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Fabrication and evaluation of matrix diffusion controlled transdermal patch of zidovudine

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ABSTRACT

The purpose of the work was to formulate and evaluate the matrix transdermal patches of Zidovudine for the controlled delivery of the drug in the body. The patches were prepared by the solvent evaporation technique using oleic acid as a permeation enhancer and PEG 400 as plasticizer. These patches were prepared in different drug and polymer (Zidovudine, HPMC, EC, Eudragit RL 100, sodium alginate and PVP) ratios with permeation enhancers and plasticizer. The drug-polymer interaction was investigated by FT-IR and the results indicated no incompatibility. Zidovudine patches were evaluated for various parameters like thickness, folding endurance, percentage moisture loss, percentage moisture absorption, drug content uniformity, in vitro diffusion studies using Franz diffusion cell in Phosphate Buffer pH 7.4 for 10 hrs. The results of the preliminary trials indicate the drug-polymer ratio affected the characteristics of the patches. The formulation 3 ratio 10: (9:1) of Zidovudine: Ethylcellulose patch with permeation enhancer oleic acid showed best result among all formulations.

Keywords: Zidovudine, transdermal, Franz diffusion

INTRODUCTION

Transdermal drug delivery is the non-invasive delivery of medications from the surface of skin-the largest and most accessible organ of human body- through its layers, to the circulatory system. TDDS offers many advantages over conventional injection and oral methods. It reduces the load that the oral route commonly places on the digestive tract and liver. Designing and development of transdermal patches can be described as state of the art [1].

The current transdermal delivery systems have evolved as a successful alternative to systemic drug delivery. Compared to oral dosage forms, these systems offer not only improved patient compliance, but also superior uniformity of drug concentrations in plasma throughout their duration of use. Most transdermal patches are designed to release the active ingredient at a zero-order rate for a period of several hours to days following application to the skin [2].

Recently there has been an increasing awareness that the benefits of intravenous drug infusion can be closely duplicated, without its potential hazards, by continuous transdermal drug administration through skin [3].

The annual number of AIDS deaths can be expected to increase for many years to come, unless more effective and patient compliant anti-retroviral medications are available at affordable prices. The major drawbacks of anti retroviral drugs for the treatment of AIDS are their adverse side effects during long-term therapy, poor patient compliance and huge cost of the therapy [4].

Zidovudine is the FDA approved drug for clinical use for the treatment of HIV infection, AIDS and AIDS-related conditions either alone or combination with other antiviral agents. However, patients receiving zidovudine frequently develops anemia and leucopenia. The side effects of zidovudine are dose dependent and a reduction of the total administered dose reduces the severity of the toxicity [5].

The aim of this present work is to formulate a transdermal patch of Zidovudine using various polymers. Transdermal patches were prepared with the aim to reduce first pass metabolism and thereby increasing the bioavailability of the drug. It also reduces the frequency of dosing which in turn improve patient compliance and reduce fluctuation in plasma drug levels.

MATERIALS AND METHODS

Materials

Zidovudine was obtained as a gift from Aurobindo Pharma Pvt Ltd., India. HPMC K4M was obtained as gift sample from Colorcon Asia Pvt. Ltd., Mumbai, India. Ethyl cellulose was gifted by Maan Pharmaceuticals Ltd., Ahmedabad, India. Eudragit RL 100, was obtained as gift from Mission Pharma Ltd, Indore, India. Sodium Alginate was obtained as a gift sample from Loba Chemie Pvt. Ltd., Mumbai. PEG 400 was gifted by S.D. Fine chemicals, Mumbai. Oleic acid was gifted by Sigma Chemicals Ltd., Ahmedabad, India. All other chemicals are of either analytical or Pharmacopoeial grade.

