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Research Article

Preparation of Aloe Vera Gel Containing Solid Lipid Nanoparticles for Treatment of Eczema

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Abstract

Atopic dermatitis, also known as eczema, is a chronic skin disorder that occurs as a result of many diseases and genetic factors. Decreased filaggrin and ceramide levels in the epidermis are considered the prime pathogenesis of atopic dermatitis.Aloe vera contributes to the treatment of atopic dermatitis thanks to its anti-inflammatory, moisturizing and immune response regulating properties. SLN were characterized using UV-Visible Spectroscopy, Fourier Transform Infrared Spectroscopy (FTIR), Scanning Electron Microscopy (SEM). BMV-loadedSLN (BMV-SLN) was analyzed by FTIR and SEM. Release of BMV from nanoparticles and its free solution form was also achieved. The gel formulation of BMV-SLN was developed using Carbopol 940 and Aloe vera. BMV bound to SLN with 87% efficiency, and controlled release of BMV from the nanoparticles was observed. BMV-bound SLN gel was formulated at pH 5.9. This gel formulationhavethe potential to be used in treatment problems caused by atopic dermatitis.

Keywords: Eczema, solid lipid nanoparticle, betamethasone valerate, Aloe vera gel.

Egzema Tedavisine Yönelik Katı Lipid Nanopartiküller İçeren Aloe Vera Jel Hazırlanması

Öz

Egzama olarak da bilinen atopik dermatit, birçok hastalık ve genetik faktör sonucu oluşan kronik bir cilt rahatsızlığıdır. Epidermisteki azalmış filaggrin ve seramid düzeyleri, atopik dermatitin ana patogenezi olarak kabul edilmektedir. Aloe Vera, anti-inflamatuar, nemlendirici ve immun yanıtı düzenleyici düzenleyici özellikleri sayesinde atopik dermatitin tedavisine katkıda bulunur. SLN, UV-Görünür Spektroskopisi, Fourier Dönüşümlü Kızılötesi Spektroskopisi (FTIR), Taramalı Elektron Mikroskobu (SEM) kullanılarak karakterize edilmiştir. BMV yüklüSLN (BMV-SLN), FTIR ve SEM ile analiz edilmiştir. BMV-SLN'nin jel formülasyonu, Carbopol 940 ve Aloe vera kullanılarak geliştirilmiştir. BMV, SLN'ye %87 verimlilikle yüklenmiştir ve nanopartiküllerden BMV'nin kontrollü salımı gözlemlenmiştir. BMV yüklü SLN jeli, pH 5,9'da formüle edilmiştir. Bu jel formülasyonun atopik dermatitin neden olduğu sorunların tedavisinde kullanılma potansiyeli olduğu söylenebilmektedir.

AnahtarKelimeler: Egzama, katı lipid nanopartikül, betametazonvalerat, Aloe vera jel.

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1. Introduction

Atopic dermatitis, also known as atopic eczema, is a chronic inflammatory skin disorder caused by the interaction between multiple genetic and environmental factors. It is characterized by itchy and scaly skin lesions, often localized on the flexural surfaces of the body [1].Today, the prevalence of atopic dermatitis worldwide is increasing significantly. The disease occurs in 20% of children and 1%-3% of adults)[2].It causes difficulties in the daily lives of patients, reduces their quality of life, and limits their mobility. Atopic dermatitis is a chronic inflammatory skin condition that requires a multifaceted approach to treatment.The aim of treatment is to restore epidermal barrier function and reduce skin inflammation. This can be achieved by moisturizing the skin and using topical anti-inflammatory agents such as topical corticosteroids and calcineurin inhibitors[3].

Betamethasone Valerate is a highly potent topical corticosteroid. Betamethasone is a topically inactive synthetic corticosteroid. To be effective topically, it needs to be administered in the form of esters such as betamethasone 17-valerate or betamethasone 17,21-dipropionate. The esterified form usually has an increased lipophilic structure, which allows the drug molecule to better penetrate through the lipid membrane of the skin. It helps to relieve swelling and irritation of the skin. Since its effects on humans and animals are well known, it is frequently used in adults and children.[2]

Nanoparticles, solid lipid nanoparticles, nanosuspension, nanoemulsion and nanocrystals are important drug delivery systems developed using nanotechnology principles[4]. Solid lipid nanoparticles (SLNs) are aqueous colloidal dispersions with sizes ranging from 10 to 1000 nanometers, consisting of a matrix of solid, biodegradable lipids. SLNs have been developed for penteral, oral, rectal, dermal, and pulmonary applications. SLNs are widely preferred due to their properties such as excellent biocompatibility, lack of biotoxicity, controlled drug release and drug targeting, increased drug stability, high drug carrying capacity, and better transport of lipophilic drugs [5].

Gel formulations are one of the forms of medication used in the treatment of atopic dermatitis. Gels contain active ingredients dissolved or dispersed in a matrix containing water and other solvents. The use of gel formulations in treatment has many advantages. They are easy to apply and quickly absorbed, as well as ensuring that the active ingredients of the product are effectively absorbed, and the symptoms of the disease are relieved. However, there are some important points to consider. Gels are affected by heat and humidity, so the product should be stored at the appropriate temperature.In conclusion, gel formulations are an effective treatment method in the treatment of atopic dermatitis[6].

