Evaluation of the Adhesion Properties of Salbutamol Sulphate to Inhaler Materials

F. Podczeck[1,2]

Received November 18, 1997; accepted February 20, 1998

KEY WORDS: powder inhalations; inhaler devices; gelatin capsules; adhesion; salbutamol sulphate.

INTRODUCTION

The development of dry powder inhalations as a suitable dosage form involves not only the manufacture of a balanced powder mixture to be inhaled, but also the use of an efficient inhaler device. Inhaler devices for dry powders were initially developed for patients who have problems coordinating inspiration and actuation of metered dose inhalers. The breath actuation of a dry powder inhaler was thought to be a major step forward in overcoming such problems (1). To date, several dry powder inhalers are on the market, which are different, for example, in their air flow resistance, (2) and in the way the air passes the device when emptying the single dose unit during inhalation. These two differences explain variations in the loss of drug in the device (3). However, a further difference is in the packaging, which contains the single dose units. Some inhalers use hard gelatin capsules (e.g. Spinhaler®, Inhalator M®, Rotahaler®), while others use polyamide/aluminium foil blisters (Diskhaler®, Diskus®). Steckel & Müller (4) compared several inhaler devices. Apparently, those devices using gelatin capsules showed a higher loss than those using polyamide/aluminium foil blisters. Also, the Turbuhaler®, which uses neither of these single dose containers, was characterized by a slightly larger loss in the device. These authors attributed this effect to the previously mentioned reasons, but did not provide any experimental measurement for the adhesion forces involved. However, it appears likely that drug is also lost due to adhesion to the capsule shell wall and the inhaler device walls, but to date, no comparison of the adhesion properties of drug particles to hard gelatin capsule shells and inhaler device materials has been performed.

MATERIALS AND METHODS

Salbutamol sulphate (batch WNC80006; Glaxo-Wellcome Research and Development, Ware, UK) has been used as a model drug. Its mean particle size (equivalent circle diameter) was 2.68±1.54 μm (Image analyzer Seescan Solitaire 512; Cambridge, UK). Inhaler device surfaces used were PVC, Polythene, and Acetal® (Hoechst AG, Frankfurt, Germany). Gelatin capsule shells could not directly be used, because they do not provide a flat surface for adhesion force measurements. Thus, gelatin films were obtained (Capsugel, Colmare, France), which are equal in composition and physical properties to hard gelatin capsules made by the same company. The 4 types of gelatin film used are (1) plain gelatin, i.e. no additives, (2) transparent yellow, which contained 0.05% quinoline yellow as a colorant, (3) white opaque, which contained 2% titanium dioxide as pigment, and (4) blue opaque, which contained 1% titanium dioxide as pigment and 0.13% indigo carmine as colorant.

The adhesion force measurements were undertaken using the centrifuge method previously described by Podczeck & Newton (5). The gelatin films were glued onto support disks, whereas the inhaler device materials were cut into disks of appropriate size. Particles were adhered to the surfaces and subjected initially to a press-on force. They were detached from the surfaces by applying a series of spin-off forces, until a complete adhesion force distribution had been obtained. The adhesion force distributions were evaluated using the median adhesion force and the interquartile range (spread). The results are the mean and standard deviation of 4 replicates, thus representing the adhesion force distribution of about 2000 particles.

The surface roughness of the test materials was obtained using a non-contact laser profilometer (UBM, Ettlingen, Germany). An area of 3×6 mm was measured using a resolution of X=500 points/mm and Y=20 points/mm on four different disks per surface material.

