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DESIGN AND INVITRO CHARACTERIZATION OF RIVASTIGMINE TRANSDERMAL PATCHES

P.Umadevi [1*], I.Nagaraju [2] and K. Ravi kumar [3]

[1]Department of Pharmaceutics, Geethanjali College of Pharmacy, Keesara, Hyderabad

[2]Assistant Professor, Department of Pharmaceutics Geethanjali College of Pharmacy, Keesara, Hyderabad

[3]Principal, Geethanjali College of Pharmacy, Keesara, Hyderabad

Abstract

In present study transdermal drug delivery of Rivastigmine was developed 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 HPMCk$_4$M and HPMCk15M.Transdermal patches were prepared by employing solvent casting method. Propylene glycol and Tween80 were selected as permeation enhancer and plasticizer. Formulations were prepared with the varying concentrations polymers ranging from F1-F12.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.

Key words: *Rivastigmine, transdermal patches, HPMCk$_4$M and HPMCk15M*

Corresponding author:

P.Umadevi

Department of Pharmaceutics,
Geethanjali College of Pharmacy,
Keesara, Hyderabad,Telangana.
Email ID: umadeviparunandi@gmail.com

QR code

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INTRODUCTION:

The idea of delivering drugs through skin is old, as the use is reported back in 16th century B.C. Today the transdermal drug delivery is well accepted for delivering drug to systemic circulation.

Until recently, the use of transdermal patches for pharmaceuticals has been limited because only a few drugs have proven effective delivered through the skin typically cardiac drugs such as nitroglycerin and hormones such as estrogen.

Definition: 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.

The first Transdermal drug delivery (TDD) system, Transderm-Scop developed in 1980, contained the drug Scopolamine for treatment of motion sickness. The Transdermal device is a membrane-moderated system. The membrane in this system is a microporous polypropylene film. The drug reservoir is a solution of the drug in a mixture of mineral oil and polyisobutylene. This study release is maintained over a one-day period.

Non-medicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists of two major sub-categories — therapeutic and cosmetic), aroma patches, weight loss patches, and patches that measure sunlight exposure[1-3].

Basic components of TDDS [4-6]: The components of transdermal devices include:

1. Polymer matrix or matrices
2. The drug
3. Permeation enhancers
4. Other excipients

1. Polymer matrix: The polymer controls the release of the drug from the device. The following criteria should be satisfied for a polymer to be used in a transdermal system.

1. Molecular weight, glass transition temperature and chemical functionality of the polymer should be such that the specific drug diffuses properly and released through it.
2. The polymer should be stable, non-reactive with the drug, easily manufactured and fabricated into the desired product; and inexpensive.
3. The polymer and its degradation products must be non-toxic or non-antagonistic to the host.
4. The mechanical properties of the polymer should not deteriorate excessively when large amount of active agent is incorporated into it.

- Possible useful polymers for Transdermal devices are

1. Natural polymers:cellulose derivatives,zein, gelatin, shellac, waxes, proteins, gums and their derivatives, natural rubber, starch etc.
2. Synthetic elastomers: polybutadiene, hydrin rubber, polysiloxane, silicone rubber, nitrile, acrylonitrile, butyl rubber, styrenebutadiene rubber, neoprene etc.
3. Synthetic polymers: polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethyl methacrylate, epoxy etc.

2. Drug: For successful development of transdermal drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of a drug for transdermal delivery

- **Physicochemical properties of Drug :**
  1. The drug should have a molecular weight less than approximately 1000 daltons
  2. The drug should have affinity for both lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.
  3. The drug should have a low melting point (<200^{o}c)
- **Biological properties of Drug :**
  1. The drug should be potent with a daily dose of the order of a few mg/day
  2. The half-life ($t_{1/2}$) of the drug should be short.
  3. The drug must not induce a cutaneous irritant or allergic response.
  4. Drugs, which degrade in the GI tract or are inactivated by hepatic first-pass effect, are suitable candidates for transdermal delivery.
  5. Tolerance to the drug must not develop under the near zero-order release profile of transdermal delivery.

4. Permeation Enhancers: These are the compounds, which promote skin permeability by altering the behaviour of skin as a barrier to the flux of a desired penetrant. The flux, j, of drugs across the skin can be written as:

$$J = d\, dc/dx \text{ ------- } (1)$$

Where d is the diffusion coefficient and is a function of the size, shape and flexibility of the diffusing molecule as well as the membrane resistance; c is the concentration of the diffusing

species; x is the spatial coordinate. Thus enhancement of flux across membranes depends on the considerations of:

a. Thermodynamics (lattice energies, distribution coefficients)
b. Molecular size and shape
c. Reducing the energy required to make a molecular hole in the membrane

. Other excipients:

4.1 Adhesives: The fastening of all transdermal devices to the skin has so far been done by using a pressure sensitive adhesive. The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device and extending peripherally. Both adhesive systems should fulfill the following criteria.

