DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 11(2&3), 607-633 (1985)

CONTENT UNIFORMITY OF ETHINYLOESTRADIOL TABLETS 10 μG: EFFECT OF VARIATIONS IN PROCESSING ON THE HOMOGENEITY AFTER DRY MIXING AND AFTER TABLETING

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ABSTRACT

The effect of numerous processing factors such as mixer geometry and design, power input, time of dry and wet mixing on the content uniformity of tablets containing potent drugs have been studied. Cohesive drug powders and excipients have been used.

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0363-9045/85/1102-0607$3.50/0

Results show that pharmaceutically acceptable homogeneity is achieved after dry mixing for 7 hours in the Lödige-Morton mixer. It is shown that there is no significant improvement of homogeneity on increasing the time of wet mixing in excess of 5 minutes, and the rate of breakdown of the drug agglomerates and dispersion of individual particles, under the experimental conditions, is very slow. The high energy input exerted by ball milling markedly improves the homogeneity of the powder mixes and the content uniformity of tablets. After 15 minutes of dry mixing, the state of homogeneity of the powder mix containing cohesive drug powder in minute amounts in cohesive excipient is not influenced by the type of mixer.

INTRODUCTION

Content uniformity of tablets containing potent drugs (e.g. ethinyloestradiol 10 µg tablets) is dependent on the dispersion of drug particles into the excipients.

At the high levels of dilution that occur with potent drugs (e.g. 1:5000), the drug must be finely divided if reasonable standards of homogeneity are to be satisfied (1,2). As the particle size of the drug is decreased, the homogeneity is improved in accordance with random mixing theory until a critical or

minimum particle size d'_c is reached (3). For batches containing drug particles of size less than d'_c poor homogeneity is obtained. This is because drug particles become very fine which exhibit cohesive properties with a tendency to form agglomerates. The presence of drug agglomerates leads to positively skewed distributions, poor homogeneity and consequently poor content uniformity of tablets (3-8).

The critical particle size of drug powder (or critical mixing diameter of drug particles), d'_c is a minimum value which appears to be associated with a change of the shape of the distribution from normal to positively skewed (3,9).

The rationale of proposing the critical particle size d'_c is to help in choosing the proper particle size distribution of drug powder which produces unit doses with pharmaceutically acceptable content uniformity.

The value of d'_c for ethinyloestradiol powders mixed with cohesive lactose powder (the volume weighted volume mean diameter of cohesive lactose = 23 μm) in the Lödige-Morton mixer for 15 minutes was found to be 22 μm (9).

In addition to the cohesiveness of the drug powders the critical particle size of drug particles, d'_c will depend upon numerous factors such as mixer

geometry and design, power input, time of dry and wet mixing, and nature and particle size of excipients (9).

The nature and particle size of excipients effect the dispersal of drug agglomerates into component particles (3,5,6,10-13). Thus the critical particle size of drug particles, d'_c is to some extent dependent upon the size and physical characteristics of the excipient particles (10).

The object of this study is to investigate the effect of processing factors such as mixer geometry and design, power input, and time of dry and wet mixing on the value of d'_c. It is also investigating the relevance of these factors to the content uniformity of ethinyloestradiol tablets.

EXPERIMENTAL

Materials and Methods:

Cohesive lactose (C1, Lactose 350A grade) was obtained from Unigate Food Ltd., England. Ethinyloestradiol cohesive powder was obtained by further grinding of the powdered drug (laboratory prepared, 9) using pestle and mortar. Ethinyloestradiol free flowing powder was obtained from Organon Laboratories Ltd., England.

The full particle size distribution was evaluated for each powder, using microscope counting

for cohesive ethinyloestradiol and cohesive lactose powders. For the free flowing ethinyloestradiol powder Coulter Counter model B (Coulter Electronics, luc., Fla., U.S.A.) was used. The volume weighted volume mean diameter, d'_m and simply called the effective mixing diameter, was calculated for each powder by the method described by Orr and Sallam (14). The densities were found to be 1.23 and 1.54 g/ml for ethinyloestradiol and lactose powders.

Preparation and Sampling of the Powder Mixes:

Mixing Apparatus and Operations:

Three mixing machines were used as follows:

1- Lödige-Morton Mixer (Morton Machine Co. Ltd., Wishaw, Scotland).

