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EFFECT OF FLOWING ADJUVANTS ON THE HOMOGENEITY AND THE KINETICS OF MIXING OF LOW DOSAGE COHESIVE POWDER MIXTURES

Louis H.Cartilier and André J.Moës
Laboratoire de pharmacie galénique et de biopharmacie-C.P 207
Institut de pharmacie
Université Libre de Bruxelles
Campus de la Plaine,1050-Bruxelles,Belgique

ABSTRACT

One of the major problems encountered in powder mixing, depending on the properties of the constituents of the mix is the inability of low-power mixers to break down powder agglomerates.

The effects of the addition of two flowing adjuvants(colloidal Aluminium oxide and Aerosil-200^{R})on the homogeneity of cohesive powder mixtures and on the kinetics of mixing were investigated.

It was demonstrated that colloidal Aluminium oxide increases the degree of homogeneity of a 1 % Triamteren-200 mesh lactose mixture blended in a Turbula T2 C mixer,when an appropriate concentration of the adjuvant,corresponding to that which produces the best flowing properties of the excipient was used. Aerosil-200^{R} did not enhance the homogeneity of the mix.

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INTRODUCTION

Solid-solid mixing is a fundamental step in the pharmaceutical industry;the most important function of these mixing operations is to ensure the content uniformity,especially in the production of low drug content dosage forms.

Two major problems encountered in powder mixing,depending on the properties of the constituents of the mix,are segregation(1) and the inability of mixers to break down powder agglomerates(2).

Micronized powder particles possess intrinsic cohesional properties and adhere to large particles of a second constituent;this is called an ordered mixture.

Since an ordered system is not prone to segregation,unless the particle-particle bonds can be broken easily,segregation is not the major problem for micronized powders(3).

Nevertheless,the high tendency of micronized powders to agglomerate produces generally poorly homogenized mixes,especially when low drug contents are concerned.

Lacey(4)considered that there are 3 principle mechanisms for mixing:(I)convective mixing,in which there is bulk transfer of particles from one part of the mix to another;(II)diffusive mixing,which involves the distribution of particles over freshly formed surfaces;and(III)shear mixing,by the setting up of slip planes within the powder mass.

With cohesive powder mixtures,the problem is to overcome the lack of relative movement between particles,which is the necessary initial condition prior to a mixing process(5).

The low-power mixers are not able to separate cohesive powders to their elementary particles,so that agglomerates still exist and do not permit the relative movement between particles to occur(6); the consequence is a very bad homogeneity for these mixtures(7). The effects of the addition of two flowing adjuvants(Aerosil-200^{R} and colloidal Aluminium oxide)on the homogeneity of cohesive powder mixtures were investigated in this study.

MATERIALS AND METHODS

Triamteren(S.K.F.Rit,Genval,Belgium)was used as the fine-powder active constituent.The granulometric characterization of Triamteren was performed by Scanning Electron Microscopy and sieving analysis(30 gr.of Triamteren were sieved during 1 hour in a Rhewum type A2 sieving apparatus).

A 200 mesh lactose(D.M.V.Holland)was used as the excipient.Its particle size distribution was established by optical microscopy.

Two flowing adjuvants were used in this study:colloidal Aluminium oxide(Degussa,Frankfurt,R.F.A.),a glidant with very good anti-static properties(8)(Specific area-B.E.T. :100 ± 15 m^2/g;mean particle diameter:20 nm)and Aerosil-200^{R}(Degussa,Frankfurt,R.F.A.) (Specific area-B.E.T. :200 ± 25 m^2/g;mean particle diameter:12 nm).

A 1 % w/w drug concentration was chosen in all experiments.

The influence of the adjuvant concentration on the rheological properties and the homogeneity of powder mixtures was studied.

The rheological properties of excipient-adjuvant mixtures were determined using a stamp volumeter method(J.E.L. STAV 2003, Engelsmann,Ludwighaven,R.F.A.).The variation of the Hausner ratio

($R_H = V_0/V_{1250}$)was studied versus the adjuvant concentration;the R_H minimum value was obtained with the adjuvant concentration that produces the best flowing properties.

Mixing was carried out in a Turbula mixer T2 C type(W.A.Bachofen, Switzerland)rotating at 30 r.p.m.The load was 600 g,which corresponds approximatively to a 50 % loading volume(9).

Two mixing processes were used in this study:

A)The total amount of the adjuvant was previously mixed with the 200 mesh lactose;then,this premix was mixed with Triamteren.

