 0 for no erythema; Score 1 for Mild erythema (barely perceptible- light pink); Score 2 for Moderate erythema (dark

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pink); Score3 for Severe erythema (Extreme redness). The conducted study in present work was approved by IAEC CPCSEA/311/18/2009-10

RESULTS AND DISCUSSION

Evaluation of Preliminary formulations

HPMCK15 is hydrophilic polymer and was reported as release retardant of a drug [12]. The purpose of present study was to prolong the release of a drug upto 10-12hrs from the transdermal patch. Hence hydrophobic polymer Eudragit RL 100 was incorporated along with HPMCK15; since had reported to has more water permeation properties [13]. Thus it was expected that it may serve as porous matrix releasing more amount of drug from patch. The permeation data clearly indicated that the highest permeation rate was obtained from formulation F3 as expected due to highest proportion of Eudragit RL100 than F1 and F2 which was essential for faster drug release and hence permeation. The appearance and mechanical properties of formulation F4 were not upto the mark and hence the formulation was rejected.

Effect of penetration enhancers on the In vitro skin permeation of Ropinirole HCl through the rat skin

The purpose of developing the TDDS for Ropinirole HCl was to attain minimum effective concentration as early as possible and maintain it for a prolong period. Thus there was a need of penetration enhancer to load the drug in systemic circulation and ensure quick onset of action which would be followed by sustained release of a drug from formulation. The results of permeation studies after addition of penetration enhancers are reported in figure number 2.

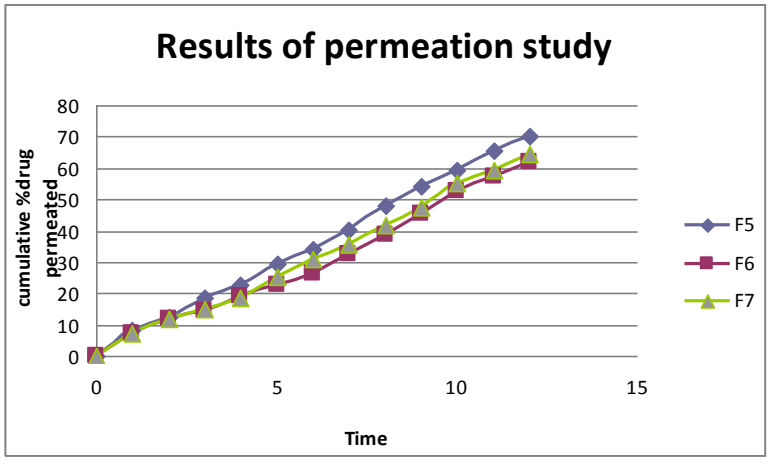

Figure 2. Results of permeation studies for F5-F7

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The permeation data was also analyzed for the parameters like Flux, permeability coefficient and the results are reported in table number 4. The steady state flux achieved from formulation containing DMSO was highest (194 µg/cm^2/h) as compared to ethanol (170 µg/cm^2/h) and SLS (178 µg/cm^2/h). Highest permeation coefficient was achieved using DMSO in formulation. The evaluation results revealed that flux of F5 was highest than other formulations and rate of passage of drug through membrane was highest as well, as indicated by its Permeability coefficient value. Flux and permeability coefficient values were found to be highest for formulation containing DMSO among all permeation enhancer tested. This could be explained by the fact that DMSO is a powerful dipolar aprotic solvent which forms an association complex through dipole-dipole interactions and through hydrogen bonding interactions which are stronger than those formed between water molecules. Skin penetration enhancement produced by DMSO involves changes in protein structure and may also be related to alterations in stratum corneum lipid organization besides any increased drug partitioning effects [14]. Since barrier capacity of the skin is due to integrity of stratum corneum, increase in permeation of a drug is obvious when DMSO is used as a penetration enhancer.

