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Review

Formulation and Characterization of Transdermal Patches for Controlled Delivery of Fravotriptan for the Treatment of Migraine

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Abstract

The present study focuses on the formulation and characterization of transdermal patches for the controlled delivery of Fravotriptan, a selective 5-HT1B/1D receptor agonist used in the treatment of migraine. Due to its short half-life and extensive first-pass metabolism, the oral delivery of Fravotriptan often results in reduced bioavailability and frequent dosing. To overcome these limitations, transdermal drug delivery systems (TDDS) offer a promising alternative by maintaining sustained drug release, enhancing patient compliance, and minimizing systemic side effects.

In this research, transdermal patches were formulated using varying concentrations of hydrophilic (HPMC E15) and hydrophobic Ethyl cellulose and Eudragit RL100, EC) polymers through the solvent casting method. Polyethylene glycol 400 (PEG-400) was employed as a plasticizer to improve flexibility and mechanical strength. The prepared patches were subjected to various physicochemical evaluations, including thickness, weight uniformity, folding endurance, tensile strength, moisture content, moisture uptake, drug content uniformity, pH, and in vitro drug release studies using Franz diffusion cells.Among all the formulations, the optimized patch demonstrated uniform thickness, high folding endurance, suitable drug content, and sustained drug release up to 12 hours, following Higuchi kinetics, suggesting a diffusion-controlled release mechanism. The optimized patch also exhibited good physical stability during short-term storage conditions.

This study successfully demonstrates the potential of transdermal patches as an effective system for the controlled and sustained delivery of Fravotriptan, offering a patient-friendly approach for the management of migraine.

Keywords: Fravotriptan, migraine, transdermal patches, controlled release, HPMC, Eudragit RL100 and Ethyl cellulose.

1. INTRODUCTION

Transdermal patch (Skin patch) uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the Bloodstream. Some drugs must be combined with substances, such as alcohol, that increase their ability to penetrate the skin in order to be used in a skin patch. Drugs administered through skin patches include scopolamine (for motion sickness), nicotine (for quitting smoking), estrogen (for menopause and to prevent osteoporosis after menopause), nitroglycerin (for angina), and lidocaine to relieve the pain of shingles (herpes zoster). Molecules of insulin and many other substances, however, are too large to pass through the skin. Patches applied to the skin eliminate the need for vascular access by syringe or the use of pumps. Transdermal patches were developed in the 1970s and the first was approved by the FDA in 1979 for the treatment of motion sickness.[1-3] It was a three-day patch that delivered scopolamine. In 1981, patches for nitroglycerin were approved, and today there exist a number of patches for drugs such as clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, oestradiol, oxybutinin, scopolamine, and testosterone. There are also combination patches for contraception, as well as hormone replacement.[4,5] Depending on the drug, the patches generally last from one to seven days. The major advantages provided by transdermal drug delivery include the following: improved bioavailability, more uniform plasma levels, longer duration of action resulting in a reduction in dosing frequency, reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval compared to a decline in plasma levels with conventional oral dosage forms. Transdermal patches have been useful in developing new applications for existing therapeutics and for reducing first-pass drug-degradation effects. Patches can also reduce side effects; for example, oestradiol patches are used by more than a million patients. annually and, in contrast to oral formulations, do not cause liver damage. of two major sub-categories - therapeutic and cosmetic), aroma patches, weight loss patches, and Non medicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists patches that measure sunlight exposure. [6,7]

Definition:

A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream.

Advantage and Disadvantage:

Advantages:

i) They can avoid gastrointestinal drug absorption difficulties covered by gastrointestinal pH, enzymatic activity and drug interaction with food, drink and other orally administration drug.

ii) They can substitute for oral administration of medication when the route is unsuitable as with vomiting and diarrhea.

iii) To avoid the first pass effect e.g. Transdermal Nitroglycerin. It is rapidly metabolized by the liner when taken orally.

iv) They are noninvasive, avoiding the inconvenience of parenteral therapy.

v) They provided extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration e.g. Tradermal clonidine day.

vi) The activity of drugs having a start half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.

vii) Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.[8,9]

