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ROTARY MACHINE INSTRUMENTATION FOR PRODUCTION PURPOSES WITH PARTICULAR REFERENCE TO QUALITY ASSURANCE

Trevor M. Jones

Director of Technical Development - The Wellcome Foundation Limited, Dartford, Kent.

Visiting Professor - Chelsea School of Pharmacy (Kings College) - The University of London.

INTRODUCTION

Quality Assurance may be regarded as the totality of those design and operation activities giving rise to an assurance of reproducible and reliable product performance. In the field of tabletting technology this is particularly important due to the high outputs now achievable from modern compaction machinery coupled with the low doses of potent new drug substances and the need to control processes to ensure reproducible bio-pharmaceutical characteristics in the final product.

In consequence, during recent years, attention has been turned from sophisticated means of controlling the final product in the laboratory (Quality Control) to an greater emphasis on the design of correct operating conditions together with their monitoring and control in routine production. Such procedures are relevant at all stages during the manufacture of tablets.

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This paper concentrates on methods used for instrumentation of the compaction process in rotary tablet machines. It should be remembered, however, that the monitoring and control of the compaction process is no substitute for adequate product design and monitoring and control of the earlier stages of process, particularly granulation and drying. Whereas appropriate instrumentation of the compaction process can accommodate certain variability in the bulk characteristics of the formulation or its components, it is essential that the product being compressed is formulated in such a manner that variations in process technique (eg. as a result of manufacturing in different locations or using different equipment) are accommodated. In general, provided sufficient attention is given during the formulation stage to raw material variability and the process of preparing the final granule is controlled within tight limits, the compaction process should be relatively trouble free requiring only minimal control. Failure to achieve reproducible formulation characteristics prior to compression can lead to the necessity of considerable intervention at the compaction stage where the degrees of freedom to influence product properties are limited.

The advent of relatively cheap micro electronic technology coupled with significant advances in data acquisition and high speed computing have led, in recent years, to the availability of techniques of providing rapid information during the compaction process as well as providing more detailed records of quality control and assurance. As this trend continues the acceptability of records in electronic form will require further discussion.

DESIGNING ROTARY MACHINES FOR OPTIMUM QUALITY ASSURANCE

The last decade has seen a revolution in the appearance of rotary tablet machines which has been stimulated by international considerations of safety, efficiency and Good Manufacturing Practice.

The materials of construction of modern machines coupled with paint free and ledge free surfaces make clean down routines and the avoidance of dust build up more simple.

By enclosing the compaction process within glass fronted cabinets, environmental emission of powder particles is reduced (or eliminated) leading to greater operator safety and reduction of cross contamination.

Several machines now permit ease of access to the compaction chamber resulting in reduced changeover times and ease of engineering maintenance. In addition, "modular" units within the compaction chamber can be removed between production runs thus further reducing changeover time.

Although dust extraction at its point of creation has been a feature of compaction for several decades, the well sealed compaction machines of current day technology coupled with advances in air handling further assist in environmental protection.

These design features (several of which are easily monitored by appropriate instrumentation) coupled with the monitoring of the compaction process itself lead to the possibility of reduced supervision which, especially for highly potent drug substances, can result in unmanned operation using remote control. It is possible to consider operating several machines from a central (distant) console thus increasing productivity and further reducing exposure of operators to hazards.

MONITORING MACHINE PERFORMANCE

Until recently, tablet machines were driven by a primary motor with little or no ancillary electrical systems. In consequence, measurement of the power consumed by the primary motor could be regarded as an overall indication of machine efficiency coupled with operator observation of the process. Nowadays, machines are fitted with a variety of additional motors controlling or assisting machine performance by, for example, force feeding of powders into the dies, regular lubrication of punch guides. Furthermore, air handling support systems and force: weight monitors (see below) also involve electric motors.

The performance of these motors can be monitored routinely such that if performance deviates from normality, warning lights or audible systems can be activated, or alternatively, machine operations stopped.

