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STABILITY STUDY OF LIQUID PARAFFIN ORAL EMULSION (CREMAFFIN)

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ABSTRACT

Stability studies ensuring the maintenance of product quality, safety and efficacy throughout the shelf life are considered as pre-requisite for the acceptance and approval of any pharmaceutical product. These studies are required to be conducted in a planned way following the guideline issued by ICH, WHO and or other agencies. Importance of various methods followed for stability testing of pharmaceutical products, guideline issued for stability testing and other aspects related to stability of pharmaceutical products have been presented in a present review.

Keywords: Stability, Stability studies, Stability testing

INTRODUCTION

Stability testing of pharmaceutical products is a complex set of procedures involving considerable cost, time consumption and scientific expertise in order to build in quality, efficacy and safety in a drug formulation. Stability of a pharmaceutical product may be defined as the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, toxicological, protective and informational specifications. In other words, it is the extent to which a product retains, within the specified limits, throughout its period of storage and use, the same properties and characteristics possessed at the time of its packaging. Stability testing thus evaluates the effect of environmental factors on the quality of the a drug substance or a formulated product which is utilized for prediction of its shelf life, determine proper storage conditions and suggest labeling instruction. Creamaffin as an emulsion, is a thermodynamically unstable system consisting of at least two immiscible liquid phases, one of which is dispersed as globules in the other liquid phase, stabilized by the presence of an emulsifying agent.

1. Emulsion stability refers to the ability of an emulsion to resist change in its properties over time.
2. There are four types of instability in emulsions: flocculation, creaming, coalescence, and Ostwald ripening.
3. Flocculation occurs when there is an attractive force between the droplets, so they form flocs, like bunches of grapes. Coalescence occurs when droplets bump into each other and combine to form a larger droplet, so the average droplet size increases over time
4. Emulsions can also undergo creaming, where the droplets rise to the top of the emulsion under the influence of buoyancy, or under the influence of the centripetal force induced when a centrifuge is used.
5. An appropriate "surface active agent" (or "surfactant") can increase the kinetic stability of an emulsion so that the size of the droplets does not change significantly with time. It is then said to be stable.

Objectives: The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product as the Drug products varies with time, Under the influence of a variety of enviromental factors such as temperature, humidity and light. To establish a re-test period for the drug substance. And also shelf life for the drug product and recommended storage condition. Emulsifying

agents are needed to decrease the surface tension and to stabilize the droplets.

TABLE 17-3. *Classification of Surfactants for Pharmaceutical Emulsions*

	*Typical Representatives**	*Utility*
Anionic Group		
Carboxylic acids	Soap	T
	Lactylates	TO
	Polypeptide condensates	T
Sulfuric acid esters	Sulfated monoglycerides	TO
	Alkyl sulfates	TO
Alkyl and alkyl-aryl sulfonates	Dodecylbenzene sulfonates	T
Phosphoric acid esters	Trioleyl phosphate	T
Substituted alkyl amides	Sarcosinates	TO
	Taurates	T
Hemiesters	Sulfosuccinates	TO
Cationic Group		
Amines	Alkoxyalkylamines	T
Quaternaries	Benzalkonium chloride	T
Amphoteric Group		
Ammonium carboxylates	N-alkylaminoacids	TO
Ammonium phosphates	Lecithin	TOP
Nonionic Group		
Polyalkoxyethers	Polyoxyethylene alkyl/aryl ethers	T
	Polyoxyethylene polyoxypropylene block polymers	TOP
Polyalkoxyesters	Polyoxyethylene fatty acid esters	TO
	Polyoxyethylene sorbitan acid esters	TO
Polyalkoxyamides		T
Fatty acid esters of polyhydric alcohols	Sorbitan esters	TO
	Glyceryl esters	TO
	Sucrose esters	TO
Fatty alcohols	Lauryl alcohol	T

*Illustrative examples only.
T = some representatives useful in topicals.
O = some representatives useful in oral preparations or ingested drugs.
P = some representatives useful in parenterals.