Disadvantages:

i) Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.

ii) Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's imperability.

iii) Some drugs e.g. scopolamine transdermal patch placed behind the ear, it is uncomfortable.

iv) Long time adhere is difficult. [10]

Materials and methods

Frovatriptan	Sura Labs
HPMC (mg)	Merck Specialities Pvt Ltd
Methyl cellulose (mg)	Merck Specialities Pvt Ltd
EudragitL100 (mg)	Merck Specialities Pvt Ltd
Ethanol (ml)	Merck Specialities Pvt Ltd
Propylene glycol (ml)	Merck Specialities Pvt Ltd
DMSO	Merck Specialities Pvt Ltd

EQUIPMENTS

Double beam UV Visible Spectrophotometer Lab India UV 3000
Digital weigh balance Sartourious
FTIR Spectrophotometer Bruker
Magnetic Stirrer 2MLH
Remi Equipments, Mumbai, India.
Franz diffusion cell
Remi Equipments, Mumbai, India.

METHODOLOGY

Compatibility study

FTIR study:

The infrared spectrum of the pure Frovatriptan sample was recorded and the spectral analysis was done. The dry sample of drug was directly placed after mixing and triturating with dry potassium bromide.

Formulation of transdermal patches

Preparation of blank patches:

Polymers of single or in combination were accurately weighed and dissolved in respective solvent and then casted in a Petri-dish with mercury as the plain surface. The films were allowed to dry overnight at room temperature.

Formulation of Drug Incorporated Transdermal Patches:

The matrix-type transdermal patches containing Frovatriptan were prepared using different concentrations of ethyl cellulose and Eudragit S 100. The polymers in different concentrations were dissolved in the respective solvents. Then the drug was added slowly in the polymeric solution and stirred on the magnetic stirrer to obtain a uniform solution. Propylene glycol was used as plasticizers. Propylene glycol was used as the penetration enhancer. Then the solution was poured on the Petri dish having surface area of 78 cm2 and dried at the room temperature. Then the patches were cut into 2x2 cm^2 patches. Drug incorporated for each 2x2 cm^2 patch was 8 mg. the formulation table is given in table no. 6.3.

Table 7.1: Formulation of Frovatriptan Patches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Frovatriptan	10	10	10	10	10	10	10	10	10
HPMC (mg)	5	10	15	-	-	-	-	-	-
Ethyl cellulose (mg)	-	-	-	5	10	15	-	-	-
EudragitL100 (mg)	-	-	-	-	-	-	5	10	15
Ethanol (ml)	8	8	8	8	8	8	8	8	8
Propylene glycol (ml)	6	6	6	6	6	6	6	6	6
DMSO	3	3	3	3	3	3	3	3	3
Glycerin (Drops)	1	1	1	1	1	1	1	1	1
Water (ml)	10	10	10	10	10	10	10	10	10

Evaluation Parameters of patches

Physical evaluations

a. Thickness[47]

The thickness of films was measured by digital Vernier calipers with least count 0.001mm. The thickness uniformity was measured at five different sites and average of five readings was taken with standard deviation.

b. Folding endurance

The folding endurance was measured manually for the prepared films. A strip of film (4x3 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance.

c. Weight variation[47]

The three disks of 2*1 cm^2 was cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch- to- batch variation.

d. Drug content Determination

The prepared drug contained patches specified surface area (2 cm^2) were cut and dissolved in (5% of methanol contained) 100ml of pH 7.4 phosphate buffer, and vigorously shaked for 12hrs, and then sonicated for 15 minutes, centrifuged at 5000 rpm for 30 min. Filter the drug contained polymeric solution through 42 number whatmann filter paper, then 1ml of the filtrate was taken in a test tube and dilute it for five times with same solvent by using double beam Uv-Visible

spectrophotometer to determined drug content at λmax 303 nm. Respected Placebo patch was taken as a blank solution.