The Aloe vera plant has been used for centuries for its health, beauty, medicinal and skin care properties.It contains 77 potentially active compounds, including vitamins, enzymes, minerals, fatty acids, sugar, lignin, saponin, salicylic acid and amino acids.Thanks to the substances it contains, it has healing, protection from ultraviolet and gamma rays, anti-inflammatory,

antiviral, moisturizing, anti-aging, antiseptic and immune system effects.Aloe vera is used in atopic dermatitis due to its anti-inflammatory, moisturizing and immune response regulating effects [7].

The values that make this study unique can be considered as the preparation of the gel form ofdrug loaded solid lipid nanoparticles, making it easy to apply, increasing the speed of action, efficacy and absorption of the drug from the skin. It is thought that solid lipid nanoparticles could affect the area where the drug should affect at higher rates, reducing the drug dosage that should be used in the treatment, thus protecting patients from possible side effects and providing a positive effect on their economic situation by using the drug for a shorter period of time. In addition the anti-microbial, anti-inflammatory, wound healing, antioxidant and immune-boosting properties of the Aloe vera extract could reduce the treatment of the factors that cause the disease and the possibility of the disease recurring.

The advantage of the study compared to the currently used treatments is that it is loaded into a delivery system, allowing the drug to affect the treated area directly, effectively, quickly and in a controlled manner, thus shortening the recovery period of the patients. Compared to the drug loaded treatment systems used with the Aloe vera gel in its content, it contributes to the healing of the disease with its anti-inflammatory and moisturizing effects. It is shown that this formulation, prepared in a simple and economical way, could contribute to human health by treating the pain, itching and problems that prevent patients from daily life due to eczema more effectively and in a shorter time.

2. Materials and Methods

2.1 Materials

Betamethasone 17-Valerate (BMV), Cetyl Palmitate (CP), Polysorbate 80 and Acetonitrile were purchased from Sigma- Aldrich. Carbopol 940 was bought from Acros Organics and Triethanolamine (TEA) was purchased from Carlo Erba. All other chemicals used were of analytical grade and were used without any further processing or purification.

2.2 Synthesis of Solid Lipid Nanoparticles

Solid lipid nanoparticle synthesis was performed following procedure reported by Ak. et al., 2021 [8]. Solid lipid nanoparticles were formulated using combination of the two techniques named high shear homogenizer and ultrasonication. Aqueous phase, containing Tween- 80, was heated up to 65℃ in water bath. 100 mg cetyl palmitate (lipid phase) was heated up to the same temperature separately. Two hot phases were then mixed together just before homogenization, and pre-emulsion was achieved using a high-speed homogenizer (Ultraturrax, Isolab) at 22000 rpm for 2 min. This pre-emulsion continued to be homogenized for 1 min in a sonic bath. Subsequently, the emulsion was quickly cooled to 4℃. The emulsion was left until it reached room temperature. In order to obtain pure nanoparticles, they were placed in a pre-heated

dialysis membrane (12000-14000 MWCO) (Sigma-Aldrich) and they weredialyzed against 50 mL of pure water at room temperature for 4 hours [9].

2.3 Encapsulation of BMV into SLN

The same techniques used for preparing drug- free SLN were applied for the formulation of SLN loaded with BMV. BMV solutions prepared with acetonitrile to final concentrations of 0.25, 0.5, 0.75, 1, 1.25 mg/mL were added to the melten lipid phase at 65 °C and the procedure above was applied. Dialysisprocedure was performed to remove free drug and to determine drug loading efficiency. 2 mL of drug loaded SLN were placed in a pre-heated dialysis membrane and dialysis was performed against 50 mL of d-water at room temperature for 4 hours [9]. The dialysis samples analyzed by UV- VIS spectrophotometer (Cary UV Vis 60 spectrophotometer)using calibration graph at 236 nm.The drug loading efficiency (DLE %) was given by the formula 1:

$$\text{Drug loading efficiency (DLE)}(\%) = \frac{[(\text{Initial drug amount}(\mu g) - \text{Unbound drug amount}(\mu g)]}{[\text{Initial drug amount}(\mu g)]} \text{x}100 \quad (1)$$

2.4 Characterization Studies

The chemical structures of dried SLN and BMV-loaded SLN were analyzed using fourier transform infrared spectroscopy (FTIR). The sample was compressed into a transparent disk and scanned from 4000 to 400 cm^{-1} using an average of 16 scans, with a resolution of 1 cm^{-1}. Scanning electron microscopy (SEM) was used to determine the morphological structure and size of gold-coated SLN and gold-coated drug-loaded SLN.

