CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.804920

Available online at: http://www.iajps.com *Research Article*

FORMULATION AND INVITRO EVALUATION OF OXYBUTYNIN TRANSDERMAL PATCH

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Abstarct:
The present study was aimed to develop transdermal drug delivery of Oxybutynin 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 polymers eudragit L100 and eudragit S100.Transdermal patches were prepared by employing solvent casting method. Propylene glycol and Tween80 were selected as permeation enhancer and plasticizer. 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 were found to be with in the pharmacopeial limits, invitro drug release studies by using dialysis membrane. Among all the 12 formulations F6 formulation which contain HPMC K4M 300mg and Eudragit L-100 60mg had shown 94% cumulative drug release with in 12 hours. And compared to HPMC K15M, HPMC K4M showed better drug release profile. For F6 formulation release kinetics were plotted and the Regression coefficient value was found to be high for Korsmeyer-peppas release model i.e., 0.9892. The n value was found to be 0.6203 which indicates the drug release pattern was found to be non-Fickian diffusion.

Key words: *Oxybutynin, Matrix type, Transdermal patches.*

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Please cite this article in press as Aduri Prakash Reddy et al, ***Formulation and Invitro Evaluation of Oxybutynin Transdermal Patch****, Indo Am. J. P. Sci, 2017; 4[05].*

INTRODUCTION:

Transdermal therapeutic systems are defined as self-contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation (USP 25).Transdermal patch is a medicated adhesive pad that is designed to release the active ingredient at a constant rate over a period of several hours to days after application to the skin. It is also called skin patch. A transdermal patch uses a special membrane to control the rate at which the drug contained within the patch can pass through the skin and into the bloodstream.Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. Is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. The main disadvantage to transdermal delivery systems stems from the fact that the skin is a very effective barrier; as a result, only medications whose molecules are small enough to penetrate the skin can be delivered in this method.

Oxybutynin (OXB) is a tertiary amine that has anticholinergic and direct spasmolytic effects on the bladder smooth muscle. It is widely used in the treatment of various forms of urinary incontinence and overactive bladder. Particularly, Oxybutynin (OXB) effectively treats neurologically caused bladder disorders.

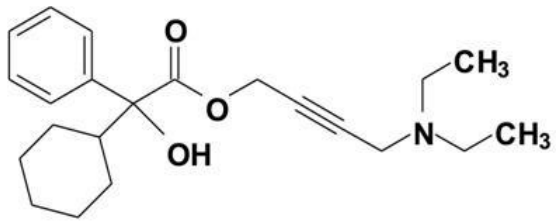

Fig 1: structural formula of oxybutynin

However, after oral administration of Oxybutynin (OXB), many patients discontinue its use because of unacceptable anticholinergic side effects such as dry mouth, dizziness, blurred vision, and constipation. In some cases, the adverse side effects are severe enough to persuade the patient to discontinue treatment.(2)These side effects have been associated with the presence of active metabolite of Oxybutynin, N-desethyloxybutynin (N-DEO),which circulates in concentrations approximately 4 to 10 times those of the parent compound. Presystemic metabolism of Oxybutynin (OXB) occurs primary because of extensive hepatic first-pass metabolism with a small contribution by intraluminal gastrointestinal metabolism, resulting in oral bioavailability of approximately 6% of the oral dose.(3)To reduce or even eliminate systemic anticholinergic adverse effects of Oxybutynin, novel anticholinergic agents and dosage forms have been currently developed that may avoid the hepatic first-pass metabolism so they exhibit the pharmacological effects. In fact, it has been shown that transdermal adhesive matrix patches of Oxybutynin (OXB) avoids that extensive presystemic metabolism, and directly introduces the drug into blood stream, and consequently enhances the bioavailability.(4) However, the skin irritation caused by the transdermal adhesive matrix patches remain to be a problem. Sometimes the irritation may discourage patients to discontinue the treatment, particularly for the long-term users.(5)Thus, the needs still remain for the improved formulations of Oxybutynin (OXB), which may significantly reduce the adverse side effects and skin irritation.

