Research Article

FORMULATION, DEVELOPMENT, AND IN VITRO CHARACTERIZATION OF PRAMIPEXOLE TABLETS FOR SUSTAINED RELEASE DRUG DELIVERY SYSTEM

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ABSTRACT

The objective of the present study was to design and evaluate sustained release matrix tablets of Pramipexole dihydrochloride, a non-ergoline dopamine agonist used in the management of Parkinson's disease and restless legs syndrome. Sustained drug delivery is crucial in chronic neurological disorders to ensure consistent therapeutic levels, minimize side effects, and improve patient adherence. Conventional dosage forms of Pramipexole necessitate frequent dosing due to its relatively short half-life (~8 hours), which can lead to fluctuations in plasma concentration and increased risk of adverse effects. To address these limitations, matrix tablets were formulated using various grades of hydrophilic polymer Hydroxypropyl Methylcellulose (HPMC K4M, K15M, and K100M) and Eudragit polymers (L-100 and S-100) in different ratios, combined with excipients like microcrystalline cellulose (MCC), PVP K30, talc, and magnesium stearate. The direct compression method was employed for tablet preparation. Pre-compression blends were evaluated for micromeritic properties, and the compressed tablets underwent standard post-compression tests including hardness, friability, drug content uniformity, and thickness. In vitro dissolution studies were carried out in simulated gastric and intestinal fluids using USP Type II dissolution apparatus. Drug release data were analysed using various kinetic models (zero- order, first-order, Higuchi, and Korsmeyer-Peppas) to understand the mechanism of release. The results demonstrated that formulations containing higher viscosity grades of HPMC (particularly K100M) and combinations with Eudragit showed a more controlled and prolonged drug release up to 12 hours. FTIR studies confirmed the absence of drug-excipient interactions, and short-term stability studies indicated the physical and chemical stability of the optimized formulation under accelerated conditions. This study successfully establishes a promising sustained release oral formulation of Pramipexole that can potentially enhance therapeutic efficacy, reduce dosing frequency, and improve the quality of life in patients suffering from Parkinson's disease.

KEY WORDS

Pramipexole, FTIR Studies, Polymers, Direct compression technique, In vitro drug release kinetics

INTRODUCTION

Oral drug delivery method is the most widely utilized routes for administration among all alternatives that have been explored for systemic delivery of drug via various pharmaceutical products of different dosage forms.[1] Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopoeia, Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drug or a mixture of drugs, with or

without diluents.[2] Pramipexole (2-amino-4,5,6,7-tetrahydro-6-propylamino-benzethiazole-dihydrochloride) is indicated for the treatment of PDs, alone or in combination with levodopa. Its introduction in PDs therapy effectively reduced the dose of levodopa by approximately 30%, thus diminishing the common side effects from levodopa treatment.[3] The present study was the development and invitro characterization of pramipexole tablets for a sustained release drug delivery system.

MATERIAL

Pramipexole was obtained from Hetero Lab, HYD. HPMC, Eudragit and PVPk30 were procured from Synpharma Research Labs, Hyderabad, other chemicals and reagents used were of analytical grade.

METHODOLOGY

FTIR:[4]

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany (Alpha T). The potassium bromide pellets were prepared on KBr press by grounding the solid powder sample with 100 times the quantity of KBr in a mortar. The finely grounded powder was then introduced into a stainless-steel die and was compressed between polished steel anvils at a pressure of about 8t/in^2. The spectra were recorded over the wave number of 8000 to 400cm^{-1}.