2.5 In vitro Drug Release

In vitro drug release studies were performed using the dialysis membrane with an MWCO value of 12000-14000 (Sigma-Aldrich) in 10 mL 10 mM phosphate buffer (pH 7.4) and 10 mL10 mM acetate buffer (pH 5.5). 2 mL of BMV-loaded SLN dispersion was taken into the dialysis membrane and dialyzed at 300 rpm at 32°C and 37°C for 48 hours. At the intervals of 0.5, 1, 2, 4, 6, 8, 24 and 48h, all dialysis media replaced with a fresh buffer at the same temperature[10].The amount of released BMVwas determined using UV- VIS spectrophotometer at 236 nm. Cumulative drug release was calculated using the following formula 2:

$$\text{Cumulative release}(\%) = \frac{\text{Amount of drug released}(\mu g)}{\text{Initial drug amount}(\mu g)} \text{x}100 \quad (2)$$

In vitro free drug release studies were performed using the dialysis membrane in 10 mL 10 mM phosphate buffer (pH 7.4) and 10 mL 10 mM acetate buffer (pH 5.5). BMV was prepared in a mixture of acetonitrile and distilled water 1:1 (v/v) with final concentration 1mg/mL.1 mL ofdrug solution was taken into the dialysis membrane and dialyzed at 300 rpm at 37°C for 24 h. At the intervals of 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 24h, all dialysis media replaced with a

warm fresh buffer at the same temperature[10].The amount of released BMVwas determined and cumulative drug release was calculated using formula (2).

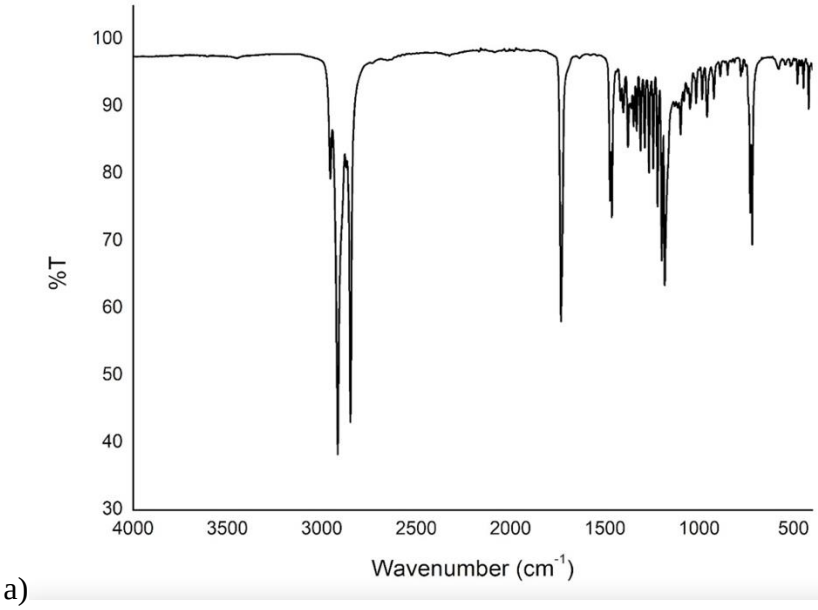
2.6 Preparation of Aloe Vera Gel Formulation Containing BMV-SLN

Carbopol 940, prepared as 1% (w/v), was stirred with a magnetic stirrer for 24 h[11].In order to form the gel structure TEA was added to the Carbopol 940, which was stirred with the magnetic stirrer at 3000 rpm and the pH was adjusted to 6.00[12].Aloe vera leaves were washed with chlorinated water, cut and the gel inside was collected.The obtained gel was homogenized with a blender. After the homogenization process, the obtained extract was filtered and stored at +4°C[13].5 g of the prepared carbopol gel was taken and 1, 2, 2.5 and 3 mL of Aloe vera extract and 1.8 mg (optimized amount) of BMV containing nanoparticle dispersion were added into the gel. The formulations were evaluated based on pH and spreadability.

3. Results and Discussion

3.1 Synthesis and Characterization of Solid Lipid Nanoparticles

In this study, solid lipid nanoparticles consisting of cetyl palmitate lipid as a solid core coated with aqueous surfactant were obtained. Solid lipid nanoparticles were synthesized by high-speed homogenization and ultrasonication at temperatures above the melting temperature to ensure homogenization of the lipid emulsion [14]. FTIR spectra of the obtained SLN and cetyl palmitate are shown in Figure 1. Several peaks were observed in the FTIR spectrum of SLN in the spectrum range of 400-4000 cm^{-1}.The peak at 1734 cm^{-1} corresponded to C=O tension, the peak at 1462 cm^{-1} was ascribed to C–H bending, the peak at 1090–1300 cm^{-1} corresponded to C–O stretching which were also seen in FTIR data of cetyl palmitate, Tween- 80. The peaks at 2916 and 2848 cm^{-1} were related to aliphatic C–H stretching. The characteristic peaks of cetyl palmitate and Tween 80 are also present in the spectrum of the obtained solid lipid nanoparticles (SLNs), resulting in similar spectra for cetyl palmitate and SLNs. The results are consistent when compared with similar studies [15].



