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Formulation and Evalution of Rivastigmine Oral Controlled Release Tablets

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A B S T R A C T

Immediate-release products result in relatively rapid drug absorption and onset of accompanying pharmaco-dynamics effects. After absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Hence greater attention is being paid on development of oral controlled release drug delivery systems. In the present study controlled release matrix tablets of Rivastigmine was formulated using different concentration of rate releasing polymers i.e. Kollidon-SR, HPMC K15M and HPMC K4M for extending the drug release up to 12 hrs. All the prepared formulations (F1-F10) were evaluated for the different physico chemical properties, which showed better results. Among all the formulations (F1-F10), it was observed that F-10 showed better dissolution profile with 94.32% drug release and followed Hixon-Crowel kinetics. Hence drug release was found to be dissolution controlled and directly proportional to cube root of time.

Keywords: Controlled drug release, Rivastigmine, Hydroxy propyl methyl cellulose (HPMC), Patient Compliance etc

A R T I C L E I N F O

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1. Introduction

Controlled release dosage form is a dosage form that releases one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ [1- 3]. Controlled release

dosage forms provide better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. [3,4] Rivastigmine tartrate is a cholinesterase inhibitor which is used to treat mild to moderate Dementia (Alzheimer's disease). In Alzheimer's disease lower levels of ACH (acetyl cholinesterase) leads to impaired memory (dementia) and learning. Thus Rivastigmine tartrate is used in the treatment of mild to moderate dementia of Alzheimer's disease. [5]

Rivastigmine tartrate has a half life of 1.5 Hrs, so in the present research work an attempt was made to formulate oral controlled release dosage form by using various polymers like Kollidon-SR, HPMC K15M and HPMC K4M to extend the drug release and to improve patient compliance by decreasing the dosage frequency.

2. Materials and Methods

Materials:

Rivastigmine Hydrogen Tartrate was obtained from Novartis, Bangalore. HPMC K4M, HPMC K15M was obtained from Apex Pharmaceuticals Chennai. Kollidon-SR form BASF Group. Magnesium stearate from Vasa pharma chem. P.Ltd, Ahmadabad. Talc, PVP K30 was procured from Colorcon, Ahmedabad. All the other chemicals used were of analytical grade.

Methods:

Pre formulation studies: [6]

It is "an investigation of physical and chemical properties of a drug substance alone and when combined with excipients".

Color, odor, taste and appearance:

The color, odor and taste of the drug were recorded using descriptive terminology.

Melting point determination:

Melting point of the drug sample was determined by capillary method by using melting point apparatus. The reported and observed melting point is shown in Table.

Determination of solubility:

The solubility of the Rivastigmine was determined by adding excess amount of drug in the solvent and equilibrium solubility was determined by taking supernatant and analyzing it on Lab India, double beam spectrophotometer.

% solubility = sample absorbance /standard absorbance × dilution factor ×100

Drug–Excipient compatibility studies: Compatibility studies conducted to investigate and predict physico chemical interaction between drug substance and excipients and therefore to select suitability of chemically compatible excipients. Compatibility studies were performed by preparing compatibility blends at different ratios of different excipients with drug based on tentative average weight. Together the mixture placed in two vials. One set of vials were stored at 2-8 ^{0}C as control. The set was stored at 40^{0}C/75% RH. The caps of the vials which were kept at 40^{0}C/75% RH were punctured for the permeation of moisture. The vials observed after every week and compared with vials kept at 2-8^{0}C as control for any physical incompatibility like lump formation, color change.

Fourier Transformation Infra-red (FT-IR) analysis:

Rivastigmine hydrogen tartrate discs were prepared by pressing the Rivastigmine with potassium bromide and the spectra between 4000^{-1}cm –500^{-1}cm was obtained under the operational conditions. The absorption maxima in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum represented in Table 4 & Fig 1-6 respectively. Infra-red spectroscopy analysis was performed by Fourier Transformation Infrared Spectrophotometer.

