Design and Invitro Evaluation of Transdermal patches of Tacrine

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ABSTRACT

Tacrine *is a centrally acting acetylcholinesterase inhibitor and indirect cholinergic agonist (parasympathomimetic). It was the first centrally acting cholinesterase inhibitor approved for the treatment of Alzheimer's disease. It also acts as a histamine N-methyltransferase inhibitor.In present study transdermal drug delivery of Tacrine was developed to overcome the first pass metabolism and to reduce frequency of dosing compared to oral route. Oral drug delivery system has various drawbacks like poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient. Matrix type of transdermal patches was developed by using xanthan gum, chitosan and HPMC K100M polymers. Transdermal patches were prepared by employing solvent casting method. Drug excipient compatibility studies were carried out by using FTIR, and it was observed that there were no interactions. Formulations were prepared with the varying concentrations polymers ranging from F1-F9, and all the formulations were evaluated for various physical parameters Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake, Moisture content and Swelling study and all the results were found to be with in the pharmacopeial limits, invitro drug release studies by using dialysis membrane. Among all the 9 formulations F5 formulation which contain Chitosan 150 mg had shown 97.52% cumulative drug release with in 12 hours.*

Key Words: Tacrine , *xanthan gum, chitosan and HPMC K100M, Transdermal patches*

Introduction

In the early stage of transdermal drug fabrication for AD, tacrine was one of the experimental drugs. Tacrine is a reversible cholinesterase inhibitor; its passive diffusion was difficult because of the lipophilic and weak base property. Therefore, the transport was done with the utilization of ion-exchange fibers and iontophoresis. In an iontophoresis system, there were an anode with cationic or neutral therapeutic agents and a cathode with anionic therapeutic agents, which were utilized under an external electric field. The drugs had the same polarity with the electrode and were driven into the skin by electrorepulsion and electroosmosis. With electron repulsion, cationic drugs were driven into and through the skin by the anode (active electrode), which also extracted anions from the tissue underneath the skin into the anode.

Materials

Tacrine, Chitosan, Xanthan gum, HPMCk100M, Ethanol, Dichloromethane, Propylene glycol

Tween-80all the chemicals used were laboratory grade.

Methodology& Formulation

Formulation:

- **Development of Transdermal patches :** Transdermal drug delivery patches were prepared by solvent casting method.
- **Solvent casting method :** Transdermal patches were prepared according to the formula shown in Table 3.3. Xanthan gum, Chitosan and HPMCK100 M were weighed in requisite ratios and they were then dissolved in dichloromethane and ethanol as solvent using magnetic stirrer. Tacrine (100 mg), Propylene glycol and Tween 80 was added to the above dispersion under continuous stirring. The uniform dispersion was poured in the petri plate. The rate of evaporation of solvent was controlled by inverting cut funnel over the patches. After 24h, the dried films were taken out and stored in desiccator.

Table 1 : Formulations of Tacrine Transdermal Patch

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Drug(mg)	100	100	100	100	100	100	100	100	100
2	Xanthan gum (mg)	100	150	200	-	-	-	-	-	-
3	Chitosan (mg)	-	-	-	100	150	200	-	-	-
4	HPMCK100 M(mg)	-	-	-	-	-	-	100	150	200
5	Dichloromethane(ml)	8	8	8	8	8	8	8	8	8
6	Ethanol(ml)	8	8	8	8	8	8	8	8	8
7	Propylene glycol(ml)	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
8	Tween-80(ml)	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2

All ingredients are expressed in mg only

Evaluation of prepared tablets

The formulated patches were studied for their Physical appearance, Thickness, Weight variation, Flatness, Folding endurance, Moisture uptake, Moisture content,Drug content determination, Evaluation of Transdermal patch by permeation studies.

