

STABILITY OF EMULSION

The stability of an emulsion must be considered in terms of physical stability of emulsion system and the physical and chemical stability of the emulsion component including pharmacologically active ingredients, if any.

Definition: A physically stable emulsion component may be defined as a system in which the globules retain their initial character and remain uniformly distributed throughout the continuous phase.

Symptoms of instability

As soon as an emulsion has been prepared, time and temperature dependent processes occur to effect its separation. During storage, an emulsion's stability is evidenced by (i) creaming, (ii) flocculation and / or (iii) coalescence.

CREAMING

Creaming is the upward or downward movement of dispersed droplets related to the continuous phase due to the difference of density between two phases.

N.B. The downward creaming is also called sedimentation. Generally the term "sedimentation" is associated with the downward movement of solid particles in suspension.

Creaming is undesirable in a pharmaceutical product where homogeneity is essential for the administration of correct and uniform dose. It may still be pharmaceutically acceptable as long as it can be reconstituted by a modest amount of shaking. However, in case of cosmetic products creaming is usually unacceptable because it makes the product inelegant.

Creaming or sedimentation brings the particle closer together and may facilitate a serious problem of coalescence.

The rate at which a spherical droplet or particle sediments in a liquid is governed by Stoke's equation.

$$v = \frac{d^2(\rho_1 - \rho_2)g}{18\eta}$$

where v = velocity of creaming
 d = diameter of globule
 ρ_1, ρ_2 = densities of dispersed phase and continuous phase respectively
 η = viscosity of the continuous medium

A consideration of this equation shows that the rate of creaming will be decreased by:

- (i) reduction of droplet size
 - (ii) a decrease in the density difference between the two phases
 - (iii) increase in the viscosity of the continuous phase
- *Reduction in droplet size* is done by using an efficient homogeniser or colloid mill. There are, however, technical difficulties in reducing the diameter of droplets to below about 0.1 μm .
 - Stoke's equation predicts that no creaming is possible if the specific gravities of the two phases are equal. A few successful attempts have been made to equalize the densities of the oil and aqueous phase. This method is of little use in pharmaceutical practice because, it usually involves the addition of substances those are unacceptable in pharmaceutical preparations.
 - The most frequently used approach is to raise the viscosity of the continuous phase although this can be done to the extent that the emulsion still can be removed readily from its container and spread on the body surface conveniently.

FLOCCULATION

Flocculation of the dispersed phase may take place before, during or after creaming.

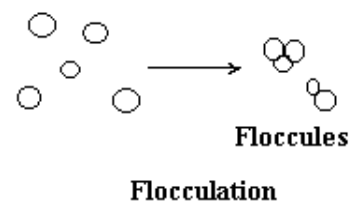
Flocculation is reversible aggregation of droplets of the internal phase in the form of three-dimensional clusters.

In the floccules the droplets remain aggregated but intact. The droplets can remain intact when the mechanical or electrical barrier is sufficient to prevent droplet coalescence.

e.g. if an insufficient amount of emulsifier is present, emulsion droplets aggregate and coalesce.

The reversibility of this type of aggregation depends on the strength of the interaction between particles, as determined by:

- (i) the chemical nature of the emulsifier,
- (ii) the phase-volume ratio, and
- (iii) the concentration of dissolved substances, especially electrolytes.

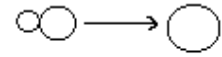


The viscosity of an emulsion depends to a large extent on flocculation, which restricts the movement of particles and can produce a fairly rigid network. Agitation of an emulsion breaks the particle-particle interactions with a resulting drop of viscosity; i.e. shear thinning.

COALESCENCE

Coalescence is a growth process during which the emulsified particles join to form larger particles.

Any evidence for the formation of larger droplets by merger of smaller droplets suggests that the emulsion will eventually separate completely.



Coalescence

The major factor which prevents coalescence in flocculated and deflocculated emulsions is the mechanical strength of the interfacial barrier. Thus macromolecules and particulate

solids forms thick interfacial film – and hence natural gums and proteins are useful as auxiliary emulsifiers when used at low level, but can even be used as primary emulsifiers at higher concentrations.

Any agent that will destroy the interfacial film will crack the emulsion. Some factors are:

- (i) the *addition of a chemical* that is incompatible with the emulsifying agent. Examples include surfactants of opposite ionic charges, addition of large ions of opposite charge, addition of electrolytes such as Ca and Mg salts to emulsions stabilized with anionic surfactants.
- (ii) *Bacterial growth*: Protein materials and non-ionic surfactants are excellent media for bacterial growth.
- (iii) *Temperature change*: Protein emulsifying agent may be denatured and the solubility characteristics of non-ionic emulsifying agents change with a rise in temperature. Heating above 70°C destroys almost all emulsions. Freezing will crack an emulsion; this may be due to the ice-crystals disrupting the interfacial film around the droplet.

EVALUATION OF EMULSION

SHELF LIFE

The final acceptance of an emulsion depends on stability, appearance, and functionality of the packaged product.

There is no quick and sensitive methods for determining potential instability in an emulsion are available to the formulator. To speed up the stability test program the emulsion is subjected to various stress conditions.

The stress conditions normally employed include:

- (i) aging and temperature
- (ii) centrifugation, and
- (iii) agitation

Aging and temperature

It is routine to determine the shelf life of all types of preparations by storing them for varying periods of time at temperatures that are higher than those normally encountered. A particularly useful means of evaluating shelf life is cycling between two temperatures preferably between 4⁰ and 45⁰C.

