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Research Article

Formulation Development and *In Vitro* Characterization of Oral Floating *In Situ* Gelling Liquid System of Rivastigmine Tartrate

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ABSTRACT

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The main aim of the study was to develop a stable gastroretentive *In situ* gel of Rivastigmine tartrate for Geriatric patients in the treatment of Alzheimer's disease. Rivastigmine tartrate oral *In situ* gel was formulated by pH-triggered ionic gelation using various gelling polymers such as Sodium alginate, Gellan gum and Iota carrageenan along with HPMC K4M as release retardant. Prepared formulations were evaluated for Physical appearance, Pourability, pH, viscosity, *In vitro* gelation study, *In vitro* buoyancy study, Density, Gel strength, Percentage water uptake, Drug content and *In vitro* drug release. All the parameters showed differences based on the combination and concentration of polymers used. The pH and drug content of the formulations ranged from 6.94 - 7.39 and 98.04 - 99.83 % respectively. All the formulations showed floating lag time of less than 2 minutes and the duration of floating was greater than 12 hours. *In vitro* drug release study showed that only the Formulations F9 and F10 released 99.91 % and 91.11% of drug respectively at the end of 12 hours, while the other formulations showed more than 90% of drug release even before the period of 12 hours. *In vitro* release kinetic study of the optimized formulation F9 showed that the formulation followed Zero-order kinetics and Non-Fickian diffusion mechanism. The stability studies indicated that the optimized formulation F9 remained stable at the end of 3 months. The formulated gastroretentive *In situ* gel prolonged the gastric residence time resulting in controlled delivery of the drug.

INTRODUCTION

Oral drug administration still remains the route of choice for the majority of clinical applications. Oral delivery of drugs with a narrow absorption window in gastrointestinal tract is often limited by poor bioavailability with conventional dosage forms due to incomplete drug release and short residence time at the site of absorption. *In situ* gel forming systems have been widely investigated as vehicles for controlled drug delivery. Since the administration of highly viscous gel formulations by oral route is difficult, it is preferred that a liquid drug-polymer formulation would gel at the targeted site, since *In situ* gelling systems undergo reversible sol-gel transitions in response to temperature, pH, or ion composition of the fluids.

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Drug retention and bioavailability can be achieved by gelation [1, 2]. Gastroretentive floating *In situ* gel refers to a polymer solution of low viscosity which upon coming in contact with the gastric fluids undergoes a change in polymeric conformation and a viscous strong gel of density lower than the gastric fluids is formed. Gastroretentive *In situ* gelling system helps to increase the bioavailability of drug compared to the conventional liquid dosage form. The gel formed from *In situ* gelling system, being lighter than gastric fluids, floats over the stomach contents, produces gastric retention of the dosage form and increase gastric residence time, resulting in prolonged drug delivery in the gastrointestinal tract [3, 4].

Rivastigmine, a drug extensively prescribed for the treatment of mild to moderate Alzheimer's disease, has recently been recommended for the treatment of mild to moderate dementia associated with Parkinson's disease as well [5]. Rivastigmine has an elimination half-life of about

1.5 - 2 hours. The efficacy of rivastigmine is dose-related, with the total oral dose ranging between 6 and 12 mg administered 2 to 3 times a day [6]. Rivastigmine is associated with severe central cholinergic gastrointestinal (GI) side effects [7, 8]. A rapid increase in brain acetylcholine levels has been believed to precipitate these side effects [9, 10]. Moreover, the twice or thrice daily dosage regimen associated with a drug like Rivastigmine tends to reduce its patient compliance. Hence, the above limitations can be overcome by administration of Rivastigmine tartrate in the form of oral floatable *In situ* gel.

MATERIALS AND METHODS

Rivastigmine tartrate was gifted by Dr Reddys Laboratories Pvt. Ltd. Sodium alginate, Gellan gum and Iota carrageenan were obtained from Signet Chemical Corporation Pvt. Ltd. Hydroxy Propyl Methyl Cellulose (HPMC) K4M, Calcium carbonate, Sodium bicarbonate and Sodium saccharin were obtained from Saimirra Innopharm. Sodium Citrate, Methyl Paraben Sodium and Propyl Paraben Sodium were obtained from Pharmafabrikon Pvt. Ltd. Deionized water was purchased from Lab Chemicals.

Drug-Excipient Compatibility Studies

Fourier transform infrared (FTIR) spectroscopy was performed by dispersing the sample (drug alone, Mixture of drug and excipients and the optimized formulation) in Potassium Bromide (200– 400 mg) using a Shimadzu FTIR 8400 Spectrophotometer from 4000 to 400/cm region, the spectrum was recorded [11].

Preparation of Calibration Curve for Rivastigmine Tartrate

Rivastigmine tartrate solutions were prepared at concentrations ranging from 100-500 µg/ml. The absorbance was measured at 263 nm against the reagent blank [12]. Then, Calibration curve was plotted by taking Concentration on X-axis and Absorbance on Y-axis.

