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Research Paper

Lactose Contaminant as Steroid Degradation Enhancer

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Purpose. By pharmaceutical processes and in the presence of solid excipients physical–chemical changes are known to occur, leading to increased rate of chemical degradation. The purpose of this work was to determine the critical aspects in the stability of a steroid in the presence of a commonly used excipient, lactose.
Methods. A steroid was either mixed or wet granulated with lactose with different particle size.
Results. Small lactose particles lead to a higher degree of degradation. Degradation was enhanced under warm humid conditions although the presence of water alone could not account for this effect. Lactose-phosphate, a known intrinsic contaminant in lactose is demonstrated to enhance the degradation of the steroid. Stability was improved in high purity lactose and deteriorated upon extra addition of phosphates. Since the exposure to the contaminant is a function of the surface area of the lactose, particle size differences of the excipient have a clear consequence. High shear granulated lactose granules exhibit a heterogeneous composition; large granules consist of small primary particles and vice versa. It is shown that the large granules, composed of the small primary lactose particles reveal the highest degree of degradation. Granule composition dictates the stability profile of the granules.
Conclusion. The lactose contaminant and grandule composition dictates the stability profile of the granules and mixtures.

KEY WORDS: degradation; lactose; particle surface; phosphate; steroid.

INTRODUCTION

The degradation rate of a compound is related to the structural susceptibility of the substance and reaction conditions such as temperature, humidity and oxygen concentration. Unfortunately reactivity may also be enhanced by the presence of other compounds (e.g. water in wet granulation, aldehyde groups in excipients (1) or by changed physical–chemical states (e.g. as an effect of drying and tableting). The active substance and the excipients used are constantly exposed to stresses potentially leading to chemical and physical changes (2). Both high temperatures (3) and the presence of water (4–7) can induce instability. Moreover during dynamic drying processes fine particles are produced thereby increasing the potential interaction area of the drug and the excipients (8). The mechanism of chemical degradation in the solid state is described by different authors. Degradation of the solid into the gas, liquid and solid state has been distinguished (9).The theory of Prout and Tompkins is primarily used to explain solid to gas transitions. Once a molecule in the solid state has decomposed, its geometry within the lattice changes. This geometric change in the surrounding is thought to activate neighboring molecules. These activated molecules are then subject to degradation (9,10). The Leeson–Mattocks kinetics assumes that upon exposure of a solid mass to moisture, the unbound moisture forms a sorbed moisture layer, which behaves like a bulk liquid phase in which the drug substance and excipient will form a saturated solution (11). Furthermore it is assumed that the decomposition can be totally accounted for by the decomposition of the dissolved drug (9). This theory is opposed by the theory of occurrence of activated sites on the crystal surfaces. Degradation is locally enhanced by defects in the crystal lattice preferentially at the surface (10,12,13). Ahlneck and Zografi (7) proposed that small amounts of water can be absorbed in these activated sites thereby increasing molecular mobility hence increasing chemical reactivity by the plasticizing properties of the water. The role of water as solubility facilitator has then been expanded to that of a chemical reactivity enhancer. Carstensen and Pothisiri developed a model in case of decomposition of the active compound in the solid and in the dissolved state including theories of Prout and Tompkins and Leeson and Mattocks (14). Carstensen and Attarchi studied the decomposition of acetylsalicylic acid in the presence of limited amounts of water. It was hypothesized that the decomposition occurs in chains through activated molecules like the Prout–Tompkins theory (15). Activated molecules are subject to degradation by changes in the environment. Dissolved molecules provide a repository for water adjacent to these activated molecules (15).

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In the presence of solid excipients several physical chemical changes of the active substances are described leading to increased rate of chemical degradation, reduction in degree of crystallinity or the formation of molecular complexes. The excipient itself can act as a source of humidity which causes water vapor to associate with the drug and influence stability (7). The effect of excipients can also be related to the area of contact between drug and excipient, in addition to the total amount of excipient present (12).

Lactose is very often used as filler in solid state drug products; tablets, capsules and dry powder inhalers. Lactose has two isomers (α and β lactose) and has the ability to form a hydrate. It is known to occur in several crystalline states and in the amorphous state. Processing of crystalline lactose can induce failures in the crystal lattice, candidates for enhanced chemical reactivity (16) as the locally disordered regions(17) can influence the stability of drug particles. Moreover micronization of both excipient and active substance increases the surface area available for interaction. It has been discussed previously that within a granulate heterogeneity exists (8). Large granules are composed of small primary particles and small granules are composed of larger primary particles. Consequently large granules exhibit a larger internal surface than small granules, thereby theoretically enhancing degradation (8).