Therefore, in the present study, Transdermal patches were prepared according to the formula shown in Table 08. Eudragit L100, Eudragit S100 were weighed in requisite ratios and they were then dissolved in dimethyl formamide and ethanol as solvent using magnetic stirrer. Oxybutynin (100mg) with a magnetic stirrer. Propylene glycol and PEG 400 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.

EXPERIMENTAL METHOD:

Materials

Oxybutynin, Eudragit L-100, Eudragit-S100, Dimethyl formamide, Ethanol, Propylene glycol all the chemicals used were lab grade

Solvent casting method : Transdermal patches were prepared according to the formula shown in Table 08. Eudragit L100, Eudragit S100 were weighed in requisite ratios and they were then dissolved in dimethyl formamide and ethanol as solvent using magnetic stirrer. Oxybutynin (100mg) with a magnetic stirrer. Propylene glycol and PEG 400 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 Oxybutynin 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	Eudragit-L100(mg)	100	200	300	400					200
3	Eudragit-S100(mg)					100	200	300	400	200
4	Dimethyl formamide (ml)	15	15	15	15	15	15	15	15	15
5	Ethanol(ml)	10	10	10	10	10	10	10	10	10
6	Propylene glycol(Drops)	5	5	5	5	5	5	5	5	5
7	PEG 400(Drops)	20	20	20	20	20	20	20	20	

Physical appearance, Thickness, Weight variation, Flatness, Folding endurance, Moisture uptake, Moisture content, Drug content determination, In vitro permeation studies using dialysis membrane are the evaluation tests performed for the prepared patches.

RESULTS AND DISCUSSION:

Table 2: Standard graph of Oxybutynin

Concentration (µg/ml)	Absorbance
0	0
2	0.295
4	0.203
6	0.301
8	0.417
10	0.528
12	0.653
14	0.771
16	0.881

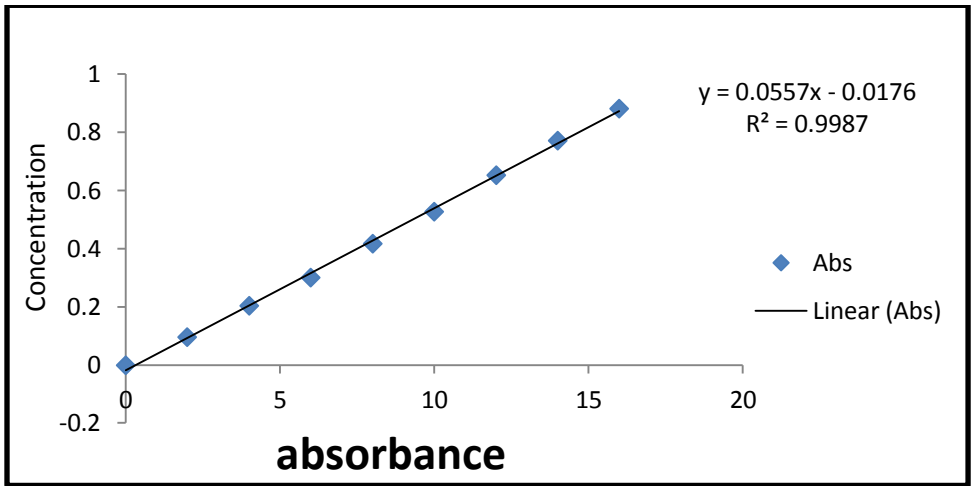

Fig 1 : Standard curve of Oxybutynin

Evaluation of Pioglitazone HCl 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 Oxybutynin Transdermal patch by physical methods

Formulation	Weight variation (mg)	Thickness (mm)	Folding endurance	Drug content (%)	Moisture uptake (%)	Moisture content (%)
F1	590.2	0.569	20	65	7.98	3.77
F2	598.3	0.520	25	65	25.05	9.2
F3	599.5	0.570	27	57.5	13.09	5.16
F4	598.3	0.596	24	60	15.63	5.66
F5	599.6	0.560	30	67.5	11.73	4.87
F6	593.1	0.517	32	92.5	19.65	12.67
F7	589.5	0.578	40	99.7	9.42	3.43
F8	591.1	0.537	37	85	10.87	4.72
F9	600	0.503	44	100	6.44	3.62

The prepared Oxybutynin Transdermal patches were evaluated for their physical parameters such as Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake, Moisture content and all the results were found to be were found to be within the pharmacoepial limits.

