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Research Article

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Contribution to the Physical Stability Study of Compounded Medications Based on Zinc Oxide, Titanium Dioxide and Precipitated Sulfur Using Emulsified Solid Fats as Vehicles

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Abstract

Background: *This investigation evaluated the physical stability of zinc oxide, precipitated sulfur and titanium dioxide suspensions using three solid fats as emulsified vehicles: stearyl alcohol, stearic acid and beeswax.*

Method: *Varying the concentration of solid fat (2%, 4%, 6%) and the agitation speed for the preparation of the emulsified vehicle (250, 500 and 750 rpm). Here 81 suspensions were prepared, 27 for each solid fat used. The apparent viscosity was measured using a Brookfield RVTD rotational viscometer. The selection of revolutions per minute and spindle used in the viscometer was carried out taking into account the need to obtain a reading in the instrument greater than 10.0, in accordance with the recommendation of the equipment manufacturer. The sediment volume was measured using identical graduated bottles.*

Results: *The effects that were studied as indicators of the physical stability of the suspensions were: sediment volume, apparent viscosity and ease of resuspension. This analysis indicated that the selection of the solid fat is a parameter significantly influential, which supports the data obtained through the investigation. Higher sediment volumes were obtained by increasing the concentration of the emulsified fat and increasing the speed of agitation, favoring thixotropic behavior in suspensions.*

Conclusion: *In terms of physical stability and ease of resuspension, the best results were obtained when emulsified stearyl alcohol was used as a vehicle.*

Keywords: Compounded Medications, Emulsions, Physical Stability, Suspensions, Solid Fats

Introduction

In current dermatological therapeutics, water-insoluble inorganic therapeutic agents such as sulfur, zinc oxide and titanium dioxide are still used. One of the most commonly used pharmaceutical forms in this field are suspensions, in both compounded medications and in products manufactured on an industrial scale.

Preferably, any suspension should form a bulky sediment that is easy to resuspend. Also, it is desirable that its rheological behavior is thixotropic.

Although there are countless excipients that can be used in suspensions, there is little information about the application of solid fat emulsions as a vehicle in topical suspensions. In this research paper, the physical stability of suspensions constituted by three solids frequently used in dermatology was evaluated. Solid emulsified fats were used as vehicles to establish the suitability of the fats, the surfactants and the process parameters that will be used in the preparation of the suspensions. The results of this study may support those who work in the formulation of these suspensions.

Importance of the Physical Stability Study of Compounded Medications

Pharmaceutical compounding is a part of Pharmacy, which is exclusive to the pharmacist, unlike others that are shared with other health professionals, such as nutrition or pharmacotherapy [1]. Compounded medications are intended for a specific patient; they are prepared by a pharmacist or under his direction to expressly comply with a detailed medical prescription [2]. It represents a tool to solve problems that occur in daily clinical practice, such as the shortage of medicines prepared by the industry, the development of medicines for rare diseases, individualized therapies in patients in special situations or the fractionation of expensive medicines [1].

Dermatological diseases are characterized by alterations in the structure and functionality of the skin. These processes can have diverse etiologies influenced by genetic, social, professional, age, race and geographic location. Individualized patient care is essential for effective treatment of dermatological diseases.

Localized treatment on the skin (epidermis and/or dermis) or mucous membranes is sought from compound medications. Dermatologists and pharmacists work closely to offer an individualized treatment that meets the patients' specific skin care needs [3,4].

Stearyl alcohol, stearic acid and beeswax in the oil phase are very important to promote skin hydration. The use of lotions and creams is typically the best way to hydrate the skin, due to the presence of moisturizers, emollients and occlusive agents [5].

Titanium dioxide and zinc oxide can be physical filters that reflect or deflect the sun's radiation, forming an opaque barrier that acts as small mirrors, providing protection against UVA, UVB, visible light and infrared [6,7]. They also have antimicrobial activity [8,9]. In combination, zinc oxide is an effective therapeutic alternative in the treatment of chronic venous ulcers, because it is effective in reducing the size of the ulcer in 63.1%, with scarring greater than 50% of the ulcers' surface after eight weeks of treatment [10]. It has also been defined as a skin protector, which is used in the treatment of diaper rash [11,12].

