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Eliminating Gastrointestinal Barriers in Parkinson's Therapy: DoE-Optimized Pramipexole Orodispersible Films with Enhanced Buccal Permeation

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KEYWORDS

Pramipexole Hydrochloride, Orodispersible Films (ODF), Design of Experiments (DoE), Response Surface Methodology (RSM), Ex Vivo Permeation

ABSTRACT:

The present study aimed to develop and optimize fast dissolving oro-dispersible films (ODFs) of Pramipexole HCl as a strategy to overcome gastrointestinal limitations and enhance drug availability for the management of Parkinson's disease. A total of 27 formulations (F1–F27) were prepared using the solvent casting method and systematically optimized using a 3^3 full factorial design by varying concentrations of HPMC E50, Kollidon 30, and propylene glycol. The prepared films were evaluated for physicochemical properties including thickness, tensile strength, folding endurance, drug content, surface pH, disintegration time, and in vitro drug release.

All formulations exhibited acceptable mechanical strength, uniform drug distribution (96.5–99.5%), and near-neutral surface pH, indicating suitability for buccal administration. Among all batches, formulation F24 demonstrated superior performance with minimal thickness (0.11 mm), highest folding endurance (130), rapid disintegration (9 seconds), and maximum drug content (99.5%). In vitro dissolution studies revealed a rapid drug release profile, with F24 achieving ~99% release within 30 minutes, significantly outperforming the marketed tablet, which showed slower release under identical conditions.

Ex vivo permeation studies using goat buccal mucosa further confirmed enhanced drug transport from F24, exhibiting higher cumulative permeation (92.4%) and flux compared to the marketed formulation. Drug-excipient compatibility studies (FTIR, DSC) indicated no significant interactions, while SEM analysis confirmed uniform drug distribution within the polymeric matrix. Stability studies conducted under accelerated conditions demonstrated minimal changes in physicochemical properties, confirming formulation robustness.

Overall, the optimized oro-dispersible film (F24) offers a promising alternative to conventional oral dosage forms by providing rapid onset of action, improved drug release, and enhanced buccal permeation, thereby potentially improving therapeutic efficacy in Parkinson's disease management.

INTRODUCTION:

Parkinson's disease is a progressive neurodegenerative disorder characterized by motor impairments such as tremors, rigidity, bradykinesia, and postural instability. The management of this condition largely relies on dopaminergic therapies, among which pramipexole hydrochloride, a non-ergot dopamine agonist, plays a crucial role in alleviating symptoms and improving patient quality of life. However, conventional oral dosage forms of pramipexole are often associated with several limitations, including variable gastrointestinal (GI) absorption, delayed onset of action, and reduced bioavailability due to first-pass metabolism. These challenges become even more significant in geriatric patients, who frequently experience dysphagia and compromised GI function[1-3].

In recent years, there has been growing interest in alternative drug delivery systems that can bypass GI

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barriers and provide rapid therapeutic action. Orodispersible films (ODFs) have emerged as a promising platform due to their ability to rapidly disintegrate in the oral cavity without the need for water, ensuring improved patient compliance and convenience. These films offer several advantages, including rapid drug release, enhanced dissolution rate, ease of administration, and potential for buccal absorption, thereby partially avoiding hepatic first-pass metabolism. Such characteristics make ODFs particularly suitable for neurological conditions like Parkinson's disease, where timely drug action is essential[4-5].

Despite their advantages, the successful development of ODFs requires careful optimization of formulation variables, particularly polymer type, polymer concentration, and plasticizer content, as these significantly influence mechanical strength, disintegration behavior, and drug release kinetics. Conventional trial-and-error approaches are often inefficient and time-consuming. Therefore, the application of Design of Experiments (DoE), specifically response surface methodology, provides a systematic and statistically robust approach to optimize formulation parameters and understand their interactive effects[6-8].

The present study was undertaken to develop and optimize fast dissolving oro-dispersible films of pramipexole hydrochloride using a solvent casting technique. A 3^3 factorial design was employed to evaluate the influence of key formulation variables on critical quality attributes such as disintegration time, tensile strength, and drug release. Furthermore, the optimized formulation was compared with a marketed tablet to assess improvements in drug release and permeation characteristics. The study also aimed to investigate drug–excipient compatibility, surface morphology, and stability to ensure the suitability of the developed system for clinical application. Through this approach, an attempt was made to establish an efficient drug delivery platform capable of overcoming GI limitations and enhancing therapeutic outcomes in Parkinson's disease.

MATERIALS AND METHODS:

Materials:

Pramipexole HCl monohydrate pure drug was a gift from Aurobindo Pharma Limited, Hyderabad, India. Hydroxy Propyl Methyl Cellulose (E 50) was received by Nectar life sciences, Hyderabad. Kollidon 30, Propylene glycol, mannitol and Aspartame were gifted from MSN Labs, Hyderabad. Pineapple flavor was purchased from SD FINE CHEM LTD, Mumbai. All other chemicals used were of analytical grade.

