ELSEVIER

International Journal of Pharmaceutics 135 (1996) 53–62

international journal of pharmaceutics

Influence of excipients and storage humidity on the deposition of disodium cromoglycate (DSCG) in the Twin Impinger

Martin A. Braun[a], R. Oschmann[b], Peter. C. Schmidt[a,*]

[a]*Department of Pharmaceutical Technology, Eberhard Karls University, Auf der Morgenstelle 8, D-72076 Tübingen, Germany*
[b]*Dr. Willmar Schwabe Arzneimittel, Willmar-Schwabe-Str. 1, D-76227 Karlsruhe, Germany*

Received 17 July 1995; accepted 12 September 1995

Abstract

The in vitro deposition pattern of disodium cromoglycate (DSCG) from a unit dose dry powder inhaler device (Microhaler®) was investigated using the Twin Impinger. Four excipients with differing particle sizes, two α-lactose monohydrate grades (Pharmatose 325 M, $x_{50} = 56.3$ μm and Granulac 220, $x_{50} = 15.6$ μm) and two dextrose monohydrate grades (Roferose FF, $x_{50} = 102.8$ μm and Roferose SF, $x_{50} = 37.4$ μm), were mixed with DSCG in the ratio 1 plus 1 and 1 plus 4 at low relative humidity. Loose spherical agglomerates were formed in a rotating drum and then the mixtures were filled into hard gelatin capsules size 3 and stored at 33 and 55% RH, respectively. The deposition pattern was investigated using the Twin Impinger at a flow rate of 60 l/min. The amount of DSCG deposited in the lower impingement chamber, corresponding to a particle size of ≤ 6.4 μm, was markedly influenced by the humidity level during storage. In all experiments, the fine particle fraction from mixtures stored at 33% RH was higher compared to those stored at 55% RH. Mixtures containing 1 part DSCG plus 1 part excipient showed higher deposition rates than the 4 + 1 mixtures. Excipients with a smaller mean particle diameter gave a higher DSCG deposition in the lower impingement chamber. Best results were obtained with the 1 + 1 mixtures of DSCG and fine lactose (Granulac 220) with 41% and DSCG and fine glucose (Roferose SF) with 38%, respectively. The results indicate that dry powder inhalations can be optimized by appropriate selection of the excipient, because its particle size distribution and its proportion in a formulation in combination with the storage humidity are important factors determining the inhalation fraction of a formulation.

Keywords: Dry powder inhalation; Microhaler®; Deposition pattern; Twin Impinger; Formulation; Storage humidity

1. Introduction

In the past years the discussion about environmental problems caused by chlorofluorocarbons (CFCs) led to a ban on CFCs in many countries (Newman, 1990). The use of CFCs will be prohibited even in medical sprays. Interest in CFC-free formulations has risen not only for environmental reasons, particularly in the treatment of lung diseases. Lahdensuo and Muittari (1986) reported

* Corresponding author.

SSDI 0378-5173(95)04337-A

that 37% of 204 asthmatic patients had problems with the coordination of actuation and inhalation from pressurized metered dose inhalers (MDI). Patients having a poor inhalation technique are likely to inhale only a small percentage of the drug dose delivered by the MDI. The output pressure and the explosive evaporation of the propellant atomize drug agglomerates, and segregated drug particles are accelerated to high velocities after the formulation has left the metering valve. These particles are much more likely to be deposited in the oropharynx by inertia than particles that travel at the same speed as the inspired air. In the case of dry powder inhalers (DPI) the energy for dispersing the powder is introduced only by the inhaled airstream and there is no additional impulse introduced to the particles by the propellant. The inhalable fraction therefore depends on the device, the inhalation effort of the patient and the powder formulation. If the drug agglomerates are dispersed completely to single particles with an aerodynamic mean mass diameter of < 7 μm, and are discharged to the inhaled air, a great percentage of the loaded dose should penetrate to the lung. In vivo studies with ^{99m}Tc-labeled drugs delivered by DPIs and MDIs showed that, depending on inhalation technique and inhaler device, drug fractions in the range of 10 to 25% could be determined in the lower airways using the gamma camera technique (Biddiscombe et al., 1993; Newman et al., 1989; Vidgren et al., 1988, 1990). These in vivo studies are very time consuming and the results are influenced by several factors related to the patients participating in the study. For example, the anatomy of the respiratory tract, the inhalation mode and the inhalation flow rate vary considerably from patient to patient. In order to detect differences between different formulations, the use of an in vitro method is preferable, because the operation parameters are standardized and the variation in deposition pattern only depends on the formulation and not on the testing system. In this work we compared several formulations containing lactose or dextrose as carrier and 20 mg of mechanically micronized DSCG as active ingredient. Using the Twin Impinger (TI, British Pharmacopoeia, 1993), we studied the impact of the type of carrier, the drug/carrier ratio and the storage humidity on the deposition pattern of the formulations. A unit dose dry powder inhaler device (Microhaler®) was used to evaluate the influence of formulation and environmental impact on the in vitro behavior of DSCG/excipient mixtures.

