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TRANSDERMAL DRUG DELIVERY SYSTEM: A RESEARCH PAPER

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ABSTRACT
The skin can be used as the site for drug administration for continuous transdermal drug infusion into the systemic circulation. For the continuous diffusion penetration of the drugs through the intact skin surface membrane-moderated systems, matrix dispersion type systems, adhesive diffusion controlled systems and micro reservoir systems have been developed. Various penetration enhancers are used for the drug diffusion through skin. In matrix dispersion type systems, the drug is dispersed in the solvent along with the polymers and solvent allowed to evaporate forming a homogeneous drug-polymer matrix. Matrix type systems were developed in the present study. In the present work, an attempt has been made to develop a matrix-type transdermal therapeutic system comprising of Rizatriptan with different concentration of various polymers alone using solvent evaporation technique. The physicochemical compatibility of the drug and the polymers was studied by infrared spectroscopy. The results obtained showed no physical-chemical incompatibility between the drug and the polymers. F1formulation has been selected as the best formulation among all the other formulations. The *in-vitro* drug diffusion studies from the formulation were found to be sustained release. All the evaluation parameters obtained from the best formulation were found to be satisfactory.The data obtained from the *in-vitro* release studies were fitted to various kinetic models like zero order, first order, Higuchi model and peppas model. From the kinetic data it was found that drug release follows peppas modelrelease by diffusion technique from the polymer.

KEYWORDS: Transdermal drug delivery, hydrophobic polymers, Rizatriptan.

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.

Rizatriptan is 2nd generation triptan with lots of benefits over other members of its category. Clinical trials have exposed that rizatriptan is effective to oral migraine specific agents in the acute migraine treatment and has more consistent long term efficacy across multiple migraine attacks.

Advantages[2,3,4,5]
1. They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH, enzymatic activity, and drug interactions with food, drink, and other orally administered drugs.
2. They can substitute for oral administration of medication when that route is unsuitable, as with vomiting and diarrhea.
3. They avoid the first-pass effect, that is, the initial pass of s drug substance through the systemic and portal circulation following gastrointestinal absorption, possibly avoiding the deactivation by digestive and liver enzymes.
4. They are noninvasive, avoiding the inconvenience of parenteral therapy.
5. They provide extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration.
6. The activity of a drugs having s short half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
7. Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.

8. They are easily and rapidly identified in emergencies (e.g., unresponsive, unconscious, or comatose patient) because of their physical presence, features, and identifying markings.
9. They are used for drugs with narrow therapeutic window. At the same time transdermal drug delivery has few disadvantages that are limiting the use of transdermal delivery.

Disadvantages[3,4,6]

1. Only relatively potent drugs are suitable candidates for transdermal delivery because of the natural limits of drug entry imposed by the skin's impermeability.
2. Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
3. The delivery system cannot be used for drugs requiring high blood levels.
4. The use of transdermal delivery may be uneconomic. For better understanding of transdermal drug delivery, the structure of skin should be briefly discussed along with penetration through skin and permeation pathways

Materials and Methods

Rizatriptan Benzoate was received as a gift sample from pharmaceutical limited Mumbai. Eudragit RL-100 from Hetero Lab. Hyderabad, India. Eudragit RS-100 from hetero Lab. Hyderabad, India. Dichloromethane Accord labs, Hyderabad, India. Menthol from merck specialities Pvt Ltd. Dibutylpthalate from merck specialities Pvt Ltd.

FORMULATION OF TRANSDERMAL PATCH

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 Rizatriptan were prepared using different concentrations of Eudragit L-100 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. Dibutylphthalate was used as plasticizers. 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 1: Formulation of Rizatriptan Benzoate patches.

INGREDIENTS	FORMULATION CODE											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Rizatriptan	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Eudragit-RL100	5	10	15	20	25	30	-	-	-	-	-	-
Eudragit-RS100	-	-	-	-	-	-	5	10	15	20	25	30
Dichloromethane	8	8	8	8	8	8	8	8	8	8	8	8
Methanol	10	10	10	10	10	10	10	10	10	10	10	10
Dibutyl Phthalate (in % w/v)	20	20	20	20	20	20	20	20	20	20	20	20

1. Physical evaluations

a. Thickness

The thickness of films was measured by digital Vernier calipers with least count0.001mm. The thickness uniformity was measured at five different sites and averageof 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

The three disks of 2*1 $cm^2$was cut and weighed on electronic balance for weightvariation test. The test was done to check the uniformity of weight and thus check thebatch- 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 15minutes, 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 226nm. 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.

% constriction = I1 – I2 X 100

I2 = Final length of each strip

I1 = Initial length of each strip

6.4.2.*In-vitro* Drug Diffusion 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±0.5^{0}C. 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 226nm

6.5. Drug release kinetics

Diffusion data of above two methods was fitted in Zero order, First

Zero-Order Kinetics

Zero order as cumulative amount of Percentage drug released vs time

C=K0t

Where K0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K0 and intercept the origin of the axes.

