

Formulation and Evaluation of Mouth Dissolving Film of Ropinirole Hydrochloride by Using Pullulan Polymers

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Abstract:

The present work aimed at preparing mouth dissolving films of Ropinirole Hydrochloride with the purpose of developing a dosage form for a very quick onset 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 pullulan and PEG 400 as plasticizer, by a solvent casting method. Formulation batches were formulated with the help of 3² full factorial designs. The fast dissolving oral films were designed using optimal design and numerical optimization technique was applied to find out the best formulation. The formulated mouth dissolving films were evaluated for physical characteristics such as uniformity of weight, thickness, folding endurance, drug content uniformity, surface pH, percentage elongation, and tensile strength, and gave satisfactory results. The formulations were subjected to disintegration, *In-vitro* drug release tests and stability study. The FTIR and DSC studies revealed that no physicochemical interaction between excipients and drug. A marked increase in the % drug release was exhibited by mouth dissolving films of Ropinirole Hydrochloride containing pullulan as a polymer at 60 sec., when compared to other polymers films. Mouth dissolving film of Ropinirole Hydrochloride containing pullulan as polymer showed 99.48 ± 0.18 % drug release at 60 sec. Mouth dissolving films of Ropinirole Hydrochloride containing pullulan showed better tensile strength (9.67 ± 0.064 g/mm²), Percentage elongation (21.59 ± 0.29 %), folding endurance (88.00 ± 1.00 No. of folds), *in-vitro* disintegration time (20.33 ± 0.57 sec.), surface pH (6.60 ± 0.10 pH), thickness (0.07 ± 0.01 mm) and percentage content uniformity (99.53 ± 0.37 %). Stability studies revealed that optimized formulation was stable. Mouth 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 along with the convenience of administration.

Keyword: Mouth dissolving film of Ropinirole Hydrochloride, Pullulan, Polyethylene glycol 400, Solvent casting method, Parkinson disease

Introduction:

Ropinirole Hydrochloride is an orally active, dopamine receptor agonist used in the treatment of Parkinson disease. Parkinson's disease is one of the most baffling and complex of neurological disorders.[1] The term parkinsonism is used for a motor syndrome whose main symptoms are tremor at rest, stiffness, slowing of movement and postural instability.[2] Ropinirole Hydrochloride is the drug of choice used in the treatment of Parkinson disease.[2,7] By definition, a solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water, is known as an oral fast-dispersing dosage form. Mouth Dissolving Film is also known as Fast dissolving film, Quick

dissolving film, Rapid dissolving film, Oral thin film (OTF), Orally Dissolving Films (ODF). Bioavailability of drug in film dosage form is greater than the conventional dosage form.[3]

Special features of Mouth Dissolving Film [4]

- Thin elegant films
- Various sizes
- Unobstructive
- Mucoadhesion
- Quick dissolving
- Fast disintegrating

- Rapid release

Advantages of Mouth Dissolving Film [5]

- Larger surface area promotes rapid disintegration and dissolution in the oral cavity.
- Oral films are flexible and thus less fragile as compared to ODTs. Hence, there is ease of transportation and during consumer handling and storage.
- Precision in the administered dose.
- No risk of choking
- Good mouth feel
- With the help of Mouth dissolving film drug delivery system those drugs can be given to the patients that are not crushed and not injected by patients.
- Improved patient compliance
- Ease of swallowing and no need of water has led to better acceptability amongst the dysphagic patients
- Dosage form can be consumed at any place and anytime as per convenience of the individual.
- Enhanced oral bioavailability of molecules that undergo first pass effect.
- Bypassing the first pass effect leads to reduction of dose which can lead to reduction in side effects associated with the molecules.
- Mouth Dissolving Films are typically the size of a postage stamp and disintegrate on a patient's tongue in a matter of seconds for the rapid release of one or more APIs.

Ideal Characteristic of a suitable Drug Candidate [5]

- The drug should have pleasant taste.
- The drug to be incorporated should have low dose up to 40 mg.
- The drugs with smaller and moderate molecular weight are preferable.
- The drug should have good stability and solubility in water as well as in saliva.

- It should be partially unionized at the pH of oral cavity.
- It should have the ability to permeate oral mucosal tissue.

Primary concerns when manufacture Mouth dissolving films [5, 6]

- **Selection of the API:** It is very important part of the process. The selection of API depends on the potency of API, dose, as well as therapeutic efficacy. Most suitable API for ODF includes anti-allergic, antihistaminic, anti-parkinson, sleeping aids and analgesic drugs are preferred selection.
- **Selection of the Film formers:** The film should be tough enough to physically handle and the robustness of the film depends on type of polymer used. Also the film has to be easily disintegrated in saliva or water to get immediate action. At least 45% w/w polymer should be present in the formulation in order to get good formulation. Along with various polymers **Pullulan**, gelatin, **HPMC** and **HPC** are the most commonly used polymers in film formulation.
- **Plasticizer:** Plasticizer provides the efficient plasticity to the ODF formulation. One has to be careful in determining the plasticizer concentration. Selection plasticizer depends on compatibility citrate, **PEG 400**, glycerin and triacetin.
- **Taste masking:** The taste masking is a prerequisite in the case of oral formulation. Natural as well as artificial sweeteners are used to improve the taste as well as intended to be dissolve and disintegrate in the oral cavity. The classical source of sugar is sucrose, fructose, glucose and dextrose. Saccharine, **Sucralose** and **aspartame** are fall in to the artificial sweetener category

