Research Article

# Design and Evaluation of Extended Release Tablets of Pramipexole dihydrochloride monohydrate

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**ABSTRACT**

The objective of the present study was to develop and characterize extended release tablets of Pramipexole dihydrochloride monohydrate to be taken once daily. The combination of different polymers like hydroxypropyl methyl cellulose (HPMC K 100M) and Eudragit L 100 in varying concentrations were studied to get the desired extended release profile over a period of 24 h. The granules were evaluated for angle of repose, bulk density, compressibility index, and drug content and found to be satisfactory. Hydroxypropylmethylcellulose (HPMC K100M) at 50% level in combination with methacrylic acid copolymer (Eudragit L100) at 2.0% level producedextended release Pramipexole dihydrochloride monohydrate matrix tablets. The drug release of optimized formulation (F7) was extended up to 24 h in vitro study. The drug release pattern from the optimized matrix formulation (F7) was diffusion controlled. The innovator product Mirapex (0.375 mg) drug release profiles are shown to be followed first order release kinetics. The results suggested that combination of hydrophilic and hydrophobic polymers used in the preparation of extended release Pramipexole dihydrochloride monohydrate tablets, is a suitable method and it can perform therapeutically better.

**Keywords:** Extended release tablets, Pramipexole dihydrochloride monohydrate, hydroxypropyl methyl cellulose, eudragit.

## INTRODUCTION

It is widely accepted that the primary cause of Parkinson's disease is a progressive degeneration of nigral dopamine neurons[1-4]. Which leads to a substantial decrease in the dopamine levels in the caudate nucleus and putamen[5-7]. A deficit of this neurotransmitter is directly linked to the appearance of numerous symptoms of this disease, such as akinesia, muscle rigidity and tremors[8-10]. Substitutive administration of levodopa (L-DOPA) is the most effective and commonly used treatment in Parkinson's disease. However, this therapeutic strategy is often complicated by severe side-effects such as psychoses, dyskinesia and on–off phenomena[11,12]. Continuous treatment with levodopa causes reduced activity after 5 to 7 years of treatment. This disadvantage of L-DOPA therapy imposes major limitations on longterm, effective application of this drug. Dopamine receptor agonists comprise a class of drugs which are efficacious in the treatment of both early and advanced stages of Parkinson's disease[13]. Pramipexole (2-amino- 4,5,6,7-tetrahydro-6-propyl-aminobenzthiazole- dihydrochloride) is a novel, highly active, full dopamine receptor agonist which acts on the D2 receptor family with a preferential affinity for the D3 type[14,15]. Pramipexole antagonizes the reserpine induced akinesia and neuroleptic-induced catalepsy[16-18]. The above data show that due to stimulation of dopamine D2 postsynaptic receptors, pramipexole appears to have a high antiparkinsonian potential[19,20,21]. It has been investigated as a monotherapy in the treatment of PD. In advanced PD the usual dose of Pramipexole is as high as 1.5 mg three to four times a day[22,23]. Pramipexole has been associated with episodes of somnolence during the daytime (referred to as sleep attacks) and other adverse effects such as abnormal behaviour, drowsiness, dizziness, fainting, hallucinations and many more. The side effects are highly dose dependent[24,25,26]. Currently there are no controlled release formulations available for pramipexole. So the major aim of the research work was to develop once a day controlled release formulations that can deliver pramipexole for period of 24hrs. This reduction in dose frequency is expected to improve patient compliance and maintain the therapeutic level of pramipexole over a prolonged period of time. This may result in reduced severity of motor fluctuations and other side effects caused by pramipexole.

## MATERIALS AND METHODS

### Materials

Pramipexole dihydrochloride monohydrate was procured from MSN labs Hyd, HPMC K4M, HPMC K15M and HPMC K100M were provided as a gift sample by colorcon. Povidone sample was procured from ISP technologies. Microcrystalline cellulose from FMC biopolymers. Other chemicals were purchased from Pure Chem. Laboratories, Pune and of analytical grade.

### Methods

Pramipexole dihydrochloride tablets were prepared by wet granulation method. The ingredients were passed through 40 mesh sieve and weighed accurately as per the manufacturing formula. Pramipexole dihydrochloride and

Povidone was dissolved in water used as binder. The binder solution was added to the contents and wet dough mass was obtained by using rapid mixing granulator. Wet mass was dried in fluid bed granulator, where temperature is maintained at 60°C in which dried granules was passed through 24 mesh sieve. Finally, milled granules were passed through 24 mesh sieve. Remaining quantity of HPMC K4M or HPMC K15M or HPMC K100M, Eudragit L-100 and colloidal silicon dioxide was mixed with the above prepared blend and final lubrication was done with magnesium stearate. All the batches were compressed on 8 station tablet compression machine (Cadmach, India).