1. Should not irritate or sensitize the skin or cause an imbalance in the normal skin flora during its contact time with the s should adhere to the skin aggressively during the dosing interval without its position being disturbed by activities such as bathing, exercise etc.
2. Should be easily removed.
3. Should not leave an un-washable residue on the skin
4. Should have excellent (intimate) contact with the skin at macroscopic and microscopic level.

The face adhesive system should also fulfill the following criteria.

1. Physical and chemical compatibility with the drug, excipients and enhancers of the device of which it is a part.
2. Permeation of drug should not be affected.
3. The delivery of simple or blended permeation enhancers should not be affected

The peripheral adhesive system is less elegant, contains several more layers, is substantially larger and is more difficult to manufacture than the face adhesive system. However, there is no need to further package the reservoir layer, containing the drug, when peripheral adhesive systems are used. The reservoir of the face adhesive system cannot be hermetically contained and therefore has to be packaged in an aluminium foil pouch. Some widely used pressure sensitive adhesives include polyisobutylenes, acrylics and silicones.

4.2. Backing membrane: Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top, and accept printing. It is impermeable substance that protects the product during use on the skin e.g. Metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate (aluminium foil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminium foil disc) etc

4.3 Release Liner: During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. Typically, release liner is composed of a base layer which may be non-occlusive (e.g. Paper fabric) or occlusive (e.g. Polyethylene, polyvinylchloride) and a release coating layer made up of silicon or teflon. Other materials used for TDDS release liner include polyester foil and metallized laminates

EXPERIMENTAL METHOD

Materials

Drug, Eudragit-L100, Eudragit-S100, Dimethyl formamide, Ethanol , Propylene glycol(Drops) all the chemicals used were lab grade

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 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. Rivastigmine (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 Rivastigmine 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,m Moisture uptake, Moisture content, Drug content determination, In vitro permeation studies using dialysis membrane, Kinetic modeling of drug release are the various evaluation tests performed for the prepared patches

RESULTS AND DISCUSSION:

Table No. 2 : Standard graph of Rivastigmine

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

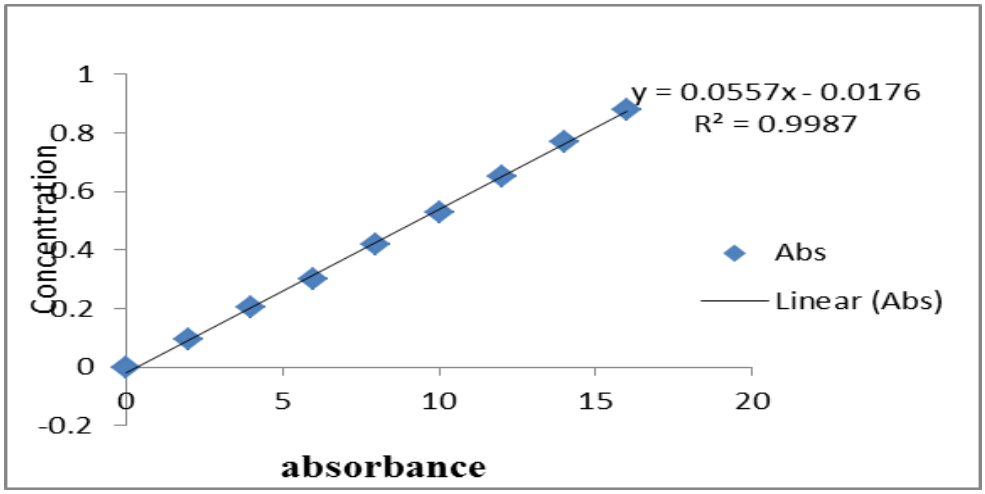

Fig 1: Standard curve of Rivastigmine

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 Rivastigmine 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 Rivastigmine 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 with in the pharmacoepial limits.

