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ORIGINAL ARTICLE

Formulation Design and Evaluation of an Emulgel Containing *Terminalia arjuna* Bark Extract for Transdermal Delivery

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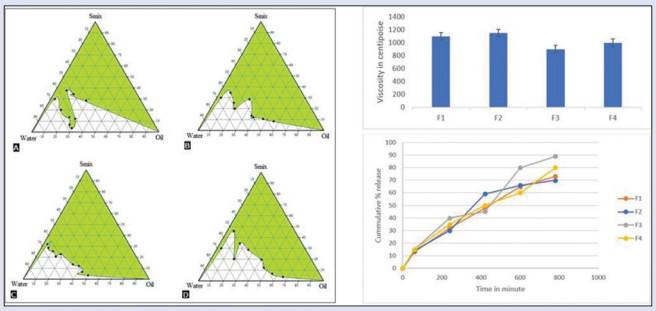
ABSTRACT

Background: *Terminalia arjuna* is used in various indigenous system of medicine such as Ayurveda, Siddha, and Unani. The traditional medical forms provide drug delivery with peaks often above the required dose and face problems such as first-pass metabolism, stability, and low therapeutic efficacy. To enhance topical delivery and to allow for controlled release, the use of *T. arjuna* bark extract emulgel was explored. **Objective:** The objective of this study is to design and develop novel emulgel formulation of *T. arjuna* bark extract for transdermal delivery. **Materials and Methods:** Pseudoternary phase diagram was developed using aqueous titration method. Appropriate amount of oil, surfactant, and cosurfactant were mixed together in accordance with obtained emulsion region in the phase diagram. The emulsion was prepared and incorporated in gel base. The four different formulations were evaluated for physical examinations, rheological studies, skin irritation studies, *in vitro* release, and *ex vivo* release studies. **Results:** The phase diagram at Km value 3 showed better emulsion existence regions. Formulation F3 showed maximum release, wherein the amount of the extract released after 720 min was 91.43%. Skin irritation test on albino rats resulted no allergic symptoms such as inflammation, redness, and irritation up to 72 h. All the prepared emulgel formulations were found to be stable on storage. **Conclusion:** It can be concluded that *T. arjuna* bark extract emulgel can be used for transdermal delivery for the treatment of chronic ailments such as pulmonary hypertension.

Key words: Emulgel, phase diagram, pulmonary hypertension, *Terminalia arjuna*, transdermal delivery

SUMMARY

- In present research, *T. arjuna* bark extract emulgel formulations were explored to enhance topical delivery and to allow for controlled release. Pseudoternary phase diagram was developed using aqueous titration method. Skin irritation and stability studies have been investigated. It can be used in chronic pulmonary hypertension to impart systematic release with long term stability.



Abbreviations used: *T. arjuna*: *Terminalia arjuna*, UV: Ultraviolet, FTIR: Fourier transform infrared, PEG: Polyethylene glycol, FD: Franz diffusion.

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INTRODUCTION

Terminalia arjuna (Roxb.) Wight and Arn., (*T. arjuna*) commonly known as "Arjuna," which has been used primarily in various cardiovascular disorders from ancient times. Many animal and clinical studies have validated its anti-ischemic, antihypertensive, antihypertrophic, and antioxidant effects. It contains useful phytoconstituents such as triterpenoids, β-sitosterol, flavonoids, and glycosides. Of this, triterpenoids and flavonoids are majorly responsible for its valuable antioxidant cardiovascular properties.[1-5] Classical conventional preparations of *T. arjuna* such as arjunaristh, arjuna ghrita, kakubhadi choorna, aravindasava, devadarvyarista, laxadi guggul, and decoction arjuna are unable to deliver medicament at a rate directed by the needs of the body, over the period of treatment.[6,7]

Pulmonary hypertension is a life-threatening disease which causes right ventricular hypertrophy and right heart failure; it probably affects around 1% of the global population. In those over 65 years of age, the prevalence is thought to be around 10%. Pulmonary vascular smooth muscle hypertrophy and increased oxidative stress are major pathological features of pulmonary hypertension.[8] In a recent study, *T. arjuna* extract showed prevention of pulmonary hypertension which may be attributed to its antioxidant as well as its effects on pulmonary arteriolar wall thickening.[9] The traditional medical forms provide drug delivery with peaks often above the required dose and face problems such as first-pass metabolism, gastritis, stability, and low therapeutic efficacy. In view of these facts, the present study was designed to deliver the medicament in controlled manner for longer duration which is an urgent need in pulmonary hypertension.

