WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 1, 815-829. Research Article ISSN 2277– 7105

DESIGN AND IN VITRO CHARACTERIZATION OF PHASE TRANSITION SYSTEM USING RIVASTIGMINE TARTRATE FOR NASAL DRUG DELIVERY SYSTEM

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Article Received on
27 October 2018,

Revised on 17 Nov. 2018,
Accepted on 07 Dec. 2018

DOI: 10.20959/wjpr20191-13824

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ABSTRACT

The aim of the present study is to overcome the limitations of nasal cavity like low residence time by using *in situ* gel forming nasal drug delivery system prepared from polymers that exhibit phase transition (Sol-Gel) and pseudo plastic behaviour to minimize interference within the mucociliary clearance. It the increasing of the delivery residence of the delivery system and enhancing bioavailability. Rivastigmine tartrate, a preferential-type central acting anti-cholinesterase, is currently used in the treatment of Parkinson. Rivastigmine tartrate is readily absorbed from gastrointestinal tract from conventional preparations and crosses the blood brain barrier. It undergoes extensive first pass metabolism in liver. With the advent of new era of pharmaceutical dosage forms, nasal drug delivery system has established itself as an integral part of novel drug delivery system. Nasal gel is prepared by using gelling agent such as Chitosan HCL, HPMC K4M, Carbopol 934, Sodium alginate, Gellun gum and Sod. β-Glycerophosphate and other excipients. It was observed that Phase transition system has best fitted to peppas model. Phase transition nasal gel has r2 value (0.9343) and n value (1.1566). Also, it was observed that nasal gel FF9 a formulation has best fitted to order release. Hence revealed that FF9 optimized formulation.

KEYWORDS: Rivastigmine tartrate, Chitosan HCL, Sod. β-Glycerophosphate, Sodium alginate.

INTRODUCTION

The nasal route is an attractive alternative to drug administration and provides a direct access to the systemic circulation. In this, drugs are administered through nasal cavity by different

dosage forms such as solution, emulsion, gel etc. and useful method for drugs having low dose and shows no or minimal oral bioavailability such as proteins and peptides. One of the reasons for the low degree of absorption of peptides and proteins via the nasal route is rapid movement away from the absorption site in the nasal cavity due to the mucociliary clearance mechanism. Presently, commercially various nasal preparation is used for systemic absorption of drug in a different pathological conditions. Various drugs in clinical use include such as Anti-Parkinson's, decongestants, antibiotics and mucolytic. The nasal cavity may also be exploited as a route of entry into the systematic circulation, either because the absorption profile of the drug is appropriate to its clinical application or destroyed in the gastrointestinal fluids or metabolized in the wall of the gastrointestinal tract or undergo extensive biotransformation by the liver during their first passage around the circulation.[1,2]

Rivastigmine is a para-sympathomimetic or cholinergic agent for the treatment of mild to moderate dementia of the Alzheimer's type and dementia due to Parkinson's disease. The reason behind choosing this drug is bioavailability of drug have approximately 36%, metabolism shows by hepatic ally (pseudo cholinesterase), this drug shows 1.5 hour biological half-life, and shows apparent volume of distribution 1.8 to 2.7 L/kg. That's way for development of phase transition system for nasal drug delivery system of Rivastigmine Tartrate was selected as active drug.

1.1. Advantages of Nasal Drug Delivery System[3,4,5]

- Availability of large nasal mucosal surface area for dose absorption.
- By pass the blood brain barrier.
- Degradation of drug observed in gastro intestinal track is avoided.
- Hepatic first pass metabolism is absent.
- Nasal bioavailability of small drug molecules is good.
- Bioavailability of large drug molecules can be increased by means of absorption enhancers.
- Convenient route for the patient on long term therapy.
- Improved bioavailability.
- Side effects are reduced due to low dose.
- A self-administration is possible.
- Direct transport into systemic circulation and central nerves system is Possible.

- The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.

1.2. Limitations of Nasal Drug Delivery System[3,4,5]

- Absorption surface area is less when compared to gastro intestinal track. Once the drug administered cannot be removed.
- High molecular weight compounds cannot be delivered by this route.
- Large interspecies variability is observed in this route.
- Normal defence mechanisms like mucociliary clearance and biliary beating affects the permeability of drug.
- Irritation of nasal mucosa by drugs like budesonide.
- Limited understanding of mechanisms and less developed models at this stage.
- Systemic toxicity occurring due to absorption enhancers is yet not established.
- Smaller absorption surface compared with gastro intestinal track.
- Possibility of nasal irritation hence inconvenient compared with oral route.
- Enzymatic barrier to permeability of drug.

1.3 Phase Transition System[6]

Phase transition system is also known as in situ system in situ is a Latin phrase which when translated literally means "In position". In situ gel is drug delivery system that is in solution form before administration in the body, but once administered, undergo gelation in situ, to form a gel.

Administration route for in situ gel are oral, ocular, rectal, vaginal, nasal, injectable and intraperitoneal routes.

