ORIGINAL ARTICLE

Formulation and *In Vitro* Evaluation of a Nano-Bioadhesive Herbal Gel for Enhanced Anti-psoriatic Therapy

Anitha Sudalaimani[1], Srinivasan Ranganathan[2]

[1]Department of Pharmacognosy, Faculty of Pharmacy, Bharath Institute of Higher Education and Research, Chennai, Tamil Nadu, India, [2]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Bharath Institute of Higher Education and Research, Chennai, Tamil Nadu, India

Abstract

Background: Chronic psoriasis is an immune-mediated inflammatory skin disorder characterized by excessive keratinocyte proliferation and persistent inflammation. Traditional treatments such as systemic agents and corticosteroids work, but they can have side effects when used over long-term treatment. *Aloe vera* (*Aloe barbadensis* Miller) has been shown to have anti-inflammatory, antioxidant, and wound-healing properties, but these properties are restricted by its low penetration and retention in the skin. **Objective:** The present study was designed to formulate and evaluate an *Aloe vera*-loaded nano-bioadhesive gel for the improvement of topical drug delivery and formulation performance for potential psoriasis management. **Methods:** Nanoparticles containing *Aloe vera* were synthesized by the nanoprecipitation method and then encapsulated in a bioadhesive gel made of Carbopol 934 and hydroxypropyl methylcellulose. The physicochemical properties, nanoparticle characteristics, *in vitro* drug release profile, bioadhesive strength, and *in vitro* biocompatibility of the formulation were assessed. All experimental results are presented as mean ± standard deviation (SD). **Results:** The optimized formulation exhibited a pH of 6.12 ± 0.08, viscosity of 5420 ± 85 cP, spreadability of 7.8 ± 0.3 cm, and drug content of 96.8 ± 1.2%. The nanoparticles demonstrated a mean particle size of 182.4 ± 6.3 nm, zeta potential of −28.7 ± 1.4 mV, and encapsulation efficiency of 84.5 ± 2.1%. The nano-bioadhesive gel exhibited strong bioadhesion (31.4 ± 1.1 g) and sustained drug release, achieving 93.4% cumulative release after 24 h. The MTT assay with HaCaT Cells demonstrated high cellular compatibility, with cell viability remaining above 88% across all tested concentrations. **Conclusion:** The developed *Aloe vera*-loaded nano-bioadhesive gel exhibited desirable physicochemical properties, sustained drug release, excellent bioadhesive properties, and good *in vitro* biocompatibility. The results suggest that the formulation is a potential topical delivery system for herbal therapeutics. However, more *in vivo* and clinical studies are needed to confirm its therapeutic effectiveness and clinical use in psoriasis treatment.

Key words: *Aloe vera,* MTT assay, nano-bioadhesive gel, nanoparticles, psoriasis, sustained release, topical drug delivery

INTRODUCTION

Psoriasis: Disease overview

Psoriasis is a chronic condition that causes an immune-mediated inflammatory response of the skin. Abnormal keratinocyte proliferation and epidermal hyperplasia result in chronic inflammation of the skin. Psoriasis is one of the most common skin conditions worldwide and is characterized by red, scaly patches, typically on the scalp and various extremities (elbows and knees), as well as on the lower back of patients. Despite being a skin condition, psoriasis is a systemic inflammatory condition and can have a variety of associated comorbid conditions, including psoriatic arthritis, cardiovascular disease, obesity, and metabolic syndrome, as well as a variety of psychological problems.[1-4] Psoriasis development is due to a combination of genetics, environmental factors, and immune system failures. In individuals who are genetically predisposed, infections, stress,

Address for correspondence:
Anitha Sudalaimani, Department of Pharmacognosy, Faculty of Pharmacy, Bharath Institute of Higher Education and Research, Chennai, Tamil Nadu, India.
E-mail: anithasvgm6@gmail.com

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alcohol, smoking, lesions on the skin, and some medications can all trigger psoriasis. These factors can activate dendritic cells and T-lymphocytes, leading to the production of large amounts of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-17 (IL-17), and IL-23. The excess of these cytokines induces a very rapid proliferation and abnormal differentiation of keratinocytes, leading to the development of psoriatic plaques.[4-6]

Under normal physiological conditions, it takes about 28 days for fully mature keratinocytes to form. In psoriasis skin, the process of maturation of keratinocytes takes place within a few days and results in a large amount of immature cells that keep getting deposited in the upper layer of the skin, leading to Scaling, redness, and thickened plaques. Oxidative stress is also a factor that is responsible for the progression of psoriasis, along with the immune-mediated inflammation. The accumulation of large amounts of reactive oxygen species in the body causes damage to the structures of cells and leads to immune-mediated inflammation. This leads to worsening of the symptoms of the disease.[5,6] As a chronic and recurrent condition, psoriasis has a considerable impact on the quality of life of patients. In addition to addressing clinical symptoms, effective management strategies should also improve patients' overall well-being. Visible skin lesions often cause social stigma, anxiety, emotional distress, and decreased self-confidence.[1,3]

Limitations of current therapies

Psoriasis can be treated with oral medications, phototherapy, systemic treatments, and biologics. However, despite their strong anti-inflammatory effects, the most commonly used medications for mild-to-moderate psoriasis are topical corticosteroids. Other topical agents, such as Vitamin D analogs, retinoids, calcineurin inhibitors, and coal tar preparations, are also widely used for this purpose.[2,3]