B)Two premixes were realized by adding 0,2 or 1,0 % w/w respectively of the flowing adjuvant to the active ingredient and to the 200 mesh lactose.In each case,the total amount of the adjuvant was mixed for 5 minutes in a Turbula T2 C mixer,rotating at 30 r.p.m. with one third of the drug or excipient respectively.This procedure was repeated twice until the whole quantity of the drug or excipient was incorporated.Then,the two premixes were mixed together and the kinetics of mixing was determined.

Process A was used to study the effect of both the nature and concentration of the adjuvant.

Process A was compared to process B only in the case of colloidal Aluminium oxide.

The composition of mixtures are summarized in Table 1.

An end-sampling thief probe(10) was used to remove ten samples from different places of the powder mixture at each sampling time; sampling times were chosen according to a geometric progression and the sample size was around 250 mg.

Table 1. Composition of mixtures

Ingredients(%)	Mixtures n° Process A 1	2	3	4	5	Process B 6	7
Triamteren	1,0	1,0	1,0	1,0	1,0	1,0	1,0
Aluminium oxide	-	0,2	1,0	-	-	0,2	1,0
Aerosil-200^{R}	-	-	-	0,2	1,0	-	-
Lactose	99,0	98,8	98,0	98,8	98,0	98,8	98,0

The Triamteren content of the samples was determined as follows: 250 mg of powder was introduced in a 100 ml volumetric flask and dissolved in 10 ml of 50 % v/v acetic acid solution;water was added to complete to 100 ml.After sedimentation of the undissolved particles,5 ml of the supernatant was withdrawn and added to 20 ml of 5 % v/v acetic acid solution.This solution was assayed by absorption spectroscopy at 356 nm.

RESULTS AND DISCUSSION

All Triamteren particles are less than a few microns(Fig.1.); hence,these may form agglomerates(Fig.2.)which will not break up in a classical low-power mixer.

Sieving analysis(Fig.3.)combined to Scanning Electron Microscopy of the obtained fractions showed that the separation of elementary particles according to their size is not possible,because agglomerates of various size are formed.

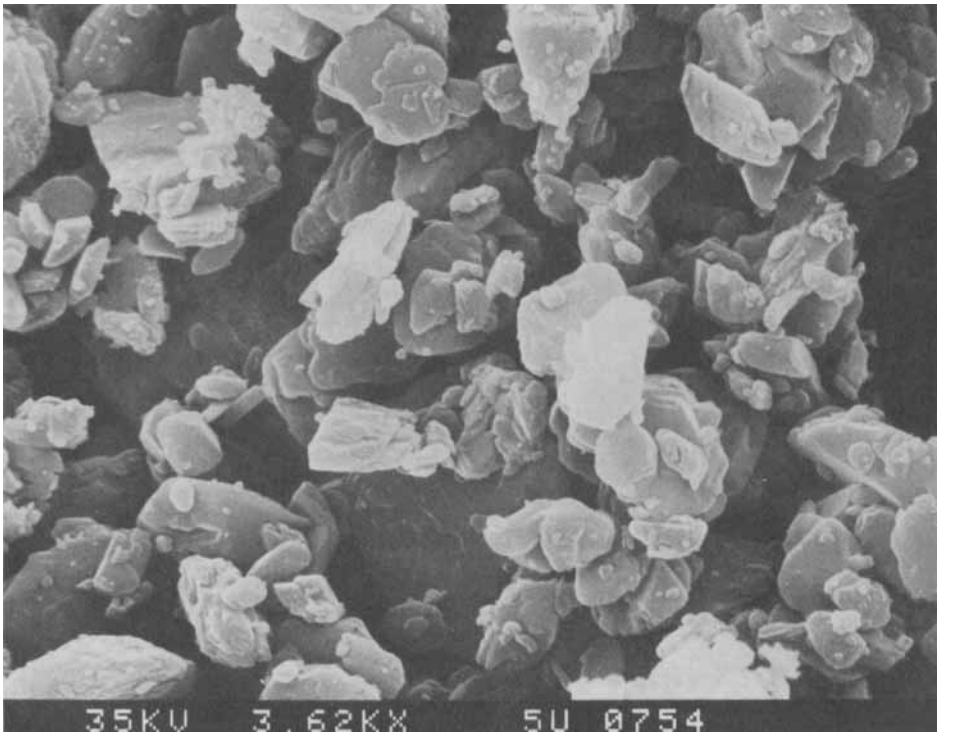

FIGURE 1
Scanning Electron Microscopy of Triamteren particles.

