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Formulation & Evaluation of Fast Dissolving Oral Thin Film of Ropinirole HCl

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Abstract: ***The present work aimed at preparing fast dissolving oral thin films of Ropinirole Hydrochloride with the purpose ofdeveloping a dosage form for a very quick onset of action, which is very convenient for administration, withoutthe problem of swallowing and using water. The film of Ropinirole Hydrochloride was prepared by usingpolymers such as polyethylene oxide and glycerine as plasticizer, by a solvent casting method. The formulated fast dissolving films were evaluated for physical characteristics such as uniformity of weight, thickness,folding endurance, drug content uniformity, surface pH and percentage elongation, tensile strength using texture analyser. The formulations were subjected to disintegration, In-vitro drug release tests. The FTIR and DSC studies revealed that no physicochemical interaction between excipients and drug. Fast dissolving film of Ropinirole Hydrochloride containing polyethylene oxide as polymer showed (99.18± 0.78%) drug release at 60 sec. Percentagecontent uniformity (99.90± 1.25%). Fast dissolving films of Ropinirole Hydrochloride can be considered suitable for clinical use in the treatment of parkinson's disease and rest leg syndrome, where a quicker onset of action for a dosage form is desirable alongwith the convenience of administration.***

Keyword: Fast dissolving film of Ropinirole Hydrochloride, Polyethylene oxide, SolventCasting method, Parkinson disease, Texture analyser, Atomic force Microscopy, XRD, and SEM (scanning electron microscopy).

1. Introduction

Fast-dissolving oral delivery systems are solid dosage forms,which disintegrate or dissolve within 1 min when placed in themouth without drinking or chewing.The first developed fast-dissolving dosage form consisted intablet form, and the rapid disintegrating properties were obtainedthrough a special process or formulation modifications. [1] Morerecently, fast-dissolving films are gaining interest as an alternativeto fast-dissolving tablets to definitely eliminate patients' fear ofchocking and overcome patent impediments.

Fast-dissolving films are generally constituted of plasticizedhydrocolloids or blends made of thereof that can be laminated bysolvent casting or hot-melt extrusion.According to the film forming material characteristics, the manufactureof the dosage forms can present different critical issues.Common problems are caused by foaming during the film formationdue to the heating of the material or solvent evaporation,the flaking during the slitting and the cracking in the cutting phase.Furthermore, the films should be stable to moisture overtime. Finally,to facilitate the handling they have to be flexible and exhibita suitable tensile stress and do not stick to the packaging materialsand fingers.Fast dissolving films offers an attractive route for systemic drug delivery. The improved systemic bioavailabilityresults from bypassing first pass effect and better permeability due to a well supplied vascular and lymphaticdrainage Also large surface area of absorption, easy ingestion & swallowing, pain avoidance make the oral mucosa avery attractive and feasible site for systemic drug delivery.[2,3]

The delivery system consist of a very thin oral strip, which is simply based on the patient's tongue or any oralmucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto site of application. It thendisintegrates and dissolves to release the medication. Ropinirole Hydrochloride is an orally active,dopamine receptor agonist used in the treatment ofParkinson disease Parkinson's disease is one themost baffling and complex of neurologicaldisorder. [4] The term parkinsonism is used for amotor syndrome whose main symptoms are tremorat rest, stiffness, slowing of movement and posturalinstability. [5] Ropinirole Hydrochloride is the drugof choice used in the treatment of Parkinsondisease.[5,6] By definition, a solid dosage form thatdissolves or disintegrates quickly in the oral cavity,resulting in solution or suspension without the needfor the administration of water, is known as an oralfast-dispersing dosage form. Mouth DissolvingFilm is also known as Fast dissolving film, Quickdissolving film, Rapid dissolving film, Oral thinfilm (OTF), Orally Dissolving Films (ODF).Bioavailability of drug in film dosage form isgreater than the convectional dosage form. [7]Oralfilms are also used for local effects like localanaesthetics for oral ulcers, toothaches, cold scarsand teething. Generally the shelf life of film is 2-3years it depends on the API added to the film butfilms are very sensitive to environmental moisture. [8]

Advantages: [9, 10, 11]

1) Oral cavity has large surface area which leads torapid dissolution and disintegration of the oraldosage form.
2) No risk of chocking.
3) OFDF is solid unit dosage form so provideaccurate dosing and great precision.
4) Due to pregastric absorption the bioavailabilityof drug is improved and fewer doses arerequired which improve the patient compliance.
5) OFDF's does not require water to swallow so ithas better acceptability among the dysphagicpatients.
6) Provide good mouth feel.
7) Oral films are flexible and less fragile ascompared to OFDF's so it can easily transporthandled and stored.

8) It avoid first pass metabolism as it directlyabsorbe from the buccal mucosa and enter intothesystemic circulation, side effects and doseare reduced.
9) Fast dissolving films disintegrate immediately within seconds when placed on tongue withoutthe need of water and release one or more API.
10) Stability of the dosage form is enhanced.

Special features of oral films:[11,16]
- Ultra thin films
- Available in various size and shape
- Unobstructive
- Rapid release and fast disintegration
- Excellent mucoadhesion

Constraints of oral film: [12-14]
- High dose cannot be incorporated.
- Drug should have low dose.
- Should have high oral bioavailability.
- Oral films have expensive packaging.