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

| Composition | F1 | F2 | F3 | F4 | F5 | F6 | F7 |
|---|---|---|---|---|---|---|---|
| | Mg/tablet | | | | | | |
| Pramipexole diHCL | 0.375 | 0.375 | 0.375 | 0.375 | 0.375 | 0.375 | 0.375 |
| MCC (Avicel PH 102) | 149.125 | 149.125 | 149.125 | 136.125 | 123.125 | 120.525 | 117.925 |
| Povidone K-30 | 2.60 | 2.60 | 2.60 | 2.60 | 2.60 | 2.60 | 2.60 |
| Purified Water | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S |
| HPMC K 4 M | 104.00 | - | - | - | - | - | - |
| HPMC K 15 M | - | 104.00 | - | - | - | - | - |
| HPMC K 100 M | - | - | 104.00 | 117.00 | 130.00 | 130.00 | 130.00 |
| Eudragit L-100 | - | - | - | - | - | 2.60 | 5.20 |
| Colloidal $SiO_2$ | 2.60 | 2.60 | 2.60 | 2.60 | 2.60 | 2.60 | 2.60 |
| Magnesium Stearate | 1.30 | 1.30 | 1.30 | 1.30 | 1.30 | 1.30 | 1.30 |
| **Tablet weight** | **260.00** | **260.00** | **260.00** | **260.00** | **260.00** | **260.00** | **260.00** |

**Evaluation of powder blend**

The powder blend used for preparation of tablets was evaluated for angle of repose, and compressibility index [9].

***Angle of repose***

10 gm of powder was passed through funnel and the pile was formed. The height and weight of the pile was measured and the angle of repose was calculated by using the formula:-

Angle of repose (θ) = tan-1 (height /radius) …….. (1)

The angle of repose less than 300 usually indicate a free-flowing material and more than 400 suggests a poorly flowing material [10].

***Carr's compressibility index***

The Carr's compressibility index was calculated by calculating the tapped and bulk density using 100 ml measuring cylinder. Compressibility is calculated by the formula.

Carr's compressibility index = (TBDLBD)/ TBD X100 …. (2)

Where, TBD is tapped bulk density and LBD is loose bulk density. A Carr's index greater than 25 is considered to be an indication of poor flowability and below 15, of excellent flowability.[11]

**Evaluation of tablets**

All the formulations were evaluated for various parameters such as hardness, friability, weight variation, % drug content, buoyancy lag time, swelling index, in-vitro drug release, release experiments, IR spectroscopy and optimized formulation were evaluated for in-vivo study.

***Hardness***

Hardness of tablets was determined using Monsanto hardness tester.

***Friability***

A sample of pre weighted 20 tablets was placed in Roche friabilator which was then operated for 100 revolutions i.e. 4 mins. The tablets were then dusted and reweighed. Percent friability (%F) was calculated as follows,

% F= (loss in weight / initial weight) x 100 …….. (3)

Conventional compressed tablets that lose less than 0.5 to 1.0% of their weight are generally considered acceptable [10, 11].

***Thickness***

Thickness of all tablets was measured using a vernier calliper.

***Weight variation***

The weight of 20 tablets was taken on electronic balance and the weight variation was calculated. The weight variation tolerance allowed for tablet weighing 324 mg and more is 5% I.P.[11].

### *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* Dissolution Studies

*In vitro* drug release studies were carried out using the USP type I (Basket) dissolution test apparatus. Operating conditions were maintained at 37± 0.50C, basket speed was 100rpm, and the dissolution medium was pH 6.8, 0.05M 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.

### Kinetic Modeling of Drug Release

The dissolution profile of all the batches was fitted to zero order, first-order, matrix, Hixon- Crowell, Korsemeyer and Peppas to ascertain the kinetic modeling of drug release. The kinetic modeling was found out by employing the PCP disso v3 software.[13]

### Infrared (IR) spectroscopy

The drug excipient compatibility and the drug polymer interaction were detected by the IR spectroscopic studies. The polymer- polymer compatibility is also found out by the IR spectroscopic studies.