Table I: List of some marketed products available as mouth dissolving film [6]

No:	Drugs	API	Manufacturer/ Distributor	Use
1.	Listerine®	Cool Mint	Pfizer, Inc.	Mouth Fresheners
2.	Benadryl	Diphenhydramine HCL (12.5 mg or 25 mg)	Pfizer	Anti allergic
3.	Suppress®	Menthol (2.5 mg)	InnoZen®, Inc.	Cough suppressants
4.	Klonopin Wafers	Clonazepam (0.125mg, 0.25mg, 0.5mg, 1mg and 2mg)	Solvay Pharmaceuticals	Treatment of anxiety
5.	Theraflu	Dextromethorphan HBR (15 mg)	Novartis	Anti allergic
6.	Orajel	Menthol/pectin (2mg/30mg)	Del	Mouth ulcer
7.	Gas-X	Simethicone (62.5 mg)	Novartis	Anti Flatuating

8.	Chloraseptic	Benzocaine/menthol (3mg/3mg)	Prestige	Sore throat
9.	Sudafed PE	Phenylephrine	Wolters Kluwer Health, Inc.	Relieving congestion
10.	Triaminic	Diphenhydramine HCL (12.5 mg)	Novartis	Anti allergic

Materials and methods:

Materials:

Ropinirole Hydrochloride, Aspartame (Sunrise Remedies Pvt. Ltd. Santej, Ahmedabad) Pullulan (Hayashibara Company Ltd, Japan) and Sucralose (Alkem Lab. Ltd. Ankleshwar, Gujarat) were obtained as a gift sample. Polyethylene glycol 400 and sodium chloride were purchased from S.D Fine Chemicals Ltd, Boisar, India. All the chemicals were used as received without any further treatment and purification.

Methods:

1. PREFORMULATION STUDIES [10]

Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms. Ideally the preformulation phase begins early in the discovery process such that the appropriate physical and chemical data is available to aid the selection of new chemical entities that enter the development process. During this evaluation, possible interaction with various inert ingredients intended for use in final dosage form was also considered in the present study. The following data must be considered.

A) Drug - Excipient Compatibility Study

Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients, which are added to facilitate administration, to promote the consistent release and bioavailability of the drug and protect it from degradation. API and excipients were been thoroughly mixed in predetermined ratio given in below table and passed through the 40# sieve. The blend was filled in transparent glass vials and were closed with gray coloured rubber stoppers and further sealed with aluminum seal and charged in to stress condition at above condition. Similarly API should also be kept at all condition as for the samples. Samples were withdrawn for analysis within two day of sampling date as per the compatibility study plan. Physical observation should be done at every week up to 1 month and FTIR studies and DSC Studies were carried out to

determine the compatibility of excipients with the drug

• Fourier transform Infrared Spectroscopy

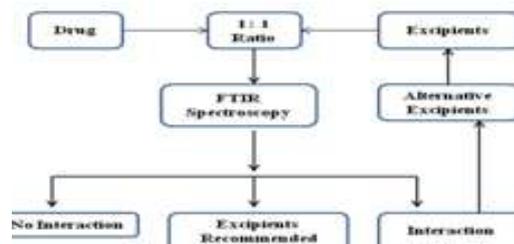


Figure I: FTIR Study

• Drug-Excipient Compatibility Studies by DSC

DSC thermograms of pure drug (Ropinirole Hydrochloride) and its physical mixture with polymers (Pullulan, HPMC, PVA) were carried out to investigate any possible interaction between the drug and the utilized polymer (Pullulan, HPMC, PVA). The selected heating rate is from 50°C to 300°C at an increase of 20°C per minute using Differential Scanning Calorimeter (shimadzu corporation, Japan).

2. ANALYTICAL METHOD DEVELOPMENT

2.1. Calibration curve of Ropinirole Hydrochloride

Calibration curve for Ropinirole Hydrochloride was developed in 6.8 pH phosphate buffer.

2.2. Calibration curve of Ropinirole Hydrochloride in phosphate buffer pH 6.8

From Standard stock solution of 100 µg/mL, appropriate aliquots were taken into different volumetric flasks and volume was made up to 10 mL with phosphate buffer pH 6.8, so as to get drug concentrations of 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 and 28 µg/mL. The absorbance of these drug solutions were estimated at λ_{max} 250 nm.