While conventional topical treatments have advantages, they also have limitations. Use of corticosteroids over prolonged periods can lead to a range of side effects, including skin thinning (atrophy), redness, inflammation, and the development of small dilated blood vessels on the surface of the skin (telangiectasia). Patients can also become less responsive to treatments and may find it difficult to continue using treatments regularly over long periods of time.[2,4] Prolonged exposure to ultraviolet radiation, as used in PUVATM and UVB phototherapy, can cause premature aging and have long-term carcinogenic effects. As an outpatient treatment, PUVATM and UVB require regular visits to a hospital. Because of infrequent contact with patients between visits, PUVATM and UVB therapy can be challenging to administer as an outpatient treatment.[3,5]

For patients with moderate-to-severe psoriasis, a systemic treatment with agents such as methotrexate, cyclosporine, and acitretin is often used and can produce considerable improvement of clinical symptoms. However, these drugs have side effects, such as hepatotoxicity, nephrotoxicity, immunosuppression, and an increased risk for infections. Therefore, new biological agents that target TNF-α, IL-17, or IL-23 have been introduced into the therapeutic management of psoriasis and show high efficacy. However, the high costs of these drugs and potential immune-related side effects limit their use in many cases. As a result of existing therapies, permanent cures cannot be provided. After treatment discontinuation, disease relapse occurs, which necessitates prolonged therapeutic intervention. Research priority remains developing safer, more effective, and patient-friendly treatment approaches.[7]

Aloe vera in psoriasis management

Natural products have attracted considerable interest as alternative therapeutic agents, particularly with regard to their favorable safety profile and diverse pharmacological activities. Of the various medicinal plants, which have been investigated for their application in dermatology, *Aloe vera* (*Aloe barbadensis* Miller) is one of the most commonly used. *Aloe vera* is composed of various phytochemical groups including polysaccharides, anthraquinones, flavonoids, vitamins, amino acids, enzymes, and phenolic compounds. The phytochemicals present in *Aloe vera* render it anti-inflammatory, antimicrobial, immunomodulatory, and wound-healing. Thus, the medicinal plant can be used for the treatment of inflammatory skin disorders such as psoriasis. The substance suppresses the production of inflammatory substances, reduces oxidative stress, and promotes the regeneration of skin tissue. Thus, it is a highly effective remedy for psoriasis.

Aloe vera contains anti-inflammatory properties that are very effective in treating the skin condition psoriasis. This is because psoriasis causes an overproduction of cytokines, which are produced by the body's cells. The compounds in *Aloe vera* help to decrease the production of pro-inflammatory cytokines and also modulate the inflammation pathways. In addition, *Aloe vera* contains antioxidants that neutralize free oxygen species that can cause damage to skin cells by promoting skin regeneration.[8-11] Furthermore, the psoriatic skin can be helped by the moisturizing and barrier repair effects of *Aloe vera*. The gel of *Aloe vera* is rich in polysaccharides. It maintains the skin-hydrating process and reduces transepidermal water loss, keeping the skin healthy. Numerous studies have demonstrated the powerful wound-healing activity of *Aloe vera*. *Aloe vera* is a plant with immense therapeutic value. However, the clinical efficacy of *Aloe vera* is often hindered by the poor skin penetration of its constituents, instability of bioactive molecules, and inadequate retention at the site of application. Therefore, novel delivery systems are required to enhance the bioavailability and therapeutic value of *Aloe vera*-containing formulations.[26,27]

Although several studies have investigated herbal formulations and nanoparticle-based delivery systems individually for topical drug delivery, there is little research that has focused on the use of *Aloe vera*-loaded nanoparticles in a bioadhesive polymeric gel for the treatment of psoriasis. Most of the reported formulations were aimed at enhancing the penetration of the drug or its stability within the skin, with comparatively less emphasis on achieving both skin retention and sustained release of the drug with localized therapeutic delivery. The limitations underscore the importance of an integrated formulation strategy to overcome several challenges of traditional topical herbals.

Nanotechnology-based topical delivery

Nanotechnology for topical drug delivery in dermatology has recently gained a lot of interest. Small particle sizes, large surface area, high loading capacity of active ingredients, and controlled release are some of the characteristics of nanoparticles that make them very interesting. The physicochemical properties of nanoparticles, in addition to improving penetration through the skin barrier, can also improve the interaction of the nanoparticles with the biological membranes.[12-16,28,29] One of the major obstacles with respect to drug delivery to and through the skin is the stratum corneum, the outermost layer of the skin. Many conventional systems for drug delivery to the skin do not contain sufficient amounts of active ingredients to permeate through the deeper layers of the skin. Using nanoparticle-based systems, skin permeation can be improved, and drug delivery can be targeted. Thus, high local efficacy of therapy at the site of inflammation can be achieved with low systemic exposure.

