International Journal of Research in Dermatology
Chinda M et al. Int J Res Dermatol. 2025 Nov;11(6):482-488
http://www.ijord.com

DOI: https://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20253295

Original Research Article

A comparative study to evaluate the Q3 characteristics of different tretinoin microspheres available in the Indian market to the innovator or the reference listed drugs

Monika Chinda[1]*, K. Balakrishna Patro[2], Ravish Qureshi[2], Amol Langde[3], Anil Kukreja[4], Hiren Patel[5]

[1]Department of Medical Affairs, Emcutix Biopharmaceutical Limited, Mumbai, Maharashtra, India
[2]Department of Formulation and Development, Encube Advance Research Center, Kalyan, Maharashtra, India
[3]Department of Analytical Services – IVRT, Encube Advance Research Center, Kalyan, Maharashtra, India
[4]Department of Clinical Research and Medical Affairs, Emcure Pharmaceutical Limited, Mumbai, Maharashtra, India
[5]Department of R&D and MSTG, Emcure Pharmaceutical Limited, Pune, Maharashtra, India

Received: 03 September 2025
Revised: 20 September 2025
Accepted: 23 September 2025

***Correspondence:**
Dr. Monika Chinda,
E-mail: monika.chinda@emcutix.com

ABSTRACT

Background: With the increasing availability of tretinoin microsphere gels in the Indian pharmaceutical market, comparative evaluation against market products and the U.S. reference listed drug (RLD) becomes essential to assess quality, safety, and performance consistency.
Methods: This study presents a comprehensive Q3 characterization a test product with 0.04% marketed by Emcutix in comparison with the U.S. RLD, retin-A micro gel, and various Indian marketed tretinoin gel brands A, B, and C (0.04% tretinoin). The evaluation focused on key physicochemical and structural attributes including appearance, texture, pH, drug content, viscosity, specific gravity, phase morphology, and in vitro release testing (IVRT).
Results: The test product 0.04% exhibited visual appearance, texture, pH, and tretinoin content similar to RLD. In contrast, the marketed products demonstrated deviations in appearance and suboptimal drug content, failing to meet USP and BP overage allowances. Viscosity (38,000 cPs) and specific gravity (1.047) of the test product 0.04% were within acceptable ranges, closely matching the RLD values. Microsphere morphology revealed well-formed, spheroidal particles in test product 0.04% and brand A formulation, while brand C and Brand B lacked such microsphere structures. IVRT profiles showed that the test product and brand A formulation showed the slowest, most sustained release, whereas brand B and brand C showed faster release kinetics, correlating with the absence of microspheres.
Conclusions: Overall, the test product gels demonstrate Q3 equivalence to the RLD and outperform Indian market products in structural and release characteristics, suggesting their suitability for bioequivalence and regulatory alignments.

Keywords: Microsphere, Tretinoin, Q3 microstructure, Similarity

INTRODUCTION

Launched nearly 55 years back, approved by Food and Drug Administration in 1971, tretinoin was the first of the retinoids channeled in the market to treat acne vulgaris. Chemically defined as vitamin A acid, tretinoin (all-trans-retinoic acid, also known as (all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8 nonatetraenoic acid.) is metabolized as retinol, a physiologically active form has also shown benefits in treating keratinizing disorders and inflammation.[1]

Tretinoin belongs to first-generation retinoids utilized in the treatment of acne vulgaris.[2] It is also used as a palliative care for treatment of photodamaged skin.[3] Tretinoin interacts with three nuclear retinoic acid receptors (RAR-α, RAR-β, and RAR-γ) but exerts its action through RAR-γ. This action activates interaction between RAR-γ with retinoid-X receptor (RXR-γ). The complex bind to the regulatory regions in DNA called the RAR response elements or RAREs. The RAREs activate gene transcriptions enabling activation of 300+ genes that alters expression of 100s of proteins.[3,4] Apart from its anti-acne potential, tretinoin is also involved in the treatment of photoaged skin, increase collagen promotion, and treats post-inflammatory hyperpigmentation, psoriasis, and skin cancers.[5-7] However, it is often associated with peeling, redness, erythema, and blisters, alongside barrier properties of the skin and its lipophilic nature, and instability due to pH, light, and oxygen that often limits the use.[8,9] The non-adherence of the patients to the treatment protocol is often associated with local irritation.[2]

