JOURNAL OF NATURAL REMEDIES
DOI: 10.18311/jnr/2024/36591
RESEARCH ARTICLE

Development and Optimisation of Olive Oil-infused Emulgel from *Andrographis* Extract Using Quality by Design (QbD) Methodology

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Abstract

Background: Andrographolide, the primary active constituent in *Andrographis* extract, exhibits poor aqueous solubility, necessitating a novel formulation strategy for effective dermal delivery. **Aim:** To formulate and optimise olive oil-infused emulgel from *Andrographis* extract. **Methods:** Various emulgel formulations were prepared using different combinations of oil and Carbopol 940. The formulations were assessed for visual inspection, pH, spreading ability, extrudability, viscosity, drug content, and *in vitro* drug release. The optimal formulation (AEE 6) was identified using design expert software based on the evaluated parameters. **Results:** The emulgel formulations demonstrated varied properties based on the combinations of oil and Carbopol 940 used. The optimized formulation (AEE 6) showed favourable stability under accelerated conditions, maintaining stability across all assessed physicochemical parameters. **Conclusion:** The emulgel formulation approach successfully addressed the poor aqueous solubility of andrographolide, enhancing its permeation for dermal delivery. The selected formulation (AEE 6) demonstrated optimal characteristics and stability, making it a promising candidate for effective dermal delivery of *Andrographis* extract.

Keywords: Andrographolide, Characterisation, Emulgel, QbD, Responses

1. Introduction

Andrographis paniculata, a renowned medicinal herb with long history of traditional use worldwide, has been used for treating various disorders such as gastrointestinal disorders, respiratory infections, cancer, diabetes, thrombosis, hypertension, fever, and herpes[1]. Widely utilized in *Ayurvedic* medicine, it is recognized for its antioxidant and anti-inflammatory properties, aerial parts of the plant; particularly the leaves, stems and roots are commonly utilized as folk medicine in Asia and Europe[2]. Previous phytochemical investigations on both aerial parts and roots of *A. paniculata* have identified with various bio actives. Among them, andrographolide (Figure 1), the diterpene found in *A. paniculata*, is considered the principal bioactive compound of this plant species[3].

Andrographolide, a bioactive compound found in the labdane diterpenoidal lactone derived from the medicinal plant *A. paniculata* of the Acanthaceae family, can be extracted through various methods such as column chromatography, microwave extraction, and supercritical fluid extraction techniques[4]. It exhibits diverse biological activities[5]

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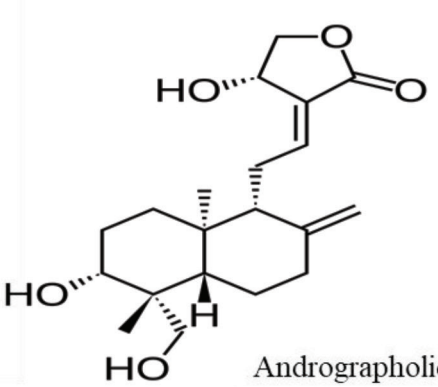
Article Received on: 16.02.2024 Revised on: 28.06.2024 Accepted on: 16.07.2024

Andrographis paniculata



Andrographolide

Figure 1. *Andrographis* plant and its active constituent.

such as anti-oxidant, anti-fungal, anti-viral, and anti-cancer, hepato protective *etc*. However, it's potential for topical formulations, especially in addressing skin cancer and other dermatological disorders, remains underexplored. This gap in knowledge serves as motivation to explore andrographolide further, taking into account its solubility and logP parameters[6], to develop innovative topical formulations. Nanotechnology has gained attention in dermatological formulations due to its ability to enhance drug delivery, stability and therapeutic efficacy. Emulgel, which combines nanotechnology-based nano emulsions with conventional hydrogel systems, shows promise for topical applications[7]. This approach allows for controlled release of active compounds, ensuring prolonged skin contact and desired outcomes. Quality by Design (QbD) is a unique approach used in product development, focusing on understanding and controlling formulation and manufacturing processes to ensure product quality[8]. QbD methodologies involve identifying critical quality, material attributes and process parameters to develop a robust and consistent product[9]. This study evaluates a novel emulgel formulated with andrographolide using a QbD approach. Integrating QbD principles into the formulation process enhances product quality and performance, while streamlining development by reducing the need for extensive trial-and-error testing. Ultimately, this research aims to provide insights into rational design and optimization, contributing to the development of safe and effective products tailored to address various topical concerns.