The objective of the current study was to investigate the influence of physical state and excipient characteristics on the stability of a steroid.

THEORY

Many steroids are known to degrade under influence of oxygen. In Fig. 1 the assumed degradation reactions of the compound used in this study are shown. The degradation into the primary degradation products is started by enolization of the active substance. The enolized molecule is more vulnerable to oxidative degradation. The enolization of the steroid can theoretically be enhanced both in acid or basic environment. From the transition products alcoholic and ketonic degradation products are formed. However the complete mass balance of the degradation reaction is not known. The decrease in steroid content is therefore appointed as main degradation criterion and not the formation of degradation products.

MATERIAL AND METHODS

Excipient Powder Mixtures

A steroid hormone, Org 30659 (Diosynth, Oss, The Netherlands), was mixed (1 mg. g^{-1}) with α-lactose monohydrate (Pharmatose 200 M), micronized α-lactose monohydrate (both DMV-Fonterra, Veghel, The Netherlands), ultra-pure lactose (Fluka, Biochemika, Sigma-Aldrich, Buchs, Germany) and $CaHPO_4$ dihydrate (Chem. Fabrik Budenheim, Budenheim, Germany).

Samples were prepared in threefold. The samples were either mixed in a Turbula Mixer or mixed with a mortar and pestle for 30 min. For the lactose mixtures the distribution of the steroid was determined by NIR Imaging (Sapphire Go NIR Imager, Spectral Dimensions Inc, Olney, USA, operated with Isys Software 4.0, 1,100–2,500 nm, normalized second derivative spectra (Savitsky–Golay)). In case of an inhomogeneous distribution the steroid could be visualized and detected as clumps in the lactose. The mixtures were stored in open containers at 40°C and 75% relative

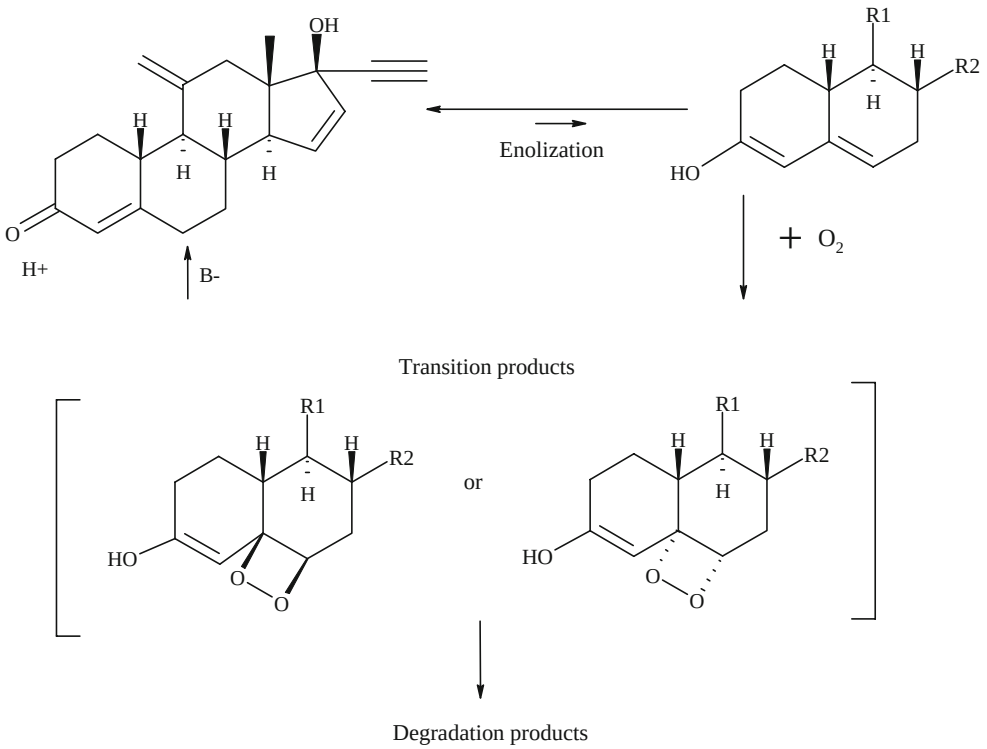

Fig. 1. The enolization of the steroid Org 30659. Enolization is enhanced in the presence of acidic (H^+) or basic (B^-) components. Upon enolization the molecule is susceptible to oxidative degradation.

