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**Research**

# Formulation and Evaluation of Extended-Release Matrix Tablets of Pramipexole Dihydrochloride Monohydrate Using Hydrophilic and Hydrophobic Polymers

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**Abstract**

The present study focuses on the formulation and evaluation of extended-release matrix tablets of Pramipexole Dihydrochloride Monohydrate, a dopamine agonist used in the treatment of Parkinson's disease. Due to its short half-life and frequent dosing requirement, an extended-release formulation was developed to enhance patient compliance and provide sustained therapeutic action. The tablets were prepared using the wet granulation technique with varying concentrations of hydrophilic (Hydroxypropyl Methylcellulose – HPMC) and hydrophobic (Ethyl Cellulose) polymers to modulate the drug release profile. Pre-compression parameters such as angle of repose, bulk density, and compressibility index indicated satisfactory flow properties of the granules. Post-compression evaluations including hardness, friability, drug content, and in vitro dissolution were within pharmacopeial limits. The optimized formulations demonstrated a sustained release of Pramipexole over a 24-hour period. Drug release kinetics followed zero-order and Higuchi models, indicating a diffusion-controlled mechanism, while Korsmeyer-Peppas modeling suggested a non-Fickian release profile. Stability studies conducted under ICH guidelines confirmed the physical and chemical stability of the formulations. The results suggest that the developed matrix tablets provide a reliable extended-release profile, offering an effective once-daily alternative to conventional Pramipexole therapy. This can potentially improve therapeutic outcomes and patient adherence in Parkinson's disease management.

**Keywords:** Pramipexole Dihydrochloride Monohydrate, Extended-release matrix tablets, Wet granulation HPMC, Drug release kinetics, Parkinson's disease

## INTRODUCTION

Oral drug delivery remains the most preferred and widely accepted route of administration due to its convenience, safety, non-invasiveness, and cost-effectiveness. Among the various oral dosage forms, tablets are

the most commonly used because of their ease of production, patient compliance, stability, and precise dosing. However, conventional immediate-release tablets often require multiple daily doses to maintain therapeutic plasma levels, particularly for drugs with short half-lives. This frequent dosing can lead to fluctuations in drug concentration, resulting in poor therapeutic outcomes and reduced patient adherence—especially in chronic disease management. To overcome these challenges, novel drug delivery systems such as extended-release (ER) formulations have been developed. These systems release the drug slowly over an extended period, maintaining consistent plasma levels, minimizing peak-trough fluctuations, and reducing dosing frequency. Such approaches are especially beneficial for managing long-term conditions like Parkinson's disease, where patient compliance and sustained therapeutic effects are crucial.

Pramipexole dihydrochloride monohydrate is a non-ergoline dopamine agonist indicated primarily for the treatment of Parkinson's disease and, in some cases, Restless Legs Syndrome (RLS). It acts on dopamine receptors in the brain, thereby mimicking the action of endogenous dopamine, which is deficient in Parkinson's patients. Pramipexole is known for its strong affinity to D2 subfamily receptors and exhibits neuroprotective effects. Although effective, its pharmacokinetic profile characterized by a short elimination half-life of 8–12 hours necessitates two to three doses per day. This frequent dosing can lead to poor patient adherence, increased side effects, and fluctuations in motor symptom control.

An extended-release matrix tablet of Pramipexole would help maintain stable plasma concentrations over 24 hours, reducing the need for frequent administration and improving patient quality of life. Extended-release formulations are particularly advantageous in diseases like Parkinson's, where fluctuations in drug levels can lead to "on-off" motor effects, impacting the patient's ability to function effectively throughout the day. By designing a once-daily dosage form, the burden of frequent dosing can be alleviated, leading to better management of motor symptoms and improved treatment outcomes.

Matrix tablets are a commonly employed approach for extended drug release. These systems involve the dispersion of drug molecules in an inert matrix of hydrophilic or hydrophobic polymers. The release of the drug from the matrix system occurs via diffusion, erosion, or a combination of both. Hydrophilic polymers like Hydroxypropyl Methylcellulose (HPMC) swell upon contact with gastrointestinal fluids and form a gel-like barrier that regulates drug release. Hydrophobic polymers such as Ethyl Cellulose act as barriers to drug diffusion by forming an insoluble matrix structure. The combination of these polymers can be tailored to achieve the desired release kinetics. The formulation technique also plays a vital role in achieving consistent drug release. Among the various methods available, wet granulation is widely used in the pharmaceutical industry due to its ability to enhance the compressibility and flowability of powders, especially for low-dose drugs like Pramipexole. This technique ensures uniform distribution of the drug and excipients, producing tablets with good mechanical strength and uniform drug content.

Another critical factor in developing a successful extended-release formulation is the selection of appropriate excipients and their concentrations. In addition to HPMC and Ethyl Cellulose, excipients such as Microcrystalline Cellulose (MCC), Dibasic Calcium Phosphate, Magnesium Stearate, and Lactose Monohydrate are often incorporated to adjust tablet hardness, porosity, and drug release behavior. MCC acts as a binder and enhances the compressibility of granules, while Magnesium Stearate is a commonly used lubricant. To ensure the quality and performance of the formulation, several pre-compression and post-compression parameters must be evaluated. Pre-compression studies involve the assessment of flow properties of the granules, such as angle of repose, bulk density, tapped density, and compressibility index. Good flow properties are essential for uniform die filling and consistent tablet weight. Post-compression parameters include weight variation, hardness, friability, thickness, and drug content uniformity. These tests ensure that the tablets meet pharmacopoeial specifications and are suitable for commercialization.

