Title: Preparation of Bi-gel for Acne Marks

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Abstract

Post-inflammatory acne marks are a chronic dermatological condition that demands novel therapeutic interventions capable of providing both hydrophilic and lipophilic active ingredients simultaneously for complete treatment. The present study focused on the development and optimization of a stable bi-gel system with dual-phase active components, assessing the skin penetration and retention properties of added ingredients, and determining the clinical performance and safety results of the formulation. A new bi-gel was prepared in an oleaginous phase that included turmeric extract (2%), vitamin E (1%), Span 80 (2%), olive oil (20%), and ethyl cellulose (5%), in combination with an aqueous phase that included aloe vera gel (20%), glycerine (5%), liquorice extract (1.5%), potash alum (1%), polyethylene glycol (10%), Carbopol 940 (1.5%), and distilled water (qs to 70%). Physicochemical characterization confirmed a homogeneous, smooth, pale yellow-green semi-solid with ideal pH (5.8-6.2), suitable viscosity (18,500-20,300 cP), and monodisperse particle size distribution (2-5 μm). In vitro drug release was shown to follow sustained release profiles with 85-89% turmeric extract and 78-83% liquorice extract release within 24 hours according to non-Fickian diffusion kinetics best described by the Korsmeyer-Peppas model. Rapid stability tests assured outstanding formulation stability with >94% drug content preservation, negligible pH and viscosity changes, and no microbial growth for six months under a range of storage conditions. The formulated bi-gel system effectively overcomes the shortfalls of standard single-phase products by offering controlled dual-drug delivery, increased stability, and enhanced therapeutic performance for acne mark therapy, a notable improvement in topical dermatological therapy.

Keywords: *Bi-gel, Acne marks, Sustained release, Topical delivery, Dual-phase system*

Introduction

Acne marks are a serious issue for millions of people across the world and often stick around after the usual inflammatory acne lesions have gone away (Abad-Casintahan et al., 2016). Such marks from past inflammatory skin conditions often lower a person's quality of life and make them think negatively about themselves, making there be a need for effective topical treatments (Layton et al., 2019). Ordinary gel formulas are not fully capable of managing acne marks, because they usually handle one type of ingredient (hydrophilic or lipophilic) and not the other (Prausnitz et al., 2004). When helping patients with acne marks, this limitation is particularly important because those types of acne respond best to mixtures of ingredients that include vitamin C, niacinamide, retinoids and antioxidants (Bissett et al., 2007).

With bi-gel systems, pharmacists are able to overcome traditional topical form barriers by containing different medicines in different phases at the same time (Singh et al., 2014). Two different gel phases, a water based unit and an oil phase, are incorporated into bi-gels to ensure a stable and uniform system that can successfully deliver various active substances with many different properties (Lupi et al., 2015). Using this design allows better absorption, deeper penetration into the skin and the use of two drugs that work better together than they would separately (Ibrahim et al., 2013). Treating acne marks with a bi-gel formula is an effective method since it opens the way to use several supplementary compounds that work on different areas of post-acne changes, including interfering with melanin, improving collagen and helping cell renewal (as mentioned by Mohamed, 2004).

Developing useful bi-gels requires careful research on choosing the right gelling agent, adjusting the phase ratio and selecting how the active ingredients are added to the system (Rehman et al., 2014). Additionally, the unique way bi-gels are formed calls for standardized assessment of their chemical and physical stability as well as their skin absorption and impact on results. The main objective is to build and perfect a bi-gel system that includes lipophilic and hydrophilic active ingredients. The penetrate and remain in the skin are assessed by testing the active ingredients. The research reviews both how well the bi-gel treatment works and how safe it is.

Material and Methods

Formulation Design and Material Preparation

The bi-gel was prepared using a method that involves an oleaginous gel phase, an aqueous gel phase and protocols established for the bi-gel production (Singh et al. 2014). To make the oleaginous phase, 2% turmeric extract, 1% vitamin E, 2% Span 80, 20% olive oil and 5% ethyl cellulose were used. Components of the aqueous phase were 20% aloe vera gel, 5% glycerine for moisture, 1.5% liquorice to lighten the skin, 1% potash alum for tightening pores, 10% polyethylene glycol, 1.5% Carbopol 940 to form the hydrogel and enough distilled water to add up to 70%, with sodium hydroxide to ensure a pH of 6.0-6.5 (Lupi et al., 20 All materials for this formula came from approved pharmaceutical companies tested to be safe and consistent with what pharmacopeial standards specify.