First order kinetics

First order as log cumulative percentage of log (%) cumulative drug remaining vs time,

Log C = Log Co − kt / 2.303

Where C0 is the initial concentration of drug, k is the first order constant, and t is the time.

Higuchi Model

Higuchi's model as cumulative percentage of drug released vs square root of time

Q = K t 1/2

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Kors meyer Peppas equations

Korsmeyer peppas equation used to determine the mechanism of drug release form the polymer matrix of the tablet. Log cumulative percentage of drug released VS Log time, and the exponent n was calculated through the slope of the straight line.

Mt/M∞=Ktn

Where Mt/M∞ is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/polymer system, and n is an exponent that characterizes the mechanism of release of tracers. For cylindrical matrix tablets, if the exponent n = 0.45, then the drug release mechanism is Fickian diffusion, and if 0.45 < n < 0.89, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release.

6.6. Compatibility study

FTIR study

The infrared spectrum of the pure Rizatriptan 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.

RESULT AND DISSCUSSION

Table 2: Compare patch batch F1 is plane patch without penetration enhancer F3 is 10% methanol and F5 is 10% eucalyptus oil.

S.N.	Time in hrs	Plane patch CDR	10% Eucalyptus oil CDR	10% Menthol CDR
1.	1	0	0	0
2.	2	05.06	07.58	08.58
3.	3	06.99	07.99	08.99
4.	4	09.91	09.91	09.91
5.	5	10.69	11.69	12.69
6.	6	26.52	26.82	28.82
7.	7	32.54	34.54	36.54
8.	8	47.44	47.44	49.44
9.	9	49.22	50.22	52.22
10.	10	51.45	53.45	54.45
11.	11	61.47	63.47	65.47
12.	12	63.22	65.22	69.22

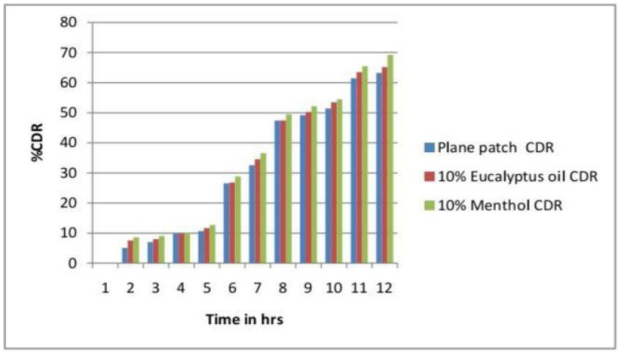

Figure 1.

***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 ^{o}C. The diffusion was carried out for 12 h and 5 ml sample was withdrawn at an interval of 1 h.

Table 3: *In vitro* drug permeation of Rizatriptan containing different concentrations of Eudragit-RL.

Time (hr)	F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0
2	0	0	0	0	0	0
3	15.20	22.00	16.78	13.04	16.44	16.54
4	20.09	28.75	23.03	20.61	21.80	22.20
5	28.77	30.42	30.43	24.68	29.08	29.44
6	36.28	39.25	38.17	29.30	35.44	35.87
7	44.93	48.77	43.39	36.94	51.36	42.76
8	47.75	52.42	46.45	42.22	55.91	50.62
9	51.11	55.38	54.91	49.35	59.41	58.26
10	53.71	59.22	59.38	53.55	62.53	62.79
11	59.99	62.01	61.99	57.01	65.01	64.02
12	62.34	64.91	65.51	65.66	67.42	69.44

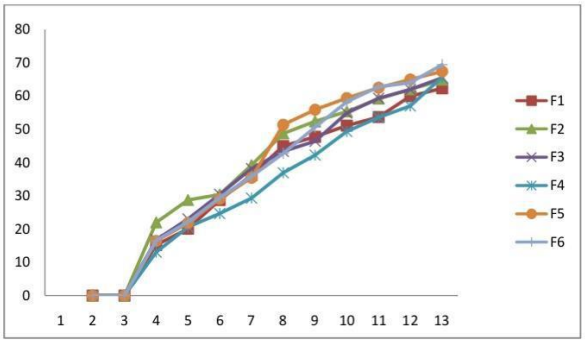

Figure 2: Cumulative% drug permeation of Rizatriptanpatch (F1, F2,F3, F4, F5 and F6).

The formulations F1 to F6 were prepared by different concentrations of Eudragit-L100 (0.5%, 1% 2%,3%,4%, and 5%), the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. At low polymer concentration the drug permeation is more within 12 hours it was total amount of drug was permeated. The 0.5% concentration of polymer was showed maximum drug released at 12 hors 98.29%. The 2% concentration of polymer was showed maximum drug release 86.19 at desired time period. Hence in that 6 formulation F1 formulations showed total drug release at desired time period.

Table 4: *In vitro* drug permeation of Rizatriptan containing different concentrations of Eudragit-S100.

