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# A FACTORIAL STUDY, FORMULATION AND EVALUATION ROPINIROLE HYDROCHLORIDE TRANSDERMAL FILMS

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## ABSTRACT

The present work aimed at preparing transdermal films of Ropinirole Hydrochloride with the purpose of developing a dosage form for a sustain release of action, which is very convenient for administration, without the problem of swallowing and using water. The films of Ropinirole Hydrochloride were prepared by using polymers such as HPMC K4M and PEG 400 as plasticizer, by a solvent evaporation method. Formulation batches were formulated with the help of $3^2$ full factorial designs. The transdermal films were designed using optimal design and numerical optimization technique was applied to find out the best formulation. The formulated Transdermal films were evaluated for physical characteristics such as uniformity of weight, thickness, folding endurance, drug content uniformity, surface pH, percentage and tensile strength and gave satisfactory results. The formulations were subjected to, *In-vitro* drug release tests. The IR and UV studies revealed that no physicochemical interaction between excipients and drug. Transdermal flim containing HPMC K4M showed 98.19% drug release. Transdermal films of Ropinirole Hydrochloride containing HPMC showed better tensile strength (9.67 ± 0.064g/mm2), folding endurance (162 No. of folds), surface pH (6.60 ± 0.10 pH), thickness (0.61 mm) and percentage content uniformity (98.19%). Stability studies revealed that optimized formulation was stable. Transdermal films of Ropinirole Hydrochloride can be considered suitable for clinical use in the treatment of parkinson's disease and rest leg syndrome, where a sustain release of action for a dosage form is desirable along with the convenience of administration.

**KEYWORD:** Ropinirole Hydrochloride, HPMC K4M, Polyethylene Glycol 400, Solvent Evaporation method, Parkinson disease.

## TRANSDERMAL DELIVERY SYSTEM

Any drug delivery system aim is to provide a therapeutic amount of drug to the proper site in the body and then maintain desired drug concentration. Drugs are administered by various routes such as oral, parental, nasal, transdermal, rectal, intravaginal, ocular etc. Among all of them, oral route is most common and popular but this route of administration have some drawback like first pass metabolism, drug degradation in gastrointestinal tract due to pH, enzyme etc. To overcome these drawback, a novel drug delivery system (controlled drug delivery system) was developed in which a polymer(natural or synthetic) combined with a drug in such a way that drug is released from the material in a predesigned manner. The discovery of Transdermal drug delivery system(TDDS) is a breakthrough in the field of controlled drug delivery system. It become a great field of interest. TDDS are 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. In 1965 Stoughton first conceived of the percutaneous absorption of drug substances. FDA approved the first Transdermal system Transderm-SCOP in 1979. FDA approved this for the prevention of nausea and vomiting.

In TDDS, the drug is mainly delivered through the skin with the aid of transdermal patch which is a medicament adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and to the blood stream. Now a day TDD is a well-accepted means of delivering many drugs to the systemic circulation in order to achieve a desired pharmacological outcome. The success of this approach is evidenced by the fact that there are currently more than 35 TDD products approved in the USA for the treatment of conditions including hypertension, angina, female menopause, severe pain states, nicotine dependence, male hypogonadism, local pain control and more recently, contraception and urinary incontinence.

## ADVANTAGES

1. Transdermal medication delivers a steady infusion of a drug over an extended period of time.
2. Transdermal delivery can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug e.g., gastro-intestinal irritation, low

absorption, decomposition due to hepatic "first-pass" effect, formation of metabolites that cause side effects, short half-life necessitating frequent dosing etc.

3. They are non invasive, avoiding the inconvenience of Parenteral therapy
4. The drug input can be terminated at any point of time by removing transdermal film
5. The simplified medication regimen leads to improved patient compliance and reduced inter & intra – patient variability.
6. Self administration is possible with these systems.
7. They can be used for drugs with narrow therapeutic window.
8. Longer duration of action resulting in a reduction in dosing frequency.
9. Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.