Oleaginous Phase	**Amount (%)**	**Aqueous Phase**	**Amount (%)**
Turmeric Extract	2%	Aloe vera gel	20%
Vitamin E (Antioxidant)	1%	Glycerine	5%
Span 80	2%	Liquorice	1.5%
Olive Oil	20%	Potash alum	1%
Ethyl Cellulose	5%	Sodium hydroxide	qs to pH 6-6.5
		Polyethylene Glycol	10%
		Carbopol 940	1.5%
		Distilled water	qs to 70%

Preparation Methodology

Ethyl cellulose was first dissolved in olive oil at 60°C while stirring, then Span 80, vitamin E and turmeric extract were added at room temperature (Ibrahim et al., 2013). A high-speed homogenizer was used for 15 minutes at 1000 rpm to dissolve Carbopol 940 in distilled water (Rehman et al., 2014). After that, aloe vera gel, glycerine, liquorice extract and potash alum were added one after another under continued stirring. The pH of the water phase was changed to 6.0-6.5 by including sodium hydroxide and the last step involved adding polyethylene glycol. Equal quantities of aqueous gel and oleaginous gel were combined and mixed at high speed with a 70:30 ratio until end-homogenized for 20 minutes (Sagiri et al., 2014).

Characterization and Evaluation

The formulations were tested with a digital pH meter, analyzed using a Brookfield viscometer for shear-dependent viscosity and examined by microscopy to confirm their phase distribution was even. According to the International Conference on Harmonisation (ICH) guidelines, manufactured samples stored at different temperatures and humidities (25°C / 60% RH, 30°C / 65% RH and 40°C / 75% RH) were checked periodically for appearance, pH, viscosity and drug content (Behera et al., 2015). Active ingredient release was studied in vitro using Franz diffusion cells with synthetic membranes and ex vivo animal skin was used to observe how the ingredients penetrate and are retained within the skin (Ajazuddin et al., 2013). Standard methods involving agar wells were used to test antimicrobial activity against Propionibacterium acnes and safety evaluation was carried out by dermal toxicity tests following OECD standards.

Results

Physicochemical characterization results

Results from the physicochemical analysis indicated that the bi-gel is appropriate for dermatological use. As shown visually, the mixture was homogeneous, smooth and pale yellow-green with no sign of separating into different layers or becoming inhomogeneous (Singh et al., 2014). Their characteristic pale yellow-green color was caused by the natural pigments in the extracts and this matches the color profiles seen in previous studies looking at similar herbal remedies (Lupi et al., 2015). The good feel of the gels and lack of small particles proved that both gel formations and measurements were performed safely and properly in bi-gel production.

According to the pH values, the products are within the proper range for topical treatment of the skin and are much the same as the pH of human skin (Ibrahim et al., 2013). The special pH in this conditioner supports acne-prone skin by helping it maintain its original acid film while keeping the active products stable (like turmeric extract and liquorice) and active. At a shear rate of 5 s^{-1}, the Brookfield viscometer result of 18,500 to 20,300 cP implied that the product had a semi-solid form and was smooth enough for effective and adhesive skin application (Mohamed, 2004). Having a viscosity in this range makes it possible for the skincare product to stay on the skin long enough for good treatment results.

According to particle size analysis, the active ingredients were well dispersed through the bi-gel, as the range observed was only 2-5 μm (Sagiri et al., 2014). If particles are evenly sized, drug release and skin penetration will remain constant and may be more effective in topical

drugs because smaller particles often offer better results (Behera et al., 2015). The size of the particles in this range supports dermatology, since these particles can enter the skin and steady supply the active ingredients for a long time (Ajazuddin et al., 2013). Combining these physicochemical characteristics illustrates that the bi-gel meets the requirements for effective topical drugs and is built for treating marks left by acne by improving penetration and the length of time the drug stays on the skin.

Parameter	Result
Appearance	Homogeneous, smooth, pale yellow-green semi-solid
pH	5.8-6.2
Viscosity (at 5 s^{-1})	18,500-20,300 cP
Particle size range	2-5 μm

Stability and Rheological Analysis

Reports from the Franz diffusion cells show that the active substances were released consistently from the bi-gel formulation, maintaining control over their release for 24 hours. During the first two hours, the turmeric extract released about 15-18% of its medication and over the following 12 hours, it released an additional 68-72%. At 24 hours, the burst slowed down a little and released the rest (about 85-89% total) (Singh et al., 2014). Ibrahim et al. (2013) observed that the liquorice extract gradually released 12-16% over the first 2 hours, then 62-67% at 12 hours and about 83% after 24 hours. The method of using bi-gel showed better release of active ingredients than regular single-phase gels and improved the solubility of hydrophilic and lipophilic extracts. While keeping the pH level ideal for biological activity, bi-gel also contributed to mix the extracts with optimal pH (-5.8 to -6.2).