FABRICATION OF TRANSDERMAL PATCHES [6, 7, 8, 9]

The membrane type transdermal patches containing Zidovudine prepared using different ratios of HPMC, Ethyl cellulose, Eudragit RL 100, sodium alginate with PVP. The polymers were dissolved in suitable solvent in required amount mixed well by using magnetic stirrer. Zidovudine was added slowly to the polymer solution and mixed thoroughly to obtain uniform solution. PEG 400 is used as plasticizer and oleic acid is used as permeation enhancer. The polymeric solution was poured into Petri plate placed in a level, hard rigid surface. Solvent evaporation was controlled by covering with placement of funnel in its inverted position. After 24 hrs the films were removed and kept in desiccators. These films were wrapped in aluminium foil packed in self sealing cover and kept in desiccators. The composition of various formulations was given in the following table.

Table-1: Fabrication of Zidovudine Matrix Transdermal patches

Ingredients	F1 10: (9:1)	F2 10: (8:2)	F3 10: (9:1)	F4 10: (8:2)	F5 10:(9:1)	F6 10:(8:2)	F7 10:(9:1)	F8 10:(8:2)
Zidovudine	100	100	100	100	100	100	100	100
HPMC	90	80						
Ethyl cellulose			90	80				
Eudragit L 100					90	80		
Sod. Alginate							90	80
PVP	10	20	10	20	10	20	10	20
PEG 400 (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Oleic acid (ml)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

RESULTS AND DISCUSSION

COMPATIBILITY STUDY OF DRUG AND THE POLYMER [10]

FTIR absorption spectra: 2 mg of the substance being examined was triturated with 300mg to 400mg of finely powdered and dried potassium bromide. This quantity was usually sufficient to give a disc of 13 mm diameter and a spectrum of suitable intensity. The mixture was grinded carefully, spread it uniformly in a suitable die, and submit in a *vacuo* to a pressure of about 800 Mpa (8t.cm⁻²). The same product was repeated for the polymer and the physical mixture of drug and the polymers.

Fig. 1: FT-IR of pure Zidovudine

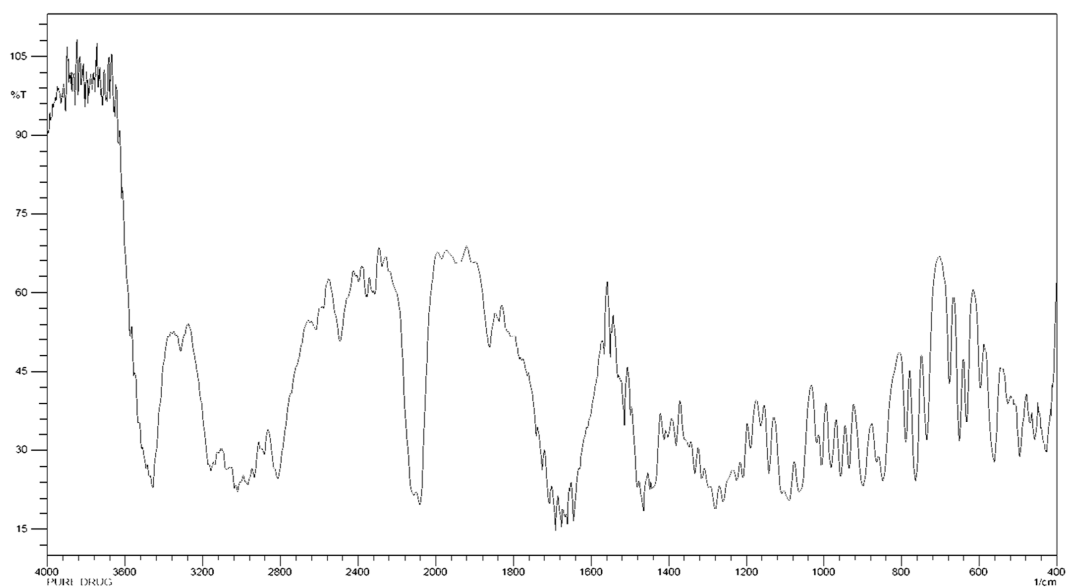
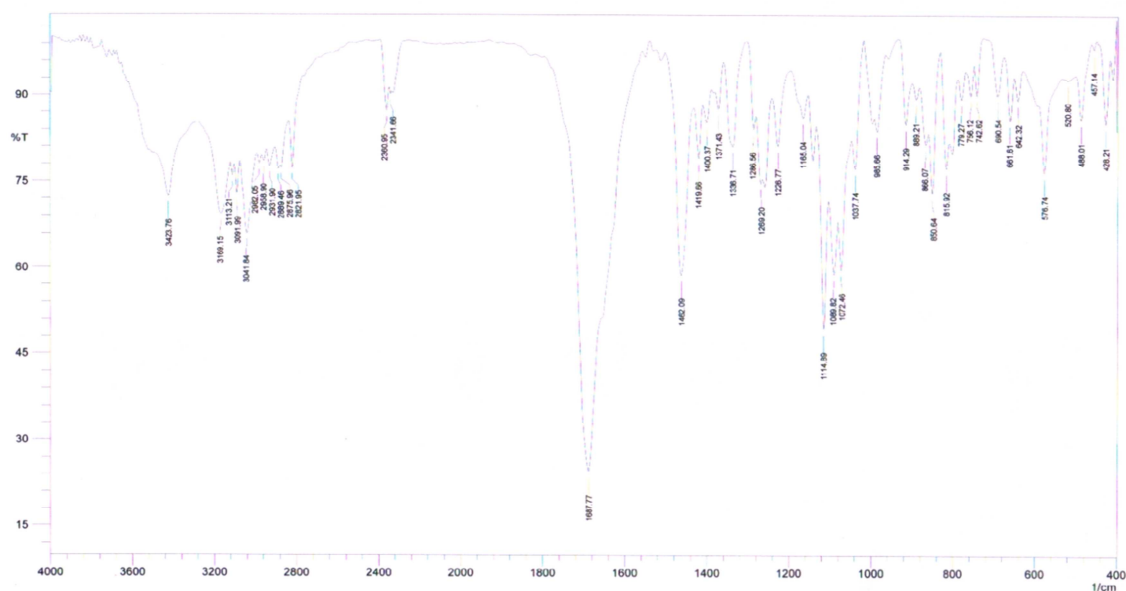