Tablet formulation:

Formulation of Pramipexole Dispersible Tablet by Direct-Compression:

Composition of preliminary trials for Pramipexole Tablet by direct compression is shown in table. All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-8 station with 6mm flat punch, B tooling. Each tablet contains 2.5 mg Pramipexole and other pharmaceutical ingredients.[5]

Table-1: Formulation of Pramipexole sustained release tablets

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pramipexole	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
HPMC K4M	5	10							
HPMC K15M			5	10					
HPMC K100M					5	10			
Eudragit L-100							5	10	
Eudragit S-100									10
PVP K30	5	5	5	5	5	5	5	5	5
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2
MCC	QS	QS	QS	QS	QS	QS	QS	QS	QS

Evaluation parameters:

Preformulation Studies of Tablets

Weight variation:

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P. [6]

Hardness:

Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm2.[7]

Thickness:

Three tablets were selected randomly from each batch and thickness was measured by using Vernier Calliper.[8]

Friability (F):

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at the height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.[9]

***In-Vitro* drug release:[10]**

Release of the drug in vitro, was determined by estimating the dissolution profile.

Dissolution test:

USP II Paddle apparatus was used and paddle was allowed to rotate at 50 rpm, acid buffer 0.1N HCL (pH 1.2, 900 ml) was used as a dissolution medium. After 2hrs 6.8pH phosphate buffer as dissolution medium.

Assay:

10 tablets were weighed and triturated. The tablet triturate equivalent to 10 mg of the drug was weighed accurately, dissolved in pH 1.2 buffer and diluted to 100 ml with the same. Further dilutions were done suitably to get a concentration of 10 µg/ ml with simulated gastric fluid pH Absorbance was read at 230 nm against the reagent blank, and the concentrations of PRAMIPEXOLE in µg/ ml was determined by using the regression equation.

Y = 0.007x + 0.001

Drug content in mg / tablet = conc. Mg/ml * dilution factor

% Drug content = drug content in mg * 100 / label claim. Drug- excipient compatibility studies by

Application of Release Rate Kinetics to Dissolution Data:[11]

Various models were tested for explaining the kinetics of drug release. To analyse the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-

order, first order, Higuchi, and Korsmeyer-Peppa's release model.

Zero order release rate kinetics:

To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$F = Ko\ t$$

Where, 'F' is the drug release at time 't', and 'Ko' is the zero-order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$$Log\ (100-F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k\, t1/2$$

Where, 'k' is the Higuchi constant.

In Higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppa's release model:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppa's equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$Mt/ M\infty = K\, tn$$

Where, Mt/ M∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the

diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fiskian release, the value of n falls between 0.5 and 1.0; while in case of Fiskian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for case II transport, n > 1. In this model, a plot of log (Mt/ M∞) versus log (time) is linear.

Hixson-Crowell release model:

$$(100\text{-}Qt)1/3 = 1001/3 – KHC.t$$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

