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FORMULATION AND DEVELOPMENT OF CONTROLLED RELEASE TABLET USING OPTIMIZATION APPROACH FOR ALZHEIMER'S DISEASE

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ABSTRACT

This research work aims to optimize and formulate the controlled release tablet of Rivastigmine Tartrate using 3^2 factorial design by direct compression method to provide controlled release of drug at the desired site of absorption. The preformulation studies were carried out in terms of test for identification (physical appearance, melting point, IR spectrum) solubility profile. The tablets were prepared by direct compression method. The 3^2 full factorial design was used to study the effect of independent variables (Carbopol 971 & HPMC K15 M) on dependent variable (drug dissolution, floating time and bioadhesive strength). Tablets were prepared using these polymers, with the ratios of drug to polymer kept as 1:3. The preliminary and screening studies were performed using different polymers Carbopol 971, Carbopol 934, HPMC E5 LV and HPMC K 15 M. The polymers Carbopol 971 P and HPMC K 15M promised excellent properties for controlled release and muco-adhesion. Sodium bicarbonate at the concentration of 12% w/w was found to be ideal in achieving the buoyancy and 9 batches were made using 3^2 factorial design. The batch F1 with Carbopol 971 P (35mg) and HPMC K 15 M (20mg) showed the best *ex-vivo* muco-adhesion result with (20.03gm) which released 98% of drug in 12 hrs. The research work resulted into the successful formulation of floating bioadhesive tablet with excellent ex-vivo muco-adhesive properties, which might circumvent the problems in treatment of Alzheimer's disease.

KEYWORDS: Rivastigmine Tartrate, HPMC K15 M, Carbopol 971, 3^2 factorial design, bioadhesive strength.

1. INTRODUCTION

Conventional oral drug delivery system (DDS) is complicated by limited gastric residence time (GRT). Rapid GI transit can prevent complete drug release in absorption zone & reduce the efficacy of the administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine. To overcome these limitations, various approaches have been proposed to increase gastric residence of drug delivery systems in the upper part of GIT includes gastro retentive drug delivery system (GRDDS). Among the GRDDS, floating drug delivery system (FDDS) have been the most commonly used.[1] Floating system are low density system which have adequate buoyancy to float over the gastric region and stay floating in the stomach without affecting gastric emptying time for a prolonged period time. Floating can be achieved by incorporating stomach filled with air, vacuum and inert gas.[2]

Rivastigmine is a cholinergic or parasympathomimetic agent for the treatment of mild to moderate dementia of the Alzheimer's type. Rivastigmine is a cholinesterase inhibitor that inhibits both acetylcholinesterase and butyrylcholinesterase.[3] Its short half-life (1.5hr), dosing frequency (two to four times day) & local action in stomach make rivastigmine ideal candidate for floating drug delivery system.[4]

2. MATERIALS AND METHODS

Material

Rivastigmine tartrate was obtained as gift sample from Alembic Pharmaceuticals Ltd. Vadodara, Gujrat. Carbopol 971 and HPMC K15 M were obtained from Ambika lab, Indore. Other ingredients and excipients used were laboratory analytical grade.

Methods

Preformulation of drug

Objective of pre-formulation study is to develop the elegant (stable, safe and effective) dosage form by establishing compatibility with the other ingredients and to establish physico-chemical parameters of new drug substance. The preformulation studies were carried out in terms of tests for identification (physical appearance, melting point, IR spectra and UV spectrum), solubility profile.

Identification of drug

Organoleptic parameters of Rivastigmine Tartrate were checked by visual inspection. The melting range of Rivastigmine Tartrate was determined using open capillary method. The drug powder was packed into capillary and melting range was determined in thiel's tube.[5]

The solubility of Rivastigmine Tartrate was tested in various common solvents. A small quantity of drug was dissolved in 5 ml, until the drug was saturated in solvents and kept for 24 hrs at room temperature. The solution was filtered and solubility was observed by the UV spectroscopy.[6]

Small quantity of Rivastigmine Tartrate was placed on holder and the FTIR spectrum of drug was recorded in the wave number region of 400-4000cm-1 on FTIR spectrophotometer (Shimadzu Affinity 1).[7]

Calibration curve by U.V. spectroscopy method

a. Preparation of stock solution of Rivastigmine Tartrate in 0.1N HCL

Rivastigmine Tartrate was accurately weighed (100mg) and transferred to a 100ml volumetric flask. To this, 50ml 0.1 N HCL was added to dissolve the drug and the volume was made up to 100ml with 0.1 N HCL to prepare a 1000µg/ml solution. Then 1ml of this stock solution was pipette into a 10ml volumetric flask and volume made up to the mark with 0.1 N HCL to prepare a 100µg/ml solution. It was scanned on a double- beam UV- visible spectrophotometer (Shimadzu 1800) between wavelength 200-400 nm and UV spectrum was recorded.