Formulation Development

Ten formulations (F1, F2, F3, F4, F5, F6, F7, F8, F9 & F10) of varying constituents were prepared. Formulation was done by wet granulation followed by direct compression. Drug and polymer (HPMC K4M, HPMCK15M and KOLLIDON-SR combination) pass through 40 # mesh separately and then transfer it to poly bag and mix it for 3 minutes. Binder (PVPK-30) dissolved in isopropyl alcohol which is used as a granulating agent. Above drug-polymer blend is granulated by using binder solution. Add other excipients to the above mixture. Finally add the Glidant (Magnesium Stearate) and Lubricant (Talc) to the above blend mix it for 2 min. Composition is shown in table no-1.

Evaluation Parameters [7]

Angle of Repose (θ):

The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

Angle of repose (θ) = tan-¹ (h/r)

Where, θ = angle of repose, h = height of pile, r = radius of the base of the pile.

Bulk density [8]:

Bulk density is ratio of given mass of powder and its bulk volume. Bulk density was determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduated cylinder or through volume measuring apparatus in to cup.

Bulk density = M / V0

Where, M= mass of the powder, V0=bulk volume of the powder.

Tapped density:

A known quantity of powder was transferred to a graduated cylinder and volume V0 was noted. The cylinder fixed to a density determination apparatus, tapped for 200 times then reading was observed. The density is achieved by mechanically tapped by a measuring cylinder containing the powder sample. After observing the initial volume the cylinder is mechanically tapped and volume reading were taken until little further volume changes is observed.

Tap density = M / $V_{r,}$ Where, M = mass of the powder, V_r = final tapping volume of the powder.

Compressibility index and Hausner ratio:

Basic methods for the determination of compressibility index and Hausner ratio: While there are some variations in the method of determining the compressibility index and Hausner ratio, the basic procedure is to measure the unsettled apparent volume, (V_O), and the final tapped

volume, (V_f), of the powder after tapping the material until no further volume changes occur. The compressibility index and the Hausner ratio are calculated as follows:

Compressibility index = 100 × Vo-V_f/Vo, Hausner ratio = Vo/V_f

Where, V_o = apparent volume, V_f= final tapped volume.

Evaluation of Tablets [9, 10]:

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, Friability, Buoyancy test and in-vitro dissolution characters.

1. Physical Appearance:

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, color, presence or absence of odor, taste etc.

2. Size & Shape:

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or Vernier calipers. Tablet thickness should be controlled within a ± 5% variation of standard value.

3. Weight variation test:

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

4. Content Uniformity: Randomly select 30 tablets. 10 of these assayed individually. The Tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labeled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labeled content. If these conditions are not met, remaining 20 tablets assayed individually and none may fall outside of the 85 to 115% range.

5. Friability: A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked. The percentage friability was determined by the formula

% friability = (W_1-W_2) / W_1 X 100

Where, W_1 = Weight of tablets before test, W_2 = Weight of tablets after test

6. Hardness

The hardness of the tablet was determined by Monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet, and a zero reading is taken. The upper plunger is then forced against a spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded and the zero reading is deducted from it ten tablets from each batch were selected and evaluated, and the average value with standard deviation was recorded.

7. Swelling Study [11]:

The floating tablets were weighed individually (designated as W_0) and placed separately in glass beaker containing 200 ml of 0.1 N HCl and incubated at 37°C±1°C. At regular 1-h time intervals until 24 h, the floating tablets were removed from beaker, and the excess surface liquid was removed carefully using the tissue paper. The swollen floating tablets were then re-weighed (Wt), and % swelling index (SI) was calculated using the following formula.

SI (%) = (Wt – W_0/ W_0) x 100

Where, W_t – weight of tablets at time't', W_0 – weight of tablets at time '0'

9. Drug release

The drug release from the Rivastigmine tablets was investigated in a USP-II (paddle) apparatus, 900 ml of 0.1N KH_2PO_4 (50 rpm, 37°C). At predetermined time intervals, 5-ml samples were withdrawn and take 1ml sample and diluted to 10 ml and then analyzed with UV spectrophotometry at λ_{max}=220 nm.

10. Characterization of Rivastigmine hydrogen tartrate Tablets

Fourier Transform Infrared Spectroscopy (FT-IR)

The samples of pure Rivastigmine and HPMC K15M, Kollidon-SR, HPMC K4M, Rivastigmine+HPMC K15M, Kollidon-SR, HPMC K4M & all physical mixtures with Rivastigmine ewere prepared in the form of KBr pellets and subjected for scanning from 4000 cm^{-1} to 400 cm^{1} using FT-IR spectrophotometer.