RESULTS AND DISCUSSION

FTIR

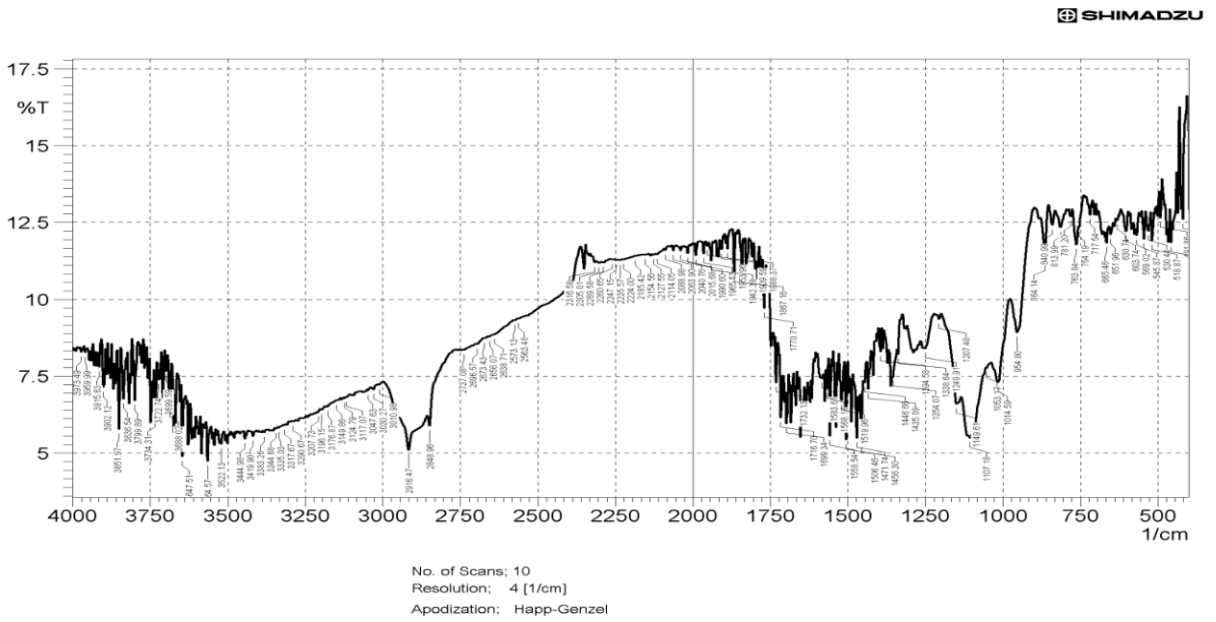

Fig-1: FTIR spectrum of pure drug

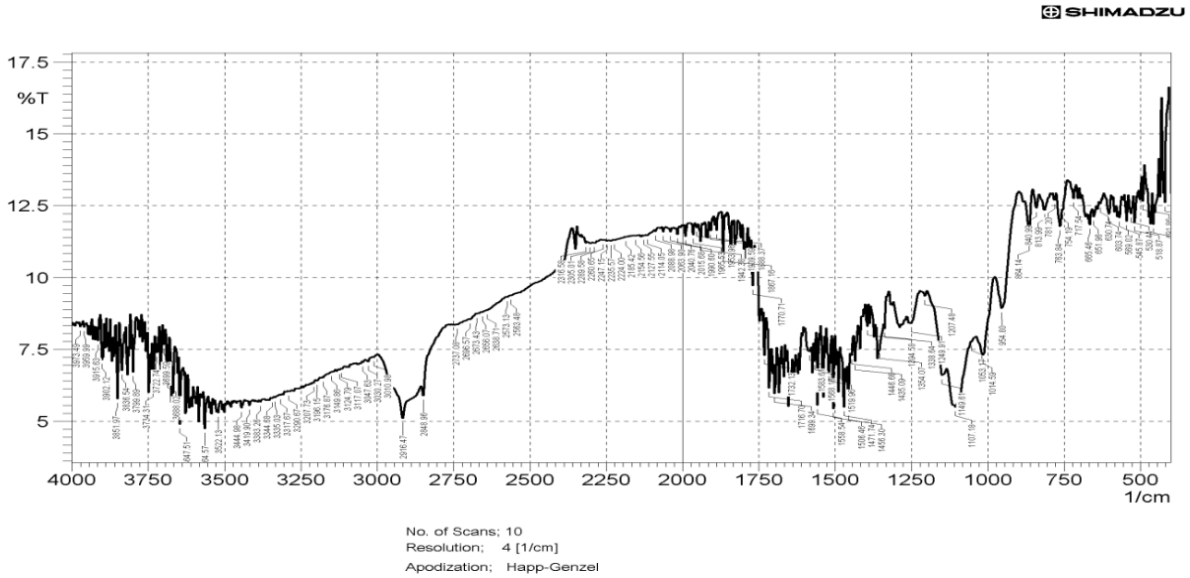

Fig-2: FTIR spectrum of optimized formulation

Evaluation parameters

Table-2: Evaluation parameters of Tablets

post-compression parameters:

F. No	Weight variation (mg)	Hardness (kg/cm²)	Thickness (mm)	Disintegration Time (min)	Friability (%)	Assay (%)
F_1	25	3.2	1.59	13	0.43	86.96
F_2	24	3.9	1.64	12	0.34	89.10
F_3	25	3.4	1.59	9	0.49	91.25
F_4	26	3.7	1.58	12	0.47	88.63
F_5	24	3.3	1.59	16	0.49	90.12
F_6	25	3.5	1.64	11	0.34	88.09

Weight variation test:

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 2. The average weight of the tablet is approximately in range of 24 to 26, so the permissible limit is ±10%. The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test:

Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data were shown in Table 2. The results showed that the hardness of the tablets is in range of 3.3 to 3.7 kg/cm², which was within IP limits.

