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Research

Formulation and biopharmaceutical evaluation of a transdermal patch containing letrozole

Posina Rakshitha*[1], B. Deekshi Gladiola [1], Dr. Cheepurupalli Prasad[1]

[1]Department of Pharmaceutics, Pydah College of Pharmacy Patavala, Andhra University, Kakinada, Andhra Pradesh, India

*Author for Correspondence: Posina Rakshitha
Email: posinarakshitha1@gmail.com

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Abstract

The skin can be used as the site for drug administration for continuous transdermal drug infusion into the systemic circulation. For the continuous diffusion penetration of the drugs through the intact skin surface membrane-moderated systems, matrix dispersion type systems, adhesive diffusion controlled systems and micro reservoir systems have been developed. Various penetration enhancers are used for the drug diffusion through skin. In matrix dispersion type systems, the drug is dispersed in the solvent along with the polymers and solvent allowed to evaporate forming a homogeneous drug-polymer matrix. The results obtained showed no physical-chemical incompatibility between the drug and the polymers. L5 formulation has been selected as the best formulation among all the other formulations. 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 like zero order, first order, Higuchi model and peppas model. From the kinetic data it was found that drug release follows Zero order kinetics model release by diffusion technique from the polymer.

Keywords: Letrozole, Transdermal drug delivery.

INTRODUCTION

Controlled drug delivery

Treatments of acute and chronic diseases have been accomplished by delivery of drugs to patients using various pharmaceutical dosage forms. These dosage forms are known to provide a prompt release of drug. But recently several technical advancements have been done and resulted in new techniques for drug delivery. These techniques are capable of controlling the rate of drug release.

The classification of controlled drug delivery can be given as follows.

1. Rate-preprogrammed drug delivery systems
2. Activation-modulated drug delivery systems
3. Feedback-regulated drug delivery systems
4. Site-targeting drug delivery systems

Out of these classes first class contains new drug delivery systems as transdermal delivery, intra uterine delivery, ocular inserts, and sub dermal implants. The transdermal drug delivery has advantage to deliver medicines via skin to systemic circulation at a predetermined rate and maintain therapeutic concentration for prolong period of time.

Transdermal drug delivery: An Introduction

The idea of delivering drugs through skin is old, as the use is reported back in 16th century B.C. Today the transdermal drug delivery is well accepted for delivering drug to systemic circulation. Until recently, the use of transdermal patches for pharmaceuticals has been limited because only a few drugs have proven effective delivered through the skin typically cardiac drugs such as nitroglycerin and hormones such as estrogen. Transdermal therapeutic systems are defined as self-contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation.

The first Transdermal drug delivery (TDD) system, Transderm-Scop developed in 1980, contained the drug Scopolamine for treatment of motion sickness. The Transdermal device is a membrane-moderated system. The membrane in this system is a microporous polypropylene film. The drug reservoir is a solution of the drug in a mixture of mineral oil and polyisobutylene. This study release is maintained over a one-day period. Non-medicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists of two major sub-categories — therapeutic and cosmetic), aroma patches, and weight loss patches, and patches that measure sunlight exposure. Transdermal drug delivery has many advantages over conventional drug delivery and can be discussed as follows.

Structure of skin

An average adult skin has a surface area of approximately 2 square meters and receives about one third of the blood circulating through the body. It is one of the most readily accessible organs of the human body with a thickness of only a few millimeters (2.97+/-0.28 mm). Its major roles are to regulate body temperature, protect tissues from infection, prevent fluid loss, and cushion internal structures.

The skin is a multilayered organ composed of many histological layers. It is generally described in terms of three major tissue layers.[6,9,10.]

- **The epidermis** – thin protective outer layer.
- **The dermis** – the tough elastic second layer.
- **The hypodermis** – layer of fatty and connective tissue.

The Epidermis

The outer (epidermal) layer of the skin is composed of stratified squamus epithelial cells. The multilayered envelope of the epidermis varies in thickness, depending on cell size and then number of cells and then number of cell layers, ranging from about 0.8mm on the palms and the soles down to 0.66mm on the eyelids. Cells which provide epithelial tissue differ from those of all other organs provide epithelial tissue differ from those of all other organs in that as they change in an ordered fashion from metabolically active and dividing cells to dense, dead, keratinized protein.

