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MICROMIXING OF ORAL CONTRACEPTIVES

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ABSTRACT

The role of the mixing process and the influence of the different processing steps on the homogenous distribution and accurate dosage of small amounts of norethisterone acetate and ethinyl estradiol, as models of classical type contraceptives, was studied.

The multistage mixing technique of 1 part norethisterone acetate and 1 part ethinyl estradiol in 55 and 1100 parts respectively of tablet filling material using a Lödige-mixer (type F.M. 130D.) showed a reasonable degree of homogenity after 2400 revolutions of the final mixing step. Wet granulation, mixing with the external phase, and compression developed partial segregation in the system which was within tolerable limits.

Statistical treatment of the results indicated that the maximum deviation developed through mixing, granulation, mixing with the external phase, compression, sampling and analysis was within $\pm$ 5% for norethisterone acetate and $\pm$ 10% for ethinyl estradiol. Therefore, the critical tolerance limits specified for a sample of 20 tablets will not be exceeded.

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INTRODUCTION

There is a slight but increased risk of thrombo-embolic disorders in patients taking oral contraceptives and this appears to be related to the estrogen content[1].

Hypertension due to oral contraceptives appeared also to be related to the estrogen content[2].

Spellacy et al.[3] considered that the small but significant increase in blood sugar and insulin concentrations in healthy women taking an oral contraceptive of the combined type were due to the progestogen.

Progestogen-only contraceptives prevented intra-uterine pregnancy but not tubal pregnancy; therefore, patients using these oral contraceptives and found to be pregnant should be considered to have an increased risk of ectopic pregnancy[4].

Some side-effects are considered to result from the relative balance of estrogenic and progestogenic effects of particular products.

Impairment of tolerance to glucose might be the result of plasma-hydrocortisone concentrations increased by the estrogen component of the oral contraceptive[5].

Beck[6] found that serum-triglyceride concentrations were increased by estrogen and this effect was reversed by nortestosterone derivatives.

Therefore, a strict control on the content of oral contraceptives was demanded, since the many official tests may allow considerable variation in individual unit doses.

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Train[7] pointed out the close relation between mixing and the accuracy of dosage of potent drugs. Variation in the potency was attributed to a mixing problem rather than any other causes met in the processing steps.

Tawashi and Speiser[8] studied the role of the mixing process from the initial segregation to the random equilibrium state with reserpine as a model of a potent drug. They studied also the influence of the different processing steps on homogenity and accurate dosage of reserpine in tablets.

As no information is available in the literature about the problem of micromixing of oral contraceptives, i.e., the homogenous distribution of a small amount - up to 0.05 mg - of a hormone in a large bulk of filling material, it is the purpose of this work to study the role of the mixing process and the influence of the different processing steps on homogenity and accurate dosage of norethisterone acetate and ethinyl estradiol.

EXPERIMENTAL

Materials

The following materials were used: norethisterone acetate micro 20, ethinyl estradiol micro 20, lactose, corn starch, poly-N-vinylpyrrolidon 25, talc, magnesium stearate, isonicotinic acid hydrazide, ethyl alcohol, hydrochloric acid, boric acid, sodium hydroxide, sulfanilic acid and sodium nitrate. All these materials were either U.S.P. or analytical grades.

Apparatus

1 - Gebr-Lödige Paderborn Mixer, Type F.M. 130D., West Germany.

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2 - Manesty Oscillating Granulator, England.

3 - Circulating Air Drying Cabinet with trays.

4 - Kilian Rotary Tablet Machine, Siemens, West Germany.

5 - Perkin-Elmer UV-VIS Spectrophotometer, Type 550 S.

Processing Steps

The contraceptive tablets were prepared according to the following formula for an individual tablet:

norethisterone acetate (micro 20)	1.000 mg
ethinyl estradiol (micro 20)	0.050 mg
lactose	32.100 mg
corn starch	18.000 mg
poly-N-vinylpyrrolidon 25	2.100 mg
talc	1.650 mg
magnesium stearate	0.100 mg

A sufficient quantity of each material was used to produce a batch of 800,000 tablets.

1. Dry Mixing:

Step I) 0.8 kg norethisterone acetate, 0.04 kg ethinyl estradiol and 5 kg of lactose were mixed in a polyethylene bag and were passed over a 0.5 mm-screen into the Lödige-mixer where 20.68 kg of lactose had been placed after it had been passed over a 2 mm-screen. The substances were mixed for 15 minutes during which 10 samples, each weighing about 300 mg, were taken from the mixing chamber every 5 minutes. These time periods corresponded to 800, 1600 and 2400 revolutions. The samples were withdrawn from the mixing chamber from fixed regions uniformly located within the

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mixer[8]. The samples were analyzed spectrophotometrically and the amount of norethisterone acetate in each sample was determined from a calibration curve made at a wave length of 380 mμ and that of ethinyl estradiol from another calibration curve made at a wave length of 490 mμ. The procedure adopted in analysis was that of CID Co.[9].