Sulfur precipitated in ointments (5% and 10%) are widely used for the treatment of scabies in infants under 2 months and pregnant women [13,14]. This is a parasitic disease with more than 300 million cases in the world [15]. It can also be used for the treatment of acne, blackheads, fungus and pimples [16].

Aspects about Physical Stability of Suspensions

In compounded suspensions, the correct formulation must meet certain criteria. The dispersed particles must have a size that does not cause them to settle rapidly in the container. If there is sedimentation, the sediment must not form a hard paste but must be capable of redispersion with minimal effort by the patient [17].

Another desirable feature is that the suspension particles flocculate [18]. The particles should not bind tightly or form a hard and dense paste. The sediment might be easy to redisperse, re-forming the original suspension. There should be rapid sedimentation and the presence of an evident clear supernatant region [19].

Thixotropy is particularly useful in the formulation of pharmaceutical suspensions and emulsions since they must easily tip over on their containers. This implies low viscosity, which causes rapid sedimentation of solid particles in suspensions and rapid cream formation in emulsions. If the suspension or the emulsion have thixotropic behavior, the agitation temporarily breaks the structure of the formulation reducing the apparent viscosity, which allows it to tip over easily. Once the product is on the shelf, the viscosity slowly increases again preventing sedimentation and suspended particles to paste. This forms cream between the emulsion droplets, which cause the suspended particles to be trapped again in the plastic matrix [17].

Materials and Methods

In this research paper, the physical stability of suspensions of zinc oxide, precipitated sulfur and titanium dioxide in vehicles prepared by emulsification of three solid fats was evaluated, considering the effect of formulation and process variables.

The following methodology aspects are listed below:
The following hardly wettable solids were studied:
- Zinc oxide
- Precipitated Sulfur
- Titanium dioxide

The basic qualitative formula of the vehicle is as follows:
- Active ingredient
- Solid Fat
- Nonionic surfactants
- Glycerin
- Preservatives
- Water

The solid fats studied are the following:
- Stearyl alcohol
- Stearic acid
- Bee wax

The following non-ionic surfactants were used:
- Tween 80
- Ceteareth 20 (Eumulgin B2)
- Ceteareth 12 (Eumulgin B1)
- Span 60

The selection of these surfactants and the weighted amounts calculation was made based on the HLB required and the HLB of the surfactants in each case.

The effects that were evaluated as indicators of the physical stability of the suspensions are the following:
1. Volume of sediment versus time (determined every 15 days).
2. Apparent viscosity (measured at the beginning and end of the study).
3. Ease of resuspension (made four months after the preparation was done).

The apparent viscosity was measured using a Brookfield RVTD rotational viscometer. The selection of revolutions per minute and spindle used in the viscometer was carried out taking into account the need to obtain a reading in the instrument greater than 10.0, in accordance with the equipment manufacturer's recommendation.

The sediment volume was measured using graduated bottles of identical dimensions. The resuspension facility was determined by shaking the bottle 5 times by simple inversion and observing if no sediment remained adhered to the bottom of the container.

The formulation and process variables that were studied are the following:
1. Type of solid fat.
2. Solid fat concentration (2%, 4%, 6%).
3. Agitation speed for emulsion preparation (250, 500,750 rpm).

The following variables were kept constant:
1. Concentration of the active ingredient: 5%.
2. Glycerin concentration: 10%.
3. Surfactant concentration: 2%.
4. Emulsification temperature: 75 ° C.
5. Volume to prepare: 90 mL.
6. Observation time: 4 months.
7. Observation interval: every 15 days.

General Procedure for Preparing Suspensions

1. The solid fat is melted together with the surfactants at 75 ° C.
2. Water is heated to 75 ° C.
3. Both phases are mixed (normal emulsification) using an electric

stirrer with adjustable speed, maintaining the stirring until room temperature is reached.

4. The parabens are dissolved in glycerin.
5. The solution of parabens and glycerin is mixed in a mortar with the solid to be suspended until a homogeneous paste is obtained.
6. The emulsion obtained in step three is added on the dispersion of the solid in glycerin. It is mixed in the mortar.
7. Pack in graduated glass uniform size jars (see materials).

Notes

- The solid was previously screened by a 710-micron sieve.
- Tables 1, 2 and 3 detail the suspension formulations. Eighty-one suspensions were prepared, 27 for each solid fat used.

