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Research paper

Physical stability of redispersible dry emulsions containing amorphous sucrose

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Abstract

The objective of the present study was to estimate the stability of redispersible dry emulsions containing amorphous sucrose. Dry emulsions were prepared by spray drying liquid o/w-emulsions in a laboratory spray dryer. The effect of hydroxypropyl methylcellulose (HPMC) on the glass transition temperature T_g of spray dried sucrose-HPMC mixtures, relative to the T_g of amorphous sucrose, was investigated. For the sucrose-HPMC mixtures the values of T_g followed the ideal Gordon-Taylor equation up to 30% HPMC. For dry emulsions containing 40% HPMC, 30% lipid and 30% sucrose, the T_g was increased by 12°C relative to the T_g of amorphous sucrose. The stability of the dry emulsions was investigated by a conventional stability study and by an enthalpy relaxation study. The measured enthalpy recovery of amorphous sucrose below T_g was used to calculate molecular relaxation time parameters based on the Williams-Watts equation. The molecular mobility of amorphous sucrose at temperatures 50°C below T_g was low and negligible with respect to the shelf life stability. It was concluded that the dry emulsions are physically stable with respect to the lifetime of a pharmaceutical product when stored in dry condition and at temperatures up to 28°C.

Keywords: Dry emulsion; Sucrose; Hydroxypropylmethylcellulose (HPMC); Glass transition temperature; Stability; Molecular mobility; Amorphous; Enthalpy relaxation

1. Introduction

Liquid emulsions have distinct advantages over other oral dosage forms by improving the bioavailability and by reducing the side effects, but the number of emulsion formulations currently in use are few compared with other oral dosage forms. The lack of usage is due to physical-chemical stability and compliance problems. Packages are often big and must be stored at low temperatures.

Dry emulsions are prepared by drying liquid o/w-emulsions containing a solid carrier in the aqueous phase. The solid carrier provides the dry emulsions with bulk and mass. Dry emulsions are lipid-based powder formulations from which an o/w-emulsion can be reconstituted in vivo [1–3] or in vitro [2,4–18].

From a pharmaceutical point of view, dry emulsions are attractive because they are physically and microbiologically stable solid formulations, which are easy to administer in the form of powders as capsules and tablets. Like o/w-emulsions, dry emulsions represent a potential oral drug delivery system for lipophilic and low-soluble drug substances [1–3,6–9,12,15–18] and for drug substances needing protection against light [10] or oxidation [19].

Previous studies have shown that dry emulsions having a lipid content of up to 40% dry powder mass are physically stable [20]. These dry emulsions were prepared by spray drying liquid o/w-emulsions containing fractionated coconut oil dispersed in aqueous solutions of hydroxypropylmethylcellulose (HPMC). Unfortunately, the dry emulsions were cohesive powders having poor flow properties. The cohesiveness was reduced by addition of sucrose [21], meaning that the processing properties of the dry emulsions were improved.

Preparation of dry emulsions by spray drying transforms sucrose into an amorphous state, which exhibits a strong tendency to crystallise when stored at temperatures above the glass transition temperature T_g. The relationship between T_g and the stability of amorphous solids is complex. The molecular mobility decreases as the temperature decreases, particularly below T_g, thereby slowing molecular diffusion and reducing the rate of crystallisation. It is clear that storage below T_g under dry conditions is advantageous,

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though not a guarantee, for stability. Amorphous solids may be physically stabilised when combined with a polymer (an antiplasticizer) having a higher T_g, making up an amorphous solid solution [22–24]. The combined system is expected to have a T_g between those of the individual components and a different degree of molecular mobility at a particular temperature and relative humidity [24].

From enthalpy relaxation studies, the molecular mobility can be estimated from the calculated molecular relaxation time parameters τ and β based on the Williams-Watts equation. This equation was originally developed to describe non-symmetrical dielectric relaxation behaviour and is frequently applied to quantify the relaxation process in amorphous solids [24–28]. Studies have shown that the molecular mobility becomes negligible from 50°C below T_g, because the molecular mobility is too low to initiate crystallisation within the expected lifetime of amorphous pharmaceutical products [25,28–29].

The objective of the present study was to investigate the physical stability of redispersible dry emulsions containing amorphous sucrose and to find the temperature range at which the molecular mobility decreases to a level where it becomes negligible with respect to the expected lifetime of pharmaceutical products. The physical stability of the dry emulsions, the effect of HPMC on T_g and the molecular mobility of amorphous sucrose below T_g were investigated.