Stratum germinativum (basal layer)

The basal cells are nucleated, columnar, and about 6 microns wide, with their long axis at right angles to the dermoepidermal junction; they connect by cytoplasmic intercellular bridges. Mitosis of the basal cells constantly renews the epidermis and this proliferation in healthy skin balances the loss of dead horny cells from the skin surface. The epidermis thus remains constant in thickness. Below the basal cell layer lies the complex dermoepidermal junction, which constitutes an anatomic functional unit. The junction serves three functions of dermal-epidermal adherence, mechanical support for the epidermis, and control of the passage of cells and some large molecules across the junction.

Stratum spinosum (prickle cell layer)

As the cells produced by the basal layer move outward, they alter morphologically and histochemically. The cells flatten and their nuclei shrink. These polygonal cells are called as prickle cells because they interconnect by fine prickles.

Stratum granulosum (granular layer)

As the Keratinocytes approach the surface, they manufacture basic staining particles, the keratohyalin granules. It was suggested that these granules represent an early form of keratin 3, 4. The term transitional zone is convenient region between living cells and dead keratin.

MATERIALS

Letrozole-Procured From Sigma Laboratories Bangalore, India. Provided by SURA LABS, Dilsukhnagar, Hyderabad, HPMC K100 M-Hetero Labs.Hyderabad,India, Polyvinyl Alcohol-Hetero Labs.Hyderabad,India , Polyvinylpyrrolidone-Accord labs, Secunderabad, PEG-200(ml)-Merck Specialities Pvt Ltd, Dimethylsulphoxide(ml)-Merck Specialities Pvt Ltd, Methanol(ml)-Merck Specialities Pvt Ltd.

METHODOLOGY

Analytical method development

UV scan

A 100mg of Letrozole was accurately weighed and was first dissolved in 35ml methanol solution. The solution was then diluted using phosphate buffer (pH- 7.4) to 100 ml. (stock solution-I). Take 10ml solution from stock solution 1 and volume make up to 100ml with phosphate buffer to get 100 µg/ml concentrations (stock solution-II). Take 10 ml solution from stock II and volume make up to 100 ml with buffer to get 10 µg/ml. 10 µg/ml solution was scanned from 200-400nm.

Construction of calibration curve

A 100mg of Letrozole was accurately weighed and was first dissolved in 35ml methanol solution. The solution was then diluted using phosphate buffer (pH- 7.4) to 100 ml. (stock solution-I). Take 10ml solution from stock solution 1 and volume make up to 100ml with phosphate buffer to get 100 µg/ml concentrations (stock solution-II). It was further diluted with phosphate buffer pH – 7.4 to get solutions in concentration range of 2,4,6,8 and 10 µg /ml. The absorbances of these solutions were determined spectrophotometrically at 235 nm.

Preformulation study

Colour, Odour, Taste and Appearance: The drug sample was evaluated for its Colour, Odour and Appearance.

Melting point determination: Melting point of the drug sample was determined by capillary method by using melting point apparatus.

Determination of solubility: The solubility of Letrozole was determined by adding excess amount of drug in the solvent.

The Letrozole has very low aqueous solubility. Its solubility is not reported in any official book, so determination of solubility is important. The solubility was determined in distilled water and phosphate buffer pH 7.4. The procedure can be detailed as follows. Saturated solution of Letrozole prepared using 10 ml. of distilled water/ phosphate buffer pH 7.4 in 25 ml volumetric flasks in triplicate. Precaution was taken so that the drug remains in medium in excess. Then by using mechanical shaker, the flasks were shaken for 48 hours. The sample withdrawn (1ml after filtration) was diluted with appropriate medium and analyzed by using UV spectrophotometer at 235nm and 245 nm for phosphate buffer and distilled water respectively.

Formulation of transdermal patches

Preparation of blank patches

Polymers of single or in combination were accurately weighed and dissolved in respective solvent 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 Drug Incorporated Transdermal Patches

The matrix-type transdermal patches containing Letrozole were prepared using different concentrations of HPMC K100 M, Polyvinyl Alcohol and Polyvinylpyrrolidone. The polymers in different concentrations were dissolved in the respective solvents. Then the drug was added slowly in the polymeric solution and stirred on the magnetic stirrer to obtain a uniform solution. PEG-200 was used as plasticizers. Then the solution was poured on the Petri dish having surface area of 78 cm2 and dried at the room temperature. Then the patches were cut into 2x2 cm^2 patches. Drug incorporated for each 2x2 cm^2 patch was 8 mg. the formulation table is given in table no. 6.1.