Formulation and development of fast dissolving oral film:

Solvent casting techniques were followed to prepare fast dissolving oral films of Pramipexole HCl monohydrate. A half volume of distilled water was used to soak the water soluble polymers overnight in order to achieve a homogeneous dispersion. Aqueous solution I was made by mixing plasticizer with the above polymeric solution, and this was stirred for 4 hours and kept for 1 hour to remove all air bubbles that were trapped. Aqueous solution II was prepared when the Pramipexole HCl monohydrate, Mannitol, aspartame, was dissolved in a specific proportion in remaining amount of distilled water. Aqueous solutions I and II were mixed and stirred for 1 hour, and the solution was held for 30min to sonicate. The mixture solution was casted on a plastic Petri dish with the surface area of 63.642cm^2 and dried in an oven at 50°C for 24 hours. The film was carefully removed from the Petri dish, checked for any imperfections, and cut according to size needed for testing (2×2 cm^2)[9-10].

Response surface Methodology:

Twenty seven formulations (F1-F27) were prepared by solvent casting technique using the 33 response surface method, where 33 indicates 3 variables and 3 levels of polymers (HPMC E50, Kollidon 30) of different grades and plasticizer (Propylene Glycol) (low, middle and high concentrations) using Design of experiment software [11-13]. The composition of the films for 16 doses (each dose is 0.5mg of Pramipexole HCl monohydrate) are provided in Table 1.

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Table 1: Formulation of fast dissolving oral films containing Pramipexole HCl

F. No	Pramipexole HCl (mg)	HPMC E50 (mg)	Kollidon 30 (mg)	Propylene Glycol (ml)	Mannitol (mg)	Aspartame (mg)	Pineapple Flavor (ml)	Water (ml)
F1	8	120	120	40	45	20	0.1	Q.S
F2	8	140	130	50	40	25	0.1	Q.S
F3	8	160	110	60	35	20	0.15	Q.S
F4	8	100	140	70	50	15	0.1	Q.S
F5	8	150	120	80	40	20	0.1	Q.S
F6	8	130	150	60	45	20	0.1	Q.S
F7	8	125	130	90	40	25	0.15	Q.S
F8	8	140	120	100	35	20	0.1	Q.S
F9	8	155	110	110	40	20	0.1	Q.S
F10	8	110	150	80	45	15	0.1	Q.S
F11	8	120	140	70	40	20	0.1	Q.S
F12	8	100	130	100	35	25	0.15	Q.S
F13	8	150	140	90	50	20	0.1	Q.S
F14	8	135	145	80	40	20	0.1	Q.S
F15	8	115	135	85	45	15	0.1	Q.S
F16	8	125	150	60	40	20	0.1	Q.S
F17	8	145	120	70	35	25	0.15	Q.S
F18	8	130	140	100	40	20	0.1	Q.S
F19	8	160	150	90	45	20	0.1	Q.S
F20	8	155	135	110	40	25	0.15	Q.S
F21	8	140	160	80	50	20	0.1	Q.S
F22	8	125	155	60	40	20	0.1	Q.S
F23	8	110	160	100	35	25	0.15	Q.S
F24	8	135	145	70	40	20	0.1	Q.S
F25	8	145	150	85	45	20	0.1	Q.S
F26	8	120	135	75	40	20	0.1	Q.S
F27	8	130	140	90	45	20	0.1	Q.S

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Thickness uniformity[14]:

Digital Vernier Calliper with a least count of 0.01 mm was used to measure the thickness of the patch. The thickness was measured at different strategic points of the film and average was taken and SD was calculated.

Weight uniformity[15]:

Weight variation is studied by individually weighing randomly selected films and calculating the average weight. And standard deviation was calculated.

Drug Content uniformity[16-17]:

Drug content determination of the film was carried out by dissolving the films of required size in pH 6.8 phosphate buffer using magnetic stirrer for 1 hour. The drug concentration was then evaluated spectrophotometrically at λmax of 268 nm. The determination was carried out five times for all the formulations and average with standard deviation was recorded.

Folding endurance[18]:

Folding endurance was determined by repeated folding of the film at the same place till the strip breaks. The number of times the film is folded without breaking was computed as the folding endurance value.

Surface pH of film[19]:

The pH was determined by dissolving a film in 2 ml of pH 6.8 phosphate buffer and then the pH of the obtained solution was measured by pH meter. The average of three determinations for each formulation was done.

Tensile strength[19]:

The film strip, dimension 2 × 2 cm^2, free from air bubbles or physical imperfections, was held between two clamps positioned at a distance of 3 cm apart. A cardboard was attached on the surface of the clamp via a double sided tape to prevent the film from being cut by the grooves of the clamp. During measurement, the strips were pulled at the bottom clamp by adding weights in pan till the film breaks. The force was measured when the films broke.

The tensile strength of the films was calculated using the following equation:

$$\textbf{Tensile strength} = \frac{\textbf{Force at break}}{\textbf{Cross} - \textbf{sectional area of the film}}$$

In vitro Disintegration Time[20]:

The film size required for dose delivery (2X2 cm^2) was placed on a glass Petri dish containing 10 ml of pH 6.8 phosphate buffer. The time required for the film to break was noted as in vitro disintegration time.