2. Materials and methods

Mechanically micronized disodium cromoglycate (lot number 5700-U-09-02, Francis Chemicals, Italy) was used as received. The drug was stored in a desiccator at room temperature over silica gel to preserve the initial water content at 4.6%. Two grades of α-lactose monohydrate, Pharmatose 325M (DMV, NL-Veghel) and Granulac 220 (Meggle, D-Wasserburg), and two dextrose monohydrate types, Roferose FF and Roferose SF (both Roquette, D-Frankfurt), were used as supplied. The water content measured as the mean of three determinations by means of Karl-Fischer titration was 5.28% for Granulac 220, 5.34% for Pharmatose 325M, 9.13% for Roferose SF and 9.30% for Roferose FF. Hard gelatin capsules (SnapFit™ size 3, Capsugel, B-Bornem) and the excipients were stored in tightly closed containers at room temperature. Potassium dihydrogen phosphate, disodium hydrogen phosphate, magnesium chloride, magnesium nitrate and methanol (all analytical grade) were supplied by Merck, D-Darmstadt. The powder mixtures were prepared in a 50 ml polyethylene screw capped container with a PTFE inlay in the cap.

2.1. Preparation of the powder inhalations

To prepare mixtures containing 80 and 50% DSCG respectively, 6 g DSCG plus 1.5 g excipient and 5 g DSCG plus 5 g excipient, accurately weighed, were premixed in the mixing vessel by shaking manually for 5 min. Drug agglomerates were then destroyed by passing the mixture through a 500 μm sieve. The premix was again transferred to the mixing vessel and mixed in a Turbula (Bachofen, CH Basel) for 30 min at 42 rpm. In order to achieve an acceptable flowability,

the powder was passed through a 500 μm sieve and then transferred to a 100 ml glass vessel. This container was placed in a horizontal drum mixer without baffles rotating at 30 rpm for 15 min. The powder mixture aggregated and soft agglomerates were formed. Fifty hard gelatin capsules were filled with a powder load containing 20 mg DSCG per unit. Immediately after filling, they were transferred to desiccators containing saturated $MgCl_2$ and $Mg(NO_3)_2$ solutions, respectively, to store them at two humidity levels of 33 and 55% RH. All preparation steps except weighing and mixing were performed in a glove box, where the relative humidity was kept at $\leq 10\%$.

2.2. Dry powder inhaler (microhaler®)

All experiments were conducted using a unit dose dry powder inhaler (Microhaler®, Pearce, 1989). Fig. 1 presents a view of this inhaler in an opened position exhibiting the working principle of the device. The rear part on the left hand side is joined to the front part on the right with an integral hinge (7). By flapping the front part to the rear part, a dispensing chamber (1) and air inlet channels (2) are formed by the curved flanges (3) projecting from the inner surface of the two halves of the device. A locking mechanism holds the parts tightly together so that the air drawn through the mouthpiece enters the inhaler only at the three air inlets. The pierced capsule (4) is placed into the rear part of the dispensing chamber and the device is closed. The air entering through the inlet channels forces the capsule to rotate and the powder is ejected to the airstream. The grid (6) at the front part prevents the capsule from being sucked through the mouthpiece and destroys large agglomerates.

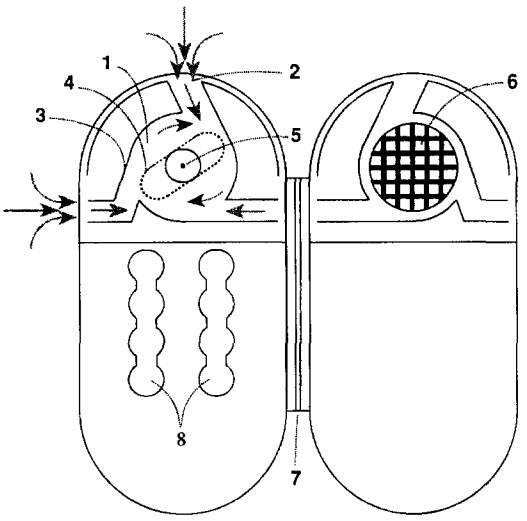

Fig. 1. Rear view of the Microhaler® in the opened position. (1) Cylindrical dispensing chamber; (2) air inlet; (3) curved flanges; (4) rotating capsule; (5) metal pin for piercing the capsule; (6) air outlet with separation grid to mouthpiece; (7) integral hinge; (8) capsule holder (two days' supply).