1.4 Advantages of Phase Transition (*In situ*) forming Gel

The various advantages of *in situ* gel are

1) Ease of administration

2) Improved local bioavailability

3) Reduced dose concentration Reduced dosing frequency

4) Improved patient compliance and comfort

5) Its production is less complex and thus lowers the investment and manufacturing cost.

2. MATERIALS AND METHODS

2.1. Reagents and Chemicals

Standard drugs of Rivastigmine tartrate were kindly supplied as a gift sample by Sun Pharm Vadodara, Gujarat all the materials used in the study are Chitosan HCL Merk Pharm, Ahmedabad, Gujarat, HPMC K4M Colorcon Asia Pvt. Limited, Goa, Carbopol 934 Dr. Reddy's Research & Development, Hyderabad, Sodium alginate, Gallum gum and Sod. β-Glycerophosphate Himedia Lab. Pvt. Limited.

2.2. Instrumentation

The various apparatus used were like Electronic Balance (Model No.AW-220 and BX –6205 Pioneered (OHAUS), USA.), FTIR Spectrophotometer (Model -84005, Shimaduzu Asia Pacific Pvt Ltd. Singapore.), Brookfield Viscometer (Brookfield RVDE 230), Assembly for gel Strength Measurement, Assembly for Mucoadhesion Force Measurement, Franz Diffusion Cell (Laboratory fabricated assembly).

2.3. Formulation of Rivastigmine tartrate nasal gel

Table 1: Factorial Batch Formulation of Phase Transition System.

	Formulation Code with Their Quantity								
Name of Ingredient	**FF1**	**FF2**	**FF3**	**FF4**	**FF5**	**FF6**	**FF7**	**FF8**	**FF9**
Drug (mg)	150	150	150	150	150	150	150	150	150
Chitosan HCl (mg)	100	100	100	100	100	100	100	100	100
Sodium Alginate (mg)	20	30	40	20	30	40	20	30	40
Gellan Gum (mg)	20	20	20	30	30	30	40	40	40
Sod β-Glycerophosphate(mg)	432	432	432	432	432	432	432	432	432
Benzaalkonium Chloride (w/v)	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Water for Injection (ml)	10	10	10	10	10	10	10	10	10

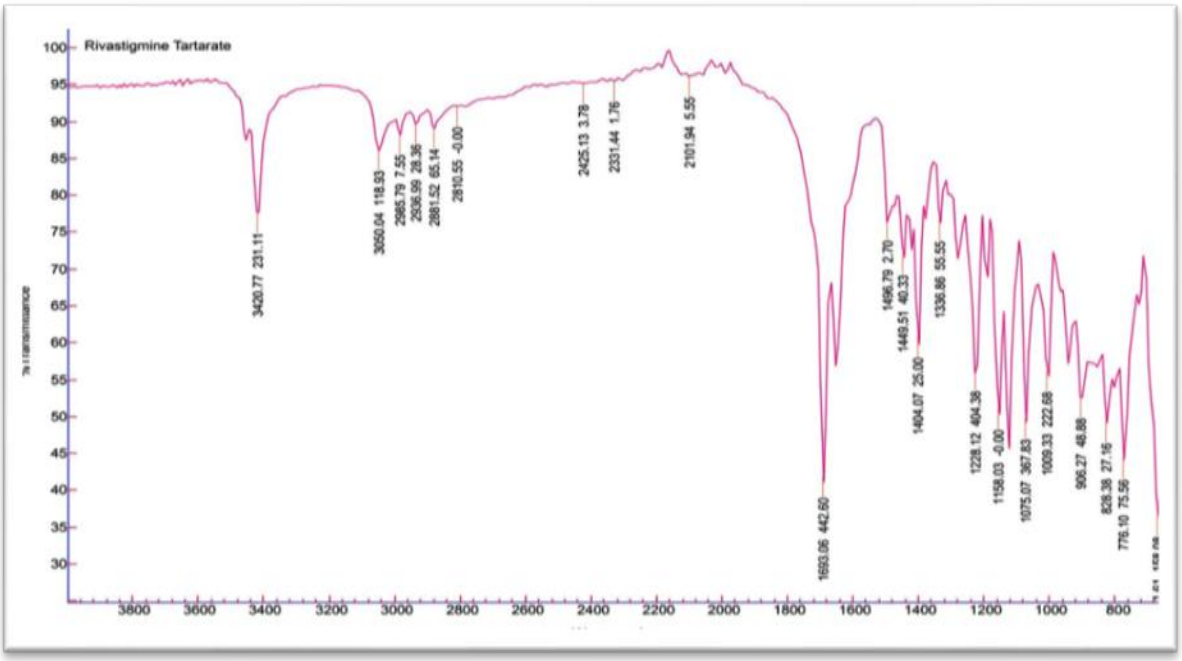
2.4. Factorial Batch for Formulation of Phase Transition System

The formulation of phase transition system were prepared by employing gellan gum, sod alginate, and using chitosan hydrochloride as mentioned in the Table 1 was prepared by dissolving the chitosan hydrochloride and hydroxy propyl methyl cellulose K4M in the distilled water and to that resultant solution, weighted quantity of drug Rivastigmine Tartrate was dissolved and cooling up to 4°C. To this solution sodium β-glycerophosphate solution was added drop by drop with continuous stirring and the volume was made up with sterile water for injection. The final pH of the formulation was adjusted to 6.8-7.2.