Preparation of Oral *In Situ* Gel of Rivastigmine Tartrate

Sodium Alginate, Gellan Gum, Iota Carrageenan, HPMC K4M, Sodium Citrate, Calcium Carbonate, Sodium bicarbonate, Sodium Saccharin, Propylparaben sodium and Methylparaben sodium were weighed accurately. Various concentrations of gelling polymer (Sodium Alginate or Gellan Gum) for the formulations F1 to F10 as given in the Table 1 were dissolved in deionized water with a weighed amount of Sodium Citrate on a magnetic stirrer at 70°C. Iota carrageenan solution was prepared separately by dissolving in deionized water containing Sodium Citrate and heating to 80º C while stirring. In another beaker, the required quantity of release retardant polymer HPMC K4M was soaked in deionized water until completely dissolved. Then, all three solutions were mixed together with continuous stirring. After the above solution has cooled down to 40°C, Calcium Carbonate, Sodium bicarbonate and Rivastigmine tartrate were added. Sodium Saccharin and Preservatives were mixed. Finally, the volume was adjusted with the deionized water, and the resultant solution was stirred well and stored in amber-coloured bottles until further use [13].

Table 1: Composition of the *In situ* gelling formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Rivastigmine tartrate (mg)	60	60	60	60	60	60	60	60	60	60
Sodium alginate (%w/v)	1.0	-	0.5	-	1.0	-	1.0	-	0.5	0.5
Gellan gum (%w/v)	-	0.3	0.15	-	-	0.3	-	0.3	0.15	0.15
Iota carrageenan (%w/v)	-	-	-	0.25	0.2	0.2	0.25	0.25	0.2	0.25
HPMC K4M (%w/v)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Sodium citrate (%w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Calcium carbonate (% w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium bicarbonate (% w/v)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Sodium Saccharin (% w/v)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Methyl paraben sodium (% w/v)	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09
Propyl paraben sodium (% w/v)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Deionized water (to produce ml)	100	100	100	100	100	100	100	100	100	100

Characterization of *In Situ* Gel

Visual Appearance

All the formulations were visually inspected for their appearance, clarity, and consistency.

Measurement of pH

The pH for each of the formulations was measured using a calibrated pH meter. The readings were recorded three times for each of the formulations and the averages of the readings were considered [14].

***In Vitro* Gelation Study**

1 ml of the formulation was introduced into a 15 ml test tube containing 5 ml of simulated gastric fluid (pH 1.2) at 37°C. The formulation was released slowly from the pipette positioned facing the surface of the fluid in the test tube. When the formulation comes in contact with the medium, sol-gel transition results in the formation of the gel. The *In vitro* gelling capacity was investigated based on the stiffness of gel as well as the duration for which the gel remains as such in the medium.

In vitro gelling capacity was mainly divided into three categories based on gelation time and the time period the formed gel remains in the medium [14].

- (+): Gels in few seconds, disperse immediately
- (++): Gelation immediate remains for few hours
- (+++): Gelation after few minutes remains for extended periods

Determination of Viscosity

Viscosities of the formulations were determined with the help of Brookfield's digital Viscometer at 50 rpm, repeated thrice with fresh samples and the average of the readings was considered [14].

***In Vitro* Buoyancy Study**

The studies were conducted in a United States Pharmacopoeia (USP) Type II dissolution apparatus using simulated gastric fluid (pH 1.2) as the medium at 37 ± 0.5°C. About 10 ml of the *In situ* gel formulation was placed in the medium. The time taken by the *In situ* gel formulation to float on the surface of the medium (floating lag time) and time period for which the formulation remained buoyant (duration of floating) was noted [15].

Measurement of Water Uptake by the Gel

In situ gel was formed in 40 ml of 0.1N Hydrochloric Acid (HCl), pH 1.2. The gel formed was then separated and the excess buffer was blotted out using Whatman filter paper. The initial weight of the gel was noted and then 10 ml of distilled water was added. At periodic intervals, water was decanted and then reweighed and the difference between initial and final weight was calculated [16].

Measurement of Density of Gel

In situ gel formed 0.1N HCl was taken in measuring cylinder and the weight of the gel was measured. Using the weight as well as the volume of the gel, the density was calculated. This method was followed for all the formulations [16].

Measurement of Gel Strength

30 g of the gel formed in 0.1 N HCl was taken in a beaker and a 50 g weight was placed on the centre of the gel surface and allowed to penetrate through the gel. The time taken by the weight to penetrate 5 cm down through the gel was noted for all the formulations. The method was repeated thrice for each fresh formulation and the average time was noted [16].

Determination of the Drug Content

5 ml of the formulation equivalent to 3 mg of the drug was added to 80 ml 0.1N HCl (pH 1.2) in a 100 ml standard flask and stirred for 1 hour in a magnetic stirrer. After 1 hour, the solution was filtered and diluted with 0.1 N HCl (pH 1.2). The drug concentration was then determined by Ultraviolet (UV) - visible spectrophotometer at 263 nm against a suitable blank solution [16].

***In Vitro* Drug Release Study of the *In Situ* Gel Formulation**

The dissolution studies were performed using a USP type II (paddle method) dissolution apparatus. 500 ml of 0.1 N HCl (pH 1.2), maintained at 37ºC was used as the dissolution medium. The stirring rate was adjusted to 50 rpm. This speed was believed to simulate the *in vivo* existing mild agitation and was slow enough to avoid the breaking of the gelled formulation. At predetermined time intervals, 10 ml samples were withdrawn and replaced with fresh dissolution medium, filtered through Whatman filter paper, diluted, and assayed at maximum absorbance at 263 nm using UV-Visible Spectrophotometer [16].

Release Kinetics of the Optimized Formulation

To study the *In vitro* release kinetics of the optimized formulation of Rivastigmine tartrate

oral *In situ* gel, data obtained from dissolution study were plotted in various kinetics models [17].

Zero-Order Equation

The zero order release can be obtained by plotting cumulative % percentage drug released vs. time in hours. It is ideal for the formulation to have a release profile of zero order to achieve pharmacological prolonged action.

$$C=K_0t$$

Where K_0= Zero order constant, t= Time in hours.

