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Formulation and evaluation of controlled release matrix tablets of rivastigmine

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ABSTRACT

Rivastigmine is used to treat dementia (a brain disorder that affects the ability to remember, think clearly, communicate, and perform daily activities and may cause changes in mood and personality) in people with alzheimer's disease the main objective of the present study was to develop control release formulation by using natural polymers i.e guar gum, locust bean gum and karaya gum. Direct compression technique was used to prepare tablets which were evaluated for pre compression and post compression parameters. Nine formulations were prepared which f1-f3 were prepared using guar gum, f4-f6 by locust bean gum and f7-f9 by karaya gum. F6 was selected as the best formulation which controls the drug release up to 99.82% in 12hrs.

Keywords: Rivastigmine, Guar Gum, Locust Bean gum and Karaya gum

INTRODUCTION[1-9]

Controlled 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. 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.

The first Controlled 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.

Controlled 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 Controlled or Controlled 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, Controlled 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.

Controlled 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 Controlled 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.

The above factors need serious review prior to design.

Introduction of matrix tablet as Controlled release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and Pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused

greater attention on development of Controlled release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of Controlled release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed.

In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the Controlled release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.

Rationale for extended release dosage forms[10-12]

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. 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).

The Controlled plasma drug levels provided by extended-release products oftentimes eliminate the need for night dosing, which benefits not only the patient but the caregiver as well.

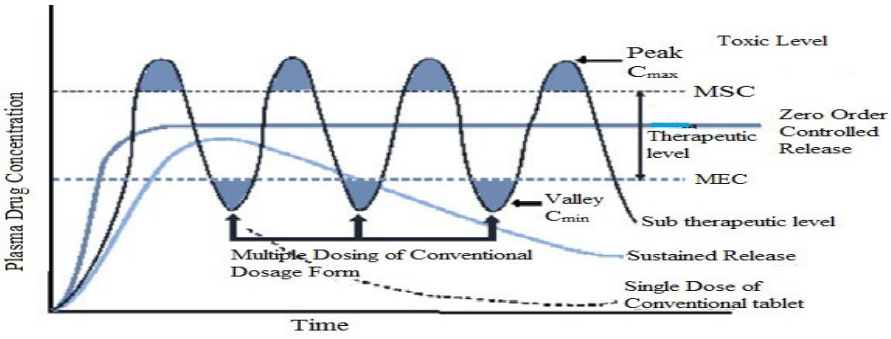

Figure 1: Hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of Controlled and controlled delivery formulations.

Drawbacks of Conventional Dosage Forms[13]

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
2. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
3. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

Aim and objective

Aim of the work

Aim of the study is to formulate and evaluate Rivastigmine Controlled release tablets using different polymers.

Objective of the Study

- ✓ To Formulate Controlled release Tablets Of Rivastigmine for the treatments of mild to moderate Alzheimer's disease and Parkinson's.
- ✓ To formulate sustained release tablets by using different types of polymers.
- ✓ To evaluate pre and post compression evaluation parameters
- ✓ To perform Drug and Excipient compatibility studies (FTIR)
- ✓ To perform various quality control evaluation parameters for the prepared tablets.

The main objective of this study is to extend the drug release there by reducing the frequency of dosage.

MATERIALS AND METHOD MATERIALS

Rivastigmine was Provided by SURA LABS, Dilsukhnagar, Hyderabad . Guar Gum ,Locust Bean gum, Karaya gum, PVP K30,Magnesium stearate,Talc and MCC was gift sample from Merck Specialities Pvt Ltd, Mumbai, India ,

Methodology

Table 1: Formulation composition for tablets

INGREDIENTS (MG)	FORMULATION CODE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rivastigmine	5	5	5	5	5	5	5	5	5
Guar Gum	3	6	9	-	-	-	-	-	-
Locust Bean gum	-	-	-	3	6	9	-	-	-
Karaya gum	-	-	-	-	-	-	3	6	9
PVP K30	5	5	5	5	5	5	5	5	5
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	5	5	5	5	5	5	5	5	5
MCC	78	75	72	78	75	72	78	75	72
Total weight	100	100	100	100	100	100	100	100	100

RESULTS AND DISCUSSION

The present study was aimed to developing Controlled release tablets of Rivastigmine using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method

Graphs of Rivastigmine were taken in Simulated Gastric fluid (pH 1.2) and in p H 6.8 phosphate buffer at 220 nm and 222nm respectively.