Flatness: A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

$$\% \text{ constriction} = I1 - I2 \text{ X } 100$$

I2 = Final length of each strip
I1 = Initial length of each strip

***In-vitro* Drug Diffussion Study:**
The in vitro study of drug permeation through the semi permeable membrane was performed using a franz type glass diffusion cell. The modified cell having higher capacity (25 ml) is used to maintain sink condition. This membrane was mounted between the donor and receptor compartment of a diffusion cell. The transdermal patch was placed on the membrane and covered with aluminum foil. The receptor compartment of the diffusion cell was filled with isotonic phosphate buffer of pH 7.4. The hydrodynamics in the receptor compartment were maintained by stirring with a magnetic bead at constant rpm and the temperature was maintained at 37±0.5ºC. The diffusion was carried out for 12 h and 1 ml sample was withdrawn at an interval of 1 h. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal. The samples were analyzed for drug content spectrophotometrically at 305 nm

8. RESULTS AND DISCUSSION

Initially the drug was tested by UV to know their significant absorption maximum which can be used for the diffusion study of the drug.

8.1. Analysis of drug:
A. UV scans:
The lambda max of Frovatriptan was found to be 305 nm.
B. construction of calibration curve:

Table 8.1: Standard graph of Frovatriptan

Concentration(µg/ml)	Absorbance (at 305 nm)
0	0
5	0.131
10	0.258
15	0.376
20	0.488
25	0.614

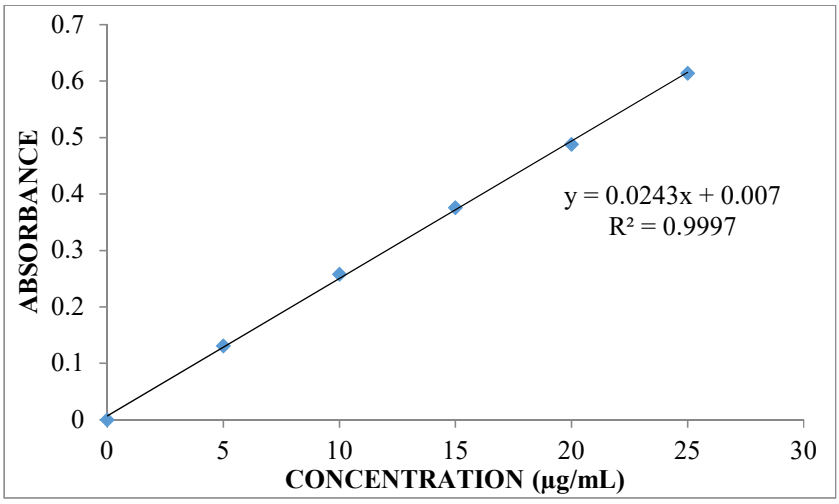

Figure 8.1: Standard calibration curve of Frovatriptan

8.2. Pre formulation study

Totally, nine formulation trials were done with the aim to achieve the successful matrix type Frovatriptan transdermal patches. The blend trials prepared for the drug was evaluated for various physical parameters and content uniformity of drug by UV.

A. Colour, odour, taste and appearance

Table 8.2: Results of identification tests of drug

Parameter	Frovatriptan
Color	White
Odor	Odorless
Taste	Bitter
Appearance	A white powder

B. Melting point determination:

Table 8.3: Results of melting point determination tests of drug

Drug	Reported melting point
Frovatriptan	172-174 ^{0}C

C. Determination of solubility:

Table 8.4: Solubility Determination

solvent	Drug solubility(mg/ml)
Distilled water	0.0177 mg/mL

8.3 Evaluation of Patch

The formulations F1 to F9 were varying in thickness when compared to other formulations which is due to the variation in the polymer concentration. Which shows the increase in polymer concentration increases the thickness of patch. For all other formulations it was found to be in between 0.051±0.006 to 0.059±0.001mm.

All formulations from F1 to F9 Shows weight variation in between 116±2.60 to 120±6.14mg.

Folding endurance from formulations F1 to F9 was found to be in between 70 ± 5.16 to 79 ± 2.53 which can withstand the folding of the skin.

All formulations showed % drug content from 95.26 ±2.10 to 99.43 ±9.99.

