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A semi-empirical model of aerosol deposition in the human respiratory tract for mouth inhalation

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A mathematical model for regional deposition of aerosols following inhalation via mouth has been developed. The model is in the form of algebraic equations which make it particularly efficient for computation of deposition of polydisperse aerosols. The parameters of the model were derived from average experimental data for 'head' and tracheobronchial deposition which were supplemented by results of previous theoretical calculations and mass balance considerations. An example is presented to illustrate an application of the model to a problem in formulation of inhalation aerosols. To make the calculations more reliable for particular patho-physiological groups of patients, some modifications of the parameters used in the model are necessary. The model may be suitable, e.g. for testing the changes in regional deposition which would be likely to result from modification of particle size and related formulation properties of inhalation aerosols.

Therapeutic aerosols are examples of systems typically exhibiting a fairly high degree of polydispersity (Mercer et al 1968a,b; Hallworth & Andrews 1976; Hallworth & Hamilton 1976; Davies et al 1978; Ruffin et al 1978; Groom et al 1980). The aim of this work has been to combine experimental and, where appropriate, theoretical results for deposition of monodisperse aerosols in the human respiratory tract into a set of algebraic equations which could be used for predictions of deposition of polydisperse aerosols with the minimum amount of computing involved.

METHODS

The starting point was the semi-empirical model proposed by the TASK group (Task Group on Lung Dynamics, 1966, 1967) for nasal inhalation. Mercer's method (Mercer 1975) for conversion of data for the nasal route into values for deposition during mouth inhalation was followed with some modifications. Unless stated otherwise, the assumptions of Mercer were made. In particular, it was assumed, as did the authors of experimental deposition data (Lippmann 1977; Stahlhofen et al 1980), that deposition 'above' the trachea takes place only during inspiration. In contrast to the TASK group approach, in which a number of equations had to be solved for deposition at each individual value of the aerodynamic diameter, curve-fitting of theoretical and experimental data was used. This diminishes the potential for deposition calculations under physiological conditions different from those used for the curve-fitting; however, a substantial saving in calculations is gained when the model is applied to polydisperse aerosols.

The mathematical model developed consists of algebraic equations relating deposition in various parts of the respiratory tract directly to the aerodynamic diameter D, defined as 'the diameter of a unit sphere with the same settling velocity as the particle in question' (Task Group on Lung Dynamics 1966). Because the deposition equations for different ranges of D have been derived from various sources, the slopes of the deposition functions change discontinuously at certain values of D whilst the actual deposition values form continuous sequences. It is important to bear in mind the above mentioned discontinuity when an integration routine is selected for application of the model.

The depositions in tracheobronchial and pulmonary regions for nasal inhalation, TBN and PN (Table 1 in the Task group publication 1966) were converted to the corresponding quantities for mouth inhalation, TBM and PM, using the formula*

$$\text{TBM or PM} = (\text{TBN or PN})(1-N)^{-1}(1-M) \quad (1)$$

N is the fraction of the inhaled dose deposited in the nasopharynx during nasal breathing, and M is the fraction deposited above the trachea (i.e. in the

* The formula presented by Mercer (1975) on p. 675 of his paper for 'deposition in the designated compartments relative to the number of particles entering the trachea', has a printing error. The correct expression has the form of eqn 1 above without the last term (1 − M).

'head') during mouth breathing. For N we employed the empirical equation of Pattle (1961)

$$N = -0.62 + 0{\cdot}475 \log (D^2F) \quad (2)$$

The average inspiratory flow rate, F, was calculated from

$$F = 2 \times TV \times f \quad (3)$$

The TASK group used respiratory frequency f = 15 min^{-1}; the corresponding F values for their tidal volumes TV = 0·75, 1·45 and 2·15 dm^3 are F = 22·5, 43·5 and 64·5 $dm^3\ min^{-1}$. Lippmann (1977) found that his experimental data for M could be described by a function similar to equation 2. The following equations were obtained from Lippmann's eye-fit to his results for non-smokers:

$$\text{For } (0 \leqslant M < 0{\cdot}1)\text{: } M = M1 = -0{\cdot}2674 + 0{\cdot}1337 \log (D^2 F) \quad (4)$$

$$\text{For } (0{\cdot}1 \leqslant M \leqslant 1{\cdot}0)\text{: } M = M2 = -1{\cdot}983 + 0{\cdot}758 \log (D^2 F) \quad (5)$$

