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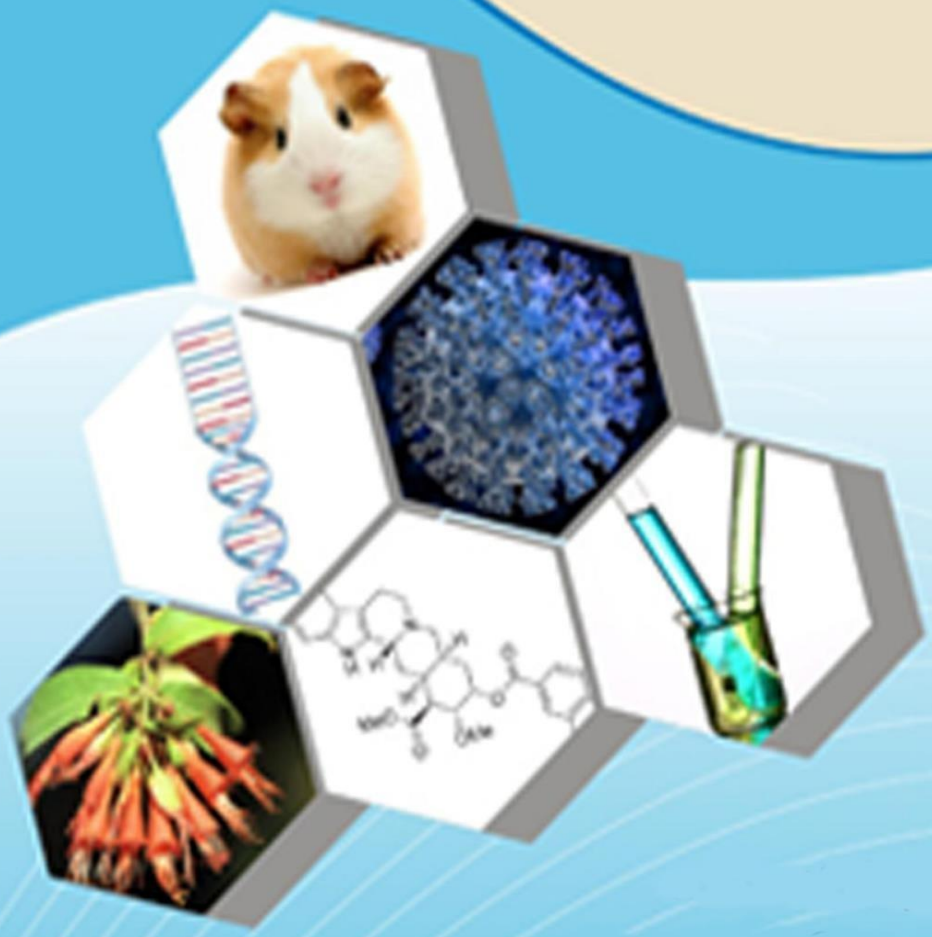

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FORMULATION AND EVALUATION OF ZIDOVUDINE TRANSDERMAL PATCHES

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ABSTRACT

The objective of present study was to develop matrix type transdermal therapeutic systems of Zidovudine using various such as sodium alginate, HPMCK5M and Ethyl cellulose polymers as matrix formers. Results revealed that prepared patches showed good physical characteristics and no drug-polymer interaction was observed. The in vitro release study revealed that F2 formulation showed maximum release in 8 hrs. Formulation F2 was subjected for accelerated stability studies. The F2 formulation was found to be stable as there was no drastic change in the Physico-chemical properties of the patches, which was also confirmed by FTIR. Thus, conclusion can be made that stable transdermal patches of Zidovudine has been developed. F2 formulation showed highest cumulative percentage drug release of 99.32% were obtained during in vitro drug release studies after 8 hrs. The release of Zidovudine appears to be dependent on lipophilicity of the matrix. Moderately lipophilic matrices showed best release. The predominant release mechanism of drug through the fabricated matrices was believed to be by diffusion mechanism. Based upon the in vitro dissolution data the F2 formulation was concluded as optimized formulation.