First Order Equation

The graph was plotted as log % cumulative drug remaining vs. time in hours.

$$Log\ C= log\ C_0- Kt/2.303$$

Where C_0= Initial concentration of the drug, K= First order, t= Time in hours.

Higuchi Kinetics

The graph was plotted with % cumulative drug released vs. square root of time

$$Q = Kt^{½}$$

Where K= constant reflecting design variable system (differential rate constant), t= Time in hours.

Hixson and Crowell Erosion Equation

To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using the Hixson and Crowell rate equation. The graph was plotted by the cube root of % drug remaining vs. time in hours.

$$Q_0^{1/3} – Qt^{1/3} = K_{HC}t$$

Where Qt= amount of drug released in time t, Q_0= Initial Amount of drug, K_{HC}= Rate constant for Hixson Crowell equation.

Korsmeyer - Peppas Equation

To evaluate the mechanism of drug release, it was further plotted in Korsmeyer - Peppas equation as Log cumulative % of drug released Vs. Log time.

$$M_t/M_\alpha = Kt^n$$

Where M_t/M_α = Fraction of drug released at time t, t = Release time, K= Kinetics constant (Incorporating structural and geometric characteristics of the formulation), N= Diffusional exponent indicative of the mechanism of drug release.

Stability Studies

The optimized formulation of the *In situ* gel was placed in an amber colour bottle. It was tightly sealed. The stability study was carried out as per the International Council for Harmonization (ICH) guideline, i.e., Accelerated temperature 40 ± 2 °C / 75 ± 5 % RH for 3 months. Samples were withdrawn periodically (0 and 90 days) and evaluated for visual appearance, pH, floating behaviour, gelling capacity, drug content as well as *In vitro* drug release [18].

RESULTS AND DISCUSSION

Drug-Excipient Compatibility Studies

FTIR spectra of drug and optimized formulation are given in Fig. 1 and Fig. 2. Chemical compatibility of drug with excipients using FTIR spectroscopy shows no disappearance of characteristic peaks of drug as given in Table 2. This suggests that there is no interaction between the drug and the excipients.

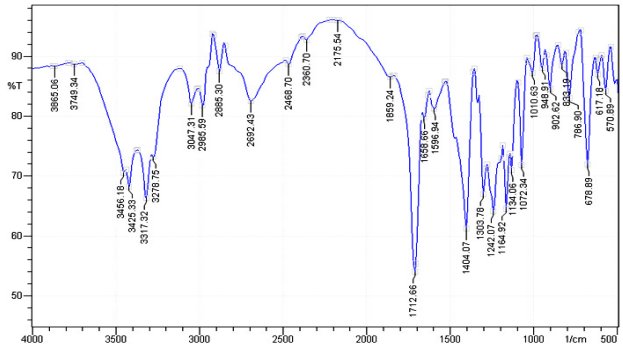


Figure 1: FTIR spectra of Rivastigmine tartrate

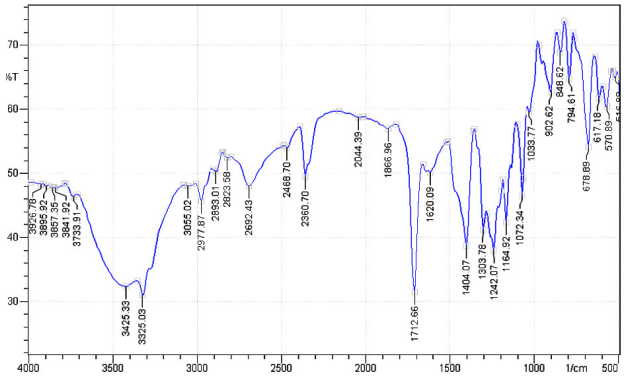


Figure 2: FTIR spectra of optimized formulation

Table 2: Major IR peaks of Rivastigmine tartrate and optimized formulation

Samples	Major peaks (wave numbers cm^{-1})
Pure drug (Rivastigmine tartrate)	3425.33, 2885.30, 1658.66, 1164.92, 678.89
Optimized Formulation (F9)	3425.33, 2893.01, 1620.66, 1164.92,678.89

Calibration Curve of Rivastigmine Tartrate

The Calibration curve of Rivastigmine tartrate was determined by UV spectrophotometric method at 263 nm and the results are given in Table 3 and Fig.3.It was found that the solutions of Rivastigmine tartrate in 0.1 N HCl (pH 1.2) showed linearity (**R^2=0.9997**) in absorbance at concentrations of 100 to 500 µg/ml and obeys Beer - Lambert's Law.

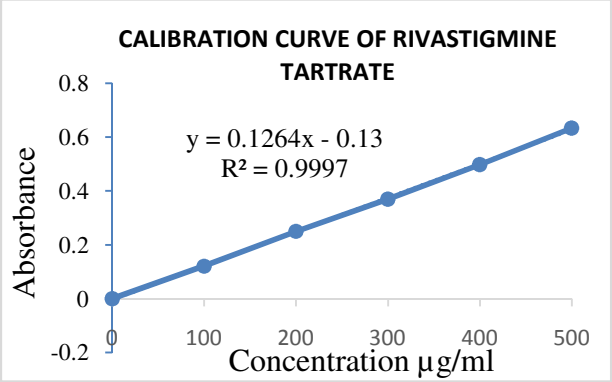


Figure 3: Calibration curve of Rivastigmine tartrate

Table 3: Concentration and absorbance of Rivastigmine tartrate

Concentration (µg/ml)	Absorbance at λ263 nm
0	0
100	0.1210 ± 0.005
200	0.2504 ± 0.01
300	0.3699 ± 0.01
400	0.4987 ± 0.02
500	0.6342 ± 0.01