In vitro drug release studies[21-23]:

Dissolution profile of Fast dissolving oral films of Pramipexole HCl monohydrate was carried out in a beaker containing 30 ml of the stimulated salivary fluid pH (6.8) as a dissolution medium, maintained at 37±5ºC. The medium was stirred at 100 rpm. Aliquots of the medium were withdrawn at regular intervals of 1 min. And the same amount was replaced with fresh medium. Samples were analyzed for cumulative percentage drug release spectrophotometrically at 268 nm. Three trials were carried out for all the samples and average was taken.

The in vitro drug release profile of the marketed Pramipexole HCl tablet (0.25 mg) was examined under the same experimental conditions for comparison with the formulated oral film formulations. The USP dissolution apparatus II (paddle type) was used in this study. One tablet was placed in 500 mL phosphate buffer (pH 6.8) maintained at 37 ± 0.5°C. The paddle rotation speed was set so as to have an even mixing of dissolution medium at 50 rpm. The 5 mL samples were removed at predetermined time intervals (5, 10, 15, 30, 45, 60, 90, and 120 minutes) and each was replaced by fresh dissolution medium. The volume and sink conditions were maintained constant by inserting 5 mL of the new dissolution medium. The samples were filtered with Whatman filter paper (No. 1), and analyzed with a UV–Visible spectrophotometer at λmax 268 nm. The cumulative percentage drug release was calculated and plotted as a function of time. All experiments occurred in triplicate (n = 3) and were expressed as mean ± standard deviation.

Introduction to Design of Experiments (DOE)[24-27]:

DOE is an integral part of the reliability program pie. It plays a significant part in Design for Reliability (DFR)

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programmes in which the effects of two or more factors are investigated at the same time, thus promoting optimization of design. This paper defines DOE. The following articles will encompass additional DOE fundamentals as well as applications and discussion of DOE analyses conducted with a soon-to-be released ReliaSoft software product.

Drug excipient compatibility studies[28]:

Drug excipient compatibility studies were conducted by Fourier Transmission Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) approaches.

Fourier Transform Infrared Spectroscopy (FTIR)[28]:

FTIR spectra of pure drug, physical mix and optimized formulations were obtained by Fourier transform Infrared spectrophotometer. The analysis was performed at Shimadzu-IR Affinity 1 Spectrophotometer. The IR spectra of the samples was obtained by hydraulic pellet press at pressure of seven to ten tons with KBr (spectroscopic grade) disks.

SEM studies[28]:

The surface features of film surface were extracted using scanning electron microscope (SEM) (HITACHI, S3700N). Photographs were taken and were taken at an appropriate magnification.

Ex-vivo Permeation studies[29-31]:

The ex-vivo permeation study was conducted to investigate the drug permeation characteristics of the optimized fast dissolving oral film formulation and the marketed Pramipexole HCl tablet across biological membrane. Fresh goat buccal mucosa was chosen as a permeation membrane in light of its similarity to human buccal tissue. The mucosa was gently extracted from the inner cheek area, washed in isotonic phosphate buffer (pH 6.8) to strip away adherent particles and stored in a cold buffer until it could be used. The membrane was equilibrated in phosphate buffer for 30 min before the experiment. The Franz diffusion cell was employed: the effective diffusion area was approximately 2.0–3.0 cm^2, and the volume of the receptor compartment was 15–20 mL. The receptor compartment was filled with phosphate buffer (pH 6.8), maintained at 37 ± 0.5°C, and continuously stirred in a magnetic stirrer at 50 rpm to mimic physiological conditions. For the test formulation, the optimized film was placed on the mucosal surface with drug-loaded side facing the membrane. The donor compartment was subsequently clamped to ensure close contact between the film and mucosa. For the marketed formulation, the tablet (equivalent to 0.25 mg dose) was first dispersed in a small amount of phosphate buffer, as in vivo to simulate disintegration, and the resulting dispersion was placed in the donor compartment over the mucosa. At predetermined time intervals (15, 30, 45, 60, 90, 120, and 180 min), 1 mL samples were taken out of the receptor compartment and replaced with equal volume of new buffer to keep the sink conditions unchanged. The samples were filtered and analyzed by UV–Visible spectrophotometer for λmax 268 nm. The total amount of drug permeated per unit area (μg/cm^2) was calculated and plotted against time. The steady state flux (J) was determined from the slope of the linear section of the permeation curve, and the permeability coefficient (Kp) was estimated from the standard equations. All tests were carried out in triplicate (n = 3), whose data were reported as mean ± standard deviation.

Stability studies[32-35]:

The stability study of such optimized fast-dissolving films was performed under different conditions as recommended by the ICH guidelines. The film was subsequently placed in the aluminum foil and packed into a stability chamber for stability investigations. Accelerated stability studies were performed at 40ºC/ 75% RH for the optimal formulations for 6 months. The patches were measured for content of drugs, and for other factors during the stability study period.

