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Research Article

FORMULATION, DEVELOPMENT AND EVALUATION OF TRANSDERMAL PATCHES FOR ANTI-CANCER DRUG

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Abstract

The purpose of the work was to formulate and evaluate the transdermal patches for Anti-cancer drug. Transdermal patches were formulated by solvent evaporation method. Transdermal patches were evaluated for various parameters like thickness, folding endurance, percentage moisture loss, percentage moisture absorption, drug content uniformity, stability studies and *in vitro* permeation test. All formulations possess excellent physicochemical properties with good physical stability. Permeation study was performed by using modified Franz diffusion cells. On the basis of drug release and physicochemical values, formulation FT1 was shows higher percentage of drug release at 24 hours.

Keywords: Transdermal patches, Polymer, *In vitro,* Franz diffusion cells

Introduction

Transdermal route is, therefore, a better alternative to achieve constant plasma levels for prolonged periods of time, which additionally could be advantageous because of less frequent dosing regimens. To provide continuous drug infusion through an intact skin, various transdermal systems have been designed for topical application and it control the delivery of drug and its permeation via the skin tissue. Historically, developments related to TDDS have been incremental, concentrating on overcoming issue related with the skin barrier properties, minimizing skin irritation and improving the outlook related with passive patch systems. TDDS defined as self-contained, discrete dosage form applied to the unharmed skin then it deliver the drug, via skin at controlled manner in the systemic circulation. Transdermal drug delivery via the skin provides a suitable route of administration for a various clinical indications.

A pharmaceutical scientist focuses the development of transdermal drug delivery over the last 25 years. The skin offers a large and easily penetrable surface for drug delivery. Transdermal routes, from that of other routes are quite non-invasive, like simple adhesion of a "Patch" similar as that of application of a Band-Aid. A transdermal drug delivery systems transfer a precise dose of drug through the skin and into systemic circulation. [1-8]

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Methotrexate2 (MTX) {(2S)-2-[[4-[(2, 4-diaminopteridin-6-yl) methylethylamino] benzoyl] amino] pentanedioic acid)} is a folic acid derivative and a folic acid antagonist. In the cell it is a competitive inhibitor of the dihydrofolate reductase2. The inhibition of the reduction of dihydrofolate to tetrahydrofolate causes blocking of the DNA synthesis. It is widely used in the treatment of leukemia, lymphoma3, choriocarcinoma, head and neck cancer6 and osteogenic sarcoma. It is also used for the treatment of various autoimmune diseases, e.g., rheumatoid arthritis8, 9 and psoriasis and for the prevention of graft-versus host disease12, 13 after transplantation. MTX is a key drug in the curative regimen of children with acute lymphocytic leukemia.

Methotrexate (MTX) is an antifolate drug used to treat various types of cancer such as breast, lung, head and neck, bladder, lymphoma, leukemia, osteosarcoma and trophoblastic neoplasms. As like other drugs, MTX is also a safer drug in low doses and well tolerated in the treatment of certain autoimmune diseases. It blocks and inhibits the synthesis of purines and pyrimidines which are responsible for the efficacy and toxicities of the drug in the cancer therapy [9-11]

Materials and Methods :

Preparations of Transdermal patches [12-16]

The matrix type transdermal patches of Methotrexate were prepared by solvent evaporation technique by using different ratio of ethylcellulose (EC) and polyvinylpyrrolidone K-30 (PVP) polymers. The polymers EC and PVP were weighed and mixed in different ratios by keeping the total polymers weight at 1.6 g added in a chloroform solvent using magnetic stirrer. The dibutyl phthalate 30% w/w of polymer was incorporated as plasticizer. Drug 20 % w/w of polymer weight was added slowly to the polymers solution and mixed thoroughly by continuous stirring for 30 minutes to obtain a homogenous solution. The five formulations were prepared by using same drug and different polymers ratio without permeation enhancer in order to determine the optimum combination of drug and polymers. On the basis of preliminary studies, the optimized polymers ratio 3:2 (EC:PVP) were mixed with the different permeation enhancers like DMSO, Tween-80, eucalyptus oil and olive oil. The permeation enhancers were added in three different concentrations *i.e.* 2%, 5% and 10% w/w of total

polymers weight for each. The resulting drug-polymers solution was poured in petridish of 64 cm^2.

