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STUDIES RELATING TO THE CONTENT UNIFORMITY OF ETHINYLOESTRADIOL TABLETS 10 UG: EFFECT OF PARTICLE SIZE OF ETHINYLOESTRADIOL.

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ABSTRACT

Ethinyloestradiol is formulated in minute amounts, e.g. 10 µg per tablet of 50 mg weight. Experiments to relate the shape of the distribution curve and the extent of homogeneity to the particle size of ethinyloestradiol were performed.

Results showed that on comparison of values of C_R (the coefficient of variation for a random mix), with C_p and C_t (the coefficients of variation for powder mix and

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tablets respectively), for the batches containing the large particle size fractions of drug the values are as predicted by random mixing theory. As the particle size of the drug is decreased, the values of C_p and C_t also decrease in accordance with random mixing theory until a critical particle size d'_c is reached. For batches containing drug particles of size less than d'_c then both C_p and C_t increase with decreasing particle size. This change is associated with a change to a positively skewed distribution because of the cohesive properties of fine powders and their tendency to form agglomerates which remain undispersed in the excipients. Above d'_c the rate limiting step in powder mixing is randomisation and below it the rate limiting step in achieving the required homogeneity is the breaking down of the drug agglomerates. In addition to its effects on the magnitude of C_p and C_t, the particle size of ethinyloestradiol has a marked influence on the shape of the distribution curve.

INTRODUCTION

It is well known that the distribution of drugs in tablets depends upon mixing criteria (1,2). The homogeneity of a mix is dependent upon the association of one species with another species. Until Hersey (3) introduced the concept of ordered mixing, mixing processes were defined in terms of randomisation (4-7). Recently Egermann (8) has shown that ordered mixing can not be attained under real mixing conditions. However, random

mixing is frequently attained with pharmaceutical powder mixes. This is because pharmaceutical powder mixes usually contain cohesive powders with different particle size distributions, particle shape, density and flow characters. The random mixing theory shows that at the high level of dilution of drug in excipient, e.g. ethinyloestradiol 10 μg tablets each of 50 mg weight, to attain acceptable content uniformity, the drug must be very fine. However, this increases the cohesion of particles which impairs the efficiency of the mixing process and promotes the presence of agglomerates; hence, gives rise to a positively skewed distribution (9-15). It can be assumed that the rate limiting step in the mixing of small amounts of a fine cohesive powdered drug will be the rate of breakdown of agglomerates into their component particles. Despite the considerable amount of research undertaken in the field of powder mixing there is still little published data concerning the shape of the distribution curve obtained in practice as compared to the normal distribution that is often associated with random mixing.

This study relates the shape of the distribution curve and the extent of homogeneity to the particle size of ethinyloestradiol. It also relates the degree of skewness to the particle size characteristics and bulk properties of the drug and explains the results in terms of random mixing theory.

EXPERIMENTALS

Materials:

The formula for ethinyloestradiol tablets 10 μg used throughout this study is outlined in table 1. This formula was based on that currently being used by a manufacturer (Manufacturer E, (13) to make ethinyloestradiol tablets and known to cause problems of content uniformity in certain instances.

Powder Binary Mixes:

Eleven batches of powder mix were prepared using 11 fractions of ethinyloestradiol of different particle size ranging from very fine cohesive powder to a free flowing powder consisting of large particles as described by Sallam (16). Cohesive lactose (lactose 350A grade) was used for preparing these batches.

The full particle size distribution was evaluated for each powder and the volume weighted volume mean diameter (d'_m) was calculated (17). The source of Lactose B.P. (Unigate Ltd) and of Potato Starch B.P. (B.D.H.) used throughout this investigation was kept constant. The d'_m value of lactose was found to be 23 μm. Density of ethinyloestradiol was determined and found to be 1.23 g/cc, while that of lactose was 1.54 g/cc.

Preparation of Powder Mix:

A Lödige-Morton (Morton Machine Company, Wishaw, Scotland) of 4.8 litres capacity was used. Double plough

TABLE 1.

Formula for Ethinyloestradiol Tablets 10 µg Based on that Supplied by Manufacturer E (13).

1-	Ethinyloestradiol	0.200 g.	
2-	Lactose	790.0 g.	
3-	Potato Starch	130.0 g.	
			- Dry mixing.
4-	Starch Mucilage.	Q.S.	
			- Wet granulation.
			- Tray drying for 1 hour at 60°C.
			- Dry granulation.
5-	Magnesium Stearate	10.0 g.	
6-	Potato Starch to	1000.0 g.	
			- Mixing.
			- Compression, tablet weight, 50 mg.

shaped shovels are connected to a shaft which rotates inside the mixing drum at 240 r.p.m.

Operation was performed by placing 920 g of excipient, consisting of 790 g cohesive lactose and 130 g of starch, in the drum which gave a volumetric fill of approximately 60% of total capacity. The ethinyloestradiol powder 0.20 g was placed on top of the excipient. The drum was attached to the mixer and clipped into position. The mixer was operated for 15 minutes.

Sampling of the Powder Mix:

The drum was carefully lowered off the mixer unit and any powder adhering to the blades of the shaft was scraped off with a spatual into the drum. The powder bed was levelled to a uniform height and 50 spot samples were withdrawn using a sample-thief. The sample thief was of the concentric cylinder type and the design of thief and the sampling technique was as described by Orr and Shotton (9). The scale of scrutiny was equivalent to a target weight of 50 mg. The actual weight of each spot-sample varied within a sample of 50 spot-samples. The standard deviation was in the range 6.9-13.8 mg and the mean weight in the range 56–64 mg.

