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FORMULATION AND *IN VITRO* EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF ENTACAPONE USING HYDROPHILIC POLYMERS

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Abstract:

The present study focuses on the formulation and in vitro evaluation of sustained release matrix tablets of Entacapone, a selective and reversible catechol-O-methyltransferase (COMT) inhibitor used in the management of Parkinson's disease. Due to its short biological half-life and frequent dosing requirements, the development of a sustained release formulation was undertaken to enhance patient compliance and maintain steady plasma drug levels.

Matrix tablets were prepared using various hydrophilic polymers such as Hydroxypropyl Methylcellulose (HPMC), Carbopol, and Sodium Carboxymethyl Cellulose (NaCMC) by direct compression method. The pre-compression parameters (bulk density, tapped density, Carr's index, Hausner ratio, and angle of repose) and post-compression parameters (hardness, thickness, friability, weight variation, drug content) were evaluated and found to be within acceptable limits.

In vitro drug release studies were carried out using USP dissolution apparatus, and the results showed that the rate of drug release was significantly influenced by the type and concentration of polymer used. Among the various formulations, E4 exhibited a sustained drug release up to 12 hours, releasing approximately 99.95% of the drug and followed Higuchi and Korsmeyer-Peppas kinetics, indicating a diffusion-controlled release mechanism.

The study concludes that hydrophilic polymers can effectively sustain the release of Entacapone from matrix tablets, offering a promising approach for the development of oral sustained release formulations to improve therapeutic efficacy and patient adherence.

Keywords: *Entacapone sustained release matrix tablets*

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1. INTRODUCTION:

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body[1]. This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action[2, 3]. The term therapeutic substance also applies to an agent such as gene therapy that will induce in vivo production of the active therapeutic agent. Sustained release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect[4]. The advantage of administering a single dose of a drug that is released over an extended period of time to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use[5, 6].

The first sustained release tablets were made by Howard Press in New Jersy in the early 1950's. The first tablets released under his process patent were called 'Nitroglyn' and made under license by Key Corp. in Florida.

Sustained release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.
The goal in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or to a specified target organ[7, 8].

Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. There are certain considerations for the preparation of extended release formulations:

- ✓ If the active compound has a long half-life, it is sustained on its own,
- ✓ If the pharmacological activity of the active is not directly related to its blood levels,
- ✓ If the absorption of the drug involves an active transport and
- ✓ If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose.
- ✓

1.1. Rationale for extended release dosage forms:

Some drugs are inherently long lasting and require only once-a-day oral dosing to sustain adequate drug blood levels and the desired therapeutic effect. These drugs are formulated in the conventional manner in immediate release dosage forms. However, many other drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results. Multiple daily dosing is inconvenient for the patient and can result in missed doses, made up doses, and noncompliance with the regimen[10,11]. When conventional immediate-release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys (troughs) associated with the taking of each dose . However, when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. For example, if doses are administered too frequently, minimum toxic concentrations of drug may be reached, with toxic side effects resulting. If doses are missed, periods of sub therapeutic drug blood levels or those below the minimum effective concentration may result, with no benefit to the patient. Extended-release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. Typically, extended-release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period (Fig.1).

7. METHODOLOGY:

Materials used in the work

1	HPMC K 4M	Provided by SURA LABS, Dilsukhnagar, Hyderabad.
2	Sodium Carboxymethyl Cellulose	Panchi Chemicals Pvt Ltd, Mumbai
3	Carbopol	Alkem Labs Pvt, Ltd, Mumbai.
4	PVP K 30	Sd fine Chem.Ltd. Mumbai
5	Talc	SD Fine chemicals, Mumbai

LIST OF EQUIPMENTS USED

Weighing Balance	Sartourius
Tablet Compression Machine (Multistation)	Lab Press Limited, India.
Hardness tester	Monsanto, Mumbai, India.
Vernier callipers	Mitutoyo, Japan.