In recent years, there has been great interest in the use of emulsified gel, which allows the formulation of stable emulsion for transdermal application.[10] It has several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, long shelf life, bio-friendly, and transparent which can protect first-pass effect and control the rate of release.[11]

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To the best our knowledge, no report is available in the previous literature on the formulation containing *T. arjuna* bark extract to fill the gap of traditional medical forms through systematic transdermal release in less amount of medicament for longer duration of action with long-term stability, which is a current global requirement in pulmonary hypertension. The aim of this work was to design and develop the *T. arjuna* bark extract emulgel formulation for transdermal delivery. The physical examinations, rheological studies, skin irritation studies, *in vitro* release, and *ex vivo* release studies of the prepared emulgels were also evaluated.

MATERIALS AND METHODS

Plant material

The stem bark of *T. arjuna* was collected from Sahyadri valley, Western Maharashtra region, Kolhapur District (Maharashtra, India) in 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.

Extraction process

The collected *T. arjuna* barks were cut into small pieces. The bark parts were dried in an incubator for 7 days at 40°C, crushed in an electrical grinder and then the powder was separated. A total of 1 kg of *T. arjuna* bark powder was washed in 4 l of petroleum ether for 24 h to remove the greasy-pigmented nonpolar materials. Then, the petroleum ether was discarded and residue was dissolved in 5 l diethyl ether for 2 h in a Soxhlet apparatus. The extract was filtered through Whatman No. 1 filter paper and the resulting filtrate was dried in the air. The ether solid extract was dissolved in 3 l acetone for 1 h in a Soxhlet apparatus. Then, the extract was filtered through Whatman No. 1 filter paper and the resulting filtrate was dried under reduced pressure at 40°C on a rotary evaporator. The acetone solid extract was dissolved in 2 l methanol and was dried in the air. The methanol extract was stored in refrigerator. Percent of yield was calculated[12] as follows:

Extract yield %= (W1/W2) × 100

where W1 is net weight of powder in grams after extraction and W2 is total weight of bark powder in grams taken for extraction.

Phytochemical screening

Preliminary screening of secondary metabolites such as alkaloids, flavonoids, saponins, phytosterols, lactones, terpenoids, and glycosides was carried out according to the common phytochemical methods.[13]

Determination of total flavonoid content

Aluminum chloride colorimetric method was used for flavonoids determination.[14] About 1 ml of the *T. arjuna* extract/standard of different concentration solution was mixed with 3 ml of methanol, 0.2 ml of aluminum chloride, 0.2 ml of 1 mol/l potassium acetate, and 5.6 ml of distilled water. It remained at room temperature for 30 min. The absorbance of the reaction mixture was measured at 415 nm with spectrophotometer against blank. Methanol served as blank. The total content of flavonoid compounds in extracts in quercetin equivalents was calculated by the following equation:

C = (c × V)/m

where C is the total content of flavonoid compounds, mg/g extract, in quercetin equivalent; c is the concentration of quercetin established from the calibration curve in mg/ml, V is the volume of extract in ml, and m is the weight of crude extract in g.

Ultraviolet visible spectroscopic analysis

The obtained *T. arjuna* bark extract was subjected for determination of absorbance maxima by dissolving concentrated extract in methanol solvent. Ultraviolet (UV) spectrum of *T. arjuna* extract in methanol has shown in [Figure 1]. The absorbance values at different concentration of *T. arjuna* extract in methanol and phosphate buffer pH 7.4 by double-beam spectrophotometer (Jasco V630) are shown in [Tables 1 and 2], respectively.

Fourier transform infrared spectrophotometer study

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}.

Solubility determination in various oil, surfactant, and cosurfactant

To find out appropriate solvents with good solubilizing capacity of *T. arjuna* extract, the saturation solubility of *T. arjuna* extract was investigated in various oils such as olive oil, cremophor ELP, isopropyl myristate, and some surfactants and cosurfactants including tween 80, captex 8000, maisnee, Polyethylene glycol (PEG) 400, PEG 600, and transcutol by shake-flask method. An excess amount of *T. arjuna* extract was added to vial containing 5 ml of each selected solvent. After sealing, the mixture was vortexed using a cyclomixer for 10 min to facilitate

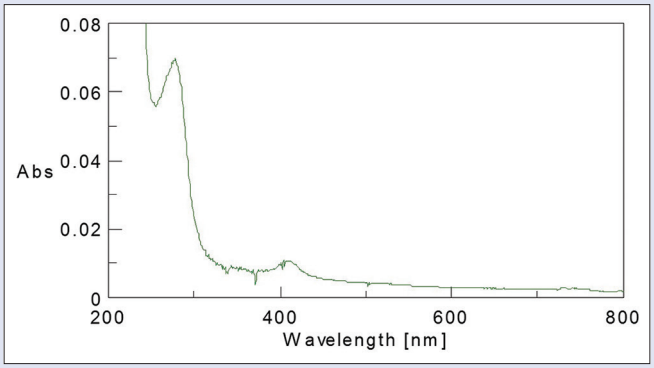

Figure 1: Ultraviolet spectra of *T. arjuna* bark extract

Table 1: The absorbance values at different concentration of *Terminalia arjuna* bark extract in methanol

