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Research Article

ACCELERATED STABILITY TESTING OF ANTI-AGING CREAM: FORMATION OF MYRISTIC ACID AND STEARIC ACID AS DEGRADATION PRODUCTS

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ABSTRACT

Objective: This study aimed to determine the stability of anti-aging cream using the accelerated stability test and calculating the levels of myristic acid and stearic acid as degradation products.

Methods: Optimum conditions and validation methods for the mixture of myristic acid and stearic acid were determined to obtain a valid method for determining the levels of degradation products in anti-aging cream. Derivatization was performed with the Lepage esterification method, which uses methanol-toluene 4:1 (v/v) and acetyl chloride catalysts. The analysis was performed using gas chromatography (GC) Shimadzu GC-17A system with an HP-1 column and flame ionization detection.

Results: The column temperature was 120°C, with an increase of 10°C/min (up to 160°C) followed by an increase of 3°C/min (up to 220°C; maintained for 5 min) and an increase of 10°C/min (up to 260°C; maintained for 5 min). The injector and detector temperatures were 260°C and 280°C, respectively, with a flow rate of 1 mL/min. The retention times of myristic acid and stearic acid were 16.655 min and 28.169 min, respectively, with tailing factor values of 0.734 and 0.943, respectively. Validation results fulfilled our acceptance criteria, which obtained linearity for myristic acid at y=9.6483+190.78x, with a correlation coefficient (r) value of 0.9997, limit of detection (LOD)=0.0013 parts per million (ppm), and limit of quantification (LOQ)=0.0042 ppm. The linearity for stearic acid was determined at y=17.163+106.22x, with a correlation coefficient (r) value of 0.9998, LOD=0.0016 ppm, and LOQ=0.0053 ppm. Results of the anti-aging cream stability test indicated that the average remaining levels of isopropyl myristate from 0 to 3 months were 99.6283%, 99.1995%, 98.2571%, and 97.1511%, respectively. The average remaining levels of glyceryl monostearate were 99.6791%, 98.2881%, 96.2247%, and 93.7195% from 0 to 3 months, respectively.

Conclusion: The expiration date of the anti-aging cream product was then calculated using zero-order kinetics and determined to be 10 months and 9 days.

Keywords: Myristic acid, Stearic acid, Isopropyl myristate, Glyceryl monostearate, Gas chromatography, Accelerated stability test, Validation, Optimization.

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INTRODUCTION

Since ancient times, beauty has been a highly desirable trait, with skin being an outward reflection. Indeed, the skin is one part of the body where beauty can be more precisely defined. However, with age, the properties of skin can change. Indeed, extreme climate changes, high levels of pollution, smoking, hormonal changes, lifestyle, and ultraviolet (UV) exposure can all aggravate skin aging [1,2]. Characteristic signs of aging skin include reduced skin elasticity, wrinkles, and skin that appears to be thin [1].

At present, various techniques have been developed to prevent and treat skin aging, with one being the use of cosmetics [3]. Accordingly, cosmetics are widely used to overcome the problem of skin aging. Anti-aging cosmetics function to rejuvenate the skin, help remove wrinkles, and protect the skin from oxidative damage caused by UV rays [4,5]. The anti-aging products currently available on the market are generally formulated as transparent creams and gels [6]. However, cream preparations are more popular, likely because they are easy to apply and easily removed from the skin [7].

Anti-aging cream products, as well as cosmetic creams in general, are composed of two main components, namely, the oil phase and the water phase. Cream preparations generally contain >20% water content and <50% of the oil phase [8]. Some ingredients often used as oils or as the lipophilic phase in creams include ester compounds of fatty acids, including sorbitan monooleate, polyoxyl 40 stearate, glyceryl dilaurate, glyceryl oleate, glyceryl monostearate (GMS), and isopropyl myristate [9]. GMS is one of the ester fatty acid compounds used in lotions and creams as an emulsifier, stabilizer, thickener, and emollient and is the most widely sold emulsifier commercially. In addition to GMS, isopropyl myristate is an important ingredient used in cosmetics, functioning as an emollient that can restore and retain the natural softness of the skin [10]. However, when the water content is high, as in the preparation of creams under acidic conditions, the ester bonds in both GMS and isopropyl myristate become broken, which leads to their break down into various degradation products. Accordingly, isopropyl myristate breaks down into isopropanol isopropyl myristate and myristic acid, while GMS decomposes into stearic acid and glycerol [11,12]. Based on this decomposition, the stability of anti-aging cream preparations can be evaluated.