b. Preparation of calibration curve of Rivastigmine Tartrate in 0.1N HCL

Rivastigmine Tartrate was accurately weighed (100mg) and transferred to 100ml volumetric flask. To this 50ml of 0.1 N HCL was added to dissolve the drug and the volume was made up to 100ml with 0.1 N HCL to prepare 1000µg/ml solution. Then 1ml of this stock solution was pipette into a 10ml volumetric flask and volume made up to the mark with 0.1 N HCL to prepare a 100µg/ml solution. Appropriate dilutions from the stock solution were made in concentration range of 20-100µg/ml. The absorbances were noted taken against reagent blank.[8]

Partition Coefficient[6]

The partition coefficient of Rivastigmine Tartrate was examined in n-octanol: water system. It was determined by taking 10mg of drug in separating funnel, containing 10ml of n- octanol and 10ml of water. The separating funnel was shaken for 1 hour. Two phases were separated and the amount of drug in aqueous phase was analyzed spectrometrically at 263nm after appropriated dilution.

$$Partition\ coefficient = \frac{\text{concentration of drug in organic phase}}{\text{concentration of drug in aqueous phase}}$$

Formulation

Method of preparation: The tablets were prepared by direct compression method. Rivastigmine tartrate, Carbopol and HPMC were sieved through # 30 sieve. $NaHCO_3$ (Sodium bicarbonate), Magnesium stearte & MCC (microcrystalline cellulose) were sieved through #60 sieve before the use. The amount of Rivastigmine Tartrate was kept constant in each formulation (i.e. 12mg). All the materials were accurately weighed and blended using hand blender and compressed on a manual single punch tablet compression machine into 100mg tablets. 3^2 factorial design was employed for the screening of formulation and 9 formulations were prepared.

Optimization

The 3^2 full factorial design was used to study the effect of independent variables (Carbopol 971 & HPMC K15 M) on dependent variable (drug dissolution, floating time and bioadhesive strength). Tablets were prepared using these polymers, with the ratios of drug to polymer kept as 1:3.

Preliminary study for polymer identification:

Four polymers choosed Carbopol 971p, Carbopol 940, HPMC E5LV & HPMC K15M CR were chosen for formulating oral controlled release floating bioadhesive tablet of Rivastigmine Tartrate. Total 9 batches were formulated using blends of these polymer. Finally depending upon the result obtained polymer blends containing only two polymers that is Carbopol 971P & HPMC K15M CR was choosed for further study.[9]

Table 1: Factorial design batches.

Formulation code	Coded level (Amount)	
	Carbopol (mg)	HPMC (mg)
F1	1	0
F2	-1	1
F3	0	-1
F4	-1	-1
F5	1	1
F6	0	1
F7	-1	0
F8	1	-1
F9	0	0

Coded values: Carbopol 971 P: -1 (15), 0 (25), +1 (35)

HPMC K 15 M: -1 (10), 0 (20), +1 (30)

Characterization

Pre compression characterization[10]

Pre-compression parameters such as angle of repose, tapped density, bulk density, Carr's index, & Hausner's ratio were characterized for powder blend.

Flow properties

Unequal flow of powder from the hopper produce tablets with nonuniform weights. As a result, content uniformity and dose precision cannot be achieved in the production of tablets. Flow properties depend on particle size, shape, porosity and density of the bulk powder.

Angle of repose: angle of repose is defined as the maximum angle possible b/w the surface of a pile of the powder & the horizontal plane.

$$\tan\Theta = h/r$$

where h=height of pile

r = radius of the base of the pile

Θ=angle of repose

Bulk density

Bulk density depends on the density of the powder particles and on the arrangement of the powder particles. The bulk density is obtained by adding a known mass of powder to a graduated cylinder. The density is calculated by formula,

$$Bulk\ Density = \frac{Mass\ of\ Powder}{Bulk\ Volume}$$

Tapped density

The tapped density is obtained by mechanically tapping a graduated cylinder containing the sample until little further volume change is observed.

$$Tapped\ density = \frac{Mass\ of\ powder}{tapped\ volume}$$

Carr's index

The bulk and tapped density were used to calculate the carr's index and Hausner ratio to provide a measure of the flow properties and compressibility of powder.

$$Carr's\ Index = \frac{Tapped\ density - Fluff\ density}{Tapped\ density} X\ 100$$

Hausner's ratio

Hausner ratio can be used to estimate the flow characteristic of the powder.

$$\text{Hausner's ratio} = \frac{\text{Tapped volume}}{\text{Bulk volume}}$$

Post compression characterization[6]

Weight variation

Not more than two of the individual weights deviate from the average weight by more than the percent shown below & none deviates by more than twice that %.

$$Deviation\ (\%) = \frac{Average\ weight - weight\ of\ tablet}{Average\ weight} X100$$

Hardness

Hardness of tablet is defined as the force required to break a tablet a in a diametric direction. A tablet was placed b/w two anvils. Force was applied to anvils & crushing strength that causes the tablet to break was recorded. Hardness is thus the tablet crushing strength. Monsanto tester is used for hardness testing.

