ORIGINAL ARTICLE

Transdermal Delivery of Azilsartan: Formulation Strategies and Performance Evaluation

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Abstract

Aims: Matrix-type systems were developed in the present study by using various polymers including sodium carboxymethyl cellulose and eudragits with various concentrations. **Materials and Methods:** In the present work, an attempt has been made to develop a matrix-type transdermal therapeutic system comprising of Azilsartan with different concentrations of sodium carboxyl methyl cellulose and Eudragit using solvent evaporation technique. The physicochemical compatibility of the drug and the polymers was studied by infrared spectroscopy. **Results and Discussion:** The results obtained showed no physical-chemical incompatibility between the drug and the polymers. The *in vitro* drug diffusion studies from the formulation were found to be a sustained release effect. All the evaluation parameters obtained from the best formulation were found to be satisfactory. **Conclusion:** The data obtained from the *in vitro* release studies were fitted to various kinetic models; it was found that drug release follows the Peppas model release by diffusion technique from the polymer.

Key words: Folding endurance, Hydrophobic polymers, Permeable membrane, Permeation rate, Swelling effect

INTRODUCTION

Transdermal patches for anti-hypertension represent an innovative approach to managing high blood pressure by delivering medication directly through the skin. This method utilizes a patch that adheres to the skin, allowing for the continuous release of antihypertensive agents over an extended period.[1] One of the main advantages of transdermal delivery is its ability to provide a steady and controlled release of medication, which can lead to more stable blood pressure control and improved patient adherence. Patients may find this method more convenient than traditional oral medications, particularly those who have difficulty remembering to take pills regularly.[2]

Commonly used agents in transdermal patches include Clonidine, which works by stimulating receptors in the brain to lower blood pressure. The transdermal route can minimize some side effects associated with oral medications and can be particularly beneficial for individuals who experience gastrointestinal issues or have difficulty swallowing.[3] Overall, transdermal patches offer a promising alternative in the management of hypertension, catering to the needs of diverse patient populations while aiming for effective and sustained blood pressure control.[4]

Transdermal patches for anti-hypertension deliver medication through the skin to manage high blood pressure.[5] They provide a steady release of drugs, improving patient adherence by avoiding the need for daily oral dosing. Common active

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ingredients include Clonidine, which helps lower blood pressure by affecting certain receptors in the brain.[6]

MATERIALS AND METHODS

Preformulation studies

Construction of calibration curve

A 100 mg of Azilsartan was accurately weighed and was first dissolved in 35 mL methanol and the solution was then diluted using phosphate buffer (pH- 7.4) to 100 mL. Take 10 mL solution from the stock solution and volume make up to 100 mL with phosphate buffer to get 100 µg/mL concentrations. It was further diluted with phosphate buffer pH- 7.4 to get solutions in a concentration range of 5, 10, 15, 20, and 25 µg/mL. The absorbances of these solutions were determined spectrophotometrically[7] at 247 nm.

Fourier transform infrared spectroscopy study

The infrared spectrum of the pure Azilsartan sample was recorded and the spectral analysis was done. The dry sample of the drug was directly placed after mixing and triturating with dry potassium bromide.[8]