KEYWORDS: Zidovudine sodium alginate, HPMCK5M and Ethyl cellulose, solvent casting technique, in vitro drug release studies.

1. INTRODUCTION

Innovation in the pharmaceutical industry has centered around isolation and synthesis of new chemical entities. Only during the last decade we have seen emphasis placed once again on development of the dosage form, which is the physical-chemical form for administering a medicine, and we have seen the emergence of a new class of drug dosage forms that are specified by their rate and duration of drug release.[1,2] One category of such dosage forms is transdermal therapeutic system. (Others include oral, opthalmic. implatable, intranasal etc.). Transdermal drug administratino refers to the topical application of agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. Several technologies have been successfully developed to provide rate controlled transdermal delivery of drugs. Transdermal drug delivery system (TDDS) is mostly renowned as one of the most effective, appealing as well as reliable drug delivery systems. A transdermal patch is defined as a medicated adhesive patch which is placed above the skin to deliver a specific dose of medication through the skin with a predetermined rate of release to reach into the bloodstream. Delivery of drugs through the skin has been an attractive as well as a challenging area for research. Over the last two decades, transdermal drug delivery had become an appealing and patience acceptance technology as it is minimized and avoids the limitations associated with conventional as well as parenteral route of administration such as fluctuation in plasma drug concentration, pain and inconvenience of injections, and the limited controlled release options of both.[3,4,5,6] Despite early successes in transdermal patches collectively involve a relatively small portion of available dosage forms, the challenges for patch development are such as attaining sufficient skin permeability to match dose requirements, attaining optimal adhesive performance, and avoiding skin irritation upon patch application to the site. These hurdles must be overcome for the development of an efficacious transdermal delivery system.[7] The purpose of this study was to develop formulations and systematically evaluate in-vitro diffusion studies of transdermal patches of Zidovudine using different polymer and chose the polymer to develop the release of drug in immediate and sustained manner. Zidovudine

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belongs to a class of drugs known as nucleoside reverse transcriptase inhibitors-NRTIs. Zidovudine is used in pregnant women to prevent passing the HIVvirus to the unborn baby. Zidovudine transdermal patches were prepared by solvent casting technique using different patch formers polymers.

2. MATERIALS AND METHODS

2.1 Materials

zidovudine was collected as a gift sample from Hetero labs, Hyderabad and various excipients were purchased from AR chemicals, Hyderabad.

2.2 METHODOLOGY

Compatibility studies of drug and polymers[8]

In the formulation of Zidovudine patch formation, API and Excipient may interact as they are in close communication with each other, which could lead to the instability of drug. FT-IR spectroscopy was employed to ascertain the compatibility between Zidovudine and the selected polymers. The pure drug and drug with excipients were scanned separately.

Formulation design

Preparation of transdermal patches[9,10]

Transdermal patches containing Zidovudine were prepared by the solvent casting evaporation technique. The drug Zidovudine was dissolved in suitable solvent. Polymers HPMC, and Ethyl cellulose were taken in a boiling tube, to this add Zidovudine drug which was previously dissolved in methanol. PEG was taken as a plasticizer, and added to the mixture and mixed well. It was set aside for 2 hours to exclude any entrapped air and was then transferred into a previously cleaned petri plate (40cm^2), drying of patches was carried out in vacuum oven at room temperature. Dried patches were packed in aluminium foil and stored in a desiccator for further evaluation.

Table-1: Formulation Design of Zidovudine Transdermal Patches.

S. No	F. code	Drug (mg)	HPMC k5M	Ethyl cellulose
1	F1	100	100	-
2	F2	100	200	-
3	F3	100	-	100
4	F4	100	-	200

Evaluation of transdermal formulation[11,12,13]

Physico- chemical evaluation

Physical appearance

All the prepared transdermal films were observed for color, clarity, flexibility, and smoothness.