Combination of equations 1–5 facilitated the calculation of TBM and PM for aerodynamic diameters from D = 0·01 μm up to the size where TASK group's values for TBN or PN became zero. The non-linear least mean square program of Metzler (1969), NONLIN, was used to fit the curves of TBM and PM vs. D. The rational functions describing these curves are given below. There is a 'kink' in the PM curve for TV = 0·75 dm^3 at D = 0·06 μm which consistently caused a deterioration in the goodness of the fit. It was therefore decided for this particular tidal volume to approximate PM in the range 0·01 μm ⩽ D⩽ 0·06 μm by a straight line. This simplification has no effect on calculations for typical pharmaceutical aerosols because usually only a negligible amount of drug is contained in the fraction below D = 0·06 μm. The difference between the 'actual' and fitted fractional deposition values was at most 0·02; the fitted curves showed no oscillations at intermediate values of D.

At this stage, experimental results for tracheobronchial deposition were introduced thus: Lippmann (1977) found that when the tracheobronchial deposition was expressed as the deposition fraction, TBT, of those particles which enter the trachea, i.e.:

$$TBT = TBM\,(1 - M)^{-1} \text{ or } TBN\,(1 - N)^{-1} \quad (6)$$

then TBT was again a linear function of the logarithm of the 'impaction parameter' D^2F. From Lippmann's eye-fit for non-smokers, the slope of the line was calculated as 0·68. Stahlhofen et al (1980) found that their data showed a similar slope but, generally, they found somewhat lower values for TBT. Lippmann's data began at approximately TBT = 0·1. Therefore, the TASK model detailed above had to be used from D = 0·01 μm up to the size D = DT1 at which TBT became approximately 0·1. A nearest higher value of TBT derived from the TASK data was then substituted into the equation:

$$I = TBT - 0{\cdot}68 \log (D^2 F) \quad (7)$$

The intercept I for each tidal volume was thus calculated. The curves describing TBM above the size DT1 therefore have the form

$$TBM = [I + 0{\cdot}68 \log (D^2 F)] \cdot [1{\cdot}0 - M] \quad (8)$$

A further cut-off diameter had to be introduced at the point D = DT2 when all particles entering the trachea deposited in the tracheobronchial region, i.e. when

$$I + 0{\cdot}68 \log (D^2 F) = 1{\cdot}0 \quad (9)$$

For diameters greater than DT2, therefore,

$$TBM = 1{\cdot}0 - M \quad (10)$$

A natural constraint on any deposition model is that the sum of fractions of the inhaled dose deposited in all compartments must not exceed unity. In the present model, this was accomplished first by putting the pulmonary deposition equal to

$$PM = 1{\cdot}0 - M - TBM \quad (11)$$

from D = DP2 where the sum of the unadjusted PM plus (M + TBM) became greater than 1·0. From the point D = DP3 where either the sum (M + TBM) alone exceeded unity (DP3 = DT2 for TV = 1·45 & 2·15 dm^3), or, before that, PM derived from the TASK model reached zero (DP3 = DP2 for TV = 0·75 dm^3), PM was put as PM = 0. These last impositions upon the model at large values of aerodynamic diameters caused only minor modifications in the predicted values of TBM and PM. However, they did introduce a guarantee of correct mass balance necessary for any applications of the model. Both the TASK group (1966) and Mercer (1975) corrected the total deposition by a small term TV/(TV + 0·05) where 0·05 dm^3 represented the volume of the nasopharynx which, supposedly, would not contain any aerosol. This minor, and somewhat arbitrary, correction was felt to unnecessarily complicate the present model, and it was therefore omitted.