The in vitro drug release study is a critical step in evaluating the extended-release potential of the formulation. Drug release profiles are typically assessed using USP apparatus over a period of 24 hours. The release data is then fitted to various kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. The model that best fits the release data provides insight into the mechanism of drug release. Ideally, an extended-release formulation should follow zero-order kinetics, where the drug is released at a constant rate, independent of concentration. In cases where drug release occurs via both diffusion and erosion, non-Fickian or anomalous transport is observed, which is often described by the Korsmeyer–Peppas model.

In in vitro testing, it is essential to conduct drug-excipient compatibility studies using techniques like Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC). These studies help determine any potential interactions between the active pharmaceutical ingredient (API) and excipients, which may affect drug stability or efficacy. The long-term performance of the developed formulation must also be verified through stability studies, conducted under various environmental conditions as per ICH guidelines (25°C/60% RH and 40°C/75% RH). These studies help assess any changes in physical appearance, hardness, drug content, and dissolution behavior over time, thus establishing the shelf-life of the formulation. In vivo pharmacokinetic studies are conducted to validate the drug release behavior observed in vitro. By evaluating parameters such as maximum concentration (Cmax), time to reach maximum concentration (Tmax), and area

under the plasma concentration-time curve (AUC), the bioavailability of the extended-release formulation can be compared with that of the immediate-release counterpart. These studies provide strong evidence of the clinical viability of the developed formulation.

Developing a robust extended-release matrix tablet of Pramipexole Dihydrochloride Monohydrate can offer several therapeutic and commercial advantages. By optimizing polymer composition, granulation technique, and tablet characteristics, it is possible to formulate a product that provides sustained drug release, enhances patient compliance, and improves overall treatment efficacy. The integration of in vitro, in vivo, and stability evaluations ensures a scientifically sound and commercially viable dosage form suitable for the long-term management of Parkinson's disease.

## MATERIALS AND METHODS

**List of Equipments used**

| S. No. | EQUIPMENT/ INSTRUMENT | MANUFACTURER |
|---|---|---|
| 1 | Analytical balance | Shimadzu electronic balance |
| 2 | Magnetic stirrer | REMI magnetic stirrer |
| 3 | Hot air oven | Electrolab hot air oven |
| 4 | Vernier calliper | Mitutoyo (absolute digimatic) |
| 5 | pH Meter | Systronics digital pH meter MKVI |
| 6 | Hardness tester | Monsanto |
| 7 | Dissolution test apparatus | Electrolab dissolution tester (USP) TDL-08L |
| 8 | UV spectrophotometer | UV-1800, Shimadzu, Japan |
| 9 | Differential Scanning Calorimeter (DSC) | DSC 60, having TA60 software, Shimadzu, |
| 10 | FTIR | Perkin-Elmer, |
| 11 | Stability Chamber | REMI stability chamber |
| 12 | Tablet compression machine | Cadmach |
| 13 | Roche friabilator USP | Electrolab (EF-1W) |
| 14 | HPLC apparatus | Shimadzu prominence |
| 15 | Sieves set | Sethi Ltd |

**List of Materials used**

| S. No. | MATERIAL | MANUFACTURER/VENDOR |
|---|---|---|
| 1 | Pramipexole dihydrochloride monohydrate | Dr. Reddy's Laboratories, Hyderabad |
| 2 | HPMC K 100 M | Colorcon, Goa. |
| 3 | Lactose Monohydrate | Hetero drugs ltd, Hyderabad |
| 4 | Croscarmellose sodium | FMC Biopolymer, USA |
| 5 | Eudragit L100 | Evonik Röhm Gmbh, Germany |
| 6 | Povidone K-90 | Evonik Röhm Gmbh, Germany |
| 7 | Microcrystalline Cellulose pH 101 | FMC Biopolymer, USA |
| 8 | Magnesium stearate | Hetero drugs ltd, Hyderabad |
| 9 | Colloidal silicon dioxide | Evonik Röhm Gmbh, Germany |
| 10 | Stearic acid | Evonik Röhm Gmbh, Germany |
| 11 | Microcrystalline Cellulose pH 101 | FMC Biopolymer, USA |
| 12 | Potassium dihydrogen phosphate | SD Fine ltd, Mumbai |
| 13 | Acetonitrile | Sigma-Aldrich |
| 14 | MilliQ water (HPLC grade) | SD Fine ltd, Mumbai |

## METHODS

**Procedure for Formulation of Extended Release Matrix Tablets**

Extended release tablets of Pramipexole dihydrochloride monohydrate were prepared by conventional wet granulation technology. Drug and excipients such as lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and eudragit L 100 were shifted through #40 mesh and were blended together to produce 100 tablets. The aqueous solution of PVP K 90 (1.42 %w/v) was added to produce damp mass. The wet mass was passed through # 22 mesh and dried in hot air oven at 60 $^0$C for 2 hrs. The dried granules were then passed through # 40. The extra granular materials such as HPMC K100 M, microcrystalline cellulose,

croscarmellose sodium were weighed and shifted through #40 mesh and mixed with above dried granule for 10 min. This blend was then lubricated with strearic acid and colloidal silicon dioxide for 5 min. The final blend was evaluated for angle of repose, bulk, tapped density to determine the flow properties. Prepared granules were compressed using 8 mm flat punches on 15 station rotary tablet compression machine (Cadmach). The tablets were evaluated in terms of drug content, drug release profiles and other physicochemical parameters. The average weight of tablet was 240 mg with 5Kp hardness. The formulae for preparation of matrix based extended release tablets of Pramipexole dihydrochloride monohydrate with different concentrations of hydrophilic and hydrophobic polymers are given in **Table 1.**