The aluminum foil was uniformly spread on petridish on which drug-polymers solution was poured. The rate of evaporation was controlled by inverting a funnel over the petridish and the solvent was allowed to evaporate for 24 h at room temperature. After 24 h, the films were collected and a wax paper was applied on other side of the films as a release liner to complete the formulation

Evaluation of Transdermal Patches[12-19]

Thickness of patches

The thickness of Patches were measured by digital vernier calipers with least count 0.001mm at three different sites average of three reading was taken with standard deviation.

Weight variation

The three disks of 3.14 cm^2 were 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.

Drug content

Accurately weighed patches were individually dissolved in minimum quantity of methanol and made volume up to 100 ml with PBS pH 7.4 solutions; 10 ml was transferred to flask and made volume 100 ml. The absorbance was recorded. The blank solution was

made in the same manner except the patches without drug were used.

Percentage Moisture content

The films were weighed & placed in desiccators containing calcium chloride at 40^0c in a dryer for at least 24 hrs or more until it gives a constant weight. The % of moisture content was the difference between constant weight taken and the initial weight and as reported with percentage by weight moisture content.

Percentage Moisture absorption/uptake

The films of which the size 3.14cm^2 were put in a desiccators with silica gel for 24 hrs and weighed the patches were transferred to another desiccators containing saturated solution of KCL(84% RH) after equilibrium was attained. Patches were taken out and weighed. Moisture uptake was calculated with following formula

Swelling index

The patches of 3.14 cm^2 were weighed and added into Petri dish which contains 10 ml double distilled water and were permeated to absorb moisture at a fix time interval check the increase weight of the patches. Continue this process till same weight observed until weight remaining the same over a period of time. Swelling index (% S) was determined by applying the formula.

S (percentage) = Wt – Wo / Wo x 100

Where, S percent swelling, Wt patch weight at time t.

Wo patch weight at time zero.

Folding endurance

This was obtained by constantly folding one patch at the same place without breaking gave the value of folding endurance. This test performed to check folding ability of transdermal patches also indicate brittleness of patches, more brittle patch when folding endurance value.

Percentage Elongation

A film strip (4 x 1cm) was cut on a glass plate with a sharp blade. The % elongation break is to be determined by observing the length just before the breaking point with formula by pointer on the graph paper.

% Elongation = [Final length – Initial length] * 100/Initial length

Tensile Strength

The tensile strength of the patches was found by the apparatus and the design of instrument such that, it had one wooden frame that horizontally placed having fixed scale. On the top of frame two clips were attached to hold patches that under study. From two clips one clips fixed & other moved. Instrument also has pulley to hold weight a patch, weight applied to one end of pulley and other end attached to the fixed clip. During the test wooden platform not dislocate from the original place so platform was fixed carefully to avoid dislocation. Three patches were cut for study having 3.14 cm^2 sizes. Thickness and width of patches were noted at three sizes and calculated average value. Rate of stress changes was maintained constant with the addition of 0.5g per 2 minutes. The elongation was observed and the total weights taken were used for calculation.

Formula for tensile strength :

Tensile strength= F/a.b (1+L/l)

Where,

F is the force required to break; ‘a’ is width of film; ‘b’ thickness of film; L is length of the film; l is an elongation of film at break point.

In-vitro permeation studies

Franz diffusion cell (fabricated in our Lab.) with a diameter 3.7 cm was used in in-vitro release studies. A glass tube with both end open, 10 cm height and 3.7 cm outer diameter was used as a permeation cell. A transdermal patch sample was accurately placed on a semipermeable cellophane membrane to occupy a circle of 3.7 cm diameter. The loaded membrane was stretched over the lower open end of a glass tube of 3.7 cm diameter and made water tight by rubber band. The tube (donor compartment) was immersed in a beaker containing 100 ml of phosphate buffer pH 6.8 (receptor compartment) .The cell was immersed to a depth of 1 cm below the surface of buffer. The system temperature was maintained at 37°±1° and speed was maintained at 30 rpm throughout the experiment by magnetic stirrer. The samples 3 ml were withdrawn at different time intervals and analyzed without dilution or filtration for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.

Stability studies

As per ICH Guidelines of Accelerated stability studies were performed at the different storage condition $25^{O}C\pm2^{0}c$ temp., 60%±5% RH and $40^{O}C\pm2^{0}c$ temperature, 75%±5% RH, for 90 days on optimized formulation batches (FT5).The parameters studied for stability studies are thickness, drug content, moisture content and uptake, weight variation, folding endurance, Tensile strength, % elongation and swelling index.