Roche Friabilator Labindia, Mumbai, India
DissolutionApparatus Labindia, Mumbai, India
UV-Visible Spectrophotometer Labindia, Mumbai, India
pH meter Labindia, Mumbai, India
FT-IR Spectrophotometer Bruker, Alpha

Analytical method development:
Determination of Wavelength:
10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

Determination of Calibration Curve:
10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared and those concentrations absorbance were found out at required wavelength.

Formulation development of Tablets:
All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 6.3. The tablets were prepared as per the procedure given below and aim is to prolong the release of Entacapone. Total weight of the tablet was considered as 400mg.

Procedure:
1) Entacapone and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Table 7.3: Formulation composition for tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Entacapone	100	100	100	100	100	100	100	100	100
HPMC K 4M	50	100	150	-	-	-	-	-	-
Sodium Carboxymethyl Cellulose	-	-	-	50	100	150	-	-	-
Carbopol	-	-	-	-	-	-	50	100	150
PVP K 30	20	20	20	20	20	20	20	20	20
Talc	15	15	15	15	15	15	15	15	15
Magnesium Stearate	10	10	10	10	10	10	10	10	10
Lactose	QS	QS	QS	QS	QS	QS	QS	QS	QS
Total Weight	400	400	400	400	400	400	400	400	400

Drug – Excipient compatibility studies
Fourier Transform Infrared (FTIR) spectroscopy:
The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany(Alpha T).The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm^{-1} to 400cm^{-1}

8. RESULTS AND DISCUSSION:

8.1. Analytical Method

Table 8.1: Observations for graph of Entacapone in 0.1N HCl (310nm)

Conc [µg/ml]	Absorbance
0	0
2	0.115
4	0.214
6	0.315
8	0.405
10	0.511

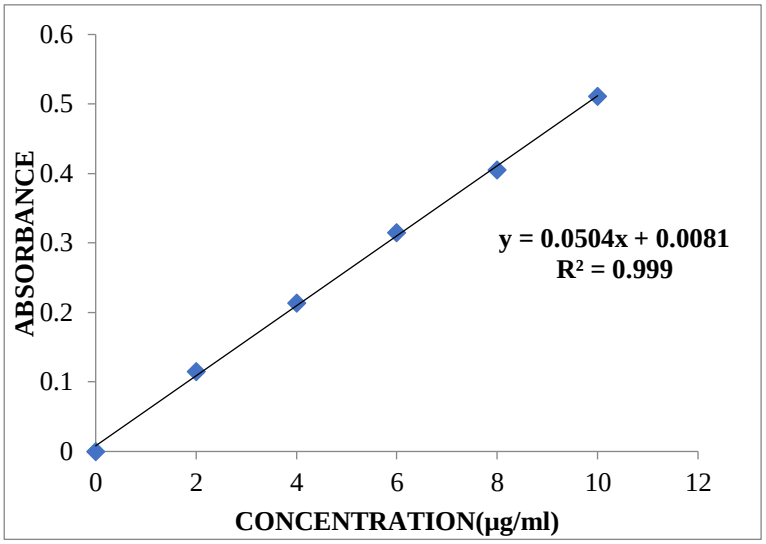

Figure 8.1: Standard graph of Entacapone in 0.1N HCl

Table 8.2: Observations for graph of Entacapone pH 6.8 phosphate buffer (247nm)