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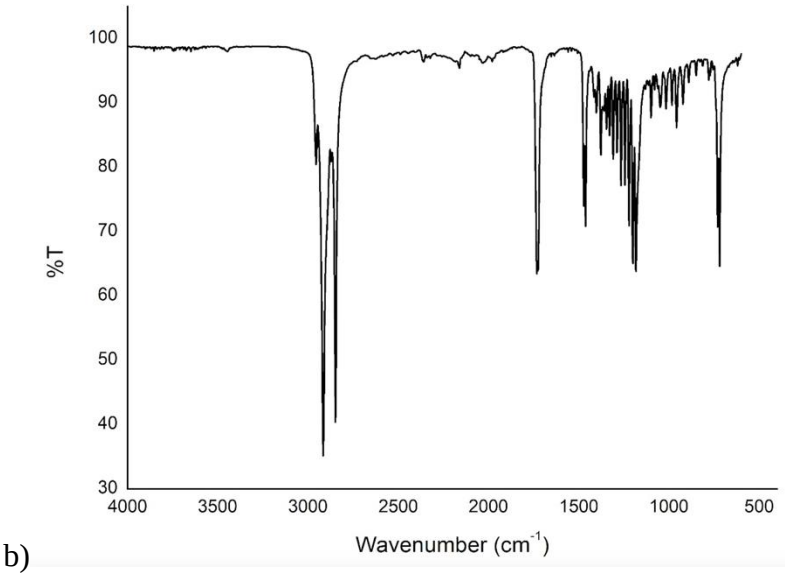


b)

Figure 1. FTIR spectra of a) solid lipid nanoparticles and b) cetyl palmitate.

The morphology of the nanoparticles was investigated by the SEM imaging method and shown in Figure 2. According to the shape, the average size of the nanoparticles was determined to be approximately 200 nm and the structure was found to be spherical, flat and smooth, which is consistent with similar studies in the literature [8].

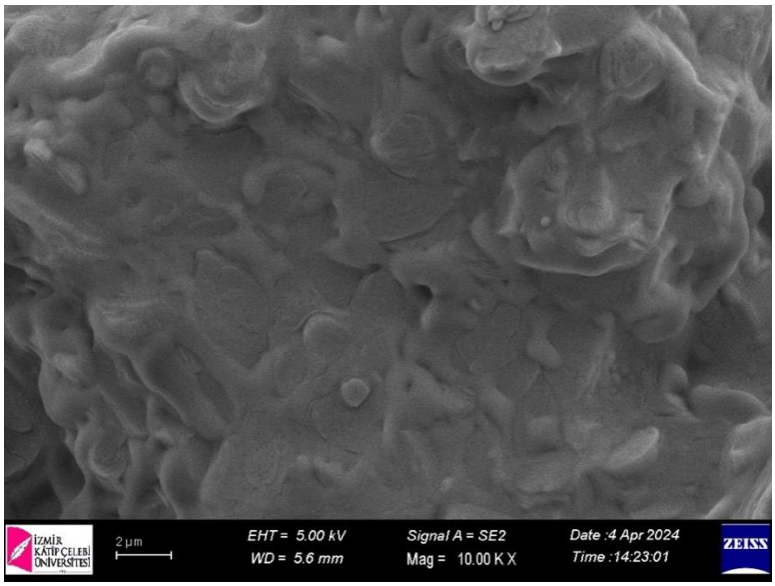


Figure 2. SEM image of solid lipid nanoparticles.

3.2 Encapsulation of BMV into SLN

For the calibration curve of Betamethasone valerate, which has low water solubility, the main stock drug was prepared inacetonitrile-distilled water 1:1 (v/v) mixture and dilutions were made from the main stock at concentrations of 5, 10, 15, 20, 25, 30, and 35µg/mL[16].The maximum absorbance peak of the drug was determined as 236 nm. The R^2 of the BMV standard graph was found to be 0.9997. The calibration curve of the drug is given in Figure 3.

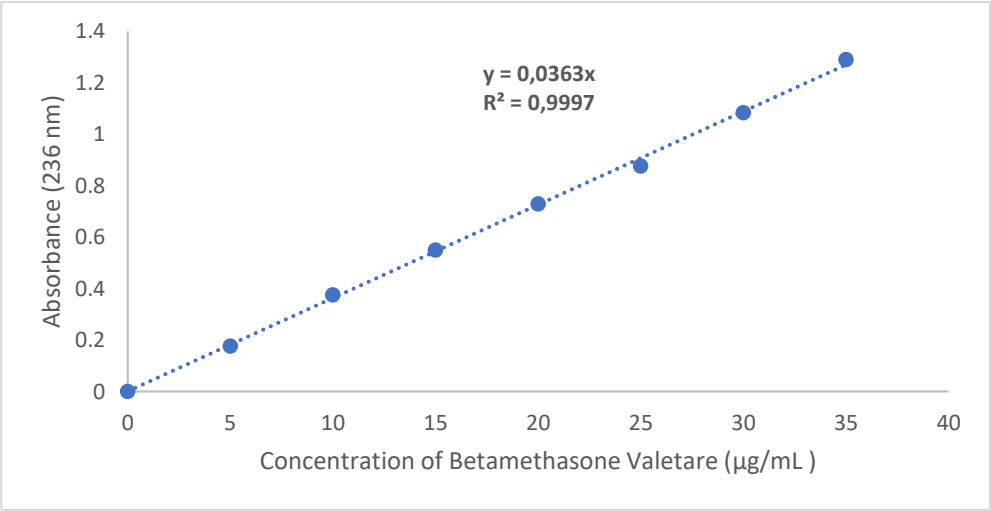


Figure 3. Betamethasone valerate calibration curve.