*All values are expressed as mean ± SD, n=3

Physical Appearance of Rivastigmine Tartrate Oral *In Situ* Gel

The visual appeal of the formulation is an important parameter as it has an impact on patient compliance. All the formulations were subjected to visual appearance and results are given in Table 4. All the prepared formulations had a dull-white appearance. The formulations were free-flowing and did not produce any gelation at room temperature as shown in Fig. 4.

pH of Rivastigmine Tartrate Oral *In Situ* Gel

The pH of all the formulations was found to be satisfactory in the range of 6.94 - 7.39 as depicted in Table 4. The pH of all the formulations was within the orally acceptable range (i.e. salivary pH range: 6.2 - 7.6). Therefore, it will not cause any irritation on the administration of the formulations.

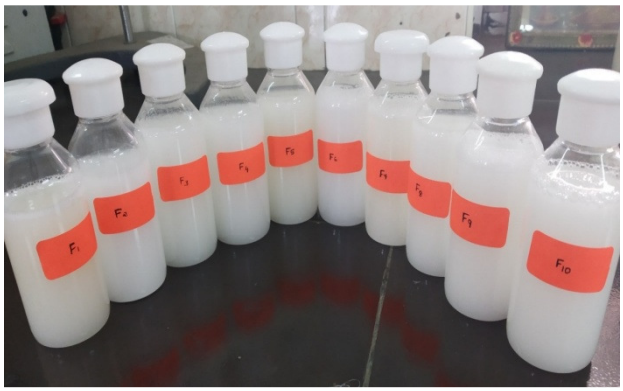
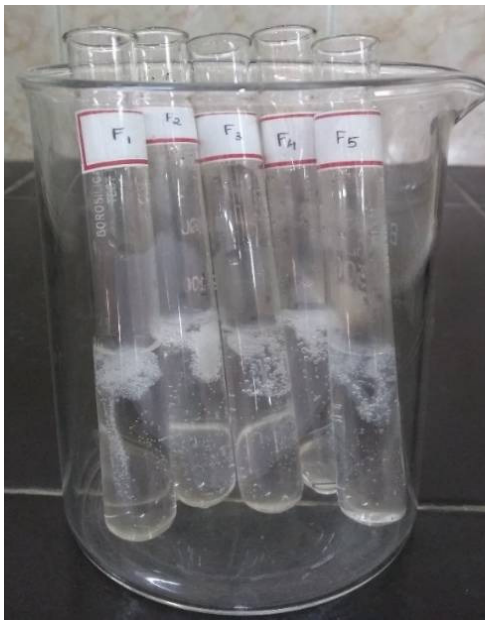


Figure 4: Prepared formulations of Rivastigmine tartrate oral *In situ* gel



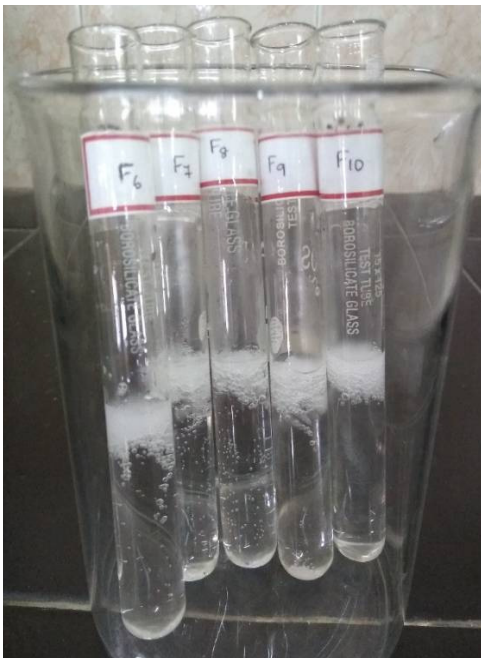


Figure 5: *In vitro* gelation study of the In situ gel formulations

Table 4: Visual appearance, pH and Gelling capacity of the Prepared In situ gel

S.No.	Formulation Code	Appearance	Pourability	pH*	Gelling capacity
1	F1	Dull - white	Pourable	6.94 ± 0.02	+++
2	F2	Dull - white	Easily Pourable	7.18 ± 0.02	+++
3	F3	Dull - white	Easily Pourable	7.33 ± 0.02	+++
4	F4	Dull - white	Easily Pourable	7.08 ± 0.02	+
5	F5	Dull - white	Pourable	7.16 ± 0.02	+++
6	F6	Dull - white	Pourable	6.98 ± 0.02	+++
7	F7	Dull - white	Pourable	7.20 ± 0.02	+++
8	F8	Dull - white	Pourable	7.28 ± 0.02	+++
9	F9	Dull - white	Easily Pourable	7.39 ± 0.02	+++
10	F10	Dull - white	Pourable	7.05 ± 0.02	+++

*All values are expressed as mean ± SD, n=3

In Vitro Gelation Study of Rivastigmine Tartrate Oral *In situ* Gel

The Gelation characteristics of the formulations were assessed in 0.1N HCl (pH 1.2) on an ordinal scale ranging between + and +++ as shown in Table 4. All the formulations had undergone sol-to-gel transition on contact with the gelation medium in the presence of gel-forming polymers as shown in Fig. 5. The *In situ* released calcium ion from calcium citrate complex gets entrapped in polymeric chains resulting in the cross-linking of polymer chains to form a gel matrix. Thus, stiff gels were formed with all the formulations containing polymers such as Sodium alginate and Gellan gum as the main polymer with or without Iota Carrageenan, except formulation F4 containing only Iota-carrageenan as the gelling polymer where the gel formed dispersed rapidly.