Tableting:

Tableting was done by conventional wet granulation process, and then compression on Manesty F3 (Manesty Machines Ltd, Speke, Liverpool) using a 3/16 inch punch and die set. After compression the tablets were mixed well and then a sample of 50 tablets was obtained by removing at random, tablets from the bulk container. Each tablet was weighed individually (Oertling R42 balance, London), and placed in a small stoppered glass tube and kept for analysis.

Analytical Assessment of Samples:

A semi-automated analytical technique for the determination of ethinyloestradiol in the powder spot samples

and tablets was used. Sample solutions in aqueous methanol (60% v/v), were first prepared, then fed into the Auto-Analyser II (Technicon Instruments Co. Ltd., Basingstoke). The analysis was based on an acid induced fluorescence in methanolic solution of ethinyloestradiol by 60% v/v. sulphuric acid in methanol (16). The fluorescence was measured at an excitation wavelength of 462 nm and an emission wavelength of 490 nm. The overall analytical precision which includes errors in weighing of the spot-sample or tablet, volumetric measurements, extraction technique, and use of the Auto-Analyser was estimated by experiment to have a coefficient of variation not more than 1.7%.

RESULTS AND DISCUSSION

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

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

n is number of degrees of freedom and r=2 for m_2 and r=3 for m_3. For a symmetrical distribution, if all of the observations are considered, $\sqrt{b_1}=0$; for a positively skewed distribution $\sqrt{b_1} > 0$. However, the value of $\sqrt{b_1}$ calculated for a sample of observations from a symmetrical distribution will not be exactly zero.

Pearson and Hartley (18) gave the probability of various departures from zero for a normal distribution. 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.

Effect of Particle Size of Ethinyloestradiol on the Homogeneity after Dry Mixing and after Tableting:

Powder Mixes:

From results (Table 2) the shape of the distribution for ethinyloestradiol content can be classified into two types:

1- Distributions which are approximately symmetrical and approach a normal distribution (at P = 0.01). The plot of log C_p versus log d'_m of ethinyloestradiol exhibits linearity similar to that predicted for a random mix(Fig.1).

2- Distributions which exhibit asymmetry characterised by positively skewed distribution.

When log C_p is plotted versus log d'_m for all powder mixes (Fig. 1), the graph exhibits a minimum value. This minimum value appears to be associated with a change of the shape of the distribution from normal to positively skewed. It is proposed that this minimum value occurs at a critical particle size, d'_c. Values of $d'_m < d'_c$ result in positively skewed distribution. On the other hand, values of $d'_m > d'_c$ result in distributions appro-

TABLE 2

Summary of Experimental Data: Effect of Particle Size of Ethinyloestradiol on the Homogeneity after Dry mixing and after Tableting.

Batch No.	EE	Ethinyloestradiol $\sum$ (fw) in ng	d'_m in µm	Powder mix µg.g^{-1} C_p	$\sqrt{b_1}$	Tablets µg.g^{-1} C_t	$\sqrt{b_1}$
B3	EE3	281244	759	94.7	3.483	59.0	3.34
B5	EE5	13538	276	51.0	0.032	63.5	0.625
B6	EE6	358	82.2	27.0	- 0.325	25.3	- 0.257
B8	EE8	116	56.4	9.7	- 0.325	8.1	0.350
B7	EE7	66.1	46.8	10.9	0.177	7.2	0.329
B10	EE10	34.3	37.6	7.8	1.132	5.2	0.162
B11	EE11	14.1	28.0	4.1	- 0.320	4.1	1.607
B9	EE9	11.3	26.0	6.4	0.250	4.9	0.508
B12	EE12	6.6	21.7	38.6	5.792	3.6	0.153
B13	EE13	1.5	13.2	52.2	3.666	5.8	0.622
B14	EE14	0.31	7.9	131.5	5.851	11.4	3.753

EE = Ethinyloestradiol particle size fraction. $\sum$ (fw) = the effective mean particle weight; d'_m = the volume weighted volume mean diameter; C_p = the experimental coefficient of variation for ethinyloestradiol in the powder mix; C_t = the experimental coefficient of variation of ethinyloestradiol in the tablets; the data in µg.g of tablet or powder mix give an indication of the homogeneity of the drug within the tablet mass or powder mix; that is independent of variation in tablet or spot sample weight; $\sqrt{b_1}$ = the coefficient of skewness, for a normal distribution and a sample size of 50 the limiting values of $\sqrt{b_1}$ are 0.533 and 0.787 P = 0.05 and 0.01 respectively (18).

aching normality, so long as the particle is not so large that the weight of an individual particle apporaches the labelled content of drug in a tablet. When this occurs the distribution will tend to be positively skewed (e.g. B3).