The ideal properties of drug for thedevelopment of oral strips formulation:
a. The drug should have low dose.
b. The dug have extensive high first passmetabolism.
c. It should be non-bitter.
d. It should have quick onset of action.
e. The dug should have high solubility and high permeabilility (BCS class I).

Applications: [14-17]
a. Oral films are preferred for local action and alsoto manage pain, allergies, sleeping difficulty andCNS disorders.
b. Dissolvable films are feasable for topicalapplication for wound care as analgesics orantimicrobial agents.
c. Oral films are applicable to enhance thebioavailability of poorly bioavailable drugs.
d. Taste masking of bitter drugs.
e. Dissolvable films are loaded with sensitivereagents to allow controlled release whenexposed to a biological fluids or to create isolation barriers for seperating multiple reagents to enable a timed reaction with adiagnostic device.

Primary concerns when manufacture Fast dissolvingfilms [18, 19]

Selection of the API: It is very important partof the process. The selection of API dependson the potency of API, dose, as well astherapeutic efficacy. Most suitable API for ODF includes anti-allergic, antihistaminic, anti-parkinson, sleeping aids and analgesicdrugs are preferred selection.

Selection of the Film formers: The filmshould be tough enough to physically handleand the robustness of the film depends on typeof polymer used. Also the film has to beeasily disintegrated in saliva or water to getimmediate action. At least 45% w/w polymershould be present in the formulation in orderto get good formulation. Along with various polymers Pullulan, gelatin, HPMC and HPCare the most commonly used polymers in film formulation.

Plasticizer: Plasticizer provides the efficientplasticity to the ODF formulation. One has tobe careful in determining the plasticizerconcentration. Selection plasticizer dependson compatibility citrate, PEG 400, glycerine and triacetin.

Taste masking: The taste masking is aprerequisite in the case of oral formulation.Natural as well as artificial sweeteners areused to improve the taste as well as intendedto be dissolve and disintegrate in the oralcavity. The classical source of sugar issucrose, fructose, glucose and dextrose.Saccharine, Sucralose and aspartame are fallin to the artificial sweetener category.

2. Materials and Methods

Ropinirole were received as gift sample from **wockhardt pharma , Aurangabad,** India. Polyethylene oxide (Aldrich Chemicals, Mumbai, India), Glycerine (Loba chemie, Mumbai, India) were purchased for carrying out various experiments.All other chemical were commercially available and used as received.

Methods
Pre-formulation studies
FTIR Spectroscopy
The FTIR spectrum of Ropinirole was recorded using FTIR spectrophotometer. The drug: KBr in a ratio of 1: 99 was taken & pallet was prepared using KBr press. This pallet was analyzed under IR spectrophotometer.

Drug-Excipient Compatibility Studies by DSC
DSC thermograms of pure drug (Ropinirole Hydrochloride) and its physical mixture with polymers (Ropinirole, PEO) were carried outto investigate any possible interaction between thedrug and polymer. The selected heating rate is from 50^0C to300^0C at an increase of 20^0C per minute usingDifferential Scanning Calorimeter (shimadzu corporation, Japan).Differential scanning calorimetric (DSC) measurements were performed using a DSC in a temperature range of 25–250^0C at a heating rate of 10^0C/min in nitrogen gas. The melting points were calculated using a Stare Software from Mettler Toledo.

Standard Calibration curve for Ropinirole in phosphate buffer of pH 6.8
100 mg Ropinirole was accurately weighted & transferred to 100ml volumetric flask. Add sufficient quantity of phosphate buffer (pH 6.8) to dissolve drug & diluted to volume with phosphate buffer to give stock solution containing 1000µg/ml. 10ml of above stock solution was taken in 100ml volumetric flask appropriately diluted with phosphate buffer to obtain a concentration of 100µg/ml.2, 4, 6, 8, & 10µg/ml prepared using stock solution of 100µg/ml. The above solutions were analyzed by U. V. Spectrophotometer at 250 nm. Phosphate buffer was used as a blank during spectrometric analysis.

Preparation of fast dissolving film by solvent casting method
Fast dissolving films of Ropinirole HCl were prepared by solvent casting technique using film forming polymer. Required amount of Polyethylene oxide according to the

formulation table was weighed accurately and soaked aside for 1hour for swelling of polymer. Simultaneously Ropinirole HCl was weighed accurately and dissolved in 5ml of distilled water in another beaker. Then drug solution was added to the polymer solution and Glycerin was added as plasticizer and Sorbitol as sweetener, Citric acid as saliva stimulating agent mixed thoroughly with the help of magnetic stirrer. The above solution was sonicated for 20 min for removal of air bubbles. The glass mould (petridish) having diameter 9.5cm was placed over a flat surface and the resulting 10 ml solution with the help of measuring cylinder was transferred into petridish slowly drop by drop and was spread uniformly. Funnel was inverted and placed over the petridish to have uniform evaporation. The petridish containing polymeric solution of drug was kept for 24 hours at room temperature for drying. The area of each film is 1x2 means $2cm^2$, so here we use the petridish having a diameter 9.5cm, radious 4.5cm so area of petridish was found to be,

Area of Petridish = πr^2

$=3.14x22.56$

$=70.84cm^2$

From the above calculation it was concluded that the each pertidish contain 35 films so formula was developed as per 35 films for one batch.