3 RESULT AND DISCUSSION

3.1 IR Spectroscopy

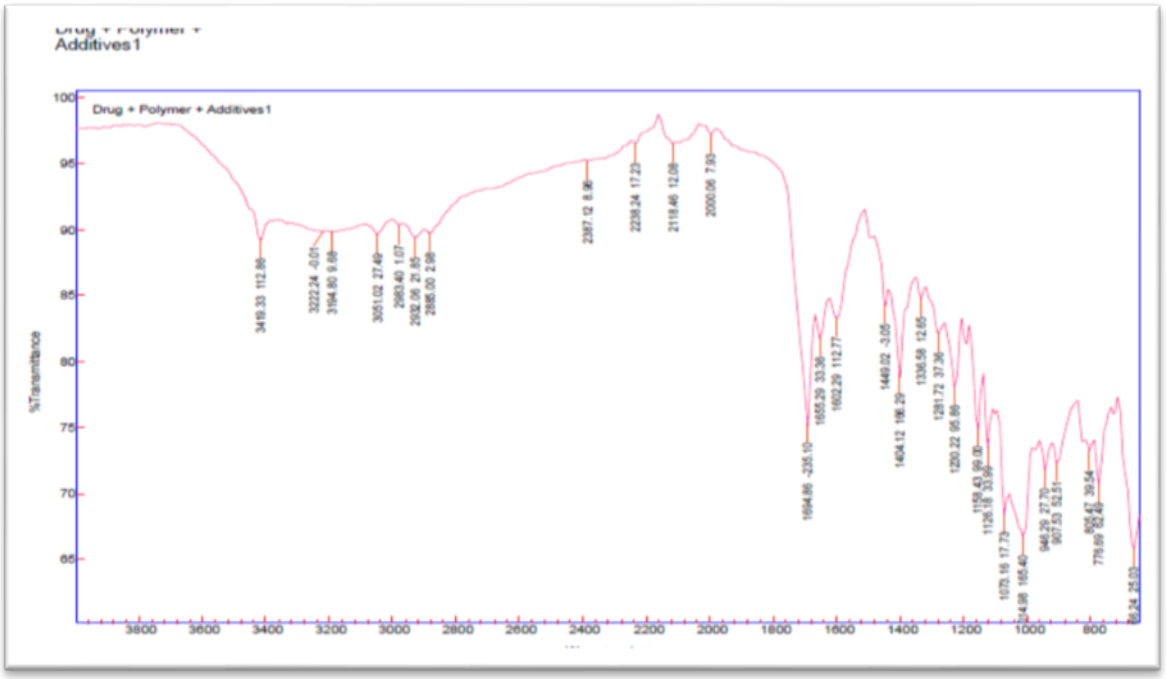
3.1.1 FTIR Study of Rivastigmine Tartrate



Graph 1: FTIR Spectra of Rivastigmine Tartrate.

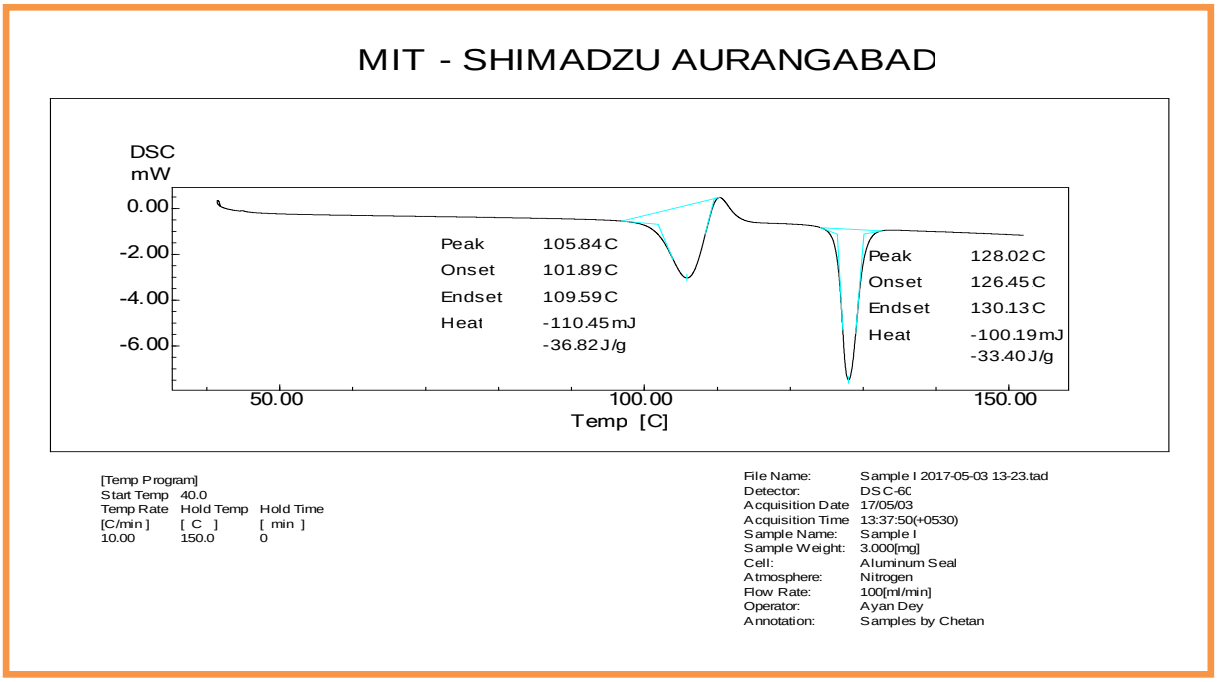
3.1.2 Drug-Excipients Interaction Studies

