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Research Article

TERMINALIA ARJUNA TRANSDERMAL MATRIX FORMULATION CONTAINING DIFFERENT POLYMER COMPONENTS

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ABSTRACT

Objective: The objective of this research work was to prepare a transdermal matrix formulation containing different polymer components for topical delivery.

Methods: *Terminalia arjuna* bark extract loaded transdermal patches were prepared using solvent casting technique with different amount of chitosan and Eudragit RL 100 batches were prepared according to 3^2 factorial designs.

Results: The transdermal patches prepared were evaluated for different physicochemical properties, determination of drug content, *in vitro* diffusion study, *ex vivo* study, skin irritation study, and stability study. Infrared studies indicate the absence of chemical interaction or any changes in the chemical composition of extract during the preparation of transdermal patch. *In vitro* diffusion study and *ex vivo* diffusion study of optimized batch S3 showed drug releases to 74.56–69.12%, respectively, up to 12 h. Skin irritation study indicates that the extract and excipients used in the patch do not show any irritating effect on the skin. All the prepared transdermal matrix formulations were found to be stable on storage.

Conclusion: It can be concluded that prepared matrix formulation containing different polymer components can be used for transdermal delivery for the treatment of chronic ailments such as cardiovascular disorder.

Keywords: Chitosan, Eudragit RL 100, *Terminalia arjuna,* Transdermal.

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INTRODUCTION

Transdermal matrix system (TMS) encompasses the uniform dispersion of drug in the polymeric matrix that has a hydrophilic or hydrophobic identity. TMS has been showing an increased interest than other delivery methods, one of which is to avoid the metabolism of the first pass effect on the liver and able to deliver the drug in a controlled manner directly to the blood vessels. Transdermal administration can give local therapeutic effect as well as a systemic effect [1-3]. TMS imparts a leading advantage beyond injectables and oral routes by elevating patient compliance, minimize dosing frequency, painless, and cost effective. TMS can deliver medicines through the skin portal to systemic circulation at a predetermined rate over a prolonged period [4].

Terminalia arjuna is a deciduous and evergreen tree, which has been used in heart failure, ischemia, cardiomyopathy, atherosclerosis, myocardium necrosis, blood diseases, anemia, venereal, and viral disease. It is used in the treatment of several ailments and showed hypocholesterolemic, antibacterial, antimicrobial, antitumoral, antiallergic, antifeedant, antifertility, and anti-HIV activities. *T. arjuna* stem bark contains glycosides, ample quantities of flavonoids, tannins, and minerals [5-8]. Phytoconstituents of *T. arjuna* have been well reported to exert antioxidant, anti-inflammatory, lipid-lowering effect, and cardiotonic effect [9].

Over the past few decades, polymers such as guar gum, chitosan, carrageenans, sodium alginate, pectin, xanthan gum, gellan gum, and agar have been widely used which can be used in various ways in the formulation of targeted and controlled drug delivery systems as they have different derivatizable groups, a wide range of molecular weight, and varying chemical composition. Chitosan is a linear polysaccharide composed of randomly distributed β-(1-4) linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit) produced by the deacetylation of chitin [10]. The amino group in chitosan has a pKa value of around 6.5, which leads to a protonation in acidic to a neutral solution with a charge density dependent on pH and the degree of acetylation value which makes chitosan water soluble and bioadhesive that readily binds to negatively charged surfaces such as mucosal membranes. The properties of chitosan allow it to be used in transdermal drug delivery effectively. Eudragit RL 100 (ERL 100) is a copolymer of acrylic acid and methacrylic acid esters with a low content in quaternary ammonium groups. Presence of ammonium groups makes the polymer into salts and increases the permeability. Hence, the combination of chitosan and ERL 100 will greatly helpful for transdermal application in terms of mucoadhesive property, drug diffusion, and permeability.