Table 1: Formulation of Letrozole Patches

INGREDIENTS	FORMULATION CHART								
	L1	L2	L3	L4	L5	L6	L7	L8	L9
Letrozole	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

HPMC K100 M	4.5	8.10	12.15	-	-	-	-	-	-
Polyvinyl Alcohol	-	-	-	4.5	8.10	12.15	-	-	-
Polyvinylpyrrolidone	-	-	-	-	-	-	4.5	8.10	12.15
PEG-200(ml)	8	8	8	8	8	8	8	8	8
Dimethylsulphoxide(ml)	3	3	3	3	3	3	3	3	3
Methanol(ml)	10	10	10	10	10	10	10	10	10

RESULTS AND DISCUSSIONS

Initially the drug was tested by UV to know their significant absorption maximum which can be used for the diffusion study of the drug.

Analysis of drug

UV scan

The lambda max of Letrozole was found to be 235 nm.

construction of calibration curve

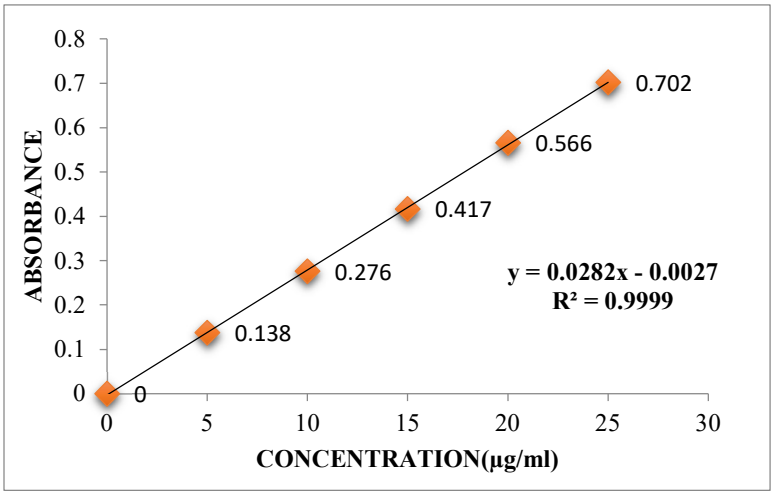

Fig 1: Standard calibration curve of Letrozole

Preformulation study

Totally, Nine formulation trials were done with the aim to achieve the successful matrix type Letrozole transdermal patches. The blend trials prepared for the drug was evaluated for various physical parameters and content uniformity of drug by UV.

Colour, odour, taste and appearance

Table 2: Results of identification tests of drug

Parameter	Letrozole
Color	White
Odor	Odorless
Taste	Bitter
Appearance	A whity powder

Melting point determination

Table 3: Results of melting point determination tests of drug

Drug	Reported melting point
Letrozole	184-185^{0}c

Determination of solubility

Table 4: Solubility Determination

solvent	Drug solubility(mg/ml)
Distilled water	0.0403
Ph 7.4 phosphate buffer	78.3

Evaluation of Patch

The formulations F1 to F9 were varying in thickness when compared to other formulations which is due to the variation in the polymer concentration. Which shows the increase in polymer concentration increases the thickness of patch. For all other formulations it was found to be in between 0.041±0.007 to 0.051±0.004 mm. All formulations from L1 to L9 shows weight variation in between 72 ±6.79 to 78 ±2.41 mg. Folding endurance from formulations L1 to L9 was found to be in between 81 ± 2.34 to 89 ± 2.15 which can withstand the foldings of the skin. All formulations showed % drug content from 96.01 ± 2.24 to 99.65 ± 2.71.

Table 5: Evaluation of patches

Formulation Code	Average weight(mg)	Thickness (mm)	Folding endurance	Flatness (%)	Flatness (%)	% Drug Content
L1	73±2.02	0.041 ±0.002	82 ± 0.14	98	Transparent	96.2 ± 2.10
L2	76 ±4.12	0.045±0.006	85 ± 2.10	100	Transparent	99.11 ± 0.45
L3	75 ±1.21	0.050±0.002	86 ± 3.17	97	Transparent	99.65 ± 2.71
L4	75 ±5.41	0.046±0.006	82 ± 3.11	98	Transparent	96.01 ± 2.24
L5	72 ±7.11	0.047±0.001	81 ± 2.34	100	Transparent	97.31 ± 3.73
L6	75 ±3.05	0.043±0.005	89 ± 2.15	99	Transparent	98.35 ± 0.59
L7	72 ±6.79	0.045±0.003	83 ± 2.36	99	Transparent	96.11 ± 1.24
L8	78 ±2.41	0.044±0.002	85 ± 2.04	100	Transparent	98.65 ± 1.57
L9	75 ±5.14	0.049±0.004	81 ± 2.96	98	Transparent	99.12 ± 2.54

***In vitro* diffusion study**

All the formulation *in vitro* diffusion study was carried out by using Franz type diffusion cell under specific condition such as temp maintained at 32 □ 0.5 °C. The diffusion was carried out for 12 h and 5 ml sample was withdrawn at an interval of 1 h.