There is an urgent need of developing a formula that will allow tretinoin to work at its maximum capacity without affecting the skin in a negative manner. To bridge this therapeutic gap, several researches have been undertaken to minimize the safety risks associated with tretinoin in its original chemistry. Topical liposomal tretinoin variants were developed and tested for retention and achieved satisfactory clinical outcomes for treating acne, particularly comedones. The liposomal system delivered tretinoin through gel formulations in a prolonged fashion and also was retained in skin by 2-fold means as compared to plain gel.[10] Yet another drug delivery system used for tretinoin are nanolipid carriers. A study reports its clinical intervention stating that the effect was optimal as compared to nascent drug and the levels of plasma tretinoin after 8 weeks remained lower than the toxic levels.[11] Another study reports microencapsulation method where tretinoin was encapsulated in silica shell (0.01-100 µm in diameter). This permitted sustained release of the active ingredients through microchannels in the skin and reduced skin irritation. The same study utilized both tretinoin and benzyl peroxide to work simultaneously without affecting tretinoins chemistry due to oxidative attack done by benzyl peroxide.[12] Another study explored the function of microemulsion composed of water, isopropyl alcohol, and tween-80 as a tretinoin solubilizer and penetration enhancer. The study further evaluated the release profile of tretinoin through carbopol and xanthum gum-based formulae invitro through synthetic membrane and ex-vivo through porcine ears skin to deliver isotretinoin in a sustained manner.[13]

One such delivery systems are microparticles or Microsponges® which are free flowing, insoluble in water, spherical particles which do not penetrate the skin but allow sustained release of tretinoin to eventually reduce its irritation. The sizes of the particles typically vary from 5-300 µm and with a pore size of 0.25 µm allowing incorporation of actives, cosmetic ingredients, and fragrances for sustained diffusion.[14] However, it is crucial to analyze the manufacturing method and formulation characteristics, Q3 attributes, interaction of tretinoin with microspheres, experimental conditions such as solvent type, concentration of drug etc. to ensure optimal efficacy and performance with minimum adverse effects. Practical interactions of microspheres with the skin was limited and hence they are formulated in gels or creams or similar semisolid formulae.[15]

To address the demand for stable, effective, and safe tretinoin formulations, Encube developed tretinoin microsphere gel. The primary aim of this study was to assess the test product, Flawlizo microsphere gel (0.04% tretinoin) and compare its Q3 microsimilarity structural characteristics with those of reference listed drugs (RLD), ensuring its pharmaceutical equivalence with products in the Indian market. This article provides insights into the performance, quality, delivery efficiency, and overall benefits of the test products.

METHODS

The Flawlizo Microsphere 0.04% tretinoin gel (test product) was prepared in-house by Encube. The study was conducted in Encube Advance Research Center and was conducted from January to February, 2025. All the chemicals used were of analytical grade and/or LC-MS grade. Brand A 0.04%, brand B 0.04%, and brand C 0.04% were procured from a local pharmacy in Mumbai, India. The test product with 0.04% were analysed for Q3 parameters with a view of using these tests was surrogate to *in vivo* performance against market samples.

Preparation of tretinoin microparticles loaded gel 0.04%

Tretinoin microsphere gel is an aqueous gel formulation in which tretinoin-loaded microspheres are uniformly dispersed. The microspheres are prepared using a solvent evaporation technique designed to achieve controlled drug delivery and improve patient tolerability. In this process, tretinoin is dissolved in a suitable organic solvent and incorporated into an acrylate copolymer matrix through mixing, followed by solvent evaporation and drying to obtain microspheres encapsulating the drug. These dried microspheres, serving as the functional form of the API, are subsequently incorporated into an aqueous gel base to yield the final formulation.

