

Development of niacinamide and calendula oil anti-acne gel using carrageenans as gelling agents.

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Abstract

The objective of this research work was to formulate an anti-acne gel consisting carrageenan as gelling agent, Niacinamide and calendula oil as acne controlling agents. In this present work, effect of calendula oil alone was ascertained in treatment of acne, in addition to comparison of anti acne properties of niacinamide and calendula oil combination. Six formulations of gels were formulated and evaluated. Out of 6 formulations, the first three formulations (F1, F2 and F3) were carried out using niacinamide as active substance and carrageenan as gelling agent, the other three formulation (F4, F5 and F6) were carried out using niacinamide and calendula oil in combination as active substances and carrageenan as gelling agent. FTIR studies confirmed that there was no distinguishable physical or chemical interaction between drug and excipients used for this study of anti acne gel formulations. All formulations were evaluated for general appearance, viscosity, pH, drug content, spreadability, invitro diffusion studies and anti microbial studies. Results showed, using a combination of calendula oil and niacinamide proved effective treatment of acne than calendula oil used alone or niacinamide used alone. The prepared anti acne gels were characterized by Fourier transform infrared (FT-IR) spectroscopy, In – Vitro diffusion profile and anti microbial studies. All the gel formulations showed more than 60 percentage drug release within 180 minutes, which was far better when compared to drug release profile of pure drug. By this study, it can be concluded that calendula oil in combination with acne treating drugs can be used as a conjunction in the formulation of gels. The anti microbial spectra of the drug could be improved by this methodology by more than 1.5 times due to improved permeability when compared to pure drug. This combination of calendula oil and niacinamide, using carrageenan as gelling agent can be further exploited for the successful treatment of acne.

Keywords: Niacinamide, Anti acne gels, Carrageenan, Gelling agent, Calendula oil.

Accepted on March 03, 2021

Introduction

Gels have better potential as a vehicle to administer the drug topically in comparison to ointment because they are non-sticky, require low energy during the formulation, stable and have aesthetic value. Gels are transparent to opaque semi solids containing a high ratio of solvent to gelling agent. Gels tend to be smooth, elegant, non greasy and produce non greasy effect and utilize better drug release when compared to semi solid formulations.

The gels are prepared by adding a gelling agent (gelator) which could be natural, synthetic or semi-synthetic polymer or low molecular weight small molecules, into an organic, inorganic or aqueous solvent or solvent systems. The polymer in gels acts as the backbone of the gel matrix. The polymeric meshwork gives gel its structural strength, increased adherence to the surface where applied and decreased permeation of the larger molecules hence making the retention possible. The concentration of the gelling agents is mostly less than 10%, usually in 0.5% to 2.0% range, with a few exceptions [1]. Different kinds of transdermal preparations like lotions, creams, ointments, patches, gels etc. are available; out of which gel is preferred due to more stability and better application

property. The rigidity of a gel is attributed to the presence of a network formed by the interlinking of gelling agent particles. The nature of the particles and the kind of force involved in the linkages, determines the structure of the network and the properties of gel.

Acne is medically known as Acne vulgaris. It is a skin disease that involves the oil glands situated at the base of hair follicles. It is very common and affects almost all adolescents and also the adults in their lives. It is not responsible for impairment of overall health but it is not trivial disease. It affects the patient by producing cutaneous scars which may last for lifetime [2]. It also results in varied number of psychological problems which may lead to low confidence and self esteem. The clinical symptoms of acne are inflammatory lesions, non inflammatory lesions, various degrees of scarring and seborrhea. Acne mostly affects the body parts having maximum density of the pilosebaceous units, such as, face, neck, shoulders, upper chest and back [3]. Acne medications work by reducing oil production, speeding up skin cell turnover, fighting bacterial infection or reducing inflammation, which helps prevent scarring. The most common topical medications used for management of acne include retinoids and retinoid like drugs (tretinoin, adapalene and tazarotene); Antibiotics

(Clindamycin with benzoyl peroxide, erythromycin with benzoyl peroxide); Salicylic acid, azelaic acid, Dapsone 5 % gel, and many other chemical therapies like laser, photodynamic therapy, chemical peel, extraction of white heads/black heads, steroid injection, most of which are expensive and ineffective [4].

