DESIGN AND CHARACTERIZATION OF TRANSDERMAL PATCHES FOR SUSTAINED DRUG RELEASE (RIVASTIGMINE)

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1. Long-Acting Rivastigmine Transdermal Patch - Computational Design

ABSTRACT:
The purpose of the study was to use computational simulation to develop a long-acting patch of rivastigmine (RVS). Patch formulations were screened including pressure sensitive adhesive (PSA), pharmaceutical excipients, and controlled release membranes using transfer simulation based on a mathematical model. Rat in vitro permeation showed excellent correlation with in vivo deconvolution profile (R^2=0.998). The patch transferred RVS at a relatively uniform speed with high skin permeation 2531.2±142.46 μg/cm² in 72 h. Pharmacokinetic data confirmed stable plasma concentrations over 72 h, with prolonged Tmax (11.20±1.79 h) and MRT0-t (33.91±5.33 h). Cmax was controlled with AUC0-t (267.34±24.46 h•ng/ml), closely comparable to commercial Exelon® Patch. The study underscores the potential of computer-aided design for promnesic transdermal delivery.

KEYWORDS : Focused on 72-hour sustained release, used modeling to optimize PSA + membrane, achieved Exelon®-comparable AUC with flatter plasma profile.

2. Chitosan Microparticle-Based Rivastigmine Transdermal Patch

ABSTRACT:
Rivastigmine (RVT) is anti-Alzheimer with low bioavailability and short elimination half-life due to first-pass metabolism. RVT is hydrophilic with low skin permeability. PLGA NPs were prepared by nano-precipitation and chitosan (CH) NPs by ionic gelation. Optimized PLGA NPs: PS 291.3 nm, PDI 0.296, %EE 75.31%. CH NPs: PS 339.3 nm, PDI 0.264, %EE 83.91%. DSC showed RVT dispersed as amorphous state. In vitro release: PLGA NPs 52.7±1.07% and CH NPs 75.02±0.97% in 24 h vs 92.21±1.11% from drug solution in 2 h. Optimized NPs were incorporated in patches. In vitro pork ear skin permeation: steady-state flux of PLGA NP patch (PPN) 223.64 μg/cm²•h and CH NP patch (PCN) 265.18 μg/cm²•h vs 55.01 μg/cm²•h for pure RVT patch. Flux of PPN and PCN was 4.06 and 4.82 fold higher than pure drug patch. The developed patch could be a potential alternative for Exelon® patch.

KEYWORDS: Nanoparticle-in-patch approach. Chitosan NPs gave highest flux, 4.8x better permeation than plain RVT patch, sustained release over 24 h.

3. Review: Clinical Use of Rivastigmine Patch

ABSTRACT:
Rivastigmine transdermal patch (Exelon® patch) for mild to moderate Alzheimer's disease was effective in improving cognitive and global function, and generally well tolerated in a large, well designed trial The patch had good skin adhesion and favorable skin tolerabilityCurrent evidence suggests rivastigmine transdermal patch is an effective treatment option with potential for improving compliance and sustained clinical benefit due to ease of use and favorable tolerability.
Why it matters for design: This is the benchmark Exelon® patch 9.5 mg/24 h. New designs compare Cmax, AUC, Tmax, and adhesion to this referenceWant me to pull full-text PDFs or more recent 2024-2025 papers on novel approaches like microneedles or transethosomes for rivastigmine too?

1. INTRODUCTION

Alzheimer's disease (AD)

Alzheimer's disease (AD) (named after the German psychiatric Alois Alzheimer) is the most common type of dementia and can be defined as a slowly progressive neurodegenerative disease characterized by neuritic plaques and neurofibrillary tangles (Figure 1) as a result of amyloid-beta peptide's (Aβ) accumulation in the most affected area of the brain, the medial temporal lobe and neocortical structures [1]. Alois Alzheimer noticed a presence of amyloid plaques and a massive loss of neurons while examining the brain of his first patient that suffered from memory loss and change of personality before dying and described the condition as a serious disease of the cerebral cortex. Emil Kraepelin named this medical condition Alzheimer's disease for the first time in his 8th edition psychiatry handbook [2,3]. Progressive loss of cognitive functions can be caused by cerebral disorder like Alzheimer's disease (AD) or other factors such as intoxications, infections, abnormality in the pulmonary and circulatory systems, which causes a reduction in the oxygen supply to the brain, nutritional deficiency, vitamin B12 deficiency, tumors, and others [4,5].

1.1.1 Alzheimer's Disease Diagnostic Criteria

A patient suspected to have AD should undergo several tests, including neurological examination, magnetic resonance imaging (MRI) for neurons, laboratory examinations such as vitamin B12, and other tests besides the medical and family history of the patients [8]. Vitamin (vit.) B12 deficiency has been long known for its association with neurologic problems and increasing risks of AD, according to some studies. A special marker of vit. B12

Stages of Alzheimer's Disease

Alzheimer's disease is commonly classified into stages based on severity:

1.1.1 Mild (Early Stage): Memory lapses and mild cognitive difficulties.

1.1.2 Moderate (Middle Stage): Increased confusion, behavioral changes, and difficulty performing daily tasks.

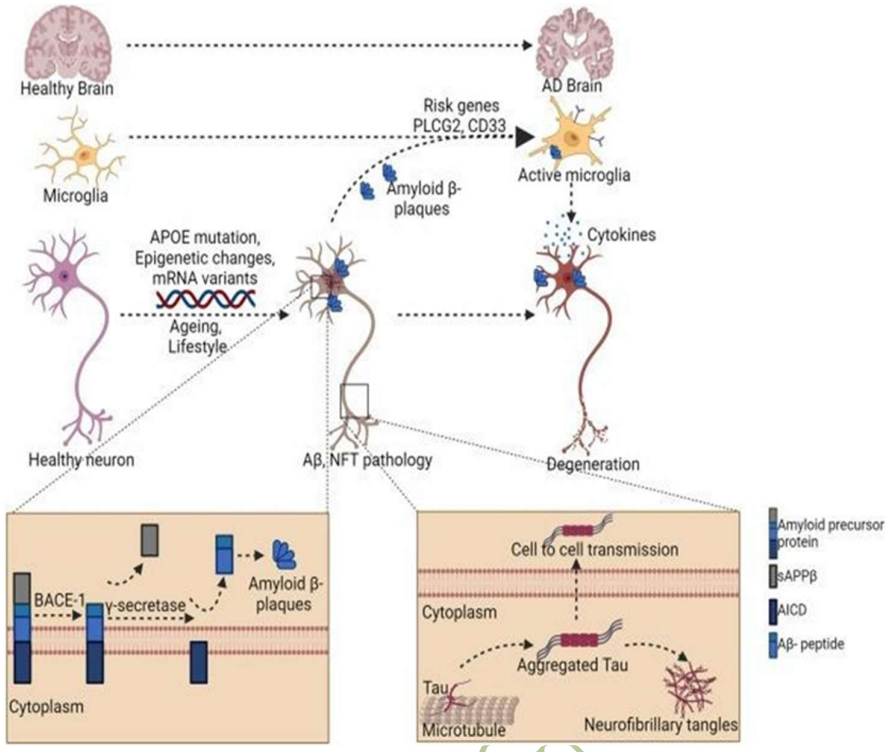
1.1.3 Severe (Late Stage): Significant memory loss, inability to communicate effectively, and complete dependence on caregivers.[27]

1.2 Current Treatment Options for Alzheimer's Disease

At present, there is no complete cure for Alzheimer's disease. The currently available therapies are primarily aimed at symptomatic management and slowing the progression of cognitive

decline. These treatments focus on improving neurotransmitter balance, particularly within the cholinergic and glutamatergic systems, which are significantly impaired in Alzheimer's disease.

Fig 1: Pathogenesis of AD



1.3 Causes and Risk Factors of Alzheimer's Disease

AD has been considered a multifactorial disease associated with several risk factors (Figure 2) such as increasing age, genetic factors, head injuries, vascular diseases, infections, and environmental factors (heavy metals, trace metals, and others). The underlying cause of pathological changes in Alzheimer's disease (Aβ, NFTs, and synaptic loss) is still unknown. Several hypotheses were proposed as a cause for AD but two of them are believed to be the main cause: some believe that an impairment in the cholinergic function is a critical risk factor for AD, while others suggest that alteration in amyloid β-protein production and processing is the main initiating factor. However, at present, there is no accepted theory for explaining the AD pathogenesis [22]

1.4 Signs and Symptoms of Alzheimer's Disease

Alzheimer's disease is a progressive neurodegenerative disorder characterized by gradual decline in cognitive and functional abilities. The clinical manifestations vary among individuals but primarily affect memory, reasoning, language, behavior, and spatial awareness. Symptoms worsen over time and eventually interfere with daily activities. Early medical evaluation is essential when dementia-like symptoms are observed.[22]

1.4.1 1.1.1 SKIN

Two systems in the human body shield the body from the elements, including dangerous organisms found in the surroundings. The external system keeps germs and other microorganisms out of the body. Through a variety of methods, the internal immune system attacks and eliminates germs and other microorganisms that have already infiltrated the body. The largest external defence system is the skin. The skin covers the entire body and shields the underlying structures from harm and microbial invasion. It has sensitive nerve endings that allow it to distinguish between touch, warmth, and pain. Additionally, depending on the surroundings, it controls body temperature between 30 and 400 degrees Celsius [43].

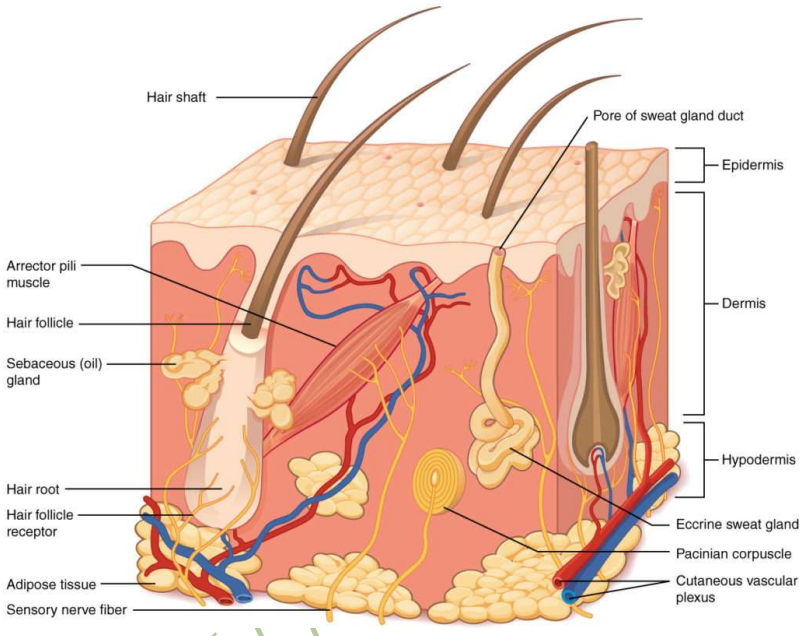


Fig 2: Structure of Skin

1.4.1.1 Structure of Skin

With a surface area of between 1.5 to 2 square meters in adults, the skin is the biggest organ in the body. It has auxiliary features like glands, hairs, and nails in some places. The three layers are the dermis (middle layer), hypodermis (innermost layer), and epidermis (outer layer covering dermis) [44].