It has a total capacity of 4.8 litres. Double plough shaped shovels are connected to a shaft which rotates inside the mixing drum at 240 rev/min. Mixing machine may be operated in two modes, one with the drum stationary and the other with the drum rotating. However, throughout this study the drum was kept stationary. The mixing unit may be turned vertically in order to attach or to remove the mixing drum.

Operation was performed by placing 920 g of excipient (790 g of lactose and 130 g of potato starch) in the drum which filled approximately 60% by volume of the capacity of the mixer. Ethinyloe-

stradiol powder (0.2 g) was then placed on top of the excipient. The drum was then attached to the mixing unit and clipped in position. The mixer was operated for 15 minutes. The drum was carefully taken off the mixer unit and any powder adhering to the blades of the shaft was scraped off with a spatula into the drum. The powder bed was levelled to a uniform height and 50 spot samples were withdrawn. For studying the rate of dry mixing 50 spot samples were withdrawn from the powder bed after 15 minutes, 1 hour, 7 hours and 24 hours.

2- Y - Cone Mixer (made by the workshop of the Faculty of Pharmacy, Sunderland Polytechnic).

It consists of a polythene Y shaped cone of a capacity of about 1.5 litre mounted on a rotating unit (Apex Construction Ltd, London) so that it can be rotated horizontally in the plane of the Y - cone, and the speed was adjusted to rotate at 25 rev/min.

285 g of excipient (245 g of lactose and 40 g of potato starch) was placed in the mixer and then ethinyloestradiol powder was added into the centre of the powder bed and mixed for 15 minutes. Twenty five spot samples were withdrawn from each side.

3- Duplex Mixer or Z - Blade Mixer (Morton Machine Co. Ltd., Wishaw, Scotland).

It has a capacity of 2.5 litres and consists of a tank with a round semicylindrical bottom and two

arms of Z - shape, turning around in opposite directions at the same speed. During the run the tank is covered with a lid. When it is emptied the lid is removed and the body of the tank is tipped.

920 g of excipient (790 g of lactose and 130 g of potato starch) was placed in the tank, then ethinyloestradiol powder (0.2 g) was added and mixed for 15 minutes. After which, the powder bed was levelled to a uniform height and 50 spot samples were withdrawn.

Effect of Method of Mixing

Powder mixing by trituration using a ball mill was compared with that for the Lödige-Morton mixer. 0.300 g of ethinyloestradiol was placed with 150.0 g of starch (potato) into the ball mill, placed on a roller (Pascall Engineering, England) and milled for 1 hour. 100 g of the powder mix was then transferred to the drum of the Lödige-Morton mixer which contained 30 g starch and 790 g of the cohesive lactose (lactose 350 A grade) and then mixed for 15 minutes. Two batches were prepared using two different fractions of ethinyloestradiol, the cohesive fraction and the free flowing fraction. When the cohesive lactose (lactose 350 A grade) was triturated with ethinyloestradiol in a ball mill, a powder cake was formed, however no caking was observed if starch was used instead of lactose.

Sampling of the Powder Mix:

The sample thief was of the concentric cylinder type and the design of thief and the sampling technique were as described by Orr and Shotton (4).

For the Lödige-Morton mixer the depth of powder mix was 10 cm, and five sample depths were used. Operating with a sampling grid of 55 holes this gave a possible 275 different sampling positions, i.e. 1-55 at depth 1, 56 - 110 at depth 2, 111 - 165 at depth 3, 166 - 220 at depth 4 and 221 - 275 at depth 5. Fifty numbers were chosen randomly from a set of numbers 1 - 275 and samples were removed from positions according to their numbers. In the case of the Y - cone mixer, 25 spot samples were withdrawn from each side of the Y to give a total of 50 spot samples. These were withdrawn from different depths each of 2 cm deep and chosen randomly in a similar manner of that of the Lödige-Morton mixer. Similarly 50 spot samples were withdrawn from the powder mix mixed by the Duplex mixer.

The scale of scrutiny was equivalent to a target weight of 50 mg which was equivalent to the weight of ethinyloestradiol 10 μg tablet. The actual weight of each spot sample was not exactly 50 mg and varied within a sample of 50 spot samples, the standard deviation was in the range of 6.9 - 13.8 mg and the mean weight in the range of 56 - 64 mg.