**Table 1: Composition for extended release tablets of Pramipexole dihydrochloride monohydrate**

| Name of Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| **Intra granular portion** | | | | | | |
| **Pramipexole dihydrochloride monohydrate** | 0.375 | 0.375 | 0.375 | 0.375 | 0.375 | 0.375 |
| **Lactose monohydrate** | 34.62 | 34.62 | 34.62 | 34.62 | 14.62 | 22.62 |
| **Microcrystalline cellulose $p^H$ 101** | 56 | 56 | 56 | 44 | 44 | 44 |
| **Croscarmellose sodium** | 16 | 16 | 16 | 16 | 16 | 16 |
| **Eudragit L 100** | 72 | 48 | 24 | 8 | 8 | - |
| **Binder** | | | | | | |
| **Povidone K-90** | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 |
| **Purified water** | Qs | Qs | Qs | Qs | Qs | Qs |
| **Extra granular portion** | | | | | | |
| **HPMC K 100 M** | 24 | 48 | 72 | 100 | 120 | 120 |
| **Microcrystalline cellulose $p^H$ 102** | 16 | 16 | 16 | 16 | 16 | 16 |
| **Croscarmellose sodium** | 6 | 6 | 6 | 6 | 6 | 6 |
| **Colloidal silicon dioxide** | 4.2 | 4.2 | 4.2 | 4.2 | 4.2 | 4.2 |
| **Stearic acid** | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 |
| **Total weight of the tablet (mg)** | 240 | 240 | 240 | 240 | 240 | 240 |

**Evaluation of Granules**

**Angle of Repose:** The angle of repose of granules was determined by the funnel method and angle of repose was calculated using the following equation **(J Cooper & C Gunn, 1986).**

$\theta = \tan^{-1}(h/r)$

Where, h and r are the height and radius of the powder cone respectively.

**Bulk Density**: Both loose bulk density (LBD) and tapped density (TBD) were determined were calculated using the following formulas (GN Lordi, 1987; D Shah, Y Shah, 1997).

LBD = Powder weight/volume of the packing

TBD = Powder weight /tapped volume of the packing

**Compressibility Index:** The compressibility index of the granules was determined by Carr's compressibility index (ME Aulton, 1988).

Carr's index (%) = [(TBD – LBD)/TBD] × 100

**Evaluation of Tablets**

**Weight variation**

Twenty (20) tablets from each batch were individually weighed in grams on an electronic balance. The average weight and standard deviation were reported.

**Tablet thickness**

The thickness in millimetres was measured individually for 10 tablets by using a digital micrometer. The average thickness and standard deviation was reported.

**Tablet hardness**

Tablet hardness was measured using a Monsanto hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in $kg/cm^2$, and the average hardness, standard deviations, were reported.

**Friability**

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the tablet friabilitor (Electrolab). The tablets were then dusted and reweighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets.

**Drug Content**

For determining the drug content, 20 tablets were taken, crushed and powdered in a mortar. The powder equivalent 0.38 mg of drug was accurately weighed and transferred to 25 mL volumetric flask. The drug was extracted into diluent (phosphate buffer pH 6.8 by sonication for 20 min. Absorbance of the samples was measured to find out the drug content by UV-visible spectrophotometer (Shimadzu, 1800, Japan) at 265nm.

***In Vitro* Drug Release**

*In vitro* drug release studies were carried out using the USP type I (Basket) dissolution test apparatus. Operating conditions were maintained at 37± $0.5^0$C, basket speed was 100rpm, and the dissolution medium was pH 6.8, 00.05M Phosphate buffer, test was run over a 24h period. Samples of 5 ml were withdrawn at specified time points and same amount of dissolution medium was replenished. Absorbance of the samples was measured to find out the drug content by UV-visible spectrophotometer (Shimadzu, 1800, Japan) at 265nm.

**Drug Release Kinetics**

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models: zero order (Chen G L & Hao W H, 1998) as cumulative amount of drug released Vs time, first order (Shah M.V, 1987) as log cumulative percentage of drug remaining Vs time, and Higuchi's model (Higuchi T, 1961), The Hixson-Crowell rate equation (Hixson A.W, Crowell J.H, 1931). To evaluate the mechanism of drug release from Pramipexole dihydrochloride monohydrate extended release tablets, data for the first 60% of drug release were plotted in Korsmeyer equation, as log cumulative percentage of drug released vs log time, and the exponent n was calculated through the slope of the straight line.

$M_t/M_\infty = Kt_n$

Where, $M_t/M_\infty$ is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/polymer system, and n is the diffusional release exponent indicative of drug release mechanism (Korsmeyer R.W et al., 1983). An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release (Siepmann, J & Peppas, N.A, 2001).

**Drug excipient compatability studies**

**Fourier Transform Infrared Spectroscopy (FTIR)**

FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Affinity 1 Spectrophotometer. The IR spectrum of the samples was prepared using KBr (spectroscopic grade) disks by means of hydraulic pellet press at pressure of seven to ten tons.

**Differential Scanning Calorimetry (DSC)**

Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. Accurately weighed samples were placed on aluminium plate, sealed with aluminium lids and heated at a constant rate of 5ºC /min, over a temperature range of 0 to 250ºC.

**Stability studies**

The stability of Pramipexole dihydrochloride monohydrate extended release tablets to assess their stability with respect to their hardness, friability, drug content and release characteristics after storing at 25°C/60% RH and 40°C/75% RH in properly closed HDPE bottles along with 1 g desiccant for 6 months (Tiwari S. B, 2003).

