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Original Research Article

Development of a Transdermal Delivery System for Tacrine

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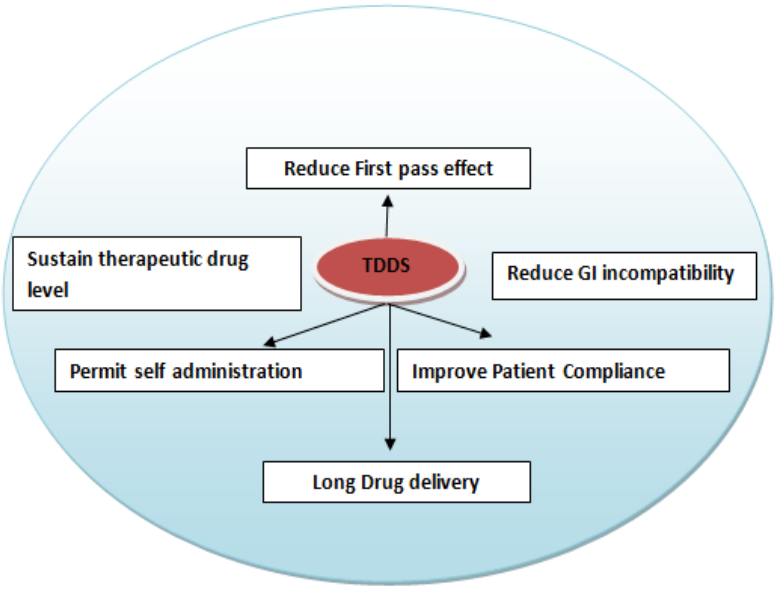
Abstract: Tacrine has several mechanisms of action. The putative primary mechanism of action of tacrine for Alzheimer's disease is reversible inhibition of acetylcholinesterase (AChE), which thus slows the breakdown of the chemical messenger acetylcholine (ACh) in the brain. Tacrine also inhibits butyrylcholinesterase activity. In accumulation, tacrine blocks sodium and potassium channels. Tacrine also acts as a histamine N-methyltransferase inhibitor. This study was carried out to develop matrix based transdermal patches containing Tacrine to overcome the first pass metabolism and to reduce frequency of dosing compared to oral route. . Matrix type of transdermal patches was developed by using Methocel K4M, Methocel K15M, Methocel K100M and Xanthan gum polymers. Transdermal patches were prepared by employing solvent casting method. Drug excipients 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-F16, 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 within the pharmacopeial limits, invitro drug release studies by using dialysis membrane. Among all the 16 Tacrine transdermal patches formulations F5 formulations which contain Methocel K15M 100 mg had shown 97.61% % cumulative drug release within 12 hours.

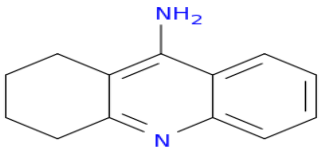
Keywords: Tacrine, Transdermal patches, Methocel K4M, Methocel K15M, Methocel K100M and Xanthan gum.

INTRODUCTION

Transdermal drug delivery systems (TDDS) are definite as self contained, discrete dosage forms which, when functional to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation. The Transdermal route of administration is predictable as one of the potential route for the local and systemic delivery of drugs. In evaluation to conventional pharmaceutical dosage forms. TDDS offer much compensation, such as elimination of first pass metabolism, sustained drug delivery, reduced frequency of administration, reduced side effects and improved patient compliance [1-4]. The biological properties of drug for preparing transdermal patch should be of short $t_{1/2}$, should not produce sensitive to response and the drug should be potent with a daily dose of the order of a few mg/day [5]. Substances which provisionally diminish the impermeability of the skin are recognized as permeation enhancers [6]. As the epidermis is the main barrier for penetration of the drug, numerous chemical enhancers such as sulphoxide, alcohols, fatty acids, polyols, ureas and physical enhancers such as sonophorosis, electroporation, iontophorosis, magnetophorosis have been used in TDDS [7-12].



Tacrine has several mechanisms of action. The putative primary mechanism of action of tacrine for Alzheimer's disease is reversible inhibition of acetylcholinesterase (AChE), which thus slows the breakdown of the chemical messenger acetylcholine (ACh) in the brain. Tacrine also inhibits butyrylcholinesterase activity. In accumulation, tacrine blocks sodium and potassium channels. Tacrine also acts as a histamine N-methyltransferase inhibitor [13].

Description of Tacrine [14]	
Synonym	Tetrahydroaminacrine1,2,3,4-TETRAHYDRO-9-ACRIDINAMINE
IUPAC	1,2,3,4-tetrahydro-9-acridinamine monohydrochloride monohydrate
Molecular Formula	$C_{13}H_{14}N_2$•HCl•H_2O
Molecular Weight	252.74
Structure	
Mechanism of action	Reversible cholinesterase 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.

MATERIAL AND METHOD

Preformulation study

Preformulation studies were primarily done to investigate the physicochemical properties of drug and to establish its compatibility with other excipients.

Selection of drug and other ingredients

Tacrine was selected as model drug based on its physico-chemical and biological properties and also based on its suitability for Transdermal drug delivery system.

Methocel K4M, Methocel K15M, Methocel K100M and Xanthan gum were selected as matrix forming polymers.

Propylene glycol was selected as permeation enhancer and plasticizer.