11. Kinetic Analysis of i*n-Vitro* Release Rates of Floating Tablets of Rivastigmine [12,13]: The results of *in vitro* release profile obtained for all the formulations were plotted in modes of different data treatment like, Zero order kinetic model – Cumulative % drug released versus T, First order kinetic model – Log cumulative percent drug remaining versus T, Higuchi's model – Cumulative percent drug released versus square root of T, Korsmeyer equation / Peppa's model – Log cumulative percent drug released versus log T, Hixoncrowell erosion equation –cube root of percentage drug remaining vs. time

Stability studies [14].

The optimized formulation of Rivastigmine were packed in strips of 0.04 mm thick aluminium foil laminated with poly vinyl chloride by strip packing and these packed formulations were stored in ICH certified stability chambers maintained at 40°C and 75% RH for 1 month (zone III conditions as per ICH Q1 guidelines). The samples were withdrawn periodically and evaluated for their hardness, content uniformity and for in vitro drug release. Selected Formulation was subjected to stability studies as per ICH guidelines.

Following conditions were used for Stability Testing.

a. 25^0C/60% RH analyzed every 15 days for period of one month.
b. 30^0C/75% RH analyzed every 15 days for period of one month.
c. 40^0C/75% RH analyzed every 15 days for period of one month.

3. Results and discussions

Prefoermulation Studies

Physical characteristics:

Table 2: Results of organoleptic properties of drug

S. No	Parameter	Drug
1	Color	White
2	Odor	Odorless
3	Taste	Bitter
4	Appearance	Powder

Melting point determination: Drug: Rivastigmine

Table 3: Results of Melting point of drug

Reported Melting Point	Observed Melting Point
123-125^{0}C	123.68^{0C}

Determination of solubility: The solubility of the Rivastigmine was determined and found to be freely soluble in Water, soluble in Ethanol, methanol & Acetonitrile slightly soluble in Octanol and very slightly soluble in Ethyl- Acetate. Solubility of Rivastigmine in 0.1 N KH_2PO_4 was found to be 0.78 mg/ml at 37°C.

Fourier transformer infrared spectroscopy (FT-IR)