humidity or 5°C at ambient humidity (80% RH) for a total of 6 or 8 months. At 0, 2, 4, 6 and 8 months the mixtures were analyzed with HPLC/UV detection to quantify remaining content and degradation products (reversed phase HPLC C-18 column, column temperature 30°C, eluent methanol/water (55/45, *v/v* %), flow 1.5 ml. min^{-1}, UV detection 240 nm, injection volume 10 μl). The mixtures were analyzed with differential scanning calorimetry to detect changes in excipient characteristics and to detect presence of disordered structures. (Mettler Toledo DSC 822e, open pans, 25°C–250°C, 10°C. min^{-1}, nitrogen flow 40 $ml.min^{-1}$). No changes were observed upon storage. The micronized lactose did not contain amorphous structures at the start of the experiments.

Water vapor sorption isotherms of both the lactose 200 M and micronized lactose were collected by water sorption analysis. (DVS-1 Surface Measurement Systems, Alperton, UK).

Granules

Org 30659 was mixed with lactose 200 M (1 mg. g^{-1}) in a high shear granulator (Gral 10, Colette, Wommelgem, Belgium) for a total of 15 min (mixer velocity 313 rpm). The powder was granulated for 5 min (mixer velocity 313 rpm, chopper velocity 1,500 rpm). Water (140 ml) was used as the binding liquid. The granules were dried for 4 h under vacuum at 40°C (Elbanton, Kerkdriel, The Netherlands). Granules were sieved with a Retsch control 200 '*g*' sieve, (Haan, Germany). Size fractions were collected and stored at 5°C ambient relative humidity (80% RH), 40°C ambient relative humidity (18% RH) and 40°C, 75% relative humidity in open containers. At 0, 1 and 2 months the steroid content was determined with the HPLC/UV method as described above.

Liquid Dispersions

Liquid dispersions of the steroid in water or saturated lactose solution were prepared in sixfold in two concentrations: 0.01 and 0.1 mg. ml^{-1}. The saturated lactose solution was prepared by dissolving lactose 200 M. The lactose solution was mixed for 24 h before the dispersion was filtered. The clear solution was used for preparing the steroid fluid dispersions. Solubility of the steroid is 50 μg. ml^{-1} at room temperature. At 40°C in all cases Org 30659 was fully dissolved. 20 ml of the liquids was stored in closed 50 ml glass vials at 40°C. At 0, 2 and 10 months the samples were analyzed with the above described HPLC method. The closed glass vials were only opened for sampling purposes for less than 2 min. Na_2HPO_4. $2H_2O$ (Sigma-Aldrich, Buchs, Germany, analytical grade) was added after 2 months storage to a concentration of 0.1 M.

Influence of pH on Stability in Water

NaOH 0.1 M and HCl 0.1 M were used to obtain aqueous solutions with pH 3, 4, 5, 7 and 8. Org 30659 was dissolved in the solutions and stored at 40°C for 3 months. At 0 and 3 months steroid content was determined. pH was determined with the Inolab pH/Cond Level 1 (WTW, Weilheim, Germany).

BET Surface Analysis

BET surface analysis was performed on a Tristrat 3000 (V6.00A, Micromeritics, Norcross, USA). The analysis adsorptive was N_2.

Lactose-Phosphate and Phosphorus Content Determination

Lactose-phosphate content was performed at Food Science Australia by direct capillary electrophoresis by the method as developed by Lifran *et al.* (18) (Beckman Coulter P/ACE™ MDQ series, Fullerton, USA). Detection was carried out by UV detection at 280 nm. Samples were run in duplicate.

Inorganic phosphorus content was determined by Flow Injection analysis using a Lachat Instrument (Hach Company, Loveland, USA) and the spectrophotometric method based on the reduction of molybdenum blue by an acidic reagent at Food Science Australia (19).

Phosphorus content of the saturated lactose solutions of both lactose 200 M and ultra-pure lactose was determined by ICP-atomic emission spectrometry based on the reduction of molybdenum blue (Perkin Elmer, Optima 4300 DV, emission wavelength 213.62, 214.91 and 178.22 nm). Determination was done in duplicate.

