Available online on 15.11.2014 at http://jddtonline.info
Journal of Drug Delivery and Therapeutics
Open access to Pharmaceutical and Medical research

RESEARCH ARTICLE

DESIGN, OPTIMIZATION, DEVELOPMENT AND EVALUATION OF ONCE A DAY CONTROLLED RELEASE FORMULATION OF RIVASTIGMINE TARTRATE

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ABSTRACT:

Rivastigmine, an Anti-Alzheimer's drug suffer from a major limitation of sever GI adverse events such as nausea, vomiting, diarrhea, loss of appetite, weight loss and increase dosing frequency [1]. The present work aim at design, optimization and development of rivastigmine once a day controlled release formulation to minimize the above limitation and increase patient's compliance. Based on the target in-vitro release profile derived from pharmacokinetic simulation [2], a once a day matrix tablet with the simulated dose was developed. The simple direct compression process was followed as a manufacturing process, the percentage of Polymer HPMC K100M, Polyethylene oxide (Polyox WSR303) and insoluble excipients microcrystalline cellulose used in the formulation were optimized using 2^3 full factorial design. The formulations were then evaluated for the physical characteristics of blend, tablets, swelling index, percentage of erosion, drug release and release rate kinetics. The quadratic model was suggested, contour and 3D graphs were generated. The optimized formulation was subjected to stability studies. The final optimized formulation showed a comparative release profile similar to that the desired in-vitro target release profile, which followed zero order release kinetics and a stable formulation.

Keywords: Controlled Release Formulation, Rivastigmine Tartrate, HPMC K100M, Polyethylene oxide (Polyox WSR303), microcrystalline cellulose

INTRODUCTION

Rivastigmine is indicated for the treatment of mild to moderate dementia associated with Parkinson's diseases. The dementia of Parkinson's disease is purportedly characterized by impairments in executive function, memory retrieval, and attention, in patients with an established diagnosis of Parkinson's disease [3]. Currently, oral solution (2mg/mL base), capsules (12 mg/day) and transdermal dosage form (4.6mg/24h, 9.5mg/24h and 13.3mg/24h) are approved in USA for the symptomatic treatment of mild to moderate AD [3, 4]. Analysis of data from the clinical trial investigation suggested that rivastigmine may also benefit patients even at more advance stages of diseases [5]. Increased dosing frequency of twice a day dosage regimen, GI side effects associated with the large fluctuation in the plasma level limits its usage [6]; hence need for once a day controlled release formulation of rivastigmine which will reduce the larger fluctuation in plasma level and thereby increasing patient's compliance.

MATERIALS AND METHODS:

Materials

Rivastigmine tartrate is obtained from Orchid Healthcare, Hydroxy propylmethylcellulose (HPMC K Methocel 100M) and polyethylene oxide (Polyox WSR303) was obtained from Colorcon Asia Private Limited (India), Microcrystalline cellulose (Avicel PH 112) is received from signet Chemical Corporation Private Limited (Mumbai, India), Colloidal silicon dioxide (Aerosil 200) was purchased from Evonik Industries (Mumbai, India) and Magnesium stearate (vegetable source) was purchased from Ferro corporation (Cleveland, USA).All other chemicals and reagents used were of high analytical grade.

Methods

Manufacturing procedure of CR tablets of Rivastigmine

Based on the simulated dose calculation the required quantity of Rivastigmine tartrate is taken in the unit composition of the controlled release formulation of Rivastigmine tartrate and is represented in the table-1.

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Table 1: Manufacturing Formula

S.No	Ingredients /Specification	Qty/Unit (mg)	Percentage (%)
01	Rivastigmine tartrate USP	17.4$	8.7
02	Anhydrous lactose NF (Supertab 21AN)	#	#
03	Microcrystalline cellulose NF (Avicel PH112)	27.5 – 47.5	13.75 – 23.75
04	Hydroxy propylmethylcellulose USP (Methocel K100M)	60 – 100	30 – 50
05	Polyethylene oxide NF (Polyox WSR 303)	20 – 28	10 – 14
06	Colloidal silicon dioxide NF (Aerosil 200M)	2.0	1
07	Magnesium Stearate NF (Vegetable source)	1.5	0.75
	Total (mg)	200	

$ - Qty of rivastigmine tartrate equivalent to rivastigmine 10.9 mg
# - Qty of anhydrous lactose to be adjusted based on the potency of rivastigmine tartrate and in-order to maintain the constant average weight.

The controlled release matrix tablets of rivastigmine were prepared by a simple direct compression process.

Step: 1 Rivastigmine, Polyethylene oxide (WSR 303) and microcrystalline cellulose (Avicel PH 112) are weighed accurately and sifted together through #30 ASTM sieve.

Step: 2 Hydroxypropyl methylcellulose (HPMC, Methocel K100M)) and lactose anhydrous (Supertab 21 AN) are weighed accurately and sifted together through #30 ASTM sieve mesh.

Step: 3 The material of Step 1 and Step 2 are blended in a double cone blender for 20 minutes.

Step: 4 The weight quantity of colloidal silicon dioxide (Aerosil 200) and magnesium stearate are sifted together through # 60 mesh.

Step: 5 The material of step 3 is lubricated with step 4 material by blending for 10 minutes in a double cone blender.

Step: 6 The above step 5 material is compressed into tablets using 8.1 mm circular flat faced beveled edge tooling.