The stability test is composed of a series of tests aimed at obtaining information on the stability of pharmaceutical products, to determine their shelf life and expiration date under certain packaging and storage conditions [13]. The long-term stability test is often performed to produce more significant degradation data for preparation [14]. However, this stability test takes a long time to determine the expiration date, which precludes timely cosmetic notification processes for production. Therefore, the preferred stability test is the accelerated method, which requires shorter test times, where the decomposition may cause the consistency of the cream to change [13,14]. Therefore, in this study, we performed the accelerated stability test at 40°C±2°C and a relative humidity of 70±5% to accelerate the expiration date of

the product. Data acquisition was based on the remaining isopropyl myristate and GMS in the product at 0, 1, 2, and 3 months.

In previous studies, stability tests were conducted on cosmetic preparations using the accelerated method for 90 days, a temperature of 40°C, and a relative humidity of 75%. In addition, tests were performed at room temperature. After the test, the physical properties of the preparation, such as organoleptic, pH, viscosity, and the levels of active substances were observed [2]. While there has been an increasing use of anti-aging creams, little data exist on the stability of the chemicals in these creams; thus, it is necessary to study the components of cream preparations.

In this study, accelerated stability testing was conducted on the preparation of anti-aging creams containing isopropyl myristate and GMS as their base components. The stability of the anti-aging cream was judged by determining the residual isopropyl myristate levels, based on the formation of myristic acid, and the residual GMS levels, based on the formation of stearic acid. Considering the fatty components of the cream, gas chromatography (GC) methods were chosen as the best technique. Indeed, GC is the method most often used for the analysis of fatty acids and is very sensitive for their identification and quantification [15]. However, fatty acids detected using GC processes first require derivatization to lower their boiling point, and the response to the detector used [16]. In this study, derivatization was performed using the Lepage esterification method, followed by analysis using GC.

METHODS

Samples

The anti-aging cream used for accelerated stability testing at 0, 1, 2, and 3 months was composed of a formulation of glycolic acid (10%), Lanette O (5%), isopropyl myristate (5.5%), GMS (4.5%), emulgade SE-PF (3.5%), propylene glycol (5%), glycerin (5%), methylparaben (0.01%), propylparaben (0.002%), and water (ad 100%).

Chemical material

A myristic acid standard (Natural Oleochemicals Sdn Bhd), stearic acid standard (Edenor), isopropyl myristate standard (Oleon), GMS standard (Evonik), acetyl chloride (Merck), methanol p.a (Merck), toluene p.a (Merck), potassium carbonate (Merck), nitrogen (UHP dan HP), and hydrogen (UHP) were all of reagent grade or higher.

Chromatographic condition

Shimadzu GC-17A systems are equipped with a flame ionization detector, a capillary column with a length of 30 m and an inside diameter of 0.25 mm, film thickness of 0.25 µm with a stationary phase HP-1, and carrier gases of nitrogen and hydrogen. The solution class GC data processor had an initial column temperature of 1200°C, which was increased 10°C/min (up to 160°C), then raised 3°C/min (up to 220°C; maintained for 5 min). Then, the temperature was raised 10°C/min (up to 260°C; maintained for 5 min). The injector and detector temperatures were set at 260°C and 280°C, respectively. The carrier gas flow rate was 1.0 mL/min.

Preparation of potassium carbonate solution (6%)

Approximately 6 g of K2CO3 was carefully weighed and placed into a 100 mL volumetric flask, followed by dilution with distilled water to mark the boundaries of the flask.

Preparation of the myristic acid stock solution

Approximately 25 g of myristic acid standard was carefully weighed and placed into a 25 mL volumetric flask followed by dilution with methanol-toluene 4:1 (v/v) to mark the boundaries of the flask.

Preparation of the stearic acid stock solution

Approximately 25 g of the stearic acid standard was carefully weighed and placed into a 25 mL volumetric flask followed by dilution with methanol:toluene 4:1 (v/v) to mark the boundaries of the flask.