Concentration [µg/ml]	Absorbance
0	0
2	0.109
4	0.222
6	0.331
8	0.438
10	0.547

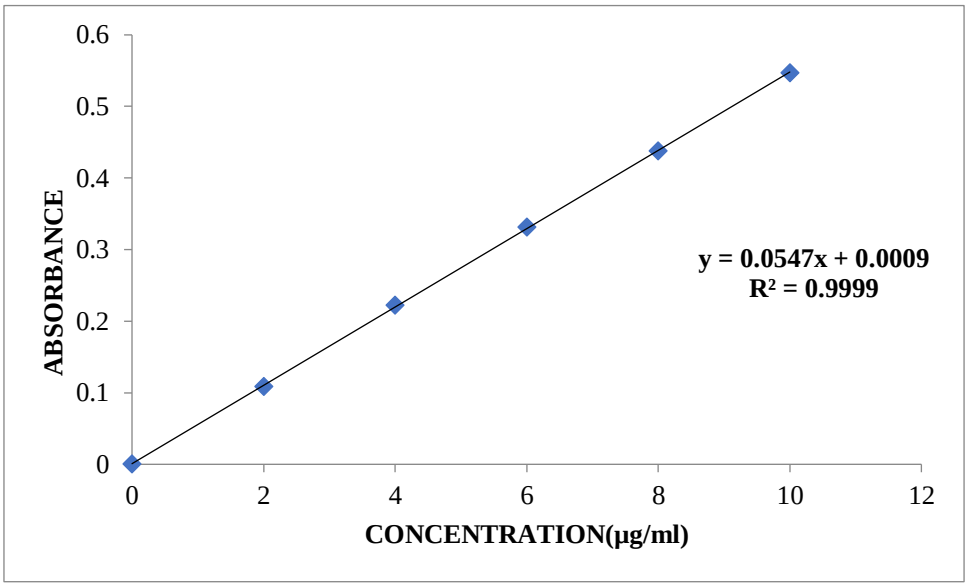

Figure 8.2: Standard graph of Entacapone pH 6.8 phosphate buffer (247nm)

8.2. Preformulation parameters of powder blend

Table8.3: Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
E1	31.68±0.5	0.44±0.145	0.56±0.13	21.42±0.2	1.27±0.1
E2	22.56±0.4	0.42±0.17	0.52±0.18	19.23±0.1	1.23±0.2
E3	30.24±0.4	0.48±0.195	0.56±0.1	14.28±0.1	1.16±0.1
E4	23.85±0.1	0.37±0.160	0.45±0.2	17.77±0.1	1.21±0.1
E5	25.52±0.4	0.50±0.108	0.63±0.2	20.63±0.2	1.26±0.1
E6	28.73±0.2	0.52±0.135	0.59±0.2	11.86±0.3	1.13±0.1
E7	27.58±0.9	0.36±0.096	0.41±0.69	12.19±0.1	1.13±0.1
E8	24.72±0.2	0.39±0.110	0.42±0.9	7.14±0.2	1.07±0.4
E9	31.44±0.14	0.42±0.07	0.54±0.10	22.22±0.1	1.28±0.1

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.36±0.096 to 0.52±0.135 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.41±0.69 to 0.63±0.2 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 25 which show that the powder has good flow properties. All the formulations has shown the Hausner ratio below 1.333 indicating the powder has good flow properties.

8.3. Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

8.4. *In vitro* quality control parameters for tablets

Formulation codes	Average weight(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
E1	398.12	4.43	0.32	2.85	97.63
E2	399.35	4.74	0.15	2.15	99.54
E3	300.22	4.26	0.14	2.89	99.85
E4	300.08	4.21	0.18	2.72	98.81
E5	398.37	4.48	0.38	2.92	98.53
E6	397.59	4.21	0.29	2.22	97.91
E7	398.76	4.78	0.37	2.93	99.76
E8	399.31	4.15	0.44	2.88	98.54
E9	398.53	4.36	0.53	2.76	97.83

***8.4. In-Vitro* Drug Release Studies**

Table 8.5: Dissolution Data of Entacapone Tablets

Time(Hrs)	E1	E2	E3	E4	E5	E6	E7	E8	E9
0	0	0	0	0	0	0	0	0	0
0.5	12.88	15.82	08.96	19.71	17.47	17.23	12.85	17.51	16.32
1	16.08	22.71	13.12	29.32	26.32	28.61	18.55	22.87	19.13
2	19.47	29.98	19.52	38.17	34.85	31.84	25.36	29.32	23.74