Preparation of Phosphate Buffer pH 6.8

Accurately measured 250 ml of 0.2 M potassium dihydrogen phosphate in a 1000 ml of volumetric flask and added 195.5 ml of 0.2 M sodium hydroxide and then water was addedto make up the volume and adjusted pH 6.8 by using 0.2 M potassium dihydrogen phosphate/sodium hydroxide.

2.2) Construction of standard graph of tacrine

Standard graph of tacrine was plotted in PBS pH 6.8. Tacrine was estimated spectrophotometrically at λ_{max} of 254nm.

Preparation of standard solution

Stock solution - I was prepared by dissolving tacrine 100 mg in 100 ml of buffer, so as to get a solution of 1 mg/ml concentration. Then stock solution - II was prepared by taking 10 ml from the previous stock solution i.e. stock solution - I and dissolved in 100 ml of buffer, so as to get a solution of 100 µg/ml concentration. Accurately measured aliquot portions of standard drug solution, from stock solution -II were taken, like 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml and 1 ml were transferred in to 10 ml volumetric flasks and were diluted up to the mark with buffer pH 6.8 Absorbance of each solution was measured at λ_{max} 254 nm nm against buffer pH 6.8 as the blank, by using UV-spectrophotometer. A graph was plotted by taking concentration of drug vs absorbance was plotted.

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 1.Methocel K4M, Methocel K15M, Methocel K100M and Xanthan gum were weighed in requisite ratios and they were then dissolved in dimethyl formamide and ethanol as solvent using magnetic stirrer.. Propylene glycol 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 patches were taken out and stored in desiccator.

Table-1: Formulations of tacrine Transdermal Patches

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
1	Drug(mg)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
2	Methocel K4M(mg)	100	200	300	400	-	-	-	-	-	-	-	-	-	-	-	-
3	Methocel K15M(mg)	-	-	-	-	100	200	300	400	-	-	-	-	-	-	-	-
4	Methocel K100M(mg)	-	-	-	-	-	-	-	-	100	200	300	400	-	-	-	-
5	Xanthan gum (mg)	-	-	-	-	-	-	-	-	-	-	-	-	100	200	300	400
6	Dimethyl formamide (ml)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
7	Ethanol(ml)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
8	Propylene glycol(Drops)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Evaluation of Transdermal patch by physical methods

Physical appearance, Thickness, Weight variation, Folding endurance, Moisture, Moisture content and Drug content determination were carried out.

Evaluation of Trandermal patch by permeation studies

Permeation studies were carried out on Franz diffusion cells. The Franz diffusion cell contains two compartments, the donor and receptor compartment. The receptor compartment is mm and holds a volume of 15 ml. The receptor compartment is attached to a collecting tube which allows easy collection of hourly sample while the process of diffusion. The donor and the receptor compartment are held together with help of a clap. The total area of the receptor compartment that is exposed to the Transdermal patch for diffusion is 3.83 cm^2.

***In-vitro* permeation studies using dialysis membrane**

In-vitro permeation of tacrine from Transdermal patches through dialysis membrane (Hi-Media) with molecular weight cut off of 12000 was studied. The membrane was mounted over a Franz diffusion cell and a Transdermal patch. The receiver compartment of the diffusion cell was filled with 15.0 ml of PBS pH 6.8 and the setup was placed over a magnetic stirrer with temperature maintained at 37^0C. Samples of 3 ml were withdrawn and replenished immediately from the receiver compartment at 1, 2, 3, 4, 6 and 12h. They were stored in refrigerated condition till the analysis was performed. The content of Tacrine in the samples was analyzed by UV-Visible spectrophotometer. The concentrations of drug were determined at 254 nm.

Kinetic modeling of drug release [15-16]

Mechanism of drug release: Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

A. Zero order release model: To study the zero–order release kinetics the release rate data are fitted to the following equation.

$Q= K_{0\,t}$

Where, Q= amount of drug released at time t

K_0=zero order release rate constant

The plot of % drug release versus time is linear.

B. First order release model: The release rate data are fitted to the following equation

$\ln (100-Q) = \ln 100- k_1 t$

Where, Q= percent drug release at time t

K_1= first order release rate constant

The plot of log % drug release versus time is linear.

C. Higuchi's Release Model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation

$Q= K_H t^{1/2}$

Where, Q= percent drug release at time t

K_H= Higuchi's (diffusion) rate constant

In Higuchi's model, a plot of % drug release versus square root of time is linear.

D. Korsmeyer-peppas release model: The release rate data were fitted to the following equation

$F= (M_t/M) = K_m t^n$

Where, M_t= drug release at time t

M= total amount of drug in dosage form

F= fraction of drug release at time t

K_m=constant dependent on geometry of dosage form

n=diffusion exponent indicating the mechanism of drug release.

If n is equal to 0.89, the release is zero order. If n is equal to 0.45 the release is best explained by Fickian diffusion, and if $0.45 < n < 0.89$ then the release is through anomalous diffusion or non-fickian diffusion (Swellable& Cylindrical Matrix).In this model, a plot of log (M_t/M) versus log (time) is linear.

Drug excipients interaction studies

FT-IR spectrum interpretation

IR spectral analysis was carried out using FT-IR by the KBr disc method. The sample and KBr were triturated and compressed to get the discs. The samples of pure drug, dummy formulation and optimized formulation were analysed between wave numbers 4000.0 and 400.0 cm^{-1}.