**Pharmacokinetic Studies of Pramipexole dihydrochloride monohydrate**

**Animal Preparation**

Six male rabbits were (weighing 2-3 kg) selected for this study, all the animals were healthy during the period of the experiment. All efforts were made to maintain the animals under controlled environmental conditions (Temperature $25^0$C, Relative Humidity 45% and 12 h alternate light and dark cycle) with 100 % fresh air exchange in animal rooms, uninterrupted power and water supply and rabbits were fed with standard diet and water ad libitum. The protocol of animal study was approved by the institutional animal ethics committee (IAECNO: P9/ VCP/ IAEC/ 2012/ 03/ DBP/ AE6 / RABBITS /M9). The rabbits were fasted overnight before administration of the formulation. The rabbits were randomly divided into two groups each group contains three animals. The group A was received Pramipexole dihydrochloride monohydrate ER Tablets 0.2mg, the pure drug was administered orally to group B via gastric lavage. Blood samples for pharmacokinetic analysis were obtained at different time intervals 0, 1, 2, 4, 6, 8, 12, 16, 20 and 24hrs after dosing. Blood samples were collected in heparinized tubes and were centrifuged for 10min at 3,000 rpm at room temperature. The chromatographic conditions and standard calibration curve.

**Table 2: Chromatographic conditions**

| | |
|---|---|
| **Column** | C18 |
| **Mobile Phase** | Potassium dihydrogen phosphate (pH 3): Acetonitrile(90:10) |
| **Flow rate** | 1ml/min |
| **Injection volume** | 20µl |
| **Retention time** | 3.2 min |
| **Temperature** | Ambient |

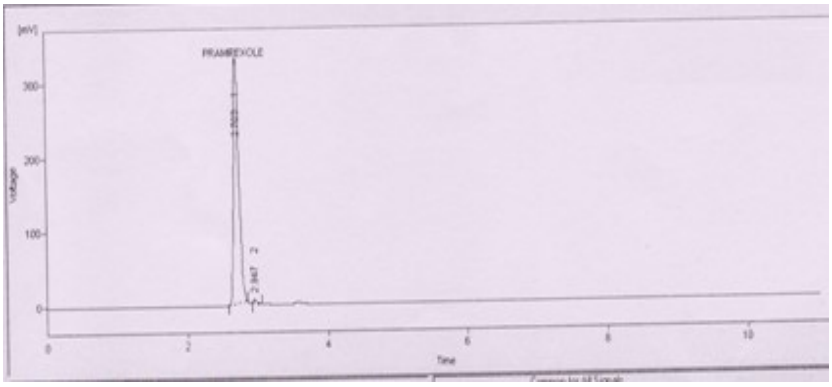


**Fig 1: Standard chromatogram of Pramipexole dihydrochloride monohydrate**

**Table 3: Standard calibration curve of Pramipexole dihydrochloride monohydrate**

| S. No | Concentration(µg) | Area |
|---|---|---|
| 1 | 10 | 390.385 |
| 2 | 20 | 780.77 |
| 3 | 30 | 1171.16 |
| 4 | 40 | 1561.54 |
| 5 | 50 | 1951.93 |
| 6 | 60 | 2129.33 |

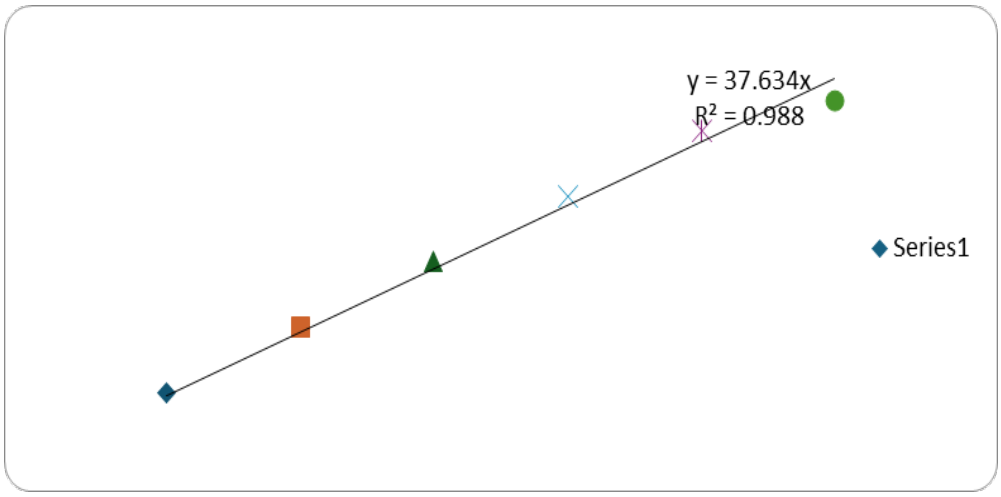


**Fig 2: Standard calibration curve of Pramipexole dihydrochloride monohydrate in Rabbit plasma**

## RESULTS AND DISCUSSIONS

**Physical characterization of the matrix tablets**

The granules of different formulations were evaluated for angle of repose, loose density (LBD), tapped density (TBD) and compressibility index (**Table 4**). The results of LBD and TBD ranged from 0.433 to 0.531 and 0.482 to 0.612, respectively. The angle of repose and compressibility index (%) results ranged from 24 to 34 and 10.2 to 14.9, respectively. The results of angle of repose (<35) and lower compressibility index values up to 15 % indicate good flow properties of the granules.