RESULTS AND DISCUSSION

During breath actuation of a dry powder inhaler, particles are accelerated by the air stream and likely to collide with the inhaler device walls. The force acting on a particle during collision can be calculated from (6):

$$F_{acc} = \frac{\pi}{6} d_p^3 \rho_p \frac{dv_{rel}}{dt} \quad (1)$$

where F_{acc} is the force of acceleration, d_p is the particle diameter, ρ_p is the particle density, v_{rel} is the average velocity of the air stream, and t is the time of acceleration. In the in vitro-experiments to test the performance of dry powder inhalers, a volume flow between 28.3 and 90 l/min usually is used. The average velocity of the air stream can be calculated from the volume flow as follows:

$$V_{rel} = \frac{V_{vol}}{t \cdot A} \quad (2)$$

where V_{vol} is the volume flow, t is the flow time (to be assumed 1 s for inhalation), and A is the cross area, through which the air stream passes (1 m^2). Steckel & Müller (4) used 30 l/min to test the Inhalator M® and some other devices. This is equivalent to a value of F_{acc} of 2.72×10^{-9}N. It appeared therefore reasonable to use a similar press-on force in the adhesion experiments. The centrifuge allows increases in centrifugal speed in steps of 1000 rpm. The nearest press-on force that could be achieved was 2.67×10^{-9}N, a value which can be considered to be satisfactorily close to the value of F_{acc} used by Steckel & Müller (4). Due to the large adhesion forces obtained under this condition, a second reduced press-on force

[1] Department of Pharmaceutics, The School of Pharmacy, University of London, UK.

[2] To whom correspondence should be addressed. (e-mail: podczeck@cua.ulsop.ac.uk)

0724-8741/98/0500-0806$15.00/0

Table I. Median Adhesion Force (F_{ad}) and Interquartile Range (*IQR*) of Salbutamol Sulphate Adhered to Various Inhaler Device Surfaces and Gelatin Films F_{on}, Press-on Force

	F_{on}			
	1.50×10^{-9}N		2.67×10^{-9}N	
Surface	$F_{ad}[\times10^{-9}N]$	IQR $[\times10^{-9}N]$	$F_{ad}[\times10^{-9}N]$	IQR $[\times10^{-9}N]$
Transp. yellow	11.35±2.61	23.70±5.00	22.42±3.77	38.28±3.66
Plain gelatin	12.60±3.73	27.34±3.19	17.46±0.83	33.54±4.12
White opaque	9.65±1.54	25.74±8.06	33.67±1.33	71.50±4.06
Blue opaque	26.26±0.20	51.28±5.34	34.27±7.52	70.52±1.92
PVC	2.26±0.49	8.32±1.36	5.37±1.75	19.33±1.24
Acetal	5.27±0.29	16.87±2.80	12.44±4.30	33.04±9.09
Polythene	11.12±2.89	27.32±8.46	12.03±0.26	29.49±2.95

of 1.50×10^{-9}N was additionally tested. This reduced press-on force reflects situations of simple mechanical powder and inhaler handling. The median adhesion forces observed and the interquartile ranges are listed in Table I.

Using the lower press-on force, PVC and Acetal surfaces provided the lowest median adhesion force, whereas the median adhesion forces and interquartile ranges obtained on all other surfaces except for blue gelatin are statistically the same (ANOVA). In contrast, the adhesion force between drug and blue gelatin surfaces is comparatively high. However, using the press-on force of 2.67×10^{-9} N simulating air stream impingement, the adhesion forces obtained on plastic inhaler device surfaces are significantly lower than those found on gelatin surfaces. If the gelatin surfaces are to be used and a low adhesion force achieved, plain gelatin appears to be the most appropriate form, and transparent yellow gelatin might also be a possible packing material. However, those gelatin capsules containing the pigment obviously gave a poorer performance for the use as single dose units in dry powder inhalers.

