J Young Pharm, 2020; 12(2) Suppl: s45-s50
A multifaceted peer reviewed journal in the field of Pharmacy
www.jyoungpharm.org | www.phcog.net

Original Article

Formulation and Evaluation of Zidovudine Transdermal Patch using Permeation Enhancers

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ABSTRACT
Objective: The objective of this research was to study the permeation of zidovudine using permeation enhancers. **Methodology:** Transdermal patches were formulated using permeation enhancer namely T-Anethole. Zidovudine patches were prepared by solvent casting method. **Results:** The prepared patches were evaluated for drug content, thickness and weight variation folding endurance, moisture uptake, water vapor transmission, *ex-vivo* permeation study and skin irritation study. Fourier Transform Infrared revealed no interaction among the drug, polymers and terpene used in the present study. Different formulations were prepared and variations in drug release profiles were observed. About 67.42% of drug release was observed for TPS control patch (without permeation enhancer) whereas for TPS4 patch containing t-anethole as permeation enhancer, drug release at the end of 8h was found to be 93.21%. The *ex vivo* permeation studies were performed in 7.4 phosphate buffer saline using a Franz diffusion cell. The skin irritation test was performed on rabbits and these results suggested that both placebo and drug-loaded films produced negligible erythema. *Ex vivo* studies indicated that formulation TPS4 shown better release of zidovudine for 8 hrs with flux 614.05μg/cm²/hr. **Conclusion:** The transdermal patches of zidovudine using permeation enhancers done successfully.

Key words: Zidovudine, Permeation, Anethole, Permeation enhancer, Flux.

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DOI: 10.5530/jyp.2020.12s.45

INTRODUCTION

Zidovudine (Retrovir), a nucleoside reverse transcriptase inhibitor, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. The apparent volume of distribution of zidovudine, following oral administration, is 1.6 ± 0.6 L/kg; and binding to plasma protein is low, <38%. After oral administration, it is rapidly absorbed from the gastrointestinal tract with a peak serum concentration occurring in about 1 h. However, oral bioavailability of AZT is not very high, with a range of 52% to 75%, due to the first-pass metabolism and the mean half-life is approximately 1 hr.

In order to maintain therapeutic levels, large doses should be given frequently in oral route.[1] This dosage often causes toxic levels in blood and severe adverse effects such as granulocytopenia or anemia occurs. The side effects of AZT are usually associated with excessive plasma level of AZT immediately after intravenous or oral administration. Therefore, when compared to a delivery from oral pathway, delivery from the transdermal route may be helpful in maintaining suitable plasma concentration and in improving bioavailability and patient compliance and avoiding side effects. Zidovudine (AZT) is a polar molecule, diffusion of AZT across highly lipophilic stratum corneum is poor and below the level to achieve effective therapeutic plasma concentration. Hence, using terpenes (anethole) along with polyol such as propylene glycol and polyethylene glycol as penetration enhancers could be an effective in achieving therapeutic plasma levels for AZT.[2-4]

MATERIALS AND METHODS

Materials

Zidovudine was obtained from Aurobindo pharmaceuticals. Terpene was obtained from Alfa aesar Johnson Matthey Chemicals India Pvt. Ltd. PVA was obtained from NP Chemicals, PVP was obtained from Yarro Chemicals, Propylene glycol was obtained from Otto,. Eudragit RL 100 was purchased from Evonik industries, HPMC was brought from Burgoynr Burbidges % Co. All other chemicals were of analytical grade.

Methods

Preparation of transdermal patches

Dose calculations of drug[5-7]

Transdermal dose = oral dose * bioavailability

Transdermal dose = 40*65/100=26 mg

Diameter of Teflon plate: 6cm

Area of petri plate= 28.26 sq.cm

No. of 2.3*2.3 cm area films in a petri plate =28.6/5.3 =5.33

Each film contains 26mg drug, drug to be taken per petri plate= 5.33*26=138.58 mg (139 including practical loss).

Preparation of patches[8,9]

All the ingredients were weighed accurately and dissolved in a suitable solvent with continuous stirring. Then plasticizer was added to the above solution. The resultant solution was stirred for 15 min to get a clear solution and was kept aside for some time to get a bubble free solution, these solutions were casted slowly on a Teflon plate with a continuous flow to avoid bubble formation and the plates were kept at room temperature for 24 hrs. An inverted funnel was placed over the plate to control the rate of drying. (Table1)

After 24 hr, formed patch was taken out and checked for its complete dryness. The dried patch was gently separated from the Teflon plate and

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Figure 1: Prepared transdermal patch of Zidovudine.

cut into separate patches 2.3cm*2.3cm area. (Figure 1) The patches were preserved by wrapping in aluminum foil. These patches were used for evaluation tests further.