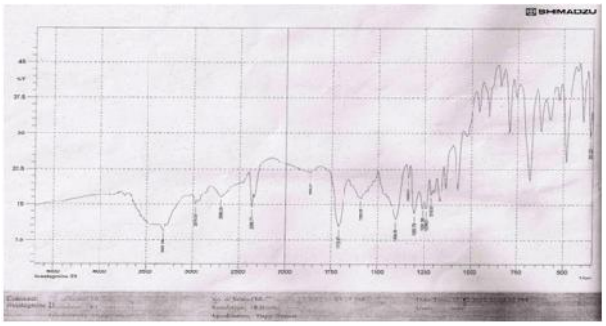

Fig 1: FTIR spectra of pure Rivastigmine hydrogen Tartrate

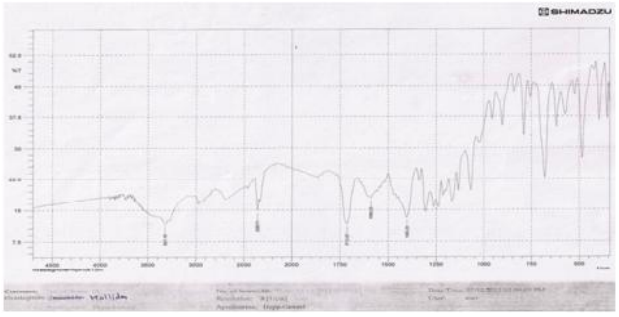

Figure 2: FTIR spectra of Rivastigmine and Kollidon-SR physical mixture

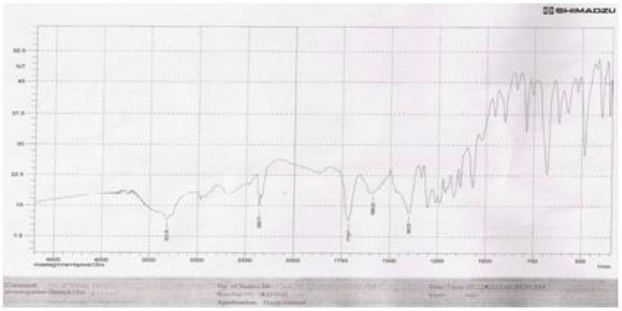

Figure 3: FTIR spectra of Rivastigmine and HPMC K15M physical mixture

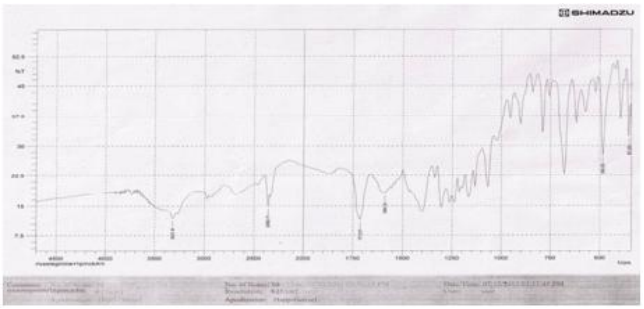

Figure 4: FTIR spectra of Rivastigmine and HPMC K4M physical mixture

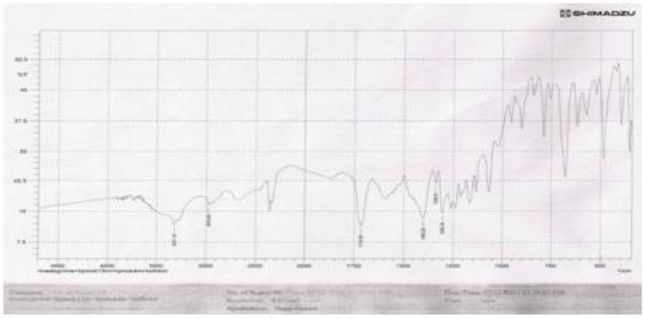

Figure 5: FTIR spectra of Rivastigmine, HPMC K 4M, HPMC K 15M & Kollidon-SR Physical mixture

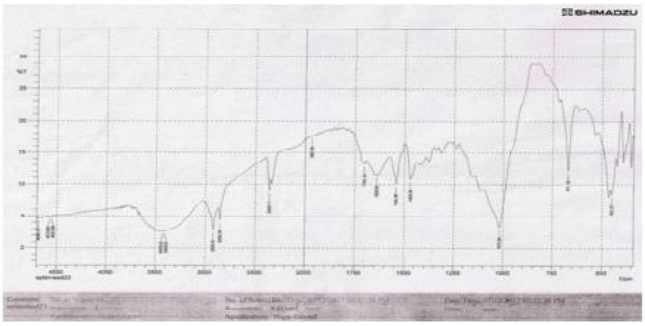

Figure 6: FTIR spectra of Optimized formula physical mixture

Fourier transformer infrared spectroscopy

The FTIR spectra of pure Rivastigmine and HPMC K15M, Kollidon SR, PVP K30 & physical mixtures with Rivastigmine are shown in Fig 24. The IR spectrum of pure drug and physical mixture of drug and polymer of optimized formulation were studied. The characteristic absorption peaks of Rivastigmine were obtained at 3251.76 cm^{-1}, 2854 cm^{-1}, 1694 cm^{-1}, 1651cm^{-1}, 1320 cm^{-1}, 1156cm^{-1}.

The peaks also obtained in the spectrum of each physical-mixtures of the optimized formulation. By correlating Rivastigmine peaks of pure drug spectrum with physical mixtures of the optimized formulation it was found that the drug is compatible with the formulation components. Results are shown in table-4 and Fig 1-6.

Inference:

The overall observation of infrared study suggested that formulation development of drugs in combination with excipients, functionalities of drugs was unreacted and hence contribution of drugs along with excipients can be formulated safely.

Evaluation of pre-compression parameters of Matrix tablets of Rivastigmine: Rivastigmine hydrogen tartrate controlled release Matrix tablets were prepared by Wet granulation followed by direct compression method using 6-8 mm punch, adjusting the hardness between 6-10 kg/cm^2. All the tablets white in color, round, cylindrical with smooth surfaces.