RESULT AND DISCUSSION

Tacrine is a effective inhibitor of cholinesterases (acetylcholinesterase and butyrylcholinesterase) that shows limiting clinical claim by liver toxicity. Although this, analogues of tacrine are considered as a model inhibitor of cholinesterases in the therapy of Alzheimer's disease. To overcome liver toxicity and improve patient compliance an attempt had been made to developed the transdermal drug delivery of Tacrine was developed to conquer the first pass metabolism and to reduce frequency of dosing compared to oral route. The preformulation of Tacrine carried out to generate useful data needed in developing stable and safe dosage forms that can be manufactured on a commercial scale. Matrix type of transdermal patches was developed by using Methocel K4M, Methocel K15M, Methocel K100M and Xanthan gum polymers. Transdermal patches were prepared by employing solvent casting method. Drug excipient compatibility studies were carried out by using FTIR (Fig. 11-12). The figure is the FT- IR spectrum of the optimized formula by which the compatability of the drug to all other excipients can be known by the wave numbers which are present. It was observed that there were no interactions. Standard graph of tacrine was plotted in PBS pH 6.8. Tacrine was estimated spectrophotometrically at λ_{max} of 254 nm(Table 2 & Fig 1). Formulations were prepared with the varying concentrations polymers ranging from F1-F16(Table 1), 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 within the pharmacopeial limits. The result was tabulated in table 3. *In-vitro* drug release studies by was carried out using dialysis membrane. Among all the 16 tacrine transdermal patches formulations F5 formulation which contains Methocel K15M 100 mg had shown 97.61% cumulative drug release within 12 hours. The prepared tacrine transdermal patches were evaluated for *in-vitro* diffusion studies. Among all the 16 formulations F5 formulation which contain Methocel K15M 100mg had shown 97.61% cumulative drug release within 12 hours. The result showed in the table 3 and fig 1-6.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.The result was tabulated in the table 5 and fig. 7-10.In the formulations prepared with MethocelK15M 100mg has shown highest drug release compared to the other formulations, hence they were considered as the optimized formulations and selected for further *in-vivo* studies.

CONCLUSION

The present study established that tacrine can be formulated in matrix-based transdermal patches with *in-vitro* experiment. For further exploration of the possibility of the patches *in-vivo* study should be carried out.

Table-2: Standard graph of Tacrine

Concentration (µg/ml)	Absorbance (nm)
0	0
0.2	0.175
0.4	0.398
0.6	0.599
0.8	0.781
1	0.947

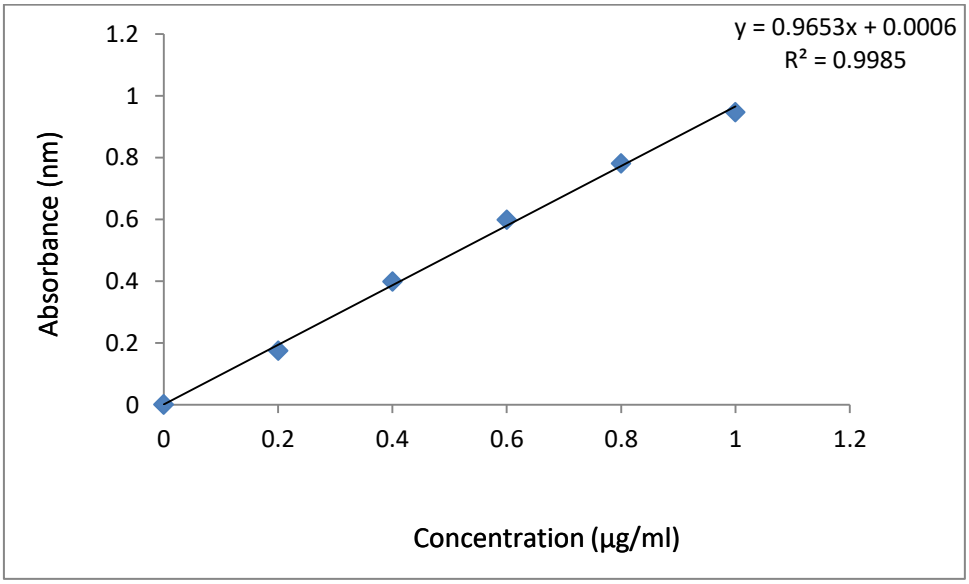


Fig-1: Standard curve of Tacrine

Table-3: Evaluation of Tacrine Transdermal patches by physical methods

Formulation	Thickness (mm)	Folding endurance	Drug content (%)	Moisture uptake (%)	Moisture content (%)	Weight Variation
F1	0.3515	200	99.16	4.86	4.99	217
F2	0.3507	203	97.63	5.16	5.13	314
F3	0.3489	199	97.83	5.08	4.98	411
F4	0.3513	215	98.52	4.79	4.85	513
F5	0.3498	195	97.12	5.14	4.96	212
F6	0.3507	201	98.83	4.89	4.95	311
F7	0.3493	212	99.15	5.06	5.12	415
F8	0.3503	205	99.07	4.96	4.94	518
F9	0.3485	192	97.88	4.95	4.87	210
F10	0.3505	198	99.01	4.87	5.13	311
F11	0.3511	201	98.13	5.14	5.08	417
F12	0.3489	205	97.99	4.87	4.95	515
F13	0.3510	213	98.54	4.86	5.04	218
F14	0.3497	187	97.76	4.99	5.04	311
F15	0.3503	195	99.07	5.04	4.99	416
F16	0.3496	212	97.99	5.03	4.95	519

Table-4: Evaluation of tacrine trandermal patches by In-vitro permeation studies using dialysis membrane

