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EFFECT OF ACTIVE RAW MATERIAL VARIABILITY ON TABLET PRODUCTION: PHYSICOCHEMICAL, PHYSIOCOMECHANICAL AND PILOT PLANT STUDIES.

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ABSTRACT

Batch-to-batch variation in an active raw material was evaluated following a production process change by the raw material supplier. Physicochemical and physicomechanical tests were applied and indicated that polymorphism or solvate formation was not occurring but changes in crystal properties in terms of size and degree of aggregation were involved. Other more subtle differences in crystal properties were also possible.

The deleterious effect of the raw material process change on tablet production was noted and a method of overcoming the problem identified.

The necessity for comprehensive preformulation studies including physicomechanical screening is underlined. Such studies are also necessary if changes in raw material production methods occur to avoid process problems related to the marked batch-to-batch variation that can occur in these instances.

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INTRODUCTION

Recent reviews[1,2] have indicated that the batch-to batch variation in raw material properties and variation between lots from different suppliers can lead to processing difficulties or variability in the properties of finished products. Such variability may be marked by significant changes in raw material properties arising from modification of the raw material manufacturing processes. Such changes may occur during the early development stages of an active drug, or when a supplier identifies a more economic route to a raw material, whether active or excipient ingredient of a formulation. However, more subtle variability in materials can occur without the process changes indicated and still result in problems for formulators and production units.

One example of excipient raw material variability that has received a good deal of attention is the tablet lubricant magnesium stearate, where variability in raw material properties may lead to tablet hardness and dissolution problems. A review of studies on the variability of this material has recently appeared[3]. For other excipients, indentation hardness and tensile strength tests on compacts have demonstrated notable inter-batch variation in microcrystalline cellulose, sucrose, spray-dried lactose and modified starch[4].

Outside polymorphism and solvate formation there are few reports on interbatch variation in active ingredients of formulations and the effects of this variation on subsequent product properties and performance. Some workers have reported on the deliberate physical manipulation of active ingredients to modify, for example, dissolution propertes [6,7,8]. If such modification is inadvertently and occasionally introduced into a raw material process this may manifest itself as a significant interbatch variation. Subtle process changes may have marked effects on active ingredients as indicated by studies carried out on ibuprofen[5].

Mechanical property changes in ibuprofen compacts could be produced simply by alteration in the crystallisation rate of raw material. Although particle size differences may have been involved in the change in mechanical properties observed, it is likely that dislocation density also varied in the crystals.

Whilst physicochemical preformulation screening is practiced universally within the pharmaceutical industry, physicomechanical screening may be applied to a lesser extent perhaps only being applied where a problem may exist. For example, a physicomechanical quality control test may be introduced during the early development of a formulation to avoid processing or quality problems, e.g. flow tests for direct compression formulation components, surface area test for drugs where dissolution rate may be a problem. Tests may need to be instituted at a later stage of product development where an unexpected problem arises or a raw material process change is notified.

The present work illustrates the practical use of physicochemical, physicomechanical and pilot plant studies in combination to examine raw material variability of an active ingredient of a formulation following the notification of a raw material process change by the supplier.

EXPERIMENTAL

Materials

The active ingredient investigated was the antibacterial agent trimethoprim. This and all other formulation components were of pharmacopoeial grade. The batches of trimethoprim were selected to examine differences between old and new process materials, where a change in the preparation method for the active had been instituted by the supplier.

Physicochemical Tests

Differential scanning calorimetry (DSC) was carried out on a Perkin Elmer DSC2 instrument using approximately 10mg. of sample in open aluminium pans. The heating rate was $10^{\circ}C$ per minute and the range setting was 10mCal. per

second. The temperature range studied was 30°C to 300°C.

Infra-red spectra were recorded in Nujol mulls on a Pye SP 1000 spectrophotometer.

Powder X-ray diffraction curves were obtained on a Phillips type 120-101-11 instrument using nickel filtered Cu-K_α radiation.

Physicomechanical Tests

Particle size analysis was undertaken using a Malvern 3600D laser light scattering powder particle size analyser. The instrument was fitted with a 63mm. focal length lens. Samples were dispersed in a saturated solution of trimethoprim in water containing 1.0% $^{w}/_{v}$ sodium lauryl sulphate as a wetting agent. An ultrasonic probe was applied to the suspension for varying time periods up to a maximum of 55 minutes. At various time points samples were pumped through the flow cell of the instrument for sizing. Results were supplied by the instrument in hte form of a computer print-out.