METHODS

Stability testing is a routine procedure performed on drug substances and products and is employed at various stages of the product development.

1. Real-Time stability testing
2. Accelerated stability testing
3. Retained sample stability testing
4. Cyclic temperature stress testing.

Physical stability of emulsion

Creaming: **Creaming is the upward movement of dispersed droplets of emulsion relative to the continuous phase (due to the density difference between two phases)**

Stoke's law: dx/dt = d2 (□i-□e)g/18□
dx/dt = rate of setting
D = diameter of particles
ρ = density of particles and medium
g = gravitational constant
η = viscosity of medium

- Breaking, coalescence, aggregation
- Breaking is the destroying of the film surrounding the particles.
- Coalescence is the process by which emulsified particles merge with each to form large particles.
- Aggregation: dispersed particles come together but do not fuse.
- The major fact preventing coalescence is the mechanical strength of the interfacial film.

Phase inversion: An emulsion is said to invert when it changes from an o/w to w/o or vice versa.

Preservation of emulsions

- Growth of microorganisms in emulsions
- Preservatives should be in aqueous phase.
- Preservatives should be in unionized state to penetrate the bacteria
- Preservatives must not bind to other components of the emulsion

Methods of emulsion preparation

- Continental or dry gum method

- English of wet gum method
- Bottle or Forbes bottle method
- Auxiliary method
- In situ soap method

- Cremaffin (400 ml) (Liquid Paraffin, Milk of Magnesia) from Abbott India Ltd
- Manufacturer: Abbott
- Contents: CREMAFFIN oral emulsion: liquid paraffin 3.75 mL, magnesium hydroxide 11.25 mL/15 mL.
- Indications: Symptomatic relief of constipation in patients with cardiovascular disease, hernia, anorectal disorders & post-operative conditions.
- Dosage: Adult & child over 12 yrs: 7.5-15ml; child 5-12 yrs: 5-10ml; child 2-5: 2.5-5ml. Dose best taken at bedtime preferably with water & if necessary, again in the morning or as reqd.
- class: Laxative, purgative

This study was carried out by Dry gum method (4:2:1 method).

- In a mortar, the 1 part gum (e.g., acacia) is levigated with the 4 parts oil until the powder is thoroughly wetted; then the 2 parts water are added all at once, and the mixture is vigorously and continually triturated until the primary emulsion formed is creamy white.
- Additional water or aqueous solutions may be incorporated after the primary emulsion is formed. Solid substances (e.g., active ingredients, preservatives, color, flavors) are generally dissolved and added as a solution to the primary emulsion. Oil soluble substance, in small amounts, may be incorporated directly into the primary emulsion. Any substance which might reduce the physical stability of the emulsion, such as alcohol (which may precipitate the gum) should be added as near to the end of the process as possible to avoid breaking the emulsion. When all agents have been incorporated, the emulsion should be transferred to a calibrated vessel, brought to final volume with water, then homogenized or blended to ensure uniform distribution of ingredients.

Preparing emulsion by dry gum method

- Cod liver oil 50 mL
- Acacia 12.5 g
- Syrup 10 mL
- Flavor oil 0.4 mL
- Purified water, qs ad 100 mL
- Accurately weigh or measure each ingredient
- Place cod liver oil in dry mortar
- Add acacia and give it a very quick mix
- Add 25 mL of water and immediately triturate to form the thick, white, homogenous primary emulsion
- Add the flavor and mix
- Add syrup and mix
- Add sufficient water to total 100 mL

Figure 1: Stability chamber for stability testing.

