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PHARMACOKINETIC SIMULATION TO DETERMINE TARGET *IN VITRO* DRUG RELEASE PROFILE FOR RIVASTIGMINE CONTROLLED RELEASE FORMULATION

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ABSTRACT

Rivastigmine, an anti-Alzheimer's drug, is effective in the treatment of mild to moderate dementia. Oral immediate release (IR) formulation suffers from limitation like severe GI adverse effects which may even result in treatment interruption, like vomiting, diarrhea and anorexia resulting in wide fluctuations in drug plasma levels and calling for altered frequency of dosing. Even the Novel Drug Delivery System such as transdermal formulation suffers from poor patient compliance. The present work aims at pharmacokinetic simulation to determine the required dose and target *in vitro* drug release profile required for the development of once a day controlled release drug delivery system (CRDDS) of Rivastigmine with a steady state maximum and minimum plasma concentrations (Css max and Css min) similar to that of a transdermal formulation with reduced frequency of dosing and GI adverse events. Using zero order and absorption models, dose and the *in vitro* drug release rate per hour for controlled release formulation of Rivastigmine were found to be 10.9 mg and 0.48 mg h^{-1} respectively. There is a rapid decline in the fluctuation index of controlled release formulations of rivastigmine, 0.73 as compared to 6.53 of IR formulation, indicating more constant plasma concentrations than the IR formulation, thereby reducing the adverse event. Based on the simulation study, the feasibility of Controlled release formulation of Rivastigmine is explored with a predetermined target *in vitro* release profile and dose prior to initiation of the formulation development, thereby reducing the cost and development timelines.

KEYWORDS: Rivastigmine, Pharmacokinetic simulation, Controlled release, Target Invitro drug release

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INTRODUCTION

The oral route of drug administration is most preferred, convenient, and cost effective. Various technological advancements eliminated the drawbacks of oral conventional drug delivery systems (Immediate release dosage forms), and have led to the development of oral controlled drug delivery systems that could provide a number of therapeutic benefits[1]. A controlled drug delivery system is usually designed to deliver the drug at a particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. This predetermined rate of drug release is based on the desired therapeutic concentration and the drug's pharmacokinetics. Alzheimer's disease (AD) is the most common cause of progressive mental deterioration in elderly people.It is characterized by impaired neuronal signaling, leading to a slow and progressive decline in cognition functional activity and behavior. Although the etiology of the disease is not clearly established, one cause of the disease is believed to be based on the cholinergic hypothesis. Acetylcholine (ACh) is the primary neurotransmitter that facilitates learning and increases attention[2,3]. Among the different types of drugs that are used to enhance cholinergic neurotransmission, cholinesterase inhibitors (ChEIs) have been shown to be effective in treating symptoms of mild to moderate AD. Rivastigmine tartrate (RT) is a carbamate derivative that reversibly inhibits the metabolism of aceylcholinesterase (AChE) and it is chemically known as (S) – N-Ethyl-N-methyl-3-[1-(dimethylamino)ethyl]-phenyl carbamate hydrogen-(2R,3R)- tartrate[3]. The drug is available in various dosage forms such as immediate release capsules, oral solution and Transdermal patch (as rivastigmine). Immediate release dosage forms such as capsules and oral solutions have the limitation due to GI adverse reactions such as nausea, vomiting, diarrhea, anorexia, dehydration due to prolonged vomiting or diarrhea, poor patient compliance due to multiple dosing and attention required by caregivers[4]. The Transdermal dosage forms have limitation such as skin reactions, loss of patch before its usual replacement time, poor patient compliance, ensuring patients or caregivers receiving instruction on proper dosing and administrations [4, 5, 6]. The GI side effects of rivastigmine cause large fluctuation in plasma level with the rapid rise in plasma level (C_{max}) and then rapid fall in plasma level (C_{min}) for immediate release capsules with a high fluctuation index (FI_{IR}). The adverse events can be reduced by reducing C_{max}, increasing the time to reach the maximum plasma concentration (t_{max}) and thereby reducing the fluctuation index[7]. Hence the ideal pharmacokinetic profile would be to maintain a steady state plasma concentration with reduced fluctuation index (FI). Rivastigmine is reported to be well absorbed from the across the GIT[8]. The objective of the current study is to determine the required target *in vitro* drug release profile via pharmacokinetic simulation with a reduced fluctuation index and to develop a once daily controlled drug release formulation of rivastigmine tartrate, thereby reducing the dosing frequency, GI adverse events and eventually increasing patient compliance.