Appearance and texture

The test formulation and marketed products were evaluated based on their visual and sensory characteristics, including colour, clarity, texture, and odour. Observations such as these, help define the overall aesthetic quality of the product.

For example, the US RLD retin-A micro gel is described as an opaque gel with a white to very pale-yellow appearance.

Tretinoin content

The percentage of tretinoin in all formulations was analyzed using an HPLC method. The assay of tretinoin in pharmaceutical dosage forms is performed using a validated reverse-phase high-performance liquid chromatography (HPLC). The column used is C18 column (150×4.6 mm, 5 µm) with a mobile phase containing acetonitrile and water in the ratio 850:150 (v/v), added 5 ml of glacial acetic acid, delivered at a flow rate of 1.5 ml/min and ambient column temperature of 25 °C. Detection is carried out using a UV detector at 353 nm for tretinoin, with a typical run time of 10 minutes and an injection volume of 20 µl. Samples are prepared by accurate weighing, extracted with diluent such as methanol and ethyl acetate in the ratio (50:50) (v/v), sonicated, and filtered through a 0.45 µm PTFE filter. Method is validated as per ICH guidelines, the method is stability-indicating and suitable for release, stability studies, and quality control testing.

pH measurement

pH is a critical parameter in determining the microstructural similarity of products and is essential for minimizing potential side effects. pH measurements for the samples and generic products were recorded using a calibrated pH electrode (Make: Thermo Scientific, Model: Orion Versa Star Pro) with standard buffer solutions at 25°±2°C.

Viscosity

Viscosity was measured using a viscometer (Make: Brookfield. Model: RVDV II+ Pro Viscometer). Approximately 50 g of the gel formulation was placed in a beaker and equilibrated at 25±1 °C using a water bath prior to measurement.

Viscosity was measured at a fixed spindle speed of 5 rpm. The spindle was carefully immersed to the appropriate depth, ensuring no contact with the beaker walls or bottom. Measurements were performed, and the viscosity was recorded in centipoise (cP). Along with visual appearance, viscosity plays a key role in the product's aesthetic appeal and user acceptance.

Specific gravity

The specific gravity of the product was recorded versus the generic product using the instrument Make: Anton Par, Model: DMA 4100M. The specific gravity of the topical gel formulation was determined using a digital density meter (Anton Paar, Model: DMA 4100M) based on the oscillating U-tube principle. Approximately 1–2 ml of the sample was carefully introduced into the U-tube using a clean, dry syringe, ensuring no air bubbles were present. Measurements were conducted at a controlled temperature of 25.00±0.05 °C. The specific gravity was calculated as the ratio of the measured density of the sample to that of water at the same temperature (typically 0.997047 g/cm³ at 25 °C) and reported as a dimensionless value.

Morphological evaluations

The particle size distribution of tretinoin microspheres incorporated in the gel formulation was determined using a laser diffraction technique on the Malvern Mastersizer 3000 (Malvern P analytical). A sample equivalent to 250 mg of Tretinoin microsphere gel was accurately weighed into a 100 ml glass beaker. To aid dispersion, few drops of surfactant were added to the sample, and a uniform paste was prepared by gentle mixing with a glass rod. Subsequently, 20 ml of purified water was added to the paste and the mixture was stirred thoroughly to achieve preliminary dispersion. The resulting dispersion was subjected to external probe sonication for few minutes, ensuring that the microspheres were adequately dispersed without disruption of their structure. After sonication, the sample was transferred to the Mastersizer 3000 dispersion unit and the measurement was carried out. The data for particle size was expressed in terms of D10, D50, D90 that represents diameters below which 10%, 50% or 90% of the population fall respectively.