Concentration (µg/ml)	Absorbance
10	0.02
20	0.06
30	0.10
40	0.13
50	0.16

Table 2: The absorbance values at different concentration of *Terminalia arjuna* bark extract in phosphate buffer pH 7.4

Concentration (µg/ml)	Absorbance
10	0.06
20	0.11
30	0.15
40	0.20
50	0.24

proper mixing of *T. arjuna* extract with the vehicles. Mixtures were kept for 72 h at ambient temperature to attain equilibrium, and afterward, mixtures were centrifuged at 2000 rpm for 15 min, followed by filtration through membrane filter (0.45 μm). Aliquots of supernatant were diluted with methanol and drug content was quantified using UV-visible double-beam spectrophotometer (Jasco V-630) against methanol as blank solution at λ_{max} 276 nm.[15]

Pseudoternary phase diagram

The emulsion existence region was determined by constructing pseudoternary phase diagrams. Phase diagrams were constructed using Chemix School 3.51 software (Arne Standnes, Bergen, Norway) to define the extent of the emulsion regions, that is, proportion, in which the three essential components must be mixed to form a transparent, clear, single phase, homogeneous, and stable emulsion. Based on the solubility study of extract, oils, surfactants, cosurfactants, and aqueous phase were used for construction of phase diagram. Surfactant and cosurfactant (Smix) in each group were mixed in different weight ratio of (1:1, 2:1, 3:1, and 4:1). For each phase diagram, Smix and oil ratios were mixed thoroughly in different weight ratio from 9:1 to 1:9 (9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9) in different glass vials. Pseudoternary phase diagram was developed using aqueous titration method. Water was added dropwise with constant stirring on six station magnetic stirrers (Spectralab, Whirlmatic, India) until homogeneous dispersion or solution was obtained. After each addition, the system was examined for appearance and flow property. The end-point of the titration was the point in which the solution becomes cloudy or turbid. The quantity of aqueous phase required to achieve turbidity point was noted. Slow titration with aqueous phase is performed to each weight ratio of Smix and oil.[16]

Formulation of emulsion

To prepare *T. arjuna* extract loaded emulsion, appropriate amount of oil, surfactant, and cosurfactant were mixed together in accordance with obtained emulsion region in the phase diagram and equilibrated with gently vortexing together the initial concentrate. The appropriate amount of *T. arjuna* extract was dissolved in the oil phase followed by addition Smix to prepare initial preconcentrate. The blend was mixed using high-speed homogenizer up to 10 min as the extract was resinous in nature. The dropwise addition of water was done to resulting mixture till emulsion was formed.

Preparation of hydrogel

Hydrogel was prepared using 0.5% of carbopol grades 934. Carbopol was dissolved in purified water and left overnight for swelling, then the pH of the hydrogel was adjusted to 6–6.5 using triethanolamine.

Formulation of emulgel

Different formulations of emulgel based on the better emulsion existence regions were prepared by incorporating emulsion with addition of glutaraldehyde for 10 min into hydrogel at high-pressure homogenization in ratio of 1:1.[17] The composition of different formulations has been discussed in Table 3.

Table 3: Composition of different formulation batches

Ingredients	F1	F2	F3	F4
Terminalia arjuna extract (mg)	500	500	500	500
Carbopol 934 (%)	0.5	0.5	0.5	0.5
Olive oil (%)	10	10	10	10
Tween 80 (%)	30	35.5	45	52.5
Propylene glycol 400 (%)	10	12.5	15	17.2
Ethanol (%)	2	2	2	2
Methyl paraben (%)	0.005	0.005	0.005	0.005
Glutaraldehyde (%)	0.05	0.05	0.05	0.05
Triethanolamine (ml)	qs	qs	qs	qs
Water (% w/w)	50	50	50	50

Evaluation of emulgel

The prepared emulgel formulations were inspected visually for their color, appearance, consistency, and drug content.[17] Drug content was measured by dissolving known quantity of emulsion in methanol and stirring for 4 h. Absorbance was measured at 276 nm in UV/visible spectrophotometer.

