Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 339 (2007) 189–196
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Predictive stress tests to study the influence of processing procedures on long term stability of supersaturated pharmaceutical o/w creams

Peter Fischer[a], Andreas Eugster[b], Erich J. Windhab[a], Michael Schuleit[b,*]

[a] *Swiss Federal Institute of Technology (ETH Zürich), Institute of Food Science and Nutrition, Schmelzbergstrasse 9, 8092 Zürich, Switzerland*
[b] *Novartis Pharma AG, Pharmaceutical & Analytical Development, P.O. Box, 4002 Basel, Switzerland*

Received 9 March 2006; received in revised form 12 January 2007; accepted 2 March 2007
Available online 12 March 2007

Abstract

Partial coalescence in emulsions is a destabilization mechanism whereby the droplets retain their individual identity but there is a molecular contact between their content. This process can occur under fluctuating temperatures and/or shear stress, which effects the stability and quality of emulsions. In the case of topical drug delivery systems, in particular supersaturated oil-in-water (o/w) creams, the molecular exchange of dissolved drug from one droplet to the other is a critical issue because it can induce drug crystallization and enhance crystal growth. In this work two approaches to address the problem are reported: the stability of the emulsion in relation to (i) shear exposure and (ii) temperature cycling. Some ideas on how this approach can be used to identify critical process parameters and predict long term stability of supersaturated emulsions are discussed.

Keywords: Partial coalescence; Emulsion processing; Cream; Temperature cycles; Rheology; Emulsion stability

1. Introduction

An emulsion is a fine dispersion of one liquid in a second immiscible liquid. Pharmaceutical creams are semi-solid emulsions which are widely used as a means of altering the physical properties of the skin and as vehicles for the delivery of drugs (Peramal et al., 1997). They need to fulfill several criteria such as the right consistency, safety of the excipients, stability of the immobilized drug and long term physical stability against, e.g. coalescence and crystallization.

Emulsion destabilization mechanisms such as creaming, aggregation, or coalescence disturb and eventually destroy the microstructure (Binks, 1999; McClements, 2004; Walstra et al., 2005). This has a tremendous impact on the desired functionality of the emulsion such as drug delivery properties. In fact the microstructure of pharmaceutical emulsions is of essential importance and has been the subject of considerable studies, both for the purposes of optimizing their physical properties and also for the understanding of the mechanisms to incorporate and release drugs (Eccleston, 1984; Mueller-Goyman and Frank, 1986).

Besides coalescence, emulsion stability can also be affected by changes in the dispersed phase such as fat crystallization or gelation (Coupland, 2002; Rousseau, 2000; Walther et al., 2004). The physical stability of emulsions, in particular of the dispersed droplet phase, is an important factor when considering supersaturated pharmaceutical formulation as drug delivery concepts. The supersaturation concept is used to enhance the skin permeation of lipophilic drugs (Moser et al., 2001). In these formulations physical stability does not include exclusively the physical state of the dispersed emulsion droplets, it also considers the physical state of the drug, which poses a certain thread to emulsion stability. In other words, destabilization phenomena such as flocculation or coalescence, where the droplets get in close contact, might initiate drug crystallization, which in turn might have a negative impact on the bioavailability of the drug substance. In this case both classical coalescence and crystallization of the dispersed phase will lead to an additional destabilization mechanism called partial coalescence (Van Boekel and Walstra, 1981). During partial coalescence, the emulsion droplets retain their shape, but there is a molecular contact between the droplets leading to

* Corresponding author. Tel.: +41 61 324 2699; fax: +41 61 324 7293.
E-mail address: michael.schuleit@novartis.com (M. Schuleit).

0378-5173/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2007.03.013

exchange of the dispersed phase material between the droplets favoring, e.g. crystal growth. Partial coalescence is difficult to identify because the microscopic appearance of the droplets seems not to be affected (especially when dealing with emulsions containing high volume fractions). For example one do not observed macroscopic phase separation typical for classical coalescence.

Many manufacturing processes involving mixing, pumping, stirring or, in our case, filling affect the microstructure by destabilizing the emulsion system, which might reduce shelf-life and performance of the final product (Windhab et al., 2005; Vanapalli and Coupland, 2001; Vanapalli et al., 2002; Hetzel et al., 2000). For this reason emulsion instability acceleration techniques such as (i) subjecting the formulation to temperature changes as well as temperature cycling (freeze thaw) (Thanasukarn et al., 2004; Cramp et al., 2004), (ii) application of high centrifugal forces to detect separation of the emulsion, (iii) application of rheological shear stress (Tadros, 2004), and (iv) subjecting the emulsion to vibration, and successive investigation of the artificially aged emulsion by microscopy have been employed to predict long term stability of the final product.

In this work, we examine both coalescence and crystal formation of supersaturated oil-in-water emulsions creams, which have been processed under various pumping and filling conditions occurring in pharmaceutical processing. The semi-solid cream has been analyzed right after manufacture showing well-dispersed semi-solid emulsion droplets free of drug crystals. However, after several months of storage under ambient conditions (25 °C and 30% humidity) drug crystals, which significantly exceed the size of the dispersed droplets, have been observed. The amount of crystals depends on the manufacturing conditions and, as a consequence, we assume that drug crystallization and crystal growth is not due to the high concentration in the emulsion droplets, but rather to a mechanically initiated crystallization process favored by the process conditions. In this case, predictive investigations that allow to study the impact of manufacturing procedures on (i) the physical state of the emulsion and on (ii) the physical state of the drug itself on a short time scale is of practical interest and relevance for formulation scientists.