FTIR Spectra of Drug and Polymers



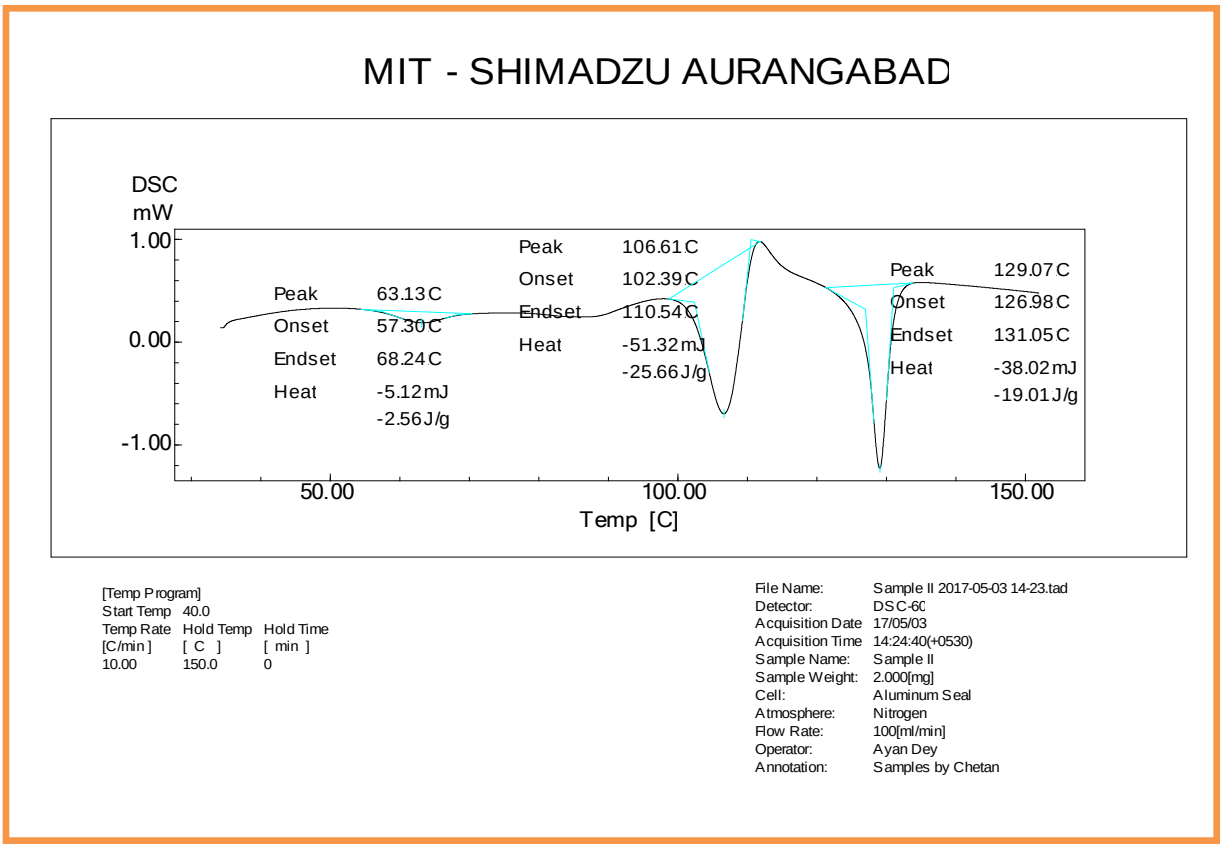
Graph 2: FTIR Spectra of Drug and Polymer.

3.1.3 Differential Scanning Calorimeter Analysis



Graph 3: DSC Spectra of Rivastigmine Tartrate.

3.1.4 DSC spectra of Drug and Polymer Interaction



3.2 Factorial Batches for Phase Transition System

3.2.1 Evaluation

Table 1: Factorial Batches for Phase Transition System.