In addition, potentially catastrophic failure of the process of compaction as a result, say, of totally inefficient lubrication or mechanical parts seizing or failing during operation can be avoided by monitoring motor overload.

MONITORING LUBRICATION

Mechanical lubrication of rotary tablet machines can be divided conveniently into three groups, viz:

a. Transmission
b. Ancillary components
c. Tooling

The type of monitoring device used will depend upon the particular system involved but could include pressure monitoring, measurement of temperature changes, conductivity and machine performance indices.

Perhaps the commonest system used is that of monitoring oil pressure to determine the changes which require the addition of further lubricant or sudden shortages which could give rise to severe damage of machine parts.

Lubrication of tooling can be effected by secondary evaluation of, for example, lubrication jets or machine performance.

Temperature measurements during compaction

Since all compaction processes involve the expenditure of work in order to form coherent compacts, forces exerted by axial pressure in the confined space of a die result in the generation of heat which is conducted gradually through machine parts and results in a rise in machine temperature.

In addition, the process of ejection of tablets from dies requires boundary lubrication conditions to exist at the tablet die wall interface which, although met in certain circumstances by the materials being compressed, invariably require the addition of lubricants such as magnesium stearate.

Inefficient lubrication - for example due to poor mixedness of an added lubricant or by grade variability - can be monitored by measurement of the force of ejection or by direct temperature measurement.
Temperature measurement can be divided into two categories, viz;

a. Continuous temperature measurement.

There are now available a variety of sophisticated, relatively cheap, transducers that can be fitted to machine parts (eg. a die surface) continuously to monitor temperature changes during compaction. Thermistors have proved useful in this context as have semi-conductor temperature gauges.

b. Single point temperature evaluation.

Alternatively, temperature sensitive compounds - usually existing as liquid crystals - can be painted onto machine parts and changes in their appearance detected by visual or photographic means. (In addition, these compounds might be included, experimentally, within formulations to detect overall temperature rises during compaction). These liquid crystalline materials - characterised by differences in their lattice structures - show changes in their visible spectrum particularly when using the cholesteric mesophase.

A further method that might be used is the application of infra-red thermography to monitor either a sample of tablets abstracted from the machine during routine compaction or alternatively, static or moving machine parts.

Nurnberg and Hopp have shown that overall temperature rises of upto 20°C can be recorded depending upon the energies expended during compaction.

Clearly, the ability to shut down processes which are likely to go out of control is an important means of avoiding product and machine failure.

Ejection Force Monitoring

The friction between a compact and a die wall can be monitored by measuring continuously the force required to eject tablets.

This has been achieved by instrumenting the ejection cam of the machine such that the force required to lift the bottom punch is measured and action points established at certain threshhold levels of ejection force.

(In addition, in the development phase of a product, the choice and optimisation of a lubricant and its method of incorporation can be studied in this manner).

Unfortunately, the point of contact between a bottom punch and the ejection cam will vary according to the shape and profile of the punch head and, in particular, the position of the bottom pressure roll. In consequence, it is necessary to measure separately the force exerted by any given punch rather than the summation of events resulting from, say, two punches rising up the ejection cam at the same time. This can be achieved by dividing the cam into small segments such that the force exerted by a single punch only is measured. By this means, individual ejection forces can be measured and the changes in machine and product performance monitored.

PUNCH TIGHTNESS MONITORS

Sticking of punches during routine tabletting operations can arise from two sources, viz;

a. Increased friction in punch guides.

b. Fusion of punch tips within the die.

In the former case this may arise as a result of inefficient lubrication of the guide tracks, improper punch: bore tolerance due to imperfect tools or the presence of powder from the formulation within the guide tracks.

In the latter case, fusion may be the result of compact: punch face adherence, damaged punch tips, or inadequate formulation lubrication.

In either case punch tightness may arise on an individual punch, or pair of punches, or a number of punches around the turret.

