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ORIGINAL ARTICLE / ÖZGÜN MAKALE

DEVELOPMENT AND *IN VITRO* EVALUATION OF *OLEUM ROSMARINI* BASED TOPICAL EMULGEL FORMULATION FOR RHEUMATIC DISEASE

ROMATİK HASTALIKLARA YÖNELİK OLEUM ROSMARİNİ BAZLI TOPİKAL EMÜLJEL FORMÜLASYONUNUN GELİŞTİRİLMESİ VE İN VİTRO DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: *In this study, it was aimed to develop a topical emulgel formulation from o/w type emulsions containing Oleum rosmarini, to be used in the treatment of rheumatoid arthritis.*
Material and Method: *Carbopol 996 and HPMC were used as the water phase and Oleum rosmarini was used as oil phase in the emulsion combinations containing oil, surfactant, copolymer and plasticizer at different rates over different polymer concentrations, to select the appropriate formulation with in vitro formulation studies. Organoleptic controls of the selected formulations were made and characterizations were made in terms of pH, texture profile analysis, rheology evaluation and thermodynamic stability.*
Result and Discussion: *The pH value of the optimized formulations was in the range of 5.5-6.5. The formulations were obtained homogeneously, and no phase separation was observed. It has been observed that the emulgels provide suitable viscosity, flow properties, mechanical properties and have high stability for topical application.*
Keywords: *Essential oil, rheumatoid arthritis, Rosmarinus officinalis, topical emulgel*

ÖZ

Amaç: *Bu çalışmada romatoid artrit tedavisinde kullanılmak üzere Oleum rosmarini içeren y/s tipi emülsiyonlardan topikal bir emüljel formülasyonunun geliştirilmesi ve in vitro karakterizasyonu amaçlanmıştır.*
Gereç ve Yöntem: *In vitro formülasyon çalışmaları ile uygun formülasyonun seçilmesi amacıyla farklı polimer konsantrasyonlarında farklı oranlarda yağ, yüzey aktif madde, kopolimer ve plastizer içeren emülsiyon kombinasyonlarında su fazı olarak Carbopol 996 ve HPMC, yağ fazı olarak Oleum rosmarini kullanılmıştır. Seçilen formülasyonların organoleptik kontrolleri yapılmış ve pH, tekstür profili analizi, reoloji değerlendirmesi ve termodinamik stabilite açısından karakterizasyonları gerçekleştirilmiştir.*
Sonuç ve Tartışma: *Optimize edilen krem formülasyonların pH değeri 5.5-6.5 aralığında olup, formülasyonlar homojen bir şekilde elde edilmiş ve herhangi bir faz ayrımı gözlenmemiştir. Emüljellerin topikal uygulama için uygun viskozite, akış özellikleri, mekanik özellikler gösterdiği ve yüksek termodinamik stabiliteye sahip olduğu belirlenmiştir.*
Anahtar Kelimeler: *Esansiyel yağ, romatoid artrit, Rosmarinus officinalis, topikal emüljel*

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INTRODUCTION

Rheumatoid arthritis is a multisystem disease of unknown cause, characterized by inflammation of the synovial membrane, leading to progressive destruction of joint cartilage, bone erosion, and chronic deformities that may also involve internal organs. Because chronic pain is a common symptom in most rheumatic diseases and the restrictive effect of pain, pain relief is one of the primary goals of antirheumatic treatment goals [1]. *Rosmarinus officinalis* (rosemary) is a medicinal plant originating from the Mediterranean and grown worldwide. Several phytocompounds with pharmacological activities can be isolated from essential oils and extracts of *Rosmarinus officinalis*. Some characteristic chemical constituents of this oil include 1,8-cineole, α-pinene, camphor, bornyl acetate, borneol, camphene, α-terpineol, limonene, and myrcene [2].