### Evaluation of powder blend

### *Angle of repose*

Angle of repose of all the powder blends was obtained within the range of 20-30$^0$. This indicates that all the powder blends shows good flow property.[11]

### *Carr's compressibility index*

The compressibility index of all the powder blends was obtained below 10. The compressibility index indicates the good flowability of the powder blend [10].

### Evaluation of tablets

### *Infrared (IR) spectroscopic study of the formulation*

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.

### *IR Spectroscopic study of drug, polymer and formulations*

The formulations containing the polymers showed all the prominent peaks of Pramipexole dihydrochloride with no change in the intensity of the peaks. This indicates that there is no interaction between the excipient and drug that can affect the efficacy of drug.

### *In Vitro Dissolution Studies*

The drug release patterns from all the formulations are shown in tables 4. The percent drug release after 24 hours is as shown in figure 1.

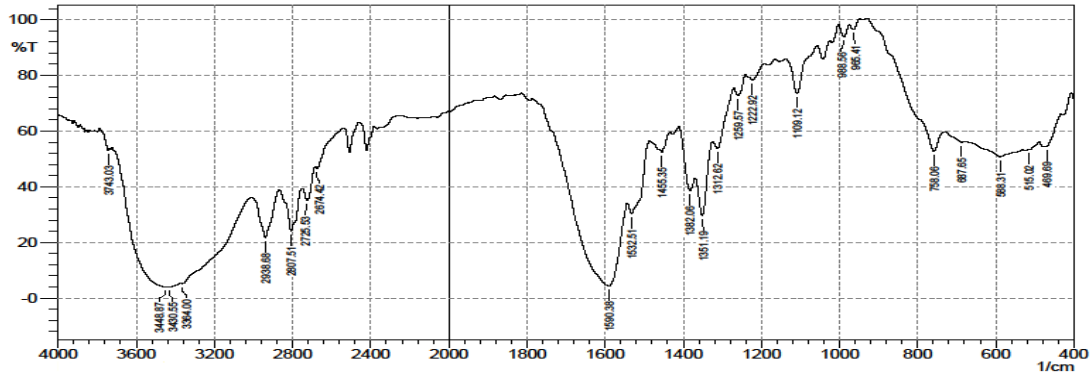
The drug release profile of formulations F1- F7 indicates that as the concentration of polymers increases, the drug release decreases. From the comparison of release profile of all the batches, it was observed that the formulations containing combination of polymers shows retardation of drug release to greater extent than formulations containing single polymer. The batches F1-F6, fail to comply with standards for drug release as mentioned for Modified release tablet in USP29.

### Stability study

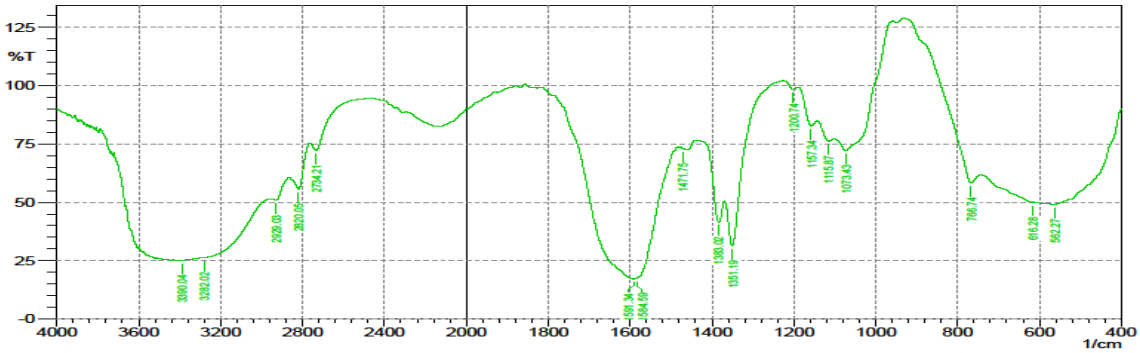
There was no significant difference in physical nature, % drug content and amount of Pramipexole dihydrochloride released from F7 after storing for 6 months at normal conditions and for 3 month at 40$^0$ C temperature 75 % relative humidity.