<u>Three different storage condition for stability testing</u>

- Long term 25±2°C/60±5% RH
- Intermediate 30±2°C/65±5% RH
- Accelerated 40±2°C/75±5% RH

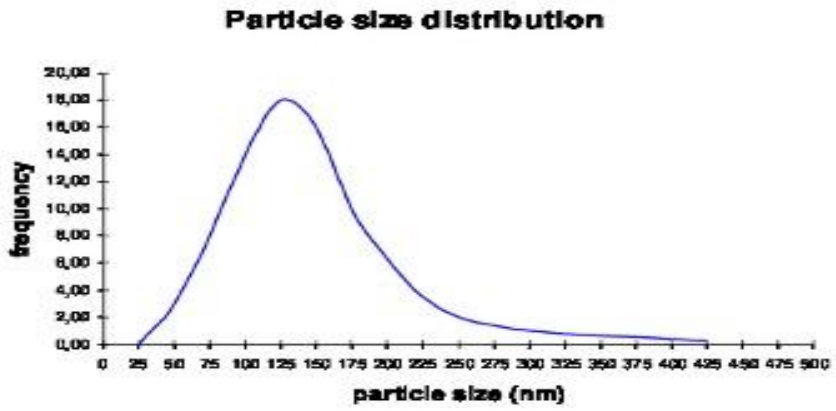
The storage conditions to be selected are based upon the climatic zone in which the product is intended to be marketed or for which the product is proposed to be filed for regulatory approval. General recommendations on the storage conditions have been given by ICH, CPMP and WHO. The abridged/indicative ICH and WHO storage conditions for drug products have been given.

RESULTS

IPQC test for stability testing:

1. Appearance: In a graduated glass cylinder or transparent glass container
2. Color
3. Odor
4. Taste

5. pH value: pH meter
6. Viscosity: Brookfield viscometer
7. Particle size: Optical microscopy, Sedimentation method , Conductivity method (coulter counter method)
8. Density: specific gravity bottle
9. Drug content uniformity.



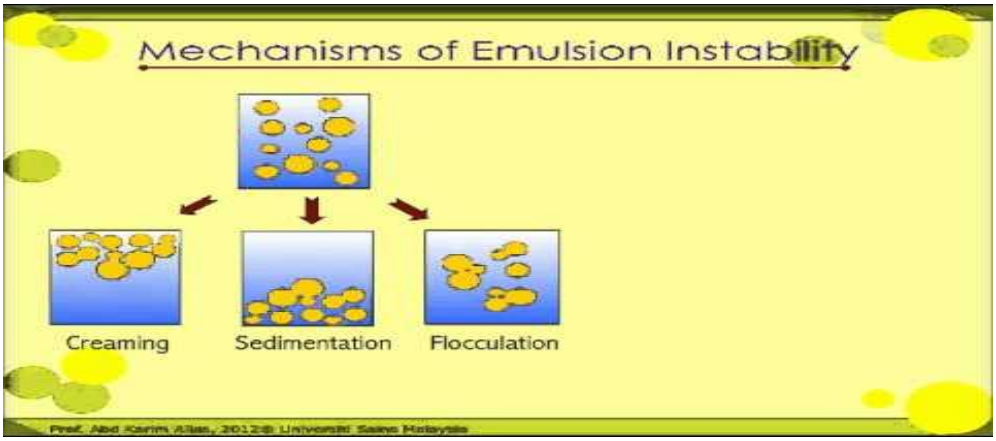


Table 1: Evaluation data for cremaffin; Temp: 25±2°C/60±5% RH.

Evaluation parameter	Market product(cremaffin)					
	0 day	7 day	15 day	21 day	30 day	45 day
Organoleptic propertise						
Color	white	White	white	white	white	White
Odor	Minty	Minty	Minty	Minty	Minty	Minty
Taste						
Appereance	good	good	good	good	good	Good
pH value	10	10	10	10	10	10
Viscosity (cps)	499.9	499.9	499.9	499.9	499.9	499.9
Density	0.9337	0.9337	0.9337	0.9337	0.9337	0.9337
Content of uniformity	uniform	uniform	uniform	uniform	uniform	uniform
Particle size(µm)	13.2	12.5	12.7	11.5	13.5	12.2

Table 2: Evaluation data for cremaffin; Temp: 30±2°C/65±5% RH.