RESULTS AND DISCUSSION

The general form of the equations derived as described above are now presented. The actual parameter values are in Table 1. To reduce the amount of computation, equations 4, 5 and 8 have

Table 1. Parameters for equations 12–22 in the text for the three tidal volumes used in the model.

Parameters	Tidal volume (dm³) 0·75	1·45	2·15
Head deposition:			
A1	−0·0866	−0·0483	−0·0255
A2	−0·958	−0·7410	−0·6114
Tracheobronchial deposition:			
B1	−1·5758	−2·3058	−0·51409
B2	6·3568	8·7217	11·4455
B3	−0·50348	−0·22301	1·5257
B4	1·1422	1·0496	−0·13754
B5	207·057	277·727	494·469
B6	−44·9747	−71·8424	−186·993
B7	3·4805	9·2269	34·8649
B8	−0·5135	−0·4154	−0·2914
Pulmonary deposition:			
C1	−1·9446	−4·8067	−3·1810
C2	3·9034	10·2572	10·8935
C3	−0·34757	1·0164	0·77426
C4	1·0399	1·5052	1·3357
C5	8·2507	−10·6135	−4·2879
C6	0·0025967	54·3737	63·5294
C7	0·275705	−25·8617	−36·2478
C8	0·04063	5·0927	7·5831
Cut-off diameters (μm)			
DM1	2·108	1·516	1·246
DM2	4·990	3·587	2·946
DM3	19·568	14·073	11·559
DT1	3·000	2·500	2·000
DT2	13·400	10·983	8·900
DP1	0·06	0·01	0·01
DP2	10·730	6·200	3·100
DP3	10·730	10·983	8·900

been expanded, with the appropriate values of F for each tidal volume substituted from equation 3.

'Head' deposition:

$$M = 0, \text{ for } 0{\cdot}01\ \mu m \leq D < DM1 \quad (12)$$

$$M = A1 + 0{\cdot}2674 \log D, \text{ for } DM1 \leq D < DM2 \quad (13)$$

$$M = A2 + 1{\cdot}516 \log D, \text{ for } DM2 \leq D \leq DM3 \quad (14)$$

$$M = 1{\cdot}0, \text{ for } D > DM3 \quad (15)$$

Tracheobronchial deposition:

$$TBM = (1{\cdot}0 + B1 \times D + B2 \times D^2 + B3 \times D^3)/(B4 + B5 \times D + B6 \times D^2 + B7 \times D^3) \text{ for } 0{\cdot}01\ \mu m \leq D \leq DT1 \quad (16)$$

$$TBM = (B8 + 1{\cdot}36 \log D)(1{\cdot}0 - M) \text{ for } DT1 < D \leq DT2 \quad (17)$$

$$TBM = 1{\cdot}0 - M, \text{ for } D > DT2 \quad (18)$$

Pulmonary deposition:

$$PM = 0{\cdot}4902 + 1{\cdot}58 \times D, \text{ for } 0{\cdot}01\ \mu m \leq D \leq 0{\cdot}06\ \mu m, TV = 0{\cdot}75\ dm^3 \text{ only} \quad (19)$$

$$PM = \frac{(1{\cdot}0 + C1 \times D + C2 \times D^2 + C3 \times D^3)}{(C4 + C5 \times D + C6 \times D^2 + C7 \times D^3 + C8 \times D^4)} \text{ for } DP1 < D < DP2 \quad (20)$$

$$PM = 1{\cdot}0 - TBM - M, \text{ for } DP2 \leq D \leq DP3 \quad (21)$$

$$PM = 0{\cdot}0, \text{ for } D < DP3 \quad (22)$$

The results generated from equations 12–22 are shown graphically in Fig. 1A–C.