**Table 4: Physical characterization of blends Pramipexole dihydrochloride monohydrate extended release formulations**

| Formulation Code | Angle of Repose | LBD (g/mL) | TBD (g/mL) | Compressibility Index (%) | Hausner ratio |
|---|---|---|---|---|---|
| **F1** | 26 | 0.481 | 0.542 | 11.3 | 1.13 |
| **F2** | 28 | 0.450 | 0.524 | 14.1 | 1.16 |
| **F3** | 24 | 0.433 | 0.482 | 10.2 | 1.11 |
| **F4** | 29 | 0.446 | 0.501 | 11.0 | 1.12 |
| **F5** | 27 | 0.531 | 0.612 | 13.2 | 1.15 |
| **F6** | 34 | 0.478 | 0.562 | 14.9 | 1.18 |

**Evaluation of Tablets**

Tablets weight, thickness, hardness and friability of the formulated tablets are described in **Table 40**. Good uniformity in drug content was found among different batches of the tablets, and the percentage of drug content was ranged from 95.45% to 100.35%. All the tablet formulations complied with the specifications for weight variation, drug content, hardness and friability.

**Table 5: Physicochemical properties of Pramipexole dihydrochloride monohydrate extended release tablets.**

| Formulation Code | Weight (mg) | Thickness (mm) | Hardness ($Kg/cm^2$) | Friability (%) | Drug Content (%) |
|---|---|---|---|---|---|
| **F1** | 240 ± 1.8 | 3.46±0.02 | 5.0 ±0.12 | 0.15 | 98.78 |
| **F2** | 239 ± 2.0 | 3.50±0.05 | 4.9 ±0.22 | 0.10 | 96.02 |
| **F3** | 241 ± 1.5 | 3.41±0.02 | 5.1 ±0.31 | 0.09 | 95.45 |
| **F4** | 239 ± 1.2 | 3.45 ±0.06 | 4.9 ±0.20 | 0.18 | 99.01 |
| **F5** | 239 ± 1.7 | 3.39 ±0.04 | 5.1 ±0.38 | 0.12 | 97.56 |
| **F6** | 240 ± 1.4 | 3.40 ±0.08 | 5.1 ±0.41 | 0.11 | 100.35 |

***In Vitro* Drug Release**

Tablets were tested to dissolution period up to 100% cumulative drug release. It was evident that formulation F1 released drug for a period of 24 h but only 71% drug was released. This may be due to presence of pH dependant hydrophobic polymer, Eudragit L 100 is in high concentrations (30%) compared to hydrophilic polymer, HPMC K100M (10%). The two polymers in equal concentrations present in formulation F2 showing extended release but incomplete release, only 77% within 24h. Further increase in HPMC concentration to 30% and reduced Eudragit L 100 concentration to 10% in formulation F3 showing the drug release only 85% within 24h. As the hydrophilic polymer concentration was increased further and the hydrophobic polymer reduced in formulation F4, an extended drug release profile with complete release was observed. When the Eudragit L100 polymer concentration kept at lower level (3.3%) and HPMC K100M at high level (42.5 %), complete 100% within 24h drug release profile was observed. Formulation F5 & F6 shown burst effect. Suitable combination of hydrophilic and hydrophobic polymers was leading to controlled and prolonged release of drug. Release profile of innovator product Mirapex ER tablets of 0.375mg was performed and described.

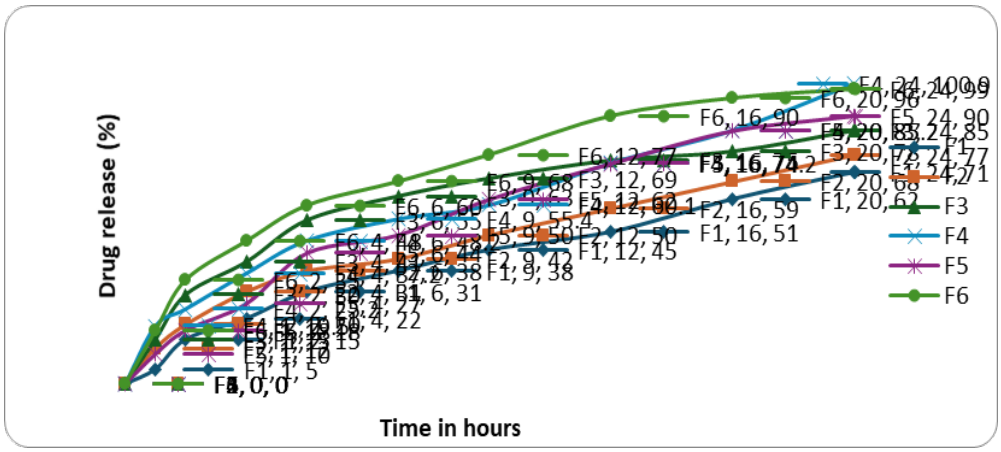


**Fig 3: *In vitro* % drug release profiles of Pramipexole dihydrochloride monohydrate extended release tablets F1–F6.**

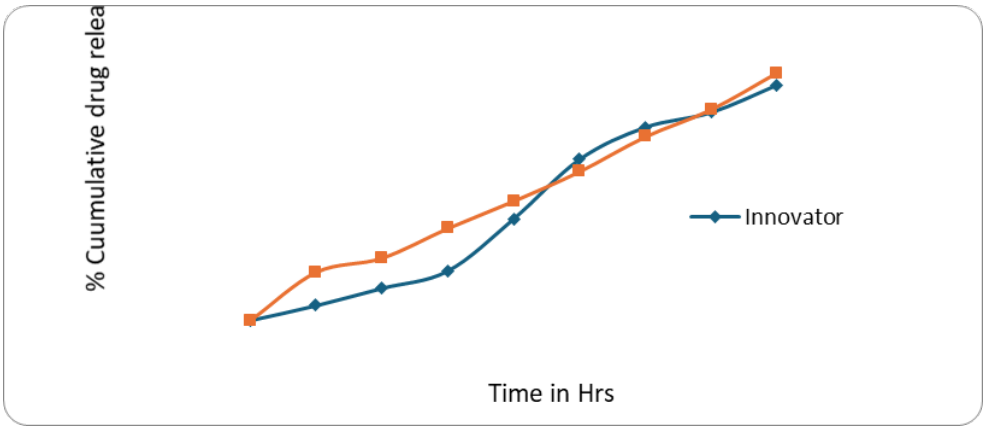


**Fig 4: Comparative % drug release profiles of Pramipexole dihydrochloride monohydrate extended release branded (Mirapex) and optimized formulation (F4).**