**Table 2:** Evaluation results of formulations F1-F8

| Batch No | Blend Parameters | | | | | Physical Parameters of Tablets | | |
|---|---|---|---|---|---|---|---|---|
| | Angle of Repose | Bulk density (gm/ml) | Tapped density (gm/ml) | Hausner ratio | Compressibility Index | Hardness (N) | Friability (%) | Average weight (mg) |
| F1 | 21.5 | 0.483 | 0.543 | 1.12 | 11.04 | 160 ± 4 | Nil | 260.00 ± 1.52 |
| F2 | 22.5 | 0.453 | 0.553 | 1.22 | 18.08 | 165 ± 2 | Nil | 260.00 ± 1.42 |
| F3 | 29.8 | 0.432 | 0.587 | 1.35 | 26.40 | 162 ± 3 | Nil | 260.00 ± 1.35 |
| F4 | 24.3 | 0.442 | 0.572 | 1.29 | 22.72 | 161 ± 4 | Nil | 260.00 ± 1.25 |
| F5 | 22.8 | 0.412 | 0.528 | 1.28 | 21.96 | 159 ± 3 | Nil | 260.00 ± 1.92 |
| F6 | 21.2 | 0.437 | 0.534 | 1.22 | 18.16 | 158 ± 5 | Nil | 260.00 ± 1.12 |
| F7 | 21.3 | 0.467 | 0.566 | 1.21 | 17.49 | 160 ± 5 | Nil | 260.00 ± 1.46 |




**IR Spectra of Pramipexole dihydrochloride monohydrate**




**IR Spectra of Pramipexole dihydrochloride monohydrate formulation**

**Table 3**: *In vitro* drug release of formulations F1- F7.

| Formulation | % Drug Release | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 hrs | 2 hrs | 4 hrs | 6 hrs | 9 hrs | 12 hrs | 16hrs | 20 hrs | 24 hrs |
| **F1** | 67.8 | 76.4 | 79.7 | 84.3 | 92.8 | 97.2 | 99.2 | 99.4 | 99.5 |
| **F2** | 57.4 | 68.1 | 76.5 | 81.1 | 88.4 | 94.5 | 96.1 | 99.4 | 99.4 |
| **F3** | 49.8 | 59.9 | 67.3 | 72.1 | 82.4 | 86.7 | 90.6 | 91.6 | 93.4 |
| **F4** | 39.7 | 48.6 | 56.9 | 63.7 | 73.6 | 77.5 | 83.5 | 87.6 | 92.4 |
| **F5** | 32.8 | 40.9 | 49.5 | 57.9 | 67.5 | 71.6 | 82.8 | 85.9 | 92.6 |
| **F6** | 27.5 | 34.7 | 43.9 | 53.4 | 63.9 | 69.7 | 76.4 | 81.4 | 93.6 |
| **F7** | 20.4 | 27.8 | 39.7 | 48.2 | 53.8 | 64.9 | 74.8 | 84.8 | 96.7 |
| **Innovator** | 21.2 | 28.4 | 37.8 | 46.7 | 50.6 | 59.0 | 72.5 | 80.7 | 94.5 |