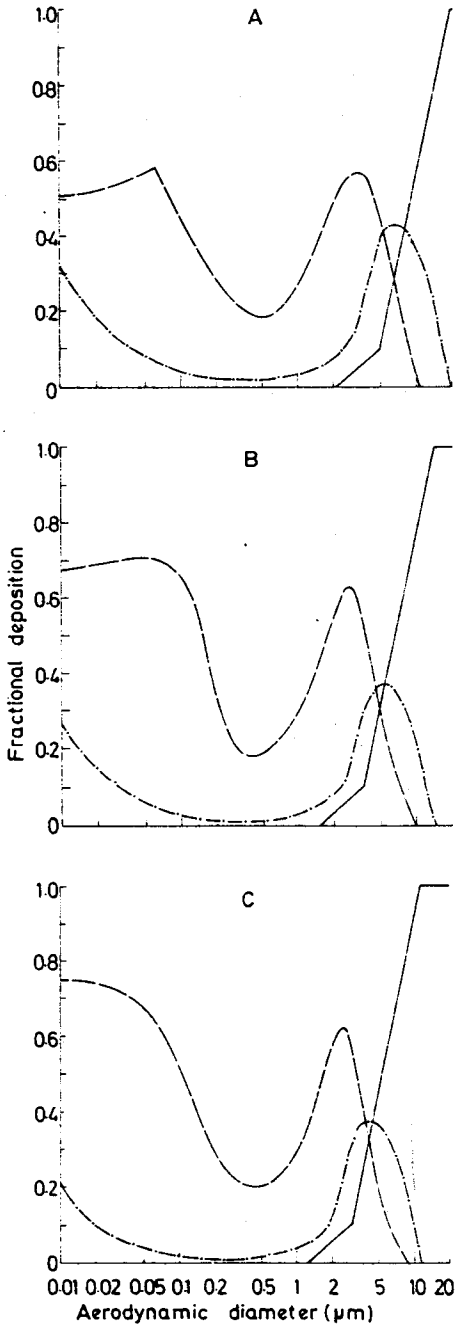

Fig. 1A, B, C. Regional deposition of monodisperse aerosols following mouth inhalation in the 'head' (——), tracheobronchial (–·–) and pulmonary (– – –) compartments vs aerodynamic diameter. Tidal volume 0·75 dm³ (A), 1·45 dm³ (B), 2·15 dm³ (C).

Application of equations 12–22 can be illustrated by the following examples: we shall compare the regional deposition of two aerosols with log-normal distribution, LN, with the same degree of polydispersity characterized by the geometric standard deviation $\sigma g = 3$ but differing in the drug mass median aerodynamic diameter (Byron et al 1977) MMD. This parameter for the first aerosol is chosen to be 4 μm, i.e. near the maxima of tracheobronchial and pulmonary depositions. MMD for the second aerosol is put equal to 10 μm. Thus, the comparison of the regional deposition of these two aerosols could be a simplified analogy of the effects of an increase in MMD due to coagulation of suspended drug particles in pressurized aerosols, poor regeneration of the primary particle size distribution, incomplete evaporation of the propellant before the entry of the aerosol into mouth, or rapid condensation of water and formation of equilibrated aqueous droplets from the powder aerosol containing a water-soluble drug (Groom & Gonda 1980; Groom et al 1980). The fractions, Y, of the dose depositing in the three respiratory regions can be calculated from the product LN times the compartmental deposition probability R (given by either M, TBM or PM in eqn 12–22) integrated with respect to the aerodynamic diameter:

$$Y = \int_{-\infty}^{\infty} LN(MMD,\sigma g,D) \cdot R(D)dD \qquad (23)$$

LN has the form:

$$LN = (\sqrt{2\pi}\, D \ln \sigma g)^{-1} \exp[-0{\cdot}5(\ln D - \ln MMD)^2/(\ln \sigma g)^2] \qquad (24)$$

The differences between the regional depositions of the two aerosols are contrasted in Table 2. It is apparent that the aerosol with MMD = 10 μm is likely to be captured in the 'head' region to a much greater extent than an aerosol which would be presented to the respiratory tract with the intended MMD = 4 μm preserved. The increase in 'head' deposition is largely mirrored by a reduction in pulmonary deposition. On the other hand, the tracheobronchial deposition seems quite insensitive to this effect. The exhaled fraction is not included in Table 2; the present model makes no allowance for a prolonged breath-holding manoeuvre (Byron et al 1977; Newman et al 1979) which would reduce the exhalation of small particles (Palmes et al 1967, 1971).