The positively skewed distribution of drug content for value of d'_m less than d'_c can be explained in terms

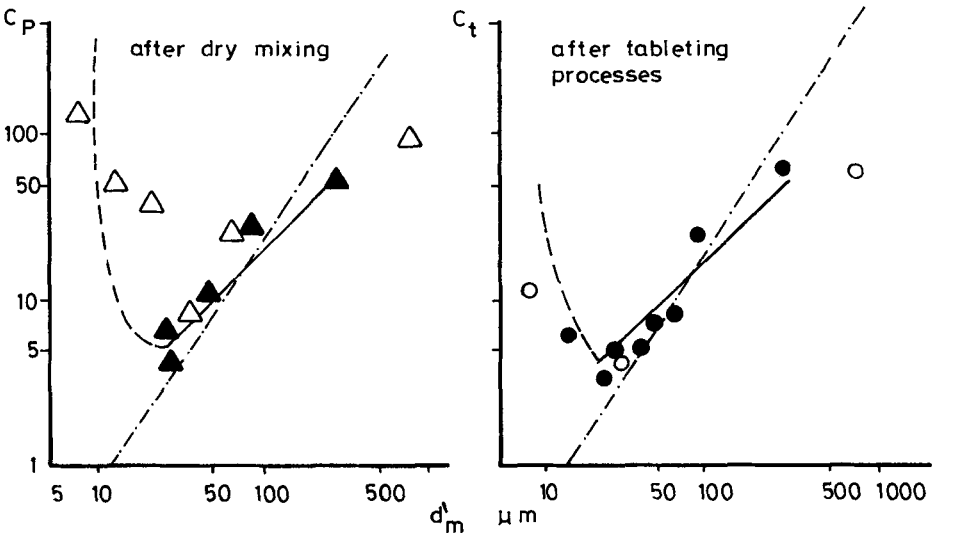


FIG. 1 : RELATIONSHIP BETWEEN HOMOGENEITY AND PARTICLA SIZE OF ETHINYLOESTRADIOL AFTER DRY MIXING AND AFTER TABLETING PROCESSES.
(-·-·-) , THEORETICAL RANDOM MIX ; (——) LINEAR REGRESSION ON EXPERIMENTAL DATA (FROM TABLE 2) ▲ ● , APPROACHING NORMALITY : △ ○ , POSITIVALY SKEWED.

of the cohesive properties of fine powders and their tendency to form agglomerates. For a fine cohesive powder, in many cases, the particle size distribution in the powder mix is not the distribution of sizes of the individual component particles but will consist of some primary particles and also particles in association with other particles in form of agglomerates. The particle/agglomerate size distribution due to the presence of agglomerates of differing size is likely to be markedly asymmetrical with a highly positive skew or possibly bi-modal with a distribution of primary particles and a distribution of agglomerates. Considerable energy will

be required, in this case, to give a dispersion composed of single component particles.

It is important to realise that for any one value of d'_m there are an infinite number of particle size distributions. Since the cohesiveness of a powder will, to a large extent, depend upon the percentage of the finer particles in the distribution as opposed to the value of d'_m which depends upon the percentage of the larger particles in the distribution it can be seen that it is possible to have powder of the same d'_m but of varying degrees of cohesiveness. Thus for any mix the critical particle size, d'_c cannot be defined absolutely.

In addition to the cohesiveness of the drug particles the critical particle size, d'_c will depend upon numerous factors such as mixer geometry and design, power input, time of mixing, nature and particle size of excipients (19, 20).

The rate limiting step for batches containing ethinyloestradiol with a value of d'_m greater than d'_c will be randomisation. While for powder mixes containing ethinyloestradiol with a value of d'_m less than d'_c the rate limiting step will be the breakdown of agglomerates. As powder mixing approaches a state of complete randomness the ratio $\bar{C}_p/C_R$, approaches unity.

Table 3 shows the degree of mixedness obtained for those batches where the distribution approaches normality. Markedly better homogeneity than that expected is achieved for B5, which is believed to be due to substantial

TABLE 3

The Effect of Particle Size on the Degree of Mixedness ($\bar{C}_p/C_R$) for those batches approaching normality.

Batch No.	EE d'_m in μm	C_R	$\bar{C}_p$	$\bar{C}_p/C_R$	$\bar{C}_p/C_R$ for 50 samples and 95% confid. limits.
B5	276	111.6	51.00	0.38	0.32 - 0.47
B6	82.2	18.14	26.92	1.48	1.24 - 1.84
B8	56.4	10.33	9.56	0.93	0.78 - 1.15
B7	46.8	7.80	10.83	1.39	1.17 - 1.72
B11	28.0	3.60	3.78	1.05	0.88 - 1.30
B9	26.0	2.46	6.18	2.51	2.11 - 3.11

The values of $\bar{C}_p/C_R$ indicate that, with the exception of B9 the above powder mixes approach the state of randomness (for 95% confidence limits).
EE = ethinyloestradiol; d'_m = the volume weighted volume mean diameter; C_R = the coefficient of variation for a random mix calculated by Poole et al. equation (6); $\bar{C}_p$ = the coefficient of variation of ethinyloestradiol in the powder mix excluding other sources of variation.

breakdown of the individual component particles because of the shear mixing effect produced by the Lodige-Morton mixer. Whilst the ratio $\bar{C}_p/C_R$ is useful for comparing exprimental homogeneity with that for a random mix, it is not suitable for pharmaceutical purposes. For example the B5 powder mix approaches randomisation, however the $\bar{C}_p$ value indicates gross inhomogeneity which is unacceptable for producing ethinyloestradiol tablets. A mixing index based on the acceptable coefficient of variation C_A is more relevant for pharmaceutical purposes. If a value C_A is arbitrarily chosen as 5% (21) then as powder mixing approaches acceptability, the ratio $\bar{C}_p/C_A$ approaches unity as shown in Fig 2. 1. Thus batches producing values of $\bar{C}_p/C_A$ far from unit can be identified, e.g. B3 and B5, this is not the case for the mixing ratio $\bar{C}_p/C_R$ as shown in Fig 2.2.

