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Research Paper

Formulation of shea butter Nanoparticle containing griseofulvin: a combination of antifungal and anti-inflammatory treatments

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Abstract

Nanomedicine has been a booming industry with the development of nanovectors to encapsulate water-soluble or amphiphilic molecules for drug delivery. As the new therapeutic agents synthesized are increasingly lipophilic, the development of new nanoparticulate vectors allowing their transport and targeting is now a major challenge. These particles are lipid nanoparticles, a few hundred nanometers in diameter, stabilized by a layer of surfactants composed of castor oil and stealth agents. Solid lipid nanoparticles based on shea butter, stabilized by cremophor® ELP, encapsulating griseofulvin, were formulated by the temperature phase inversion method. The shea butter nanoparticles thus obtained were the subject of characterization relating to: determination of the morphology, size, polydispersity index, pH and zeta potential. The results confirm the stability of our preparations. The anti-inflammatory activity of shea butter being known, the tests were carried out on mice. The inflammation was induced by a solution of croton oil acetone. There is a very big improvement in anti-inflammatory activity. This is due to better penetration of the preparation through the different layers of the skin. Griseofulvin release studies have been carried out on our various preparations. Systems designed as reservoirs of active ingredients and intended for a priori controlled release obey kinetics of the order of one-half (½) corresponding to a proportionality between the quantity released and the square root of time. Shea butter in nanoparticulate forms has thus enabled us to considerably prolong the release of griseofulvin.

Keywords: Nanoparticles; Shea Butter; Inflammation; Griseofulvin.

INTRODUCTION

In the pharmaceutical field, nanoparticles (nanospheres and nanocapsules) are widely used for the vectorization of active ingredients. During the last decades, a significant number of research works have been cited in the literature mainly focusing on the resolution of the problems related to the administration of active molecules by topical route, to the stability, to the poor bioavailability and to the efficacy [1–5].

A promising strategy for solving these problems is to encapsulate the active ingredients in vectors thus allowing their protection, their targeting and a controlled release of the molecule of interest to the target organ [6–9].

The introduction of colloidal vectors has led to a revolution in therapy over the past two decades. It is now established that the use of these vectors not only improves the therapeutic efficacy, but also reduces the side effects of the active substance. A wide variety of colloidal vectors have been introduced into the therapeutic field to meet the challenge of improving the bioavailability of hydrophobic active ingredients [10–13]. These vectors are classified according to the nature of the matrix used for their preparation. They are mainly based on lipids, synthetic polymers or biopolymers (polysaccharides and proteins) [14–18].

Polymeric nanoparticles are colloidal nanovectors composed of biodegradable polymers. The major problem with using these particles is that their production often requires toxic crosslinking agents and carcinogenic monomers. Complete removal of these constituents is difficult [19–21].

Lipid nanovectors were introduced to overcome the toxicological problems of polymeric nanovectors. There is a lot of research on lipid systems, such as liposomes, nanoemulsions, micelles, and solid lipid nanoparticles (SLNs, Solid Lipid Nanoparticles) [22,23].The particles formed from solid lipids have been formulated in order to obtain systems that limit the mobility of the active principle within the vectors. The low mobility of the molecule of interest in the solid lipid core gives these systems good stability compared to emulsions [24,25]. This makes SLNs interesting for a vectorization allowing a controlled release of the actif principle. SLNs are thus colloidal nanovectors used to encapsulate hydrophobic active principles and to a lesser extent hydrophilic active principles [24,26–28]. Shea butter was

used as a solid lipid in this study. Shea butter is used in cosmetics as a moisturizer. The presence of unsaponifiables (sterols, phenolic compounds, etc.) gives shea butter anti-inflammatory and antioxidant properties, which makes it interesting for medical and cosmetic applications [16,29]. In this context, the overall objective of this work relates on the one hand to the formulation of a vectorization system in the form of solid lipid nanoparticles (SLNs) based on shea butter. On the other hand, the study of the anti-inflammatory activity of nanoparticles in comparison with raw shea butter as well as the study of the release of the active principle in the nanoparticles.