Table No. 4: Evaluation of Rivastigmine 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

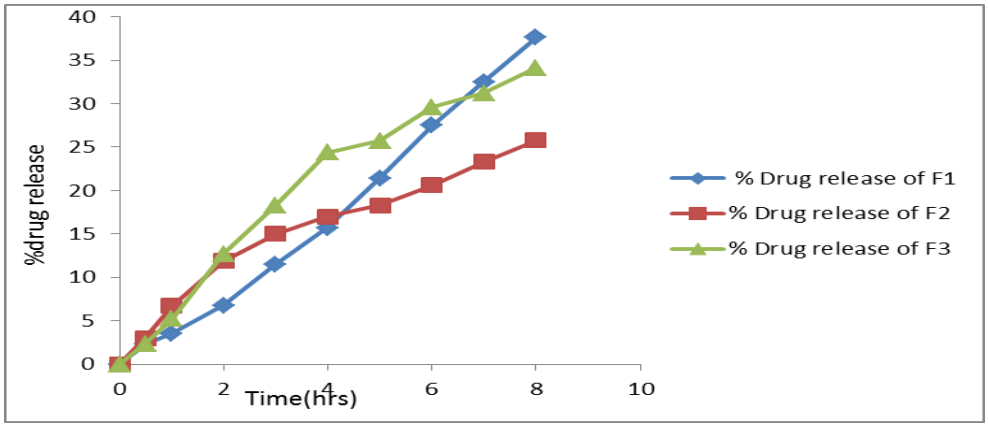

Fig 2: %ge drug release of F1, F2, F3

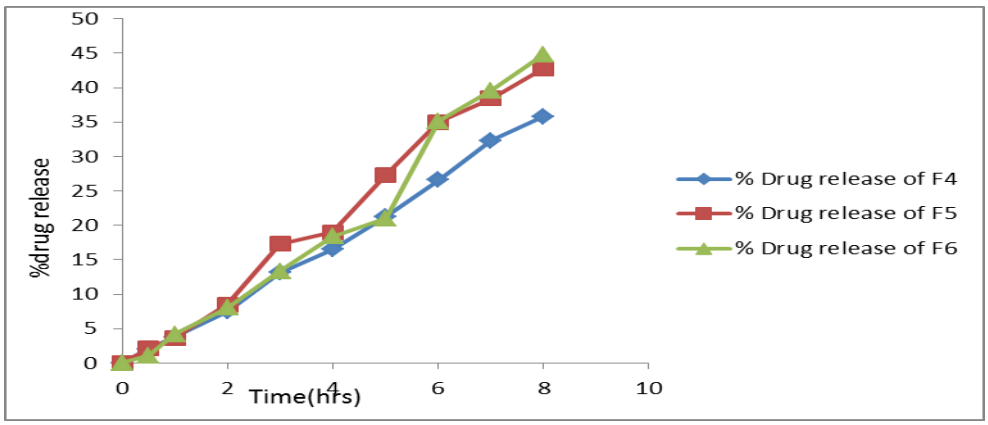

Fig 3: %ge drug release of F4, F5, F6

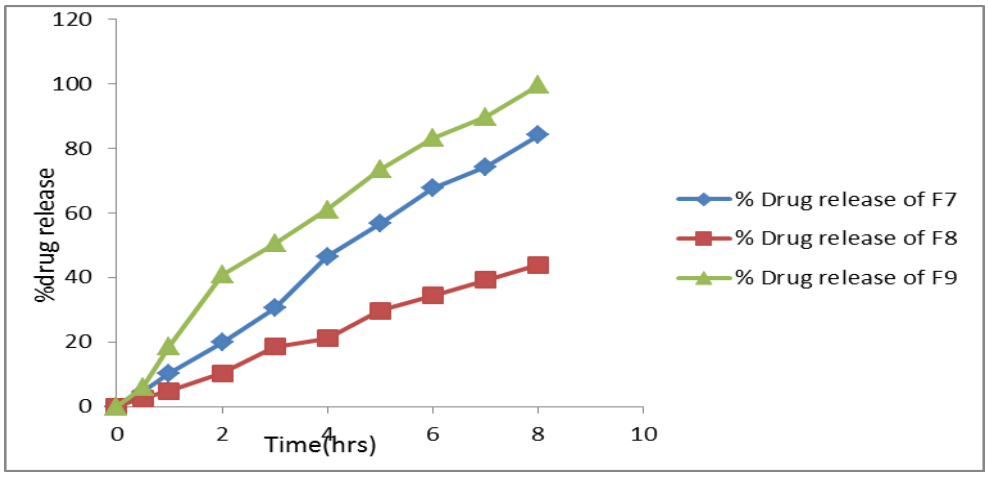

Fig 4: %ge drug release of F7, F8, F9

The prepared Rivastigmine 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 No. 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