Rheological study

The viscosity of the formulated batches was determined using a cone and plate viscometer with Spindle 7 (viscometer Brookfield RVDV-I Prime). The assembly was connected to a thermostatically controlled circulating water bath maintained at 25°C. The formulation was added to a beaker covered with thermostatic jacket. Spindle was allowed to move freely into the emulgel and the reading was noted.[18]

Skin irritation test

Institutional ethics committee permission was obtained as per the Committee for the Purpose of Control and Supervision of Experiments on Animals (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 prepared emulgel 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.[19]

In vitro release studies

The *in vitro* release studies were carried out using a Franz diffusion (FD) cell. The formulation was applied on 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 % release was calculated.[20]

Ex vivo release study

The *ex vivo* release study was carried out in a FD cell using the skin. Male goat free from any visible sign of disease was selected. The goat dorsal skin was brought from slaughterhouse. The dorsal hair was removed and the skin was washed with distilled water. 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. 1 g emulgel was spread. 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. PCP Disso V3 (BVDU, PCP, Pune) software was used to study the flux coming out from the emulgel.[20]

Stability studies

The prepared emulgels were packed in aluminum collapsible tubes (5 g) 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 physical appearance, pH, rheological properties, and extract content.[21]

RESULTS AND DISCUSSION

Phytochemical screening

The phytochemical analysis of the *T. arjuna* extract was carried by the common phytochemical methods.[13] It showed the presence of different groups of secondary metabolites such as alkaloids, flavonoids, saponins, phytosterols, lactones, terpenoids, and glycosides. *T. arjuna* has medicinal and economic value due to the presence of secondary metabolites showing biological activities in human and animal body.[4,5]

Determination of total flavonoid content

The total flavonoid content of the *T. arjuna* extract was estimated using aluminum chloride colorimetric technique.[14] The total flavonoid content was found to be 199.00 mg quercetin equivalent/g of dried extract. Due to the presence of free-radical scavenging action of the flavonoid content in *T. arjuna*, it acts as strong antiproliferative and antioxidant agent.[3] Furthermore, prevention of pulmonary hypertension may be attributed to its antioxidant potential through pulmonary arteriolar wall thickening.[9]

Ultraviolet-visible spectroscopic analysis

The UV-visible spectrum of *T. arjuna* extract in methanol has absorption band at 240–276 nm and at 350–400 nm. These absorption bands were characteristic for flavonoids and its derivatives, which typically consist of two absorption maxima in the ranges 240–285 nm (band II) and 300–380 nm (band I).[22] The precise position and relative intensities of recorded maxima in the spectrum indicated that flavonoid was a predominant ingredient of extract. The graph of absorbance versus concentration shown in Figure 1 for *T. arjuna* was found to be linear and obeys Beer–Lambert's law in the concentration range of 10–50 µg/ml. The λ_{max} of the extract was found to be 276 nm. Calibration curve of extract in methanol and phosphate buffer pH 7.4 is shown in Figures 2 and 3, respectively. Both curves were found to be linear.

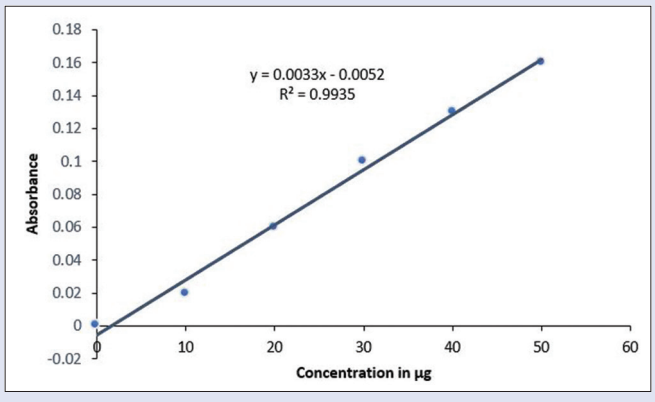

Figure 2: Calibration curve of *T. arjuna* bark extract in methanol

Fourier transform infrared spectrophotometer study

The 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) which confirms the presence of alcohol, ether function groups, and aromatic ring.[17] FTIR spectrum of *T. arjuna* bark extract has shown in [Figure 4].

Solubility determination in various oil, surfactant, and cosurfactant

Solubility of *T. arjuna* extract in various oils such as olive oil, cremophor ELP, isopropyl myristate, and some surfactants and cosurfactants including tween 80, captex 8000, maisnee, PEG 400, PEG 600, and transcutol has been discussed in Table 4. Solubility of *T. arjuna* in olive oil, tween 80, and PEG 400 was found to be 110.3 mg/ml, 65.55 mg/ml, and 70.25 mg/ml, respectively. *T. arjuna* extract is lipophilic in nature. Olive oil consists of oleic acid (up to 83%), with smaller amounts of other fatty acids including linoleic acid (up to 21%) and palmitic acid (up to 20%) which is lipophilic in nature, while tween 80 and PEG 400 are hydrophilic surfactants. Tween 80 is derived from polyethoxylated sorbitan and oleic acid. Hydrophilic groups in tween 80 are polyethers also known as polyoxyethylene groups, which are polymers of ethylene oxides.[23] From the results, it can be depicted that *T. arjuna* extract is comparatively more soluble in olive oil, tween 80, and PEG 400, respectively.