Invitro drug release test

In vitro release of tretinoin from different formulation was evaluated by using a nylon membrane, with pore size 0.45 µ (Make: mdi). The membrane was mounted on modified Franz diffusion cells (Vertical Modified Franz Diffusion Cells, Logan Corporation, System 913A-12)). Based on Tretinoin solubility receptor media containing ethanol, acetonitrile and propylene glycol solution was chosen as the receptor fluid. Then, 1.0 g of the formulations was applied with in the donor compartment and the diffusion cells covered with an aluminum foil to prevent light exposure. The temperature was maintained at 32.0±1°C on the membrane surface with water bath temperature slightly higher to maintain the membrane surface temperature. Sampling was done at 1.0, 2.0, 3.0, 4.0,5.0 and 6.0 hour and at each point, 0.5 ml aliquots were drawn from the receiver compartment. After that, an equivalent volume of receptor fluid was put back to the receiver compartment to keep sink condition. The profile of release was then plotted.

RESULTS

In the current study, a preliminary screening of the Q3 attributes for the product under examination were compared with retin-A micro gel, a reference listed drug (RLD), and competitors of Indian market brand A 0.04%, brand B 0.04%, brand C 0.04 The Q3 attributes tested for sample product versus RLD were texture and appearance, pH, viscosity, and specific gravity. Microsphere morpohology and IVRT was not performed for the RLD. For the ease of comparison, the data from the literature shall be extracted. A complete comparison of the test product 0.04% with competitors of Indian market (brand

A 0.04%, brand B 0.04% and Brand C 0.04%), was done for all the Q3 parameters and IVRT.

Characterization of appearance and texture

Both the product and RLD showed similar physical appearance, color, and texture. Both showed opaque, white-to very pale-yellow appearance. The test product with 0.04% tretinoin was also compared with market competitors of India. The appearance of brand A and brand B was off-white opaque; brand C was light yellow transparent gel (Figure 1).

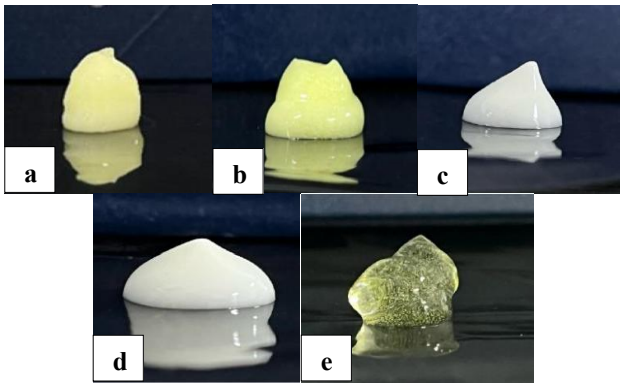

Figure 1: Physical appearance of the gels, (a) RLD retin-A micro gel lot: 8127510, (b) test product 0.04% lot: FND-0225/02, (c) brand A 0.04%, (d) brand B 0.04%, and (e) brand C 0.04%).

Evaluation of tretinoin content

The percent drug content by HPLC assay with respect to the product specifications was estimated for the retin-A micro gel (RLD) and other marketed products (brand A 0.04%, brand B 0.04% and brand C 0.04%). The percent drug content of tretinoin for the test product (0.04%) was 106.3% contains drug overages required to match the product stability. The RLD also showed 103.4% tretinoin content. Brand A 0.04% and brand B 0.04% showed 90.5% and 89.8% (~90%) drug content. Likewise, brand C 0.04% also showed 98.1% drug content without any overages.

pH

The pH of the test product 0.04% was 4.8 and falls within the ideal pH range required for anti-acne formulae. The RLD, retin-A micro gel also exhibited a pH of 5.08. The marketed products showed slightly higher pH. Brand A 0.04% exhibited the highest pH of 5.88, followed by brand B 0.04% with a pH of 5.55 and brand C 0.04%, with a pH 5.55.

Viscosity and specific gravity

All the tested samples exhibited viscosity within the limits of 30000-100000 cPs as mentioned for high viscosity formulations (Table 1).

