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Formulation development & characterization for rivastigmine controlled release tablets

B. Sujatha, Mohammed Omar*, Ramya Sri. S

Department of Pharmaceutics, Arya College of Pharmacy, Sangareddy, Telangana, India.
SuraPharma Labs, Dilsukhnagar, Hyderabad, Telangana-500060, India.

Address of Correspondence: Mohammed Omar

ABSTRACT

In this study an attempt was made to formulate and evaluate controlled release matrix tablets of Rivastigmine using Ethyl cellulose, HEC 2M and HPC 2M as the retardant polymer. Tablets were prepared by direct compression technique. Tablets were evaluated for parameters such as weight variation, hardness, friability and drug content. All the formulations showed compliance with pharmacopoeial standards. *In vitro* release studies were performed using USP type II apparatus (paddle method) in 900 mL of 0.1N HCl at 50 rpm for 2 hours and remaining 10 hours 6.8 Phosphate Buffer. The release kinetics was analyzed using the zero-order, first order, Higuchi, and Korsmeyer-Peppas equations to explore and explain the mechanism of drug release from the matrix tablets. *In vitro* release studies revealed that percent drug release increased with increase of polymer loading. Based on the dissolution data F-6 formulation (HEC 2M) was selected as the best formulation. The drug release profile of the best formulation was well controlled and uniform throughout the dissolution studies.

Keywords: Rivastigmine, Ethyl cellulose, HEC 2M and HPC 2M and controlled release tablets.

INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, convenient and safe due to its ease of administration, patient acceptance, and cost effective manufacturing process. Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption.[1,2,3]

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 locally to specified target organ. Greater attention is paid on development of oral controlled release drug delivery systems due to flexibility in designing of dosage form. The main challenges to oral drug delivery systems are to deliver a drug at therapeutically effective rate to desirable site, modulation of GI transit time and minimization of first pass elimination. Control release dosage form provides better maintenance of optimal and effective drug level for prolonged duration with less dosing frequency and side effects.[4,5]

Historically, oral drug administration has been the predominant route for drug delivery. It is known to be the most popular route of drug administration due to the fact the gastrointestinal physiology offers more flexibility in dosage form design than most other routes. A major challenge for the pharmaceutical industry in drug development is to produce safe and efficient drugs, therefore properties of drugs and the way in which they are delivered must be optimised.

A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time The goal of such systems is to provide desirable delivery profiles that can achieve therapeutic plasma levels. Drug release is dependent on polymer properties, thus the application of these properties can produce well characterised and reproducible dosage forms.[6]

The basic rationale of a controlled release drug delivery system is to optimize the biopharmaceutics, pharmacokinetics, and pharmacodynamics properties of a

drug in such a way that its utility is maximized through reduction in side effects and cure or control of disease condition in the shortest possible time by using smallest quantity of drug, administered by most suitable route. The immediate release drug delivery system lacks some features like dose maintenance, controlled release rate and site targeting. An ideal drug delivery system should deliver the drug at a rate dictated by the need of body over a specified period of treatment.

MATERIALS AND METHODS

Rivastigmine Provided by SURA LABS, Dilsukhnagar, Hyderabad. Ethyl cellulose from Research Lab Fine Chem Industries, Mumbai. HEC 2M from Research Lab Fine Chem Industries, Mumbai. HPC 2M from Research Lab Fine Chem Industries, Mumbai. PVP K30 from Shakti Chemicals, Mehsana, India. Magnesium Stearate from Merck Specialities Pvt Ltd, Mumbai, India. Lactose from S. D. Fine Chemicals Ltd., Mumbai, India. Aerosil from S. D. Fine Chemicals Ltd., Mumbai, India.

METHODOLOGY

Analytical method development

Determination of absorption maxima

100mg of Rivastigmine pure drug was dissolved in 100ml of Methanol (stock solution) 10ml of above solution was taken and make up with100ml by using 0.1 N HCL (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml) and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400nm.

Preparation calibration curve

100mg of Rivastigmine pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCL (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 2, 4, 6, 8 and 10 µg/ml of Rivastigmine per ml of solution. The absorbance of the above dilutions was measured at 220 nm by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Formulation development of Tablets

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Rivastigmine. Total weight of the tablet was considered as 60 mg.