Since the direct application of essential oils might irritate the skin, topical application of essential oils requires the design of suitable carriers to eliminate irritating effects and improve patient compliance. Gels are semi-solid dispersions with many benefits, but there are still a lot of restrictions when they relate to how hydrophobic pharmaceuticals can be distributed. To overcome these restrictions, hydrophobic pharmaceuticals can be combined in an emulsion before being added to gels, which are known as emulgels [3]. Emulgels combine the advantages of emulsions with gel technology. Emulgels are oil-in-water (o/w) or water-in-oil (w/o) emulsion-type semi-solid dosage forms with an opaque appearance in which the therapeutic ingredient is encapsulated in the internal phase, permeates through the external phase, and eventually absorbs into the skin to produce a controlled effect [3]. The penetration-enhancing effect of emulgel-based essential oil formulations helps active phytochemicals penetrate the skin. In addition to acting as a matrix for essential oil delivery, emulgels shield the volatile oils from decomposition.

Along with the oil phase content, gelling agents are the key ingredients for the development of emulgels. A variety of gelling agents are utilized, including natural, semi-synthetic, and synthetic types. As a result of the main drawback of natural gelling agents' high microbial breakdown susceptibility, semisynthetic and synthetic gelling ingredients are increasingly utilized in the formulation of emulgels, including hydroxypropyl methylcellulose (HPMC) and carbopol polymers [4].

The aim of this study is to develop an alternative emulgel formulation with HPMC and carbopol as gelling agents, and the *Oleum rosmarini* due to its anti-inflammatory and analgesic effects in the treatment of rheumatoid arthritis; and to investigate its *in vitro* characterization.

MATERIAL AND METHOD

Materials

HPMC, Carbopol 996, triethanolamine (TEA), Tween 20, and propylen glycol were bought from Sigma-Aldrich (USA). *Oleum rosmarini* was bought from Talya Bitkisel (Antalya, Turkey).

Methods

Formulation Studies

Emulgel formulations were prepared by the emulsification technique. Carbopol 996 and HPMC were used as the water phase, and *Oleum rosmarini* was added as the oil phase. Tween 20 was applied as a surfactant, while propylene glycol was added as a plastizer. Different ratios of the formulation ingredients were evaluated, given in Table 1.

Among the formulations that are suitable in terms of the specified features, the most ideal formulation in which the active ingredient *Oleum rosmarini* was used highest and the excipients were used less was determined [5,6].

Based on the determined F33 formulation, 6 more formulations were prepared by making changes to various components, as presented in Table 2.

Table 1. Composition of different emulgel formulations prepared in preformulation studies

Code	Water Phase				Oil Phase		
	Carbopol (g)	**HPMC (g)**	**TEA (g)**	**Distilled water (qs)**	***Oleum rosmarini* (g)**	**Tween 20 (g)**	**Propylene glycol (g)**
F1	1.0	2	-	100	20	3	5
F2	0.5	2	-	100	20	3	5
F3	0.1	2	-	100	20	3	5
F4	1.0	5	-	100	20	3	5
F5	0.5	5	-	100	20	3	5
F6	0.1	5	-	100	20	3	5
F7	1.0	2	0.50	100	20	3	5
F8	0.5	2	0.25	100	20	3	5
F9	0.1	2	0.10	100	20	3	5
F10	1.0	5	0.50	100	20	3	5
F11	0.5	5	0.25	100	20	3	5
F12	0.1	5	0.10	100	20	3	5
F13	1.0	2	-	100	20	6	5
F14	0.5	2	-	100	20	6	5
F15	0.1	2	-	100	20	6	5
F16	1.0	5	-	100	20	6	5
F17	0.5	5	-	100	20	6	5
F18	0.1	5	-	100	20	6	5
F19	1.0	2	0.50	100	20	6	5
F20	0.5	2	0.25	100	20	6	5
F21	0.1	2	0.10	100	20	6	5
F22	1.0	5	0.50	100	20	6	5
F23	0.5	5	0.25	100	20	6	5
F24	0.1	5	0.10	100	20	6	5
F25	1.0	2	-	100	30	3	5
F26	0.5	2	-	100	30	3	5
F27	0.1	2	-	100	30	3	5
F28	1.0	5	-	100	30	3	5
F29	0.5	5	-	100	30	3	5
F30	0.1	5	-	100	30	3	5
F31	1.0	2	0.50	100	30	3	5
F32	0.5	2	0.25	100	30	3	5
F33	0.1	2	0.10	100	30	3	5
F34	1.0	5	0.50	100	30	3	5
F35	0.5	5	0.25	100	30	3	5
F36	0.1	5	0.10	100	30	3	5
F37	1.0	2	-	100	30	6	5
F38	0.5	2	-	100	30	6	5
F39	0.1	2	-	100	30	6	5
F40	1.0	5	-	100	30	6	5
F41	0.5	5	-	100	30	6	5
F42	0.1	5	-	100	30	6	5
F43	1.0	2	0.50	100	30	6	5
F44	0.5	2	0.25	100	30	6	5
F45	0.1	2	0.10	100	30	6	5
F46	1.0	5	0.50	100	30	6	5
F47	0.5	5	0.25	100	30	6	5
F48	0.1	5	0.10	100	30	6	5