Thickness:

Thickness of three tablets of each batch was checked by using Vernier Caliper. The result showed that thickness of the tablet is raging from 1.58 to 1.64.

Friability:

Tablets of each batch were evaluated for percentage friability and the data were shown in the Table 2. The average friability

of all the formulations lies in the range of 0.34 to 0.59% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

***In vitro* disintegration time:**

Tablets of each batch were evaluated for in vitro disintegration time and the data were shown in the Table. The results showed that the disintegration time of prepared tablets were in the range of 9 to 16 min

Assay: Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 86.96-91.25 %.

***In vitro* Dissolution studies:**

In vitro dissolution studies were carried out by using 500ml of 0.1 N HCl in USP dissolution apparatus 2 hours after that using 6.8ph phosphate buffer by using paddle method. The dissolution studies were carried out for about 8hrs min.

Table-3: *In vitro* dissolution data

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	20.22	14.26	15.02	17.21	14.66	16.22	21.10	19.50	23.54
2	32.65	20.65	22.55	29.53	28.44	25.45	32.86	31.88	38.33
3	49.68	39.29	40.89	40.12	43.85	36.89	43.24	49.28	44.25
4	55.24	59.55	48.22	56.84	65.88	42.83	66.49	61.11	51.01
5	60.35	77.58	54.48	66.85	79.25	58.46	74.85	78.96	66.86
6	74.24	80.65	59.77	76.63	96.12	62.70	84.25	82.58	78.98
7	88.28	98.63	66.62	85.12		75.23	95.57	94.66	84.26
8	97.55		74.35	97.70		84.26			96.99
9			88.99			97.99			
10			98.43						

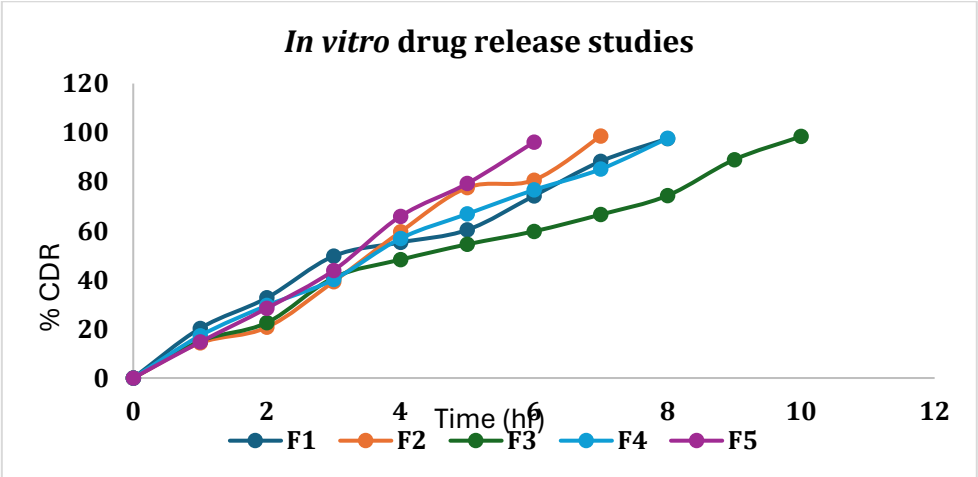

Fig 3: Cumulative drug release of formulations(F1-F5)