Tableting:

Conventional tableting processes were performed as follows:

1- Wet Granulation

The powder mixture was placed in the Duplex mixer and sufficient granulating agent (5% w/v starch mucilage) was added while mixing at fast speed for 5 minutes until a suitable consistency was obtained. The volume of starch mucilage was recorded. The wet mass was passed through the granulator (Jackson Crockatt Ltd, Glasgow) fitted with a 710 μm aperature screen.

2- Drying

Granules were dried out for 1 hour at 60^{0} C in the Mitchell Drying Oven (Mitchell Dryers, Manchester).

3- Dry Granulation

Dry granules were passed through the Jackson Crockatt granulator fitted with a 355 μm aperture screen.

4- Lubrication

Dry granules were placed in a 2 litre powder jar with 1% w/w magnesium stearate and the rest of the starch to make 1 kg formula. The jar was placed on a roller (Pascall Engineering, England) and mixed for 20 minutes.

5- Tableting

The lubricated granules were placed in a hopper and compressed on a single punch machine, Manesty F3 (Manesty Machines Ltd, Speke, Liverpool) using a 3/16 inch punch and die set. The tablet fill weight was adjusted to give 50 mg tablets. A sample of 50 tablets were withdrawn randomly from the bulk containers.

Effect of Time of Wet Mixing on the Content Uniformity of Tablets

Using cohesive ethinyloestradiol powder and the cohesive lactose (lactose 350 A grade) another two different batches of tablets were made under the same conditions except time of wet granulation was varied, 15 minutes for one batch and 30 minutes for the second one.

Analytical Method:

A semi-automated analytical technique for the single assay of EE powder samples and tablets was used. Sample solutions were first prepared, then fed into the Auto-Analyser II (Technicon Instruments Co. Ltd., Basingstoke). The analysis was based on an acid-inducing fluroescence in methanolic solution of ethinyloestradiol by 60% v/v sulphuric acid in methanol. The fluorescence was measured at an excitation wave length of 462 nm and emission wave

length of 490 nm (9). The overall analytical precision which includes errors in weighing of samples, volumetric measurements, extraction technique and use of the Auto-Analyser was estimated to be equivalent to a coefficient of variation of 1.7%.

RESULTS AND DISCUSSION

The results expressed as μg of ethinyloestradiol per tablet give an indication of the variation in doses that occurs whereas the data expressed as μg per gram of powder or tablet give an indication of the homogeneity of the drug variation in spot sample or tablet weight.

The degree of skewness is assessed by calculating the statistic $\sqrt{b_1}$ often referred to as the coefficient of skewness where:

$$\sqrt{b_1} = \sqrt{m_3^2 / m_2^3} \quad \text{where } m_r = \sum_{i=1}^{n} \frac{(x_i - \bar{x})^r}{n}$$

n = number of degrees of freedom, and r = 2 for m_2. and r = 3 for m_3.

The limiting values for a normal distribution, for a sample size of 50 are 0.533 and 0.787 for P = 0.05 and 0.01 respectively (15).

Effect of Increasing Mixing Energy on the Homogeneity After Dry Mixing and After Tableting.

Increasing the mixing energy was achieved by three different methods as follows:

1. By increasing the time of dry mixing, Spot samples were withdrawn at different times; 15 minutes (B1), 60 minutes (B2), 420 minutes (B3) and 1440 minutes (B4). Tablets were made from B1 and B4 powder mixes.

2. By increasing the time of wet mixing; 5 minutes (B1), 15 minutes (B5) and 30 minutes (B6).

A cohesive ethinyloestradiol powder was used for the above mentioned studies.

3. By using a ball mill, which produces a high energy input, prior to dry mixing in the Lödige-Morton mixer. Two batches were prepared, the first one used coarse free flowing drug powder (B7b) and the second one cohesive agglomerated drug powder (B8).

Effect of time of dry mixing on the Homogeneity of Powder Mix and Tablets (Rate of Dry Mixing)

From Table 1, it would appear that the breakdown of agglomerates, under the experimental conditions, is time dependent, considerable breakdown of agglomerates being achieved in 420 minutes. When the mean drug content approaches a value consistent with the target value (217 $\mu g.g^{-1}$ powder) and the coefficient of variation has a value of 4.2, the homogeneity would appear to be pharmaceutically acceptable, although a time of dry mixing of 7 hours

TABLE 1

Summary of the experimental data of the effect of dry mixing on the homogeneity of powder mix and tablets of ethinyloestradiol.