Table 6: *In vitro* drug permeation of Letrozole containing different concentrations of HPMC K100 M

Time (hr)	L1	L2	L3	L4	L5	L6	L7	L8	L9
0	0	0	0	0	0	0	0	0	0
1	9.57	15.98	6.14	5.12	8.85	7.14	10.18	12.72	10.64
2	13.26	21.33	11.56	11.69	13.47	15.26	17.39	19.61	18.14
3	20.93	26.78	19.79	18.82	16.44	18.58	21.54	21.43	24.98
4	27.72	31.71	26.62	26.11	23.86	21.31	28.07	28.32	29.64
5	33.90	39.46	31.22	30.87	29.71	26.10	32.97	35.11	31.78
6	40.10	43.99	36.72	31.98	36.11	35.71	37.65	41.94	36.97
7	45.39	49.87	42.73	37.24	43.75	51.29	43.17	47.89	47.14
8	48.83	53.31	49.31	48.36	68.93	63.12	52.35	51.21	57.87
9	56.44	57.56	56.78	57.33	78.24	72.86	57.96	67.34	63.75
10	62.29	60.76	62.40	74.98	81.39	77.67	61.31	76.14	75.24
11	66.14	64.14	78.52	85.71	92.59	81.12	74.46	83.58	85.33
12	70.36	75.97	81.42	90.27	99.81	97.49	83.22	87.12	92.44

The formulations L1 to L3 were prepared by different concentrations of HPMC K100 M (4.5, 8.10, 12.15mg) 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 hours it was total amount of drug was permeated.

The 8.10mg concentration of polymer was showed maximum drug released at 12 hours 99.81 %. The 4.5mg concentration of polymer was showed maximum drug release 90.27 at desired time period. Hence in that 3 formulation F5 formulations showed total drug release at desired time period.

The formulations L7 to L9 were prepared by different concentrations of Polyvinylpyrrolidone (4.5, 8.10, 12.15mg) the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. The 8.10mg (L8) concentration of polymer was showed maximum drug release 87.12 within 12 hours. The 4.5mg (L7) concentration of polymer was showed maximum drug released at 12 hours 92.44%. The 12.15mg (L9) concentration of polymer was showed less drug release 75.97 at 12 h. Among all 9 formulations L5 formulation showed good drug permeation from the patch. Among all *in vitro* evaluation parameters L5 formulation passed all evaluation parameters.

Kinetic models for Letrozole

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.

Table 7: Kinetics data of L5 Letrozole patch

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	**0**	0			2.000				100	4.642	4.642	0.000
8.85	1	1.000	0.947	0.000	1.960	8.850	0.1130	-1.053	91.15	4.642	4.500	0.141
13.47	2	1.414	1.129	0.301	1.937	6.735	0.0742	-0.871	86.53	4.642	4.423	0.219
16.44	3	1.732	1.216	0.477	1.922	5.480	0.0608	-0.784	83.56	4.642	4.372	0.270
23.86	4	2.000	1.378	0.602	1.882	5.965	0.0419	-0.622	76.14	4.642	4.238	0.403
29.71	5	2.236	1.473	0.699	1.847	5.942	0.0337	-0.527	70.29	4.642	4.127	0.515
36.11	6	2.449	1.558	0.778	1.805	6.018	0.0277	-0.442	63.89	4.642	3.998	0.644
43.75	7	2.646	1.641	0.845	1.750	6.250	0.0229	-0.359	56.25	4.642	3.832	0.810
68.93	8	2.828	1.838	0.903	1.492	8.616	0.0145	-0.162	31.07	4.642	3.144	1.498
78.24	9	3.000	1.893	0.954	1.338	8.693	0.0128	-0.107	21.76	4.642	2.792	1.850
81.39	10	3.162	1.911	1.000	1.270	8.139	0.0123	-0.089	18.61	4.642	2.650	1.992
92.59	11	3.317	1.967	1.041	0.870	8.417	0.0108	-0.033	7.41	4.642	1.950	2.692
99.81	12	3.464	1.999	1.079	-0.721	8.318	0.0100	-0.001	0.19	4.642	0.575	4.067