Results & Discussion

Table 2: Standard graph of Tacrine

Concentration (µg/ml)	Absorbance (nm)
1	0.159
2	0.305

3	0.487
4	0.612
5	0.813

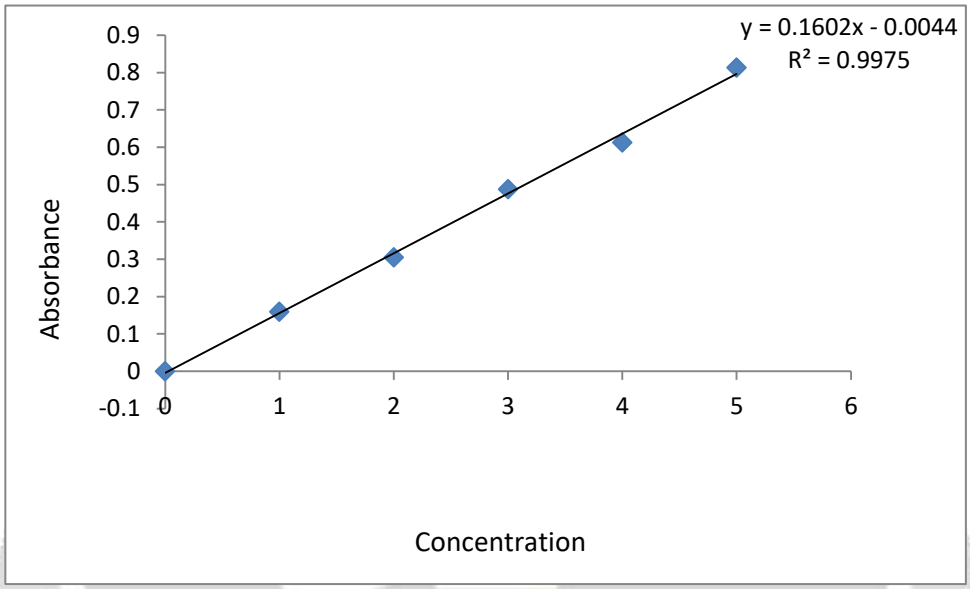

Fig 2 : Standard curve of Tacrine

Evaluation of Tacrine Transdermal patches :

Physical appearance : All the Transdermal patches were visually inspected for colour, clarity, flexibility.

Flatness : All the Transdermal patches was found to be flat with out any foams.

Table. 3 : Evaluation of Transdermal patch by physical methods

Formulation	Thickness (mm)	Folding endurance	Drug content (%)	Moisture uptake (%)	Moisture content (%)	Weight Variation
F1	0.3489	190	98.54	4.08	4.77	215
F2	0.3491	195	97.65	5.12	5.02	267
F3	0.3531	107	97.05	4.09	5.16	314
F4	0.3496	204	99.85	4.63	4.87	216
F5	0.3512	192	97.25	5.03	5.11	268
F6	0.3471	204	98.32	4.65	4.59	316
F7						

	0.3522	193	971.7	5.02	3.99	217
F8	0.3493	186	98.35	3.97	4.32	265
F9	0.3511	204	99.04	5.04	4.81	318

The prepared Tacrine Transdermal patches were evaluated by physical methods such as Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake and Moisture content and all the results were found to be with in the pharmacopeial limits.

Table 4 : Evaluation of Trandermal patch by In-vitro permeation studies using dialysis membrane

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	7.84	10.43	6.95	9.05	7.83	6.98	5.23	7.82	10.56
1	14.76	19.58	13.71	18.27	13.95	11.34	10.28	13.34	16.64
2	21.07	26.31	20.42	23.51	20.42	20.17	17.32	19.92	23.81
3	28.34	32.81	27.81	31.08	28.54	27.53	25.91	27.35	31.52
4	34.21	38.42	33.79	38.56	37.28	34.81	33.56	35.82	37.81
5	39.56	43.61	39.48	45.71	45.22	38.51	38.01	40.51	45.37
6	44.08	48.92	44.52	52.73	51.05	43.29	44.08	47.86	50.91
7	51.83	54.73	48.71	60.21	58.43	48.17	49.53	54.72	59.63
8	55.01	59.21	55.19	64.58	65.47	54.92	54.91	60.35	68.42
9	56.92	65.82	63.27	70.42	74.09	58.31	59.67	67.51	74.51
10	61.95	69.51	69.56	75.61	83.43	63.19	68.83	72.58	80.75
11	67.81	74.92	74.03	78.92	90.26	69.52	74.41	78.53	84.63
12	75.69	81.27	79.26	82.35	97.52	76.43	80.59	83.76	87.52