Batch No.	Time of dry mixing in min.	Powder mix $\mu g.g^{-1}$ C_p	$\sqrt{b_1}$	Tablets $\mu g.g^{-1}$ C_t	$\sqrt{b_1}$
B1	15	131.5	5.851	11.4	3.753
B2	60	13.6	5.710	-	-
B3	420	4.2	-0.068	-	-
B4	1440	2.3	-0.133	3.2	0.312

The cohesive fraction of ethinyloestradiol (d'_m, the effective mixing diameter = 7.9 μm) and CL (cohesive lactose, d'_m = 23.1 μm) are used for all batches. C_p $\mu g.g^{-1}$ and C_t $\mu g.g^{-1}$, the coeffecients of variation of ethinyloestradiol/gram of powder and tablet mass respectively. For anormal distribution and a sample size of 50 the limiting values of $\sqrt{b_1}$ (the coefficient of skewness) are 0.533 and 0.787 for P = 0.05 and 0.01 respectively (15).

in industry would not be economical. The value of C_p is however significantly better (F-test at P = 0.05) after 1440 minutes of dry mixing. The distribution of drug content changes from positively skewed (15 min. and 60 min. of dry mixing) to symmetrical after increasing the time of dry mixing to 420 and 1440 minutes, as the processes of breaking down agglomerates and dispersion of detached particles continue to take place.

The value of $\bar{x}$, the mean drug content, for powder mixes of B1 and B2 (15 min. and 60 min. of dry mixing respectively) is smaller than the target value (217 $\mu g.g^{-1}$ powder) because some of the drug powder still remains in the form of agglomerates. Such agglomerates are few in number relative to the excipient particles, therefore the probability of withdrawing spot samples containing agglomerates is very small which results in the value of $\bar{x}$ being less than the target value. As the breakdown of agglomerates continues with increasing time of dry mixing so, the value of $\bar{x}$ increases ($\bar{x}$=214 $\mu g.g^{-1}$ powder).

In conclusion, the positive skewness of batches containing cohesive drug powder is due to the presence of agglomerates of the drug not being completely dispersed into their components. Therefore the rate limiting step in mixing minute amounts of agglomerated drug powder, is the breakdown of agglomerates into their individual particles thus allowing subsequent randomisation or possibly ordered mixing to take place. It is also shown that by increasing the time of dry mixing 6 to 24 hours, the value of d'_c decreases to, or even less than, 7.9 μm.

The homogeneity of the ethinyloestradiol content in tablets after 15 and 1440 minutes of dry mixing

follows the same pattern for the powder mixes (Table 1). The powder samples of B2, B3 and B4 are withdrawn from the same powder mix at 60, 420 and 1440 minutes of dry mixing, therefore one batch of tablets can only be prepared at the end of the dry mixing cycle, i.e. B4 tablets. B1 (15 min. dry mixing) is another powder mix which was used to prepare B1 tablets. This has been done because the study is mostly concerned with the relationship between the time of dry mixing and the breakdown of drug agglomerates. Thus, two batches of tablets prepared at the beginning and at the end of the dry mixing cycle are considered reasonable to show the effect on tablets.

Effect of Time of Wet Mixing Process on the Homogeneity of Drug Content in Tablets Prepared From Cohesive Drug Powder

The results shown in Table 2 suggest that there is no significant improvement of homogeneity on increasing the time of wet mixing in excess of 5 minutes and thus the rate of breakdown of agglomerates and dispersion of individual particles, under the experimental conditions, is very slow. Assuming C_p and $\sqrt{b_1}$ of the B1 powder mix as values for wet mixing and further tableting processes at zero time, they are included in Table 2. It is therefore suggested that tableting

TABLE 2

Summary of the experimental data of the effect of wet mixing on the homogeneity of cohesive ethinyloestradiol in tablets.