3. PREPARATION OF MOUTH DISSOLVING FILM BY SOLVENT CASTING METHOD

The MDF of Ropinirole hydrochloride using polymers were prepared by solvent casting method. An aqueous solution of the polymers was prepared in distilled water. Ropinirole hydrochloride was

added to the aqueous polymeric solution. This was followed by addition of plasticizers like PEG 400. Sweeteners like aspartame and sucralose were also added to the above solution. Citric acid and flavour were also mixed with it. The solution was casted on a petridish (diameter 9 cm) and dried at room temperature for 24 hr. The film was carefully removed from the petridish, checked for any imperfections and cut into the required size to deliver the equivalent dose (3 x 2 cm²) per strip. The samples were stored in a dessicator at relative humidity 30-35 % until further analysis. [11]

4. PREPARATION OF MOUTH DISSOLVING FILM OF ROPINIROLE HCL BY USING 3² FULL FACTORIAL DESIGNS

4.1. Optimization of Mouth dissolving Film Formulation Using 3² Full Factorial Designs

It is desirable to develop an acceptable pharmaceutical formulation in shortest possible time using minimum number of man-hours and raw materials. Traditionally pharmaceutical formulations after developed by changing one variable at a time approach. The method is time consuming in nature and requires a lot of imaginative efforts. Moreover, it may be difficult to develop an ideal formulation using this classical technique since the joint effects of independent variables are not considered. It is therefore very essential to understand the complexity of pharmaceutical formulations by using established statistical tools such as factorial design. In addition to the art of formulation, the technique of factorial design is an effective method of indicating the relative significance of a number of variables and their interactions. [14]

The number of experiments required for these studies is dependent on the number of independent variables selected. The response (Y_i) is measured for each trial.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where Y is the dependent variable, b₀ is the arithmetic mean response of the nine runs and b_i is

Table IV: Formulations of Mouth dissolving film using pullulan as polymer

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ropinirole HCL(mg)	32	32	32	32	32	32	32	32	32
Pullulan (mg)	200	300	400	200	300	400	200	300	400
PEG 400 (mg)	112.8	112.8	112.8	169.2	169.2	169.2	225.6	225.6	225.6
Citric Acid (mg)	70	70	70	70	70	70	70	70	70

the estimated coefficient for the factor X_i. The main effects (X₁ and X₂) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X₁X₂) show how the response changes when two factors are simultaneously changed.

A 3² randomized full factorial design was utilized in the present study. In this design two factors were evaluated, each at three levels, and experimental trials were carried out at all nine possible combinations. The design layout and coded value of independent factor is shown in Table 4.11 and Table 4.12 respectively. The factors were selected based on preliminary study. The concentration of Plasticizer PEG 400 (X₁) and concentration of Polymer (X₂) were selected as independent variables. The formulations of the factorial batches (F1 to F 27) are shown in Table: 4.13, 4.14 & 4.15.

Table II: 3² Full Factorial design layout

Batch code	X ₁	X ₂
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1

Table III: Coded value for plasticizer conc. & polymer concentration

Coded value	Concentration of Plasticizer (mg)	Concentration of Polymers Concentration (mg)
-1	112.8	200
0	169.2	300
1	225.6	400

Aspartame (mg)	20	20	20	20	20	20	20	20	20
Sucralose (mg)	30	30	30	30	30	30	30	30	30
Strawberry (mL)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Distilled Water (mL)	10	10	10	10	10	10	10	10	10

5 EVALUATION OF MOUTH DISSOLVING FILMS OF ROPINIROLEYDROCHLORIDE

5.1. Measurement of mechanical properties of the film [11, 12]

Tensile strength of films was determined using an apparatus fabricated in laboratory. A small film strip ($3 \times 2 \text{ cm}^2$) was cut and fixed to assembly. The weight required to break the film was noted and simultaneously film elongation was measured with the help of pointer mounted on the assembly. Measurements were done in triplicate for each batch. The mechanical properties tensile strength and % elongation were calculated for the mouth dissolving film from the above measurements. Tensile strength is the ratio of maximum stress applied to a point at which the film specimen breaks and can be computed from the applied force at rupture to the crosssectional area of the fractured film as a mean of three measurements and described in the equation-

$$\text{Tensile strength} = \frac{\text{Force at break (N)}}{\text{Initial cross sectional area of the film (mm}^2\text{)}}$$

Percentage elongation was calculated by the following equation-

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



Figure II: Image of instrument used for measurement of mechanical properties

5.2. Folding Endurance

This test was performed by cutting the mouth dissolving film of size $3 \times 2 \text{ cm}^2$. The films were folded at same place until it breaks apart. [13]

5.3. *In-vitro* disintegration studies

Disintegration time study was slightly modified to mimic the *in-vitro* and *in-vivo* conditions. For the study, film as per the dimensions ($3 \times 2 \text{ cm}^2$) required for dose delivery were placed on a stainless steel wire mesh containing 10 mL distilled water. Time required for the film to break and disintegrate was noted as *in-vitro* disintegration time. Since, the film is expected to disintegrate in the mouth in presence of saliva; only 10 mL of medium was used. [14]

5.4. Weight variation test

$3 \times 2 \text{ cm}^2$ film was cut at three different places in the cast film. The weight of each film strip was taken and then weight variation observed. [15]

5.5. Surface pH Measurement

The surface pH of Mouth dissolving film is determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the oral mucosa, it is determined to keep the surface pH as close to

neutral as possible. A combined pH electrode is used for this purpose. Film is slightly wet with the help of water. The pH is measured by bringing the electrode in contact with the surface of the oral film. This study is performed on three films of each formulation and mean \pm S.D calculated. [16]