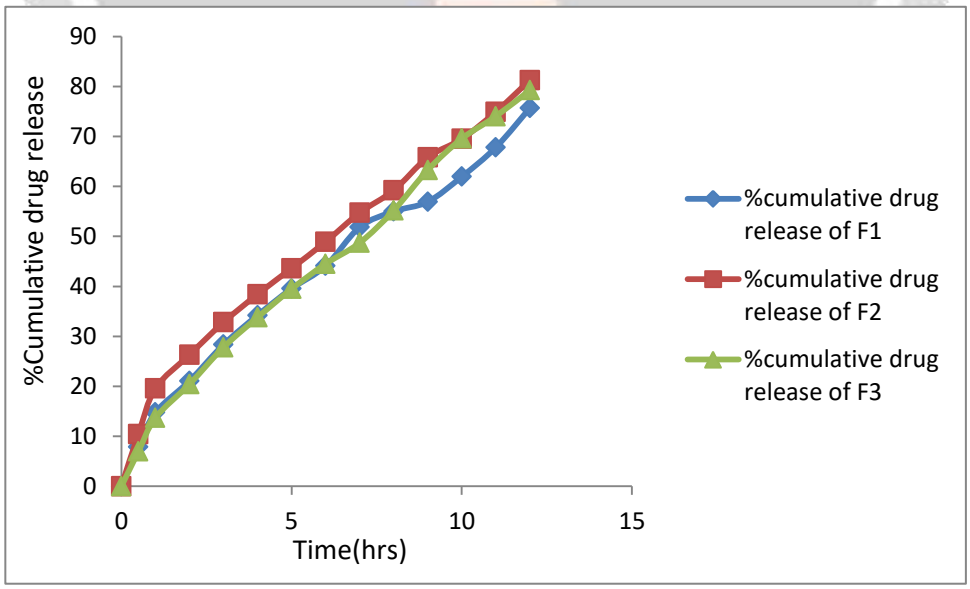

Fig 2: Dissolution profile of F1, F2, F3 formulations.

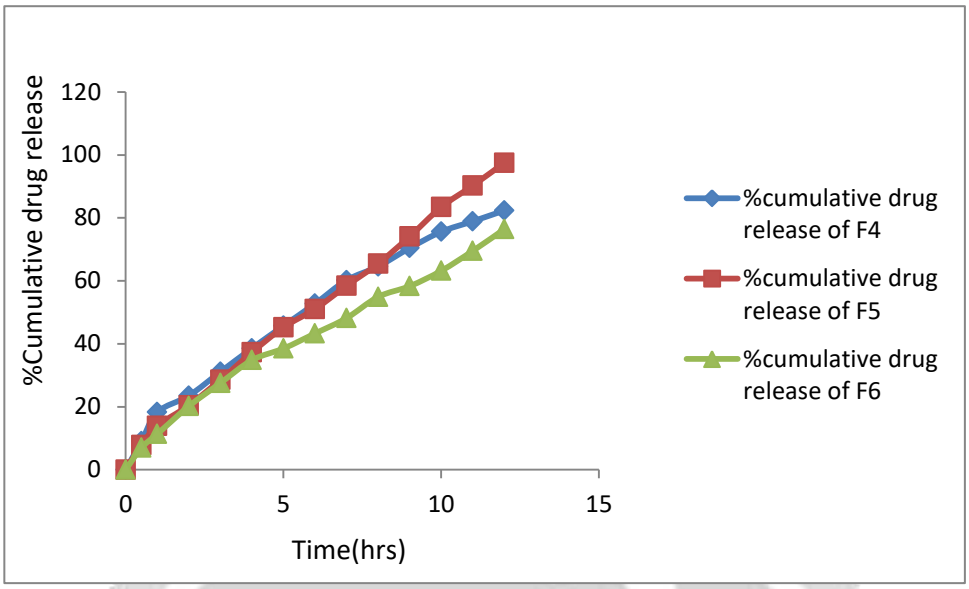

Fig3: Dissolution profile of F4, F5, F6 formulations.