Niacinamide/nicotinamide/niacin/vitamin B3 is a water-soluble vitamin that works with the natural substances in your skin to help visibly improve the appearance of enlarged pores, uneven skin tone, fine lines and wrinkles, dullness, and a weakened surface.

Calendula oil is natural oil extracted from marigold flowers (*Calendula officinalis*). Calendula oil may have antifungal, anti-inflammatory, and antibacterial properties that might make it useful in healing wounds, soothing eczema, and relieving diaper rash. Carrageenan works as a thickening agent, binder and hair conditioning agent. It has excellent water binding properties, as well as the ability to form gels at room temperature. Cosmetic manufacturers value this ingredient because it can thin under stress and then recover its consistency once the stress is removed. In the present study, an attempt is made to use carrageenan as gelling agent to formulate anti acne gel. In addition to niacinamide, calendula oil and carrageenan, are investigated for synergistic effect as anti acne gel formulation.

Materials and Methods

All the materials used for the research were of analytical grade purity. Niacinamide was a kind gift from Quiver technologies. Organic calendula oil was purchased from local market. Carrageenan was obtained as gift samples from Signet chemical corporation pvt. Ltd. And Aquarev industries, Gujarat; Glycerine, sodium benzoate and oleic acid were obtained from S D Fine Chemicals, Mumbai. Distilled water was used to prepare aqueous solutions and was obtained by a suitable process.

Determination of λ max

To find out the λ max of niacinamide, a stock solution of 1 mg/ml was prepared by dissolving 100 mg of drug in small quantity of methanol and diluted with 100 ml of phosphate buffer (pH 6.8). The stock solution was serially diluted to get solutions in the range of 2-12 μ g/ml and λ max of the solution was found out by scanning from 200 - 400 nm.

Determination of Calibration Curve

The stock solution was serially diluted to get solutions in the range of 2-10 μ g/ml and λ max of the solution was found out. The absorbances of the different diluted solutions were measured in a UV-Visible spectrophotometer at 267 nm. A calibration curve was plotted by taking concentration of solution in X axis and absorbances in Y axis and correlation coefficient 'r' was calculated.

Determination of melting point

The melting point of the drug has been determined by taking a small amount of the drug in a capillary tube that was closed at one end. The capillary tube was placed in a thermionic melting point apparatus and, the temperature at which the drug melted was noted. Averages of three readings were taken.

Drug excipients interaction study by FTIR

FTIR emission spectrometer (Shimadzu, Japan) was used to record the FTIR spectrum of the drugs from 400 to 4000 cm^{-1} to confirm compatibility between the excipients used and pure drug in the formulation. FTIR spectra of pure drug, along with physical mixture of polymers and drug were taken separately. The sample was grounded with KBr and pressed to a suitable size disk for measurement.

Preparation of gels [5,6]

6 gel formulations were prepared using carrageenan as gelling agent in three different concentrations. Required quantity of gelling agent was weighed and dispersed in a small quantity of distilled water to form a homogeneous dispersion. The drug (only niacinamide in F1, F2 and F3, niacinamide in combination with calendula oil in formulations F4, F5 and F6) was dissolved in suitable solvent (propylene glycol or ethanol) and added to the above solution. Other excipients (glycerin, sodium benzoate) were also added with continuous stirring. Measured amounts of oleic acid were used to enhance permeability. pH of the gel was brought to skin pH. The final weight of the gel was adjusted to 10 g with distilled water. The gels were stored in wide mouthed bottles until further use (Table 1).

Formulation code	Ingredients						
	Niacinamide	Calendula oil	Carrageenan	Glycerin	Sodium benzoate	Oleic acid	Distilled Water
F1	1.5g	--	0.5g	5ml	0.1g	0.4g	q.s to 10 ml
F2	1.5g	--	0.75g	5ml	0.1g	0.4g	q.s to 10 ml
F3	1.5g	--	0.9g	5ml	0.1g	0.4g	q.s to 10 ml
F4	1.25g	0.25 g	0.5g	5ml	0.1g	0.4g	q.s to 10 ml
F5	1.25g	0.25 g	0.75g	5ml	0.1g	0.4g	q.s to 10 ml
F6	1.25g	0.25 g	0.9g	5ml	0.1g	0.4g	q.s to 10 ml

Table 1. Formulation table of anti-acne gels.