Friability

Weigh 10 tablets and place in a friabilator chamber rotated at 25 rpm and they are dropped on distance of 6 inches. The chamber is allowed to rotate for 100 revolutions. Then the tablets are removed, dusted and again the weight is taken. The difference in the weigh is calculated and the weight loss should not be more than 1%.

Thickness

The thickness of tablets was performed on 20 tablets from each formulation. Vernier caliper was used for the study.

The Buoyancy lag time and total floating time

The Buoyancy lag time & total floating time were determined by immersion of tablets of different formulation in 0.1 N HCL at 37±.5°C.

Swelling Property

Swelling property was determined by dissolution apparatus. Tablets were introduced in dissolution apparatus containing 900ml of 0.1 N HCL at 50 rpm. The tablets at definite intervals & swollen weight of each tablets was determined by formula.

$$\text{Swelling Index} = \frac{Wt - Wo}{Wo} X100$$

Wt= weight of tablet at time t

Wo= weight of tablet before immersion

Drug content

20 tablets of F1 were taken randomly & crushed in pestle-mortar. The weight equivalent to one tablet was taken in volumetric flask (100ml) & dissolved in 0.1 N HCL and filtered. This solution was analyzed in UV spectrophotometer at λmax 263nm.

Dissolution study

The *in-vitro* dissolution study of tablets were determined by using USP type 2 (Paddle type) dissolution apparatus. For dissolution, 0.1 N HCL was taken as media and the rotation speed was kept at 50rpm at 37±0.5°C in 900ml of distilled water.

***Ex-vivo* mucoadhesive strength**[11]

Mucoadhesive strength of the tablet formulations was determined by modified physical balance. The assembly consists of a modified double beam physical balance in which left sided pan is removed and attached with glass slide with an additional weight is added with slide to balance the weight of both the pan. Fresh intestine mucosa of goat was used as membrane obtained from local slaughter house and kept in kerb solution during transportation and 0.1 N HCL was use for moistening the mucosa. The underlying mucous membrane was separated with the use of surgical blade and tied with the glass slide with the

help of thread. Now the prepared tablet was made to stitch with the wooden block and made contact with the mucous membrane and the tablet. The additional weight was increased on the right pan until the tablet detach from the membrane and the weight used was noted as mucoadhesive strength in grams and force of adhesion was calculated.

Optimization

A 3^2 factorial design was used to study the effect of independent variables selected as Carbopol971 (X1) and HPMC K 15M (X2) on the dependant variables drug dissolution, floating time and bioadhesive strength. The statistical model incorporating interactive and polynomial terms was used to evaluated the responses.[9]

$$Y= b_0 + b_1X_1+ b_2 X_2+ b_{12}X_1X_2 + b_{11} X_1^2 + b_{22} X_2^2$$

Table 2: Responses as per factorial design.*

Run	Factor 1 A:Carbopol mg	Factor 1 B:HPMC mg	Response 1 Drug release 12h (%)	Response 2 Floating time (hrs)	Response 3 Bioadhesive strength (gm)
1	1	0	103.1	18.32	20.3
2	-1	1	73.02	24.21	14.52
3	0	-1	74.98	13.25	9.36
4	-1	-1	76.12	11.23	5.02
5	1	1	93.42	28.21	24.12
6	0	1	81.23	24.25	22.17
7	-1	0	82.09	14.15	11.24
8	1	-1	90.67	15.36	14.25
9	0	0	89.67	17.38	16.56

*All batches contained 12 mg Rivastigmine Tartrate, 11% magnesium stearate, 12% sodium bicarbonate, A is the percentage of carbopol, and B is the percentage of HPMC.

Stability Studies

Tablet of formulation F1 were subjected to chemical stability testing. Tablet was kept in 10ml glass vials and vials are plugged and sealed. Vials are kept at 40˚C±2°C and 75± 5%RH. The samples were withdrawn at different time intervals and drug contents were determined by UV spectrophotometric analysis. The initial drug content was considered as 100.00%.

3. RESULT AND DISCUSSION

Organoleptic parameters

Table 3: Organoleptic Parameters.