Characterization of phase states and structural organization of matter

The morphology and size distribution of microspheres were also analyzed. In the case of the brand A 0.04%, microscopic evaluation revealed the presence of extremely fine, insoluble particles dispersed uniformly within the gel matrix, indicative of well-formed microspheres with a D90 value of 36 µm. Conversely, the brand B and brand C displayed irregular, crystalline particles that lacked the characteristic appearance of microspheres.

Further particle size analysis using Malvern instrumentation showed that these particles dissolved readily in aqueous dispersants, suggesting they are non-polymeric and confirming the absence of true microspheres in these formulations. In contrast, the test product 0.04% exhibited evenly dispersed, almost spheroidal particles with a D90 of 53 µm, supporting the identification of a true microsphere-based gel system (Figure 2).

IVRT evaluations

The release profiles of the four 0.04% tretinoin gels show distinct differences in their drug release behaviour. The test product 0.04% exhibited the slowest release, with a gradual increase from 10.4% at 1 hour to 33.9% at 6 hours and a low slope value of 36.48. Brand A 0.04% demonstrated a moderate release rate, starting similarly to the test product at 0.04% but reaching 44.9% by 6 hours with a slope of 55.88, suggesting a balance between onset speed and tolerability. Brand B has a relatively fast release profile, reaching 61.4% at 6 hours with a slope of 87.8, indicating moderate control over drug diffusion. Brand C shows the fastest release, with a rapid increase after 2 hours reaching 83.1% at 6 hours and a high slope of 129.8 (Table 2 and Figure 3).

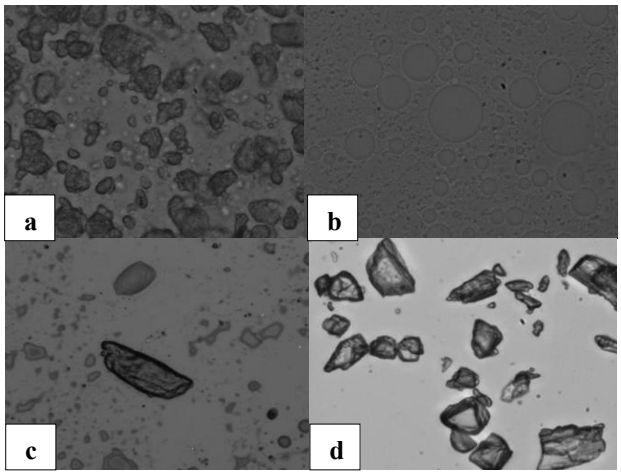

Figure 2: Phase state analysis of the gels, (a) test product 0.04% lot: FND-0225/02, (b) brand A 0.04%, (c) brand B 0.04%, and (d) brand C 0.04%).

Table 1: Viscosity and specific gravity of the gels.

Product details	RLD retin-A micro gel lot: 8127510	Test product 0.04%, lot: FND-0225/02	Brand A 0.04%	Brand B 0.04%	Brand C 0.04%
Viscosity	51,000	38,000	34,800	21,600	62,800
Specific gravity	1.064	1.047	0.9902	1.0155	1.0058

*Limit: 30000 to 100000 cps based on IH method development.

Table 2: IVRT analysis of the gels.

Time (hours)	Test product 0.04% Lot: FND-0225/02	Brand A 0.04%	Brand B 0.04%	Brand C 0.04%
	% Release of tretinoin			
1	10.4	10.0	8.6	7.5
2	16.4	18.9	15.6	28.0
3	21.3	27.8	25.2	53.2
4	25.8	35.0	41.9	74.6
5	29.6	40.2	53.0	81.0
6	33.9	44.9	61.4	83.1
Rate of release (slope): µg/cm² /√t	36.48	55.88	87.8	129.8