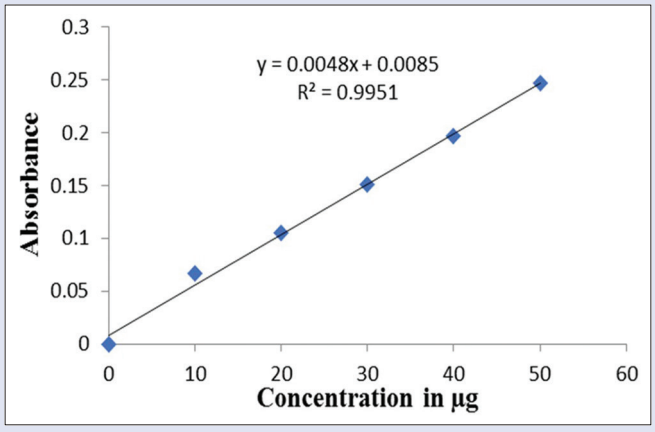

Figure 3: Calibration curve of *T. arjuna* bark extract in phosphate buffer 7.4 pH

Table 4: Solubility of *Terminalia arjuna* extract in various oil, surfactant, and cosurfactant

Oil		Surfactant		Cosurfactant	
Name	Solubility (mg/ml)*	Name	Solubility (mg/ml)*	Name	Solubility (mg/ml)*
Olive oil	110.3	Tween 80	65.55	PEG 400	70.25
Cremophor ELP	50.36	Captex 8000	52.68	PEG 600	59.98
Isopropyl Myristate	45.72	Maisnee	48.41	Transcutol	54.03

*All measurements were triplicate. PEG: Polyethylene glycol

Pseudoternary phase diagram

The pseudoternary phase diagram of surfactant tween 80 and cosurfactant PEG 400 in different weight ratio was constructed and system of highest water absorption (highest emulsion region) selected for formulation.[16] Phase diagrams were constructed using Chemix School 3.51 software. The phase diagram at Km value 3 showed better emulsion existence regions than Km value 1, 2, and 4 which did not show further increase in emulsion existence region. The physical state of the emulsion was marked on a pseudo-three-component phase diagram with one axis representing aqueous phase, the other representing oil, and the third representing a mixture of surfactant and cosurfactant at fixed weight ratios (Smix ratio). Phase diagrams at different Km values have been shown in [Figure 5].

Evaluation of emulgel

Emulgel formulations were yellowish white, viscous, and creamy with a smooth homogeneous texture and glossy appearance. Consistency of all F1 to F4 formulations was found to be excellent. Results have been discussed in Table 5. The study showed the drug content from its emulsified gel formulation F1 to F4 was 98.20% ± 0.17%, 97.50% ± 0.22%, 100.20% ± 0.16%, and 99.10% ± 0.12%, respectively. The drug content was within the range of 70%–100%.[17]