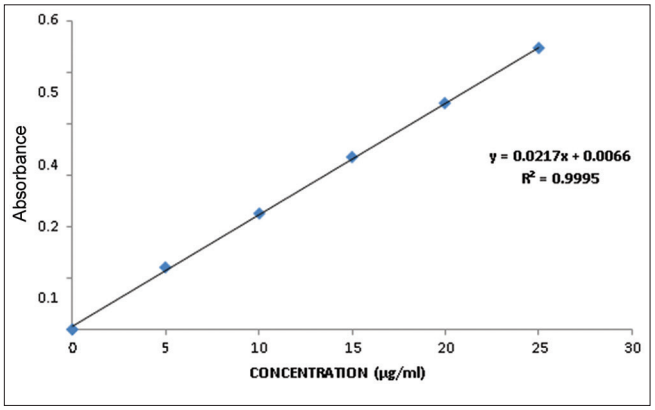

Figure 1: Standard calibration curve of Azilsartan

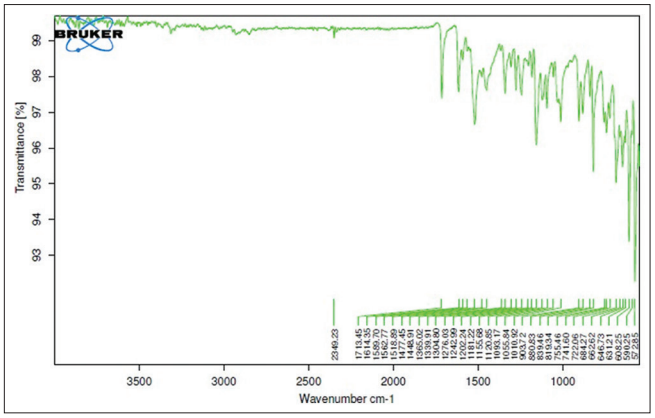

Figure 2: Fourier transform infrared spectroscopy spectrum of pure Azilsartan drug

Formulation of transdermal patches

Preparation of blank patches

Polymers of single or in combination were accurately weighed and dissolved in respective solvents and then casted in a petri dish with mercury as the plain surface. The films were allowed to dry overnight at room temperature.

Formulation of Azilsartan transdermal patches

The matrix-type transdermal patches containing Azilsartan were prepared using different concentrations of Eudragit L-100 and Eudragit S-100. The polymers in different concentrations were dissolved in the respective solvents.[8] Then the drug was added slowly into the polymeric solution and stirred on the magnetic stirrer to obtain a uniform solution. Dibutyl phthalate was used as a plasticizers.[9] Then the solution was poured on the petri dish having surface area of 78 cm[2] and dried at room temperature. Then the patches were cut into 2 × 2 cm^2 patches. Polymer incorporated Azilsartan transdermal patches compositions are given in Table 1.

Evaluation of transdermal patches

Weight variation

The three disks of 2 × 2 cm^2 were cut and weighed on an electronic balance for weight variation test. The test was

