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Formulation and evaluation of in-situ gel for otic administration of Rivastigmine for the treatment of Alzheimerś Disease

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ABSTRACT

The present study successfully demonstrated the formulation and evaluation of a pH-sensitive in situ gel for the otic delivery of Rivastigmine, aimed at enhancing therapeutic outcomes in the management of Alzheimer's disease. The Insitu gel system, was prepared using Carbopol 934 and Sodium Alginate were used as gelling agents, which exhibited excellent sol-to-gel transition at physiological pH, making it suitable for otic administration.
HPMC was used viscosity enhancer, along with PEG-400 and Methyl Parabenworked as excipients, which contributed toget the desired physicochemical properties of the formulation. The optimized formulation showed satisfactory gelation capacity, suitable viscosity, and showed sustained drug release over an extended period of time, which is crucial for maintaining therapeutic drug levels and reducing dosing frequency.
In vitro evaluation results validated the potential of this delivery system to provide controlled and localized release of Rivastigmine, minimizing systemic side effects and improving patient compliance.
Among all the 9 formulations, F5 showed most promising results of atmost standard. Overall, this pH-triggered in situ gel offers a novel and reliable approach for non-invasive, sustained delivery of Rivastigmine via the otic route.
Future studies involving stability of the formulation, in-vivo evaluation and pharmacokinetic analysis are recommended to further establish the clinical potential of this formulation.

KEYWORDS: Ideal Properties Of Polymer, Preparation Of In Situ Gel.

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INTRODUCTION

In-situ gel is a soft, stable, semi solidlike material which consists of at least two components, one of them being a liquid, present in hefty quantity.

The "in situ gel" system has become one of the most effective novel drug delivery methods due to its unique "Sol to Gel" transition property which aids in the controlled and sustained release of the medications which helps in reducing dosing frequency and increasing patient compliance.

Before administration, in-situ gelling system is in solution form; nevertheless, under certain physiological conditions, it will show excellent sol to gel transition.

Number of variables such as temperature, pH shift, solvent exchange, UV light, and the presence of certain molecules or ions, may affect the sol-gel transition. For the creation of sustained delivery vehicles for bioactive compounds, drug delivery systems with the aforementioned "sol to gel transition" characteristics can be frequently employed.[1]In situ gels are the solutions or suspensions that undergo transition at the site of administration due to various physiochemical changes such as slight change in pH, temperature variation, ionic concentration, UV radiation, presence of specific molecules, or ions, external stimulus, etc.[2]
In situ gel produces a constant plasma drug profile in the body by achieving sustained drug release, so it is attached and well absorbed in gel form and is known for prolonged therapeutic action due to the presence of mucin. The drug delivery systems have various properties of sol to gel transition which can be widely incorporated for sustained delivery vehicle preparation of bioactive moiety.[3]

In situ gels, are used for oral, buccal, subcutaneous, transdermal, intraperitoneal, ocular, nasal, rectal, vaginal, and parenteral routes. From a manufacturing point, it is less complicated and hence is used in cost reduction. In the discovery phase, the gel formulations are used to enhance the local and systemic exposure of potential lead compounds, which is ideal for establishing animal models for various conditions quickly. Despite the massive diversity of gels, a particular class of gels, namely novel polymer gels, are in the focus of pharmaceutical research during the last decades.[4]

The "in situ gelling system" offers a number of benefits, such dosing compliance, reduction in dosing frequency, and even provide drug protection from various environmental factors.

Both natural and synthetic origin of polymers can be utilised for oral, otic, transdermal, buccal, intra peritoneal, parenteral, rectal and vaginal routes, undergoing sol to gel transformation.Natural polymers incorporated in in-situ gelling systems include pectin, chitosan, alginic acid, guar gum, carbopol, xyloglucan, xantham gum, HPMC, poloxamer, and others.[2]

Advantages of in-situ gel	**Disadvantage of in-situ gel**
Controlled and prolonged release of drug[5]	It requires high levels of fluid[9]
Ease of administration[6].	The medication is more prone to deterioration in its sol form.[10]
Can be administered in unconscious patients[7], [8]	Eating and drinking is avoided as it may effect the drug delivery. [11]
Dosing frequency reduction and drug toxicity.	Smaller dosing regime.
Non-invasive technique.	Drug loading limitation, especially for hydrophobic drugs.
Increased bioavailability	Premature dissolution due to low mechanical strength.