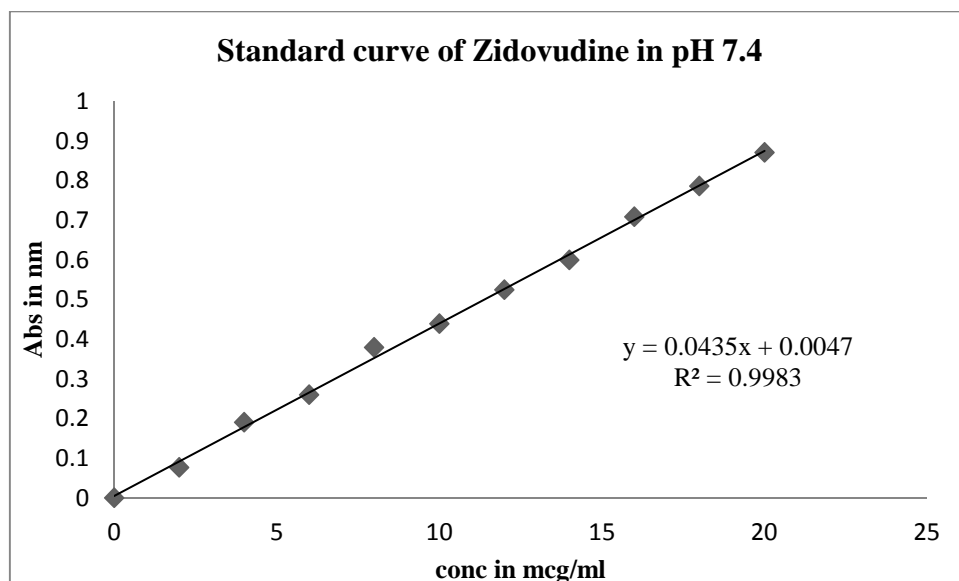
Fig. 2 FT-IR of Zidovudine + Ethyl Cellulose +PVP



Calibration curve for Zidovudine

Standard Curve of Zidovudine in Phosphate Buffer 7.4 was determined by plotting absorbance (nm) versus concentration ($\mu\text{g/ml}$) at 267 nm and it was found to follow the Beer's law in the range 2-20 $\mu\text{g/ml}$. The results obtained are as follows:

Fig. 3: Standard Calibration Curve of Zidovudine in Phosphate Buffer pH 7.4



PHYSICOCHEMICAL EVALUATIONS OF THE TRANSDERMAL PATCHES [7, 11, 12, 13, 14, 15, 16]

Thickness of the patch

Thickness of the patch was measured by using 'Screw gauge' in mm.

