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IN VITRO AND IN VIVO DEPOSITION OF DRUG PARTICLES INHALED FROM PRESSURIZED AEROSOL AND DRY POWDER INHALER

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ABSTRACT

Disodium cromoglycate particles were labelled with a pure γ-radiator ^{99m}Tc using a novel co-precipitation technique based on spray drying. Metered dose aerosols as well as a dry powder dosage form were prepared using these labelled drug particles. Fractional deposition of the drug particles was determined in vivo by means of gamma camera. Inhalation patterns of seven healthy volunteers were compared to deposition patterns evaluated in vitro using a modified cascade impactor. On average only 9 per cent of the aerosol dose deposited in a whole lung area

and about 81 per cent in the upper airways of the volunteers. The in vitro results showed clearly greater deposition of the drug particles into the imitated bronchial and alveolar stages. The physiological factors of the human respiratory tract as well as the individual differences in the inhalation techniques seemed to have a significant influence to the deposition and aerodynamic behaviour of the inhaled drug particles. The in vitro results indicated, however, the similar differences between the two inhalation dosage forms as the in vivo evaluation did.

INTRODUCTION

Metered dose aerosols are primarily used to deliver antiasthmatic agents into the respiratory tract. The active substance is commonly suspended in liquided chlorofluorocarbon propellants and packed into a compact aerosol container. Through the metering valve patients can deliver an accurate dose of the drug during their inspiration. Although the metered dose aerosols are apparently easy to use, many patients found it difficult to release the aerosol dose in co-ordination with their inspiration (1). Using dry powder inhalers asthmatic patients can activate the delivery of the drug dose with their own inspiration (2). Thus dry powder inhalation has become an alternative drug delivery system to aerosol

therapy, especially for the patients who are not able to use metered dose inhalers correctly (3).

The efficiency of the inhalation therapy is usually evaluated by measuring the therapeutical response of the inhaled drug doses (4-7). For studying the dispersing ability of different dosage forms and differently constructed inhalation aids this kind of clinical studies are, however, very laborious and expensive to perform. Furthermore they do not give accurate information from the deposition of the drug particles in the respiratory tract.

In the formulating work of the new inhalation product it is very important to be able to screen the inhalation behaviour of the drug particles reliably with a suitable in vitro method. Different kinds of simulated respiratory systems which imitate respiratory airways have been constructed using metal, glass or plastic tubes (8,9). Perhaps the most frequently used in vitro method bases on the cascade impaction (10). This technique enables the collection of the aerosol cloud through a simulated throat in a way which imitates the in vivo situation. In the cascade impactor larger particles with sufficient inertia are impacted on the upper stages whereas finer particles are penetrated to the lower stages of the separator. Compared to the human respiratory tract all the in vitro models are of course very simplified. The number of levels of branching of the respiratory airways is limited and the airway surface is unnatural.

Practically all in vivo deposition studies have been performed using radiotracer techniques. Chemical labelling of the drugs commonly used in a management of asthma is often impossible because these molecules rarely contain an element with can be labelled with a suitable gamma radiator, which can be detected outside the body using gamma camera (11). Therefore non-medical Teflon particles labelled with ^{99m}Tc have been used as model particles in these studies (12-14).

Presupposition for the use of in vitro methods in the research and development work of inhalation dosage forms is that the results of in vitro test are relevant for predicting the behaviour of inhaled drug particles in the human respiratory tract. In this study the drug particle deposition after administration of the drug dose from a metered dose aerosol and from a dry powder inhaler was evaluated using both in vitro and in vivo methods. Deposition was analyzed in vitro using the modified cascade impactor. For the in vivo study the radioactive disodium cromoglycate particles were prepared using a novel labelling method based on spray drying technique (15). Fractional deposition patterns after inhalation of drug doses by seven healthy volunteers were obtained in vivo using a gamma camera. Special attention was paid for evaluating the correlation between the in vitro and in vivo deposition patterns of the two different inhalation dosage forms.

MATERIALS AND METHODS

Labelling and evaluation of the drug particles

Disodium cromoglycate (BP 1980, Chemisell, Italy) was dissolved in 50 ml of water to give a 6 % w/w solution. 1 ml of 0.9 % w/w sodium chloride solution containing ^{99m}Tc was added to the drug solution. This mixture was spray dried (Buchi Minispray drier, type 190, FRG) at the feed rate of 60 ml/min. The air input temperature during drying was about 180 ^{0}C and the outlet temperature was about 80 ^{0}C. The throughput of air was 2.4 m^{3}/min and the nozzle air pressure was 800 Nl.