Folding endurance

Folding endurance of the patches was determined by repeatedly folding at the same place till it broke. The number of times the patch could be folded at the same place without breaking is the folding endurance. This was repeated on all the patches for three times and the mean values plus standard deviation was calculated.

Thickness of the film

The thickness of each film was measured by using screw gauze. The thickness was measured at three different places on each film and the average thickness of the film was taken as the thickness of the film.

Weight uniformit

The prepared patches are to be dried at 60^{0}C for 4hrs before testing. A specified area of 4.52 cm^2 of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Drug content

The formulated transdermal films were assayed for drug content in each case. Three patches from each formulation were assayed for content of drug. Each formulation was casted in triplicate and one film from each was taken and assayed for content of drug.

Moisture absorption studies

The films were weighed accurately and placed in a desiccators containing aluminium chloride to maintain 79.50% RH. After 3 days, the films were taken out and weighed. The percentage of moisture uptake was calculated using the following formula.

$$\text{Perentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture loss studies

Three films were weighed individually and kept in a desiccator containing calcium chloride at 37^{0}C for 24 hrs. Then the final weight was noted when there was no further change in the weight of the patch. The percentage of moisture loss was calculated using the following formula.

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

***In-vitro* Drug release studies**

The *in-vitro* study of drug permeation through the Dialysis membrane was performed using a modified Franz type glass diffusion cell. The modified cell having higher capacity is (10 ml) is used to maintain sink condition. The samples were analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.

Percentage of drug release was determined using the following formula.

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$$\text{Perentage drug release} = \frac{Da}{Dt} \times 100$$

Where, Dt = Total amount of the drug in the patch
Da = The amount of drug released

Stability studies[14]

Optimized medicated films were subjected to short term stability testing. The transdermal films were sealed in aluminium foils and kept in a humidity chamber maintained at 40 ± 2 ^{0}C and 75 ± 5% RH for 1 month as per ICH guidelines. Changes in the appearance and drug content of the stored films were investigated after storageat the end of every week.

3. RESULTS AND DISCUSSION

Drug - excipient compatibility studies

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

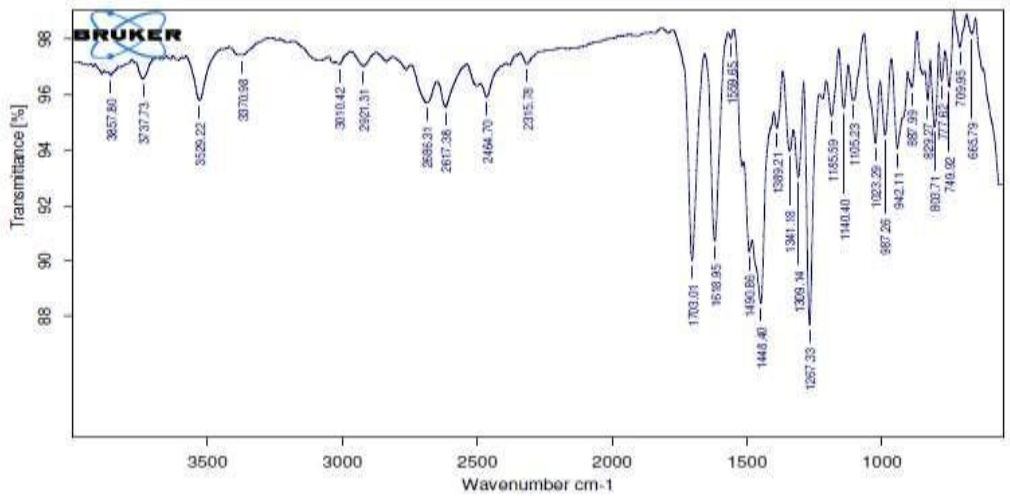

Fig. 1: FTIR spectra of pure drug.