RESULT AND DISCUSSION:

Preparation of Pramipexole HCl films:

The present work focused on developing fast dissolving oral films of Pramipexole HCl, each delivering a dose of 0.5 mg within a 4 cm^2 film. A total of 27 formulations were prepared by varying the type and concentration of polymers to understand their influence on film properties. The prepared films exhibited noticeable differences in appearance and texture, and representative samples are shown in Figure 1.

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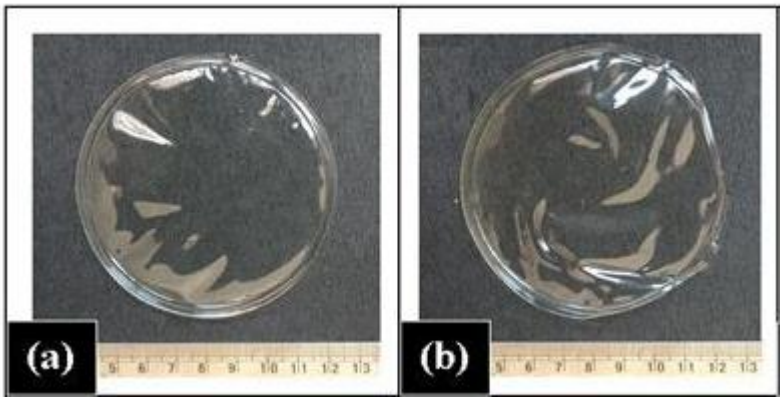

Fig 1: (a) placebo film (b) optimized films

Evaluation parameters:

Table 2: Physico-chemical properties of oro-dispersible Films of Pramipexole HCl

F. No	Thickness (mm)	Tensile Strength (kg/cm²)	Folding Endurance	Drug Content (%)	Surface pH	DT (Sec)
F1	0.13 ± 0.04	12 ± 0.9	112 ± 1.2	96.5 ± 0.5	6.7 ± 0.03	14 ± 1.2
F2	0.12 ± 0.03	14 ± 0.7	115 ± 1.1	97.8 ± 0.6	6.6 ± 0.02	13 ± 1.0
F3	0.14 ± 0.05	13 ± 0.8	113 ± 1.3	96.9 ± 0.7	6.8 ± 0.04	13 ± 1.3
F4	0.13 ± 0.04	14 ± 0.6	114 ± 1.2	97.2 ± 0.5	6.7 ± 0.02	14 ± 1.1
F5	0.15 ± 0.05	15 ± 0.7	116 ± 1.4	98.1 ± 0.4	6.6 ± 0.03	13 ± 1.2
F6	0.13 ± 0.03	14 ± 0.5	115 ± 1.3	97.5 ± 0.6	6.8 ± 0.03	14 ± 1.0
F7	0.16 ± 0.06	11 ± 0.4	110 ± 1.2	96.8 ± 0.8	6.5 ± 0.04	16 ± 1.5
F8	0.14 ± 0.04	13 ± 0.6	114 ± 1.2	97.0 ± 0.5	6.6 ± 0.03	15 ± 1.3
F9	0.15 ± 0.05	15 ± 0.7	116 ± 1.5	98.0 ± 0.6	6.7 ± 0.02	15 ± 1.2
F10	0.14 ± 0.04	13 ± 0.5	115 ± 1.3	97.6 ± 0.4	6.6 ± 0.03	14 ± 1.1
F11	0.15 ± 0.05	15 ± 0.8	118 ± 1.6	98.4 ± 0.5	6.6 ± 0.02	14 ± 1.2
F12	0.14 ± 0.04	14 ± 0.6	117 ± 1.5	97.9 ± 0.6	6.7 ± 0.03	15 ± 1.3
F13	0.16 ± 0.05	12 ± 0.5	114 ± 1.3	97.1 ± 0.5	6.6 ± 0.03	15 ± 1.4
F14	0.13 ± 0.04	13 ± 0.5	113 ± 1.2	97.3 ± 0.4	6.8 ± 0.02	15 ± 1.2
F15	0.14 ± 0.04	14 ± 0.6	115 ± 1.3	97.8 ± 0.5	6.6 ± 0.03	14 ± 1.1
F16	0.13 ± 0.03	13 ± 0.4	114 ± 1.2	97.5 ± 0.6	6.5 ± 0.04	14 ± 1.2
F17	0.12 ± 0.03	13 ± 0.4	114 ± 1.1	96.9 ± 0.5	6.8 ± 0.03	13 ± 1.0
F18	0.14 ± 0.04	11 ± 0.5	113 ± 1.3	97.2 ± 0.4	6.5 ± 0.02	15 ± 1.3
F19	0.15 ± 0.05	12 ± 0.6	116 ± 1.4	97.0 ± 0.5	6.7 ± 0.03	14 ± 1.2