Scanning electron microscopy was carried out by Structure Probe Inc., Metuchen, New Jersey, U.S.A. and photographs with magnifications in the range x 100 to x 10,000 were obtained.

Compaction studies were carried out on an Instron 1122 Universal Testing Instrument equipped with a compression/tension load cell. Trimethoprim powder (0.30g.) was transferred to a 0.956cm. diameter die and compressed between the upper and lower punches. The upper punch was fixed to the load cell on the moving crosshead of the Instron. Punches and dies were lubricated by direct application of a film of magnesium stearate powder. Compaction force (kg.) was measured directly on the Instron and from this compaction pressure was calculated. Two contact times, defined[9] as the time during which the upper punch exerts a force on the die contents, were used, being 1 second and 30 seconds. Heckel [10] plots were calculated to compare plastic deformation of the trimethoprim samples[11].

Stress relaxation studies were carried out by compressing a sample in the die and arresting the moving upper punch at a fixed depth during compression and measuring the force on the punch over a period of time. Percentage relative stress relaxation was calculated as the ratio of the fall off in pressure during a defined time period (30 seconds) to the maximum applied pressure expressed as a percentage. This was carried out at several different compaction pressures for each trimethoprim batch examined. Compaction and stress relaxation studies were also carried out on milled new process materials prepared and characterised as described below.

Pilot Laboratory Studies

Formulations of new and old process active material were tableted on an instrumented Manesty F3 machine equipped with an upper piezoelectric load cell. Load cell signals were amplified via a Kiag-Swiss charge amplifier and data were collected and processsed by an AIM 65 microcomputer to yield applied peak compression force. Apart from trimethoprim other ingredients in the formulations were identical. A wet granulation procedure was employed to prepare tablets. Tablet crushing strength was measured on a Sleuniger hardness tester, yielding results in Strong-Cobb units.

To study size reduction effects, new process material was milled using an Apex hammer mill equipped with a 60 mesh screen. Particle sizes of new process material after this milling operation was compared with that of old process material by an air permeametry method (Fischer sub-sieve sizer) and the mean sizes calculated were found to be of the same order (18-23 microns). Tablets were made with the size reduced new process material and compared with tablets made from unmilled new process trimethoprim and from old process raw material.

Dissolution testing was carried employing USP XX method 1 with 1000ml. of 0.1N hydrochloric acid in each vessel. Samples of dissolution medium were withdrawn at

intervals, filtered and assayed by spectrophotometry.

RESULTS AND DISCUSSION

During studies on a trimethoprim tablet formulation, the raw material supplier changed to a new process of preparation. This change immediately manifested itself in poor compression properties of the trial formulation.

Physicochemical preformulation screening studies were applied to compare old and new process materials. Infra-red spectra, differential scanning calorimetry and powder X-ray diffraction indicated that polymorphs or solvates were not responsible for the change in processing properties. It has previously been reported that trimethoprim polymorphs may be differentiated by their infra-red spectra and powder X-ray diffraction curves[12,13]. In addition to infra-red spectroscopy and X-ray diffraction studies, thermal analysis would be expected to reveal the presence of a solvate by the occurrence of a desolvation endotherm.

Old and new process materials showed a shift in their size distribution to a smaller median diameter with increasing exposure to sonication in the Malvern 3600D analyser. Old process material showed a rapid initial breakdown to an apparent primary state whereas new process material was broken down less readily (Fig. 1). This suggested that weakly bonded aggregates may be present in old process material. Scanning electron microscopy of batches of old and new process material indicated that the old process material consisted of aggregates of fine crystalline material (Fig. 2A) whereas large crystals were in evidence in the new process material (Fig. 2B).