**DISADVANTAGES**

1. The drug must have some desirable physicochemical properties for penetration through stratum corneum and if the drug dose required for therapeutic value is more than 10mg/day, the transdermal delivery will be very difficult.
2. Only relatively potent drugs are suitable candidates for TDDS because of the natural limits of drug entry imposed by the skin's impermeability.
3. Some patients develop contact dermatitis at the site of application for one or more of the system components, necessitating discontinuation.
4. Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.
5. The barrier function of the skin changes from one site to another on the same person, from person to person and with age.
6. Many drugs especially drugs with hydrophilic structures permeate the skin too slowly may not achieve therapeutic level.
7. The drug, the adhesive or other excipients in the patch formulation can cause erythema, itching and local edema.

**MATERIALS AND METHODS**

**Materials** Ropinirole Hydrochloride was received as a gift sample from Orchid Chemicals & pharmaceuticals Ltd,(Aurangabad, India). HPMC K4M and PEG 400 were obtained from Mukta engg pvt Ltd shrirampur All other ingredients used were of pharmaceutical grade.

## METHODS

### Preparation Of Transdermal Film

### 1. Preparation of blank films

Transdermal films were prepared using HPMC K4M, by solvent casting method method. The polymers were weighed in requisite ratio and dissolved in Methanol. Proper amount of PEG added with the help of micropipette. PEG in 20%, 30% and 40% w/w of polymer composition was used as plasticizer. Homogeneous dispersion was formed by stirring with a mechanical stirrer. The uniform dispersion was then poured into a glass ring mould of 6 cm diameter with surface area of 28.26 cm which was placed in a petri dish. The solvent was allowed to evaporate under ambient conditions (Temperature:60 C) for 4 hr in Hot air oven. Films were lifted from the glass ring mould and initially observed for properties such as removal from glass rings, clarity, flexibility and stickiness, surface gloss etc. These patches were kept in desiccators for 2 days for further drying and wrapped in aluminum foil, packed in self-sealing covers.

### 2. Formulation of Medicated films

Transdermal films containing Ropinirole Hydrochloride were prepared using different ratio of HPMC K4M, combination by solvent evaporation method. The polymers were weighed in requisite ratio and dissolved in Methanol. Proper amount of PEG added with the help of micropipette. PEG 40% w/w total weight of polymer composition was used as plasticizer. Methanol was added 10 ml of the total weight of polymers; homogeneous dispersion was formed by slow stirring with a mechanical stirrer. The uniform dispersion was then poured into a glass ring mould of 6 cm diameter placed in a Petri dish. The solvent was allowed to evaporate under ambient conditions (Temperature: 60 C) for 4 hr. Aluminum foil was used as backing membrane and prepared film was stored in desiccators until used.

### Preparation Of Transdermal Film Of Ropinirole Hydrochloride By Using $3^2$ Full Factorial Designs

**Optimization study in brief:** The $3^2$ full factorial design was applied to formulations. The two factors were concentrations of HPMC K4M and PEG. The three levels of each factor were three different concentrations of HPMC K4M and PEG. So, nine formulations were evaluated for in vitro evaluation parameters and optimized formulation was selected.

**Table No. 1: Independent Variables.**

| Factor | Name | units | Minimum -1 | Medium 0 | Maximum +1 | Level |
|---|---|---|---|---|---|---|
| A | PEG | Ml | 3 | 4 | 5 | Levels: 3 |
| B | HPMC, K4M | Mg | 100 | 200 | 300 | Levels: 3 |

**Table No. 2: Factor combination as per the$3^2$full factorial design.**

| Independent Variable | F1 | F2 | F3 | F4 | F6 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| X1 (PEG) | -1 | -1 | -1 | 0 | 0 | 0 | +1 | +1 | +1 |
| X2 (HPMC K4M) | -1 | 0 | +1 | -1 | 0 | +1 | -1 | 0 | +1 |

**Table no 3: Composition of transdermal films of Ropinirole Hydrochloride.**

| Sr. No. | INGRIDIENT | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Ropinirole Hydrochloride | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| 2 | HPMC K4M | 100 | 200 | 300 | 100 | 200 | 300 | 100 | 200 | 300 |
| 3 | PEG | 3 | 3 | 3 | 4 | 4 | 4 | 5 | 5 | 5 |
| 4 | Methanol | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

## EVALUATION OF TRANSDERMAL FILMS

### 1. Physical appearance

Films of each formulation were randomly selected and inspected visually as well as by touch for texture.