Solid lipid nanoparticles containing initial dose of BMV at 0.25, 0.50, 0.75, 1.00 and 1.25 mg/ml were prepared. Drug loading efficiencies of the prepared BMV loaded nanoparticles were calculated. The obtained results shown in Table 1.The nanoparticle group (initial BMV dose of 1mg/mL) with the highest drug binding efficiency was selected as optimum for further studies. As reported by Md S.thedrug/polymermassratiostestedwere 0.5:1, 0.25:1, 0.17:1, 0.125:1, and 0.1:1. The obtained result depicts that 0.5:1 (drug/polymer) ratiowasfoundtohavethehighest %EE of 94.39 ± 1.10% whereas 0.1:1 has theleastencapsulation

of 62.43 ± 6.99%. It can be seenthat an increase in drug/polymermassratioresults in an increase in EE. Hence, thisprovesthattheincreasingamount of drug in theorganicphaseremarkablyinfluencesthe EE duetothehigherinteractionbetweenthedrugandthepolymer[17].

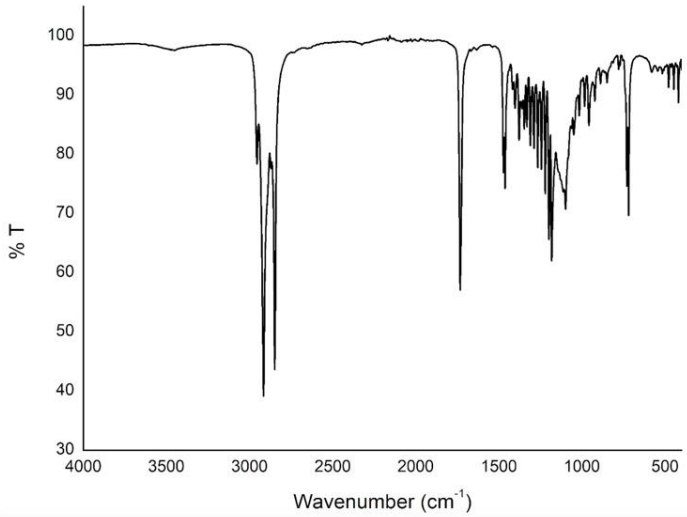
Table1.Encapsulation efficiencies(%) of drug at different concentrationsinto solid lipid nanoparticles.

Initial BMV Concentration (mg/mL)	Loaded DrugConcentration (mg/mL)	Encapsulation Efficiency (%)
0.25	0.15	58
0.50	0.37	74.5
0.75	062	82.1
1	0.90	89.4
1.25	1.10	88.2

3.3 Characterization of BMV loaded SLN

As reported by Pandey et al. the characteristics peaks of BMV appeared at 3422 cm^{-1} (–OH stretching), 2955 cm^{-1} and 2872 cm^{-1} (–CH stretching), 1731 cm^{-1} (C=O stretching), 1616 cm^{-1} (C=C stretching), and 1298 cm^{-1} and 1264 cm^{-1} (–CF stretching)[18].The FTIR spectrum of BMV-SLNis represented in Fig. 4. According to FTIR spectrum analysis of BMV-SLN, 2916 and 2847 cm-1 (C-H tension band), 1732 cm-1 (C=O tension band), 1464 cm-1 (C-H bond bending band), 1099 and 1182 cm-1 (C-O bond tension band), 730 cm-1 (C-H bond bending vibration) were observed. Spectral analysis showed that the BMV-SLN specific functional groups on the surface of the nanoparticles exhibited almost the same chemical properties as cetyl palmitate and exhibited the main characteristic peaks of the entrapped drug. This study indicates that there is no molecular interaction that could change the chemical structure of BMV[19].

a)



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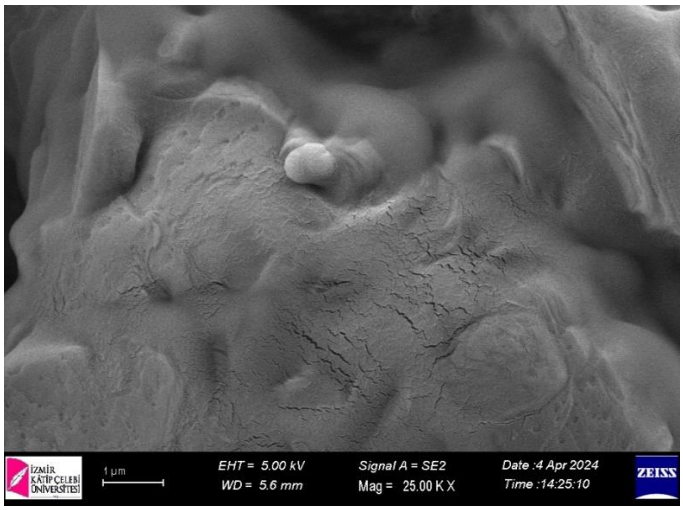


Figure 4. a) FTIR spectrum and b) SEM image of betamethasone valerate loaded solid lipid nanoparticles.