Formula was developed for 35 films and each film contains 2 mg of RopiniroleHCl.

Table 1: Formulation Batches of Fast Dissolving Oral Film of Ropinirole HCl

Sr.no	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Ropinirole (mg)	70	70	70	70	70	70	70	70	70
2	PEO(mg)	150	150	150	200	200	200	250	250	250
3	Glycerin(ml)	0.1	0.2	0.3	0.1	0.2	0.3	0.1	0.2	0.3
4	Citric acid(mg)	25	25	25	25	25	25	25	25	25
5	Sorbitol(mg)	20	20	20	20	20	20	20	20	20
6	Strawberry (ml)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
7	D\W	10	10	10	10	10	10	10	10	10

3. Evaluation of Fast Dissolving Films of Ropinirole HCl

Mechanical properties

Mechanical properties of films were evaluated using a Brookfield, USA texture analyzer equipment equipped with a 5Kg load cell. Films are held between two clamps positioned between 3cm. During measurement the films were pulled at rate of 2mm/sec. The force and elongation were measured when film breaks. Three mechanical properties namely tensile strength, elastic modulus and % elongation were calculated.

Tensile strength

Tensile strength is calculated by formula,

$$\text{Tensile strength} = \frac{\text{Load at failure}}{\text{Film thickness} \times \text{film width}} \times 100$$

% Elongation

It is calculated as,

$$\%\,\text{Elongation} = \frac{\text{Increase in length}}{\text{Original length}} \times 100$$

Figure1: Image of CT3 texture analyser used forMeasurement of mechanical properties.

Folding Endurance

This test was performed by cutting the mouthdissolving film of size 1×2 cm^2. The films werefolded at same place until it breaks apart. [20]

In-vitro disintegration studies

Disintegration time study was slightly modified tomimic the in-vitro and in-vivo conditions. For thestudy, film as per the dimensions 1×2 cm^2required for dose delivery were placed on astainless steel wire mesh containing 10 ml distilledwater. Time required for the film to break anddisintegrate was noted as in-vitro disintegrationtime. Since, the film is expected to disintegrate inthe mouth in presence of saliva; only 10 ml ofmedium was used. [21]

Weight variation test

1×2 cm^2film was cut at three different places inthe cast film. The weight of each film strip wastaken and then weight variation observed. [22]

Surface pH Measurement

The surface pH of Mouth dissolving film isdetermined in order to investigate the possibility ofany side effects in vivo. As an acidic or alkaline pHmay cause irritation to the oral mucosa, it isdetermined to keep the surface pH as close to neutral as possible. A combined pH electrode isused for this purpose. Film is slightly wet with thehelp of water. The pH is measured by bringing theelectrode in contact with the surface of the oralfilm. This study is performed on three films of eachformulation and mean ± S.D calculated. [23]

Thickness Test

The thickness of the film can be measured bymicrometer screw gauge at different 5 strategiclocations. This is helpful in determination ofuniformity in the thickness of the film & this isdirectly related to the accuracy of dose in the film. [24]

Uniformity of drug content

A film of size 1×2 cm^2 is cut and put in 30 ml ofvolumetric flask containing solvent. This is thenshaken in a mechanical shaker for 1 hr to get ahomogeneous solution and filtered. The drug is determined spectroscopically after appropriate dilution. [25]

In-vitro dissolution studies

The in-vitro dissolution studies were conductedusing simulated saliva (300 ml). The dissolutionstudies were carried out using USP dissolution apparatus XXIV (Electrolab, Mumbai, India) at 37± 0.5^0C and at 50 rpm using specified dissolutionmedia. Each film with dimension 1×2 cm^2 wasplaced on a stainless steel wire mesh with sieveopening 700µm. The film sample placed on thesieve was submerged into dissolution media.Samples were withdrawn at 0, 15, 30 and 60 sec.time intervals and filtered through 0.45µmwhatman filter paper and were analyzed spectrophotometrically at 250 nm. To maintain thevolume, an equal volume of fresh dissolution medium maintained at same temperature was addedafter withdrawing samples. The absorbance valueswere converted to concentration using standardcalibration curve previously obtained byexperiment. The dissolution testing studies wereperformed in triplicate for all the batches.[21]

Scanning Electron Microscopy (SEM) [26]

The surface morphology of the fastdissolving film was observed with scanning electronmicroscope, (JEOL 5400, Tokyo, Japan).The samples were attached to the slab surfaceswith double-sided adhesive tapes and the scanningelectron photomicrograph was taken at 1000x magnification.

X-ray Diffractograms of Films

Powder X-ray diffraction spectra of the drug-loaded Mouth Dissolving films were prepared using a Rigaku DMAX powder diffractometer (J) with Cu–Ka radiation and a monochromator on the diffracted beam.

Atomic force Microscopy (AFM)

AFM topographic images of film were taken on a multimode AFM attached to a Nanoscope III electronics. The AFM probes used for this study were rectangular silicon probes with a nominal spring constant of 40 nN/nm.