### 1. Thickness

Five films of each formulation were taken and the film thickness was measured by Using micrometer screw gauge at different strategic locations (5 locations). Mean thickness and standard deviation were calculated.

### 2. Surface pH of films

The surface pH of films was determined to investigate the possible side effect because of change in pH. The film to be tested was placed in a test tube and was moistened with 1.0 ml of distilled water and kept for 30 second. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibrating for 1 min. The average of three determinations for each of the formulation was taken and standard deviation was also calculated.

### 3. Drug content uniformity

Content uniformity is determined by estimating the API content in individual strip. Three films from each formulation were took and individually dissolved in 50 ml of 6.8 pH

phosphate buffer to give solutions of 10µg/ml concentration. These solutions were filtered and absorbance of each solution was recorded at 250 nm (λ max of Ropinirole Hydrochloride) using the blank film solution as a blank. The percentage drug content was determined. Mean of the percentage drug content and standard deviations were calculated. The Limit of content uniformity is 85-115%.

**4. Folding endurance**

Three films of each formulation of 4cm$^2$(2× 2 cm) were cut by using sharp blade. Folding endurance was determined by repeatedly folding a small strip of film at the same place till it break. The number of times, the film could be folded at the same place without breaking gave the value of folding endurance. The mean value of three readings and standard deviation were calculated.

**5. Drug release study**

Dissolution bath apparatus 2 with mini was used to perform the release test for patches. The patches were fixed at baskets and placed at the bottom of the vessel in quantity 50mL at pH 7.4 phosphate buffer. The patches were glued to metal disks and placed at the bottom of the vessel at pH 7.4 phosphate buffer with its release surface up.

**6. Tensile strength**

To determine tensile strength of transdermal films in the transdermal patch were sandwiched individually by corked liner iron plates. One end of the film was kept fixed with the help of iron screen and other end was connected to freely movable thread over a pulley. The weight was added gradually to the pan close with the hanging end of the thread. A pointer on the thread used to measure the elongation of the film. The weight just sufficient to break the film was noted, the tensile strength can be calculated using the following equation.

Tensile strength = Maximum applied force/ Minimum cross sectional area

= m × g / b × t kg / mm²

Where, m- mass in kg g- Acceleration due to gravity at 980 cm/ sec²

## RESULTS AND DISCUSSIONS

## PREFORMULATION STUDY

### Preformulation Study of Drug

### I. Organoleptic properties

The Sample of drug received was studied for its organoleptic characters such as color, odour, appearance. The result are presented in the following Table.

**Table no 4: Organoleptic properties of Ropinirole Hydrochloride.**

| Properties | Observed Result | Reported Result |
|---|---|---|
| Color | White | White |
| Odour | Odorless | Odorless |
| Appearance | Fine powder | Fine powder |

### II. Solubility of Ropinirole Hydrochloride

Ropinirole Hydrochloride was found to be soluble in water Solubility of Ropinirole Hydrochloride were shown in Table.

**Table No. 5: Solubility of Ropinirole Hydrochloride.**

| Solvent | Observed Solubility (mg / mL) | Reported Solubility (mg/mL)[69] |
|---|---|---|
| Water | 120 | 133 |

### III. Melting point

Melting point of Ropinirole Hydrochloride observed was as shown in Table 8.

**Table No. 6: Melting point of Ropinirole Hydrochloride.**

| Sr no | Method | Observd M.P | Reported M.P |
|---|---|---|---|
| 1 | Thieles tube | $248^0$ C | $243^0$C-$250^0$C |

### UV Spectrophotometric analysis of Ropinirole Hydrochloride

The UV spectrum was recorded in the range 200-400 nm. The wavelength of maximum absorption (λmax) was determined from the scan and then further preparation of (standard) curve was carried out at the detected wavelength of maximum absorption (λmax).