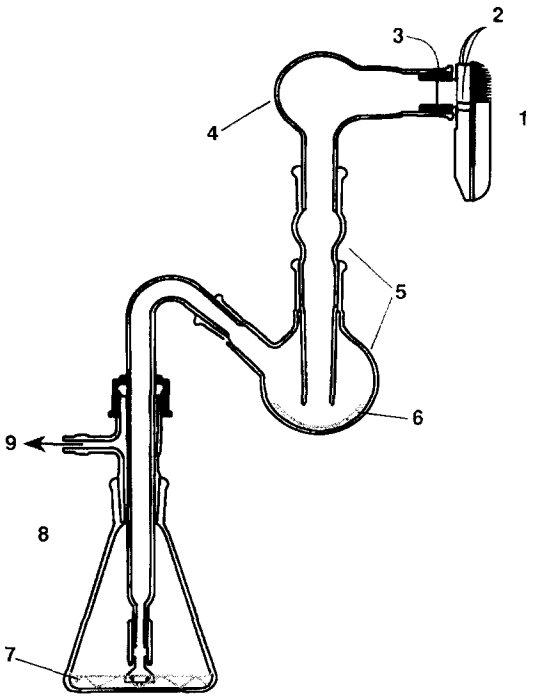

Fig. 2. Side view of the Twin Impinger with Microhaler® attached. (1) Microhaler®; (2) air inlets; (3) connecting adapter; (4) upper impingement chamber (50 ml round bottomed flask); (5) middle impingement chamber (glass tube and 100 ml round bottomed flask); (6) phosphate buffer solution (10.0 ml); (7) phosphate buffer solution (40 ml); (8) lower impingement chamber (bent glass tube and 250 ml conical flask); (9) outlet to vacuum pump (60 l/min).

2.3. Assessment of the in vitro aerosol deposition

The deposition behavior of the dry powder inhalations was evaluated with the TI depicted in Fig. 2. It consists of an artificial glass lung and a vacuum pump connected to the lower impingement chamber. Starting the pump it draws air through the glass lung and the attached inhaler so that the powder load is dispensed into the air stream. On its way to the outlet of the apparatus, the powder load is separated according to the diameter of the particles by inertia. Depending on the mass, the shape, the density and the speed of a particle, it will impact on a different part of the impinger. The upper and the middle impingement chambers mimic the throat and the upper airways. With a cut-off diameter of 6.4 μm, particles with a mean mass aerodynamic diameter (MMAD) lower than this value are likely to reach the lower chamber (Hallworth and Westmoreland, 1987). This portion of the powder cloud is considered to be the 'inhalable' or 'fine' particle fraction. After phosphate buffer solutions (pH 7.4) have been introduced into the middle (10.0 ml) and lower impingement chambers (40 ml), the vacuum pump is operated for 10 s to adjust the air flow to a value of 60 l/min. Then the capsule with the powder mixture is taken from the storage chamber. With the metal pin of the Microhaler®, the capsule is pierced at the top and bottom and placed into the dispensing chamber of the inhaler. On starting the vacuum pump, the capsule content is discharged to the bypassing turbulent air stream. For a few capsules stored at 55% RH, the operation time of 5.0 s was not sufficient, because large agglomerates sometimes blocked the small dispensing holes of the capsule and a considerable portion of the powder load remained in the capsule. In these cases the pump was operated for another 5.0 s to empty the capsule. At the end of each single experiment the inhaler is disconnected and the apparatus is disassembled. The inner surfaces of the three impingement chambers are washed separately with phosphate buffer solution pH 7.4. The washings are collected in graduated flasks. The residue in the capsule adhering to the inner capsule wall is washed and collected in a graduated flask in the same way. After adjusting to volume, the solutions are diluted to receive a DSCG concentration, which is within the calibrated range of 0.5–2.0 mg/100 ml. The drug content is determined spectrophotometrically at 238 nm using a PE 550S spectrophotometer (Perkin-Elmer, D-Überlingen). The constituents used did not interfere with DSCG absorbance at the wavelength chosen. The distribution of DSCG in the TI (deposition pattern) and the remainder in the capsule and the inhaler device were calculated from these data. Each test was performed three times and results are expressed as the percentage of drug dose filled into the capsules (loaded dose).