4. Results and Discussion

Drug-Excipient Compatibility Studies byFT-IR

Pure drug Ropinirole Hydrochloride spectra showed sharp characteristic peaks at 1350 cm^{-1}(CH_3 bending), 1456 cm^{-1}(C=C stretching), 1700 cm^{-1} (C=O stretching) and 3150 cm^{-1}(N-H stretching) in shown (fig.2, 4). All the above characteristic peaks of drug appear in the spectra of all other spectra of drug with polymer mixtures and formulations of mouth dissolving film at the same wave number, indicating no modification or no interaction between the drug and the excipients.

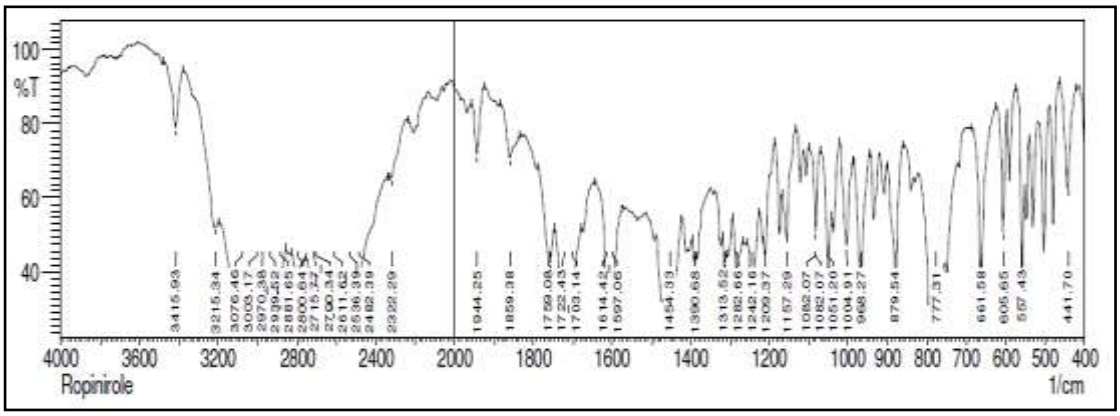


Figure 2: FTIR spectra of Ropinirole HCl

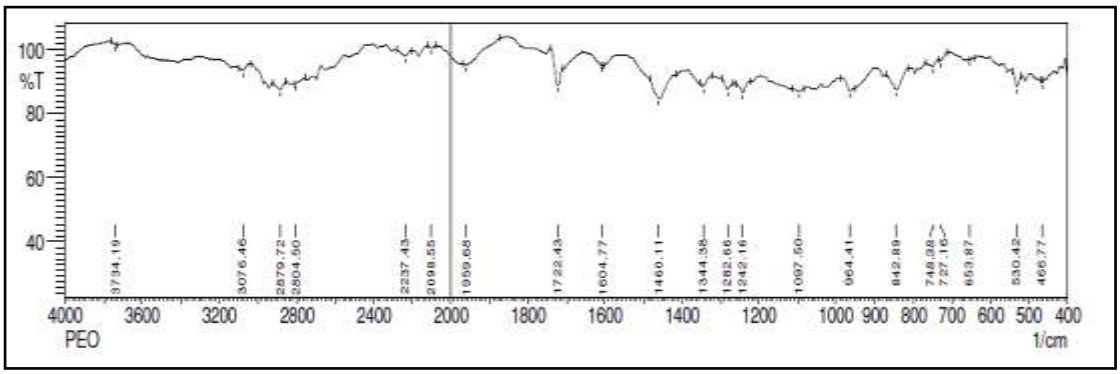


Figure 3: FTIR spectra of Polyethylene Oxide

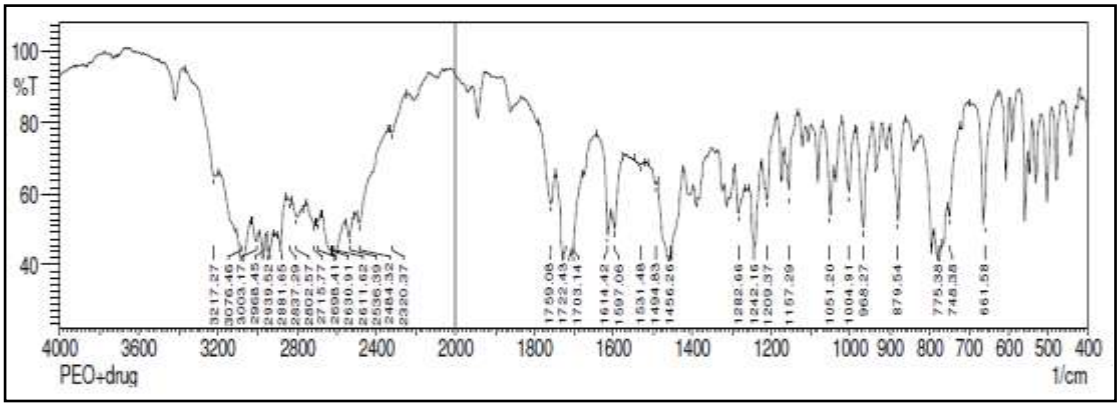


Figure 4: FTIR spectra of Ropinirole HCL&Polyethylene Oxide

DSC studies of RopiniroleHCl:

Samples were analyzed by DSC using shimadzu corporation, Japan. The samples were placed into a pieced aluminium sample container. The studies were performed under static air atmosphere in the temperature range of 50^0 C-300^0 C at a heating rate of 10^0C per min. The peak temperatures were determined after calibration with a standard. The DSC thermograph of ropinirole hydrochloride exhibits endothermic peak at 244.41^0C (figure 5, 6) corresponding to its melting point. All polymer anddrug mixtures showed endothermic peak 240^0C to255^0C range. So, results indicate that weakinteraction occurs between drug and polymer.