3	26.74	37.21	25.54	45.85	39.63	44.54	34.74	36.85	28.89
4	32.11	43.87	29.31	54.13	43.25	49.87	39.25	43.78	37.64
6	39.69	48.92	36.28	58.87	49.85	55.25	46.85	49.72	52.99
7	45.39	52.39	43.72	65.47	57.36	63.98	54.78	57.25	63.41
8	54.74	58.11	49.62	69.52	65.81	76.74	63.58	66.32	69.52
9	59.98	64.84	56.49	76.21	72.99	79.87	74.62	73.95	77.87
10	67.28	69.74	62.68	89.13	78.41	88.33	82.73	86.12	82.74
11	76.57	79.44	73.59	95.84	89.13	93.25	89.91	99.31	86.11
12	83.35	92.89	89.78	99.95	95.08	97.22	96.44	98.63	93.35

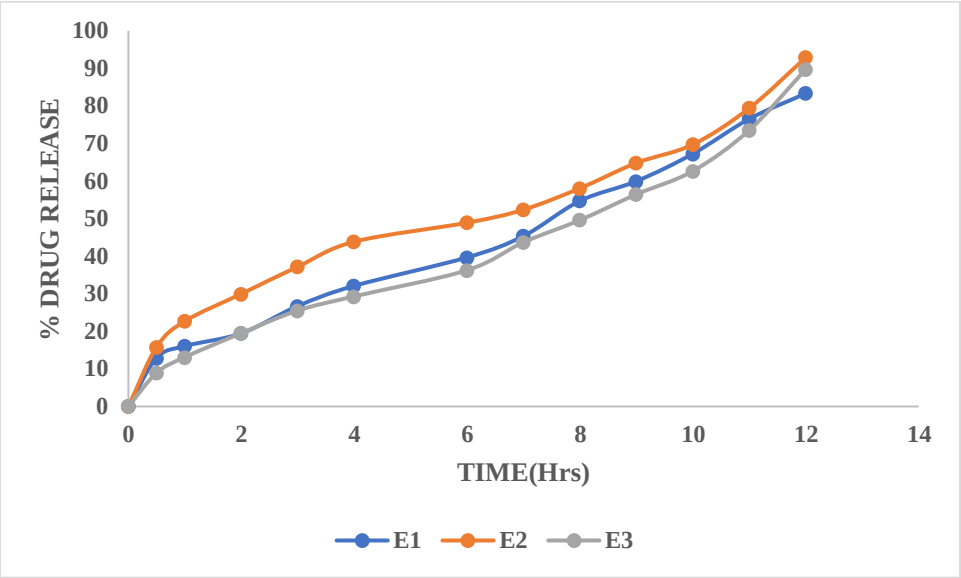

Fig 8.3: Dissolution profile of Entacapone (E1- E3 formulations).

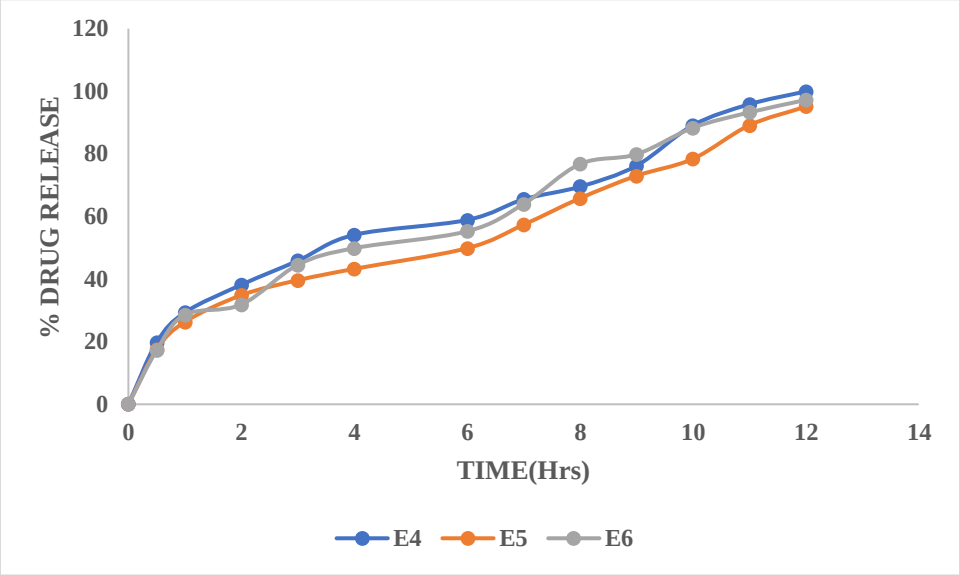

Fig8.4: Dissolution profile of Entacapone (E4 - E6 formulations)