Viscosity of Rivastigmine Tartrate Oral *In Situ* Gel

The results of viscosity measurement of all the formulations are shown in Table 5. All formulations exhibited good consistency, which was dependent on the concentration of gelling agents. The increase in viscosity was observed in formulations containing a high concentration of Sodium alginate and Gellan gum. Formulations containing a combination of polymers i.e. Sodium alginate and Gellan gum along with Iota carrageenan showed less viscosity than the formulations with a high concentration of single polymer.

In vitro Buoyancy of Rivastigmine Tartrate Oral *In situ* Gel

The time taken by the formulation to emerge on the surface of the medium is the floating lag time and the time period for which the formulation constantly floated on the surface of the medium is known as floating duration. The results of buoyancy studies are given in Table 5. All the *In situ* gel formulations had a floating lag time of <2 min and all the formulations floated for more than 12 h. Therefore, the extended duration of floating may be responsible for the controlled release of the drug.

Density of Rivastigmine Tartrate Oral *In Situ* Gel

Density is an important evaluation parameter in floating drug delivery. For the formulation to float on the gastric contents, it should have a density less than or equal to that of the gastric contents (~1.004 gcm^{-3}). The density of all the formulations as given in the Table 5 is less than that of the gastric fluid. As a result, the floating of the gastroretentive *In situ* gel is promoted in the stomach.

Measurement of Gel Strength of Rivastigmine Tartrate Oral *In Situ* Gel

Gel strength indicates the tensile strength of the gelled mass where the ability of the gelled mass to withstand the peristaltic movement in *in vivo* is demonstrated. Table 5gives the gel strength of all the formulations. All the formulations showed good gel strength which ranged from as low as 14.7 s for formulation F4 which contains only Iota-carrageenan as the main polymer to higher values of 44.3 s and 52.6 s for formulations F9 and F10 respectively, which contains a combination of three polymers i.e. Sodium Alginate, Gellan gum and Iota carrageenan. When the gel strength is more, the formulation may retain its consistency for a prolonged period of time. Thus, the release of the drug may also be prolonged.

Table 5: Viscosity, Floating study, Density, Gel strength and Drug content of *In situ* gel

S.No.	Formulation Code	Viscosity (centipoise)*	Floating lag time (s)*	Floating duration (hrs)	Density (g/cm³)*	Average gel Strength (s)*	Drug content (%)
1	F1	186 ± 2.65	13 ± 2	>12	0.659 ± 0.001	20.3 ± 0.6	98.20
2	F2	165.67 ± 1.53	15 ± 4	>12	0.641 ± 0.002	17.6 ± 1.15	98.04
3	F3	111.33 ± 2.62	12 ± 2	>12	0.461 ± 0.002	29.7 ± 0.58	98.20
4	F4	67 ± 4.58	8 ± 2	>12	0.303 ± 0.001	14.7 ± 0.58	98.36
5	F5	238.33 ± 2.52	20 ± 4	>12	0.734 ± 0.001	29.3 ± 1.53	98.04
6	F6	208.67 ± 2.52	12 ± 2	>12	0.648 ± 0.001	23.6 ± 1.15	98.51
7	F7	253.33 ± 6.03	16 ± 2	>12	0.771 ± 0.001	34.3 ± 1.53	98.69
8	F8	236.67 ± 4.16	22 ± 4	>12	0.658 ± 0.001	29.0 ± 1.00	98.36
9	F9	175.67 ± 3.51	13 ± 2	>12	0.486 ± 0.001	44.3 ± 1.53	99.83
10	F10	194.33 ± 3.21	17 ± 2	>12	0.532 ± 0.001	52.6 ± 1.53	99.53

*All values are expressed as mean ± SD, n=3

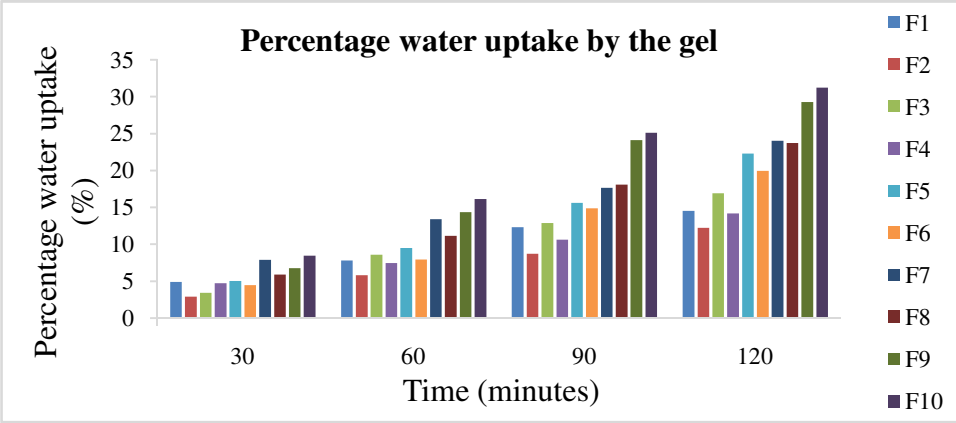


Figure 6: Percentage water uptake of *In situ* gel formulations

Drug Content of Rivastigmine Tartrate Oral *In Situ* Gel

Drug content is one of the important evaluation parameters for any type of dosage form. The percentage drug content of the formulations is given in Table 5. The percentage drug content of all the formulations was in the range of 98.04 - 99.83 % indicating the uniform distribution of drugs in all formulations.