IDEAL PROPERTIES OF POLYMER:

1. The polymer should adhere to the mucosal membrane.
2. It should not have any adverse effects and should be highly compatible.
3. It ought to behave in a pseudoplastic manner.
4. The ideal pseudoplastic behaviour of the polymer should be able to reduce viscosity as the shear rate increases.
5. It is better to have good optical clarity and tolerance.
6. It ought to affect the behaviour of tears. [12]

PREPARATION OF IN SITU GEL:

The polymer may differ based on the development of in situ gelling systems. The polymeric solution was prepared by dispersing required quantities of polymers and copolymers in distilled water using a magnetic stirrer until the polymers completely dissolve. After the preparation of an aqueous drug solution, transferred to a primarily prepared polymeric solution with continuous stirring until to get a homogeneous solution, and then add excipients based on the delivery system. Finally, make up the volume with distilled water.[13]

APPROACHES OF IN SITU GELS

There are three generally defined mechanisms used for triggering the insitu gel formation of biomaterial:
A. Physiological stimuli (eg., temperature and pH)
B. Physical stimuli (eg., solvent exchange or diffusion and swelling)
C. Chemical stimuli (eg., enzymatic, chemical and photo-initiated polymerization)[6], [14]

DISEASE PROFILE:

Alzheimer's disease (AD) (named after the German psychiatric Alois Alzheimer) is the mostcommon type of dementia and can be defined as a slowly progressive neurodegenerative diseasecharacterized by neuritic plaques and neurofibrillary tangles as a result of amyloid-betapeptide's (Aβ) accumulation in the most affected area of the brain, the medial temporal lobe andneocortical structures.

There are two types of neuropathological changes in AD which provide evidence about diseaseprogress and symptoms and include: (1) positive lesions (due to accumulation), which are characterizedby the accumulation of neurofibrillary tangles, amyloid plaques, dystrophic neurites, neuropilthreads,and other deposits found in the brains of AD patients. In addition to (2) negative lesions (due tolosses), that are characterized by large atrophy due to a neural, neuropil, and synaptic loss. Besides,other factors can cause neurodegeneration such as neuroinflammation, oxidative stress, and injury ofcholinergic neurons.[15]

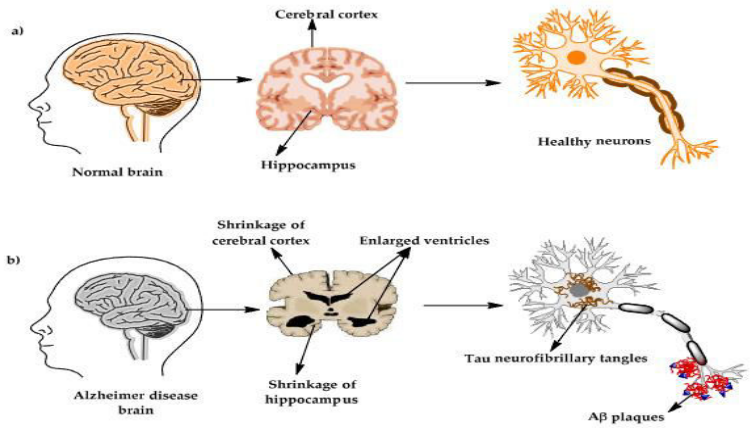


Fig.4 The physiological structure of brain and neurons in (a) Healthy Brain and (b) Alzheimer's Disease Brain [15]

The Stages of Alzheimer's Disease

The clinical phases of Alzheimer's disease can be classified into:

(1) Pre-clinical or the pre-symptomatic stage, which can last for several years or more. This stage is characterized by mild memory loss and early pathological changes in cortex and hippocampus, with no functional impairment in the daily activities and absence of clinical signs and symptoms of AD.

(2) The mild or early stage of AD, where several symptoms start to appear in patients, such as a trouble in the daily life of the patient with a loss of concentration and memory, disorientation of place and time, a change in the mood, and a development of depression.

(3) Moderate AD stage,in which the disease spreads to cerebral cortex areas that results in an increased memory loss with trouble recognizing family and friends, a loss of impulse control, and difficulty in reading, writing,and speaking.