Procedure

1) Rivastigmine 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 1: Formulation composition for tablets

INGREDIENTS	FORMULATION CHART								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rivastigmine	3	3	3	3	3	3	3	3	3
Ethyl cellulose	5	10	15	-	-	-	-	-	-
HEC 2M	-	-	-	5	10	15	-	-	-
HPC 2M	-	-	-	-	-	-	5	10	15
PVP K30	5	5	5	5	5	5	5	5	5
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Lactose	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Aerosil	3	3	3	3	3	3	3	3	3
Total weight	70	70	70	70	70	70	70	70	70

All the quantities were in mg; Total Tablet Weight = 60 mg

Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the

individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Table 2: Pharmacopoeial specifications for tablet weight variation

Average weight of tablet (mg) (I.P)	Average weight of tablet (mg) (U.S.P)	Maximum percentage difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = [(W1-W2) / W] × 100

Where, W1 = Initial weight of three tablets
W2 = Weight of the three tablets after testing

Determination of drug content

Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of drug were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with media. The solution was suitably diluted and the absorption was determined by UV – Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

In vitro drug release studies Dissolution parameters

Apparatus -- USP-II, Paddle Method
Dissolution Medium -- 0.1 N HCL, pH 6.8 Phosphate buffer
RPM --50
Sampling intervals (hrs) -- 0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature -- 37°c $\pm$ 0.5°c

Procedure

900 ml 0f 0.1 HCL was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°C $\pm$ 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCL were removed and pH 6.8 phosphate buffer was added process was continued from up to 12 hrs at 50 rpm. At definite time intervals withdrawn 5 ml of sample, filtered and again 5ml media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at 220 and 225 nm using UV-spectrophotometer.

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 400 cm^{-1}.

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 225 nm respectively.

Preformulation parameters of powder blend

Table 3: Pre-formulation parameters of Core blend

Formulations	Bulk Density (gm/cm^2)	Tap Density (gm/cm^2)	Carr's Index (%)	Hausner ratio	Angle Of Repose (Ɵ)
F1	0.532	0.657	19.45	1.17	25.8^0
F2	0.476	0.594	25.22	1.24	27.5^0
F3	0.456	0.633	27.51	1.38	29.5^0
F4	0.488	0.685	24.84	1.40	29.7^0
F5	0.461	0.661	27.75	1.43	29.9^0
F6	0.588	0.720	22.24	1.22	26.8^0
F7	0.567	0.705	18.33	1.24	27.3^0
F8	0.543	0.711	17.13	1.30	28.4^0
F9	0.477	0.660	23.52	1.38	29.6^0

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 0.456 to 0.588 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.594 to 0.720 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between "13.7 to 27.7" which show that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 1.17 to 1.40 indicating the powder has good flow properties.

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	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	69.25	3.6	0.71	2.10	98.48
F2	70.10	3.9	0.53	2.61	99.32
F3	68.37	4.0	0.34	1.98	96.74
F4	69.65	4.1	0.43	2.14	97.43
F5	65.82	3.5	0.31	2.88	99.25
F6	70.23	4.3	0.29	1.86	98.41
F7	68.79	3.7	0.50	2.34	99.69
F8	69.28	4.6	0.34	1.87	98.43
F9	69.57	3.2	0.30	1.97	99.24

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

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	16.58	10.28	14.87	8.23	10.92	08.86	11.81	7.53	6.19
1	20.17	16.81	20.15	11.35	18.65	17.23	18.27	15.63	15.91
2	25.98	21.96	26.10	23.78	24.34	28.82	26.33	19.95	20.16
3	32.14	27.55	32.64	38.96	30.11	31.61	33.46	30.36	28.97
4	40.81	34.10	40.72	42.53	35.82	36.28	38.97	37.13	35.43
5	45.16	46.29	46.25	59.29	41.37	48.13	45.73	41.82	41.81
6	57.27	51.91	51.39	62.41	49.20	53.29	51.21	47.51	46.78
7	62.70	57.83	56.21	67.50	55.73	57.62	57.34	51.68	53.45
8	69.32	62.91	60.98	71.24	62.90	65.81	64.76	58.25	56.22
9	73.98	67.30	68.75	78.36	66.35	69.72	72.62	63.36	62.71

10	76.25	75.14	72.96	89.91	73.12	78.96	79.07	69.51	67.68
11	80.11	83.22	86.21	96.76	80.98	83.70	83.77	78.95	71.39
12	85.74	91.73	97.89		86.25	98.92	90.19	85.26	78.17

From the dissolution data it was evident that the formulations prepared with Ethyl cellulose polymer (high concentrations) were able to retard the drug release up to desired time period i.e., 12 hours.

The Formulation Containing HEC 2M in 15mg Concentration Showed good retarding nature with required drug release in 12 hours i.e., 98.92 %.

Whereas the formulations prepared with HPC 2M were retarded the drug release in the concentration of 5 mg (F7 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 90.19 % in 12 hours with good retardation.

From the above results it was evident that the formulation F6 is best formulation with desired drug release pattern extended up to 12 hours.

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 ss.