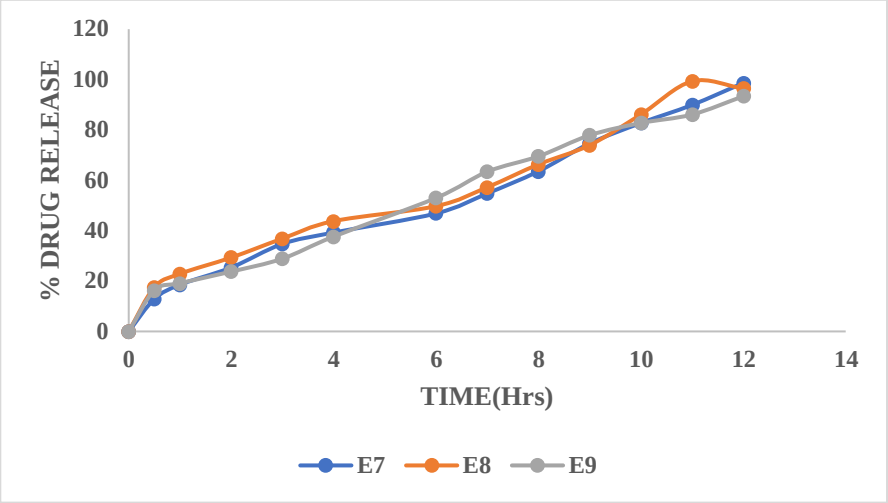

Fig8.4: Dissolution profile of Entacapone (E7 - E9 formulations)

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze 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.

Table 8.7: Release Rate Kinetics to Dissolution Data

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	%) REL	LOG (T	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
19.71	1	1.000	1.295	0.000	1.905	19.710	0.0507	-0.705	80.29	4.642	4.314	0.328
29.32	2	1.414	1.467	0.301	1.849	14.660	0.0341	-0.533	70.68	4.642	4.135	0.507
38.17	3	1.732	1.582	0.477	1.791	12.723	0.0262	-0.418	61.83	4.642	3.954	0.687
45.85	4	2.000	1.661	0.602	1.734	11.463	0.0218	-0.339	54.15	4.642	3.783	0.858
54.13	5	2.236	1.733	0.699	1.662	10.826	0.0185	-0.267	45.87	4.642	3.580	1.062
58.87	6	2.449	1.770	0.778	1.614	9.812	0.0170	-0.230	41.13	4.642	3.452	1.190
65.47	7	2.646	1.816	0.845	1.538	9.353	0.0153	-0.184	34.53	4.642	3.256	1.385
69.52	8	2.828	1.842	0.903	1.484	8.690	0.0144	-0.158	30.48	4.642	3.124	1.518
76.21	9	3.000	1.882	0.954	1.376	8.468	0.0131	-0.118	23.79	4.642	2.876	1.766
89.13	10	3.162	1.950	1.000	1.036	8.913	0.0112	-0.050	10.87	4.642	2.215	2.426
95.84	11	3.317	1.982	1.041	0.619	8.713	0.0104	-0.018	4.16	4.642	1.608	3.033
99.95	12	3.464	2.000	1.079	0.540	8.329	0.0100	0.000	0.05	4.642	0.368	4.273