To address the aging phenomena of processed supersaturated pharmaceutical formulations and in particular the fat crystal growth leading to partial coalescence we have defined a number of rheological experiments, which are believed to mimic the process conditions such as pumping or filling (Macosko, 1994). We demonstrate that steady shear and large amplitude oscillatory shear flow (LAOS) experiments based on the strain unit concept are valuable tools to simulate manufacturing conditions on a small scale in the laboratory. In combination with traditional temperature cycling tests therefore a comprehensive set of accelerated tests have been applied to a pharmaceutical cream formulation. We will discuss the obtained results towards presenting a predictive tool for both the evaluation of critical process parameters and as a tool for rational formulation screening. The remaining of the manuscript will present a brief introduction into partial coalescence and shear-induced crystallization. The material and method section introduces in particular the rheological experiments and the strain unit concept before the results are presented and discussed.

2. Background of partial coalescence and shear-induced crystallization

Recent literature indicates that partial coalescence in food-based oil-in-water emulsion frequently goes along with crystallization of the lipid phase.

Partial coalescence is a process where a fat crystal from one partially crystalline droplet penetrates into the matrix fluid and/or into the liquid region of another partially crystalline droplet (Van Boekel and Walstra, 1981). A number of studies have been carried out to elucidate the factors that influence the susceptibility of food based oil-in-water emulsions to partial coalescence, with the major factors being the solid fat content, the composition of the interfacial membrane surrounding the droplets (Boode et al., 1991; Walstra et al., 2005), droplet size and shear rate (Boode et al., 1993, 1991). It has been shown that milk fat globules are stable to coalescence when at rest, but unstable under Couette flow (Van Boekel and Walstra, 1981). It was argued that the presence of shear forces increases the rate of collision between droplets and therefore leads to greater tendency towards partial coalescence (Jeelani and Hartland, 1993).

Shear-induced crystallization or shear-enhanced crystallization of fats or lipids is found mainly for food materials such as monoglycerides or triglycerides (e.g. milk fats or cacoa fats) (Sato, 2001 and references therein, Narine and Marangoni, 1999; Mazzanti et al., 2004). The influence of pure and mixed monoglycerides on the emulsion stability was studied by, e.g. Davies et al. (2001). Although in this study the monoglycerides were used as emulsifier (i.e. at small volume fractions) emulsion stability was correlated to crystal formation. In contrast to shear-induced crystallization in long-chain polymer systems it is assumed that it is not the alignment due to shear or strain but rather the interaction probability of the small fat molecule, which is enhanced by the flow (Kumaraswamy, 2005).

The exact temperature of the onset of fat crystallization has been shown to depend on droplet size, presence of impurities and type of emulsifier (Boode and Walstra, 1993). It was also shown that the addition of a small fraction of solid fat droplets to a liquid oil emulsion increased the isothermal crystallization rate of the liquid portion (McClements et al., 1990). The effect of shear rate on the crystallization onset temperature of a sample of confectionary fat shows an acceleration of lipid crystallization by flow (Garbolino et al., 2000). In light of these results it is very likely that fat crystals and the way they crystallize significantly affects emulsion destabilization, i.e. favoring partial coalescence.

However, the knowledge of the influence of the fat properties on the emulsion stability is very limited. The higher the amount of solid fat the greater the proportion of the number of crystals that may protrude from globules causing them to be less stable. It is still unclear in the literature whether there is a minimum and an optimum solid fat content with respect to partial coalescence. Even the number of crystals present in the fat globules is unknown (Boode et al., 1993; Walstra et al., 2005).

The presence of a crystal network connecting the individual droplets allowing the molecular exchange of the droplet's dispersed phase may have a considerable effect on both the emulsion stability and the stability of the immobilized drug. It is known that supersaturated formulations as used in this work are thermodynamically unstable and it is not surprising that the drug re-crystallizes over time. However, similar to the work on food emulsions the relationship between the number of crystals, process conditions and partial coalescence as well as information on the size of the crystal, which exceed the size of the droplets keeps elusive.

3. Materials and methods

3.1. Material

The materials used for the preparation have been: oleyl alcohol (Cognis), triglycerides medium chained (Sasol), glycerol monostearate (Danisco), cetyl alcohol (Cognis), stearyl alcohol (Cognis), sodium cetostearyl sulphate (Cognis), benzyl alcohol (Merck), citric acid (Merck) sodium hydroxide (Merck), propylene glycol (Hedinger) and water. All materials were used as received.

3.2. Flow measurements and strain unit concept

A standard rotational rheometer equipped with a plate–plate geometry (MCR 300, Anton-Paar Physica Rheometer) was used to perform the rheological experiments. The geometry has a diameter of 50 mm and a Peltier element was used to heat or cool the measuring cell as well as the sample volume. The entire cell is covered by an insulation jacket and mounted on an anti-vibration table (Newport Corp.).

Crystal formation is expected to be initiated by high gradient shear flow during the pumping and filling of the emulsion. The motion of the valve is an oscillatory motion between the filling position and the pumping position (see Fig. 1A). During the filling, especially in the valve, high shear rates (10,000 s^{-1} and more) are imposed on the sample. Such shear rates are not easily obtained in rotational rheometers since sample can be expelled from the gap or undergo heating and eventually degradation.