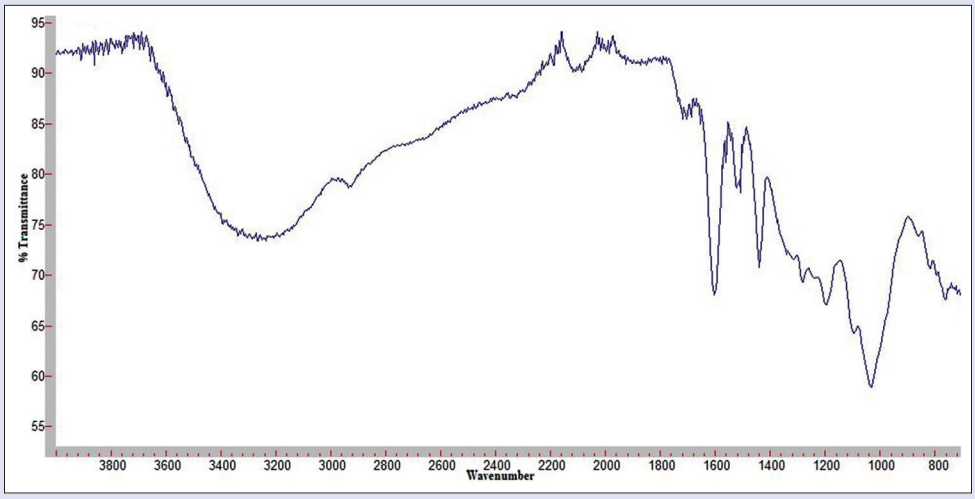

Figure 4: FTIR spectrum of *T. arjuna* bark extract

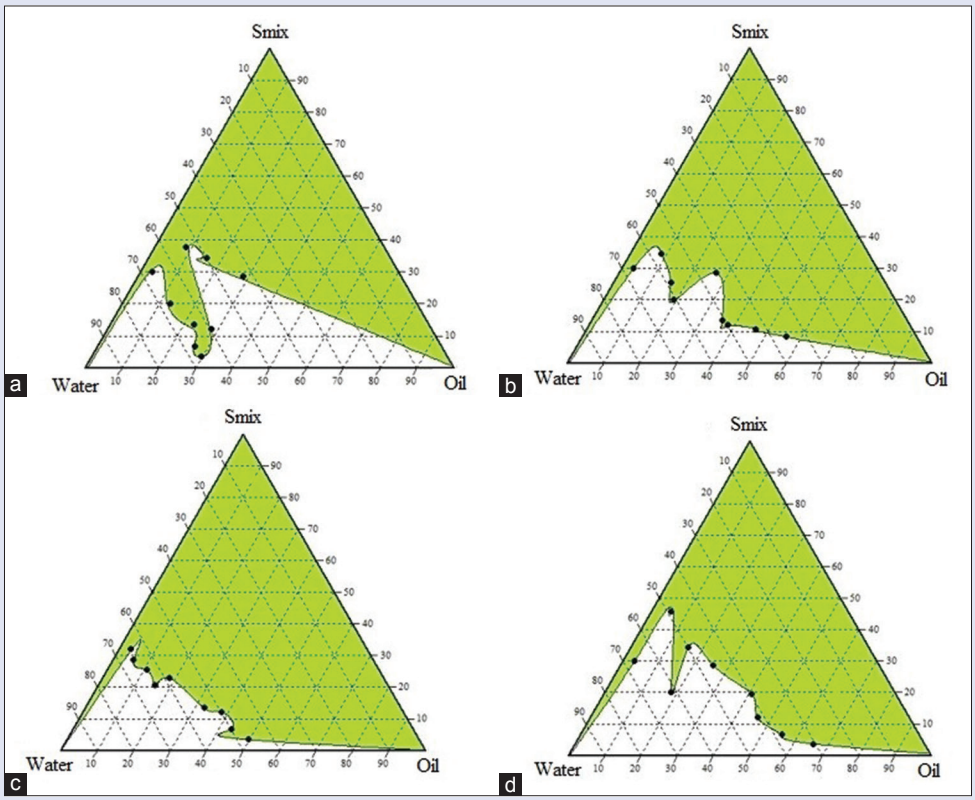

Figure 5: (a) Phase diagram at Km = 1 (b) Phase diagram at Km = 2 (c) Phase diagram at Km = 3 (d) Phase diagram at Km = 4

Rheological study

Rheological study tests were performed at 100 rpm for 10 min.[18] Viscosity of all F1 to F4 emulgel formulations was found in the range of 800 cp to 1200 cp. Results are depicted in [Figure 6].

Skin irritation test

The test sites were examined for dermal reactions in accordance with the Draize scoring criteria.[19] No allergic symptoms such as inflammation, redness, and irritation appeared on albino rats up to 72 h.

In vitro release studies

The study showed the release of the drugs from its emulsified gel formulation can be ranked in the following descending order: F3>F4>F1>F2, where the amounts of the extract released after 720 min were 91.43%, 84.23%, 76.86%, and 74.65%, respectively [Figure 7]. Formulation F3 showed better release than other formulations, this may be due to appropriate Smix and oil proportion.[20] Results are given in Table 6.

Ex vivo release study

The study showed the release from its emulsified gel formulation F1 to F4 were 73.33%, 70.98%, 89.32%, and 80.02%, respectively, in 720 min [Figure 8]. F3 showed better release than other formulations; this may be due to the uniform globule size formation based on proportion of Smix and oil selection in emulsion region of the phase diagram.[20] Transdermal diffusion flux measures the amount of substance that will flow through a small area during a time interval. Flux was obtained from the slope values plotted for amount diffused per unit area against time. PCP Disso V3 software was used to study the flux. The flux of the formulation was in the range of 61.55–339.56 μg/cm^2/min.[24] The results are shown in Table 7.

Table 5: Physical parameters of formulation batches

Formulation	Color	Homogeneity	Consistency	Phase separation
F1	Pale yellow	Excellent	Excellent	None
F2	Pale yellow	Excellent	Excellent	None
F3	Pale yellow	Excellent	Excellent	None
F4	Pale yellow	Excellent	Excellent	None

Table 6: Data for *in vitro* cumulative percentage extract release of formulations F1-F4

Time (min)	F1 (%)	F2 (%)	F3 (%)	F4 (%)
60	13.02±0.002	14.56±0.026	15.33±0.010	15.32±0.009
240	32.49±0.002	33.98±0.030	35.50±0.003	35.01±0.012
420	49.26±0.036	49.38±0.003	44.58±0.005	54.78±0.055
600	65.32±0.005	69.90±0.005	78.55±0.025	64.58±0.022
720	76.86±0.021	74.35±0.010	91.43±0.002	84.23±0.015