Determination of optimum conditions

To determine the optimum conditions for testing, as much as 1.0 mL of each test solution of 4 parts per million (ppm) was pipetted and mixed. The solution was then placed in a test tube stoppered and shaken with a vortex. Acetyl chloride (1 µL) was then added slowly while stirring. The tube was sealed while shaking occasionally. Furthermore, 5.0 mL of 6% potassium carbonate solution was slowly added. The tube was then tightly closed and centrifuged at 3000 rpm for 5 min. The top layer (toluene phase), containing the methyl ester mixture of myristic acid and stearic acid, was injected (1 µL) into the GC system. Optimum conditions for analysis were assessed by retention time, the number of theoretical plates (N), height equivalent to a theoretical plate, tailing factor, and the best separation resolution in Table 1.

Analysis of the effect of heating time on placebo

The placebo, weighing as much as 200 mg, was then fed into a 100 mL measuring flask and dissolved in 4:1 (v/v) methanol: toluene, up to the boundary marker. Then, 200 µL of acetyl chloride was added slowly while stirring. The tube was then placed into a water bath at 100°C for 10 min, 5 min, and without heating. The tube was then sealed while shaking occasionally. 5 mL of 6% potassium carbonate solution was then slowly added. The tube was then tightly closed and centrifuged at 3000 rpm for 5 min. The top layer (toluene phase), containing the methyl ester mixture of myristic acid and stearic acid, was injected (1 µL) into the GC system. Based on the results of our analysis, the peak area and comparative peak areas of myristic acid and stearic acid were recorded with each variation in conditions.

Analysis of the addition of acetyl chloride to placebo

The placebo, weighing as much as 200 mg, was then fed into a 100 mL measuring flask and dissolved in 4:1 (v/v) methanol: toluene, up to the boundary marker. Acetyl chloride was then added slowly while stirring, with the variation of addition volume being 10 µL, 5 µL, and 1 µL. The tube was sealed while shaking occasionally. Furthermore, 5.0 mL of 6% potassium carbonate solution was slowly added. The tube was then tightly closed and centrifuged at 3000 rpm for 5 min. The top layer (toluene phase), containing the methyl ester mixture of myristic acid and stearic acid, was injected (1 µL) into the GC system. Based on our results of the analysis, the peak areas of myristic acid and stearic acid were observed for each variation.

System conformity test

Sample preparation was performed in accordance with procedures for determining the optimum conditions for analysis. The injection of each solution was performed up to 6 times. The results of the analysis were recorded and the coefficient of variation was counted (% KV). The acceptance criteria of %KV were 2% or less.

Validation of the GC analytical method

Linearity test of myristic acid and stearic acid

Test solutions of myristic acid and stearic acid (10 ppm) were prepared at 100 µL and 500 µL. Aliquots (1.0, 2.0, 4.0, and 8.0 mL) were then inserted into a 10 mL measuring flask. A sufficient volume of methanol:toluene solution 4:1 (v/v) was used to obtain standard solutions of concentration: 0.1; 0.5; 1; 2; 4; and 8 ppm.

Detection limit test (LOD) and quantitation limit (LOQ)

The LOD and LOQ were calculated statistically by linear regression calibration curves. The calculation results were equal to the value of

Table 1: Variation of initial column temperature and flow rate for determining the optimum conditions for analyzing myristic acid and stearic acid content

Initial column temperature (°C)	Flow rate (mL/minute)
100	1.0
120	1.2
140	1.5

Table 2: Optimization of analysis condition for mixture of myristic and stearic acid

	Initial column temperature (°C)								
	100			120			140		
	Flow rate (mL/min)								
	1.0	1.2	1.5	1.0	1.2	1.5	1.0	1.2	1.5
Retention time (min)	19.057	18.001	16.842	16.655	15.438	14.218	13.629	12.477	11.166
Peak area (μV/s)	689	557	804	749	658	1001	1302	1237	1587
Theoretical plate (N) (plates)	480866	424006	391146	391327	332864	232531	202990	185770	115155
HETP (cm)	0.0062	0.0071	0.0077	0.0077	0.0090	0.0129	0.0147	0.0161	0.0260
Resolution	163.61	163.36	159,61	145.00	145.17	115.35	55.51	51.082	44.616
(Tf)	0.73	0.76	0.94	0.81	0.84	0.81	0.80	0.71	0.77

b in the straight-line equation y=a+bx, whereas the standard deviation of the blank was equal to the residual standard deviation (Sy/x) [17].