2. Materials and Methods

2.1 Materials

Andrographis extract was gifted by natural remedies, India. Carbapol and olive oil were procured from Loba Chemicals in Mumbai. Methyl paraben and propyl paraben were sourced from Vasa Chemicals in Bangalore, and tri-ethanolamine was obtained from Merck Chemicals, Mumbai. EDTA and DMSO were obtained from Merck in Germany.

2.2 Methods

2.2.1 Compatibility Studies

For exploring the chemical interactions between andrographolide and the excipients of the emulgel formulation, Fourier-transform Infrared Spectroscopy (FTIR) was employed using a bruker-alpha instrument from Ettlingen, Germany. The FTIR analysis encompassed a wave number range from 4000 to 400 cm^{-1}. The samples subjected to FTIR analysis included pure andrographolide, individual drug excipients such as olive oil and carbapol, a physical blend of these excipients, and the final emulgel formulation.

2.2.2 Experimental Design by Using Design Expert

A factorial design was used, where a two-level two-factorial method with carbapol (A) and olive oil (B) concentrations designated as independent variables were set at low level (-1) (Carbapol-0.5%, olive oil-3%) and high-level (+1) (Carbapol-1.5%, olive oil-9%). The dependent variables comprised spreadability (Y1), extrudability (Y2), viscosity (Y3), and drug release at 10 hours (Y4). The software, Design-Expert1 (Version 11,

State-Ease, Inc.) was used in the optimization process involved in the formulation of *Andrographis* extract-loaded emulgels comprised of a design matrix with five experimental runs. Linear equations for the response variables were suggested by the software.

2.2.3 Preparation of Emulgels

The modified method involved formulating emulgels[10], concerning the previous research work. Based on the design obtained from the design expert, 5 formulations were prepared. Olive oil was chosen for the oil phase. The gel base was formulated by blending carbopol-934 (0.5, 1, 1.5 %) with water till it attained homogeneity. Triethanolamine was subsequently added to adjust the pH (5.8-6.3). For the oil phase, 0.5% of span 80, dissolved in 3.75% of olive oil, 0.04-0.12 % of *Andrographis* extract was incorporated. In the aqueous phase, 0.25% of tween 80, 2.5% of propylene glycol, 1.25% glycerine,0.02% of both methylparaben and propyl paraben were dispersed in water in suitable proportions. Both phases were heated to 45-55°C. The oily phase was gradually mixed with the aqueous phase under stirring speed of 250 rpm to ensure uniform emulsification[11]. Finally, *Andrographis* extract loaded emulgel was then prepared by blending the gel phase and emulsion phases in equal parts using homogenization with a speed of 1000 rpm.

2.2.4 Physico Chemical Evaluation Parameters

Physical examination of the emulgels includes color, odour, texture, uniformity, phase seperation. The following studies were explored to know the quality of the formulations. Further, pH determination with 1% aqueous solution[12] of the emulgel formulation by pH meter was done. Viscosity by spindle 6 at 10 rpm[13] was used for viscosity determination. Spreadability was measured by standard procedure[14] from the literature by placing the emulgels formulations in between the glass slide, extrudability of the emulgels were done to know the amount of emulgel[15], which can be extruded from the packed containeror aluminium tubes under stipulated time with standard formula. *In vitro* drug release profiling was done using the dialysis membrane[16] and the drug release data were fitted in various kinetic models to know the pattern of drug release. The evaulation details were systematically done and the responses were analysed through design expert to predict the optimised formulation[17]. The same procedure as that of the emulgels AEE1-AEE5 was followed for optimised formulatiion of AEE6 for further evaluations along with stability studies.