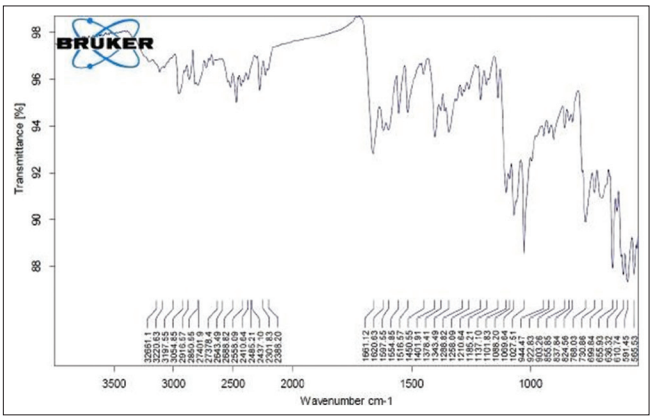

Figure 3: Fourier transform infrared spectroscopy of optimized formulation

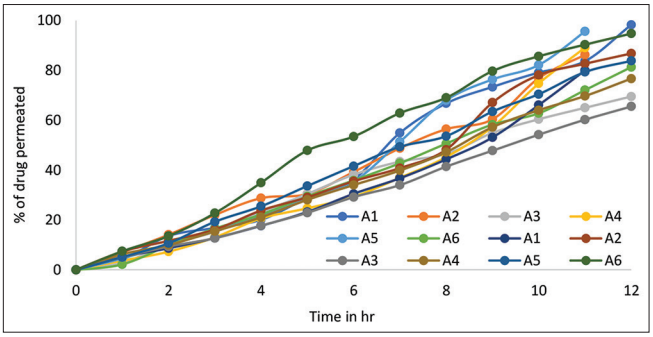

Figure 4: Cumulative % drug permeation of Azilsartan patch

Table 1: Formulation of Azilsartan transdermal patches

Ingredients	Formulation code											
	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12
Azilsartan (mg)	40	40	40	40	40	40	40	40	40	40	40	40
Sodium carboxy, methyl cellulose (mg)	100	100	100	100	100	100	100	100	100	100	100	100
Eudragit-L100 (mg)	5	10	15	20	25	30	-	-	-	-	-	-
Eudragit-S100 (mg)	-	-	-	-	-	-	5	10	15	20	25	30
Dichloromethane (mL)	8	8	8	8	8	8	8	8	8	8	8	8
Methanol (mL)	10	10	10	10	10	10	10	10	10	10	10	10
Dibutyl phthalate (in%w/v)	20	20	20	20	20	20	20	20	20	20	20	20

Table 2: Evaluation of transdermal patches

Formulation code	Average weight (mg)	Thickness (mm)	Folding endurance	Flatness (%)	Appearance	% Drug content
A1	75±1.05	0.046±0.003	81±0.15	100	Transparent	89.74±1.57
A2	78±5.36	0.049±0.008	86±1.39	99	Transparent	88.28±0.45
A3	71±2.84	0.051±0.004	85±2.26	100	Transparent	87.69±2.21
A4	75±5.41	0.041±0.009	80±1.84	100	Transparent	85.1±2.61
A5	77±9.18	0.049±0.004	82±3.10	99	Transparent	89.2±3.87
A6	79±4.69	0.041±0.007	89±2.15	100	Transparent	88.35±0.59
A7	70±9.58	0.047±0.001	84±2.36	99	Transparent	89.11±2.34
A8	76±3.86	0.045±0.009	87±2.04	100	Transparent	87.1±2.10
A9	74±7.29	0.048±0.006	82±2.96	100	Transparent	88.48±0.44
A10	79±6.85	0.043±0.001	88±4.64	99	Transparent	87.10±2.91
A11	76±8.94	0.049±0.006	83±1.72	100	Transparent	88.87±2.48
A12	78±8.49	0.047±0.005	87±2.68	100	Transparent	89.45±2.61

done to check the uniformity of weight and thus check the batch-to-batch variation.[10]

Thickness

The thickness of the films was measured by digital Vernier calipers with the least count of 0.001 mm. The thickness uniformity[11] was measured at five different sites and an average of five readings was taken with standard deviation.

Folding endurance

The folding endurance was measured manually for the prepared films. A strip of film (2 × 2 cm) was cut evenly and repeatedly 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.[12]

Drug content

The prepared drug contained patches with specified surface area (2 × 2 cm^2) were cut and dissolved in (5 mL of methanol contained) 100 mL of pH 7.4 phosphate buffer and vigorously shaked for12 h and then sonicated for 15 min, centrifuged at 5000 rpm for 30 min. Filter the drug-contained polymeric solution through 42 number Whatman filter paper, then 1 mL of the filtrate was taken in a test tube and diluted it for 5 times with the same solvent by using double beam ultraviolet (UV)-visible spectrophotometer to determine drug content at λmax 247 nm. The respected placebo patch was taken as a blank solution.[13]

Flatness

A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with a flatness study. For flatness determination, one strip is cut from the center and two from each side of the patches. The length of each strip is measured and variation in length is measured by determining percent constriction.[14] Zero percent constriction is equivalent to 100% flatness.

% constriction = I1–I2 × 100

I2 = Final length of each strip; I1 = Initial length of each strip.