Keeping in mind that the shear rate imposed to a sample can be expressed as the deformation multiplied by the shearing time it is possible to impose significant deformation to the le by shearing the material for a long time. As long as the sample is not destroyed it can be assumed that the overall strain (expressed as strain unit = shear rate times elapsed time) does not depend on the shear rate or the time alone but rather on the product of both. This is expressed by the "strain units" concept, which allows the comparison of experiments performed at high shear rate over short times (i.e. in the filling valve) with experiments at moderate or low shear rate over longer time intervals (i.e. in the plate–plate geometry).

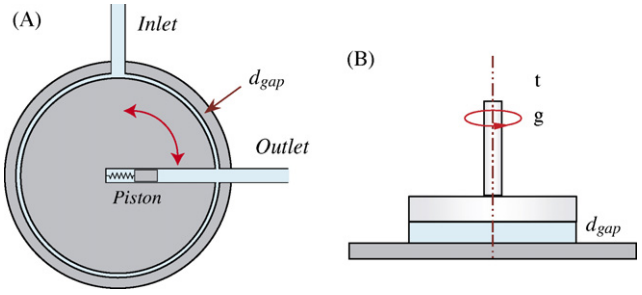

Fig. 1. Set-up: (A) schematic of the filling device and (B) the rheometrical shear cell (plate–plate geometry).

Two rheological experiments were designed to simulate the flow conditions during filling procedure. Shear flow experiments where shear rate is imposed and kept constant during the course of experiment and large amplitude oscillatory shear (LAOS) experiments. In the latter case the movement of the filling valve is simulated by the large deformation experiment. Even though the shear gap in the valve (see Fig. 1A) is in the order of 3 μm and the shear gap in the plate–plate geometry is set to 50 μm (see Fig. 1B) strains, i.e. the total deformation can be adjusted according to the "strain unit" concept.

For the shear flow experiments a gap of 50 μm was chosen to guarantee a proper rheometrical flow and also a sufficiently high shear rate of 62,800 s^{-1}, which is comparable to the shear rate of the valve. The following shear rate profiles were performed at 22 and 30 °C: 1000 s^{-1} for10 s (strain units: 10,000); 1000 s^{-1} for 1000 s (strain units: 100,000); 62,800 s^{-1} for 10 s (strain units: 628,000); 62,800 s^{-1} for 100 s (strain units: 6,280,000). LAOS experiments were performed for the same gap size at frequency of 10 and 100 rad/s and different deformation, i.e. strain of 500, 1000, and 2000%. The duration of experiments were 10 and 100 s.

The non-sheared emulsion sample was obtained directly from production and stored at 4 °C. Appropriate sample volumes for rheological investigations were taken from the storage container and tempered in the rheometer prior to the experiments. Sheared sample was taken directly from the outer rim of the geometry and stored in plastic vials. Eight rheological experiments at each investigated shear rate were needed to collect a sufficient amount of sample of approximately 0.5 g. Before and after aging the samples the formation of crystals is investigated by Zeiss microscopy and can be correlated to the shear treatment.

3.3. Temperature cycling experiments

The formulations undergo temperature cycling tests from 5 to 40 °C for a period of 1-month storage 12 h at each temperature step.

3.4. Microscopy

The samples have been examined using a Zeiss Axioplan microscope under polarized light. About 10–25 mg of the cream has been placed on a microscopic slide. Subsequently the slide was covered and compressed with a 200 g mass for 2 min in order to ensure constant material thickness.

3.5. Determination of drug solubility

Drug solubilities were determined after 24-h equilibration at 25 °C, using a standard HPLC system, e.g. Hewlet Packard 1100, with UV detection at 210 nm. A reversed phase column, e.g. Nucleosil 100-5 C18 AB, 5 m, maintained at 60 °C was used. The mobile phase consisted of water, acetonitrile, *t*-butylmethylether and phosphoric acid (85%) and gradient with increasing amount of acetonirile was chosen.

3.6. Preparation of the cream

The cream was made by stirring oil phase at 80 °C containing oleyl alcohol, triglycerides, glycerol monostearate, cetyl alcohol stearyl alcohol and the drug until a clear solution was obtained. In parallel an aqueous phase consisting of citric acid, sodium hydroxide, sodium ceteostearyl sulphate, and water was prepared. Both clear solutions were mixed and stirred until a homogeneous solution was obtained, which subsequently was quenched to 20–25 °C.

4. Results

4.1. Shear flow and LAOS measurements

Both shear flow and LAOS experiments were performed to simulate the flow-induced crystallization of the sample in the valve. Shear rate profile of 10,000, 100,000, 628,000, and 6,280,000 strain units were imposed to the sample. The results are shown in Fig. 2. Fig. 2A shows the viscosity at $T = 22$ °C for the different shear profiles as a function of time (i.e. strain units). The transient behavior at 1000 s^{-1} shows a pronounced thinning effect (thixotropy) in the first 50 s and a leveling out at around 80 s. Orientation effects during flow are the reason for such behavior. At higher shear rates of 62,800 s^{-1} a lower viscosity is observed and a less pronounced start-up behavior. Similar to the experiments at low shear rate the viscosity is leveling out after a few seconds. At a temperature of $T = 30$ °C the flow behavior of the sample shows the sample trends and almost the same values as for 22 °C (Fig. 2B). Higher temperatures were not investigated due to the formation of a lubricating oil film that reduces the contact between sample and lower plate (plug flow condition as a violation of rheometrical flow field).