Percentage Water Uptake by Rivastigmine Tartrate *In situ* Gel

Percentage water uptake by the gel plays an important role in determining the release of the drug from the polymer matrix which involves the penetration of water into the matrix and simultaneous release of the drug through diffusion or dissolution. The percentage water uptake of all the formulations is given in Fig. 6. When compared with other formulations, F9 and F10 showed a better water uptake of 29.27% and 31.22% respectively. The high water uptake may be because of the high swelling capacity of the polymers used. The formulations F9 and F10 contain a combination of Sodium alginate, Gellan gum, Iota carrageenan and HPMC K4M. This results in high water uptake.

In Vitro Dissolution Study of Formulated Rivastigmine Tartrate Oral *In Situ* Gel

The results of *In vitro* drug release study of the *In situ* gel formulations are given in Fig. 7 and Fig. 8. From the *In vitro* drug release studies of the *In situ* gel formulations (F1 - F10), it was observed that only the Formulations F9 and F10 containing the combination of all three polymers (Sodium Alginate, Gellan gum and Iota carrageenan) provided prolonged release of the drug up to 12 hours. Other formulations (F1 - F8) released the drug even before the period of 12 hours. Formulation F9 containing Sodium alginate (0.5 % w/v), Gellan gum (0.15 % w/v) and Iota carrageenan (0.2 % w/v) showed 99.91 % of drug release at the end of 12 hours. Formulation F10 containing Sodium alginate (0.5 % w/v), Gellan gum (0.15 % w/v) and Iota carrageenan (0.25 % w/v) showed 91.11 % of drug release at the end of 12 hours.

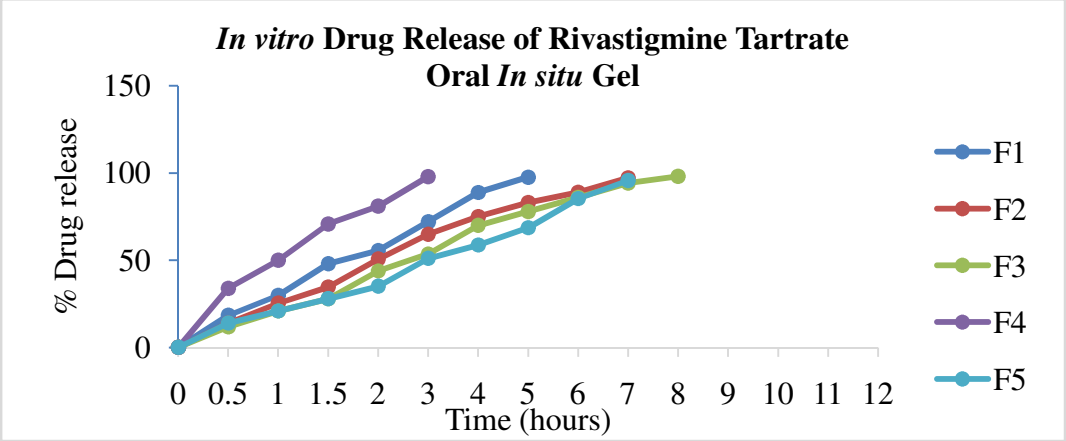


Figure 7: *In vitro* drug release study of *In situ* gel formulations (F1 - F5) of Rivastigmine tartrate

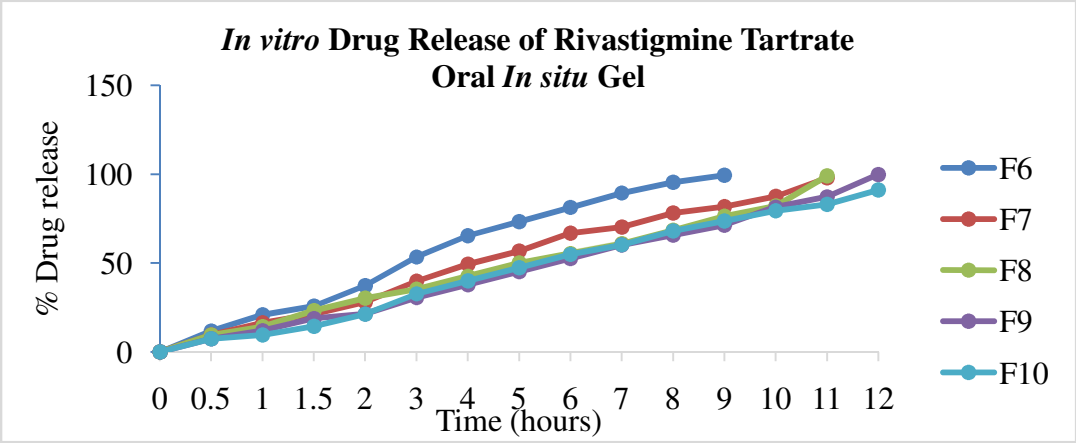


Figure 8: *In vitro* drug release study of *In situ* gel formulations (F6 - F10) of Rivastigmine tartrate

Selection of Optimized Formulation

Based on the *In vitro* drug release studies of the *In situ* gelling formulations, formulation F9 and F10 were considered to be suitable for providing prolonged delivery of Rivastigmine tartrate as it extended the drug release up to 12 hours. Comparing other evaluation parameters like pourability, viscosity, density and drug content of both the formulation F9 and F10, the formulation F9 was found to be a better formulation than F10. Hence, Formulation F9 is chosen as the optimized formulation.