METHODS

Pharmacokinetic Simulation Model

The intermittent Zero order release model (CRDDS) as described by Ritschel[9] was used for all simulations. The controlled drug release formulation envisioned, shall release the drug at a zero order rate (R^O) for the period of time (t del) shorter than the selected dosing interval (τ). After termination of release the drug concentration in blood decays according to the drug's elimination rate constant (Kel) The calculation for simulation was carried out using Microsoft Excel in a step wise manner. As a first step the pharmacokinetic parameters, steady state plasma concentration for 3mg IR capsules were derived from the pharmacokinetic parameter simulation of 1.5 mg Rivastigmine IR capsules obtained (linear pharmacokinetic up to 3mg dose) from the reported study, and literature value of the Cmax of transdermal

dosage form[10, 11]. In the second step the dose of the drug (D) and the final zero order release rate (R^O) required to achieve target steady state plasma concentration of controlled release formulation of rivastigmine tartrate were calculated. The third step involves the determination of target *in vitro* release profile for Controlled release drug delivery system (CRDDS) using the determined zero order release rate.

Step 1

Simulation of Plasma Concentration Profile of IR Formulation

Based on the reported data and literature on the pharmacokinetic parameters of 1.5 mg immediate release capsules (Table-1) the pharmacokinetic parameters of 3mg immediate release capsules are calculated as there is pharmacokinetic linearity up to 3mg (double the dose).

Table-1

Pharmacokinetic parameters of 1.5 mg immediate release capsules.

Parameters	Reported data
Cmax (Maximum plasma drug concentration)	5580.4 pg/mL
Tmax (Time to reach maximum plasma drug concentration)	1 hr
AUC $_{0-Inf}$ (Area under the plasma concentration curve extrapolated to infinite time)	10250.7 pghr/mL

Calculation of Elimination rate constant (Kel)

The terminal disposition or elimination rate constant was determined from the elimination half-life ($t_{1/2}$) using Eq:1 and is used to predict the blood level – time profile.

$$\text{Elimination rate constant (Kel)} = \frac{0.693}{t\ 1/2} \qquad (Eq.\ 1)$$

Calculation of volume of distribution (V_z)

The Volume of distribution is the proportionality constant relating the amount of drug in the body to the measured concentration in the blood. It was calculated from the dose (D), bioavailability fraction (f), Area under the curve (AUC $_{0\ -\ inf}$) and Kel. Since the AUC $_{0\ -\ inf}$ represents only the bio available fraction, f was assumed to be 1 (100%) in Eq. 2

$$\text{Volume of distribution (Vz)} = \frac{Dose\ (D)\ x\ f}{AUC\ (0-Inf) x\ Kel} \qquad (Eq.\ 2)$$

The steady state maximum and minimum plasma concentration of IR formulation (C_{ss} max and C_{ss} min) were derived after simulation of IR 1.5 mg capsules based on principles of superposition. To determine the steady state concentration expected after 4 repeated dose at 12 hours interval for 2 days and an accumulation table was constructed[9].

Fluctuation index for IR formulation (FI_{IR}) was calculated at a dosing interval of 12 hours using the equation (Eq.3) represented below,

$$\text{Fluctuation Index (FI)} = \frac{Css\ \max(\text{IR}) - Css\min(IR)}{AUC/\tau} \qquad (Eq.\ 3)$$

Based on the simulation data of 1.5 mg IR capsules and on the reported literature on the maximum concentration (C_{max}) of 3 mg capsule twice daily being approximately 70% higher than using 9.5

mg/24 patch of transdermal dosage form[10,11], the desired maximum and minimum steady state concentration for Controlled release formulation is finalized for further steps.