1.1.1.1 Appendageal Route

Also known as shunt routes, these include permeation through sweat glands and hair follicles with their associated sebaceous glands.. For instance, on the forehead, approximately 13.7% of the surface area is available as follicles, while this figure remains close to 0.1% for forearm skin [52].

1.8.2.3 Transcellular Route

In this pathway, drugs pass through the corneocytes. These cells contain highly hydrated keratin, providing an aqueous environment for hydrophilic drugs. This route requires the drug to partition into and diffuse through both the keratin-filled corneocytes and the intercellular lipids [53].

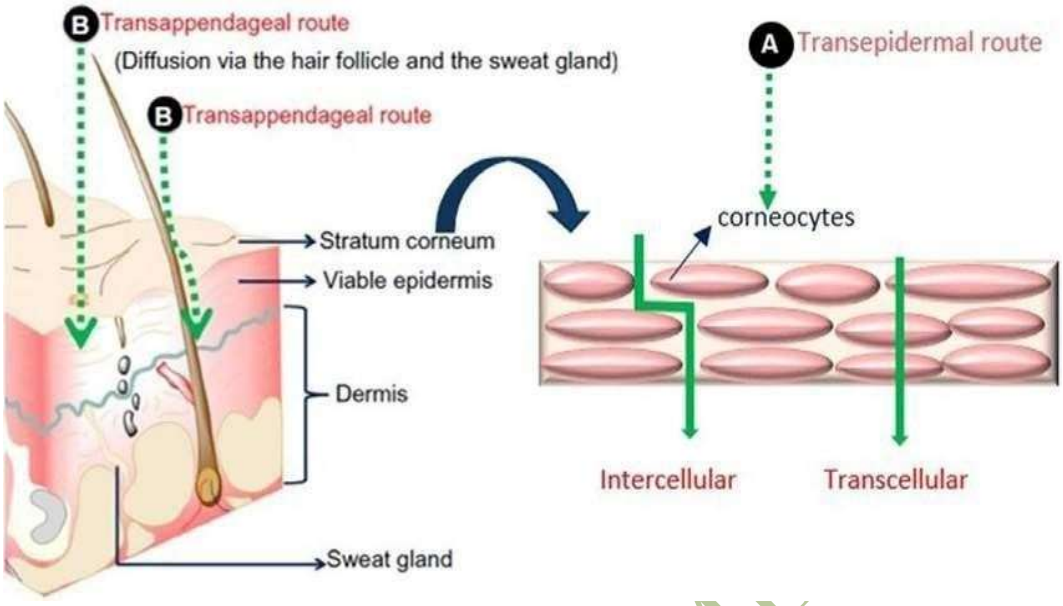


Fig 4: Schematic of skin penetration routes

- The interdigitating nature of corneocytes creates a winding path for drug permeation, unlike the more direct transcellular route.

The intercellular domain consists of alternating structured bilayers, requiring drugs to repeatedly partition into and diffuse through both aqueous and lipid domains.

1.9.1 Transdermal Patch Design

Transportation of drug across the skin is affected by various factors, such as skin permeability, area, and duration of application, as well as metabolic activity of the skin (i.e., first pass metabolism). In fact, every drug has its unique properties, which can affect transdermal delivery. To achieve adequate skin absorption and penetration, the drug should be non-ionic and relatively lipophilic to cross the skin barrier. [60] Molecules larger than 500 Daltons make it difficult to cross the stratum corneum, and ideally the therapeutic dose of the drug should also be less than 10 mg per day.

1.9.2 Basic Component of Transdermal Patch

Transdermal patches typically consist of several layers that are designed to deliver the medication through the skin and into the bloodstream. Figure 1 illustrates the basic component of a medicated patch. The specific composition and structure of the patch may vary depending on the drug being delivered and the desired rate of drug release. [61]

Fig 5: Basic component of a transdermal medical patch

The backing layer is the outermost layer of the patch and serves to protect the other layers from the environment. This layer is usually made of a flexible, waterproof material such as polyethylene or polypropylene. The adhesive layer serves to attach the patch to the skin and keep it in place. It usually consists of a strong, hypoallergenic adhesive that is gentle on the skin. The drug layer contains drugs that are delivered through the skin. It is formulated to release the drugs at a constant rate over a period of time. The rate-controlling membrane serves to control the rate at which the drugs are released from the patch. Membranes are usually made of semi-permeable materials that allow the drugs to pass through the membrane at a controlled rate. Linen acts as a protector for the patch and adhesive. The patch must be removed before being applied to the skin surface. [62]

1.9.3 Types of Transdermal Patches

In general, there are four main type of transdermal medical patches (drug-in adhesive, reservoir, matrix, and micro-reservoir systems), as shown in Figure 2. Most commercially available patches are categorized as reservoir or matrix systems [64].

Fig 6:Types of transdermal patches: (A) drug-in adhesive system; (B) Reservoir system; (C) matrix system; (D) Micro-reservoir system

6. 1 MATERIALS

6. 1.1 List of Materials

Table 1: Details of drug

Drug sample	Rivastigmine
Supplied by	Pharmensure, Mumbai

Table 2: List of Materials

Sr. No.	Material	Manufacturer Name	Supplied By
1	HPMC E5	Cosmo Chem Pvt. Ltd.	Solanki Enterprises
2	PVP K30	Cosmo Chem Pvt. Ltd.	Solanki Enterprises
3	PEG 400	Research Lab Fine Chem Industries, Mumbai	Solanki Enterprise, Pune
4	Dimethyl sulfoxide (DMSO)	Research Lab Fine Chem Industries, Mumbai	Solanki Enterprise, Pune
5	Ethanol	Research Lab Fine Chem Industries, Mumbai	Solanki Enterprise, Pune
6	Phosphate Buffer Saline (PBS, pH 7.4)	Cosmo Chem. Pvt. Ltd.	Solanki enterprises
7	Dialysis Membrane (MWCO 1000 Da)	Cosmo Chem. Pvt. Ltd.	Solanki enterprises
8	Deionized Water	Cosmo Chem. Pvt. Ltd.	Solanki enterprises
9	Methanol	Research Lab Fine Chem industries ,Mumbai	Solanki enterprise pune