Optimization of quantity of Polymers Hypromellose (HPMC), polyethylene oxide (PEO) and insoluble filler microcrystalline cellulose using 2^3 full factorial design:

A 2^3 full factorial design was selected to optimize three variables viz., rate controlling polymer Hypromellose (HPMC), matrix forming polymer polyethylene oxide (PEO) and an insoluble filler microcrystalline cellulose (Avicel PH112). In these 2^3 full factorial design each variables were evaluated at 2 levels and experimental trails were conducted for all possible 8 combinations and a triplicate centre point run was also executed to determine the signal to noise ratio. The response was analyzed for ANOVA using Design Expert, Stat-Ease, Inc, version 9.0.1.0. A mathematical equation was generated for each response parameter. The mathematical models were tested for significance. Response surface plots were generated for response to study the behavior of the system. The 2^3 full factorial design for factorial batches are presented in the Table -2

Table 2: 2^3 full factorial design for factorial batches:

Run Order	Formulation code	Variable in coded form			Factor 1	Factor 2	Factor 3
		Factor 1	Factor 2	Factor 3	A Hypermellose (mg)	B Polyethylene oxide (mg)	C Microcrystalline cellulose (mg)
1	RIV-CR/001	+1	+1	+1	100	28	47.5
2	RIV-CR/002	-1	-1	-1	60	20	27.5
3	RIV-CR/003	0	0	0	80	24	37.5
4	RIV-CR/004	-1	+1	-1	60	28	27.5
5	RIV-CR/005	0	0	0	80	24	37.5
6	RIV-CR/006	+1	+1	-1	100	28	27.5
7	RIV-CR/007	-1	+1	+1	60	28	47.5
8	RIV-CR/008	0	0	0	80	24	37.5
9	RIV-CR/009	+1	-1	+1	100	20	47.5
10	RIV-CR/010	-1	-1	+1	60	20	47.5
11	RIV-CR/011	+1	-1	-1	100	20	27.5

Determination of Physical characteristic of Blend:

The interparticulate interactions that influence the bulking properties of a powder are also the interactions that interfere with powder flow, a comparison of the bulk and tapped densities can give a measure of the relative importance of these interactions in a given powder. Such

a comparison is often used as an index of the ability of the powder to flow [7].

Bulk density and Tap density:

Bulk density is determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder (*Method I*). An accurately weighed (M) quantity of powder is poured into the graduate measuring cylinder and carefully the powder is leveled without compacting. The unsettled apparent volume (V_o) to the nearest graduated unit is measured. The bulk density is expressed in g per mL (Eq.1) and is measured in replicate.

$$Bulk\ Density = \frac{Mass\ (M)}{Volume\ (Vo)} \text{ (Eq.1)}$$

Tap density is determined by mechanically tapping the cylinder containing powder sample. After observing the initial volume (V_o), the cylinder is mechanically tapped using Electrolab tap density apparatus (ETD-1020, Electrolab India) and the volume reading are taken until little further volume changed is observed. (i.e) final tapped volume (V_f). The tap density is expressed in g per mL (Eq.2) and is measured in replicate.

$$Tap\ Density = \frac{Mass\ (M)}{Volume\ (Vf)} \text{ (Eq.2)}$$

Measure of Powder Compressibility:

The *Compressibility Index* and *Hausner Ratio* are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the *Compressibility Index* and the *Hausner's Ratio* represented by the equation 3 and 4 respectively.

$$Compressibilty\ Index = \frac{100\ (Vo - Vf)}{Vo} \text{ (Eq.3)}$$

$$Hausner's\ Ratio = \frac{Vo}{Vf} \text{ (Eq.4)}$$

The compressibility index (Carr's Index) values are represented in the scale of flowability table 3

Table 3: Scale of flowability

Flow Characteristics	Compressibility Index (%)	Hausner's ratio
Excellent	≤ 10	1.00 – 1.11
Good	11 – 15	1.12 – 1.18
Fair	16 – 20	1.19 – 1.25
Passable	21 – 25	1.26 – 1.34
Poor	26 – 31	1.35 – 1.45
Very poor	32 – 37	1.46– 1.59
Very, very poor	> 38	> 1.60

Evaluation of Controlled Release Matrix Tablets of Rivastigmine tartrate [8, 9]:

Weight Variation: The representative twenty tablets samples from each formulation trails were weight using balance (MIRAS, Sartorius Mechatronics India, Pvt ltd). The average weight and standard deviation are calculated and are represented in the table-4.

Thickness: The representative ten tablets samples from each formulation trails were measured using (VK200, Varian Inc, Cary, NC, USA). The average thickness and standard deviation are calculated and are represented in the table-4.

Hardness: The representative ten tablets samples from each formulation trails were measured using (VK200, Varian Inc, Cary, NC, USA). The average hardness and standard deviation are calculated and are represented in the table-4.

Friability Test: The whole tablets corresponding as near as possible to 6.5 g were taken from each formulation trails and are dedusted prior to testing. Accurately weighed tablets are placed in the drum of friabilator (EF-2, Electrolab, Mumbai, India) and the apparatus is operated at 25 rpm for 4 minutes (i.e., 100 revolutions). The tablets were then dedusted and reweighed. The friability is calculated as a percentage weight loss and is represented by the equation (Eq 5). The friability observed is represented in the table -4.

$$Friability\ (\%\ w/w) = \frac{W1-W2}{W1} x100\ \ (Eq.5)$$

Whereas,

W_1 – Weight of Initial tablets

W_2 – Weight of final tablets after 100 revolution.