RESULTS AND DISCUSSION

NIR analysis of the steroid lactose blends made using the Turbula revealed that the steroid forms agglomerates within the excipient powder. This compromised the uniform distribution of the steroid in powder and granule masses, thus affecting sampling for analysis negatively. Moreover, it makes predication of drug excipient interaction very unreliable. Mixing of the powders by hand with a mortar and pestle provided a homogenous mixture. The powder samples were

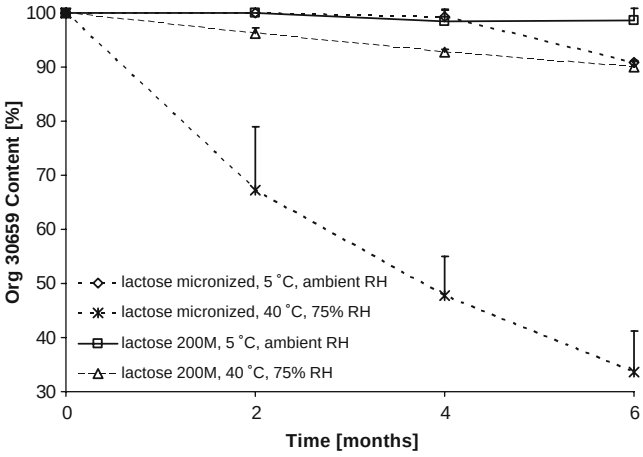

Fig. 2. Degradation of the steroid mixed either with lactose 200 M or micronized lactose mixtures (content 1 mg. g^{-1}). The powder mixtures are stored at 40°C, 75% RH or 5°C, ambient RH. Samples are presented including SD. At 5°C, ambient humidity conditions, no degradation of Org 30659 was observed. In the absence of lactose at 40°C, 75% RH Org 30659 did show a minimal degradation, smaller than the observed degradation in the presence of lactose (content 97.2% after 6 months storage at 40°C, 75% RH).

stored at 40°C, 75% RH and 5°C, ambient RH. For the last condition ambient RH corresponds to a relative humidity of 80%. As shown in Fig. 2 the steroid degraded most in the mixtures of micronized lactose when stored at warm humid conditions. For clarity reasons only the mixtures where degradation was observed are shown. At 5°C and ambient relative humidity no degradation was observed except for the micronized lactose mixture. The results show that particle size and temperature both influenced the degradation.

Org 30659 is vulnerable to oxidative degradation. Oxidative degradation itself may be enhanced by temperature, humidity and oxygen concentration (20). The amount of oxygen available for oxidation is considered as a constant factor under these experimental conditions. Based upon the known role of water in degradation kinetics the amount of adsorbed water was determined for both lactose 200 M and the micronized lactose. It is known that the packing density or very low amounts of amorphous structures affect the adsorption of moisture significantly (21). Literature data on moisture isotherms are highly inconsistent. This is ascribed to the various methods of free moisture content determinations. Recently, the influence of particle size and analysis temperature on lactose moisture isotherms has been investigated (21).

Drugs in solid dosage forms decompose in most cases much more slowly than the same drugs in suspension or solution form. The reason for this is that molecules in solids are fairly well fixed in space, whereas in solution they are subject to random movement, so that the interaction possibilities are greater (7). As seen in the introduction, several degradation models have been proposed to explain observed degradation phenomena. Degradation is often ascribed to the presence of water on the surface of the solid particles. The exact role of water in the degradation reactions differs. As seen in Fig. 3 the lactose particle size has minor influence on the water adsorption. The isotherms of lactose 200 M are highly comparable to the data presented by Bronlund and Paterson (21). The micronized lactose absorbs twice as much water as lactose 200 M at the current constant storage conditions (75% RH). It can be calculated that only a small fraction of the steroid (~0.01%) can be dissolved in this quantity of water. It is assumed that both in micronized lactose and lactose 200 M the Org 30659 will be dissolved to the same concentration (up to saturation level) and that even when a limited amount of water is available for interaction this amount is higher for micronized lactose than for lactose 200 M. Therefore it is not likely that the difference in these amount of dissolved Org 30659 (factor 2 between lactose 200M and micronized lactose) can account for the sevenfold higher degradation of the steroid in the presence of micronized lactose.

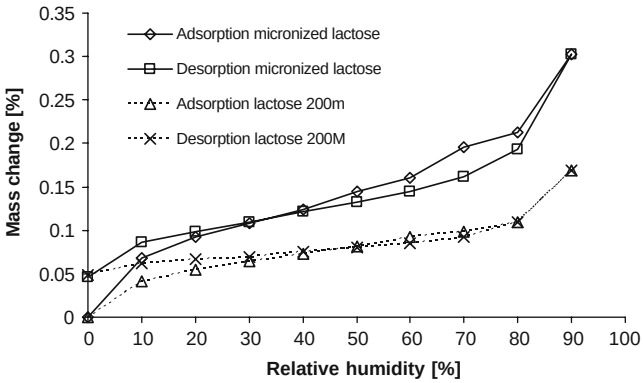

Fig. 3. Moisture isotherms of lactose 200 M and micronized lactose at 25°C.