The scanning electron micrograph taken from the spray dried disodium cromoglycate particles is in Fig. 1. The arithmetic mean diameter was evaluated microscopically measuring the Feret diameter of 400 particles. The value of the arithmetic mean diameter with the standard error of the mean was 2.8 +/- 0.04 microns. The behaviour of the particles in human respiratory tract is dependent besides on the particle size also on the density and shape of the particles. Thus it is customary to define an aerodynamic diameter to describe the size of particles moving in the airstream. The aerodynamic diameter is usually calculated by multiplying the value of the arithmetic diameter by the square root of the effective particle density. The value of mean aerodynamic diameter for spray dried disodium cromoglycate particles was 3.8 +/- 0.05 microns.

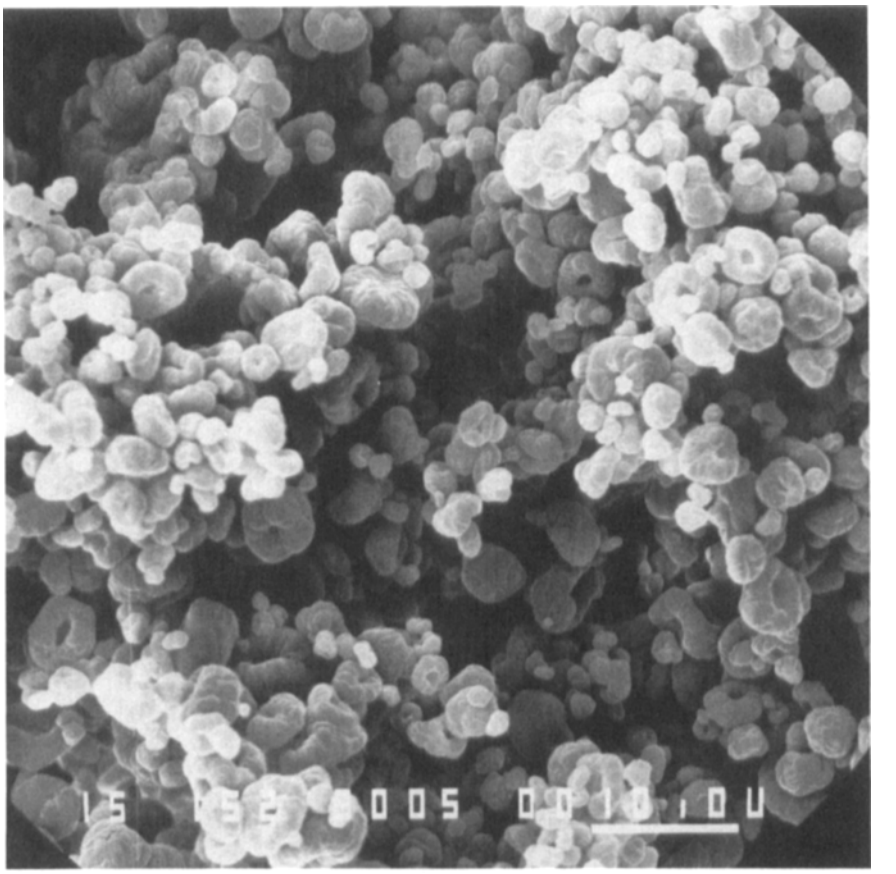

Figure 1

Scanning elctron micrograph of spray dried disodium cromoglycate. Bar = 10 μm.

Preparation of metered dose aerosol and dry powder dosage form

Firstly, 100 mg of sorbitan trioleas (Span 85, Atlas, Belgium) was dissolved in 20.7 g of liquided propellant dichlorodifluoromethane (Freon P12). Secondly, 6.21 g of liquided dichlorotetrafluoroethane (Freon P114) was added

into the mixture of P12 and Span 85 at the temperature of -70 ^{0}C. Thirdly, 2.53 g of ^{99m} Tc-labelled disodium cromoglycate was dispersed in the above mentioned solution using the homogenizer (Ultra Turrax, type TP 18-10, IKA Werk, FRG). The samples of 8.28 g of the suspension were filled into metal aerosol containers (Presspart, UK). The containers were closed with 50 µl metering valves (Riker, UK). 7.24 g of P12 was filled through the metering valve. Each dose contained 1 mg of ^{99m} Tc-labelled disodium cromoglycate with the activity of about 400 kBq (10 µCi).