Swelling and Erosion:

A Swelling and matrix erosion study was performed as per the method reported [10, 11]. The matrix tablets from the (B.No: RIV-CR/003) center point formulation trial (n=3) were subjected to dissolution using USP type –II (paddle) (Disso 2000, Lab India). The accurately weight tablets (W_1) are dropped into the dissolution vessel containing 500 mL of purified water, paddle rotated at 50 rpm and maintained at a temperature of 37°C±0.5°C. At selected time intervals over a period of 24 hours, the swollen /hydrated tablets were removed carefully and wiped gently to remove surface water and weighed (W_2). The matrix erosion is determined by weighing swollen / hydrated tablets and is then subjected to drying in an oven at a temperature of about 60°C until a constant mass was achieved to determine the weight loss (W_3).

The swelling index and matrix erosion are calculated using the equation 6 & 7.

$$\text{Swelling Index (\%)} = \frac{Weight\ of\ swollen\ \ tablet\ \ at\ \ specfied\ \ time\ \ interval\ \ (W2) - Initial\ \ weight\ of\ \ tablet\ \ (W1)}{Initial\ \ weight\ of\ \ tablet\ \ (W1)} \text{ x 100 (Eq.6)}$$

$$\text{Erosion (\%)} = \frac{Intial\ \ weight\ of\ \ tablet\ \ (W1) - Weight\ of\ \ tablet\ \ after\ \ drying\ \ (W3)}{Initial\ \ weight\ of\ \ tablet\ \ (W1)} \text{ x 100 (Eq.7)}$$

 ISSN: 2250-1177 CODEN (USA): JDDTAO

In vitro dissolution studies

The invitro dissolution studies were carried out using USP –II (Paddle), with 500mL of purified water as dissolution media and at stirring speed of 50 rpm of paddle (Lab India dissolution apparatus, 2000 series). The tablets were placed in a dissolution vessel containing media, maintained at a temperature of 37°C±0.5°C. A 5mL of sample is collected at appropriate time interval (2, 4, 6, 12, 15, 20 and 24 hours) from the dissolution vessel and then replaced with equivalent volume of dissolution media in order to maintain the constant volume (sink condition). The samples were then analyzed using validated HPLC method [12].

Drug Release Kinetics [13]

The invitro drug release data of a few selected batches were tested with the help of DD solver, for the mathematical model such as zero-order, first order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell equations.

Zero-order equation:

The equation is used to represent the dissolution of drug from the dosage form that do not disintegrate and release the drug slowly.

$$Q_t = Q_0 - K_0 t \quad \text{(Eq 8)}$$

Where Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in solution (most of time Q_0=0) and K_0 is the zero order rate constant expressed in unit concentration /time. A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

First order equation [14]:

The release behavior of first order equation expressed as follows,

$$\text{Log } Q_t = \text{Log } Q_0 + K_1 t / 2.303 \quad \text{(Eq 9)}$$

Where Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution and K_1 is the first order release constant. A graph of log cumulative percentage of drug remaining vs time yields a straight line with a slope of –K / 2.303**.**

Higuchi Model [15]

The Higuchi model describes drug release as a diffusion process based on the Fick's law, square root time dependent. The equation is as follows,

$$Q = K\sqrt{t} \quad \text{(Eq 10)}$$

Where Q is the amount of drug dissolved at time t, K is the constant reflecting the design variables of the system. The data obtained were plotted as cumulative percentage drug release versus square root of time.

Hixson-Crowell Model [16]

The equation describes the release from systems where there is a change in surface area and diameter of particles or tablets. The particles regular area is proportional to the cube root of its volume. The equation is expressed as follows,

$$W_0^{1/3} - W_t^{1/3} = \kappa t \quad \text{(Eq 11)}$$

Where W_0 is the initial amount of drug in the dosage form, W_t is the remaining amount of drug in the dosage form at time t and k (kappa) is a constant incorporating the surface-volume relation. A graphic of the cubic root of the drug percentage remaining in the matrix versus time is plotted.

Korsmeyer – Peppas Equation [17]

The mechanism of drug release can be determined using the well known exponential equation

$$\text{Log } (M_t/M_f) = \text{Log } k + n \text{ Log } t \quad \text{(Eq 12)}$$

Where Mt is the amount of drug released at time t; Mf is the amount of drug released after infinite time; k is a release rate constant, incorporating structural and geometric characteristics of the tablet; and n is the release exponent indicative of the mechanism of drug release. Each formulation data are plotted as log percentage of drug dissolved verses log time.

- If n = 0.45 indicates Fickian diffusion
- If 0.45<n<0.89 indicates anomalous diffusion or non- Fickian diffusion.
- If n = 0.89 and above indicates case-2 relaxation or super case transport-2.
- Anomalous diffusion or non-fickian diffusion refers to combination of both diffusion and erosion controlled rate release.
- Case-2 relaxation or super case transport-2 refers to the erosion of the polymeric chain.

Stability Studies

The stability studies were carried out as per International conference on Harmonization (ICH) guidelines [18]. The optimized formulation (RIV-CR/003) is packed in HDPE bottle and is charged in stability chamber (Newtronic, India) both Accelerated (40°C/75 % RH) and long term condition (25°C/60%RH). The stability samples are then evaluated for Assay, Water content, dissolution and related substances.