Batch number and time of wet mixing.	C_t $\mu g.g^{-1}$	$\sqrt{b_1}$ $\mu g.g^{-1}$
B1 powder mix (0 minutes)	131.5	5.851
B1 tablets (5 minutes)	11.4	3.753
B5 tablets (15 minutes)	8.1	1.799
B6 tablets (30 minutes)	11.2	2.980

The cohesive fraction of ethinyloestradiol (d'_m the effective mixing diameter = 7.9 μm) and CL (cohesive lactose, d'_m = 23.1 um) are used for all batches. C_t ug.g^{-1}, the coefficient of variation of ethinyloestradiol/gram of tablet mass. The C_p of powder mix for B1 is considered as the C_t at zero time of wet mixing.
For a normal distribution and a sample size of 50 the limiting values of $\sqrt{b_1}$ (the coefficient of skewness) are 0.533 and 0.787 for P = 0.05 and 0.01 respectively (15).

processes other than wet mixing, e.g. granulating the wet mass by passing through smaller mesh sieves, dry granulation process and further mixing of the granules with lubricant and the rest of the excipients, contribute markedly to improving the homogeneity of ethinyloestradiol in the tablets. This could be the reason why C_t values of B1, B5 and B6 (5, 15 and 30 min. of wet mixing respectively) are significantly less than C_p of B1.

Effect of Increasing Energy Input by Ball Milling Prior to Dry Mixing in the Lodige-Morton Mixer

The high energy input exerted by ball milling markedly improves the homogeneity of the powder mix prepared from either coarse particles or cohesive ethinyloestradiol fraction as shown in Table 3. In both instances this is due to the breakdown of the particles or agglomerates with subsequent dispersion of the finer particles produced.

The value of C_p depends on this reduction and the new particle size distribution. The values of C_p and C_t are markedly reduced which leads to the assumption that random mixing has been achieved.

In order to determine the value of d'_m of ethinyloestradiol after ball milling the following equation is used:

$$C_R = 100 \sqrt{\frac{\Sigma (fw)_x}{Mx}} \qquad \text{(Ref. 2)}$$

$$\Sigma (fw)_x = 1/6 \cdot \pi \cdot \rho \cdot (d'_m)^3$$

Where:

C_R is the coefficient of variation for a random mix. $\Sigma (fw)_x$ is the effective mean particle weight of the drug. (d'_m) is the volume weighted volume mean diameter and simply called the effective mixing diameter.

TABLE 3

Summary of the experimental data showing the effect of increasing energy input by ball milling prior to dry mixing in the Lödige-Morton mixer.

Batch number	EE d'_m μm	Powder mix μg.g^{-1} C_p	$\sqrt{b_1}$	Tablets μg.g^{-1} C_t	$\sqrt{b_1}$
B7a* without ball milling.	759 Coarse	94.5	3.483	59.0	3.334
B7b with ball milling.	759 Coarse	3.1	0.505	1.9	0.184
B1 without ball milling.	7.9 Cohesive	313.5	5.851	11.4	3.753
B8 with ball milling.	7.9 Cohesive	3.2	1.179	2.9	0.028

EE = ethinyloestradiol size fraction; d'_m = the effective mixing diameter.
C1 (cohesive lactose, d'_m = 23.1 μm) is used for all batches.
C_p μg.g^{-1} and C_tμg.g^{-1}, the coefficients of variation of ethinyloestradiol/gram of powder and tablet mass respectively.
(*) From reference 16.

(M) is the weight of the sample taken from the mix.

(x) is the proportion of the drug in the powder mix.

(ρ) is the density of the drug.

Therefore, the value of d'_m could be assumed to be within the range of 6.9 to 22.9 μm (for C_t = 1.9 and C_p = 3.1 respectively). This is an assumption in order to indicate the magnitude of reduction of coarse ethinyloestradiol powder (d'_m = 759 μm) after ball milling for 1 hour.

After ball milling, the powder mix containing cohesive drug particles exhibits positive skewness, while the value of C_p is very small. This may be due to the presence of agglomerates. However, the comparison between the minimum and the maximum drug content for batches prepared without ball milling and batches prepared with ball milling will give an indication of the efficiency of ball milling in breaking down drug agglomerates. In the case of the powder mix prepared without ball milling, the range of drug content is 84 - 1585 $\mu g.g^{-1}$ contrasting with 193 - 235 $\mu g.g^{-1}$ for the powder mix prepared by ball milling. The mean drug content $\bar{x}$ for powder mix of 81 is 165μg^{-1} but 207 $\mu g.g^{-1}$ for the powder mix of 88. All of the above factors indicate that ball milling efficiently breaks down drug agglomerates and helps individual particles to become detached from each other and be dispersed into the excipients. However, the positively skewed

distribution of the powder mix B8 with a small C_p value of the small range between the minimum and the maximum drug content indicates that small agglomerates are still present undispersed and could be randomly distributed in the powder mix.