2. Materials and methods

2.1. Materials

HPMC (Pharmacoat® 606) Shin-Etsu (Japan) having a viscosity of 6.1 mPas (2% w/v solution) at 20°C, fractionated coconut oil (Miglyol® 812 N) Condea (Germany) and sucrose, Danisco Sugar (Denmark) were used.

2.2. Preparation of dry emulsions, amorphous sucrose and mixtures

Liquid o/w-emulsions with 20% dry powder mass were prepared so dry emulsions contained 40% HPMC, 30% fractionated coconut oil and 30% sucrose. The fractionated coconut oil and the aqueous solution containing dissolved HPMC and sucrose were homogenised in a high speed colloid mill, Ultra-Turrax® T25 basic (IKA Labortechnik, Germany) for 3 min at 24 000 rpm. Aqueous sucrose solutions with 50% dry powder mass, as well as aqueous mixture with 20% dry powder mass containing sucrose and HPMC at various ratios, were prepared.

The liquid o/w-emulsions and aqueous solutions of sucrose and sucrose-HPMC mixtures were spray dried in a laboratory spray dryer, Mobil Minor (Niro Atomizer, Denmark). The dryer operates co-currently, has a rotary atomizer and a flow of drying air at approximately 135 kg/h. The inlet air temperature was 120°C, the outlet air temperature was held at 75°C, and the rotation rate of the rotary cup atomizer was 25 000 rpm. In the spray drying process, the atomizer was cooled by water.

2.3. Reconstitution

A total of 1.0 g of dry emulsion was suspended in 4.0 ml of distilled water in a 17 ml container. After 1 h of rotation at approximately 20 rpm (comfort Heto Mastermix rotator), samples were withdrawn for further characterisation.

2.4. Storage of dry emulsions, amorphous sucrose and mixtures

Dry emulsions, amorphous sucrose and amorphous sucrose-HPMC mixtures were stored at ambient temperature in desiccators over dry silica gel. Samples were taken out to be stored for 6 months at ambient temperature and 40°C in 75% relative humidity, created by a saturated NaCl solution.

2.5. Study design

A three-step study plan was set up. The first step, the reconstitution properties of the dry emulsions and the degree of crystallisation of amorphous sucrose in the dry emulsions upon ageing were investigated. The degree of crystallisation was determined by differential scanning calorimetry (DSC) analysis as the ratio between the melting enthalpy of sucrose in the dry emulsions and crystalline sucrose. The dry emulsions were heated from 25 to 225°C and the enthalpy of melting was determined as the area of the endotherm.

Subsequently, the ability of HPMC to raise T_g of amorphous sucrose-HPMC mixtures, relative to the T_g of amorphous sucrose was investigated. T_g of different sucrose-HPMC mixtures was calculated applying the Gordon-Taylor equation and measured experimentally by DSC analysis. The midpoint T_g was determined. The samples were heated from 25 to 100°C, and then kept at 100°C for 40 min to ensure dry samples (the chemical stability of sucrose was not affected). Cooled to 25°C and subsequently heated a second time to 225°C during which the midpoint T_g was determined [24,29–32]. The experiment was performed twice.

Finally the physical stability of amorphous sucrose and the dry emulsions were estimated by an enthalpy relaxation study. From the measured enthalpy recovery at T_g, the mean relaxation time parameters τ and β were calculated applying the Williams-Watts equation.

By DSC analysis, the midpoint T_g, the enthalpy recovery ΔH and the change in heat capacity at T_g (ΔC_p) for the samples were determined. The samples were heated from 25 to 21–22°C above T_g and then cooled to 0°C to form a sample with a standardised thermal history. The samples were then heated to a storage temperature of 20, 30 or 50°C below T_g and were held isothermally at that temperature for 1, 2, 4, 8 or 16 h. The samples were subsequently cooled and then heated through T_g to 225°C. During the final heating scan, the pronounced endothermic relaxation peak located at the end of the glass transition region was analysed [24–25,29,31,33]. Each experiment was performed twice.