(4) Severe AD or late-stage, which involves the spread of the disease to the entire cortex area with a severe accumulation of neurotic plaques and neurofibrillary tangles, resulting in a progressive functional and cognitive impairment where the patients cannot recognize their family atall and may become bedridden with difficulties in swallowing and urination, and eventually leading to the patient's death due to these complications.[15]

DRUG AND EXCIPIENT PROFILE

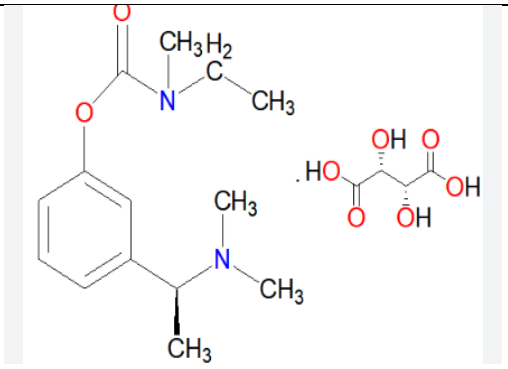
RIVASTIGMINE TARTRATE

It is one of the new generation of Ach E and butyrylcholinesterase (BuChE) inhibitors that were approved in 2000 under the name of Exelon, when it proved great efficacy against various stages of AD.

It is a reversible inhibitor of AChE produced from carbamates that preferentially affects the central nervous system (CNS) and has demonstrated effectiveness against both AD and PD. The medicine is marketed under the brand Exelon, although its generic name is Rivastigmine. It functions as a reversible cholinesterase inhibitor and is a semisynthetic pharmaceutical derivative of eserine (physostigmine), a parasympathomimetic alkaloid that was extracted from *Physostigmavenenosum*seeds. Rivastigmine is a relatively weak inhibitor because of its unique mechanism of action, which involves a delayed covalent reaction with the active site of Ach E and BuCh E through its carbamate structure.

Rivastigmine's carbamate structure, which is its pharmacophore, is what gives it its Ach E and BuCh E inhibitory action both in vitro and in vivo.[16]

S.NO	CATERGORY	DESCRIPTION
1.	Drug	Rivastigmine Tartrate
2.	Chemical Formula	C14H22N2O2.C4H6O6
3.	Mol. Wt.	400.4
4.	Chemical Name	Ethylmethylcarbamic acid',3-[(S)T (diinethylamino)ethyl]phenyl ester, (2R,3R)-2,3-dihydrbxybutanedioate

5.	Structure	
6.	Therapeutic Category	Cholinesterase Inhibitors, Parasympathomimetic Agent
7.	Description	A white to off white powder
8.	Identification	A. Determine by infrared absorption spectrophotometry. Compare the spectrum with that obtained with rivastigmine tartrate IPRS or with the reference spectrum of rivastigmine tartrate. B. The principal peak obtained with the test solution corresponds to principal peak in the chromatogram obtained with reference solution (c).,
9.	Solubility	Water soluble
10.	Adverse Effects	• Nausea • Vomiting • Loss of appetite • Headache • Confusion
11.	Uses	• Dimentia • Alzheimer's Disease • Parkinson's Disease

Excipients-
CARBOPOL/CARBOMER
Synonyms: Acrypol; Acritamer; acrylic acid polymer; carbomera
Functional Category: Bioadhesive material; controlled-release polymer; emulsifying agent; emulsion stabilizer; rheology modifier; stabilizing agent; suspending agent; tablet binder.
pH: 2.5-3.0
Description: Carbomers are white-colored, 'fluffy', acidic, hygroscopic powders with a characteristic slight odor.

SODIUM ALGINATE
Synonyms: Alginatosodico; algin; alginic acid, sodium salt
Molecular Weight: 216.12 g/mol
Functional Category: Stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity increasing agent.

Description: Sodium alginate occurs as an odorless and tasteless, white to pale yellowish-brown colored powder.
HYDROXY PROPYL METHYL CELLULOSE

Synonyms: Hypermellose, hypromellosum, Methocel, methylcellulose propylene glycol ether
Molecular Weight: 1261.44g/mol
Functional Category: Bioadhesive material.
POLYETHYLENE GLYCOL.
METHYL PARABEN(preservative).

RESULT AND DISCUSSION

PREFORMULATION STUDIES OF RIVASTIGMINE

1. **Organoleptic Properties:** The organoleptic properties of the drug sample were observed as shown in the table. It was observed that the organoleptic properties of the drug comply with the standards. This can be used as a preliminary identification tool of drugs.