Since the transient data for all shear rates and temperatures investigated superimpose, the strain unit concept can be utilized. As a consequence, only the total deformation, i.e. strain imposed on the sample is important and not individual parameters such as time of flow and shear rate. Different geometrical and technical restrictions of both the valve and the rheometer (different gap size and applicable shear rate) can therefore be adjusted and subsequent experiments such as LAOS are guaranteed to exactly simulate the stress profile of the valve motion. Again the actual shear time and magnitude in the valve was higher than in the rheometer but using the strain unit equivalent a similar total deformation can be achieved.

Many fluids behave as viscoelastic liquids, which means that their inner composition is comprised of structures (macromolecules, droplets, particles) showing viscous and additional elastic properties. To investigate the viscoelastic properties of the sample an oscillating shear stress is imposed on the sample and the resulting oscillatory deformation and phase shift between both properties is measured. This information is used to calculate the storage modulus $G'(\omega)$ (describes elastic properties) and the loss modulus $G''(\omega)$ (describes viscous properties).

In Fig. 3 storage and loss modulus from LAOS experiments ($\omega = 10$, 100 rad/s, $\gamma = 500$, 1000, 2000%, $t = 10$, 100 s) are reported for $\omega = 100$ rad/s as a function of time. In all cases the loss modulus is larger than the storage modulus indicating a pronounced viscous behavior of the sample. Similar to Fig. 2 a slight decrease of both loss and storage modulus is observed for the first 40 s while later on the response functions level out. As indicated in Fig. 3B an increased temperature is not influencing the rheological response function. The thixotropic behavior during the first 40 s could be again due to the start-up of the rheometrical flow.

In summary, the rheological experiments provide well-known sheared samples of the pharmaceutical cream to be investigated further in temperature cycling test. As discussed in the following sections we are able to establish a correlation of the shear exposure (expressed via the strain unit) and the destabilization of the cream due to partial coalescence.

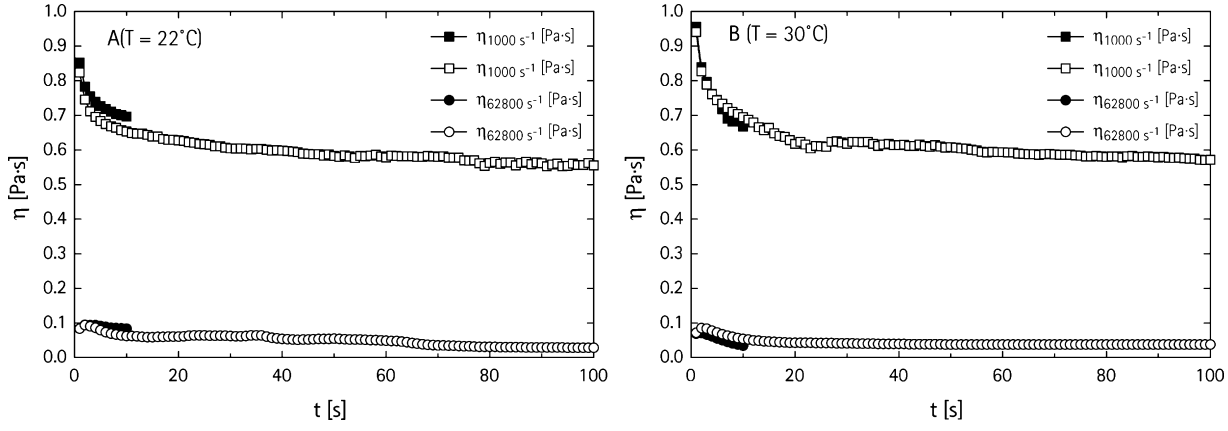

Fig. 2. Viscosity as function of time for different shear rates at (A) 22 °C and (B) 30 °C.

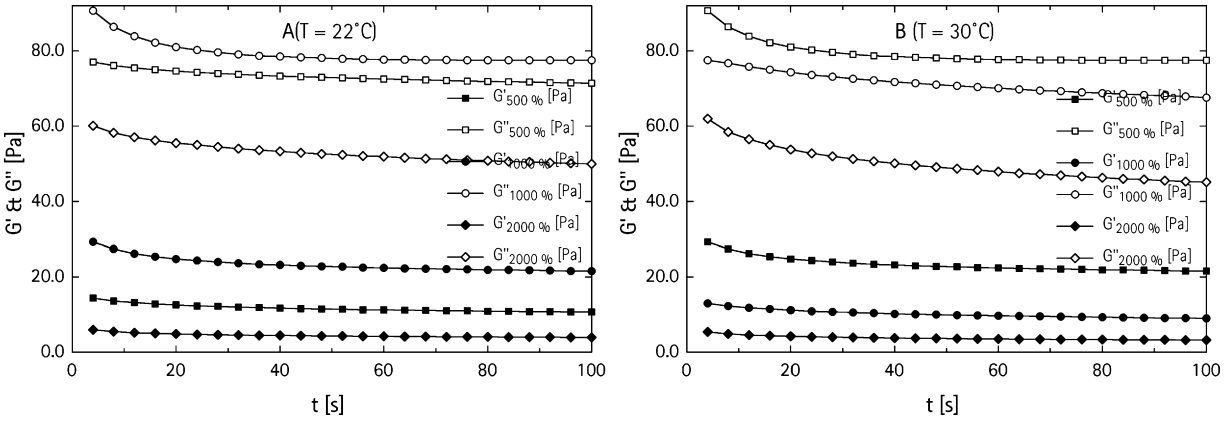

Fig. 3. Storage and loss moduli as function of time for different deformations at (A) 22 °C and (B) 30 °C ($\omega = 100$ rad/s).