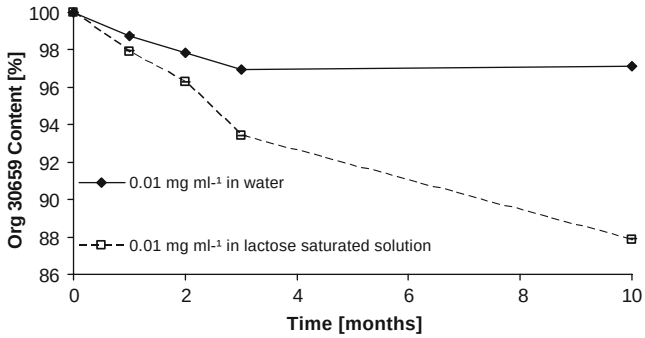

Fig. 4. Degradation of Org 30659 in water or saturated lactose solution stored at 40°C in closed vials. Saturated lactose solutions are prepared out of lactose 200 M. Data points are shown including SD.

The degradation of the steroid in water and in saturated lactose solution was assessed. Although solubility of Org 30659 is only 0.050 mg. ml^{-1} at room temperature, the steroid was dissolved completely in water or lactose solution of 40°C. As seen in Fig. 4, degradation of the steroid in water is minimal. In contrast, in the presence of lactose the steroid degrades significantly. Obviously it is not the dissolved state, but the presence of lactose that enhances degradation. If the degradation in powders and in solution is compared several aspects have to be considered; the solubility of oxygen in water of 40°C is only 2. 10^{-4} M, whereas air contains 4. 10^{-2} M O_2. In solution 3.2. 10^{-2} M Org 30659 (0.01 mg. ml^{-1} Org 30659) *versus* 2. 10^{-4} M molecular oxygen could be available for the oxidative degradation. In solution availability of oxygen may therefore limit degradation in both types of solutions.

The Leeson–Mattock kinetic model assumes that degradation only occurs for the active compound in the dissolved state (9,11). As seen in Fig. 2, degradation in powder is much higher than in solution. If it is assumed that the availability oxygen in solution and in the water layer adsorbed onto the powder surface is similar, the Leeson–Mattock kinetics can not be applied to the current data set.

As it was observed that the degradation of the steroid is enhanced in solutions containing dissolved lactose, the cause of this catalyzing effect was studied. The pH of the solution could significantly enhance the degradation (Fig. 1) and therefore the pH of the lactose solution was considered. pH values of several types of lactose and $CaHPO_4$ in saturated solution were determined. $CaHPO_4$ was chosen as excipient with a known relatively high surface pH (22). Saturated lactose solutions exhibited a pH value of 3.6 to 4 at room temperature, whereas the $CaHPO_4$ in solution had a pH value of 7.4. The low (surface) acidities for lactose have been reported earlier (23,24). The low values can not be explained by the physico-chemical properties of lactose (pK value 13.6 (25)) but have been ascribed to the presence of lactose-phosphate (25). The presence of the steroid did not influence the pH of the solution significantly. It should be noted that the buffer capacity of the solutions is very low. All lactoses

used, with the exception of the micronized lactose, pass the test on the acidity as described in the Ph. Eur. (26). The direct influence H^+ and OH^- was determined by dissolving the steroid in water with pH 4, 5, 7 and 8 adjusted with either HCl or NaOH 0.1 M. Remarkably no significant effect upon the degradation profile could be observed. Degradation varied between 0% and 4% without a correlation to increasing or decreasing pH values (data not shown). It is possible that this pH range is too limited. Upon storage pH of lactose solutions dropped to 3.1. This is lower than the lowest value in the range of solutions used. Based upon the observation that pH did not clearly affect the degradation pattern the possibility that lactose-phosphate could act as catalyzer was explored. Stability of the steroid was also tested in solution in the presence of lactose, phosphates and the combination of the two substances. The steroid (0.01 mg. ml^{-1-1}) was dissolved in a saturated lactose solution (based upon lactose 200 M).

As depicted in Fig. 5 after 2 months $Na_2HPO_4 \cdot 2H_2O$ was added to one part of the lactose solutions. To verify the effect upon addition of phosphates the composition of the other part of the samples was not changed.

In the presence of $CaHPO_4$ the degradation profile of the steroid is quantitatively highly comparable to the degradation in micronized lactose in the solid state (data not shown). This result seems to indicate that the presence of phosphates may lead to this significant degradation. Phosphate groups coupled to monosaccharides are known to catalyze enolization in bio-molecules (27,28). Based upon the results in the current study it was therefore assumed that phosphate could also act as a catalyst for enolization under the observed conditions (see Fig. 1).