The dry powder mixture was prepared mixing equivalent amounts of disodium cromoglycate and lactose (Ph. Eur., D.M.V., Holland) with a Turbula mixer (type 2P, Switzerland). Forty milligrammes of the mixed powder were filled into the hard gelatin capsules. Each dose unit contained 20 mg of active substance. In the in vivo deposition studies with the dry powder dosage form every capsule contained, on average, an activity of 8 MBq (200 µCi).

The in vitro inhalation test

The in vitro deposition of disodium cromoglycate particles delivered either from a metered dose aerosol through the conventional aerosol actuator with a short plastic mouthpiece (Orion Plastic Department, Finland) or from a dry powder I.S.F.-inhaler (I.S.F., Italy) was

tested with a modified cascade impactor (Sierra Andersen 1 ACFM Nonviable Ambient Particle Sizing Sampler, USA) fitted with a vacum pump and an air flow meter. A simulation of an upper airway was constructed with the bent metal tube. The human respiratory cycle was imitated using an air flow of 60 l/min and an air flow period of 2 s. One hundred aerosol doses or five dry powder drug doses both corresponding 100 mg of disodium cromolgycate were delivered through the imitated throath into the cascade impactor. Room air with the relative humidity of 40 per cent was used as carrier gas.

After inhalation the inhalation devices, the throat and separator stages of the sampler were carefully washed with purified water. After evaporating the water, the samples were diluted to measuring volume with phosphate buffer and analyzed spectrophotometrically at 238 nm. Five determinations were performed.

The in vivo inhalation test

Seven healthy volunteers took part in the in vivo inhalation test. Before inhalation the lung function was measured and the 80 per cent lung volume from the maximum vital capacity was carefully trained. It was noticed that all the volunteers were able to repeat this volume with a lower deviation than five per cent. The inhalation was done using approximately the velocity of 55-70 1/min. Inhalation was followed by five seconds of breath-holding.

Just before the gamma camera measurement either ten doses from the metering dose aerosol or one dry powder drug dose were taken as carefully as possible by the 80 per cent depth of the breath from the maximum forced inspiratory volume. The volunteers inhaled the aerosol doses with the controlled closed mouth technique (16).

The measurements of deposition were done with the large field gamma camera (General Electric, type 400T, Wisconsin, USA) equipped with a low energy all purpose collimator. The energy window was 10 % for the ^{99m}Tc-energy peak (140 keV). All measurements were done for each person in the anteroposterior and posteroanterior view in the same measurement geometry for 5 minutes per view in the sitting position. The data were collected to the Gamma-11-system with PDP 11/34 computer (Digital Equipment Corp., Massachusetts, USA) with 64 x 64 collection matrix. All the results were calculated after correction of the backgroung radiation and time decay of ^{99m}Tc. The geometric mean counts were calculated for the lung region and the results were listed for the actuator and lungs as well as for the upper airways. For the individual correction of attenuation in different body thicknesses the point source measurement in opposite site of the subject was done. The correction factor for the dose measured in air were solved with the calibration curve, which was measured in various depths of water as an attenuation and scattering material. Ten puffs of aerosol

deposit an initial lung burden of 400 kBq (100 μCi) ^{99m}Tc, and the radiation dose to the lung resulting from this amount of activity does not exceed 4 mrad. The same radiation dose to the lungs after administration of one dry powder drug dose 800 kBq (200 μCi) does not exceed 8 mrad.

RESULTS AND DISCUSSION

Using a labelling technique based on spray drying it was well possible to draw conclusions of the deposition of the drug particles in device, upper airways and lungs (Fig. 2). In this study as low activities as 100 μCi and 200 μCi were used and thus it was not possible to separate the bronchial and alveolar stages of the respiratory tract. There existed, however, relatively large deviations between the deposition patterns of the individuals which indicate differences in anatomical and physiological factors as well as in the inhalation techniques (Fig. 3). On the other hand, the deviations in drug deposition results obtained from the repeated in vitro inhalations were relatively small. During the cascade impactor test the air flow penetrates through the stationar sampler with a quite constant velocity. Thus the drug particles seemed to deposite in a repetable way in the different stages of imitated respiratory tract.