***In Vitro* Release Kinetics of Optimized Formulation**

The *In vitro* release of optimized formulation F9 data was fit into various kinetic models such as Zero order, First order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas kinetics as shown in Fig. 9 - 13to find out the mechanism of drug release from Rivastigmine tartrate oral *In situ* gel.

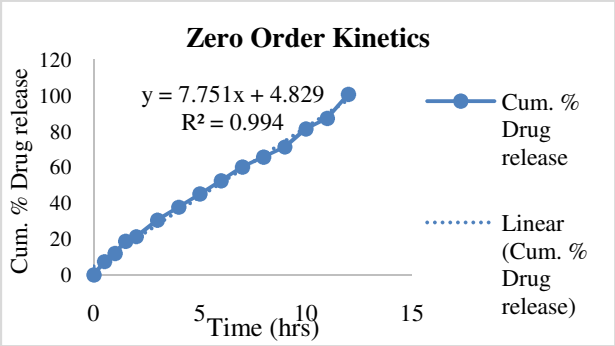


Figure 9: A plot of zero order kinetics of optimized formulation (F9)

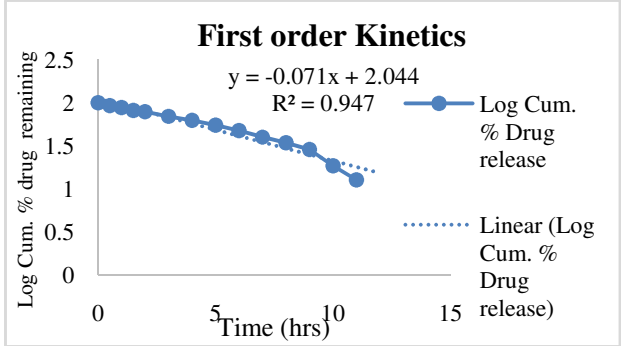


Figure 10: A plot of first order kinetics of optimized formulation (F9)

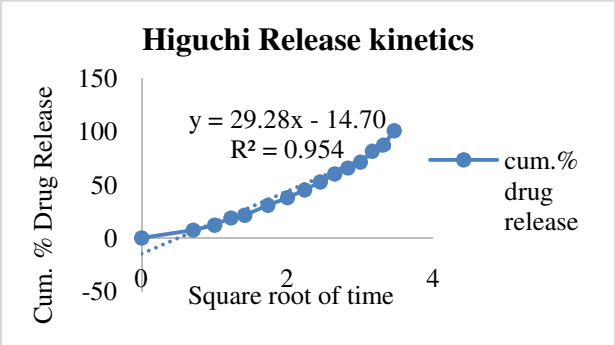


Figure 11: A plot of Higuchi kinetics of optimized formulation (F9)

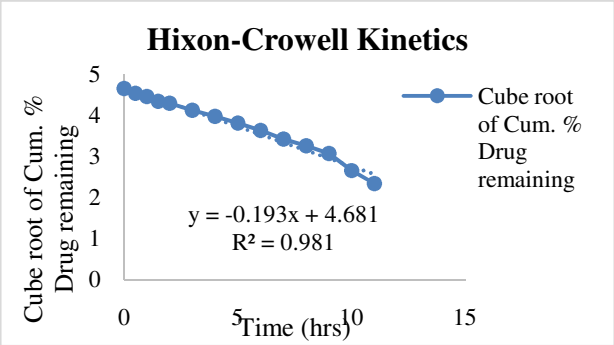


Figure 12: A plot of Hixon-Crowell kinetics of optimized formulation (F9)

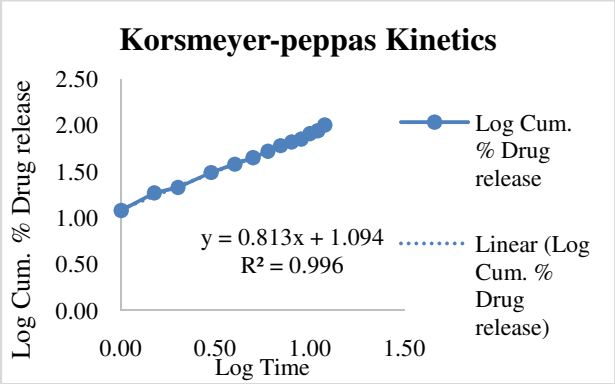


Figure 13: A plot of Korsmeyer-Peppas kinetics of optimized formulation (F9)

The coefficient of determination (R^2) was taken as criteria for choosing the most appropriate model. The R^2values of various models are given in Table 6.

Table 6: R^2Values of various Kinetic Models of Optimized formulation (F9)

Kinetic Models	Coefficient of Determination (R^2)
Zero-order	0.9944
First Order	0.9475
Higuchi	0.9542
Hixon-Crowell	0.9815
Korsmeyer - Peppas	0.9968

A good linearity was observed with the zero order (R^2=0.9944). The slope of the regression line from the Higuchi plot (R^2=0.9542) and Hixson-Crowell plot (R^2=0.9815) indicates the rate of drug release follows both diffusion and dissolution mechanisms. The slope of the Korsmeyer-Peppas plot (n= 0.8133) was found to be more than 0.45 indicating Anomalous diffusion (Non-Fickian diffusion). Thus, the release kinetics of the optimized formulation showed zero order drug release with Non-Fickian diffusion mechanism.