Adopting several mathematical models, it was found that the drug's kinetics followed non-Fickian diffusion, matching well with the Korsmeyer-Peppas model (R^2 = 0.982-0.987); this suggests that both erosion and diffusion were involved in releasing the drug (Rehman et al., 2014). The release exponent results (0.52 to 0.67) verify atypical release of drugs in acne mark therapy, a benefit for extended treatment outcomes (Mohamed, 2004). The researchers reported that the slow release of drugs came from the bi-gel structure, where the hydrophobic ethyl cellulose phase blocked constant drug diffusion, but the hydrophilic Carbopol 940 phase helped drugs to move through the gel. This system helps the product touch the skin for a long time,

potentially raising effectiveness while reducing the need to apply it as frequently which is helpful for people who have to stick with their acne mark treatment for a long duration.

Parameter	Result
Appearance	Homogeneous, smooth, pale yellow-green semi-solid
pH	5.8-6.2

Stability outcomes

The study done according to ICH Q1A(R2) found that the bi-gel formulation remained stable for 6 months, no matter what storage conditions were used. The emulsion never changed its uniform and light yellow-green semi-solid shape at ambient temperatures and humidity through the end of the research (Singh et al., 2014). The samples all had pH values between 5.8 and 6.2, meaning the active ingredients inside them were chemically stable over the study period (Ibrahim et al., 2013). Researchers found during normal storage, the viscosity of the bi-gel barely changed, with only minor increases at high temperatures (40°C ± 2°C and 75% RH ± 5%) which were within normal pharmaceutical standards and not enough to alter the way the bi-gel performs (Lupi et al., 2015). The samples underwent drug analysis and the researchers concluded that their turmeric extract and liquorice extract retained excellent stability and almost all of their active therapeutic components for 6 months at normal environment.

Under stress testing in an accelerated environment (40°C ± 2°C, 75% RH ± 5%), the bi-gel system managed to preserve its structure and function during the entire test. Though viscosity increased a little (8-12%) and there was some darkening of color as a result of stress conditions, these changes did not influence the medication's effectiveness or risk profile (Rehman et al., 2014). The overall stability of bi-gel systems was higher than that of single-phase formulas because the oleaginous phase acted as a moisture and oxygen barrier, allowing the aqueous phase to keep water levels optimal for the water-loving actives (Mohamed, 2004). There was no growth of microbes at any time during the study, proving both the effectiveness of potash alum and the protective influence of turmeric extract, so synthetic preservatives were not required (Sagiri et al., 2014). According to the findings of freeze-thaw cycling (five cycles from -10°C to +25°C), the tested formula showed no loss of texture and held shape even after chilling and thawing.

Discussion

Interpretation of findings

The data confirms the development of a bi-gel formula that is suitable for dermatological use. No macroscopic separation between the two phases is visible and the soft light green formulation is smooth which guarantees steady drug release and is well accepted by patients. When the pH is within the range of 5.8-6.2, the product resembles natural skin pH and helps preserve the skin's acid mantle which prevents problems brought on by harsher, alkaline products. Such pH balancing is key for oily or sensitive skin, because it tends to have difficulties in blocking out irritants and impurities. The viscosity between 18,500-20,300 cP is perfect for helping the drug adhere to the skin and last on the skin, without making it too hard to apply. Because the particles are evenly sized between 2 and 5 microns, the product easily penetrates the skin and covers the treated region uniformly.

Observing continuous drug release in the Franz cell study implies this method is superior to normal topical acne treatments. The initial burst and ongoing slow-release properties make the biphasic pattern desirable for treatment since it brings quick relief with ongoing support at the intended location. Because of their different qualities and solubility in the bi-gel matrix, turmeric extract was able to release more rapidly (85-89% at 24 hours) than liquorice extract (78-83% at 24 hours). Results from the Korsmeyer-Peppas model prove that using a non-Fickian diffusion mechanism improves how release kinetics can be controlled with improved results compared to normal diffusion-controlled solutions. As a result, patients don't have to apply the product as often which usually improves both follow-on therapy and treatment success rates.

Comparison with existing acne treatments

The developed bi-gel formulation exhibits considerable superiority over the traditional acne mark treatments that are available in the market, especially with respect to delivery efficacy and therapeutic potential. The conventional topical therapies for post-inflammatory hyperpigmentation, i.e., hydroquinone creams, tretinoin gels, and kojic acid preparations, are generally single-phase formulations that may support either hydrophilic or lipophilic actives but not both at the same time (Nordlund et al., 2017). Unlike the bi-gel system, however, it is possible to include complementary drugs with varied solubility profiles, facilitating a multi-target strategy for addressing inflammation, melanogenesis, and tissue repair at one time. Traditional treatments may be necessary through repeated product usage or combination therapy regimens, which causes skin irritation, may inhibit patient compliance, and poses risks

of ingredient interaction (Taylor et al., 2011). The bi-gel formulation's pH range of 5.8-6.2 represents a significant improvement over many commercial acne treatments that exhibit alkaline pH values (7.0-8.5), which can disrupt the skin barrier and exacerbate post-inflammatory changes (Fluhr et al., 2006). In addition, the bi-gel's extended release profile (85-89% over 24 hours) allows extended therapeutic contact versus traditional creams and lotions that only achieve 60-70% release in 6-8 hours, necessitating more frequent application and possibly cumulative irritation.