1- EXPERIMENTAL SECTION

1-1 Raw material

The raw materials used for the formulation of nanoparticles were: unrefined shea butter, purchased from women producers of Kedougou (South-East of Senegal), a non-ionic surfactant, Cremophore (Kolliphor® ELP (BASF)), distilled water.

1-2 Animal

Albino mice weighing between (20 – 31g) obtained from Pasteur Institute of Dakar were used. The animals were housed in a cage under conditions of 25±2°C temperature, 12 h light cycle and provided with food and water *ad libitum*.

1-3 Methods.

1.3.1 Lipid nanoparticles preparation

The lipid nanoparticles were obtained by a phase inversion method described in the literature. After various tests using a three-dimensional diagram (Figure 1), a stable dispersion was obtained with: 57.14% of crude shea butter, 14.26% of Cremophor and 28.57% of distilled water. The surfactant (Cremophor®ELP) was mixed under stirring in with the shea butter which has been melted at a temperature below 60 °C. When the mixture became completely homogeneous, the temperature was brought to 80 ° C. This oily phase was then added abruptly in the aqueous phase at 0 °C. Stirring was maintained at 350 rpm 60 °C for 10 minutes. This resulted in the formation of lipid nanoparticles which were then distributed in test tubes and left out of light and at room temperature.

	Témoin	Tube with griseofulvin
Shea butter (g)	10	10
Crémophor (g)	2.5	2.5
Water (ml)	5	5
Griséofulvin (mg)	00	25

1.3.2. shea butter Lipid nanoparticles characterizations

1.3.2.1. Size distribution and ζ potential measurements shea butter lipid nanoparticles

Size distributions, polydispersity indexes (PDI) and zeta potentials were determined with a NanoZS (Malvern Instruments, Orsay, France), by dynamic light scattering (DLS), and measurement of the electrophoretic mobility of the nano-emulsion droplets, respectively. All experiments were performed in triplicate

1.3.2.2 Macroscopic examination of shea butter Lipid nanoparticles

The shea butter nanoparticles are left to stand in the dark and at room temperature in 15 ml conical tubes with lids. This visual inspection makes it possible to highlight certain phenomena of instabilities such as sedimentation, flocculation and coalescence.

1.3.2.3. Microscopy of shea butter Lipid nanoparticles

A droplet of the suspension on a slide covered with a coverslip then place on the stage. The observation was made at the 40X objective. The device is equipped with software that allows you to directly photograph the image observed by the microscope. The image of the droplets obtained is analyzed using software that allows the size of the droplets to be determined by delimiting the diameter of the droplets.

1.3.3 pH determination shea butter Lipid nanoparticles

The determination of the pH of the solutions is based on the measurement of the potential between two electrodes immersed in a solution rich in H^+ ions.

After having calibrated the pH meter with solutions of known pH, the electrode is dipped in a 15 ml conical tube containing the preparation to be studied. Like conductivity, care should be taken to immerse the electrodes to the level of the emulsified phase for tubes with sedimentation. The reading is taken a few minutes after inserting the electrode.

1.3.4 Conductivity measurement of shea butter Lipid nanoparticles

It is based on measuring the electrical resistance of a solution located between 2 plates coated with platinum black. Depending on the concentration of ions present, the solution will have a more or less important conductivity.

In a 15 ml tube fitted with a screw cap containing the preparation to be studied, the conductivity cell is introduced. In the presence of a conductive preparation, the conductimeter displays a value corresponding to the conductivity and expressed in Siemens per meter ($S.m^{-1}$). In the case of tubes showing sedimentation, immerse the conductive cell to the level of the emulsified fraction.

1.3.5 Topical anti-inflammatory test

Topical anti-inflammatory activity was evaluated in croton oil induced ear edema in the experimental mice model [30].

The mice were divided into 3 batches of 5:

- Batch 1: control group
- Batch 2: treated group with raw shea butter
- Batch 3: treated group with virgin shea butter nanoparticles

In control group, the mice were treated locally with 10 µl of 1% croton oil in alcoholic solution applied to the right inner ear.