Values are expressed as mean±SD (n=3). SD: Standard deviation

Table 7: Data for *ex vivo* cumulative percentage extract release of formulations F1-F4 and transdermal flux

Batch	*Ex vivo* release (%)	Transdermal flux (μg/cm^2/min)
F1	73.33±0.005	138.15±0.025
F2	70.98±0.018	61.55±0.014
F3	89.32±0.010	160.19±0.033
F4	80.02±0.013	339.56±0.021

Values are expressed as mean±SD (n=3). SD: Standard deviation

Stability study

Emulgel formulations were subjected to stability studies at 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH for 3 months.[21] All the prepared emulgel formulations were found to be stable on storage for 3 months, no change was observed in their physical appearance, pH, rheological properties, and extract content.

CONCLUSION

In the coming years, transdermal delivery of potent plant extract will be used to impart systematic release in chronic therapy and for long-term stability. Equally, in the study, transdermal emulgels of *T. arjuna* extract were successfully formulated and subjected to physicochemical studies, that is, rheological studies, skin irritation studies, *in vitro* release studies, and *ex vivo* release studies through

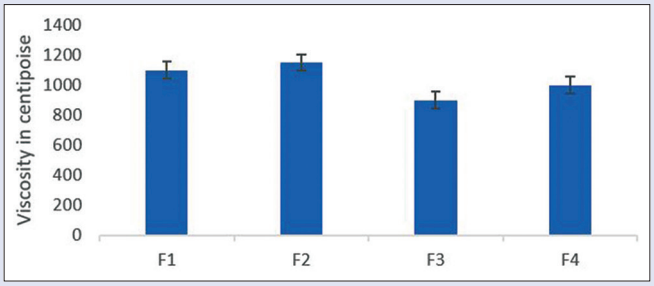

Figure 6: Viscosity of the formulations F1–F4

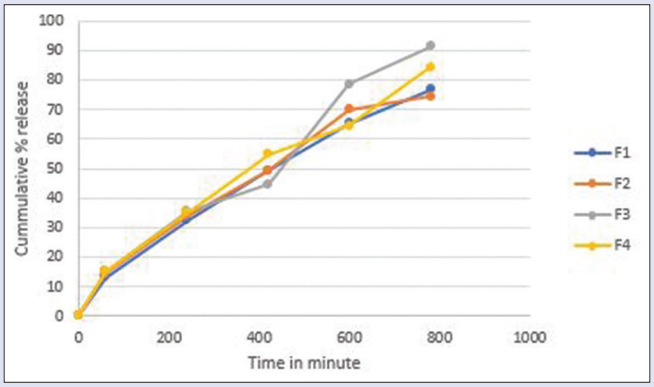

Figure 7: *In vitro* cumulative % release of formulations F1 to F4

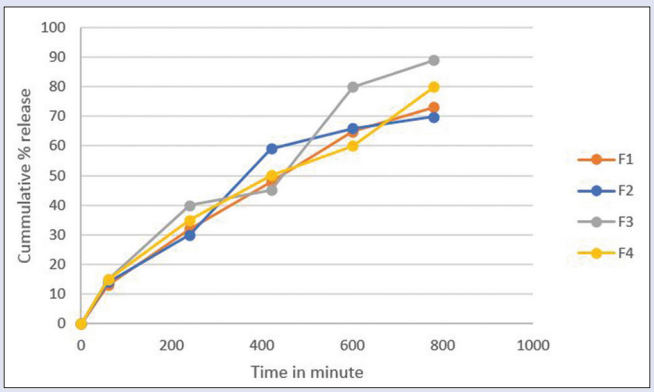

Figure 8: *Ex vivo* cumulative % release of formulations F1 to F4

skin. *In vitro* release test of formulations was performed to determine the release of extract from emulgel and duration of release. From the *in vitro* studies, formulation F3 showed maximum release of 91.43% in 720 min. *Ex vivo* drug release was also performed, in which formulation F3 showed the best release of 89.32% in 720 min. Hence, *T. arjuna* bark extract emulgel can be used for transdermal delivery for the treatment of chronic ailments such as pulmonary hypertension. However, further investigation is required to enhance the *T. arjuna* extract loading to match the human clinical dose of *T. arjuna* bark extract.