Table 8.5: Evaluation of patches

Formulation Code	Average weight(mg)	Thickness (mm)	Folding endurance	Flatness (%)	Flatness	% Drug Content
F1	120±5.93	0.056±0.004	70 ± 5.16	96	Transparent	95.26 ±2.10
F2	119±1.64	0.052±0.002	76 ± 1.52	98	Transparent	98.90 ±0.36
F3	118±0.13	0.059±0.001	72 ± 6.90	98	Transparent	97.83 ±6.29
F4	116±2.60	0.051±0.006	78 ± 0.16	94	Transparent	96.16 ±9.15
F5	119±1.89	0.053±0.004	75 ± 5.72	96	Transparent	98.97 ±4.48
F6	120±6.14	0.055±0.003	79 ± 2.53	96	Transparent	99.43 ±9.99
F7	117±2.79	0.056±0.004	76 ± 7.10	94	Transparent	98.82 ±3.15
F8	119±1.36	0.057±0.001	70 ± 9.98	97	Transparent	98.97 ±2.27
F9	118±0.42	0.054±0.004	71 ± 4.43	97	Transparent	97.34 ±7.60

***In vitro* diffusion study:**

All the formulation *in vitro* diffusion study was carried out by using Franz type diffusion cell under specific condition such as temp maintained at 32 ± 0.5 °C. The diffusion was carried out for 12 h and 5 ml sample was withdrawn at an interval of 1 h.

Table 8.6: *In vitro* drug permeation of Frovatriptan containing different concentrations of HPMC

Time (hr)	F1	F2	F3
0	0	0	0
1	27.42	25.69	21.41
2	34.39	30.09	27.69
3	47.60	42.16	38.34
4	56.51	50.65	44.61
5	67.62	63.19	50.08
6	78.37	70.67	58.39
7	85.26	78.76	64.56
8	96.78	86.54	71.98
9	99.82	92.34	86.18
10		98.54	90.14
11			97.34
12			

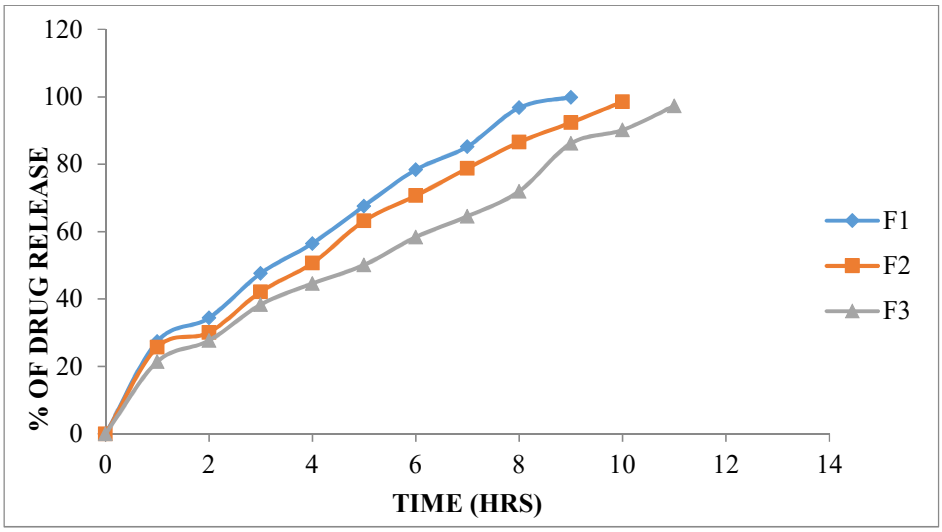

Figure: 8.2 Cumulative % drug permeation of Frovatriptan patch (F1, F2, F3)

The formulations F1 to F3 were prepared by different concentrations of HPMC (5, 10, 15mg) the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. At high polymer concentration the drug permeation is more 12 hours it was total amount of drug was permeated.