To the best of our knowledge, no report is available in literature on the well-designed transdermal matrix formulation containing *T. arjuna* extract. Conventional dosage forms of *T. arjuna* such as Arjunaristh, Arjuna Ghritha, Arvindasava, tablet, and capsule used in the treatment of different cardiovascular diseases. However, they face a problem such as first-pass metabolism, gastritis, constipation, stability, and low therapeutic efficacy. To overcome this problem, an attempt was made to prepare transdermal matrix formulation containing different polymer components to ensure satisfactory drug release with the use of polymer and thereby to avoid first-pass metabolism and prolong the duration of action for the treatment of chronic ailments such as cardiovascular disorder.

METHODS

Materials

The stem bark of *T. arjuna* was collected from Sahyadri Valley, Western Maharashtra region, Kolhapur Dist. (Maharashtra, India) in the month

of August 2016 and identification was made by Dr. M. M. Lekhak, Department of Botany, Shivaji University, Kolhapur. A voucher specimen of the plant is deposited in the herbarium, Department of Botany with an accession number DTG 001. Chitosan was provided as a gift sample from Mahtani Chitosan Pvt., Ltd., Gujarat, India, and ERL 100 from Loba Chemie Pvt., Ltd., Mumbai, India, was used. All other chemicals used were of analytical grade.

Formulation of *T. arjuna* transdermal matrix system

The transdermal patches were prepared by solvent evaporation technique. The transdermal patches were composed of Chitosan:ERL100 in requisite ratio and allowed to swell for about 6 h solvent mixture (1:1 water and methanol). 2 ml glycerin was incorporated as a plasticizer and 2 ml dimethyl sulfoxide added as permeation enhancer. The extract solution was added to the polymeric solution mixed both solutions and stirred on magnetic stirrer to an accomplished homogeneous mixture. The resulting solution was poured in a Petri dish. The solvent was allowed to evaporate at 40°C for 24 h to obtain the medicated transdermal patch. The prepare transdermal patches were store in a desiccator until further use. A total of 9 batches were prepared by 3^2 factorial design as per Table 1. Composition of S1-S9 batches is depicted in Table 2.

Physicochemical compatibility

Fourier transform infrared (FTIR) spectroscopy study was conducted with the help of Shimadzu FTIR-8400S FTIR spectrometer and spectra were recorded in the range of 4000–400 cm^{-1} [11].

Evaluation of *T. arjuna* transdermal matrix system

Visual

The visual of matrix transdermal patch parameters is color, odor, texture, and film flexibility [12].

Weight variation

The weight variation five patches were weighed on an electronic balance, and the average of weight was taken [12].

Film thickness

The thickness of films was measured by micrometer screw at five different sites, and average of five readings was taken [12].

Table 1: Formulation design of transdermal matrix system

Batch code	Independent variables	
	X_1 (Chitosan)	X_2 (ERL 100)
S1	−1	−1
S2	−1	0
S3	−1	+1
S4	0	−1
S5	0	0
S6	0	+1
S7	+1	−1
S8	+1	0
S9	+1	+1

Moisture uptake

The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight [12].

Folding endurance

The folding endurance was measured manually for prepared films. A strip of film was folded at the same place till it broke. The number of times the film can be folded at the same place without breaking was the folding endurance value [13].

Drug content

A 0.1 mm thickness of the film was cut and put it into a 100 ml phosphate buffer (pH 7.4) and ultrasonicated for 15 min with a stirrer. After filtration, the drug was estimated spectrometrically at a wavelength of 276 nm and determined the drug content compared using the calibration curve of the extract [12].

***In vitro* diffusion studies**

The *in vitro* diffusion studies were carried out using a Franz diffusion (FD) cell. *T. arjuna* transdermal matrix formulation was applied on the cellophane membrane which was placed between donor and receptor compartment of the FD cell. Phosphate buffer pH 7.4 was used as a dissolution media. The temperature of the cell was maintained at 37°C by circulating water jacket. This whole assembly was kept on a magnetic stirrer, and the solution was stirred continuously using a magnetic bead. A similar blank set was run simultaneously as a control. Sample (1 ml) was withdrawn at 60 min, 240 min, 420 min, 600 min, and 720 min and replaced with equal amounts of fresh dissolution media. Samples were analyzed spectrophotometrically at 276 nm and the cumulative percentage release was calculated [14].