Results and Discussion

Determination of Physical characteristic of Blend:

The final blend of the various formulation trials of matrix tablet were characterized with respect to bulk density, tap density, compressibility index and Hausner's ratio. Thus all the batches indicate good to fair flow properties and found to be suitable for a direct compression process of final blend. The results are presented in the table-4.

Table 4: Physical characteristics of Blend:

Formulation Trials	Bulk density (g/mL)	Tap density (g/mL)	Compressibility Index (%)	Hausner's Ratio
RIV-CR/001	0.37	0.51	27.2	1.4
RIV-CR/002	0.43	0.60	27.5	1.4
RIV-CR/003	0.41	0.52	21.6	1.3
RIV-CR/004	0.43	0.54	20.0	1.3
RIV-CR/005	0.38	0.47	19.0	1.2
RIV-CR/006	0.38	0.48	21.3	1.3
RIV-CR/007	0.39	0.51	22.4	1.3
RIV-CR/008	0.39	0.51	22.4	1.3
RIV-CR/009	0.37	0.45	19.5	1.2
RIV-CR/010	0.38	0.49	21.8	1.3
RIV-CR/011	0.43	0.52	15.9	1.2

Evaluation of Controlled Release Matrix Tablets of Rivastigmine

The each formulation trials were evaluated for parameters such as weight variation, thickness, hardness and friability. The weight variation was found to be within ± 5% and the results are represented in the table-5

Table 5: Physical characteristics of Matrix Tablet

Formulation Trials	Weight Variation (n =20)	Thickness (mm) (n=10)	Hardness (kP) ± SD (n=10)	Friability (%w/w)
RIV-CR/001	198.6 ± 2.3	3.62	8.6 ± 0.6	0.02
RIV-CR/002	201.8 ± 1.6	3.31	10.6 ± 1.1	0.01
RIV-CR/003	203.8 ± 3.0	3.47	9.9 ± 0.9	0.02
RIV-CR/004	202.5 ± 2.1	3.39	9.3 ± 1.0	0.02
RIV-CR/005	200.2 ± 1.7	3.40	10.2 ± 0.9	0.01
RIV-CR/006	201.7 ± 2.1	3.46	11.7 ± 0.9	0.03
RIV-CR/007	203.7 ± 3.0	3.46	9.8 ± 0.8	0.01
RIV-CR/008	200.6 ± 2.0	3.36	11.2 ± 0.9	0.01
RIV-CR/009	202.3 ± 2.8	3.60	9.0 ± 0.5	0.01
RIV-CR/010	203.5 ± 3.8	3.42	9.4 ± 1.0	0.02
RIV-CR/011	201.5 ± 1.5	3.43	11.5 ± 1.0	0.03

Swelling and Erosion:

The swelling of polymer occurs upon hydration, and causes increase in hydrodynamic volume as the mobility of the polymer increases [19]. The swelling profile of the center point formulation trial (B.No: RIV-CR/003) was found to be very rapid up to 6 hours and there after shows constant swelling index. The swelling index and matrix erosion profile of the Rivastigmine tartrate controlled release formulation is presented in the figure - 1 and figure-2 below.

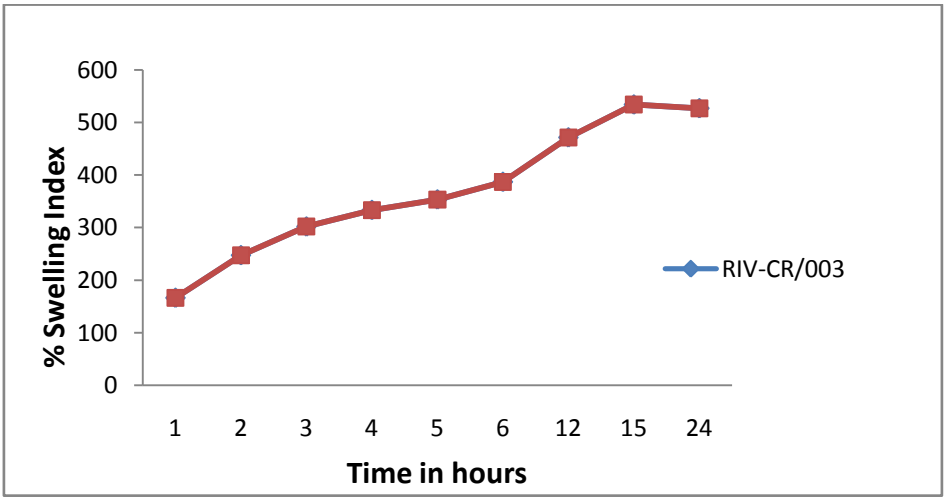

Figure 1: Swelling index Profile of the Controlled release formulation of Rivastigmine tartrate.