Table 1: Studied Suspensions' Basic Formulation Utilizing Stearyl Alcohol
Emulsified to Different Concentrations (2%, 4%, 6%) Variating Agitation Speed 8250, 500, 750 Rpm) and Active Ingredients (Zinc Oxide, Precipitated Sulfide, Titanium Dioxide)

CODE	BASIC FORMULA		
At 2% ZnO	Rx		%w/w
At 2% ZnO 250 rpm	ZINC OXIDE	....	5.000
	STEARYL ALCOHOL	....	2.000
	CETEARETH 20	....	0.970
At 2% ZnO 500 rpm	CETEARETH 12	....	1.030
	GLYCERIN	....	10.00
	METHYLPARABEN	....	0.150
At 2% ZnO 750 rpm	PROPYLPARABEN	....	0.050
	DISTILLED WATER	....	80.80
At 4% ZnO	Rx		%w/w
At 4% ZnO 250 rpm	ZINC OXIDE	....	5.000
	STEARYL ALCOHOL	....	4.000
	CETEARETH 20	....	0.970
At 4% ZnO 500 rpm	CETEARETH 12	....	1.030
	GLYCERIN	....	10.00
	METHYLPARABEN	....	0.150
At 4% ZnO 750 rpm	PROPYLPARABEN	....	0.050
	DISTILLED WATER	....	78.80
At 6% ZnO	Rx		%w/w
At 6% ZnO 250 rpm	ZINC OXIDE	....	5.000
	STEARYL ALCOHOL	....	6.000
	CETEARETH 20	....	0.970
At 6% ZnO 500 rpm	CETEARETH 12	....	1.030
	GLYCERIN	....	10.00
	METHYLPARABEN	....	0.150
At 6% ZnO 750 rpm	PROPYLPARABEN	....	0.050
	DISTILLED WATER	....	76.80
At 2% S	Rx		%w/w
At 2% S. 250 rpm	PRECIPITATED SULFUR	....	5.000
	STEARYL ALCOHOL	....	2.000
	CETEARETH 20	....	0.970
At 2% S. 500 rpm	CETEARETH 12	....	1.030
	GLYCERIN	....	10.00
	METHYLPARABEN	....	0.150
At 2% S. 750 rpm	PROPYLPARABEN	....	0.050
	DISTILLED WATER	....	80.80
At 4% S	Rx		%w/w

At 4% S. 250 rpm	PRECIPITATED SULFUR	....	5.000
	STEARYL ALCOHOL	....	4.000
	CETEARETH 20	....	0.970
At 4% S. 500 rpm	CETEARETH 12	....	1.030
	GLYCERIN	....	10.0
	METHYLPARABEN	....	0.150
At 4% S. 750 rpm	PROPYLPARABEN	....	0.050
	DISTILLED WATER	....	78.80
At 6% S	Rx		%w/w
At 6% S. 250 rpm	PRECIPITATED SULFUR	....	5.000
	STEARYL ALCOHOL	....	6.000
	CETEARETH 20	....	0.970
At 6% S. 500 rpm	CETEARETH 12	....	1.030
	GLYCERIN	....	10.00
	METHYLPARABEN	....	0.150
At 6% S. 750 rpm	PROPYLPARABEN	....	0.050
	DISTILLED WATER	....	76.80
At 2% TiO_2	Rx		%w/w
At 2% TiO_2 250 rpm	TITANIUM DIOXIDE	....	5.000
	STEARYL ALCOHOL	....	2.000
	CETEARETH 20	....	0.970
At 2% TiO_2 500 rpm	CETEARETH 12	....	1.030
	GLYCERIN	....	10.00
	METHYLPARABEN	....	0.150
At 2% TiO_2 750 rpm	PROPYLPARABEN	....	0.050
	DISTILLED WATER	....	80.80
At 4% TiO_2	Rx		%w/w
At 4% TiO_2 250 rpm	TITANIUM DIOXIDE	....	5.000
	STEARYL ALCOHOL	....	4.000
	CETEARETH 20	....	0.970
At 4% TiO_2 500 rpm	CETEARETH 12	....	1.030
	GLYCERIN	....	10.00
	METHYLPARABEN	....	0.150
At 4% TiO_2 750 rpm	PROPYLPARABEN	....	0.050
	DISTILLED WATER	....	78.8
At 6% TiO_2	Rx		%w/w
At 6% TiO_2 250 rpm	TITANIUM DIOXIDE	....	5.000
	STEARYL ALCOHOL	....	6.000
	CETEARETH 20	....	0.970
At 6% TiO_2 500 rpm	CETEARETH 12	....	1.030
	GLYCERIN	....	10.00
	METHYLPARABEN	....	0.150
At 6% TiO_2 750 rpm	PROPYLPARABEN	....	0.050
	Distilled Water	....	76.80