Table 2: Observations for graph of Rivastigmine in 0.1N HCl (220)

Concentration [µg/mL]	Absorbance
0	0
5	0.147
10	0.269
15	0.412
20	0.538
25	0.674

It was found that the estimation of Rivastigmine by UV spectrophotometric method at λ_{max} 220nm in 0.1N Hydrochloric acid had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 5-25µg/ml. The regression equation generated was y = 0.026x + 0.005

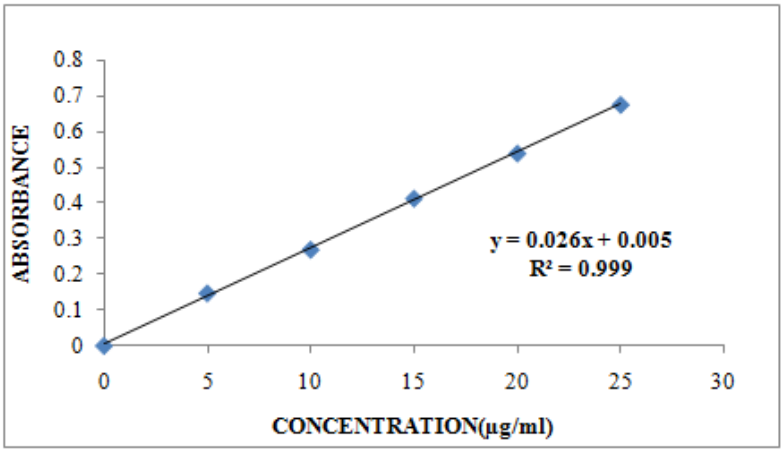

Figure 2: Standard graph of Rivastigmine in 0.1N HCl

Table 3: Observations for graph of Rivastigmine in p H 6.8 phosphate buffer (222nm)

Concentration [µg/ml]	Absorbance
0	0
5	0.178
10	0.347

15	0.523
20	0.698
25	0.845

It was found that the estimation of Rivastigmine by UV spectrophotometric method at λ_{max} 222 nm in pH 6.8 Phosphate buffer. had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 5-25µg/ml. The regression equation generated was **y** = 0.034x + 0.006.

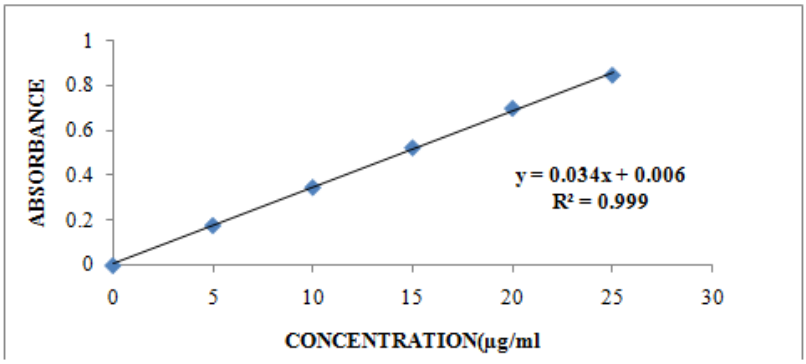

Figure 3: Standard graph of Rivastigmine pH 6.8 phosphate buffer (222nm)

Pre formulation parameters of powder blend

Table 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
F1	19.66±0.538	0.555±0.304	0.598±0.018	8.695	1.095
F2	22.7±0.933	0.524±0.141	0.593±0.334	11.11	1.133
F3	25.08±0.198	0.598±0.061	0.657±0.431	11.76	1.333
F4	21.39±0.567	0.502±0.654	0.598±0.318	17.39	1.121
F5	24.46±0.338	0.511±0.341	0.593±0.734	25.00	1.333
F6	26.75±0.735	0.574±0.3115	0.673±0.533	9.52	1.105
F7	22.12±0.244	0.582±0.758	0.641±0.290	12.50	1.142
F8	24.23±0.259	0.521±0.0534	0.581±0.941	11.53	1.130
F9	25.33±0.363	0.551±0.0821	0.555±0.304	22.22	1.285

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.