***Ex vivo* diffusion studies**

The *ex vivo* release study was carried out in a FD cell using skin. Male goat free from any visible sign of the disease was selected. The goat dorsal skin was brought from slaughterhouse. The dorsal hair was removed, and the skin was washed with distilled water. The dorsal skin of full-thickness was excised and adhering subcutaneous fat was removed. Epidermis facing the donor compartment was mounted on the donor compartment. Phosphate buffer pH 7.4 was used as dissolution media. *T. arjuna* transdermal matrix formulation was placed on the skin, which was previously equilibrated by soaking in phosphate buffer pH 7.4 for 24 h. The diffusion area of goat skin was 2.64 cm^2. The temperature of the cell was maintained constant at 37°C by circulating water jacket. This whole assembly was kept on a magnetic stirrer and the solution was stirred continuously using a magnetic bead. A similar blank set was run simultaneously. The samples were withdrawn at suitable time intervals and replaced with equal amounts of fresh dissolution media. Samples were analyzed spectrophotometrically at 276 nm [14].

Skin irritation studies

Institutional Ethics Committee permission was obtained as per the CPCSEA guidelines (Approval No: BVCPK/CPCSEA/IAEC/01/23) for carrying out the study on animals. The albino rats (average weight 200-250 gm) were divided into two groups (n=3). Group I received

Table 2: Composition of S1-S9 batches of the transdermal matrix system

Batches	S1	S2	S3	S4	S5	S6	S7	S8	S9
Chitosan (mg)	300	300	300	400	400	400	500	500	500
ERL 100 (mg)	300	400	500	300	400	500	300	400	500
Water: methanol (ml)	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1
Glycerin (ml)	2	2	2	2	2	2	2	2	2
DMSO (ml)	2	2	2	2	2	2	2	2	2
Extract solution									
T. arjuna extract (mg)	500	500	500	500	500	500	500	500	500
Water (ml)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

prepared *T. arjuna* transdermal matrix formulation and Group II received 0.8% v/v aqueous solution of formalin as a standard irritant. At 24 and 72 h, after test article application, the test sites were examined for dermal reactions in accordance with the Draize scoring criteria [15].

Stability studies

The prepared *T. arjuna* transdermal matrix formulations were packed in aluminum collapsible tubes and subjected to stability studies at 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH for 3 months. Samples were withdrawn at 15 day time intervals and evaluated for physicochemical properties and extract content [16].

RESULTS AND DISCUSSION

Physicochemical compatibility

The FTIR spectrum of pure extract showed characteristic peaks at 3386.094 cm^{-1} (broad, intermolecular hydrogen bonded, O–H stretch), 2933.937 cm^{-1} (C–H stretch), 1680.805 cm^{-1} (Aromatic C=O bend), 1439.529 cm^{-1} (C=C stretch), and 1282.533 cm^{-1} (C–O stretch). This characteristic peak may show the presence of alcohol and ethereal function groups, and also the presence of the aromatic ring. The FTIR spectrum of *T. arjuna* transdermal matrix formulation showed few minor shifting of peaks but no major changes. The FTIR spectrum of pure extract and formulation is depicted in Figs. 1 and 2, respectively.

Evaluation of *T. arjuna* transdermal matrix system

The results of the evaluation of various visual and physicochemical parameters of the *T. arjuna* transdermal matrix are presented in Tables 3 and 4.