2.2.5 Stability Studies

The stability of andrographolide in the optimized emulgel formulation (AEE 6) was evaluated through stability studies conducted under various storage conditions, including different temperatures and humidity[18].

3. Results

3.1 IR Studies

Chemical compatibilities between *Andrographis* extract, carbopol, and olive oil were evaluated using FTIR spectroscopy. IR spectra shows the peaks for free andrographolide (Figure 2B) at 3393 (hydroxyl), 1732 (carbonyl), 1031 (ether), carbopol (Figure 2A) at 32775 (hydroxyl), 1599 (carbonyl), 10289 (ether) and olive oil (Figure 2C) at 1752 (carbonyl), 1259 (ether) cm-1. The stretching peaks detected for both the physical mixture (Figure 2D) and emulgels (Figure 2E) at 3008, 3007 (hydroxyl), 1745, 1743 (carbonyl) and 1041, 1097 (ether linkage) cm-1 respectively. The absence of significant changes in these peak values indicates that there is no chemical interaction occurring during the formulation process[19], as illustrated in Figures 2A-2E.

3.2 Findings of Experimental Statistics for Optimization Studies

Based on the various responses obtained, the given equations were suggested by the design expert followed by the optimisation process.

Spreadability, Y1 = +26.38 – 3.33 A, which shows that decrease in spreadability occurs, with the increased concentration of the polymer, such as carbapol content in the emulgels formulations (Figure 3A). The model F-value of 78.62 suggests the significance of the model. It indicates a mere 1.25% probability that such a high F-value could arise from random variation. P-values < 0.0500 are indicative of significant model terms[20].

Extrudability Y2 = +27.99 - 2.94 A, implies that concentration of carbapol is inversely proportional to the extrudability of the emulgels (Figure 3B). The