Step 2

Determination of the Dose and** in vitro **Target Release Rate for the Controlled release Formulation

The estimated time for elimination (t_{elim}), (i.e.) time from termination of release to the time of next dosing, was calculated using Eq. 4[9].

$$\text{Time for Elimination (telim)} = \frac{ln\ Css\ \max - ln\ Css\ \min}{Kel} \quad (Eq.\ 4)$$

The dosing interval (τ) for the envisioned controlled release formulation is planned as 24 hours (once a day) and the estimated time span for delivery (t_{del}) of the zero order drug release is determined using Eq.5

$$\text{Estimated time span for delivery (tdel)} = \tau - \text{telim} \quad (Eq.\ 5)$$

Estimation of preliminary maintenance dose (DM_{test}), is based on the conventional dose size ($DM_{Conventional}$) of Rivastigmine Immediate release capsules of 3 mg.

$$\text{DM test} = \frac{\text{DMConventional x 0.693 x } \tau}{t1/2} \quad (Eq.\ 6)$$

It is estimated with the assumption that the system release 90% of the drug (then the driving force is exhausted), If P is 0.9 during t_{del} with a dosing interval (τ) of 24 hours.

$$\text{Preliminary zero} - \text{order release rate (R0 prelim)} = \frac{\text{DM test x F x } \tau}{t\ del} \quad (Eq.\ 7)$$

Theoretical blood concentration expected from the controlled release formulation after administration of the first dose DM_{test} were simulated using the *Eq .8*

$$\text{C (t)} = \frac{\text{R0 prelim x } \left(1 - e^{-\text{kel } \tau}\right)}{Vz \text{ x Kel}} \quad (Eq.8)$$

The C_{max} and C_{min} calculated after the first dosing interval are represented using the equation (*Eq 9* and *Eq 10)*

$$\text{C (max)} = \frac{\text{R0 prelim x } \left(1 - e^{-\text{kel tdel}}\right)}{Vz \text{ x Kel}} \quad (Eq.\ 9)$$

$$\text{C (min)} = \text{Cmax} * e^{-\text{kel } (\tau - \text{tdel})} \quad (Eq.\ 10)$$

The superposition method is used to estimate accumulation to steady state, hence the concentration expected, C(x), from the first DM_{test} to occur during subsequent dosing intervals are calculated for the times corresponding to the sampling times during the first dosing interval and is represented by the Eq. 11. The expected concentration are generated until they reach a value of <1% of Cmax.

$$C\,(x) = \; C_{min}\, x\, e^{-kel\, t} \quad (Eq.11)$$

An accumulation table is constructed with the concentration data from column DM $_{test1}$ are repeated for DM $_{test2}$, DM $_{test3}$ etc starting after 1, 2, 3 dosing intervals respectively. The last column is the sum of the values in each row listed under DM $_{test1}$ through DM $_{test3.}$ The steady state maximum (C_{ss} max) and minimum plasma concentration (C_{ss} min) achieved are derived from the accumulation table. Based on the reported literature of the transdermal dosage form[10] the desired steady state maximum (C_{ss} max) and minimum plasma concentration (C_{ss} min) are derived. The required amount of drug for the final CRDDS (DM $_{final}$) in order to achieve the desired peak steady state concentration (Css $_{max}$ desired) is calculated using the Eq.12

$$\text{DM final} = \frac{\text{Css max desired}}{\text{Css max acheived (test)}}\; DM test \;(Eq.12)$$

Then, the final release rate for the controlled release formulation is calculated using the equation Eq.13

Final zero order release rate (R^O final) = $\frac{DM\ final}{t\ del}$ (Eq.13)

Similar steps from the equations Eq.8 and Eq .11 were followed to determine the final theoretical plasma concentration expected from the final zero order release rate.

Fluctuation index for CRDDS formulation (FI_{CR}) was calculated at a dosing interval of 24 hours using the equation (Eq.14) represented below,

$$\text{Fluctation Index (FI)} = \frac{Css\ \max(CR) - Css\ \min\ (\text{CR})}{AUC/\tau}\; (Eq.14)$$

Step 3

Simulation of Target** in vitro **release profile of Controlled release Formulation.