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

Time (Hrs)	% Drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	2.31	2.98	2.36	2.06	2.10	1.11	4.43	2.59	5.86
1	3.53	6.71	5.2	3.8	3.68	4.21	10.3	4.84	18.7
2	6.78	11.9	12.7	7.48	8.50	8.01	19.8	10.3	40.9
3	11.5	18	18.3	13.1	17.3	13.3	30.5	18.6	50.5
4	15.7	2	24.4	16.5	19.0	18.4	46.4	21.1	61.0
5	21.4	18.3	25.7	21.3	27.3	21.0	56.6	29.7	73.4
6	27.5	20.6	29.6	26.6	35.0	35.1	67.6	34.3	83.1
7	32.5	23.3	31.2	32.3	38.4	39.6	74.3	39.2	89.8
8	37.6	25.8	34.1	35.8	42.8	44.8	84.1	43.9	99.6

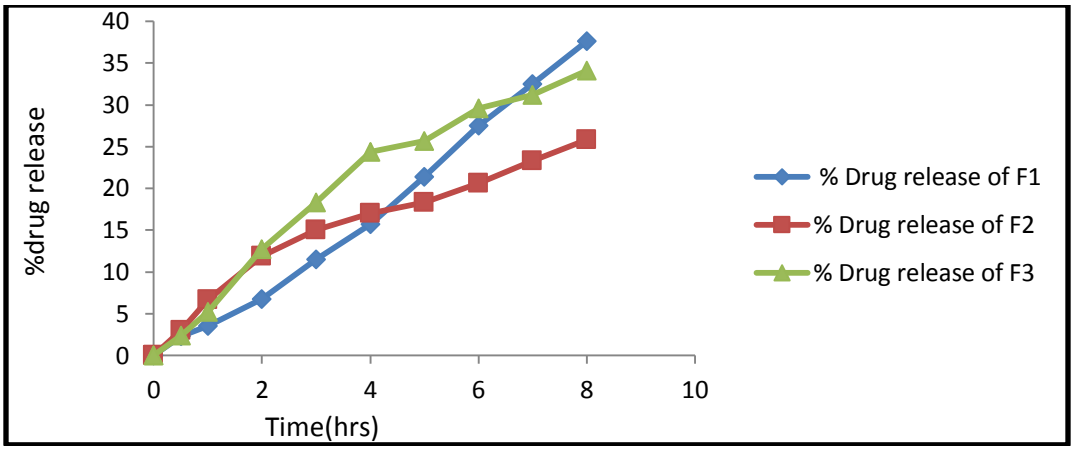

Fig 2: %ge drug release of F1, F2, F3

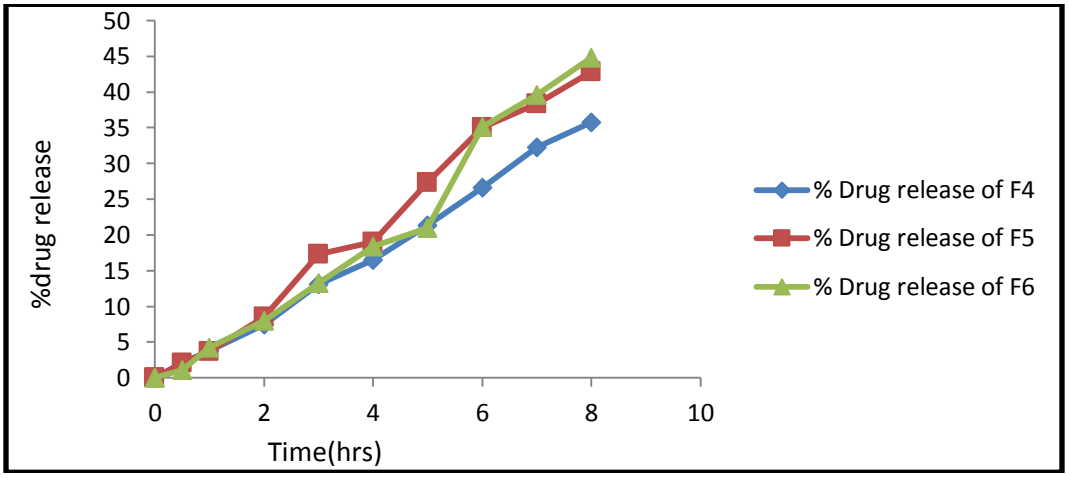

Fig 3: %ge drug release of F4, F5, F6

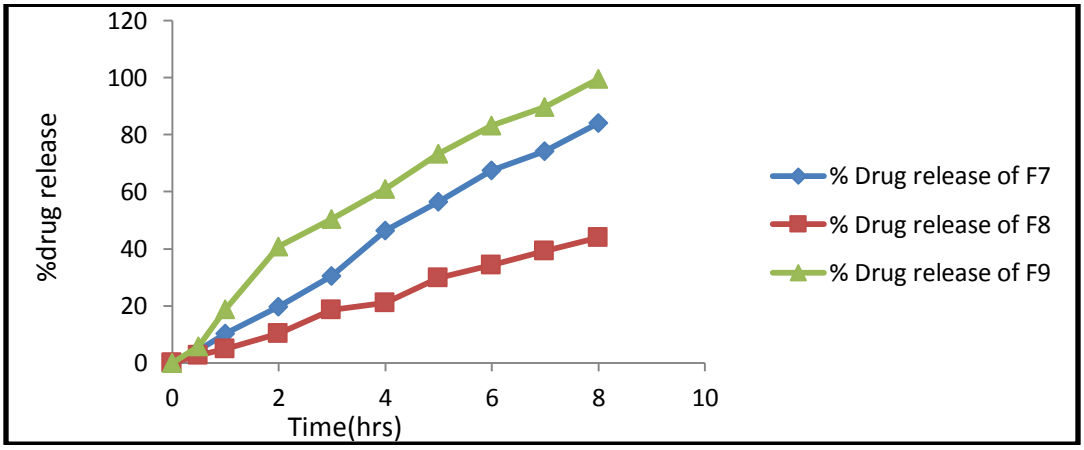

Fig 4: %ge drug release of F7, F8, F9

The prepared Oxybutynin Transdermal patches were evaluated for In-vitro permeation studies using dialysis membrane, among all the 9 formulations F9 formulation was shown 99.6% cumulative drug release within 8 hours.

Table 5: Kinetics of In-vitro permeation studies of optimized formulation

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 remain	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
5.86	0.5	0.707	0.768	-0.301	1.974	11.720	0.1706	-1.232	94.14	4.642	4.549	0.092
18.7	1	1.000	1.272	0.000	1.910	18.700	0.0535	-0.728	81.3	4.642	4.332	0.310
40.9	2	1.414	1.612	0.301	1.772	20.450	0.0244	-0.388	59.2	4.642	3.895	0.746
50.5	3	1.732	1.703	0.477	1.695	16.833	0.0198	-0.297	49.5	4.642	3.672	0.970
61.0	4	2.000	1.785	0.602	1.591	15.250	0.0164	-0.215	39	4.642	3.391	1.250
73.4	5	2.236	1.866	0.699	1.425	14.680	0.0136	-0.134	26.6	4.642	2.985	1.656
83.1	6	2.449	1.920	0.778	1.228	13.850	0.0120	-0.080	16.9	4.462	2.566	2.075
89.8	7	2.646	1.953	0.845	1.009	12.829	0.0111	-0.047	10.2	4.642	2.169	2.473
99.6	8	2.828	1.998	0.903	-0.398	12.450	0.0100	-0.002	0.4	4.642	0.737	3.905