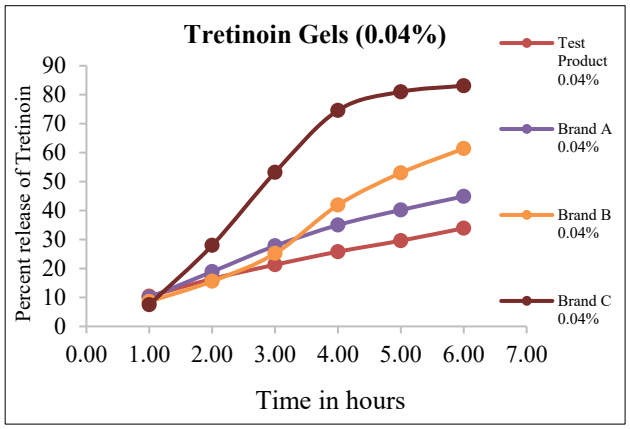

Figure 3: IVRT release profile of the gels.

DISCUSSION

While formulating any product, its pH value, texture, drug content, viscosity, and specific gravity are the risks associated with its microstructural integrity and its performance. As per FDA, the test product and the reference standard should have same physiochemical qualitative (Q1), quantitative (Q2), and structural (Q3) attributes with at least 3 batches of products and reference standards to measure invitro bioequivalence. The Q3 attributes could be but not limited to characterization of phases and visual texture and appearance, phase state, particle size, rheological behaviour, specific gravity, and IVRT.[16,17]

The characterization of appearance and texture for test product with 0.04% tretinoin was done versus the RLD, Retin-A micro gel. The product test product with 0.04% tretinoin closely matched with the description as specified in the product leaflet information as well as the upon actual comparison as seen in the current study.[18] The description for appearance and texture for market competitors did not match with the US RLD specified descriptions.[19]

Considering the instability of tretinoin by virtue of its ability to undergo thermal, oxidative, and photo degradation, the US pharmacopeia and British Pharmacopeia allows upto 35% of overages in 0.05% tretinoin solution and upto 20% overage in 0.025-0.2% strength tretinoin solutions respectively.[20] Both product and RLD contained drug overages required to match the product stability. However, it did not match requirement of overages as per US and British Pharmacopeia for the products A, B, and C. Drug content is an indicator of product efficacy suggesting that market samples do not meet the quality standards for drug content.

The pH of formulations can influence the distribution of drugs in the microstructure, alter the quantity of drug that interacts with the skin, have an effect on spreadability, solubility, stability, rheology, and dose delivery.[21] In a particular study, the diffusion of tretinoin from Carbopol gels from pH range 5.0-8.0 was studied and it was found that with increasing pH the release also increased. Most sustained release of the drug was achieved at pH 5.0 and highest release at pH 8.0.[22] Stratum corneum pH is one of several biophysical markers used to evaluate the skin's barrier function, but it stands out for reflecting a wide range of skin activities beyond just barrier integrity. It also plays a key role in the development and progression of various inflammatory and infectious skin disorders. In a study, the pH of individuals with normal skin was 4.5-5.5 for women and 4-5.5 for men, and acne-prone skin types showed higher pH indicating the range of pH of for skin is between 4.5-5.5.[23] Considering the ideal pH of skin and pH of formula with carbomers allowing sustained release, the tretinoin containing gels should match the pH requirements. Considering the association of alkalinity with acne, it is recommended that anti-acne products

should have a pH between 4.5-5.5 and test product 0.04% fit the description.

As per the document, physicochemical and structural (Q3) characterization of topical drug products submitted in abbreviated new drug applications (ANDAs), assessment of specific gravity and density is an important aspect. The air entrapped in the formula can be assessed by looking at this physical parameter. All the products matched the viscosity recommended for highly viscous formulations.[24]

According to the U.S. Food and Drug Administration (2024), an important Q3 quality attribute for evaluating tretinoin gel formulations is the assessment of phase state and the internal structural organization of the formulation.[25] As per the literature, the microparticles separated from RLD were spherical, polydisperse and free of aggregates.[14] The structural organization of test product 0.04% and brand A 0.04% matches with the RLD, but no such observations were made for brand B 0.04% and brand C 0.04%. The structural organization of test product 0.04% and brand A 0.04% matches with the RLD, but no such observations were made for brand B 0.04% and brand C 0.04%.