Time	F7	F8	F9	F10	F11	F12
1	0	0	0	0	0	0
2	0	0	0	0	0	0
3	12.73	16.13	12.70	15.46	19.27	22.72
4	17.65	23.80	17.74	21.10	25.49	34.94
5	23.22	29.10	22.88	28.10	33.63	47.88
6	28.49	35.54	29.18	34.02	41.60	49.46
7	31.73	39.81	33.99	39.85	49.35	51.87
8	37.30	42.21	41.40	47.21	53.61	54.01
9	42.10	53.06	47.78	57.23	57.49	58.70
10	46.08	58.10	54.20	61.04	62.45	61.64
11	53.99	61.64	60.21	65.71	66.33	66.31
12	64.21	65.78	65.52	68.69	70.50	70.75

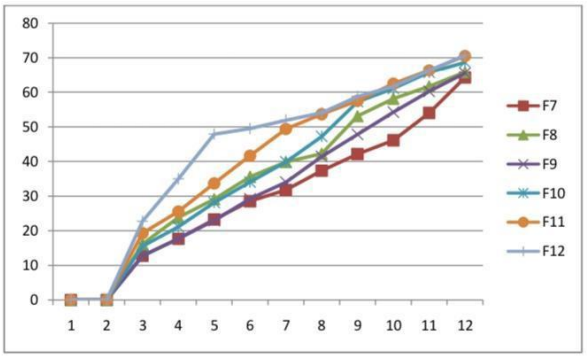

Figure 3: Cumulative % drug permeation of Rizatriptanpatch (F7, F8, F9, F10, F11 and F12).

The formulations F7 to F12 were prepared by different concentrations of Eudragit-S100 (0.5%, 1% 2%, 3%, 4% and 5%), the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. The 0.5% (F7) concentration of polymer was showed maximum drug release 79.99 within 11 hours. The 1% (F8) concentration of polymer was showed maximum drug released at 12 hors 86.78%. The 2% (F9) concentration of polymer was showed less drug release 62.15 at 10 h. The 3% (F10) concentration of polymer was showed maximum drug released at 12 hours 76.69%. The 4% (F11) concentration of polymer was showed maximum drug released at 12 hours 83.80%. The 5% (F12) concentration of polymer was showed maximum drug released at 12 hours 94.75%.

Hence in that 6 formulations F12 formulations showed total drug release at desired time period.

Among all 12 formulations F1 formulation showed good drug permeation from the patch.

Among all *in vitro* evaluation parameters F1 formulation passed all evaluation parameters.

7.4 Kinetic models for Rizatriptan

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.

Table 5: Kinetics data of F8 Rizatriptanpatch.

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
4.22	1	1.000	0.625	0.000	1.981	4.220	0.2370	-1.375	95.78	4.642	4.575	0.066
13.57	2	1.414	1.133	0.301	1.937	6.785	0.0737	-0.867	86.43	4.642	4.421	0.220
16.78	3	1.732	1.225	0.477	1.920	5.593	0.0596	-0.775	83.22	4.642	4.366	0.276
20.09	4	2.000	1.303	0.602	1.903	5.023	0.0498	-0.697	79.91	4.642	4.307	0.334
28.77	5	2.236	1.459	0.699	1.853	5.754	0.0348	-0.541	71.23	4.642	4.145	0.496
36.28	6	2.449	1.560	0.778	1.804	6.047	0.0276	-0.440	63.72	4.642	3.994	0.647
54.93	7	2.646	1.740	0.845	1.654	7.847	0.0182	-0.260	45.07	4.642	3.559	1.083
66.75	8	2.828	1.824	0.903	1.522	8.344	0.0150	-0.176	33.25	4.642	3.216	1.426
73.37	9	3.000	1.866	0.954	1.425	8.152	0.0136	-0.134	26.63	4.642	2.986	1.655
79.12	10	3.162	1.898	1.000	1.320	7.912	0.0126	-0.102	20.88	4.642	2.754	1.888
83.69	11	3.317	1.923	1.041	1.212	7.608	0.0119	-0.077	16.31	4.642	2.536	2.106
98.29	12	3.464	1.993	1.079	0.233	8.191	0.0102	-0.007	1.71	4.642	1.196	3.446

CONCLUSION

In the present investigation an attempt has been made to design and develop the formulation of Rizatriptan patches using different types of polymers by solvent evaporation technique and mercury substrate method. The drug used isthe best studied for therapy in treating migrane.

Rizatriptan was successfully formulated as controlled release transdermal patches, which prevents the frequency of administration and gives good patient compliance.

From the experimental results obtained, F1formulation has been selected as the best formulation among all the other formulations.The *in-vitro* drug diffusion studies from the formulation were found to be sustained release. All the evaluation parameters obtained from the best formulation were found to be satisfactory.

The data obtained from the *in-vitro* release studies were fitted to various kinetic models like zero order, first order, Higuchi model and Peppas model.

From the kinetic data it was found that drug release follows peppas model release by diffusion technique from the polymer.

Based on the observations, it can be concluded that the attempt of formulation and evaluation of the Rizatriptan patches was found to be successful in the release of the drug for an extended period of 12hrs.

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