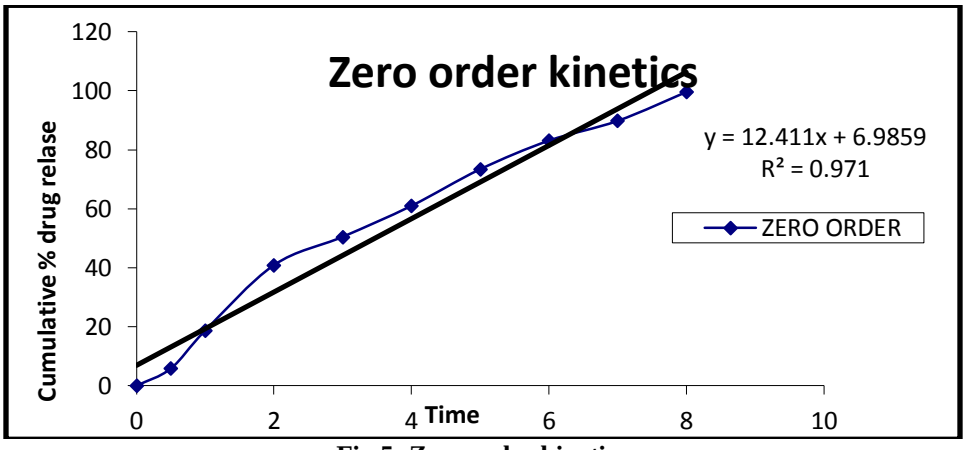

Fig 5: Zero order kinetics

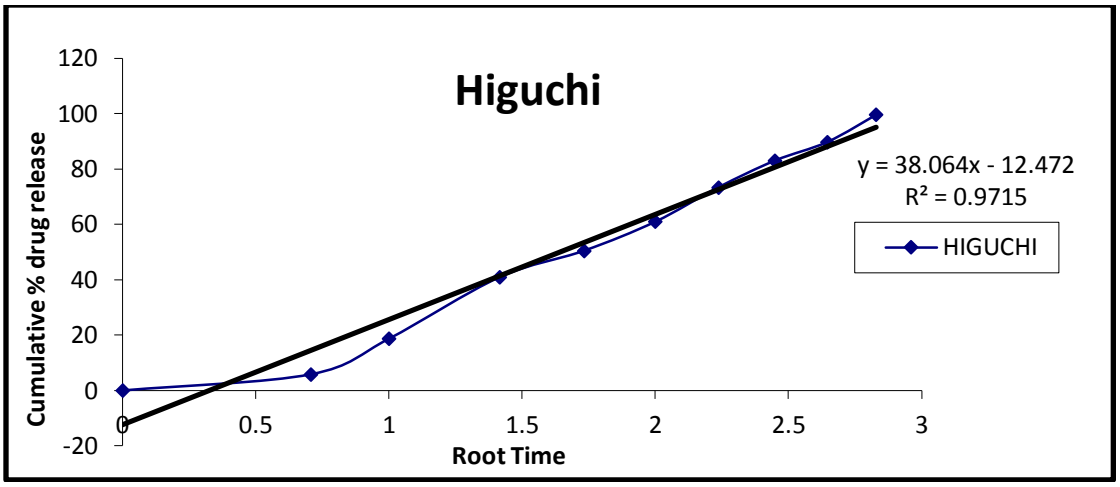

Fig 6 : Higuchi plot

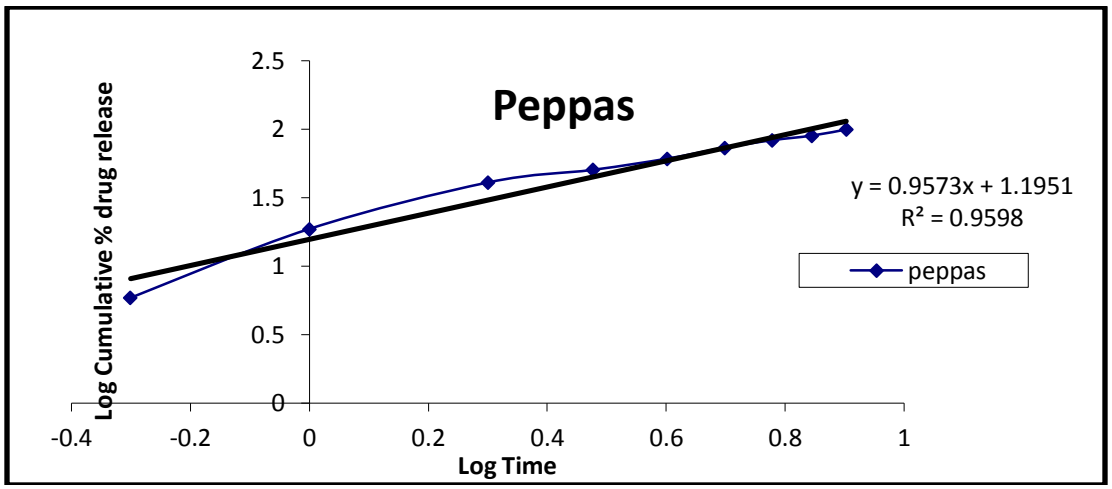

Fig 7 : Peppas plot

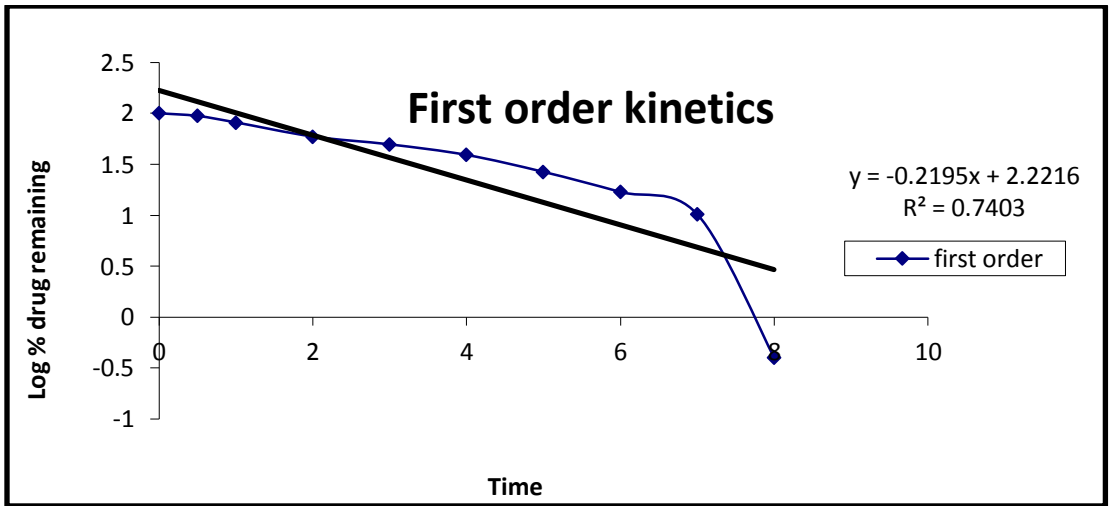

Fig 8 : First order kinetics

The kinetics of In-vitro permeation studies using dialysis membrane for F9 formulation was plotted and the F9 formulation followed the Higuchi mechanism of drug release.

SUMMARY & CONCLUSION:

In present study transdermal drug delivery of Oxybutynin 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 polymers eudragit L100 and eudragit S100.Transdermal patches were prepared by employing solvent casting method. Propylene glycol and Tween80 were selected as permeation enhancer and plasticizer. 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 were found to be within the pharmacopeial limits, invitro drug release studies by using dialysis membrane. And f6 showed the better drug release. For F6 formulation release kinetics were plotted and the Regression coefficient value was found to be high for Korsmeyer-peppas release model i.e., 0.9892. The n value was found to be 0.6203 which indicates the drug release pattern was found to be non-Fickian diffusion.

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