the corresponding acids at the daily doses indicated: diclofenac (1–10 mg kg^{-1}); indomethacin (2 mg kg^{-1}); tolmetin (60 mg kg^{-1}). These acetate esters showed impressive stability in aqueous dispersions, with very little hydrolysis under neutral conditions (5 days, 20 °C, pH 6·0) as indicated by t.l.c. analysis.

Esters of acidic NSAI drugs may not always be fully effective anti-inflammatory agents compared with their parent acids e.g. benorylate (Brooks & Buchanan 1976; Rainsford & Whitehouse 1977) or the triglyceride ester of aspirin (Kumar & Billimora 1978). Thus the principle of esterification of acidic NSAI drugs to reduce gastric ulcerogenic activity (and still retain full therapeutic effectiveness inherent in the parent acids) will depend on the capacity of the particular ester to release the active drug after absorption through the gastric mucosa. Relatively rapid hydrolysis occurs after absorption of aspirin methyl ester (Rainsford & Whitehouse 1976; Rainsford et al 1980) and the carbonate esters of aspirin (Dittert et al 1968). Rapid metabolic hydrolysis would likewise be expected to occur with the methyl esters of the benzoates and arylacetates studied here. The principle of blocking the acidic moiety of NSAI drugs with such moderately labile groups or formation of cyclic (Edelson et al 1975; Sofia et al 1975) or other derivatives (Sinkula 1975) to produce latent forms (pro-drugs) appears a most effective means of reducing interaction of the irritant NSAI acids in the acidic millieu of the stomach with drug sensitive mucosal (Rainsford 1975a) and parietal cells (Rainsford & Brune 1976; Brune et al 1977). While the methyl esters of acidic NSAI drugs have still to be fully evaluated for intrinsic toxicity (e.g. from formation of one-carbon metabolites of the methyl moiety) it has been found that the methyl ester of aspirin is less toxic than aspirin after long-term oral administration to rats and pigs (Rainsford & Whitehouse 1980).

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On the accuracy of displacement measurements by instrumented single-punch machines

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The physical phenomena of the compression process have been much studied over the last three decades. Brake (1951) introduced equipment for measurement of compressional forces in tableting. Higuchi and his co-workers also developed equipment for the same purpose (Higuchi et al 1952, 1953). For the first time in pharmacy they introduced a system for measuring displacement of the punch during the compression process (Higuchi et al 1954). This was achieved by means of an inductive displacement transducer mounted onto the upper punch system. This kind of connection has been shown to be useful in routine observation of the tableting process.

De Blaey & Polderman (1970) introduced another kind of displacement measuring system. In this equipment the displacement transducer unit was linked to the machine part holding the upper punch, but the essential inductive part was firmly linked to the lower punch. Thus, this equipment takes into account the change of the distance between the punches due to the movement of the lower punch. From the technical point of view this system is more difficult to construct than the system

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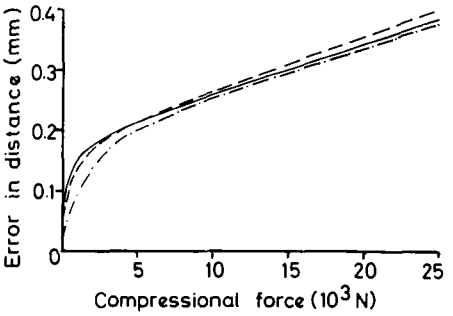

FIG. 1. Error in distance with 13 mm punches. — · — · — Lead tablet method. – – – – Punches against punches at maximum compressional force method. ——— Punch against punch at different compressional forces method.

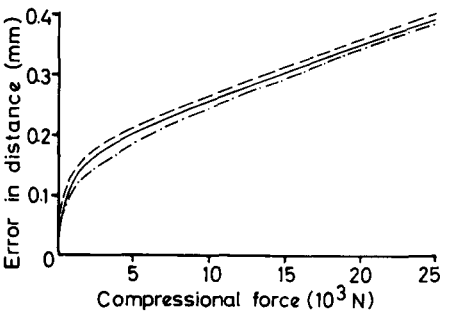

FIG. 2. Error in distance with three punch series by the use of punch against punch at different compressional forces method. — · — · — 8 mm punch. – – – – 13mm punch. ——— 20 mm punch.

linked only to the upper punch. Ho et al (1979) have shown that great errors exist in distance measurements carried out by the latter method. We have found the same in our equipment (Puumalainen et al 1978), which has the displacement measuring unit mounted relatively far from the surface of the upper punch. This unit is connected to the arm which moves the upper punch.

As a starting point we assumed that the greatest error in distance measurement must be the looseness in the machine itself and between the punches and their fitting sets. This kind of error ought to exist even at relatively low compressional forces. Secondly, errors must also be due to the elastic deformation of the punches and other parts of the machine. These errors become distinctive at relatively high compressional forces.

The basic assumptions were tested by three different methods. First a lead tablet was compressed so that it filled the die exactly. This tablet was compressed with gradually increasing forces. The thickness was measured with a micrometer screw at several points of the lead tablet after compressing it at different compressional forces. The thickness values were compared with those obtained by displacement transducer system. For each compressional force the difference was regarded as the error of the distance measuring system. Lead was chosen as the test material because it has a particularly small elastic recovery. The other two methods involved measuring the distance values recorded using the displacement transducer when the punches were just in contact as compared to the distance values recorded under compression. In the second method, the distance was recorded at maximum compression forces whereas in the third method the values were determined in a single compression cycle at a variety of compressional forces. All the above-mentioned experiments were carried out using 13 mm punches.