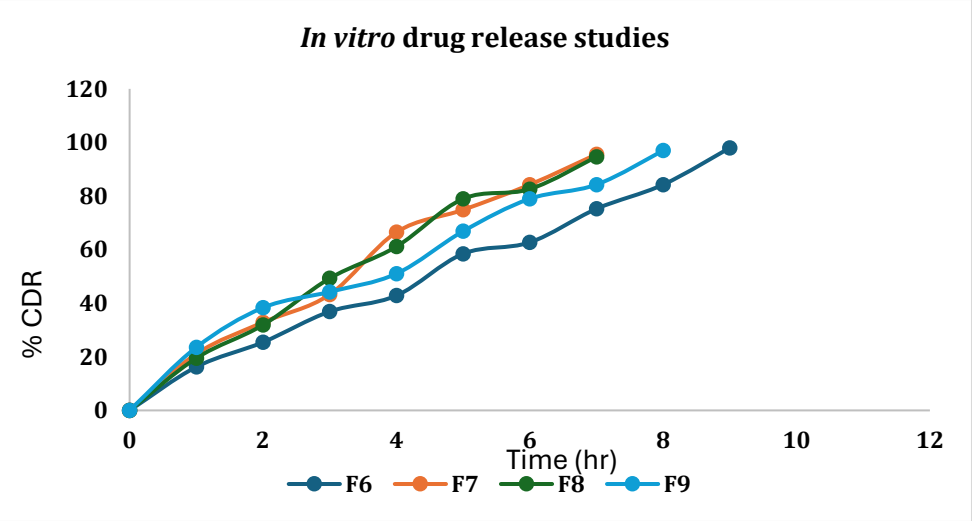

Fig 4: Cumulative drug release of formulations(F6-F9)

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyses the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order kinetics