Preparation of Azt Loaded Transdermal Patches using Combination of Synthetic Polymers

Physicochemical Evaluation of Transdermal Patches

Patches were evaluated for their visual inspection, film formation, weight variation, folding endurance, content uniformity, assay, thickness, drug content, *in-vitro* studies, *ex-vivo* studies, skin irritation studies and stability studies.[10-16] Results were given in Table 5 and 6

(A) Visual inspection and film formation

The patch was evaluated visually for its clarity, transparency and stickiness. If it was satisfactory, then it was taken for further evaluation. If the patches were not satisfactory, then they were discarded.

(B) Assay

The assay was performed to ensure the drug loading in each patch. The assay was performed by taking out a 5.29 cm^2 (2.3cm*2.3cm) area of patch from the whole patch. It is dissolved in 100ml of phosphate buffer saline pH 7.4 with the aid of stirring. The volumetric flask was kept on a magnetic stirrer for 6 hr and sonicated for 15 mins for mixing. The solution was filtered through the Whatman filter paper, diluted appropriately and the drug content was measured spectrophotometrically against corresponding placebo patches at a wavelength of 267.6nm.

(C) Thickness variation test

The thickness of the patches was measured at three different points using a micrometer screw gauge and mean values were calculated.

(D) Weight variation test

This test ensures the uniformity of the formed patch. From the whole patch three small pieces were cut randomly, each of 4cm^2 (2*2cm) area and were weighed individually. The standard deviation from the mean value was reported.

(E) Folding endurance

Folding endurance of patches was determined by repeatedly folding a small strip of patch till it broke; the number of times, the patch could be folded at the same place without breaking gave the value of folding endurance.

(F) Moisture content

The prepared films weighed individually and kept in a dessicators containing calcium chloride at room temperature for 24 hr. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content was calculated by following formula.

% Moisture content= [Inital weight – Final weight / Final weight] × 100

(G) Moisture uptake

Weighed films were kept in desicators at room temperature for 24hr. These were taken out and exposed to 84% relative humidity using saturated solution of potassium chloride in a desicators until a constant weight is achieved.

% Moisture uptake= [Final weight – Initial weight / Initial weight] × 100

(H) Water Vapor Transmission Rate (WVTR) studies

Glass vials of equal diameter were used as transmission cells. The transmission cells were washed thoroughly and dried in oven at 100°C for some time. About 1g anhydrous calcium chloride was placed in the cells and respective polymer film (1 sqcm) was fixed over the brim. The cells were accurately weighed and kept in a closed desicator containing saturated solution of potassium chloride (200 ml) to maintain a relative humidity of 84%. The cells were taken out after 24h and weighed after storage. The amount of water vapor transmitted was found using the following formula.

$$WVT=WL/S$$

Where,

W= water vapor transmitted in gm,

L= thickness of the film in cm,

S= exposed surface area in square cm.

Table 1: Formulation of Zidovudine patch using different synthetic polymers with t-anethole as permeation enhancer.

Ingredients	TPS1	TPS2	TPS3	TPS4	TPS5	TPS6	TPS7	TPS8	TPS9
Zidovudine	138	138	138	138	138	138	138	138	138
PVA (mg)	100	200	300	-	-	-	100	100	100
PVP K30 (mg)	400	300	200	-	-	-	-	-	-
Eudragit RL 100 (mg)	-	-	-	400	300	200	-	-	-
HPMC E 15LV(mg)	-	-	-	100	200	300	-	-	-
Na CMC (mg)	-	-	-	-	-	-	100	200	300
T-Anethole	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Solvent (10ml)	water	Water	water	Dcm:Et	Dcm:Et	Dcm:Et	water	water	water
Plasticizer	glycerol	glycerol	glycerol	PG	PG	PG	PG	PG	PG

NOTE: All the ingredients are dissolved in 10 ml of solvent

Dcm:Et-Dichloromethane:ethanol in 1:1 ratio

It is expressed as the number of grams of moisture gained/h/cm^2.