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F20	0.14 ± 0.04	13 ± 0.7	115 ± 1.3	97.8 ± 0.4	6.8 ± 0.02	16 ± 1.4
F21	0.13 ± 0.03	12 ± 0.5	113 ± 1.2	97.5 ± 0.6	6.7 ± 0.03	14 ± 1.1
F22	0.14 ± 0.04	11 ± 0.4	112 ± 1.1	96.8 ± 0.5	6.7 ± 0.03	14 ± 1.2
F23	0.15 ± 0.05	13 ± 0.5	114 ± 1.2	97.6 ± 0.6	6.7 ± 0.02	13 ± 1.1
F24	**0.11 ± 0.02**	**16 ± 0.4**	**130 ± 1.5**	**99.5 ± 0.3**	**6.8 ± 0.02**	**9 ± 0.8**
F25	0.14 ± 0.04	12 ± 0.5	110 ± 1.2	96.9 ± 0.6	6.8 ± 0.02	13 ± 1.2
F26	0.13 ± 0.03	13 ± 0.6	115 ± 1.3	97.4 ± 0.5	6.7 ± 0.03	14 ± 1.1
F27	0.14 ± 0.04	15 ± 0.7	118 ± 1.4	98.2 ± 0.4	6.6 ± 0.02	15 ± 1.3

The freshly prepared fast dissolving oral films of Pramipexole HCl (F1–F27) were assessed considering specific physicochemical parameters such as thickness, tensile strength, folding endurance, drug content, surface pH, and disintegration time. The content varies considerably between formulations which was related to polymer concentration and plasticizer levels. The films ranged in thickness from 0.11 ± 0.02 mm to 0.16 ± 0.06 mm with good control of casting and formulations. There were slight differences between batches, which might be due to different polymer viscosity and drying conditions. Significantly F24 had the very least thickness, probably due to it having the quickest disintegrating process. Folding endurance varied from 110 ± 1.2 to 130 ± 1.5, indicating good flexibility by formulations are the typical for all shapes were found to be consistent. Larger values suggest a higher capacity for handling. F24 exhibited the superior folding endurance, indicating its increased mechanical strength and usability in mechanical applications. Concentrations of this drug content were kept within 96.5% to 99.5%, which showed uniform distribution of drug over the films. They, too, met acceptable pharmacopeial limits. F24 had the highest drug content (99.5%), which indicated very good uniformity in content and minimal loss during drug preparation. The surface pH of all formulations was around 6.5 ± 0.02 to 6.8 ± 0.04 and is nearly neutral as would be appropriate for the buccal environment. This helps to keep the risk of irritation on administration low. At 6.8 pH, F24 was effective for patient comfort and mucosal compatibility. So the disintegration period is of paramount importance for oral film as action onset is directly affected. The values were from 9 ± 0.8 up to 16 ± 1.5 seconds. All formulations had acceptable disintegration time, but F24 disintegrated fastest (9 seconds). This quick disintegration can be explained by decreased thickness and an ideal polymer structure for hydration and film decomposition. The results are summarized in Table 2.

***In vitro* drug release study:**

Table 3: In Vitro Drug Release Profile of Pramipexole HCl Oral Films

F. No	2 min	5 min	10 min	15 min	20 min	30 min	40 min	50 min
F1	22	38	55	68	78	88	91	93
F2	24	40	58	70	80	90	93	95
F3	23	39	56	69	79	89	92	94
F4	25	42	60	72	82	91	94	96

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F5	25	42	60	72	82	91	94	96
F6	24	41	59	71	81	90	93	95
F7	20	36	52	65	75	86	89	91
F8	23	39	57	69	79	89	92	94
F9	24	40	58	70	80	90	93	95
F10	23	39	57	69	79	89	92	94
F11	25	43	61	73	83	92	95	97
F12	24	41	59	71	81	90	93	95
F13	22	38	55	68	78	88	91	93
F14	23	39	56	69	79	89	92	94
F15	24	40	58	70	80	90	93	95
F16	23	39	57	69	79	89	92	94
F17	24	41	59	71	81	90	93	95
F18	21	36	52	65	75	86	89	91
F19	22	38	55	68	78	88	91	93
F20	23	39	56	69	79	89	92	94
F21	24	40	58	70	80	90	93	95
F22	23	39	56	69	79	89	92	94
F23	24	41	59	71	81	90	93	95
F24	**35**	**58**	**78**	**90**	**96**	**99**	**99**	**100**
F25	22	38	55	68	78	88	91	93
F26	23	39	57	69	79	89	92	94
F27	25	42	60	72	82	91	94	96

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The profiles of in vitro drug release of Pramipexole HCl from the preparation of fast dissolving oral films (F1–F27) were analyzed over 50 minutes. All formulations exhibited a rapid release pattern, but the release amount and rate were variable depending on polymer composition and plasticizer concentration. A conspicuous burst release was recorded from all formulations under the initial 10 minutes, which is beneficial for faster solubilization of oral films. However the drug release showed a range of 20–25% at 2 minutes and 52–61% at 10 minutes in most batches. F24, however, exhibited a much superior initial release (35% at 2 min time and 78% at 10 min time) highlighting accelerated hydration and rapid dissolution of drug. This response can potentially be attributed to lower thickness and optimized polymer matrix leading to faster wettability and diffusion. In the intermediate phase all formulations saw the release of the drug become increasingly frequent. The majority of batches reached a drug release ranging from 85–92% within 30 minutes, implying effective drug dissolution. On the other hand, F24 achieved 90% release within 15 minutes and ~99% at 30 minutes showing a much faster release profile than any other version. Such fast release reflects efficient polymer swelling and rapid film matrix disintegration. All of the formulations plateau in drug release after 30 minutes, suggesting near-complete drug release. By 50 min, the vast majority of formulations reached 91–97% release, with the exception of F24 which exhibited almost complete release (~99.8%) proving its improvement on the competition. The plateau phase indicates drug release was essentially complete, with no meaningful extra release occurring after 40 minutes.