The glass transition temperature of a mixture $T_{g(mix)}$ is expressed by the Gordon-Taylor equation Eq. (1), which assumes that two components are miscible and that the free volumes of the components are additive [34]

$$T_{g(mix)} = \frac{w_1 \times T_{g1} + K \times w_2 \times T_{g2}}{w_1 + K \times w_2} \quad (1)$$

w_1 and w_2 are the mass fractions of each component and T_{g1} and T_{g2} are the respective glass transition temperatures. Applying free volume theory, the constant K is calculated by the Simha-Boyer rule Eq. (2) [35]

$$K \approx \frac{T_{g1} \times \rho_1}{T_{g2} \times \rho_2} \quad (2)$$

ρ_1 and ρ_2 are the density of both components.

By DSC analysis an endothermic relaxation peak accompanying the glass transition is generated as a consequence of enthalpy recovery. The intensity of the peak depends on the storage conditions. The maximum enthalpy recovery ΔH_∞ can only be determined accurately at ageing temperatures near T_g [36]. However, assuming that the heat capacity change ΔC_p is independent of the temperature, an approximate value of ΔH_∞ for a particular ageing temperature T can be calculated from Eq. (3)

$$\Delta H_\infty = (T_g - T) \times \Delta C_p \quad (3)$$

ΔC_p is the change in heat capacity at T_g. From ΔH_∞ the extent to which a material relaxes $\phi(t)$ is calculated under any given time t and temperature T conditions from Eq. (4)

$$\phi(\mathrm{t}) = 1 - \frac{\Delta \mathrm{H_t}}{\Delta \mathrm{H_\infty}} \quad (4)$$

ΔH_t is the measured enthalpy recovery under those conditions and is obtained by calculating the area under the endothermic relaxation peak. The mean molecular relaxation time constant τ is calculated applying the Williams-Watts equation [37] Eq. (5)

$$\phi(\mathrm{t}) = \exp\left((-\mathrm{t}/\tau)^\beta\right) \quad (5)$$

β is a relaxation time distribution parameter with a value between 0 and 1. A β value of unity corresponds to a single relaxation time of an exponential type.

The mean relaxation time constant τ and the relaxation time distribution parameter β are calculated from the experimental enthalpy recovery data. An iterative non-linear regression procedure is applied to estimate the best fit to the data applying Quattro® Pro Version 7 (Corel, Canada). The initial parameters provided are $\tau = 100$ and $\beta = 0.5$ for all samples.

2.6. Differential scanning calorimetry (DSC)

The physical state of sucrose in the dry emulsions, amorphous sucrose and the sucrose-HPMC mixtures was determined by differential scanning calorimetry applying a DSC 7 equipped with an instrument controller TAC 7/PC (Perkin Elmer, Denmark) and a cooling accessory Ultra-Kryomat® Rul 80 (Lauda, Germany). A total of 10–20 mg of samples were weighed and analysed in 40 μl aluminium pans with holes and the effluent gas was dry nitrogen. The scanning rate was 20°C/min. The instrument was calibrated towards indium and zinc.

2.7. Thermogravimetric analysis (TGA)

The moisture content in the dry emulsions, amorphous sucrose and sucrose-HPMC mixtures was determined by thermogravimetric analysis (TGA) applying a TGA 7 equipped with a TAC 7/PC instrument controller (Perkin Elmer, Denmark). Samples (15.00–20.00 mg) were placed in the sample pan and the effluent gas was dry nitrogen. The scanning rate was 10°C/min in the scan range 50–200°C. The moisture content was determined as the weight loss between 50 and 120°C. The instrument was calibrated towards alumel and nickel in addition to a furnace and weight calibration.

2.8. Droplet size

The droplet size distribution of the reconstituted o/w-emulsions was determined by laser diffraction applying a Mastersizer S (Malvern Instruments Ltd., UK). A reverse Fourier optic lens with a 300 focal length was used, covering the size interval 0.05–880 μm. The refractive index of lipid was 1.4500, the absorption value was 0.1 and the refractive index of water was 1.3300. The droplet size distribution was determined on the basis of the volume distribution. The volume weighted median diameter d(v, 0.5), was applied to characterise the droplet size. The width of the droplet size distribution was expressed by the SPAN-value.

2.9. Scanning electron microscopy (SEM)

The outer macroscopic structure of the dry emulsions was examined by scanning electron microscopy applying a JMS-5200 scanning electron microscope (Jeol, Japan). Prior to microscopy, samples were coated with gold/palladium by sputtering for 300 s in a BioRad, E5200 Auto Sputter Coater. The samples were scanned at a voltage of 15 kV.