The thickness of all tablets was found to be in the range of 2.51-2.59 mm and hardness was found to be in the range of 6-9 kg/cm^2 in all the formulations, the MCC and HPMC together showed good binding properties. In all the formulations, the %friability was (0.22-0.41) below 1% as per USP. The average weight was found to be 99-101 mg which will be within the given limits. Hence all the tablets were found to show less weight variation. Results are shown in table no 6,7. The drug content of all formulations ranged from 94% to 100%, which is within the specified USP limits. Swelling index was found to range from 146% to 156%, which shows that the formulations swell to a certain degree after coming in contact with the simulated Intestinal P^H 6.8. Also the swelling index of tablets without HPMC K4M, HPMC K15M showed lower % swelling index than that of the tablets with HPMC K4M, HPMC K15M because of the fact that the polymers are are swellable in nature. The results of formulations containing both HPMC K15M and HPMC K4M showed more values of swelling index than that of the ones containing HPMC K15M& HPMC K4M alone because of the fact that the polymers showed good swelling properties in the later periods of time. i.e., these polymers enhancing controlled release of the Matrix Tablets for a period of 12hrs.

The *in- vitro* drug release of tablets has shown a profound effect on the choosing of the type of polymers and their concentrations. Initially, the drug release using Kollidon-SR without HPMC K15M, and HPMC K4M were compared to see how effectively they could retard the drug release. From the %CDR data of all the formulations, the polymer HPMC K15M, HPMC K4M & Kollidon-SR showed desirable drug release. Hence HPMC K15M, HPMC K4M & Kollidon-SR in equal concentrations was chosen to make the final formulae as a retarding polymer. The additional use of Kollidon-SR was taken into account as the hydrophilic polymer (HPMC K15M), although was able to retard the drug release in the initial stage, could not show effective retardation of controlled drug release in the later stage. Hence, in the later stages of dissolution study, the tablets started to release more amount of drug in controlled fashion. The % Cumulative drug release of all the formulations F1-F10 were within the range of 94.32% to 99.89% for 12 hrs. The optimized formulation F10 showed a %drug release of 94.32% for 12 hrs which shows controlled release compare to all other formulation. Results are shown in table no 8,9 and Fig no 7,8.

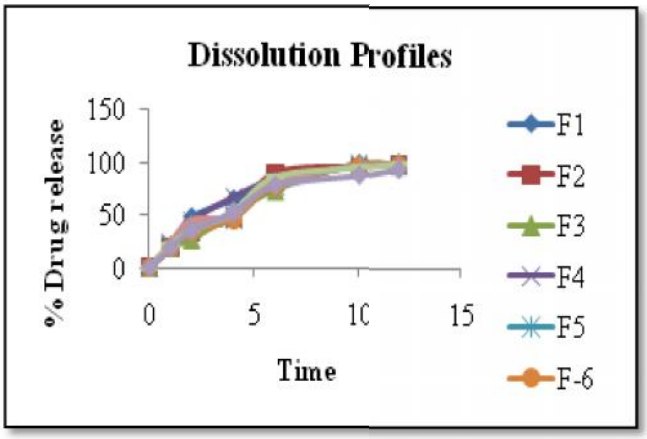

Figure 7: Comparative in- vitro drug release profiles of Rivastigmine Hydrogen Tartrate formulations (F1-F10)

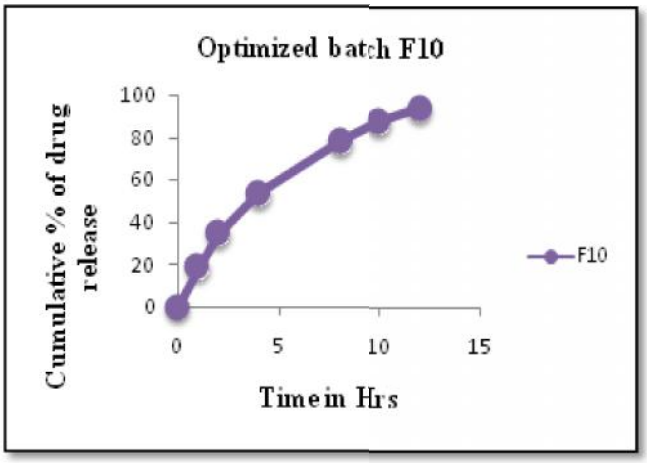

Figure 8: In-Vitro Release Profile of Optimized Batch (F10)