Based on the final zero order release rate (R^O final) and the final dose (DM $_{final}$), the percentage of drug released (%R) at time t is represented using the Eq.15.

$$\text{Percentage of drug releasd (\%R)} = \frac{Ro\ final\ \text{x time}}{DM\ final}\; (Eq.15)$$

RESULTS & DISCUSSION

The results of the pharmacokinetic parameters of the Rivastigmine IR formulation estimated using the equation 1 to 2 and are listed in the Table 2. The pharmacokinetic parameters of Rivastigmine 1.5 mg IR capsules were extrapolated to Rivastigmine 3mg IR capsules as it has linear pharmacokinetics up to a dose of 3 mg

Table 2
Pharmacokinetic parameters of Rivastigmine IR 1.5 mg and 3mg IR capsule formulation

Pharmacokinetic Parameter	Results	
Dose (D)	1.5 mg	3 mg
Maximum plasma concentration (C_{max})	5580.4 pg/mL	11160.8 pg/mL
Time to reach maximum plasma concentration (t_{max})	1.0 hrs	1.0 hrs
Elimination rate constant (k_e)	0.8 hr^{-1}	0.8 hr^{-1}
R^2	0.996	0.996
Half Life ($t_{1/2}$)	0.896 hr	0.896 hr
Area under the plasma concentration curve from administration to last observed concentration at time t (AUC_{0-t})	10248.4 pghr/mL	20496.7 pghr/mL
Area under the plasma concentration curve from last observed concentration at time (t) to extrapolated to infinite time (AUC_{t-inf})	2.3 pghr/mL	4.6 pghr/mL
Area under the plasma concentration curve extrapolated to infinite time AUC_{0-inf})	10250.7 pghr/mL	20501.4 pghr/mL
Volume of distribution Vz (L)	189.2 L	189.2 L
Maximum steady state plasma concentration (C_{ss} max)	5581.21 pg/mL	11162.4 pg/mL
Minimum steady state plasma concentration (C_{ss} min)	1.8 pg/mL	3.6 pg/mL

The plasma concentration profile of 1.5 mg IR formulation is provided in the figure below, (Fig - 1) and the simulated plasma concentration profile achieved upon multiple dosing of 1.5 mg at 12 hours intervals for 2 consecutive days is depicted in table3 and figure -2. The c_{max} was achieved within 1 hour and found to have a fast elimination due to shorter half life ($t_{1/2}$) of 0.9 hours, and hence found to have higher fluctuation index (FI_{IR}) due to large difference in the Maximum and minimum steady state plasma concentration. The fluctuation index of IR capsules formulation calculated using the Eq.3 at a dosing interval of 12 hours is 6.53.