2.10. Density

The density of the dry emulsions, amorphous sucrose and HPMC was determined at ambient temperature by helium pycnometry applying an AccuPyc 1330 pycnometer (Micrometritics Ltd., UK). An equilibration rate at 0.7 kPag/min was applied and for one determination each sample was measured seven times.

Table 1
Droplet size distribution of liquid o/w-emulsions after reconstitution, the moisture content and crystallisation of amorphous sucrose in the dry emulsions[a]

Ambient temperature, 75% RH					40°C, 75% RH			
Time (month)	Crystallinity (%)*	Moisture content (%)*	d(v, 0.5) (μm)	SPAN	Crystallinity (%)*	Moisture content (%)*	d(v, 0.5) (μm)	SPAN
0	–	2.0	1.71 (0.04)	1.47 (0.05)	–	2.0	1.71 (0.04)	1.47 (0.05)
1	–	1.6	1.69 (0.01)	1.43 (0.01)	–	2.0	1.67 (0.02)	1.45 (0.02)
2	–	1.5	1.64 (0.03)	1.46 (0.02)	4	2.9	1.60 (0.01)	1.47 (0.01)
3	–	1.6	1.64 (0.00)	1.53 (0.02)	13	4.0	1.63 (0.02)	1.43 (0.01)
4	–	1.8	1.68 (0.00)	1.28 (0.00)	18	5.0	1.62 (0.01)	1.43 (0.02)
5	<1	2.2	1.65 (0.02)	1.44 (0.01)	23	6.0	1.62 (0.05)	1.42 (0.06)
6	<1	2.4	1.69 (0.07)	1.51 (0.07)	25	6.0	1.67 (0.05)	1.53 (0.05)

[a] The values are the mean value of two determinations and the values in brackets are the difference between the two determinations. *One determination.

3. Results

3.1. Stability of dry emulsions

Table 1 shows that during storage at 75% relative humidity, the moisture contents of the dry emulsions were increased from 2.0 to 2.4% at ambient temperature and to 6.0% at 40°C. The crystallisation of amorphous sucrose was initiated after 5 months of storage at ambient temperature and after 2 months at 40°C. At the end of the storage period the degree of crystallisation was below 1 and 25%, respectively. The reconstitution properties of the dry emulsions were not affected by the crystallisation of amorphous sucrose. The dry emulsions were able to reconstitute the original o/w-emulsion in water after 6 months of storage in 75% relative humidity at ambient temperature and 40°C. As seen in Fig. 1, the outer structure of the dry emulsions was not changed after storage in 75% relative humidity at 40°C for 6 months. The dry emulsions still consisted of well-separated spherical particles with shallow dents, seen to be deeper and more abundant in the smaller particles.

3.2. The effect of HPMC on T_g

Fig. 2 shows a plot of T_g values of sucrose-HPMC mixtures as a function of their compositions. The graph includes the values calculated by the Gordon-Taylor equation using values from Table 2. The experimental determined T_g values of the sucrose-HPMC mixtures were very close to the T_g of pure sucrose.

3.3. Molecular mobility below T_g

Fig. 3 shows the enthalpy recovery of amorphous sucrose and the dry emulsions as a function of ageing time at different ageing temperatures below T_g. The enthalpy recovery increased with increasing ageing time and temperature in a non-linear way. The enthalpy recovery was lower for the dry emulsions even though the ageing temperatures were higher.

Fig. 4 shows the extent of relaxation of amorphous sucrose and the dry emulsions in terms of $\phi(t)$ as a function of the ageing time at different ageing temperatures below T_g. There was a significant reduction in the extent of relaxation for amorphous sucrose and the dry emulsions at temperatures 50°C below T_g, and the values were almost identical. For the dry emulsions, values of °(t) were lower than for amorphous sucrose at temperatures 20 and 30°C below T_g.