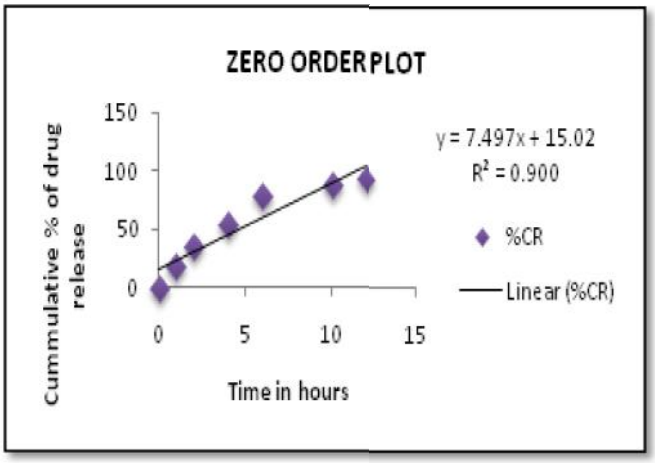

Figure 9: In-vitro release profile of Optimized batch (F10) according to Zero order kinetics

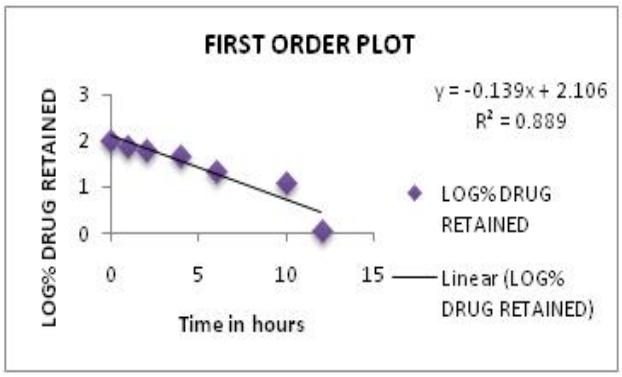

Figure 10: In-vitro release profile of Optimized batch (F10) according to first order kinetics

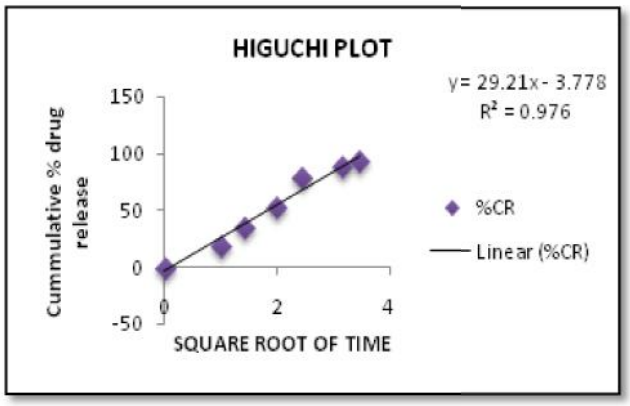

Figure 11: In-vitro release profile of Optimized batch (F10) according to Higuchi kinetics

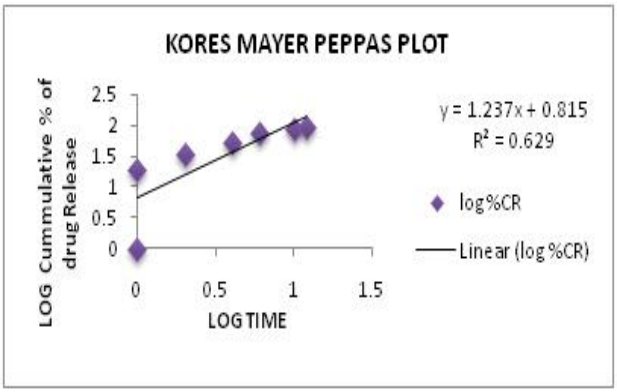

Figure 12: In-vitro release profile of Optimized batch (F10) according to Hixon-Crowell Kinetics

Kinetic Modelling and Mechanism of Drug Release:

The release kinetics of all the dosage forms was calculated using zero-order, first-order, higuchi and kosermeyer-peppas. All the formulations were found to follow zero-order release kinetics. The dissolution data when fitted into Kosermeyer-peppas model, which indicates that the release was governed by diffusion, polymer relaxation, and erosion. When the data was fitted in higuchi model, the formulations showed diffusion type of drug release. The optimized formulation F10 was found to exhibit zero–order which shows that the diffusion along with polymer relaxation and polymer diffusion of drug from the tablet. Different kinetic models were applied for best formulation and n value obtained is 1.237 and R^2 is 0.629 indicating Super Case - II transport. Results are shown in fig no 9-12 and table no-13.