Organoleptic Properties of Drug

S.NO	PROPERTIES	STANDARD	OBSERVATION
1	Appearance	Fine Powder	Fine Powder
2	Odour	Odourless	Odourless
3	Color	White to off-white	White

2. **Solubility Studies:** 10mg drug was added in various 2ml solvents and solubility was observed as shown the table.

Solubility Analysis

S.NO.	SOLVENT	SOLUBILITY
1	Water	Very soluble
2	Ethyl acetate	Slightly soluble
3	Ethanol	Soluble

3. **Melting Point:** The melting point of Rivastigmine tartrate was determined by the capillary tube method and it was found to be 125°C. This value is the same as that in the literature citation.

4. **Partition Coefficient:** The partition coefficient of Rivastigmine determination study was done with Toulene and Water. The P value of Rivastigmine was found to be 1.81. This indicates that Rivastigmine is moderately lipophilic.

5. **Identification of drug using FT-IR:** The acquired FT-IR of the medication demonstrates the identification of distinct functional groups that were compared with the reference spectra, and no significant difference was seen, confirming the purity of powder of Rivastigmine tartrate.

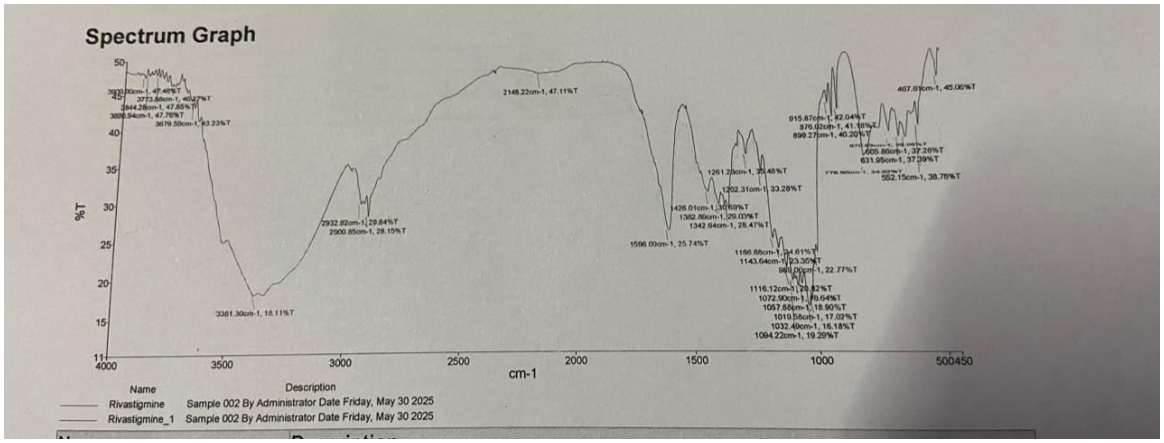


Fig.5 FTIR spectrum of Rivastigmine

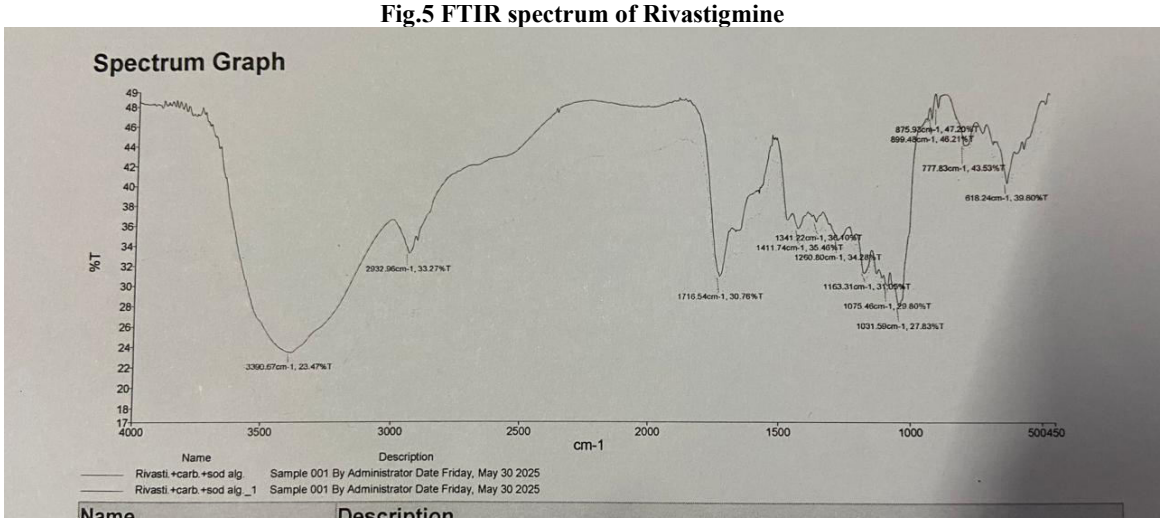


Fig.6 FTIR spectrum of physical mixture of Rivastigmine, Carbopol and Sodium alginate