Tablets:

Results for the tablets follow the same pattern as those for the powder mixes as shown in Table (2) and Fig. 1. Fig 3 shows values of C_p and C_t plotted against their corresponding d'_m values on a log - log scale. A regression line is drawn through values of C_p and C_t approaching a normal distribution (at P=0.01). This indicates that results approach those predicated by random mixing theory, and follow the same pattern as discussed before. Line A-B in Fig.3 indicates the increasing values of C_p and C_t with further decreasing values of d'_m. It

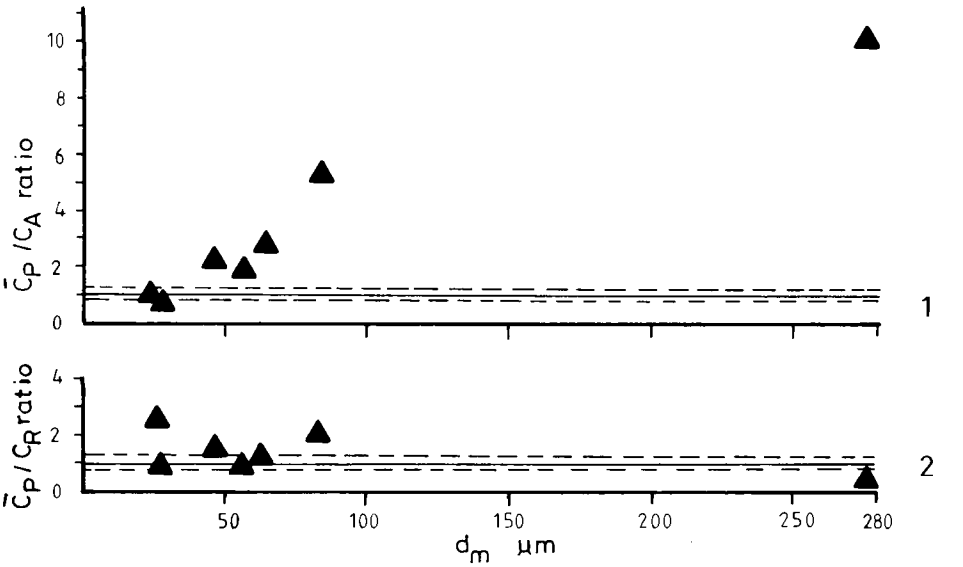


FIG. 2 COMPARISON OF THE EFFICIENCY OF MIXING INDICES WITH RESPECT TO PHARMACEUTICAL PURPOSES.

FIG. 2.1 MIXING INDEX BASED ON THE ACCEPTABLE COEFFICIENT OF VARIATION, C_A (5%).

FIG. 2.2 MIXING INDEX BASED ON THE COEFFICIENT OF VARIATION FOR A RENDOM MIX, C_R .

(-----) , INDICATES THE RATIO FOR 50 SAMPLES AND 95% CONFIDENCE LIMITS.

$\bar{C}_p$, THE COEFFICIENT OF VARIATION OF DRUG IN THE POWDER MIX EXCLUDING OTHER SOURCES OF VARIATION.

is emphasised that this line is only an indication of the relationship, due to the grossly non-normal distribution obtained with a sample of 50, which is inadequate for giving an accurate estimate.

Comparison of the values of C_p with the values of C_t suggest that further tableting processes play an important role in improving drug homogeneity and in the dispersal of agglomerates as values of C_p decrease considerably

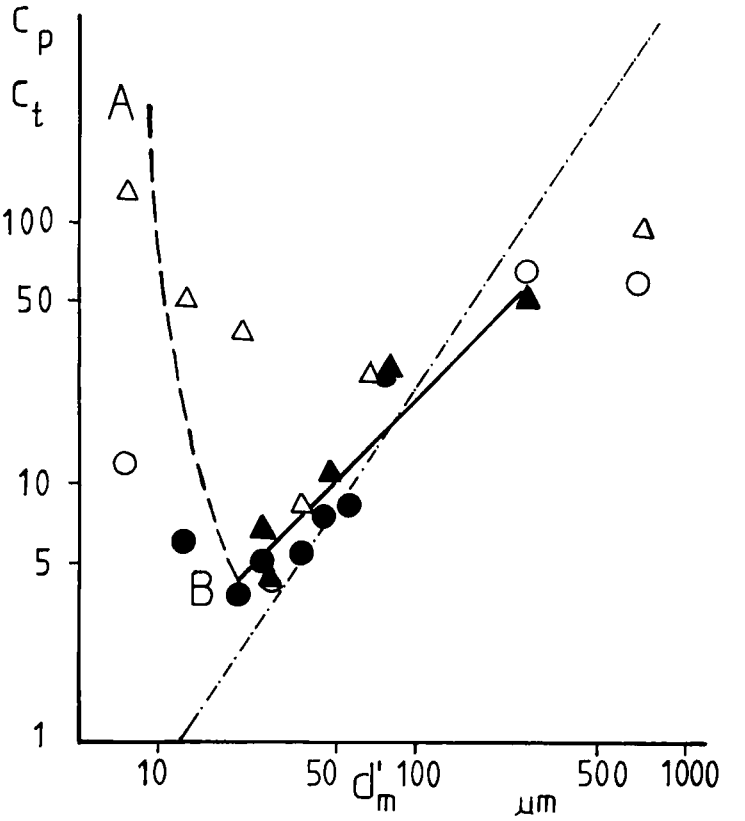


FIG.3 : GRAPHICAL REPRESENTATION OF THE RELATIONSHIP BETWEEN THE HOMOGENEITY EXPRESSED AS C_p AND C_t AND THE PARTICLES SIZE OF ETHINYLOESTRADIOL.