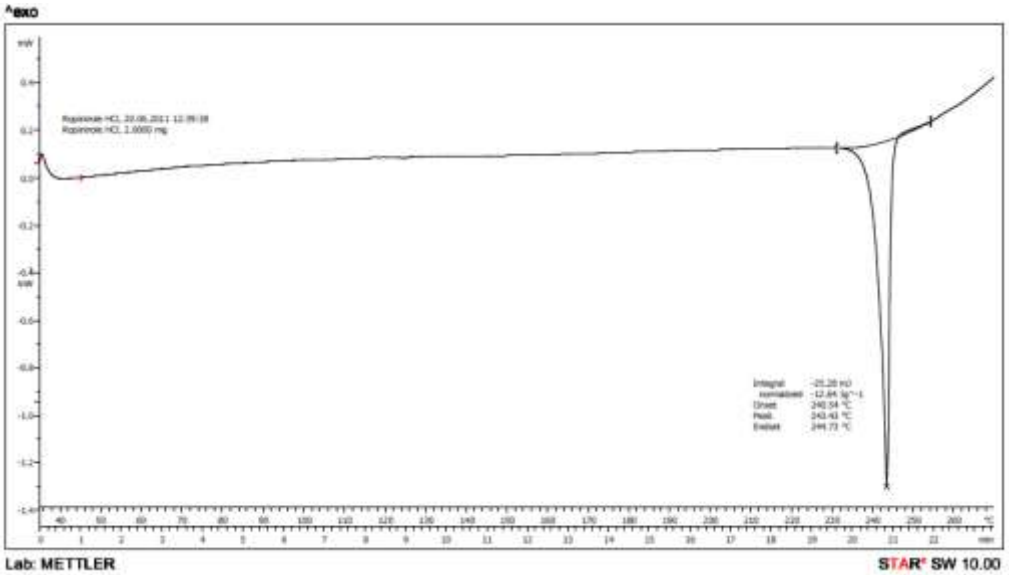


Figure 5: DSC thermogram of RopiniroleHCl

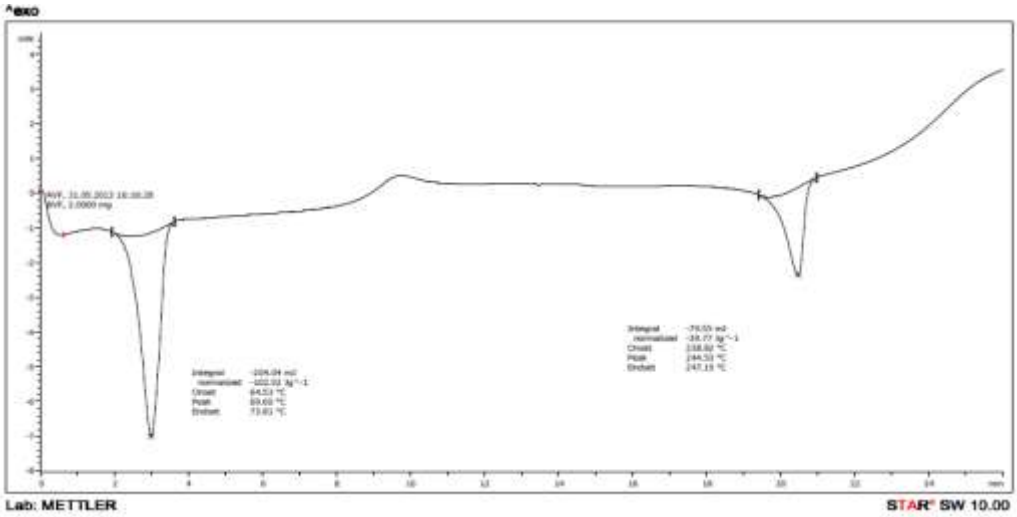


Figure 6: DSC thermogram of Ropinirole HCL and Polyethylene Oxide

Calibration curve of Ropinirole Hydrochloride in Phosphate buffer pH 6.8

Graph of absorbance Vs concentration was plotted and found to be linear over the range of 2 to 10 µg/ml indicating it is compliance with Beer's and Lambert's law with r^2 value 0.995 . Results are shown in (table no. 2 and fig. 7).

