J. Pharm. Pharmacol. 1983, 35: 320–321
Communicated November 10, 1982

0022–3573/83/050320–02 $02.50/0

A proposed consolidation parameter for powders

N. A. ARMSTRONG*, N. M. A. H. ABOURIDA, A. M. GOUGH, *Welsh School of Pharmacy, U.W.I.S.T., Cardiff, U.K.*

The formation of tablets from powdered or granular systems depends on the formation of interparticulate bonds, the nature and strength of which will depend on the chemical properties of the substance in question. However, consolidation is an essential preliminary so as to bring the particles into close enough proximity for these forces to act. A number of methods have been suggested to quantify the consolidation process. For example, equations have been proposed linking applied force to the relative density of the consolidated mass (Kawakita & Ludde 1970). An alternative approach has been to construct the so-called 'force displacement curve' and derive from it some values which serve to characterize the curve. The best known of these is to measure the area under the force-displacement curve, which dimensionally is equivalent to work (de Blaey & Polderman 1971). However none of the suggested methods takes into account the time over which the force was applied, yet it is known that time dependent effects do occur on consolidation (David & Augsberger 1977; Rue & Rees 1978; Armstrong et al 1982). Compression problems encountered in transferring a tablet formulation from one form of tablet press to another have been attributed to the different time and rate of application of force between, for example, rotary and eccentric tablet presses.

* Correspondence

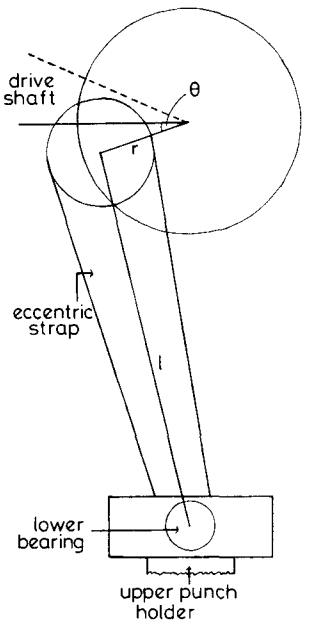

FIG. 1. Diagrammatic representation of drive shaft, eccentric strap and upper punch assembly of an eccentric tablet press.

A suggested alternative approach is to measure the power expended in the compression process. The unit of power, the watt, is defined as the power dissipated when 1 joule is expended for 1 second (Jerrard & McNeill 1971), and so equals the area under the force-displacement curve divided by the time over which the force is applied, i.e.

$$\left(\int_{D_1}^{D_2} F.dD - \int_{D_2}^{D_3} F.dD\right)/t$$

where F = applied force, t = time, D_1 = displacement when F deviates from zero, D_2 = maximum punch displacement, D_3 = punch displacement when F returns to zero.

Whilst the time over which the force is applied can be measured conventionally, linking the output of the force and displacement transducers to a micro computer (Armstrong & Abourida 1980) affords a more accurate measure. In this apparatus, the signal from each transducer is sampled sequentially at a rate determined by a clock operating a multiplexer device. Thus, if the transducer data are printed out, the time which elapses between successive values from any particular transducer represents a known time interval, and the number of lines of printout is thus directly related to the time over which the force was applied.

An alternative derivation of the same parameter can be obtained as follows.

The units of power are J s^{-1}, which can be expressed as N m s^{-1}, i.e. a product of the force and the speed at which that force is applied.

Fig. 1 represents the drive shaft, eccentric sheave, eccentric strap and upper punch holder of an eccentric tablet press. The position of any component below the lower bearing (e.g. the punch tip) at any point during one rotation of the drive shaft is given by equation 1.

$$y = a + r \sin(90 + \omega t) + \sqrt{l^2 - r^2 \cos^2(90 + \omega t)} \quad (1)$$

where ω is the angular velocity of the shaft, t is time, a is the position of that component when $\theta = 0$. θ, r and l are defined in Fig. 1.

If t is arbitrarily put to zero when $\theta = 90°$, i.e. at maximum displacement of the punch, then by differentiation, the velocity of the punch tip at any value of θ is given by equation 2.

$$\frac{dy}{dt} = \omega r \cos\theta \left(1 + \frac{r \sin\theta}{\sqrt{l^2 - r^2 \cos^2\theta}}\right) \quad (2)$$

Thus when θ is 90°, the velocity is zero, whilst maximum velocity (ωr) is achieved when θ is 0°.

From a knowledge of the speed of rotation of the shaft, and the time interval represented by each line on the computer printout, the angular displacement θ and hence the punch velocity can be calculated for any point in time represented by a given line on the computer printout.