Table 8.6: *In vitro* drug permeation of Frovatriptan containing different concentrations of Ethyl cellulose

Time (hr)	F4	F5	F6
0	0	0	0
1	32.26	27.92	22.92
2	48.78	32.65	30.36
3	55.36	43.89	37.61
4	67.23	54.32	44.53
5	76.98	62.87	51.88
6	87.46	67.90	64.46
7	95.68	75.36	71.87
8	98.14	82.77	79.29
9		89.53	86.14
10		97.91	92.49
11			96.73
12			98.87

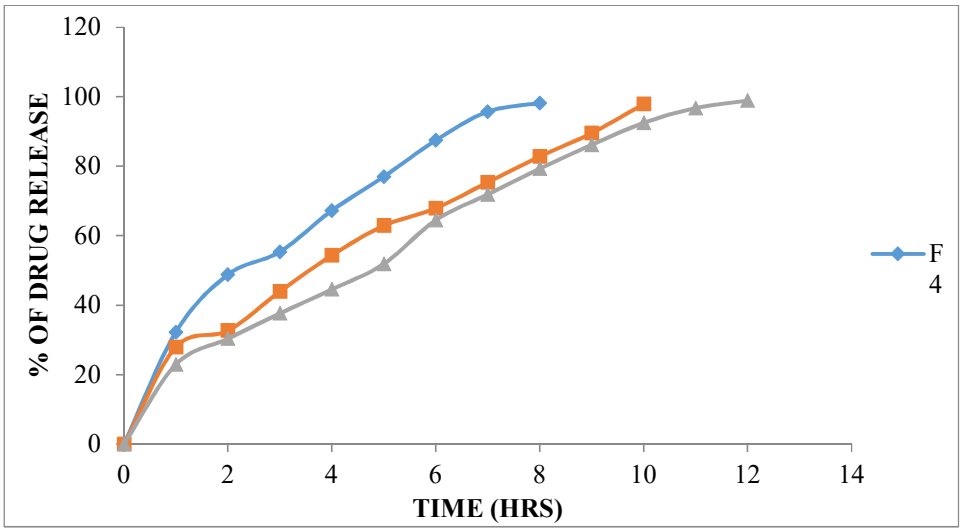

Figure: 8.3 Cumulative % drug permeation of Frovatriptan patch (F4, F5, F6)

The 5mg concentration of polymer was showed maximum drug released at 8 hours 98.14 %. The 10mg concentration of polymer was showed maximum drug release 97.91 at 10 hours. Hence in that 3 formulations F6 formulations showed total drug release at desired time period.

Table: 8.8 *In vitro* drug permeation of Frovatriptan containing different concentrations of EudragitL100

Time	F7	F8	F9
0	0	0	0
1	36.54	30.14	25.30
2	46.41	38.79	31.26
3	55.05	46.23	36.71
4	61.60	52.90	43.82
5	67.35	57.44	50.19
6	75.12	64.15	56.53
7	89.28	73.20	64.75
8	95.46	77.38	72.89
9	96.65	83.02	79.93
10		92.11	85.42
11		98.97	90.82
12			95.36

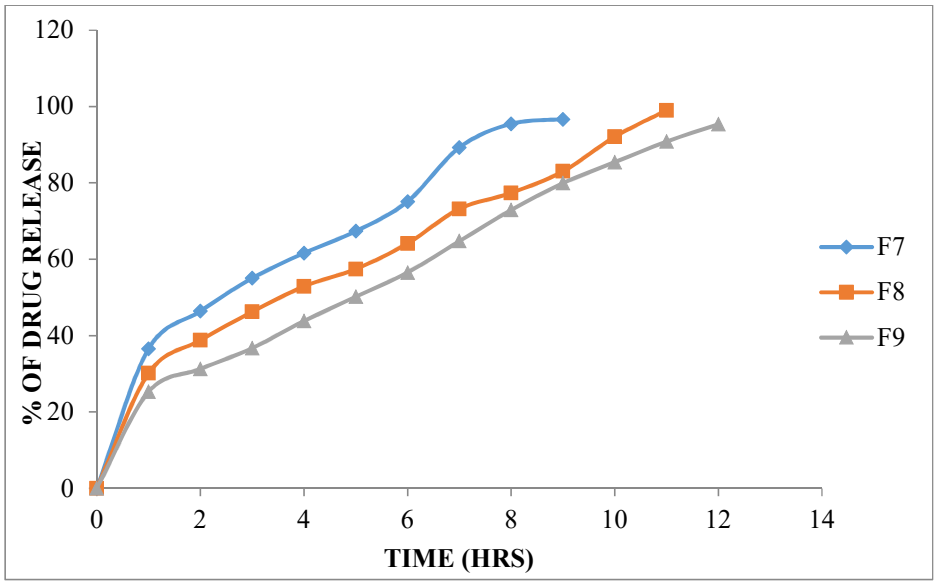

Figure: 8.4 Cumulative % drug permeation of Frovatriptan patch (F7, F8, F9)

