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Original Article

DEVELOPMENT AND EVALUATION OF CYCLODEXTRIN NANOSPONGES-BASED TOPICAL FORMULATION OF TAZAROTENE

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ABSTRACT

Objective: Tazarotene is used as a topical retinoid for the treatment of acne, psoriasis and sun-damaged skin. But its topical formulation has many side effects, including itching, burning, dryness, redness, stinging, rash blistering, skin discoloration, peeling at the site of application and low bioavailability. The present study focuses on the reduction of side effects and enhancement of solubility and topical bioavailability of tazarotene by using cyclodextrin-based nanosponges.

Methods: Nanosponge of tazarotene were prepared by lyophilization method. The physiochemical characterization of plain nanosponges and drug-loaded nanosponges were performed using Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), and X-ray Diffractometer (XRD) studies. The drug-loaded nanosponges were incorporated into a carpool-based gel formulation. The prepared formulation was evaluated for viscosity, dissolution and stability. FTIR, DSC and XRD studies confirmed the formation of inclusion complex of tazarotene with nanosponges.

Results: The particle size of the drug-loaded nanosponges was found to be in the range of 156.72 to 163.48 nm. Transmission Electron Microscopy (TEM) images revealed the regular spherical shape of both the nanosponges that are unaffected even after drug encapsulation. The pH of the gel formulations was found to be in the range of 5.86 to 6.46. The gel formulation resulted in the diffusion of drug in controlled manner for up to 24 h. The *in vitro* dissolution studies revealed that nanosponges-based topical formulation had better results than the marketed product.

Conclusion: Thus, the study showed that nanosponge-based gel formulation can be a possible alternative to conventional formulations of tazarotene with enhanced bioavailability and skin retention characteristics for topical application.

Keywords: Tazarotene, Retinoids, Nanosponges, Carbopol-946, Diffusion

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INTRODUCTION

The retinoid acetylenic class includes tazarotene. Topical therapy of mild to severe plaque psoriasis, acne vulgaris, and photoaging is facilitated by its use. Under skin and plasma conditions, tazarotene, a prodrug, is de-esterified to produce tazarotenic acid, the physiologically active form [1]. Only the retinoic acid receptors, RAR-β and RAR-γ, are specifically bound by tazarotene. According to Kassir M *et al.* [2, 3], this medication is used topically to treat mild-to-moderate cases of facial acne vulgaris and plaque psoriasis, which affects over 20% of the body surface. Along with thorough skin care and sun protection, tazarotene is also used as an adjuvant implementation for specific clinical indicators of chronically photodamaged skin, such as benign facial lentigines, mottled facial hypopigmentation as well as hyperpigmentation, and facial fine wrinkles [4].

As a third-generation retinoic acid medication, tazarotene has been shown to have anti-inflammatory, normalizing-of-differentiation, and organizational-reconstruction properties. According to preliminary research, tazarotene can encourage angiogenesis and wound healing [5, 6]. The main pharmacologic effects of tazarotene, which include anti-inflammatory properties, reversal of keratinocyte hyperproliferation, reduced hyperkeratinization, and normalisation of cellular differentiation, are what make it a therapeutically effective treatment for acne vulgaris. According to several studies [7-9].

Numerous formulation approaches were recently used to provide delivery systems for tazarotene, including creams, foams, gels, liposomes, microemulsions, proniosomal gels, ethosomal-gels, nanosponge and noisome-based gels, electrospun membrane systems, and Poly lactic-co-glycolic acid (PLGA) nanoparticles [10]. To enhance patient adherence and results, decrease irritation, and promote comfort and convenience, A brand-new formulation of 0.1% short-contact tazarotene lotion was developed. The efficacy of this formulation was suggested by the well-tolerated findings of twice-daily administration [11].

Individuals with acne vulgaris who use topical tazarotene report significant reductions in both inflammatory and non-inflammatory acne lesions. A once-daily 6 mg dose for 24 w resulted in an 86% reduction in the count of nodulocystic lesions on the face, a 55% reduction in the count of papules and pustules, and a 72% reduction in the count of non-inflammatory lesions on the face. This oral formulation of tazarotene has now additionally shown effectiveness toward pustules, nodulocystic lesions, papules and non-inflammatory acne lesions [12].