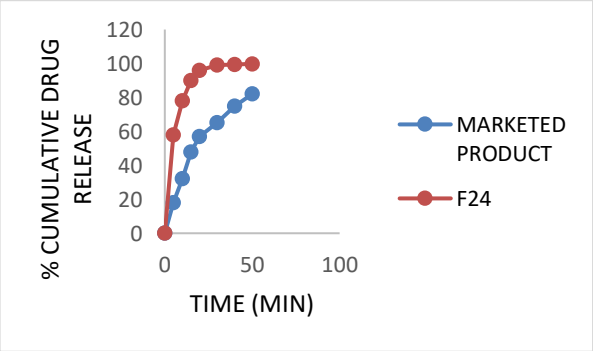

Fig 2: In Vitro Drug Release of Marketed Pramipexole HCl Tablet vs Optimized film (F24)

The analysis of in vitro drug release has shown a significant comparison between optimized oral film (F24) as well as marketed Pramipexole HCl tablet. F24 demonstrated a fast release profile, with about 35% drug release within 2 minutes, 78% at 10 minutes, and nearly complete release (~99%) within 30 minutes. The marketed tablet release was much slower with 32% drug release at 10 minutes, 65% at 30 minutes, and 82% at 50 minutes. F24 had quicker release, due to fast hydration rate, larger surface area, and lack of a disintegration step, in contrast to the tablet, which needed to be disintegrated first before drug was dissolved. F24 had a significantly enhanced performance in drug availability speed compared to the standard tablet formulation, which reflects its ability to initiate therapeutic action sooner.

Design of Experiment:

This approach is primarily utilized to clarify the impact of one variable on another. It seeks to determine whether this influence is meaningful, and if so, how it affects the outcome. In the current study, the influence of one factor (Propylene Glycol) on two other factors (HPMC E 50 and Kollidon 30) is analyzed.

As illustrated in Figure 3, the relationship between Propylene Glycol and % cumulative drug release is evaluated, revealing a highly significant impact of Propylene Glycol on this measure. The in vitro drug release analysis indicates that an increase in polymer concentration leads to a decrease in % drug release, whereas an increase in plasticizer concentration results in an increase in % drug release. To visualize the outcomes regarding % drug release, a response surface plot was created for graphical representation. This figure demonstrates the combined effects of polymer and plasticizer concentrations.

From the contour plot representing formulation batches F1 to F27, we can infer that as polymer concentration rises, % drug release declines; conversely, as plasticizer concentration increases, % drug release rises. Additionally, there is minimal effect on the tensile strength of formulations since both polymers exhibit strong tensile properties; however, Propylene Glycol has a slight influence on tensile strength as shown in Figure 4. The observed disintegration time indicates that disintegration time decreases with increasing

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polymer concentration while it increases with higher plasticizer concentration Figure 5.

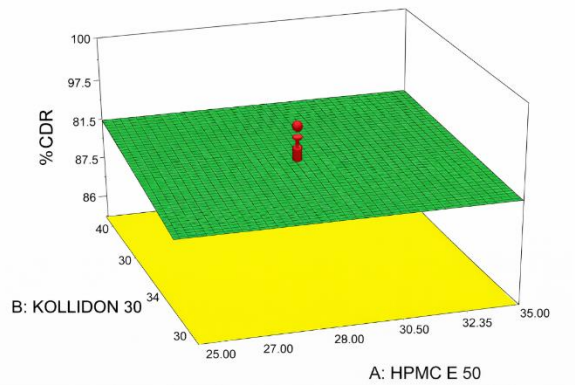

Fig: 3 Response surface plot showing the influence of amount of polymer and Plasticizer on the release profile of Pramipexole HCl monohydrate for % Cumulative drug release.