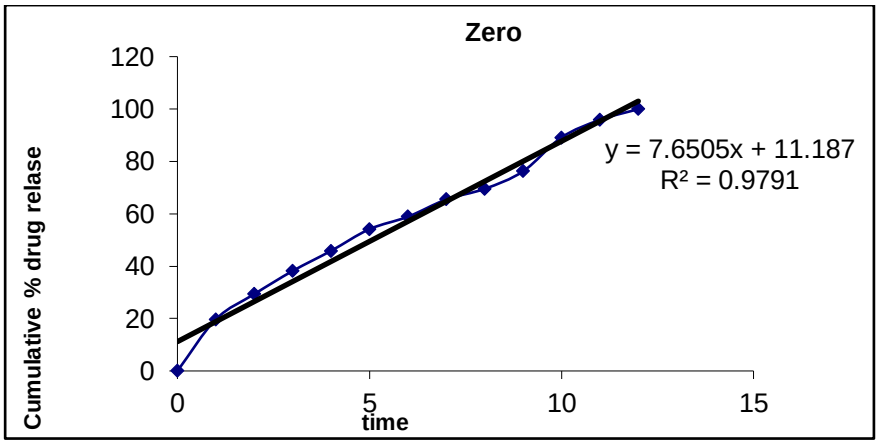

Fig 8.5 : Zero order release kinetics graph

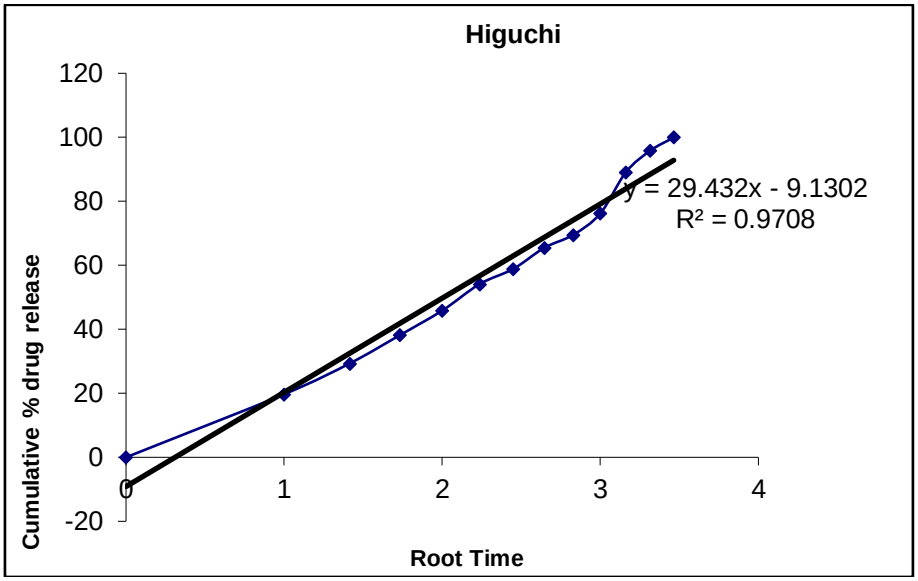

Fig 8.6: Higuchi release kinetics graph

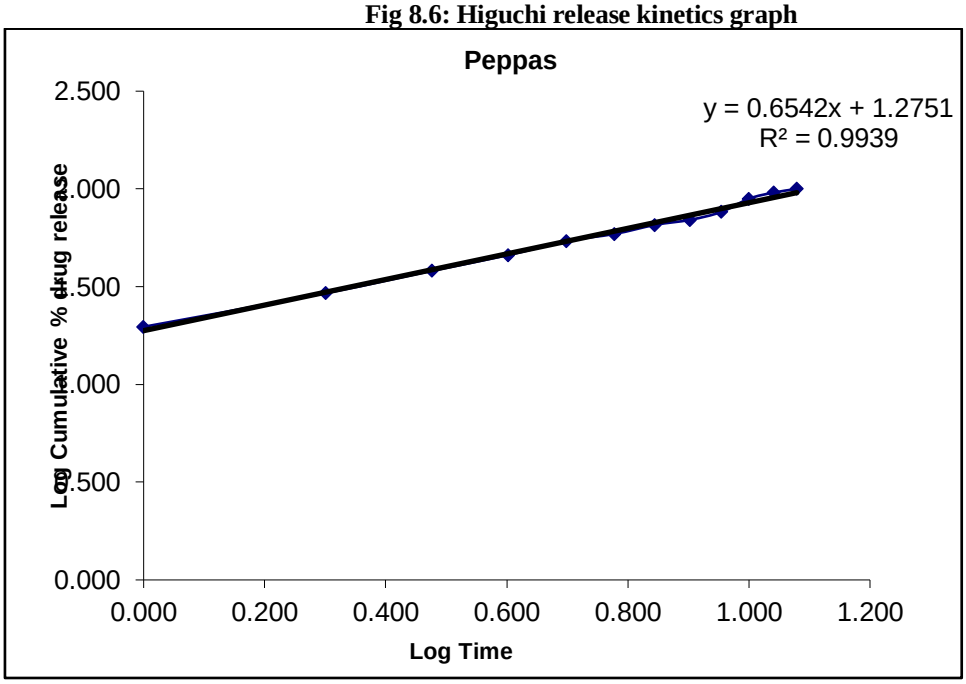

Fig 8.7: Kars mayer peppas graph