Table 2: Sedimentation Volume (In Cubic Centimeters) with Respect to the Time (In Days) of Stearyl Alcohol Suspensions

Suspensions	Sedimentation Volume							
	15 Days	30 Days	45 Days	60 Days	75 Days	90 Days	105 Days	120 Days
At 2% ZnO 250 rpm	17.8	17.2	16.4	16.1	16.0	15.3	15.0	14.1
At 2% ZnO 500 rpm	30.3	29.3	27.1	26.9	25.2	25.1	24.3	23.8
At 2% ZnO 750 rpm	58.6	58.0	57.9	56.3	56.3	55.9	55.4	55.1
At 4% ZnO 250 rpm	41.5	39.2	37.8	36.0	34.6	34.1	33.7	32.9
At 4% ZnO 500 rpm	48.2	46.5	45.8	45.4	45.3	45.1	44.9	44.5
At 4% ZnO 750 rpm	59.0	58.3	57.3	57.2	57.1	56.8	56.6	56.4
At 6% ZnO 250 rpm	44.4	44.1	42.1	40.2	39.1	39.0	38.9	38.8
At 6% ZnO 500 rpm	56.2	56.2	55.8	55.7	55.0	54.0	54.0	53.9
At 6% ZnO 750 rpm	46.4	44.0	43.8	42.6	42.1	41.5	41.0	40.7
At 2% TiO_2 250 rpm	27.4	2.6	2.1	1.8	1.5	1.2	1.2	1.2
At 2% TiO_2 500 rpm	40.4	39.7	37.9	36.7	35.9	34.8	34.5	34.0
At 2% TiO_2 750 rpm	73.5	73.5	72.7	72.3	71.5	71.5	71.2	70.9
At 4% TiO_2 250 rpm	10.3	8.5	8.2	7.8	6.5	6.3	6.2	6.0
At 4% TiO_2 500 rpm	51.7	51.3	51.0	50.3	49.7	49.5	49.1	48.5
At 4% TiO_2 750 rpm	60.0	59.2	57.3	56.4	55.9	55.3	55.0	54.9
At 6% TiO_2 250 rpm	23.7	22.3	21.7	21.2	20.8	19.9	19.5	19.2
At 6% TiO_2 500 rpm	48.3	48.0	47.3	46.5	46.2	45.9	45.4	44.0
At 6% TiO_2 750 rpm	43.6	41.7	38.0	36.7	35.4	35.2	34.3	33.9
At 2% S. 250 rpm	4.6	4.4	3.8	3.5	2.9	2.5	2.0	1.9
At 2% S. 500 rpm	4.4	4.3	3.3	2.9	2.6	2.3	2.1	2.1
At 2% S. 750 rpm	6.2	5.9	5.8	5.3	5.0	4.9	4.9	4.8
At 4% S. 250 rpm	4.2	4.1	3.5	3.2	3.0	3.0	3.0	2.8
At 4% S. 500 rpm	4.7	4.3	4.2	4.1	3.9	3.3	3.1	2.2
At 4% S. 750 rpm	7.7	7.2	6.8	6.3	6.1	5.6	5.3	4.9
At 6% S. 250 rpm	3.5	3.2	3.0	3.0	2.9	2.5	2.5	2.3
At 6% S. 500 rpm	4.9	4.5	4.6	4.2	4.0	3.8	3.5	3.5

At 6% S. 750 rpm	22.9	22.7	21.9	20.2	20.1	20.0	19.9	19.9

Table 3: Initial and Final Apparent Viscosity in Centipoise of Sterile Alcohol Suspensions. Observation Time: One Hour