Batch Code	pH	Drug Content (%)	Gellation Time (Min)	Gellation Temp (^{0}C)	Viscosity Before Gel (Cp)	Viscosity After Gel (Cp)	Mucoadhsive Time (Min)	Mucoadhesive Strength (Dyne/cm^2)
FF1	7.03 ± 0.0577	97.66 ± 1.5275	7.95 ± 0.4479	39.00 ± 1.5275	70.00 ± 2	71.00 ± 1	6.91 ± 0.8337	26.76 ± 1.0901
FF2	7.06 ± 0.1155	98.00 ± 1.7320	8.70 ± 0.5084	40.33 ± 1.5275	71.00 ± 1	70.33 ± 2.5166	8.0333 ± 0.6168	27.35 ± 1.0171
FF3	7.23 ± 0.0577	97.66 ± 1.5257	9.04 ± 0.6683	41.00 ± 1	73 ± 1	74.33 ± 1.1547	8.67 ± 0.8311	27.98 ± 1.5032
FF4	7.2 ± 0.1	98.66 ± 0.5773	7.95 ± 0.4834	40.33 ± 1.5275	70.66 ± 1.1547	72.00 ± 2	7.33 ± 0.5658	27.05 ± 1.7201
FF5	7.03 ± 0.0577	97.66 ± 1.1547	8.72 ± 0.4129	40.66 ± 1.1547	75.66 ± 1.5275	76.00 ± 2	7.93 ± 0.6484	29.21 ± 1.4698
FF6	7.2 ± 0.01	97.66 ± 1.5275	9.02 ± 0.6087	44.33 ± 1.5275	80.66 ± 1.547	81.00 ± 1.7320	7.64 ± 1.0257	28.72 ± 1.2061
FF7	7.13 ± 0.0577	98.33 ± 1.1547	8.08 ± 0.7769	43.33 ± 2.5166	76.66 ± 2.5166	77.00 ± 2.6457	9.30 ± 0.4701	29.53 ± 1.0500
FF8	7.2 ± 0.1	97.33 ± 1.5275	8.66 ± 0.6089	45.00 ± 2	81.33 ± 1.5275	79.66 ± 1.5275	9.01 ± 0.6348	30.49 ± 1.1064
FF9	7.16 ± 0.1528	98 ± 1	9.71 ± 0.4787	47.00 ± 2	85.66 ± 1.1547	85.66 ± 0.5773	9.68 ± 0.5040	32.56 ± 0.7836

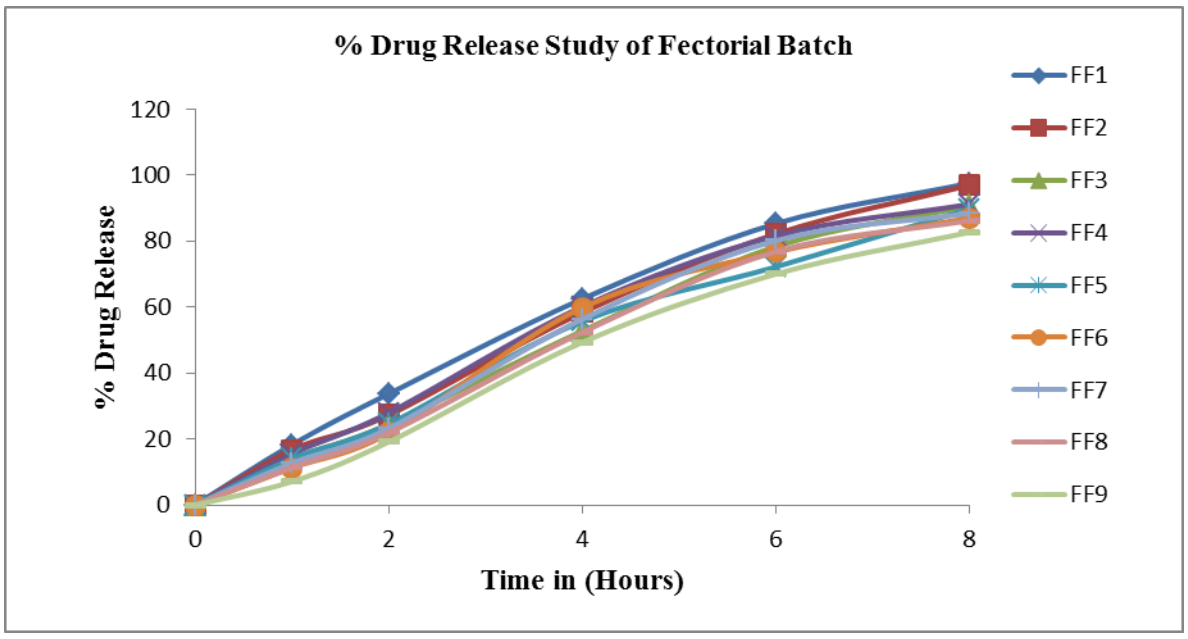
It was observed that Mucoadhesive Time of formulation from (FF1 to FF8) was in range of (6.91 ± 0.8337) to (9.68 ± 0.5040) min all formulation has good Mucoadhesive Time properties. It was observed that Mucoadhesive Strength of formulation from (FF1 to FF8) was in range of (26.76 ± 1.0901) to (32.56 ± 0.7836) Dyne/cm^2 all formulation has good Mucoadhesive Strength properties. It was concluded that formulation containing polymers Sodium alginate, Gallan gum for Phase Transition System has shown good mucoadhesive time, mucoadhesive strength, and drug content in Factorial batch.