Table2: Standard Calibration Curve ofRopiniroleHCl in Phosphate buffer pH 6.8

Sr.no	*Concentration*	*Absorbance*
1	0	0
2	2	0.071
3	4	0.127
4	6	0.179
5	8	0.238
6	10	0.285

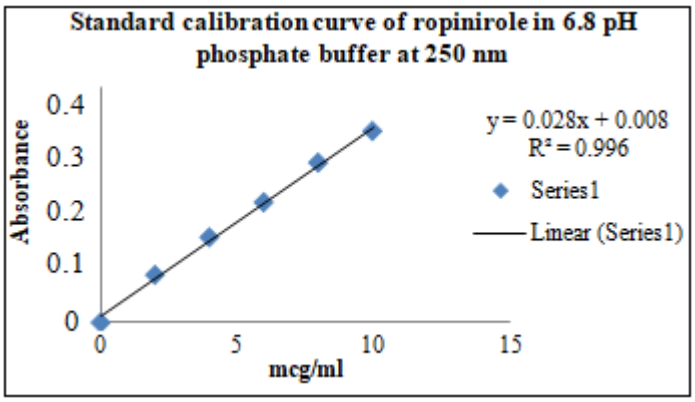


Figure 7: Calibration Curve of RopiniroleHCl in phosphate buffer pH 6.8

Table 3: Evaluation of Fast Dissolving Film Formulation Batches F1 to F9

Batches	Tensile Strength (g/mm^2)	% Elongation	Weight (mg)	Folding Endurance	In-vitro Disintegration time (sec)	Thickness (mm)	% Drug Content
F1	9.25 ± 0.038	22.29± 0.61	10.22± 0.77	97.25± 2.05	9.0± 1.00	0.05± 0.00	99.21± 0.65
F2	9.36 ± 0.112	25.82± 0.71	14.04± 1.53	105.24± 1.64	8.75± 0.00	0.06± 0.01	98.57± 0.13
F3	9.50 ± 0.050	30.62± 0.50	17.17± 0.75	92.28± 1.05	8.75± 0.57	0.05± 0.01	98.99± 1.25
F4	9.63 ± 0.070	33.99± 0.88	12.13± 0.50	99.78± 1.00	9.05± 0.58	0.05± 0.02	98.58± 0.71
F5	11.08 ± 0.094	37.21± 0.90	14.92± 0.60	94.67± 2.67	9.08± 0.00	0.05± 0.00	98.68± 0.67
F6	12.10 ± 0. 111	39.80± 0.78	18.12± 1.53	94.30± 3.25	9.25± 1.00	0.05± 0.01	99.90± 1.25
F7	13.25 ± 0.158	48.21± 0.20	13.06± 1.28	85.00± 1.67	8.75± 0.00	0.06± 0.01	98.87± 0.25
F8	14.63 ± 0.091	50.93± 1.00	15.79± 0.28	88.20± 1.64	8.50± 0.58	0.06± 0.02	99.15± 0.26
F9	16.39 ± 0.115	52.56± 0.55	18.45± 0.53	98.90± 2.30	9.25± 1.00	0.06± 0.01	99.25± 0.13

Note: All values are mean ± SD, (n = 3)

Evaluation parameter

In vitro disintegrating time for fast dissolving film of PEO was ranges from 8.75± 0.00 to 9.25± 1.00 sec. Drug content in the films was evaluated and the values were found to be between 98.00 to 99.91 % shown in (table 3). All the fast dissolving formulations of different polymers are show thickness value in the range of 0.05 ± 0.00 to 0.06 ± 0.02 mm.

Weight variation measurement

A result showed that as the concentration ofpolymer increases weight of film also increases shown in (table 3).

Surface pH

Surface pH of all fast dissolving films preparedby using PEO was found to be in therange of 6.0 to 7 pH, which was close to the neutralpH, which indicated that films may have lesspotential to irritate the sublingual mucosa, andhence, more acceptable by the patients.

Folding endurance

The flexibility of film is an important physical character needed for easy application on the site of administration. The flexibility of films can be measured quantitatively in terms of folding endurance and is determined by repeatedly folding the film at 180^0 angle of the plane at the same plane until it breaks. The number of times the film is folded without breaking is computed as the folding endurance value. A result shown in (table 3) that as the concentration of polymer and plasticizer increases, folding Endurance of fast dissolving film increases.

Dissolution Studies

The studies of the formulation Batches from F1-F9 were carried out to know the in-vitro drug release pattern and the procedure was carried out as the procedure discussed earlier. The drug release at different time intervals was determined and calculated to know the release at variable concentration of polymers used. The results obtained were converted in the form of % drug release. The result was showed in (Table No.4 and Fig.No.8) Complete drug release with in 1 min.

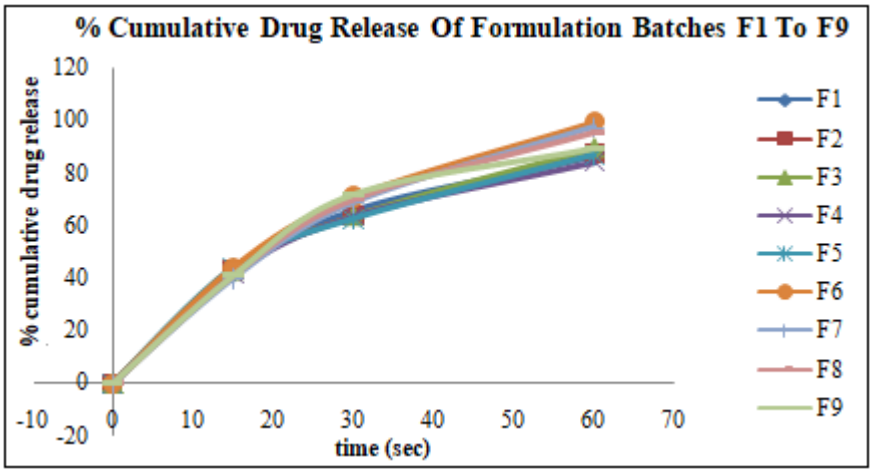


Figure 8: Dissolution profile of formulation batches F1 to F9

Table 4: Cumulative % Drug Release*(SD) of Oral Fast Dissolving Film of Ropinirole.