Similar to other topical retinoids, the most frequent side effect is local irritation, which can include erythema, burning, mild to moderate pruritis, and desquamation. Tazarotene does not appear to have any systemic adverse effects due to its very low systemic absorption. Accordingly, it is advised that tazarotene be applied topically for the management of acne vulgaris and psoriasis [13]. When developing topical formulations, the stability of tazarotene is a major challenge in addition to the reported formulations' performance variations. When exposed to oxygen and acids, they show severe chemical instability; when exposed to light, they show photo instability. Accordingly, it is crucial to enhance the topical delivery of tazarotene and lessen its side effects by using a suitable carrier with the desired skin-targeting qualities. This will help to improve user compliance with the novel regimen and significantly lessen adverse reactions [14-16]. Nanotechnology's advantages over modern delivery techniques have shown considerable potential and influence on the management of medicinal medicines. Nanoscale carriers, including cyclodextrin-based nanosponges, represent a novel class of strongly cross-linked polymer structures with nanosized gaps that may be filled with a variety of active moieties (both hydrophilic and hydrophobic). These nanosponges can also be added to creams and gels to administer medications topically. Nanosponges are a somewhat promising therapy option for skin

problems despite their little exploration. If properly entrapped, drug distribution from topical gel was also enhanced by drug-targeting nanosponges. Literature has indicated the use of nanosponges for topical medication administration, namely for resveratrol, γ-oryzanol, quercetin, diclofenac sodium, and babchi oil [17-21]. Skin permeation studies in diclofenac sodium-loaded nanosponge gel and cream gels significantly retarded the drug permeation through skin while enhancing its concentration in viable epidermis and stratum corneum, confirming the localization of highly penetrating drugs in external layers of skin [22]. Therefore, tazarotene loading and release from cyclodextrin nanosponges might be a potential way to improve skin penetration.

MATERIALS AND METHODS

Materials

In Hyderabad, India, Dr. Reddy's Laboratory Ltd. gave a complimentary sample of tazarotene. An β-Cyclodextrin (Complexol-B) sample was provided to us at no cost by Gangwal Chemicals Pvt. Ltd. located in Mumbai, India. In Milan, Italy, we purchased diphenyl carbonate from Sigma Aldrich. All of the other materials and reagents used in the study were of the analytical variety. The Milli Q water (Millipore) was used for the experiments. The dialysis membrane, which has a molecular weight cutoff of 12 kDa, was purchased from Hi-media Pvt. Ltd., located in Mumbai.

Instrumentation

The characterization and analysis of materials were conducted using several advanced instruments. Transmission Electron Microscopy (TEM) was performed using the JEM-2000 EXII from JEOL, providing detailed imaging at the nanometer scale. Differential Scanning Calorimetry (DSC) was carried out with the Perkin Elmer DSC/7, allowing precise thermal analysis of material properties. Structural information was obtained using the Bruker D8 Advance X-ray Diffractometer (XRD), which offers high-resolution diffraction data. Particle size and zeta potential measurements were conducted with the Mastersizer 2000-Zeta Sizer from Malvern Instruments Ltd, ensuring accurate characterization of dispersions. Fourier Transform Infrared Spectroscopy (FTIR) was performed using the Tensor 27 FTIR from Bruker Optics, enabling identification of chemical functionalities within the samples. These instruments collectively provided comprehensive insights into the materials under investigation.

Table 1: Molar ratios and cross-linker and cyclodextrin concentrations

S. No.	Type of nanosponge	Molar ratio	Concentration of β cyclodextrin (g)	Concentration of carbonyldiimidazole (g)
1	NS1	1:2(β-CD: CDI)	2.274	2.484
2	NS2	1:4(β-CD: CDI)	2.274	4.968
3	NS3	1:8(β-CD: CDI)	2.274	9.936

NS: Plain Nanosponges, β-CD: β cyclodextrin, CDI: Carbonyldiimidazole

Table 2: Nanosponges percent drug loading

S. No.	Name of the formulation	Drug loading (%)
1	TZNS1	22.54±2.67
2	TZNS2	44.38±3.12
3	TZNS3	38.67±1.88

The results were reported as mean±SD (n = 3), TZNS1: Tazarotene loaded Nanosponges 1, TZNS2: Tazarotene loaded Nanosponges 2, TZNS3: Tazarotene loaded Nanosponges 3

Table 3: Particle size, zeta potential and polydispersity index of plain and drug-loaded nanosponges

Sample	Meanhydrodynamic diameter±SD (nm)	Polydispersity index	Zeta potential (mV)
NS2	139.34±3.2	0.18±0.005	-22.18±1.3
NS3	155.72±4.5	0.26±0.005	-26.34±1.1
TZNS2	156.72±8.2	0.25±0.005	-21.55±2.2
TZNS3	163.48±4.7	0.21±0.005	-23.12±2.7

The results were reported as mean±SD (n = 3), NS2: Plain Nanosponges 2, NS3: Plain Nanosponges 3, TZNS2: Tazarotene loaded Nanosponges 2, TZNS3: Tazarotene loaded Nanosponges 3