3.3 Diffusion Study

Table 2: *In-Vitro* Drug Release Factorial Batch.

Time (Hours)	% Cumulative Drug Release								
	FF1 ± SD	FF2 ± SD	FF3 ± SD	FF4 ± SD	FF5 ± SD	FF6 ± SD	FF7 ± SD	FF8 ± SD	FF9 ± SD
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	17.69 ± 0.4793	16.36 ± 0.7181	12.65 ± 1.3080	15.19 ± 0.7899	13.86 ± 0.6914	11.90 ± 0.7018	12.26 ± 0.8453	11.96 ± 0.5344	7.68 ± 0.7590
2	32.43 ± 1.1786	27.21 ± 0.3782	25.00 ± 0.7846	21.17 ± 0.7962	23.88 ± 1.0527	23.04 ± 1.3779	24.99 ± 1.1232	23.08 ± 1.5217	18.22 ± 1.0234
4	61.56 ± 0.8100	58.20 ± 0.2599	53.63 ± 0.9010	61.00 ± 1.1810	55.93 ± 1.8614	60.80 ± 1.4408	58.38 ± 0.7698	54.22 ± 1.7103	50.86 ± 1.8426
6	85.15 ± 0.4426	81.72 ± 1.2115	79.56 ± 1.4638	81.43 ± 1.0500	71.75 ± 1.1572	77.00 ± 0.7971	80.71 ± 0.6278	77.93 ± 1.3442	70.52 ± 0.6807
8	97.22 ± 0.9032	96.82 ± 0.4677	91.48 ± 0.9625	91.04 ± 0.5134	89.44 ± 1.1071	88.52 ± 1.6209	87.99 ± 0.4568	87.74 ± 1.3120	83.14 ± 0.4358

N=3



Graph 5: *In-Vitro* Drug Release Study of Factorial Batch.

Cumulative % Drug Release of Phase Transition System (FF1-FF9) was found to be range (97.22 ± 0.9032) (8 hours) to (83.14 ± 0.4358) (8 hours). It was observed that Cumulative % Drug release depend on concentration of polymer Sodium alginate and Gellun gum. Here, as

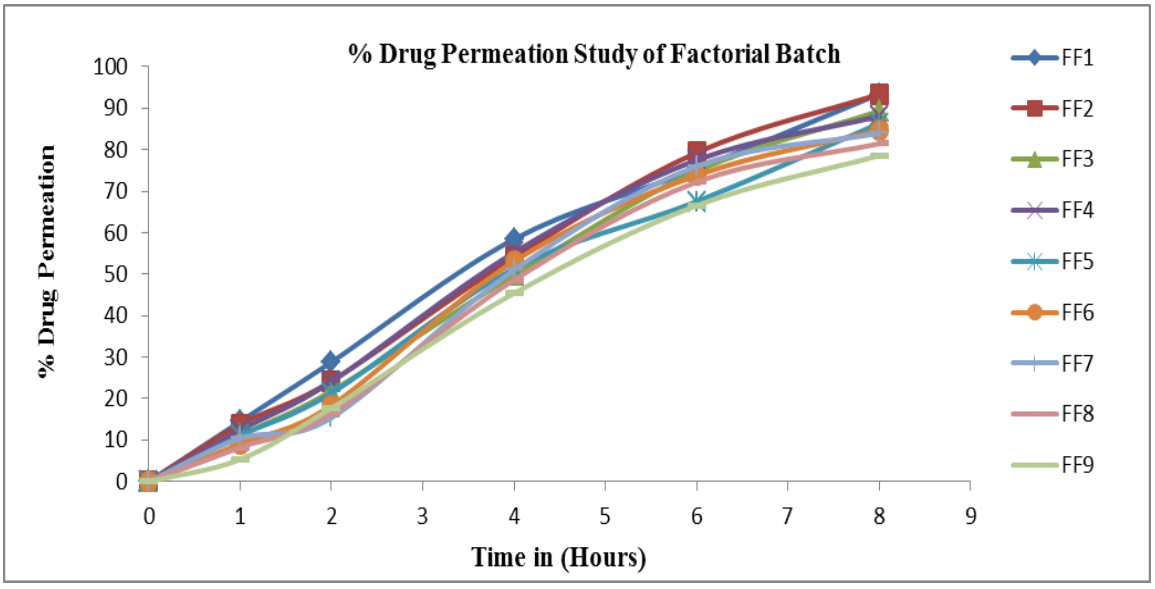
concentration of polymer increases % drug release time of formulation also decreases. In this formulation batch (FF1) (97.22 ± 0.9032) both Sodium alginate and Gellan gum have less concentration shows that more drug release as compared to (FF9) (83.14 ± 0.4358) Gellan gum and Sodium alginate have more concentration batch.

3.3 Permeation Study

Table 3: *In-Vitro* Drug Permeation Study of Factorial Batch.