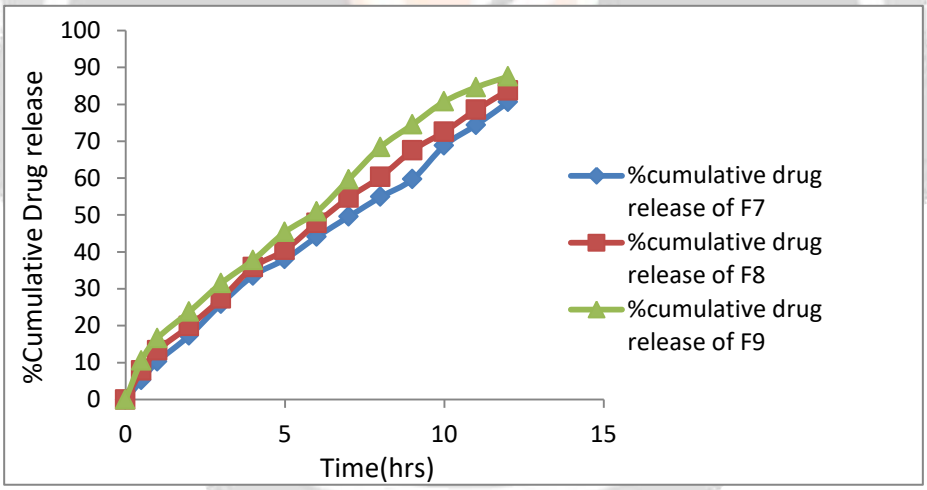

Fig4: Dissolution profile of F4, F5, F6 formulations.

The prepared Tacrine Transdermal patches were evaluated for In-vitro diffusion studies. Among all the 9 formulations F5 formulation which contain Chitosan 150mg had shown 97.52% cumulative drug release with in 12 hours.

Table 4.4 : kinetics of In-vitro permeation studies using dialysis membrane

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN
0	0	0			2.000
7.83	0.5	0.707	0.894	-0.301	1.965
13.95	1	1.000	1.145	0.000	1.935
20.42	2	1.414	1.310	0.301	1.901
28.54	3	1.732	1.455	0.477	1.854
37.28	4	2.000	1.571	0.602	1.797
45.22	5	2.236	1.655	0.699	1.739
51.05	6	2.449	1.708	0.778	1.690
58.43	7	2.646	1.767	0.845	1.619
65.47	8	2.828	1.816	0.903	1.538
74.09	9	3.000	1.870	0.954	1.413
83.43	10	3.162	1.921	1.000	1.219
90.26	11	3.317	1.955	1.041	0.989
97.52	12	3.464	1.989	1.079	0.394