5.6. Thickness Test

The thickness of the film can be measured by micrometer screw gauge at different 5 strategic locations. This is helpful in determination of uniformity in the thickness of the film & this is directly related to the accuracy of dose in the film. [17]

5.7. Uniformity of drug content

A film of size $3 \times 2 \text{ cm}^2$ is cut and put in 30 mL of volumetric flask containing solvent. This is then shaken in a mechanical shaker for 1 hr to get a homogeneous solution and filtered. The drug is determined spectroscopically after appropriate dilution. [18]

5.8. Taste evaluation

Taste acceptability was measured by a taste panel (n=5) with 3 mg drug and subsequently film sample containing 3 mg drug held in mouth until disintegration, then spat out and the bitterness level was then recorded. The volunteers were asked to gargle with distilled water between the drug and film sample administration. The scale for the bitterness study was as follows: [14]

- + = very bitter
- ++++ = tasteless/taste masked
- ++ = moderate to bitter
- +++++ = excellent taste masking
- +++ = slightly bitter

5.9. *In-vitro* dissolution studies

The *in-vitro* dissolution studies were conducted using simulated saliva (300 mL). The dissolution studies were carried out using USP dissolution apparatus XXIV (Electrolab, Mumbai, India) at $37 \pm 0.5 \text{ }^\circ\text{C}$ and at 50 rpm using specified dissolution media. Each film with dimension ($3 \times 2 \text{ cm}^2$) was placed on a stainless steel wire mesh with sieve opening $700\mu\text{m}$. The film sample placed on the sieve was submerged into dissolution media. Samples were withdrawn at 0, 15, 30 and 60 sec. time intervals and filtered through $0.45\mu\text{m}$ whatman filter paper and were analyzed spectrophotometrically at 250 nm. To maintain the volume, an equal volume of fresh dissolution

medium maintained at same temperature was added after withdrawing samples. The absorbance values were converted to concentration using standard calibration curve previously obtained by experiment. The dissolution testing studies were performed in triplicate for all the batches. [14]

5.10. Environment scanning electron microscopy (ESEM)

The surface morphology of the film was observed using Environment scanning electron microscope (Philips, XL 30, The Netherlands). The film sample was placed in the sample holder and the photomicrographs were taken using tungsten filament as electron source and GSE detector at 65x and 350x magnification. [14]

5.11. Stability Study of Mouth Dissolving Film of Ropinirole Hydrochloride

Stability of a drug has been defined as the ability of a particular formulation in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability study is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. Recommended storage conditions, re-test periods and shelf-lives are to be established. The International Conference of Harmonization (ICH) Guidelines titled, "stability testing of New Drug substance and products" (QIA) describes the stability test requirements for drug registration application in the European Union, Japan and the United States of America. ICH specifies the length of study and storage conditions

Long-term testing: $-25 \text{ }^\circ\text{C} \pm 2 \text{ }^\circ\text{C} / 60 \% \text{ RH} \pm 5\%$ for 12 months.

Accelerated testing: $-40 \text{ }^\circ\text{C} \pm 2 \text{ }^\circ\text{C} / 75 \% \text{ RH} \pm 5\%$ for 6 months.

Accelerated Stability studies were carried out at $40 \text{ }^\circ\text{C} / 75 \% \text{ RH}$ for the best formulations for 1 month.

Method:

The best formulation was assessed their accelerated stability with respect to their 1 appearance, *in-vitro* disintegration time, surface pH & drug release characteristics after storing them at $40 \pm 2 \text{ }^\circ\text{C} / 75 \pm 5 \% \text{ RH}$ for 1 month. [28]

Results & Discussion:

A) Drug-Excipient Compatibility Studies by FT-IR

a) Fourior Transform Infrared Spectroscopy

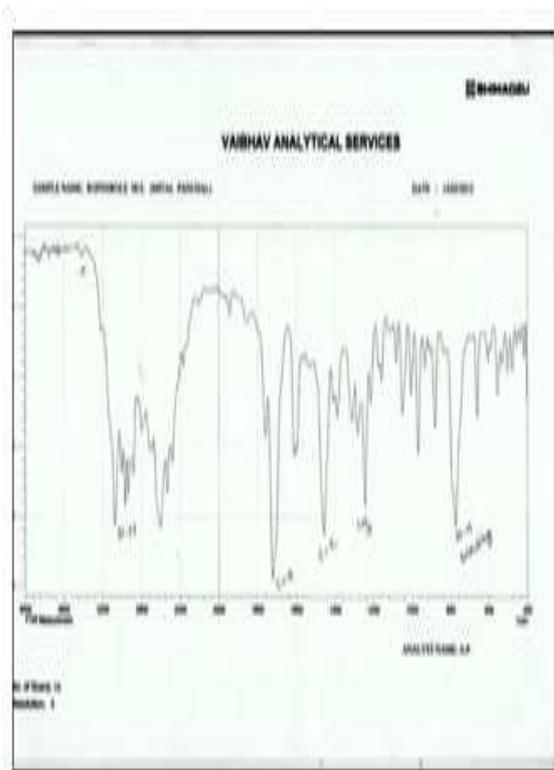


Figure III: FT-IR Spectra of Ropinirole Hydrochloride

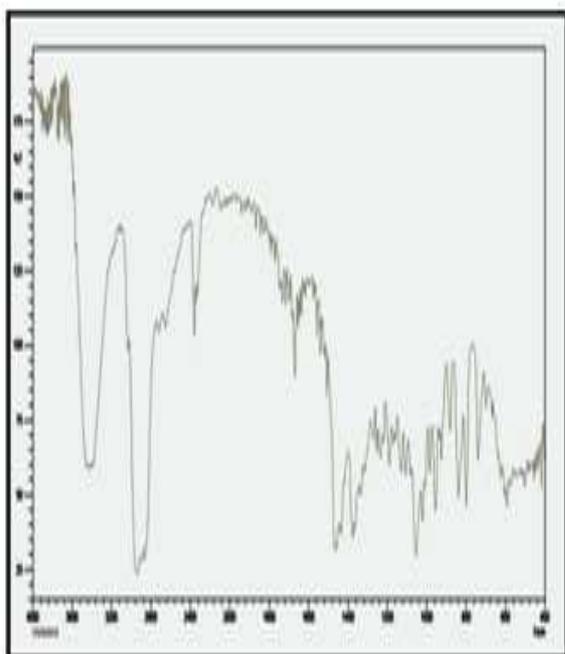


Figure IV: FT-IR Spectra of Ropinirole Hydrochloride with Pullulan Polymer

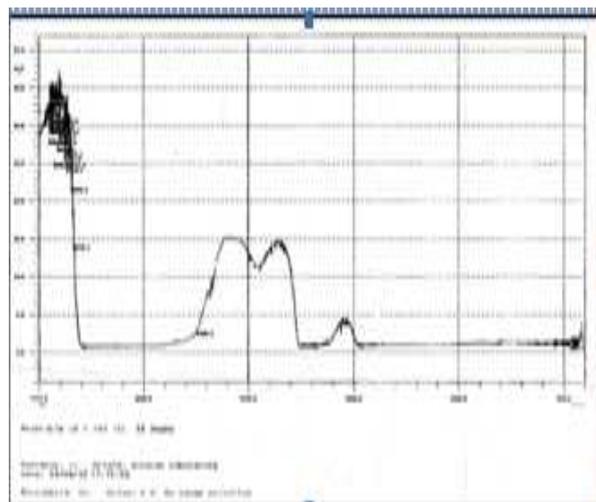


Figure V: FT-IR spectra of mouth dissolving film of Ropinirole HCL prepared by using pullulan as polymer

Pure drug Ropinirole Hydrochloride spectra showed sharp characteristic peaks at 1350 cm^{-1} ($-\text{CH}_3$ bending), 1456 cm^{-1} (C=C stretching), 1700 cm^{-1} (C=O stretching) and 3150 cm^{-1} (N-H stretching). 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 interaction between the drug and the excipients.

From this it can be concluded that the drug has maintained its identity without losing its characteristic properties. It will not show any adverse effect in action of the formulation and helps to study desired parameters in the present study.

b) Drug-Excipients Compatibility Studies by Differential Scanning Calorimetry Study

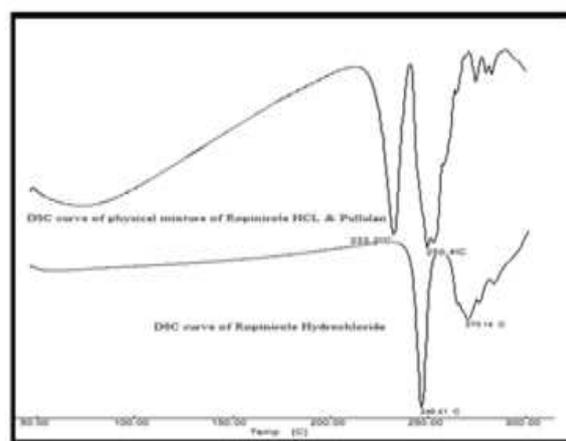


Figure VI: DSC spectras of Ropinirole Hydrochloride and Physical mixture of Ropinirole Hydrochloride and Pullulan

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 50⁰ C-300⁰ C at a heating rate of 20⁰C per min. The peak temperatures were determined after calibration with a standard.

The DSC thermograph of ropinirole hydrochloride exhibits endothermic peak at 246.41 °C corresponding to its melting point. All polymer and drug mixtures showed endothermic peak 240 °C to 255 °C range. So, results indicate that weak interaction occurs between drug and polymer

B) Calibration curve of Ropinirole Hydrochloride in Phosphate buffer pH 6.8

Table V: Absorbance-concentration data for standard curve of Ropinirole Hydrochloride