Figure 1
Plasma concentration profile of 1.5 mg IR capsule formulation

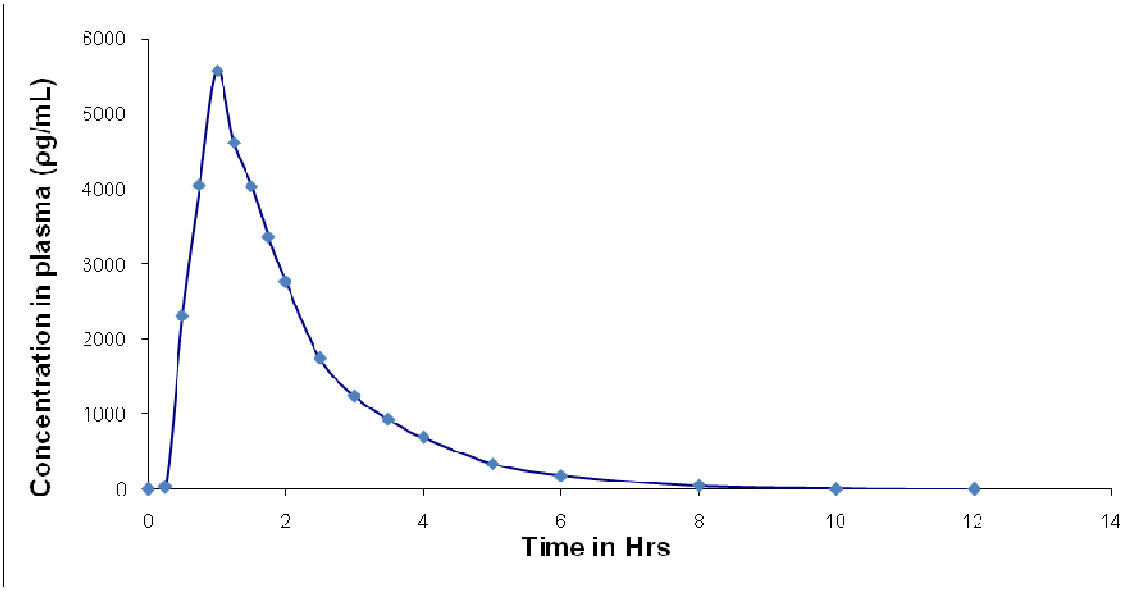
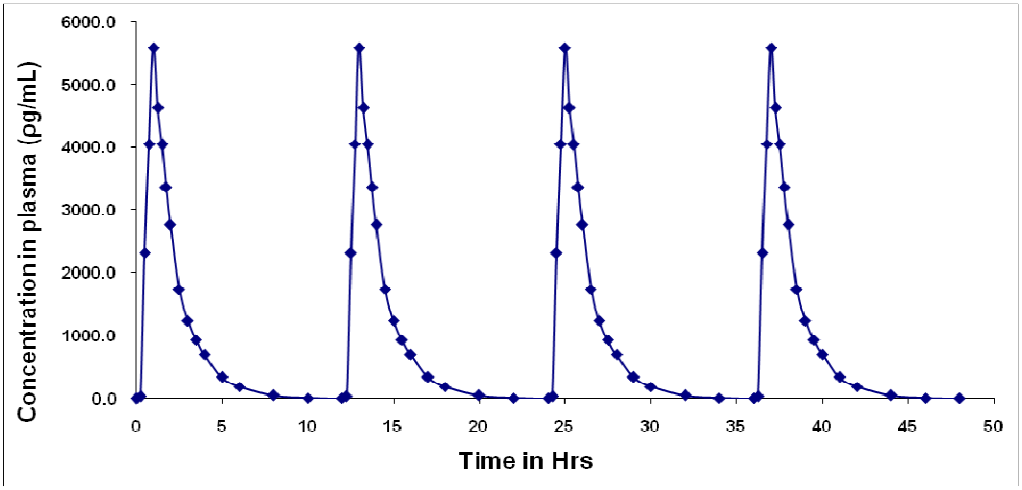


Table 3
Simulated plasma concentration of Rivastigmine IR formulation at a dosing interval of 12 hours for a period of 2 days.

Plasma concentration (ρg/mL) of IR formulation of Rivastigmine 1.5 mg capsules				
Days	Day -1		Day -2	
Time (h)	Dose 1	Dose 2	Dose 3	Dose 4
0.25	30.1	31.6	31.6	31.6
0.5	2318.6	2319.9	2319.9	2319.9
0.75	4046.3	4047.3	4047.3	4047.3
1	5580.4	5581.2	5581.2	5581.2
1.25	4622.2	4622.9	4622.9	4622.9
1.5	4043.5	4044.0	4044.0	4044.0
1.75	3360.3	3360.8	3360.8	3360.8
2	2767.3	2767.6	2767.6	2767.6
2.5	1739.8	1740.1	1740.1	1740.1
3	1239.7	1239.9	1239.9	1239.9
3.5	924.0	924.1	924.1	924.1
4	693.8	693.9	693.9	693.9
5	340.9	340.9	340.9	340.9
6	183.1	183.2	183.2	183.2
8	50.2	50.2	50.2	50.2
10	10.2	10.2	10.2	10.2
12	1.8	1.8	1.8	1.8

Figure 2
Simulated plasma concentration profile of 1.5 mg IR capsule formulation upon multiple dosing.



The desired maximum and minimum steady state concentration for the envisioned controlled release formulation is derived from the 9.5 mg/24 patch of Transdermal dosage forms as the measured exposure of the trans dermal dosage form is close to 3 mg twice daily IR formulation with the reduced side effects and lower fluctuation index[10,11]. Therefore the desired steady state C_{max} is 3300 ρg/mL and the desired steady state C_{min} is 1100 ρg/mL (i.e) 1/3rd of the desired C_{max} is selected as a target to reduce fluctuation and GI adverse events. The estimated time for elimination (t_{elim}), time span for delivery (t_{del}), preliminary maintenance dose (DM_{test}), preliminary zero-order release rate (R^0 prelim) and the theoretical blood

concentration expected from the controlled release formulation using the equation (Eq. 4 to Eq. 11) are presented in the below table 4.