Table 2. Formulations prepared by changing the component amounts over the F33 formulation

Code	Water Phase				Oil Phase		
	Carbopol (g)	**HPMC (g)**	**TEA (g)**	**Distilled water (qs)**	***Oleum rosmarini* (g)**	**Tween 20 (g)**	**Propylene glycol (g)**
F49	0.1	2	0.1	100	30	1	5
F50	0.1	2	0.1	100	30	3	2.5
F51	0.1	2	0.1	100	30	3	10
F52	0.1	2	-	100	30	1	5
F53	0.1	2	-	100	30	3	2.5
F54	0.1	2	-	100	30	3	10

Characterization of the Emulgels

Organoleptic Properties

Various organoleptic properties, including appearance, homogeneity, phase separation, spreadability, and immediate skin feeling upon application, were examined for every formulation. Visual assessments were made of appearance and phase separation properties. Sensory characteristics were assessed by rubbing emulgels into the skin on the dorsal side of the hand or between two fingers [7]. Homogenity was evaluated by pressing a standard amount (100 mg) of the formulations between the thumb and the index finger in order to notice the consistency of the emulgel and whether any coarse particles were being adhered to or removed from the finger [8].

pH

pH values of the emulgels were determined with a digital pH meter (Mettler Toledo, Switzerland) in triplicate, and average values with standard deviations were recorded [9].

Texture Profile Analysis (TPA)

The mechanical properties of the emulgels, including hardness, adhesiveness, cohesiveness, and compressibility, were evaluated using a texture analyzer (TA.XT.PlusC, Stable Micro System, Haslemere, Surrey, UK), equipped with a 5 kg load cell. The tests were performed with a Perspex probe having a 10 mm diameter (SNSP/10, h : 10 mm) and 20 g of each emulgel formulation placed into a suitable beaker at 25 ± 0.5 °C. The pre-test, test, and post-test speeds were 2 mm/s each, with a trigger force of 0.001 N. The compression depth in each test was 10 cm, and the delay period between two compressions was 10 s. All measurements were done in triplicate for each formulation, and the Texture Exponent Connect 8.0.5.0 software package was used to determine the mechanical properties of the emulgels [10].

Rheological Properties

Rheological measurements, including shear stress, shear rate, and apparent viscosity, were performed using a cone and plate Brookfield rheometer (Brookfield DV3THACJ0, Middleboro, MA, USA) in triplicate in a temperature-controlled environment at 25 ± 0.5 °C, and rotational speed was ranged from 10-100 rpm. Data were obtained by the RheoWin 4.87.0006 (Haake®) software [9].

Stability Evaluation

The prepared emulgel formulations were characterized in heating-cooling cycles and centrifuge conditions to evaluate their thermodynamic stability. The samples were evaluated in terms of phase separation and physical appearance under stress conditions. Emulgels were incubated at 4 and 40 °C (24 h) for 3 cycles and examined for phase separation. Additionally, a centrifuge test was performed for 10 minutes at 3500 rpm with 3 repetitions [11].