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	7.10	9.50	8.91	9.12	9.92	8.86	7.32	9.94	9.69	9.51	8.52	7.63	9.68	8.21	7.87	6.87
1	14.18	21.56	15.72	20.26	15.86	13.42	12.26	15.36	18.72	15.43	20.34	17.68	17.42	14.32	15.06	13.52
2	21.20	28.42	22.43	25.54	22.41	22.17	19.34	21.93	25.83	24.20	28.13	24.51	28.26	21.58	22.32	19.31
3	28.78	34.79	29.10	33.05	30.52	29.53	27.91	29.37	33.54	32.86	37.38	30.26	34.07	26.54	28.42	25.24
4	36.52	40.43	35.77	40.56	39.37	36.81	35.56	37.83	39.81	40.57	44.26	36.21	42.39	33.57	34.35	33.36
5	42.67	45.62	41.48	47.80	47.29	40.52	40.13	42.52	47.36	48.42	52.87	45.09	50.31	39.64	41.16	38.19
6	46.73	51.90	46.63	54.83	53.11	45.38	46.07	49.85	52.89	53.21	59.51	52.23	57.24	46.31	47.40	45.06
7	53.68	56.83	50.72	62.21	60.42	50.16	52.54	56.91	61.74	58.43	65.23	58.52	64.76	52.86	53.06	50.41
8	58.96	61.20	57.16	66.58	68.46	57.91	56.93	62.37	70.42	64.27	73.26	63.08	71.37	58.27	59.28	57.32
9	63.92	67.82	65.28	72.41	76.07	61.32	61.68	69.65	76.54	71.42	77.18	70.52	75.43	64.20	64.42	64.68
10	69.86	71.53	71.56	78.63	85.43	66.18	70.91	74.58	82.61	76.23	83.47	79.34	81.29	70.32	68.21	70.51
11	73.19	76.91	76.12	81.92	92.28	72.51	76.43	80.63	86.73	80.56	88.30	87.32	84.12	79.62	72.34	79.43
12	80.07	83.28	81.27	85.30	97.61	78.42	82.58	85.76	90.38	5.12	91.21	94.62	90.57	85.07	76.32	86.19

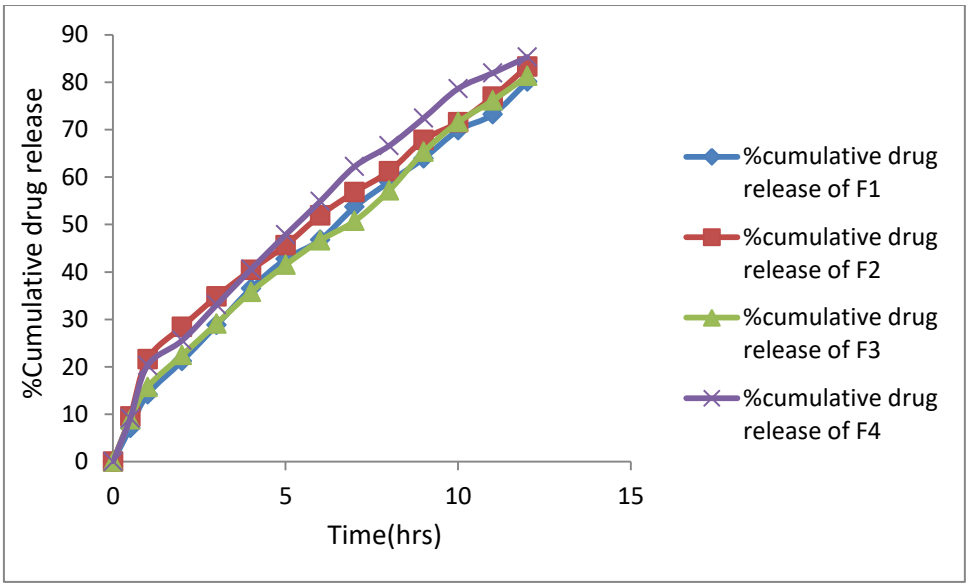


Fig-2: Dissolution profile of F1, F2, F3, F4 formulations.