Table 4
Pharmacokinetic parameters derived from the Eq.4 to Eq.11

Parameters	Results
Time for elimination (t_{elim})	1.42 hr
Time span for delivery (t_{del})	22.58 hr
Preliminary maintenance dose (DM_{test})	55.69 mg
Preliminary zero-order release rate (R^0 prelim)	2.47 mg hr^{-1}
Maximum steady state plasma concentration achieved (C_{ss} Max)	16853.7 ρg/mL
Minimum steady state plasma concentration achieved (C_{ss} Min)	9076.9 ρg/mL

It is evident from the above data, the maximum and minimum steady state achieved is much higher than the IR formulation and from desired maximum (3300 ρg/mL) and minimum (1100 ρg/mL) steady state derived from the Transdermal dosage form of 9.4 mg/24 patch. The final dose (DM_{final}) and final zero order release rate (R^O_{final}) derived using the Eq.12 and 13 are tabulated in the table 5

Table 5
Pharmacokinetic parameters derived using the Eq. 12 and 13

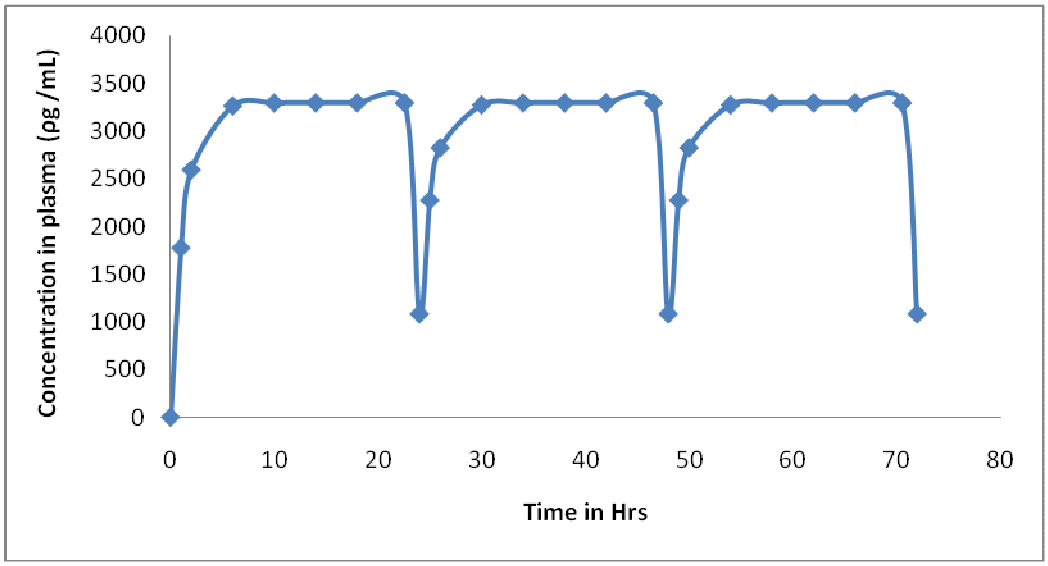
Parameters	Results
Final dose (DM_{final})	10.9 mg
Final zero order release rate (R^O_{final})	0.48 mg hr^{-1}

The multiple dose plasma concentration profile of controlled release formulation derived based on the accumulation to steady state for a zero –order CRDDS according to the superposition method is shown in table -6 and figure- 3.

Table 6
Simulated plasma concentration of Rivastigmine controlled release formulation at a dosing interval of 24 hours for a period of 3 days.