S. No.	Parameters	Observation
1.	Colour	White
2.	Odour	Odorless
3.	Nature	Powder

Melting Point determination

Table 4: Melting point of Rivastigmine Tartrate.

S. No.	Drug	Melting Point	
		Standard[5]	Experimental±3
1	Rivastigmine Tartrate	123-125°C	122-125°C

Solubility studies of Rivastigmine Tartrate

Table 5: Solubility studies in various solvents

S. No.	Solvents	Solubility
1	Water	620 mg/ml
2	Ethanol	30 mg/ml
3	Acetonitrile	50 mg/ml

Infra-Red Spectroscopy (IR)

For characterization of pure Rivastigmine Tartrate FTIR studies were carried out. The observed and reported characteristic peaks of functional group have been shown in table 6 and FTIR spectrum is shown in (Fig.1).

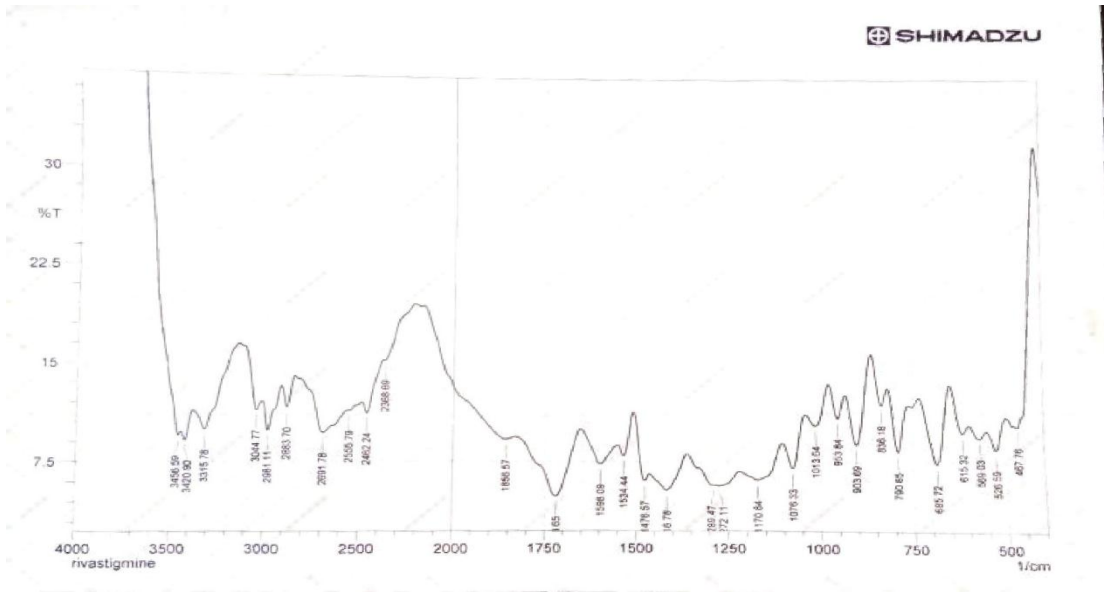


Fig 1: Infra-Red Spectrum of Rivastigmine Tartrate.

Table 6: Interpretation of the IR Spectra of Rivastigmine Tartrate.

S.N.	Obtained peak (cm^{-1})	Reference peak (cm^{-1})[7]	Interpretation
1	679.72	669.31	Meta di substituted aromatic ring
2	1618.65	1633.50	Conjugated esters
3	3315.78	3313.90	Primary amines
4	3429.59	3411.9	N-C stretching
5	1159.76	1152.84	Aliphatic amines

Calibration curve by U.V. spectroscopy method

Preparation of stock solution of Rivastigmine Tartrate

Rivastigmine Tartrate shown absorbance at 262nm in 0.1N HCL (Fig.1). While reported λ max of drug is 263nm.

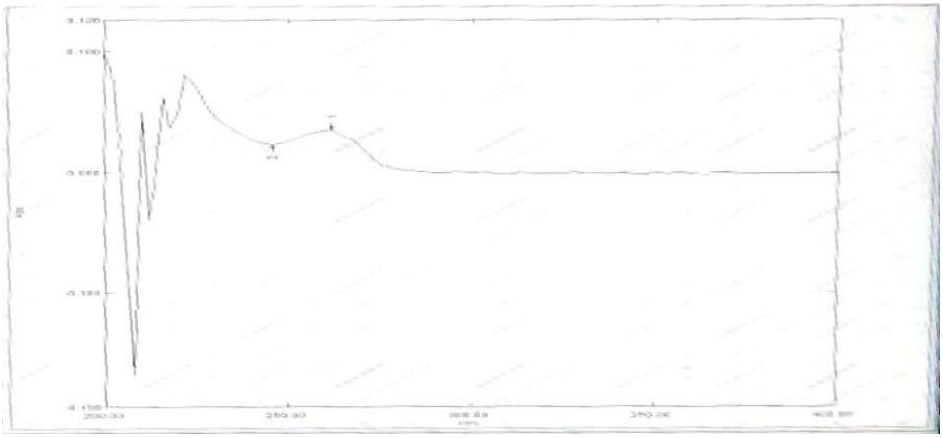


Fig. 2: UV spectrum of Rivastigmine Tartrate.

