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Effect of powder inhaler design on drug deposition in the respiratory tract

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Summary

Disodium cromoglycate particles were labelled with pure γ-radiator, ^{99m}Tc, using the co-precipitation technique based on spray drying. Radioactive drug particles were mixed with lactose carrier and filled into hard gelatin capsules. Seven healthy volunteers inhaled drug doses using Spinhaler, I.S.F., Berotec, and Rotahaler dry powder devices. The fractional deposition of drug particles in the upper airways and lung region were monitored using a gamma camera. The fraction of the dose retained in the powder inhaler was the smallest for I.S.F. and especially for Berotec inhalers. These devices have narrower air channel constructions with a smaller wall surface area than the Spinhaler and Rotahaler devices. Thus the sticking of the drug particles onto the plastic walls was less probable for the first-mentioned devices. The drug particles from all the dry powder inhalers seemed to be more able to follow the inspired air stream without depositing in the upper airways than previously documented for pressurized metered dose aerosols. I.S.F. and Berotec inhalers with narrow air channels gave the greatest lung deposition of the inhaled drug particles. Thus the design of the dry powder inhaler was noticed to have a remarkable effect both on the emptying of the capsules as well as on the redispersion of the powder mixture.

Introduction

Pressurized metered dose aerosols are primarily used in inhalation therapy of asthma. The administration of antiasthmatic agents from pressurized aerosols requires the co-ordination of the dose delivery with the inspiration. On average, 14% of asthmatic patients have been found to misuse their metered dose aerosols (Crompton, 1982). The dry powder inhalers have been introduced in order to avoid this synchronizing problem as well as to reduce the non-therapeutic fraction of the drug dose deposited in the mouth and oesophagus.

Dry powder dosage forms are generally formulated by mixing the cohesive micronized drug particles with the larger carrier particles. Thus it is possible to enhance the flowability of powder mixtures and therefore to enable the accurate filling of gelatin capsules primarily used as unit dose system in the dry powder dosage form. Lactose is a commonly used carrier. During the inhalation, the drug particles are dispersed from their agglomerations or from the surface of carrier particles by the energy of the inspired air flow. Redispersed small drug particles should be deposited in

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the therapeutically significant regions of the lungs. This separation stage is the critical phase from the point of view of drug response (Byron, 1986). It has been pointed out that the particle size of drug particles should be under 7 μm for accomplishing the penetration into the therapeutically significant region of the respiratory tract (Davies et al., 1976).

Before the inhalation, the drug capsules must be inserted in the dry powder inhaler and either opened or pierced by the patient. For delivering the inhalation drug dose several devices with different constructions have been introduced. The first dry powder inhaler introduced by Bell et al. (1971) is called the Spinhaler. In this device a gelatin capsule is connected with a rotor and pierced with metal needles. During the inhalation the capsule revolves with the rotor and the powder disperses through the holes on the sides of capsule walls into the relatively wide air channels. It has been noticed that the walls of the gelatin capsule vibrate with a high frequency when the air flow rate exceeds 35 litres/min (Bell et al., 1971). This flow rate is the minimum for generating the effective dispersion of the fluidized powder mixture into the inhaled air. In another powder inhaler, marketed by I.S.F., the gelatin capsule is pierced at both ends by the means of small needles (Cocozza, 1976). During the inhalation the capsule rotates in a small chamber like a propeller and the powder disperses through the holes into the inspired air. Both Spinhaler and I.S.F. inhalers are commercially used for delivering disodium cromoglycate powders.

Using a powder inhaler introduced by Steil (1975), drug powder is inhaled through the pierced holes of the stationary capsule. In this device no mechanical movements exist during the inhalation and thus the only factor for redispersing the powder mixture is the energy of the inspired air flow. The bronchodilator agent, fenoterol, is administered in powder form using this inhaler. In this paper this device is called Berotec inhaler according the the trade mark of fenoterol products.

Using the Rotahaler inhaler, gelatin capsules are divided into two halves by twisting the segments of the device (Power and Dash, 1985). The opened halves are dropped into a relatively large chamber and drug powder is liberated for inhalation. The Rotahaler is used for the administration of potent drugs such as salbutamol and beclomethasone dipropionate.

The efficiency of the inhalation therapy is usually evaluated by measuring the therapeutic response of the inhaled drug dose. In numerous studies an equal clinical response of the conventional aerosol and dry powder drug forms has been detected (Hetzel and Clark, 1977; Harris and Rothwell, 1981; Boner et al., 1985). For studying the in vivo dispersing ability of different drug forms and differently constructed inhalers these kinds of clinical studies are, however, very laborious and expensive to perform and furthermore they do not give accurate information from the deposition of drug particles in the respiratory tract.