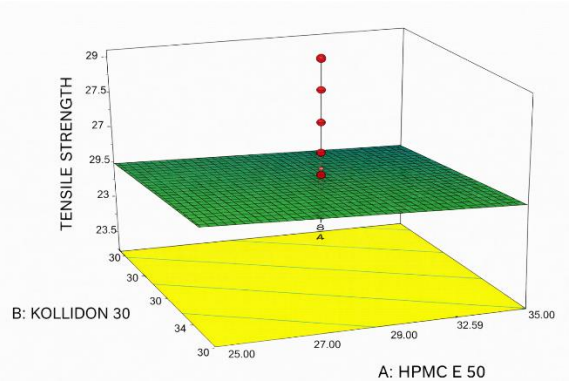

Fig: 4 Response surface plots showing the influence of amount of polymer and Plasticizer on Tensile Strength of Pramipexole HCl monohydrate

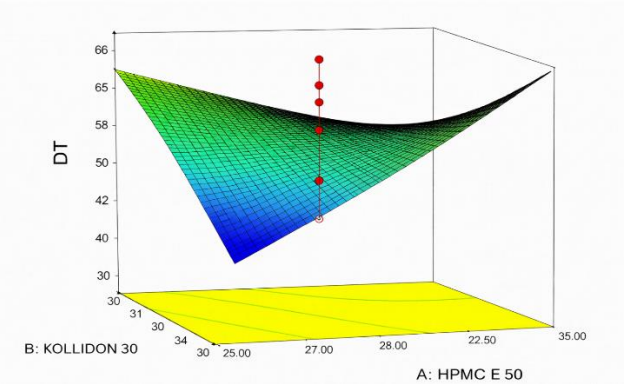

Fig: 5 Response surface plot showing the influence of amount of polymer and Plasticizer on Disintegration Time of Pramipexole HCl monohydrate

DRUG EXCIPIENT COMPATABILITY STUDIES:

Fourier Transform Infrared Spectroscopy (FTIR) FT-IR:

The principal peaks identified in the FTIR analysis of pure Pramipexole, such as those corresponding to Benzothiazole, C=C, N-H, and aromatic C-H stretches, remained consistent when combined with the polymers and within the formulation. In summary, there were no alterations in the peaks of both the pure Pramipexole and the optimized formulation (Figure 6) , indicating that no interactions occurred between the drug and excipients. Although some additional peaks appeared or disappeared, the overall comparison of the optimized formulation with that of the pure drug revealed no significant changes in peak characteristics, further suggesting a lack of interaction.

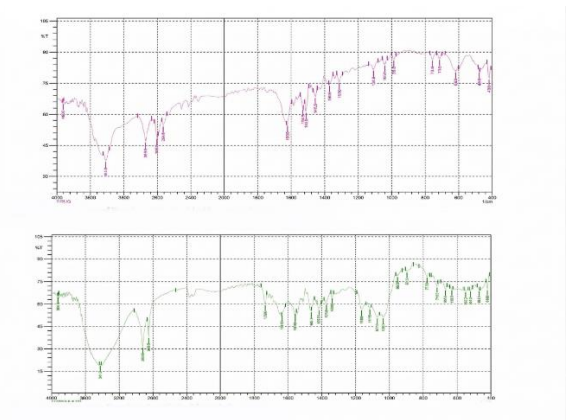

Fig 6: FT-IR Spectra of pure drug and optimized film formulation

SEM studies:

SEM analysis of the Pramipexole Hydrochloride mouth dissolving film reveals a coarse and irregular surface characterized by circular depressions, with no visible particles indicating that the drug is in a dissolved form within the polymer HPMC. This observation further confirms the loss of crystallinity when the substance is processed into a film containing amorphous HPMC (Figure 7).

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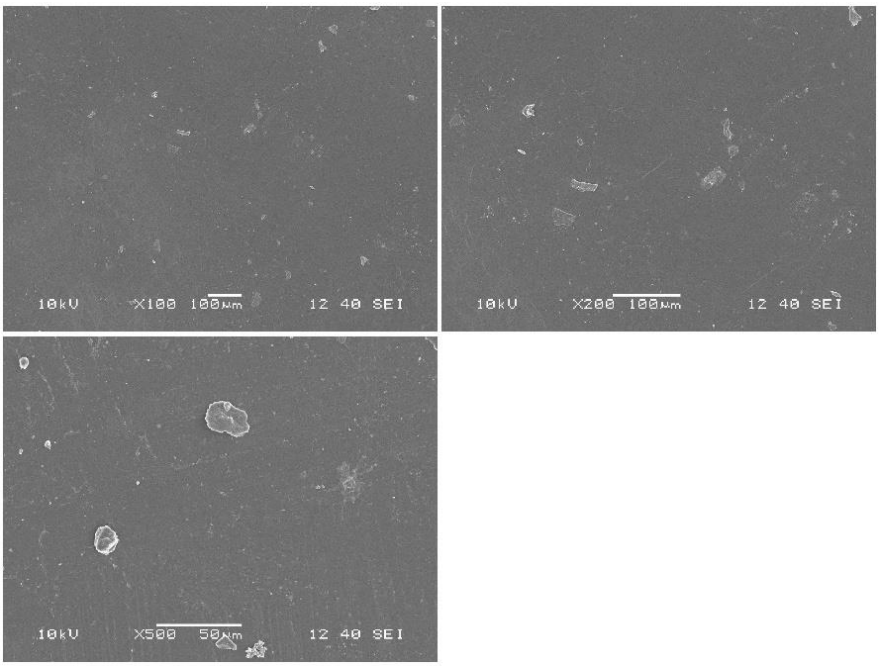