Folding endurance

The folding endurance was measured manually for the prepared film. A strip of film was cut evenly and 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.

Weight variation

The study was carried out by taking the weight of randomly selected five films from each batch with the help of electronic balance. The average weight of a film was calculated.

Percentage of moisture absorbed

To check the physical stability of the film in high humidity condition, accurately weighed film were placed in a desiccators containing saturated solution of Aluminium chloride (79.5% relative humidity) for 3 days. The films were reweighed and percentage moisture absorption was calculated using the formula.

$$\text{Percentage moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percentage of moisture lost

To check the extent of moisture loss from freshly prepared film, accurately weighed films were placed in a desiccator containing fused anhydrous calcium chloride for 72 hrs. After 72 hrs, the films were reweighed and percentage moisture loss was calculated using the formula.

$$\text{Percentage moisture lost} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Drug content uniformity

The prepared patch was cut into small pieces and put into 100 ml dissolution or diffusion medium used respectively and stirred continuously using a mechanical stirrer and sample was withdrawn at the end of three hours and the drug content was determined, spectrophotometrically at 267 nm.

In-vitro drug diffusion studies [17, 18, 19]

The in-vitro diffusion studies were performed by using Franz diffusion cell with a receptor compartment capacity of 20 ml. The egg membrane was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were cut and placed over the drug release membrane and the receptor compartment of the

diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm. The sample of 2 ml were withdrawn at the time interval of 1 hr to 10 hrs and analyzed for drug content spectrophotometrically at 267 nm.

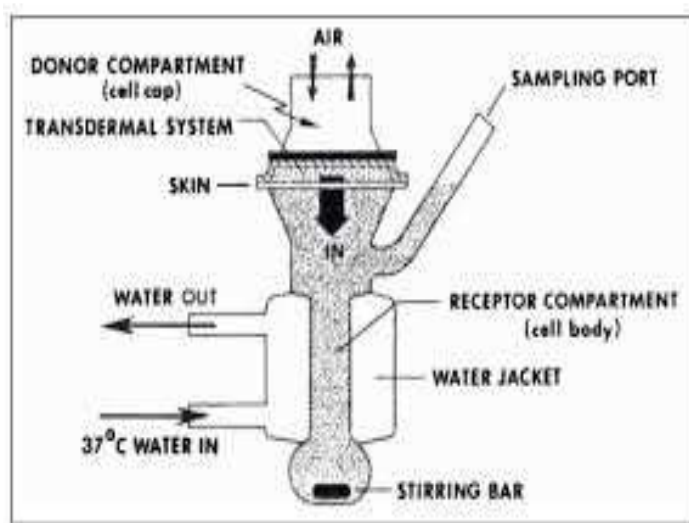


Fig 4: Modified Franz diffusion cell

The following table shows the physicochemical evaluation like the thickness, weight variation, folding endurance, percentage moisture absorbed, percentage moisture lost, drug content uniformity, and in-vitro % drug diffusion studies.