The mean particle size and the particle size distribution of the 200 mesh lactose(Fig.4.)were determined by optical microscopy :

$$d_g = 7,0 \pm 2,4 \ \mu m$$

The R_H minimum value of the excipient-adjuvant mixtures indicates the adjuvant concentration which has to be used to get the best flowing properties(Fig.5.).According to these results,we decided to study the mixing characteristics of powders containing 0, 0,2 and 1,0 % of additives.

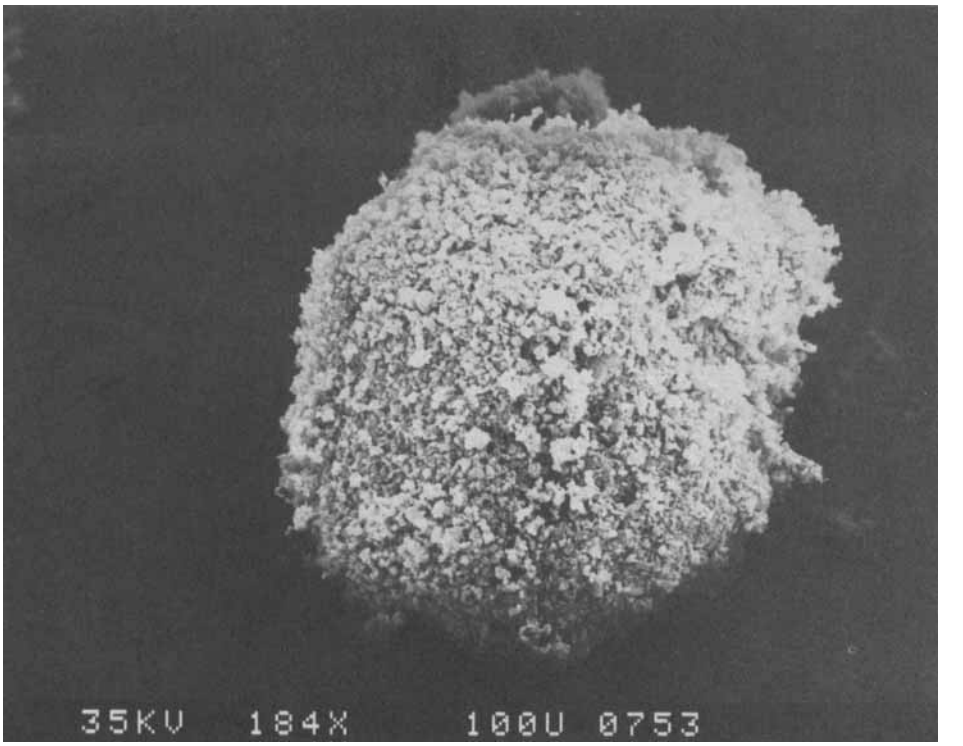

FIGURE 2
Scanning Electron Microscopy of Triamteren agglomerates.

At each sampling time,10 samples were analysed and the average mean content of Triamteren $\bar{X}_{10}$,and the standard deviation S_{10} were calculed.

Mixture homogeneity was appreciated by using a mixing index that takes into account $\bar{X}_{10}$,S_{10},the number of samples,and the content uniformity limits(11).

The quality of a product which is represented in this case by the content uniformity may be specified by an interval of variation. This interval is bounded by "tolerance limits".

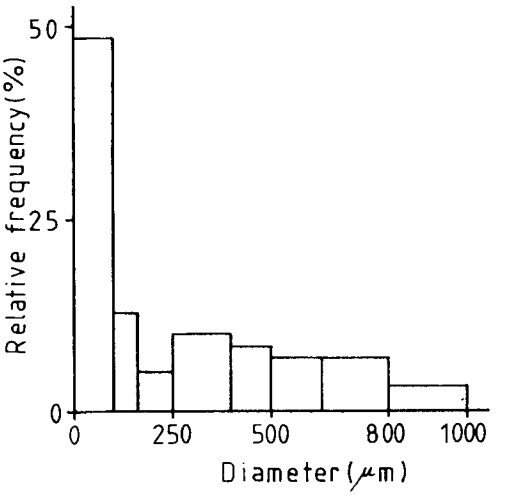

FIGURE 3

Sieving analysis of Triamteren.