Suspensions	Inicial (cp)	Rheological Behavior	Final (cp)	Rheological Behavior
At 2% ZnO 250 rpm	42 100 rpm spindle 3	Non-Thixotropic	151-120 100 rpm spindle 3	Thixotropic
At 2% ZnO 500 rpm	36 100 rpm spindle 3	Non-Thixotropic	93-76 100 rpm spindle 3	Thixotropic
At 2% ZnO 750 rpm	207-172 100 rpm spindle 3	Thixotropic	193-148 100 rpm spindle 3	Thixotropic
At 4% ZnO 250 rpm	137 100 rpm spindle 3	Non-Thixotropic	87 100 rpm spindle 3	Non-Thixotropic
At 4% ZnO 500 rpm	179-159 100 rpm spindle 3	Thixotropic	110 100 rpm spindle 3	Non-Thixotropic
At 4% ZnO 750 rpm	267-219 100 rpm spindle 3	Thixotropic	187-161 100 rpm spindle 3	Thixotropic
At 6% ZnO 250 rpm	78-100 50 rpm spindle 3	Rheopectic	74-98 50 rpm spindle 3	Rheopectic
At 6% ZnO 500 rpm	128-204 50 rpm spindle 3	Rheopectic	224-266 50 rpm spindle 3	Rheopectic
At 6% ZnO 750 rpm	3710-2320 20 rpm spindle 3	Thixotropic	600-760 50 rpm spindle 3	Rheopectic
At 2% TiO_2 250 rpm	41 100 rpm spindle 3	Non-Thixotropic	40 100 rpm spindle 3	Non-Thixotropic
At 2% TiO_2 500 rpm	26 100 rpm spindle 3	Non-Thixotropic	34 100 rpm spindle 3	Non-Thixotropic
At 2% TiO_2 750 rpm	116-78 100 rpm spindle 3	Thixotropic	71-61 100 rpm spindle 3	Lightly Thixotropic
At 4% TiO_2 250 rpm	131-51 100 rpm spindle 3	Thixotropic	37 100 rpm spindle 3	Non-Thixotropic
At 4% TiO_2 500 rpm	139-58 100 rpm spindle 3	Thixotropic	132-44 100 rpm spindle 3	Thixotropic
At 4% TiO_2 750 rpm	276-218 100 rpm spindle 3	Thixotropic	192-172 100 rpm spindle 3	Thixotropic
At 6% TiO_2 250 rpm	39 50 rpm spindle 3	Non-Thixotropic	39 100 rpm spindle 3	Non-Thixotropic
At 6% TiO_2 500 rpm	60-46 50 rpm spindle 3	Thixotropic	73-59 100 rpm spindle 3	Thixotropic
At 6% TiO_2 750 rpm	1580-972, 972-1112, 1112-618 50 rpm spindle 3	Complex behavior	161-104 100 rpm spindle 3	Thixotropic
At 2% S. 250 rpm	34 100 rpm spindle 3	Non-Thixotropic	64-54 100 rpm spindle 3	Lightly Thixotropic
At 2% S. 500 rpm	28 100 rpm spindle 3	Non-Thixotropic	55-42 100 rpm spindle 3	Thixotropic
At 2% S. 750 rpm	114-74 100 rpm spindle 3	Thixotropic	135-69 100 rpm spindle 3	Thixotropic
At 4% S. 250 rpm	72-52 100 rpm spindle 3	Thixotropic	55-37 100 rpm spindle 3	Thixotropic
At 4% S. 500 rpm	73-55 100 rpm spindle 3	Thixotropic	63-52 100 rpm spindle 3	Thixotropic
At 4% S. 750 rpm	116-79 100 rpm spindle 3	Thixotropic	120-83 100 rpm spindle 3	Thixotropic

At 6% S. 250 rpm	36 50 rpm spindle 3	Non-Thixotropic	39 100 rpm spindle 3	Non-Thixotropic
At 6% S. 500 rpm	56-46 50 rpm spindle 3	Thixotropic	94-68 100 rpm spindle 3	Thixotropic
At 6% S. 750 rpm	1228-404 50 rpm spindle 3	Thixotropic	183-94 100 rpm spindle 3	Thixotropic

Results and Discussion

Suspensions with Stearyl Alcohol

Resuspension problems were found for zinc oxide at the lowest concentration of stearyl alcohol at 250 rpm and 500 rpm ; also, titanium dioxide 2% at the three speeds studied and 4% at 250 rpm and 500 rpm showed resuspension problems. There were no sediments difficult to resuspend in any sulfur suspension at the three concentrations of stearyl alcohol (6%), for zinc oxide and titanium dioxide.