Table 4: Dissolution profile of tazarotene from different formulations

Time (h)	Cumulative drug release (%)				
	Pure drug	TZNS2	Gel formulation of plain drug	Gel formulation of TZNS2	Marketed formulation (Tazorac®gel)
0	0	0	0	0	0
0.25	0.83±0.23	7.108±1.22	1.78±0.38	5.156±0.58	4.56±0.78
0.5	1.32±0.42	11.214±1.58	3.02±0.44	8.243±0.92	7.32±0.97
0.75	1.68±0.38	13.782±2.36	4.17±0.62	11.512±1.78	11.54±1.24
1	1.89±0.52	16.326±2.58	5.24±0.76	12.982±1.24	16.42±0.94
2	2.78±0.76	28.568±1.84	8.12±0.88	20.712±1.96	28.16±1.18
3	3.67±0.45	39.542±1.72	10.25±0.57	27.056±1.59	39.38±1.76
4	4.76±0.58	49.876±1.58	11.89±1.63	35.897±3.42	48.42±1.38
6	6.12±1.05	73.764±1.94	13.48±1.24	48.021±2.87	57.16±1.62
8	9.32±0.92	89.182±2.78	15.29±1.32	61.982±3.42	65.37±2.34
12	13.42±1.23	98.564±4.12	19.12±2.96	86.123±5.12	69.89±3.42
18	17.12±1.46	99.826±3.56	23.57±2.89	94.187±3.36	71.23±3.76
24	19.76±1.37	99.965±2.12	27.52±2.04	99.879±4.78	73.14±4.56

The results were reported as mean±SD (n = 3), TZNS2: Tazarotene loaded Nanosponges 2

β-Cyclodextrin nanosponges (NS) preparation

As indicated in table 1, three different varieties of Cyclodextrin Nanosponges (CDNS); 1:2, 1:4, and 1:8 were created by adjusting the molar ratios of cyclodextrin and cross-linker. The molar ratios and concentrations of the cyclodextrins and crosslinker that were used are listed in table 1. 1,1-carbonyldiimidazole was used as a crosslinker in this study. To sum up, anhydrous Dimethyl Formamide (DMF) partly dissolved β-Cyclodextrin. 1, 1-After adding carbonyldiimidazole to this reaction mixture, it refluxed for six hours at 90 °C in an oil bath while being stirred. After the reaction was finished and washed with water several times, the resulting product was refined by the process of soxhlet extraction employing ethanol for up to eight hours. The resulting white powder was then pounded in a mortar after being dried for the whole night at 60 °C in an oven. Water was used to distribute the resulting fine powder. By using lyophilization, the colloidal portion that was still suspended in water was extracted. After being vacuum-dried, the resulting nanosponges were kept at 25 °C until they were needed again in a desiccator [23, 24].

Tazarotene loaded nanosponges preparation

As previously mentioned, freeze-drying was used to create cyclodextrin nanosponges loaded with tabarotene [25, 26]. Using a magnetic stirrer, 100 mg of CDNS were adjourned in 50 ml of Milli Q water. The mixture was sonicated for 10 min and stirred at 500 rpm for 24 h after 50 mg of tazarotene was added. By centrifuging the solutions for 10 min at 2,000 rpm, the simple medicine was extracted from the suspensions as a residue below the colloidal supernatant. Using a lyophilizer (LARK INDIA) set to operate at 13.33 mbar of pressure at-20 °C, the excess liquid were lyophilized. The finished goods were kept for further research in a desiccator. The compositions of tazarotene-loaded nanosponges were emerged varied depending on the kind of nanosponges, were given the names TZNS1, TZNS2, and TZNS3. The following formulas were used to determine the loading capacity and encapsulation efficiency:

$$\text{Encapsulation efficiency} = \frac{\text{Actual amount of tazarotene loaded in CDNS}}{\text{Amount of tazarotene fed for loading}} \quad \ldots\ldots(1)$$

$$\text{Loading capacity} = \frac{\text{Actual amount of tazarotene loaded in CDNS}}{\text{Weight of tazarotene loaded CDNS}} \quad \ldots\ldots(2)$$

Plain nanosponges and drug-loaded nanosponges characterization

The drug-loaded and plain nanosponges were measured for zeta potential, polydispersity index, and particle size distribution using a Mastersizer 2000 (Malvern Instruments Ltd, Worcestershire, UK). Both drug-loaded and plain nanosponges were examined morphologically using transmission electron microscopy (JEM-2000 EXII; JEOL, Tokyo, Japan). The FTIR spectra of plain nanosponges, tazarotene, and tazarotene-loaded nanosponges complexes were acquired using the potassium bromide disc method, with a range of 4000 to 600 cm−1, using the Tensor 27 FTIR Spectrophotometer (Bruker Optics, Germany). The 2θ range of 2.5° to 60° was scanned at a rate of 5 °/min using a Bruker D8 Advance X-ray diffractometer to capture the X-ray powder diffraction patterns of tazarotene, drug-loaded nanosponges (TZNS2, TZNS3), and plain nanosponges (NS2, NS3). A Perkin Elmer DSC/7 differential scanning calorimeter (Perkin-Elmer, CT-USA) equipped with a TAC 7/DX instrument controller was used to perform differential scanning calorimetry research on tazarotene, plain nanosponges (NS2, NS3), and tazarotene loaded nanosponge complexes (TZNS2, TZNS3). The gadget was calibrated using indium using measurements of the melting point and heat of fusion. A heating rate of 10 °C/min was employed in the 30–400 degree Celsius temperature range. An empty pan was used as the standard reference, while standard Perkin-Elmer aluminum sample pans were used. Five-milligram samples were analyzed in triplicate under nitrogen purge.