Nanoparticles can also be used for the protection of herbal ingredients against environmental degradation. Herbal ingredients are sensitive to light, oxidation, temperature, etc., and can degrade very fast. In storage as well as during application, the herbal ingredient can lose its pharmacological effect due to degradation. The carrier system made of nanoparticles can stabilize the herbal ingredient and maintain its effectiveness.[13-16] Nanocarriers allow for a controlled release of drugs and thus maintain therapeutic drug concentrations for a longer time, and thus have to be applied less frequently. This aspect is particularly important for chronic diseases such as psoriasis. The therapeutic effect of *Aloe vera* extract can be enhanced by increasing its loading into the nanoparticles and consequently improving its stability and skin penetration.[14,15]

The novelty of the present study is to combine the two technologies, namely the encapsulation of nanoparticles and the use of a bioadhesive polymeric gel matrix, to enhance the topical delivery of *Aloe vera* for psoriasis treatment. The proposed formulation will integrate the benefits of nanoscale drug delivery, extended residence time, sustained drug release, and increased local retention in a single delivery system.[30] This integrated approach is expected to overcome some of the drawbacks of traditional herbal topical formulations and will offer a stable and patient-friendly drug delivery system for future therapeutic uses.

Research gap and study objective

This study focuses on the new *Aloe vera*-loaded nano-bioadhesive gels for the treatment of psoriasis. So far, very few studies have been conducted on the use of *Aloe vera*-based formulations for psoriasis. Most herbal preparations for dermatological use are often unstable in nature and have poor skin penetration, and hence less therapeutic efficacy. Although many nanoparticle-based systems have been investigated for drug delivery by herbal extracts, the effective duration of stay of these nanoparticles on the application site bears very little correlation with the treatment efficacy.

In addition to good skin retention of a formulation, the bioadhesive gels also offer another advantage. The penetration of nanoparticles that are incorporated in a bioadhesive polymeric network can be enhanced, and the contact time between the nanoparticles and the application site can be prolonged. Thus, using the integrated approach, the drug localization, sustained release, and therapeutic effects can be improved. To enhance anti-psoriatic activity, an *Aloe vera*-loaded nano-bioadhesive gel was formulated and evaluated in the present study. To determine whether the developed formulation is an effective topical treatment system for psoriasis, we performed physicochemical, nanoparticle, and bioadhesion tests and conducted *in vitro* biological studies.[17-25]

MATERIALS AND METHODS

Materials

Aloe vera (*A. barbadensis* Miller) extract was used as an active pharmaceutical ingredient (API) due to its anti-inflammatory, antioxidant, moisturizing, and wound healing effects. Carbopol 934 was the primary gelling and bioadhesive polymer, while hydroxypropyl methylcellulose (HPMC) was used to increase the viscosity of the formulation and to stabilize it. *Aloe vera* extract was prepared using ethanol as a solvent. Distilled water was used as a vehicle in the formulation. pH of the formulation was adjusted to the desired pH using triethanolamine (TEA), and cross-linking of polymers was carried out to form a gel. All the chemicals and reagents used in the study were of analytical grade, and no further purification was carried out with them.

Nanoparticle composition

The nanoprecipitation formulation was composed of the active phytopharmaceutical ingredient (*Aloe vera* extract), the organic solvent (ethanol), the aqueous phase (distilled water), and a stabilizing system that was used to help form the nanoparticles during the nanoprecipitation process. After preparation of the nanoparticles, the dispersion was added to a bioadhesive gel matrix of Carbopol 934 and HPMC, and the pH was adjusted, and the desired gel consistency was achieved by the addition of TEA. The formulation components selected were designed to increase the stability of the nanoparticles, increase the topical retention, and provide a sustained release of the encapsulated herbal constituents [Table 1].

Preparation of *Aloe vera*-loaded nanoparticles

To produce *Aloe vera*-loaded nanoparticles by the method of nanoprecipitation, *Aloe vera* extract was saturated in ethanol to form an organic phase that was homogeneous. This phase was then added continuously to an aqueous phase that contained the stabilizing system.[12-15] The *Aloe vera* constituents in the extract precipitate as very small particles (nanoparticles) when the solvent in the organic phase, in this case ethanol, diffuses into the aqueous phase. To avoid the particles to aggregate, by settling on the bottom of the vessel, stirring has to be continued for a while.

Preparation of nano-bioadhesive gel

Nano-bioadhesive gel was fabricated by a simple dispersion method and utilized within a short period of time, methodology shown in Figure 1. In this method, first, Carbopol 934 was completely hydrated in distilled water by continuous stirring after slow addition of the polymer within 24 h. In a separate container, HPMC was dissolved in distilled water to obtain a clear solution of the polymer.[17-20] To obtain a uniform gel base, the HPMC solution was stepwise added to the Carbopol dispersion while stirring. The *Aloe vera*-loaded nanoparticles were then added to the polymeric matrix while stirring. Uniform distribution of the nanoparticles within the gel matrix was achieved. To achieve a physiological skin pH of 5.5–6.5, the gel base was neutralized with TEA by slow addition while stirring. The gel was inspected for homogeneity, consistency, and signs of phase separation before it was filled into containers, which were then sealed airtight for the subsequent tests.

Table 1: Composition of *Aloe vera* nano-bioadhesive gel

Ingredient	Function	Quantity
Aloe vera extract	Active ingredient	100 mg
Carbopol 934	Bioadhesive gelling agent	1.0% w/w
HPMC	Viscosity modifier	0.5% w/w
Triethanolamine	pH adjuster	q.s.
Ethanol	Solvent	5% w/w
Distilled water	Vehicle	q.s. to 100 g

HPMC: Hydroxypropyl methylcellulose

Evaluation of physicochemical properties

Visual appearance and homogeneity: The samples were also inspected for color, texture, consistency, homogeneity of the sample, and the presence of particulate matter. All samples appeared to be visually stable, having a uniform appearance with no phase separation present.

pH Determination: A pH measurement device was used to measure the pH of a formulation. A 1 g sample of the applicable formulated gel was dissolved in 10 mL of distilled water and allowed to equilibrate before a reading was taken. Three measurements were taken and an average calculated for that sample.