(----), THEORETICAL RANDOM MIX;(——) LINEAR REGRESSION ON EXPERIMENTAL DATA OF POWDER AND TABLETS APPROACHING NORMALITY. ▲ ● , APPROACHING NORMALITY; △ ○ , POSITIVELY SKEWED. LINE A-B INDICATES THE INCREASING VALUES OF C_p AND C_t WITH FURTHER DECREASING VALUES OF d'_m.

after wet granulation and further processing. When F-values (Table 4) are examined it is interesting to note that there is little difference between C_p and C_t values for powder mixes approaching a normal distribution but there is a big difference between C_p and C_t values for those powder mixes exhibiting a positively skewed distribution. This

TABLE 4

F - values for variance ratio of C_p and C_t for ethinyloestradiol batches, B1 to B14.

Powders approaching normality				Powders exhibiting skewness			
Batch No.	C_p	C_t	F	Batch No.	C_p	C_t	F
B5	51.5	63.5	1.06	B3	94.7	59.0	1.73
B6	27.0	25.3	1.18	B10	7.8	5.2	2.9
B8	9.7	8.1	1.54	B12	38.6	3.6	88
B7	10.9	7.2	2.4	B13	52.2	5.8	76
B11	4.1	4.1	1.19	B14	131.5	11.4	96
B9	6.4	4.9	2.8				

F = 1.60, variance ratio for a sample size of 50 and 95% confidence limits (22). C_p = the experimental coefficient of variation of ethinyloestradiol in the powder mix; C_t = the coefficient of variation of ethinyloestradiol in the tablets. C_p and C_t are expressed as $\mu g.g^{-1}$ of the powder and the tablet mass respectively.

indicates that the processes involved in tableting subsequent to dry mixing are influential in breaking down agglomerates. In conclusion, from Fig.3 incidence of skewness is coincident with the minimum of the log particle size/log C_p or C_t curve. This is the rationale for suggesting a test for skewness in compendial methods.

The powder mix B3 (containing EE3) exhibits a positively skewed distribution. This is not due to the presence of agglomerates of drug particles in the EE3 powder because it consists of coarse, free flowing particles, and in fact the ratio of $\bar{C}_p/C_R$ indicates a homogeneity better than that expected for a random mix. For the situation where the number of drug particles in the powder mix, is small and the number of the excipient particles remains enormously large as in B3, the distribution of the number of particles of EE3 in the powder mix corresponds to a Poisson distribution. In this case the Poisson distribution is positively skewed, and as the number of particles increases, the degree of skewness declines, approaching the symmetrical pattern of the normal distribution. The distribution of ethinyloestradiol in the powder mixes B3, B5 and B6 follows the same pattern, i.e. changing from a positively skewed distribution for B3 to the symmetrical pattern of the normal distribution for B6 as indicated by the frequency histograms (B3, B5 & B6, Fig.4) and the values of $\sqrt{b_1}$ of powder mixes (Table 2). The tablets of B3, B5 and B6 also follow the same pattern of distributions as for their powder mixes.