Preparation of calibration curve of Rivastigmine Tartrate in 0.1N HCL

A linear relationship was obtained in Beer-Lamberts plot of Rifabutin (y =0.001x+0.002, R^2=0.999). The calibration data is given in Table 3 and graph obtained after plotting absorbance (y) vs. concentration (x) is shown in Fig.3.

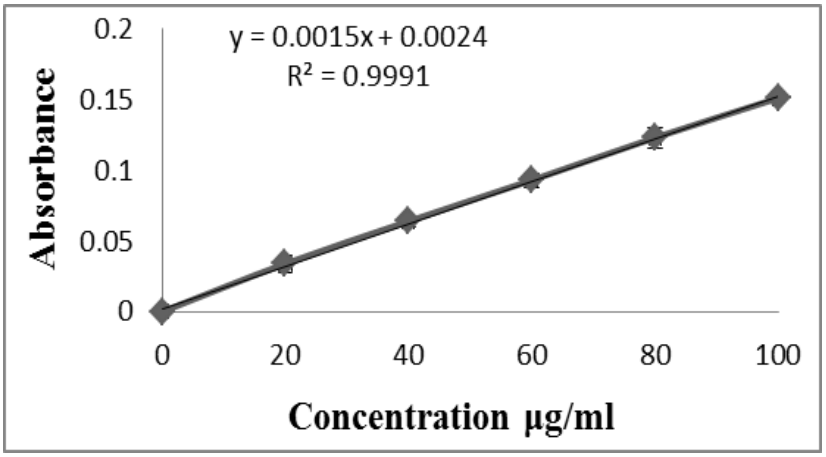


Fig 3: Calibration curve of Rivastigmine Tartrate in 0.1 N HCL.

Partition coefficient

Partition coefficient was found by shake flask method.

Table 7: Partition Coefficient

S. No.	Medium	Partition Coefficient (n-octanol/aq. Phase)	
		Observed	Reported[5]
1.	n-octanol : water	2.58	2.61

Pre compression characterization

Table 8: Pre-compression characterization.

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index (%)	Hausner Ratio	Angle of Repose
F1	0.358	0.433	17.32	1.20	36.77
F2	0.365	0.464	21.33	1.27	32.33
F3	0.385	0.449	14.25	1.16	36.18
F4	0.343	0.437	21.51	1.27	34.88
F5	0.369	0.465	20.64	1.26	31.65
F6	0.278	0.420	33.80	1.51	37.64
F7	0.299	0.473	36.78	1.58	32.62
F8	0.315	0.400	21.25	1.26	35.75
F9	0.335	0.423	20.80	1.26	36.13

Post compression characterization

Table 9: Post compression characterization.

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
F1	99±.49	2.59±.01	7.51±.91	0.34±.43
F2	100±.01	2.51±.04	7.54±.42	0.31±.46
F3	101±.02	2.56±.06	8.34±.23	0.37±.41
F4	100±.04	2.54±.09	8.74±.78	0.29±89
F5	103±.01	2.53±.01	8.54±.41	0.21±.67
F6	97±±.05	2.51±.02	9.01±.10	0.38±.56
F7	100±.01	2.56±.03	9.05±.44	0.35±.57
F8	101±.03	2.59±.01	8.31±.27	0.24±.43
F9	99±.06	2.56±.02	8.30±.28	0.26±.23

Table 10: Buoyancy Lag Time & Total Floating Time.

S. No.	Formulation code	Buoyancy lag time (sec)	Total floating time (hrs.)
1	F1	70±3	18.32±0.6
2	F2	300±2	24.21±0.1
3	F3	240±1	13.25±0.3
4	F4	60±2	11.23±0.2
5	F5	60±4	28.21±0.6
6	F6	290±3	24.25±0.4
7	F7	30±1	14.15±0.2
8	F8	120±1	15.36±0.9
9	F9	180±4	17.38±0.1

Table 11: Swelling Property of F1 batch.

S. No.	Time (hrs.)	Swelling Index (F1)
1	15	70±0.12

Table 12: Drug content of F1 batch.