The preparations were applied on the left inner ear of mice. On the right inner ear, 10 µl of 1% croton oil in alcoholic solution and the preparations were also applied.

The treated animals were anesthetized with ethyl ether using a funnel 6 h after treatment. The ears were immediately cut along the cartilage and weighed immediately with a precision balance. The mice were then sacrificed.

Topical anti-inflammatory activity was evaluated using the following formulae:

$$F1 = \%\ INCREASE\ (\%INC) = \frac{RE\ Weight\ -LE\ Weight}{LE\ Weight} \times 100$$

RE: right ear; LE: left ear

$$F2 = \%\ INHIBITION\ (\%\ INH) = \frac{Mean\ \%\ INC\ control\ - Mean\ \%\ INC\ treated\ lot}{Mean\ \%\ INC\ control} \times 100$$

Percentage increase expresses the intensity of the inflammation in the right ear. The percentage inhibition of edema evaluates the power of inhibition of edema by raw shea butter and virgin lipid nanoparticles.

1.3.6. In vitro release study

As a model drug soluble in oil, griseofulvin was encapsulated in shea butter Lipid nanoparticles at 0.33mg/mL. The solubilization of griseofulvin in Labrafac® WL 1349 was carried out by using a thermomixer (Thermomixer C Eppendorf) at 37°C for 15min. The griseofulvin release profiles were characterized by dialysis (2mL of loaded shea butter Lipid nanoparticles at a concentration in solution equal to 0.33mg/mL, and the dialysis tubing as Spectra-Por, regenerated cellulose, cut-off: 12 −14kDa). Dialysis was done in 300mL, magnetically stirred at 100rpm. In PBS at pH=6.8. Aliquots of 5mL were regularly collected from the dissolution medium, and analyzed by UV spectrophotometry (UV Thermo Scientific Evolution 300). Absorbance values were monitored in a quartz cuvette at 286.5nm in PBS respectively. Sink conditions were maintained by replacing 5mL of the release medium with fresh media at each sampling point. This allowed the determination of the cumulative drug amounts released from nanoemulsions. UV–vis absorption spectra of shea butter Lipid nanoparticles were recorded on sample solutions using a UV spectrophotometer with a wavelength range of 180–500nm at 0.2nm sampling interval. All experiments were performed in triplicate.

1.3.7 Statistical analysis

The results were expressed as mean ± standard error at mean. An analysis of variance (ANOVA) was performed to verify the homogeneity of the groups. A Student's test was used to highlight the existence of a significant difference between the different groups with a threshold of significance $p < 0.001$.

2. RESULTS

2.1 Preparation shea butter Lipid nanoparticles

Different proportions were used in the formulation study using a three-dimensional diagram. After various tests, the stable proportion was:

- 57.1% raw shea butter
- 17.5% cremophor
- 28.6% water

Tridimensional diagrammed

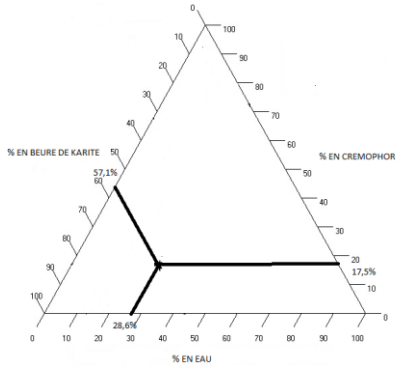

Figure 1: Representation of the three-dimensional diagram

2.2 Shea butter Lipid nanoparticles characterizations

2.2.1 Microscopy of shea butter Lipid nanoparticles

Microscopic observation of lipid nanoparticles is difficult by optical microscopy due to the small size of the particles. In **Figure 2** is shown the microscopic imaging of our suspension of lipid nanoparticles.

