

STABILITY OF PHARMACEUTICAL PRODUCTS

Abstract

The world of drug delivery is getting every day more efficient with new product forms, which are directly targeting the deficient organs. Colloidal systems such as emulsions (simple or multiple) or nanoparticle suspensions are now widely used as drug carriers or nutritional solutions in this respect. These new product forms allow better targeting and assimilation for the patient, and give rise to new solutions for drug designers. However, the stability of these inherently unstable colloidal systems makes them complex to formulate and study.

The Turbiscan[®] technology is a unique and complete tool, which enables the study of the colloidal dispersions stability without any dilution or modification of the product. Destabilization processes can be identified and quantified easily up to 50 times earlier than the naked eye. Determining shelf life can be automated *via* the use of the ageing station, Turbiscan ags.

Keywords: emulsion, suspension, nanoparticles, shelf life, stability, Turbiscan[®].

Introduction

Many products available in the pharmaceutical industry are liquid dispersions (cream, syrup, suspension, aerosol etc.), even if tablets remain the most common product form. The stability of these formulations is not only critical from the esthetical side, but more importantly from the health point of view, as an unstable product can lead to serious health issues, even to death (e.g. particle size increase in a parenteral emulsion can lead to embolism).

The Turbiscan[®] range provides the formulator with a complete set of tools to investigate the stability of formulations developed. The different instability phenomena (creaming, sedimentation, flocculation, coalescence) can be identified and quantified *via* different parameters, allowing an objective analysis to be made. Shelf life can be determined up to 50 times earlier than visual observation, allowing the development time for new products to be significantly reduced. The stability measurements can also be completely automated using the robotized ageing station, Turbiscan ags.

Experimental procedure

1. Principle of the measurement

The heart of the optical scanning analyser, Turbiscan[®], is a detection head, which moves up and down along a flat-bottom cylindrical glass cell (Figure 1)¹⁻². The detection head is composed of a pulsed near infrared light source ($\lambda = 880$ nm) and two synchronous detectors. The transmission detector (at 180°) receives the light, which goes

through the sample, while the backscattering detector (at 45°) receives the light scattered backward by the sample. The detection head scans the entire height of the sample, acquiring transmission and backscattering data every 40 μ m. The Turbiscan LAB can be thermo-regulated from 4 to 60°C and linked to a fully automated ageing station (Turbiscan ags) for long-term stability analyses. Increasing temperature is the ideal parameter to accelerate destabilisation processes, while maintaining realistic testing conditions.

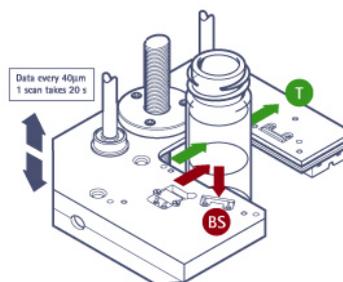


Figure 1. Principle of Turbiscan[®] measurement

The Turbiscan[®] makes scans at various pre-programmed times and overlays the profiles on one graph in order to show the destabilisation. Graphs are usually displayed in reference mode, whereby the first profile is subtracted to all other profiles, in order to enhance variations. A stable product has all the profiles overlaid on one curve (Figure 2), as an unstable formulation shows variations of the profiles (Figure 3). Backscattering and/or transmission fluxes are shown in ordinate and the height of the cell in abscissa (Figure 2 and 3). The first profile is displayed in pink, the last one in red.