The formulations F7 to F9 were prepared by different concentrations of Eudragit L (5, 10, 15mg) the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. The 5mg (F7) concentration of polymer was showed maximum drug release 96.65 within 9 hours. The 10mg (F8) concentration of polymer was showed maximum drug released at 11 hours 98.97 %. The 15mg (F9) concentration of polymer was showed less drug release 95.36 at 12 h.

Among all 9 formulations F6 formulation showed good drug permeation from the patch.
Among all *in vitro* evaluation parameters F6 formulation passed all evaluation parameters.

8.4. Kinetic models for Frovatriptan

Various models were tested for explaining the kinetics of drug release. To analyse 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.

Table: 8.9 Kinetics data of F6 Frovatriptan patch

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
22.92	1	1.000	1.360	0.000	1.887	22.920	0.0436	-0.640	77.08	4.642	4.256	0.386
30.36	2	1.414	1.482	0.301	1.843	15.180	0.0329	-0.518	69.64	4.642	4.114	0.527
37.61	3	1.732	1.575	0.477	1.795	12.537	0.0266	-0.425	62.39	4.642	3.966	0.675
44.53	4	2.000	1.649	0.602	1.744	11.133	0.0225	-0.351	55.47	4.642	3.814	0.828
51.88	5	2.236	1.715	0.699	1.682	10.376	0.0193	-0.285	48.12	4.642	3.637	1.004
64.46	6	2.449	1.809	0.778	1.551	10.743	0.0155	-0.191	35.54	4.642	3.288	1.354
71.87	7	2.646	1.857	0.845	1.449	10.267	0.0139	-0.143	28.13	4.642	3.041	1.600
79.29	8	2.828	1.899	0.903	1.316	9.911	0.0126	-0.101	20.71	4.642	2.746	1.895
86.14	9	3.000	1.935	0.954	1.142	9.571	0.0116	-0.065	13.86	4.642	2.402	2.305
92.49	10	3.162	1.966	1.000	0.876	9.249	0.0108	-0.034	7.51	4.642	1.958	2.683
96.73	11	3.317	1.986	1.041	0.515	8.794	0.0103	-0.014	3.27	4.642	1.484	3.157
98.87	12	3.464	1.995	1.079	0.053	8.239	0.0101	-0.005	1.13	4.642	1.042	3.600