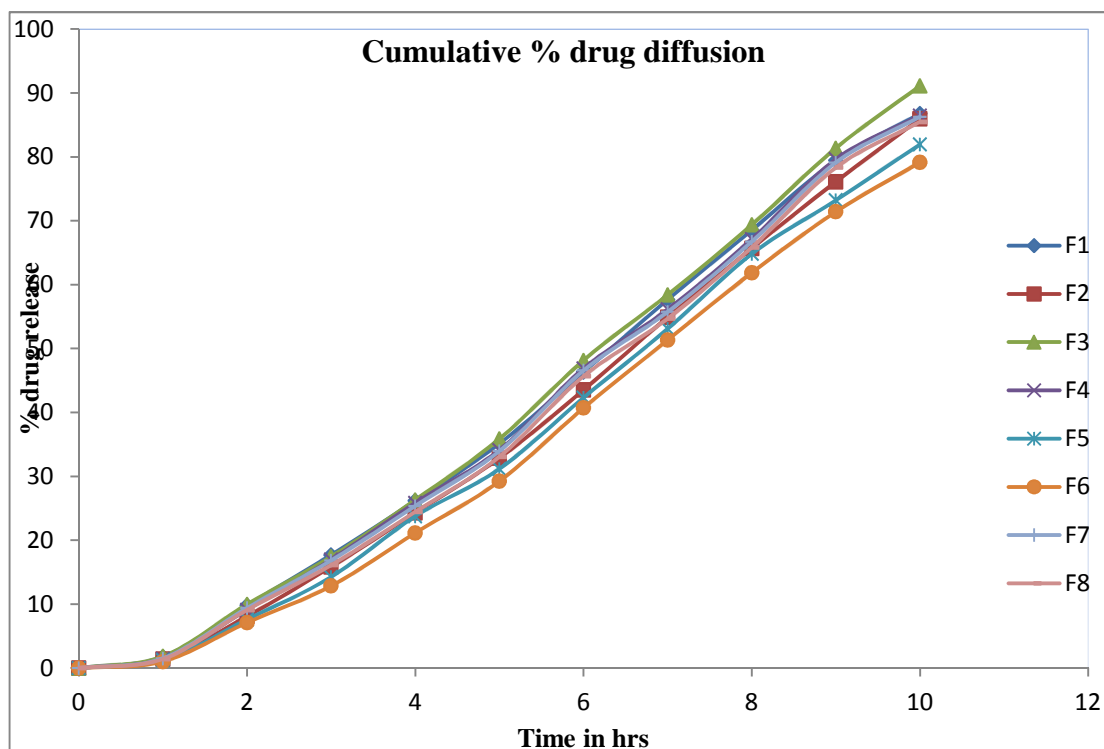


Fig. 5 Cumulative % drug diffusion

Table 2: Physicochemical Evaluation of the prepared Transdermal patches

F. Code	Thickness (mm)	Weight variation (mg/cm ²)	Folding endurance	% Moisture absorbed	% Moisture lost	Drug Content (%)	% Drug diffusion in 10 hrs
F ₁	0.71	11.41	9	2.48	1.08	97.7	86.77
F ₂	0.78	11.21	11	2.35	1.01	96.3	85.96
F ₃	0.75	11.37	10	1.85	1.06	99.1	91.11
F ₄	0.83	11.19	13	1.72	1.03	98.2	86.48
F ₅	0.18	7.62	12	1.83	0.67	98.4	81.96
F ₆	0.17	7.84	13	1.71	0.64	98.6	79.15
F ₇	0.19	8.39	10	1.79	0.68	97.3	67.79
F ₈	0.22	8.47	12	1.68	0.66	97.1	66.13

CONCLUSION

In this study, the zidovudine patches were prepared by various combinations of HPMC, EC, ERL, PVP, Sodium alginate and EC polymers. The reasons for choosing these polymers were their ease of preparation with solvent evaporation method and the release modifying characteristics of these polymers. All the films prepared had various degree of sustained release effect on the in vitro release of Zidovudine. However, by using only Ethylcellulose and PVP polymer in the patches, cumulative released amounts of drug were highest (F3). This could be attributed to the hydrophilic nature and swelling of polymer. Zidovudine released rapidly from ethyl cellulose and PVP patch than the other patches because pores of the polymer should have expanded by swelling effect. Thus, it was thought that the films prepared with ethylcellulose and PVP polymers in the ratio of 1:(9:1) had better release properties and can be improved in further studies for transdermal delivery either by using permeation enhancers or combining these polymer with suitable alternative polymer which could be prepared with solvent evaporation method.

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