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Research Paper

Development of the Formula and Characterization of Tretinoin Nanostructured Lipid Carriers (NLC) With Precirol®Ato5 Using the Sonicator Probe Method

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ABSTRACT: *The most widely used vitamin A derivative for mild to severe acne is tretinoin. However, it is lipophilic (LogP 6.3). Tretinoin must be transformed into liquid lipids and nanostructured lipid carriers (NLC) based on Precirol®ATO5 and stabilized by surfactants to address permeability and stability concerns.* ***Method:*** *Heat homogenization and sonication with a sonicator probe were used to formulate tretinoin into NLC. Precirol®ATO5, Myritol®, and Tego®care were the materials utilized. Particle size, polydispersity index, zeta potential, adsorption effectiveness, and morphological measurements were then used to describe NLC.* ***Results:*** *The characterization results showed that NLC tretinoin has a particle size of < 300 nm for two measurements over 30 days, a polydispersity index value of 0.5, a zeta potential range of 42.8 to 58.3 mV, and an efficiency entrapment value of >80% for all formulas. And a spherical shape emerged from the morphology data.* ***Conclusion:*** *The findings demonstrate that tretinoin's nanostructured lipid carriers provide favourable characterization outcomes.*

KEYWORDS: *Tretinoin, Precirol®ATO5, NLC*

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I. INTRODUCTION

The human body comprises a variety of organs, each of which contains a network of distinct cells with distinct forms and functions. [1]. Teenagers who have acne may experience psychological and emotional issues, making it a severe issue. As a result of blocked hair follicles, overactive sebaceous glands, blocked sebum production, and increased Propionibacterium acnes activity in the sebaceous unit, acne-like lesions (papules, comedones, pustules, and nodules) develop [2]. 85% of young adults between the ages of 12 and 25 have acne vulgaris, according to the Global Burden of Disease (GBD) research. About 40 and 80 percent of Southeast Asian people have acne vulgaris [3]. Oral and topical anti-acne therapies are available. The most widely used topical treatment for mild to moderate acne is tretinoin, a vitamin A derivative utilized in one of the first-line topical therapies [4]. A retinoid called tretinoin, or trans-retinoic acid, is frequently used for proliferative and inflammatory skin conditions such as psoriasis, acne, and epidermal skin cancer [5]. Retinoic acid works by attaching to the nuclear membrane Retinoid Acid Receptor (RAR), which normalizes the differentiation and cohesion of corneocytes and follicular keratinocytes, encourages comedolytic activity and inhibits conidiogenesis. Mainly, tretinoin binds to the three RARs (RAR -α, β, and γ) with considerable affinity. Tretinoin has also been demonstrated to reduce the production of neutrophil oxygen free radicals and suppress the expression of TLR2 (Toll-Like Receptor 2) in monocytes. The physical characteristics of tretinoin are as follows: it has a high melting point of 180–182 °C, indicating a crystalline structure, and a log P value of 6.3, indicating poor solubility and low permeability. Therefore, tretinoin requires a new method of drug delivery [6].

In recent years, many studies have been conducted on nanocarrier systems. One of the nanocarriers is called NLC (Nanostructured Lipid Carriers). NLC enables adaptive medication release and increases drug absorption in a way that is impossible with traditional formulations. NLC may also pass through the skin's SC barrier. NLC can be utilized for topical therapy for skin illnesses and increase therapeutic efficacy since it typically accumulates in the skin [7].

II. MATERIALS AND METHODS

Materials

Tretinoin (Beaute Lab) is the active component, and the other ingredients include distilled water (PT. Merapi Utama Pharma), methanol PA (Merck, Germany), Myritol® liquid lipid (PT. BASF Indonesia), Tego®care surfactant (Evonik Industries, Singapore), and solid lipid Precirol®ATO5 (PT. Gattefose).

Methods

FT-IR (Fourier transform infrared)

The samples evaluated were Tretinoin, Precirol®ATO5, and a combination of Tretinoin and Precirol®ATO5. After being initially ground into a powder, the substance is placed in the FTIR device, where the Agilent Cary 630 instrument reads the sample. Results from the sample spectrum are contrasted [8].