Table 6: Release kinetics data for optimised formulation

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
8.86	0.5	0.707	0.947	-0.301	1.960	17.720	0.1129	-1.053	91.14	4.642	4.500	0.141
17.23	1	1.000	1.236	0.000	1.918	17.230	0.0580	-0.764	82.77	4.642	4.358	0.284
28.82	2	1.414	1.460	0.301	1.852	14.410	0.0347	-0.540	71.18	4.642	4.144	0.497
31.61	3	1.732	1.500	0.477	1.835	10.537	0.0316	-0.500	68.39	4.642	4.089	0.552
36.28	4	2.000	1.560	0.602	1.804	9.070	0.0276	-0.440	63.72	4.642	3.994	0.647
48.13	5	2.236	1.682	0.699	1.715	9.626	0.0208	-0.318	51.87	4.642	3.729	0.912
53.29	6	2.449	1.727	0.778	1.669	8.882	0.0188	-0.273	46.71	4.642	3.601	1.040
57.62	7	2.646	1.761	0.845	1.627	8.231	0.0174	-0.239	42.38	4.642	3.486	1.155
65.81	8	2.828	1.818	0.903	1.534	8.226	0.0152	-0.182	34.19	4.642	3.246	1.396
69.72	9	3.000	1.843	0.954	1.481	7.747	0.0143	-0.157	30.28	4.642	3.117	1.525
78.96	10	3.162	1.897	1.000	1.323	7.896	0.0127	-0.103	21.04	4.642	2.761	1.881
83.7	11	3.317	1.923	1.041	1.212	7.609	0.0119	-0.077	16.3	4.642	2.535	2.106
98.92	12	3.464	1.995	1.079	0.033	8.243	0.0101	-0.005	1.08	4.642	1.026	3.616

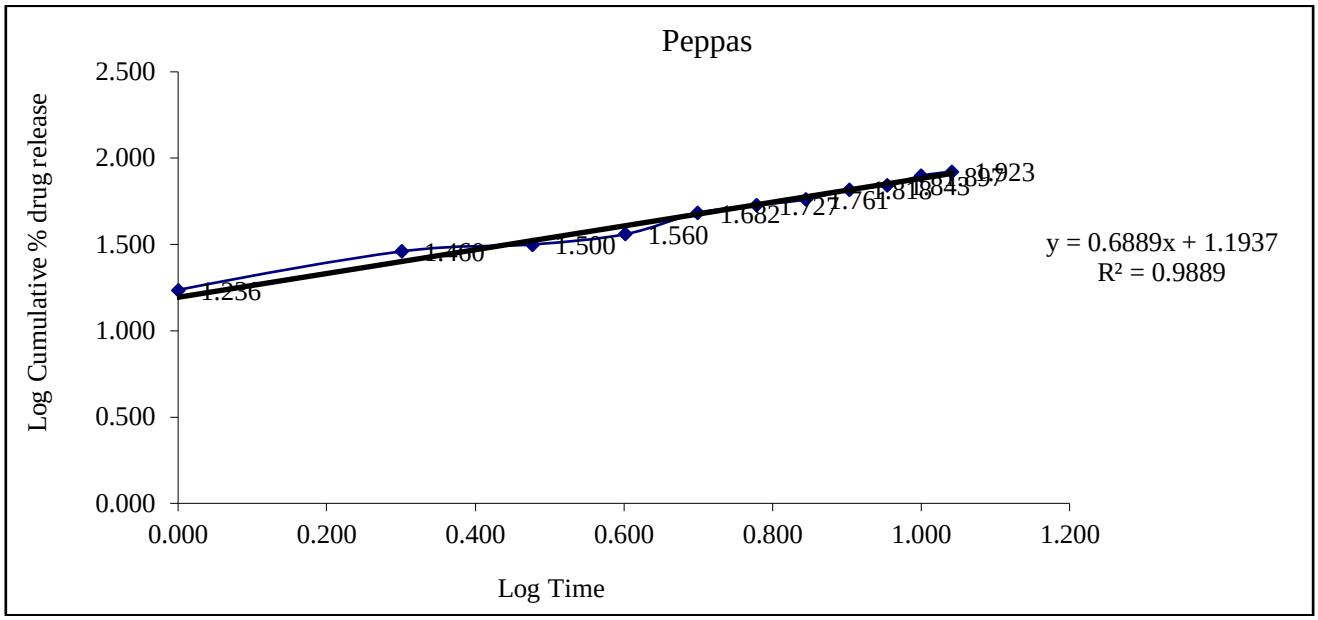

Fig 1: Kars mayer peppas graph

From the above graphs it was evident that the formulation F6 was followed Peppas release kinetics.