2.4. Shape of formulation agglomerates

The shape and the distribution of DSCG and excipient particles in drug/carrier agglomerates were evaluated using a scanning electron microscope (DSM 940 A, Carl-Zeiss, D-Oberkochen). After coating the specimens with gold for 240 s in a BIO-RAD sputter-coater (BIO-RAD, D-München), they were transferred to the microscope and pictures were taken at the acceleration voltage of 5 kV.

2.5. Particle size distribution

The particle size distributions of the micronized drug and the excipients were determined with a Sympatec HELOS laser diffraction spectrometer equipped with a RODOS dry powder dispersing system (both Sympatec, D-Clausthal-Zellerfeld). The samples were fed to the dispersing airstream using a funnel connected to the injector of the RODOS. Depending on the diameter of the injector nozzle and the pressure and speed of the passing airstream, the dispersing force and the powder concentration in the airstream could be adjusted. The pressure at which only agglomerates are dispersed without destroying single particles was evaluated. With this pressure being too low, a bimodal volume particle size distribution is measured and, by increasing it step by step, the peak at larger particle diameter values disappears. At a certain point, when the agglomerate peak has disappeared, the fine particle fraction starts to

increase because of particle fracture caused by the high force input of the dispersing airstream. For the measurements, the dispersing pressure was set to a value so that only agglomerates, but not the particles themselves, were destroyed. In the case of DSCG a dispersing pressure of 2500 hPa was found to be appropriate, while for the excipients, 1000 hPa was adequate. The fineness and the particle size distribution width of the compounds were characterized by calculating two values: the x_{50} value and the x_{90}/x_{10} ratio. The first value represents the particle size below which 50% of the particles based on their volume are found (mean particle size). The latter is calculated by dividing the x_{90} by the x_{10} value, indicating a narrow distribution for values near 1.

2.6. Water content

The water content of the excipients and the DSCG used was determined using a SET/MET-Titrino 702 (Metrohm, CH-Herisau) in combination with Karl-Fischer equipment. The titration vessel was equipped with an Ultra Turrax T25 (IKA Labortechnik, D-Staufen) to accelerate the dissolution of the substances in the solvent methanol. Prior to the titration, the Ultra Turrax was operated for 60 s. The platinum electrode was set to a current of 40 μA and the titration was stopped when meeting two criteria: the drift was < 14 μl/min *and* the sensor electrode potential did not exceed a value of 220 mV. All titrations were performed with the titrant Hydranal composite 5 (Riedel de Hæn, D-Seelze).

3. Results and discussion

3.1. Particle size distribution of DSCG and carrier materials

The particle size of the active ingredient in a dry powder inhalation is one of the major determinants for an effective inhalation therapy. For this reason it is important to measure the particle size distribution of the drug used in the formulation. Fig. 3 shows the cumulative volume particle size distribution of the DSCG. Particles exceeding a size of 7 to 10 μm are not likely to reach the lower airways as they impact on the surface of the throat and upper airways by inertia. Therefore, carrier materials with a particle size distribution starting at a value above 10 μm are preferred, because side effects in the lower airways caused by these particles are minimized. Fig. 3 also shows the cumulative particle size distributions of the excipients used. Granulac 220 (Gr 220) with a median particle diameter determined as being 15.6 μm and an x_{90}/x_{10} ratio of 20.99 is a very fine lactose grade with a wide particle size distribution. A considerable fraction of particles < 6.4 μm is present. The second lactose type, Pharmatose 325M (Ph 325M), shows a much narrower distribution with an x_{90}/x_{10} ratio of 4.14, a median particle size of 56.3 μm and a negligible amount of particles < 6.4 μm. It is a more homogeneous excipient compared to Gr 220. The two dextrose grades Roferose SF (Ro SF) and Roferose FF (Ro FF) show about the same distribution width with an x_{90}/x_{10} ratio of 8.90 and 8.09, respectively, but the median particle size differs markedly with $x_{50} = 37.4$ μm for Ro SF and $x_{50} = 102.8$ μm for Ro FF. With the selection of two different kinds of excipients at four different particle size distributions, carrier influences on the in vitro deposition of DSCG could be evaluated.