Step II) 14.4 kg of corn starch and 1.68 kg of PVP 25 were added into the Lödige-mixer and the substances were mixed for 15 minutes, during which 10 samples, each weighing about 500 mg, were taken every 5 minutes corresponding to 800, 1600 and 2400 revolutions. The samples were withdrawn and analyzed in the same way as described before.

2. Granulation:

The powder blend was kneaded with 8.5 kg of demineralized water and the moist mixture was granulated over a 2 mm-perforated disk of the Manesty granulator. The granules were dried on trays in the circulating air drying cabinet at 50°C until a water content of 6.5% to 7.5% was obtained. This usually occurred within 24 hours. The dried granules were then equalized over a 1 mm-screen of the Manesty granulator. Ten samples from the dried granules, each weighing about 500 mg, were withdrawn and analyzed in the same way as before.

3. Granulation+external phase:

The dried granules were mixed in the Lödige-mixer together with 1.32 kg talc and 0.08 kg of magnesium stearate - after the latter had been passed over a 0.5 mm-screen - for 5 minutes corresponding to 800 revolutions. Ten samples from the mixture,

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each weighing about 500 mg, were withdrawn and analyzed in the same way as before.

4. Compression:

The granules with the external phase - corresponding to a batch of 800,000 tablets - were compressed in the tabletting machine to cores 5 ± 0.25 mm in diameter, with convex radius of 3 mm and height of 3-3.1 mm and each weighing 55 ± 5.5 mg. The norethisterone acetate content was individually analyzed by taking 10 randomly chosen cores while the ethinyl estradiol content was analyzed by taking 80 randomly chosen cores where every 8 cores were analyzed individually.

The results obtained in the different processing steps were statistically treated to evaluate the degree of homogenity of the hormones within the filling material. The results and their corresponding treated data are compiled in Table 1 and Figure 1.

RESULTS AND DISCUSSION

A quantitative measure of the degree of mixing is generally accomplished by the arbitrary choice of a statistical function that indicates the uniformity of composition of the powder bed[10]. In this investigation the relative standard deviation, $S_{rel.}$, and the relative standard deviation of the mean, $S_{\bar{x}\ rel.}$, are taken as criterion for the degree of homogenity[11,12].

The mixing of very small amounts of norethisterone acetate and ethinyl estradiol in a relative large bulk of filling material - 1 part in 55 with the former and 1 part in 1100 with the later -

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Process		No. of revolutions	Hormone	Samples										$\bar{x}$	S_{rel}	$S_{\bar{x}rel}$
				1	2	3	4	5	6	7	8	9	10			
Dry Mixing	I	800	N	101.5	115.7	101.5	110.8	119.7	105.5	105.8	108.1	99.8	93.6	106.2	7.76	2.46
			E	105.4	100	79.1	93.1	74	108.4	99.1	80.1	92	72	90.3	13.20	4.17
		1600	N	111.1	106.5	105.5	99.8	105.5	101.2	99.5	103.1	96.9	103.8	103.3	4.12	1.30
			E	101.4	88.5	95.9	93.8	92.4	90	88.7	102	93.8	97.3	94.4	4.84	1.53
		2400	N	102.5	99.2	103.5	102.5	100.5	99.2	97.2	95.2	96.5	92.2	98.9	3.61	1.14
			E	97.8	94.1	95.6	101.5	92.6	98.6	95.6	94.6	101	91.8	96.3	3.32	1.05
	II	800	N	103.9	107.5	105.2	98.2	99.6	99.6	100.6	99.2	60.5	94.9	96.9	13.31	4.21
			E	89.1	91.2	105.1	103.6	91.2	85.9	90.2	112.4	100.9	90.7	96	8.73	2.77
		1600	N	90.3	100.9	92.3	90	88.7	90.3	88.3	93.3	88.3	88.3	91.1	3.86	1.22
			E	86.9	89.1	105.1	105.8	100.7	86	90	104.9	106	100.7	97.5	8.47	2.68
		2400	N	96.3	96.6	96.9	103.9	93.9	93.9	93.9	95.9	96.3	96.6	96.4	2.90	0.92
			E	103.9	100	98.7	86.1	91.3	94.8	91.7	97.2	85.6	109.9	95.9	7.66	2.42
Granulation		——	N	98.3	92	95.9	100.6	93.3	91.6	99.6	91.3	91.6	93.9	94.8	3.56	1.13
			E	90.9	96.7	83.5	105.8	84.3	97.6	86.5	90	107.8	89.3	93.2	8.51	2.69
Granules + External Phase		800	N	101	106.3	104.6	104	97.4	97.4	104.6	97.4	97.7	99.7	101	3.57	1.13
			E	84.2	99.3	98.7	80.8	96.7	89.2	86.2	80.6	88.7	105	90.9	8.48	2.68
Compression		——	N	103.8	98.7	96.8	101.6	106.2	101	94.5	102.6	98.7	98.7	100.8	4.29	1.36
			E	86.1	84.8	93.5	90.2	86.7	98.7	93.7	85.5	88.4	93	90.1	4.55	1.44