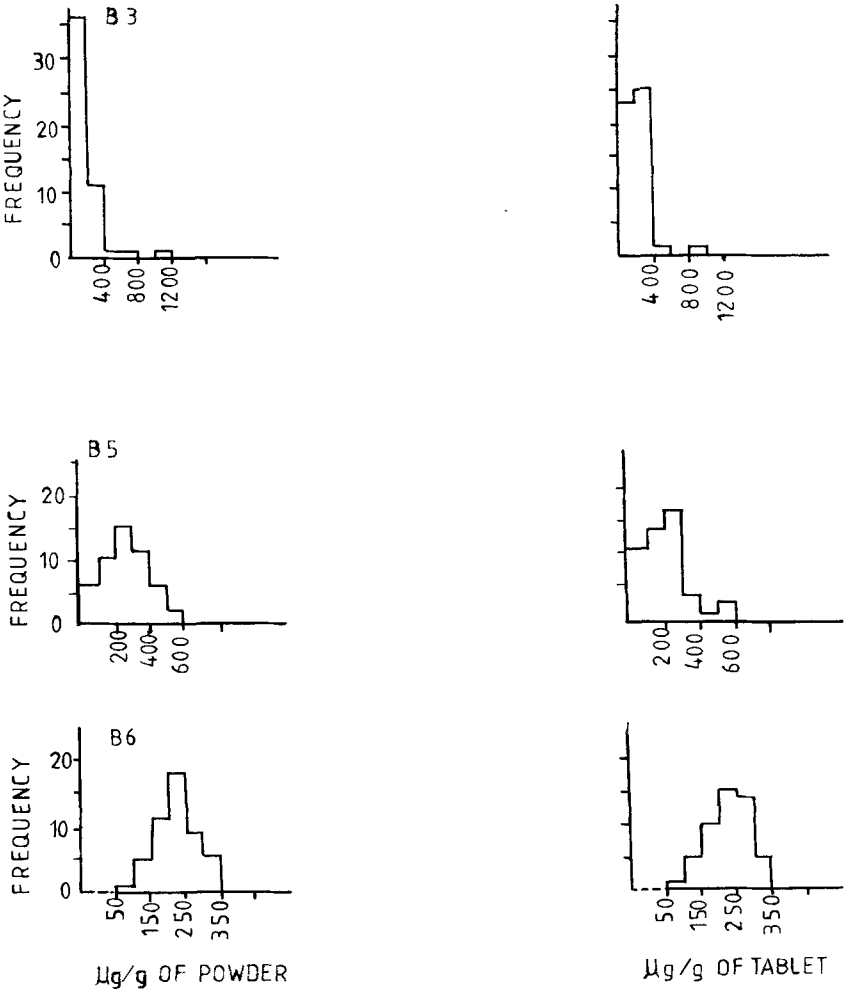


FIG. 4: HISTOGRAMS BASED ON SINGLE POWDER SPOT SAMPLE/TABLET ASSAY RESULTS FOR SAMPLES FROM B3, B5 AND B6. THE HISTOGRAMS ARE CONSTRUCTED ON DIFFERENT SCALES TO ILLUSTRATE THE SHAPE OF EACH DISTRIBUTION.

Effect of Particle Size of Ethinyloestradiol on the Shape of the Distribution Curves

In addition to the magnitude of C_t and C_p, the value of d'_m has a marked influence on the shape of the distribution curve, this is illustrated in Fig.5 and Table 5.

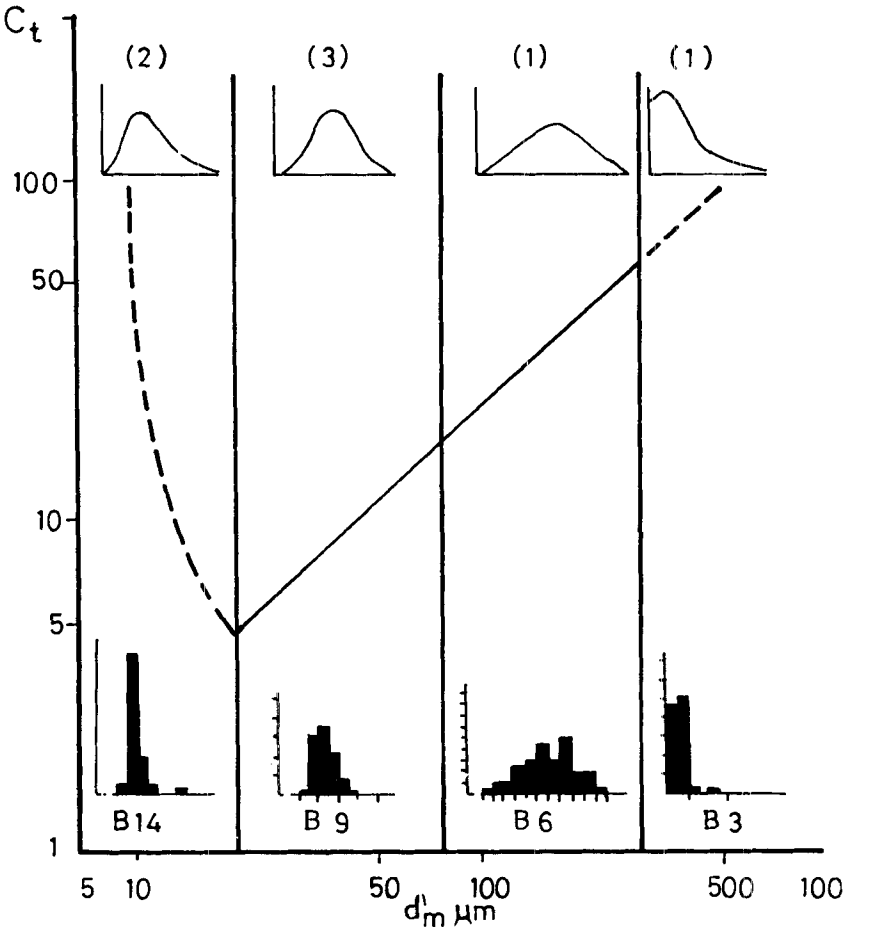


FIG.5 : RELATIONSHIP BETWEEN PARTICLE SIZE OF ETHINYL-OESTRADIOL, VALUE OF C_t AND THE SHAPE OF THE DISTRIBUTION CURVES OF DRUG CONTENT IN TABLETS.

(———), LINEAR REGRESSION ON EXPERIMENTAL DATA FROM FIG.1

(----), INDICATES POSITIVELY SKEWED DISTRIBUTIONS.

(1),(2) AND (3) ARE EXPLAINED IN THE TEXT.

TABLE 5

Summary of results of C_p and C_t for 50 spot samples or tablets divided into 5 consecutive subgroups of 10 to show the distribution in batches prepared from different ethinyloestradiol powders.

