The effect of mesh size on disintegration time measurements

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During the course of a wider investigation the meshes from five disintegration testers (Manesty Tablet Disintegration Unit) were studied to ascertain their compliance with the B.P. specification. These testers were taken from production departments and laboratories. Meshes had been replaced during the course of their normal use and it was found that some of the meshes on the machines at the time of the study did not comply with the B.P. requirements. A comparative study was then made to find out whether the different meshes gave rise to significant differences in disintegration times.

The aperture size and wire diameter of the meshes in use were measured using a travelling microscope. Two types of mesh were found to be fitted to the machines, denoted below by A and B. The results of the measurements are shown in Table 1. A plot of the mesh measurements on probability paper was linear showing their distribution to be normal and a comparison with the B.P. specification was therefore carried out using Student's *t*-test.

Table 1. Measurements on two mesh sizes found to be in use on disintegration testers. Mesh A complies with B.P.

Mesh	Aperture size (mm)	Standard deviation (mm)	Wire diam. (mm)
A	1·71	0·07	0·89
B	1·87	0·08	0·67

The B.P. requirements for sieve number 1·70 are as follows: Aperture size = 1·70 mm; wire diameter =0·80 mm. The average aperture size should not be greater or less than the nominal value (1·70 mm) by more than the tolerance (0·051 mm). It can be seen that the above mean aperture size of mesh A lies within the B.P. band 1·649–1·751 mm whilst that of mesh B does not. From the *t*-test it was concluded that it was 98% certain that mesh A fulfilled the B.P. requirements and 99·9% certain that mesh B did not.

Of the five machines being investigated two were fitted solely with mesh A, two with a mixture of meshes A and B and one solely with mesh B. One of the machines fitted only with mesh A was taken and its disintegration times compared with those obtained when all its gauzes had been changed to mesh B. By carrying out such a comparison, other variables between machines remained unchanged.

A single batch of sugar-coated tablets was used for the tests. Random samples were taken from the bulk by means of a spinning riffler and the disintegration times of these determined according to B.P. recommendation. The results of these tests are shown in Table 2.

Comparing the two sets of measurements it can be seen that there was a difference of about 15% between the means. However there is a great deal of dispersion in the data and it is therefore not obvious that it is significant. A histogram of the measurements with mesh A showed the distribution to be positively skewed with a skewness coefficient of 1·9. The main body of the distribution was skewed and outliers were also present. The distribution was not significantly improved by plotting in logarithmic form.

Table 2. Comparison of disintegration times of tablets randomly sampled from the bulk obtained using two different meshes on the same machine.

	No. of measurements	Mean (min)	Interquartile range (min)
Machine with Mesh A	105	5·50	3·08
Machine with Mesh B	95	4·77	2·75

Most of the tests of significance, e.g. Student's *t*, are only valid if the distributions do not differ greatly from normal distributions. In this case, with such marked skewness, it was decided to use one of the distribution-free tests which make no such requirements on the form of the distribution being considered. The Rank Sum Test is one of these. Observations from the two populations being compared (sample sizes n_1 and n_2) are combined and arranged in order of increasing size from smallest to largest. Rank 1 is assigned to the lowest, 2 to the next lowest etc. The sum of the ranks for both populations are then calculated and the smallest, R, compared with the value M_α obtained for two samples n_1 and n_2 at a significance level α, from tables. If R is less than M_α then the test is significant at the α level. The results of comparing the disintegration times obtained using mesh A and then mesh B on the same machine by means of the Rank Sum Test are shown in Table 3.

It can be seen that there is a difference between the two meshes significant at the 0·05 level. Thus the differences between the disintegration times of the two meshes are shown to be real, despite the large scatter.

From January 1st 1979 the B.P. test is to be superceded by the European Pharmacopoeia Test. The principle of testing will remain the same although a number of changes will be made, including an alteration in the specified mesh size. Despite these changes this

Table 3. Results of Rank Sum Test of significance for disintegration times obtained with two different meshes, A and B. A difference significant at the α level exists if the parameter $M_\alpha > R$ the Rank Sum.