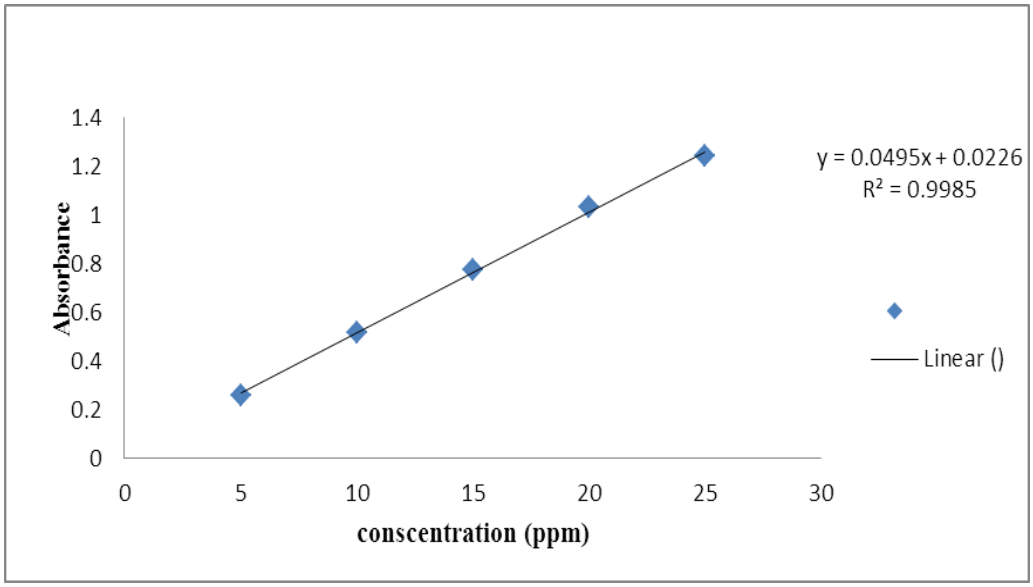


**Fig no 1 Construction of Beer's Lamberts plot in distilled water.**

**IR spectrum interpretation**

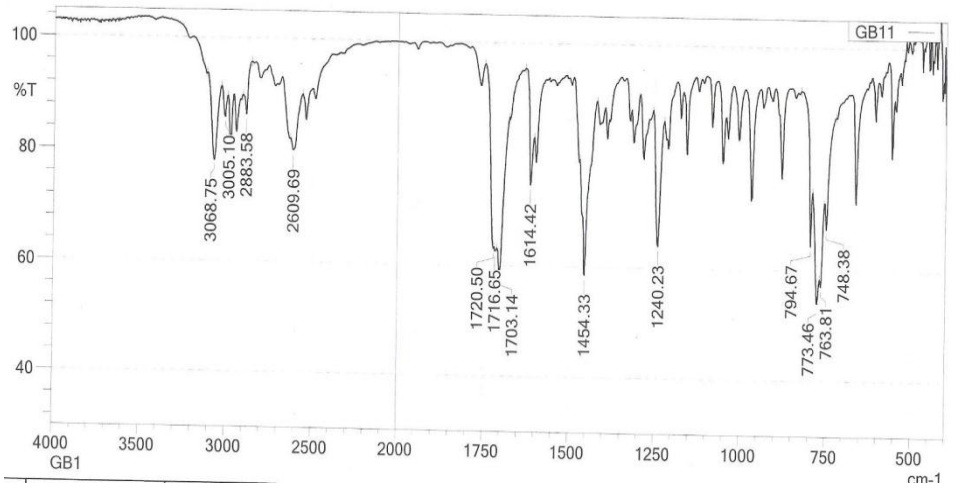


**Fig no 2. IR spectrum of Ropinirole Hydrochloride.**

**Table No. 7: Interpretation of IR.**

| Sr. No. | Functional group | Frequency ($cm^{-1}$) |
|---|---|---|
| 1 | Amines(N-H) | 3068 |
| 2 | Esters(C=O) | 1770.50 |
| 3 | Alkyl(CH) | 3005 |
| 4 | C=C | 1454.33 |
| 5 | Nitrile | 124..23 |