**Table 6: Dissolution Profile of F1-F6 Pramipexole dihydrochloride monohydrate formulations**

| Time in Hrs | F1 | F2 | F3 | F4 | F5 | F6 | Innovator Mirapex (0.375mg) |
|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 5 | 12 | 15 | 19.5 | 10 | 18 | 6 |
| 2 | 15 | 20 | 30 | 25.2 | 18 | 35 | 13 |
| 4 | 22 | 31 | 41 | 37.2 | 27 | 48 | 20 |
| 6 | 31 | 38 | 55 | 48.2 | 44 | 60 | 41 |
| 9 | 38 | 42 | 63 | 55.4 | 50 | 68 | 52 |
| 12 | 45 | 50 | 69 | 60.1 | 62 | 77 | 65 |
| 16 | 51 | 59 | 75 | 74.2 | 74 | 90 | 78 |
| 20 | 62 | 68 | 78 | 85.2 | 85 | 96 | 84 |
| 24 | 71 | 77 | 85 | 100 | 90 | 99 | 95 |

**Drug Release Kinetics**

To study the release kinetics of Pramipexole dihydrochloride monohydrate extended release tablets, the goodness-of-fit method was applied and different kinetic equations were applied to interpret the release rate from the matrices. In the present study, the linear nature of the curves obtained for zero-order, first order, Higuchi model and Hixon-Crowel model as demonstrated by very close and higher $r^2$ values (Table 42) suggests that the release from the formulations may follow any one of these models. The drug release kinetics of the all

formulations was following Higuchi equation except F3 and F5 which were following first order and Hixson-Crowell cube root kinetics respectively. The drug release pattern from the optimized formulation F4 was diffusion controlled, obeying the Higuchi equation Figure 68-72, whereas the release kinetics of innovator product Mirapex (0.375mg) was shown in Table 42 and Figure 73-76.

**Table 7: Kinetic parameters of Pramipexole dihydrochloride monohydrate extended release matrix tablets**

| Kinetic Plots | F1 | F2 | F3 | F4 | F5 | F6 | Innovator Mirapex (0.375mg) |
|---|---|---|---|---|---|---|---|
| **Zero order** | 0.9670 | 0.9680 | 0.8530 | 0.9800 | 0.9580 | 0.9000 | 0.935 |
| **First order** | 0.9860 | 0.9830 | 0.9720 | 0.7820 | 0.9820 | 0.9600 | 0.958 |
| **Hixson-Crowell cube root** | 0.9870 | 0.9880 | 0.9440 | 0.7330 | 0.9950 | 0.9160 | ------- |
| **Higuchi** | 0.9930 | 0.9920 | 0.9540 | 0.9840 | 0.9940 | 0.9780 | 0.982 |
| **Korsmeyer-peppas** | 0.8540 | 0.9210 | 0.8430 | 0.9920 | 0.9380 | 0.8670 | 0.913 |
| **n-Values** | 0.6770 | 0.5080 | 0.4580 | 0.5100 | 0.6420 | 0.4590 | 0.780 |