Higher sediment volumes are obtained by increasing the concentration of stearyl alcohol and increasing the speed of agitation. However, in the case of zinc oxide and titanium dioxide with 6% stearyl alcohol, higher volumes of sediment are obtained at 500 rpm, than at 750 rpm.

Regarding rheological behavior using stearyl alcohol as emulsified fat in the vehicle, it is important to point out that the changes occur in some cases after aging for 4 months at room temperature (25-30 °C).

Secondly, there is a tendency to get non-thixotropic suspensions when preparing the vehicle at a low 250 rpm agitation speed, while at the highest 750 rpm speed, thixotropic suspensions are obtained.

Finally, the appearance of rheopexy from zinc oxide was observed at high concentrations of stearyl alcohol.

It is not possible to establish other general trends due to the complex rheological behavior of some samples. Especially sample A (6% TiO2 750 rpm) which was prepared again, obtaining the same results.

The phase division in the emulsified vehicle seems to be related to the difficulty in resuspension for titanium dioxide, at a low and intermediate concentration of stearyl alcohol (2 and 4%), while in other cases, phase separation of the vehicle does not imply difficulty in resuspension.

The presence of hazy supernatant fluid is usually an indicator of the existence of deflocculated suspensions capable of forming compact sediment that is difficult to resuspend and attaches to the bottom of the container. This situation occurred in zinc oxide suspensions at a low concentration of stearyl alcohol (2%) and at a low (250 rpm) and intermediate (500 rpm) stirring speed. There is also a relationship between the difficulty of resuspension and the turbidity of the supernatant in three of the suspensions of titanium dioxide, but it is difficult to establish the influence of the concentration of stearyl alcohol and the speed of agitation in this case.

Neither the presence of foam, nor the appearance of the sediment surface, allows to establish any kind of relationship with the process parameters and the ease of resuspension.

In general terms, it can be said that the resuspension facility is favorable in the case of stearyl alcohol when using intermediate and high concentrations (4% and 6%) of the solid fat and high agitation speed (750 rpm).

Table 4: Qualitative Observations of Stearyl Alcohol Suspensions

Suspensions	Foam presence	Hazy supernatant liquid	Phase division in the emulsified vehicle	Growth of Microorganisms in Culture	Sediment with regular surface	Easy resuspension
At 2% ZnO 250 rpm	NO	YES	NO	NO	YES	NO
At 2% ZnO 500 rpm	NO	YES	NO	NO	YES	NO
At 2% ZnO 750 rpm	NO	YES	NO	NO	YES	YES
At 4% ZnO 250 rpm	NO	YES	YES	NO	YES	YES
At 4% ZnO 500 rpm	NO	YES	NO	NO	YES	YES
At 4% ZnO 750 rpm	YES	YES	NO	NO	YES	YES
At 6% ZnO 250 rpm	YES	YES	NO	NO	YES	YES
At 6% ZnO 500 rpm	YES	YES	NO	NO	YES	YES

At 6% ZnO 750 rpm	YES	YES	YES	NO	YES	YES
At 2% TiO_2 250 rpm	YES	NO	YES	NO	NO	NO
At 2% TiO_2 500 rpm	YES	NO	YES	NO	YES	NO
At 2% TiO_2 750 rpm	YES	YES	YES	NO	YES	NO
At 4% TiO_2 250 rpm	YES	YES	YES	NO	YES	NO
At 4% TiO_2 500 rpm	NO	YES	NO	NO	YES	NO
At 4% TiO_2 750 rpm	NO	YES	NO	NO	YES	YES
At 6% TiO_2 250 rpm	NO	YES	NO	NO	YES	YES
At 6% TiO_2 500 rpm	YES	YES	NO	NO	YES	YES
At 6% TiO_2 750 rpm	YES	YES	YES	NO	YES	YES
At 2% S. 250 rpm	NO	NO	YES	NO	YES	YES
At 2% S. 500 rpm	NO	NO	YES	NO	YES	YES
At 2% S. 750 rpm	NO	NO	YES	NO	YES	YES
At 4% S. 250 rpm	NO	NO	YES	NO	YES	YES
At 4% S. 500 rpm	NO	NO	YES	NO	YES	YES
At 4% S. 750 rpm	NO	NO	YES	NO	YES	YES
At 6% S. 250 rpm	YES	YES	YES	NO	YES	YES
At 6% S. 500 rpm	YES	NO	YES	NO	YES	YES
At 6% S. 750 rpm	YES	YES	YES	NO	YES	YES