In Fig. 1 the distance error measured by the different methods is plotted against the compressional force. The errors in distance are of the same magnitude in spite of the way of measuring.

Whether different punch series change the magnitude of the distance error was also investigated. The third method was used to determine the errors with 8 and 20 mm punches. Table 1 shows the values of the power curve constants and the equation for the linear part of the power curve. The power curve is the equation showing the best correlation to the distance error values. Fig. 2 shows the errors graphically.

Changing the punch series caused only a relatively small alteration to the errors. Therefore it could be assumed that the steep rise of the error curve is caused by the looseness of the tablet press. It seems that the linear part of the curve, with high compressional forces, reasonably follows the metallic deformation according to Hooke's law (cf. Table 1).

The changing of the punch series in our experiments had no practical effect on the error, and therefore the distance correction can be made in all cases with the aid of the same equation. This was determined with the equations from different punch series according to the third method. The mean of the values obtained was

Table 1. The empirical equations for the error in distance. The constants of the equations are valid for different punch series and for different methods. The figures have been calculated from three experiments each containing 10 observation points. Y is the error in distance. X is the compressional force. r^2 is regression coefficient (indicating how well the plots fix the equation).

Measuring method	$Y = aX^b$ $a \cdot 10^{-3}$	b	r^2	$Y = cX + d$ (*) $c \cdot 10^{-5}$	d	r^2
13 mm punches						
1.	0·291	0·489	0·984	0·809	0·176	0·995
2.	1·142	0·346	0·941	0·811	0·177	0·995
3.	0·866	0·377	0·974	0·913	0·174	0·999
20 mm punches						
3.	1·158	0·340	0·995	0·892	0·169	0·999
8 mm punches						
3.	0·720	0·387	0·994	0·922	0·152	0·999

* X is over 5000 N.
1. Lead tablet method.
2. Punches against punches at maximum compressional force method.
3. Punch against punch at different compressional forces method.

calculated and the correction equation for our tablet machine was obtained from the formula

$$Y = 0{\cdot}00915\ X^{0{\cdot}368}$$

For practical purposes the mean value of the upper and the lower punch forces can be used as X in the previous equation. This approximation is valid if the percentage of the die wall friction is not high. In the case of high friction the entire system would have to be analysed to study the effects of the great force differences between the upper and lower punch.

When account is taken that the distance resolution in our tablet press is 0·02 mm, the accuracy of the correction equation can be regarded as sufficient for this system.

In conclusion, the mounting of the displacement transducer system far from the surface of the upper punch causes a relatively great error in measured distance values and hence significant differences may be obtained in compaction studies. Using the proposed empirical correction equation, it is possible to obtain more precise values which approach those obtained with more complicated mounting systems.

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The quantitative determination of cephalexin by proton magnetic resonance spectroscopy

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For cephalexin [7-(D-2-amino-2-phenylacetamido)-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0.] oct-2-ene-2-carboxylic acid] the official methods of analysis (British Pharmacopoeia 1973; Code of Federal Regulations 1977) are the microbiological agar diffusion assay and/or the iodometric assay. Other assays include i.r. spectrophotometry (Casu & Ventura 1974), column chromatography (Tortolani & Romagnoli 1976), u.v. spectroscopy (Wahbi & Unterhalt 1977), fluorometry (Yu et al 1977), high performance liquid chromatography (Hartmann & Rodiger 1976; Carroll et al 1977), and gas-chromatography (Nakagawa et al 1978). The nuclear magnetic resonance method presented here provides a specific, rapid quantitative analysis for this compound, which compares well with the official microbiological and iodometric assays.

Materials. Cephalexin formulations were obtained from commercial sources in Italy (Glaxo, Lilly, Dukron), chemicals and intermediates were Pierrel's products. Deuterium oxide, 20% deuterium chloride (99·9% isotopic purity for both), 40% sodium hydroxide—d_1 (99% isotopic purity) were purchased from E. Merck, Darmstadt, Germany and sodium 3-trimethylsilylpropionate-2,2-3,3-d_4 was obtained from Merck, Sharp & Dohme, Montreal, Canada. 3-picoline and 36% hydrogen chloride were regent grade (C. Erba, Milan, Italy).

Method. Approximately 80–150 mg of cephalexin (drug substance) or 150–250 mg of capsule contents were accurately weighed into a 5 ml flask, then 1 ml of the internal standard solution (approximately 30 mg ml^{-1} of 3-picoline in deuterium oxide or distilled water) was added. Deuterium chloride (or hydrogen chloride) was added until a complete solution was obtained by gentle swirling. For intermediates, samples were treated as before but were dissolved by careful addition of 10% sodium hydroxide-d_1 (in deuterium oxide). If an opalescence was present, samples were centrifuged, pipetted into a 5 mm i.d. n.m.r. tube and sodium 3-trimethylsilylpropionate-2,2-3,3-d_4 was added.

Spectra were recorded on a Varian T-60 n.m.r. spectrometer using a 250 s scan time and a sweep width of 100 Hz between 80 and 180 Hz. The methyl peaks of 3-picoline and of cephalexin (about 150 and 126 Hz respectively) were carefully integrated five times. The amount (%) of cephalexin in a sample was calculated as follows, using the average integral value:

$$\%\ \text{Cephalexin} = \frac{Ac}{As} \times \frac{Ws}{Wc} \times \frac{MWc}{MWs} \times 100$$

Ac = integral value for cephalexin; As = integral value for standard; Ws = weight of internal standard in 1 ml; Wc = weight of cephalexin; MWc = molecular weight of cephalexin; MWs = molecular weight of standard.

The n.m.r. spectrometry has been applied to the identi-

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