Batch No.	EE, d'_m in μm.	C_p/C_t μg.g^{-1}		Subgroup No. 1-10	11-20	21-30	31-40	41-50
B3	EE3, 759	C		58.3	62.2	50.1	53.0	131.1
		C_t^p		30.2	84.3	27.8	41.7	59.9
B5	EE5, 276	C		68.4	58.9	40.6	35.8	51.3
		C_t^p		48.1	39.2	74.5	73.2	75.5
B6	EE6, 82.2	C		36.1	25.1	30.1	19.6	23.4
		C_t^p		24.1	28.1	24.7	28.7	24.5
B14	EE14, 7.9	C		29.7	5.0	40.2	176.7	76.7
		C_t^p	a-	2.1	20.4	6.1	7.6	7.2
			b-	4.0	5.9	2.6	6.0	3.9
B26	EE14, 7.9	C		41.0	55.8	129.4	121.0	58.5
		C_t^p		5.6	16.1	18.4	12.1	54.3
B27	EE14, 7.9	C		32.1	26.1	72.4	42.8	98.5
		C_t^p		2.8	6.0	5.6	44.9	3.7
B9	EE9, 26.9	C		5.2	3.7	6.3	4.0	6.1
		C_t^p		5.0	3.4	4.7	3.8	5.6
B19	EE14, 7.9	C		3.4	3.2	6.9	4.5	4.6
		C_t^p		1.0	2.4	3.8	4.8	3.6
E	Coarse	C_t		65.7	71.1	47.4	57.8	65.4

(a) = B14a, the first 50 tablets of B14 and (b) = B14b, the second 50 tablets of B14.
E = the commercial ethinyloestradiol tablets 10 μg B.P. The ethinyloestradiol fraction used for preparing this batch was obtained from the manufacturer.

Batches prepared from free flowing, slightly cohesive and very cohesive fractions of ethinyloestradiol are chosen to illustrate the effect of particle size of ethinyloestradiol on the shape of the distribution curve. Each group of 50 samples of powder mix or tablets is divided into 5 consecutive subgroups of 10 to investigate the distributions within them as shown in Table 5. This is because the value of C_p or C_t for 50 samples does not give any indication of the type of distribution whether it is unimodal or bimodal, while the values of C_p or C_t for the subgroups would give. Examples are B3 and B27 both with high C_t values and positive skewness. When the values of subgroups are examined, they suggest different types of distributions as shown later. The difference is more obvious in the tablets than in the powders. In the case of tablets three types of distribution have been characterised as follows:

1. Distribution Characteristic for Batches Prepared from Free Flowing Ethinyloestradiol Fractions

When the tablets are prepared from free flowing ethinyloestradiol fractions, the values of C_t for subgroups are characterised by being similar but of a high magnitude. This indicates the presence of one type of distribution, i.e. unimodal distribution. Such a type of distribution can be either positively skewed (e.g. B3) or approaching normal distribution (e.g. B5 and B6 at $P = 0.01$) as explained before.

2. Distribution Characteristic for Batches Prepared from Cohesive Ethinyloestradiol Fractions

In the case of tablets prepared from very cohesive ethinyloestradiol fractions, e.g. B14, B26 and B27 (Table 5) the majority of subgroups produce low C_t values which indicates better homogeneity. However, there are possibly more, subgroups which produce very high C_t values due to the presence of tablets containing high drug content. For example, in the case of B27 tablets, the third 10 tablets have a C_t value of 44.9 while the other subgroups have values for C_t in the range of 2.8 to 6.0. Similarly, batches B14, B26 produce C_t values for the subgroups in the same order as shown in Table 5.

It can be suggested that for the tablets prepared from fine cohesive drug fractions, the distribution of ethinyloestradiol content in tablets is a bimodal one composed of a unimodal distribution of tablets containing primary drug particles in excipient and of a unimodal distribution of agglomerates and primary drug particles in excipient. However, because of the small number of tablets sampled, the shape of the distribution tends to be positively skewed rather than bimodal.

3. Distribution Exhibits Nonskewness (Approaching Normality) and Low C_t Values

When tablets are prepared from slightly cohesive or noncohesive ethinyloestradiol fractions, or when the agglomerates of the cohesive fraction are efficiently

broken down and dispersed in the excipients, the results are characterised by the following:

a. Low C_t values for all subgroups almost of the same magnitude, e.g. C_t values for subgroups of B9 are within the range of 3.4 to 5.6 and for B19 from 1.0 to 4.8.

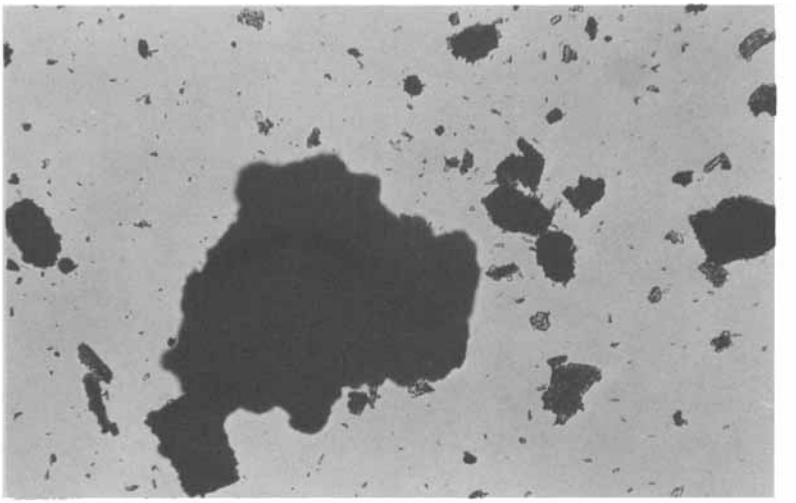
b. The distribution of ethinyloestradiol content in tablets is mostly consistent with normality. This suggests that it shows a unimodal distribution with good homogeneity. Thus, Fig 5 can be used as a guideline to show the relationship between both the values of C_t and the shape of the distribution and the particle size of of ethinyloestradiol. As the commercial batch of ethinyloestradiol tablets (batch E(13) produces high C_t with markedly positive skewed distribution it is interesting to apply this approach to investigate the particle size distribution of ethinyloestradiol used to prepare it. When the value of C_t for the subgroups (Table 5) are examined it is found to be of the same pattern as B3 tablets, i.e. high C_t values of similar magnitude and markedly positive skewed distribution. This suggests that the particle size distribution of ethinyloestradiol used to prepare the tablets in batch (E) is similar to that of B3 (EE3). To investigate the validity of this suggestion, ethinyloestradiol powder used to prepare batch (E) has been obtained from the manufacturer and examined microscopically. It is interesting to find that it has similar particle size

