

Formulation Development And Invitro Evaluation Of Matrix Type Transdermal Drug Delivery System Using Cetyl Pyridinium

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Abstract

At present, the most common form of delivery of drugs is the oral route, its advantage of easy administration. It also has significant drawbacks –poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes, which can be both cost prohibitive and inconvenient. To overcome these difficulties there is a need for the development of new drug delivery system; which will improve the therapeutic efficacy and safety of drugs.

Hence in present work, an attempt is been made to provide development and optimization a matrix type Transdermal drug delivery system using water insoluble polymers with model drug as Cetylpyridinium and to study the effect of various concentration of polymers on In-vitro membrane permeation studies.

Keywords: Cetylpyridinium , TDDS.

Introduction

Oral drug administration has been the predominant route for drug delivery over decades. Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration [1-2]. Delivery of drugs through the skin has been always a challenging area for research due to barrier properties exhibit by the outermost layer of skin stratum corneum. In the last two decades, the transdermal drug delivery system has become a proven technology that offers significant clinical benefits over other dosage forms. Because transdermal drug delivery offers controlled as well as predetermined rate of release of the drug into the patient, it able to maintain steady state blood concentration. It's a desirable form of drug delivery because of the obvious advantages.

Example. Convenient and pain-free self-administration for patients, avoidance of hepatic first-pass metabolism and the GI tract for poorly bioavailable drugs over other routes of delivery.

CPC, an amphiphilic quaternary compound, has been used extensively in oral hygiene formulations. Valuable, properties of

CPC include solubility in water and alcohol, as well as its ability to reduce surface tension. A number of laboratory studies are available in the literature that report the broad spectrum activity of CPC on a range of organisms, including bacteria and yeast found in dental plaque [3-5]. a moderate plaque inhibition was obtained when CPC was applied twice daily as a mouthwash [6].

Materials and Methods Materials

Cetylpyridinium Chloride, potassium dihydrogen phosphate and lactose were purchased from pharmatech laboratories, Hyderabad. Eudragit-L100, Propylene Glycol, Dimethyl formamide, Ethanol. All chemicals and solvents were of analytical grade. Freshly double distilled water was used in the experiments.

Preparation of Phosphate Buffer pH 7.4: 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 added to make up the volume and adjusted pH 7.4 by using 0.2 M potassium dihydrogen phosphate/sodium hydroxide.

Preparation of standard solution: Stock solution - I was prepared by dissolving Cetylpyridinium 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 0.8 ml, 1 ml, 1.2 ml, 1.4 ml and 1.6 ml were transferred in to 10 ml volumetric flasks and were diluted up to the mark with buffer pH 7.4. Absorbance of each solution was measured at λ_{max} of 270 nm against buffer pH 7.4 as the blank, by using UV-spectrophotometer. A graph was plotted by taking concentration of drug vs absorbance was plotted.

Development of Transdermal patches: Transdermal drug delivery patches were prepared by solvent casting method.

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	20

Table 1: Formulations of Cetylpyridinium Transdermal Patch

Evaluation of Transdermal patch by physical methods

- **Physical appearance:** All the Transdermal patches were visually inspected for color, clarity, flexibility & smoothness.
- **Thickness:** This thickness of the patches was assessed at 3 different points using screw gauze. For each formulation, three randomly selected patches were used.
- **Weight variation:** The three disks of 2x2 cm² 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 variation²⁷.
- **Flatness:** Longitudinal strips were cut out from each patch, one the centre and two from either side. The length of each strip was measured and the variation in the length because of uniformity in flatness was measured by determining present constriction, considering 0% constriction equivalent to 100% flatness⁴¹.
- **Folding endurance:** The folding endurance was measured manually for the preparation patch. A strip of the films (4x3 cm) was cut evenly and repeatedly folded at the same place till it is broken⁴².
- **Moisture uptake:** The percent moisture absorption test was carried out to check the physical stability and integrity of the patch at high humid conditions. In the present study the moisture absorption capacities of the patch were determined in the following manner. The patches were placed in the desiccators containing 200 ml saturated solution of potassium chloride, to get the humidity

inside the desiccators at 84 % RH. After 3 days the films were taken and weighed the percentage moisture absorption of the patch was found⁴².

- **Moisture content:** The patches were weighed individually and kept in a desiccators containing fused calcium chloride at 40 °C for 24 h. The patches were reweighed until a constant weight was obtained. Moisture content was calculated in percentage based on the difference between the initial and the constant final weights of the patches⁴⁶.

- **Drug content determination:** The patch of area 3.83 cm² was cut and dissolved in PBS pH 7.4. Then solvent ethanol and dimethyl formamide, to make polymer soluble, were added to the mixture and the remaining volume was made up with PBS pH 7.4 to 100 ml in 100 ml volumetric flask. Then 1 ml was withdrawn from the solution and diluted to 10 ml. The absorbance of the solution was taken at 310 nm and concentration was calculated. By correcting dilution factor, the drug content was calculated.