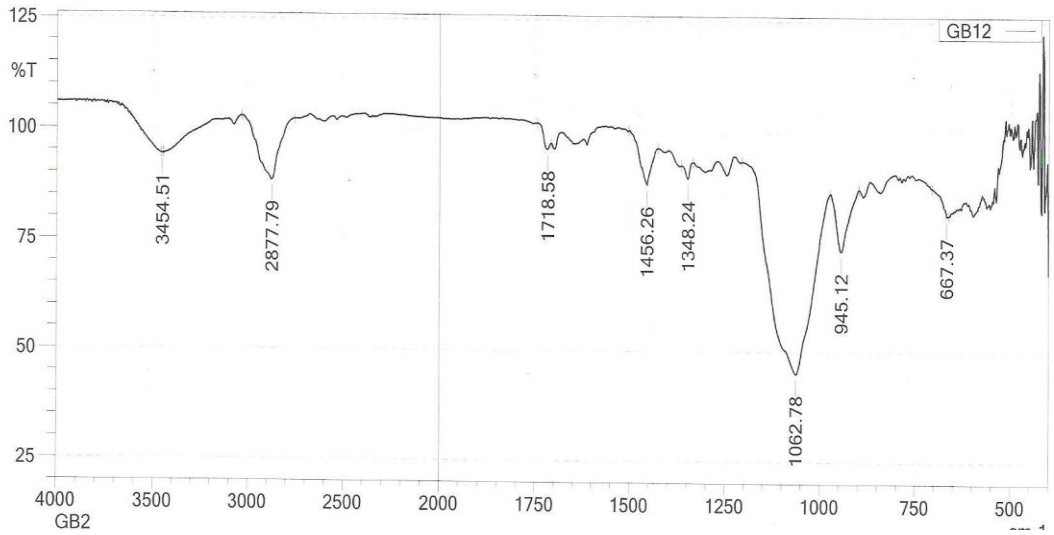


**Fig no 3 IR spectra of Ropinirole Hydrochloride with HPMC K4M.**

**Table No7: IR spectrum interpretation of Ropinirole Hydrochloride with HPMC K4M.**

| Sr. No. | Functional group | Frequency (cm-1) |
|---|---|---|
| 1 | Amines | 3464 |
| 2 | Alkyl | 7877.79 |
| 3 | C=C | 1456.26 |

**Table No. 8: Evaluation parameters of formulations.**

| Formulation | Tensile strength | Thickness† (mm | Folding Endurance | Surface pH | Drug Content uniformity % |
|---|---|---|---|---|---|
| F1 | 9.19 | 0.61 | 150 | 6.3 | 94.11 |
| F2 | 9.33 | 0.73 | 133 | 6.3 | 93.52 |
| F3 | 9.53 | 0.86 | 120 | 6.4 | 92.35 |
| F4 | 9.67 | 0.58 | 155 | 6.4 | 94.70 |
| F5 | 10.8 | 0.72 | 140 | 6.2 | 92.94 |
| F6 | 12.03 | 0.93 | 128 | 6.6 | 93.52 |
| F7 | 13.21 | 0.65 | 162 | 6.1 | 92.35 |
| F8 | 15.60 | 0.74 | 142 | 6.7 | 94.70 |
| F9 | 16.33 | 0.90 | 137 | 6.6 | 91.17 |