Table: 4. *In vitro* quality control parameters for tablets

Formulation codes	Average Weight (mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	98.22	2.45	0.26	1.59	99
F2	99.42	2.39	0.48	1.43	98
F3	100.88	2.41	0.52	1.48	97
F4	97.33	2.49	0.34	1.57	99
F5	99.86	2.35	0.21	1.65	99
F6	100.14	2.31	0.49	1.42	98
F7	102.28	2.47	0.38	1.68	97
F8	98.47	2.56	0.45	1.52	98
F9	99.38	2.47	0.29	1.49	99

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

In Vitro Drug Release Studies

Table 5: Dissolution Data of Rivastigmine Tablets Prepared With Guar Gum

TIME (hr)	F1	F2	F3
0	**0**	**0**	**0**
0.5	6.38	10.82	15.12
1	15.69	19.65	22.92
2	27.42	28.29	33.58
3	34.88	35.78	40.21
4	41.37	43.33	46.78
5	48.68	47.18	49.99
6	53.78	55.74	57.63
7	59.12	62.43	65.58
8	64.93	67.28	69.14
9	71.51	73.52	76.92
10	75.79	79.92	81.79
11	81.48	83.44	86.54
12	85.62	88.81	89.25

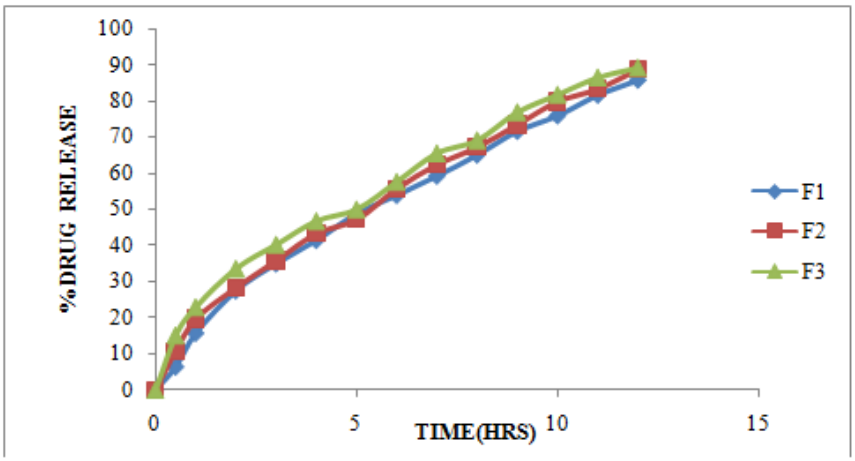

Fig 4: Dissolution profile of Rivastigmine (F1, F2, and F3 formulations).

Table 6: Dissolution Data of Rivastigmine Tablets Prepared With Locust Bean gum

TIME (hr)	F4	F 5	F 6
0	0	0	0
0.5	17.35	19.22	21.11
1	25.04	27.81	29.62
2	36.82	39.64	41.73
3	43.43	46.42	48.58
4	48.23	53.28	56.12
5	52.98	57.72	59.38
6	59.77	64.83	66.92
7	68.62	70.13	73.36
8	73.14	78.84	79.48
9	77.86	82.73	85.63
10	83.49	86.68	89.32
11	88.28	91.18	92.24
12	90.53	94.42	99.82

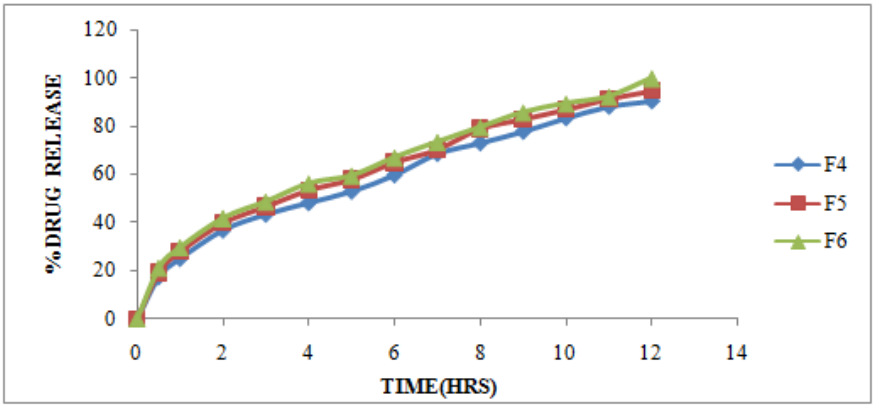

Fig 5: Dissolution profile of Rivastigmine (F4, F5, and F6 formulations)