RESULT AND DISCUSSION

Rosemary essential oil is reported to have many biological activities such as antioxidant, anticarcinogenic, antibacterial, analgesic and antimicrobial, antifungal, antioxidant, and anti-inflammatory activities [12,13]. Among the chemical components of rosemary essential oil, 1,8-cineole, α-pinene, camphor, bornyl acetate, borneol, camphene, α-terpineol, limonene, β-pinene, β-caryophyllene, and myrcene compounds are defined as the characteristic components of this oil [2]. The pharmacological activities of *Rosmarinus officinalis* essential oil are attributed to its 1,8-cineole, camphor, and α-pinene components. *Rosmarinus officinalis* is employed in traditional medicine for its antiinflammatory, analgesic, and antibacterial properties in muscles and joints [14]. Because of its antiinflammatory and antiarthritic properties, *Rosmarinus officinalis* has shown promise in modulating rheumatoid arthritis, with the *in vivo* studies in the literature [15].

Topical application stands out in terms of providing the opportunity to administer drugs with a non-invasive method and also with its advantages, such as not being exposed to first pass metabolism, reduced side effects, ease of application, and also removal, thus improving patient compliance [16,17]. Recently, delivery of bioactive molecules derived from medicinal plants by the topical formulations gained increasing interest due to improving the biological qualities and bioavailability of the plant constituents in treatment of various conditions [18].

One of the formulations developed for topical application is emulgels. Emulgels are described as semi-solid emulsions of either the w/o or the o/w type dosage forms, with consistency varying according to the type of oil and gelling agent used [19]. Emulsions are heterogeneous systems in which one phase is finely dispersed in another, and the dispersed phase can be hydrophobic-based (w/o) or aqueous-based (o/w) [20]. Oil-in-water emulsions are widely used in various industrial applications, such as the food industry, pharmaceutical, or cosmetic fields [21]. In our study, o/w emulsion-type emulgel formulations were developed as Carbopol 996, HPMC, and TEA in the water phase; Tween20, propylene glycol, and rosemary oil were used as the oil phase.

Rosemary oil is included in the formulation as the active ingredient and is added to the internal phase due to its volatile properties. In all developed emulgel formulations, the inner phase is determined as the oil phase and the continuous phase as the water phase.

Carbopol is a high molecular weight synthetic polymer of acrylic acid that helps formulate low-irritating topical dosage forms, providing good characteristics, skin feel, and drug penetration properties [22]. The most appealing features of carbopol as a mucoadhesive agent for topical application are that it is less costly, non-irritating, biodegradable, and not absorbed into the body [23].

HPMC is one of the most frequently used cellulosic polymers available to develop topical drug delivery systems. HPMC can be employed for emulsification, adhesion, thickening, film formation, and gelation, depending on the molecular weight and viscosity selected. It is composed of linked polymeric units that hold onto water, making it a great hydrophilic gel-forming polymer [24]. Furthermore, HPMC exhibits minimal drug interaction and has been shown to promote bioadhesion and local drug delivery by improving retention [25].

Surfactants are components that enable the formation of stable emulsions. While o/w emulsions are prepared with hydrophilic surfactants, w/o emulsions are prepared with lipophilic substances. Surfactants are adsorbed at the oil-water interface, reducing the interfacial tension and ensuring stable mixing of water and oil [26]. In recent years, surfactants such as polysorbates (Tweens) and co-surfactants such as propylene glycol have been used widely in the formulations [27,28].

Propylene glycol is a widely used excipient in many cosmetics, topical skin preparations, medications, and foods [29]. It is known that this excipient is safe to use even at high concentrations. Although it acts as a co-solvent in some preparations, it is also preferred in many formulations due to its skin care properties [30]. Due to the advantages of propylene glycol, such as being safe at high concentrations and being widely used, a fixed concentration of propylene glycol was used in our formulations.

Tween 20 was used as a surfactant in the developed formulations. The HLB value of Tween 20 is known to be approximately 16.7 [31]. This value ensures that the hydrophilic feature of the substance is high and that it has the ability to make water into the outer phase of the formulation [32]. As a

surfactant, Tween 20 has the ability to mix with both phases. While preparing the formulations, it was dispersed in the oil phase. Surfactants found in topical formulations can increase skin permeability and affect the physicochemical properties of the formulation, as well as causing skin irritation [33]. For this reason, surfactant concentrations were used within confidence limits when developing the formulation.