**Table no 9: Drugrealease data of formulations formulations F1,F2,F3,F4, F5, F6, F7, F8 and F9.**

| TIME (In Mins) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| **5** | 4.21 | 3.59 | 3.56 | 4.43 | 3.17 | 2.51 | 3.90 | 2.13 | 2.82 |
| **10** | 9.02 | 7.92 | 7.15 | 11.19 | 7.47 | 6.51 | 9.85 | 9.01 | 6.81 |
| **15** | 16.53 | 13.44 | 12.67 | 22.25 | 12.4 | 13.32 | 19.61 | 15.89 | 11.55 |
| **30** | 26.95 | 23.20 | 22.43 | 34.83 | 23.46 | 23.04 | 32.03 | 26.22 | 19.09 |
| **45** | 44.64 | 39.96 | 38.46 | 52.28 | 39.56 | 37.03 | 52.9 | 39.42 | 33.36 |
| **60** | 69.09 | 63.88 | 59.31 | 72.85 | 59.88 | 57.85 | 73.72 | 61.1 | 54.25 |
| **120** | 98.19 | 92.11 | 82.519 | 97.21 | 90.04 | 84.06 | 96.87 | 89.73 | 82.21 |

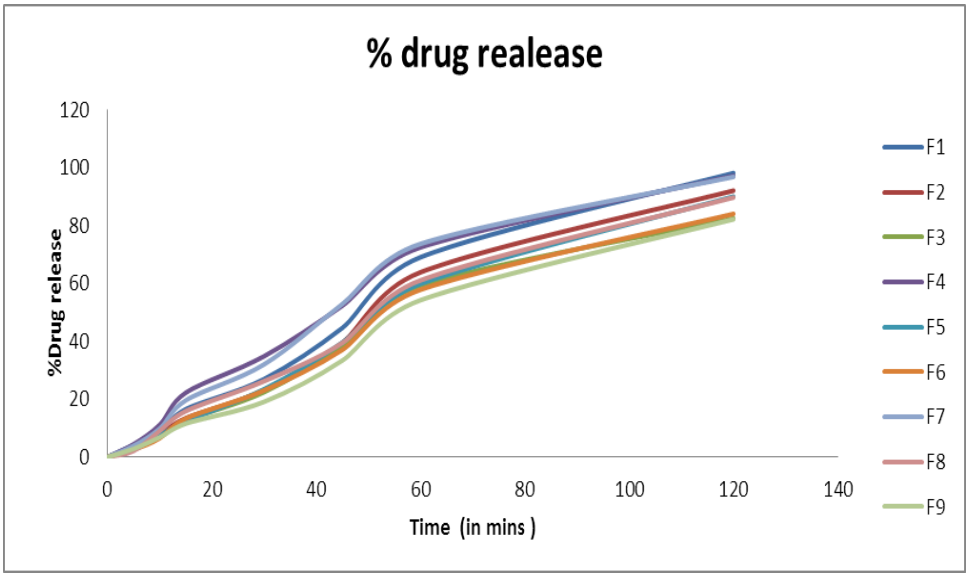


**Fig no 4 % Drug released profiles of formulations F1,F2,F3,F4, F5, F6, F7, F8 and F9.**

## SUMMARY AND CONCLUSION

From all observations and results obtained it can be concluded that All the prepared formulations show satisfied organoleptic properties. Ropinirole Hydrochloride was initially characterized for its preliminary studies such as organoleptic properties, melting point, solubility, UV Spectroscopy, IR studies. As no unaccountable peaks was observed in IR analysis, so it confirmed the purity of developed formulations and no interaction of excipients with drug. Transdermal films were prepared by solvent-evaporation method using hydrophilic film forming polymer HPMC K4M and PEG as plasticizer. Films prepared were smooth and elegant in appearance and showed no visible cracks; were uniform in thickness, weight and drug content.

Optimization of Transdermal flim was carried out using $3^2$ factorial design, with independent variables as concentration of HPMC K4M ($X_1$) and concentration of PEG ($X_2$). This design was employed to study the effect of independent variables on various dependent variables such as *In vitro* drug release at 120min., Thickness and folding endurance. The nine formulations prepared were subjected to physical evaluation parameters like physical appearance, thickness, surface pH measurement, drug content uniformity and folding endurance.

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