Tazarotene gel formulation preparation

As mentioned before [27], Carbopol® Ultrez 10 NF Polymer (Lubrizol Corp, Wickliffe, Ohio) was used to create the gel base formulation for the tazarotene-loaded nanosponges. Using a magnetic stirrer, the polymer was combined with distilled water after being soaked in water for two hours to produce a homogenous gel foundation of 1% w/w. 1% w/w triethanolamine, 2% w/w N-methyl-2-pyrolidone, and 2% w/w propylene glycol were added to the previously described gel base while stirring continuously. Tanzarotene-loaded nanosponges were ultimately added to the prepared gel base in order to get 1% w/w tazarotene in the gel foundation. The preparation of the tazarotene reference formulation (control) involved mixing ordinary tazarotene with the gel basis mentioned above.

Gel formulations evaluation

pH determination

A digital pH metre (HI 98107, Hanna Instruments, India) was used to measure the gel's pH (10% w/w). pH 4 and pH 7 buffers were used to standardize the pH before use. (Bachhav YG and Patravale VB 2009).

Determination of spreadability

The spreadability of the gel was determined using the following technique: Over the 0.5 g of gel, a second glass plate was placed inside a 1 cm-diameter circle that had been previously marked. A 500 g weight was placed on the upper glass plate and left for five minutes. After three repetitions of the experiment, the mean diameter was determined by noting the increase in diameter caused by the gels spreading [28].

Nanosponges-based gel rheological studies

For rheological investigations, A helipath stand-equipped Brookfield Viscometer LVDV-IIIU (Brookfield Engineering LABS, Stoughton, USA) was used. A T-C spindle was used to measure the dial reading after 30 g of the sample were added to glass beaker and permitted to equilibrate to 5 min at 0.5, 1, 2.5, and 5 rpm. At every speed, the corresponding dial reading from the viscometer was noted. For every spindle speed drop, the dial reading that matched it was noted. The values were taken in triple at the ambient temperature [29].

Drug release in *in vitro*

Franz diffusion cell that has been modified was used for the *in vitro* release research. A synthetic dialysis membrane with a 2.4 nm pore size and a 12000 Da molecular weight cut-off was employed. After washing the dialysis membrane tubing under running water for three to four hours in order to eliminate glycerol, the tubing was treated for one minute at 80 °C with a 0.3% w/v sodium sulfide solution in order to eliminate sulfur compounds. After acidifying it with a 0.2% (v/v) sulfuric acid solution and rinsing it with hot water to remove the acid, it was then cleaned for two minutes in 60 °C hot water. Before dialysis, the dialysis membranes were then immersed in the diffusion medium Phosphate buffered saline (PBS) with a pH of 6.8 for a whole night [30].

Drug diffusion study

The donor compartment was coated with a formulation corresponding to 10 mg of tazarotene, whereas 100 ml of 6.8 pH phosphate buffer were placed inside the receptor chamber. 3.79 cm2 is the diffusion area. Teflon-coated magnetic stirring bars were used to agitate the fluid in the receptor side at 100 rpm while keeping it at 37±2 °C throughout the experiment. After achieving enough dilution, a 5 ml aliquot was taken out at predetermined intervals and subjected to UV spectroscopic analysis. The amount of drug released from the membrane is divided by the area of drug release (Q/A) to determine the drug flux. The Q/A vs time plot was plotted. The graph's slope reveals the flow [31].

Study of long-term stability

Using the identical formulas used in the photodecomposition tests, stability investigations were carried out. The formulations were kept in the dark and at room temperature for three months in stoppered containers. At the appropriate times, aliquots (40–50 mg) were removed from the emulsions and placed into calibrated flasks (20

ml). The sample underwent sonication to remove ethanol, were diluted to volume, and finally filtered using 0.45 µm membrane filters. A UV spectrophotometer was used to analyse the samples in order to determine the amount of residual tazarotene. According to Neves AR *et al.* 2016 [32], every measurement was done in triplicate.

Data analysis

At least three replications of each experiment were conducted. The statistical program Statistical Package for the Social Sciences (SPSS) 12.0 was used to conduct the comparisons. The one-way analysis of variance ANOVA (SPSS package) was utilized for statistical analysis, and the data were reported as the mean±standard deviation (SD) of the mean. When $p<0.05$ was reached, statistical significance was determined. From the results, it is evident that there is a significant difference (*$p<0.005$) between the pure tazarotene gel and tazarotene-loaded nanosponges gel. The data were subjected to ANOVA (Graph Pad Prism, software), it was found that the F ratio was 3.0 (fc<ft). So there is a significant difference between the pure tazarotene and tazarotene loaded nanosponges gel.(tab.1)tazarotene loaded nanosponges gel shows effective inhibition when compared to the marketed gel and pure tazarotene gel (tazarotene loaded nanosponges gel>marketed gel>pure tazarotene gel)

RESULTS AND DISCUSSION

According to Anandam S. and Selvamuthukumar S., 2014 [33], nanosponges are a novel kind of totally biocompatible cross-linked polymer that have excellent encapsulation and high solubilization capacities for a variety of compounds. They provide a new and practical drug delivery nanocarrier due to their adaptability and affordable manufacture. In this work, we examine the topical administration of the anti-psoriatic medication tazarotene via nanosponges for specific skin delivery. Over the past ten years, several attempts have been made to improve the process of creating and using nanosponges.