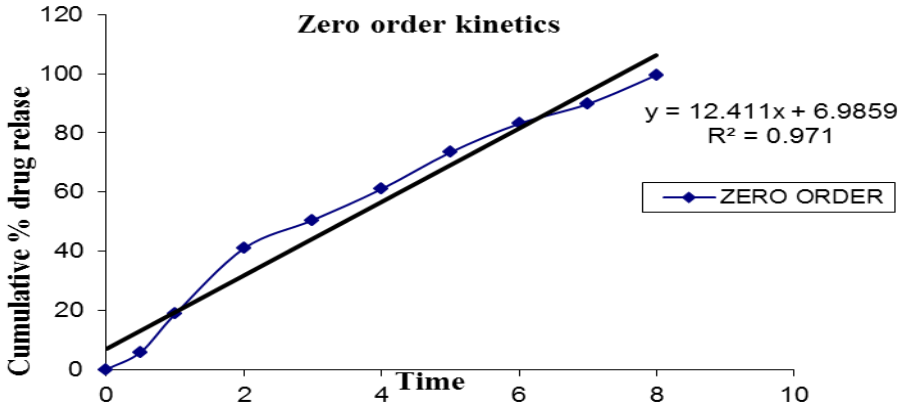

Fig 5 : Zero order kinetics

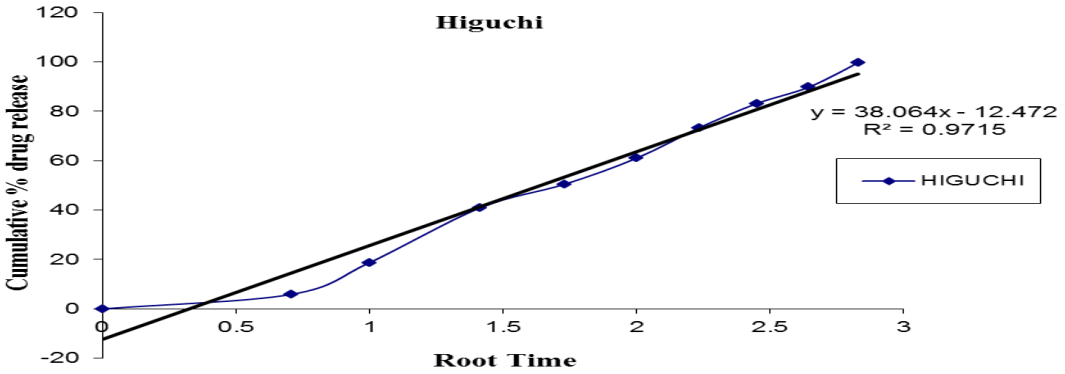

Fig 6 : Higuchi plot

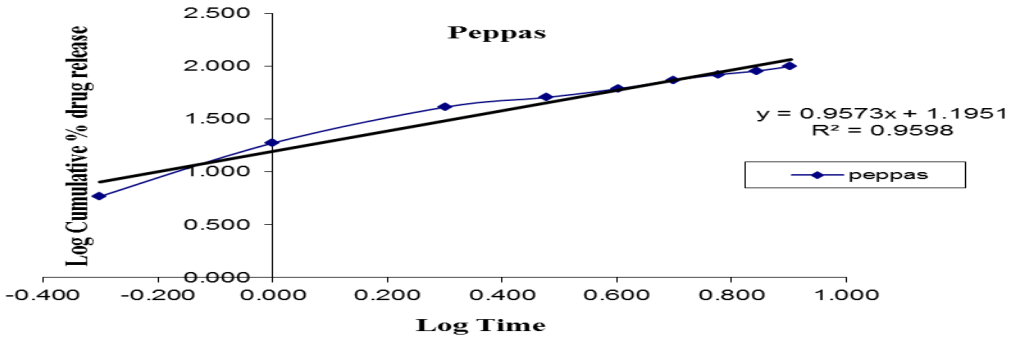

Fig 7 : Peppas plot

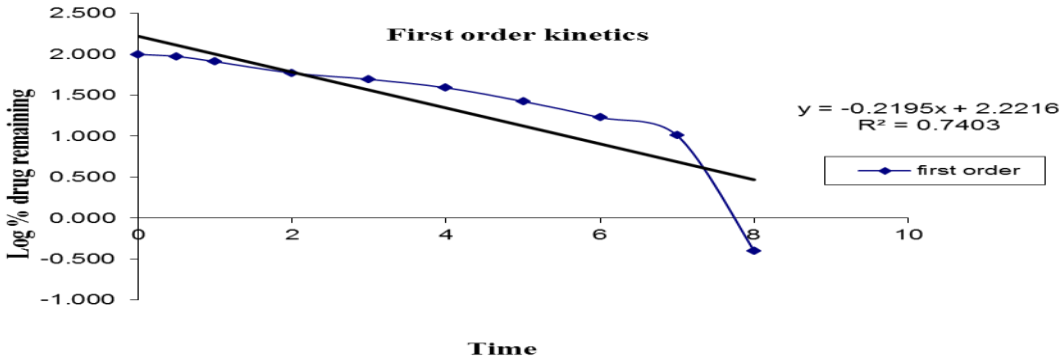

Fig 8 : First order kinetics

The kinetics of In-vitro permeation studies using dialysis membrane for F12 formulation was plotted and the F12 formulation followed the Higuchi mechanism of drug release.

Drug excipients interaction studies: FT-IR spectrum interpretation: IR spectral analysis was carried out using FT-IR by the KBr disc method and the results showed that there are no interactions between drug and excipients. The results were attached in the Annexure.

SUMMARY & CONCLUSION

In present study transdermal drug delivery of Rivastigmine 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 HPMCk_4M and HPMCk15M.

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-F12, 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.

REFERENCES:

1.Chien Y.W. “Novel Drug Delivery Systems”, 2nd Edition, Drugs and Pharmaceutical Sciences, 50.
2.En.wikipedia.org/wiki/Transdermal_Drug_Delivery
3.GeetaAggarwal, Dr. SanjuDhawan. Development Fabrication and Evaluation of Transdermal Drug Delivery System - A Review. Pharmainfo_net.mht 2009; 7 (5).
4.Finnin B C, Morgan T M, Transdermal penetration. J Pharm Sci. Oct 1999; 88 (10):955-958.
5.Allen L V, Popovich N G, Ansel H C, Ansel’s Pharmaceutical Dosage Forms and Drug Delivery Systems, 8th Edition, Lippincott Williams & wilkins, 2005:298- 315.
6.Barry B.Transdermal Drug Delivery. In Ed: Aulton M E, Pharmaceutics: The Science of Dosage Form Design, Churchill Livingston. 2002:499-533
7.Cleary G W, Transdermal controlled release systems. Medical Applications of Controlled Release. 1:203-251.