Characterization and evaluation of anti-acne gels [7,8]

General appearance

Texture, clarity of the gel was evaluated in terms of stickiness and grittiness by mildly rubbing the gel between two fingers. Consistency and odor were also evaluated by physical observation.

Rheological measurement

Viscosity of all the batches of soft gels was measured using Brookfield DV-II viscometer. Viscosity of all the formulations of topical gels was measured using spindle number S63 at the rotation of 50 rpm at room temperature. The viscosity measurements were made in triplicate using fresh samples each time.

pH of the anti-acne gel

The pH of topical gel was measured using Electroquip Digital pH meter at room temperature.

Drug content

Gel equivalent to 10 mg of topical gel was taken in 100 mL volumetric flask and dissolved in 50 ml of water with vigorous shaking for 5-10 minutes. Finally the volume was made up to mark with water. Then it was analyzed using UV spectrophotometer at 267 nm.

Spreadability

The spreadability of the gel formulation was determined, by measuring diameter of 1 gm gel between horizontal plates (20×20 cm²) after 1 minute. The standardized weight tied on the upper plate was 125 gm.

In Vitro Diffusion using Franz Diffusion cell

The lower abdominal skin of Albino mice, weighing 20-25 gm of 8-10 week old was shaved using hand razor and skin was cleansed with hot water cotton swab. 1 gm of gel was applied uniformly to skin. The skin was mounted between the compartments of the Franz diffusion cell with anti-acne gel facing the donor compartment. Reservoir compartment was filled with 100 ml phosphate buffer of pH 6.8.

The study was carried out at $37 \pm 1^\circ\text{C}$ and speed was adjusted until the vortex touches the skin and it carried out for 150 minutes. 2 ml of sample was withdrawn from reservoir compartment at 30 min interval and absorbance was measured spectrophotometrically at 267 nm. Each time the reservoir compartment was replenished with 2 ml volume of phosphate buffer pH 6.8 solution to maintain constant volume (Figure 1).



Figure 1. In Vitro diffusion testing using Franz diffusion cell.

Anti microbial study of anti acne gels using Cup and plate Assay method [9]

Solid agar media solution was sterilized for 15 min at 121°C at 15 lb pressure in autoclave for about 20 min. Sterilised media was cooled at room temperature and the gram negative strain (*Escherichia Coli*) was dispersed in the medium and then the medium was poured in to petriplates and allowed it cool until it solidifies at room temperature. Cups were bored in each petridish with the help of sterile steel bore of 6 mm at the centre and calculated concentration of the standard drug (Amoxicillin), gel formulation (F1-F6) and niacinamide pure drug were placed in the bores and incubated the petri plates for 72 h at 37°C in incubators. Then the zone of inhibition was observed and radius of zone was determined.

Stability studies

All topical anti acne formulations were subjected to stability study using humidity controlled stability chamber [10,11]. Formulations were stored in stability testing chamber for two months. Physical evaluation of the stability was carried out by visual inspection, pH measurements and spectrophotometric analysis of the drug content.

Results and Discussion

Absorption maxima (λ_{max}) for Niacinamide

From the stock solution 1 mg/ml niacinamide in pH 6.4 phosphate buffer, suitable dilutions was made with distilled water to get a concentration 12 $\mu\text{g/ml}$ and scanned for maximum absorbance using UV - visible spectrophotometer in the range from 200-400 nm. The absorption maximum was found to be 267 nm and hence the same was used as λ_{max} for the estimation of niacinamide in the study (Figure 2).

Citation: Maddukuri S, Devi GL, Metta S, et al.. Development of niacinamide and calendula oil anti-acne gel using carrageenans as gelling agents. *Allied J Med Res* 2021;5(2):1-29.