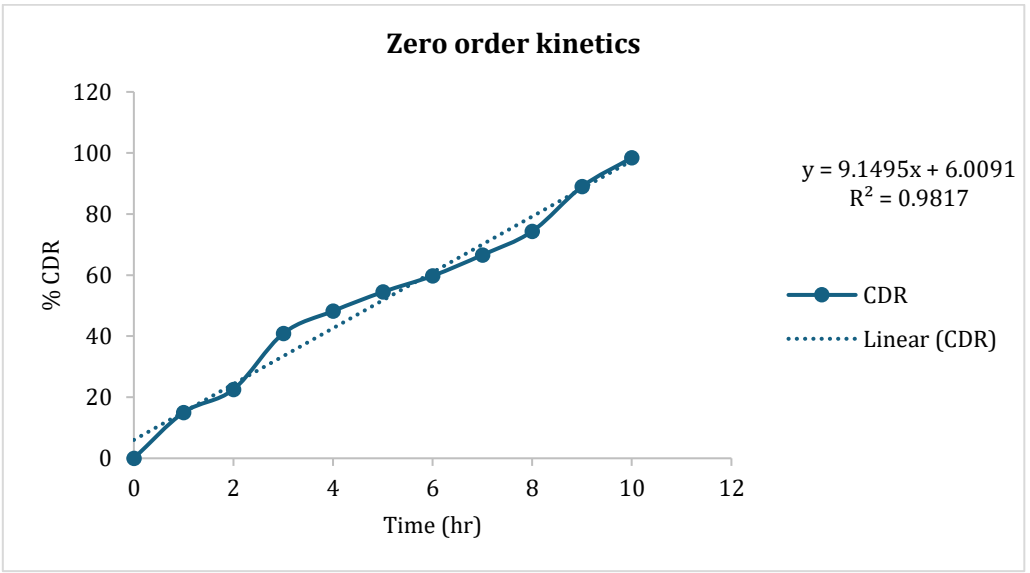

Fig-5: Zero order kinetics of optimized formulation

First order kinetics

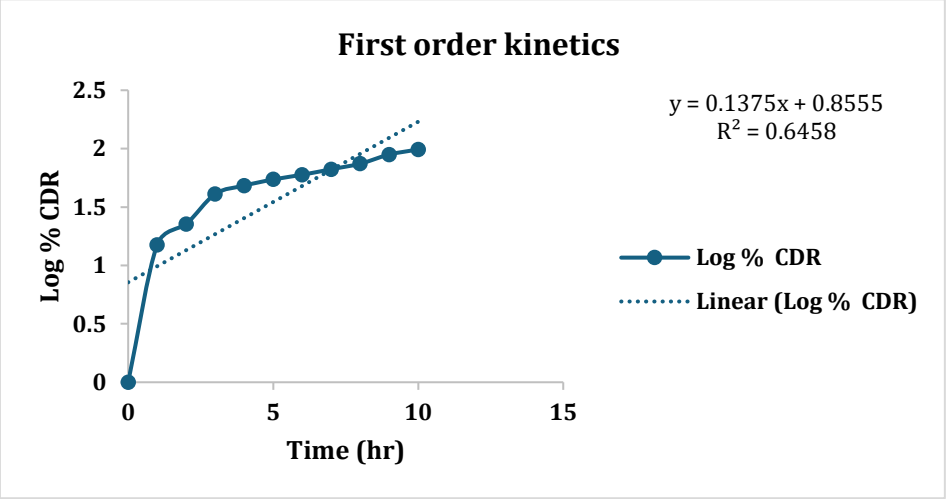

Fig-6: First order kinetics of optimized formulation

Higuchi model

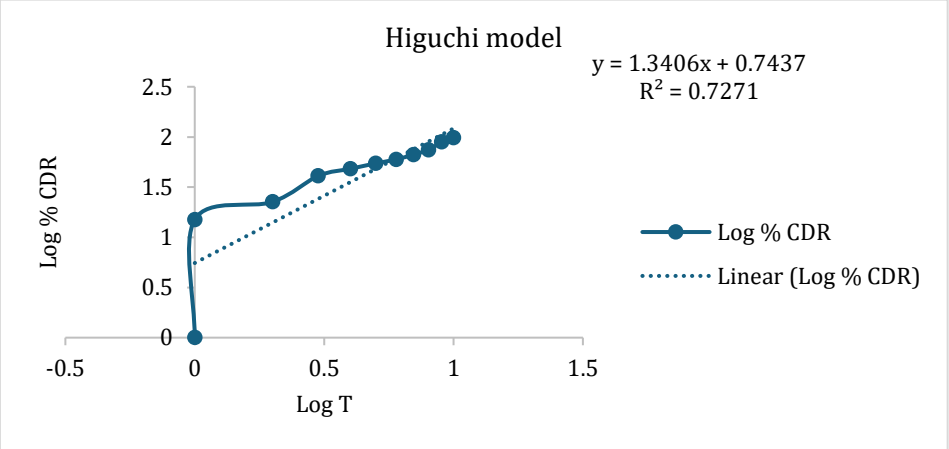

Fig-7: Higuchi model of optimized formulation

Korsmeyer peppas

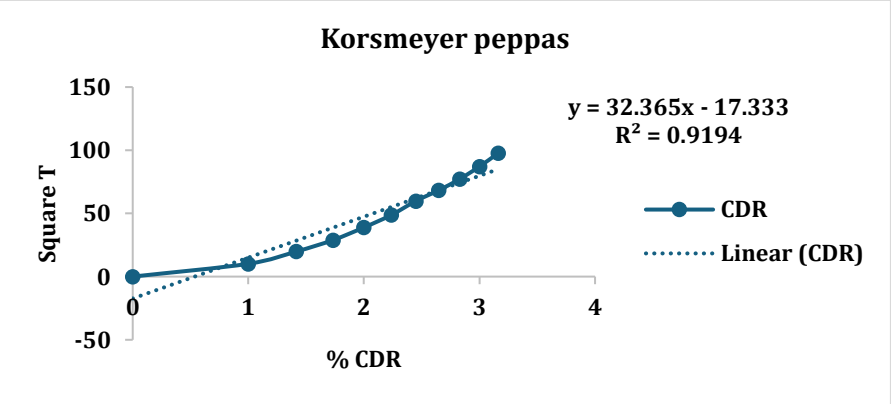

Fig 8: Korsmeyer peppas model of optimized formulation

CONCLUSION

In the present work, an attempt has been made to develop sustained release tablets of Pramipexole. Different grades of hydroxy propyl methyl cellulose and different grades of eudragit polymers used. All the formulations were prepared by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F3 formulation showed maximum % drug release i.e., 98.43 % in 8 hours hence it is considered as an optimized formulation.

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