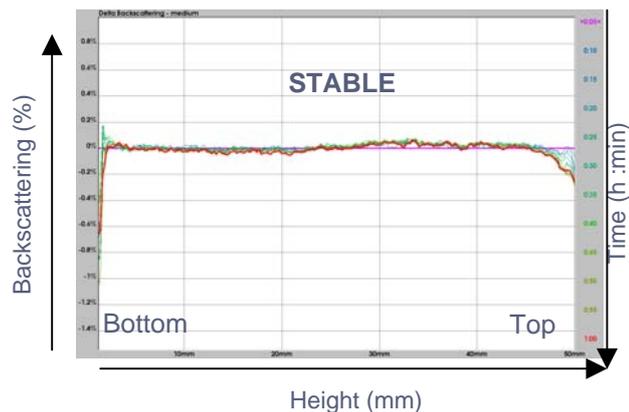


Figure 2. Superposition of scans with time for a stable sample

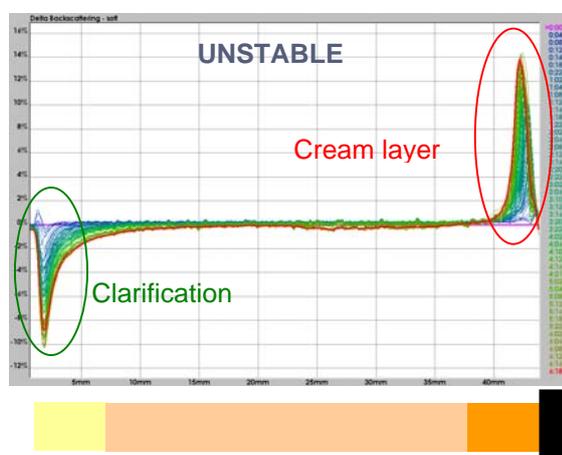


Figure 3. Superposition of scans with time for an unstable sample (creaming)

2. Instability detection

The measurement principle of the Turbiscan® range is based on multiple light scattering (MLS), where the photons are scattered many times by the particles / droplets of the dispersions before being detected by the backscattering detector. The intensity of the light backscattered by the sample depends on three parameters: the diameter of the particles, their volume fraction and the relative refractive index between the dispersed and continuous phases. Therefore, any change due to a variation of the particle size (flocculation, coalescence) or a local variation of the volume fraction (migration phenomena: creaming, sedimentation) is detected by the optical device.

a. Particle size variation

Figure 4, the variation of the backscattering level is shown as a function of the particle diameter for a fixed volume fraction of latex particles.

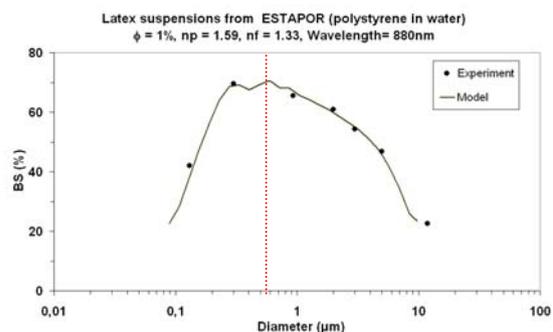


Figure 4. Backscattering level versus diameter for latex particles at 1%

The curve obtained is a bell shaped curve, where the top is linked to the wavelength of the incident light (880 nm). For particles smaller than the incident light (left part of the curve), an increase of particle size is showed by an increase in backscattering. For particles bigger than the incident light (right part of the curve), an increase in size leads to a decrease in backscattering.

On the Turbiscan® profiles, the particle size variations are displayed by a variation of the backscattering level over the total height of the sample (Figure 5).

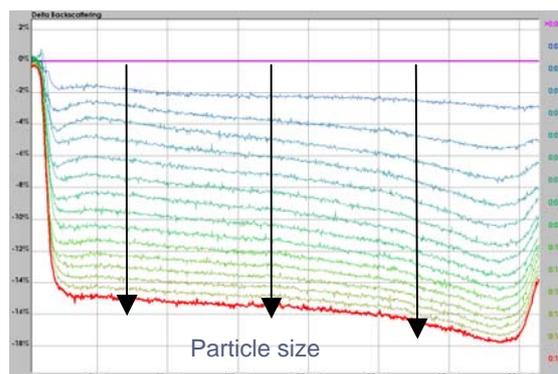


Figure 5. Typical profiles for flocculation phenomenon (initial size = 1µm)

b. Migration phenomena

Migration phenomena (sedimentation or creaming) lead to local variation of the concentration of particles in the sample.

Figure 6, the variation of transmission and backscattering levels are shown as a function of the volume fraction for a fixed diameter of latex particles.

If the concentration of particles is smaller than the critical concentration ϕ_c , the product can be considered as diluted and the transmission level decreases with an increase in concentration.

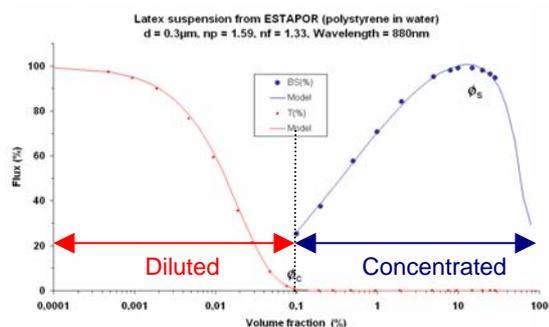


Figure 6. Transmission (red) and backscattering (blue) levels versus volume fraction for latex particles of $0.3 \mu\text{m}$

When the concentration is sufficient ($\phi > \phi_c$), there is no transmission signal (opaque product) and the backscattering level increases with an increase of the volume fraction.