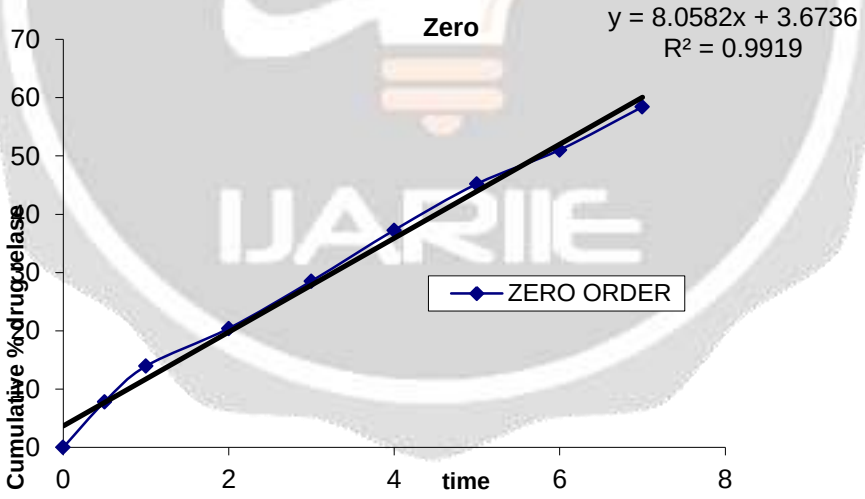

Fig 5 : Zero order kinetics

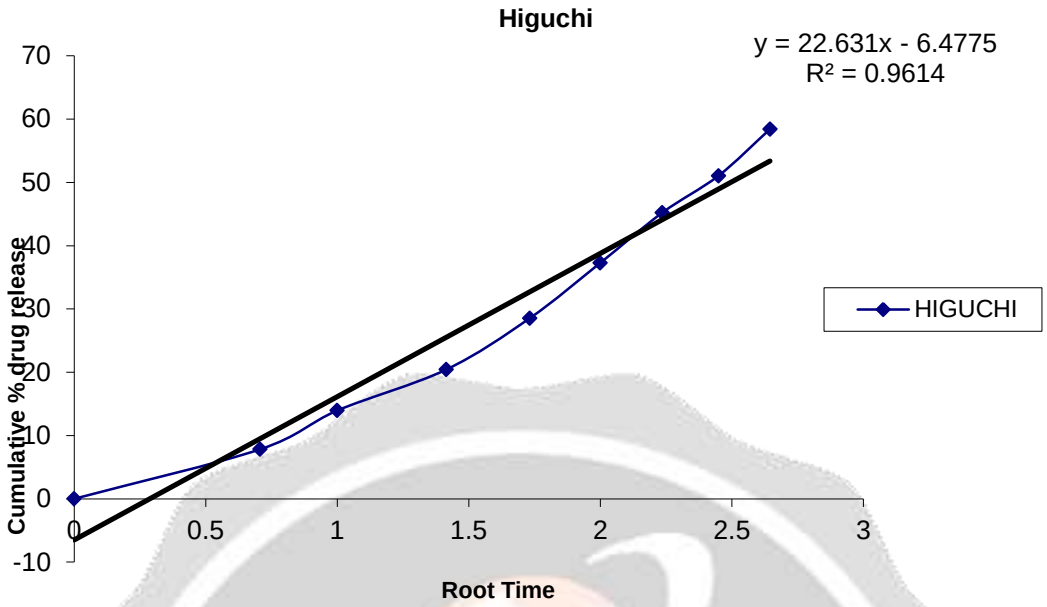

Fig .6 : Higuchi plot

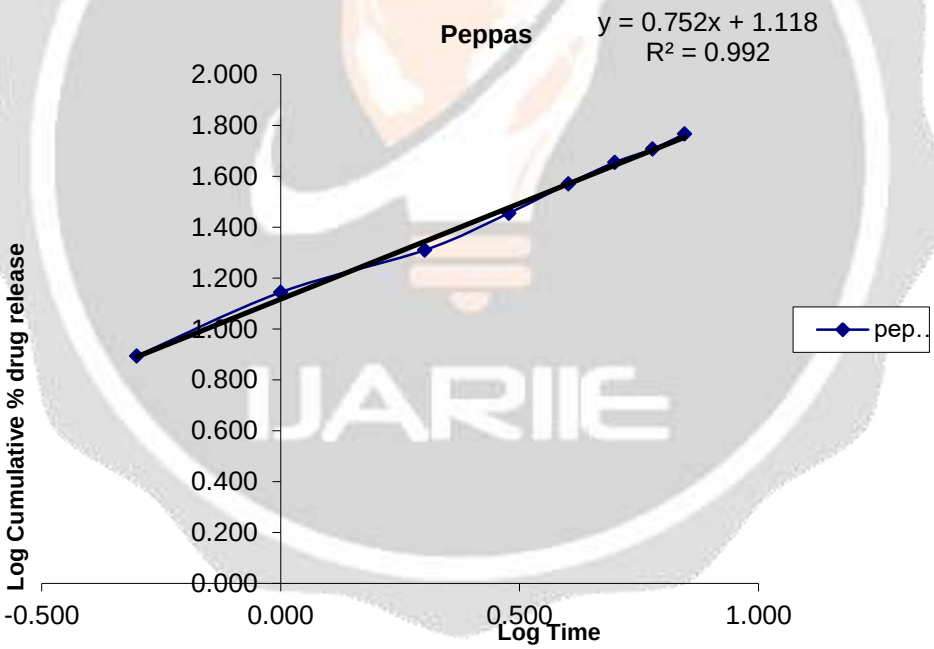

Fig 7 : Peppas plot

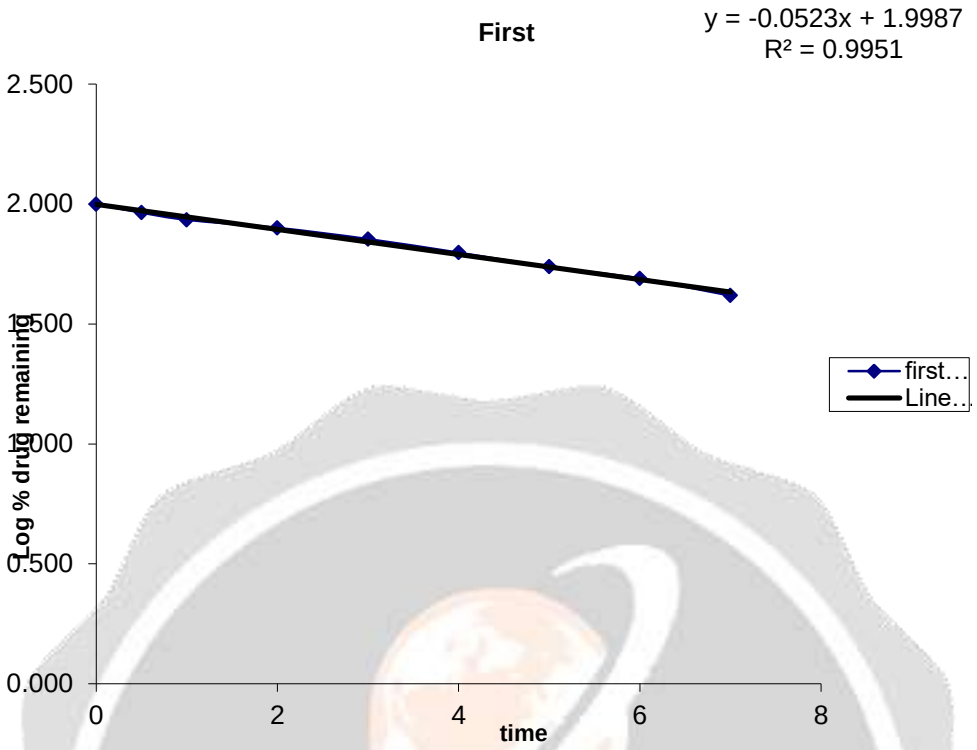

Fig 8 : First order kinetics

The kinetics of In-vitro permeation studies using dialysis membrane for F5 formulation was plotted and the Regression coefficient value was found to be high for first order release model i.e., 0.995.

Conclusion

In present study transdermal drug delivery of Tacrine was developed to overcome the first pass metabolism and to reduce frequency of dosing compared to oral route. Oral drug delivery system has various drawbacks like poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient. Matrix type of transdermal patches was developed by using xanthan gum, chitosan and HPMC K100M polymers. Transdermal patches were prepared by employing solvent casting method. Drug excipient compatibility studies were carried out by using FTIR, and it was observed that there were no interactions. Formulations were prepared with the varying concentrations polymers ranging from F1-F9, and all the formulations were evaluated for various physical parameters Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake, Moisture content and Swelling study and all the results were found to be with in the pharmacopeial limits, invitro drug release studies by using dialysis membrane. Among all the 9 formulations F5 formulation which contain Chitosan 150 mg had shown 97.52% cumulative drug release with in 12 hours.

Bibilography

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