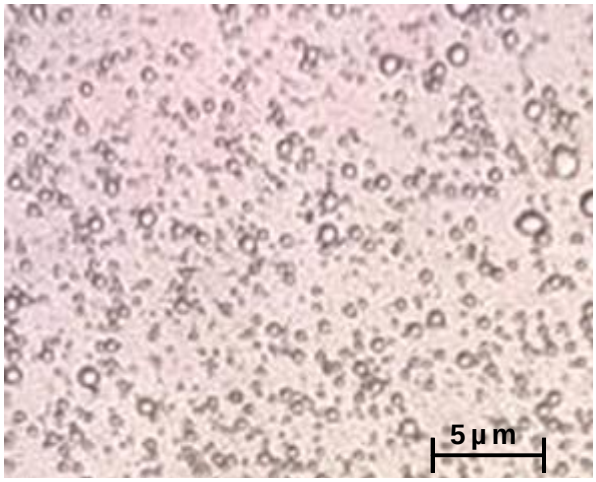

Figure 2: Microscopic image of lipid nanoparticles

2.2.2 Size distribution and ζ potential measurements of shea butter Lipid nanoparticles

The average size of the nanoparticles was determined by dynamic light scattering using the Zetasizer. On the tables and the following figure, we present the size distribution obtained

Table 1 : average size of the nanoparticles anr PDI

Tubes	T1	T2
	402,3 nm	531,2nm
Tailles	402nm	498,7
	405nm	486,2nm
Average	403,1nm	505,36nm

Tubes	T1	T2
	0,299	0,212
PDI	0,204	0,224
	0,246	0,221
Average	0,216	0,219

Figure 3: Size distribution of nanoparticles by volume.

The determined Zeta Potential gives values between -5 and -7mV. This demonstrates good stability of the prepared nanoparticles.

2.3 pH determination of Pickering emulsion

The pH measurements were carried out on D1, D7, D14, D21, and D28. The results are shown in **Figure 4** below.

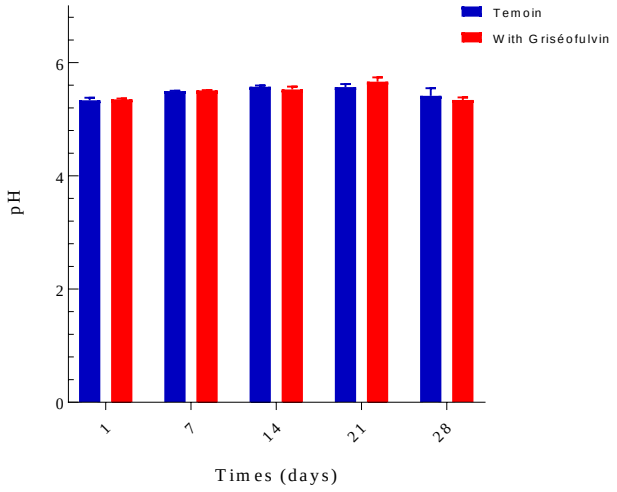

Figure 4: pH evolution of emulsions as a function of time

2.4 Conductivity measurement of Pickering emulsion

The conductivity measurements were taken on D1, D7, D14, D21, and D28 (Figure 5). The results give conductivity values of less than 0.2 mS / cm for all the preparations.

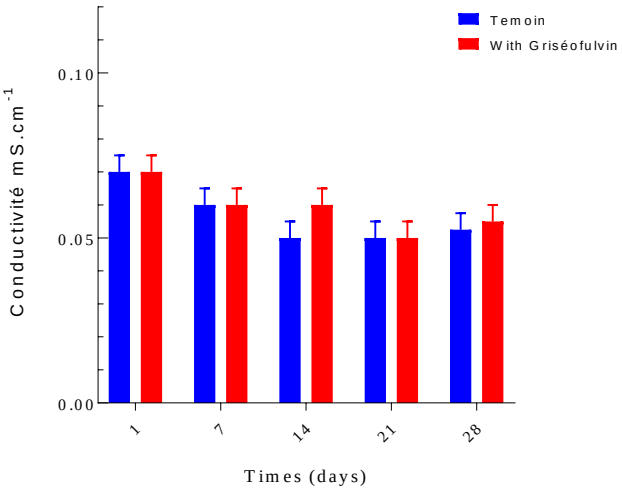

Figure 5: Measurement of conductivities of emulsions as a function of time

2.5. Topical anti-inflammatory test

The percentage of increase (% INC) in the ear calculating with the formula F1 express the intensity of the inflammation. The percentage increase of the edema induced by the alcoholic solution of croton oil (control) is 122.78 (**Table 2**).