Table 3 shows the calculated values of the molecular relaxation time parameters τ and β based on Williams-Watts equation at different ageing temperatures. For both

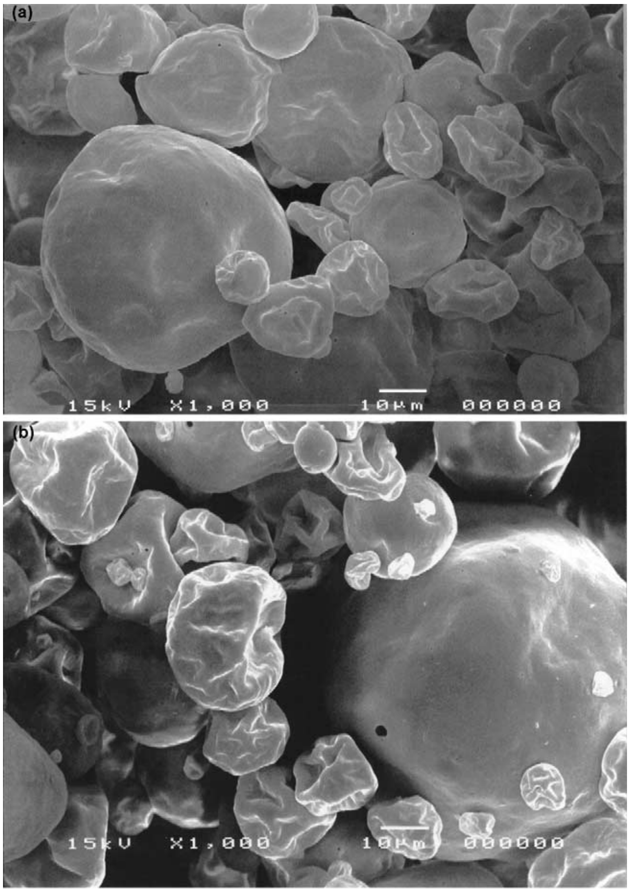

Fig. 1. Scanning electron micrograph of the dry emulsion: (a) before storage; and (b) after 6 months of storage in 75% relative humidity at 40°C. Bar = 10 μm.

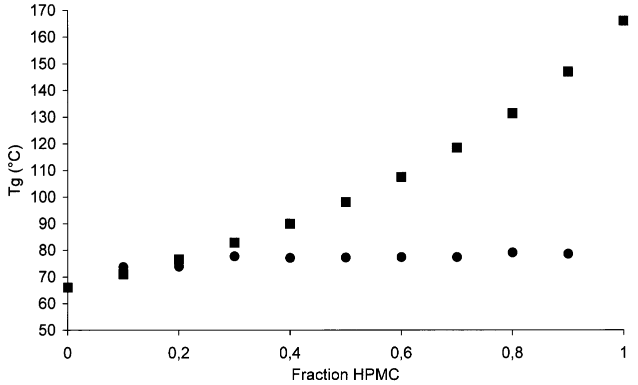

Fig. 2. T_g values of sucrose-HPMC mixtures as a function of composition: ● represent measured values and ■ represent calculated values from the Gordon-Taylor equation.

amorphous sucrose and the dry emulsions, values of τ increased with lower ageing temperatures.

4. Discussion

Values of T_g for the various sucrose-HPMC mixtures remain equal and very close to the T_g of amorphous sucrose. T_g increased by 12°C relatively to amorphous sucrose with HPMC concentration up to 30% HPMC. At higher concentration deviations from the Gordon-Taylor equation were seen. This indicates a non-ideal mixing above 30% HPMC. Sucrose was shown to be miscible with HPMC during the DSC scan by a single glass transition temperature T_g and by the fact that no other thermal transitions reflecting crystallisation were observed at HPMC concentrations above 30%. Mixing HPMC with sucrose may introduce a considerable excess of free volume to the mixture due to the larger molecular size. Thus the T_g of the mixture is less elevated than calculated by Gordon-Taylor equation [29]. Crystal inhibition is obtained despite an apparent lack of antiplasticizing (i.e. T_g-elevating) effects [22], and consequently the effect of the polymer is not linked directly to T_g, so other factors may be involved. For the dry emulsion containing 40% HPMC, T_g was also increased by 12°C relatively to amorphous sucrose. Dry emulsion containing 40% HPMC instead of 30% HPMC was selected due to stability of the liquid o/w-emulsion but also to be sure that crystal inhibition of amorphous sucrose was obtained.

Table 2
The glass transition temperature (T_g), the change in heat capacity (ΔC_p) at T_g and the density of the dry emulsions, amorphous sucrose and HPMC[a]

Materials	T_g (°C)	ΔC_p (J/g°C)	Density (g/cm^3)
Dry emulsions	78 ± 3.3	0.156 ± 0.002	1.20 (0.00)
Amorphous sucrose	66 ± 3.0	0.545 ± 0.002	1.53 (0.00)
HPMC	166 (0.6)	0.098 (0.000)	1.29 (0.00)

[a] The values for T_g and ΔC_p for the dry emulsions and amorphous sucrose are mean values of 30 determinations. The other values are the mean value of two determinations and the values in brackets are the difference between the two determinations.