X-Ray Diffraction

To assess the crystallinity of the substance utilized at an angular velocity of 1° per minute using a cobalt radiation source, samples tested Tretinoin, Precirol®ATO5, and a combination of Precirol®ATO5 and Tretinoin were recorded using X-ray Diffraction at 20%–50% intervals [9].

Manufacture of NLC Tretinoin

Using a thermal homogenization technique to create NLC and an ultrasonication probe at a temperature of 70 °C after that, Use a magnetic stirrer (IKA® C-Mag H54) and distilled water to dissolve the surfactant at or below 70 degrees Celsius. Phase A and B are blended after adding the active ingredients and heating Precirol®ATO5 until it melts on the magnetic stirrer. The following phase involves utilizing probe ultrasonication to lower the particle size [10].

Characterization of Tretinoin NLCs

Particle size, polydispersity index, and zeta potential were the characteristics used to characterize tretinoin NLC. A Malvern ZSP Zetasizer (UK) was used to take measurements. 1 mL of the NLC sample, 10 mL of aqua dest, a disposable cuvette, a dip cell electrode, and room temperature were used to make the measurements. The measurements are then analyzed. This measurement was done three times [11].

A transmission electron microscope (JEM-1400 Flash Electron Microscope, JEOL Ltd.) was used to create the morphology of tretinoin NLC. Take one drop of the NLC sample, distribute it on a 300-mesh copper grid covered with a carbon membrane, and allow it to dry after first diluting it with 10 mL of distilled water. Both samples and photographs were examined [10].

Efficiency Entrapment

1.5 mL of Tretinoin NLC was collected and then placed in a vivaspin (Vivaspin®, Göttingen, Germany) to calculate efficiency entrapment. After that, it underwent a 3-hour centrifugation process at 12,000 rpm. The supernatant from the centrifugation results was also obtained and examined using a UV spectrophotometer (Shimadzu UV-1800) at the maximum wavelength to determine the amount of adsorbed tretinoin. Efficiency Entrapment, or EE, uses the following formula [8].

$$\%EE = \frac{Initial\ amount\ of\ the\ drug - free\ unentrapped\ drug}{Initial\ amount\ of\ the\ drug}\ x\ 100\%$$

Morphology of Nanocarriers

One drop of the NLC sample was applied to a 300-mesh copper grid covered with a carbon membrane after being diluted with 10 mL of aqua dest. Wait till it dries. After inspecting the sample, several shots are taken at various magnifications to provide images with the necessary resolution for analysis [10]

III. RESULTS

This FT-IR test aims to ascertain the compatibility of the materials used in the production of NLC and whether or not interactions between the molecules of each material occur. The appearance of additional peaks in the material mixture indicates the presence of material interactions. This circumstance suggests that the material combination is incompatible [8]. This FT-IR test aims to ascertain the compatibility of the materials used in the production of NLC and whether or not interactions between the molecules of each material occur. The emergence of new peaks in the material mixture indicates the presence of material interactions. This scenario

hints at the incompatibility of the material combination [12]. When combined with the Precirol®ATO5 utilized, FT-IR data in the 1500–500–1 range demonstrate no appreciable difference between the peaks of the properties of the active component tretinoin. These findings demonstrate the suitability of the material utilized, and the absence of any additional peaks shows that tretinoin and Precirol®ATO5 do not interact (Fig. 1).