Particle size distribution changes might influence die packing and hence compression properties, dependent upon the compaction mechanisms involved. Recent work has demonstrated this for some excipient materials[14]. To evaluate this for the trimethoprim samples Heckel plots were constructed (Fig. 3) and areas under the curves at

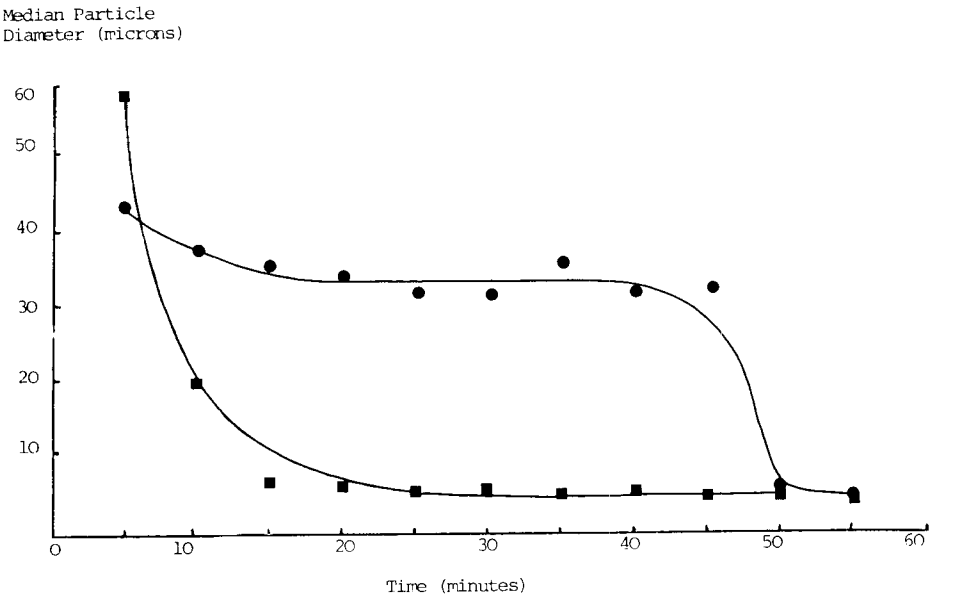


FIGURE 1

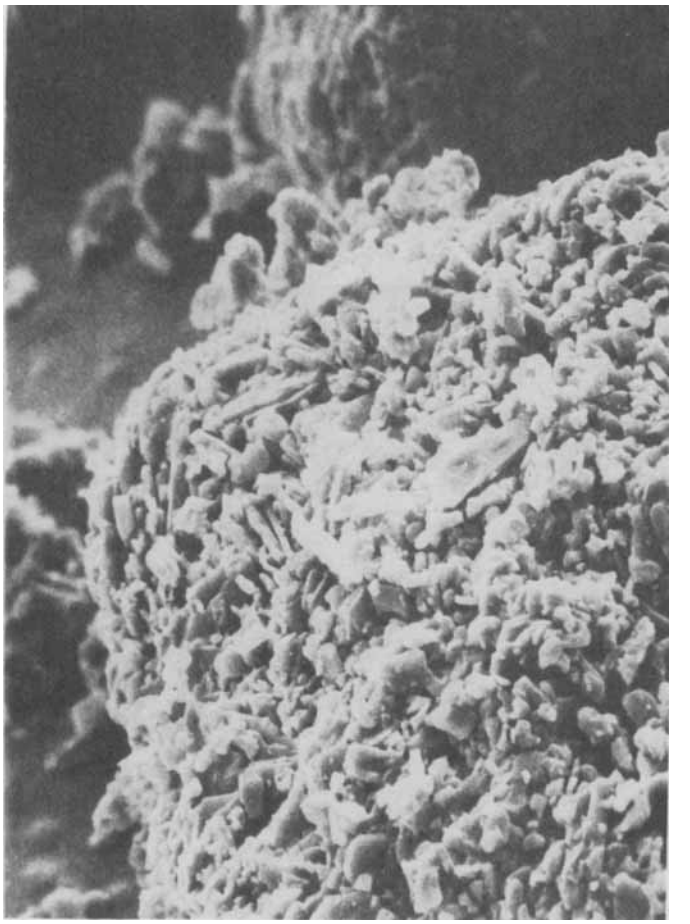
Plot of median particle diameter versus time of ultra sound exposure in Malvern 3600D for old and new process material:

■ old process material; ● new process material

the two contact times calculated. The percentage relative stress relaxation was also determined to aid in compaction process elucidation (Table 1).

The AUC for the Heckel plots indicate equivalent curves representing deformation of materials mainly by brittle fracture or by plastic deformation with time independent stress relaxation. The values obtained for % relative stress relaxation support the latter phenomena with values of 32-44% representative of materials undergoing plastic deformation e.g. (microcrystalline cellullose: 20%, Sta-Rx 1500 25%)[15]. To further support these data it would be necessary to run studies at compaction pressures higher than 30 MNm^{-2} but due to limitations imposed (25 MNm^{-2}) by capping of new process materials, 30 MNM^{-2} was the maximum compaction pressure used.