distribution to EE3 as shown by the photomicrographs of both powders (Fig. 6).

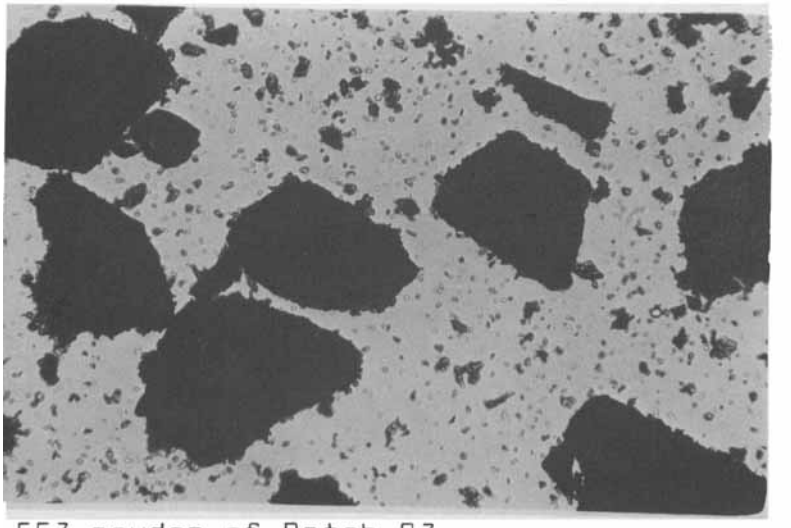
For powder mixes the shape of the distribution curve can be classified as for tablets but with some differences in the case of the cohesive ethinyloestradiol fractions. It is not easy to differentiate between powder mixes prepared from EE3, the free flowing fraction, and those prepared from the cohesive ethinyloestradiol fractions, EE4 and EE14. They produce similar C_p values for subgroups and positively skewed distributions. This means that for powder mixes of the cohesive ethinyloestradio fractions, the distribution is most probably a unimodal one because most of the drug particles still adhere together in the from of agglomerates. Such agglomerates are present in smaller numbers relative to the large number of the excipient particles which results in a Poisson distribution. Therefore, the type of the distribution of agglomerates in the powder mix will be similar to that of the powder mix containing the free flowing ethinyloestradiol fraction (EE3).

Content Uniformity of Tablets According to USP 1985:

The content uniformity test of USP 1985(23) has been applied. Although the test becomes more stringent however, it could only detect the tablets batches which are characterised by gross inhomogeneity and large variations between individual results (24). Many batches although having pharmaceutically unacceptable homogeneity they pass



EE powder of Batch (E).



EE3 powder of Batch B3.

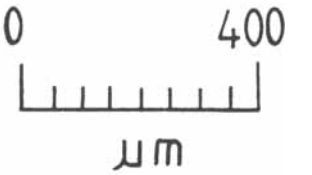


Fig. 6. Photomicrographs of the Ethinyloestradiol Powder Used in the Preparation of the Commercial Tablets (E) and B3 (EE3).

the test, e.g. B14b and B27. The problem in determining the content uniformity of such tablets is that there is a possibility of withdrawing samples of tablets that tend to show only a distribution approaching normality. In addition the sample size of 10 in the first step of the test is not sufficient to detect the presence of unit dosage containing high drug content in a batch of tablets. A positively skewed distribution should be regarded as unacceptable since, owing to the nature of the distribution it is highly likely that a number of tablets in the batch will contain relatively enormous doses of the drug. To overcome this problem a test which includes an examination of the type of distribution is desirable and hence increasing sample size is required.

CONCLUSIONS

Particle size of the ethinyloestradiol is shown to be of prime importance in determining the content uniformity of tablets manufactured using a conventional wet granulation process. In general the particle size effects both the degree of variation between tablets and the shape of the distribution curve. Reducing the particle size of a drug will, by increasing the number of individual component particles, increase the potential for a high degree of homogeneity. However it will, due to the cohesiveness of fine powders and the greater likelihood of persistent agglomerates, increase the potential for gross nonuniformity in the final dosage form.

It should be emphasised that it is difficult to design a content uniformity test for tablets containing minute amounts of potent drugs. Therefore, it is important to design both the formulation and the processing in order to guarantee the breakdown of the drug agglomerates and dispersion of individual particles into the excipients. However, the design of an efficient content uniformity test and a proper formulation and processing should be considered in order to safeguard against the presence of unit doses having high drug contents. This is of particular relevance to Good Manufacturing Practice and quality control specifications for content uniformity of tablets and capsules.

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