Batches	In-vitro percentage drug release at 60 sec.
F1	86.21± 0.31
F2	87.24± 0.18
F3	89.30± 0.36
F4	84.15± 0.71
F5	86.83± 0.36
F6	**99.18± 0.78**
F7	97.53± 0.55
F8	95.47± 0.57
F9	89.30± 0.92

Environment scanning electron microscopy (ESEM)

SEM of optimized the film at 1000X magnification showed smooth surface with some little pores and without any scratches or transverse striations as shown in(fig. 9).

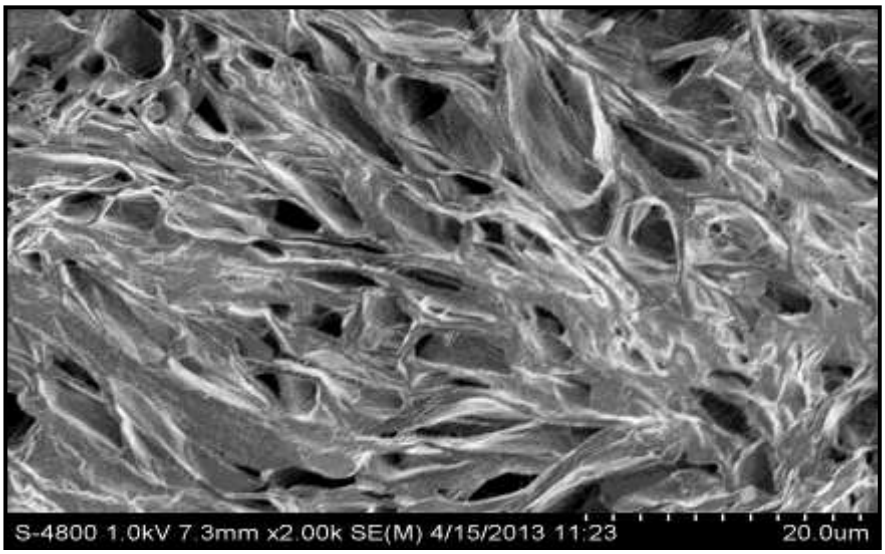
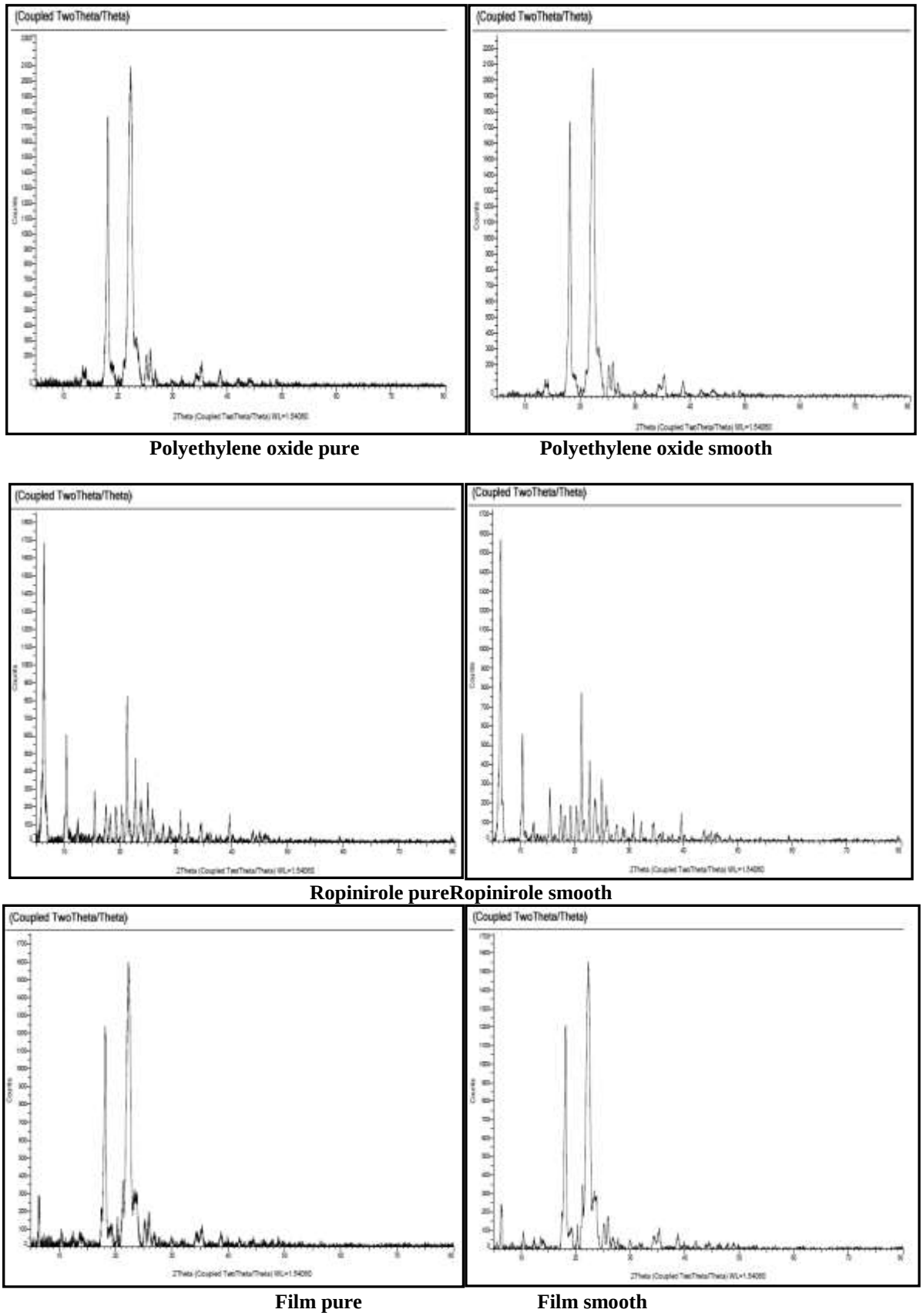