Ex-vivo Permeation Studies

Preparation of goat skin for *ex-vivo* studies

Fresh abdominal skin of the goat was collected from the slaughter house. Abdominal skin hair was removed using an animal hair clipper, a portion of skin was separated andadipose tissue was surgically removed and dermis side was wiped with isopropyl alcohol to remove residual adhering fat.The skin was washed with phosphate saline buffer (PBS) pH 7.4 and was stored at −20°C and used within four days.[17-19]

Ex-vivo Permeation studies using goat skin

For the permeation studies locally fabricated Franz diffusion cells with 25 ml receptor volume were used. The thawed rat skin was mounted onto diffusion cell such that the dermis side was in constant contact with receptor solution. Patch was applied to the stratum corneum facing the donor compartment and the receptor fluid was agitated at 100 rpm by magnetic stirrer and the temperature was maintained at 32±0.5°C. 1 ml sample was withdrawn at predetermined time intervals for 8 hrs and drug content was analyzed by UV-VIS double beam spectrophotometer at 267.6 nm.[20,21]

Calculation of permeability parameters

(A) Steady state flux (µg/cm^2/hr)

Steady state flux (Jss) is defined as the rate of diffusion or transport of a substance through a permeable membrane. After reaching the steady state of drug permeation, the flux was calculated using the following equation.

$$Jss = \frac{dM}{s} dt$$

dM-amount of drug permeated

S-unit cross-section area

t -time (t).

The steady state flux obtained by plotting the cumulative amount of drug permeated in micrograms per square centimeter versus time in hours and the slope is the flux. Lag time is X intercept of this graph.[22,24]

(B) Permeability coefficient (cm/hr)

The permeability coefficient (Kp) was calculated with the following equation:

$$Kp = \frac{Jss}{cv}$$

Where, cv is the total donor concentration of the formulation[25]

(C) Enhancement ratio

Enhancement ratio (ER) used to evaluate the effect of permeation enhancer on the diffusion and permeation of selected drug molecules and is calculated by

$$ER = \frac{\text{Jss of drug with enhancer}}{\text{Jss of drug alone}}$$

Where, Jss - Steady state flux[26]

(D) Lag time (min)

Lag time is the time required for the drug to get released from the reservoir. It is calculated by plotting the cumulative amount of drug permeated v/s time. The x-intercept value gives the lag time.

Calculation of model dependent kinetics for prepared patch formulations

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, to study the drug release from the dosage form.[27-29]

Drug kinetics

In order to understand the mechanism and kinetics of drug release from the drug reservoir through rate controlling membrane, the *in-vitro* data was related with the following mathematical models as shown in Table 2 and 3.

Skin Irritation Studies

Skin irritation studies were performed on rabbits after the approval by the Institutional animal Ethical Committee (IAEC) in G. Pulla Reddy College of Pharmacy, Registration number 320/CPCSEA and ID no: GPRCP/IAEC/10/18/02/PCE/AE-4.

A primary skin irritation test was performed.Since, skin is the vital organ through which the drug is transported. The test was carried out on two healthy rabbits weighing between 1.5-2 kg. The test was conducted on an unbraided skin of rabbits. The unbraided skin was cleaned with rectified spirit for placing the patches. The control patch was placed on the left dorsal surface of each rabbit, whereas the test patch with the drug was placed on the right dorsal surface of the same rabbit and the other rabbit was kept as control. The patches were removed after 24 hrs and the skin was examined for erythema/ oedema.[30,31]

Table 2: Model dependent kinetics.[32-34]

Model	Equation	Plot of graph	Parameters
Zero order	$Q_t = Q_0 + K_0 t$	% drug release versus time	K_o - release rate constant
First order	$\ln Q_t = \ln Q_0 + K_1 t$	log % drug release versus time	K1- release rate constant
Higuchi release	$Q_t = K_H t^{1/2}$	% drug release versus square root of time	K_H-Higuchi constant
Korsmeyer-Peppas	$Q_t/Q_\infty = K_k t_n$	log % drug release versus log time	n–release exponent

Regression coefficient (r^2) was calculated for all the formulations. Release component "n" was calculated from Korsmeyer-peppas equation. These calculations were carried out using MS-office excel.