4.2. Coalescence and crystal formation due to mechanical stress test (rheological experiments)

The high volume concentration of the semisolid cream (see Fig. 4) will potentially increase particle aggregation and might lead to the loss of the colloidal particulate structure during the pharmaceutical process, which in turn might favor drug re-crystallization. The above described rheological experiments are valuable tools to mimic pharmaceutical processes such as mixing, pumping, stirring or filling. However, the investigated samples received after the preparation process meet the specification of the required product in particular the drug product was free of drug crystals and the microscopic investigations confirmed the presence of dispersed colloidal emulsion droplets (Fig. 4).

As a reference, the sample illustrated in Fig. 4 is considered as a treated but un-aged sample. The solubility of the drug in different solvents is shown in Table 1. In the model experiments described here the concentration of the drug (10 mg/g) is significantly exceeding the calculated drug solubility in the cream following the concept of supersaturation frequently used as passive skin penetration enhancement (Moser et al., 2001).

However, the initial part of the experimental plan of applying accelerated aging tests was devoted to the analysis of the flow behavior of semi-solid emulsion and its dependence on the temperature as summarized in Table 2.

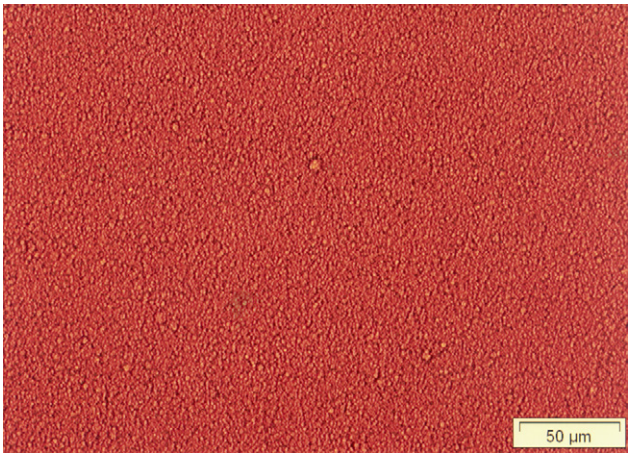

Fig. 4. Microscopic picture of a native o/w emulsion.

Table 1
Drug solubility data

Solvent	Solubility (g/100 ml) at 25 °C
Water	<0.01
Acetone	>25
n-Octanol	0.37
Propylenglycol	0.11
Ethanol/water, 1:1	0.05
Cream (mg/g)	6*

* Calculated value.

By increasing the temperature two effects have been observed as shown in Figs. 5 and 6. First, needle shaped crystals have been observed, which refer to the re-crystallized drug substance as confirmed with RAMAN spectroscopy (data not shown). Second, the droplet size distribution of the emulsion and the average diameter of the droplets are effected by shear and temperatures. The presence of drug crystals indicate that emulsion destabilization has occurred. However, a clear relationship between classical destabilization mechanism such as flocculation or coalescence could not be made. The observation of some larger droplets indicate partial coalescence and/or coalescence.

A prerequisite of emulsion destabilization such as partial coalescence or coalescence is the interaction between the emulsion droplets, which is promoted by high shear rates. During partial coalescence several droplets aggregate to form a cluster but each droplet remains intact and their contents do not mix. It is assumed that in this particular case the diffusion of oil soluble drug monomers from one droplet to the other is inhibited.

Table 2
Observed crystals as a function of strain units (with increasing temperature an increasing number of crystals could be found)

Strain units	22 °C	30 °C	40 °C
1,000	No crystals	No crystals	Crystals
10,000	No crystals	Crystals	Crystals
62,800	No crystals	Crystals	Phase separation
6,280,000	No crystals	Crystals	Phase separation

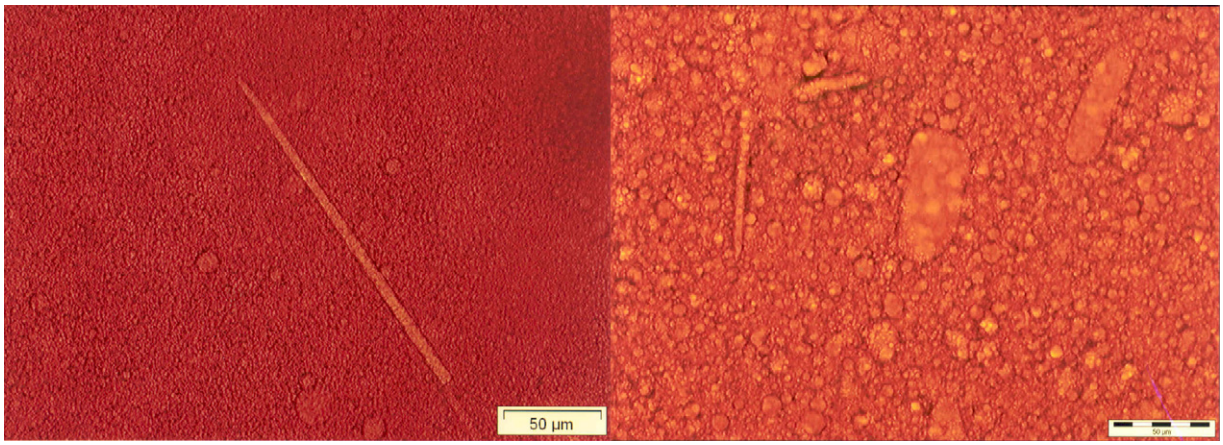

Fig. 5. Emulsion stressed at strain units (left) 100,000 and (right) 6,280,000 (strain units = 1000 s^{-1} × 100 s = 100,000 and 62,800 s^{-1} × 100 s = 6,280,000 at 30 °C). The amount of crystals as well as droplet size increases with increasing strain units.