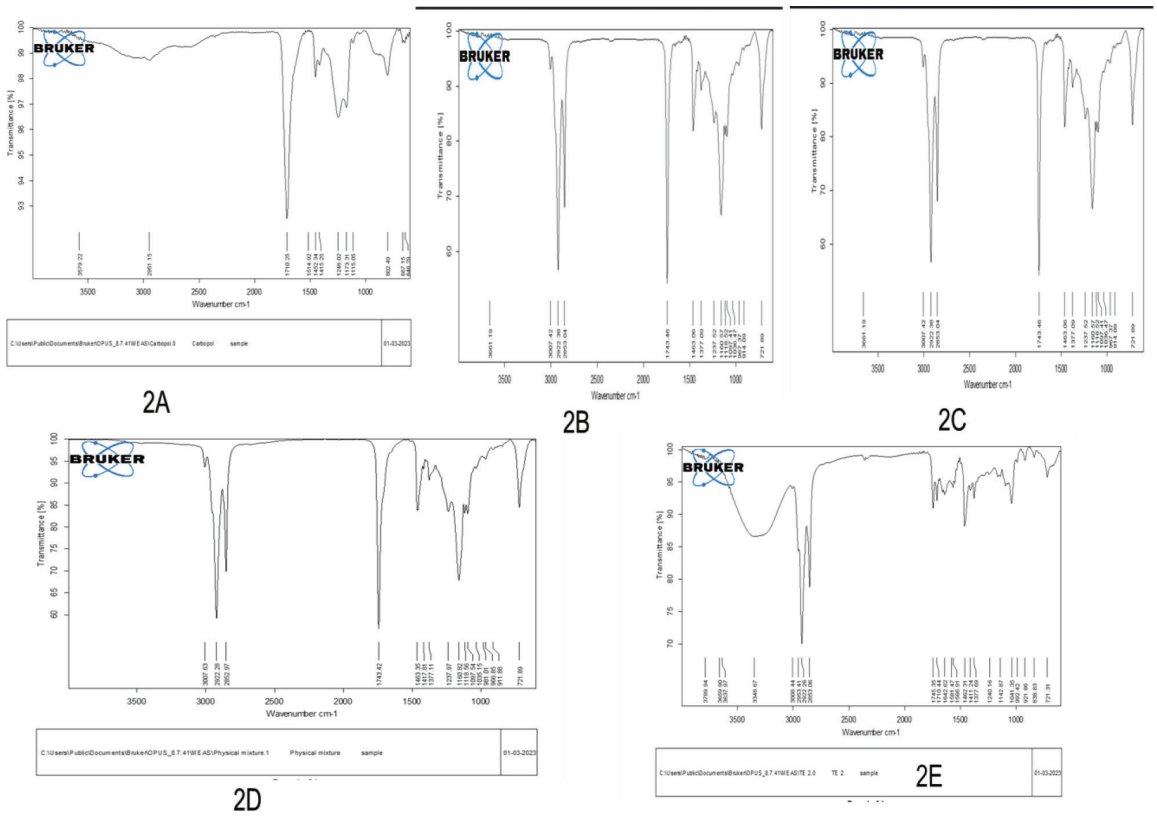


Figure 2A-2E. IR spectra of carbapol, extract, olive oil, physical mixture, emulgel.

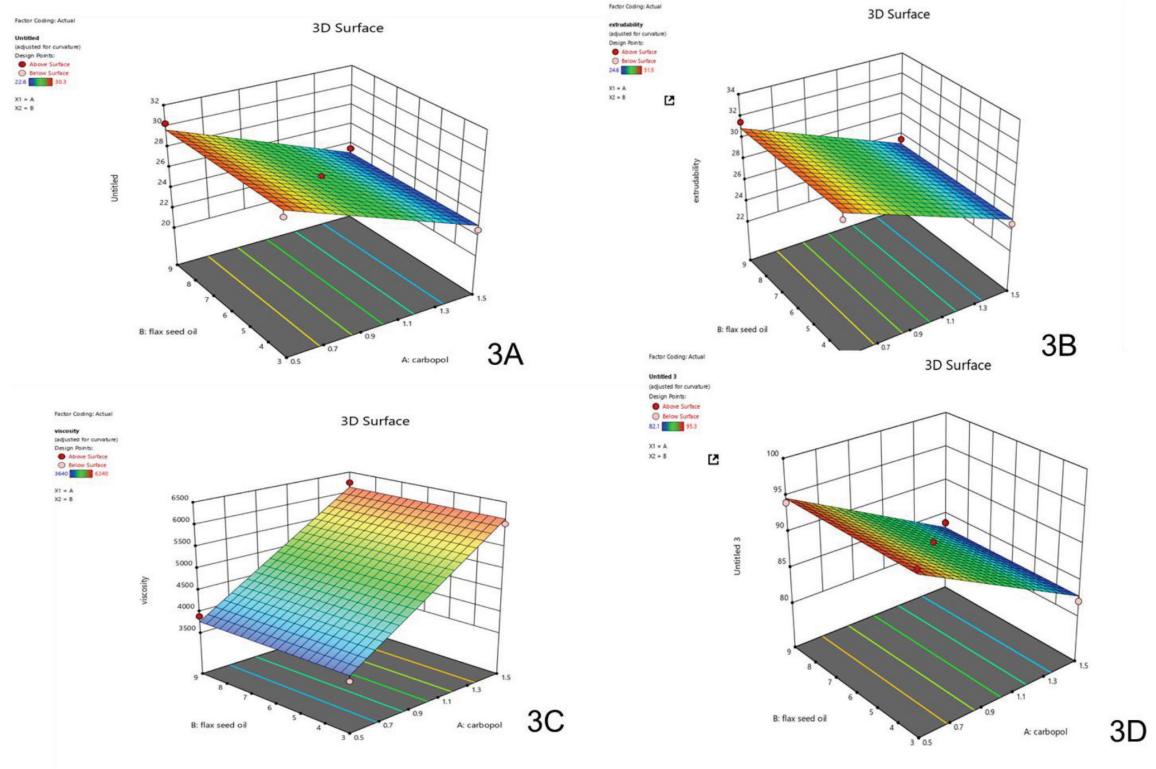


Figure 3A-3D. Impact of independent factors on spreadability (Y1), extrudability (Y2), viscosity (Y3), drug release 10hrs (Y4).