Table 5: Comparison of 4% stearyl alcohol prepared suspensions at 750 rpm

Suspensions	Easy Recovery	Initial apparent viscosity (cp)	Initial rheological behavior	Final apparent viscosity (cp)	Final rheological behavior	Sediment volume (cm^3)
At.4%ZnO 750 rpm	Yes	267-219	Thixotropic	187-161	Thixotropic	59
At.4%TiO_2 750 rpm	Yes	276-218	Thixotropic	192-172	Thixotropic	60
At.4% S 750 rpm	Yes	116-79	Thixotropic	120-83	Thixotropic	7.7

Stearic Acid Suspensions

Resuspension difficulties occurred in all cases for zinc oxide and titanium dioxide, while sulfur suspensions could easily be resuspended.

Higher and decreasing or stable in time sediment volumes at the lowest agitation speed (250 rpm) were obtained with zinc oxide, being the greater and more stable sediment at the high concentration (6%) of stearic acid. In the case of titanium dioxide, in some cases an increase in the sediment volume was observed over the time, while in other cases the opposite was observed, being difficult to establish a tendency in this regard.

In the case of sulfur, there is a slight increase in the sediment volume over the time and few differences in relation to the concentration of solid fat and the speed of agitation.

On the other hand, stearic acid does not allow obtaining thixotropic suspensions and apparent viscosities showed little or no differences at the beginning and end of the study period (4 months), and for all cases it ranges between 19-35 centipoise.

In all suspensions prepared with stearic acid, hazy supernatant liquid and phase separation in the emulsified vehicle were obtained. The turbidity of the supernatant is consistent with the increase in the sediment volume observed in several cases, which gives suspicion of the deflocculated suspension formation.

In general terms, stearic acid emulsion is not an appropriate vehicle for zinc oxide or titanium dioxide, while sulfur forms suspensions that, despite their low sediment volume, easily resuspend and are not influenced by solid fat concentration and agitation speed.

Beeswax Suspensions

When Titanium dioxide is used, beeswax as emulsified fat does not allow obtaining suspensions with a sediment that is easy to resuspend. Only an easy resuspension for zinc oxide was obtained using beeswax at the highest concentration (500 and 750 rpm). All sulfur suspensions were resuspended without difficulty.

In relation to the volume of sediment there is no clear trend regarding the effect of the concentration of beeswax and the speed of agitation.

It can be affirmed in the case of zinc oxide that only the combination of high concentration of beeswax (6%) and the intermediate speed of agitation (500 rpm) allow obtaining a high sediment volume (40-50 cm 3). With titanium dioxide, a higher sediment volume was obtained with a high concentration of beeswax (6%) and at a high stirring speed (750 rpm). Sulfur suspensions have a lower influence of the agitation speed on the sediment volume over time as the concentration of beeswax increases.

With respect to rheological behavior, all suspensions prepared with beeswax are non-thixotropic except for the three suspensions of zinc oxide with the high concentration (6%) of beeswax. Of these three suspensions, the one that was prepared at 250 rpm lost its thixotropic behavior after four months according to the result obtained. The other two suspensions (C. 6% ZnO 500 rpm, C.6% ZnO 750 rpm) retained thixotropic behavior with an increase in apparent viscosity and were the only Zinc oxide suspensions that were easily resuspended. The Zinc Oxide suspension with 6% beeswax prepared at 500 rpm was more viscous and had a greater sediment volume.

In all beeswax suspensions a hazy supernatant liquid was obtained that could indicate the formation of deflocculated suspensions.

Phase separation in the emulsified vehicle was absent in all zinc oxide suspensions. Phase separation of the vehicle was observed in the titanium dioxide suspension with the low concentration (2%) of beeswax and low agitation speed (250 rpm) and the suspension with high concentration (6%) of beeswax and high agitation speed (750 rpm). All sulfur suspensions presented phase separation in the emulsified vehicle.