6.1.2 List of Softwares Used:

Table 3: List of softwares used

Name of Software	Version
Design of Expert	13.0.5

6.1.3 List of Instrument

Table 4: List of Instruments

Sr. No.	Instrument / Equipment Name	Company	Model Number
1.	UV-Visible spectroscopy	Jasco v-630	B206461148
2.	High speed homogenizer	REMI	RQ-127A/D
3.	Centrifuge	Eltek	OC 2F
4.	FTIR	FT/IR-4600typeA	F193061786
5.	XRD	Bruker D8 Advance	D8 Advance Series
6.	Franz diffusion cell	DBK	210796
7.	Analytical balance	wensar	KAB2L

Drug Profile

1] Rivastigmine

Molecular Weight : 250.3367 g/mol

Chemical Formula: $C_{14}H_{22}N_2O_2$

Synonyms: Rivastigma

Brand Name: Exelon, Nimvastid.

Structure of Rivastigmine

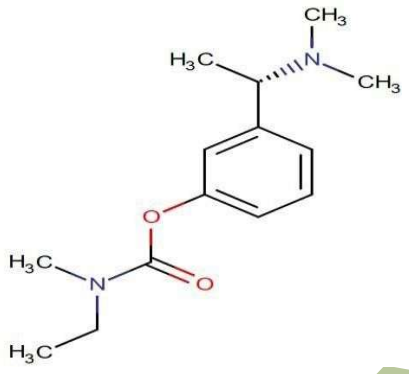


Fig 7 : Structure of Rivastigmine

Solubility:

Freely soluble in water across physiological pH ranges

Pharmacodynamics

Rivastigmine is a parasympathomimetic and a reversible cholinesterase inhibitor.

Mechanism of action

Rivastigmine is a carbamate derivative that is structurally related to physostigmine, but not to donepezil and tacrine.

Volume of distribution

1.8 to 2.7 L/kg

Metabolism

Rivastigmine is rapidly metabolized by cholinesterase-mediated hydrolysis.

Route of elimination

Rivastigmine is extensively metabolized primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite NAP226-90. Renal excretion of the metabolites is the major route of elimination. Less than 1% of the administered dose is excreted in the feces.

Half-life: 1.5 hours

Application

Rivastigmine is mainly used to treat:

- Alzheimer's disease – Improves memory and thinking in mild to moderate cases.

Parkinson's disease dementia – Helps manage cognitive symptoms in Parkinson's patients. [105]

Table 5: List of Independent and Dependent variables in Box–Behnken design

Independent variables	Low value (-1)	High value (+)
Polymer concentration (HPMC E5, % w/w)	2	6
Plasticizer concentration (PEG 400, % w/w)	10	30
Permeation enhancer (DMSO, % w/w)	1	5
Dependent variables	Constraints	
Moisture Content (%)	Maximize	
Drug Content Uniformity (%)	Maximize	
In-vitro Drug Release (%)	Minimize	

Table 6: DOE Suggested and Experimental batches

Formulation Code	Rivastigmine (mg)	HPMC E5 (% w/w)	PVP K30 (% w/w)	PEG 400 (% w/w)	DMSO (% w/w)	Ethanol
F1	4.5	2	4	10	3	10
F2	4.5	4	4	10	5	10
F3	4.5	6	4	30	3	10
F4	4.5	2	4	20	5	10
F5	**4.5**	**4**	**4**	**20**	**3**	**10**
F6	4.5	2	4	20	1	10
F7	4.5	4	4	30	5	10
F8	4.5	6	4	20	1	10
F9	4.5	6	4	20	5	10
F10	4.5	6	4	10	3	10
F11	4.5	4	4	10	1	10
F12	4.5	2	4	30	3	10
F13	4.5	4	4	30	1	10

7.1 PREFORMULATION STUDY OF RIVASTIGMINE

7.1.1 Identification of drug

Appearance

Active pharmaceutical ingredient: Rivastigmine

Appearance: A white to beige

Odor: **Odorless**

Taste: Strong, unpleasant taste

Solubility: Practically soluble in water, pH 7.4 and 1.2.

Fig 8: Rivastigmine

7.1.2 Melting Point

Table 7: Melting point of Rivastigmine

Drug	Observed	Reported
Rivastigmine	126^{0}C ± 0.0011	124 -129 ^{0}C

Conclusion-

The observed melting point of Rivastigmine was found to be 126°C**,** which falls within the reported range of 230-242ºC. This close agreement confirms the purity and identity of the sample, as the melting point is a critical parameter in assessing a drug's physicochemical properties.