Several machines incorporate force monitors within the lifting cams which alert the operator to excess lifting forces resulting from tightness within the punch guides of the turret. When such problems are detected it is common practice to shut down the machine, remove the punches one-by-one, cleaning down the system completely before restarting the operation of compaction. These procedures result in considerable loss of output due to prolonged down-times. In addition, unless each and every punch is carefully inspected the problem may recur soon after start-up.

Furthermore, such monitoring systems, although measuring tightness within the guides, do not detect fusion within the die cavity. In consequence, expensive failure of tooling (and potentially major parts of compaction machines) can occur unless fusion within the die is also detected.

We have developed a system which is capable of monitoring both causes of punch tightness and identifying the individual punches concerned (Ho <u>et al</u> (1983)).

The system consists of the insertion of additional cams, (made of Nylatron) on both top and bottom punch stations. Each cam is instrumented with strain gauges to detect the forces required to move the punches immediately following their maximum depth of travel, ie. both within the die and after removal from the die through the punch guides.

A control module, linked to proximity detectors, permits the detection of the particular punch causing the problem; this information being displayed numerically such that the operator can free the offending punch avoiding prolonged downtime.

TABLET THICKNESS MONITORING

Tablet thicknesses is clearly an important parameter in efficient packaging operations; in particular during blister packing operations and in slat counters used for bottle filling.
Ideally, the design of a formulation should accommodate variability in excipient characteristics and in process variables to ensure that irrespective of compression force, provided a coherent compact is formed, the tablet will be of adequate thickness for such packaging operation. However, if this is not the case, tablet thickness must be carefully controlled during manufacture. It should be remembered, however, that increasing compaction force to reduce tablet thickness can result in changes in internal porosity within the compact which may result in inferior disintegration/disaggregation/dissolution properties. In addition, increased compaction force can exceed critical failure stresses within the compact leading to actual or incipient lamination. In the latter case problems may not be apparent during compaction but occur during subsequent packaging.

Few devices exist for an adequate measurement of tablet thickness during compaction. Those machines fitted with such monitors usually measure the distance between the upper and lower pressure roll axes and, by assuming constancy of punch length, infer an actual tablet thickness at the point of compression.

It should be appreciated that such measurements of thickness are relatively poor indices of eventual tablet properties since tablet tooling can and does vary in absolute length and, more importantly, elastic recovery following compaction results in considerable expansion of tablets both immediately following the removal of compacting forces and during subsequent storage prior to packing.

Provided these effects have been quantified adequately then it is possible to use these arbitrary measurements of "in-die" tablet thickness as a guide to tablet thickness reproducibility.

TABLET WEIGHT CONTROL

Despite considerable advances in machine instrumentation, it is arguable that the majority of tablets produced in the world are still controlled for weight by the operator abstracting the sample at reasonably frequent time intervals during the production run, weighting 20 tablets and making appropriate adjustments, if necessary, to the machine. Invariably such "in-process" records are supplemented by final Q.C. checks where further samples are abstracted from the final bulk of tablets and their weight distribution characteristics determined. Most compaction machine manufacturers, however, now provide systems for weight monitoring and control based upon two principals viz;