Figure 9: ESEM of optimized batch film at 1000xmagnification

X-ray Diffractograms of Film, drug and polymer

XRD analysis was performed to study the crystal structure of drug in the film. (Fig. 10)shows the spectra for drug compared when these drugs are incorporated into PEO films. The spectra obtained demonstrate that the drug in film has crystalline characteristics that are preserved during processing. PEO resulted in significant increase the ropinirole bioavailability as compared to plain drug.



Polyethylene oxide pure **Polyethylene oxide smooth**

Ropinirole pureRopinirole smooth

Film pure **Film smooth**

Figure 10: X-ray diffractograms

Atomic Force Microscopy

Ropinirole fast dissolving film obtained for various concentration of plasticizer condition were subjected to topographic analysis by means of atomic force microscopy. Fast dissolving film indicates variations in experimental condition were not sufficient to affect shape dramatically. (Fig.11) Also shows the height and amplitude of single fast dissolving film.

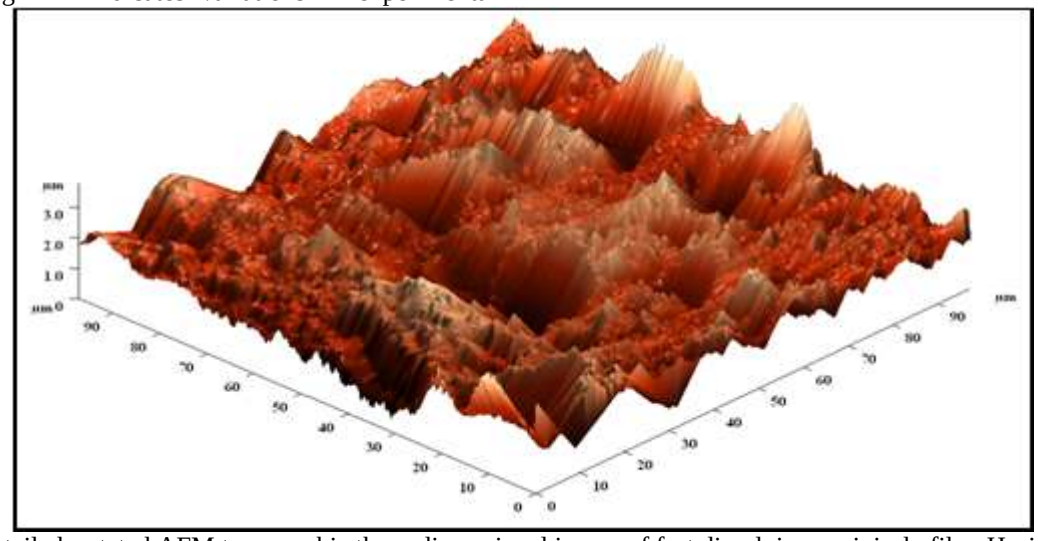


Figure 11: Detailed, rotated AFM topographic three-dimensional image of fast dissolving ropinirole film. Horizontal, vertical and surface distance is shown

5. Conclusion

In present work, a Ropinirole HCl was selected for this investigation as novel drug dosage form for paediatric, geriatrics, and also for general population to improve bioavailability by preventing first pass metabolism, rapid onset of action. The main objective of study was to formulate and evaluate fast dissolving oral film of Ropinirole HCl by using polymer polyethylene oxide and plasticiser glycerine by solvent casting method.

Polyethylene oxide was found to be compatible with Ropinirole HCl, which was confirmed by FTIR spectroscopy. All formulations (F1 to F9) were evaluated for weight variation, thickness, drug content, disintegration time. Results of folding endurance, % elongation and tensile strength proved by texture analyser that when concentration of plasticiser and polymer are increased the flexibility of film also increases. From all evaluation parameter it was found that batch F6 show good physical appearance, texture and flexibility. Hence F6 batch can be selected as best batch. Results of In vitro drug release study reveals that batch F6 shows maximum drug release (99.18± 0.78%) within 60 seconds.

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