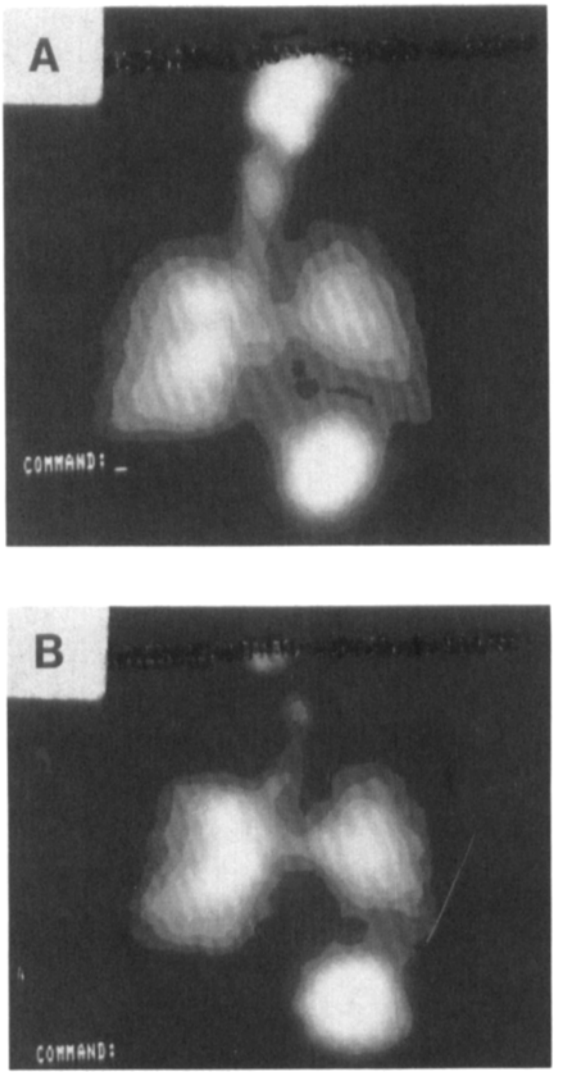

Figure 2

Typical gamma camera photograph from the deposition of ^{99m}Tc-labelled particles of disodium cromoglycate in the respiratory tract of one of the human volunteers after administration from the pressurized aerosol (A) and from the dry powder inhaler (B).