When the concentration of particles becomes too high ($\phi > \phi_s$), the backscattering level starts to decrease as the distance between particles is smaller than the wavelength of incident light. This phenomenon is called dependent diffusion and is mostly observed for small particles ($< 1 \mu\text{m}$).

On the Turbiscan® profiles migration phenomena are displayed by local variations of the backscattering. Figure 7, the backscattering level decreases at the top (right part of the graph), due to a decrease of the concentration of particles, hence a clarification, while it increases at the bottom due to the increase of particle concentration consecutive to the sediment formation. It is interesting to note that there is no variation in the middle of the sample, indicating no particle size variation.

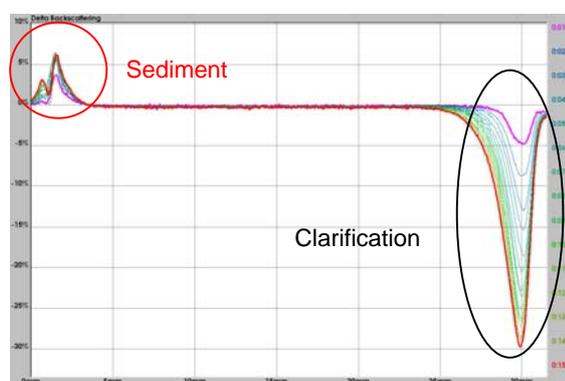


Figure 7. Typical backscattering profiles for a sedimentation phenomenon.

3. Materials

In this paper, results from different pharmaceutical products are presented. These products have been analysed at different temperatures.

For each experiment, the sample was shaken before use and 7 or 20 mL (for the Turbiscan Classic and LAB respectively) was sampled in a borosilicate glass cell. The cell is then closed with a stopper and placed in the Turbiscan®.

Results and Discussion

1. Stability of nanoparticles from emulsions

Nanoparticles are used as carriers for drug delivery as they enable to protect the drug from degradation and if the particle is properly grafted it can be used for triggered release in order to deliver the drug in the right place at the right time. Nanoparticles are commonly produced from nanoemulsions, as it enables to obtain control size and shape particles. It is therefore necessary to control the stability of these nanoemulsions in order to obtain homogeneous nanoparticles.

Gref *et al.*^{3,4} report the preparation of nanoparticles from emulsions containing copolymers (dextran and polycaprolactone) with various solvents. After sonication a nanoemulsion is obtained and the nanoparticles are formed after evaporation of the solvent (migration of the copolymers at the interface and solvent evaporation). Nanoparticles of around 100nm can be obtained *via* this process. Depending on the solvent used to prepare the emulsion, different stability profiles are observed.

First, with methylene chloride, where the copolymer is fairly soluble, the profiles (Figure 8) show a large coalescence together with sedimentation of the droplets (methylene chloride is more dense than water). At the bottom, we can also see that the sediment layer is coalescing.

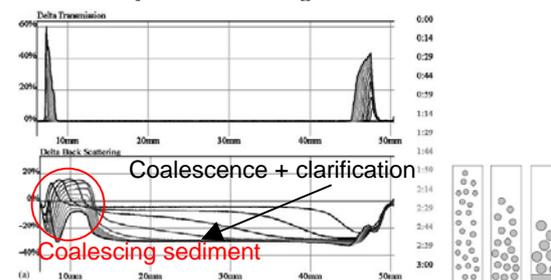


Figure 8. Turbiscan profiles for methylene chloride nanoemulsion

Using ethyl acetate instead of methylene chloride (Figure 9), no size variation is seen in the sample (no backscattering variation in the middle). Only creaming is visible (ethyl acetate is less dense than water). The clarification is visible both in backscattering and transmission.

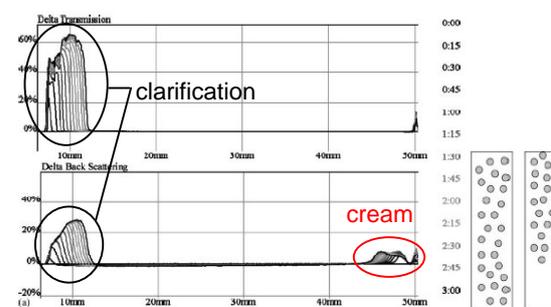


Figure 9. Turbiscan profiles for ethyl acetate nanoemulsion

In the preparation of nanoparticles from nanoemulsion droplets, it is important to control the size of the droplets, as they are directly related to the size of the particles formed. Therefore, it is important to avoid all aggregation phenomenon in the emulsion, in order to obtain controlled size nanoparticles. Using ethyl acetate as solvent leads to more stable nanoemulsions, hence better nanoparticles.