8.Vyas S P, Khar R K, Controlled Drug Delivery: Concepts and Advances, VallabhPrakashan, 1st Edition. 2002:411-447.
9.Barry B W; “Dermatological Formulations: Percutaneous Absorption”, Drugs and pharmaceutical sciences, MARCEL DEKKER, INC. 1983; 18:1-39.
10.Wilson K J W, Waugh A. Eds, “Ross and Wilson: Anatomy and Physiology In Health And Illness”, 8th Edition, Churchill Livingstone. 1996:360-366.
11.Tortora G, Grabowski S. The Integumentary system.In: Principles of Anatomy and Physiology. 9th edition. John Wiley and Sons Inc. 150-151.
12.Megha F. Wilkosz, BS, PharmD Candidate Robin H. Bogner, PhD Transdermal Drug Delivery PART 1: current status 28(4) and (5).
13.EseldinKeleb, Rakesh Kumar Sharma, Esmaeil B mosa, Abd-alkadar Z aljahwi Transdermal Drug Delivery System- Design and Evaluation. International Journal of Advances in Pharmaceutical Sciences 2010; 1: 201-211.
14.Heather A.E. Benson Transdermal Drug Delivery: Penetration Enhancement Techniques Current Drug Delivery, 2005; 2: 23-33.
15.MohitSoni,Sandeep Kumar and Dr. G.D. Gupta Transdermal Drug Delivery: A Novel Approach to Skin Permeation Journal of Pharmacy Research 2009, 2(8),1184-1190.
16.Ramesh panchagnula Transdermal delivery of drug. Indian Journal of Pharmacology 1997; 29: 140-156.
17.BharkatiyaM,Nema RK skin penetration enhancement techniques J.young pharm. 2010;1(2):110-115.
18.Gattani SG, Gaud RS, Chaturvedi SC. Formulation and evaluation of Transdermal films of ondansetron hydrochloride. Indian Drugs. 2006; 43(3):245-9.
19.Gwak H S, Oh IS, Chun I K, In-vitro percutaneous absorption of ondansetron hydrochloride from pressure-sensitive adhesive matrices through hairless mouse skin, Arch Pharm Res, 2003; 26 (8): 644-8.
20.Gwak H S, Oh IS and Chun I K, Transdermal delivery of ondansetron hydrochloride: effects of vehicles and penetration enhancers, Drug DevInd Pharm, 2004; 30(2):187-94.