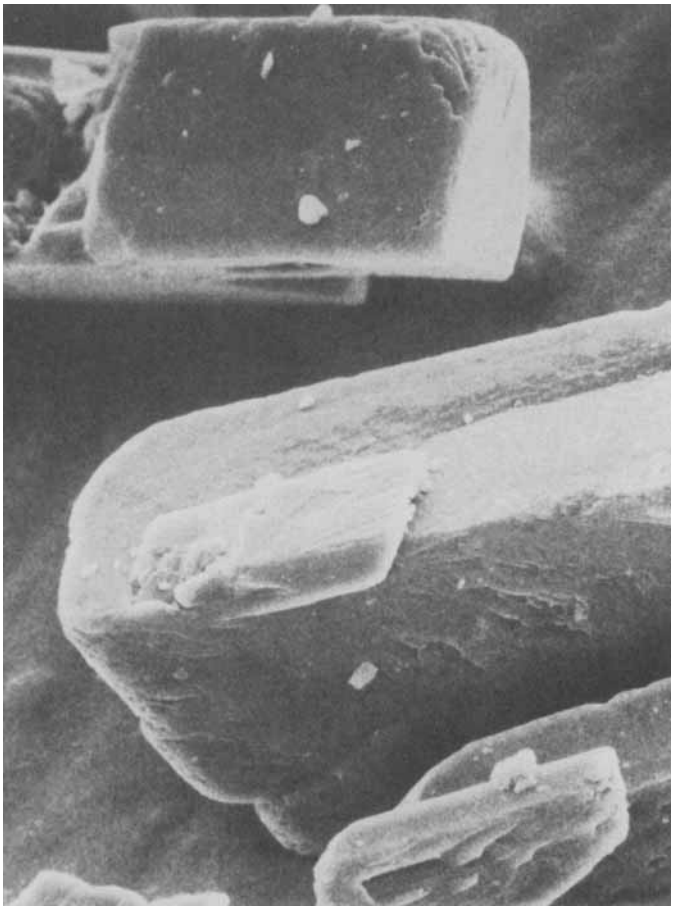
Thus it would appear that the materials compact



A

Figure 2. Scanning electron micrographs of A) 'old process' material and B) 'new process' material. Magnification x 350.

mainly by plastic deformation with the new process causing an inherent increase in plasticity. From the ratio of AUC's at two contact times the compaction of milled new process is less time dependent than unmilled process with a ratio of 1:1 cf. 1:1.08 which possibly explains the eradication of capping which the old process did not exert either (1:1.03). Thus milling appears to improve compaction characteristics of new process material.



B

Figure 2 continued.

This observation that milling the material improved its compression properties was applied in pilot laboratory studies and tablet formulations containing old process, new process and milled new process materials were compared. Plots of tablet hardness versus applied compression force (Fig. 5) indicated that milling the new process material gave tablets of improved physical properties, although tablet properties were not identical