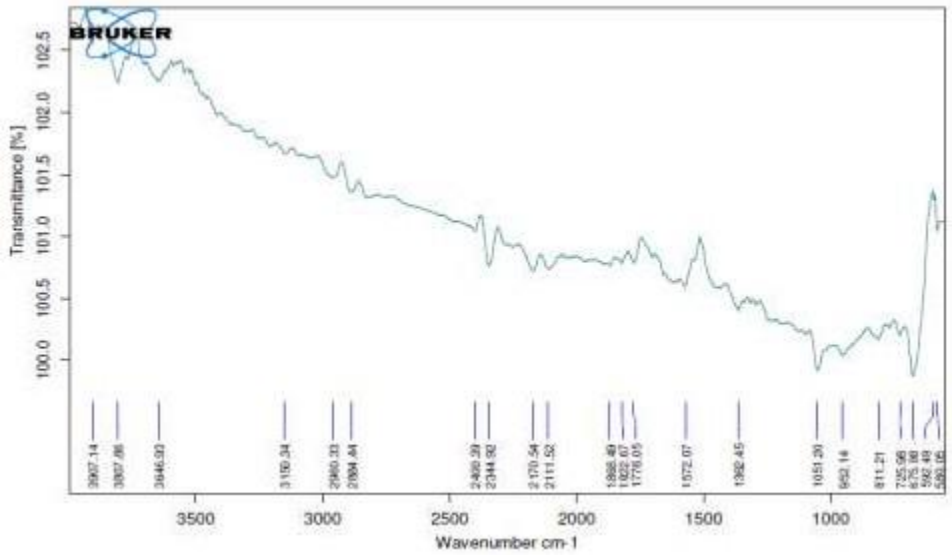

Fig. 2: FTIR Spectra of physical mixture of drug and excipients.

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of Pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks were obtained as above and as they were in official limits (±100 cm^{-1}) the drug is compatible with excipients.

Physical appearance and surface texture of Transdermal patches

These parameters were checked simply with visual inspection of patches and by feel or touch. The observation reveals that the patches are having smooth surface and they are elegant in appearance.

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Weight uniformity of Transdermal patches
The weight of the patches was determined using digital balance and the average weight of all patches.

Thickness of Transdermal patches
The thickness of the patches was measured using screw gauge and the average thickness of all patches.

Folding endurance of Transdermal patches
The folding endurance gives the idea of flexible nature of patches. The folding endurance was measured manually, patches were folded repeatedly till it broke, and it was considered as the end point. The folding endurance was found optimum and the patches exhibited good physical and mechanical properties and the average folding endurance of all patches.

Drug content uniformity of Transdermal patches
RanolazineTransdermal patches prepared with various polymers were subjected to the valuation for uniform dispersion of drug throughout the patch. In each case three patches were used and the average drug content was calculated.

% Moisture loss
The moisture content in the Transdermal patches ranged from 8.75 to 8.96%. The moisture content in the formulations was found to be increased by increase in the concentration of polymers.

%moisture absorption
The moisture absorption in the Transdermal patches ranged from 9.92 to 10.52%.

Swelling index
The swelling index in the Transdermal patches ranged from 14.58to 15.98 %.

Table 2: Physicochemical evaluation data of Zidovudine transdermal Patches.

Thickness (mm)	0.2	0.32	0.26	0.28
Weight variation (mg)	51.24	54.28	48.93	49.93
Drug content Uniformity	98.3	89.96	92.26	96.41
Folding endurance	81	83	76	77
% Moisture loss	8.86	8.93	8.78	8.96
%Moisture absorption	10.19	10.21	10.52	10.26
Swelling index	15.2	15.11	15.85	15.98

Drug release studies
Table 3: *In vitro* release data of film F_1 to F_4.