Table 1

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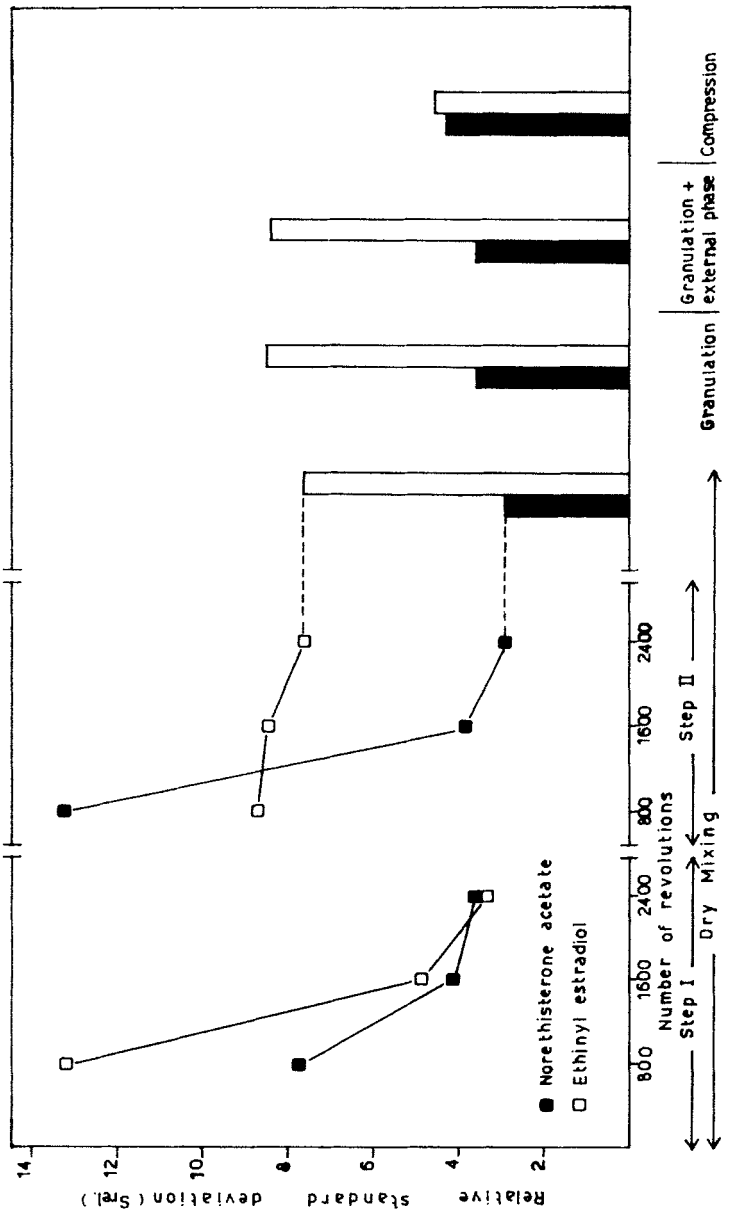

Figure 1: Effect of the different processing steps on the distribution of norethisterone acetate and ethinyl estradiol.

puts the mixing performance of the system under severe testing conditions.

Table 1 and Figure 1 illustrate that during the first step of powder mixing and after 1600 revolutions a reasonable degree of homogenity is attained, as indicated by the marked decrease in $S_{rel.}$ and $S_{\bar{x}\ rel.}$ of both hormones. After 2400 revolutions a further, but small, decrease in $S_{rel.}$ and $S_{\bar{x}\ rel.}$ of both hormones is observed.

During the second step of powder mixing and after 800 revolutions a marked segregation developed in the system, as indicated by the marked increase in $S_{rel.}$ and $S_{\bar{x}\ rel.}$ of both hormones. This behavior is not surprising, because the ratio of the ingredients to be mixed is one of the important factors which affect markedly the degree of homogenity. After 1600 revolutions a marked decrease in $S_{rel.}$ and $S_{\bar{x}\ rel.}$ of norethisterone acetate is observed and after 2400 revolutions a further, but small, decrease in $S_{rel.}$ and $S_{\bar{x}\ rel.}$ is observed. In case of ethinyl estradiol a small decrease in $S_{rel.}$ $S_{\bar{x}\ rel.}$ is observed after 1600 and 2400 revolutions. This is because of the very small amount of this hormone in relation to the large bulk of filling material at this step.