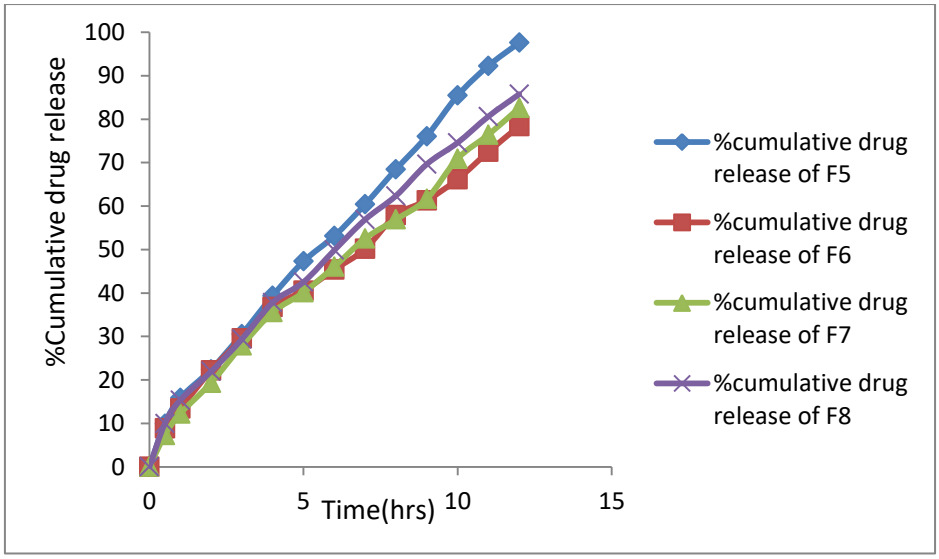


Fig-3: Dissolution profile of F5, F6, F7,F8 formulation

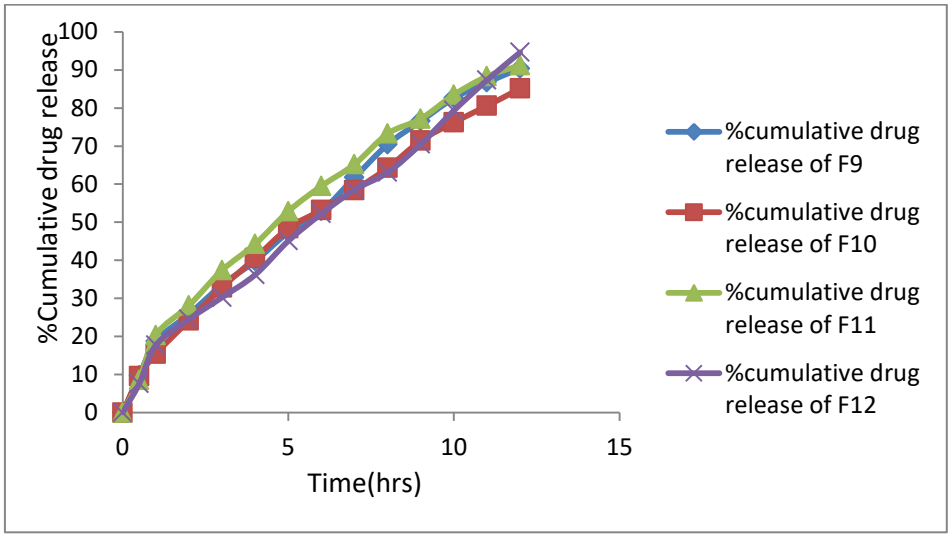


Fig -4: Dissolution profile of F9, F10, F11, F12 formulations.

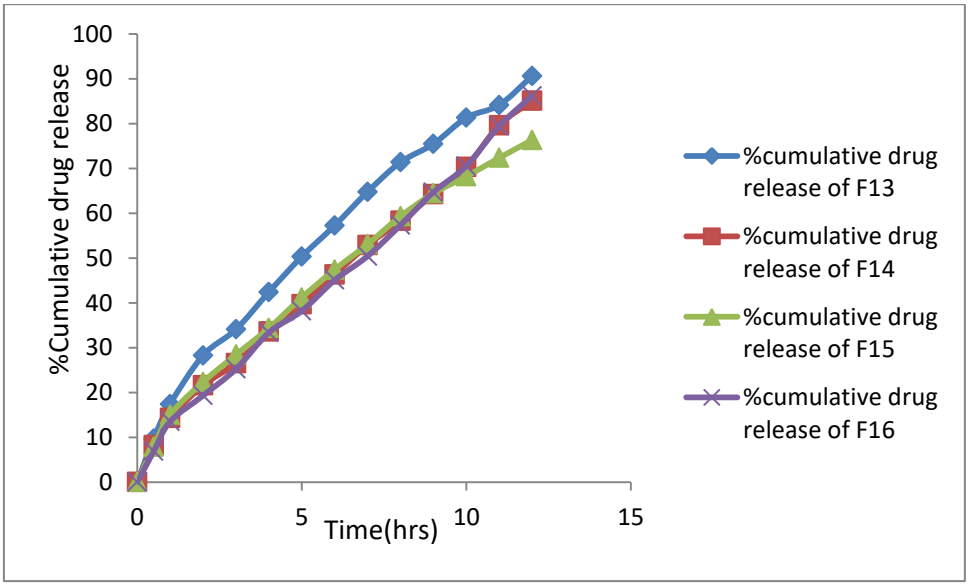


Fig -5: Dissolution profile of F13, F14, F15, F16 formulations.