Experimentally, at high volume fraction the presence of partial flocculated aggregates cannot be easily detected by classical microscopic investigations.

Another typical observation, i.e. the formation of crystals exceeding the size of the partial coalesced droplets, which has been made throughout the work, is shown in Fig. 5. Although main parts of the emulsion seemed to be in a well-dispersed state, drug monomer diffusion to the crystal seems to be possible. Hence, the size of the re-crystallized drugs should correlate with the dimension of the dispersed droplets. Since crystals exceed significantly the size of the droplets the increase of monomer concentration, which can facilitate drug re-crystallization in a supersaturated environment, is the driving force for crystal formation. Depending on the size of the coalesced or partially coalesced aggregates the crystals could exceed the size of the merged emulsion droplets.

The drug substance used in this work is poorly water-soluble (Table 1) and the drug concentration in the continuous water phase can be neglected (data not shown). This information temps us to assume that drug diffusion occurred via the emulsion droplets, which is confirmed in Fig. 6. It could be nicely seen that the needle shaped drug is located in the interior of merged emulsion oil droplets. It has to be noted that the viscosity of the cream decreases significantly with increasing temperatures and at 40 °C the emulsion exhibits rather fluid-like more than viscous behavior. With respect to the physical–chemical properties of the drug we conclude that the accelerated re-crystallization process is mainly affected by the structural fluctuation of the emulsion droplets and drug diffusion to the drug substance nucleus in other words crystallization occurs via the emulsion droplets.

4.3. Effect of temperature cycling tests on emulsion stability

To obtain more information about the emulsion structure and its dependency on temperature and temperature cycling the rheological pre-stressed emulsion underwent temperature cycles from 5 to 40 °C within 24 h for a period of 1 month. This type of test are frequently used in pharmaceutical industry as accelerated tests in order to predict the long term stability in particular shelf-life of the investigated product.

The impact of the thermal stress on the dispersity of the emulsion droplets is shown in Fig. 7. The obtained pictures illustrate

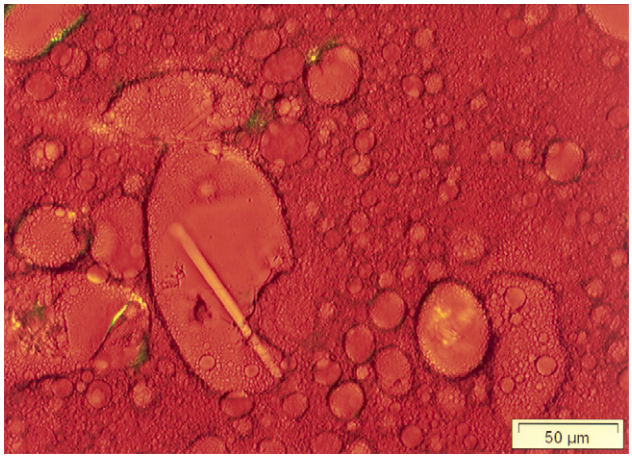

Fig. 6. Emulsion stressed at shear rate $\gamma = 1000\ s^{-1}$ and duration $t = 100$ s (strain units = 1000 s^{-1} × 100 s = 100,000 at 40 °C).

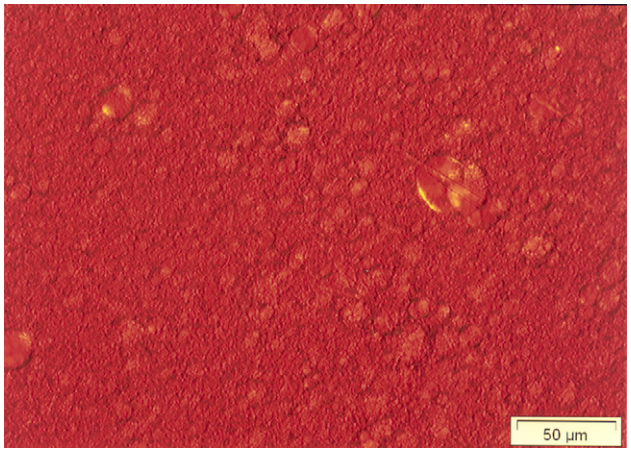

Fig. 7. Emulsion stressed at 6,280,000. The previous stable emulsion at 22 °C showed droplet flocculation as well as droplet coalescence during cycling test. In parallel a significant number of drug crystals have been observed.