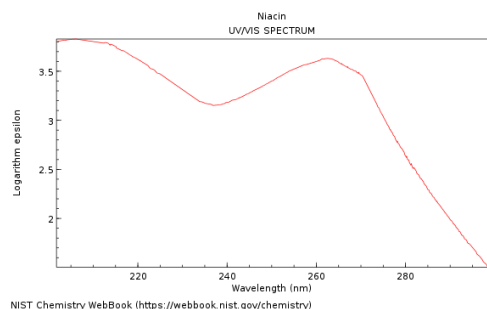


Figure 2. UV Spectrum of niacinamide.

Calibration curve of niacinamide

The stock solution of niacinamide in pH 6.4 phosphate buffer and further dilution in distilled water showed good linearity ($r^2 = 0.999$) over the concentration range of 4- 20 $\mu\text{g/ml}$ at λ_{max} 267 nm (Figure 3).

Figure 3. Standard calibration curve of niacinamide.

Melting point determination

The melting point of niacinamide was determined by capillary method. The melting point of niacinamide was found to be 128 $^{\circ}\text{C}$. It complies with standards thus indicating the purity of the drug sample.

FTIR studies

FTIR was performed for the pure drug, calendula oil, carrageenan, tween 80 and physical mixture of drug and polymers to detect any sign of interaction which would be reflected by a change in the position or disappearance of any characteristic peaks of the compound.

The IR spectra of the pure niacinamide had shown characteristic peaks at 3083.38 due to CH aromatic stretch, 3335.62 due to NH secondary stretch, 1718.26 cm^{-1} due to C=O stretch and 1248.86 cm^{-1} due to C-N stretch and CH₃ rock.

The IR spectra of the physical mixtures of pure drug along calendula oil, carrageenan, tween 80 were also recorded and the spectra showed the presence of characteristic peaks of both pure drug and polymers, thereby confirming the compatibility between them.

The IR spectra showed neither shift nor disappearance of characteristic peaks suggesting that there was no interaction between drug and excipients used for preparation of anti-acne gels (Figure 4).

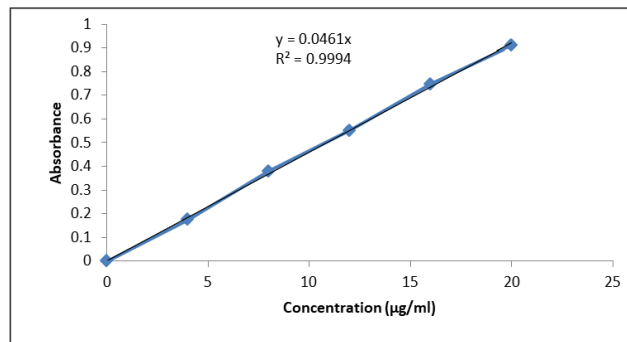


Figure 4. IR Spectra of Drug and excipients.

Evaluation Studies

General appearance: Texture, clarity of the gel was evaluated in terms of stickiness and grittiness by mildly rubbing the gel between two fingers [12]. Gel was found to be creamy and translucent. No grittiness and tackiness was found in all formulations.

Viscosity measurement: Viscosity of all anti acne gel formulations were measured using brookefield viscometer, model DV II. Viscosity of all anti acne gel formulations ranged from 3.67-4.82 Pa.sec.

pH: pH of the final gel has a lot of impact on stability, acceptability of the anti acne gel formulations [13]. Since, it is intended to be applied to the facial skin, pH of the final formulation was closely monitored using digital pH meter and found to be 7 ± 0.2 .

Drug content: All the six formulations of anti acne gels, Drug content was estimated by SHIMADZU-1700 UV spectrophotometer at λ_{max} 267 nm. The results were in the official limits (table 2).

Spreadability: Spreadability test was carried out for all the formulations; spreadability of the gel formulation was found decreasing with increase in the concentration of the gelling agent [14].

Evaluation Property	F1	F2	F3	F4	F5	F6
General Appearance	Creamy, translucent	Creamy, translucent	Creamy, translucent	Creamy, translucent	Creamy, translucent	Creamy, translucent
Rheology (Pas)	3.65	3.87	4.82	3.55	3.69	4.025
pH	6.94	6.92	6.95	7.02	6.55	6.98
Drug content	97.54	98.15	99.05	99.74	99.42	99.88
Spreadability (cms)	8.2	7.9	8.4	9.1	9.2	8.8

Table 2. Evaluation properties of anti-acne gels.