6. Standard curve of Rivastigmine at 220nm

The standard curve of Rivastigmine was prepared in distilled water. Beer's Lambert Law was in the concentration of 10-50µg/ml. The absorbance at different 0concentrations is shown in the table below.

Absorbance at different Concentrations

S.NO	CONCENTRATION (µg/ml)	MEAN ABSORBANCE
1	2	0.2623
2	4	0.3573
3	6	0.5940
4	8	0.6752
5	10	0.9887
6	12	1.1397

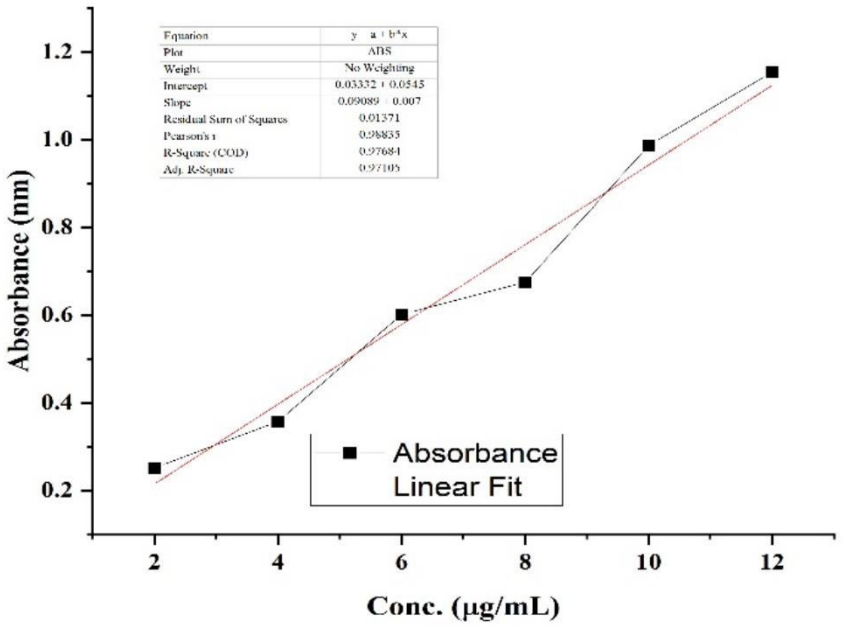


Fig.7 Calibration curve of Rivastigmine in Water

EVALUATION PARAMETERS OF PREPARED INSITU GEL.

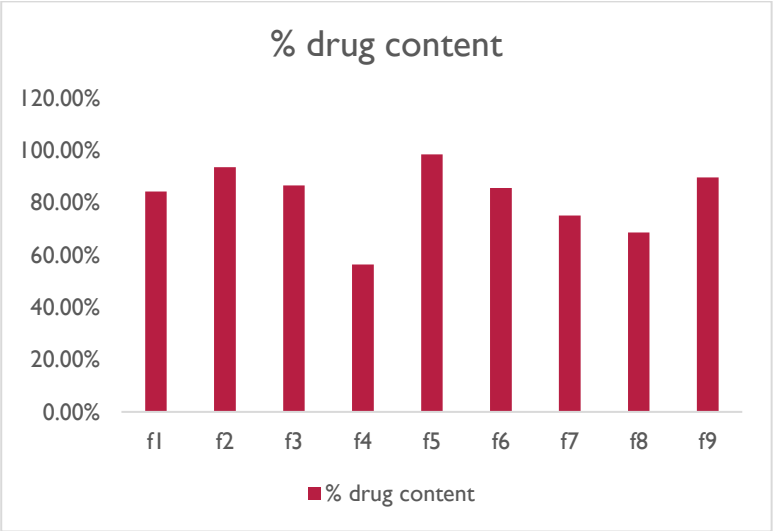
Formulation	LOR	ARITY	pH	Gelling /time (sec)	Viscosity (at spindle no 62)	Spread ability (cm)
F1	ite	ar	**6.0**	**No gelation.**	**10320.6CP**	**13.83**
F2	ite	ar	**6.3**	**No gelation.**	**12346.9CP**	**13.16**
F3	ite	ar	**5.9**	**Immediate(9s)**	**13245.07CP**	**12.33**
F4	ite	ar	**6.0**	**Immediate(12s)**	**13367.2CP**	**10.16**
F5	ite	ar	**6.4**	**Immediate(6s)**	**13567.1CP**	**16.83**
F6	ite	ar	**6.9**	**Immediate(5s)**	**24637.9CP**	**12.66**
F7	ite	ar	**6.8**	**Already gelled**	**35467.8CP**	**13.16**
F8	ite	ar	**6.0**	**Already gelled**	**65757.8CP**	**12.03**
F9	ite	ar	**6.8**	**Already gelled**	**75844.3CP**	**11.28**