To test the influence of lactose-phosphate highly purified lactose was tested. In comparison to the saturated solution of lactose 200 M (54 μg mL^{-1} PO_4^{3-}) or micronized lactose (44 μg mL^{-1} PO_4^{3-}), high purity lactose saturated solution contained only 17 μg mL^{-1} PO_4^{3-}. The pH of the saturated solution was 4.8. This indicates a diminished presence of lactose phosphate in the lactose. No degradation was observed during 3 months in the high purity lactose, whereas only limited degradation (1%) was observed from the fourth month at storage at 40°C and 75% RH. This degradation was smaller than the degradation seen in lactose 200 M (8%) whereas the particle size is comparable after mixing with mortar and pestle; lactose 200 M $d_{3,2}$ 10 μm ($d_{4,3}$ 49.7μm), high purity lactose $d_{3,2}$ 13.1 μm ($d_{4,3}$ 51.6 μm). In lactose 200 M up to 10% degradation occurred, after 6months storage under the same conditions. The difference between the lactose samples was the lactose-phosphate content. In the high purity purer lactose less degradation is seen.

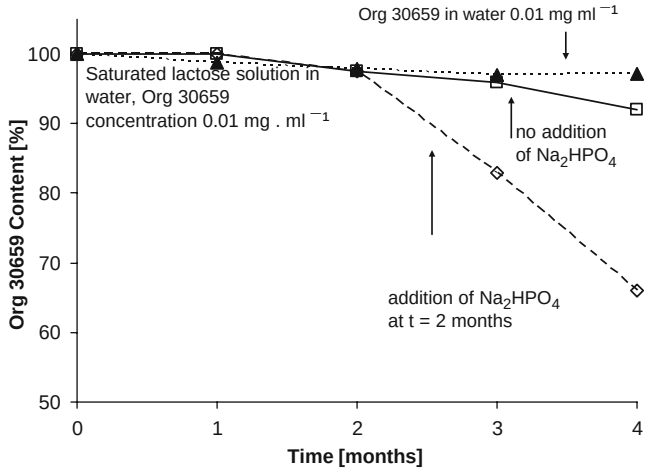

Fig. 5. Degradation of Org 30659 in saturated lactose solution. After 2 months Na_2HPO_4 is added to half of the samples. All samples are continuously stored at 40°C, 75% RH. As a reference the degradation of Org 30659 dissolved in water is shown.

Known contaminants of lactose are riboflavin, potassium chloride and lactose-phosphate (29). In literature riboflavin and potassium chloride are not known as reactive impurities or as enolization enhancers. Recently the presence of trace levels of hydroxyperoxides (30) and aldehydes (1) has been acknowledged. Hydroxyperoxides are detected at a level of <10nmol g^{-1} (≅3.6 ppm) in lactose. Hydroperoxides are known to enhance oxidative degradation (30). However the oxidative degradation of Org 30659 is initially dependent on the enolization of the molecule (Fig. 1). Hydroperoxides are not identified as enolization enhancers. Furthermore in lactose only formaldehyde and no other aliphatic aldehydes were detected at a low level of 0.1μg g^{-1} (≅0.1ppm) (1). In dibasic calcium phosphate aldehydes were not detected, whereas it was shown in the current study that the degradation profile of Org 30659 was quantitatively highly comparable in calcium phosphate and micronized lactose. The influence of aldehydes on stability was therefore also excluded.

Pharmaceutical grade lactose is contaminated with 270 to 400ppm lactose phosphate (29). Lactose-phosphate is already present in milk (25,29,31) and is known as a natural crystallization growth retarder (25). Upon crystallization the lactose-phosphate is preferentially integrated in the crystals in layers. This monolayer can be covered again by lactose-phosphate-free lactose molecules (29). Upon increasing crystallization time relatively more lactose-phosphate is included in the crystals (25,29). It can be considered as a standard contaminant as even a large number of washes (29) or recrystallizations (25) can not remove the lactose-phosphate. Lactose-phosphate is labile under elevated temperature or acidic conditions. It is easily hydrolyzed to lactose and PO_4^{3-} (18). Upon milling of the crystals the lactose-phosphate layers will be preferentially exposed at the surface. Subsequently less battered crystals with larger particle size will expose relatively less lactose-phosphate at the surface than the small micronized particles. The processing 'history' of particles therefore determines the amount of lactose-phosphate. In turn this determines the free organic phosphor content.