As far as the authors know, no comparison studies concerning the effect of the construction of the dry powder inhaler on the respiratory tract deposition of inhaled drug particles have been published. Recently Vidgren et al. (1987a) have described a new method for evaluating the actual deposition of radioactively labelled drug particles into the human respiratory tract. This method is based on the labelling of drug particles using the spray drying technique and it is equally suitable for detecting the deposition of drug particles after administration either from metered dose aerosols or from dry powder devices (Vidgren et al., 1987b and c).

In this study disodium cromoglycate particles were labelled with a pure γ-radiator, ^{99m}Tc. Labelled disodium cromoglycate particles were mixed with lactose carrier and inhaled by 7 healthy volunteers using 4 powder inhalers. After inhalation, fractional deposition patterns of radioactive drug particles were determined by the means of a gamma camera.

Materials and Methods

Labelling and evaluation of the drug particles

Disodium cromoglycate (BP 1980; Chemisell, Italy) particles were labelled using the spray drying technique previously described by Vidgren et al. (1987a). Spray drying method as well as the

physical properties of the labelled drug particles are described in the above-mentioned article. The mean aerodynamic diameter with the standard error of the mean for the spray-dried disodium cromoglycate particles labelled by this method was 3.8 ± 0.05 μm.

Preparation of the dry powder capsules

Equivalent amounts of ^{99m}Tc-labelled disodium cromoglycate particles and 325 mesh α-lactose monohydrate particles (DMV, Veghel, Holland) were mixed for 15 min in a 250 ml glass vessel (Turbula, type 2P mixer, Switzerland). Forty mg of the mixed powder per capsule were filled into hard gelatin capsules with a suitable size for each device. Each delivered dose thus contained 20 mg of labelled disodium cromoglycate. This amount as well as the drug–lactose share used are the same as mentioned in the British Pharmacopoeia under the monograph "Sodium cromoglycate insufflation". The amount of the active substance was also the same as declared for the commercially available dry powder preparation (Lomudal, Fisons, U.K.) containing disodium cromoglycate. The radioactivity of the content of one gelatin capsule was about 8 MBq (200 μCi).

Delivery of the inhalation doses

Seven healthy informed volunteers took part in the inhalation test which was conducted under medical supervision. Before inhalation, the lung function was measured and the 80% lung volume of the maximum vital capacity was carefully trained. It was noticed that all the volunteers were able to repeat this volume with lower deviation than 5%.

The dry powder packed in the gelatin capsules was delivered with the following commercial inhalers: Spinhaler (Fisons, U.K.), I.S.F. Inhaler (I.S.F., Italy), Berotec Inhaler (Boeringer-Ingelheim, F.R.G.) and Rotahaler (Glaxo, U.K.). Every patient had own powder inhalers for ensuring that the delivering devices were dry and clean. The content of one capsule was administered from the powder inhaler as carefully as possible by the 80% volume of the breath from the maximum forced vital capacity. The inhalation was done using approximately a flow rate of 55–70 litres/min. Inhalation was performed twice and followed both times by 5 s of breath-holding. The activity retained in a dry powder inhaler was measured immediately after the inhalation.

Measurement and calculation of the deposition

The measurements of deposition by the means of gamma camera were done as described previously by Vidgren et al. (1987a). The radiation dose to the lung resulting from one dry powder capsule does not exceed 8 mrad.

Statistical testing

The experimental data were not assumed to be normally distributed and the Kruskal-Wallis nonparametric test was used for analysis of variance by ranks.

Results and Discussion

The deposition of inhaled drug particles in the human respiratory tract is strongly dependent on the inhalation technique, the formulation factors as well as on the construction of the powder inhaler. Depending on the chemical and physical nature, especially on the particle size of the materials used in formulations, there exist different cohesive and attractive forces between the drug particles and between the drug and carrier particles. These forces induce the particles to adhere more or less firmly together. During the inhalation the only available energy for emptying the gelatin capsules and for dispersing the micronized drug particles from their agglomerations and from the surfaces of carrier particles is the energy of the inspired air flow. Depending on the formulation of the inhaled powder mixture the differently effective air flow is required for dispersing the dry powder mixture. It has been pointed out that turbulent air flow is more effective than laminar flow for dispersing the powder mixture (Moren et al., 1985). The high air velocities are more prone to induce turbulent air flow than low velocities (Barrow, 1973). The velocity of the inspired air flow as well as the inspired air volume are, however, limited. Thus the air channels of the inhaler should induce enough strong movements

in the passing air flow for the dispersing of the particles.