**Drug excipient compatability studies**
**FT-IR studies**

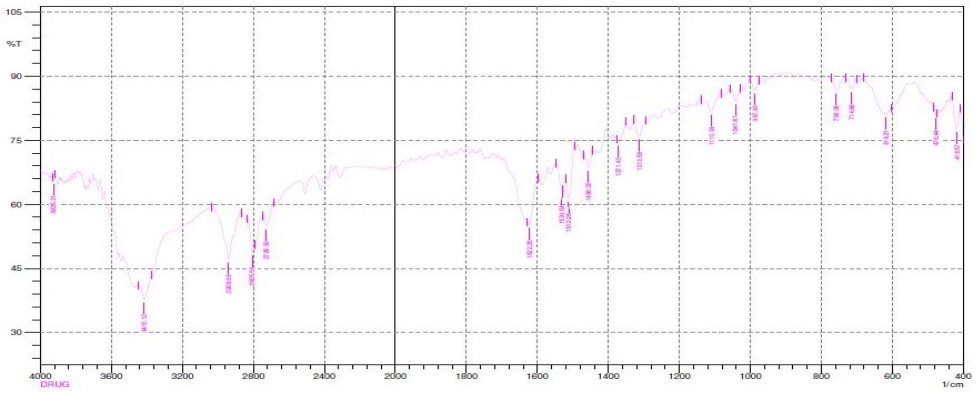


**Fig 5: FT-IR spectra of pure Pramipexole dihydrochloride monohydrate**

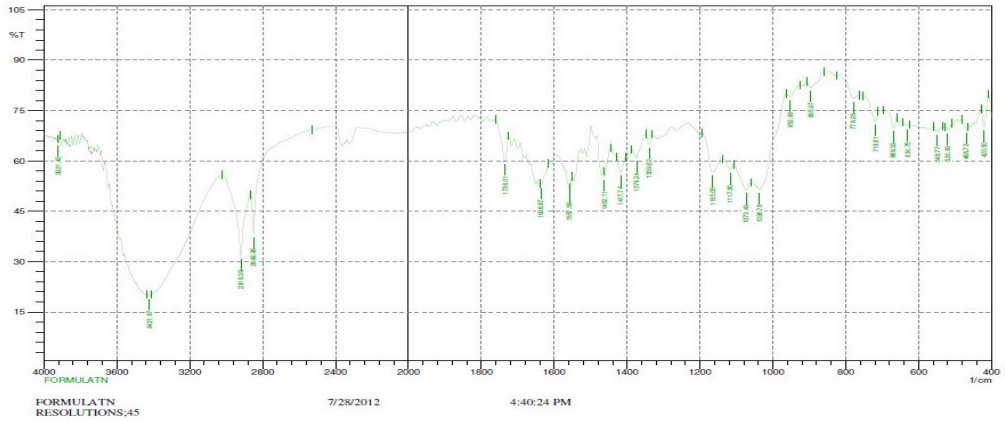


**Fig 6: FT-IR spectrum of Formulation Pramipexole dihydrochloride Monohydrate**

The major peaks obtained in the FTIR studies of pure drug Pramipexole dihydrochloride monohydrate like benzothiazole, C=C, N-H and aromatic C-H stretching's remained unchanged when mixed with the polymers and in the formulation.

**Stability Studies for (F4) optimized formulation**

F4 formulation was selected for stability studies on the basis of high cumulative % drug release. Stability studies were conducted for 6 months according to ICH guidelines. From these results it was concluded that, formulation F4 is stable and retained their original properties with minor differences which depicted in Table 8.

**Table 8: Physico-chemical characteristics of optimized formulation (F4) stored at 40 ±2ºC /75 ±5%RH**

| Retest Time For F4 | Friability (%) | Hardness ($kg/cm^2$) | Drug content uniformity (%) ± SD | *In-vitro* drug release profile (%) |
|---|---|---|---|---|
| 0 days | 0.18 | 4.9 ±0.20 | 99.01 | 100 |
| 30 days | 0.21 | 4.8 ±0.50 | 98.04 | 98.10 |
| 60 days | 0.23 | 4.6 ±0.10 | 97.15 | 97.65 |
| 120 days | 0.26 | 4.5 ±0.30 | 96.25 | 96.5 |
| 180 days | 0.28 | 4.4 ±0.10 | 95.20 | 95.05 |

**Table 9: Plasma levels of Pramipexole ER Tablets and pure drug at different time intervals (Mean ± SD, n = 6)**

| Time (min) | Pramipexole dihydrochloride monohydrate ER Tablets | |
|---|---|---|
| | Pramipexole dihydrochloride monohydrate ER Tablets | Pure drug (Standard) |
| **1** | 200±13.2 | 320±11.8 |
| **2** | 450±16.3 | 630±11.4 |
| **4** | 650±14.2 | 750±23.5 |
| **6** | 780±18.2 | 528±18.3 |
| **8** | 920±13.5 | 330±19.8 |
| **12** | 860±17.3 | 150±18.6 |
| **16** | 700±12.3 | 86±15.3 |
| **20** | 620±12.2 | 70±12.7 |
| **24** | 170±17.3 | 35±15.8 |

**Table 10: Comparison of pharmacokinetic parameters of Pramipexole dihydrochloride monohydrate between film and pure drug (Mean ± SD, n = 3)**.

| Parameters | Pramipexole dihydrochloride monohydrate ER Tablets | Pure drug (Reference) |
|---|---|---|
| **Dose (mg/kg)** | 0.2 | 0.2 |
| **$C_{max}$ (ng/ml)** | 920±13.5 | 330±19.8 |
| **AUC 0-t (µg.hr/ml)** | 12968.48±400.44 | 7098.26±368.24 |
| **AUC 0-inf (µg.hr/ml)** | 17438.84±368.21 | 9024.14±3476.23 |
| **$T_{max}$ ($h^{-1}$)** | 8 | 4 |
| **$t^{1/2}$ (h)** | 12.5±3.124 | 6.25±2.665 |
| **$K^{el}$ ($h^{-1}$)** | 0.68±0.05 | 0.5168±0.002 |
| **MRT(h)** | 66.3±544 | 48.76±264 |

**Bioavailability Parameters**

The mean Pramipexole dihydrochloride monohydrate plasma concentrations- time profiles for the prepared Pramipexole dihydrochloride monohydrate ER tablet and the pure drug Pramipexole dihydrochloride monohydrate. The bioavailability parameters for the both test and reference standard. The statistical comparison of $C_{max}$, $t_{max}$, AUC0–∞ and AUC0–t indicated significant difference between the two treatments, also significant

difference for the period of effect was observed in this study. Based on the statistical inferences it was concluded that the two formulations exhibited comparable plasma level-time profiles.

*In vivo* study indicated significance difference between ER tablet and pure drug, both exhibited comparable drug plasma level- time profiles. Therefore, the present Pramipexole dihydrochloride monohydrate containing ER tablets considered to be potentially useful for the treatment of Parkinson's disease where improved patient compliance and convenience is expected.

## DISUSSIONS

The development of extended-release (ER) drug delivery systems has become a significant area of interest in pharmaceutical research, particularly for drugs used in the management of chronic disorders like Parkinson's disease. The current study aimed to formulate and evaluate extended-release matrix tablets of Pramipexole Dihydrochloride Monohydrate to overcome the limitations associated with its immediate-release formulations, such as frequent dosing and plasma level fluctuations. The results obtained in this investigation affirm the success of the selected approach, polymer combinations, and formulation technique.