Concentration (ig/mL)	Absorbance			Average (± S.D.)
	I	II	III	
0	0.000	0.000	0.000	0.000 ± 0.000
1	0.501	0.499	0.500	0.500 ± 0.001
2	0.078	0.079	0.076	0.078 ± 0.002
4	0.124	0.123	0.124	0.123 ± 0.001
6	0.189	0.190	0.189	0.189 ± 0.001
8	0.255	0.255	0.255	0.255 ± 0.000
10	0.328	0.330	0.330	0.330 ± 0.001
12	0.398	0.395	0.397	0.397 ± 0.002
14	0.462	0.461	0.461	0.461 ± 0.000
16	0.512	0.510	0.509	0.510 ± 0.002
18	0.597	0.595	0.596	0.596 ± 0.001
20	0.627	0.627	0.625	0.627 ± 0.001
22	0.680	0.680	0.680	0.680 ± 0.000
24	0.715	0.714	0.717	0.715 ± 0.002
26	0.797	0.797	0.796	0.797 ± 0.001
28	0.858	0.859	0.857	0.858 ± 0.001

Note: Values are mean value of 3 observation (N=3), and values in parenthesis are standard deviation (± SD)

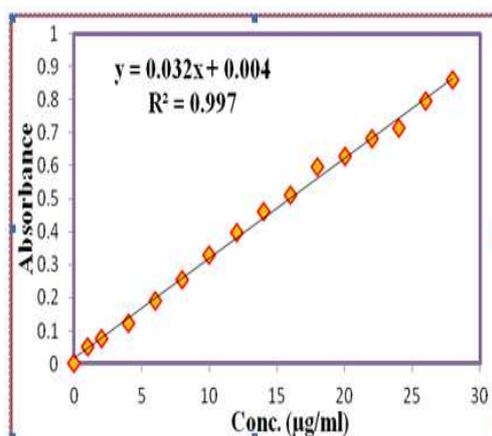


Figure VII: Absorbance-concentration profile for standard curve of Ropinirole HCL.

C) Evaluation of formulation Mouth Dissolving Films of 3² Full Factorial design**Table VI: Evaluation of Mouth Dissolving Film Formulation Batches F1 to F9**

Batch No.	Tensile Strength (g/mm ²)	% Elongation	Weight (mg)	Folding Endurance	In-vitro Disintegration time (sec)	pH	Thickness (mm)	% Drug Content	Score for Taste Masking
F1	9.19 ± 0.025	20.24 ± 1.20	63.67 ± 1.50	85.33 ± 3.21	19.67 ± 0.58	6.53 ± 0.06	0.07 ± 0.01	99.21 ± 0.48	++++
F2	9.33 ± 0.110	42.29 ± 0.88	77.50 ± 0.70	90.67 ± 3.05	22.33 ± 1.52	6.78 ± 0.08	0.08 ± 0.02	99.36 ± 0.21	+++++
F3	9.53 ± 0.080	61.10 ± 0.14	80.00 ± 0.23	94.00 ± 2.15	24.00 ± 0.00	6.83 ± 0.03	0.11 ± 0.01	99.37 ± 0.56	++++
F4	9.67 ± 0.064	21.59 ± 0.29	65.33 ± 0.68	88.00 ± 1.00	20.33 ± 0.57	6.60 ± 0.10	0.07 ± 0.01	99.53 ± 0.37	+++++
F5	10.8 ± 0.085	43.78 ± 0.45	77.66 ± 1.53	93.33 ± 3.51	22.10 ± 0.57	6.88 ± 0.13	0.09 ± 0.00	99.37 ± 1.25	+++++
F6	12.03 ± 0.112	62.05 ± 0.30	81.50 ± 0.50	96.67 ± 2.52	23.00 ± 0.00	6.95 ± 0.05	0.11 ± 0.02	99.25 ± 0.81	+++++
F7	13.21 ± 0.155	22.24 ± 0.75	65.40 ± 0.77	92.33 ± 1.64	22.00 ± 1.00	6.56 ± 0.22	0.08 ± 0.01	99.06 ± 0.67	++++
F8	15.60 ± 0.085	45.69 ± 0.81	78.00 ± 0.38	97.00 ± 1.82	23.66 ± 0.58	6.90 ± 0.15	0.09 ± 0.00	99.59 ± 0.26	+++++
F9	16.33 ± 0.121	62.94 ± 0.91	81.96 ± 0.21	104.12 ± 2.30	24.00 ± 0.00	6.86 ± 0.03	0.12 ± 0.01	99.90 ± 0.13	++++

Note: Values are mean value of 3 observation (N=3), and Values in parenthesis are standard deviation (± SD).

Tensile Strength:

We observed that increase in the concentration of polymer reflects the changes in all other variables. Specifically in the case of the polymer we observed that as the concentration of polymers increase, viscosity of the solvent system which was to be casted was increases. It affects thickness and brittleness of the film. A result showed that as the concentration of polymer increases, tensile strength of mouth dissolving film increases. A Result showed that as the concentration plasticizer increases tensile strength and % elongation of mouth dissolving film also increases.

Folding Endurance:

Folding endurance gives an indication of brittleness of the film. A result showed that as the concentration of polymer and plasticizer increases, folding Endurance of mouth dissolving film

Batch No.	In-vitro percentage drug release at 60 sec.
F1	97.58 ± 0.18
F2	86.25 ± 0.31
F3	84.51 ± 0.31
F4	99.48 ± 0.18
F5	89.69 ± 0.31
F6	86.10 ± 0.36
F7	99.52 ± 0.18
F8	89.51 ± 0.31
F9	85.89 ± 0.36

increases.