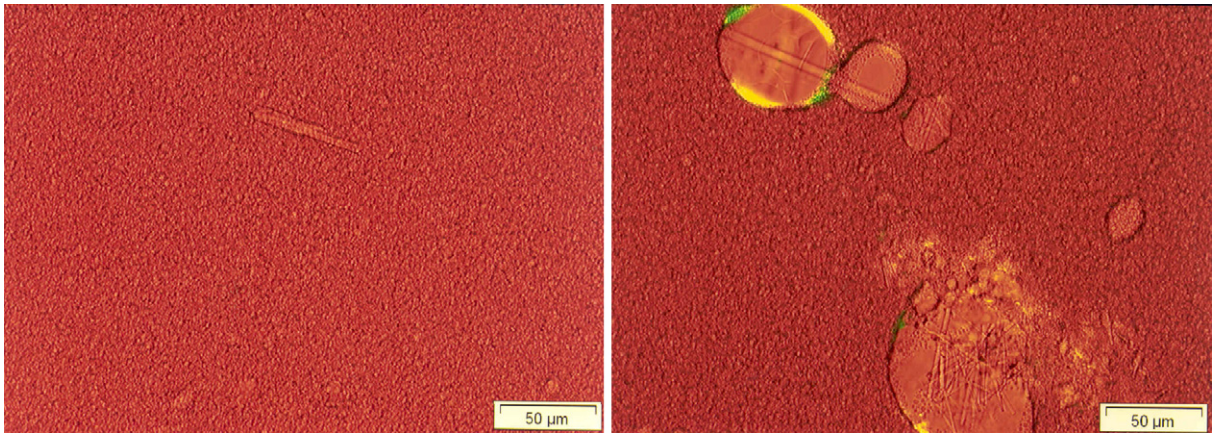

Fig. 8. Microscopic pictures of the cream matrix, which have been oscillated at 22 °C with 10 rad/s (left) and 100 rad/s (right) before the thermal stress program. The matrix is partly irreversible destroyed and a large number of crystals could be observed.

Table 3
Crystals as a function of strain units after cycling the physical stressed material 1 month from 5 to 40 °C

Strain units	22 °C	30 °C
1,000	No crystals	Increasing number of crystals
10,000	No crystals	Increasing number of crystals
62,800	Crystals	Increasing number of crystals
6,280,000	Crystals	Increasing number of crystals

that the temperature cycling test turns the formerly stable emulsion into an unstable state. This includes both experiments the shear rate (Fig. 7) as well as the oscillation measurement (see Fig. 8).

Significant parts of the emulsion show large emulsion droplets, in which small needle like drug crystals can be observed. Referring to the previous section the temperature cycling experiments confirm that as a consequence of the droplet destabilization drug crystallization occurs. This observation is in line with other studies that reported that temperature cycling led to increased viscosity in creams if the volume fraction was higher than 20%, which they attributed to partial coalescence. Furthermore repeated cycling led to the formation of larger crystalline material at the droplet interface with the consequence that partial coalescence was supported (Boode et al., 1991).

In summary, the effect of temperature cycling on the colloidal state of the emulsion cream has been studied over a period of 1 month. It could be shown that temperature cycling favored drug crystallization, which corresponds with the observation that in additional parts of the emulsion droplet destabilization occurred (see Table 3). Interesting to note is the observation that at low shear rates and ambient temperatures 22 °C the emulsion is not effected and no crystals have been observed, which point to the fact that the emulsion destabilization and hence drug crystallization is favored by process conditions.

5. Conclusion

In this work we introduced predictive stress tests aiming to study the impact of a pharmaceutical process on the long term stability of a supersaturated semisolid o/w cream.

It was shown that drug crystallization and crystal growth can be initiated via an emulsion destabilization process called partial coalescence. The partial destabilization mechanism is favored by process conditions such as pumping, filling and temperature. In an industrial environment accelerated stress tests are frequently used in order to predict long term stability of drug products. The combination of rheological and thermal accelerated stress tests in the field of emulsion cream processing introduced in this work give the pharmaceutical scientist the possibility to study these effects on a small time scale. Based on the observation he has the possibility to optimize process, emulsion properties (e.g. volume fraction) or chemical formulation at an early stage of drug product development

It is interesting to note that despite the complexity and variability of these systems the specifications for creams focus almost entirely on the chemical composition rather than on the physical properties. The results obtained in this work point clearly on a structure–property relationship, which necessities the development and use of analytical techniques for characterizing these systems from a structural point of view for both to enhance the basic understanding of the cream structure and to control the quality of the product. Structure property relationships are of fundamental importance for product quality especially in self-assembling drug delivery forms. The scientific investigation on drug delivery formulation from a structural point of view is in our opinion an underestimated subject throughout the industrial pharmaceutical world in contrast to the food industry. Novel initiatives such as PAT (process analytical technology) initiated by the FDA aim to control quality during the process by evaluating critical process parameters. This approach requires novel innovative analytical concepts in order to fulfill the upcoming needs of rational formulation and engineering screening. With respect to self-assembling systems the kinetic control of complex structures during processing will be of PAT relevance in the coming years. We believe that the type of studies performed in this work will attract increasing interest especially in the overlapping area of pharmaceutical, analytical and engineering science. However as a next step we have initiated a systematic work to study the effect of the chemical composition in the formulation in combination with fluctuating

process conditions and correlate it with the long term stability of pharmaceutical drug containing emulsion.

Acknowledgements

The authors wish to thank A. Gaillard and Y. Duchesne for performing the microscopic studies.

References

Binks, B.P., 1999. Modern Aspect of Emulsion Science. Royal Society of Chemistry, London.