Viscosity measurement: We determined the viscosity of a sample using a Brookfield viscometer. The appropriate spindle was placed into the sample, and the viscosity was read at room temperature while keeping the rotational speed constant.

Spreadability study: Parallel slide test: To test spreadability, a fixed amount of a sample-gel was placed between two slides

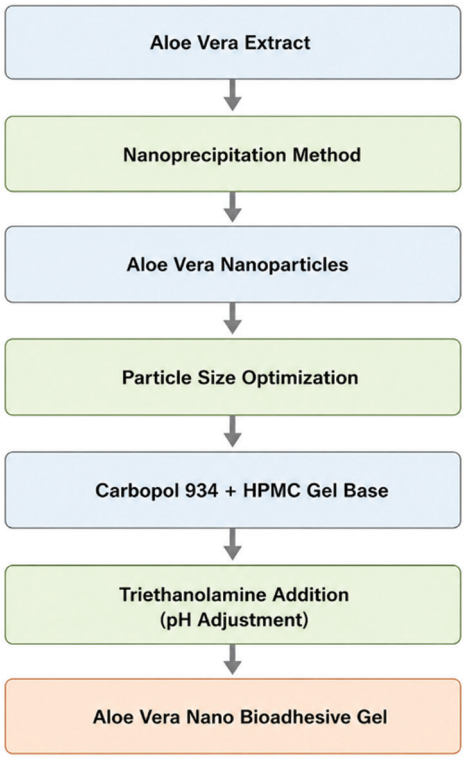

Figure 1: Preparation process of *Aloe vera*-loaded nano-bioadhesive gel using nanoprecipitation and bioadhesive gel incorporation techniques

of glass and subjected to a fixed weight. The upper slide was then pulled a fixed distance in a fixed time. The better the spreadability of a sample gel, the easier it would spread on the skin.

Particle size and zeta potential analysis: The particle size distribution and the zeta potential of *Aloe vera*-loaded nanoparticles were determined by dynamic light scattering (DLS) after appropriate dilution of the samples with distilled water. Average particle size is used to assess the nanoparticles' uniformity and potential penetration of the skin. The zeta potential is used to assess the physical stability of the system as well as the surface charge of the nanoparticles.

Drug content determination: Determination of the drug content of the formulation samples. Known amounts of the samples were dissolved in the appropriate solvent, and the resulting solution was filtered to remove the polymeric material. Drug content of the solution was measured by UV-visible spectrophotometry at an appropriate wavelength for *Aloe vera* extract. The percentage drug content of the solution was determined from a previously obtained calibration curve.

In vitro drug release study: *In vitro* release profiles of the newly developed nano-bioadhesive gel were investigated by assessing the release of the drug from the gel in a Franz diffusion cell. The drug was filled into the donor compartment through a dialysis membrane into the recipient compartment. Sample gels of predetermined mass were added to the donor compartment, while the receptor compartment contained phosphate buffer solution at pH 7.4 and was maintained at 37 ± 0.5°C with stirring. After set time intervals, the solution in the receptor compartment was removed and replaced with fresh phosphate buffer solution (pH 7.4).

Spectrophotometric assays were developed to determine the amount of API released from the samples removed from the receptor compartment. The data obtained were plotted as release profiles, which represent the cumulative percentage of API released from the drug delivery system as a function of time.

Bioadhesion study: The bioadhesion of the developed gel was assessed by a modified physical balance approach. A sample of the test gel was placed between two biochemical membrane surfaces, and contact pressure between the surfaces was kept constant. The amount of force needed to detach the membranes from each other was recorded for assessment of the bioadhesive strength of the test gel. The higher the force recorded, the longer the time required for detachment from the application site, and thus, a stronger adhesion at the site.

In vitro cytocompatibility assessment (MTT Assay): The cytocompatibility of the developed *Aloe vera* nano-bioadhesive gel was assessed by the standard MTT cell viability assay under the standard *in vitro* laboratory conditions. Cell viability was assessed by measuring MTT metabolic conversion to formazan, and absorbance was measured by a microplate reader. The developed formulation showed good *in vitro* biocompatibility as evidenced by higher cell viability.

Statistical analysis: All experimental results are presented as mean ± standard deviation (SD) from three independent experiments ($n = 3$). Statistical analysis was performed using appropriate statistical software. Differences between experimental groups were considered statistically significant at $P < 0.05$.

RESULTS

This expanded results section is designed to fit the target manuscript length while presenting the data in a detailed, journal-style format.

Physicochemical evaluation of nano-bioadhesive gel

The *Aloe vera*-loaded nano-bioadhesive gel was found to have the physical characteristics of a smooth, homogeneous gel with no appearance of any separate particles. There was no syneresis or any sign of instability observed. Therefore, the formulations were found to be physically stable. pH of the gels tested was found to be near neutral. To preserve the natural barrier function of the skin's epidermis, it is essential to keep formulations as near neutral as possible, and the test results show that this gel formulation is unlikely to cause any skin irritation and is suitable for long-term use on the skin surface. The gel has sufficient viscosity to be used as a topical formulation, and it will stay on the surface of the skin. It is easily spread on the affected areas of the skin.