model F-value of 63.94 indicates the significance of the model. It implies only a 1.53% probability that such a high F-value could occur due to random noise. P-values below 0.0500 signify the significance of model terms. In this instance, A is considered a significant model term.

Viscosity Y3 = +4947.50 + 1182.50 A, where the increase in the concentration of the carbapol leads to increase in viscosity, without any impact on the concentration of the oil. The model F-value of 201.74 highlights the significance of the model (Figure 3C). It implies only a 0.49% probability that such a high F-value could occur due to random noise. P-values below 0.0500 indicate the significance of model terms.

Drug release Y4 = +88.78 – 5.93A, the drug release demonstrates an inverse relationship with the concentration of carbapol (Figure 3D). The Model F-value of 152.22 indicates the model's significance. There's just a 0.65% likelihood that an F-value of this size could result from random variation. P-values below 0.05 imply the significance of model terms. In this case, A is considered a significant model term. P-values greater than 0.1 suggest that model terms lack significance.

3.3 Significance of the Statistical Model

The statistical analysis tool ANOVA was used for evaluating to know the significance of the linear models presented in Figures (3A-3E). The model coefficients and their corresponding p-values were examined. During the validation of statistical data for emulgel optimization, key objectives included maximizing spreadability and extrudability, minimizing viscosity and maximizing drug release after 10 hours. An optimization technique employing the desirability function within design-expert software was employed to identify the ideal values of independent experimental factors, including the concentrations of carbopol and olive oil. Based on these parameters, the recommended combination for the optimized formulation (AEE 6) was determined to be 1% carbapol (w/w) and 9% olive oil (w/w). Subsequently, all experimental evaluations were conducted using the optimized emulgels.

3.4 Physico Chemical Evaluation Parameters

The fabricated emulgels were appeared to have pale greenish in colour with uniform consistency and agreeable odour[20]. There is no phase separation was observed. The formulated emulgels (Table 1) were found to have pH range from 5.5- 6.45, spreadability of 23.5- 30.3, extrudability of 24.6 -31.5, viscosity of 3640 – 6240, drug release of 62.17% - 75. 563% (Figure 4). Based on the responses obtained, the design expert has proposed the optimised formulation and the evaluation parameters were depicted in the Table 2.

3.5 Stability Studies

The optimised emulgel formulation AEE 6 was proved to be stable without any changes in the physico-chemical parameters[21].

4. Discussion

Emulgels are the combination of emulsions and gels. Emulgels represent an innovative form of medication tailored for water-insoluble drugs with limited solubility[22]. Addressing the challenge of delivering andrographolide, the primary component of *Andrographis* extract, through emulgels proved to be a successful strategy. The formulation of emulgels was done by an experimental design generated by design software, with a factorial design selected for its simplicity and effectiveness. Five experimental designs

Table 1. Physico chemical evaluation parameters of AEE1-AEE5

Code	Carbapol (%)	Olive oil (%)	pH	Spreadability gm.cm/sec	Extrudability gm/cm	Viscosity (cp)	8 hr release %
AEE 1	0.5	3	5. 83 ± 0.6	29.1± **0.3**	30.34± **0.5**	3640± **234**	75.563
AEE 2	1.5	3	6. 08 ± 0.4	22.6± **0.4**	24.6± **0.6**	6020± 276	62.17
AEE 3	0.5	9	5. 54 ± 0.6	30.3± **0.3**	31.5± **0.4**	3890± 362	74.10
AEE 4	1.0	6	6. 45 ± 0.5	26.5± **0.2**	27.5± **0.5**	4820± **28**1	66.36
AEE 5	1.5	9	6. 29±0.4	23.5± **0.8**	25.5± **0.8**	6240± **59**5	64.67