Hence the overall power expended can be calculated by summation of the products of the force and the corresponding velocity.

The use of power, involving as it does the speed of application of the force, also satisfies the requirement that in the case of substances which consolidate by fragmentation, the kinetic energy of the moving punch will obviously influence the degree of particle fracture.

The assistance of Dr J. D. Griffiths, Department of Mathematics, U.W.I.S.T., Cardiff is gratefully acknowledged.

REFERENCES

Armstrong, N. A., Abourida, N. M. A. H. (1980) J. Pharm. Pharmacol. 32: 86P.

Armstrong, N. A., Abourida, N. M. A. H., Krijgsman, L. (1982) Ibid. 34: 9–13

de Blaey, C. J., Polderman, J. (1971) Pharm. Weekbl. 106: 57–65

David, S. T., Augsberger, L. L. (1977) J. Pharm. Sci. 66: 155–159

Jerrard, H. G., McNeill, D. B. (1971) Dictionary of Scientific Units, Chapman Hall, London.

Kawakita, K., Ludde, K. H. (1970) Powder Technol. 4: 61–68

Rue, P. J., Rees, J. E. (1978) J. Pharm. Pharmacol. 30: 642–643

J. Pharm. Pharmacol. 1983, 35: 321–322
Communicated September 9, 1982

0022–3573/83/050321–02 $02.50/0

α_2-Adrenoceptors and the delay of castor oil-induced diarrhoea by clonidine in rats

C. F. SPRAGGS*, K. T. BUNCE, *Department of Pharmacology, Glaxo Group Research Limited, Ware, Hertfordshire, SG12 0DJ, U.K.*

Although clonidine has been reported to inhibit castor oil-induced diarrhoea in rats (Lal et al 1981; Lal & Shearman 1981), the receptor type involved in this action of clonidine has not been characterized. Clonidine has been shown to be an α-adrenoceptor agonist, acting predominantly at α_2-receptors, but also having some α_1-agonist activity (Drew 1981; Doxey et al 1981). We have investigated the α-adrenoceptor subtype involved in the antidiarrhoeal action of clonidine using phenylephrine, an agonist acting at α_1-adrenoceptors (Drew 1981), prazosin, a potent α_1-adrenoceptor antagonist and yohimbine, an α_2-adrenoceptor antagonist (Drew 1981; van Meel et al 1981).

Method

Male wistar rats (approximately 200 g) were starved overnight, but allowed free access to water. The rats were injected intraperitoneally (i.p.) with 0·9% NaCl (saline) (1 ml kg^{-1}; control) or with the appropriate test drug(s). Thirty min later, each rat was dosed orally with 2 ml of castor oil and was then observed at 30 min intervals for up to 6 h for the onset of diarrhoea. This was defined as the appearance of unformed faeces and perianal staining of the fur. The data have been expressed as time to onset of diarrhoea for individual rats, with the median for each group. Statistical analysis was made using the Mann-Whitney U-test for unpaired data, as described by Siegel (1956). Two-tailed tests were used and a P value of less than 0·05 was considered to be significant. The drugs used were: clonidine (Boehringer Ingelheim Ltd.), phenylephrine (Koch-Light Laboratories Ltd), yohimbine (Sigma Chemical Co. Ltd), prazosin (Pfizer Ltd) and castor oil (BDH Chemicals Ltd).

Results

All control rats developed diarrhoea within 2 h of castor oil treatment (Fig. 1). Clonidine from 0·1 to 1·0 μmol kg^{-1} i.p. caused a dose-related delay of the onset of diarrhoea, with the highest dose preventing diarrhoea for greater than 6 h (Fig. 1). In contrast, high doses of phenylephrine (1 to 100 μmol kg^{-1} i.p.) failed to delay the onset of castor oil-induced diarrhoea (Fig. 1).

A dose of clonidine of 0·3 μmol kg^{-1} i.p., which produced a statistically significant, but submaximal delay of diarrhoea was used to investigate the effects of α-adrenoceptor antagonists. The results of these experiments are shown in Fig. 2. Yohimbine (1 to 10 μmol kg^{-1} i.p.) produced a dose-related reversal of the clonidine-induced delay of diarrhoea, the highest dose of yohimbine completely prevented clonidine's effects. In contrast, prazosin (3 to 30 μmol kg^{-1} i.p.) caused no significant reversal of clonidine's antidiarrhoeal effect. Yohimbine (10 μmol kg^{-1} i.p.) and prazosin (30 μmol kg^{-1} i.p.) alone (in the absence of

* Correspondence.