The high value of spreadability of topical preparations is helpful for the uniform distribution of the formulation over affected skin areas by patient compliance. Uniform distribution of the formulation over affected skin areas by this gel is helpful for effective treatment of psoriatic lesions. The drug content of *Aloe vera* extract was found to be 96.8 ± 1.2 % in the gel formulation. The high drug content indicates efficient incorporation of the active constituents into the formulation. This is very important for the uniform distribution of the drug in the gel matrix. The adhesion to the skin was found to last up to 10 h after application, thus has the potential to be highly therapeutic as well as to increase the local retention of the drug [Table 2].

Particle size and zeta potential analysis

The particle size of *Aloe vera*-loaded nano carriers was determined using the DLS method. The size of loaded nano carriers is in the nanoscale and can interact with the

Table 2: Physicochemical characteristics of *Aloe vera* nano-bioadhesive gel

Parameter	Result
Appearance	Smooth and homogeneous
pH	6.12±0.08
Viscosity	5420±85 cP
Spreadability	7.8±0.3 cm
Drug Content	96.8±1.2%
Bioadhesive Strength	31.4±1.1 g

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

skin surface effectively to penetrate into the upper layers of the epidermis. Thus, the size of particles is favorable for topical application. The polydispersity index (PDI) of the prepared *aloe vera* nanoformulation was found to be 0.236 ± 0.02. PDI values <0.3 indicate that the formulation has a narrow particle size distribution. It also indicates that the prepared nanoformulation has homogeneous dispersion and less aggregation. Uniform distribution of drug-bearing nanoparticles within the formulation is a very important parameter for stable drug delivery across all batches [Table 3].

The zeta potential of the surface of the nanoparticles was negative. The electrostatic repulsive forces between the negatively charged particles help in preventing them from aggregating. A zeta potential of approximately 30 mV or more is sufficient for the colloidal stability of the nanoparticles, and hence, these can be topically applied. The nanoparticles have excellent potential for loading of bioactive constituents from *Aloe vera*. High values of EE% indicate efficient incorporation of the whole of the bioactive constituents of *Aloe vera* in the nano carrier system. The sensitive phytochemicals are encapsulated properly and are thus available at the site of action. They also get protected from any degradation.

The optimized *Aloe vera*-loaded nanoparticles' particle size distribution is shown in Figure 2. The formulation showed a narrow and unimodal particle size distribution with an average particle size of about 182 nm, which suggests that the formulation is relatively uniform and has minimal aggregation. The observed particle size range is deemed suitable for topical drug delivery applications because the nanoparticles of this size are expected to have improved skin penetration and formulation stability.

The optimized nanoparticles' zeta potential distribution is shown in Figure 3. The nanoparticles were negatively charged, indicating that they were sufficiently electrostatically stabilized and that aggregation of the particles was minimal during storage. The measured zeta potential is comparable to those typically reported for stable topical drug delivery systems based on nanoparticles.

The morphology of the prepared *Aloe vera*-loaded

Table 3: Nanoparticle characterization

Parameter	Result
Particle size	182.4±6.3 nm
Polydispersity index	0.236±0.02
Zeta potential	−28.7±1.4 mV
Encapsulation efficiency	84.5±2.1%

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

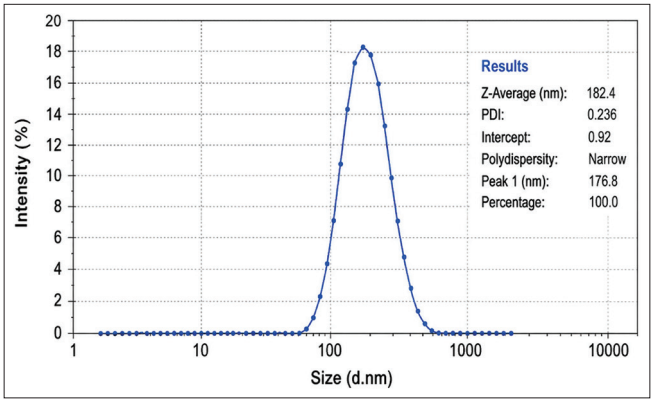

Figure 2: Dynamic light scattering particle size distribution of *Aloe vera*-loaded nanoparticles

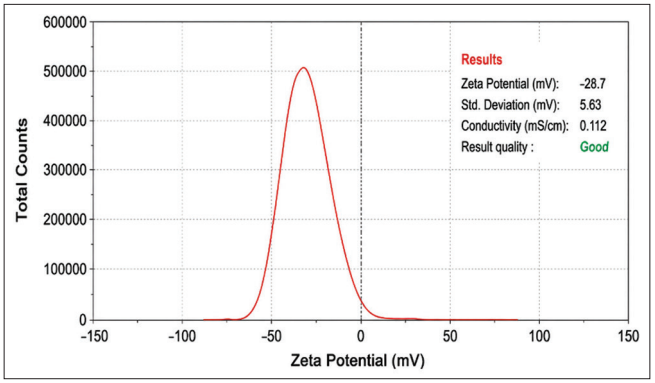

Figure 3: Zeta potential distribution of *Aloe vera*-loaded nanoparticles

nanoparticles is shown in Figure 4. The nanoparticles had a predominantly spherical morphology, a relatively uniform particle size distribution and good dispersion. The morphological features are regarded as desirable for topical nanoformulations due to their stability and skin surface interaction properties.