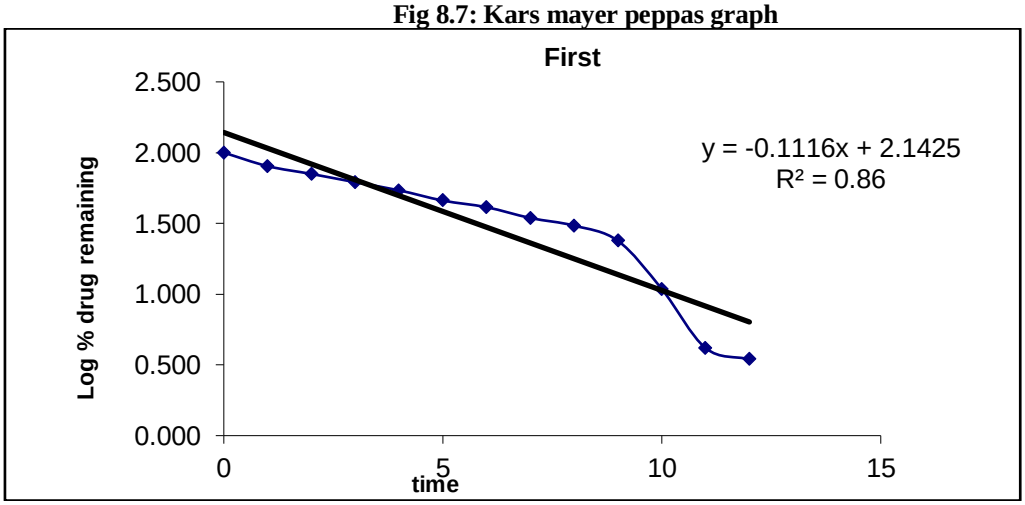

Fig 8.8: First order release kinetics graph

From the above graphs it was evident that the formulation E4 was followed Peppas release kinetics.

8.6. Drug – Excipient compatibility studies

Fourier Transform-Infrared Spectroscopy:

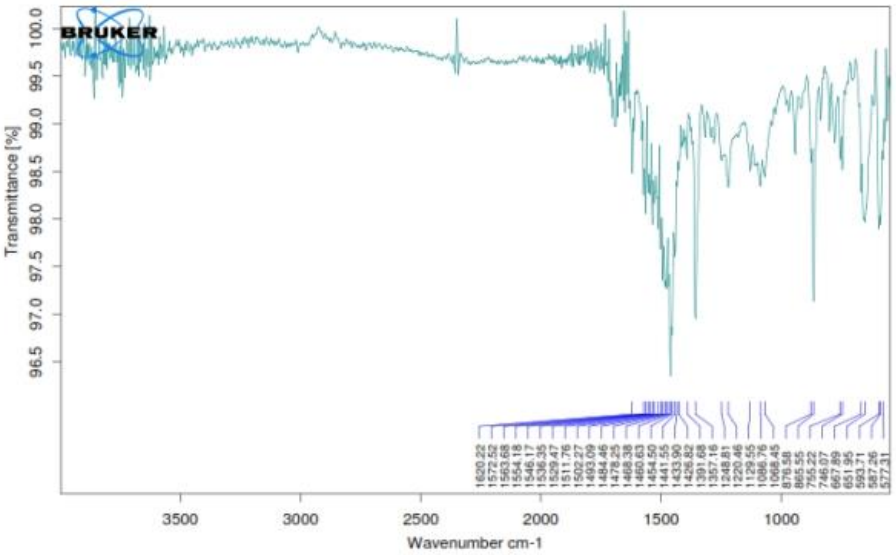

Figure 8.9: FT-TR Spectrum of Entacapone pure drug.

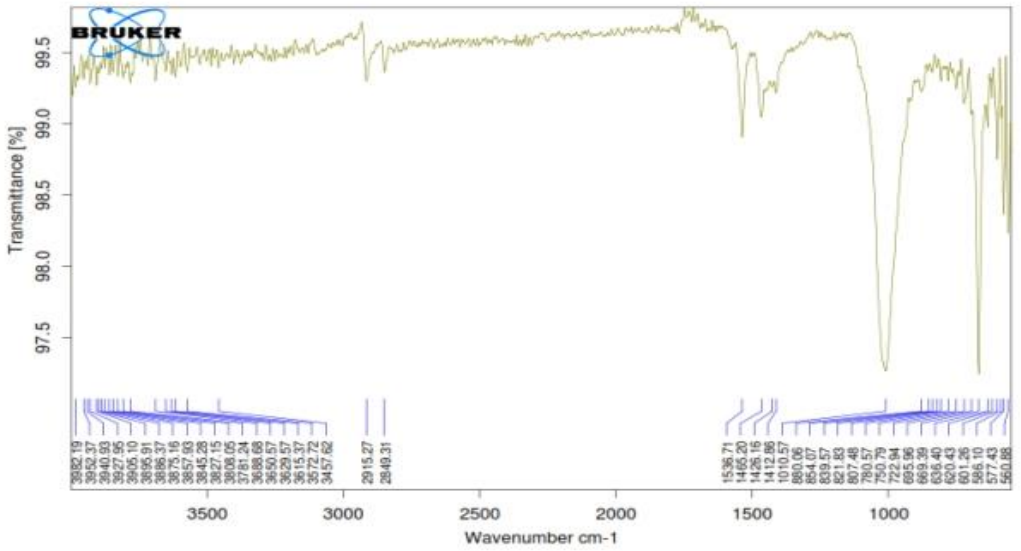

Figure 8.10: FT-IR Spectrum of Optimized Formulation

From the FTIR data it was evident that the drug and excipients doses not have any interactions. Hence they were compatible.

9. CONCLUSION:

The present study successfully aimed at the formulation and in vitro evaluation of sustained release matrix tablets of Entacapone using various hydrophilic polymers. The formulations were prepared by the direct compression method using polymers such as Hydroxypropyl Methylcellulose (HPMC), Carbopol, and Sodium Carboxymethyl Cellulose (NaCMC) in varying concentrations to modulate the drug release profile.

Pre-compression and post-compression parameters of all formulations were found to be within acceptable limits, indicating good flow properties and tablet integrity. In vitro dissolution studies revealed that the drug release was sustained over an extended period, with significant influence from the type and concentration of the hydrophilic polymer used. Among all formulations, formulation E4 exhibited the most desirable sustained release profile, releasing approximately 99.95% of Entacapone over 12 hours, and followed Higuchi and Korsmeyer-Peppas kinetic models, suggesting a diffusion-controlled release mechanism.

The study demonstrates that hydrophilic polymers are effective in controlling the release of Entacapone from matrix tablets. Hence, sustained release matrix tablets of Entacapone formulated using HPMC and other hydrophilic agents can offer a promising alternative to conventional dosing by improving patient compliance and minimizing dosing frequency in the management of Parkinson's disease.

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