3.2. Twin Impinger experiments

The adhesion and cohesion characteristics of a formulation determine the efficacy of the drug

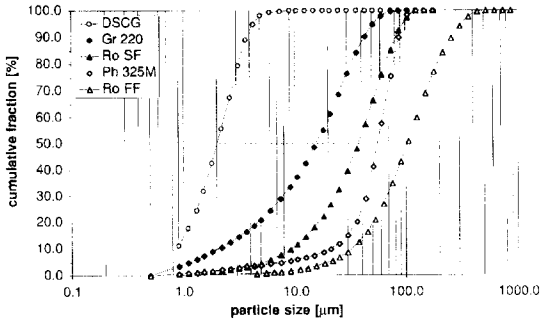

Fig. 3. Cumulative volume particle size distributions of DSCG, Granulac 220, Roferose SF, Pharmatose 325M and Roferose FF.

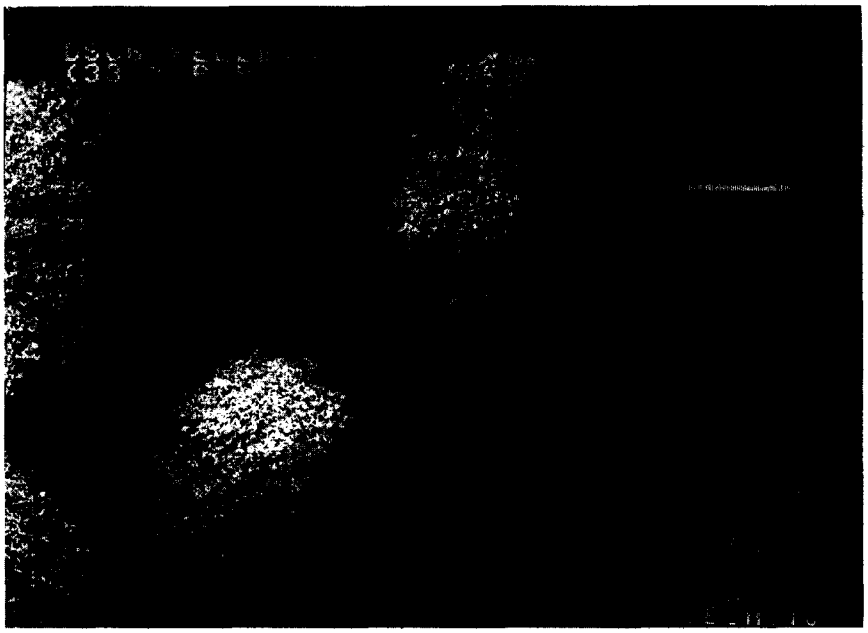

Fig. 4. SEM of pure DSCG agglomerates after storage at 33% RH (magnification 150 ×).

therapy, because only single separated drug particles are able to be delivered to the lower airways. Agglomerates consisting of only two or three DSCG particles with a resulting diameter of about 6 μm or more have a markedly reduced probability of reaching the lung because of increased inertia. Adhesion and cohesion forces are influenced by several parameters such as moisture, surface roughness, particle size, particle shape and degree of crystallinity of the compound. Particularly, the particle size and moisture content are main factors influencing the cohesiveness of a powder. This can be seen by comparing the two lactose grades used: the fine lactose type Gr 220 is a cohesive poorly flowing substance, whereas the coarser Ph 325M is a comparably excellently flowing powder. Micronized DSCG as an extremely fine material tends to adhere to almost any surface at low moisture content due to electrostatic charge, but when exposed to humid air, it becomes more and more cohesive forming agglomerates and losing its adhesion tendency. Fig. 4 shows a micrograph of round shaped DSCG agglomerates after storage at 33% RH. They exhibit a smooth surface and the diameter measured is about 250 μm. As DSCG is known to be a drug that absorbs water from the atmosphere rapidly (Cox et al., 1971; Bell et al., 1973), the increase in cohesiveness with rising moisture content must be due to the absorbed and adsorbed water, respectively. All powder mixtures were prepared with dried DSCG at low relative humidity, so that the bonds between DSCG particles could be broken during the mixing and sieving processes. At the same time, new bonds could be formed between drug and carrier particles. The number of drug/carrier bonds depends on the number of carrier particles added and this number depends on the mean particle size and the size distribution width of the carrier material. In Fig. 5 an agglomerate composed of DSCG and Ph 325M in a 1 + 1 mixture is shown. The surface of the agglomerate looks similar to that of the DSCG agglomerate shown in Fig. 4, but additionally there are some Ph 325M particles coated with DSCG. In Fig. 6 the agglomerate consisting of DSCG and Gr 220 (1 + 1) shows a rough surface with cavities and many Gr 220 particles are incorporated in the agglomerate. In the case of the Gr 220 mixture, the excipient works as a diluent separating the