In this work identical disodium cromoglycate–lactose powder mixtures were inhaled using 4 powder inhalers. Drug doses were inhaled with volume of the breath and flow rate as similar as possible to minimize the differences in the available air flow energy as well as in the inhalation techniques. Therefore it was possible to compare the ability of the differently constructed inhalation devices to deposit inhaled drug doses in the respiratory tract. It must, however, be remembered that some commercial inhalers are constructed for delivering a specially formulated drug–carrier mixture which might disperse more effectively than the test powder used in this study. Thus the results obtained using this test powder do not directly predict the efficiency of the inhalers to distribute commercial powder mixtures.

Individual results for fractional deposition in Fig. 1 point out that relatively large deviations existed between volunteers. This is partially due to the differences in inhalation techniques and partially to the differences in anatomy and functioning of the lungs. Taking into account that the same volunteers inhaled the drug doses from all the inhalers and that the standard errors of the mean for fractional deposition values in Table 1 are relatively small, reliable conclusions are, however, able to be drawn.

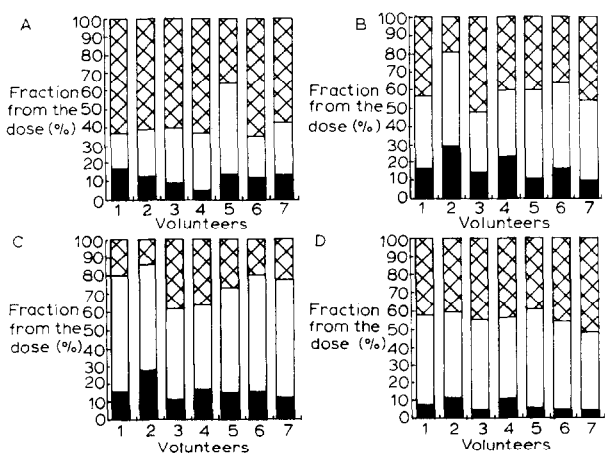

Fig. 1. Fractional deposition of ^{99m}Tc labelled particles of disodium cromoglycate separately in 7 volunteers after administration of dry powder dosage form using Spinhaler (A), I.S.F. Inhaler (B), Berotec Inhaler (C), and Rotahaler (D). Key: ■ = lungs; □ = upper airways; ⊠ = device.

TABLE 1

The mean fractional deposition ± S.E. for ^{99m}Tc-labelled particles of disodium cromoglycate after administration of dry powder drug form using 5 inhalers

Inhaler	Fraction from the dose (%)		
	Lungs	Upper airways	Device
Spinhaler	11.5 ± 3.8	30.9 ± 10.1	57.6 ± 10.2
I.S.F.	16.4 ± 2.6	44.0 ± 2.5	39.6 ± 3.9 *
Berotec	16.0 ± 2.1	59.0 ± 2.8 **	25.0 ± 3.5 **
Rotahaler	6.2 ± 2.9 *	50.1 ± 4.4 *	43.8 ± 4.5

* $P < 0.05$, ** $P < 0.01$ compared to Spinhaler (Kruskal-Wallis test), $n = 7$.

There existed significant variations of dose retainment in the powder inhalers (Fig. 1 and Table 1). The largest fraction of drug dose retained in the inhaler was in the Spinhaler powder device. The test powder impacted quite tightly along the capsule walls during the high frequency rotation of the rotor. The same kind of phenomenon has been previously documented by Bell et al. (1971). According to their study this phenomenon can be avoided using coarser carrier particles. Thus it seems that the Spinhaler device is extremely sensitive toward the formulation factors and that the test powder used in this study was not suitable to be inhaled with the Spinhaler powder device. The volunteers were able to empty the capsules quite satisfactorily using all the other 3 inhalers. The lowest amount of the drug dose was retained in the Berotec powder device. In this inhaler the pierced capsule is placed in a narrow tube where the inspired air penetrates effectively through the stationary capsule. Dry powder is liberated from the capsule straight into the air channel and follows directly the inspired air flow. All the other devices have wider air channel and chamber constructions with larger wall surfaces. Thus the adhering of drug particles into the plastic walls is more probable. Also, the chemical and physical nature of the plastic walls might be different and thus the particles may have different tendencies to adhere on the walls of the inhalers.

It has been widely documented that over 80% of the drug dose inhaled with metered dose aerosols deposited in the mucosa of the upper airways (Newman et al., 1981; Vidgren et al., 1987a and b). This might cause serious local side-effects such as candidiasis. After the swallowing also the systemic side-effects may exist. With all the dry powder inhalers the fraction of the drug dose deposited in the upper airways was significantly smaller than the previously reported results obtained after administration from the pressurized aerosols (see Fig. 1 and Table 1). The delivery of aerosol dose by the means of high pressure gives the particles a rather high velocity which leads to the inertial impaction of the particles onto the mucosa of the upper airways. In addition, the improper evaporation of the liquid propellants causes the collision of wet and relatively large droplets on the moist mucosa (Moren and Anderson, 1980). Although the relatively high velocities of inspired air flow are also needed for activating the powder dose from dry powder inhaler, the drug particles seem to be more able to follow the inspired air stream without impacting onto the airway walls.