Conclusion

The methodology used in this study allows making comparisons regarding the physical stability of zinc oxide, titanium dioxide, and precipitated sulfur suspensions, using solid emulsified fats as a vehicle.

In terms of physical stability and ease of resuspension, for the three solids studied, the best results were obtained when emulsified stearyl alcohol was used as a vehicle.

Using a 4% concentration of solid fat and stirring speed of 750 rpm, favored physical stability and ease of resuspension when using stearyl alcohol, obtaining thixotropic suspensions.

Neither stearic acid nor beeswax allowed satisfactory results in terms of physical stability and ease of resuspension applicable to the three suspended solids.

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To the department of industrial pharmacy.

References

1. Anxo FF, Miguel GB, Francisco OE, José BM, María Jesús L (2016) Challenges in masterful ophthalmic formulation. Hospital pharmacy 40: 1-2.
2. Hugo JO (2011) Use of master formulas in pediatrics. Mexico Pediatric Act 32: 175-176.
3. Maybe CC, Ivón AA (2017) Level of compliance with the Technical Health Standard No. 122 – MINSA / DIGEMID – V. 01 in prescription of dermatological magisterial formulas attended in three Specialized Pharmaceutical Offices. Lima, Peru: Wiener University.
4. Juan de Arco OZ (2016) The Masterful Formulation of the XXI Century. Current overview of the drug 40: 106-115.
5. Yunisley MR (2017) Influence of technological and formulation variables on the quality and stability of cosmetic creams. "Marta Abreu" Central University of Las Villas.
6. Elena DM, María Teresa CP, Sofía CS (2003) The sun and sunscreens. Medifam 13: 159-165.
7. Claudia SB, Isabel OC, Carlos RV, Gloria DS, Noemí A, et al. (2018) Congenital Erythropoietic Porphyria: A case report and management recommendations. Argentine Archives of Pediatrics 116: e300-e302.
8. Raquel OP, Monserrat CN (2017) Mini Vehicles for the treatment of bacterial infection EN. Spain: Complutense University of Madrid.
9. William V, Carlos DU, Karen N, Roger V, Jorge William A, et al. (2016) Study of the antimicrobial activity of thin films of silver modified titanium dioxide. Magazine of the Colombian Academy of Exact, Physical and Natural Sciences 40: 69-74.
10. Mario Adán ME, José M, Jorge CG (2016) Effect of a polysaccharide polymer with zinc oxide in reducing the size of chronic venous ulcers. Mexican Journal of Angiology. 44: 67-71.
11. María del Mar SOG, Luisa DG, Francisco Alberto CV, Verónica NR, Dulce SO, et al. (2016) Comparative efficacy study between two diapers for the prevention and treatment of diaper dermatitis. Mexico Pediatric Act 37: 310-321.
12. Olesksander N, Mohamed NB, Frédéric P (2016) Current Progress in Rheology of Cellulose Nanofibril Suspensions. Biomacromolecules 17: 2311–2320.

13. Rita del Cisne TR (2017) Protective and risk factors related to dermatological infections in children from 1 to 3 years of age in Zone 7 of Ecuador. Ecuador: National University of Loja.
14. Ministerio del Poder Popular para la Salud (2018) Guide for the syndromic management of Sexually Transmitted Infections (STIs). Bolivarian Republic of Venezuela Ministry of Popular Power for Health 2018.
15. Danilo Paúl SA (2017) Clinical and epidemiological characterization of patients with a diagnosis of scabies at the Quisapincha Health Center from 2014 to 2016. Ecuador: Autonomous Regional University of the Andes.
16. Rosa Elizabeth PC, Oscar Vinicio MP (2013) Manufacture of solid toilet soaps such as sulphurous, moisturizing and exfoliating from yausabara gel (pavonia sepium). Ecuador: Northern Technical University.
17. Riedel C, Alegria A, Colmenero J, Tordjem P (2012) Polymer Rheology by Dielectric Spectroscopy. In: Rheology, Juan De Vicente. InTech 3-28.
18. Maria PL (2020) Chapter 10: Rheology. In: Applied Physical Pharmacy, Cary M, Mansoor M, Thomas C, Third Edition. New York: McGraw-Hill 1-33.
19. Alessandra C, Jefferson L, Víctor Carlos P (2011) Rheology of high performance concrete applied in civil construction - Review. Ceramics 57: 63-75.