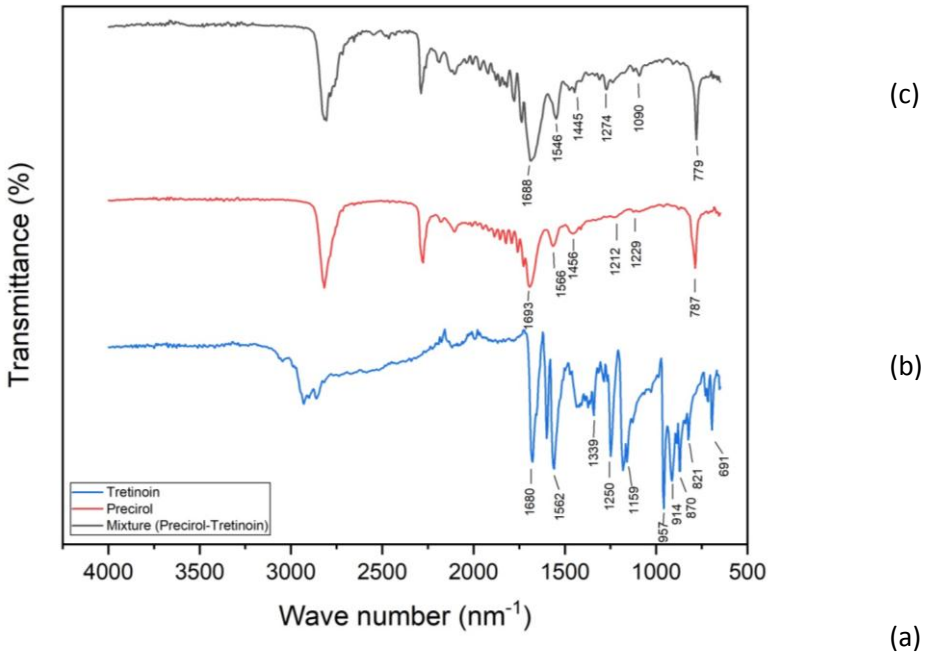

Figure 1: FTIR absorption spectra (a) Tretinoin (b) Precirol®ATO5 (c) mixture

The XRD spectra obtained in Figure 5.2 show that the results are visible at wavelengths 0-60 2 Theta, where there is a discernible difference. The amorphous form of tretinoin in the NLC is confirmed by these results, indicating the suitability of the tested material. This is due to a decrease in Tretinoin®'s crystallinity value, which is indicated by alterations in the distorted peaks in the NLC. The crystal states of tretinoin and Tretinoin® in Precirol®ATO5 are visible due to the characteristic diffraction peaks. The NLC exhibits less crystallinity due to the incorporation of Tretinoin®, as seen by its lower peak intensity. The NLC's XRD pattern thus validates Tretinoin®'s amorphous structure in the formula [13].

Tretinoin was effectively formulated into NLC using Precirol®ATO5 and stabilized by Tego®Care 450. Particle size, polydispersity index, zeta potential, and efficiency entrapment are characteristic of NLC. The measurements on F1, F2, F3, F4, and F5 were tested twice for a total of 30 days, and it can be observed from the data in Table 1 that the Tretinoin NLC sample had a particle size of around 300 nm. Particle sizes between 50 and 300 nm suggest a quick release of the medication [14].

PdI is a crucial factor in the delivery of nanosized pharmaceuticals because it prevents the unequal buildup of drug molecules on the target. PdI describes the degree of homogeneity in a system. The distribution of particles in a monodisperse system is more uniform, with a lower value of the polydispersion index [15]. The Polydispersity Index result for the Tretinoin NLC sample was less than 0.5, and the PdI test findings indicated that the sample was monodispersive. The low particle size distribution of the monodisperse system suggests that the monodisperse NLC system has a high degree of uniformity or homogeneity [16].

Zeta potential, which refers to evaluating non-aggregation and physical stability, is a crucial characteristic of NLC since it reveals the repulsion between NLC particles [17]. For nanoparticles, zeta potentials larger than -60 mV and more than -30 mV suggest excellent physical stability and strong electrostatic stabilization, respectively [12]. NLC Tretinoin exhibits zeta potential findings of > - 42 mV based on the results of the zeta potential test found in Table 1, which can guarantee stability and reduce the tendency to aggregation over time.

It can be seen from the results of the efficiency entrapment test found in Table 1 that the Tretinoin NLC sample had an efficiency entrapment result of >80%, indicating that Tretinoin NLC was in the range that

corresponds to the literature used, namely >80% [18]. Efficiency The concentration of the lipid utilized affects entrapment. Because NLC is made of two distinct lipids, an uneven gap is created in the matrix, increasing the space for the active substance. As lipid concentration rises, so does the loading capacity of the active substance [8]