Weight variation measurement

A result showed that as the concentration of polymer increases weight of film also increases.

In-vitro disintegration time

In vitro disintegrating time for mouth dissolving film of pullulan was ranges from 19.67 ± 0.58 to 24.00 ± 0.00 sec. *In vitro* disintegrating time for mouth dissolving film of HPMC 15 CPS was ranges from 34.67 ± 1.53 to 42.00 ± 1.00 sec. All the formulations found to gave minimum disintegration time as compared to other preparations.

Surface pH

Surface pH of all mouth dissolving films prepared by using different polymers was found to be in the range of 6.5 to 7 pH, which was close to the neutral pH, which indicated that films may have less potential to irritate the sublingual mucosa, and hence, more acceptable by the patients.

Thickness Measurement

Thickness of mouth dissolving film depends on the concentration of polymer. Thickness of all mouth

dissolving film was measured with micrometer screw gauge. All the mouth dissolving formulations of different polymers are show thickness value in the range of 0.07 ± 0.01 to 0.15 ± 0.02 mm. A result of thickness measurement showed that as the concentration of polymer increases, thickness of mouth dissolving film.

Content uniformity

All the mouth dissolving films were found to contain an almost uniform quantity of the drug, as per content uniformity studies indicating reproducibility of the technique. Drug content in the films was evaluated and the values were found to be between 99.36 to 100.78 % for three different cuts from each film. As per the USP requirements, the films found to meet the criteria for content uniformity. No significant difference in the drug content among the films indicated good content uniformity.

Taste masking evaluation

Taste masking was evaluated by human panel volunteers. The taste masking of all formulation was evaluated by human panel volunteers. A result shows that excellent taste masking was found in all formulations except some formulations which shows taste masked of drug bitter taste only.

In-vitro Dissolution Study:

Table VII: In-vitro drug dissolution study of formulation batches F1 to F9

Note: Values are mean value of 3 observation (N=3), and Values in parenthesis are standard deviation (± SD).

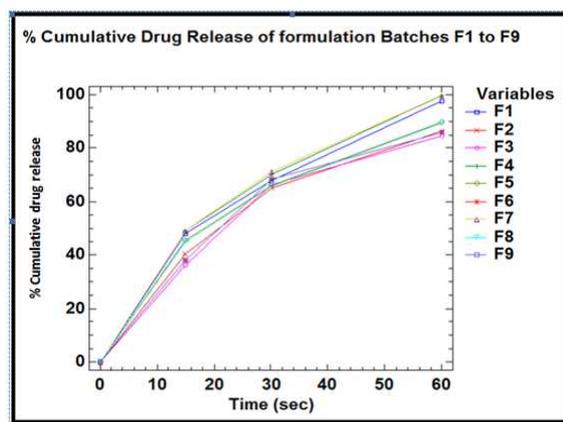


Figure VIII: Dissolution profile of formulation batches F1 to F9

Effect of Polymer concentration

In-vitro drug release study results showed that as the concentration of polymer increases, drug release of mouth dissolving films decreases.

Effect of Plasticizer concentration

In-vitro drug release study result showed that as the concentration of plasticizer increases, drug release of mouth dissolving films also increases.

Statistical Analysis:

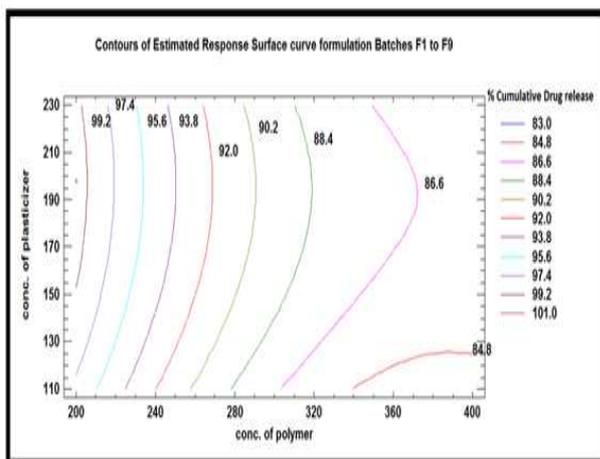


Figure IX: Contour plot of formulation batches F1 to F9

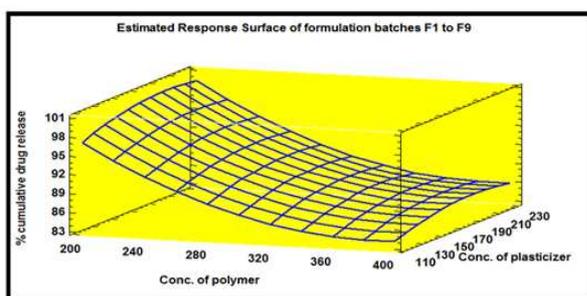


Figure X: Response surface curve of formulation batches F1 to F9

Here, contour plots, surface plots, main effect and interaction effect plots were drawn using the Statgraphic 16.1.17. These types of plots are useful in study of the effects of two factors on the response at one time.