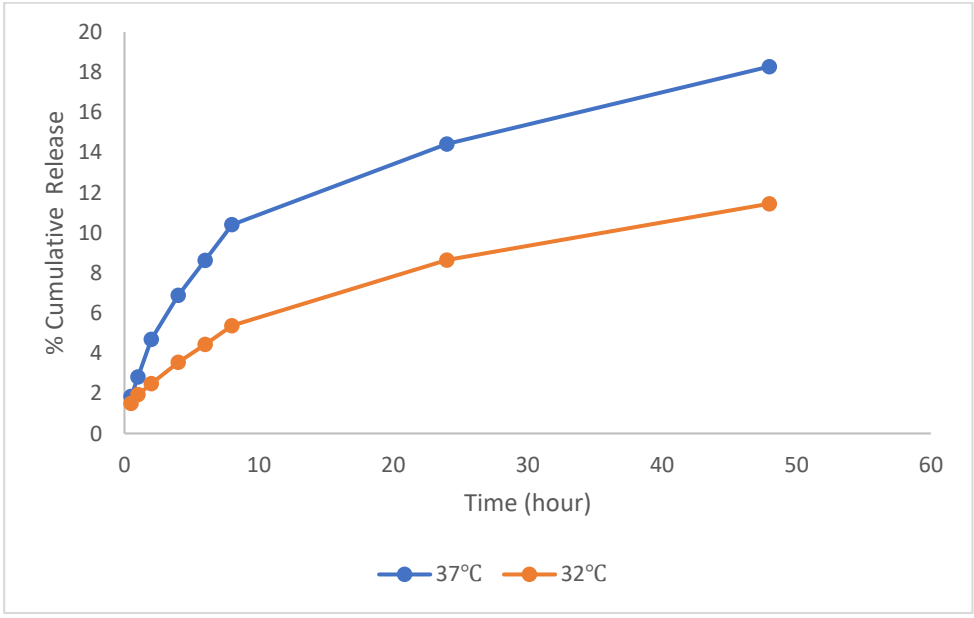
Furthermore, BMV-SLN were morphologically examined with SEM. According to the SEM image, it is seen that the nanoparticle has a shape close to spherical. The size of BMV-CPN also increased a little. According to the literature, as the amount of drug contained in the nanoparticles increases, their sizes also increase[17].

3.4 In vitro Drug Release

The in vitro drug release behaviorof nanoparticles was investigated under physiological condition (pH 7.4) and under using simulated skin surface (pH 5.5) at 37℃ and 32℃. As a result of the release, at the end of 48 hours at pH 7.4; 18.27% at 37℃, 11.44% at 32℃ BMV was released from SLN. At pH 5.5; 24.66% at 37℃, 15.89% at 32℃ BMV was released from the SLN at the end of 48 hours. The faster release of BMV in an acidic environment may be due to nanoparticle deterioration[8].The pH of the skin is acidic. Therefore, more drugs will be released from nanoparticles interacting with the skin topically and a higher concentration of

drug will reach the diseased area. The in vitro release of BMV is affected by the lipidic components of SLN, which led to a simultaneous increase in the affinity of lipophilic BMV to lipidic components and caused a relatively low release compared to free release [19].The results of the release studies are given in Figure 5.

a)



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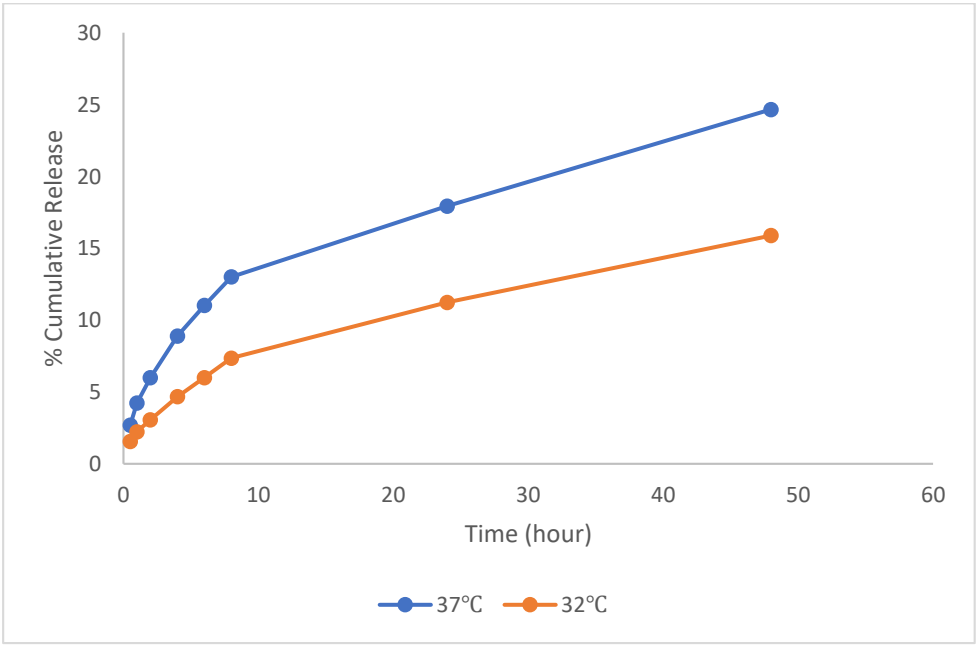

Figure 5. BMV release from nanoparticles in a) pH 7.4 and b) pH 5.5 buffer at 37°C and 32°C.