Time (hrs.)	F_1	F_2	F_3	F_4
0	0	0	0	0
1	14.90	15.58	15.80	15.56
2	26.70	25.55	26.50	25.55
3	37.89	38.55	37.70	38.25
4	48.18	48.66	44.50	47.59
5	69.75	67.55	67.65	66.55
6	76.89	80.55	71.98	78.32
7	88.86	86.99	85.32	84.28
8	91.45	95.32	88.12	92.22

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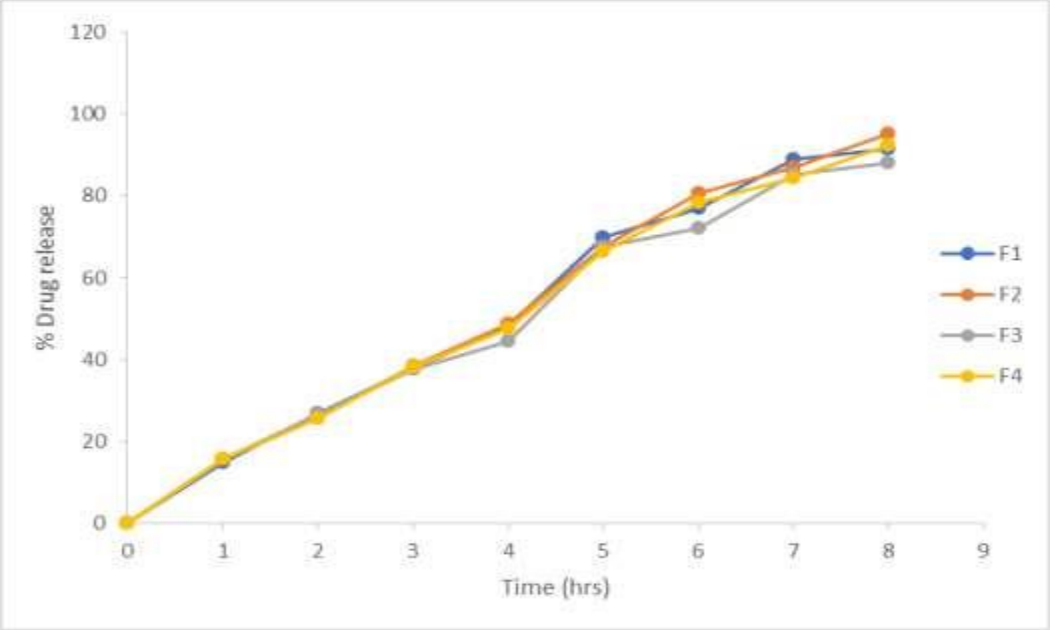

Fig. 3: In vitro drug release of (F1-F4) formulation.

Stability studies

Optimized formulations F2 was selected for accelerated stability studies as per ICH guidelines. The patches were observed for color, appearance and flexibility for a period of three months. The folding endurance, weight, drug content, % cumulative drug release of the formulation was found to be decreasing. This decrease may be attributed to the harsh environment (40^0C) maintained during the studies.

Table 4: Stability studies of optimized formulations at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months.

Formulation Code	Initial	1st Month	2nd Month	3rd Month
F2	95.32	95.20	94.74	94.35
F2	95.32	95.22	94.85	94.36
F2	95.32	95.26	94.65	94.47

4. CONCLUSION

From the obtained results, it can be concluded that, Transdermal patches of Zidovudine were formulated by solvent casting technique. The I.R spectra let out that, there was no interaction between polymers and drug. All the polymers used were compatible with the drug. Characterization parameters like thickness, tensile strength, folding endurance, percentage moisture loss indicates that films were mechanically stable. Percentage weight variation and content uniformity were found to be uniform in all the films. In-vitro drug release showed an abrupt release in the first day. There after the release profile was controlled and extended till the end of static release study, and the concentration was found to be above the minimum inhibitory concentration, which is an encouraging observation. Among the formulations, the formulated patch F_2 showed 95.32% of release. Throughout the *in-vitro* release studies, the films remained intact without any disintegration. All the patches were found to be stable over the storage period and conditions tested. Overall study suggests that among the Patch prepared F_2 was found to show the best results. Hence it was considered as optimized formulation.

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