To respond to the need of developing a formula that will allow tretinoin to work at its maximum capacity without affecting the skin in a negative manner, the current product was designed. This to bridge the therapeutic gap, to minimize the safety risks associated with tretinoin in its original chemistry. The current test product and the marketed product A showed a relatively sustained release of tretinoin indicating a controlled delivery likely designed to minimize irritation. While brands B and C showed a faster release which may provide quick therapeutic effects but also carry a higher risk of irritation.

Overall, the differences in release rates reflect varying formulation strategies, with test product favouring sustained release, brand C 0.04% focusing on rapid availability, and brand A 0.04% and brand B offering intermediate profiles suitable for different clinical needs. As per the data obtained from characterization of phase states and structural organization of matter since no microparticles were recorded for brand B 0.04% and brand C 0.04%, the high release rate of the drug from these two formulae are justified.

The test product, Flawlizo microsphere gel 0.04% exhibited comparable Q3 attributes and structural integrity to the US RLD, including similar appearance, pH, viscosity, drug content, and microsphere morphology. These findings suggest the test product is structurally robust and well-aligned with regulatory expectations. The test product showed favourable Q3 characteristics and sustained release, highlighting its potential as a high-quality tretinoin microsphere gel for clinical use. The sustained release pattern of the gel can offer safer solutions and effectiveness better suited for the Indian population.

CONCLUSION

The test product, Flawlizo microsphere gel 0.04% exhibited comparable Q3 attributes and structural integrity to the US RLD, including similar appearance, pH, viscosity, drug content, and microsphere morphology. These findings suggest the test product is structurally robust and well-aligned with regulatory expectations. The 0.04% Flawlizo microsphere gel showed favorable Q3 characteristics and sustained release, highlighting its potential as a high-quality tretinoin microsphere gel for clinical use. The sustained release pattern of the gel can offer safer solutions and effectiveness better suited for the Indian population.

ACKNOWLEDGEMENTS

The authors would like to thank Encube Advanced Research Centre and claims clinical agency to help conceptualize and provide their expertise in writing the manuscript.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Kligman AM. The growing importance of topical retinoids in clinical dermatology: a retrospective and prospective analysis. J Am Acad Dermatol. 1998;39(2 Suppl):S2-7.
2. Baldwin H, Webster G, Gold LS, Callender V, Cook-Bolden FE, Guenin E. 50 years of topical retinoids for acne: evolution of treatment. Am J Clin Dermatol. 2021;22(3):315-27.
3. Yoham AL, Casadesus D. Tretinoin. In: StatPearls. Treasure Island (FL): StatPearls Publishing. 2023.
4. Sumita JM, Leonardi GR, Bagatin E. Tretinoin peel: a critical view. An Bras Dermatol. 2017;92(3):363-6.
5. Goldfarb MT, Ellis CN, Voorhees JJ. Topical tretinoin: its use in daily practice to reverse photoageing. Br J Dermatol. 1990;122(s35):87-91.
6. Bulengo-Ransby SM, Griffiths C, Kimbrough-Green CK, Finkel LJ, Hamilton TA, Ellis CN, et al. Topical tretinoin (retinoic acid) therapy for hyperpigmented lesions caused by inflammation of the skin in Black patients. N Engl J Med.1993;328(20):1438-43.
7. Sitohang IBS, Makes WI, Sandora N, Suryanegara J. Topical tretinoin for treating photoaging: a systematic review of randomized controlled trials. Int J Womens Dermatol. 2022;8(1):e003.
8. Rahman SA, Abdelmalak NS, Badawi A, Elbayoumy T, Sabry N, Ramly AE. Formulation of tretinoin-loaded topical proniosomes for treatment of acne: in vitro characterization, skin irritation test and comparative clinical study. Drug Deliv. 2014;22(6):731-9.