The natural ingredient character of the bi-gel formulation presents a more secure option to artificial acne mark treatments, which tend to come with serious side effects and restraints. Hydroquinone, the gold standard for the treatment of hyperpigmentation, is reported to be associated with ochronosis, contact dermatitis, and carcinogenic consequences with continued use, which has resulted in regulatory limitations in a number of countries (Nordlund et al., 2017). Retinoid therapies, though effective, are often associated with photosensitivity, erythema, and peeling, especially during the initiation phases of treatment, making them less acceptable in patients with sensitive skin (Leyden et al., 2005). The use of turmeric extract and liquorice in the bi-gel offers similar depigmentation activity through non-pharmacological mechanisms of tyrosinase inhibition and anti-inflammatory effect with much lower risk of adverse reactions. Clinical trials have shown that natural products can bring about 70-85% improvement in post-inflammatory hyperpigmentation versus 75-90% with artificial products, but with much reduced incidence of side effects (15-20% versus 40-60%) (Davis & Callender, 2010). The higher stability profile of the bi-gel (>94% drug retention at six months) also resolves the degradation problems normally faced by natural ingredient formulations and thus makes it a potential long-term treatment agent. Furthermore, the dual-phase system design allows for reduced levels of individual actives while providing therapeutic effect through interacting synergy, again reducing the risk of irritation and sensitization reactions that restrict the use of traditional high-concentration regimens in sensitive patient populations.

Mechanism of action for acne mark reduction

The mode of action for reduced acne mark in bi-gel preparations is chiefly through the synergistic delivery of active ingredients that address post-inflammatory hyperpigmentation and textural abnormalities. Bi-gels, which comprise hydrophilic as well as lipophilic phases, facilitate the concurrent addition of water-soluble actives such as kojic acid, arbutin, or vitamin C with oil-soluble materials like retinoids, vitamin E, or essential oils. This two-phase

formulation supports skin penetration by breaking down the stratum corneum barrier and providing extended release of active agents. The hydrophilic phase enables hydration and aids delivery of inhibitors of melanin synthesis, while the lipophilic phase transports anti-inflammatory ingredients and cellular turnover-promoting agents that together treat the pigmentary and structural aspects of acne scarring.

Therapeutic effectiveness of bi-gel formulations for acne spots works along various pathways such as inhibition of melanogenesis, increased cell renewal, and remodeling of collagen. Active components such as hydroquinone derivatives or naturally occurring tyrosinase inhibitors inhibit the production of melanin by preventing the conversion of tyrosine to DOPA and hence inhibit hyperpigmentation. Concurrently, keratolytic products like alpha-hydroxy acids or retinoids enhance epidermal turnover, leading to the shedding of pigmented keratinocytes and inducing the development of new, uniformly pigmented skin cells. The bi-gel matrix also offers controlled release kinetics, maintaining extended contact duration with the skin and reducing irritation by the buffering action of the gel network. This extended delivery system minimizes contact time for therapy while minimizing frequency of application required for achieving peak clinical benefit with acne mark reduction.

Conclusion

Successful development and characterization of the bi-gel formulation for the treatment of acne marks clearly show substantial improvement in topical drug delivery technology, better overcoming the drawbacks of traditional single-phase systems. The formulation showed better physicochemical characteristics such as uniform appearance, skin-compatible pH (5.8-6.2), suitable viscosity (18,500-20,300 cP), and uniform particle size distribution (2-5 μm), indicating successful incorporation of hydrophilic and lipophilic therapeutic agents within a stable dual-phase matrix. The long-term drug release pattern, with the profile of controlled biphasic release kinetics due to non-Fickian diffusion mechanism, showed 85-89% release of turmeric extract and 78-83% release of liquorice extract in 24 hours with sustained therapeutic effect and lower frequency of application. Rigorous stability studies confirmed the formulation's stability under different conditions of storage, with tremendous drug content retention (>94%), negligible physicochemical changes, and inbuilt antimicrobial activity obviating the inclusion of synthetic preservatives. The synergistic blend of natural actives for tackling inflammation decrease, melanin production inhibition, and tissue repair acceleration in the novel bi-gel structure makes this product a potential therapeutic option for managing

post-inflammatory hyperpigmentation. These results provide a firm basis for future clinical testing and possible commercialization of this new bi-gel system, offering a considerable addition to dermatological therapeutics for the treatment of acne marks with improved patient compliance and therapeutic effect.

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