Syringeability: All the formulations were able to pass through 21 gauze needles easily which means each formulation passed this test.

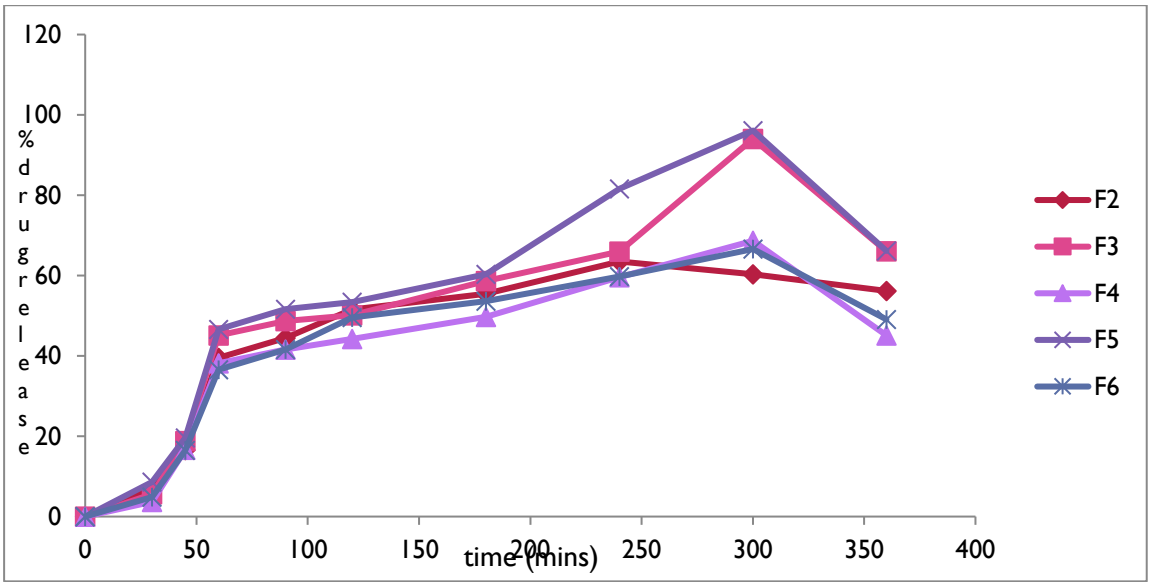
%Drug content: Since 150mg of the drug was incorporated in all the 100ml formulations, drug present in 1ml of the insitu gel comes out to be 1.5mg i.e. 1500µg/ml. This 1ml of the insitu gel is taken in 100ml volumetric flask and the volume is made up with distilled water. The concentration then becomes 1500µg/100ml i.e. 15 µg/ml. This means that theoretically the drug content in each formulation should come out to be 15 µg/ml under UV Spectrophotometer.