Characterization of the Emulgels

Within the scope of our study, organoleptic controls, pH analysis, TPA, rheological measurements, and thermodynamic stability analyses were carried out as characterization studies in the formulations. In organoleptic controls, it was examined in terms of color, spreadability, phase separation, homogeneity, and appearance.

Spreadability properties analyzed in organoleptic evaluation play a key role in defining both the efficiency of the product and its acceptance by the consumer. Reliability was evaluated at three levels: poor, moderate, and good.

Some of the emulgels developed in preformulation studies had phase separation, coarse particles, or non-ideal properties, as presented in Table 3. All optimized formulations developed in the study had a smooth texture and no evidence of phase separation. A physical evaluation was performed by pressing a small amount of the formulation between the thumb and the index finger. Based on the spreadability, appearance, homogenity, and stability, F27, F31, F32, and F33 formulations were found to be satisfactory. Among these four formulations, F33 was chosen for deriving six additional formulations (F49, F50, F51, F52, F53, and F54) by modifiying the formulation components due to having the highest *Oleum rosmarini* and the least excipient content. As a result of thermodynamic characterization studies, phase separation was observed in the F52 and F53 formulations. It was observed that other optimized formulations were homogeneous and consistent without containing any coarse particles. In terms of the immediate skin feeling after application, most formulations did not leave an oily feeling, and they are thought to be ideal in terms of spreadability.

Table 3. Organoleptic evaluation of the emulgel formulations

Formulation	Spreadability	Phase Separation	Homogenity	Immediate Skin Feel	Appearance
F1	+	No separation	Homogeneous	Poor	Good
F2	++	No separation	Not	Good	Good
F3	+++	No separation	Homogeneous	Good	Good
F4	+++	No separation	Homogeneous	Moderate	Good
F5	++	No separation	Not	Good	Poor
F6	+	No separation	Not	Moderate	Poor
F7	+	No separation	Homogeneous	Moderate	Moderate
F8	++	No separation	Homogeneous	Moderate	Moderate
F9	+++	No separation	Homogeneous	Good	Good
F10	++	No separation	Homogeneous	Good	Good
F11	++	No separation	Homogeneous	Good	Good
F12	++	No separation	Homogeneous	Good	Good
F13	+++	No separation	Homogeneous	Good	Good
F14	++	No separation	Homogeneous	Good	Good
F15	+++	No separation	Homogeneous	Good	Good
F16	+	No separation	Not	Moderate	Moderate
F17	+	No separation	Not	Poor	Poor
F18	+	Separation	Not	Poor	Poor
F19	++	No separation	Homogeneous	Good	Good
F20	+	No separation	Not	Poor	Poor
F21	+	Separation	Not	Poor	Poor
F22	+	Separation	Not	Poor	Poor
F23	+	No separation	Not	Moderate	Poor
F24	+	Separation	Not	Poor	Poor

Table 3 (*continue*). Organoleptic evaluation of the emulgel formulations

Formulation	Spreadability	Phase Separation	Homogenity	Immediate Skin Feel	Appearance
F25	+	Separation	Not	Poor	Poor
F26	+++	No separation	Homogeneous	Good	Good
F27	+++	No separation	Homogeneous	Good	Good
F28	+	No separation	Homogeneous	Good	Good
F29	++	No separation	Homogeneous	Moderate	Moderate
F30	+	No separation	Homogeneous	Moderate	Good
F31	+++	No separation	Homogeneous	Good	Good
F32	+++	No separation	Homogeneous	Good	Good
F33	+++	No separation	Homogeneous	Good	Good
F34	+	No separation	Not	Moderate	Poor
F35	+	Separation	Not	Poor	Poor
F36	++	No separation	Homogeneous	Moderate	Good
F37	++	No separation	Homogeneous	Good	Good
F38	++	No separation	Homogeneous	Moderate	Good
F39	++	No separation	Homogeneous	Moderate	Good
F40	+	No separation	Not	Poor	Poor
F41	+	No separation	Not	Moderate	Poor
F42	+	Separation	Not	Poor	Poor
F43	++	No separation	Homogeneous	Moderate	Good
F44	++	No separation	Homogeneous	Moderate	Good
F45	++	No separation	Homogeneous	Good	Good
F46	++	No separation	Homogeneous	Moderate	Good
F47	+	No separation	Not	Moderate	Moderate
F48	+	No separation	Homogeneous	Moderate	Good
F49	+++	No separation	Homogeneous	Good	Good
F50	+++	No separation	Homogeneous	Good	Good
F51	+++	No separation	Homogeneous	Good	Good
F52	+	Separation	Not	Poor	Poor
F53	+	Separation	Not	Poor	Poor
F54	+++	No separation	Homogeneous	Good	Good