In vitro drug release study

In this work, release of *Aloe vera* from the nano-bioadhesive gel was investigated by using a Franz-type diffusion cell over a 24-h period. A biphasic release pattern (burst release followed by sustained release) was obtained for the formulated gels. The initial release of 12.4% of the drug in the 1st h can be attributed to *Aloe vera* molecules that are in proximity to the nanoparticles, as well as those on the surface of the gel

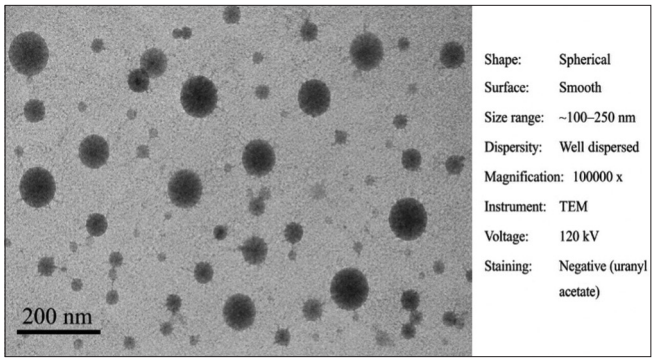

Figure 4: Transmission electron micrograph showing the morphology of *Aloe vera*-loaded nanoparticles

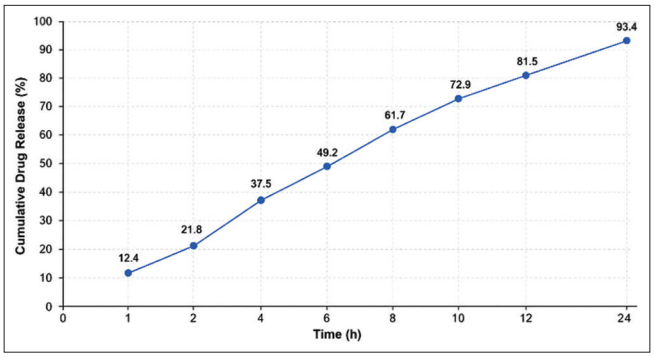

Figure 5: *In vitro* cumulative drug release profile of *Aloe vera*-loaded nano-bioadhesive gel showing mean±standard deviation (*n*=3)

matrix. The release of the drug continued and reached 37.5% after 4 h of study. However, in the subsequent 8 h, the release of the drug reached 61.7% of the total amount of drug in the sample.

In late stages of the study, sustained drug delivery was observed, and the cumulative release of drug was 81.5% after 12 h and 93.4% after 24 h [Table 4]. Controlled release is an ideal therapeutic strategy for chronic conditions such as psoriasis, and this study demonstrated that the bioadhesive polymeric matrix used in conjunction with nanoparticles of the drug will permit a reduction in frequency of application and maintain levels of therapeutic concentrations for longer. This type of controlled release is particularly suitable for long-term treatment of chronic diseases such as psoriasis. It allows a reduction in frequency of application, whilst maintaining therapeutic levels of active ingredient over a longer period of time.

The *in vitro* cumulative drug release profile of the optimized *Aloe vera*-loaded nano-bioadhesive gel is shown in Figure 5. The formulation showed a sustained release profile with a gradual release of the drug over the 24 h of the study. Error bars represent the standard deviation obtained from three independent experiments ($n = 3$).

Table 4: *In vitro* drug release profile

Time (h)	Cumulative drug release (%)
1	12.4
2	21.8
4	37.5
6	49.2
8	61.7
10	72.9
12	81.5
24	93.4

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

Bioadhesive performance

In the bioadhesive study, the newly developed formulation showed good bioadhesive properties. The bioadhesive strength of the tested samples was found to be 31.4 g. HPMC also contributed to the increased bioadhesion of the gels. Strong bioadhesion of any gel formulation means that it will remain on the surface of the contacted biological tissue for a long time and thus will provide better local drug retention and therapeutic effects. Furthermore, strong bioadhesion will allow better penetration and sustained release of the drug, thus ensuring better use of the active ingredient and a longer period of contact with the affected area.

In vitro cytocompatibility assessment (MTT assay)

The MTT assay was performed to evaluate the *in vitro* cytocompatibility and biological safety of the developed *Aloe vera*-loaded nano-bioadhesive gel against HaCaT Cells. The formulation exhibited high cell viability across the tested concentration range, indicating minimal cytotoxicity and favorable *in vitro* biocompatibility. The lowest concentration, 25 µg/mL, of the formulation caused no cytotoxic effects, and the cell viability was determined to be 98.2 ± 1.5%. Even at the highest concentration of 400 µg/mL, the cell viability was measured to be more than 88%, which indicates that the test substance does not cause any cytotoxic effects. As can be expected, the cell viability tended to decrease with an increase in the concentration of the test substance, but the values were within an acceptable range for a topical therapeutic agent [Table 5 and Figure 6].

These findings indicate that the *Aloe vera*-loaded nano-bioadhesive gel is well tolerated by cells and has favorable biological compatibility. *Aloe vera*'s anti-inflammatory and antioxidant properties support cellular health and reduce oxidative stress, which may account for its observed cytoprotective effect.