Time (Hours)	% Cumulative Drug Permeation								
	FF1 ± SD	FF2 ± SD	FF3 ± SD	FF4 ± SD	FF5 ± SD	FF6 ± SD	FF7 ± SD	FF8 ± SD	FF9 ± SD
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	14.31 ± 0.6855	12.07 ± 1.1073	11.33 ± 1.1570	12.11 ± 0.4196	11.45 ± 1.1160	8.48 ± 0.5880	11.40 ± 1.0805	8.28 ± 0.8817	5.96 ± 0.5397
2	27.49 ± 1.2015	23.22 ± 1.0588	23.01 ± 1.5483	23.34 ± 0.8007	22.43 ± 1.0553	17.43 ± 1.0269	16.97 ± 1.5052	16.14 ± 0.384	17.43 ± 1.0238
4	57.29 ± 1.1697	53.71 ± 0.3587	49.50 ± 0.9808	56.22 ± 0.8947	53.33 ± 1.7646	52.90 ± 0.7245	52.31 ± 0.9374	48.47 ± 1.0761	46.27 ± 2.3241
6	75.00 ± 0.6913	78.43 ± 0.7913	74.64 ± 0.5907	78.44 ± 1.0035	66.81 ± 0.6011	74.72 ± 1.0747	77.28 ± 1.1145	72.00 ± 1.4186	67.70 ± 1.3577
8	92.30 ± 1.1882	93.02 ± 0.7015	89.98 ± 1.6904	89.59 ± 1.7705	85.51 ± 0.7159	83.78 ± 1.1881	85.34 ± 1.7985	83.05 ± 1.6634	78.41 ± 1.0277

N=3



Graph 6: *In-Vitro* Drug Permeation Study Factorial Batches.

In Factorial batch the concentration of polymer increases the % drug permeation of drug decrease. In this formulation batch (FF2) (93.02 ± 0.7015) both Sodium alginate and Gellan gum have less concentration shows that prolong drug release as compared to (FF9) (78.41 ± 1.0277) Gellan gum and Sodium alginate have more concentration and shows controlled drug release.

3.5 Kinetic Study of Factorial Batch for Phase Transition System

Table 4: Kinetic Studies of Factorial Batch.

Batch Code	FF1	FF2	FF3	FF4	FF5	FF6	FF7	FF8	FF9
	R	R	R	R	R	R	R	R	R
Zero order	0.9779	0.9903	0.9926	0.9836	0.9919	0.9856	0.9853	0.9900	0.9919
T-test	9.364	14.288	16.306	10.908	15.659	11.657	11.519	14.005	15.616
1st order	0.9152	0.9467	0.9735	0.9820	0.9739	0.9804	0.9826	0.9815	0.9840
T-test	4.543	5.879	8.506	10.400	8.584	9.943	10.581	10.241	11.030
Matrix	0.9754	0.9586	0.9480	0.9590	0.9557	0.9428	0.9461	0.9419	0.9343
T-test	8.846	6.733	5.960	6.768	6.493	5.659	5.843	5.607	5.240
Peppas	0.9958	0.9960	0.9973	0.9942	0.9962	0.9905	0.9932	0.9949	0.9933
T-test	21.746	22.184	27.190	18.436	22.975	14.393	17.040	19.819	17.206
Hix.Crow	0.9833	0.9862	0.9908	0.9959	0.9932	0.9926	0.9917	0.9916	0.9925
T-test	10.795	11.907	14.641	22.151	17.112	16.394	15.422	15.315	16.286
Best fit model-	Peppas	Peppas	Peppas	Hix.Crow	Peppas	Hix.Crow	Peppas	Peppas	Peppas
N	0.8111	0.8792	0.9611	0.9113	0.9166	1.0407	1.0020	1.0230	1.1566
K	19.7179	16.2971	13.1891	15.2367	13.9780	11.5659	12.5072	11.4533	8.5535

It was observed that Phase transition systems (FF1 to FF9) have best fitted to peppas model. Phase transition nasal gel has r2 value (0.9343) and n value (1.1566).

3.6 Stability Study of FF9 Optimized Batch from Factorial Batch

Table 5: Stability Study of FF9 Optimized batch.

Stability (40 ± 2^0, 75±5% RH)	Drug Content (%)	Geletion Temp (^{0}C)	Mucoadhesion Strength (dyne/cm2)	%Cumulative Drug Release After 8 (Hours)
0 Day	98.90±0.23	48.03±0.88	32.86±0.739	83.42±0.225
1Week	98.74±0.42	47.75±0.76	32.75±0.387	83.42±0.278
2 Week	99.00±0.77	47.68±1.02	32.21±0.804	82.93±0.249
3Week	98.35±1.33	48.33±0.28	32.75±0.782	83.42±0.115
4Wek	98.77±0.86	47.19±0.86	32.58±0.328	83.22±0.545

Stability (25 ± 2^0, 75±5% RH)	Drug Content (%)	Geletion Temp (^{0}C)	Mucoadhesion Strength (dyne/cm2)	%Cumulative Drug Release After 8 (Hours)
0 Day	98.67±0.31	48.02±0.36	32.58±0.270	83.03±0.767
1Week	98.88±0.86	48.04±0.93	32.80±0.388	83.47±0.170