The difference between blue and white gelatin observed at a press-on force of 1.5×10^{-9} N could be due to the reduced pigment content in the blue gelatin. Titanium dioxide is known to reduce electrostatic charging (7). At higher press-on forces, i.e. under air stream test conditions, the electrostatic properties have obviously lost their importance with respect to the adhesion properties of the surfaces. The increase in adhesion force with increased press-on force is more pronounced for the gelatin surfaces than for the plastic surfaces. Gelatin films provide elastic, deformable surfaces (8). A certain amount of plastic deformation is necessary with respect to the capsule filling process and the result of the water content of the gelatin (9). Although the Youngs's moduli for the plastic surfaces are also very small, suggesting a large degree of elastic deformability (10), they were found to be rather hard (11), which suggests plastic deformation would occur to a lesser degree. Hence, the marked increase in adhesion force due to an increase in press-on force observed using gelatin surfaces might be due to their higher plasticity. The difference between the adhesion forces obtained on plastic and gelatin surfaces in general, however, appears also to be related to differences in the surface roughness. The plastic surfaces were found to have an average roughness of 0.25, 0.44, and 0.56 μm for PVC, Acetal, and Polythene, respectively. The average roughness for the gelatin surfaces increased in the order 0.50 μm (plain gelatin), 0.55 μm (transparent yellow), 0.75 μm (white opaque), and 1.11 μm (blue opaque). Increased surface roughness can increase the adhesion force between particles and surfaces if the particles are very small and thus can slip into the valleys between individual asperities (12). The adhesion force between drug and PVC surfaces was indeed the smallest, while that for blue gelatin, which had the largest surface roughness, was found to be at a maximum.

The results suggest that the loss of drug in a dry powder inhaler device can be caused by the material of the single dose containers. Hard gelatin capsules might have the potential to retain more drug due to adhesion than, for example, plastic blisters. Those gelatin capsules which contain pigments appear to be especially prone to adhesion.

REFERENCES

1. R. Fuller. Powder inhalers, past, present and future. In: *Proc. Drug Delivery to the Lungs VI,* The Aerosol Society, London, 1995, p. 53.
2. A. H. de Boer, H. M. I. Winter, and C. F. Lerk. Inhalation characteristics and their effects on in vitro drug delivery from dry powder inhalers Part 1. Inhalation characteristics, work of breathing and volunteers' preference in dependence of the inhaler resistance. *Int. J. Pharm.* **130**:231–244 (1996).
3. A. H. de Boer, D. Gjaltema, and P. Hagedoorn. Inhalation characteristics and their effects on in vitro drug delivery from dry powder inhalers Part 2. Effect of peak flow rate (PIFR) and inspiration time on the in vitro drug release from three different types of commercial dry powder inhalers. *Int. J. Pharm.* **138**:45–56 (1996).
4. H. Steckel, and B. W. Müller. In vitro evaluation of dry powder inhalers I: drug deposition of commonly used devices. *Int. J. Pharm.* **154**:19–29 (1997).
5. F. Podczeck, and J. M. Newton. Development of an ultracentrifuge technique to determine the adhesion and friction properties between particles and surfaces. *J. Pharm. Sci.* **84**:1067–1071 (1995).
6. I. Stenhouse, Fundamentals I. In: *Proc. Aerosol Measurement,* Loughborough, 1987, pp. 1–22.
7. E. T. Cole. Hartgelatinekapseln. In: H. Sucker, P. Fuchs, and P. Speiser (eds), *Pharmazeutische Technologie.* Georg Thieme Verlag, Stuttgart, 1991, pp. 319–320.
8. R. T. Jones. Gelatin: Physical and chemical properties. In: K. Ridgway (ed) *Hard Capsules: Development and Technology,* The Pharmaceutical Press, London, 1987, pp. 31–48.
9. O. Berntsson, G. Zackrisson, and G. Östling. Determination of moisture in hard gelatin capsules using near-infrared spectroscopy: applications to at-line process control of pharmaceutics. *J. Pharm. Biomed. Anal.* **15**:895–900 (1997).
10. F. Podczeck, J. M. Newton, and M. B. James. The adhesion force

of micronized Salmeterol Xinafoate particles to pharmaceutically relevant surface materials. *J. Phys. D: Appl. Phys.* **29**:1878–1884 (1996).
11. F. Podczeck, J. M. Newton, and M. B. James. The estimation of the true area of contact between microscopic particles and a flat surface in adhesion contact. *J. Appl. Phys.* **79**:1458–1463 (1996).
12. A. D. Zimon. *Adhesion of Dust and Powder,* Consultants Bureau, New York, 1982, p. 154.