Free drug release was investigated at both acidic pH and physiological pH at 37°C. At pH 7.4, more than 50% of free BMV was released in the first 2.5 hours, and 84% of free BMV was released after 24 hours. At pH 5.5, more than 50% of free BMV was released in the first 2 hours, and at the end of 24 hours, 99% of free BMV was released. The reason for testing release studies at both pH values is to show that it is suitable for physiological pH values and to show that the

gel was developed for use on the skin surface and that it was worked in an acetate buffer that is close to the skin pH value. The results of the free drug release studies given in Figure 6.

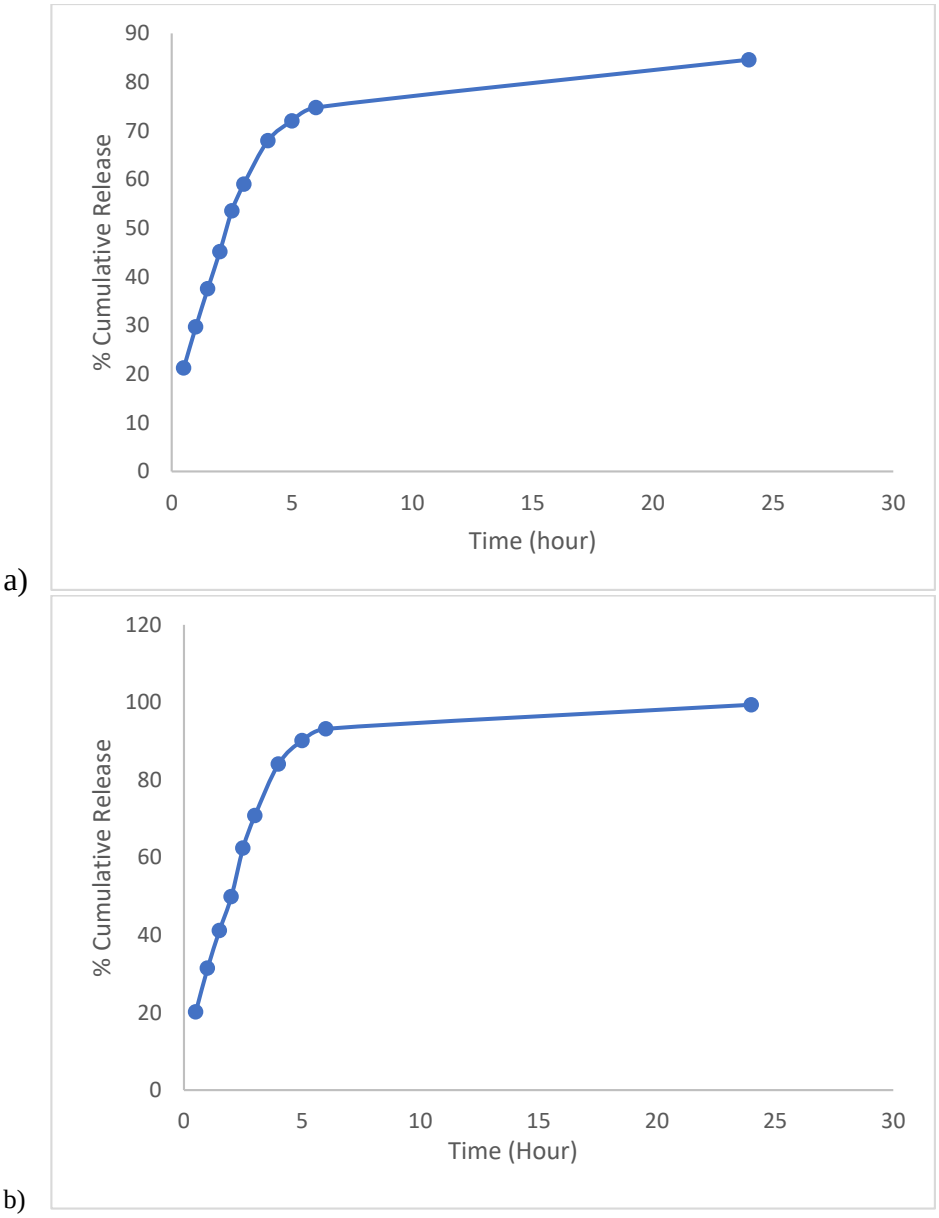

Figure 6. BMV release from free solution in a) pH 7.4 and b) pH 5.5 buffer at 37°C.