Many formulation experts are interested in cyclodextrin-based nanosponges because they can improve the solubility of drugs that are poorly soluble in water. These nanosponges can hold a broad range of medicines and create both inclusion and non-inclusion complexes with them. These nanosponges not only increase the drug's solubility but also strengthen its stability by shielding the labile groups from the stomach environment. In this investigation, β-cyclodextrin was condensation-reacted with an appropriate cross-linking agent to create cyclodextrin nanosponges. Three different molar concentrations of β-cyclodextrin and carbonyldiimidazole were used to synthesize the cyclodextrin-based nanosponges (1:2, 1:4, and 1:8). By using the freeze-drying process, tazarotene was incorporated into each of the three types of nanosponges. The amount of drug encapsulated within nanosponges, or the drug loading, was estimated by analysing a given amount of formulation in order to estimate the drug association with nanosponges. The percentage of drug association which is determined using the previously stated algorithm. Table 2 displayed the percentage of drug loading into each of the three kinds of nanosponges (TZNS1-TZNS3).

Out of the three varieties of nanosponges, TZNS2 (1:4 β-CD: DPC) had the highest loading efficiency at 44.38% w/w, whereas NS1 had the lowest at 22.54% w/w. Because TZNS2 and TZNS3 had superior solubilization and loading capabilities, they were chosen for more research. This indicates that the degree of cross-linking is a critical factor controlling how rapidly the nanosponges initiate inclusion complexation with the medicine. The kind of cross linker and ratio to β-CD have an impact on the end product's stiffness, which is ultimately related to its capacity to swell and its inclusion/release characteristics. It was expected that the concentration of cross-linker may affect the complexation ability and release properties of nanosponges. Drugs may not be incorporated in larger amounts in these types of NS because it is possible that with lesser degrees of cross-linking, the smaller amount of cross-linker may generate a network with an incomplete cyclodextrin cross-linking and with fewer sites for the drug complexation. Conversely, a higher degree of cross-linking might lead to a stronger β-CD cross-linking because of the increased cross-linker content, which would prevent some drugs from interacting with β-CD Steric effects led to a detrimental effect on the intramolecular H-bond network of individual β-CD units when the cross-linker to β-CD molar ratio was increased. It is generally accepted that swelling capacity and steric obstacles must be taken into consideration when adding the cross-linker at the ideal concentration. In addition, the molecules involved in the release can have a variety of releases; the kinetics of the releases can vary depending on the kind of nanosponges.

Based on a research of the particle sizes of both drug-loaded and plain nanosponges, low polydispersity index particles with an average size among 139 nm and 178 nm were found using the laser light scattering technique. As illustrated in the table 3, the unimodal and restricted range of the particle size distribution. If the zeta potential is high enough, the complexes should be stable with very little inclination to clump together. A narrow PI indicates the homogeneity of the colloidal suspensions. Studies using transmission electron microscopy (TEM) revealed that both nanosponges retain their regular spherical form post-drug encapsulation, depicted in fig. 1. The TEM image measurements of the particle sizes agreed with the DLS findings.

A comparison of the FTIR spectra of the complexes of TZNS2, TZNS3, tazarotene, and NS2 is presented in fig. 2. The development of cyclodextrin-based nanosponges is confirmed by the distinctive carbonate bond peak seen in nanosponges FTIR spectra, which is located between 1720 and 1750 cm^{-1}. Moreover, the C–H stretching vibration of the nanosponges was detected at 2918 cm^{-1}, the C–H bending vibration at 1418 cm^{-1}, with the C–O stretching vibration of the primary alcohol at 1026 cm^{-1}. The drug peaks in complexes broadened and disappeared, indicating modest interactions between NS and tazarotene, according to FTIR investigations. The fingerprint area, which is between 900 and 1,400 cm^{-1}, has undergone a significant modification, As per the correlation of FTIR spectra of tazarotene and complex. Tazrotene's primary distinctive peaks are caused by aliphatic C-H stretching at 2908 and 2961 cm^{-1} and aromatic C-H stretching at 3055 cm^{-1}. An absorption band at 2301 cm^{-1} is associated with the di-substituted alkyne's C=C stretching, whereas a significant absorption band at 1719 cm^{-1} is linked to the ester's C=O stretching. The band at 1585 cm^{-1} is the result of C-C aromatic stretching. Aliphatic C–H bending is responsible for the absorption bands at 1365 cm^{-1} and 1448 cm^{-1}. Aromatic C–H bending is represented by additional bands at 823 cm^{-1} and 777 cm^{-1}. In the formulas, these distinctive peaks were widened or moved, indicating clear interactions among nanosponges and tazarotene.