Table 3: Interpretation of diffusion release mechanism from "*n*" values.[35,36]

Release Exponent (n)	Drug transport mechanism	Rate as a function of time
< 0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous transport	t^{n-1}
1.0	Case-II transport	Zero order release
Higher than 1.0	Super case-II transport	t^{n-1}

Stability Studies

Stability is defined as the extent to which a product retains within the specified limits and throughout is period of storage and use *i.e.,* shelf life. Stability studies were carried out on optimized formulation according to International Conference on Harmonization (ICH) guidelines.

The formulation packed in aluminum foil was subjected to stability testing in aluminum foil for a month at room temperature. Samples were taken at regular time intervals of 15 days for over a period of 1 month and analyzed for the change in physical appearance and the drug content by procedure stated earlier. Tests were carried out in triplicate and mean value of the observed values was noted along with standard deviation.

Ex-vivo permeation rate studies such as % drug release, steady state transdermal flux (SSTF), permeability coefficient, lag time and enhancement ratio of percutaneous absorption of zidovudine were calculated.[39-41]

Evaluation Tests for Transdermal Patches Containing Synthetic Polymers

Ex-vivo Diffusion Studies of Transdermal Patch Containing Synthetic Polymers

Evaluation of Control Patch

Control patches were prepared similar to the optimized formulation TPS4 without terpene.

Evaluation and *Ex-vivo* diffusion studies were performed. The results were shown in Table 8-11.

From the results of *ex-vivo* drug release kinetics for optimized patch formulations as shown in Table 4. It was found that formulations follow first order release kinetics.

From the values of release component "*n*", it can be concluded that both the formulations have anamolous diffusional release mechanism. Drug release has shown peppas release mechanism, this may be due to presence of swelling polymers in the patch. Anamolous diffusion or non-fickian diffusion refers to a combination of both diffusion and erosion controlled release. The release process involves the penetration of solvent into the patch followed by swelling of the polymer and the diffusion of the drug dissolved in the matrix.

Stability Studies

Stability studies were done for the optimized formulation TPS4. There were no insignificant physical changes in appearance and flexibility. After subjecting the optimized formulations to the accelerated stability

Table 4: Grading scale of the Draize method.[37,38]

S.No	Grade	Formation of erythema and edema
1	0	None
2	1	Slight
3	2	Well defined
4	3	Moderate
5	4	Severe erythema and edema

Table 5: Evaluation tests for transdermal patches containing synthetic polymers.

Formulation code	Weight variation	Folding endurance	Thickness (mm)	Drug content
TPS1	133±1.7	120	0.21±0.01	97.05±2.23
TPS2	135±1	146	0.22±0.01	96.44±1.94
TPS3	134±2.08	185	0.26±0.02	95.75±3.23
TPS4	167±0.57	158	0.23±0.01	97.23±1.08
TPS5	141±0.57	130	0.23±0.02	97.60±1.87
TPS6	166±3.21	168	0.25±0.01	97.98±1.05
TPS7	76±2	285	0.16±0.01	97.27±1.90
TPS8	93.3±1.15	>300	0.17±0.01	96.89±2.9
TPS9	138.6±1.15	184	0.19±0.01	98.11±1.35

n=3, Results are the mean of triplicate observations ± S.D values.

Table 6: Evaluation tests for transdermal patches containing synthetic polymers.

Formulation code	Moisture uptake	Moisture content	WVTR (gm/cm²/hr)
TPS1	6.9±0.17	2.30±0.05	0.018
TPS2	7.42±0.41	2.27±0.2	0.032
TPS3	6.74±0.42	3.07±0.16	0.03
TPS4	2.13±0.07	1.22±0.8	0.017
TPS5	2.42±0.18	2.17±0.82	0.028
TPS6	3.23±0.04	1.82±0.24	0.019
TPS7	3.95±0.03	2.7±0.19	0.024
TPS8	2.91±0.17	1.41±0.24	0.022
TPS9	3.18±0.19	2.66±0.31	0.028

All the values are expressed as mean ± SD, n=3

Table 7: *Ex-vivo* diffusion studies of transdermal patch containing synthetic polymers.