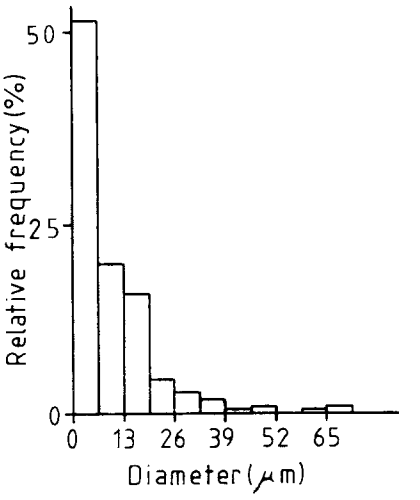

FIGURE 4

Granulometric analysis by optical microscopy of the 200 mesh lactose.

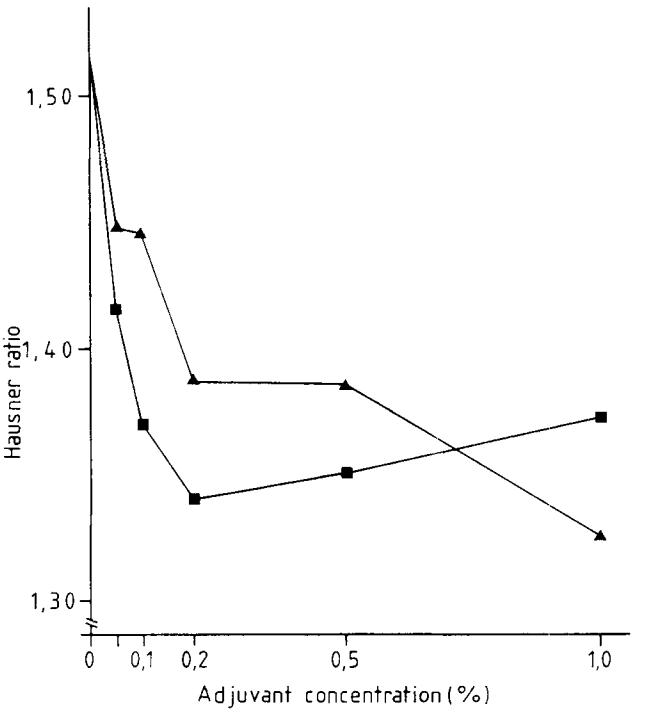

FIGURE 5

Rheological properties of the 200 mesh lactose/adjuvant mixtures;
(■ : colloidal Aluminium oxide; ▲ :Aerosil-200^{R})

A sample of size n provides an average mean content $\bar{X}_n$ and an estimation of the standard deviation S_n,so it is possible to build an interval : $\bar{X}_n \pm K.S_n$ (eq.1.);in this interval,a certain percentage of the population 100 β_p % is represented with a (100 β_t) % confidence probability(β_p is the tolerance probability and β_t the confidence probability).

The constant K is calculed so that in a great number of samples of the same size(n = 10 assays)taken from the same stable population,there is a given proportion β_t of intervals ($\bar{X}_n \pm K.S_n$)

that contains ($100\beta_p$) % of the elements of the variable X distribution(eq.2.)

$$\text{Prob}\left[\ \text{Prob}\ (\ \bar{X}_n - K.S_n < X < \bar{X}_n + K.S_n\ ) \geqslant \beta_p\ \right] \geqslant \beta_t \qquad \text{eq.2}$$

K values are given in Bowker's tables(12);they are calculated for a normal distribution of the variable X.

These tables have three entries: n, β_p and β_t (and two levels of probability: β_p,the tolerance probability,and β_t the confidence probability).

According to the U.S.P.XIX content uniformity sampling plan for tablets,the tolerance interval limits($\bar{X}_n \pm K.S_n$)are equal to $\pm$ 15 % of the theoretical content(μ_o= 100 %).

The values of β_t and β_p were fixed at the 0,90 and 0,95 levels respectively so that,in ninety percent of the cases,when removing ten samples,there is at least 95 % of the elements whose percentage lays between 85 and 115 % of the theoretical content.

In Bowker's tables, K= 3,018 for n = 10, β_p= 0,95 and β_t=0,90. Starting from equation (1) and from the previously determined value of K,the standard deviation maximum value for a sample size n = 10, σ_T was calculed.

σ_T is function of the probability levels β_t and β_p,and also function of the absolute value of the difference $d = |\bar{X}_n - \mu_o|$

$= |\bar{X}_n - 100|$

So that

$$\sigma_T = \frac{15 - |\bar{X}_{10} - 100|}{3{,}018} \qquad \text{eq.3}$$

Knowing S_{10} and σ_T,it is now possible to calculate a mixing index M,equal to S_{10}/σ_T.