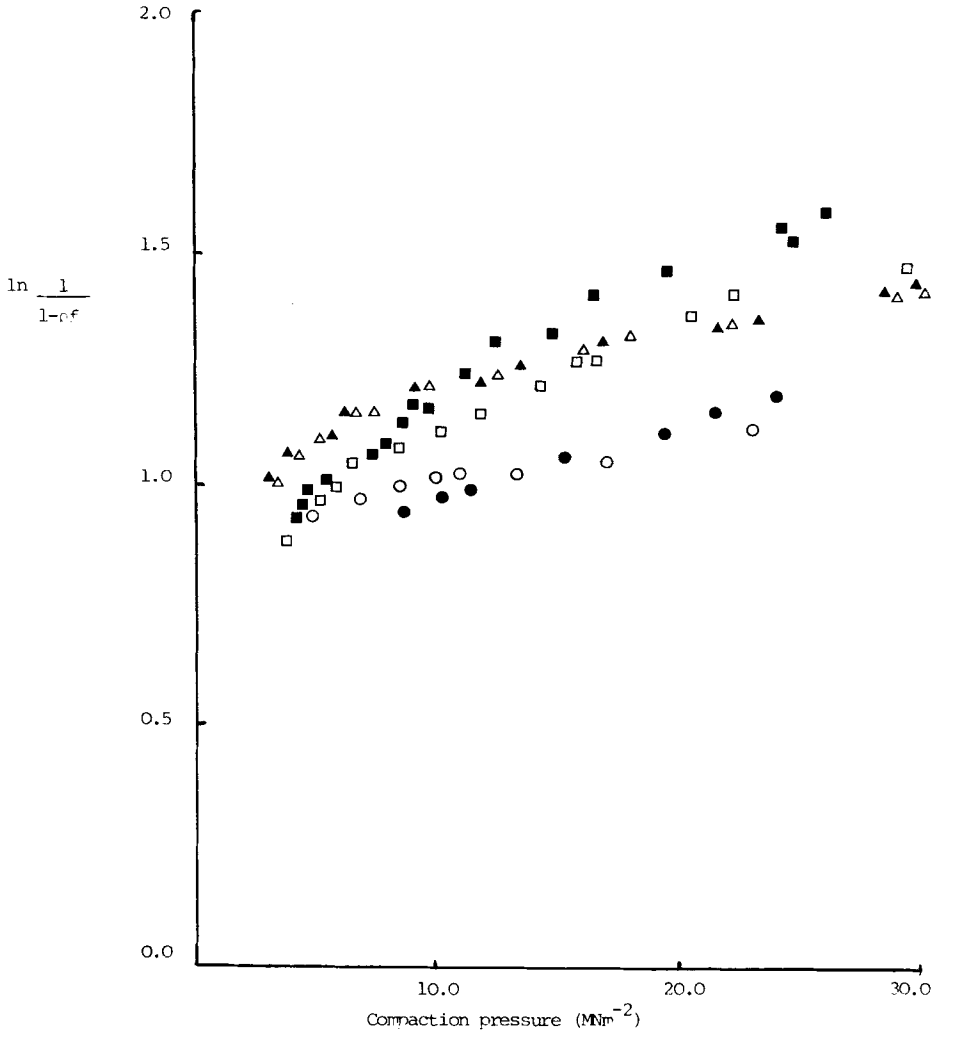


FIGURE 3

Heckel plots for old and new process material: ○ old process, 1 second contact time; ● old process, 30 second contact time; □ unmilled new process, 1 second contact time; ■ unmilled new process, 30 second contact time; △ milled new process, 1 second contact time; ▲ milled new process, 30 second contact time.

for old process and milled new process materials in spite of similar raw material particle sizes and processing conditions. Dissolution profiles for the tablets made from old and milled new process materials were very

TABLE 1

Areas under Heckel plot curves and percentage relative stress relaxation for trimethoprim raw material.

Material/ process	Ratio of AUCs 1:30 seconds	% Relative stress relaxation
Old process	1:1.03	32%
New process	1:1.08	44%*
Milled new process	1.1.00	44%

* Capping occurred at pressure greater than 25 MNm^{-2}.

similar (Table 2). Particle size differences alone may not be the only physical differences between the old and new process materials examined that leads to differences in compression properties. Changes in rate of crystallisation may be sufficient to induce alteration in the number of dislocations in a crystal and thus modify the properties of compacts made from such crystals.

In addition to physical preformulation screening techniques such as thermal analysis, powder X-ray studies and infra-red spectroscopy, physicomechanical preformulation studies of raw materials would be of great value in solid dose from development and troubleshooting. A minimum physicomechanical screening programme might include physical appearance of the material under an optical or scanning electron microscope (crystal shape and size), powder flow properties, wettability and compaction studies including time dependent stress relaxation. Other techniques may be added as required, for example, surface area where dissolution rate may be a problem with a sparingly-soluble drug. Further less readily-available as indicated in this work would help to identify such variations and contribute to the avoidance of processing problems and such tests should be especially applied where raw material process changes have been notified. The choice of tests applied may depend on the raw material