In parallel, the percentage inhibition of edema was calculated for treated groups according to the formula F2. It evaluate the power of inhibition of edema by raw shea butter and virgin lipid nanoparticles. Application of the raw shea butter significantly prevented ear edema in mice. The percentage increase of edema is 45.05±8.72 ($p<0.001$ versus control). The same profile is observed with the virgin shea butter nanoparticles, the percentage increase of edema is 46.35±7.98 ($p<0.001$ versus control) (**Table 2**). The corresponding inhibition percentages are respectively 62.80±6.55 and 60.80±7.42 (**Figure 6**).

Figures 6 represent the diagrams of percentages of inflammation inhibition (% INH) and percentages of weight increase (% AUG), respectively.

Table 2: Anti-inflammatory activies of raw shea butter and Shea butter nanoparticles

Batches (n = 5)	Ear weight average removed (g)		Increased edema (%)	Inhibition edema (%)
	Left (treated)	Rigth (untreated)		
Control	0.02	0.046	122.78±12.44	-
Raw shea butter	0.03	0.042	45.05±8.72***	62.80±6.55
Shea butter nanoparticles	0.03	0.046	46.35±7.98***	60.80±7.42

*** = p <0.001 vs control group.

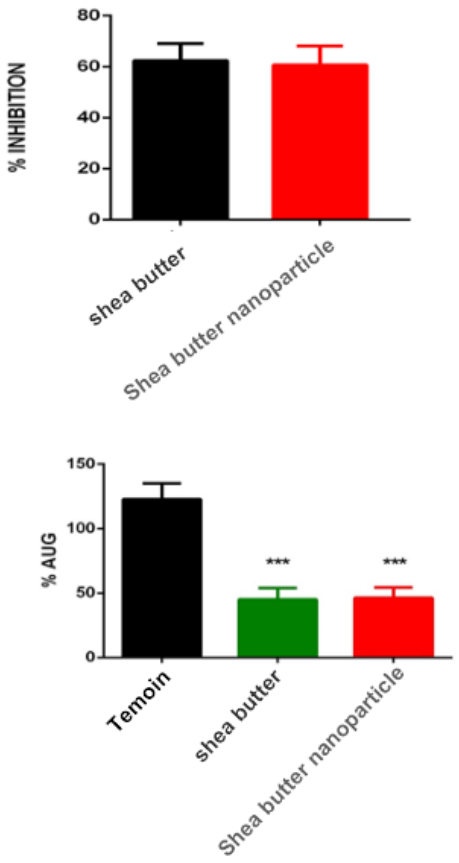

Figure 6: Diagram of percentages of inhibition and increase in weight of inflammation

The diagram of the ratio between the percentage inhibition (% INH) and the percentage of shea butter (% BK) is shown in **Figure 7.**

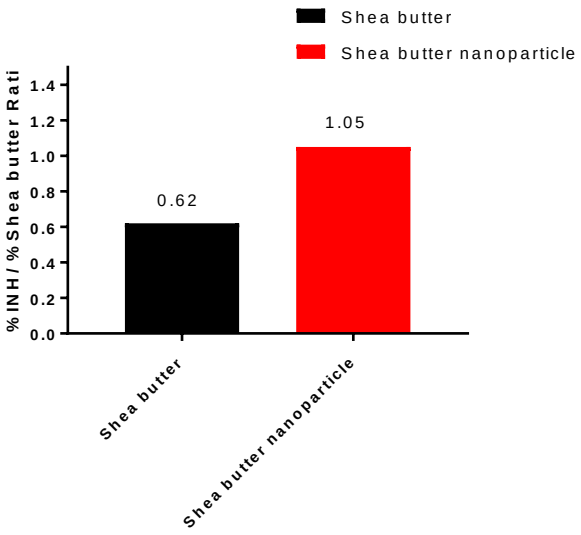

Figure 7: diagram of the ratio of percentage inhibition (% INH) / percentage of shea butter (% BK)

2.6. In vitro release study

The griseofulvin release study from crude shea butter and nanoparticles was performed. In the following figure we present the release profiles obtained in PBS.