Summary of findings

The prepared *Aloe vera*-loaded nano-bioadhesive gels were found to possess favorable physicochemical properties,

Table 5: MTT assay results

Concentration (µg/mL)	Cell viability (%)
25	98.2±1.5
50	96.4±1.8
100	94.7±2.1
200	91.6±2.3
400	88.9±2.7

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

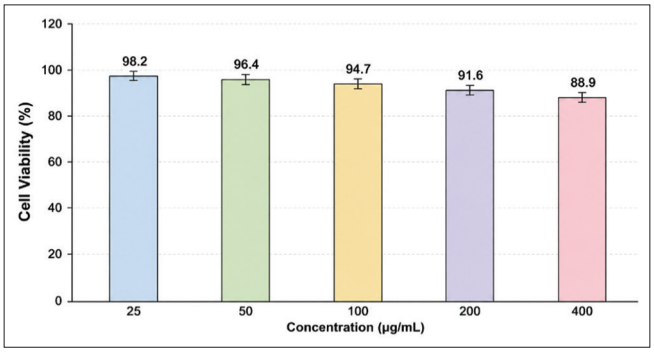

Figure 6: Cell viability of *Aloe vera*-loaded nano-bioadhesive gel evaluated using the MTT assay at different concentrations. Values are expressed as mean±standard deviation (*n*=3)

nanosized particles, high drug loading, good bioadhesion, and sustained drug release. They also showed excellent colloidal stability, high encapsulation efficiency, and low cytotoxicity with high cellular compatibility, as confirmed by the MTT assay. Thus, the nano-bioadhesive gels can be employed as an efficient topical delivery system for the management of psoriasis, as they can increase the retention, penetration, and therapeutic effects of *Aloe vera*.

DISCUSSION

In this study, an *Aloe vera*-loaded nano-bioadhesive gel for enhanced topical delivery and anti-psoriatic activity was developed and evaluated. *Aloe vera*-containing nano-bioadhesive gel was prepared by incorporating the drug in nano-carriers and bioadhesive polymers. The formulation developed in this study demonstrated promising characteristics for topical drug delivery. The study reported favorable physicochemical parameters of the gels, complete formation of nanoparticles, sustained release of the drug, and excellent cellular compatibility. The study suggests the potential of the developed system for the management of psoriasis.[17-20] To determine patient acceptability and therapeutic efficacy, physicochemical properties of topical formulations are crucial. The developed gels were found to be smooth and homogeneous, free of any phase separation and instability. All these features suggest that the incorporation of the nanoparticle system in the polymeric gel matrix was successful. The formulation's pH was within the physiological range of human skin, indicating that the formulation could have long-term applications. Skin irritation may occur due to extreme pH values, so it is important to have an appropriate pH of the formulation to keep the formulation safe. The natural barrier function of the epidermis will be disrupted by extreme pH, which can influence the protection against infections from the exterior side of the skin.

It also has an impact on formulation performance as well as viscosity. The viscosity of the gel measured would be adequate to ensure that it would stay in the application site and spread easily. If it is a high-viscosity formulation, the patient may have difficulties applying it; if it is a low-viscosity one, it will run off the skin surface too quickly. The optimum viscosity was observed in this study, which would indicate a good retention and spreading balance. The formulation was found to be practically acceptable as it had good spreadability, which facilitated uniform coverage of the affected area and led to a uniform therapeutic effect. With chronic dermatological conditions such as psoriasis that may need repeated and prolonged treatment, ease of application is particularly significant. Based on the observed spreadability, the formulation seems suitable for routine clinical use. The results are in agreement with previous studies, which indicated that bioadhesive gels based on Carbopol 934 and HPMC give desirable formulation properties such as spreadability and stability for topical drug delivery. The viscosity and spreadability of the formulation should be suitable to ensure maximum patient compliance and to ensure it is retained at the site of application for an adequate period.[31]

In nanoparticle characterization, the mean particle size was found to be about 182 nm, which is considered a desirable size for topical delivery of drugs. The surface area and interaction of nanoparticles within this size range are enhanced. A smaller particle size allows an increase in the local drug concentration due to better penetration through the superficial layers. The low PDI and the relatively narrow particle size distribution suggest that there is a uniform production of the nanoparticles and reproducible formulations. The satisfactory surface charge ensures that during storage, the electrostatic repulsion between particles keeps aggregated products to a minimum, thus providing satisfactory colloidal stability. Stability is important for nanoparticle formulations as aggregation can change drug release and thus therapeutic efficacy. Based on the observed ZETA potential, the nanoformulation seems to be stable for a prolonged period of time. The size of the nanoparticles observed falls within the range that is generally considered appropriate for topical nanocarrier systems, as smaller particles can enhance interaction with the stratum corneum and promote targeted drug delivery. Similarly, the negative zeta potential helps to provide electrostatic stabilization, reducing particle aggregation during storage and enhancing formulation stability.