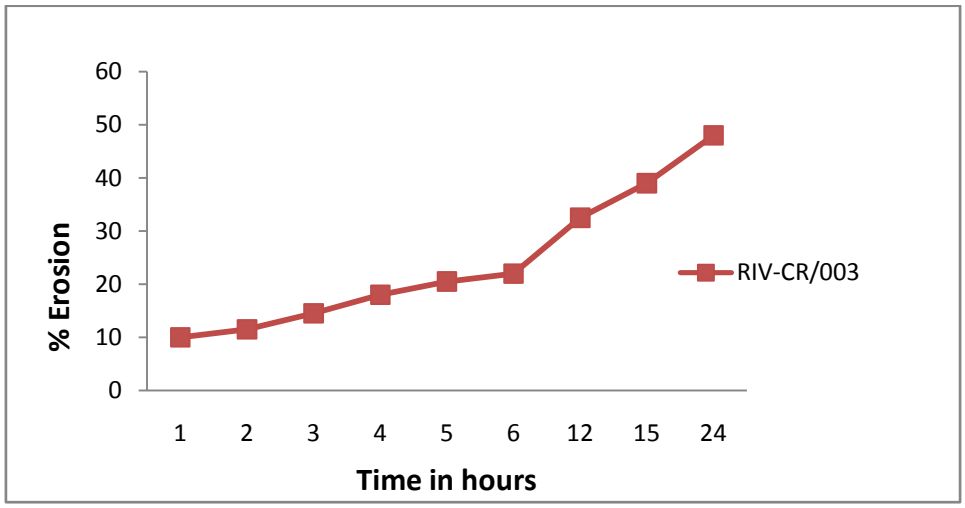

Figure-2: Matrix Erosion Profile of the Controlled release formulation of Rivastigmine tartrate.

Based on the above data the center point formulation trial (RIV-CR/003) showed a swelling index of 500 % and erosion of the matrix was observed to be 50 %.

In vitro drug release study:

The observed dissolution results and the similarity value (F2) of all the formulation trials as per experimental design are presented in the table- 6. The formulations trial (B.No: RIV-CR/002) showed higher drug release due to the lower amount of rate controlling polymers and the formulation trial (B.No: RIV-CR/001) showed lower drug release due to higher amount of rate controlling polymers. The figure -3 shows the drug release profile of the three formulation trials in comparison with the target release profile. Similarly the F2 value fails for the formulation with lower and higher amount of rate controlling polymer failed to compile the acceptable limit of ≥ 50 %.

Table 6: In-vitro release data of all formulations trials as per experimental design:

Time in hrs	Formulation Trials											
	RIV-CR/001	RIV-CR/002	RIV-CR/003	RIV-CR/004	RIV-CR/005	RIV-CR/006	RIV-CR/007	RIV-CR/008	RIV-CR/009	RIV-CR/010	RIV-CR/011	**In vitro target release**
	Cumulative percentage of drug release											
2 hr	2.1	22.3	12.4	7.2	10.2	5.6	8.2	11.8	16.5	20.5	17.4	**8.9**
4 hr	8.2	46.5	16.8	18.2	19.1	11.5	22.5	17.5	22.7	41.3	20.1	**17.7**
6 hr	13.2	51.1	33.3	33.6	30.2	14.6	33.3	31.5	30.1	47.6	34.6	**26.6**
12 hr	33.9	62.3	49.0	63.5	45.9	36.3	58.5	47.1	40.3	60.6	48.6	**53.2**
15 hr	52.7	82.3	69.3	88.6	65.8	51.9	79.9	67.8	65.9	84.6	70.2	**66.4**
20 hr	73.9	99.9	90.2	100.0	87.1	79.8	100.2	88.9	85.9	97.6	88.9	**88.6**
24 hr	88.5	99.9	98.8	101.2	99.7	89.3	101.3	101.1	96.2	102.4	95.7	**100**
F2 value	43.87	38.18	71.68	48.69	73.60	47.42	55.49	73.56	59.55	40.94	63.43	--

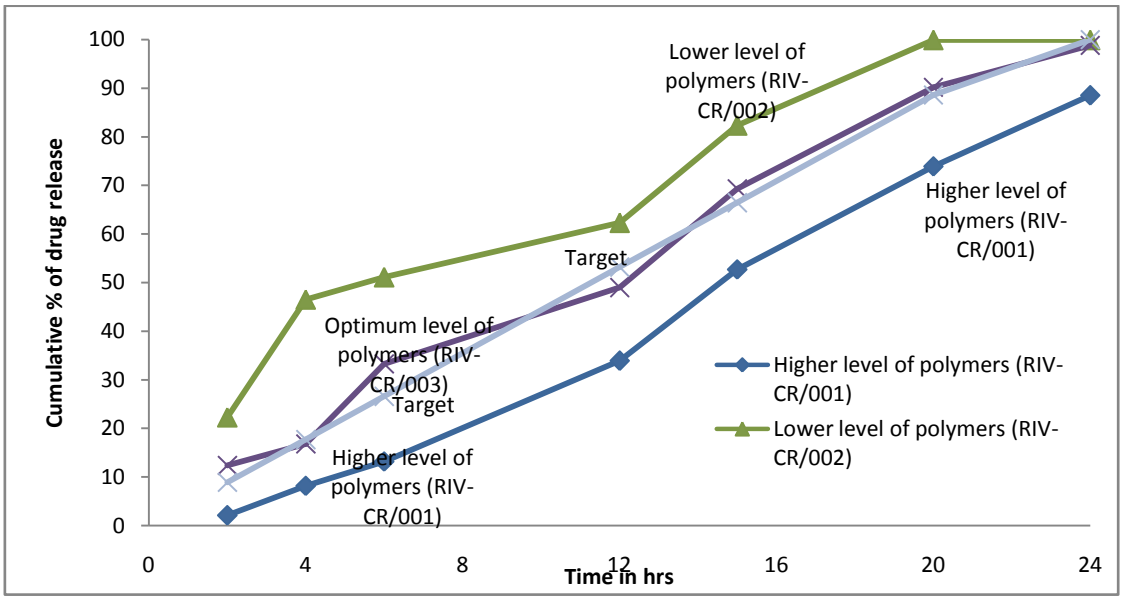

Figure 3: Drug release profile comparison of trial formulation with the target release profile.