***In vitro* diffusion studies**

The study showed the release of the drugs from its transdermal matrix formulation can be ranked in the following ascending order: S3 > S1 > S2 > S4 > S5 > S6 > S7 > S8 > S9, where the amounts of the extract released after 720 min were 74.56%, 80.32%, 82.32%, 85.25%, 85.98%, 86.17%, 91.58%, 91.68%, and 92.13%, respectively. Formulation S3

Table 3: Visual evaluation of *T. arjuna* transdermal matrix formulations

Batch	Color	Odor	Texture	Flexibility
S1	Yellowish white	Odorless	Flat surface	Flexible
S2	Yellowish white	Odorless	Flat surface	Flexible
S3	Yellowish white	Odorless	Flat surface	Flexible
S4	Yellowish white	Odorless	Flat surface	Flexible
S5	Yellowish white	Odorless	Flat surface	Flexible
S6	Yellowish white	Odorless	Flat surface	Flexible
S7	Yellowish white	Odorless	Flat surface	Flexible
S8	Yellowish white	Odorless	Flat surface	Flexible
S9	Yellowish white	Odorless	Flat surface	Flexible

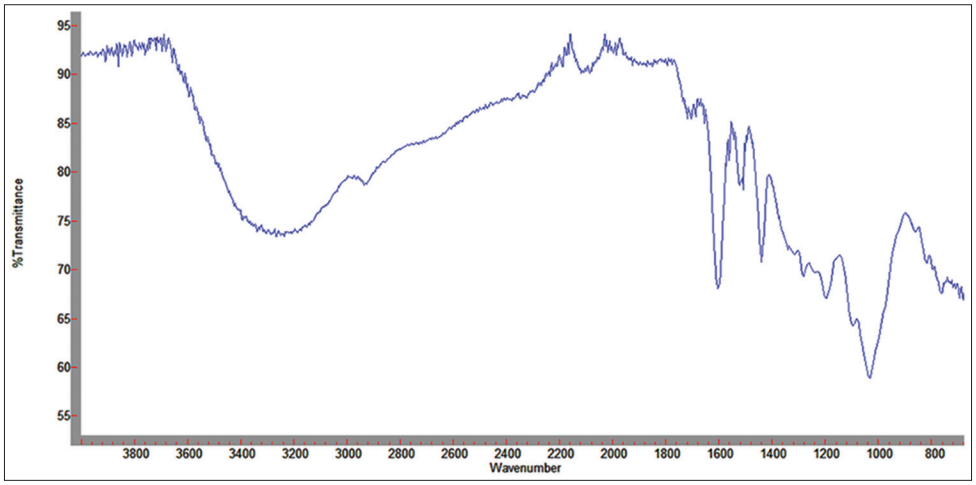

Fig. 1 The Fourier transform infrared spectrum of pure extract

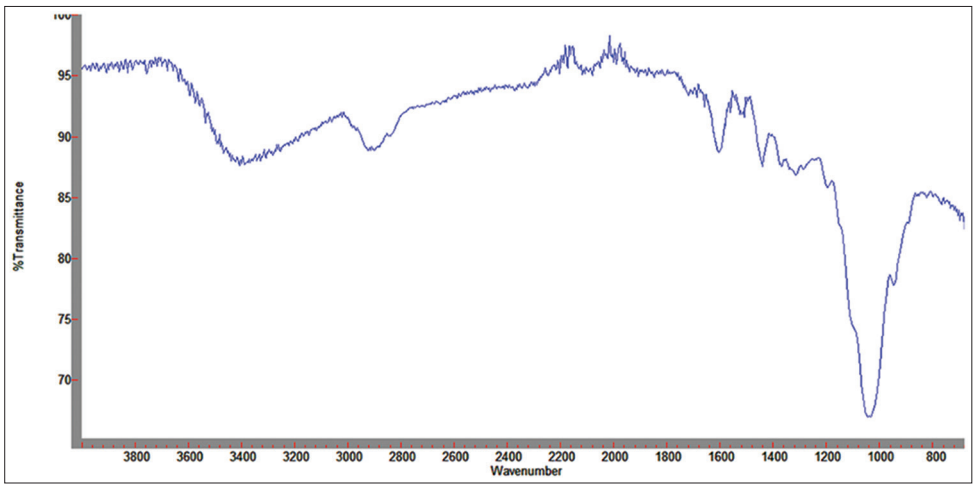

Fig. 2 The Fourier transform infrared spectrum of formulation

Table 4: Physicochemical evaluation and drug content

Batch	Physicochemical parameter				
	Tensile strength (Kg/cm^2)	Thickness (mm)	Moisture uptake (%)	Folding endurance	Drug content (%)
S1	0.112±0.02	0.12±0.02	3.14±0.005	109±1.52	97.33±0.02
S2	0.156±0.03	0.14±0.01	3.20±0.020	111±1.08	98.15±0.01
S3	0.179±0.01	0.18±0.01	2.29±0.026	120±1.08	99.65±0.01
S4	0.140±0.01	0.12±0.01	3.06±0.020	116±1.00	98.15±0.02
S5	0.124±0.02	0.13±0.02	3.07±0.028	110±1.51	97.31±0.01
S6	0.139±0.02	0.14±0.02	3.60±0.043	101±1.46	97.95±0.02
S7	0.140±0.03	0.15±0.01	4.28±0.020	105±1.21	97.64±0.01
S8	0.159±0.02	0.16±0.03	3.09±0.057	100±1.00	96.23±0.01
S9	0.189±0.01	0.22±0.01	4.22±0.005	107±1.08	99.01±0.01

*All the values are given in mean±SD (n=3), SD: Standard deviation

Table 5: Cumulative percent release

Time (min)	S1	S2	S3	S4	S5	S6	S7	S8	S9
60	10.26±0.011	11.50±0.033	11.02±0.012	12.32±0.011	13.94±0.001	14.34±0.063	15.23±0.023	15.56±0.005	17.13±0.012
240	23.20±0.001	23.01±0.012	27.47±0.011	30.12±0.014	30.44±0.001	31.11±0.011	31.32±0.002	34.01±0.012	35.15±0.015
420	44.11±0.002	46.45±0.021	46.45±0.001	47.78±0.045	48.45±0.052	48.01±0.057	48.78±0.005	51.56±0.021	52.45±0.030