No. of measurements with mesh A, n_2	= 105
No. of measurements with mesh B, n_1	= 95
Rank Sum Coefficient R	= 8549
$M_{0.10}$	= 8877
$M_{0.05}$	= 8746
$M_{0.01}$	= 8493

report will remain valid and will still be relevant to the new test.

Conclusions

Only one of the two meshes in use on disintegration testers was found to comply with the B.P. specification. As a result of comparisons carried out with a batch of sugar coated tablets, it was shown that there was a difference between the disintegration times significant at the 0·05 level. The difference in the mean values was 15% which underlines the importance of ensuring that the mesh sizes comply with the B.P. specifications.

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Influence of pimozide on the locomotor hyperactivity produced by caffeine

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Methylxanthines are known to produce various effects on the amount and turnover of putative neurotransmitters within the brain, e.g. release and enhanced turnover of noradrenaline (Berkowitz et al 1970; Waldeck 1971), increase or decrease of dopamine turnover (Corrodi et al 1972; Waldeck 1971, 1973, 1975) and decreased turnover leading to enhanced concentrations of 5-hydroxytryptamine (5-HT) (Berkowitz & Spector 1971; Corrodi et al 1972; Valzelli & Bernasconi 1973). Interactions of methylxanthines with dopa (Strömberg & Waldeck 1973) and acetylcholine (Waldeck 1974, 1975) have been also reported (for review see Eichler 1976; Waldeck 1975). Considering the diversity of these findings it is difficult to correlate any of the data with the behavioural effects of caffeine and thus to try to elucidate the basic mode of action of the drugs. Experiments from our laboratory revealed that in mice the caffeine-induced locomotor stimulation could be markedly reduced by *p*-chlorophenylalanine, a depletor of brain 5-HT, while the α- and β-adrenoceptor-blocking agents phenoxybenzamine and propranolol were ineffective in this respect (Estler 1973). On the other hand, Waldeck (1973) reported an inhibitory effect of pimozide, a dopamine antagonist, on the caffeine-produced motor excitation. Since Waldeck's (1973) results, obtained only with a high dose of pimozide and according to Andén et al (1970) might have produced unspecific effects, seemed to contradict our own findings, I have reinvestigated the effect of pimozide on the caffeine-induced motor stimulation using different doses of both drugs.

Adult male mice were kept at 25° C (room temp.) with free access to a standard diet (Herilan) and tap water. They were injected s.c. with caffeine sodium benzoate at amounts corresponding to 25 or 50 μg of the free base per g weight. Some of the animals were pretreated with 0·3 or 1·0 $\mu g\ g^{-1}$ pimozide s.c. 4 h before the administration of caffeine. Mice treated only with the same doses of pimozide or with saline served as controls. The number of animals in each treatment group ranged from 20–28. Measurements of locomotor activity of single animals were made according to Estler & Ammon (1969). The observation period was 2 h starting either immediately after the injection of caffeine or saline, respectively, or 4 h after the injection of pimozide.

Saline-treated mice placed into the activity cages showed an initial phase of increased motility (orientational hypermotility) during the first half hour. Afterwards the activity declined to a constantly low level (resting activity) (Fig. 1C). Caffeine increased the orientational and resting locomotor activity, 50 $\mu g\ g^{-1}$ being more effective than 25 $\mu g\ g^{-1}$ (Fig. 1A, B). Pimozide when given alone at a dose of 0·3 $\mu g\ g^{-1}$ did not affect the orientational and resting motility, pimozide 1 $\mu g\ g^{-1}$ depressed the orientational hypermotility but had no effect on the resting activity (Fig. 1C). When mice pretreated with pimozide 1 $\mu g\ g^{-1}$ were injected with caffeine 25 or 50 $\mu g\ g^{-1}$ 4 h later, caffeine completely lost its stimulatory effect. The lower dose of pimozide (0·3 $\mu g\ g^{-1}$) abolished the effect of the lower dose of caffeine (25 $\mu g\ g^{-1}$) but did not diminish the motor stimulation produced by 50 $\mu g\ g^{-1}$ caffeine (Fig. 1A, B).