Selectivity test

The selectivity test was carried out by preparing a standard solution of myristic acid and stearic acid, and a derivatization solution with no standard added. Each solution was injected into the GC at 1 μL under the selected analysis conditions. It was then observed whether or not other peaks appeared at the time of the retention of the methyl esters of myristic acid and stearic acid in the sample solution.

Precision accuracy test

The placebo cream, weighing as much as 200 mg, was added to each standard solution, then dissolved in a 100 mL volumetric flask using methanol:toluene 4:1 (v/v). The volume of standard solution added was calculated to obtained concentrations of 80% (3.2 μg/mL), 100% (4 μg/mL), and 120% (4.8 μg/mL).

RESULTS AND DISCUSSION

Analysis conditions optimization

Based on our experiments, the resulting optimum analysis conditions for analyzing the mixture of myristic acid and stearic acid were: An initial temperature of 120°C for the column and a mobile phase flow rate of 1.0 mL/min (Table 2). The resulting chromatogram had a fairly large peak area and relatively shorter retention time but displayed the best resolution when compared with other variations. The peak area obtained under these conditions was 749 μV/s. The retention time obtained from the chromatogram of myristic acid was approximately 16.655 min.

For stearic acid, the peak area obtained under these conditions was 451 μV/s. The retention time obtained from the chromatogram for myristic acid was 28.169 min. The retention times for myristic acid and stearic acid are known and confirmed by the analysis of each substance under the selected analysis conditions, that is, the initial temperature of the column was 1200°C and the carrier gas flow rate was 1.0 mL/min. The resultant chromatogram was obtained and myristic acid appeared at a retention time of 16.251 min, while stearic acid appeared at a retention time of 28.986 min.

System conformity test

The system suitability test should be performed first before analyzing the optimum conditions selected. A number of variations made to the equipment, as well as the analytical techniques used, were evaluated. Thus, it is necessary to test the suitability of the system to ensure the effectiveness of the operational systems and to deliver results in accordance with the purpose of the analysis. The system suitability test was performed 6 times in a row and yielded coefficients of variation for the mixture of myristic acid and stearic acid of 0.9999% and 1.0433%, respectively. Based on these experiments, our results matched the requirement that the coefficient of variation (KV) does not exceed 2%.

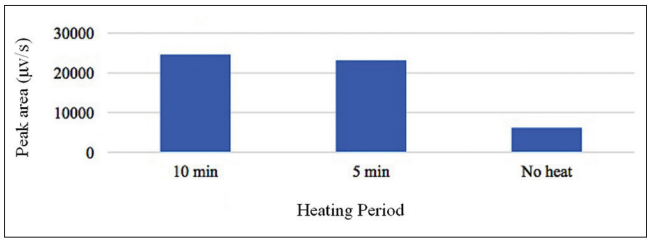

Fig. 1: Comparison of the peak area of myristic acid in the analysis of the effect of heating on the placebo

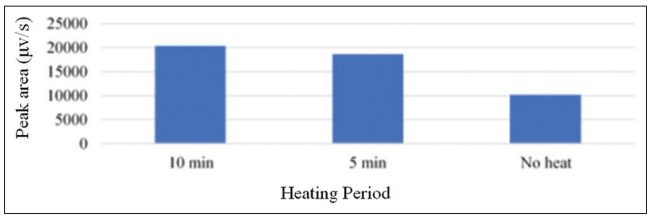

Fig. 2: Comparison of the peak area of stearic acid in the analysis of the effect of heating on the placebo

Analysis of the effect of heating on placebo

In this experiment, we analyzed the effect of heating on the placebo-based cream containing isopropyl myristate and GMS. This analysis was performed by varying the Lepage esterification procedure used, that is, by heating at 1000°C for 10 min, 5 min, and without heating. In this experiment, acetyl chloride as a catalyst was still used with an additional volume of 200 μL. The test results showed that the peak area of analysis using the same warming was slightly larger than those without the use of heating (Figs. 1 and 2). This likely occurred because in the presence of heating the reaction is catalyzed and may decompose into isopropyl myristate and GMS [18,19]. Thus, the chosen method of esterification without heating to reduce the effect of the reaction of isopropyl myristate and GMS was considered optimal.