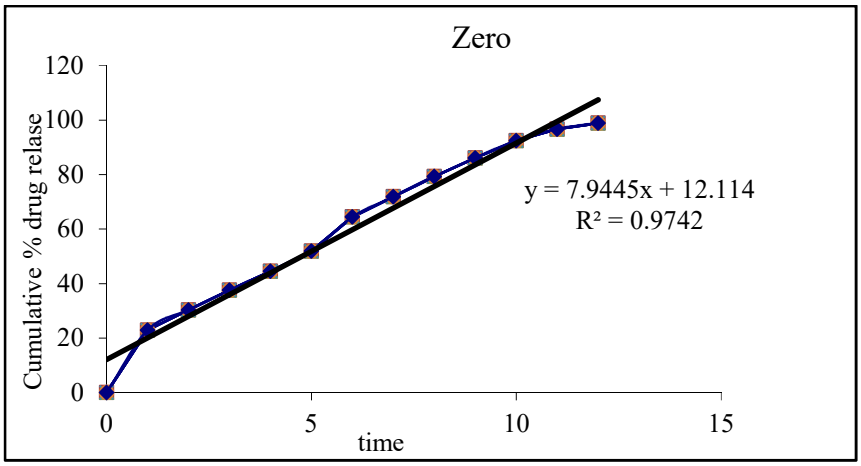

Figure: 8.5 Graph of Zero order kinetics

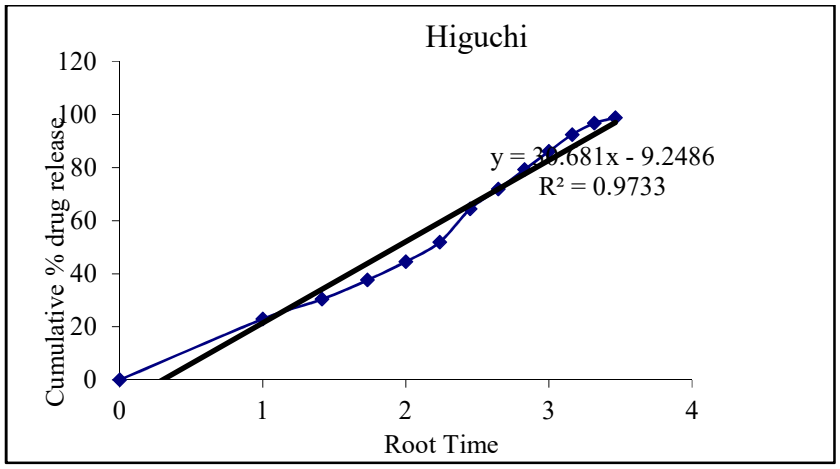

Figure: 8.6 Graph of Higuchi release kinetics

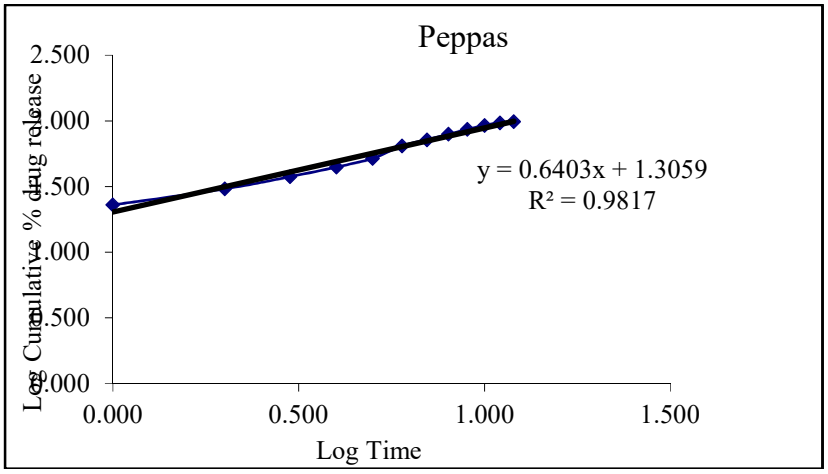

Figure: 8.7 Graph of peppas release kinetics

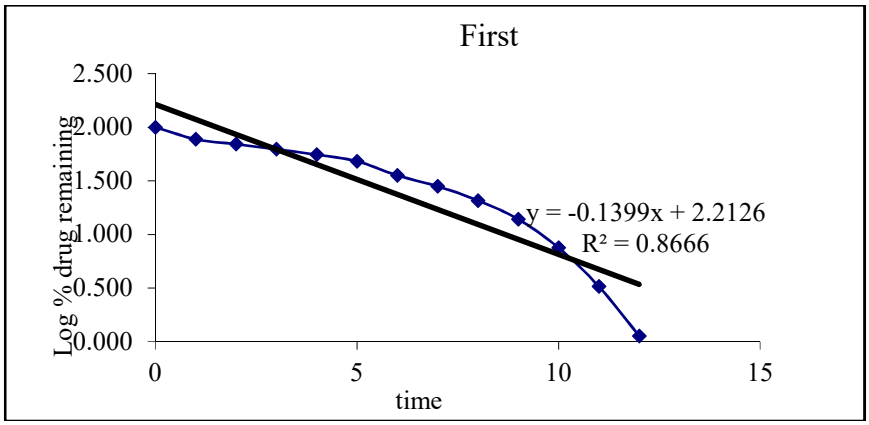

Figure: 8.8 Graph of First order release kinetics

From the above data the optimized formulation followed peppas release kinetics model rule.