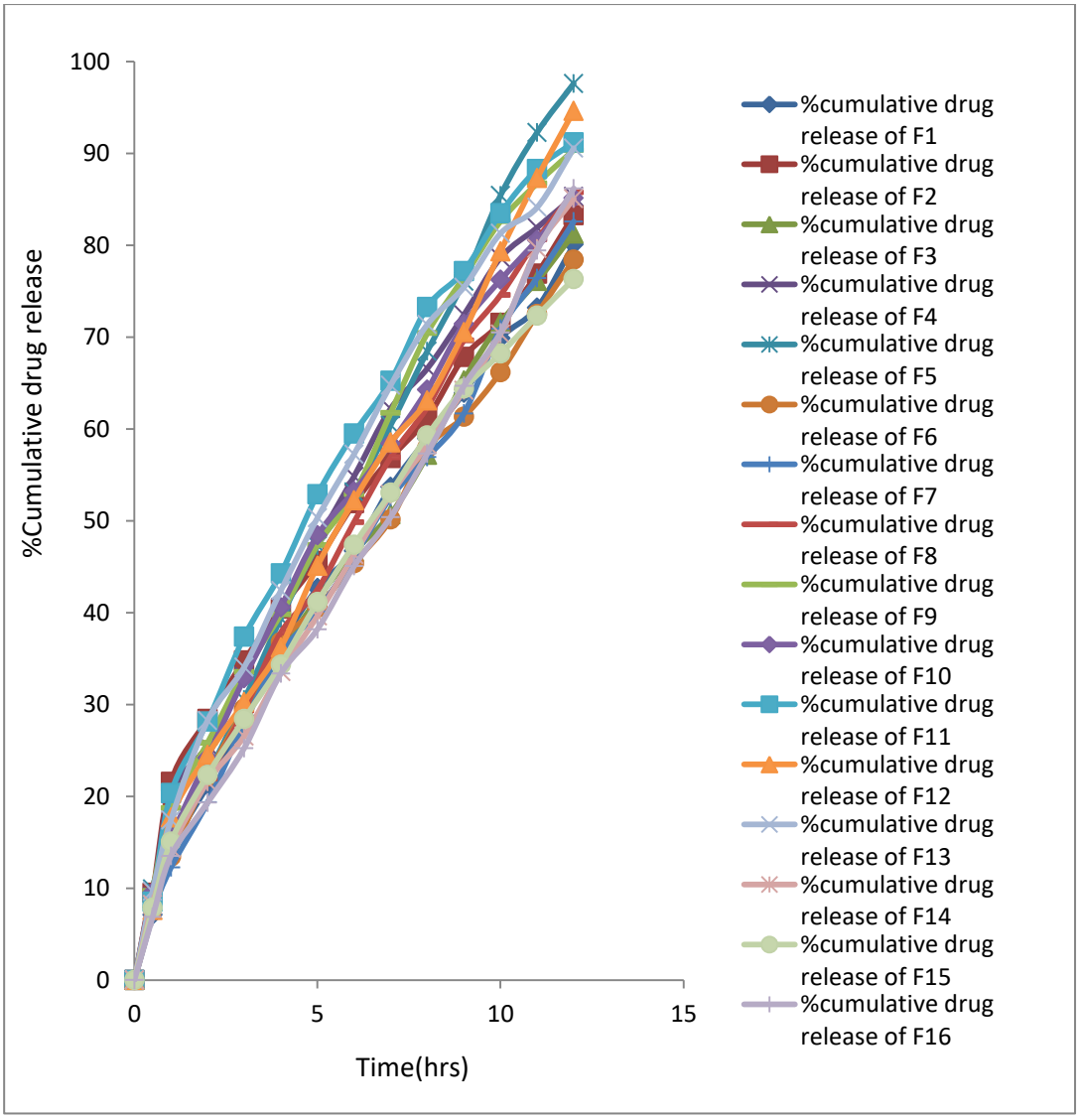


Fig-6: Dissolution profile of F1 to F16 formulations

Table-5: kinetics of In-vitro permeation studies using dialysis membrane

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%)RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM % RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
9.92	0.5	0.707	0.997	-0.301	1.955	19.840	0.1008	-1.003	90.08	4.642	4.483	0.159
15.86	1	1.000	1.200	0.000	1.925	15.860	0.0631	-0.800	84.14	4.642	4.382	0.260
22.41	2	1.414	1.350	0.301	1.890	11.205	0.0446	-0.650	77.59	4.642	4.265	0.376
30.52	3	1.732	1.485	0.477	1.842	10.173	0.0328	-0.515	69.48	4.642	4.111	0.531
39.37	4	2.000	1.595	0.602	1.783	9.843	0.0254	-0.405	60.63	4.642	3.929	0.713
47.29	5	2.236	1.675	0.699	1.722	9.458	0.0211	-0.325	52.71	4.642	3.749	0.892
53.11	6	2.449	1.725	0.778	1.671	8.852	0.0188	-0.275	46.89	4.642	3.606	1.036
60.42	7	2.646	1.781	0.845	1.597	8.631	0.0166	-0.219	39.58	4.642	3.408	1.234
68.46	8	2.828	1.835	0.903	1.499	8.558	0.0146	-0.165	31.54	4.642	3.160	1.482
76.07	9	3.000	1.881	0.954	1.379	8.452	0.0131	-0.119	23.93	4.642	2.882	1.760
85.43	10	3.162	1.932	1.000	1.163	8.543	0.0117	-0.068	14.57	4.642	2.442	2.199
92.28	11	3.317	1.965	1.041	0.888	8.389	0.0108	-0.035	7.72	4.642	1.976	2.665
97.61	12	3.464	1.989	1.079	0.378	8.134	0.0102	-0.011	2.39	4.642	1.337	3.305