Results and Discussion

Evaluation of Transdermal patches :
Physicochemical Evaluation

Table 2 and 3 shows the physicochemical evaluation like the Thickness, Folding endurance, Percentage moisture absorbed, Percentage moisture lost, Drug content uniformity.

Permeation studies and Permeation Kinetics

In-vitro drug release studies were performed by using a Franz diffusion cell with a receptor compartment capacity of 22 ml. On the basis of *in vitro* dissolution studies, the best formulations F4, FD3 and FE3 was selected from every batches for *in vitro* permeation studies across excised cellophane membrane. The samples were withdrawn at different time intervals and analyzed for drug content in U.V. Spectrophotometer at 303 nm.

The permeation enhancers like DMSO , tween-80, and eucalyptus oil were evaluated and their effectiveness was determined by comparing the *in vitro* permeation and steady state flux of Methotrexate from transdermal patches with and without enhancer (control patch). The *in vitro* permeation profile is presented in Table 3

The DMSO demonstrated a cummulative amount of drug permeated was 637.78 ± 31.63 µg/cm2 in 24 h with flux of 27.39 ± 1.76 µg/cm2/h . There was enhancement of 2.73 times. DMSO is an effective penetration enhancer that promote .

The transdermal patches containing tween-80 as permeation enhancer showed highest cummulative amount of drug permeated 1020.29 ± 40.88 µg/cm2 in 24 h with flux 43.91 ± 1.29 µg/cm2/h and enhancement of 4.36 times .

Stability Study

Stability is the essential factor for quality, safety and efficacy of product. The optimized formulations FT1 was subjected for stability studies as per ICH guidelines and observed for all evaluation parameters at a temperature of $40^{0}C$ and 75% RH, at an interval of three month. There were no physical changes in flexibility and physicochemical evaluation parameter was slightly changed.

The drug content of the patch was found 97.11, 96.91 and 96.84% after 30, 60 and 90 days respectively, indicated that no significant *(p >0.05)* change after 3 months. So on the basis of results, the optimized Methotrexate transdermal patch (FT1) was found stable enough

Conclusions

The results of Methotrexate transdermal matrix patch showed that the most promising formulation was FT1 (formulation containing EC: PVP, 3:2; Methotrexate 20%; dibutylpthalate 30% and 2% tween-80 all in %w/w). This formulation was able to deliver drug up to 24 h at a flux of 43.91 µg/cm2/h across rat skin.

Thus optimized transdermal matrix patch of Methotrexate using polymers such as EC and PVP with tween-80 as permeation enhancers demonstrated their ability to give sustained release, because of excellent release and permeation of drug and its influence on antidepressant efficacy. The developed formulation of Methotrexate is expected to improve the patient compliance, form better dosage regimen and provide maintenance therapy to patients suffering from cancer.

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Table: 1 Composition of Transdermal patches

S. No.	Formulation Code	Methotrexate (% w/w)	EC:PVP (Ratio)	Permeation Enhancer (% w/w)
1.	F1	20	4.5 : 0.5	-
2.	F2	20	4 : 1	-
3.	F3	20	2 : 1	-
4.	F4	20	3:2	-
5.	F5	20	2:3	-
6.	FD1	20	3:2	DMSO 2%
7.	FD2	20	3:2	DMSO 5%
8.	FD3	20	3:2	DMSO 10%
9.	FT1	20	3:2	Tween-80 2%
10.	FT2	20	3:2	Tween-80 5%
11.	FT3	20	3:2	Tween-80 10%
12.	FE1	20	3:2	Eucalyptus oil 2%
13.	FE2	20	3:2	Eucalyptus oil 5%
14.	FE3	20	3:2	Eucalyptus oil 10%
15.	FO1	20	3:2	Olive oil 2 %
16.	FO2	20	3:2	Olive oil 5 %
17.	FO3	20	3:2	Olive oil 10 %