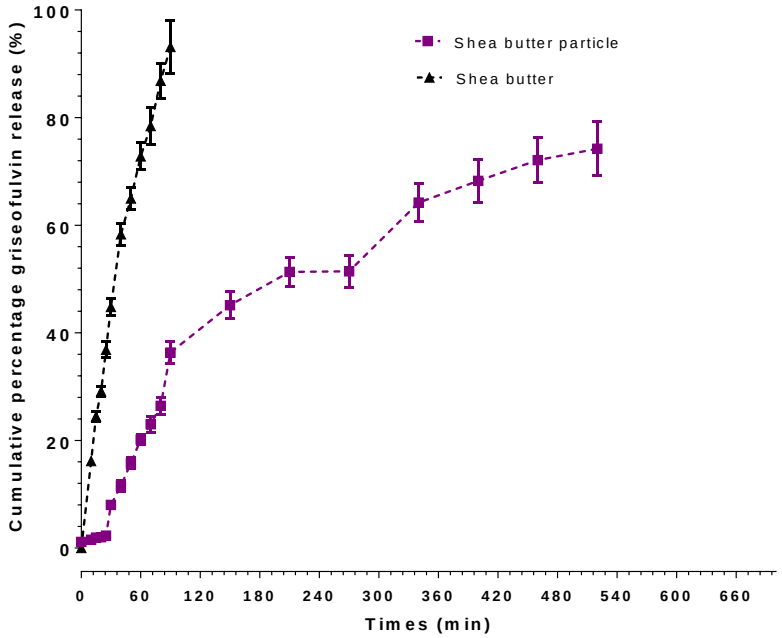

Figure 8: Percentage of griseofulvin released as a function of time

DISCUSSIONS

The main results obtained with regard to the physicochemical properties have shown that macroscopically the majority of the tubes have a homogeneous, viscous and stable appearance without formation of deposits or phase separation on visual inspection and throughout the shelf life. However, the absence or presence of a change perceived by the naked eye does not prejudge the stability of the lipid nanoparticles. This

stability is explained on the one hand by the ratio of the ternary mixture (shea butter-water stabilized by the cremophor) which gives the point of stability in the three-dimensional diagram by the phase inversion temperature method. On the other hand, the zeta potential of between -5 and -7 millivolts does not testify to a good repulsion between the lipid nanoparticles by electrostatic forces. Indeed, stability is strongly dependent on the existing electric charge at the interface between the two phases. The counterions closest to the particle are strongly retained there by electrostatic attraction. They constitute the Stern layer, so there is a second layer called the diffuse layer which does not adhere to the particle, but which forms a cloud around it and fades at a certain distance from it [31]. But this does not preclude stability due to the robustness of the method. The delicate observation of nanoparticles under microscopy does not guarantee a faithful view of the suspension of nanoparticles. However, spherical particles (lipospheres) were observed with some extensions on the surface of the particles. The particle size as a function of the composition of the ternary mixture is in agreement with the results obtained. The increase in the surfactant fraction leads to the production of smaller particles whose sizes vary between 403.1 nm and 505.36 nm with the exception of tube without griseofulvin which contains the same fraction of surfactant. This is explained by the encapsulation efficiency which thus increases with the specific surface of the particles, which encapsulation efficiency is confirmed by the study of the release of said tube as shown in figure 3.

The size of the shea butter nanoparticles is thus controlled by the quantity of surfactants capable of stabilizing the water / shea butter interface. The greater the quantity of surfactant, the greater the potentially stabilized interface, and this for a constant quantity of shea butter [16]. Thus, by using this method, it was possible to obtain nanoparticles based on raw shea butter with a size of between 400 and 500 nm. The poly dispersion index being 0.3.

Regarding the pH, the results obtained indicated an acidic character for all the tubes; with average values oscillating between 5.2 and 5.3. This confirms the possibilities of incorporating the lipid nanoparticles in supports of cream, ointment and gel types for skin application, given that the pH of the skin has a value between 5.4 and 5.9 except below the armpits, between fingers and toes.