Table 7: Dissolution Data of Rivastigmine Tablets Prepared With Karaya gum

TIME (hr)	F7	F8	F9
0	0	0	**0**
0.5	16.54	14.46	12.31
1	24.68	21.36	18.07
2	37.17	34.21	31.74
3	42.78	39.96	36.23
4	51.97	47.85	44.14
5	56.43	53.54	51.97
6	62.69	59.98	57.34
7	67.53	64.72	61.96
8	71.74	66.68	63.77
9	79.95	76.28	72.42
10	84.64	81.84	79.82
11	89.33	84.22	81.44
12	95.18	92.71	89.62

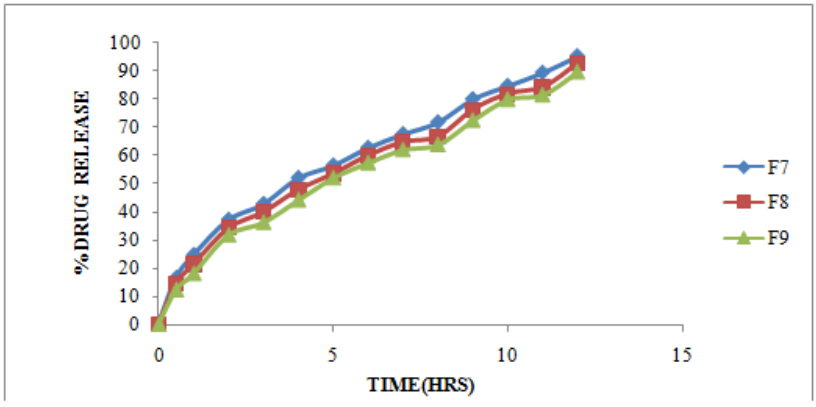

Fig 6: Dissolution profile of Rivastigmine (F7, F8 and F9 formulations)

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: Release kinetics optimised formulation data

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	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
21.11	0.5	0.707	1.324	-0.301	1.897	42.220	0.0474	-0.676	78.89	4.642	4.289	0.353
29.62	1	1.000	1.472	0.000	1.847	29.620	0.0338	-0.528	70.38	4.642	4.129	0.513
41.73	2	1.414	1.620	0.301	1.765	20.865	0.0240	-0.380	58.27	4.642	3.877	0.765
48.58	3	1.732	1.686	0.477	1.711	16.193	0.0206	-0.314	51.42	4.642	3.719	0.923
56.12	4	2.000	1.749	0.602	1.642	14.030	0.0178	-0.251	43.88	4.642	3.527	1.114
59.38	5	2.236	1.774	0.699	1.609	11.876	0.0168	-0.226	40.62	4.642	3.438	1.204
66.92	6	2.449	1.826	0.778	1.520	11.153	0.0149	-0.174	33.08	4.642	3.210	1.431
73.36	7	2.646	1.865	0.845	1.426	10.480	0.0136	-0.135	26.64	4.642	2.987	1.655
79.48	8	2.828	1.900	0.903	1.312	9.935	0.0126	-0.100	20.52	4.642	2.738	1.904
85.63	9	3.000	1.933	0.954	1.157	9.514	0.0117	-0.067	14.37	4.642	2.431	2.210
89.32	10	3.162	1.951	1.000	1.029	8.932	0.0112	-0.049	10.68	4.642	2.202	2.439
92.24	11	3.317	1.965	1.041	0.890	8.385	0.0108	-0.035	7.76	4.642	1.980	2.662
99.82	12	3.464	1.999	1.079	-0.745	8.318	0.0100	-0.001	0.18	4.642	0.565	4.077