Fig. 3 displays the tazarotene nanosponges' differential scanning calorimetry curves(TZNS2 and TZNS3), plain nanosponges (NS2 and NS3), and free tazarotene. The melting point of tazarotene, which is 98 °C, was represented by a prominent endothermic peak in its DSC spectra. The nanosponges' DSC study revealed no peak before 350 °C, indicating a high degree of thermal stability in this material. Furthermore, the tazarotene compound showed a significant exothermic peak at around 350 °C. When it comes to the freeze-dried formulations, the drug endothermal peak completely vanished. This behaviour can be seen as evidence that the formulation's constituent parts interact. This may be interpreted as a sign of inclusion complex development or medication amorphization.

To investigate the physical characteristics of tazarotene within the cyclodextrin nanosponges, XRD patterns of pure tazarotene, plain nanosponges (NS2 and NS3), and tazarotene-loaded nanosponges (TZNS2 and TZNS3) were used. The high crystalline structure of tazarotene was disclosed by a few of its characteristic peaks, as seen in fig. 2. However, the nanosponges complexes did not exhibit a single pure tazarotene characteristic peak. The absence of crystalline peaks in the tazarotene complex indicates that the medication has become amorphous inside the nanosponges' porous structure.

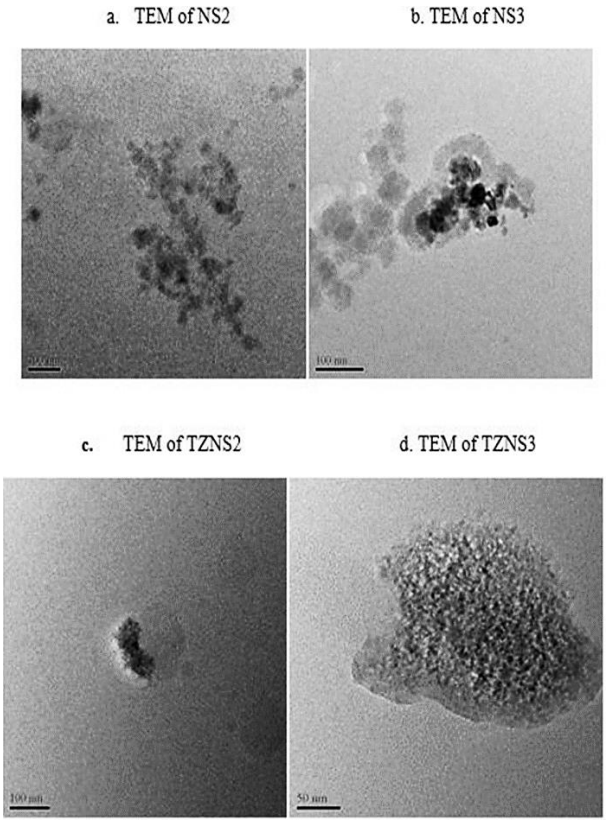

Fig. 1: TEM images of drug-loadedand plain nanosponges, TEM: Transmission Electron Microscopy, NS: Plain Nanosponges, TZNS: Tazarotene loaded Nanosponges

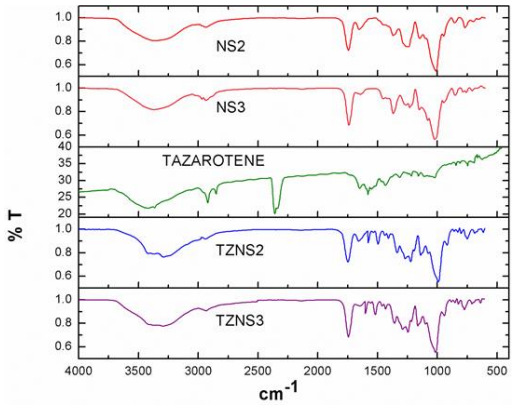

Fig. 2: Fourier transform infrared spectra of tazarotene, complexes (TZNS2 and TZNS3), and plain nanosponges (NS2 and NS3)

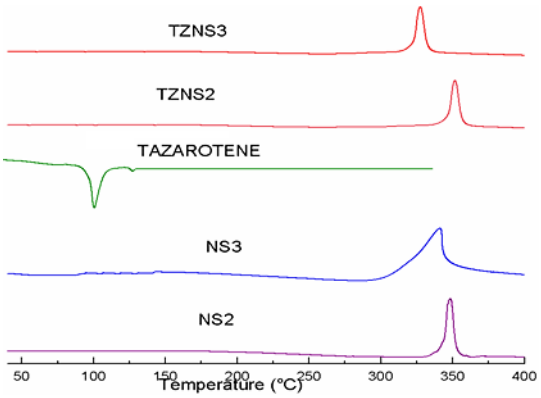

Fig. 3: The DSC thermogram of tazarotene, complexes (TZNS2 and TZNS3), and plain nanosponges (NS2 and NS3)