After dry mixing, the powder blend is granulated with water. The granulation process develops slight segregation in the system, as indicated by the small increase in $S_{rel.}$ and $S_{\bar{x}\ rel.}$ of both hormones. This behavior can be attributed to the fact that the mixed ingredients have different affinities towards the granulating liquid[8]. Lactose, corn starch and PVP 25 are better wetted by water

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than norethisterone acetate and ethinyl estradiol, therefore, the dispersion of both hormones within the granules had been affected.

After mixing the dried granules with the external phase, represented by talc and magnesium stearate, in the mixer for 800 revolutions no reasonable change in homogenity is observed which indicated complete randomization.

In the last processing step, the granules mixed with the external phase were tabletted. Compression introduces a new source of variability. Besides the mixing-unmixing problems of the active drugs developed as the materials in the hopper is subjected to vibration and stratification, there is the weight variation of the individual tablets. These factors, therefore, will be reflected in the content of both hormones in each tablet.

The specifications for norethisterone acetate and ethinyl estradiol content in each tablet of average weight are required to be within the certain fixed percentage limits of $\pm$ 10% for the first hormone and $\pm$ 15% for the second. These limits allow for variations due to the manufacturing process, to permit variation in the standard of purity and to the method of analysis. In the specified method of assay[9], 20 tablets are pulverized; the equivalent of two and eight tablets are then taken for the determination of norethisterone acetate and ethinyl estradiol respectively. A possible weakness of this method - as Tawashi and Speiser[8] said - is that variation per unit dose can be over twice or three times or more the specified limits. The presence of tablets above or below the given limit could be easily masked by the remainder of the tablets.

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In this investigation, the sample size taken for analysis during the different processing steps represents the content of one individual unit dose of norethisterone acetate and individual eight unit doses of ethinyl estradiol and not a pool representing 20 unit doses. A sample size of less than the content of eight unit doses is not valid for the spectrophotometric assay of ethinyl estradiol according to the adopted method of assay[9].

In order to know if the investigated batch complied with the specifications for drug content, the percent standard deviation due to the different sources of errors was calculated according to the following expression[13]:

$$Em = \sqrt{(S_{\bar{x}\,1})^2 + (S_{\bar{x}\,2})^2 + (S_{\bar{x}\,3})^2}$$

E_m final standard deviation of the mean.

$S_{\bar{x}\,1}$ relative standard deviation of the mean due to the manufacturing process.

$S_{\bar{x}\,2}$ relative standard deviation of the mean due to the weight variation.

$S_{\bar{x}\,3}$ relative standard deviation of the mean due to analysis.

In this investigation, $S_{\bar{x}\,rel.}$ due to manufacturing processes (mixing, granulation and compression) has been estimated as 1.36 and 1.44 for norethisterone acetate and ethinyl estradiol respectively. $S_{\bar{x}\,rel.}$ due to weight variation made by weighing 10 randomly chosen tablets for norethisterone acetate and by weighing 10 x 8 for ethinyl estradiol, were found to be 0.6 and 1.97 respectively. $S_{\bar{x}\,rel.}$ of 10 repeated determinations of pure nor-

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ethisterone acetate and ethinyl estradiol were 0.37 and 1.83 respectively. Therefore the final standard E_m will be:

$$E_m \text{ (norethisterone acetate)} = \sqrt{(1.36)^2 + (0.6)^2 + (0.37)^2} = 1.53\%$$

$$E_m \text{ (ethinyl estradiol)} = \sqrt{(1.44)^2 = (1.97)^2 + (1.83)^2} = 3.21\%$$

Saunders and Fleming[13] advocate the use of $\pm$ 3 standard deviations as approximate limits of error for a single result. Therefore, the limit of error will be 4.59% or in round figure 5% for norethisterone acetate and 9.63% or in round figure 10% for ethinyl estradiol, i.e., the investigated batch complies with the specifications for drug content and a limit of 10% for norethisterone acetate and 15% for ethinyl estradiol in the single unit dose is sufficient to allow for the different technical errors involved in the manufacturing processes.

CONCLUSION

It is obvious that norethisterone acetate and ethinyl estradiol tablets, produced in a batch size of 800,000 tablets, can easily be produced within the desired specifications for drug content. It is apparent, however, that mixing is a critical step in the production process. Lack of sufficient mixing produced relative standard deviations of over 13, which, upon further mixing was reduced to 3 or 4.

The overall final standard deviation of the mean was then reduced to 1.53% for norethisterone acetate and 3.21% for ethinyl estradiol, well within specifications. This demonstrates the validity of the micromixing technique used in the mixing process.

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