Evaluation parameter	Market product(cremaffin)					
	0 day	7 day	15 day	21 day	30 day	45 day
Organoleptic propertise						
Color	white	white	white	white	white	White
Odor	Minty	Minty	Minty	Minty	Minty	Minty
Taste						
Appereance	good	good	good	good	good	Good
pH value	10	10	10	10	10	10
Viscosity(cps)	359.9	359.9	359.9	359.9	359.9	359.9
Density	0.9337	0.9337	0.9337	0.9337	0.9337	0.9337
Content of uniformity	uniform	uniform	uniform	uniform	uniform	uniform
Particle size(µm)	12.9	13.1	12.5	11.3	13.4	12.2

Table 3: Evaluation data for cremaffin; Temp: 40±2°C/75±5% RH.

Evaluation parameter	Market product(cremaffin)					
	0 day	7 day	15 day	21 day	30 day	45 day
Organoleptic propertise						
Color	white	white	white	white	white	White
Odor	Minty	Minty	Minty	Minty	Minty	Minty
Taste						
Appereance	good	good	good	good	good	Good
pH value	10	10	10	10	10	10
Viscosity(cps)	279.9	279.9	279.9	279.9	279.9	279.9
Density	0.9337	0.9337	0.9337	0.9337	0.9337	0.9337
Content of uniformity	uniform	uniform	uniform	uniform	uniform	uniform
Particle size(µm)	12.5	12.1	11.8	12.6	12.3	12.6

DISCUSSION

From the results, it was observed that at 25±2°C/60±5% RH there was no change in organoleptic properties including color, odor, and taste, which indicates that the palatability of tested product would remain uniform throughout its shelf life.Also, there was no any significant difference in PH, viscosity, and specific gravity of samples tested at different time intervals.So, it can be inferred that the tested product is physically stable at given tested condition.

Parability of the sample was remained uniform throughout testing intervals. This indicate that the physical structure of formulation remained intact.This inference can also be supported by the physical evaluation data including average globule size and its distribution. Accelerated centrifugation study revealed stability of put only for 30 day. Samples tested only 45th day showed creaming, which indicated sign of instability.

From the results, it was observed that at 30±2°C/65±5% RH there was no change in organoleptic properties including color, odor, and taste, which indicates that the palatability of tested product would remain uniform throughout its shelf life. Also, there was no any significant difference in PH, viscosity, and specific gravity of samples tested at different time intervals. So, it can be inferred that the tested product is physically stable at given tested condition.

Parability of the sample was remained uniform throughout testing intervals. This indicate that the physical structure of formulation remained intact.
This inference can also be supported by the physical evaluation data including average globule size and its distribution. Accelerated centrifugation study revealed stability of put only for 30 day. Samples tested only 45th day showed creaming, which indicated sign of instability.

From the results, it was observed that at 40±2°C/75±5% RH there was no change in organoleptic properties including color, odor, and taste, which indicates that the palatability of tested product would remain uniform throughout its shelf life. Also, there was no any significant difference in PH, viscosity, and specific gravity of samples tested at different time intervals. So, it can be inferred that the tested product is physically stable at given tested condition. Parability of the sample was remained uniform throughout testing intervals. This indicate that the physical structure of formulation remained intact. This inference can also be supported by the physical evaluation data including average globule size and its distribution.

Accelerated centrifugation study revealed stability of put only for 30 day. Samples tested only 45th day showed creaming, which indicated sign of instability.

CONCLUSION

In a nutshell, from the results it can be concluded that the sample of CREMAFFIN® is physically stable at different conditions 25±2°C/60±5% RH, 30±2°C/65±5% RH, 40±2°C/75±5% RH for 45 days. Only it sign of instability at 45th day upon excessive centrifugation.

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