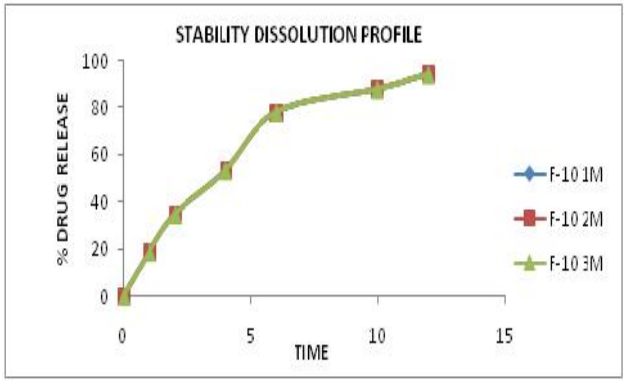

Figure 15: In vitro drug release profile of optimized formulation F10 during stability studies at 40oC and 75% RH for one month

4. Conclusion

Among all the formulations (F1-F10), it was observed that formulation-10 has shown better dissolution profile. So, Formulation-10 was found to be the best formulation among others. The kinetic treatment of the drug release data of the prepared formulations followed zero order drug release; the prepared formulations followed Hixon-Crowel profile. It indicated that drug release was dissolution controlled and directly proportional to cube root of time. Hence *F-10* was considered as formulation extending 94.32% of drug was released at the end of 12 hrs. The stability studies were carried out for period of 3 months as per ICH guidelines and were in acceptable limits.

Table 1: Composition of Rivastigmine Controlled Matrix Tablets

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)
Rivastigmine	3	3	3	3	3	3	3	3	3	**3**
Kollidon-SR	3	6	---	---	---	---	3	1.5	1.5	**2**
HPMC K 4 M	---	---	3	6	---	---	1.5	3	1.5	**2**
HPMC K 15 M	---	---	---	---	3	6	1.5	1.5	3	**2**
Microcrystalline Cellulose	87	84	87	84	87	84	84	84	84	**84**
PVP K-30	3	3	3	3	3	3	3	3	3	**3**
Magnesium Stearate	2	2	2	2	2	2	2	2	2	**2**

Talc	2	2	2	2	2	2	2	2	2	**2**
Iso Propyl Alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	**q.s**
Total wt	100	100	100	100	100	100	100	100	100	**100**

Table 4: Compatibility studies of Rivastigmine hydrogen tartrate with different excipients

API and Excipients	**API: Excipients**	**Initial Observation**	**Final observation**	
			40°C,75%RH	
			2nd week	**4th week**
Rivastigmine (API)+ Kollidon-SR	1 :1	White or almost white crystalline powder	No change in appearance	No change in appearance
API+ Micro Crystalline Cellulose	1 : 1	White colour	No change in appearance	No change in appearance
API +HPMC K4M	1 : 1	White colour	No change in appearance	No change in appearance
API+HPMC K15M	1 : 1	White colour	No change in appearance	No change in appearance
API + PVP K-30	1 : 1	White Colour	No change in appearance	No change in appearance
API + Talc	1 : 0.1	White colour	No change in appearance	No change in appearance
API+Magnesium Stearate	1:0.1	White Colour	No change in appearance	Nochange in appearance

Table 5: Data for pre-compression parameters of tablet formulations (F1-F10)