7.1.3 Solubility study of the Drug (Rivastigmine)

Table 8: Solubility study in different medium

Solubility Medium	Solubility (µg/ml)	Solubility (mg/ml)
Distilled water	2139 ± 0.0054	21.39 ± 0.0054
Methanol	2006 ± 0.0015	20.06 ± 0.0015
DMSO	1566 ± 0.0095	15.66 ± 0.0095
Phosphate buffer pH 7.4	1245 ± 0.0001	12.45 ± 0.0001
Phosphate buffer pH 1.2	1006 ± 0.0094	10.06 ± 0.0094
Phosphate buffer pH 6.8	9610 ± 0.0047	9.61 ± 0.0047

Final Equation in Terms of Actual Factors

Moisture Content	=
+25.93219	
-2.78063	HPMC E5
-0.982375	PEG 400
-4.42562	DMSO
+0.035875	HPMC E5 * PEG 400
+0.242500	HPMC E5 * DMSO
+0.028750	PEG 400 * DMSO
+0.150313	HPMC E5²
+0.018413	PEG 400²
+0.482187	DMSO²

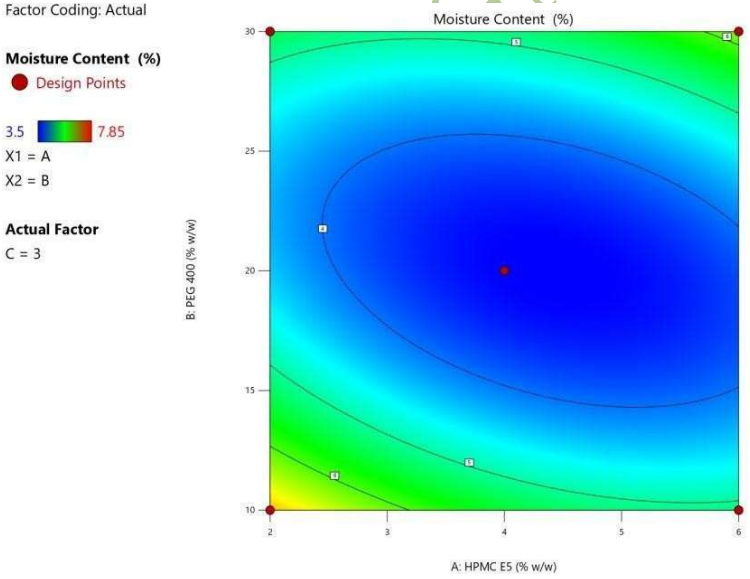


Fig 18: Counter Plot

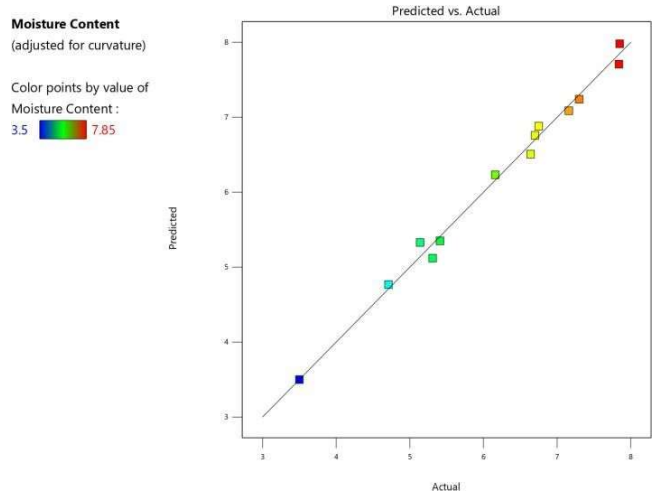


Fig 19: Predicted vs Actual plot

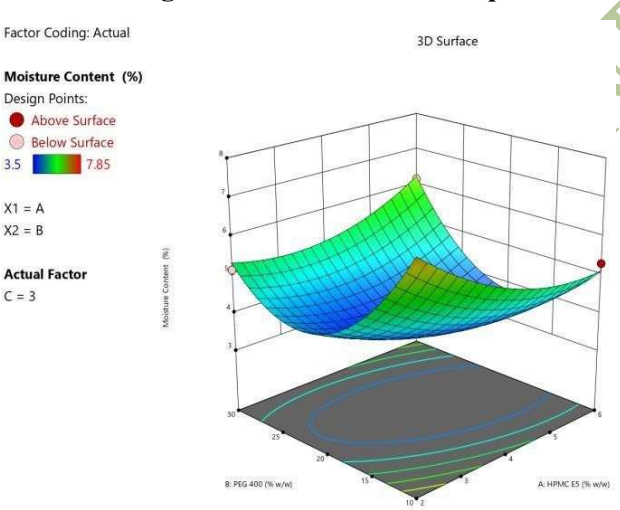


Fig 20: 3D Surface Plot

7. Drug Content Uniformity (%)

Table 23 : Drug Content Uniformity (%)

Formulation code	Drug Content Uniformity (%)
F1	86.89 ± 0.003
F2	80.5 ± 0.057
F3	78.25 ± 0.011
F4	92.62 ± 0.091
F5	93.63 ± 0.025