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Conflicts of interest

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REFERENCES

1. Ram A, Lauria P, Gupta R, Kumar P, Sharma VN. Hypocholesterolaemic effects of *Terminalia arjuna* tree bark. J Ethnopharmacol 1997;55:165-9.
2. Bachaya HA, Iqbal Z, Khan MN, Jabbar A, Gilani AH, Din IU. *In vitro* and *in vivo* anthelmintic activity of *Terminalia arjuna* bark. Int J Agric Biol 2009;11:273-8.
3. Phanikumar G, Navya K, Ramya EM, Venkataramana M, Anand T, Anilakumar KR. DNA damage protecting and free radical scavenging properties of *Terminalia arjuna* bark in PC-12 cells and plasmid DNA. Free Radic Antioxid 2013;3:35-39.
4. Dwivedi S. *Terminalia arjuna* Wight & Arn. – A useful drug for cardiovascular disorders. J Ethnopharmacol 2007;114:114-29.
5. Dwivedi S, Udupa N. *Terminalia arjuna*: Pharmacognosy, phytochemistry, pharmacology and clinical use a review. Fitoterapia 1989;5:413-20.
6. Kumar DS, Prabhakar YS. On the ethnomedical significance of the arjun tree, *Terminalia arjuna* (Roxb.) Wight and Arnot. J Ethnopharmacol 1987;20:173-90.
7. Dwivedi S, Chopra D. Revisiting *Terminalia arjuna* – An ancient cardiovascular drug. J Tradit Complement Med 2014;4:224-31.
8. Hoeper MM, Ghofrani HA, Grunig E, Klose H, Olschewski H, Rosenkranz S. Pulmonary hypertension. Dtsch Arztebl Int 2017;114:73-84.
9. Meghwani H, Prabhakar P, Mohammed SA, Seth S, Hote MP, Banerjee SK, *et al*. Beneficial effects of aqueous extract of stem bark of *Terminalia arjuna* (Roxb.), an ayurvedic drug in experimental pulmonary hypertension. J Ethnopharmacol 2017;197:184-94.
10. Gupta A, Mishra AK, Singh AK, Gupta V, Bansal P. Formulation and evaluation of topical gel of diclofenac sodium using different polymers. Drug Invention Today 2010;2:250-3.
11. Stanos SP. Topical agents for the management of musculoskeletal pain. J Pain Symptom Manage 2007;33:342-55.
12. Patil UH, Gaikwad DK. Phytochemical evaluation and bactericidal potential of *Terminalia arjuna* stem bark. Int J Pharm Sci Res 2010;2:614-9.
13. Fransworth NR. Biological and phytochemical screening of plants. J Pharm Sci 1966;55:225-76.
14. Jiao H, Wang SY. Correlation of antioxidant capacities to oxygen radical scavenging enzyme activities in blackberry. J Agric Food Chem 2000;48:5672-6.
15. Chouksey R, Pandey H, Jain AK, Soni H, Saraogi GK. Preparation and evaluation of the self emulsifying drug delivery system containing atorvastatin HMG-CoA inhibiter. Int J Pharm Pharm Sci 2011;3:147-52.
16. Bora DK, Priyanka B, Kiran B. Formulation and evaluation of self microemulsifying drug delivery systems of low solubility drug for enhanced solubility and dissolution. Asian J Biomed Pharm Sci 2012;2:7-14.
17. Khullar R, Kumar D, Seth N, Saini S. Formulation and evaluation of mefenamic acid emulgel for topical delivery. Saudi Pharm J 2012;20:63-7.
18. Bonacucina G, Cespi M, Palmieri GF. Characterization and stability of emulsion gels based on acrylamide/sodium acryloyldimethyl taurate copolymer. AAPS PharmSciTech 2009;10:368-75.
19. Pisetpackdeekul P, Supmuang P, Pan-In P, Banlunara W, Limcharoen B, Kokpol C, *et al*. Proretinal nanoparticles: Stability, release, efficacy, and irritation. Int J Nanomedicine 2016;11:3277-86.
20. Leal LB, Cordery SF, Delgado-Charro MB, Bunge AL, Guy RH. Bioequivalence methodologies for topical drug products: *In vitro* and *ex vivo* studies with a corticosteroid and an anti-fungal drug. Pharm Res 2017;34:730-7.
21. Naga Sravan Kumar Varma V, Maheshwari PV, Navya M, Reddy SC, Shivakumar HG, Gowda DV, *et al*. Calcipotriol delivery into the skin as emulgel for effective permeation. Saudi Pharm J 2014;22:591-9.
22. Tsimogiannis D, Samiotaki M, Panayotou G, Oreopoulou V. Characterization of flavonoid subgroups and hydroxy substitution by HPLC-MS/MS. Molecules 2007;12:593-606.
23. Shah AV, Desai HH, Thool P, Dalrymple D, Serajuddin ATM. Development of self-microemulsifying drug delivery system for oral delivery of poorly water-soluble nutraceuticals. Drug Dev Ind Pharm 2018;44:895-901.
24. Jagdale S, Pawar S. Gellified emulsion of ofloxacin for transdermal drug delivery system. Adv Pharm Bull 2017;7:229-39.