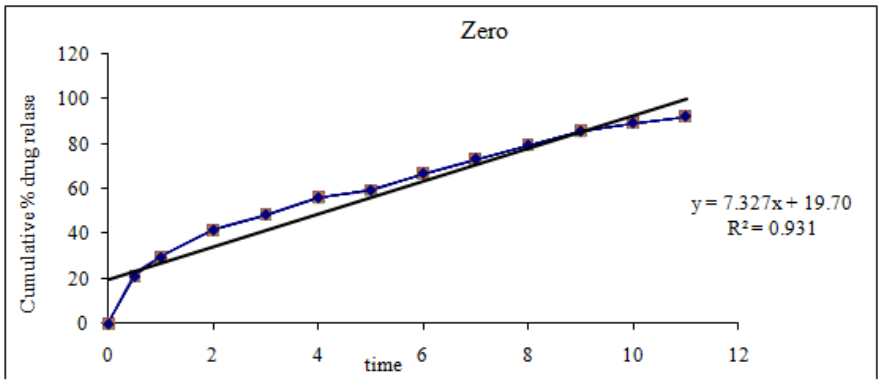

Fig 7 : Zero order release kinetics graph

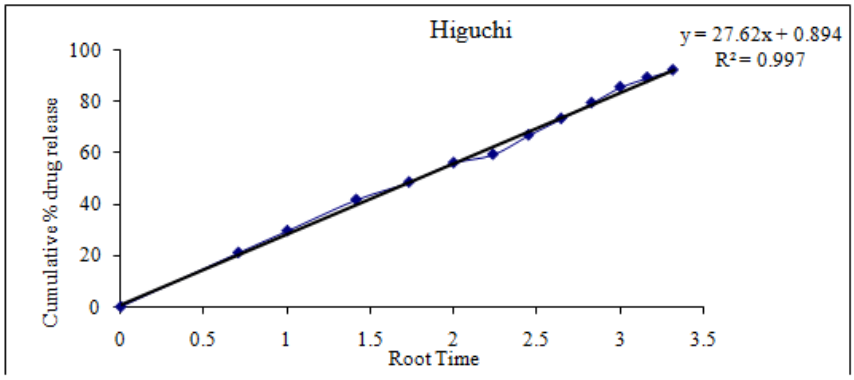

Fig 8 : Higuchi release kinetics graph

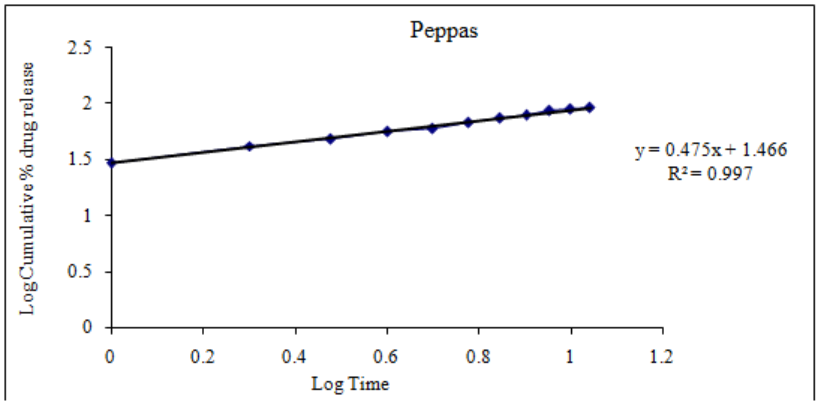

Fig 9: Kars mayer peppas graph

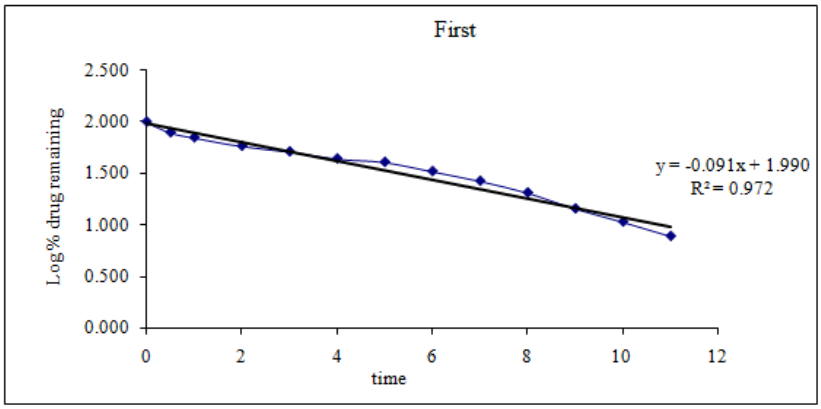

Fig 10: First order release kinetics graph

From the above graphs it was evident that the formulation F6was followed peppas order release kinetics.