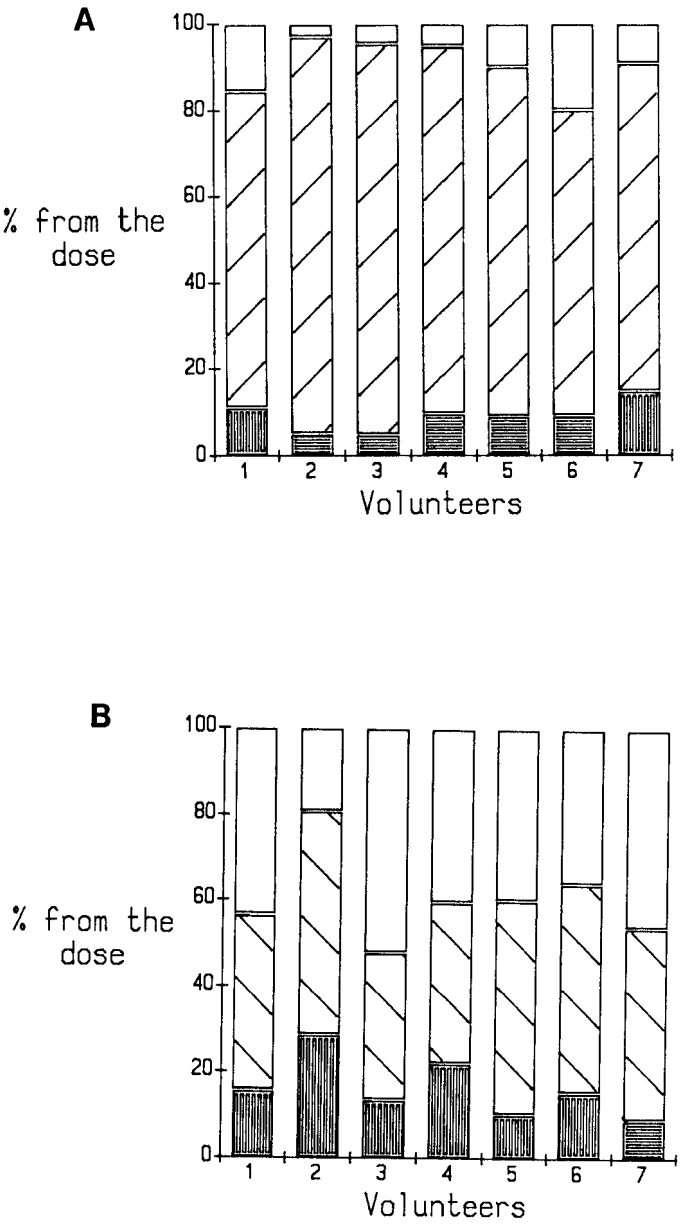

Figure 3

Fractional deposition of ^{99m}Tc-labelled particles of disodium cromoglycate separately in 7 volunteers after adminstration from the pressurized aerosol (A) and from the dry powder inhaler (B). Key: ▥, lungs; ▨, upper airways; □, device.

Only a relatively small fraction of the drug doses retained in a conventional aerosol actuator with a short plastic mouthpiece. This can be explained by the relatively high initial velocity of the drug particles after the activation of the pressurized aerosol. Thus the particles are forced effectively out from the actuator inside the cascade impactor or in the human respiratory tract. The amount of ^{99m}Tc-labelled disodium cromoglycate particles retained in the aerosol actuator during the in vivo test was slightly greater than the retained amount in the in vitro test being 9.5 and 6.4 per cent, respectively (Fig. 4). This might be mainly due to condensation of moisture on the surfaces of plastic walls of actuator during the expiration of the volunteers between the repeated inhalations of the drug doses. A much greater amount of disodium cromoglycate was retained in the powder device and on the walls of the hard gelatin capsules both in the in vitro and in vivo tests than was retained in the aerosol actuator. This is easy to understand because the technical structure of the dry powder inhaler is more complicated than that of the aerosol actuator.

On average 81.3 per cent of the radioactive drug doses administered from pressurized aerosol was deposited in the upper airways of the volunteers. Using the aerosol actuator with a short mouthpiece the delivery of aerosol spray by means of relatively high pressure led to the inertial impaction of drug particles on the moist mucose

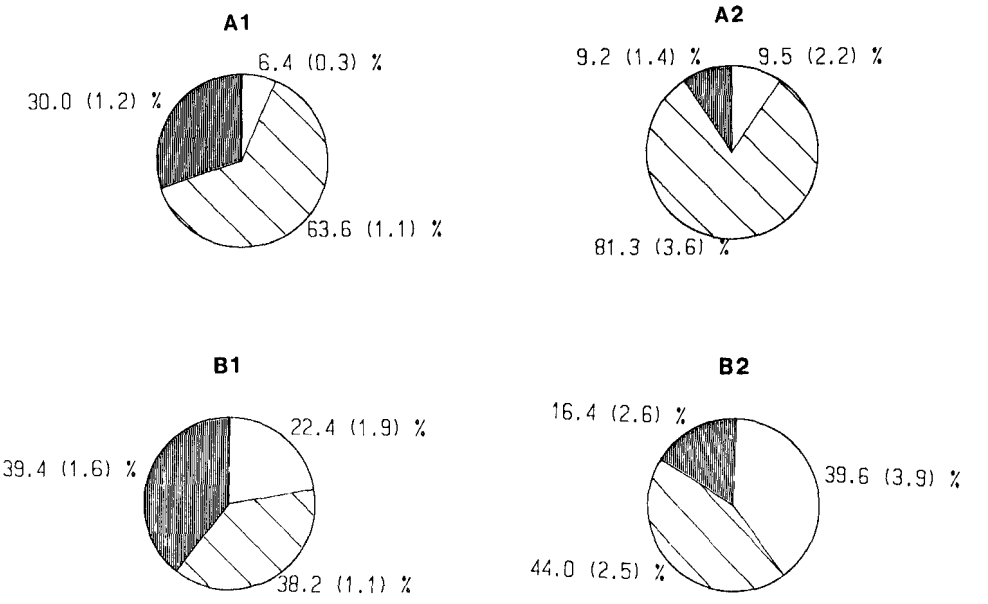

Figure 4

The mean fractional in vitro (1) and in vivo (2) deposition with the standard error of the mean of disodium cromoglycate particles after adminstration from the pressurized aerosol (A) and from the dry powder inhaler (B). Key as in Fig. 3.