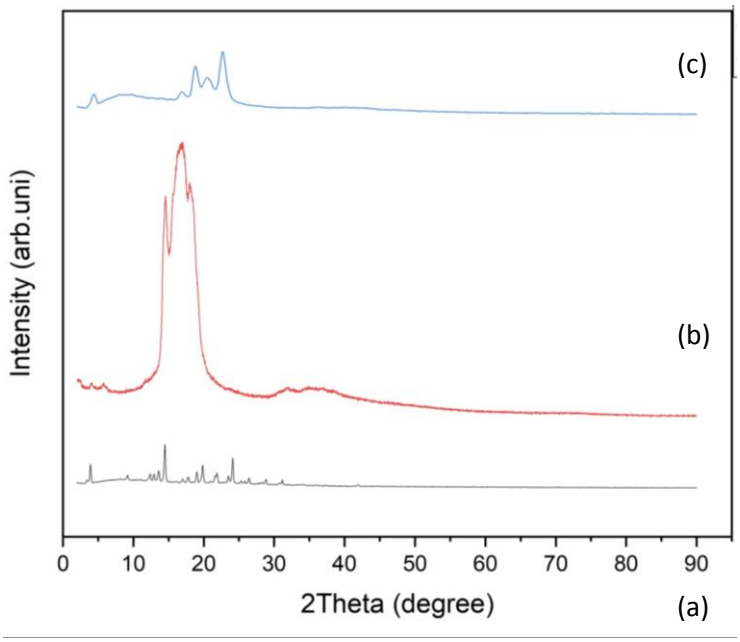

Figure 2: X-Ray Diffraction Pattern (a) Tretinoin (b) Precirol®ATO5 (c) Mixture

Table 1: NLC Tretinoin Characteristics

Formulation	Particle Size				ZP		Efficiency Entrapment	
	nm		PdI		mV		%	
Code	H1	H30	H1	H30	H1	H30	H1	H30
F1	271.47 ±10.76	271.47 ±10.76	0.43 ±0.06	0.46 ±0.04	-45.0 ±1.04	-45.2 ±07	82.911	85.911
F2	229.73 ±5.71	217.73 ±12.54	0.28 ±0.06	0.33 ±0.02	-55.8 ±1.08	-45.2± 2.52	84.842	84.842
F3	242.30 ±10.80	197.03 ±4.88	0.37 ±0.06	0.31 ±0.05	-54.4 ±1.08	-58.3 ±1.15	84.842	82.911
F4	235.43 ±3.33	273.03 ±77.40	0.24 ±0.02	0.43 ±0.29	-55.3 ±1.97	-44.2 ±2.37	83.876	84.842
F5	203.07 ±13.11	295.07 ±10.66	0.25 ±0.12	0.40 ±0.02	-48.8 ±0.72	-46.0 ±1.34	85.807	80.014

PdI: Index polydispersity, ZP: Zeta potential

Figure 3 demonstrates the spherical form and homogenous distribution of NLC tretinoin with Precirol®ATO5 based on the outcomes of the TEM test (TEM-1400 Flash Electron Microscope, JEOL Ltd.). The form and surface of spherical particles spherical shape supports good long-term release [19].

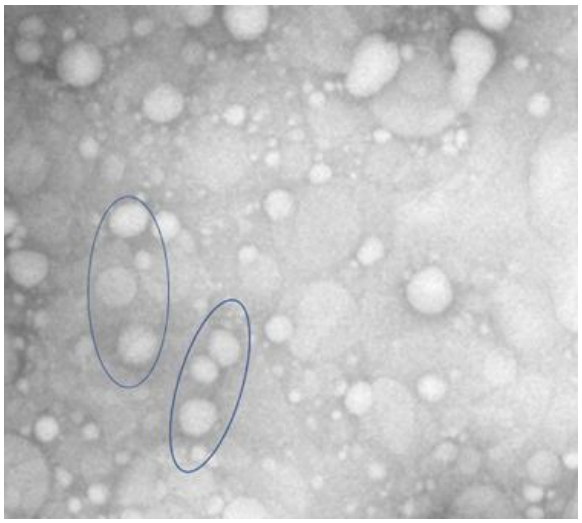

Figure 3. TEM Images

IV. CONCLUSION

Using heat homogenization and probe sonication techniques, utilizing Precirol®ATO5, Myritol®, and Tego®care surfactants, tretinoin may be formed into the Nanostructured Lipid Carriers (NLC) system. A particle size of 300 nm, a polydispersity index value of < 300 nm, a polydispersity index value of 0.5, a zeta potential value > - 42 mV, and an entrapment efficiency value of >80% are characteristics of the NLC tretinoin formulation. The morphological test is homogeneously distributed and spherical.

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