9. Rahman SA, Abdelmalak NS, Badawi A, Elbayoumy T, Sabry N, Ramly AE. Tretinoin-loaded liposomal formulations: from lab to comparative clinical study in acne patients. Drug Deliv. 2015;23(4):1184-93.
10. Patel VB, Misra A, Marfatia YS. Topical liposomal gel of tretinoin for the treatment of acne: research and clinical implications. Pharm Dev Technol. 2000;5(4):455-64.
11. Samadi A, Sartipi Z, Nasrollahi SA, Sheikholeslami B, Kashani MN, Rouini MR, et al. Efficacy assessments of tretinoin-loaded nano lipid carriers in acne vulgaris: a double blind, split-face randomized clinical study. Arch Dermatol Res. 2021;314(6):553-61.
12. Del Rosso J, Sugarman J, Green L, Lain T, Levy-Hacham O, Mizrahi R, et al. Efficacy and safety of microencapsulated benzoyl peroxide and microencapsulated tretinoin for the treatment of acne vulgaris: results from two phase 3 double-blind, randomized, vehicle-controlled studies. J Am Acad Dermatol. 2023;89(4):719-27.
13. Špaglová M, Papadakos M, Čuchorová M, Matušová D. Release of tretinoin solubilized in microemulsion from Carbopol and Xanthan gel: in vitro versus ex vivo permeation study. Polymers. 2023;15(2):329.
14. Elfakhri KH, Niu M, Ghosh P, Ramezanli T, Raney SG, Ahmed S, et al. Physicochemical and structural evaluation of microparticles in tretinoin topical gels. Int J Pharm. 2022;620:121748.
15. Elfakhri KH, Niu M, Ghosh P, Ramezanli T, Raney SG, Kamal N, et al. Understanding the impact of formulation design on microstructure and drug release from porous microparticle-based tretinoin topical gels. Int J Pharm. 2024;653:123794.
16. U.S. Food and Drug Administration. Drugs@FDA: FDA-approved drugs. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Accessed on 21 August 2025.
17. Food and Drug Administration. Draft guidance on tretinoin. 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_017579.pdf. Accessed on 21 August 2025.
18. Food and Drug Administration. Draft guidance on tretinoin. 2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020475.pdf. Accessed on 21 August 2025.
19. Bausch Health US, LLC. Highlights of prescribing information. 2025. Available at: https://pi.bauschhealth.com/globalassets/BHC/PI/Retin-A-Micro-Gel-PI.pdf. Accessed on 21 August 2025.
20. Valeant Pharmaceuticals North America LLC. Highlights of prescribing information. 2014. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020475s021lbl.pdf. Accessed on 21 August 2025.
21. Parab PV, Co BMS. Storage stable tretinoin and 4-hydroxyanisole containing topical composition. US patent US6353029B1. 2000. Available at: https://patents.google.com/patent/US6353029B1/en. Accessed on 21 August 2025.
22. Shanley A. Topical formulation: moving from art to science. PharmTech. 2025. Available at: https://www.pharmtech.com/view/topical-formulation-moving-art-science. Accessed on 21 August 2025.
23. Shin S, Kim H, Oh I, Cho C, Yang K. Development of tretinoin gels for enhanced transdermal delivery. Eur J Pharm Biopharm. 2005;60(1):67-71.
24. Prakash C, Bhargava P, Tiwari S, Majumdar B, Bhargava RK. Skin surface pH in acne vulgaris: insights from an observational study and review of the literature. J Clin Aesthet Dermatol. 2017;10(7):33-9.
25. Center for Drug Evaluation and Research. Guidances. Drugs. U.S. Food and Drug Administration. 2025. Available at: https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs. Accessed on 21 August 2025.

Cite this article as: Chinda M, Patro KB, Qureshi R, Langde A, Kukreja A, Patel H. A comparative study to evaluate the Q3 characteristics of different tretinoin microspheres available in the Indian market to the innovator or the reference listed drugs. Int J Res Dermatol 2025;11:482-8.