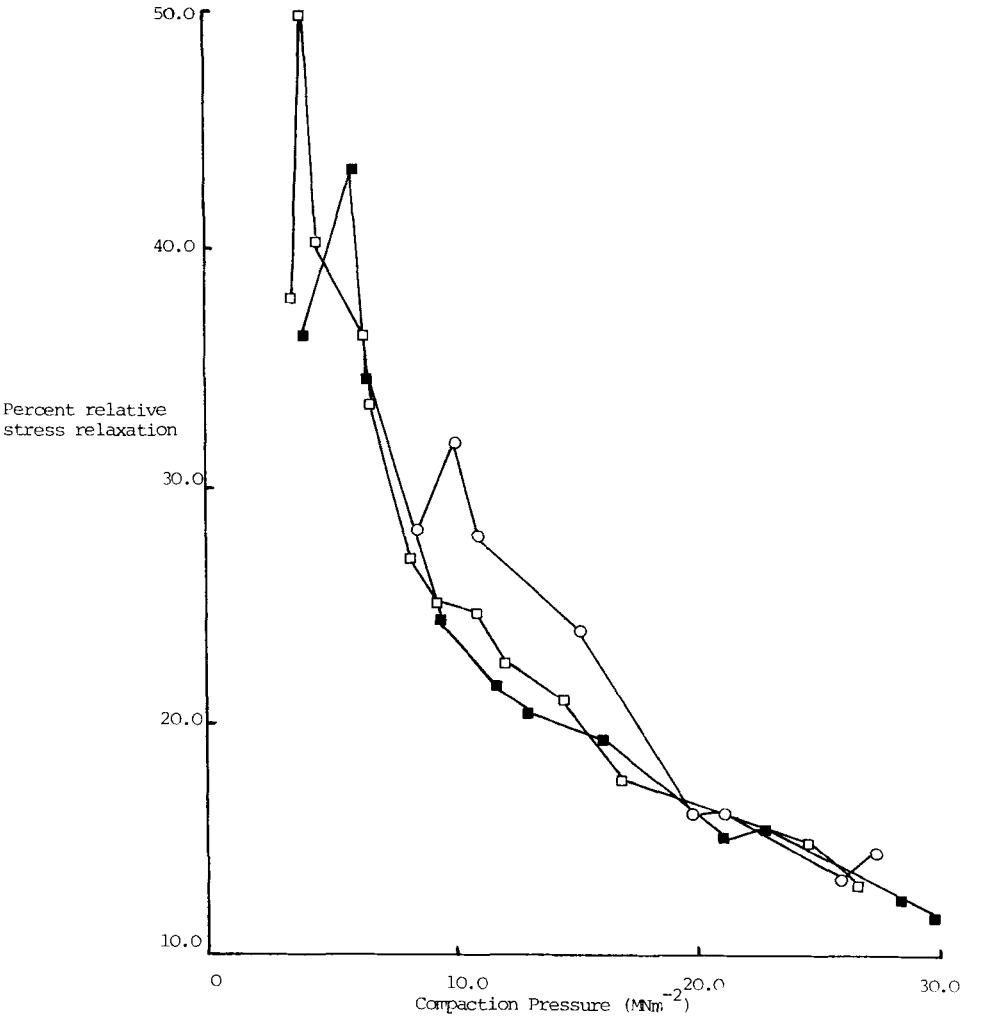


FIGURE 4

Relationship between percent relative stress relaxation and applied pressure for old and new process material;
○ old process; □ unmilled new process;
■ milled new process.

techniques such as thermosonimetry [16] and microcalorimetry [17] may be of value in the future in characterising subtle differences in crystal properties.

Interbatch variation of components of tablet formulations is becoming increasingly recognised as being important. The use of physicomechanical screening tests