layer of mouth and upper part of respiratory tract. With the cascade impaction system there can be found clearly smaller fraction from the drug dose deposited on the dry walls of the metal throat than on the moist mucose of the human upper airways. During the in vitro test the drug doses were delivered directly in the constant air flow, whereas in the in vivo test the syncronization of the dose delivery with the inspiration is demanded for achieving the drug particles to follow the inhaled air stream. The fractions of the drug doses deposited less in the upper airways of the volunteers as well as in the imitated

throat after adminstration from the dry powder inhaler than from the pressurized aerosol. This is due mainly to the difference in velocities of the drug particles administered from these two dosage forms. The speed of particles delivered from a dry powder inhaler is the same or lower than that of the flow of inspired air. Thus these particles are more prone to follow the air flow than the fast moving aerosol particles are.

The mean share of the aerosol doses deposited into the whole lung area of the volunteers was about 9 per cent (Fig. 4). Thus only a very small portion of the drug dose reached the therapeutically important region of the human respiratory tract. On the other hand, drug deposition in the imitated lung area analyzed by cascade impactor showed clearly greater deposition. On average 30 per cent of the doses was penetrated into the separator stages between 0.3 and 7.1 microns. Spray dried disodium cromoglycate particles used in this study have sufficient aerodynamic diameter for penetrating into the bronchial and alveolar regions. Thus the drug particles which were not retained in the imitated upper airways were logically deposited on the lower stages of the cascade impactor. A larger fraction from the dry powder drug doses than from pressurized aerosols deposited in the lung area of the volunteers as well as in the imitated bronchial and alveolar stages below 7.1 microns in the cascade impactor. Thus the small disodium cromoglycate particles in the dry

powder dosage form separated effectively from their agglomerations or from the surface of the coarser carrier material.

The in vitro inhalation results pointed out greater particle deposition into the whole lung area than the in vivo results. This is mostly due to the unphysiological atmosphere of the in vitro test environment. Thus the deposition patterns of the inhaled drug particles are not accurately possible to be determined using the in vitro cascade impactor method. The deposition results obtained using the in vitro method indicate, however, similar differences between the deposition patterns of the dry powder and the aerosol drug doses as the in vivo evaluation. The cascade impactor system can thus be used for comparison of deposition of inhaled drug particles administered from different inhalation dosage forms.

REFERENCES

1. G.R. Crompton, Eur. J. Respir. Dis., 63, 101 (1982).

2. J.H. Bell, P.S. Hartley and J.S.G. Cox, J. Pharm. Sci., 60, 1559 (1971).

3. G.R. Crompton, Eur. J. Respir. Dis., 63, 96 (1982).

4. R. Harris and R.P.G. Rothwell, New Zeal. Med. J., 94, 421 (1981).

5. M.R. Hetzel and T.J.H. Clark, Clin. Allerg., 7, 563 (1977).

6. A.C. Boner, E. Niero, C. Grigolini, E.A. Valletta, R. Bianzotto and D. Gabyrro, Eur. J. Respir. Dis., 66, 21 (1985)

7. P.R. Byron, Pharm. Tech., 11, 42 (1987).

8. J.J. Scierra and A. Cutie, J. Pharm. Sci., 67, 1428 (1978).

9. W.F. Kirk, J. Pharm. Sci., 61, 262 (1972)

10. G.N. Hallworth and U.G. Andrews, J. Pharm. Pharmacol., 28, 898 (1976).

11. S.P. Newman, D. Pavia, F. Moren, N.F. Sheanon and S.W. Clarke, Thorax 36, 52 (1981).

12. S.P. Newman, F. Moren, D. Pavia, F. Little and S.W. Clarke, Am. Rev. Respir. Dis., 124, 317 (1981).

13. S.P. Newman, F. Moren, D. Pavia, O. Corrado and S.W. Clarke, Int. J. Pharm., 4, 337 (1982).

14. S.P. Newman, A.B. Miller, T.R. Lennard-Jones, F. Moren and S.W. Clarke, Thorax, 39, 935 (1984).

15. M. Vidgren, A. Kärkkäinen, P. Karjalainen and P. Paronen, Int. J. Pharm., 37, 239 (1987).

16. M.R. Sears and M.I. Asher, Curr. Ther., 26, 39 (1985).