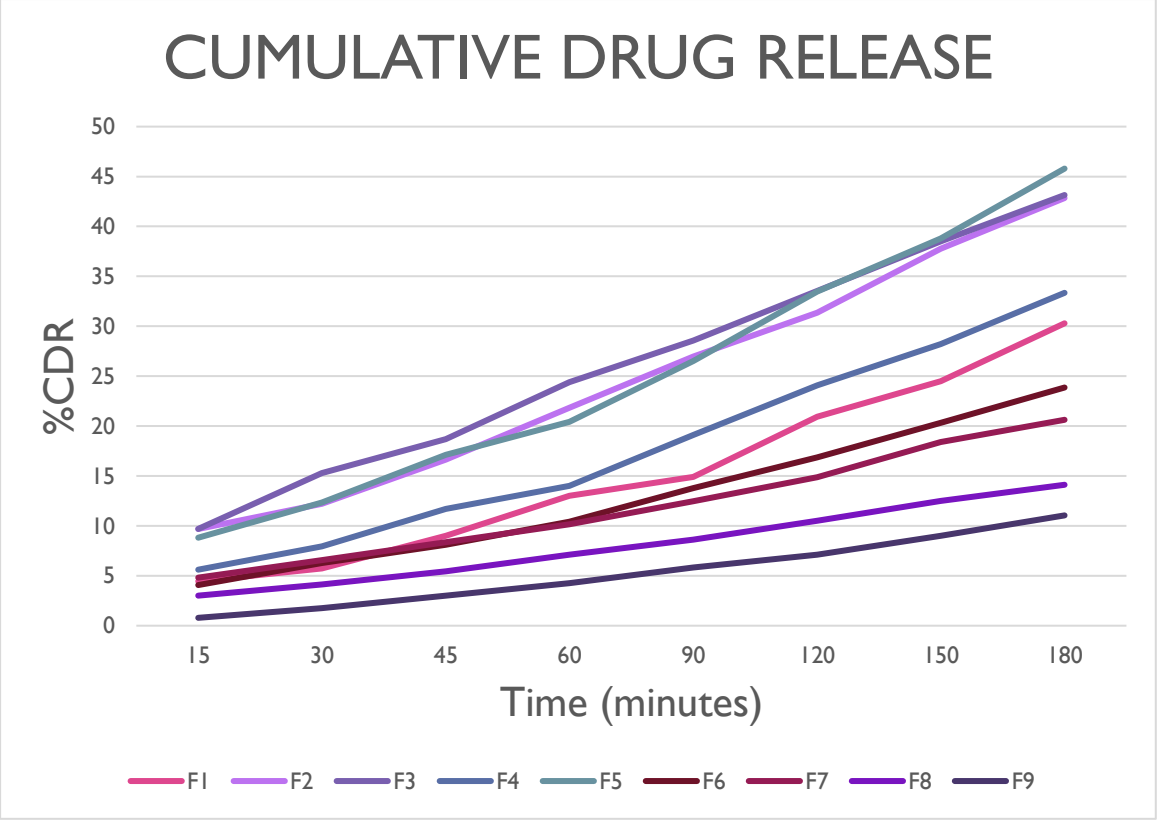
Formulation.	% drug content.
F1	**84.29%**
F2	**93.62%**
F3	**86.64%**
F4	**56.38%**
F5	**98.41%**

F6	**85.64%**
F7	**75.08%**
F8	**68.64%**
F9	**89.64%**



Franz Diffusion cell study: Formulation F1 was rejected for in vitro diffusion study due to its unstable nature at room temperature**.** Liquefaction of the gel was observed. Rest all formulations were found stable and Franz diffusion cell study was carried using cellophane membrane.





CONCLUSION

The present study successfully demonstrated the formulation and evaluation of a pH-sensitive in situ gel for the otic delivery of Rivastigmine, aimed at enhancing therapeutic outcomes in the management of Alzheimer's disease. The In situ gel system was, prepared using Carbopol 934 and Sodium Alginate were gelling agents,which exhibited excellent sol-to-gel trans at physiological pH, making it suitable for otic administration.

HPMCwas incorporated as viscosity enhancer, along with PEG-400 and Methyl Parabenas functional excipients, contributed to the desired physicochemical properties of the formulation. The optimized formulation showed satisfactory gelation capacity, suitable viscosity, and sustained drug release over prolonged period of time, which is crucial for maintaining therapeutic drug levels and thus reducing dosing frequency.

In vitro evaluation results validated the potential of this delivery system to provide controlled and localized effect of Rivastigmine, minimizing systemic side effects and improving patient compliance.

Among all the 9 formulations made, F5 showed most promising results. Overall, this pH-triggered in situ gel offers a novel and promising approach for non-invasive, sustained delivery of Rivastigmine via the otic route.

Future studies involving stability of the formulation, in vivo evaluation and pharmacokinetic analysis are recommended to further establish the clinical potential of this formulation.

To summarize, the development of Rivastigmine In situ gel for otic administration holds great potential for treatment of Alzheimer's Disease offering convenient, effective, and patent- friendly formulation.

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