Kinetic modeling of drug release

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.

- **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.

- 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.

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

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

Where, Q= percent drug release at time t

KH = Higuchi's (diffusion) rate constant

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

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

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

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 (Swella & Cylindrical Matrix). In this model, a plot of $\log(M_t/M)$ versus $\log(\text{time})$ is linear.

In vitro permeation studies using dialysis membrane:

In vitro permeation of Cetylpyridinium 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 7.4 and the setup was placed over a magnetic stirrer with temperature maintained at 37°C. 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 Cetylpyridinium in the samples was analyzed by UV-Visible spectrophotometer. The concentrations of drug were determined at 360 nm.

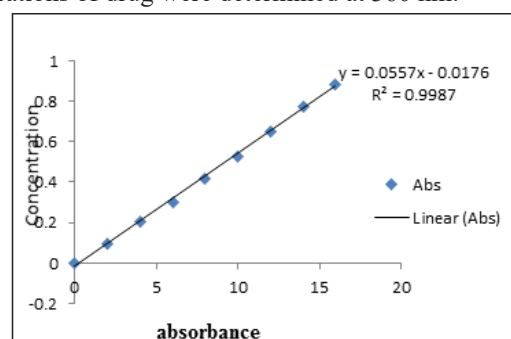


Fig No. 1: Standard curve of Cetylpyridinium

The prepared Cetylpyridinium 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 within the pharmacopial limits.

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

Table No. 2: Evaluation of Cetylpyridinium transdermal patch by physical methods.

The prepared Cetylpyridinium 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

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

Table No. 3: Evaluation of Cetylpyridinium Transdermal patch by In-vitro permeation studies using dialysis membrane.

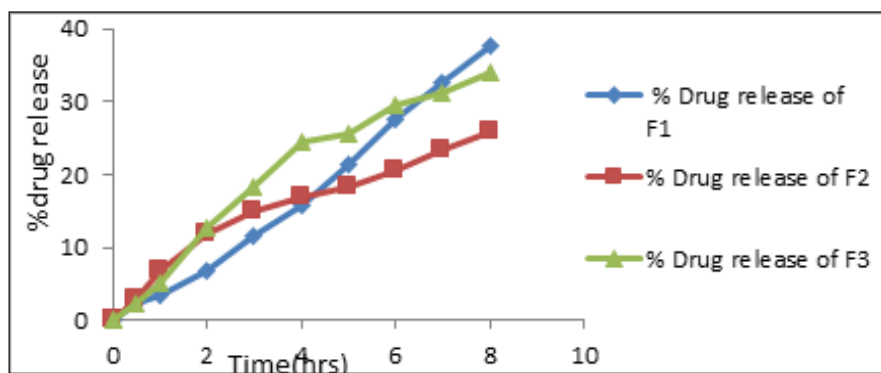


Fig No. 2: % drug release of F1, F2, F3

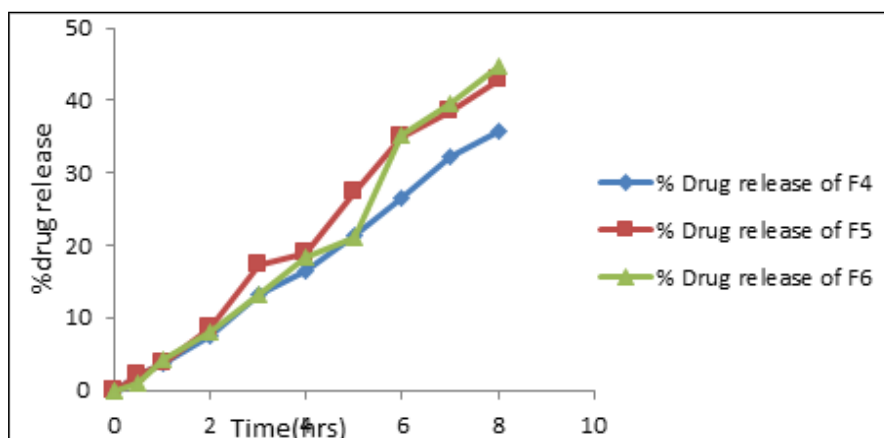


Fig No. 3: % drug release of F4, F5, F6

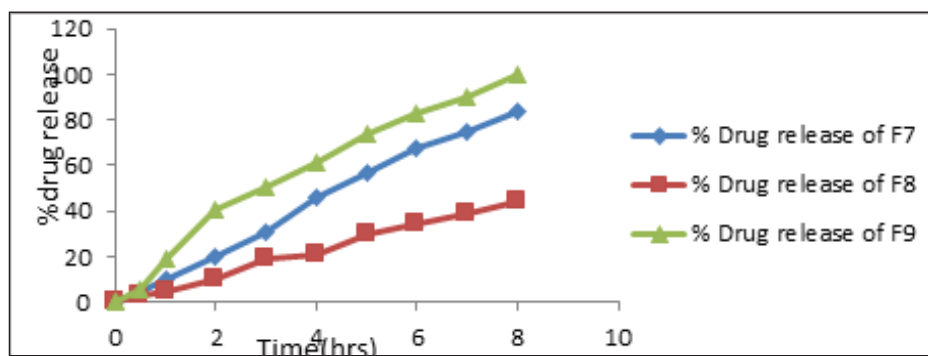


Fig No. 4: % drug release of F7, F8, F9

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.