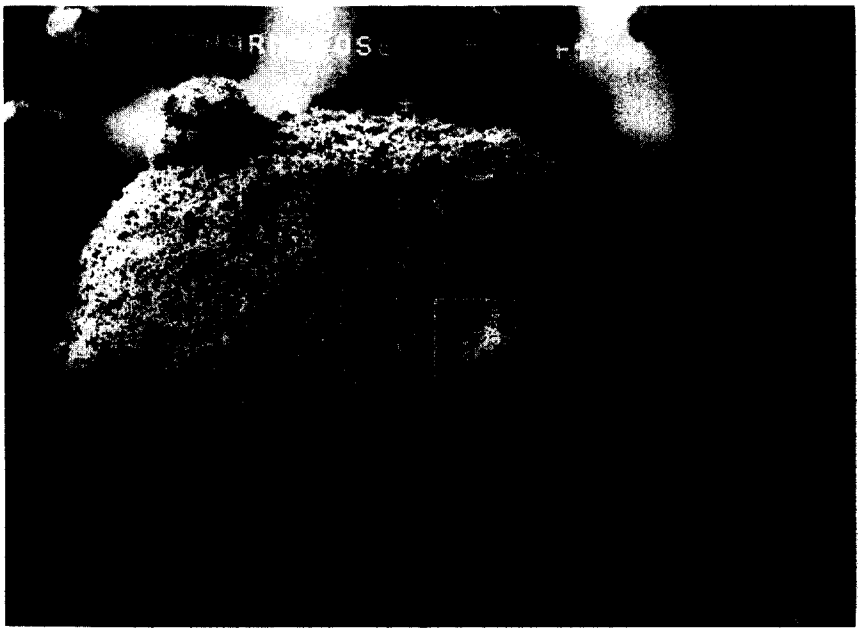

Fig. 5. SEM of an agglomerate consisting of equal parts of DSCG and Ph 325M (magnification 150 ×). An attached Ph 325M particle is marked by the white frame.

drug particles and weakening the stability of the spheres. In the DSCG/Ph 325M mix the excipient particles are attached to the agglomerate surface separating the agglomerates and improving their flowability. As most excipient particles are not incorporated in the spheres in this case, they only have little influence on the stability of the agglomerates.

The influence of humidity on the binding forces within a drug/carrier mixture could be evaluated by measuring the dispersability of the mix after storage at different humidities. If there is no influence, the amount of drug reaching the lower impingement chamber of the TI should not decrease with increasing storage humidity. However, Fig. 7 illustrates that there is a change in deposition pattern in the TI with modified storage humidity. It shows the deposition pattern of a powder blend containing equal amounts of DSCG and Ph 325M after storage for 27 days at 55% RH and at 33% RH. While the total dose, that is the sum of DSCG fractions determined in the TI and capsule, decreases with decreasing storage humidity, the fine particle fraction in the lower impingement chamber increases markedly. The portion of DSCG impinged to the upper chamber varies slightly, whereas in the middle chamber it drops from 42.8% at 55% RH to 22.7% at 33% RH. At the same time, the drug dose delivered to the lower impingement chamber and the remainder in the Microhaler® rises from 22.3 to 34.4% and from 13.5 to 25.2%, respectively. The capsule is emptied to nearly 100% in both cases. Deviating from the presented data, Vidgren et al. (1989) found no difference between DSCG/lactose blends (1 + 1) in terms of fine particle fraction delivered by a DPI device (ISF Inhalatore, Italy) after storage at different humidities. The fraction below 7.1 μm in diameter was determined as being 30.3–32.9% after the mixture was stored at 0, 20, 40, 60 and 79.5% RH for 10 days. When the same experiments were performed with spray-dried DSCG, the fine fraction decreased to 17.1 and 8.8% at the 60 and 79.5% RH level. According to Chan and Pilpel (1983), there is no change in binding properties of DSCG agglomerates with changing storage humidity. In our experiments, the increase in the lower and the decrease in the middle chamber indicate that the binding forces acting within powder agglomerates rise when the