Key-*based on polymer weight

Table 2 Physicochemical Evaluation data of Transdermal Patches

F. Code	Thickness (mm)	Weight Variation (mg)	Drug Content (%)	Flatness	Folding Endurance	Tensile Strength (kg/mm2)	pH	F. Code
F1	0.273 ± 0.014	164.87 ± 2.08	96.25 ± 0.42	100	42 ± 4.08	0.417 ± 0.02	5.8	F1
F2	0.254 ± 0.017	164.37 ± 1.48	97.26 ±1.42	100	48 ± 6.50	0.438 ± 0.04	5.8	F2
F3	0.266 ± 0.008	167.19 ± 1.88	94.12 ± 0.74	100	44 ± 3.43	0.393 ± 0.01	5.8	F3
F4	0.260 ± 0.012	165.20 ± 2.08	96.20 ± 1.11	100	39 ± 4.69	0.404 ± 0.03	5.7	F4
F5	0.268 ± 0.011	166.49 ± 1.11	95.03 ± 1.56	100	34 ± 3.08	0.357 ± 0.06	5.7	F5
FD1	0.265 ± 0.016	164.40 ± 1.89	96.78 ± 2.14	100	38 ± 5.37	0.370 ± 0.07	6.5	FD1
FD2	0.276 ± 0.010	166.72 ± 1.92	94.38 ± 0.92	100	36 ± 3.11	0.352 ± 0.03	6.6	FD2
FD3	0.269 ± 0.016	169.61 ± 2.33	96.20 ± 0.61	100	38 ± 4.15	0.346 ± 0.05	6.6	FD3
FT1	0.261 ± 0.022	165.20 ± 1.69	97.64 ± 1.04	100	37 ± 5.12	0.371 ± 0.02	6.3	FT1
FT2	0.256 ± 0.023	167.57 ± 2.12	95.68 ± 0.62	100	36 ± 3.91	0.397 ± 0.04	6.3	FT2
FT3	0.274 ± 0.013	168.97 ± 2.93	95.73 ± 1.80	100	40 ± 4.84	0.361 ± 0.02	6.4	FT3
FE1	0.246 ± 0.027	165.40 ± 2.18	98.23 ± 0.78	100	35 ± 4.32	0.394 ± 0.03	6.1	FE1
FE2	0.256 ± 0.014	167.60 ± 1.34	95.53 ± 1.21	100	38 ± 2.54	0.403 ± 0.04	6.5	FE2
FE3	0.267 ± 0.012	166.76± 2.76	97.19 ± 0.96	100	35 ± 3.63	0.372 ± 0.03	6.6	FE3
FO1	0.265 ± 0.016	168.56 ± 1.91	94.88 ± 1.13	100	36 ± 6.72	0.346 ± 0.02	5.7	FO1
FO2	0.273 ± 0.009	167.95 ± 4.32	94.58 ± 1.34	100	40 ± 3.91	0.363 ± 0.04	5.7	FO2
FO3	0.272 ± 0.014	172.01 ± 2.77	96.43 ± 0.69	100	43 ± 4.18	0.358 ± 0.05	5.7	FO3

Table 3 *In-vitro* Drug Permeation of Methotrexate from transdermal patches containing EC/PVP (3:2) and without enhancer (F4), DMSO 10% (FD3), tween-80 2% (FT1), eucalyptus oil 10% (FE3), olive oil 5% (FO2)

Time (h)	Cummulative amount of drug permeated (µg/cm2)				
	F4	**FD3**	**FT1**	**FE3**	**FO2**
1.	1.22 ± 0.38	3.42 ± 1.67	13.59 ± 2.58	6.41 ± 2.13	1.57 ± 0.48
2.	4.47 ± 1.17	14.22 ± 3.47	57.43 ± 6.97	32.34 ± 3.72	3.46 ± 0.83
3.	13.09 ± 2.90	40.20 ± 6.08	105.21 ± 8.77	87.85 ± 12.43	13.60 ± 2.70
4.	18.96 ± 2.35	73.53 ± 9.10	147.77 ± 16.06	110.32 ± 23.61	42.73 ± 5.26
5.	27.49 ± 4.59	109.02 ± 8.68	289.20 ± 36.40	143.87 ± 22.35	68.09 ± 9.29
6.	48.22 ± 3.78	141.14 ± 20.56	331.58 ± 22.47	180.30 ± 17.86	121.58 ± 31.12
8.	69.26 ± 7.90	167.06 ± 22.57	426.39 ± 32.22	257.31 ± 36.20	150.71 ± 27.90
10.	93.11 ± 13.53	232.83 ± 35.26	492.86 ± 46.76	314.89 ± 30.39	193.91 ± 15.04
12.	120.13 ± 8.10	295.92 ± 29.01	543.80 ± 29.69	484.24 ± 58.34	251.57 ± 44.28
18.	173.19 ± 17.56	438.55 ± 51.60	809.75 ± 59.61	666.23 ± 52.39	322.89 ± 62.36
24.	217.19 ± 14.33	637.78 ± 31.63	1020.29 ± 40.88	806.86 ± 60.25	437.84 ± 17.18