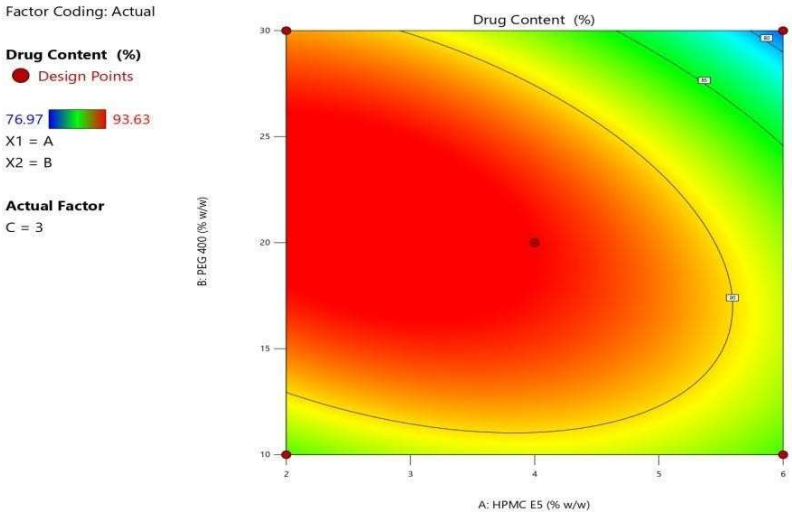


Fig 21: Counter Plot

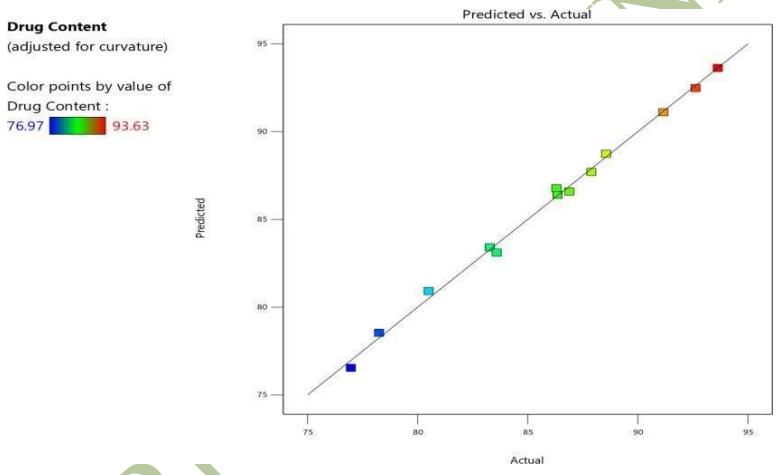


Fig 22: Predicted vs Actual plot

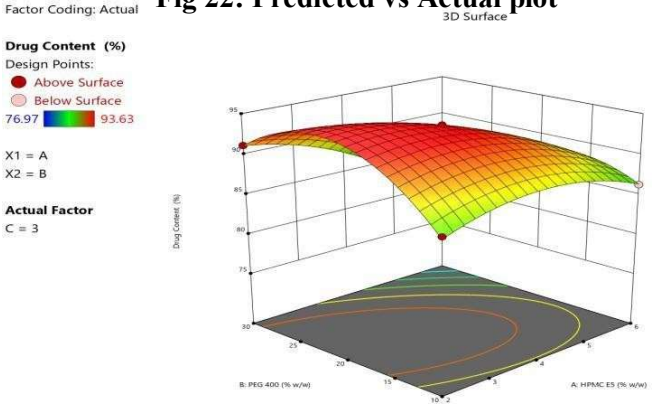


Fig 23: 3D Surface Plot

1. **In-vitro Drug Release (%)**

Table 24: In vitro Drug Release of F1 to F6

Time (Hr)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	11.97 ± 0.002	8.52 ± 0.005	11.57 ± 0.000	10.47 ± 0.000	12.51 ± 0.005	8.52 ± 0.000
4	22.85 ± 0.003	17.75 ± 0.005	20.07 ± 0.006	19.10 ± 0.007	24.58 ± 0.004	17.75 ± 0.005
6	33.80 ± 0.005	27.89 ± 0.009	31.78 ± 0.004	30.80 ± 0.008	36.80 ± 0.000	27.89 ± 0.001
8	43.76 ± 0.010	36.10 ± 0.007	41.31 ± 0.000	38.76 ± 0.009	46.98 ± 0.004	36.10 ± 0.008
12	55.62 ± 0.0369	42.89 ± 0.000	51.75 ± 0.009	48.62 ± 0.003	59.05 ± 0.001	42.89 ± 0.000
24	85.85 ± 0.127	87.11 ± 0.005	86.73 ± 0.000	82.62 ± 0.004	95.12 ± 0.005	87.2 ± 0.000

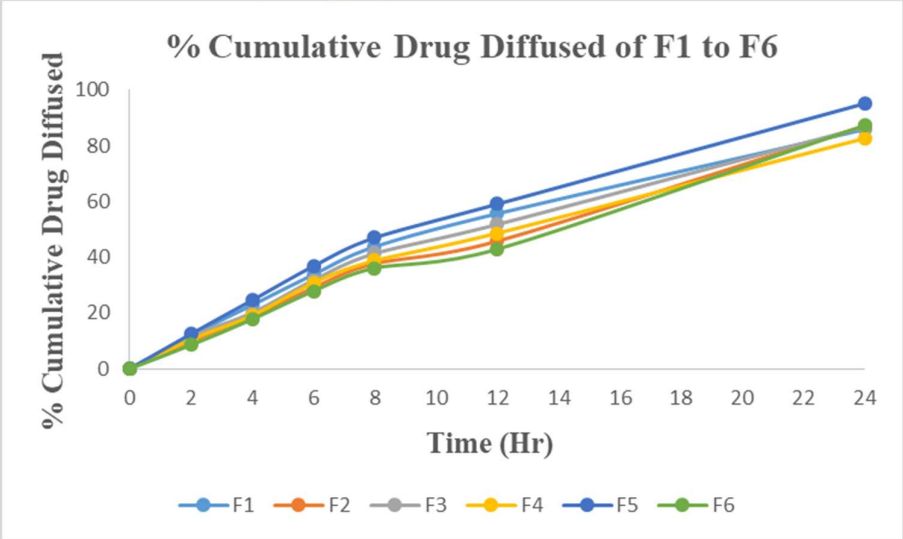


Fig 24: In vitro Drug Release of F1 to F6

Table 25: In vitro Drug Release of F7 to F13

Time (Hr)	F7	F8	F9	F10	F11	F12	F13
0	0	0	0	0	0	0	0
2	11.92 ± 0.006	10.91 ± 0.029	9.998 ± 0.014	9.627 ± 0.006	9.464 ± 0.002	8.89 ± 0.064	8.582 ± 0.001
4	23.95 ± 0.002	22.75 ± 0.035	21.02 ± 0.000	19.45 ± 0.004	17.89 ± 0.014	17.02 ± 0.074	16.74 ± 0.067
6	34.64 ± 0.000	32.63 ± 0.014	30.93 ± 0.014	29.64 ± 0.001	28.92 ± 0.057	27.93 ± 0.064	26.23 ± 0.034
8	44.99 ± 0.002	43.02 ± 0.062	41.98 ± 0.035	39.99 ± 0.003	38.56 ± 0.067	36.92 ± 0.098	35.88 ± 0.017
12	57.6 ± 0.006	55.04 ± 0.002	53.89 ± 0.025	51.6 ± 0.006	49.04 ± 0.069	47.50 ± 0.000	45.05 ± 0.067
24	81.16 ± 0.034	82.88 ± 0.000	86.9 ± 0.001	88.29 ± 0.003	80.54 ± 0.001	89.22 ± 0.002	85.41 ± 0.064