ANOVA of quadratic model for percentage drug release

ANOVA table was used to generate mathematical models. The high values of correlation coefficient for percentage of drug loaded indicate a good fit i.e. good agreement between the selected factor and response. The mathematical model was evolved by omitting insignificant term ($p > 0.05$). So, the main effect A and B were found significant as p value was < 0.05. The ANOVA response table for the quadratic model is presented in the Table no: 7 & 8 for the dissolution response at the initial phase of release (2hr) and the terminal phase of release (20 hr)

Table 7: ANOVA for selected factorial model for 2 hours of dissolution response

Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		Mean	F	p-value	
Source	Squares	df	Square	Value	Prob > F	
Model	393.565	2	196.7825	120.655	3.76E-06	significant
A-Polymer K100 M	34.445	1	34.445	21.11956	0.002497	
B-PEO WSR -303 LEO	359.12	1	359.12	220.1904	1.51E-06	
Curvature	2.218333	1	2.218333	1.360146	0.281705	
Residual	11.41667	7	1.630952			
Lack of Fit	8.83	5	1.766	1.365464	0.473918	not significant
Pure Error	2.586667	2	1.293333			
Cor Total	407.2	10				

Table 8: ANOVA for selected factorial model for 20 hours of dissolution response

Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		Mean	F	p-value	
Source	Squares	df	Square	Value	Prob > F	
Model	711.705	3	237.235	48.34985	0.000135	Significant
A-Polymer K100 M	598.58	1	598.58	121.994	3.28E-05	
B-PEO WSR -303 LEO	42.32	1	42.32	8.625059	0.026054	
AB	70.805	1	70.805	14.43046	0.008981	
Curvature	8.946818	1	8.946818	1.823413	0.225614	
Residual	29.4398	6	4.906633			
Lack of Fit	24.57	4	6.1425	2.522691	0.303469	not significant
Pure Error	4.8698	2	2.4349			
Cor Total	750.0916	10				

Factorial equation for percentage of drug loaded in terms of coded factors:

Dissolution at 2 hr = 12.2 – 2.075 *A – 6.7 *B

Dissolution at 20 hr = 90.22273 – 8.65 *A – 2.3*B– 2.975*AB

Response surface plots for the percentage of Invitro drug release:

The counter plot and 3D plot shows the effect of ratio of significant factor such as polyethylene oxide (Polyox WSR 303 and Hypromellose (HPMC K100M) on percentage of drug release at 2 hours (initial phase of release) and at 20 hours (terminal phase of drug release). As the concentration of polyethylene oxide (Polyox WSR 303) increases the percentage of drug release at 2 hours decreases significantly, probably due the higher rate of hydration and swelling of the polymer. Whereas the increase in concentration of Hypromellose (HPMC K100M) showed significant lower dissolution at the terminal phase of drug release (20 hours), which may be probably due to higher gel strength of matrix. The counter plot and 3D plot at initial release (2 hrs) and at terminal phase of release (20 hrs) are represented in the figure 4, 5, 6 and 7.

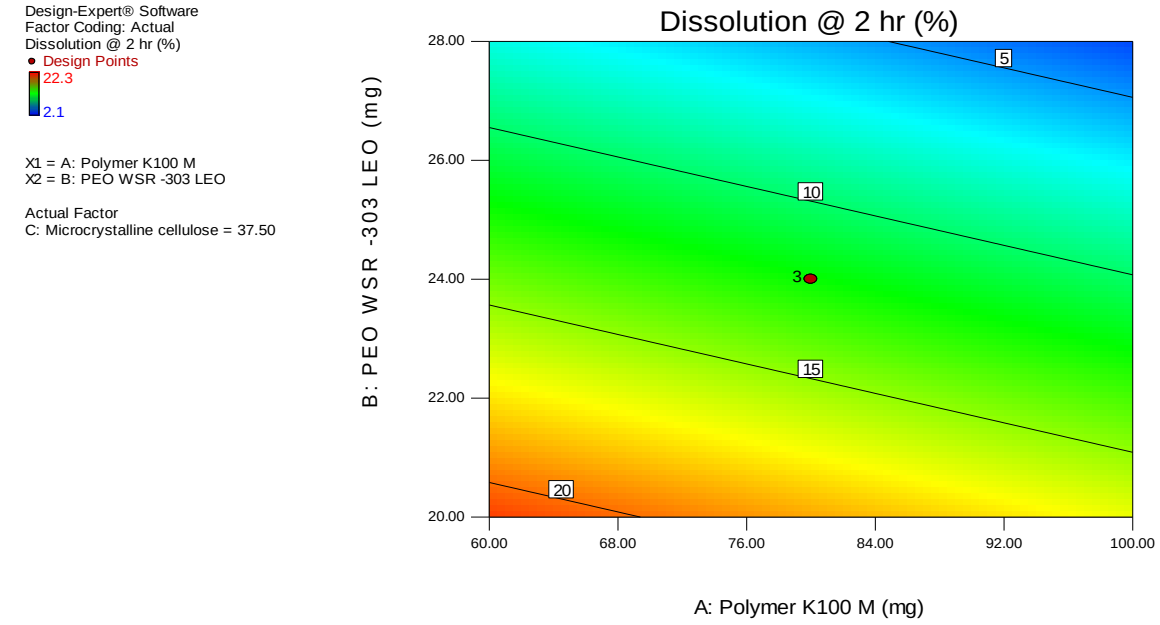

Figure: 4 Contour plot of % of Drug Release at 2 hours.