Table 7: Results of Stability studies for Optimized Formulation – F9

Parameter	Condition: 40±2ºC/75±5%RH	
	Initial	After 3 months
Visual Appearance	Dull-white	Dull-white
Pourability	Easily pourable	Easily pourable
pH*	7.39 ± 0.2	7.37 ± 0.2
Gelling capacity	+++	+++
Floating Lag time (s)*	13 ± 2	15 ± 2
Floating duration (hours)	>12	>12
Viscosity (cps)*	175.67 ± 3.51	178.3 ± 1.15
Drug content (% w/v)	98.69	98.36

*All values are expressed as mean ± SD, n=3

Table 8: Stability data for Optimized Formulation (Cumulative % drug release of Optimized formulation) - F9

Time (hours)	% Cumulative drug release	
	Condition: 40±2ºC/75±5%RH	
	Initial	After 3 months
0.5	7.42	9.61
1	12.0	16.42
1.5	18.83	25.57
2	21.39	32.66
3	30.61	42.12
4	37.81	51.74
5	45.17	62.72
6	52.55	67.11
7	60.21	72.72
8	65.72	76.33
9	71.33	82.11
10	81.46	85.77
11	87.33	91.72
12	95.52	95.50

Stability Studies

The optimized formulations (F9) subjected to stability studies as per ICH guidelines and shown in Table 7 and 8. No significant changes in Physical appearance, pH, viscosity, gelling capacity, floating lag time, drug content and *In vitro* drug release were observed at storage condition of 40°C ± 2°C / 75 ± 5% RH at the end of 3 months.

CONCLUSION

The Rivastigmine tartrate oral *In situ* gel was developed using gelling agents such as Sodium Alginate, Gellan gum, Iota carrageenan and HPMC K4M. The overall results indicate that the formulation of Rivastigmine tartrate as oral floating *In situ* gel provides controlled release of the drug. This may improve patient compliance due to the ease of administration and reduction in dosing frequency. Hence, the developed formulation can be used as an alternative to the conventional dosage form for the treatment of Alzheimer's disease in patients.

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REFERENCES

[1] Rao UG, Murari P. Buoyant sustained release drug delivery systems current potentials advancements role of polymers. Int J Comprehensive Pharm 2012; 3:1-5.

[2] Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems. Trop J Pharm Res 2008; 7:1055-66.

[3] Shah SH, Patel JK, Patel NV. Stomach specific floating drug delivery system: A review. Int J Pharm Res 2009; 1:623-33.

[4] Arunachalam A. Floating drug delivery systems. Int J Res Pharm Sci 2011; 2:76-83.

[5] Drach L.M. - Drug treatment of dementia with Lewy bodies and Parkinson's disease dementia--common features and differences. - Med. Monatsschr. Pharm 2011; 34:47-52.

[6] Kapil R, Beg S, Singh B. Alzheimer's Disease: Pathology and Treatment Strategies. Trendz in Med. World, 2011.

[7] Inglis F. The tolerability and safety of cholinesterase inhibitors in the treatment of dementia. Int. J. Clin. Pract. Suppl. 2002; 45-63,.

[8] Jhee SS, Shiovitz T, Hartman RD , Messina J, Anand R, Sramek J et al. Centrally acting antiemetics mitigate nausea and vomiting in patients with Alzheimer's disease who receive Rivastigmine. Clin. Neuropharmacol. 2002; 25:122-123.

[9] Darvesh S, Walsh R, Kumar R, Caines A, Roberts S, Magee D et al. Inhibition of human cholinesterases by drugs used to treat Alzheimer disease. Alzheimer Dis. Assoc. Disord. 2003; 17:117-126.

[10] Grossberg GT. Cholinesterase inhibitors for the treatment of Alzheimer's disease: getting on and staying on. Curr. Ther. Res. 2003; 64: 216-235.

[11] Sharma YR. Elementary Organic Spectroscopy. 4th ed. New Delhi: S. Chand; 2007.

[12] Sharmila SK, Srilakshmi M. Development and Validation of UV Spectrophotometric Method for the Estimation of Rivastigmine Tartrate in Bulk and Pharmaceutical Dosage Form. Indo American Journal of Pharmaceutical Research. 2013; 3(10): 8394-8399.

[13] Nafei AT, Khazaal N. Development and *In vitro/In vivo* Evaluation of Floating *In situ* Gelling oral liquid Extended Release Formulation of Furosemide. UK Journal of Pharmaceutical and Biosciences 2014; 2(5).

[14] Pashikanti SP, Jyothsna B. Formulation and Evaluation of Floating *In situ* Gel Of Ciprofloxacin. International Journal of Applied Pharmaceutics. 2019; 11(1): 198-204.

[15] Adimoolam S, Cindy L. Formulation And *In vitro* Evaluation Of Diclofenac Sodium *In situ* Gelling System By Fenugreek Seed Mucilage; 2017; 2: 88-100.

[16] Sindhoor M, Priya S, Maxwell A, Formulation And Evaluation Of Novel *In situ* Gel Of Lafutidine For Gastroretentive Drug Delivery. Asian Journal of Pharmaceutical and Clinical Research 2018; Vol II (8): 88-94.

[17] Dash S, Murthy PN, Nath L, Chowdhary P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Poloniae Pharmaceutica Drug research. 2010: 67(3): 213-17.

[18] WHO-GMP and ICH Stability Testing Guidelines for Drug Products. The Pharmaceutical Sciences – Pharma Pathway; 2.72-2.79.