In-vitro Diffusion studies

In vitro drug diffusion studies were carried out using USP type II tablet dissolution test apparatus paddle method at 37 ± 0.5 °C, taking 900 ml of pH 6.4 phosphate buffer as dissolution medium. Speed of rotation of the paddle was set at 50 rpm. Aliquots of 5 ml were withdrawn at a regular interval of 15 minutes and analyzed spectrophotometrically at 210 nm. The in vitro dissolution profiles of all the 6 formulations using different concentrations of gelling agents – Carrageenan and pure drug in combination with calendula oil indicated faster drug release from all the formulations and the maximum drug release was from formulations F6. Formulation F6 prepared by using combination of niacinamide and calendula oil, using gelling agent- carrageenan showed 79.29 % drug release at the end of 180 min when compared to gel formulated using only pure drug- niacinamide and carrageenan [15] (figure 5).

Figure 5. In vitro diffusion studies of anti acne gels

Antimicrobial Studies

Antimicrobial studies were carried out for all the gel formulations; Zone of inhibition was observed at F6 (6.6 cms), pure amoxicillin (8 cms) and pure form of the niacinamide (6.9 cms). The results were satisfactory. Zone of inhibition was found to be slightly higher for formulations having calendula oil, niacinamide and carrageenan as gelling agent. This slight increase in antimicrobial activity of anti acne gels having both calendula oil, niacinamide as active substances and carrageenan as gelling agent can be attributed to calendula oil and also, some reports suggest that, carrageenan has been used in skin cosmetics for its skin healing properties, hydration effects [16].

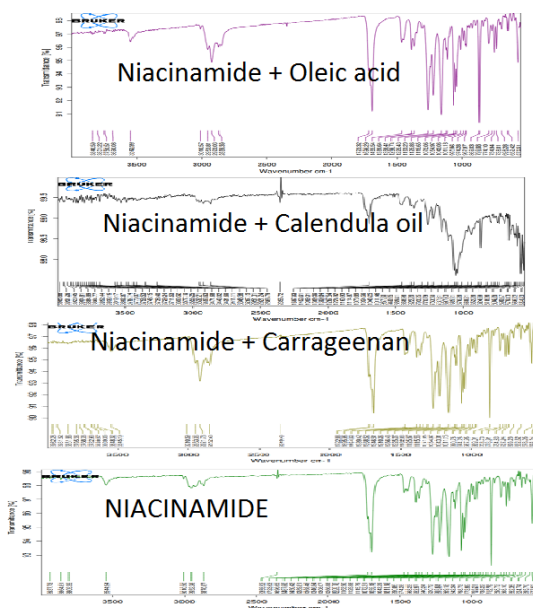


Figure 6. Antimicrobial studies using cup and plate assay method.

Stability Studies

Stability studies were carried for the most satisfactory formulation-F6, at 30 ± 2 °C for 2 months. At the end of 2 months, samples were evaluated. Drug content study showed that, there was no major change in the content drug of F6 (from 99.8 to 98%) at 30 ± 2 °C at 65 ± 5 RH and decrease at 40 ± 2 °C at 75 ± 5 RH (from 99.8 to 6%). There was no significant change in the in vitro drug diffusion study F6 (from 79.29 to 77.05%) at 30 ± 2 °C at 65 ± 5 RH. There was no major change in the parameters evaluated like drug content and in vitro drug diffusion study of F6 at 30 ± 2 °C at 65 ± 5 RH. Thus it can be concluded that, F6 is stable at 30 ± 2 °C at 65 ± 5 RH for a period of 2 months (table 3) [17].

Evaluated parameter	Initially	After 15 days	After 30 days	After 60 days
Drug content	99.8 %	99.24 %	98.25 %	97 %
Spreadability	Easily spreadable	Easily spreadable	Easily spreadable	Easily spreadable
Viscosity (Pa. Sec)	4.82	4.56	4.64	4.71
In vitro diffusion profile	79.29 %	79.05 %	78.5 %	77.05%

Table 3. Stability studies of formulation F6.