The normal effect of aging an emulsion at elevated temperature is acceleration of the rate of coalescence or creaming, and this is usually coupled with changes in viscosity.

Centrifugation

Stoke's law shows that creaming is a function of gravity (g), and an increase in gravity therefore accelerates separation. Centrifugation at 3750 rpm in a 10-cm radius centrifuge for a period of 5 hours is equivalent to the effect of gravity for about one year. Thus shelf-life under normal storage conditions can be predicted rapidly by observing the separation of the dispersed phase due to either creaming or coalescence when the emulsion is exposed to centrifugation.

Agitation

Droplets in an emulsion exhibit Brownian movement. Coalescence takes place when droplets impinge upon each other. Simple mechanical agitation contributes to the energy with which two droplets impinge upon each other.

Thus agitation can also break emulsion. A typical case is the manufacture of butter from milk.

Conventional emulsions may deteriorate from gentle rocking on a reciprocating shaker. This works in two ways:

- (i) increases the rate of impingement of droplets, and
- (ii) reduction of viscosity of a normally thixotropic system.

PHYSICAL PARAMETERS

The most useful parameters commonly are measured to assess the effect of stress conditions on emulsions include

1. phase separation,

2. viscosity,
3. electrophoretic properties, and
4. particle size analysis and particle count.

Phase separation

The rate and extent of phase separation after aging of an emulsion may be observed visually or by measuring the volume of separated phase.

A simple means of determining phase separation due to creaming or coalescence involves withdrawing a samples of the emulsion from the top and the bottom of the preparation after some period of storage and comparing the composition of the two samples by appropriate analysis of water content, oil content, or any suitable constituent.

Viscosity

The viscosity of an emulsion for the use of shelf studies is not concerned with absolute values of viscosity, but with changes in viscosity during aging. Since emulsions are generally non-Newtonian systems and the viscosity is measured by viscometer of the cone-plate type are particularly useful for emulsions, but instruments utilizing co-axial cylinders (e.g. cup and bob viscometer) are the easiest to use. The use of a penetrometer is often helpful in detecting changes of viscosity with age.

In case of w/o emulsions flocculation is quite rapid. After flocculation viscosity drops quickly and continues to drop for some time (5 to 15 days at room temperature).

In case of o/w emulsions globule flocculation causes an immediate increase in viscosity. After this initial change, almost all emulsions show changes in viscosity with time which follow a linear relationship when plotted on a log-log scale.

A practical approach for the detection of creaming or sedimentation, before it becomes visibly apparent, utilizes the Helipath attachment of the Brookfield viscometer

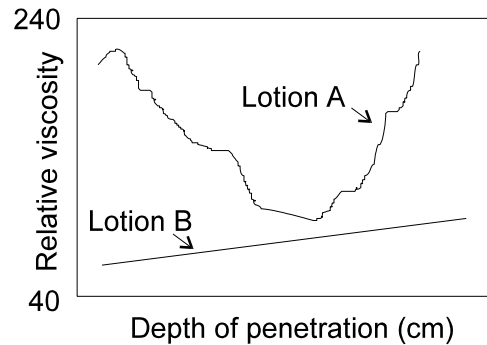
N.B. The Brookfield viscometer determines the resistance encountered by rotating spindle or cylinder immersed in a viscous material. The Helipath attachment slowly lowers the rotating spindle into the medium so that the resistance measured is always that of previously undisturbed test substances.

As a result of emulsion separation, the descending rotating spindle meet varying resistance at different levels and registers fluctuations in viscosity.

Example

Lotion A in the figure contains solids suspended in an emulsion, and the high viscosity near the top is due to non-wetted solid and creamed emulsion; the high viscosity at the lower level is due to sedimented particles.

The addition of polyoxyethylene monooleate (SAA) and methyl cellulose (viscosity enhancer) in lotion B yields a much more uniform viscosity pattern after eight weeks storage.

**Electrophoretic properties**

If the instability of the emulsion is due to flocculation only (and not due to coalescence) then the zeta potential will have to be measured.

Zeta potential can be determined with

- (i) the aid of the moving boundary method or
- (ii) more quickly and directly, by observing the movement of particles under the influence of electric current.

The zeta potential is especially useful for assessing flocculation since electrical charges on particles influence the rate of flocculation.

The measurement of electrical conductivity has been claimed to be a powerful tool for the evaluation of emulsion shortly after preparation.

Particle size number analysis

Changes of the average particle size or of the size distribution of droplets are important parameters for evaluating emulsions.

Particle size determination can be carried out by microscopic method or by electronic counting machines. (e.g. Coulter counter). Light scattering and related reflectance relationships have been used for particle size determination.

The utility of particle size for predicting or interpreting emulsion shelf-life is somewhat doubtful.

Practical recommendation for shelf-life prediction in temperate (hot and humid) zone

A typical test program for an “acceptable” emulsion (in temperate zone) may be as follows:

The emulsion should be stable with no visible signs of separation for at least:

- (i) 60 to 90 days at 45 or 50°C,
- (ii) 5 to 6 months at 37°C and
- (iii) 12 to 18 months at room temperature.
- (iv) After 1 month storage at 4°C
- (v) After 2 to 3 freeze-thaw cycles between -20 and +25°C.
- (vi) After 6 to 8 freeze-thaw cycles between 4 and 45°C with storage at each temperature for not less than 48 hours.
- (vii) No deterioration by centrifuging at 2000 to 3000 rpm at room temperature.
- (viii) No deterioration by agitation for 24 to 48 hours on a reciprocating shaker (≈ 60 cycles per minute) at room temperature and at 45°C.