Evaluation of formulations for optimized permeation

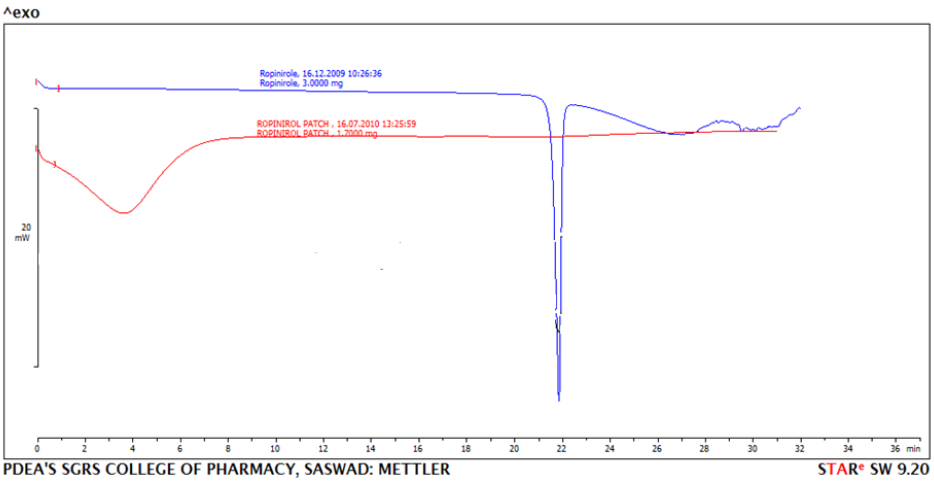

Figure 4. DSC thermogram of Ropinirole HCl and optimized transdermal patch

All patches prepared by using various concentrations of DMSO and various mixtures of HPMC K15 and Eudragit RL 100 of were transparent with smooth appearance. Uniformity in weight of patches (25mg-26mg), drug content (1.59-1.61mg/patch), thickness (0.6mm-0.7mm) indicated physical uniformity in prepared patches. Folding endurance test results indicated that patches had optimum strength ensuring their integrity and applicability. There was no weight variation in all formulations. The moisture content of the patches was low enough which ensured stability during storage. The moisture uptake of the transdermal formulations was also low, which would prevent microbial contamination and also reduces bulkiness of films. Inclusion of Eudragit in the patch also prevented crystallization of the drug aiding its release

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from the patch [15]. This fact was supported by DSC studies (figure 4). Endothermic peak of Ropinirole HCl disappeared in the mixture of patch components. This might be due to molecular dispersion of Ropinirole HCl in the polymer matrix. The F14 containing higher conc. of DMSO and higher amount of Eudragit showed 96.27% drug release in 12 hrs. This fact could be justified because of fact that the better water permeation properties of Eudragit RL 100.Thus Eudragit released the drug at faster rate and DMSO improved its penetration.

Since maximum permeation was observed from F14, this formulation was selected for skin irritation study.

Skin irritation study

(a) Tested animal: score 0 indicates no erythma (b) Standard irritant animal (0.8 %v/v formalin solution) Score3: Severe Erythema (Extreme redness)

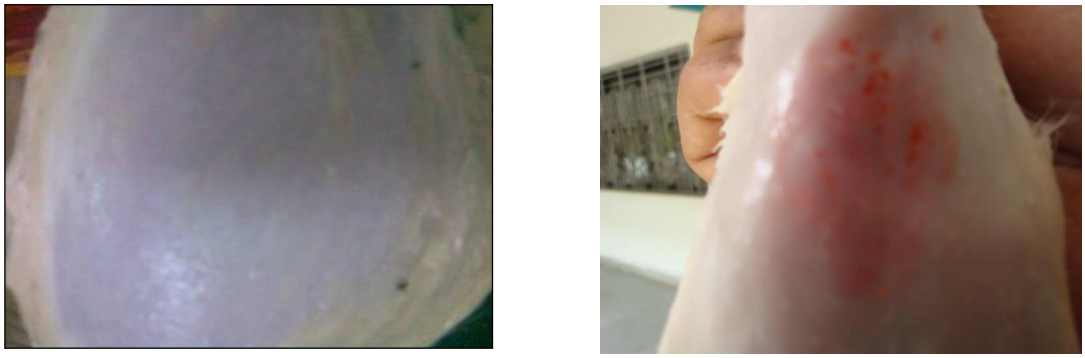

Figure 5. photographs of skin irritation studies

No erythema was found within 12 hr after application of optimized transdermal patch (F14) when compared with standard irritant. Thus this formulation was suitable for transdermal application.

CONCLUSION

Parkinson's treatment demands prolonged and sustained plasma levels of the drug which ultimately depends upon the release pattern of a drug from transdermal patch. In the present study a mixture of HPMC K15 and Eudragit RL 100 was tried to control the release of Ropinirole HCl over a prolonged period. Permeation results of optimized formulation revealed zero order release pattern. Hence this combination of polymers can be successfully manipulated to attain desired efficacy of Ropinirole HCl with minimum fluctuations in plasma levels.

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