* +++: proper spreadability, ++: moderate spreadability, +: not spreadable

Upon organoleptic evaluation, F27, F31, F32, F33, F49, F50, F51, and F54 were chosen for further studies due to their better spreadability, stability (phase separation), homogenity, immediate skin feel, and physical appearance for topical application.

pH values of the formulations were determined between 5.4±0.1 and 6.3±0.1, respectively (Table 4), and found to be suitable for topical delivery [34].

Rheological properties, depending on the formulation viscosity, elasticity, and flow model, affect the manufacturing, appearance, packaging, long-term stability, and in vivo performance of the product. Biopharmaceutical properties such as drug release and permeation may also vary depending on the rheological profile of the formulation. For these reasons, rheology behavior is an important feature to determine the compliance of semisolid formulations with quality standards appropriate to the target product profile [33]. Since viscosity can affect the release of the drug by changing the diffusion rate, it holds significance in the behavior of semi-solid formulations [16,35]. When the rheograms of the selected formulations are examined, the viscosity values of the formulations at the same shear stress are as follows in increasing order: F54, F27, F51, F33, F50, F49, F32, F31 (Table 4). It was observed that F31 and F32 formulations had a much higher viscosity value compared to other formulations against the same shear stress, and addition of the TEA increased the viscosity of the formulations [36].

It is thought that these two formulations are not suitable in terms of spreadability and will prevent the active ingredient from passing into the skin. For these reasons, therapeutic effectiveness and bioavailability may be lower compared to other formulations.

Table 4. pH and viscosity values of the emulgel formulations

Formulation	pH ± SD	Viscosity (mPa.s) ± SD
F27	5.7 ± 0.1	296 ±17
F31	6.2 ± 0.1	665 ±82
F32	6.3 ± 0.1	664 ±28
F33	6.2 ± 0.1	377 ±2
F49	5.8 ± 0.1	396 ± 12
F50	5.9 ± 0.1	353 ± 5
F51	6.1 ± 0.1	336 ± 2
F54	5.4 ± 0.1	249 ± 15

When stress is applied to topical semi-solid dosage forms by increasing the shear rate, it decreases the viscosity, which makes it easier to apply to the skin, implying a non-Newtonian behavior [37]. Therefore, a certain critical stress value (shear stress) is required for the formulation to start flowing. Below this value, the formulations show largely elastic properties, while above this value, they generally show plastic flow [38]. When the rheograms were examined (Figure 1-2), the shear rate versus shear stress was evaluated, and a system that became thinner as the stress increased was observed, and as the shear rate increased, the viscosity decreased [39]. This indicates that the prepared formulations show pseudoplastic flow properties. Significant deviations were observed in the rheograms of F31 and F32 formulations compared to other formulations, flow property was preserved in F27, F33, F49, F50, F51, and F54 formulations.