All the results obtained show that nanoparticles were formulated mainly consisting of raw shea butter. Since the anti-inflammatory activity of shea butter is known, we evaluated the activity of raw shea butter compared to that of nanoparticles. These potency tests showed anti-inflammatory activity in the ears of mice whose inflammation was induced by an alcoholic solution of croton oil. Indeed, shea butter contains unsaponifiables such as sterols, triterpene alcohols, phenolic compounds and tocopherols [32–34]. The presence of these compounds gives the shea butter interesting biological activities such as anti - inflammatory and antioxidant activity [35].

Croton oil edema anti-inflammatory activity results performed on mice show that Shea butter has an average inhibition percentage of 62.52%, virgin nanoparticles have a percentage of 60.80%. By making the ratio between the percentage inhibition of anti-inflammatory activity and the actual percentage of shea butter in the different preparations, we have ratios of 0.62 and 1.05 respectively for raw shea butter, nanoparticles based on shea butter. Thus, there is a very great improvement in anti-inflammatory activity. This may be due to a better penetration of the preparation through the different layers of the skin compared to raw shea butter. Indeed, studies show penetration of particles through the skin by intercellular pathways. This is particularly the case with ultra-flexible liposomes [36]. Hansen et al .., describe two mechanisms involved in the skin absorption of actives from particles [37] :

- Via intercellular spaces: this type of transport concerns very fine rigid particles (<10 nm) but also ultra-flexible liposomes which, in addition to passing their large size, are able to deform to slide through the intercellular channels.

- Via the hair follicle: this phenomenon has been shown to be diametrically dependent. In fact, the depth reached by the particles is a function of their size.

Prow et al. 2011 speak of an additional mechanism consisting of the internalization of nanoparticles by skin cells mainly used for topical vaccination [38].

For the release study, tubes temoin and tube with griseofulvin (shea butter nanoparticles) , released 100% after 90 minutes and 78.7% for shea butter nanoparticles respectively. These percentages of release are explained by the fact that the largest fraction of griseofulvin (lipophilic PA) is found in the hydrophobic core. Indeed the control of the release of the active principle which depends mainly on its location within the particle and the specific area for the shea butter nanoparticle. An active molecule found on the surface or in the outer envelope (enriched crown model) will be quickly released, while if it is localized in the core of the nanoparticle, its release will be prolonged. This is in perfect correlation with the cumulative release of the drug over 22 hours for Shea butter nanoparticles.

The release studies of incorporated griseofulvin show that the systems formed release up to more than 20 hours. The release profile obtained follows kinetics of the order of ½. According to the latter, unlike the ideal for controlled release systems which would be to have a constant flow of AP that is independent of time (zero order kinetics (0) difficult to obtain experimentally), the systems designed as reservoirs of Active ingredients intended for a priori controlled release obey a one-half (½) order kinetics corresponding to a proportionality between the quantity released and the square root of time.

CONCLUSIONS

The study of physicochemical parameters allowed us to assess the stability of lipid nanoparticles.On all the preparations, no instability phenomenon was observed. The microscopy shows nanospheres with some extensions on the surface of the particles. The formulated lipid nanoparticles have an average size of 400-500 nm favorable for good skin The zeta potential of between -5 and -7 mV does not induce good stability, but the robustness of the method makes it possible to guarantee lipid nanoparticles because it is low. pH measurements indicated an acidic character for all samples, however this acidity did not affect the preparations during the entire observation period The anti-inflammatory activity test of lipid nanoparticles based on crude shea butter, on mice whose inflammation with croton oil was provoked, shows good penetration of the lipid nanoparticles, which explains the similar inhibition rate. To that of raw shea butter. The kinetic profiles show a prolonged release of the active ingredient. Indeed the composition of the system used can also influence the release of the encapsulated active ingredient. Griseofulvin is a hydrophobic active principle that is poorly soluble in the aqueous phase. For this, a nonionic surfactant (Cremophor ELP) was added to improve the solubility of the active principle released.

Declaration of Competing Interest: The authors declare no conflicts of interest.

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