2. Stability of Total Parenteral Nutrition emulsions

Total Parenteral Nutrition (TNP) emulsions are used to feed patient who cannot take solid food. They are composed of all the vital components for health (lipids, carbohydrates, amino-acids, vitamins, etc.) and can be added with antibiotic, analgesic, etc. The size of the oil droplets is generally situated around 200nm. However, if coalescence or flocculation occurs, the droplet size can dramatically increase and provoke embolism. It is generally recognised that risk occurs when the size is greater than 5µm.

Pirot *et al.*⁵ report the use of the Turbiscan technology to follow the stability of TNP emulsions and show the detection of creaming at an early stage compared to visual detection (Figure 10).

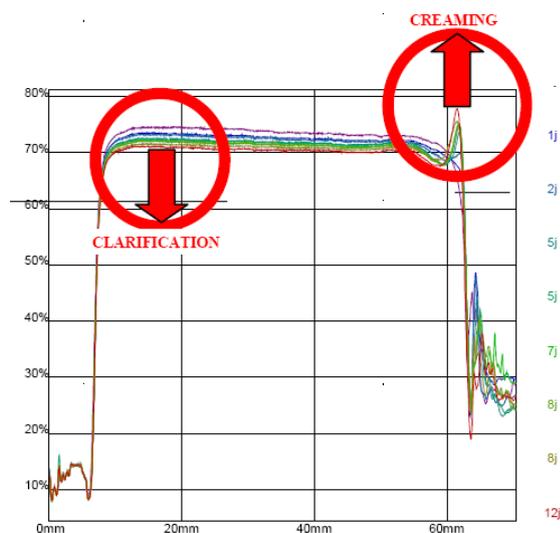


Figure 10. Backscattering profiles for TNP at 37°C.

They also studied the effect of temperature on the creaming kinetics (Figure 11), giving a linear relationship for the different formulations they analysed.

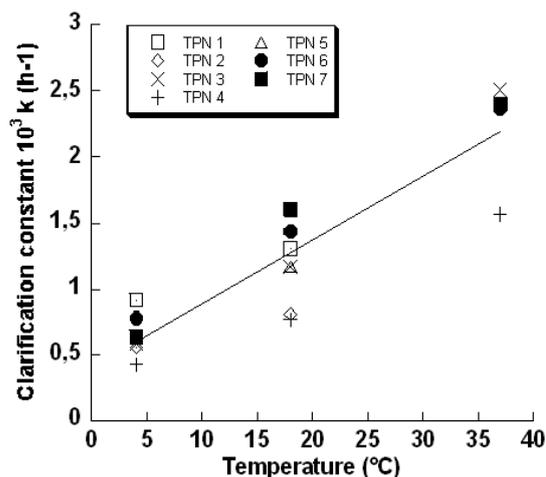


Figure 11. Linear relationship between temperature and clarification kinetics.

Adding molecules like antibiotic, salts etc. can be necessary depending on the patient requirements but this may also affect the stability of TNP emulsions. In the following graph we present analysis of a TNP emulsion where antibiotic was added (Figure 12).

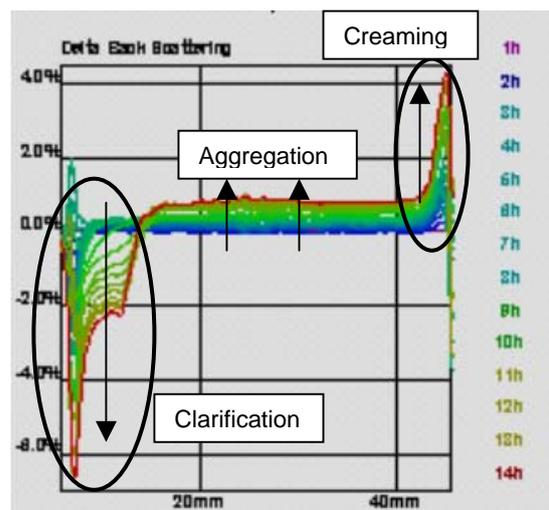


Figure 12. Delta backscattering for TNP + antibiotic

The profiles show an increase of the backscattering in the middle of the sample, which is typical of a particle size increase phenomenon (coalescence or flocculation). It is also possible to see a decrease of the backscattering at the bottom, due to a decrease of the droplet concentration in that part of the sample and simultaneously an increase at the top, as the droplets migrate from the bottom to the top, hence a creaming phenomenon.