The required homogeneity degree is obtained when M is lower than 1

It is also important to know that the mixing index has an infinite value when $|\bar{X}_{10} - 100| \geq 15$ and that we must obtain a standard deviation lower than 5 % to satisfy to homogeneity requirements ($M \leq 1$) when $\bar{X} = 100$ %.

The values of mixing indices versus mixing time obtained with the different mixtures are summarized in Table 2.

Figures 6 and 7 illustrate the kinetics of mixing for mixtures n°1 and n°2 respectively.

It should be noticed that there is considerable sampling errors in the initial stages of mixing of fine cohesive powders due to pockets of drug agglomerates that have not yet been incorporated into the bulk of the mixture(13);this must be kept in mind to explain the shape of the curves in the early moments of the experiments(14).

From the results obtained with the mixtures containing colloidal Aluminium oxide,it might be concluded that an ideal range of concentrations of the adjuvant exists to achieve homogeneity. This concentration range corresponds to that which produces the best flowing properties of the excipient(Fig.5.).

This can be explained by a decrease of the cohesiveness of the excipient powder and therefore by the enhancement of the relative movement of particles,so that the diffusion and the distribution of the drug into the bulk of the excipient are facilitated.

Furthermore,colloidal Aluminium oxide facilitates the breakdown of drug agglomerates and prevents reagglomeration.

Table 2. Mixing index versus mixing time

Time of mixing (min.)	Mixtures n° Process A 1	2	3	4	5	Process B 6	7
1	3,0	3,2	-*	-	-	3,0	7,4
2	12,3	8,9	2,5	45,5	-	2,4	25,8
4	5,7	5,9	3,3	-	7,4	2,3	5,0
8	2,1	2,1	3,4	6,4	-	1,8	3,5
16	3,9	0,9	1,8	2,8	3,4	1,3	2,1
32	2,8	1,3	6,6	-	2,2	1,0	2,8
64	3,0	0,9	3,0	2,6	2,7	1,4	1,9

* - : mixing index has an infinite value

When Aerosil-200^{R} is added to powders,no improvement of the homogeneity of mixtures is noticed(Table 2).

The difference observed between the results obtained with Aerosil-200^{R} and colloidal Aluminium oxide is probably due to the specific antistatic action of colloidal Aluminium oxide(8).

Indeed,the influence of an adjuvant on the flowing and mixing properties of powders depends on the mechanical treatment imposed to the powders;the dynamic action of colloidal Aluminium oxide on the electrostatic forces explains that this adjuvant has a good influence on the mixing process.

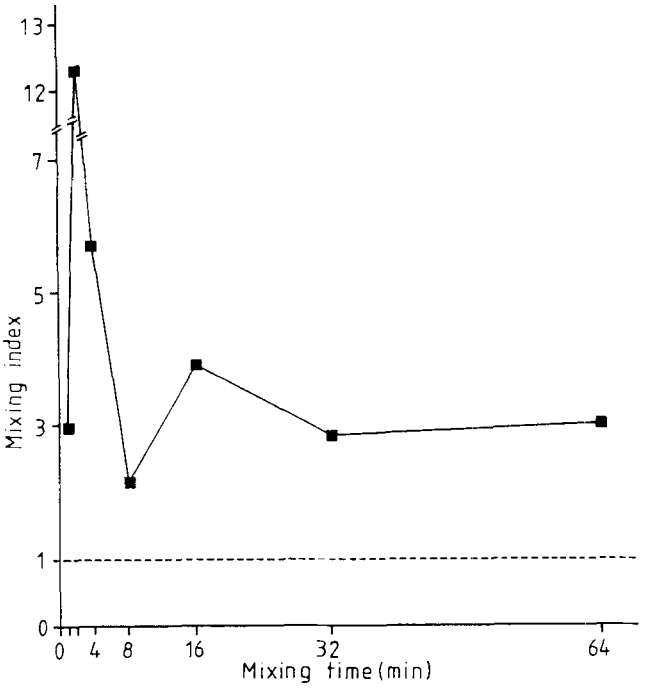

FIGURE 6

Mixing index versus mixing time
(200 mesh lactose 99 %-Triamteren 1 %).

On the contrary, Aerosil-200^{R} has a bad influence on the rheological properties of powders when a dynamic process is concerned (vibrated flow through a funnel, mixing process...).

When the mixing process B is used, the same conclusion can be drawn about the homogeneity of mixtures as far as the influence of the colloidal Aluminium oxide concentration is concerned.