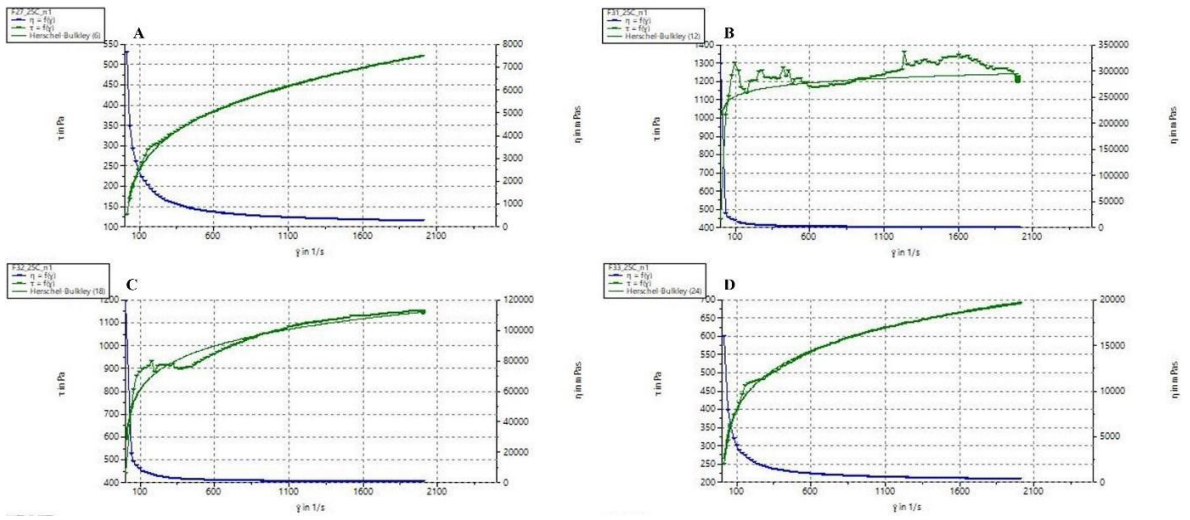

Figure 1. Rheograms of the formulations measured at 25°C. (A: F27, B: F31, C: F32, D: F33). (τ: shear stress, γ̇: shear strain, Pa: stress in pascals; x axis = γ̇ in 1/s, y axis = τ in Pa)

The most widely utilized method for analyzing the mechanical characteristics of pharmaceutical semi-solid formulations is TPA, which can be used to supplement rheological data by identifying interactions between formulation components [40]. The hardness is the force needed to atain deformation, thus involving the removal of formulation from the packaging in the first place and helping determine the degree of deformation [41]. When the hardness of the formulations is compared, it is

observed that the hardness of the F31 and F32 formulations is quite high compared to other formulations. On the other hand, the lowest hardness values were observed in F27 and F33 formulations (Table 5). The work required to overcome the attractive force between the surface of the sample and the probe is related to the adhesion parameter [42]. A high adhesion value contributes to bioavailability by increasing the retention time of the drug [43].

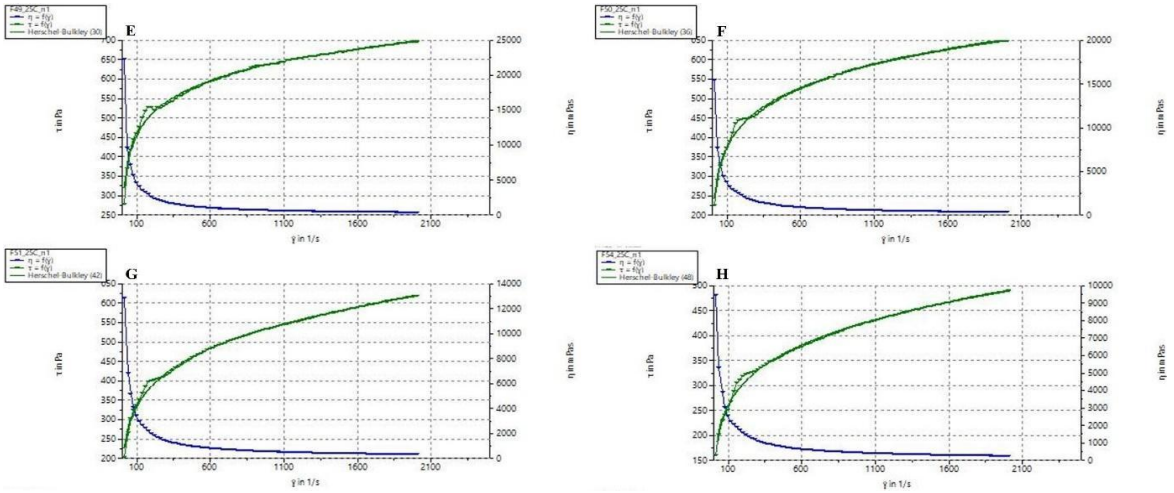

Figure 2. Rheograms of the formulations measured at 25°C. (E: F49, F: 50, G: F51, H: F54). (τ: shear stress, ɣ̇: shear strain, Pa: stress in pascals; x axis = ɣ̇ in 1/s, y axis = τ in Pa)