The lactose-phosphate content of lactose 200 M and micronized lactose powders was determined. Lactose 200 M appeared to contain a total of 476 ppm (SD 0.2) lactose-phosphate and 5.9ppm (SD 0.2) free inorganic phosphorus content as determined in the completely dissolved lactose samples. Micronized lactose contains 423ppm (SD 0.9) lactose-phosphate and 7.8ppm (SD 0.2) free inorganic phosphorus content. These data reveal that the lactose samples as such do not differ significantly in lactose-phosphate content. This essentially means that exposure of a substance to the contaminant must be related to the way the compound is mixed with the lactose particles. In other words, it is important how the substance is in direct contact with the

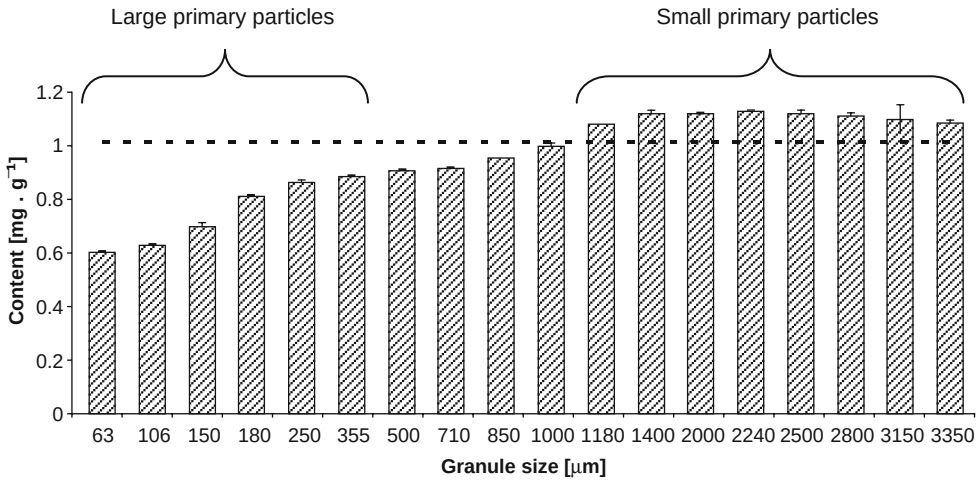

Fig. 6. The distribution of Org 30659 over the different size fractions. The large granules on the right contain more active material than the small size fractions shown on the *left*. The average concentration (1 mg. g^{-1}) is shown as the *dashed horizontal line*. Data are presented including SD. Granules are made out of lactose 200 M.

lactose particles and quantitatively speaking how large the specific surface area of the powder is. Therefore the surface area of the lactose samples was determined with gas adsorption measurements. The BET specific surface area of lactose 200 M turned out to be 0.42 m^2. g^{-1} while that of the micronized lactose was measured to be 1.45 m^2. g^{-1}. From the discussion so far it may be concluded that the lactose-phosphate contamination of the lactose is at least partially responsible for the increased degradation of the steroid. The degree in which this occurs may depend on the amount of water absorbed, but is certainly also determined by the way the steroid is exposed to the contaminant. Therefore the surface area of the lactose is an important parameter. Furthermore the presence of oxygen is a prerequisite for degradation (Fig. 1).

Inhomogeneity phenomena of high shear granulated powder mixtures have been reported extensively (8,32–35). As these have demonstrated to be dominated by particle size differences, it is interesting to check whether the current results are also visible within the granules. The granule heterogeneity is described as the result of the breakage and growth behavior within the high shear granulator (32,33,35). The consequences of these mechanisms were that large granules are composed of small primary particles and small granules are composed of large primary particles (32,35). Org 30659 is micronized. It is reasonable to assume that upon high shear granulation Org 30659 particles will behave similar to the smallest lactose particles and will be both preferentially located in the largest granule fractions. Upon granulation Org 30659 was indeed not homogeneously distributed over the size fractions. On the contrary; the steroid was preferentially located in the largest granular fractions. The larger granules contained therefore a relatively high amount of the small steroid particles. This effect is shown in Fig. 6. The smaller granules contain less active material as they are formed of the larger primary lactose particles.