Analysis of the addition of acetyl chloride to the placebo in conditions without heating

After analyzing the effect of heating on the placebo, we analyzed the effect of the amount of acetyl chloride added to the placebo. This analysis was conducted to determine whether the addition of acetyl chloride can cause isopropyl myristic and GMS to break down, which should not decompose during the preparation process. Variations in the volume used included 10 μL, 5 μL, and 1 μl. Our test results showed that the peak area decreases with the increase in volume added (Figs. 3 and 4). Thus, the optional addition volume of 1 μL, due to the smaller amount of acetyl chloride added, may minimize the possibility of reacting with the remaining isopropyl myristate and GMS. In this case, the acid reacted only with myristic acid and stearic acid as a result of the decomposition. This may occur because acetyl

Table 3: Chemical stability data of isopropyl myristate

Sample (months)	Peak area of sample (µV/s)	Peak area of placebo (µV/s)	Peak area of myristic acid as decompose product (µV/s)	Level of decompose IPM (µg/mL)	Percentage of remaining IPM	Average level of remaining IPM (%)
0	1989	1930	59	0.3063	99.7215	99.6284
	2022		92	0.5111	99.5353	
1	2076	1930	146	0.8464	99.2305	99.1995
	2087		157	0.9147	99.1684	
2	2243	1930	313	1.8830	98.2881	98.2571
	2254		324	1.9513	98.2261	
3	2439	1930	509	3.0997	97.1821	97.15105
	2450		520	3.1680	97.1200	

IPM: Integrated pest management

Table 4: Chemical stability data of GMS

Sample (months)	Peak area of sample (µV/s)	Peak area of placebo (µV/s)	Peak area of myristic acid as decompose product (µV/s)	Level of decompose GMS (µg/mL)	Percentage of remaining GMS	Average level of remaining GMS (%)
0	699	1930	38	0.2472	99.7253	99.6791
	706		45	0.3303	99.6329	
1	802	1930	141	1.4694	98.3672	98.2881
	814		153	1.6118	98.2090	
2	959	1930	298	3.3325	96.2972	96.22471
	970		309	3.4630	96.1522	
3	1151	1930	490	5.6108	93.7657	93.7196
	1158		497	5.6938	93.6734	

GMS: Glyceryl monostearate

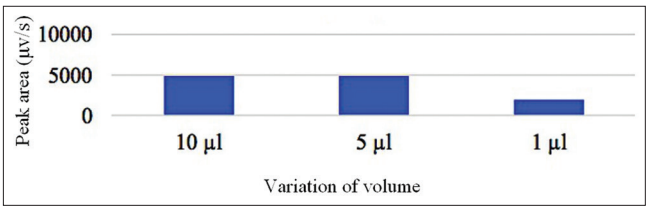

Fig. 3: Comparison of the peak area of myristic acid with additional volumes of acetyl chloride in the placebo

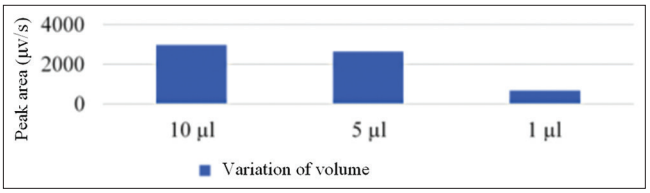

Fig. 4: Comparison of the peak area of stearic acid with additional volumes of acetyl chloride in the placebo

chloride is a strong acid that can catalyze the reaction, including both hydrolysis and esterification reactions [20].

Validation of analysis methods

Selectivity test

The selectivity test was performed by injecting the esterified product from the blank solution containing no fatty acids. The purpose of this test was to look at the possibility of a disturbance around the retention time of the fatty acid methyl esters. The results of these tests showed that the method was selective because there was no interference in the retention times of myristic acid and stearic acid.

Linearity test

The linearity test was performed by making a calibration curve by using six concentrations of the mixture of myristic acid and stearic acid, which were: 0.1, 0.5, 1.0, 2.0, 4.0, and 8.0 ppm. The regression equations for myristic acid and stearic acid were y=191.17x+7.4638 ([r]=0.9997) and y=107.06x+12.482 ([r]=0.9996), respectively. Based on these results, the linearity test was declared valid because it met the linearity criteria of having a correlation coefficient of close to 1 or >0.9990.