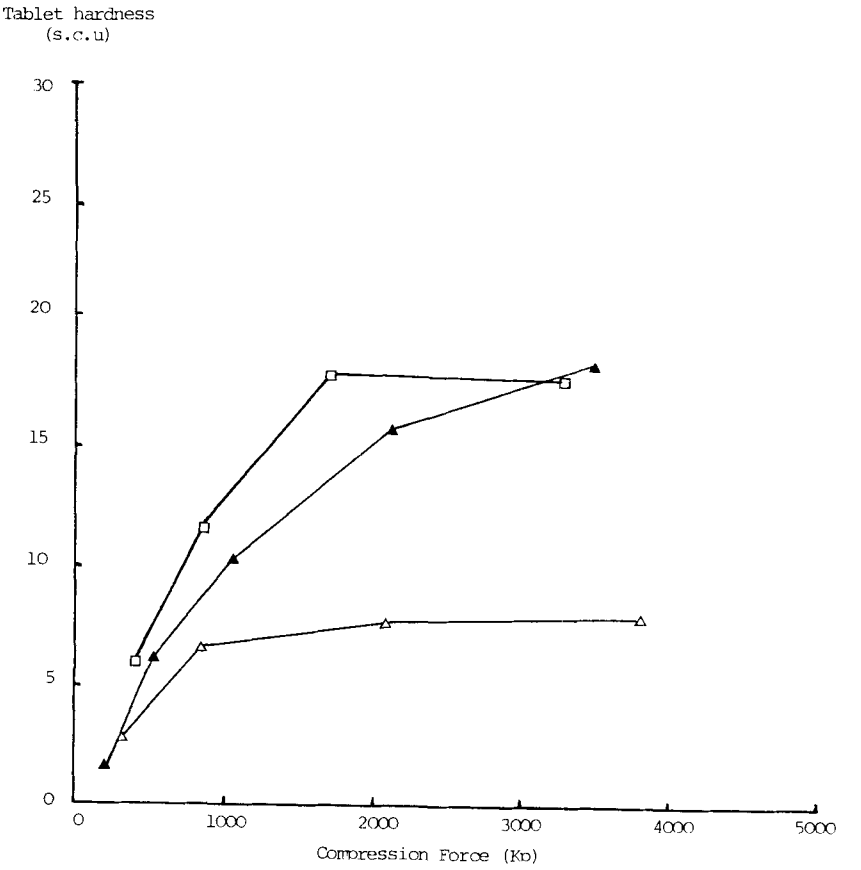


FIGURE 5

Compression force-hardness plots for old and new process material; □ old process material; △ unmilled new process material; ▲ milled new process material.

TABLE 2

Dissolution data for tablets prepared from old and new process trimethoprim batches. Figures given are percentage of label claim released at each time point. Each figure is mean from six tablets.

	Time (minutes)		
	3	10	30
Old process material	44.8	84.6	100.3
New process, unmilled	16.0	77.1	86.1
New process, milled	38.2	81.6	99.4

in question but for most materials measures of compression properties (including time dependent properties), wettability and flow would be essential. It should be noted that although interbatch variation may be considered to be most significant for direct compression formulations, it may also affect wet granulated formulations, as in the present case, although the variation in a wet granulated formulation may be more effectively masked by the remainder of the formulation.

REFERENCES

1. P. York., Int. J. Pharm., 14, 1, 1983.
2. T.M. Jones, Int. J. Pharm. Tech. Prod. Manuf. 2 17, 1981.
3. P. York, "Tablet Lubricants", in Materials used in Pharmaceutical Formulation",ed. A.T. Florence, Blackwell Scientific, Oxford, 1984.
4. E.N. Hiestand, D.P. Smith, Powder Technology, 38, 145, 1984.
5. E.N. Hiestand, G.E. Amidon, D.P. Smith, B. Tiffany, Proc. Int. Powder and Bulk Solids Handling and Processing Conference/Exhibition, Rosemont, Illinois, 1981.
6. W.L. Choice, L.E. Kyle, J. Pharm. Sci., 68, 1224, 1179.
7. A.T. Florence, E.G. Salole, J. Pharm. Pharmacol., 28, 638, 1976.
8. K.C. Lee, A.J. Hersey, J. Pharm. Pharmacol., 29, 249, 1977.
9. T.M. Jones in Formulation and Preparation of Dosage Forms, p49, ed. J. Poldeman. Elsevier, 1977.
10. R.W. Heckel, Trans. Metall. Soc. A.I.M.E., 221, 671, 1961.
11. P.J. Rue, J.G. Rees, J. Pharm. Pharmacol., 30, 642, 1978.
12. G.P. Bettinetti, F. Giordano, A. La Manna, G. Giuseppetti, J.Pharm. Pharmacol., 28, 87, 1976.
13. G.P. Bettinetti, F. Giordano, A. La Manna, G. Giuseppetti, Bull. Chim. Farm., 117, 522, 1978.

14. A. McKenna, D.F. McCafferty, J. Pharm. Pharmacol., 34, 347, 1982.
15. A.M. Delargy, Ph.D. Thesis, Queen's University of Belfast, 1983.
16. G.M. Clarke, J.E. Fairbrother, Proc. Second European Symposium on Thermal Analysis, 255-58, Heyden 1981.
17. K.Y. Chow., J. Go., M. Mehdizadeh, D.J.W. Grant, Int. J. Pharm. 20, 3, 1984.