Further processes of tableting improve the state of homogeneity of both B7b and B8 as indicated by further decrease of C_t value for B7b and a value $\sqrt{b_1}=0.028$ which is consistent with normality for B8. For B8 tablets it indicates further breakdown of agglomerates and dispersion of the detached individual particles.

In conclusion, the high energy input created by ball milling for 1 hour prior to dry mixing in the Lödige-Morton mixer, is responsible for the breakdown of agglomerates in the cohesive ethinyloestradiol powder (B8), the particle size reduction of coarse, free flowing ethinyloestradiol powder (B7b) and the dispersion of individual particles into the excipients. By such a process the value of d'_c decreases, to or may be less than, 7.9 μm which again suggests that the rate limiting step when d'_m is less than d'_c is the breakdown of agglomerates and subsequent dispersion of the individual particles into the powder mix.

Effect of Type of Mixers on the homogeneity After Dry Mixing and After Tableting.

The results for three different types of mixers, a Lödige-Morton mixer, a Y - cone mixer and a Z - blade mixer are summarised in Table 4. The cohesive fraction of ethinyloestradiol is mixed with cohesive lactose for 15 minutes by the three different mixers. The Z - blade mixer produces a powder mix with a smaller C_p value relative to the others, however all indicate gross inhomogeneity. The values of $\sqrt{b_1}$ (Table 4) indicate that the distributions are markedly positively skewed due to the presence of undispersed agglomerates. It is expected that after tableting the batch which is mixed by the Z - blade mixer (89) may produce a C_t value smaller than those mixed by the other mixers. However, this does not occur and therefore the difference in C_p could be attributed to limitations associated with sampling.

Comparison of the values of C_p, C_t and $\sqrt{b_1}$ for the batches prepared by the above mentioned mixers with those for the batch prepared by ball milling (88, Table 3) suggests that ball milling is far more efficient in breaking down drug agglomerates. However, the time of dry mixing is different, 15 minutes for batches prepared either by the Lödige-Morton mixer, the Y - cone mixer or the Z - blade mixer, but 1 hour for ball milling and 15 minutes for mixing in the Löige-Morton mixer for 88. Ball milling still

TABLE 4

Summary of the experimental data of the effect of type of mixer on the homogeneity of ethinyloestradiol after dry mixing and after tableting.

Batch	Type of mixer	Powder mix $\mu g.g^{-1}$		Tablets $\mu g.g^{-1}$	
		C_p	$\sqrt{b_1}$	C_t	$\sqrt{b_1}$
B1	Lödige-Morton mixer	131.5	5.851	11.4	3.753
B9	Y - cone mixer	111.8	3.205	29.2	4.893
B10	Duplex mixer	68.0	3.939	23.5	5.500

The cohesive fraction of ethinyloestradiol (d'_m the effective mixing diameter = 7.9 μm) and CL (cohesive lactose, d'_m = 23.1 μm) are used for all batches. C_p $\mu g.g^{-1}$ and $C_t \mu g.g^{-1}$, the coefficients of variation of ethinyloestradiol/gram of powder and tablet mass respectively. For a normal distribution and a sample size of 50 the limiting values of $\sqrt{b_1}$ (the coefficient of skewness) are 0.533 and 0.787 for p=0.05 and 0.01 respectively (15).

exhibits higher energy input which increases the rate of breakdown of agglomerates and produces better homogeneity. This can be shown by comparing results of B2 (mixing for 1 hour in the Lödige-Morton mixer) and B8 (ball milling) as shown in Table 5.

One factor influencing the rate of breakdown of agglomerates is the direct mechanical action of the

TABLE 5

Summary of the experimental data for dry mixing in the Lödge-Morton mixer and trituration by ball milling.