Cohesion refers to the internal strength of the bonds to hold the network together [44]. Among the formulations developed, the formulation with higher adhesion and lower cohesion values results in low interaction with the skin and accordingly provides high ease of application [41]. Accordingly, while the adhesion property was higher in the F31 and F32 formulations compared to the others, approximate values were observed in the other formulations, and at the same time, the cohesion value showed the lowest value in the F33 formulation. For this reason, the spreadability of the F33 formulation and therefore patient compliance is thought to be high. Formulations F31 and F32 are found to be not suitable due to their high adhesion and hardness properties (Table 5). This finding is also supported by rheology results in terms of viscosity and flow models of the formulations (Table 4, Figure 1-2).

Table 5. TPA of the emulgel formulations.

Formulation	Hardness (N) ± SD	Compressibility (N.mm) ± SD	Adhesiveness (N.mm) ± SD	Cohesiveness ± SD
F27	0.016 ± 0.001	0.019 ± 0.001	0.047 ± 0.002	0.899 ± 0.004
F31	0.152 ± 0.016	0.195 ± 0.028	0.142 ± 0.011	0.949 ± 0.047
F32	0.157 ± 0.022	0.247 ± 0.034	0.151 ± 0.018	0.936 ± 0.022
F33	0.020 ± 0.001	0.025 ± 0.001	0.060 ± 0.002	0.855 ± 0.073
F49	0.030 ± 0.001	0.041 ± 0.000	0.071 ± 0.001	0.916 ± 0.019
F50	0.022 ± 0.000	0.026 ± 0.001	0.061 ± 0.002	0.882 ± 0.014
F51	0.024 ± 0.001	0.028 ± 0.001	0.063 ± 0.000	0.878 ± 0.023
F54	0.029 ± 0.000	0.025 ± 0.001	0.054 ± 0.002	0.862 ± 0.035

Conclusion

In this study, an emulsion-type emulgel was prepared using *Oleum rosmarini* for use in the treatment of rheumatoid arthritis [18]. The prepared emulgels were evaluated in terms of pH, viscosity,

rheological properties, thermodynamic stability, organaleptic properties, and texture profile analyses. While preparing the emulgels, different proportions of HPMC, carbopol, propylene glycol, TEA, Tween 20, and rosemary oil were used, and among the formulations, characterization tests continued with F27, F31, F32, F33, F49, F50, F51, F52, F53 and F54. The stability of emulgels was tested against the stress conditions, including heating-cooling cycles and centrifuge conditions. Upon evaluation of thermodynamic stability, there was no observed phase separation except for F52 and F53 formulations. Further studies continued with F27, F31, F32, F33, F49, F50, F51 and F54. The prepared emulgel formulations showed good spreadability on the skin. In organaleptic examinations of the formulations, it was observed that they were ideal in terms of homogeneity and immediate skin feel. As a result of rheological examinations, it was observed that the optimized formulations were suitable for pseudoplastic flow type. As a result of *in vitro* characterization tests, the F33 formulation was thought to be ideal in comparison with the others. In this study, a suitable formulation in terms of its physicochemical properties was developed by using rosemary oil, an active ingredient of natural origin.

AUTHOR CONTRIBUTIONS

Concept: T.Ç., N.T., U.M.G., S.D.K.; Design: T.Ç., N.T., U.M.G., S.D.K.; Control: T.Ç., U.M.G.; Sources: U.M.G., S.D.K.; Materials: U.M.G., S.D.K.; Data Collection and/or Processing: T.Ç., N.T., U.M.G.; Analysis and/or Interpretation: T.Ç., N.T., U.M.G.; Literature Review: N.T., U.M.G.; Manuscript Writing: T.Ç., N.T., U.M.G.; Critical Review: T.Ç., N.T., U.M.G., S.D.K.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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