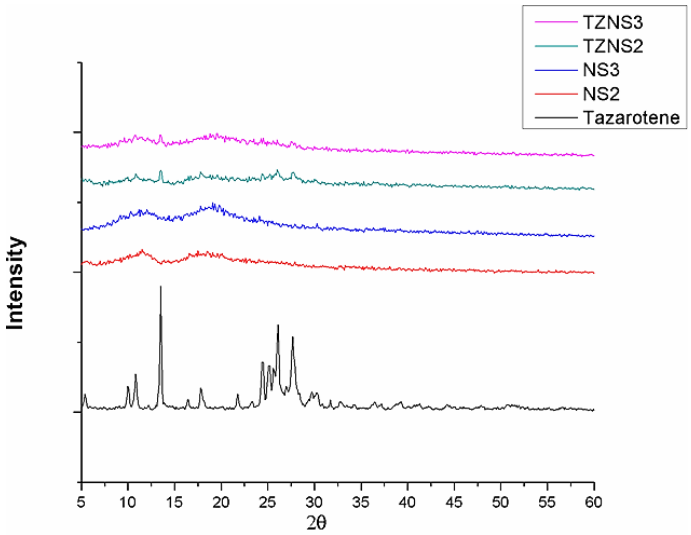

Fig. 4: X-ray reflectance spectra of tazarotene, complexes (TZNS2 and TZNS3), and plain nanosponges (NS2 and NS3)

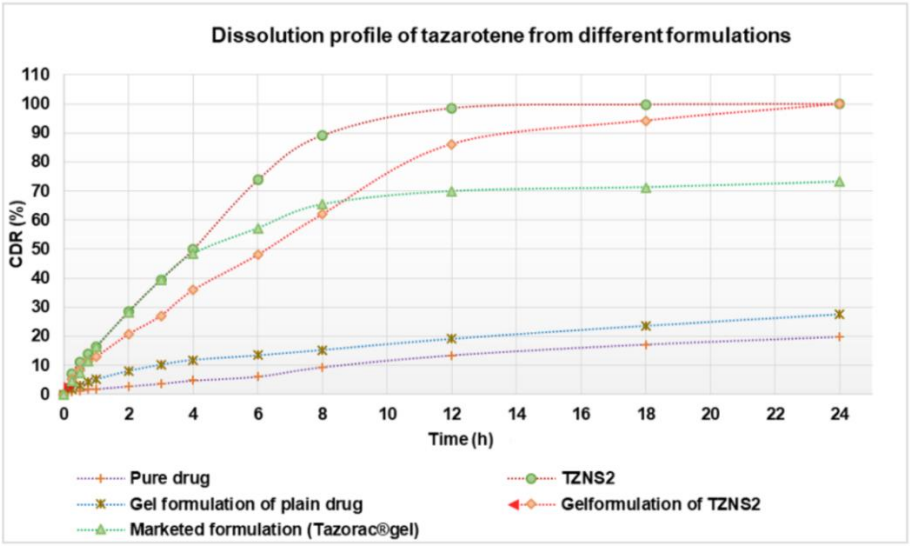

Fig. 5: Dissolution profile of tazarotene from different formulations, the results were reported (n = 3), CDR (%): Cumulative Drug Release (%)

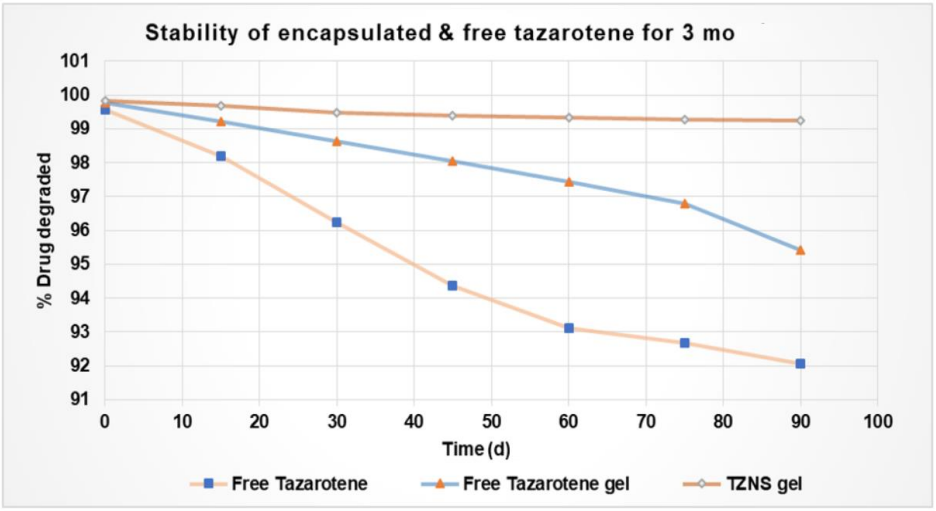

Fig. 6: Stability of encapsulated and free tazarotene for 3 mo; the results were reported (n = 3)