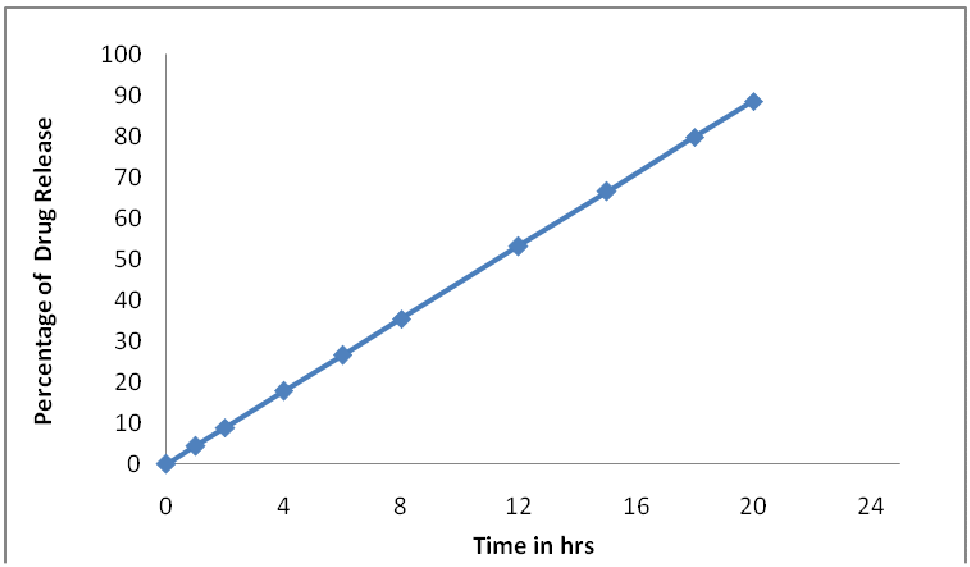
Time in hrs	Plasma concentration of CRDDS formulation of Rivastigmine			Cumulative
Days	Day –1	Day –2	Day –3	
Time(hrs)	Dose -1	Dose -2	Dose -3	
1	1777.3	-	-	1777.3
2	2597.4	-	-	2597.4
6	3268.1	-	-	3268.1
10	3298.6	-	-	3298.6
14	3299.9	-	-	3299.9
18	3300.0	-	-	3300.0
23	3300.0	-	-	3300.0
24	1083.5	-	-	1083.5
25	500.0	1777.3	-	2277.2
26	230.7	2597.4	-	2828.1
30	10.5	3268.1	-	3278.6
34	0.5	3298.6	-	3299.0
38	0.0	3299.9	-	3300.0
42	0.0	3300.0	-	3300.0
47	0.0	3300.0	-	3300.0
48	0.0	1083.5	-	1083.5
49	0.0	500.0	1777.3	2277.2
50	0.0	230.7	2597.4	2828.1
54	0.0	10.5	3268.1	3278.6
58	0.0	0.5	3298.6	3299.0
62	0.0	0.0	3299.9	3300.0
66	0.0	0.0	3300.0	3300.0
71	0.0	0.0	3300.0	3300.0
72	0.0	0.0	1083.5	1083.5

Figure 3
Simulated Plasma profile for the CRDDS formulation of Rivastigmine.



The fluctuation index of the Controlled release formulation (FI_{CR}) of rivastigmine obtained from the Eq. 14 was found to be 0.73, which is approximately 9 times lower as compared to the fluctuation index of IR formulation (FI_{IR}) 6.53. The target *in vitro* release profile of the envisioned controlled release formulation of rivastigmine derived from the Eq.15 is shown in Figure 4. The approximate time for the 25 %, 50%, 75% and 90% of drug release ($t_{25\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$) was 6 hrs, 12hrs, 18hrs and 20 hrs respectively and the drug release follows Zero order kinetic release profile.

Figure 4
Target In-vitro release profile of Rivastigmine controlled release formulation



Based on the target *in vitro* release profile, the once daily controlled release formulation for rivastigmine is developed and based on the actual drug release kinetic modeling such as Zero order, Hixson-Crowell, Weibull, Higuchi, Korsmeyer-Peppas is evaluated[12].

CONCLUSION

A systematic and scientific approach was adopted in developing a CRDDS by having a target *in vitro* release profile of Rivastigmine by Pharmacokinetic simulation using simple Microsoft excel as a tool, in place of expensive software. Simulation approaches were reported for the drugs with wide range of physico-chemical and pharmacokinetic properties such as azithromycin[13], nifedipine[14] and Acyclovir[15]. There is no currently available marketed once a day oral controlled release formulation of rivastigmine which can provide patience compliance and reduce GI adverse events; hence there is a need for this type of dosage form. Based on this pharmacokinetic simulation approach, a target in-vitro drug release profile is determined for the oral once a day controlled release formulation of rivastigmine and thereby reducing development timeline. The formulation development work is being carried out to attain the target in-vitro release profile for the envisioned controlled release formulation of Rivastigmine.

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