S. No.	Batch	Drug content (%)
1.	**F1**	**97±3**

Table 13: Dissolution profile of various batches.

Time (hrs.)	Cumulative drug release (%)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	6.99	3	6.99	2	6.99	3	2	6.99	2
2	23	13	13	8	13	18	8	23	18
3	48	28	33	28	23	23	33	36	28
4	53	33	48	33	38	48	43	49	23
6	68	48	51	48	58	58	48	58	33
8	78	68	59	68	73	68	63	69	53
10	83	71	65	71	83	73	76	78	73
12	103	73	74	76	93	81	82	90	89

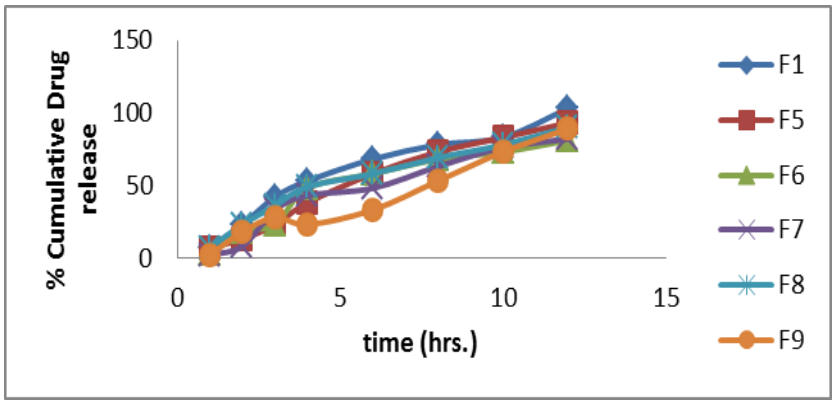


Fig 4: Dissolution profile of various batches.

***Ex-vivo* mucoadhesive strength**

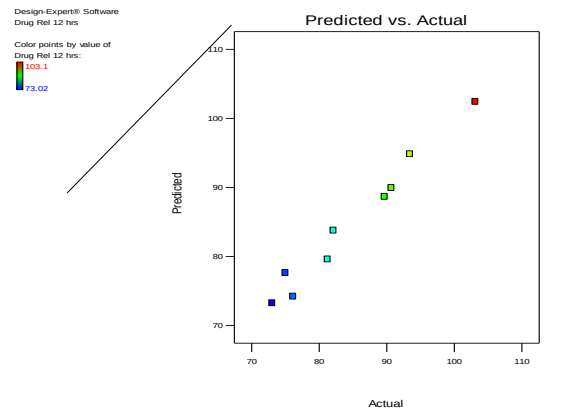
Fig 5: Determination of Bioadhesive strength by modified physical balance.

Table 14: Bioadhesive strength of the tablets.

S. No	Formulation	Bioadhesive strength (gm) ±SD
1	F1	20.03±0.5
2	F2	14.52±0.1
3	F3	9.36±0.4
4	F4	5.02±0.5
5	F5	24.12±0.1
6	F6	22.17±0.2
7	F7	11.24±0.4
8	F8	14.25±0.2
9	F9	16.56±0.2

Optimization

In vitro drug release



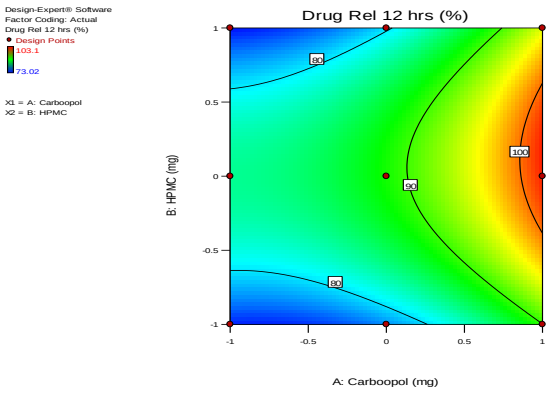


Fig 6: Predicted vs. Actual plot of *in vitro drug*. **Fig 7: Contour plot of *in vitro* drug release release.**