Compatibility studies

IR SPECTROSCOPY

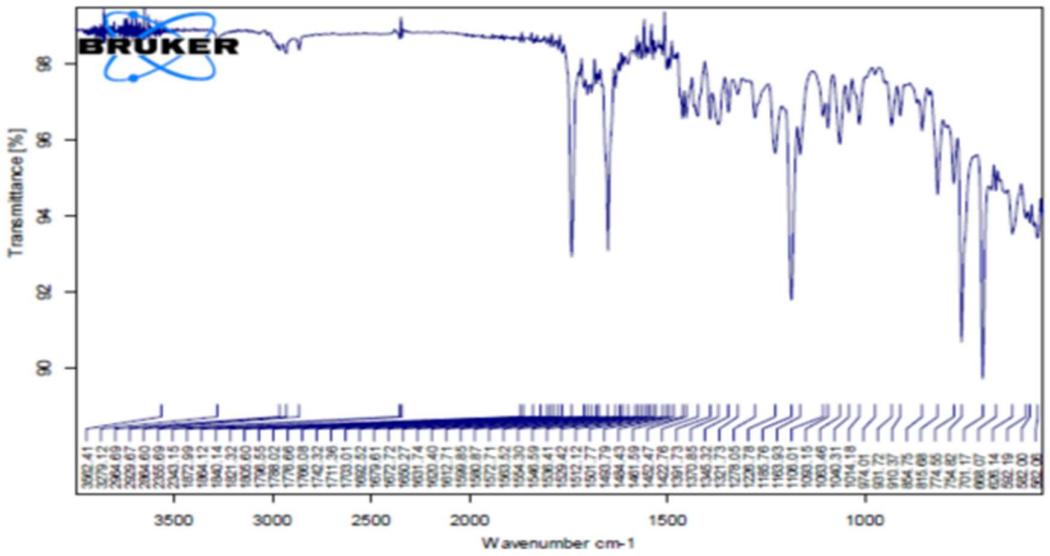

Fig 2: FTIR Spectrum of pure Letrozole drug

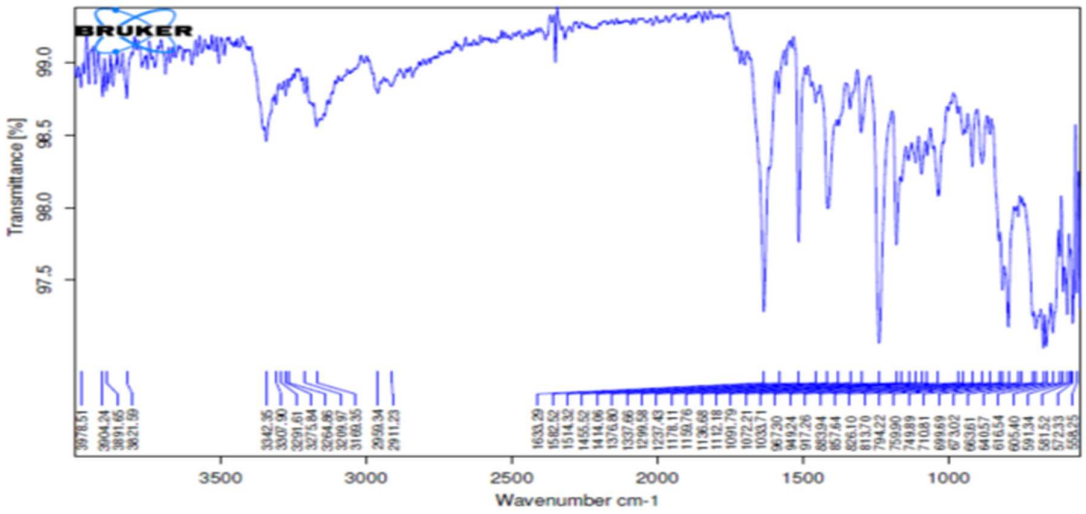

Fig 3: FTIR of Optimized formulation

The compatibility studies of the drug with excipients indicate no characteristic visual changes and no additional peaks were observed during FT-IR studies.

CONCLUSION

In the present investigation an attempt has been made to design and develop the formulation of Letrozole patches using different types of polymers by solvent evaporation technique and mercury substrate method. The drug used is the best studied for therapy in treating hormonally-responsive breast cancer after surgery. Letrozole was successfully formulated as controlled release transdermal patches, which prevents the frequency of administration and gives good patient compliance. From the experimental results obtained, L5 formulation has been selected as the best formulation among all the other formulations. 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 like zero order, first order, Higuchi model and Pappas model. From the kinetic data it was found that drug release follows Zero order 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 Letrozole patches was found to be successful in the release of the drug for an extended period of 12 hrs.

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