Figs 1–3 represent regional depositions of monodisperse aerosols. Comparison of the data in these figures with results for the polydisperse aerosols in Table 2 reveals that the width of aerosol size distribution may have a marked effect on the deposition. For example, a 'nearly' monodisperse aerosol with MMD = 10 μm would not be expected to deposit in the pulmonary region at all, except at very low tidal volumes. However, a polydisperse aerosol with the same MMD, but a distribution width characterized by $\sigma g = 3$, should have appreciable pulmonary deposition (Table 2). A more detailed analysis of this phenomenon is presented by Gonda (1981).

Table 2. Values predicted by the model equations 12–24 for deposition of two aerosols with the same geometric standard deviations but different mass median diameters. M, TB and P stand for 'head', tracheobronchial and pulmonary compartments, respectively.

Tidal volume (dm³)	0·75			1·45			2·15		
Region	M	TB	P	M	TB	P	M	TB	P
MMAD = 4 μm σg = 3	0·26	0·19	0·31	0·35	0·17	0·29	0·41	0·17	0·26
MMAD = 10 μm σg = 3	0·54	0·19	0·18	0·64	0·14	0·15	0·70	0·13	0·13

Another important feature which emerges from Table 2 is the influence of the magnitude of the tidal volume on deposition, particularly on the aerosol with MMD = 10 μm. Physiological variables, anatomical differences and breathing patterns undoubtedly affect the extent of deposition in various parts of the respiratory tract (Muir & Davies 1967; Palmes et al 1967, 1971; Lippmann & Altshuler 1976; Davies et al 1977; Heyder et al 1978). Inter-subject variations in deposition which can be classified broadly according to patho-physiological groups are well documented (Lippmann et al 1971; Thomson & Pavia 1974; Love & Muir 1976; Fazio et al 1978; Short et al 1979; Chan & Lippmann 1980). It must be emphasized, therefore, that the current version of the model will not generate reliable quantitative predictions for regional deposition in subjects with serious morphological changes of airways or abnormal breathing patterns. Chan & Lippmann (1980) suggested recently a method which accounts for variation in tracheobronchial deposition between healthy non-smokers, cigarette smokers and patients with chronic obstructive lung disease. Their method could be incorporated into equation 17. Some modification of the parameters used in the equations for pulmonary deposition would then be required as well. Further work is necessary to establish if a model of the type presented here has the capacity and flexibility to cater for different groups of subjects, particularly those affected by disorders of the respiratory tract. The model is, perhaps, sufficient already to detect the changing trends in regional deposition likely to result from modifications of particle size and related characteristics of aerosol formulation.

The parameters describing the fitted curves were derived from average results for deposition behaviour of subjects from the general population. It is envisaged therefore that the model may be useful particularly when modification of physicochemical and size characteristics of mass produced aerosols is considered with the view to optimizing the average deposition of therapeutic agents in the desired areas of the respiratory tract. For example, we suggested (Gonda & Byron 1978) that one of the reasons for poor bioavailability of inhalation aerosols lies in their potential to increase in size by condensation growth immediately after inspiration. The model provides the means to test the likely magnitude of this effect, and also a method for investigating whether changes in the particle size distribution, formulation, or both, would lead to substantial modifications of the fractions deposited in the traditionally recognised 'head', tracheobronchial or pulmonary regions of the respiratory tract.

The underlying philosophy has been to provide estimates of average deposition values for certain populations of subjects, rather than to attempt to develop models with adjustable parameters to suit individuals. This latter approach has been taken by Davies (Davies et al 1977; Davies 1980); of course, such a method requires that some experimental tests are performed on the patient. Perhaps, Davies's model could be applied to aerosol treatment in hospitals.

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