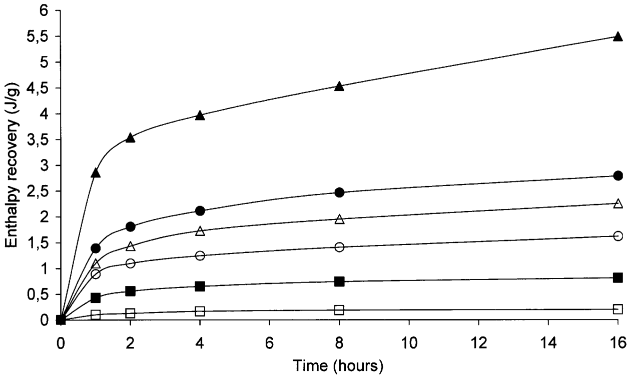

Fig. 3. Variation of enthalpy recovery (ΔH) for amorphous sucrose and the dry emulsions with time after storage at different temperatures. Ageing temperatures for amorphous sucrose: ■ 17°C (T_g – 49°C), ● 37°C (T_g – 29°C) and ▲ 47°C (T_g – 19°C). Ageing temperatures for the dry emulsions: □ 28°C (T_g – 50°C), ○ 48°C (T_g – 30°C) and △ 58°C (T_g – 20°C).

β describes the distribution of molecular relaxation times. In this study values of β were different from 1, indicating that a distribution of time scales with non-exponential behaviour was required to describe each set of data, which is typically for amorphous systems.

The mean relaxation time constant τ was found to vary from a few hours near T_g to many years at temperatures 50°C below T_g. The molecular mobility at 17°C for amorphous sucrose and at 28°C for the dry emulsions becomes negligible with respect to the shelf life stability. The estimated stability is in agreement with the results obtained from the conventional stability study. Below 1% amorphous sucrose in the dry emulsions was crystallised after 6 months of storage in 75% relative humidity at ambient temperature. In contrary, 25% of the amorphous sucrose was crystallised at 40°C. It is most likely that water acts as a plasticizer for sucrose. At elevated storage temperatures, the low amount of water required to reduce T_g [38] has profound implica-

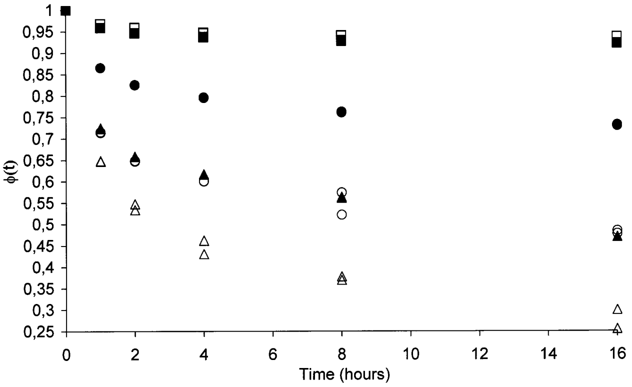

Fig. 4. The extent of relaxation for amorphous sucrose and the dry emulsions with time after storage at different temperatures. Ageing temperatures for amorphous sucrose: ■ 17°C (T_g – 49°C), ● 37°C (T_g – 29°C) and ▲ 47°C (T_g – 19°C). Ageing temperatures for the dry emulsions: □ 28°C (T_g – 50°C), ○ 48°C (T_g – 30°C) and △ 58°C (T_g – 20°C).

Table 3
Calculated molecular relaxation time values τ and β applying the Williams-Watts equation for amorphous sucrose and the dry emulsions at different ageing temperatures

Materials		Ageing temperatures		
		T_g – 20°C	T_g – 30°C	T_g – 50°C
Amorphous sucrose	τ (hours)	46	1219	10^7
	β	0.29	0.26	0.22
Dry emulsions	τ (hours)	8	51	10^7
	β	0.38	0.27	0.23

tions for accelerated stability testing of amorphous substances.

After storage for 6 months, the outer structure of the dry emulsions was not changed and the dry emulsions were able to reconstitute the original o/w-emulsion in water. The dry emulsions are physically stable with respect to the lifetime of a pharmaceutical product, when stored in dry condition and at temperatures up to 28°C.

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