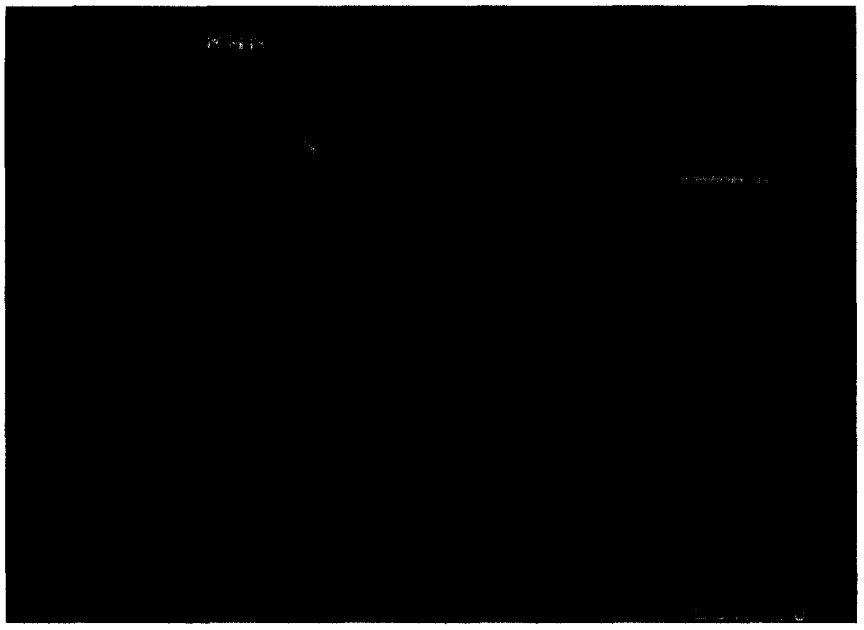

Fig. 6. SEM of an agglomerate consisting of equal parts of DSCG and Gr 220 (magnification 150 ×).

formulation is exposed to the higher humidity level. They are highly dependent on the water content of the active ingredient DSCG, because α-lactose monohydrate does not take up water in the range 33–55% RH (Callahan et al., 1982). DSCG on the other hand takes up water rapidly with increasing relative humidity. One possible explanation for the contradictory results could be the formation of soft agglomerates during our preparation process leading to a change in binding properties between the powder particles (Eaves and Jones, 1970). The other mixes evaluated show similar in vitro behavior to that of the DSCG/Ph 325M mix. Fig. 8a and Fig. 8b show the results of the determination of the fine particle fraction for all evaluated powder blends after a storage period of 27 days. The results are expressed as a percentage of the loaded dose. In all cases, there is a large influence of storage humidity on the delivery of the drug to the lower compartment of the TI, and the deposition pattern of the other formulations looks similar to those above. Fig. 8a shows the deposition pattern of the blends with α-lactose monohydrate and Fig. 8b the blends with dextrose monohydrate. It turns out that the pattern of the Gr 220 mixes is similar to that of the Ro SF mixes. Comparing the Ph 325M and Ro FF blends, a similar deposition pattern is found. In both cases the coarser excipient of the same chemical compound delivers lower DSCG amounts to the lower impingement chamber than the finer one. After storage at 33% RH, the mixes DSCG/Gr 220 (1 + 1) and DSCG/Ro SF (1 + 1) deliver very high fine particle fractions determined as being 41.1 and 37.84%, respectively.

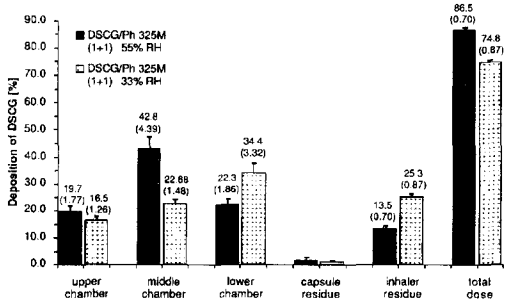

Fig. 7. Deposition pattern of the DSCG/Pharmatose 325M (1 + 1) mixture after storage for 27 days at 55% RH (■) and 33% RH (■). Bars represent the mean of three determinations, error bars = ± standard deviation.