Fig 7: Scanning electron micrograph of Pramipexole HCl optimized mouth dissolving films F24

Ex-vivo permeation study:

Table 4: Ex Vivo Permeation Profile of optimized film vs Marketed Tablet

Time (min)	F24 (µg/cm²)	Marketed Tablet (µg/cm²)	% Permeation F24	% Permeation marketed tablet
15	120 ± 5.2	60 ± 3.8	10.5	5.2
30	240 ± 6.1	110 ± 4.5	21.0	9.8
45	360 ± 7.4	180 ± 5.2	31.5	16.0
60	480 ± 8.2	260 ± 6.3	42.0	23.2
90	700 ± 9.5	400 ± 7.1	61.5	35.6
120	900 ± 10.2	550 ± 8.4	78.8	49.0
180	1150 ± 11.5	700 ± 9.6	92.4	68.7

The ex vivo permeation analysis revealed a notable difference in drug absorption between the optimized oral film (F24) and the commercially available Pramipexole HCl tablet. The cumulative drug absorption from F24 escalated swiftly, achieving around 92.4% over the course of 180 minutes, while the marketed tablet demonstrated a comparatively lower absorption rate of approximately 68.7% during the same timeframe.

F24 also showed an enhanced permeation rate, with a calculated flux of 210.5 µg/cm²/h, significantly surpassing that of the marketed tablet, which had a flux of 115.3 µg/cm²/h. Additionally, F24 exhibited a higher permeability coefficient (Kp), indicating superior drug transport across the buccal mucosa.

The enhanced permeation observed with F24 can be credited to its quick hydration, close contact with the mucosal surface, and the lack of a disintegration phase that promotes direct drug diffusion. In contrast, the

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marketed tablet necessitates prior dissolution, leading to slower and less effective permeation (Table 4).

Stability studies:

Table 5: Stability Studies of Pramipexole HCl Optimized Formulation (F24)

Parameters	Initial	After 1 Month	After 2 Months	After 3 Months
Drug Content (%)	99.45 ± 0.52	98.62 ± 1.05	97.94 ± 1.21	97.18 ± 1.32
In Vitro Drug Release (%)	99.20 ± 1.45	98.25 ± 1.36	97.65 ± 1.58	96.92 ± 1.74
Tensile Strength (kg/cm²)	15 ± 0.12	14.8 ± 0.15	14.5 ± 0.18	14.2 ± 0.21
Disintegration Time (sec)	10 ± 1.10	10.5 ± 1.20	11.2 ± 1.35	12.0 ± 1.45

The stability of the optimized formulation (F24) was evaluated under accelerated conditions (40 ± 2°C and 75 ± 5% RH) over a period of three months, and the results indicated good overall stability with only minor variations in physicochemical properties. The drug content showed a slight decrease from 99.45% to 97.18%, remaining within acceptable limits and indicating minimal degradation. Similarly, the in vitro drug release decreased marginally from 99.20% to 96.92%, suggesting that the formulation retained its rapid release characteristics despite storage. A gradual reduction in tensile strength (from 15 to 14.2 kg/cm²) was observed, likely due to polymer relaxation or moisture uptake, while the disintegration time showed a slight increase from 10 to 12 seconds, which can be attributed to minor structural changes in the film matrix. However, all parameters remained within acceptable ranges for fast dissolving oral films, confirming that F24 is physically and chemically stable under accelerated conditions and suitable for further development.

CONCLUSION:

The present study successfully demonstrated the development and optimization of fast dissolving oro-dispersible films of pramipexole hydrochloride as an effective alternative to conventional oral dosage forms. By employing a systematic Design of Experiments approach, the influence of critical formulation variables on key performance attributes was clearly understood and optimized. Among the 27 formulations developed, F24 emerged as the optimized formulation, exhibiting an ideal balance of mechanical strength, rapid disintegration, uniform drug content, and excellent surface characteristics suitable for buccal administration. The optimized film showed significantly enhanced performance compared to the marketed tablet, particularly in terms of rapid drug release and improved permeation. The absence of a disintegration step, combined with increased surface area and efficient polymer hydration, contributed to the accelerated drug release profile, with nearly complete release achieved within 30 minutes. Furthermore, ex vivo permeation studies confirmed superior drug transport across buccal mucosa, indicating the potential of the formulation to bypass gastrointestinal limitations and enhance bioavailability. Compatibility studies verified the absence of drug–excipient interactions, while SEM analysis supported the uniform dispersion of the drug within the polymeric matrix. Stability studies further demonstrated that the optimized formulation retained its physicochemical properties under accelerated conditions, confirming its robustness and suitability for further development. Overall, the developed oro-dispersible film presents a promising drug delivery platform for pramipexole, offering rapid onset of action, improved patient compliance, and enhanced therapeutic efficiency. This approach not only addresses the limitations associated with conventional oral therapy but also opens new avenues for the delivery of drugs requiring fast action and improved bioavailability in the management of Parkinson's disease.

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CONFLICT OF INTEREST STATEMENT

The author declares that there is no conflict of interest

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