Powder mix	B2	B8
$\mu g.g^{-1}$	(Lödige-Morton mixer)	(ball milling)
Minimum drug content	155	193
Maximum drug content	323	235
Mean drug content	171	207
C_p	13.6	3.2
$\sqrt{b_1}$	5.710	1.179

The cohesive fraction of ethinyloestradiol and cohesive lactose are used for all batches. B2, dry mixing in the Lödige-Morton mixer for 1 hour.
B8, ball milling for 1 hour prior to dry mixing for 15 minutes in the Lödige-Morton mixer.

mixer on the agglomerates (4, 5, and 17). From results shown in Tables 4 and 5 it is concluded that for 15 minutes dry mixing, the state of homogeneity of the powder mix containing cohesive drug powder in minute amounts in cohesive excipients is not influenced by the type of mixers. For 1 hour, ball milling for such systems produces a higher rate of breakdown of agglomerates than the Lödige-Morton mixer and this results in a better and more acceptable homogeneity.

Cohesive lactose has been used as excipient for the three batches prepared by different types of

mixers, however,it should be emphasised that excipients of other physical characteristics may exhibit different trends due to different mechanisms being predominant.

Effect on the Content Uniformity of Tablets:

The tablets produced after dry mixing of 24 hours in the Lödige-Morton mixer (B4) and after ball milling (B7b and B8) possess good content uniformity and pass the U.S.P. XX content uniformity specifications (18). Other batches possess gross nonhomogeneity and consequently produce poor content uniformity.

CONCLUSION

In formulation of ethinyloestradiol 10 μg tablets, a minimum or critical mixing diameter of drug particles d'_c was proposed (9,16). The value of d'_c is associated with the state of homogeneity which is achieved after dry mixing and tableting as shown in Fig. 1.

This study has shown that by increasing the time of dry mixing in the Lödige-Morton mixer of more than 6 hours the value of d'_c decreases to or even less than 7.9 μm. Similar result has been obtained by ball milling for 1 hour prior to dry mixing of 15 minutes in the Lödige-Morton mixer. This is because the drug agglomerates have been broken down and the individual particles subsequently dispersed into the powder mix.

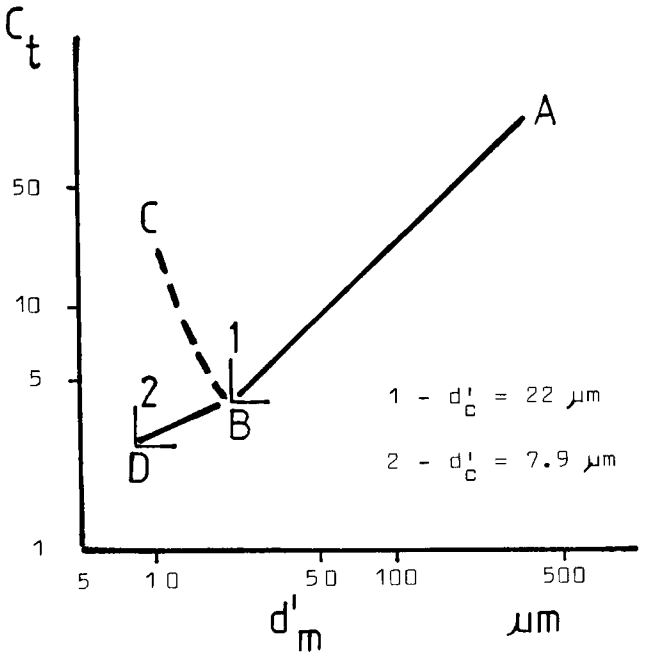

FIGURE 1

Diagram showing the effect of processing factors on the critical mixing diameter of ethinyloestradiol particles, d'_c.

(——) AB, linear regression on C_t values approaching normal distributions.
(— —) BC, positively skewed distributions.
(——) BD, by increasing time of dry mixing of 7-24 hours in the Lödige-Morton mixer, or by ball milling for 1 hour prior to dry mixing. BD is produced instead of BC.
Tablets of BD exhibit normal distributions.
d'_m = the volume weighted volume mean diameter of ethinyloestradiol.

According to the random mixing theory, when the particle size of drug is reduced from d'_c of 22 μm to 7.9 μm, the state of homogeneity will improve significantly. The content uniformity of tablets prepared has been markedly imporved and passed the compendial tests, although the time of dry mixing of 7 hours in industry would not be practical, while the ball milling method is acceptable.

Other processing factors such as time of wet mixing for more than 5 minutes and type of mixer, under the experimental conditions, do not show significant effect on the value of d'_c. Thus, they do not improve the content uniformity of ethinyloestradiol tablets prepared from cohesive ethinyloestradiol powder and cohesive lactose.

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