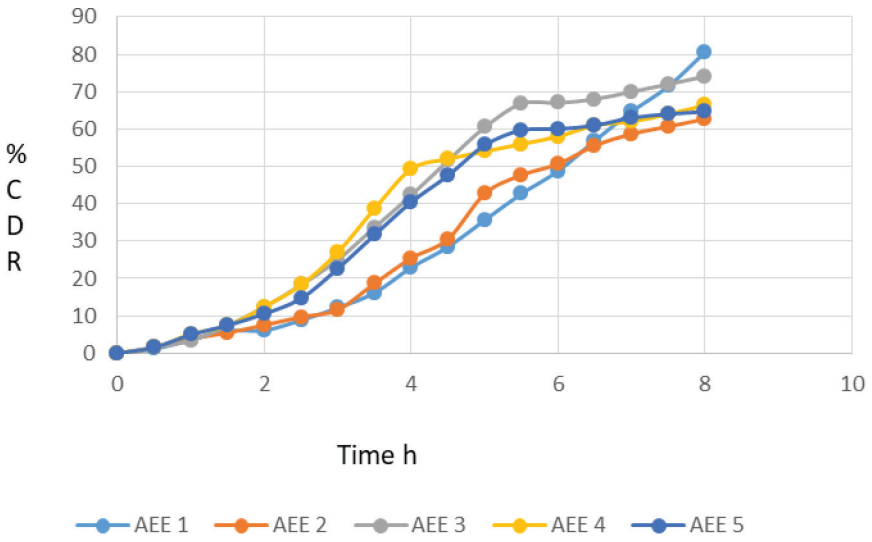


Figure 4. % Cumulative drug release (8h) of the emulgels AEE1- AEE5.

Table 2. Physico-chemical evaluation parameters of optimised formulation AEE6

Code	Carbapol (%)	Olive oil (%)	pH	Spreadability gm.cm/sec	Extrudability gm/cm	Viscosity (cp)	8 hr release %
AEE 6	1	9	5. 62 ± 0.6	29.7± **0.3**	30.92± **0.5**	3765± **234**	74.75

were developed based on varying ratios of carbopol and olive oil, pivotal factors in the formulation process. Physicochemical evaluations, aided by design software, facilitated optimization. pH measurement was essential for assessing emulgel safety and skin compatibility[23]. Spreadability and extrudability, crucial for semisolid dosage forms like emulgels, determined the formulation's quality and applicability. The optimal concentration of gelling agent significantly influenced viscosity, there by affecting drug release. The optimized emulgel formulation, comprising 1% carbopol and 0.9% olive oil, exhibited a pH of 5.62 ± 0.6, indicating compatibility with skin pH and absence of skin irritation. With a spreadability of 29.7 ± 0.3, the optimized emulgel demonstrated ideal applicability and ensured effective release of the active ingredient. Drug release primarily relied on the optimal concentration of the gelling agent or polymer employed. The viscosity of 3765 ± 234 reflected optimal andrographolide release in the emulgel formulation. The optimized emulgel, denoted as AEE 6, achieved a cumulative drug release of 74.75%, underscoring the success of this approach in delivering *Andrographis* extract. This methodological framework holds promise for formulating emulgels effectively.

5. Conclusion

In conclusion, the development of emulgels as a delivery system for andrographolide, a key constituent of *Andrographis* extract, has proven to be a successful strategy. Through careful formulation done by experimental design and physicochemical evaluations, an optimized emulgel formulation was achieved. This formulation exhibited favourable characteristics such asideal spreadability, and optimal drug release. The approach showcased in this study not only addresses the challenge of delivering poorly soluble drugs but also demonstrates the potential of emulgels as a versatile dosage form. Further research and exploration of this methodology hold promise for enhancing drug delivery systems and advancing pharmaceutical formulations.

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