The nature of the air flow can be described by the means of the Reynolds number (Barrow, 1973)

$$\text{Reynolds number} = \frac{dv\sigma}{\eta} \qquad (1)$$

where d is the tube diameter, v is the air velocity, σ is the air density and η is the air viscosity. Using this numerical parameter it is possible to separate the laminar and turbulent flow types. The large Reynolds numbers indicate turbulent air flow and the small numbers laminar air flow. The accurate calculation of the Reynolds numbers for the air flow passing through the inhalers is very difficult because of the complicated constructions of the air channels in these devices. According to the Eqn. 1 it is, however, possible to deduce that the smaller the diameter of the air channel, the more turbulent the air flow. I.S.F. and especially Berotec devices have clearly narrower air channels than Spinhaler and especially Rotahaler devices. Thus it is reasonable to assume that I.S.F. and Berotec inhalers are more prone to produce turbulent air flow and effective dispersion of powder mixtures compared to the Spinhaler and Rotahaler inhalers. The results in Table 1 confirm these assumptions. The drug particles administered either from the I.S.F. or Berotec devices deposited more drug into the whole lung area. Thus the fraction of the liberated primary drug particles which are able to be deposited in the therapeutically important lower parts of respiratory tract is larger after administration from these devices than from Rotahaler and Spinhaler devices. Furthermore, using I.S.F. and Berotec inhalers drug particles seemed to be distributed more effectively

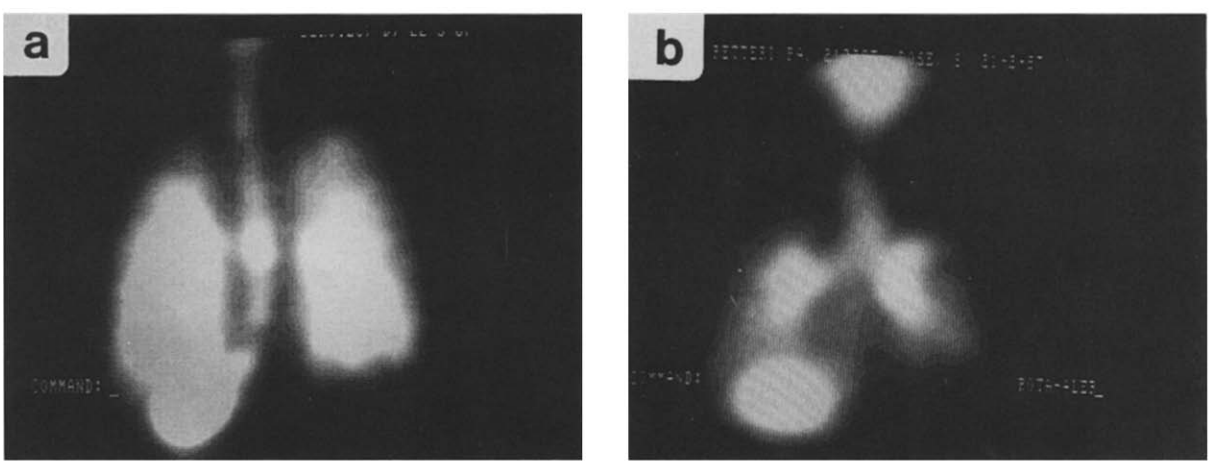

Fig. 2. Typical gamma camera photographs from the deposition of ^{99m}Tc-labelled particles of disodium cromoglycate in the respiratory tract after administration of dry powder dosage form using Berotec inhaler (a) and Rotahaler (b).

into the peripheral parts of the lungs (see Fig. 2). The fraction of the dose deposited in the lung area is smaller for Spinhaler and Rotahaler and the drug particles seemed to form a collose on the mucosa of main bronchis (see Table 1 and Fig. 2). In this study as low an activity as about 200 μCi was used and thus it was not possible to calculate accurately the activity separately in the bronchial and alveolar parts of the respiratory tract.

In conclusion, the design of the dry powder inhaler affects both the emptying of the gelatin capsules and the redispersion of the drug–carrier powder mixtures. Thus the deposition of drug particles in the respiratory tract is strongly dependent on the construction of the air channels as well as on the mechanism used for emptying the gelatin capsules.

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