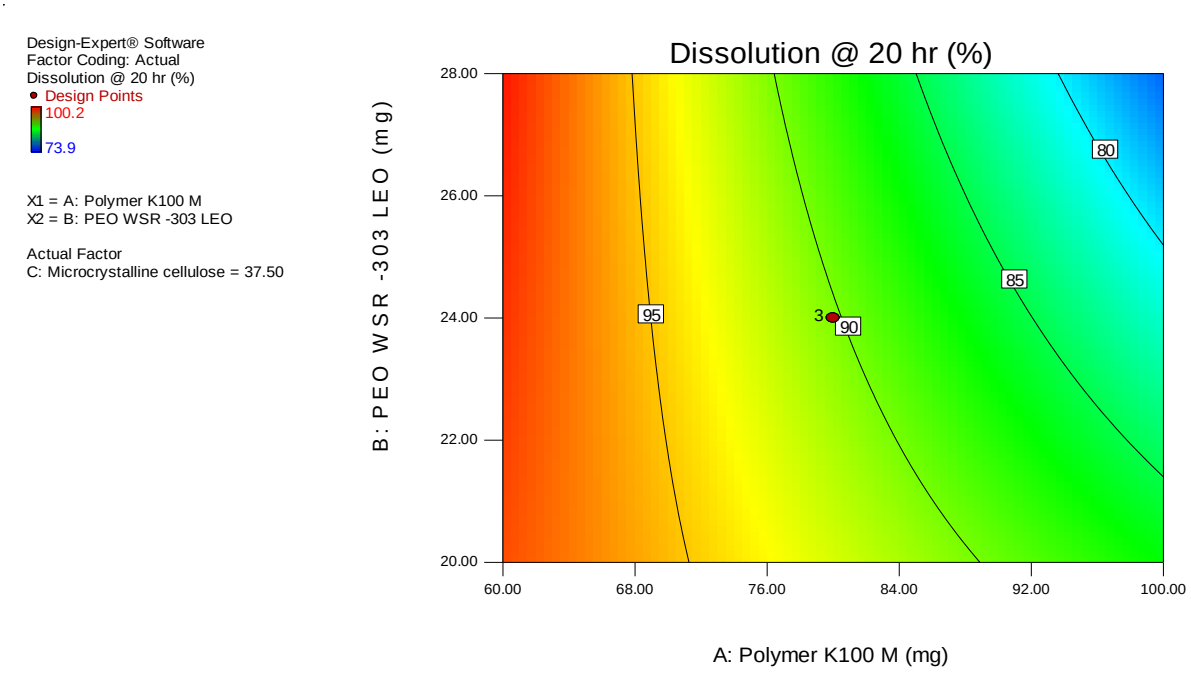

Figure: 5 Contour plot of % of Drug Release at 20 hours.

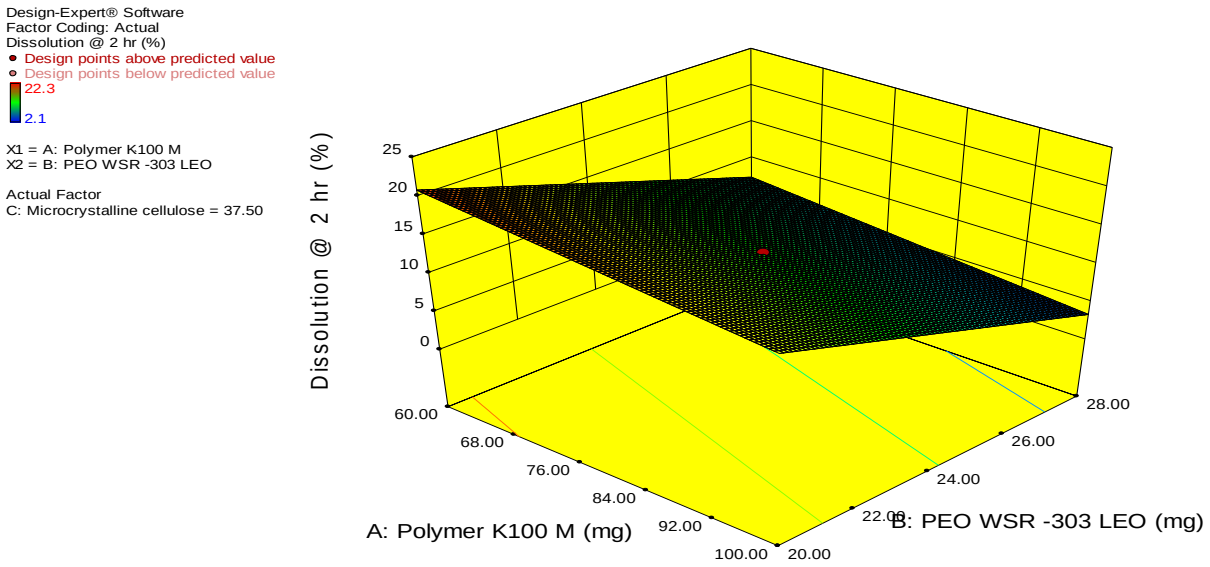

Figure: 6 3D Graph of % of Drug Release at 2 hours.