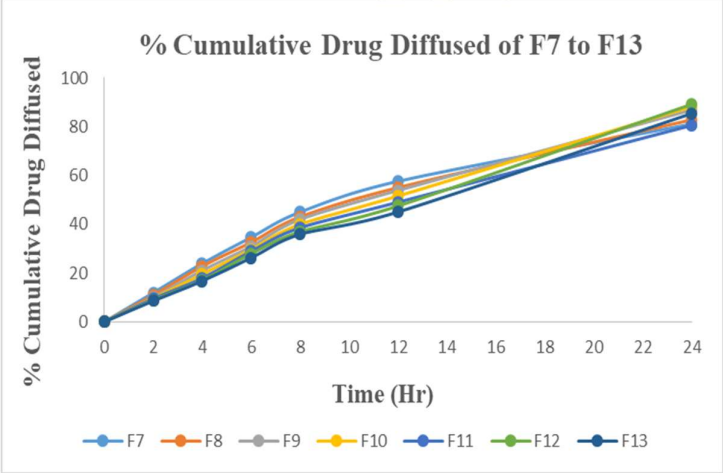


Fig 25: In vitro Drug Release of F7 to F13

Conclusion

The in vitro release study of rivastigmine transdermal patches (F1–F13) demonstrated a sustained and progressive release of the drug over 24 hours, indicating effective potential for transdermal delivery. Among the formulations F1–F6, F5 showed the highest cumulative drug release at 24 hours (95.12 ± 0.0058%), reflecting superior permeation compared to the other formulations. The release profile followed a controlled pattern, with approximately 45–

60% of the drug released within the first 12 hours, followed by a steady release up to 24 hours. Although formulations F7–F13 also exhibited sustained drug release, F5 consistently showed the highest cumulative release, confirming its optimized performance. The gradual and continuous drug release from F5 suggests it is well-suited for maintaining therapeutic plasma levels of rivastigmine while potentially reducing dosing frequency and minimizing side effects. Overall, F5 can be considered the optimized transdermal patch formulation, combining efficient drug release with improved patient compliance.

ANOVA for Quadratic model

Response 3: In-vitro Drug Release

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	175.41	9	19.49	28.10	0.0096	significant
A-HPMC E5	0.0010	1	0.0010	0.0015	0.9719	
B-PEG 400	0.0666	1	0.0666	0.0960	0.7769	
C-DMSO	0.3872	1	0.3872	0.5582	0.5092	
AB	6.08	1	6.08	8.76	0.0596	
AC	18.49	1	18.49	26.66	0.0141	
BC	29.27	1	29.27	42.20	0.0074	
A^2	22.34	1	22.34	32.21	0.0108	
B^2	45.70	1	45.70	65.88	0.0039	
C^2	115.02	1	115.02	165.83	0.0010	
Residual	2.08	3	0.6936			
Cor Total	177.49	12				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 28.10 implies the model is significant. There is only a 0.96% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case AC, BC, A^2, B^2, C^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to

support hierarchy), model reduction may improve your model.

Fit Statistics

Std. Dev.	0.8328		**R²**	0.9883
Mean	86.08		**Adjusted R²**	0.9531
C.V. %	0.9675		**Predicted R²**	0.9124
			Adeq Precision	19.9622

Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	95.12	1	0.8328	92.47	97.77	
A-HPMC E5	-0.0113	1	0.2945	-0.9483	0.9258	1.0000
B-PEG 400	0.0912	1	0.2945	-0.8458	1.03	1.0000
C-DMSO	0.2200	1	0.2945	-0.7171	1.16	1.0000
AB	-1.23	1	0.4164	-2.56	0.0927	1.0000
AC	2.15	1	0.4164	0.8248	3.48	1.0000
BC	-2.70	1	0.4164	-4.03	-1.38	1.0000
A^2	-3.13	1	0.5509	-4.88	-1.37	1.35
B^2	-4.47	1	0.5509	-6.22	-2.72	1.35
C^2	-7.09	1	0.5509	-8.85	-5.34	1.35

Final Equation in Terms of Coded Factors

In-vitro Drug Release	=
+95.12	
-0.0113	A
+0.0912	B
+0.2200	C
-1.23	AB
+2.15	AC
-2.70	BC

-3.13	A^2
-4.47	B^2
-7.09	C^2

Final Equation in Terms of Actual Factors

In-vitro Drug Release	=
+41.68406	
+5.86687	HPMC E5
+2.44987	PEG 400
+11.30563	DMSO
-0.061625	HPMC E5 * PEG 400
+0.537500	HPMC E5 * DMSO
-0.135250	PEG 400 * DMSO
-0.781562	$HPMC\ E5^2$
-0.044712	$PEG\ 400^2$
-1.77344	$DMSO^2$