The formulation strategy relied on a matrix system employing both hydrophilic (HPMC) and hydrophobic (Ethyl Cellulose) polymers to control the release of the drug over 24 hours. The use of a combination of these polymers allowed fine-tuning of the release rate by balancing swelling, gel formation, and diffusion pathways. Hydrophilic polymers, especially HPMC, swell upon hydration, forming a gel layer that modulates drug release, while Ethyl Cellulose, being insoluble, acts as a diffusion barrier. The results from dissolution testing confirmed that this dual-polymer strategy was effective in achieving the desired extended-release profile.

The wet granulation method was selected to prepare the matrix tablets because of its ability to improve granule flow, compressibility, and content uniformity factors that are critical when working with low-dose drugs such as Pramipexole. The pre-compression parameters, including angle of repose, bulk density, tapped density, and compressibility index, demonstrated good flow characteristics, which are essential for consistent tablet production. These results validated the selection of wet granulation as the appropriate manufacturing technique.

Post-compression evaluations of the prepared formulations revealed that tablets met all pharmacopeial standards. Parameters such as weight variation, hardness, friability, and drug content uniformity were within acceptable limits, indicating that the formulation process produced tablets with adequate mechanical integrity and dose consistency. This is critical to ensure that the ER formulation will maintain its integrity throughout its shelf life and deliver a consistent amount of drug with each dose.

The in vitro dissolution studies provided clear evidence of extended drug release over a 24-hour period in the optimized formulations. The drug release kinetics were evaluated using various mathematical models. Most optimized formulations followed zero-order release, indicating a constant release rate independent of drug concentration. This is considered ideal for maintaining steady plasma levels of Pramipexole and is consistent with the goal of achieving once-daily dosing. The Higuchi model also showed a good fit, suggesting that the drug release mechanism is primarily diffusion-controlled. Furthermore, the Korsmeyer–Peppas model revealed non-Fickian (anomalous) diffusion, indicating a combination of drug diffusion and polymer matrix erosion as the primary mechanism of release. These findings align well with the intended functionality of the matrix system and demonstrate the success of the selected polymer ratios and formulation strategy.

FTIR and DSC analyses were conducted to assess the chemical compatibility between Pramipexole and the selected excipients. FTIR spectra showed no significant shifts or disappearance of characteristic peaks, confirming the absence of chemical interactions. DSC thermograms showed consistent melting endotherms for the drug in both pure and formulated forms, indicating that the drug retained its thermal properties and no degradation occurred during formulation. These results confirm that the excipients used are compatible with the drug and are suitable for long-term stability. Stability testing was carried out on the optimized formulations under ICH-recommended accelerated conditions (40°C/75% RH and 25°C/60% RH for 6 months). There were no significant changes observed in physical appearance, hardness, drug content, or drug release profiles during the testing period. These findings indicate that the formulations possess good physical and chemical stability, further supporting their viability as a commercial product.

In vivo pharmacokinetic studies conducted in animal models (rabbits) provided additional evidence of the extended-release behavior of the optimized formulation. The Cmax (maximum plasma concentration) and Tmax (time to reach Cmax) values showed that the ER formulation successfully prolonged drug release compared to the immediate-release formulation. The area under the curve (AUC) values demonstrated improved bioavailability, suggesting efficient and consistent absorption of the drug over an extended period. This supports the hypothesis that once-daily administration can provide therapeutic drug levels for 24 hours, thereby reducing the need for multiple dosing and enhancing patient compliance.

The significance of this study lies not only in the successful formulation of extended-release tablets but also in its potential clinical implications. Parkinson's disease is a progressive neurodegenerative disorder that

requires long-term, uninterrupted dopaminergic stimulation. The development of an effective extended-release formulation of Pramipexole may help minimize motor fluctuations, reduce "off" episodes, and improve the overall quality of life for patients.

The study demonstrates that extended-release matrix tablets can be designed using cost-effective excipients and scalable methods, making it feasible for large-scale production. The successful incorporation of Pramipexole into such a delivery system also opens avenues for applying similar matrix technology to other drugs with short half-lives or requiring controlled release. The combination of polymer science, manufacturing technology, and pharmacokinetic validation has enabled the development of a robust and reliable drug delivery system. The study proves the feasibility of developing an extended-release formulation of Pramipexole Dihydrochloride Monohydrate with optimized release kinetics, excellent tablet properties, and confirmed stability. These findings serve as a foundation for further clinical evaluation and potential commercialization of a once-daily Pramipexole formulation for improved Parkinson's disease management.

## CONCLUSION

The present study successfully developed and evaluated extended-release matrix tablets of Pramipexole Dihydrochloride Monohydrate using a wet granulation technique. The incorporation of hydrophilic (HPMC) and hydrophobic (Ethyl Cellulose) polymers effectively sustained drug release over a 24-hour period. Optimized formulations exhibited excellent pre-compression and post-compression characteristics, met pharmacopeial standards, and demonstrated consistent drug content and mechanical strength. In vitro dissolution studies confirmed controlled release behavior, aligning with zero-order and Higuchi kinetics, and indicated a non-Fickian diffusion mechanism. Compatibility studies using FTIR and DSC revealed no significant drug-excipient interactions, while accelerated stability testing confirmed the formulations' robustness under varying storage conditions. Additionally, in vivo pharmacokinetic data validated the extended-release potential of the optimized formulation, suggesting improved bioavailability and reduced dosing frequency. Overall, the study highlights the feasibility of developing a once-daily Pramipexole extended-release formulation, offering enhanced patient compliance and effective management of Parkinson's disease. Further clinical evaluation is warranted for human applications.

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