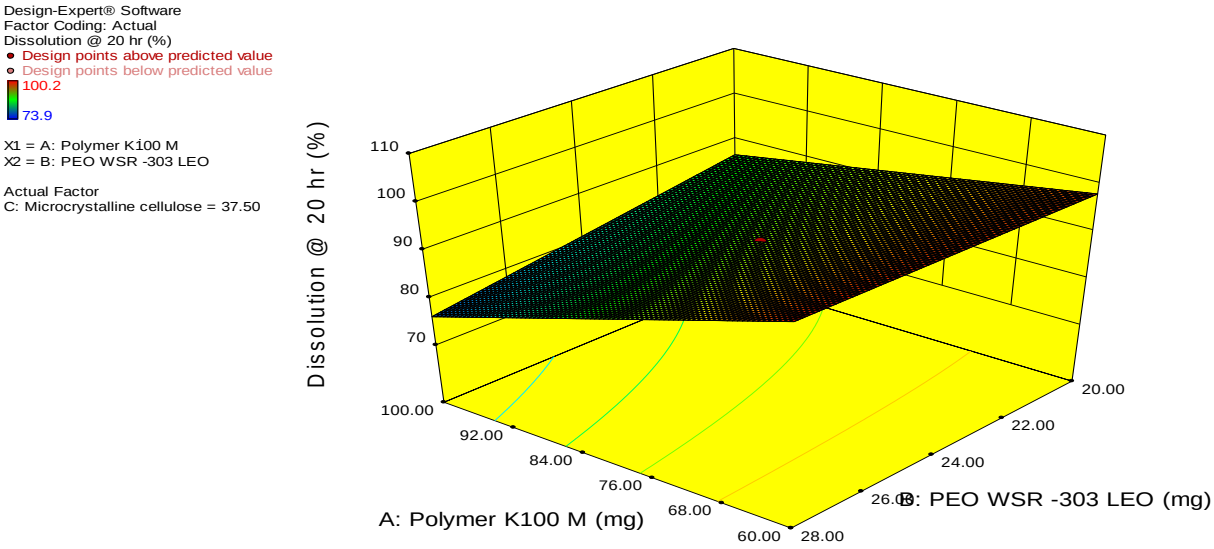

Figure: 7 3D Graph of % of Drug Release at 20 hours.

Drug Release Kinetics:

The drug release data of few selected batches were fitted to Zero-order, fist order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell equations and release kinetic data of the batches are presented in table -9. The batch with higher amount of rate controlling polymers (RIV-CR/001) and optimum quantity of rate controlling polymer (RIV-CR/003) showed best R^2 value fit for Zero order release model, whereas the release mechanism of drug transport for higher amount of rate controlling polymer was found to be erosion of polymeric chain with super case-2 transport and batch with optimum quantity of rate controlling polymers showed both diffusion and erosion controlled rate of release with an anomalous diffusion or Non-Fickian diffusion mechanism of drug transport. The batches with lower level of rate controlling polymer (RIV-CR/002) showed best R^2 value fit for first order release model with a near fickian diffusion mechanism of drug transport.

Table 9: Mathematical Modeling and drug release kinetics of controlled release formulation of Rivastigmine tartrate.

Batch No	Rate controlling polymer	Zero-order	First Order	Higuchi	Korsmeyer-Peppas	Hixson-Crowell	n	Mechanism of drug transport
RIV-CR/001	High	0.9680	0.8992	0.7255	0.9886	0.9047	1.249	super case-2 transport
RIV-CR/002	Low	0.6550	0.9254	0.9560	0.8698	0.9140	0.442	Near Fickian diffusion
RIV-CR/003	Center	0.9811	0.9175	0.8558	0.9691	0.9541	0.871	Anomalous diffusion or Non Fickian diffusion

Stability Studies

The optimized center point formulation trial (RIV-CR/003) is subjected to stability studies as per ICH (i.e) both at accelerated (40°C/75 % RH) and long term condition (25°C/60%RH) for a period of 6 months showed a stable formulation with no significant change in the Assay, water content, dissolution and related substances as compared to initial.

CONCLUSION:

A 2^3 full factorial design was applied to arrive at an optimized once daily controlled release formulation of rivastigmine tartrate with an invitro release profile similar to that of the target release profile which was derived from the pharmacokinetic simulations. The factorial design provided details of the influence of independent factors on the response. The results of analysis of variance showed that two independent variables viz, polyethylene oxide (Polyox WSR303) and hypermellose (Methocel K100M) had significant effect on the selected response at the initial phase and terminal phase of drug release respectively. It is thus concluded that by adopting a systematic approach, an optimum point can be reached in the shortest time with minimum efforts. Stability study indicated that the optimized batch was stable as per ICH stability testing conditions. Hence the once a day controlled release formulation of rivastigmine tartrate shall provide improved patients compliance by reducing GI adverse effects and dosing frequency.

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