600	62.54±0.068	63.46±0.004	60.44±0.068	67.14±0.059	68.35±0.057	68.65±0.058	74.25±0.015	75.23±0.042	78.19±0.056
720	80.32±0.011	82.32±0.011	74.56±0.055	85.25±0.078	85.98±0.001	86.17±0.001	91.58±0.003	91.68±0.011	92.13±0.035

*All the values are given in mean±SD (n=3), SD: Standard deviation

showed better prolonged release than other formulations [17]. Results are given in Table 5.

***Ex vivo* diffusion studies**

From *in vitro* diffusion studies, it is evident that batch S3 showed better drug release up to 12 h. Hence, by consideration of factorial design and overall physicochemical parameters results, batch S3 was optimized and used for *ex vivo* analysis. *Ex vivo* diffusion study of optimized S3 batch resulted in drug release 69.12±0.02% up to 12 h.

Skin irritation studies

Institutional Ethics Committee permission was obtained as per the CPCSEA guidelines. The test sites were examined for dermal reactions in accordance with the Draize scoring criteria. Skin irritation study resulted no allergic symptoms such as inflammation, redness, and irritation appeared on albino rats up to 72 h albino rats which indicate the suitability of prepared formulations for topical application.

Stability studies

T. arjuna transdermal matrix formulations were subjected to stability studies at 25°C/60% RH, 30°C/65% RH, and 40 °C/75% RH for 3 months. All the prepared formulations were found to be stable upon storage for 3 months; no change was observed [18].

CONCLUSION

In the present study, *T. arjuna* transdermal matrix formulations were prepared. On the evaluations and FTIR study, all the formulas showed good uniformity and acceptability. It was concluded that batch S3 is the optimized formulation for 12 h study period. Stability studies of the drug formulations proved that the drug was stable in the transdermal matrix formulations for the study period. Therefore, it can be concluded that the prepared transdermal matrix has the potential for transdermal drug delivery of *T. arjuna* with improved permeation profile for a longer period of time, thereby increasing the patient compliance.

AUTHORS' CONTRIBUTIONS

Both the authors were equally involved in the drafting, gathering information, and design of the framework of the manuscript.

CONFLICTS OF INTEREST

Nil.

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