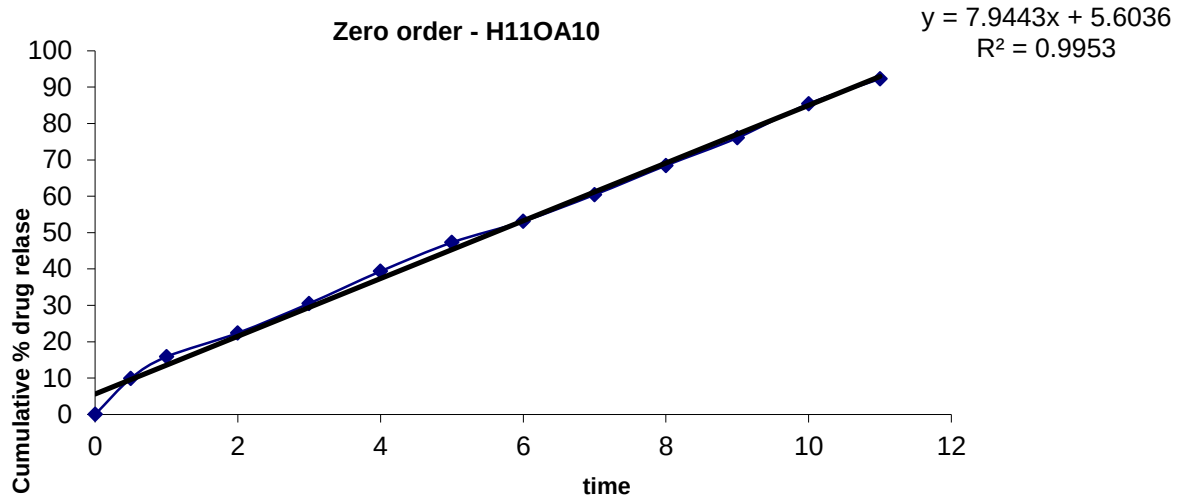


Fig-7: Zero order kinetics

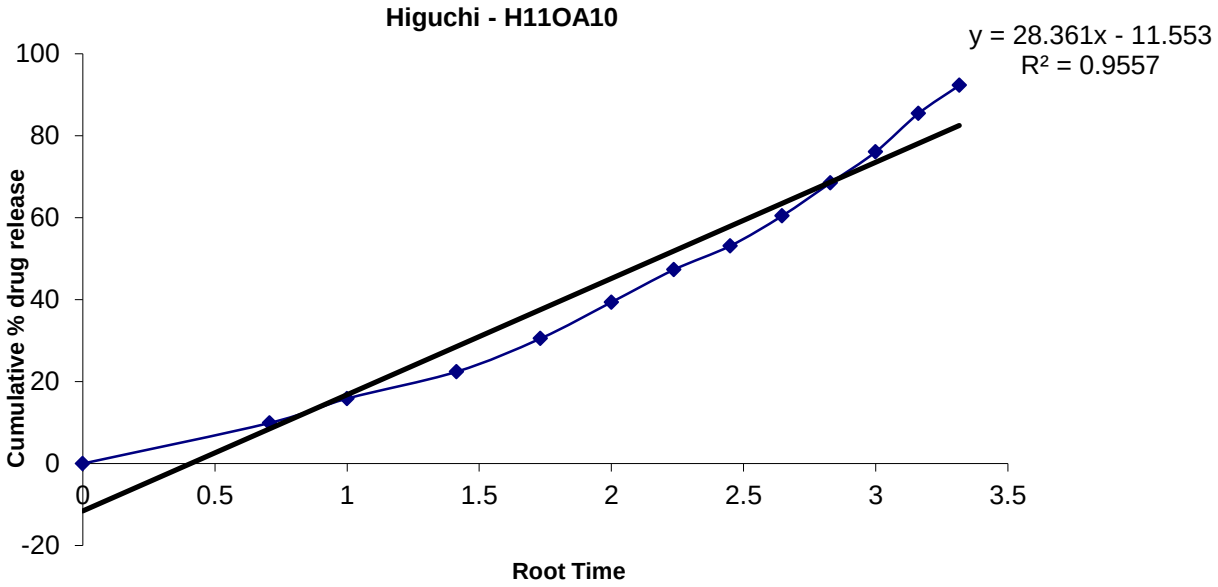


Fig-8: Higuchi plot

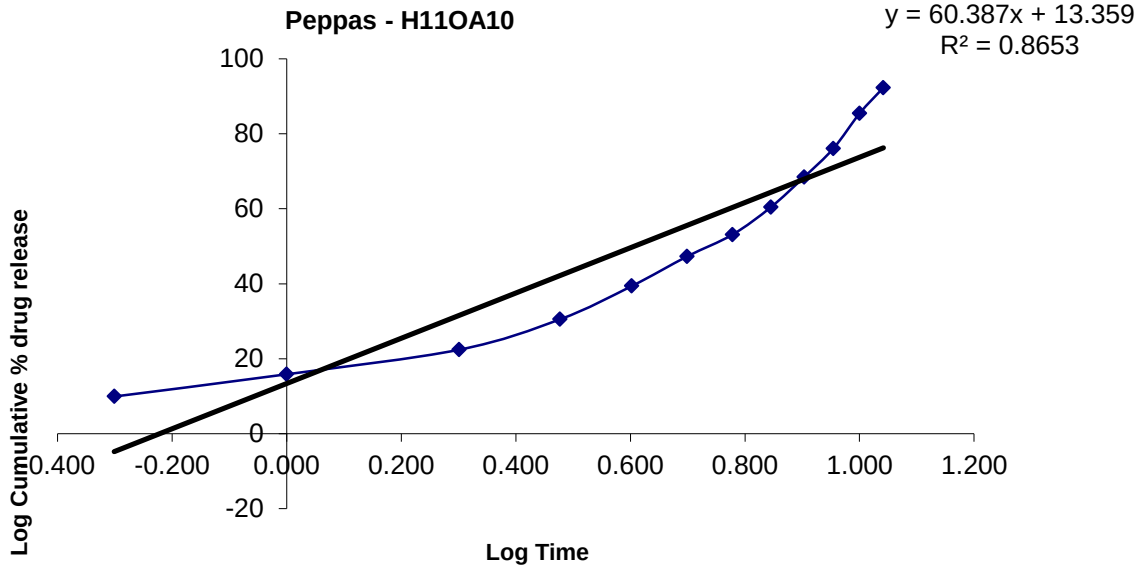


Fig-9: Peppas plot

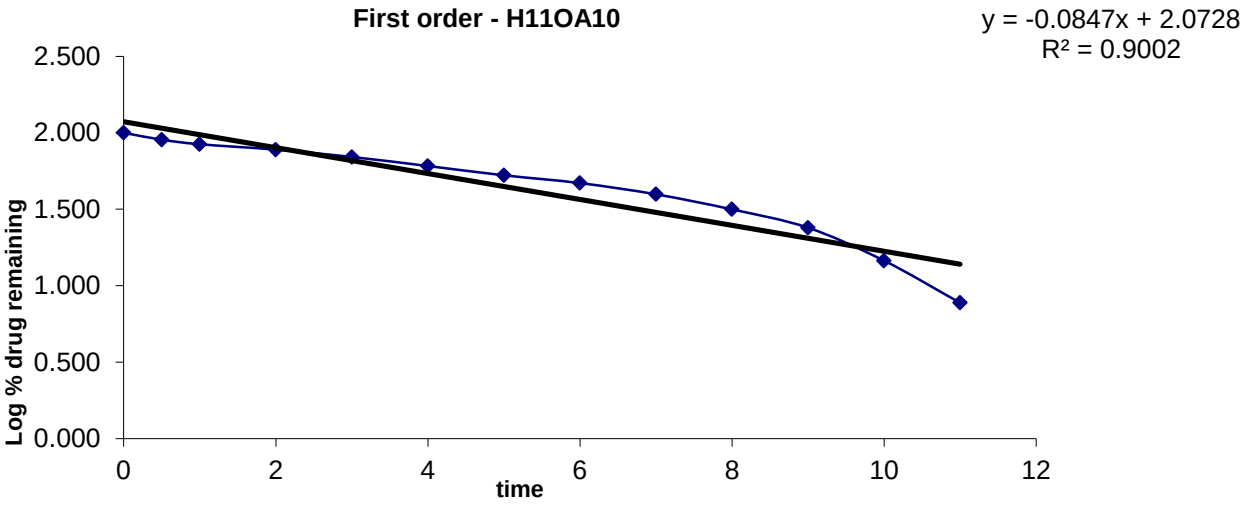