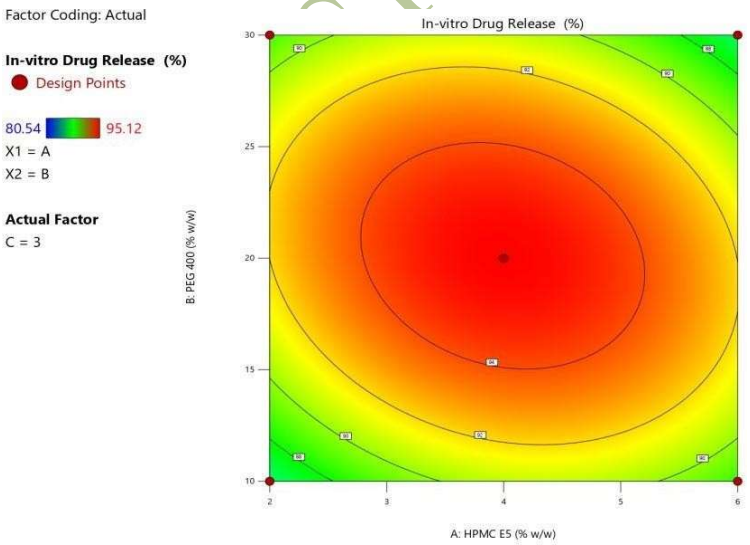


Fig 26: Counter Plot

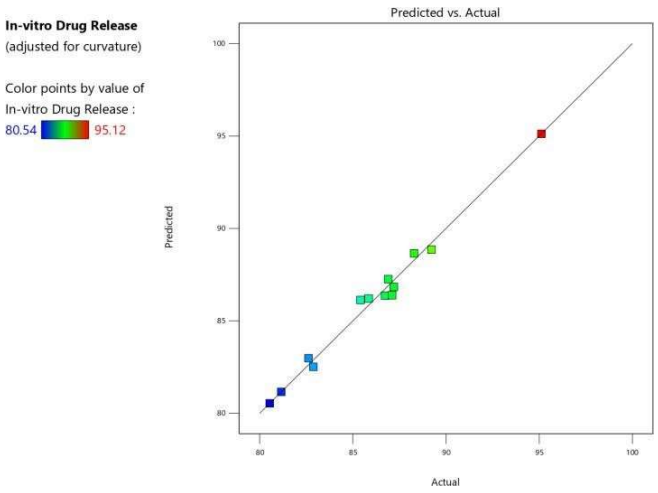


Fig 27: Predicted vs Actual plot

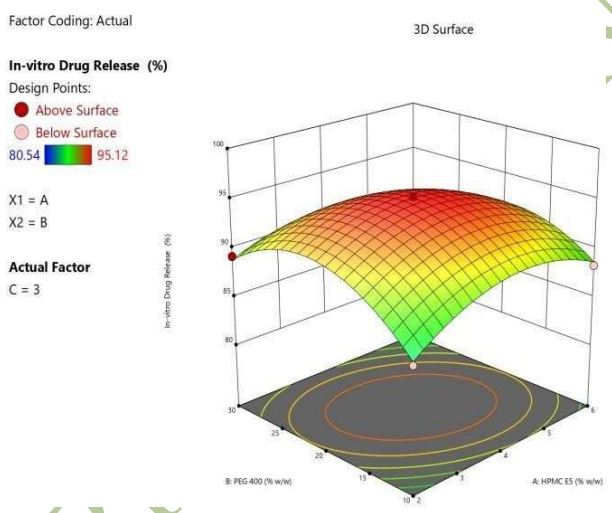


Fig 28: 3D Surface Plot

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REFERENCES

1. Diniz DP. BS Forlenza OV Alzheimer's disease. Subcell. Biochem. 2012;65:329-52.
2. Cipriani G, Dolciotti C, Picchi L, Bonuccelli U. Alzheimer and his disease: a brief history. Neurological Sciences. 2011 Apr;32(2):275-9.
3. Blass JP. Alzheimer's disease. Disease-a-Month. 1985 Apr 1;31(4):8-69.
4. Terry RD, Davies P. Dementia of the Alzheimer type. Annual review of neuroscience. 1980 Mar;3(1):77-95.
5. Rathmann KL, Conner CS. Alzheimer's disease: clinical features, pathogenesis, and treatment. Drug intelligence & clinical pharmacy. 1984 Sep;18(9):684-91.
6. Yiannopoulou KG, Papageorgiou SG. Current and future treatments in Alzheimer disease: an update. Journal of central nervous system disease. 2020 Feb;12:1179573520907397.
7. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C, Costafreda SG. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. The lancet. 2020 Aug 8;396(10248):413-46.
8. Schachter AS, Davis KL. Alzheimer's disease. Dialogues in clinical neuroscience. 2000 Jun 30;2(2):91-100.
9. Jatoi S, Hafeez A, Riaz SU, Ali A, Ghauri MI, Zehra M. Low vitamin B12 levels: an underestimated cause of minimal cognitive impairment and dementia. Cureus. 2020 Feb 13;12(2).
10. Cho,H.S.; Huang, L.K.; Lee, Y.T.; Chan, L.; Hong, C.T. Suboptimal baseline serum Vitamin B12 is associated with cognitive decline in people with Alzheimer's disease undergoing cholinesterase inhibitor treatment. Front. Neurol. 2018, 9, 325
11. McKhann, G.; Drachman, D.; Folstein, M.; Katzman, R.; Price, D.; Stadlan, E.M. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984, 34, 939–944.
12. Neugroschl J, Wang S. Alzheimer's disease: diagnosis and treatment across the spectrum of disease severity. Mount Sinai Journal of Medicine: A Journal of Translational and Personalized Medicine. 2011 Jul;78(4):596-612.
13. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack Jr CR, Kawas CH, Klunk.

Dizhen Dizhi Journal (ISSN:0253-4967)