Time (hrs)	TPS1	TPS2	TPS3	TPS4	TPS5	TPS6	TPS7	TPS8	TPS9
1	12.22±0.19	15.02±0.10	20.63±0.4	18.6±0.19	19.05±0.52	13.3±0.41	20.45±0.42	17.29±0.35	18.64±0.50
2	19.23±0.22	20.23±0.08	23.35±0.34	24.75±0.09	29.05±0.15	19.05±0.17	21.18±0.53	18.96±0.42	24.52±0.31
3	25.7±0.23	28.37±0.09	29.19±0.26	30.95±0.27	36.02±0.09	29.05±0.39	24.52±0.26	24.8±0.65	27.06±0.36
4	38.24±0.11	36.74±0.11	36.74±0.25	41.54±0.33	38.1±0.07	38.1±0.09	35.16±0.19	30.8±0.47	39.59±0.52
5	43.76±0.24	43.67±0.24	44.71±0.15	57.01±0.02	41.9±0.82	41.9±0.41	40.36±0.18	39.59±0.20	41.81±0.19
6	65.61±0.26	56.11±0.09	57.01±0.28	62.9±0.15	62.44±0.55	42.58±0.82	44.16±0.36	41.27±0.44	54.75±0.31
7	76.02±0.09	79.64±0.07	60.63±0.14	80.54±0.39	71.95±0.39	64.25±0.83	57.01±0.54	65.61±0.41	76.02±0.11
8	83.26±0.07	88.69±0.14	89.59±0.26	93.21±0.15	81±0.33	76.47±0.39	89.59±0.12	84.16±0.19	85.52±0.12

All the values are expressed as mean ± SD, n=3

Table 8: Physico Chemical parameters of control patches.

Formulation code	Weight variation (mg)	Folding endurance	Thickness (mm)
TPS	159±0.02	145	0.22±0.01

Table 9: *Ex-vivo* drug release profile of control zidovudine patch formulations.

Time (hrs)	Cumulative % drug release
	TPS
1	9.72±0.51
2	16.33±0.96
3	18.77±0.48
4	27.01±0.89
5	30.67±1.03
6	38.37±0.65
7	43.75±0.56
8	67.42±1.51

Note: All the values are expressed as mean ± SD, n=3

Table 10: flux of control formulation.

Formulation code	Flux (µg/cm2/hr)
TPS	381.15

Table 11: *Ex-vivo* drug release kinetics of optimized formulations.

Formulation code	r^2				*n*	Drug transport mechanism
	Zero	First	Higuchi	Peppas		
TPS4	0.979	0.987	0.927	0.959	0.815	Anomalous transport

Table 12: Stability study data.

Parameters	Formulation code	Initial	After 15 days	After 1 month
Folding endurance	TPS4	154	150	143
Drug content (%)	TPS4	97.05	96.23	93.02

studies, the results shown (Table 12) that there were no major changes in drug content. Hence the formulation was found to be stable.

CONCLUSION

Zidovudine transdermal patches were successfully prepared by solvent casting method using different natural and synthetic polymers using permeation enhancers and various concentrations of the same were optimized. Drug excipient compatibility studies concluded that the drug and excipient are compatible with each other. Formulations containing 4% Eudragit RL 100 and 1% HPMC (TPS4) were optimized among transdermal patch formulations containing synthetic polymers.

The prepared patches were evaluated for physico-chemical parameters to justify their suitability for transdermal use. About 67.42% of drug release was observed for TPS without permeation enhancer whereas for TPS4 patche containing t-anethole as permeation enhancer, drug release at the end of 8h was found to be 93.21%. This clearly shows the effect of permeation enhancer, t-anethole along with plasticizer propylene glycol (which is also a permeation enhancer) in the formulation in enhancing drug release.

Ex vivo studies indicated that formulations TPS4 shown better release of zidovudine for 8 hrs with flux and 614.05µg/cm2/hr. Skin irritation studies were performed and it indicated that the control and optimized patches did not cause any skin irritation. The optimized patch formulations were found to be stable for one month at room temperature.

Future Scope

Further studies are recommended to prove its therapeutic utility in animals by conducting pharmacokinetic and pharmacodynamics studies.

ACKNOWLEDGEMENT

The authors are thankful to principal and management of G. Pulla Reddy College of Pharmacy, Hyderabad for providing facilities to conduct our research.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

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Article History: Submission Date : 09-03-2020; Revised Date : 03-05-2020; Acceptance Date : 01-06-2020.
Cite this article: Mamatha J, Gadili S, Pallavi K. Formulation and Evaluation of Zidovudine Transdermal Patch using Permeation Enhancers. J Young Pharm. 2020;12(2)Suppl:s45-s50.