circuit is again completed, causing the rotary solenoid to be re-energized and the water tap closed.

To allow efficient operation of the apparatus the vacuum source, assisting the removal of liquid from tube B, should be maintained at a constant level (−10 cm water) during a series of measurements. The time for immersion of the rat foot should be standardized, 5 sec is optimal. The rate of passage of water from the burette to the foot bath should be adjusted to just less than that causing an overshoot into chamber B.

The error of the measurements when the same foot of each of ten rats was measured five times in random sequence was calculated to be 3·6%.

The advantage of this apparatus over others in common use is that speed of repetitive measurement is achieved without loss of accuracy. The components cost approximately £20 and this compares favourably with commercially available equipment.

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December 6, 1967

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Reference

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The distribution of small concentrations of active ingredients in tablet granules

SIR,—It is common practice when preparing tablets containing small quantities of potent materials to add the active ingredient in solution to an inert basis granulate to obtain even distribution. After drying, coarse aggregates are broken down by sifting and the resultant granulate is tabletted.

During the preparation of a small batch of tablets containing [4-^{14}C]-lynoestrenol, an investigation into the distribution of the lynoestrenol indicated that this was uneven when the drug was applied to the tablet granulate in ethanolic solution and after drying under an infrared lamp. All assays were made using liquid scintillation counting in a Packard Tricarb Spectrometer Model 3003, with and without an internal standard for correcting quenching, on the granulate extracted quantitatively with benzene and ether. Because of the small size of the sample, it was not possible to make a particle size evaluation, therefore samples of the coarser and very fine fractions of the granule were taken and compared with the original. The results are in Table 1. A second sample of basis granulate was prepared and reduced to a fine powder of uniform appearance before the labelled lynoestrenol was added. The distribution found is in Table 2.

TABLE 1. INFLUENCE OF PARTICLE SIZE ON LYNOESTRENOL DISTRIBUTION IN GRANULES. Added amount of labelled lynoestrenol: 2·53 mg (corresponding to 21,800 disintegrations/min) per 98·0 mg granulate.

Type of granule sample	Weight of granulate (mg)	Measured radio activity (d/min)	Calculated mg drug per 98·0 mg granulate
Coarse particles	98·0	33,400	3·89
Mixed	98·0	26,800	3·11
Mixed	98·7	26,300	3·06
Mixed	98·4	24,200	2·82
Fine	98·4	14,500	1·69

TABLE 2. LYNOESTRENOL CONTENT OF GRANULATE POWDERED BEFORE THE ADDITION OF LABELLED LYNOESTRENOL SOLUTION. Drug added: 4·83 mg (corresponding to 28,900 disintegrations/min) per 100 mg granulate.

Weight of granulate (mg)	Measured radioactivity (d/min)	Calculated drug content (mg)
91·0	26,600	4·45
95·2	26,600	4·45
96·9	27,600	4·61
100·9	30,000	5·01
103·0	27,900	4·66
106·8	31,800	5·30
109·1	31,400	5·24
111·9	30,200	5·04

Residual standard deviation of drug content about the regression line: 0·21 mg = 4·4% at arithmetic mean.

From Table 1 it can be seen that the coarser granules contained more than twice the lynoestrenol content of the fine granules. If such a granule were used in tablet manufacture then it is probable that wide variations in drug content of tablets would occur. The results in Table 2 indicate a far more even distribution of lynoestrenol. When the granulate that was initially reduced to a fine powder of uniform appearance was subjected to further size reduction, by shaking with glass beads in a closed container for 30 min, the residual standard deviation for the drug distribution was reduced to 1·3%.

Lachman & Sylwestrowicz (1964) reported a concentration of active ingredient in the larger granules when preparing tablets containing a poorly water-soluble active ingredient by moist granulation using water as the granulating agent. In that instance it was suggested that the phenomenon might be due to the drug adhering to the surface of the granules and being less easily dislodged from large granules, with a small surface area, than from the smaller ones. Further there was the possibility that the larger granules would more readily encapsulate the drug than the smaller.

We were concerned with the addition of the drug in solution. The basis granule consisted of lactose with starch as disintegrant and magnesium stearate as lubricant. It might be that the larger granules had more void spaces than the smaller granules and thus on drying the larger granules contained more ingredient than the fine granules which might have had only a surface layer. A further possibility of importance when large batches of granules are prepared could be that, before drying, the granules segregated, the larger ones rising to the surface; the active ingredient would also tend to rise to the surface by capillary action during drying.

We therefore recommend caution when this kind of procedure is used to incorporate a small quantity of potent material into a tablet granule. It would appear to be preferable to have the basis granulate in the form of uniformly sized granules, to mix these further, and possibly to reduce the particle size after drying.

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