Gel formulation characterization

Tazrotene-loaded nanosponges' gel base formulation was made using Carbopol® Ultrez 10 NF polymer in accordance with published literature. Carbopols, the most traditional base of topical preparations are still interesting for go on researching. They are acrylic acid polymers that, when hydrated by the carboxyl groups in water or an alkaline solution, create hydrogel [34]. The hydrogel used to manufacture the tazarotene-containing nanosponges is Carbopol® Ultrez 10 NF, with 2% w/w propylene glycol and 2% w/w N-methyl-2-pyrolidone added as permeability enhancers. The gel were neutralised using 1% w/w triethanolamine. The similar composition of carbopol hydrogel led to improved econazole nitrate stability and penetration in prior research [35]. It was found that the pH of the two gel compositions ranged from 5.86 to 6.46, which falls within the 3.0-9.0 typical range of skin pH. As a result, the preparation won't irritate skin.

A circle was created when a weighed amount of gel was sandwiched between two glass plates of known weight; the diameter of this circle indicates how spreadable the gel formulation is. The higher the spreadability, the bigger the diameter. The diameters of the gel formulation and ordinary tazarotene gel were determined to be 8.32±1.12 cm and 6.13±0.72 cm, respectively, showing that the gel formulation based on nanosponges had greater spreadability. This is because, instead of using a traditional gel matrix, the gel formulation has a loose gel matrix because of the oil globules.

Topical products must exhibit plastic or pseudoplastic rheological behavior and be neither too fluid nor excessively viscous in order to distribute smoothly across the skin without running. Pseudocystic behavior was demonstrated by the gel formulation, which promoted the formulation's spreading qualities and improved flow. 7.12 x 103± 0.18 x 103 cp was the viscosity of the gel formulation measured at 5 rpm.

Study of drug release

Tazarotene-drug release, TZNS (nanosponges loaded tazarotene), Gel containing plain drug, Gel containing TZNS and the marketed formulation were shown in table 4. Because the medication was not sufficiently soluble in the dissolving media, the suspension released the medicine more slowly. As a Biopharmaceutics Classification System (BCS) class II medication, the rate at which the drug may be absorbed is limited by its solubility. Fig. 1 and table 4 demonstrate increasing solubility in dissolution media by utilizing the nanosponges formulation has increased *in vitro* dissolution. The inclusion complex formed by the complicated structure of the nanosponges may be what's causing the higher dissolving rate of the medicine. Enhanced solubility was the result of the additional benefit of nano size. Given that the medication must diffuse through the gel matrix, the incorporation of drug/TZNS in the Carbopol® Ultrez 10 NF gel impeded drug release. Therefore, the drug release in gel was lower than the drug's pure form or formulation in NS after 24 h. A burst release, a drug imprisoned in an area of the body, or both might have contributed to the first high release from the NS formulation. Nevertheless, when the gel was applied, the drug's diffusion happened in a regulated way for up to 24 h, and the burst release was managed.

Using the same formulations as the photo degradation tests, ageing research was conducted to investigate nanosponges impact on tazarotene chemical stability. Fig. 6 shows the results of the analysis of the formulations for tazarotene conducted over a period of three months at ambient temperature as well as the dark. Within three months, around 7.5% of the drug from free tazarotene and 4.5% of medication from the gel formulation including non-encapsulated tazarotene were broken down. However, during the same time period, there was no discernible drop in tazarotene in the formulations that were encapsulated in nanosponge. These findings demonstrate the cyclodextrin nanosponges' protective properties.

CONCLUSION

The current work showed how to create freeze-dried nanosponges loaded with tazarotene. Studies using FTIR, DSC, and XRD verified that tazarotene and nanosponges formed an inclusion complex. The dissolution rate of the tazarotene nanosponges was significantly greater than that of the pure drug due to the formation of a high-energy amorphous state, the reduction of drug particle size, and intermolecular hydrogen bonding. It was shown that tazarotene nanosponges had an 85% relative bioavailability when compared to conventional tazarotene. The stability of the nanosponge formulations was assessed after they were integrated into a model carbopol gel formulation. The gel formulation with nanosponge base virtually entirely reduced the chemical instability of tazarotene over the three months that the formulations were stored at ambient temperature and in the dark. Every data point to a great potential of the gel formulation of tazarotene based on cyclodextrin nanosponges as a topical delivery method due to its controlled drug release, improved efficiency, and superior storage stability.

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AUTHORS CONTRIBUTIONS

Both authors contributed to the study conception and design, material preparation, data collection, and analysis. Both authors reviewed the results and approved the final version of the manuscript.

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

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