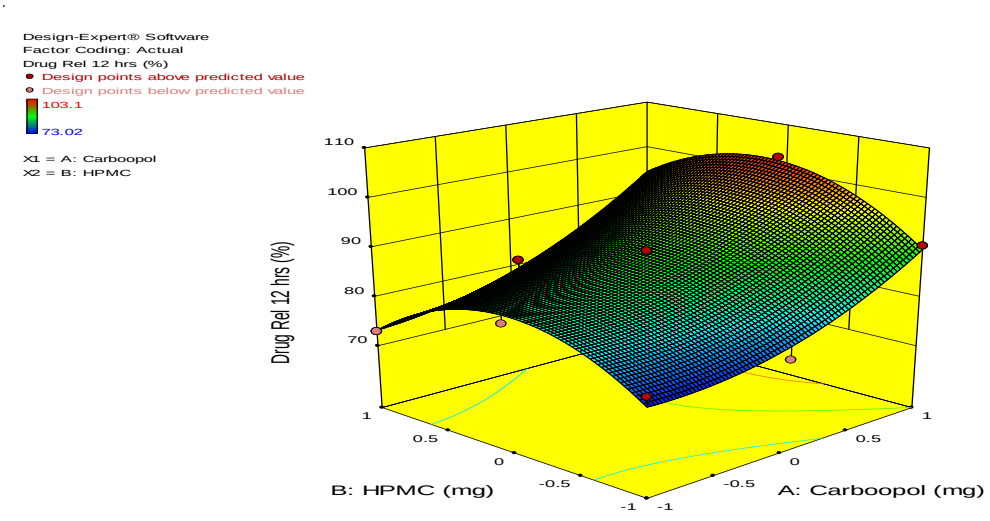


Fig 8: 3D Response surface plot of *in vitro* drug release.

Floating optimization

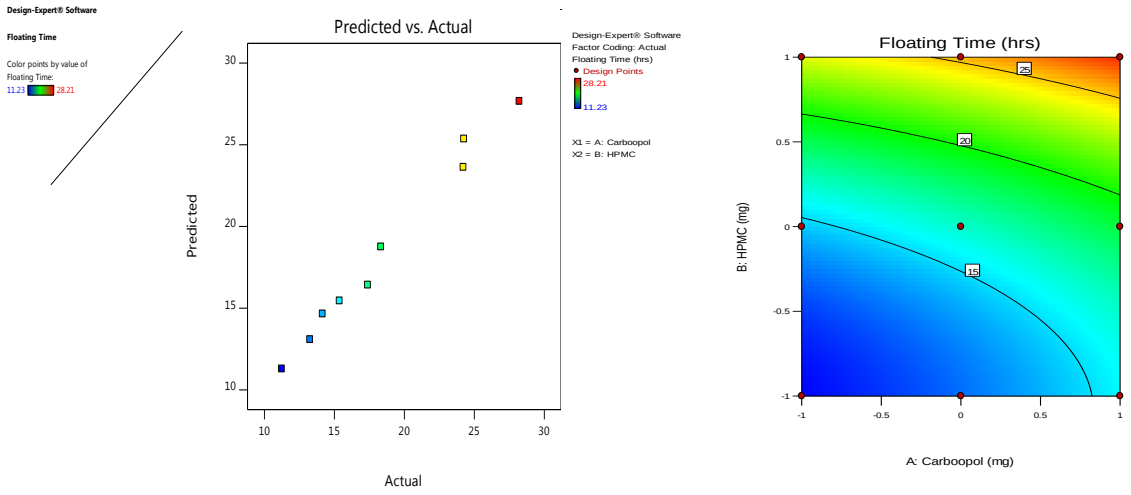


Fig 9: Predicted vs. Actual plot of floating time. Fig 10: Contour plot for floating time.

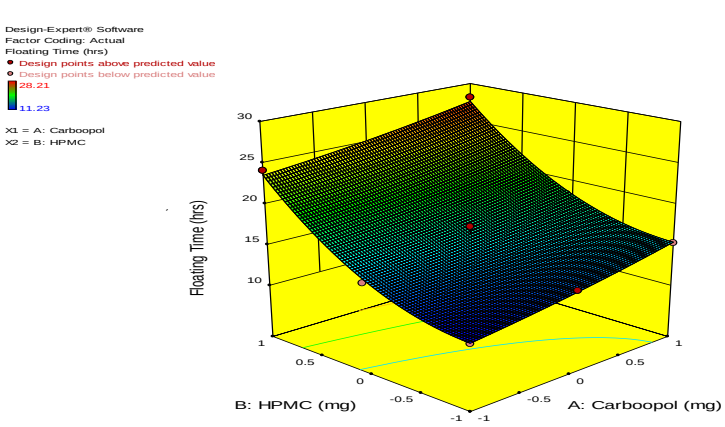


Fig 11: Response surface plot of floating time.