Formulation code	**Bulk density(g/cc)**	**Tapped density(g/cc)**	**Carr's Index**	**Hausner Ratio**	**Angle of repose(θ)**
F1	1.11	1.26	13.51	1.13	$27^0 55'$
F2	1.12	1.28	14.28	1.14	$29^o 39'$
F3	1.11	1.26	13.51	1.13	$23^o 31'$
F4	1.12	1.28	14.28	1.14	$28^0 81'$
F5	1.09	1.25	14.67	1.14	$28^0 65'$
F6	1.11	1.26	13.51	1.13	$26^0 74'$
F7	1.12	1.28	14.28	1.14	$28^o 39'$
F8	1.11	1.26	13.51	1.13	$21^0 81'$
F9	1.09	1.25	14.67	1.14	$24^0 81'$
F10	1.09	1.25	14.67	1.14	$21^0 51'$

All the formulations were evaluated for bulk density, tapped density, % compressibility, hausner's ratio and angle of repose. The results of % compressibility, hausner's ratio and angle of repose were found to be <15, <1.2 and <30 respectively. These results show that the formulations have very good flow properties. Results are shown in table no-5.

Table 6: Data for post compression parameters of tablet formulations-I (F1-F10)

Formulation Code	**Weight Variation (mg)**	**Thickness (mm)**	**Hardness (kg/cm^2)**	**Friability (%)**
F1	100±0.49	2.52±0.01	7.05±0.93	0.34±0.43
F2	99±0.49	2.59±0.09	8.03±0.59	0.41±0.21
F3	99±0.09	2.56±0.04	7.57±0.66	0.24±0.36
F4	101±0.04	2.51±0.19	8.37±0.48	0.23±0.43
F5	100±0.06	2.56±0.37	7.86±0.42	0.22±0.27
F6	100±0.05	2.59±0.08	6.39±0.49	0.33±0.67
F7	100±0.03	2.58±0.56	7.99±0.66	0.41±0.85
F8	100±0.02	2.51±0.04	8.06±0.84	0.37±0.89
F9	100±0.05	2.52±0.02	8.73±0.68	0.31±0.77
F10	100±0.01	2.53±0.02	8.35±0.68	0.28±0.78

Table 8: *In-Vitro* Dissolution Profile Data of All the Formulations

Time (Hrs)	%Drug Release									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	**0**
1	18.78	18.65	19.98	21.56	21.24	18.57	20.66	23.49	21.89	**18.89**
2	47.94	34.92	26.91	43.68	35.78	34.67	39.73	45.78	34.78	**34.78**
4	64.68	47.93	51.24	66.98	46.48	46.89	49.48	49.48	53.48	**53.48**
6	81.98	89.72	73.97	82.97	78.18	77.89	81.18	83.18	86.18	**78.18**
10	98.59	95.92	98.92	96.15	97.94	97.96	96.94	95.94	94.94	**87.94**
12	99.89	98.83	99.13	98.99	98.56	99.34	99.16	99.36	99.32	**94.32**

Table 9: In-vitro dissolution profile of Optimized batch F10

Time (Hrs)	% Drug Release F10
0	**0**
1	**18.89**
2	**34.78**
4	**53.48**
6	**78.18**
10	**87.94**
12	**94.32**

Table 10: Kinetic values obtained from different plots of formulations (F1-F10)

Formulation code	Zero-order	First-order	Higuchi	kosermeyer-peppas	
	Regression Coefficient (r^2)	Regression Coefficient (r^2)	Regression coefficient (r^2)	Slope (n)	Regression coefficient (r^2)
F1	0.863	0.969	0.971	1.249	0.608
F2	0.883	0.964	0.943	1.272	0.645
F3	0.946	0.928	0.971	1.271	0.657
F4	0.859	0.986	0.973	1.227	0.593
F5	0.928	0.957	0.971	1.235	0.622
F6	0.934	0.958	0.970	1.265	0.648
F7	0.911	0.971	0.973	1.236	0.616
F8	0.887	0.967	0.968	1.199	0.580
F9	0.894	0.967	0.966	1.24	0.617
F10	0.900	0.889	0.976	1.237	0.629

Table 14: In-vitro drug release profile of optimized formulation F10 during stability studies at 40oC and 75% RH for three months.

Time	Stability at 40^0C & 75% RH		
	F-10 1 Month	F10 2 Month	F-10 3 Month
0	0	0	0
1	18.89	18.86	18.79
2	34.78	34.75	34.74
4	53.48	53.47	53.43
6	78.18	78.16	78.14
8	87.94	87.94	87.91
12	94.32	94.32	94.3

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