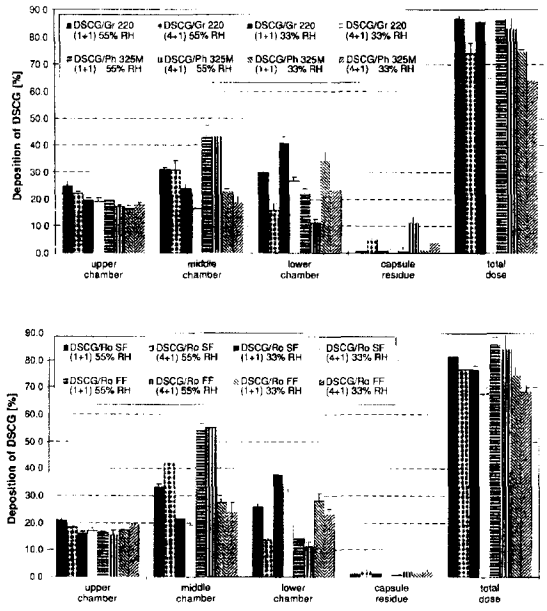

Fig. 8. (a) Deposition pattern of mixtures containing DSCG and the excipients Granulac 220 and Pharmatose 325M after storage for 27 days at 55% RH and 33% RH. Bars represent the mean of three determinations, error bars = ± standard deviation. The difference between the total dose and 100% is the remainder in the inhaler device. (b) Deposition pattern of mixtures containing DSCG and the excipients Roferose SF and Roferose FF after storage for 27 days at 55% RH and 33% RH. Bars represent the mean of three determinations, error bars = ± standard deviation. The difference between the total dose and 100% is the remainder in the inhaler device.

The extent to which a change of storage humidity affects the fine particle fraction of the evaluated powder inhalation depends on different parameters. The first parameter is the drug/carrier ratio, which is shown in Fig. 9. The fine fraction delivered by the preparation that was stored for 55 days at 55% RH is plotted as a percentage of that fine fraction found for the same preparation stored at 33% RH. The values are calculated as follows:

$$\text{Deposition change (\%)} = \frac{\text{DSCG in lower compartment at 55\% RH}}{\text{DSCG in lower compartment at 33\% RH}} \times 100$$

With this value calculated to be 79.8% in the case of the mixture DSCG/Gr 220 (1 + 1), the influence of humidity is low compared to the mixture DSCG/Ro FF (1 + 1). The latter formulation is much more affected by the humidity. After storage at 55% RH only 47.2% of the DSCG that was delivered by the same mixture stored at 33% RH is determined in the lower impingement chamber. All mixtures with low carrier percentage are affected by storage humidity to about the same extent, but again there is the same order found. Mixtures containing Gr 220 show the smallest, while the mixtures with Ro FF show the highest, change in dispersability with modified storage humidity. At both evaluated drug/carrier ratios, the mixtures containing either Ph 325M or Ro SF seem to be affected by the humidity to the same extent. The second parameter besides the drug/carrier ratio is the particle size distribution of the excipient used. The particle size distributions of the constituents in Fig. 3 show different distribution types and ranges. Gr 220 is the finest material, whereas Ro FF is the coarsest. The range of Ro SF and Ph 325M is about the same, but Ro SF has a considerably greater fine particle fraction. The in vitro testing results in Fig. 8 combined with the particle size distribution data lead to the following conclusion. It is not necessarily the chemical type, but more the physical characteristics of the excipient that determine the dispersability of a dry powder inhalation. The finer the carrier particles, the higher the number of particles per unit, and with an increasing carrier

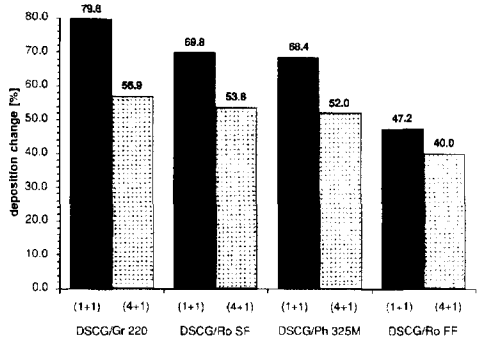

Fig. 9. Influence of storage humidity on the fine particle fraction delivered by DSCG/excipient mixtures. The values represent the percentage of the fine particle fraction of mixtures stored at 55% RH in relation to the fraction delivered after storage at 33%.

particle number, the number and size of DSCG clusters within an agglomerate decreases. Bonds between DSCG particles are stronger than bonds between DSCG and carrier particles. The excipient particles disturb the 'lattice' of DSCG particles and the agglomerates can be destroyed by the turbulent airstream that passes the rotating capsule in the inhaler device.

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