2 Week	98.99±0.76	47.71±0.52	32.21±0.804	83.13±0.812
3Week	98.59±0.24	47.49±0.37	32.75±0.782	82.31±0.177
4Wek	99.62±0.16	47.62±0.42	32.58±0.328	83.40±0.285

Stability (10 ± 2^0, 75±5% RH)	**Drug Content (%)**	**Geletion Temp (^{0}C)**	**Mucoadhesion Strength (dyne/cm2)**	**% Cumulative Drug Release After 8 (Hours)**
0 Day	98.73±0.34	48.25±0.17	32.40±0.132	83.03±0.670
1Week	99.22±0.66	48.26±0.58	32.95±0.063	83.00±0.280
2 Week	98.56±0.11	47.58±0.56	32.70±0.127	83.29±0.221
3Week	98.41±1.33	47.93±0.71	33.22±0.739	82.87±0.455
4Wek	98.77±0.85	46.99±0.66	32.62±0.357	83.22±0.606

The stability studies of optimum formulation (FF9) revealed that there is slightly reduction in drug content was observed over period of 3 month. No significant change was observed on % Drug Content, Geletion Temp, Mucoadhesion Strength and % Cumulative Drug Release (After 8 Hours) at various storing condition 40 ± 2^0, 75±5% RH, 25 ± 2^0, 75±5% RH and 10 $\pm2^0$C, 75±5% RH. Hence formulation (FF9) was found to be stable for 3 month.

4. DISCUSSION

The different polymers like Chitosan HCl, HPMC K4M, Carbopol 934, Gellan gum, Sodium Alginate, Sodium β-glycerophosphate, and Benzaalkonium chloride were used for the studies. The polymers such as Sodium Alginate and Gellan gum were used in screening of polymer and to formulate the Phase Transition System.

Formulation of phase transition system prepared the factorial batch with different polymers concentration.

The preformulation parameters like visual inspection, Melting point, detection of wavelength were evaluated FTIR and DSC study was carried out to rule out any possible interactions between the drug and the excipients. To confirming the compatibility between the selected range of the drugs and the polymers.

The Phase Transition System of *in situ* nasal gel were evaluated for their appearance pH, viscosity, drug content, gellation time, gellation temp, *in-vitro* diffusion studies, mucoadhesive strength, mucoadhesive time, gelling strength, *in-vitro* release studies, histopathology study, stability study. All the gels were transparent, homogenous, and they were found to be uniform with their drug content.

CONCLUSION

In-vitro drug release of Phase Transition System of Nasal gel for Rivastigmine Tartrate was found to be in controlled fashion. In vitro release data fitted into various kinetic models suggest that the highest correlation coefficient was showed by the drug release of formulation batches FF9 was found to be 97.22%. on the basis of drug kinetic model system FF9 having maximum r^2 value (0.9343). From evaluation of Phase transition system nasal gel formulation for factorial batch, formulation (FF9) has shown pH (7.16 ± 1.528), drug content (98 ±1), gelation time (9.71 ± 0.4787) gelation temp (47.00 ± 2), mucoadhesive time (9.68 ± 0.5040), mucoadhesive strength (32.56 ± 0.7836), viscosity before gel (85.66 ± 1.1547), viscosity after gel (85.66 ± 0.5773), drug permeation time (78.41 ± 1.0277), drug release Time (83.14 ± 0.4358), have good controlled release behaviour. Here we can conclude that from above it was calculated that Phase transition system nasal gel formulation FF9 containing sodium alginate and gellam gum which could be most promising Phase transition system gel formulation for Rivastigmine Tartrate.

Hence, finally it was concluded that the prepared Phase Transition System of Rivastigmine Tartrate may prove to be potential candidate for safe and effective drug release study over an extended period of time which can reduce dosing frequency.

ACKNOWLEDGEMENT

First and foremost, I owe my deepest gratitude to my guide, Prof. N.N. Bobade from the bottom of my heart undoubtedly for his guidance that appropriately channelized my wavering thoughts. Just the way a small bud blooms into a beautiful flower, or a caterpillar into a butterfly. I wish to extend my sincere thanks to Dr. K. K. Tapar, Principal Vidyahharti College of Pharmacy, I express my heartfelt thanks to Mr. Dr. S. D. Pande sir, Wankhede sir, Atram sir, for his constant advice.

I would like to thanks Sun Pharma Pharmaceuticals Mumbai, for providing me the gift sample of Rivastigmine Tartrate.

My heartfelt thanks to my dearest friend Prashant, Parimal, Nagesh, Vishal, Sudarshan, Keshav, Mahesh, Sarang, Dinesh, Pravin, Abhay, Abhilash, Trupti, Dipali, Sonali, Priya, Pallavi, Pooja, Riya, Naglaxmi, Shubham sir, Datta sir, Vishal sir, Varsha mam, Manisha mam, whose constant support to made this dissertation.

It is my privilege to express my heartfelt thanks to Kisan Wankhede, Vidya Wankhede and Viraj for their constant source of inspiration and encouragement throughout this course.

“Thanks” is a small word to my Father Yashvantrao, Mother Kalpana and family members for their encouragement and love that served as a source of inspiration, strength at each and every front of my life to transport my dreams in to reality.

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