In the current study we have demonstrated that degradation appears to be determined by the surface area of the

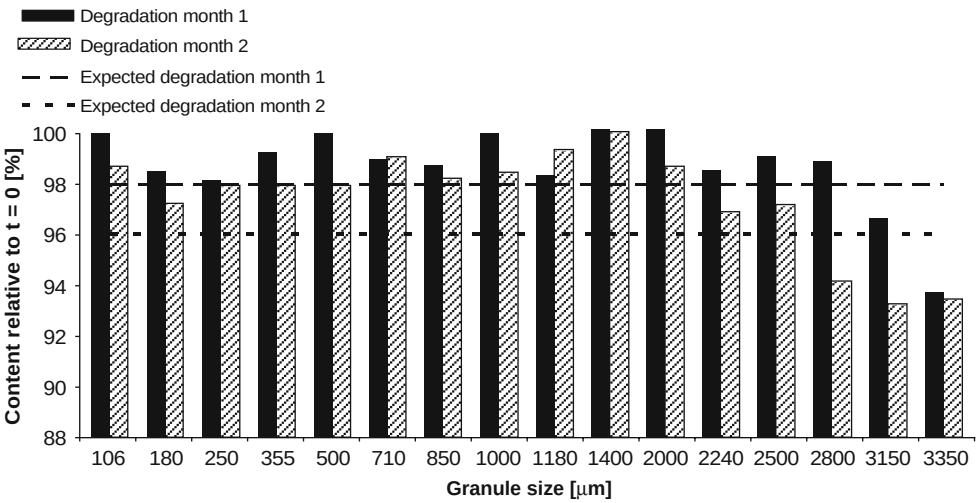

Fig. 7. The degradation of Org 30659 in the different granular size classes. The *horizontal lines* represent the degradation observed in powder mixtures of Org 30659 and lactose 200 M respectively after 1 month (98%) and 2 months (96%) of storage at 40°C, 75% RH. Granules are made out of lactose 200 M.

primary lactose particles. The direct consequence of this would be that the difference in primary particles composition for the largest and smallest granules would also affect the degradation patterns in these different granular size classes. Based upon the degradation pattern in the lactose 200 M powder mixtures the expected degradation in the granules could be determined (see Fig. 2); It was assumed that in the original powder mixture the steroid is equally exposed to all size fractions of the particle size distribution. The observed degradation then represents the average degradation. Org 30659 mixed with lactose 200 M powder showed an average degradation of 2% after 1month of storage and 4% after 2 months of storage under the same conditions (40°C, 75% RH). In Fig. 7 the degradation of the steroid in the different granule size classes is shown. The data show that degradation in the larger granules (composed of the smallest primary lactose particles) was indeed significantly larger than the degradation in the small granules. Furthermore degradation in the larger granules was significantly higher than the degradation observed in the lactose 200 M powder mixtures (Fig. 2). The difference in composition and presence of trace contaminants related to this composition is also reflected in the pH of the saturated solution of granules. A saturated solution of the largest granules has an average pH value of 4.1 (SD 0.06) whereas a saturated solution of the smallest granules exhibits a pH value of 4.5 (SD 0.28). Granule composition dictates the stability profile of the steroid granules.

The current knowledge on stability of Org 30659 related to available interaction surface can have implications for future technological development. Steroids are often used in the treatment of lung diseases. Fine lactose particles (5–8μm) have been used as component of ternary formulations in dry powder inhalers (36) used in the treatment of these lung diseases. The active substance is mixed with a coarse and very fine powder to optimize both flow properties of the powder and lung deposition. Although no definitive conclusion can be made by which mechanism fine excipient particles improve the performance of these formulations evidence of the positive influence of fine powder on the inhaled powder fraction is abundant (36). It has been stated (37) that the addition of fine particles may impair the stability of the formulation by the presence of amorphous structures in the fines. The data as presented here refute that hypothesis. At humidity levels above 75% amorphous structures (if present) re-crystallize fast. The continuous degradation during the test period stresses that even after re-crystallization significant degradation takes place. The presence of disordered structures alone can therefore not account for the observed stability problems. The detrimental effect of fine particle surfaces on the stability of the steroids as shown in this study emphasizes that further research is needed if steroids and fines are used in ternary mixtures for dry powder inhalers or granules.

CONCLUSION

The stability of Org 30659 is primarily dependent on the surface interactions with the contaminant lactose-phosphate. Larger particles with a smaller relative surface exhibit less interaction possibilities. Consequently degradation is smaller when compared to very fine particles. This particle size and surface dependent degradation profile has consequences for the stability in granules. As the composition of granules is highly heterogeneous and inter-granular composition is related to size; small granules consist of large primary particles whereas larger granules consist of small primary particles, consequently available interaction surface is also heterogeneous. The highest degree of degradation is observed in the largest granular size fraction. Granule composition determines the degradation profile of the steroid, directly related to available interaction surface.

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