• **Contour Plot**

Analysis of contour plot of formulation Batches F1 to F9, shown in Figure No: 5.17, reveals that the contour area was acceptable with % drug release value above 99 %. Thus, the working range to get an acceptable product was at the point A. Batch 4 containing pullulan as a polymer fall in the acceptable area. And it showed higher % drug release than the other batches.

• **Response Surface plot**

From the *in vitro* drug release study observed that as concentration of polymer increase, % drug release was decreased and as the concentration of plasticizer increase, % drug release was increased. But prediction of results of % drug release, response surface plot was plotted for graphical representation of results. So, figure showed common effect of plasticizer and polymer concentration. We can conclude from the contour plot for formulation batch F1 to F9 that, % drug release was decreased as the concentration of polymer increased and % drug release was increased as the plasticizer concentration increased.

Equations relating independent variables and response

The relationship between the independent variables and the response variables was estimated by subjecting the results to statistical evaluation. Statgraphics software was used to perform multiple linear regressions to determine the control factors that significantly affect the responses.

Control Factors: Polymer concentration, plasticizer concentration

Response: % drug release at 60 sec.

Table VIII: Regression analysis plots of measured response for formulation batches F1 to F9

Coefficient	Estimate
Constant	127.132
X2	-0.2844
X1	0.155969
X2 ²	0.000370
X1X2	-0.0000248
X1 ²	-0.000381

The fitted model was:

$$Y = 127.132 + 0.155969 * X1 - 0.2844 * X2 - 0.0000248 * X2 * X1 - 0.000381 * X1^2 + 0.000370 * X2^2$$

Validity of Equations:

The experimental values and predicted values of each response are shown in Table. The percentage

relative error of each response was calculated using the following equation:

$$\text{Percentage Relative Error} = \left(\frac{|\text{Predicted value} - \text{Experimental value}|}{\text{Predicted value}} \right) \times 100$$

Table IX: Response (*In-vitro* drug release) of check point batch for pullulan mouth dissolving film

Response	Experimental	Predicted values	% Relative error
Y1	99.48	99.67	0.19

The percentage relative error for the checkpoint batches were in the range of 0 to 8.5. It was concluded that the experimental values and predicted values showed good agreement with each other. This proved the validity of the equations.

Environment scanning electron microscopy (ESEM)

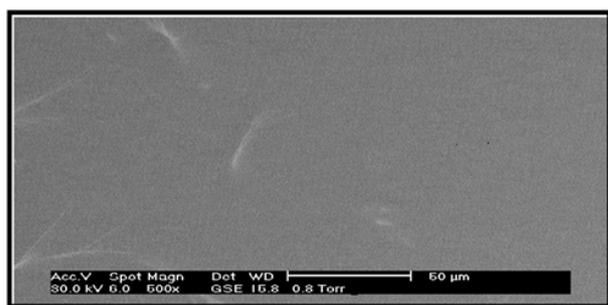


Figure XI: ESEM of batch F4 film at 500x magnification

Stability study

Table X: Evaluation of formulation F4 kept for stability at 40 °C /75 %RH

TIME (sec)	<i>In-vitro</i> Disintegration time	Surface pH	Appearance
Initial	20.33 ± 0.57	6.60 ± 0.10	White
1 month	21.20 ± 0.10	6.57 ± 0.03	Slight Yellow

Note: Values are mean value of 3 observation (N=3), and values in parenthesis are standard deviation (± SD)

Table XI: *In-vitro* drug release study of formulation F4 kept for stability at 40 °C/75 % RH

TIME (sec)	%CDR (± SD)	
	1 st Day	After 2 Month
0	0.00 ± 0.00	0.00 ± 0.00
15	48.96 ± 0.19	48.12 ± 0.19
30	70.21 ± 0.48	69.97 ± 0.52
60	99.48 ± 0.18	99.37 ± 0.36

Note: Values are mean value of 3 observation (N=3), and values in parenthesis are standard deviation (± SD)

Short-term stability studies were performed for formulation F4 at 45 ± 1°C for 1 month. The samples were analyzed for *in vitro* disintegration time, surface pH, appearance and *in vitro* drug release studies. The results are given in table no: 5.32 and 5.33. No appreciable difference was observed for the above parameters.

Photograph of formulation of mouth dissolving film



Figure XII: Photograph of mouth dissolving film containing pullulan polymer

Conclusion:

The results of the present study indicated that pullulan could be used as a film forming polymer for formulation of mouth dissolving film containing Ropinirole hydrochloride. The amount of plasticizer PEG 400 was critical for film formation and separation properties. Taste masking was achieved using combination of sweeteners, flavours and citric acid. Type of flavouring agent was critical for producing taste masking of mouth dissolving film. Acceptable mechanical properties were obtained in the batch F4 with *in vitro* disintegration time of 20 sec. The optimized batch F4 was found to be stable for a period of 1 month at 25 °C/40 %RH. One dependent variable was selected to see the effect of polymers and multiple regressions was applied. The experimental (from check point batch) and predicted (from multiple regression equation) values were close to each other. It was concluded that the check point batch

was the optimized batch with the fulfillment of all the desirability.

“Cite This Article”

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