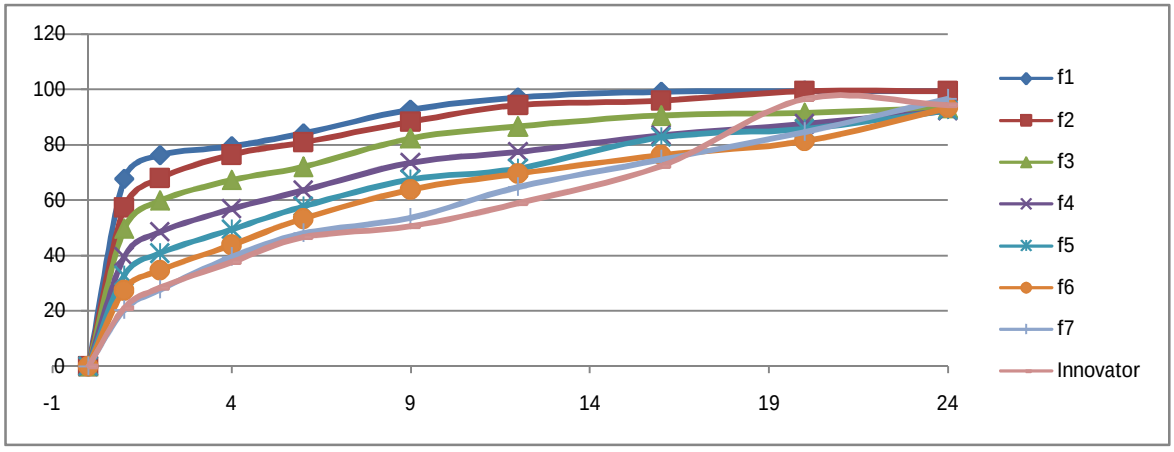
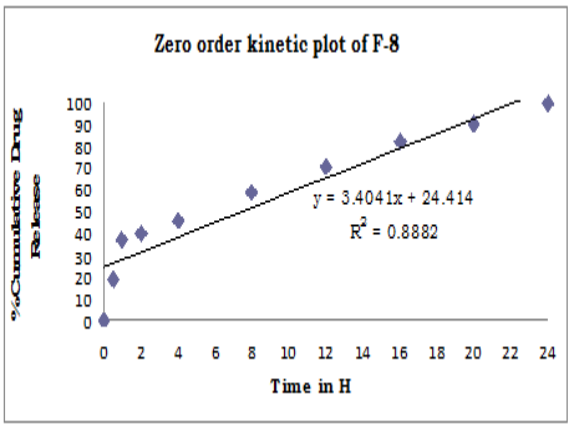
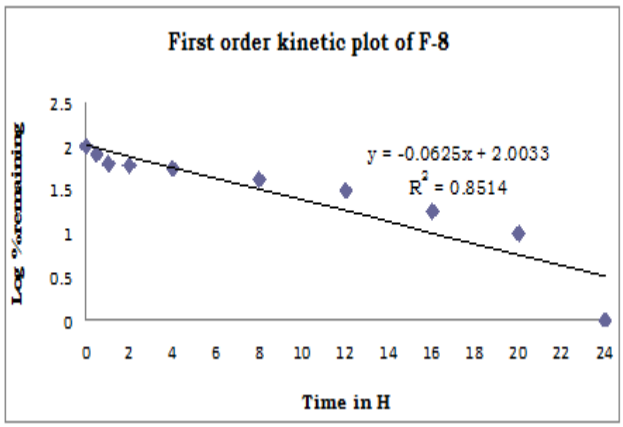


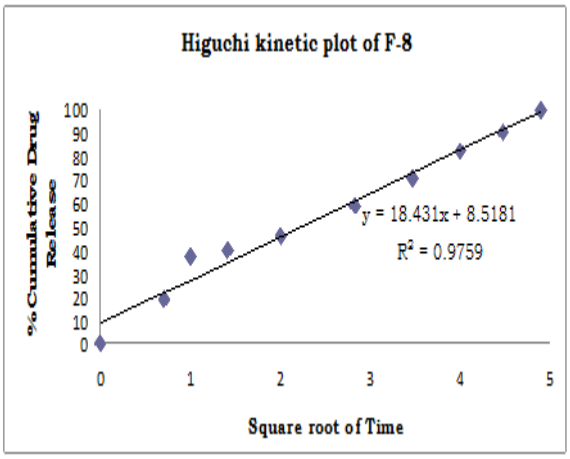

**Figure 3:** Dissolution graph of F1 – F7 trials

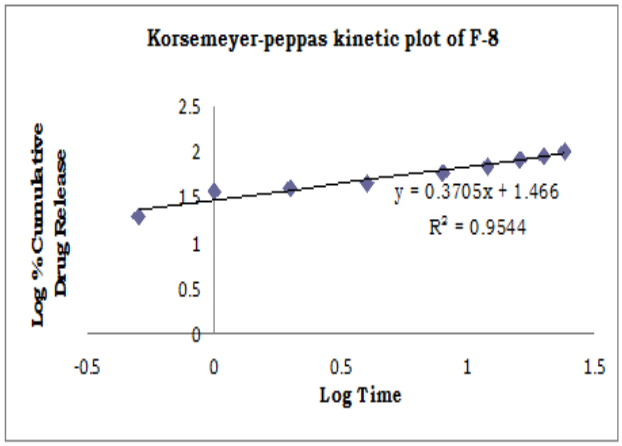
**Table 4:** Release kinetics of formulation F7

| Formulation code | Mathematical models | | | | |
|---|---|---|---|---|---|
| | Zero order | First order | Higuchi's model | Korsmeyer Peppa's model | |
| | $R^2$ | $R^2$ | $R^2$ | $R^2$ | N |
| F-7 | **0.888** | 0.851 | 0.976 | 0.954 | 0.370 |




## CONCLUSION

The results of the above study clearly indicated that Pramipexole can be formulated as extended release tablets using HPMC K 100M as retarding polymer combination with croscarmellose sodium and copovidone by wet granulation method, which will provide continuous release of drug at a predetermined rate and for a predetermined time.

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