Drug – Excipient compatability studies

Fourier Transform-Infrared Spectroscopy

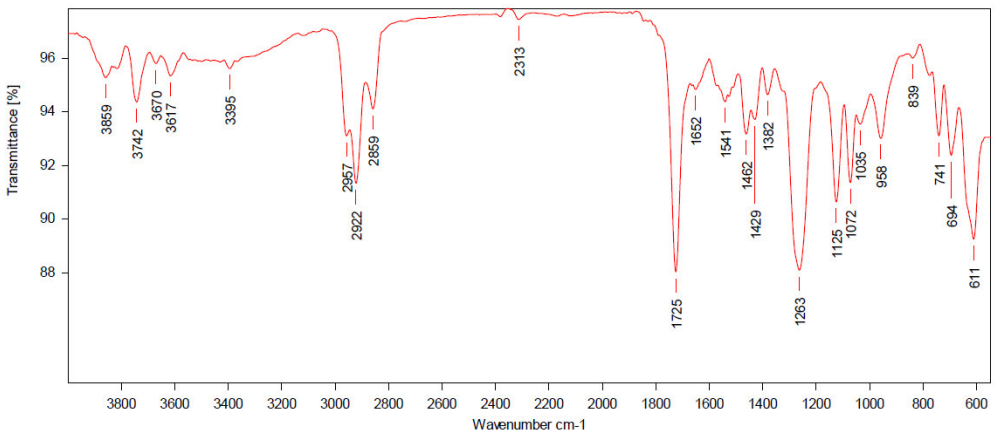

Figure 11: FT-IR Spectrum of Rivastigmine pure drug

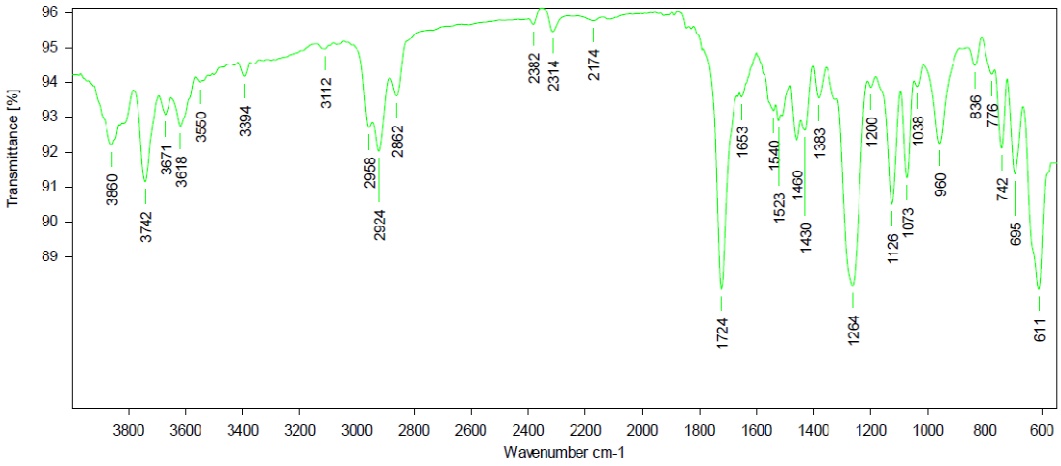

Figure 12 : FT-IR Spectrum of Optimised Formulation

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

CONCLUSION

The aim of the present study was to formulate and evaluate the control release tablets of Rivastigmine by using natural polymers to achieve prolong therapeutic effect by continuously release the medication over an extended period of time after administration of single dose. The dosage regimen is an important element in accomplishing this goal. A fixed dose of 5mg of Rivastigmine was used in the formulation. Various formulations like Guar Gum, Locust Bean gum and Karaya gum were used as release retardants to study the effect on drug release. The total weight of the tablet was 100mg. All the formulations F1-F9 passed the evaluation parameters and were found to be in limits. Among all the formulations. F6 showed the drug release of 99.82% in 12hrs and was selected as the ideal formulation

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