COMPATIBILITY STUDIES:

IR SPECTROSCOPY:

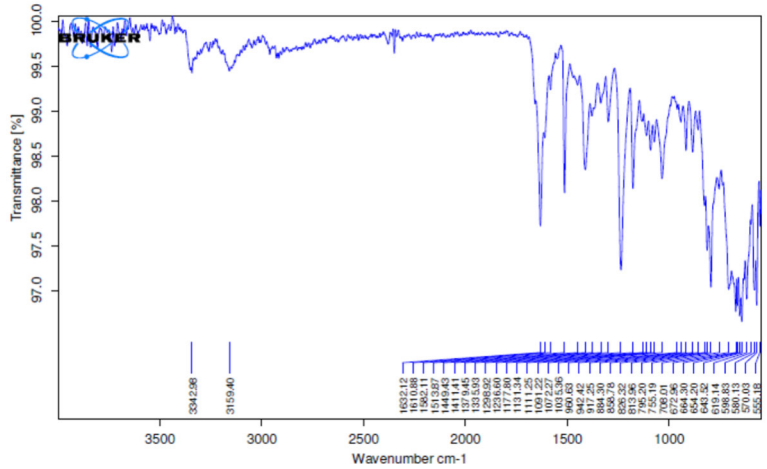

Figure 8.9: FTIR Spectrum of pure Frovatriptandrug

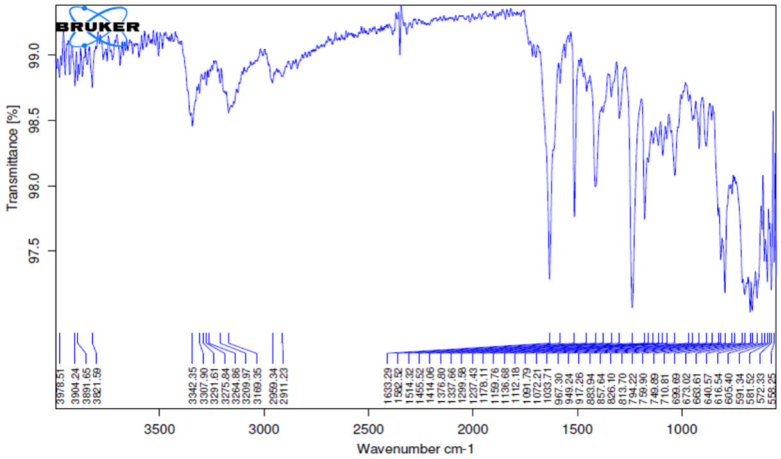

Figure 8.10: FTIR of Optimized formulation

The compatibility studies of the drug with excipients indicate no characteristic visual changes and no additional peaks were observed during FT-IR studies.

9. CONCLUSION

The present research work entitled "Formulation and Characterization of Transdermal Patches for Controlled Delivery of Frovatriptan for the Treatment of Migraine" was undertaken with the objective of developing a transdermal drug delivery system capable of providing sustained release of Frovatriptan to enhance therapeutic efficacy and patient compliance in the management of migraine.

Various transdermal patches were formulated using polymers such as Hydroxypropyl Ethyl cellulose, Ethyl cellulose and Eudragit L 100, individually and in combination, by the solvent casting technique. The prepared formulations were evaluated for their physicochemical parameters including thickness, weight uniformity, drug content, surface pH, moisture content, moisture uptake, folding endurance, and mechanical strength. All parameters were found to be within acceptable pharmacopeial limits, indicating good formulation stability and integrity.

The in-vitro drug release and permeation studies revealed that the optimized formulation exhibited a sustained and controlled release of Frovatriptan over 12hours, demonstrating a promising release profile suitable for transdermal delivery. The drug release followed a non-Fickian diffusion mechanism, suggesting a combination of diffusion and polymer matrix relaxation.

Overall, the results of the present study indicate that the formulated transdermal patches of Frovatriptan are effective in providing controlled drug delivery and could potentially reduce dosing frequency, minimize side effects associated with oral administration, and improve patient adherence in migraine therapy.

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