In vitro diffusion study

The *in vitro* study of drug permeation through the semi-permeable membrane was performed using a franz-type glass diffusion cell.[15] The modified cell having a higher capacity (25 mL) is used to maintain Sink condition. This membrane was mounted between the donor and receptor compartment of a diffusion cell. The transdermal patch was placed on the membrane and covered with aluminum foil. The receptor compartment of the diffusion cell was filled with an isotonic phosphate buffer of pH 7.4. The hydrodynamics in the receptor compartment were maintained by stirring with a magnetic bead at constant rpm and the temperature was maintained at 32 ± 0.5°C. The diffusion was carried out for 12 h and 1 mL sample was with drawn at an interval of 1 h. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.[16-18] The samples were analyzed spectrophotometrically at 247 nm.

RESULTS AND DISCUSSION

Initially, the drug was tested by UV to know their significant absorption maximum (Figure 1) which can be used for the percentage purity of the drug. Drug and excipient compatibility performed and shown in Figures 2 and 3.

The formulations A1 varying in thickness when compared to other formulations which is due to the variation in the polymer concentration.[11] Which shows the increase in polymer concentration increases the thickness of the patch. For all formulations (Table 2), it was found to be in between 0.041 ± 0.007 and 0.051 ± 0.004 mm. All formulations from A1 to A12 shows weight variation in between 70 ± 9.58 and 79 ± 6.85 mg. Folding endurance from formulations A1 to A12 was found to be in between 81 ± 0.15 and 89 ± 2.15 which can with stand the foldings of the skin. All formulations showed % drug content from 85.1 ± 2.61 to 89.74 ± 1.57.

All the formulation *in vitro* diffusion study[19] was carried out by using Franz-type diffusion cell under specific conditions such as temperature maintained at 32 ± 0.5°C. The diffusion was carried out for 12 h and 1 mL sample was withdrawn at an interval of 1 h.

The formulations A1 to A6 were prepared by different concentrations of sodium carboxymethylcellulose and Eudragit-L100 (5, 10, 15, 20, 25, 30) in a 2 × 2 cm^2 patch, the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. At low polymer concentration, the drug permeation is more within 12 h it was the total amount of drug that was permeated. The 5 mg concentration of polymer was showed the maximum drug released at 12 h 98.29%. Hence in that 6 formulations, A1 formulations showed total drug release at the desired time period. The formulations A7 to A12 were prepared by different concentrations of sodium carboxymethylcellulose and Eudragit-S100 (5, 10, 15, 20, 25, 30) in a 2 × 2 cm^2 patch the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. The 5 mg (A7) concentration of polymer was showed a maximum drug release of 79.99 within 12 h. The 10 mg (A8) concentration of polymer was showed the maximum drug released at 12 h 86.78%. The 15 mg (A9) concentration of polymer was showed less drug release 62.15 at 12 h. The 20 mg (A10) concentration of polymer was showed the maximum drug released at 12 h 76.69%. The 25 mg (A11) concentration of polymer was showed the maximum drug released at 12 h with 83.80%. The 30 mg (A12) concentration of polymer was showed the maximum drug released at 12 h 94.75%. Hence in that 6 formulations, A12 formulations showed total drug release at the desired time period. Among all 12 formulations, the A1 formulation showed good drug permeation from the patch. Among all *in vitro* evaluation parameters, the A1 formulation passed all evaluation parameters.[20]

CONCLUSION

This study aims to design and develop Azilsartan patches for hypertension treatment using various polymers through the solvent evaporation technique and mercury substrate method. Azilsartan was successfully formulated as transdermal patches, which prevents the frequency of administration and gives good patient compliance. From the experimental results obtained, the A1 formulation has been selected as the best formulation among all the other formulations (Figure 4). The *in vitro* drug diffusion studies from the formulation were found to be sustained release. All the evaluation parameters obtained from the best formulation were found to be satisfactory. The data obtained from the *in vitro* release studies were fitted to various kinetic models, such as zero order, first order, Higuchi model, and Pappas model. From the kinetic data, it was found that drug release follows the Peppas model release by diffusion technique from the polymer. Based on the observations, it can be concluded that the attempt of formulation and evaluation of the Azilsartan patches was found to be successful in the release of the drug for an extended period of 12 h.

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