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	0	0	2.000	0	0	0	100	4.642	4.64	0.000
5.86	0.5	0.70	0.76	-0.30	1.97	11.7	0.17	-1.23	94.14	4.64	4.54	0.092
18.7	1	1.00	1.27	0.00	1.910	18.70	0.053	-0.72	81.3	4.642	4.33	0.310
40.9	2	1.41	1.61	0.30	1.77	20.4	0.024	-0.38	59.2	4.64	3.89	0.74
50.5	3	1.73	1.70	0.477	1.695	16.83	0.0198	-0.297	49.5	4.64	3.67	0.97
61.0	4	2.00	1.78	0.602	1.591	15.25	0.0164	-0.215	39	4.64	3.39	1.25
73.4	5	2.26	1.86	0.699	1.425	14.68	0.0136	-0.134	26.6	4.64	2.98	1.65
83.1	6	2.44	1.92	0.778	1.228	13.85	0.0120	-0.080	16.9	4.46	2.56	2.07
89.8	7	2.64	1.95	0.845	1.009	12.82	0.0111	-0.047	10.2	4.64	2.16	2.47
99.6	8	2.82	1.99	0.903	-0.398	12.45	0.0100	-0.002	0.4	4.64	0.73	3.90

Table No. 4: Kinetics of In-vitro permeation studies of optimized formulation

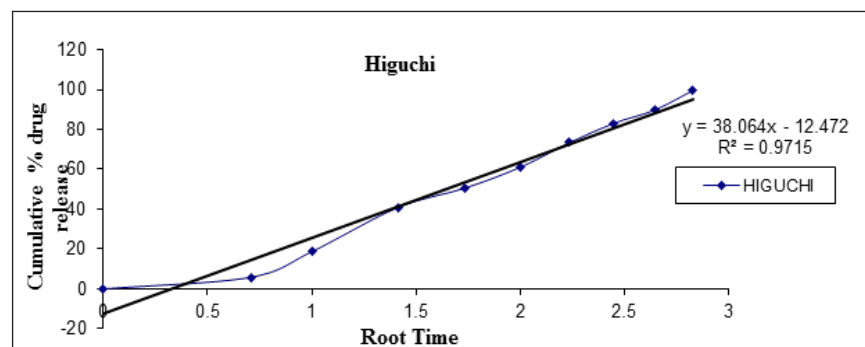


Fig No. 5: Higuchi Plot

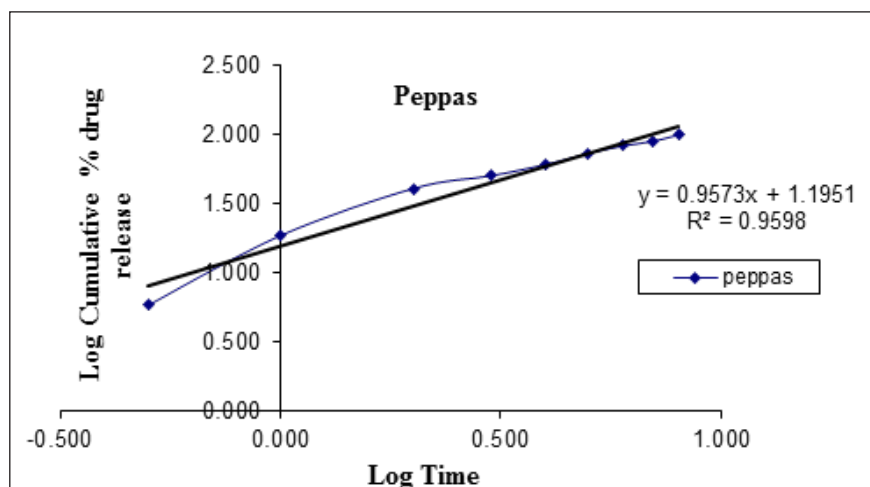


Fig No. 6: Peppas plot

Conclusion

In present study transdermal drug delivery of Cetylpyridinium 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 Eudragit-L and Eudragit-S; Transdermal patches were prepared by employing solvent casting method. Propylene glycol 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 with in the pharmacopeial limits, invitro drug release studies by using dialysis membrane. Cetylpyridinium 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.

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 0.9715.

For F9 formulation release kinetics were plotted and the Regression coefficient value was found to be high for Korsmeyer-peppas release model i.e., 0.9598.

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