Drug – Excipient Compatability studies

Fourier Transform-Infrared Spectroscopy

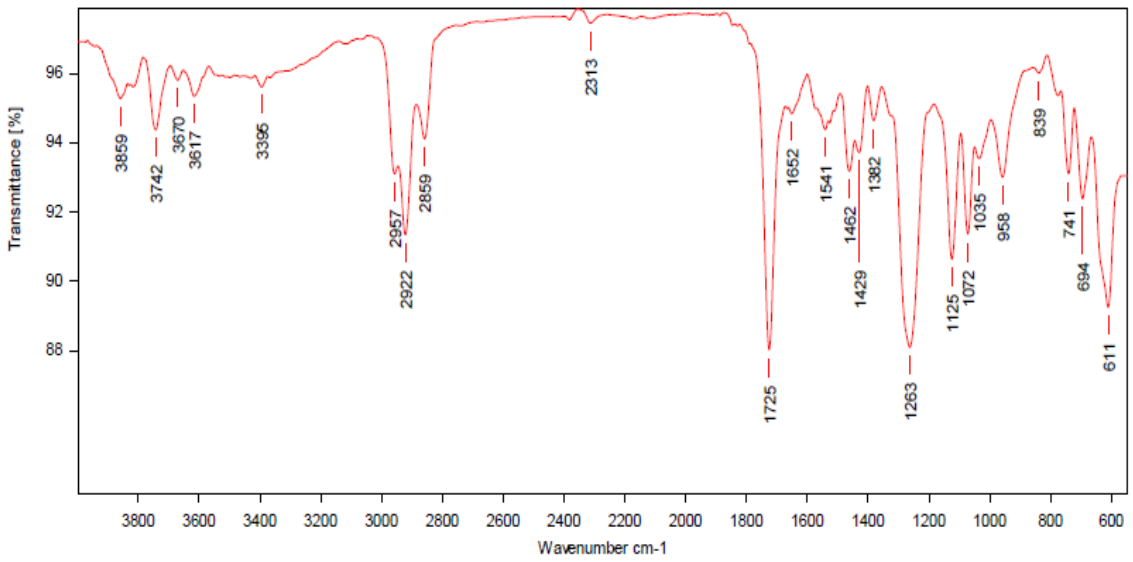

Fig 2: FT-IR Spectrum of Rivastigmine pure drug

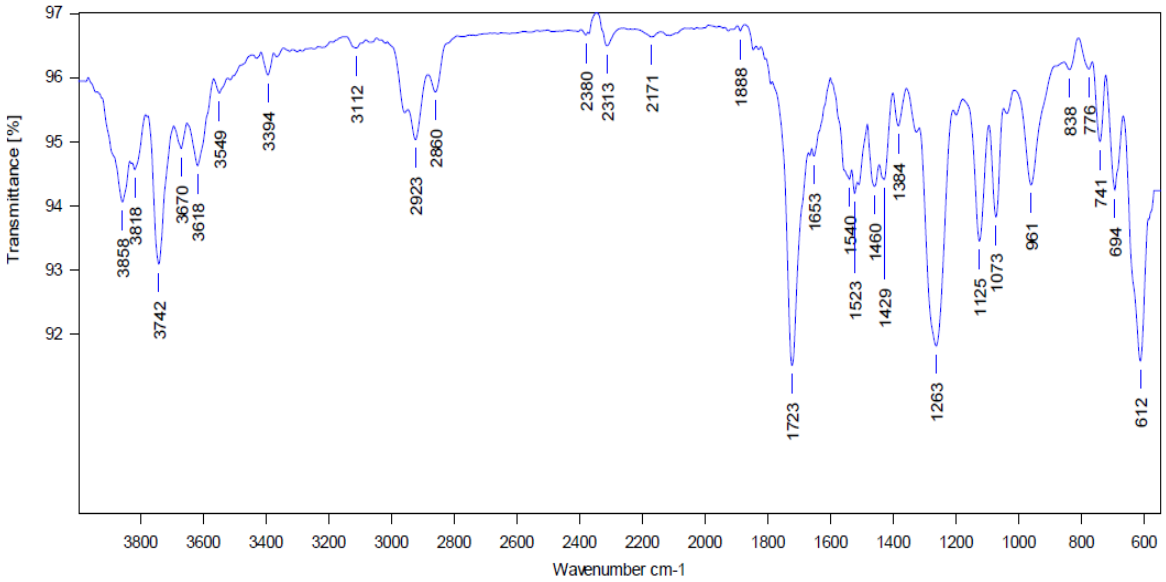

Fig 3: FT-IR Spectrum of Optimised Formulation

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

CONCLUSION

The present study was undertaken with an aim to formulate and evaluate Controlled-release matrix tablets of Rivastigmine by using different types of polymers. Compatibility study revealed that there was no interaction between the drug and the excipients in the formulation. The pre-compression and the post compression parameters are found to be within the limits. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. It can be concluded that the present study indicates that the sustained release tablets of Rivastigmine provides a better option for therapy of the several formulations investigated. Among 9 formulations, F-6 is optimized based on the cumulative % drug release is 98.92 % in 12 hours. The *in vitro* drug release data was plotted for various kinetic models. The R^2 value for optimized formulation F6 for Korsmeyer-Peppas release model was found to be 0.988.

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