Fig-10: First order kinetics

Drug compatibility studies

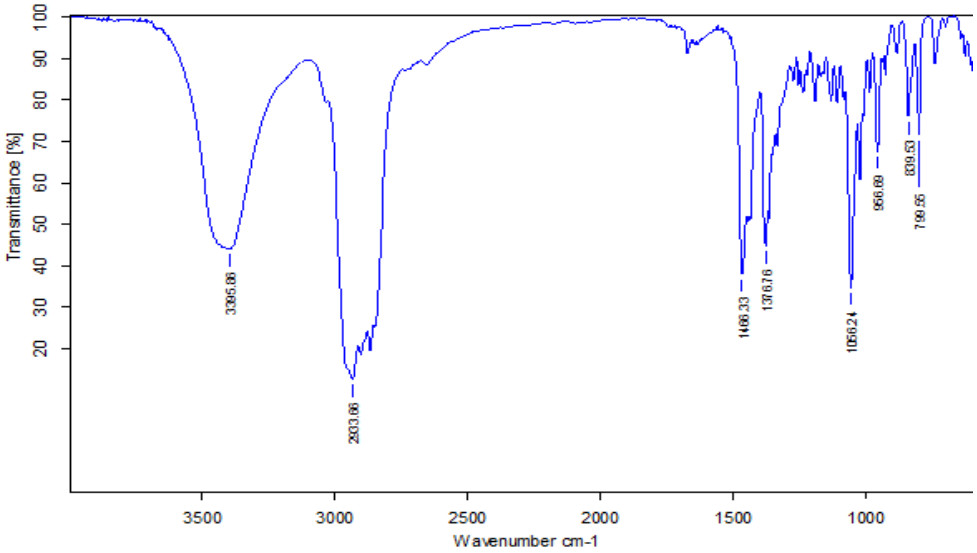


Fig-11: FTIR spectrum of pure drug

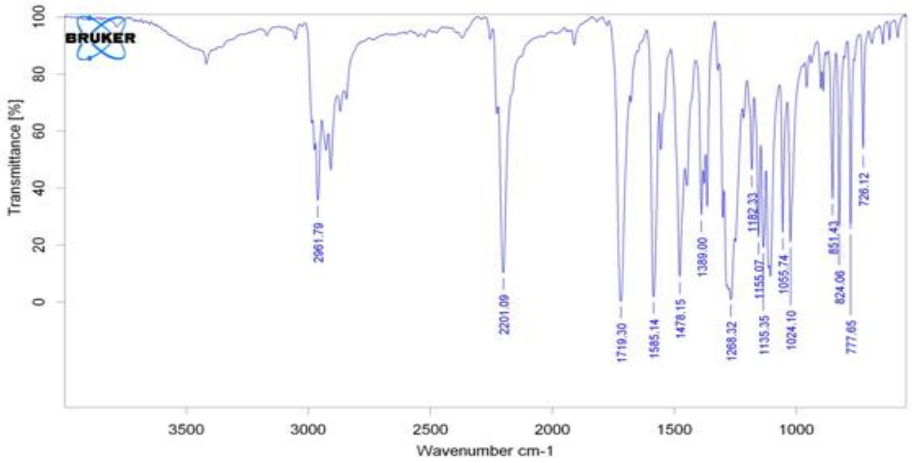


Fig-12: FTIR optimized formulation

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