In this case, it is obvious that a better homogeneity degree is achieved in the mixture after a very short mixing time(Fig.8.).

In fact, the pre-mixing of the adjuvant with the drug and the excipient respectively permits the breakdown of agglomerates and

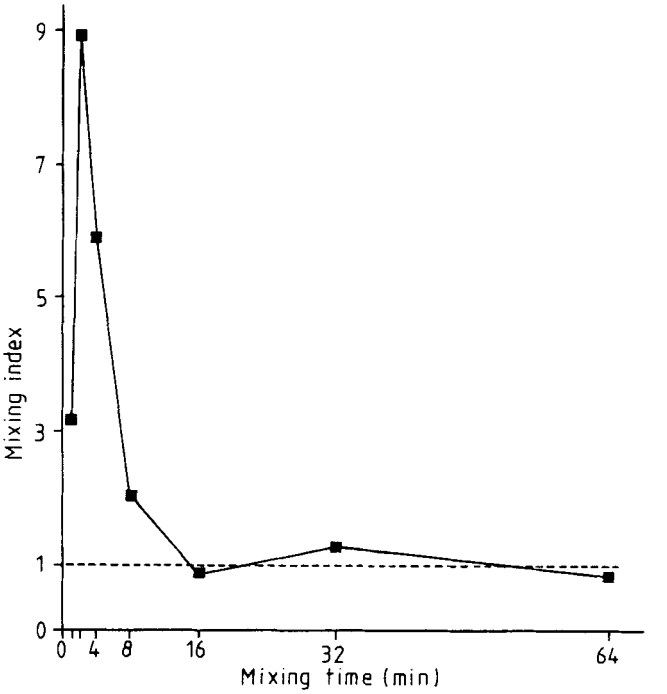

FIGURE 7

Mixing index versus mixing time;
effect of 0,2 % colloidal Aluminium oxide.

the decrease of cohesiveness of powders prior to the mixing process.

Nevertheless,the required homogeneity degree of the mixture is not reached faster than when the mixing process A is used.

CONCLUSIONS

In conclusion,it has been demonstrated that colloidal Aluminium oxide used in appropriate concentration has a good influence on the homogeneity of a 1 % Triamteren-200 mesh lactose mixture, realized with a Turbula T2 C mixer,rotating at 30 r.p.m;

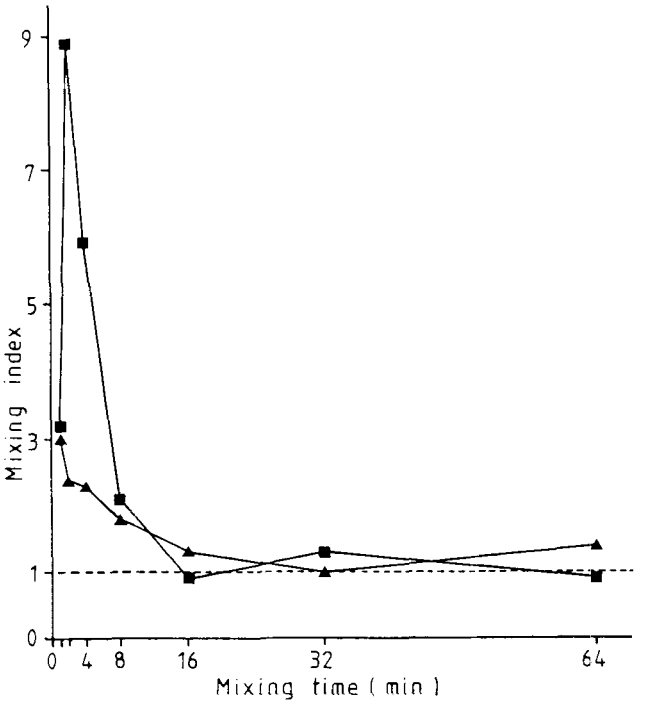

FIGURE 8

Mixing index versus mixing time;

effect of the mixing process(■ :process A; ▲ :process B).

this appropriate range of concentration is the one which gives the best flowing properties to the excipient.

Nevertheless,the addition of an adjuvant such as colloidal Aluminium oxide to improve the mixing characteristics of cohesive powders could perhaps decrease the adhesion of drug particles onto the particles of excipients.

If this happens,an ordered mixture could not be obtained and segregation of drug particles might occur on handling.

Other experiments are now being undertaken to find out how flowing adjuvants could disturb the formation of ordered mixtures.

ACKNOWLEDGMENTS

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