Conclusion

Acne Vulgaris is a chronic, inflammatory skin condition that causes spots and pimples, especially on the face, shoulders, back, neck, chest, and upper arms, caused by sensitivity to puberty related hormones (both in males and females), combined with bacteria on the skin and fatty acids within oil glands. Acne may be mild, moderate or severe with inflammatory nodules and cysts. Acne lesions include white heads, black heads, small bumps, nodules and cysts. Propionibacterium acnes (P. acnes) are the name of the bacteria that live on the skin and contributes to the infection of pimples. Only three types of drugs have proven to be effective for the treatment of acne antibiotics, benzoyl peroxide, and retinoids. Most people require at least one or two agents, depending on the severity of their acne.

Mild acne can be treated with over-the-counter (OTC) medications, such as gels, soaps, pads, creams, and lotions that are applied to the skin. Creams and lotions are best for sensitive skin. Alcohol-based gels dry the skin and are better for oily skin. Niacinamide, also known as nicotinamide, is the active form of niacin (also known as vitamin B3 or nicotinic acid). In our bodies, niacinamide is formed when we eat foods high in niacin (like liver or mushrooms). We convert the niacin into active niacinamide, which in turn acts as a precursor to the coenzymes NADH and NADPH. These coenzymes boost cellular metabolism, meaning they give our skin cells the energy to carry out their functions. In fact, they are involved in more than 40 biochemical processes, including such important jobs as DNA repair and cell turnover. Since niacinamide

readily penetrates into the skin, we don't have to rely on our diets or a dietary supplement. We can also benefit from using it topically. Niacinamide with its antimicrobial properties, can be used to treat mild to moderate acne. Calendula oil is antiseptic, antimicrobial, and has anti-inflammatory properties. The herb oil, being anti-fungal and anti-bacterial helps in treatment of acne and reduces blemishes and scars from acne. Carrageenan may actually prove beneficial to skin in several ways. In addition to its hydrating properties, it's also been found in cosmetic products for its water retaining capacity, thickening properties.

The objective of this research work was to formulate an anti-acne gel consisting of carrageenan as gelling agent, Niacinamide and calendula oil as acne controlling agents. In this present work, effect of calendula oil and carrageenan was tested in treatment of acne. Niacinamide being an already established substance in treatment of acne, effect of calendula oil and carrageenan have been studied in this research work. Six formulations of gels were formulated and evaluated. Out of 6 formulations, the first three formulations (F1, F2 and F3) were carried out using niacinamide as active substance and carrageenan as gelling agent, the other three formulation (F4, F5 and F6) were carried out using niacinamide and calendula oil in combination as active substances and carrageenan as gelling agent. Drug-excipient interaction was studied by FT-IR compatibility studies. Gel formulations were prepared according to formulation table and final weight was adjusted to 10g and stored in wide mouthed bottles, until evaluation. All formulations were evaluated for general appearance, viscosity, pH, drug content, spreadability, invitro diffusion studies and anti microbial studies. Thus, by using a combination of calendula oil and niacinamide, results of in vitro diffusion studies and anti microbial studies proved effective treatment of acne than niacinamide used alone. The prepared anti acne gels were characterized by Fourier transform infra-red (FT-IR) spectroscopy, In Vitro diffusion profile. FTIR studies confirmed that there was no distinguishable physical or chemical interaction between drug and excipients used for this study of anti acne gel formulations. Gel formulations containing niacinamide and calendula oil, in combination with carrageenan as gelling agent, were selected to be the best and can be used for further formulation and studies based on their drug diffusion profiles. All the gel formulations showed more than 60 percentage drug release within 180 minutes, which was far better when compared to drug release profile of pure drug. By this study, it can be concluded that calendula oil in combination with acne treating drugs can be used as a conjunction in the formulation of gels. The anti microbial spectra of the drug could be improved by this methodology by more than 1.5 times due to improved permeability when compared to pure drug. This combination of calendula oil and niacinamide, using carrageenan as gelling agent can be further exploited for the successful treatment of acne.

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