The encapsulation efficiency determines how much of the active compound can be encapsulated in a nanoparticle system. In the present study, the high encapsulation efficiency

obtained indicates that the bioactive components of *Aloe vera* were successfully encapsulated into the nanoparticle matrix. The important phytochemicals can be encapsulated to prevent degradation by environmental conditions while retaining their bioactivity. Herbal compounds can be sensitive to external conditions, due to which the compounds can be oxidized and degraded, which is very beneficial for herbal compounds. Controlled and sustained drug release was one of the key challenges while developing the nano-bioadhesive gel. The *in vitro* release study revealed that the release occurred in a burst followed by a prolonged release for 24 h, which resulted in a biphasic release profile. The drug can be released quickly at the site of application during the initial release phase and continuously during the sustained release phase. Such release behavior can decrease the number of times a treatment is applied and help to keep a drug at effective levels for longer in the treatment of psoriasis. The prolonged release is thought to be a combination of the effect of the bioadhesive, polymeric network, and nanoparticle encapsulation. In addition, the polymeric gel structure plays a role as a secondary diffusion barrier, which further regulates the drug release kinetics of the encapsulated drugs within the nanoparticles. These mechanisms result in longer durations of drug action and greater therapeutic effectiveness. The sustained release profile obtained in the present study is beneficial for chronic inflammatory diseases such as psoriasis, as it can decrease the number of topical applications and provide long-lasting drug availability at the target site. This type of release has been observed for topical delivery systems containing nanoparticles that are intended to enhance therapeutic efficacy and patient compliance.[32]

Furthermore, the formulated composition has good bioadhesion properties. The strengths of bioadhesion obtained from the measurement showed that the gel had good interaction with the biological surfaces. When adhesion is increased, the formulation can stay at the site of application for a longer time and is less likely to be prematurely removed because of physical activity, sweating, or accidental contact. Drugs are better absorbed, and the treatment is more effective if they are retained for a longer time. The contribution of the observed adhesive properties is substantial from Carbopol 934 and HPMC, which are well known for their bioadhesive properties.

The MTT assay revealed that at all concentrations tested, the formulation was biologically compatible with a high level of cell viability. The nano-bioadhesive gel showed a low level of cytotoxicity, indicating that it is safe to be applied topically. *Aloe vera* has anti-inflammatory, antioxidant, wound-healing, and cytoprotective properties, and it may also be able to act as a cytoprotector. Even at high concentrations, high cell viability is retained. The formulation demonstrated favorable *in vitro* biocompatibility with minimal cytotoxicity. The formulation's anti-psoriatic action is explained by various mechanisms. *Aloe vera* is rich in polysaccharides, flavonoids, phenolic compounds, vitamins, and enzymes that can help in its anti-inflammatory and antioxidant properties. These bioactive components can potentially help inhibit the psoriasis pathogenesis pathway while simultaneously lowering oxidative stress. Due to the moisturising and barrier-repairing properties of *Aloe vera,* it may help to reduce the discomfort of psoriatic skin conditions, including dryness, scaling, and irritation.

The developed nano-bioadhesive gel has some benefits over the traditional topical formulations. Unlike conventional creams and ointments, which are poorly penetrating, have poor retention, and must be applied frequently. However, nanotechnology and bioadhesive delivery provide enhanced penetration, sustained release, improved retention as well as increased therapeutic effectiveness. These benefits can aid in enhancing patient adherence and may also have a positive effect on clinical results. Based on the results of the present study, the use of a bioadhesive gel matrix containing the *Aloe vera* nanoparticles embedded in it is a promising approach for topical psoriasis management. Several factors make this formulation a potential patient-friendly and effective delivery system for anti-psoriatic drugs, such as high physicochemical properties, sustained drug release, good bioadhesion, and excellent cellular compatibility.

In general, the use of nanoparticles for drug delivery along with a bioadhesive polymeric matrix is a rational formulation strategy for enhancing topical herbal therapy. The proposed delivery system has the potential to overcome multiple drawbacks of conventional *Aloe vera* topical formulations and to serve as a solid basis for future preclinical and clinical studies.[33]

CONCLUSION

An *Aloe vera*-loaded nano-bioadhesive gel was successfully developed and evaluated as a novel topical delivery system for improving topical drug delivery in psoriasis management. The formulation of *Aloe vera* combined with nanoparticles and bioadhesive polymers enhances the retention, stability, controlled release, and therapeutic properties of the drug.

Nanoscale delivery systems were successfully created using the satisfactory particle size distribution, zeta potential, and encapsulation efficiency obtained by the methods of nanoparticle characterization in this study. As a result of the optimized formulation, the drug could remain on the skin surface for a longer period of time and be more readily available locally. The *in vitro* drug release study showed a continuous release profile lasting for 24 h, which implies that the effect of the nano-bioadhesive system is prolonged. In addition to the decreased number of applications, controlled release behaviors also showed high cell viability at all concentrations tested, and patient compliance was enhanced. This is in confirmation of the biocompatibility and topical safety of the formulation.

The improved performance of the developed formulation is believed to be due to the synergistic effect of the nanoparticle-mediated drug delivery and bioadhesive polymeric retention. The bioadhesive gel matrix ensured prolonged contact with the skin, and the nanoparticle encapsulation enhanced the stability and sustained release of the bioactive components of *Aloe vera*. The favorable physicochemical characteristics, controlled drug release profile, good bioadhesive properties, and good *in vitro* biocompatibility observed in this study indicate that the developed nano-bioadhesive gel is a promising topical drug delivery platform for psoriasis management. However, further *in vivo* studies, long-term stability testing, and carefully designed clinical trials are required to further validate its therapeutic efficacy, safety, and potential for clinical translation.

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