For the treatment of eczema, medications must be taken regularly and periodically in a certain dose. Patients usually ignore or forget this when using medications for a long time. When evaluated from this perspective, the controlled slow release of BMV allows for a uniform concentration of medication in the absorption area, allowing plasma concentrations to be maintained in the therapeutic range after absorption. In this way, the side effects of the medication are minimized and the frequency of application is also reduced.

3.5 Preparation of Aloe Vera Gel Formulation Containing BMV-SLN

The pH values of the samples prepared by adding 1, 2, 2.5 and 3 mL of Aloe vera extract and 1.8 g of BMV containing nanoparticle dispersion into 5 g of carbopol gel were measured and are shown in Table 2 and gel photographs are also displayed in Figure 7.

Table 2. Gel pH values obtained after adding Aloe vera extracts and BMV-CPN dispersion.

Contents	pH
BlankGel	6.24
1 mL Aloe vera extract - 2 mL BMV-CPN	6.05
2 mL Aloe vera extract - 2 mL BMV-CPN	5.86
2,5 mL Aloe vera extract - 2 mL BMV-CPN	5.76
3 mL Aloe vera extract - 2 mL BMV-CPN	5.66

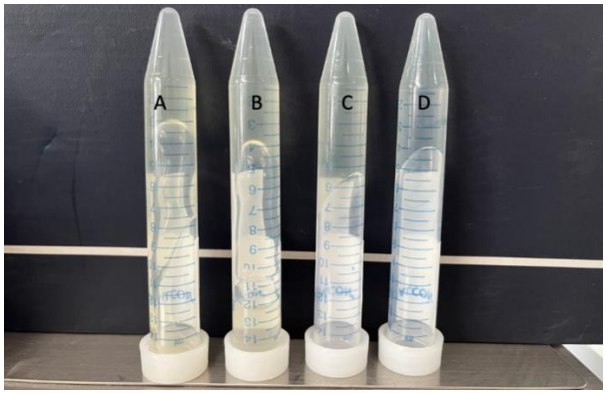

Figure 7. Gel formulation photographs; (A) 5 g gel- 3 mL Aloe vera extract- 2 mL BMV-SLN dispersion; (B) 5 g gel- 2,5 mL Aloe vera extract- 2 mL BMV-SLN dispersion; (C) 5 g gel- 2 mL Aloe vera extract- 2 mL BMV-SLN dispersion; (D) 5 g gel- 1 mL Aloe vera extract- 2 mL BMV-SLN dispersion

As seen in Table 2, 2 mL of Aloe vera extract and 2 mL of BMV-CPN dispersion were selected as optimum to be added to the gel. Other ratios can also be accepted as pH suitable for the skin, and after 2 mL of Aloe vera extract, however the fluidity of the gel increased and its structure that can be applied to the skin began to deteriorate.

Studies by Şenyiğit et al. also showed that by using the gel formulation, the concentration of betamethasone valerate can be reduced and a higher flow can still be achieved. This may be a notable advance in terms of reducing dose-dependent side effects and increasing the risk-benefit ratio of betamethasone valerate[20].The results of a randomized double-blind clinical study by Panahi et al.reported that Olivederma, a combination of Aloe vera and extra virgin olive oil, is superior to topical corticosteroids after 6 weeks of treatment in terms of disease severity, quality of life, and eosinophil count[21].The data obtained as a result of both these studies and our study show that Aloevera gel formulation can be recommended as a promising alternative system for topical application of betamethasone valerate.

4 Conclusion

In the study, solid lipid nanoparticles were synthesized using cetyl palmitate and Tween-80, and BMV, which has been proven effective to treat eczema, was encapsulated into solid lipids with high efficiency. In this way, BMV, which has a hydrophobic character, was loaded into a lipid carrier; in order to increase the speed of action, effectiveness and skin absorption of the drug.With the anti-microbial, anti-inflammatory, wound healing, antioxidant and immune-boosting properties of the Aloe vera extract, the treatment of the factors that cause the disease and the possibility of the disease recurring can be reduced. With this formulation prepared with a simple and economical method, it is shown that it will contribute to human health by treating the pain, itching and problems that prevent the daily lives of patients due to eczema more effectively and in a shorter time. The study could be used for the benefit of human health and is promising.

Hypertrophic scar inflammation in eczematous lesions creates a strong barrier for dermal penetration of drugs. To overcome this difficulty, various new topical formulations such as solid lipid nanoparticles are quite suitable systems for penetration enhancement and sustained release. It is known that these preparations are not only applied as “drug carriers” but also act as “drug depots” to release active ingredients for a long time. The gel formulation formed by adding BMV loaded SLNs to aloe vera gel was aimed to deliver the drug dermally and thus prevent hepatic first pass metabolism and extensive fluctuations in drug-plasma levels resulting from repeated oral administration of rapidly eliminated drugs. In the future, it is aimed to complete pre-phase studies by determining efficacy, toxicology and biodistribution etc. with in-vivo studies and to reveal the potential of the formulation.

Ethics in Publishing

There are no ethical issues regarding the publication of this study.

Author Contributions

HaticeÇetin:Methodology, Validation, Investigation, Writing,
Hüseyin Yılmaz: Methodology, Investigation
GülizAk:Conceptualization, Methodology, Validation, Investigation, Writing, Supervision

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