Bioadhesive strength optimization

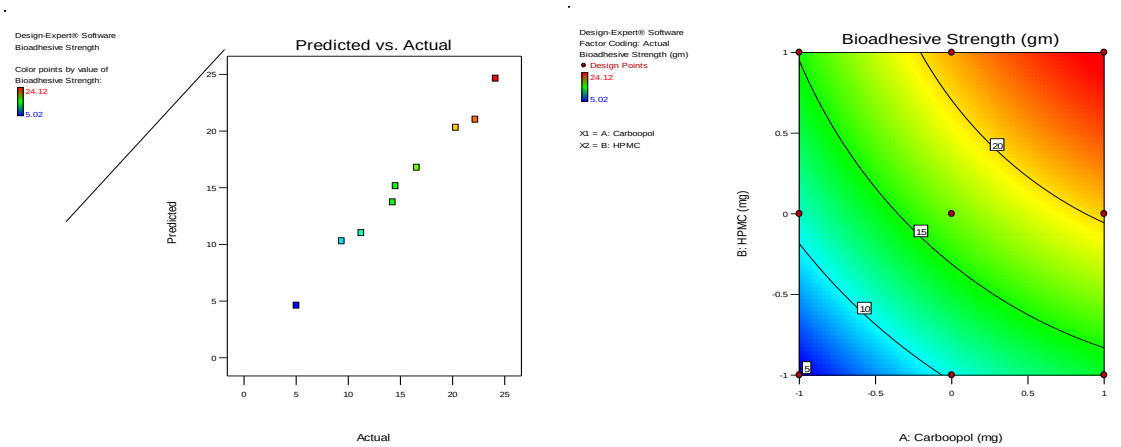


Fig 12: predicted vs. Actual plot for bioadhesive. Fig 13: Contour plot for bioadhesive strength strength.

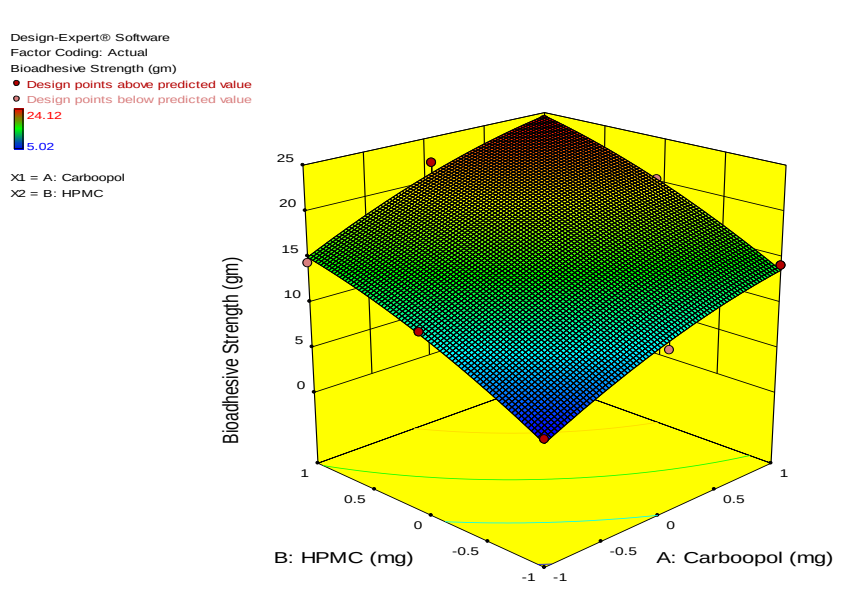


Fig 14: 3D Response surface plot of bioadhesive strength.

Table 15: Stability study data of F1.

Condition	Time (days)	% residual drug in formulation
		F1
40˚C±2°C and 75± 5%RH	0	100.00
	15	99.98
	30	99.97

4. CONCLUSION

Alzheimer's disease is a cognitive disorder that accounts for having 30 million persons suffering worldwide.[4] The current research work aimed at developing a novel drug delivery system, in the form of floating bioadhesive tablet to improve the release of drug for longer period of time to treat the Alzheimer's disease symptomatically using optimization approach. Rivastigmine Tartrate, as a cholinesterase inhibitor, suffers from problems like frequent dosing and GIT adverse effects like unbalanced plasma concentration level. The floating bioadhesive tablet of Rivastigmine Tartrate was developed to provide release in sustained manner and to reduce GI adverse effect. The preliminary and screening studies were performed using different polymers and the polymers Carbopol 971 P and HPMC K 15M promised excellent properties for controlled release and muco-adhesion. Using selected polymers, the final batches were prepared by direct compression method and were evaluated for Buoyancy lag time and total floating time, Swelling index, Drug content, Dissolution study and ex-vivo mucoadhesive strength. The batch F1 with Carbopol 971 P (35mg) and HPMC K 15 M (20mg) showed the best ex-vivo muco-adhesion result with (20.03gm) which

was desired for the formulation. The research work resulted into the successful formulation of floating bioadhesive tablet with excellent ex-vivo muco-adhesive properties, which might circumvent the problems in treatment of Alzheimer's disease.

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