Boode, K., Bisperink, C., Walstra, P., 1991. Destabilisation of o/w emulsions containing fat crystals by temperature cycling. Colloids Surf. 61, 55.

Boode, K., Walstra, P., 1993. Partial coalescence in oil-in-water emulsions. 1. Nature of the aggregation. Colloids Surf. A: Physicochem. Eng. 81, 121.

Boode, K., Walstra, P., De Groot-Mostert, A.E.A., 1993. Partial coalescence in oil-in-water emulsions. 2. Influence of the properties of the fat. Colloids Surf. A: Physicochem. Eng. 81, 139.

Coupland, J.N., 2002. Crystallization in emulsions. Curr. Opin. Colloid Interf. Sci. 7, 445–450.

Cramp, G.L., Docking, A.M., Ghosh, S., Coupland, J., 2004. On the stability of oil-in-water emulsions to freezing. Food Hydrocolloids 18, 899–905.

Davies, E., Dickinson, E., Bee, R.D., 2001. Orthokinetic destabilization of emulsions by saturated and unsaturated monoglycerides. Int. Dairy Sci. 11, 827–836.

Eccleston, G.M., 1984. Properties of fatty alcohol mixed emulsifiers and emulsifying waxes. In: Florence, A.T. (Ed.), Materials Used in Pharmaceutical Formulation, Critical Reports on Applied Chemistry, vol. 6, pp. 125–156.

Garbolino, C., Ziegler, G.R., Coupland, J.N., 2000. Ultrasonic determination of the effect of shear on liquid crystallization. J. Am. Oil Chem. Soc. 77, 157–162.

Hetzel, F., Nielsen, J., Wiesner, S., Brummer, R., 2000. Dynamic mechanical freezing points of cosmetic o/w emulsions and their stability at low temperatures. Appl. Rheol. 10, 114–118.

Jeelani, S.A.K., Hartland, S., 1993. Effect of velocity fields on binary and interfacial coalescence. J. Colloid Interf. Sci. 1566, 467–477.

Kumaraswamy, G., 2005. Crystallization of polymers from stressed melts. J. Macromol. Sci.: Polym. Rev. C45, 375–397.

Macosko, C.W., 1994. Rheology: Principles, Measurements and Applications. Wiley-VCH, Weinheim.

Mazzanti, G., Guthrie, S.E., Sirotta, E.B., Marangoni, A.G., Idziak, S.H.J., 2004. Novel shear-induced phases in cocao butter. Cryst. Growth Des. 4, 409–411.

McClements, D.J., Dickenson, E., Povey, M.J.W., 1990. Crystallisation in hydrocarbon-in-water emulsions containing a mixture of solid and liquid droplets. Chem. Phys. Lett. 174, 449–455.

McClements, D.J., 2004. Food Emulsions. CRC, Boca Rouge.

Moser, K., Kriwet, K., Kalia, Y.N., Guy, R.H., 2001. Stabilization of supersaturated solutions of a lipophilic drug for dermal delivery. Int. J. Pharm. 224, 169–176.

Mueller-Goyman, C.C., Frank, S.G., 1986. Interaction of lidocaine and lodcaine-HCl with the liquid crystal structure of topical preparations. Int. J. Pharm. 29, 147–159.

Narine, S.S., Marangoni, A.G., 1999. Relating structure of fat crystal network to mechanical properties: a review. Food Res. Int. 32, 227–248.

Rousseau, D., 2000. Fat crystals and emulsion stability—a review. Food Res. Int. 33, 3–14.

Peramal, V.L., Tamburic, S., Craig, D.Q.M., 1997. Characterisation of the variation in the physical properties of commercial creams using thermogravimetric analysis and rheology. Int. J. Pharm. 155, 91–98.

Sato, K., 2001. Crystallization behaviour of fats and lipids—a review. Chem. Eng. Sci. 56, 2255–2265.

Thanasukarn, P., Pongsawatmanit, R., McClements, D.J., 2004. Impact of fat and water crystallization on the stability of hydrogenated palm oil-in-water emulsions stabilized by whey protein isolate. Colloids Surf. A: Physicochem. Eng. 246, 49–59.

Tadros, T., 2004. Application of rheology for assessment and prediction of the long-term physical stability of emulsions. Adv. Colloid Interf. Sci. 108–109, 227–258.

Vanapalli, S.A., Coupland, J.N., 2001. Emulsions under shear—the formation and properties of partially coalesced lipid structures. Food Hydrocolloids 15, 507–512.

Vanapalli, S.A., Palanuwech, J., Coupland, J.N., 2002. Stability of emulsions to dispersed phase crystallization: effect of oil type, dispersed phase volume fraction, and cooling rate. Colloids Surf. A: Physicochem. Eng. 204, 227–237.

Van Boekel, M.A.J.S., Walstra, P., 1981. Stability of oil-in-water emulsions with crystals in the disperse phase. Colloids Surf. 3, 109.

Walstra, P., Wouters, J.T.M., Geurts, T.J., 2005. Dairy Science Technology. CRC, Boca Rouge.

Walther, B., Hamberg, L., Walkenström, P., Hermansson, A.-M., 2004. Formation of shaped drops in a fast continuous flow process. J. Colloid Interf. Sci. 270, 195.

Windhab, E.J., Dressler, M., Feigl, K., Fischer, P., Megias-Alguacil, D., 2005. Emulsion processing: from single-drop deformation to design of complex processes and products. Chem. Eng. Sci. 60, 2101–2113.