Accuracy and precision test

Based on the results of our analysis, we calculated the percentage of recovery (UPK) by comparing the results of the analysis with the actual results. The criteria of accuracy were expressed as met if the percentage recovery (% UPK) obtained was 98–102%. The precision was determined as a relative standard deviation or coefficient of variation (KV). The criteria of the precision were considered met if the method used produced a coefficient of variation (KV) of 2% or less.

Based on the results of our analysis, we obtained a value of recovery (UPK) for myristic acid and stearic acid of approximately 99.74–101.98% and 98.19– 101.51%, respectively. The value of the coefficient of variation (KV) produced for myristic acid and stearic acid was 0.49–0.89% and 1.14–1.79%, respectively. Based on these results, it can be stated that the method used to analyze the mixture of myristic acid and stearic acid met the criteria of precision (accuracy) and precision.

Existence test of free myristic acid and stearic acid on isopropyl myristic and GMS

In this study, we tested the existence of free myristic acid and stearic acid in isopropyl myristate and GMS. Based on the chromatogram of the analytical results obtained, we did not observe any free myristic acid or stearic acid in the standard isopropyl myristate and GMS. This is consistent with the information contained in the data sheet for each substance, which does not indicate the presence of free myristic acid or stearic acid in isopropyl myristic and GMS.

Data stability analysis of anti-aging cream samples

In this study, we analyzed the stability of samples of anti-aging creams after 0, 1, 2, and 3 months. Before the analysis, each sample was dissolved first using a 4:1 (v/v) methanol:toluene solution, then reacted with acetyl chloride (1 µL) and no heating. After that, 5.0 mL

of 6% solution of potassium carbonate was added and the solution was centrifuged at 3000 rpm for 5 min. The toluene layer formed was then injected into the GC system at 1 µL.

In this study, the Lepage esterification procedure used was modified for the amount of added acetyl chloride reagent, that is, from 200 µL to 1 µL and without the use of heating. This was due to the excessive use of acetyl chloride and heating time for 60 min, which can cause GMS to decompose entirely into stearic acid, as well as isopropyl myristate to decompose entirely into myristic acid. Reactions that occur as a result of the hydrolysis of the ester compound can lead to the ester compound decomposing into a carboxylic acid in the presence of a catalyst, in the form of heat or acid. If such reactions occur in a cream base that does not decompose, it can hinder the process of decomposition analysis and the stability preparation test. In samples from the monthly stability tests, there were fatty acids, namely myristic acid and stearic acid, present into the 3rd month. The levels of myristic acid and stearic acid contained in each sample as a result of decomposition were calculated using a linear regression equation with concentrations corresponding to the range of the obtained content.

Based on our analysis results the levels of isopropyl myristate and GMS decreased from 0 to 3 months. Thus, the average level of isopropyl myristate remaining in the sample was equal to 99.6283%, 99.1995%, 98.2571%, and 97.1511% from months 0 to 3, respectively (Table 3). The average GMS content remaining was 99.6791%, 98.2881%, 96,2247%, and 93.7195% from months 0 to 3, respectively (Table 4). Increased levels of isopropyl myristate and GMS were found to degrade into myristic acid and stearic acid, which can occur due to the hydrolysis reaction of the ester compound. This reaction occurs due to the water content contained in the cream, and the glycolic acid aids as a catalyst to accelerate the reaction. Thus, the longer the carboxylic acid ester compound is exposed to the water content and the acid catalyst, the more the ester compound decomposes and forms the carboxylic acid, that is, free fatty acids.

CONCLUSION

The results of the anti-aging cream stability test indicated that the average remaining levels of isopropyl myristate from 0 to 3 months were 99.6283%, 99.1995%, 98.2571%, and 97.1511%, respectively. The remaining levels of GMS were 99.6791%, 98.2881%, 96.2247%, and 93.7195 from 0 to 3 months, respectively. The expiration date of the anti-aging cream product was calculated using zero-order kinetics and determined to be 10 months and 9 days. Increased levels of isopropyl myristate and GMS degraded into myristic acid and stearic acid occur due to the hydrolysis reaction of the ester compound.

CONFLICTS OF INTEREST

All authors have none to declare.

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