3. Stability of ophthalmic suspensions

Ophthalmic suspensions are commonly used as anti-inflammatory agent for eye diseases. These suspensions have to be shaken before use, in order to redispersed the particles, which have settled at the bottom of the container. However, in some cases the sediment forms a cake at the bottom and it is

not any more possible to redisperse the drug particles, hence the product loses its curing properties. Different surfactants can be used to ensure repulsion between the drug particles, and avoid this aggregation mechanism in the sediment.

Klinke *et al.*⁶ report the sedimentation behaviour of dexamethasone suspensions formulated with different surfactants using the Turbiscan technology. Figure 13, the transmission profiles are displayed (a) with dexamethasone alone, (b) with dexamethasone + 0.01% benzalkonium chloride, and (c) with dexamethasone + 0.01% polysorbate 80.

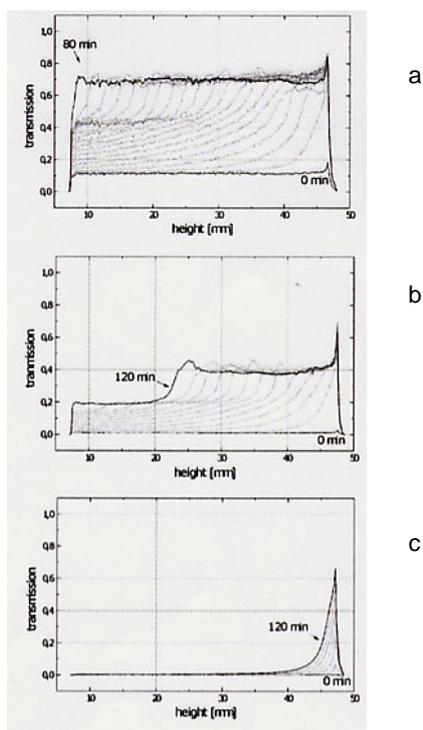


Figure 13. Transmission profiles (a) with dexamethasone alone, (b) with dexamethasone + 0.01% benzalkonium chloride, and (c) with dexamethasone + 0.01% polysorbate 80.

The shape of the clarification phase, as shown in transmission, informs about the sedimentation behaviour of the drug particles. In cases (a) and (b) the profiles show an important clarification and a step in the profile, which is characteristic of a two steps sedimentation mechanism, hence an aggregation of the sediment. In case (c), the clarification is less intense and the shape of the profile does not display any packing of the sediment. The use of polysorbate 80, is therefore the most appropriate to stabilize this suspension of dexamethasone particles.

Conclusion

The Turbiscan[®] is a flexible and complete tool, which enables to study in depth the stability of many different pharmaceutical products in order to improve the formulations regarding stability. The use of the ageing station gives an additional

dimension to the equipment, by making automatic analyses over long time and with multi-operator access.

With the Turbiscan[®], stability tests become easier and quicker, which enable to deliver new products in less time while ensuring good quality products with objective analysis.

References

1. Mengual, O., Meunier, G., Cayre, I., Puech, K., Snabre, P. (1999) Characterisation of instability of concentrated dispersions by a new optical analyser: the TURBISCAN MA 1000, Colloids and Surfaces A: Physicochemical and Engineering Aspects, 152 (1), 111-123.
2. Bru, P., Brunel L., Buron H, Cayré I., Ducarre X., Fraux A., Mengual O., Meunier G., de Sainte Marie A., (2004) Particle size and rapid stability analyses of concentrated dispersions: Use of multiple light scattering, ACS Symposium series 881ed T. Provder and J. Texter, 45-60.
3. C. Lemarchand, P. Couvreur, C. Vauthier, D. Costantini, R. Gref, "Study of emulsion stabilization by graft copolymers using the optical analyser Turbiscan" *Int. J. Pharm* 254 2003 77-82
4. C. Lemarchand, P. Couvreur, M. Besnard, D. Costantini, R. Gref, "Novel polyester-polysaccharide nanoparticles", *Pharmaceutical Research*, 20-8 2003 1284-1292
5. V. Baradel, H. Constant, F. Falson, F. Pirot "Study of Parenteral Emulsion Stability using the Optical Analyzer Turbiscan[®]", *Pharmaceutical Science Fair 2005*
6. B. Klinke, R. Süverkrüp "Sedimentation characterisation of dexamethasone ophthalmic suspensions by near infrared turbidimetry"