i. Force monitoring

ii. Individual tablet weighing and feedback

Force Control

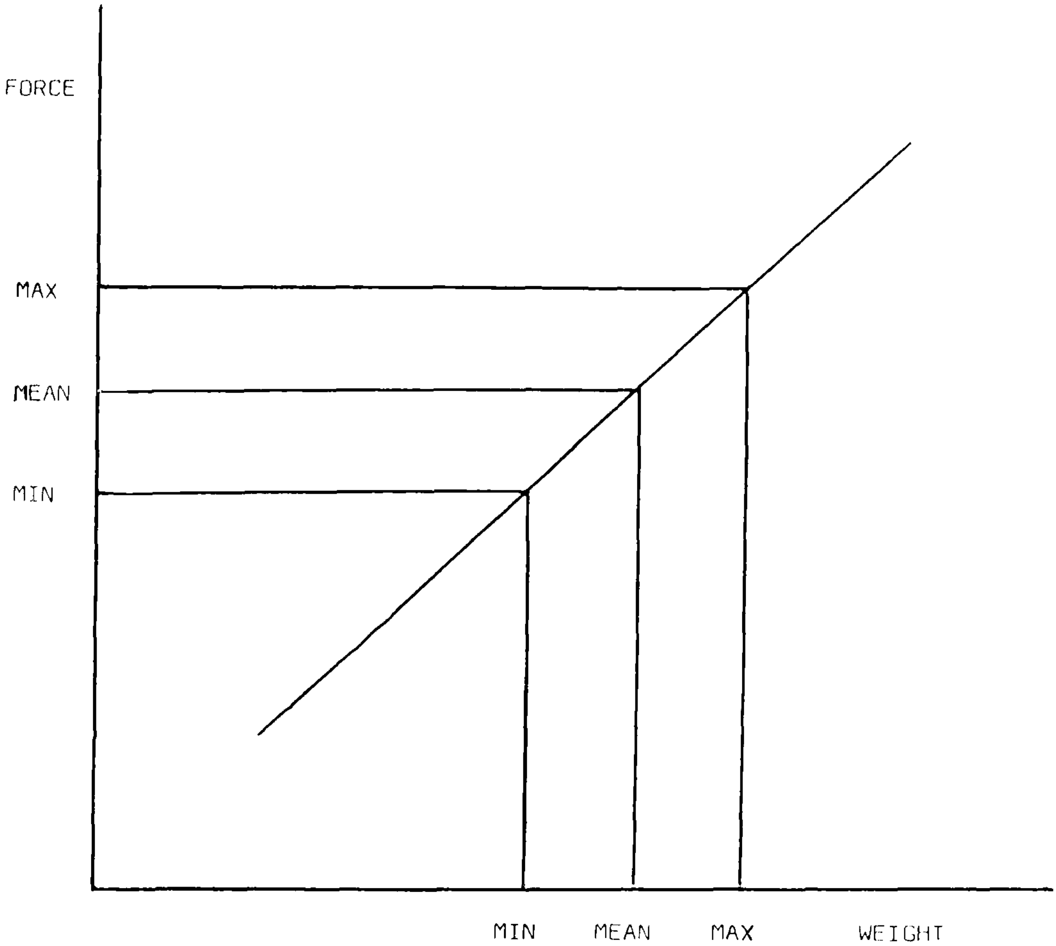
The force exerted by the upper and lower punches of rotary compaction machines can be monitored using strain gauges or piezo electric load washers attached to an appropriate part of the tablet machine. The sensitivity of such measuring devices varies from machine to machine depending upon their point of attachment. Perhaps the most appropriate place to mount force measuring devices in the majority of machines is on the roll pin or on the carriage pin. A number of authors have reviewed this subject in depth. Any given system must be capable of measuring the force exerted by each and every punch as it passes under the compression roll and should not reflect the combined effect of two or more punches.

The principal upon which weight control by force monitoring is based is that there is a fixed relationship between axial force applied and tablet weight. Thus, for an ideal bulk solid with an absolutely constant bulk density filled into die cavities of identical volume and subjected to compaction with punches of identical length, any change in force measured must reflect a change in tablet weight. It will be appreciated that real bulk solids vary in their particle size distribution within tabletting runs especially at low hopper head heights and that, furthermore, due to some segregation occurring during hopper discharge and feed frame movement, uniform bulk densities are usually not possible throughout a run. In addition, even with adequate care of tablet tooling slight variation in punch length will occur which, although paired appropriately, will lead to slight variation in applied force from die to die.

Two point force control

Early systems where tablet weight was controlled by force monitoring involved the establishment of a maximum and minimum force of compaction. On setting up a machine, the operating characteristics were adjusted first to give the correct target weight and then to increase the axial force to provide tablets of desirable characteristics (eg. breaking strength).

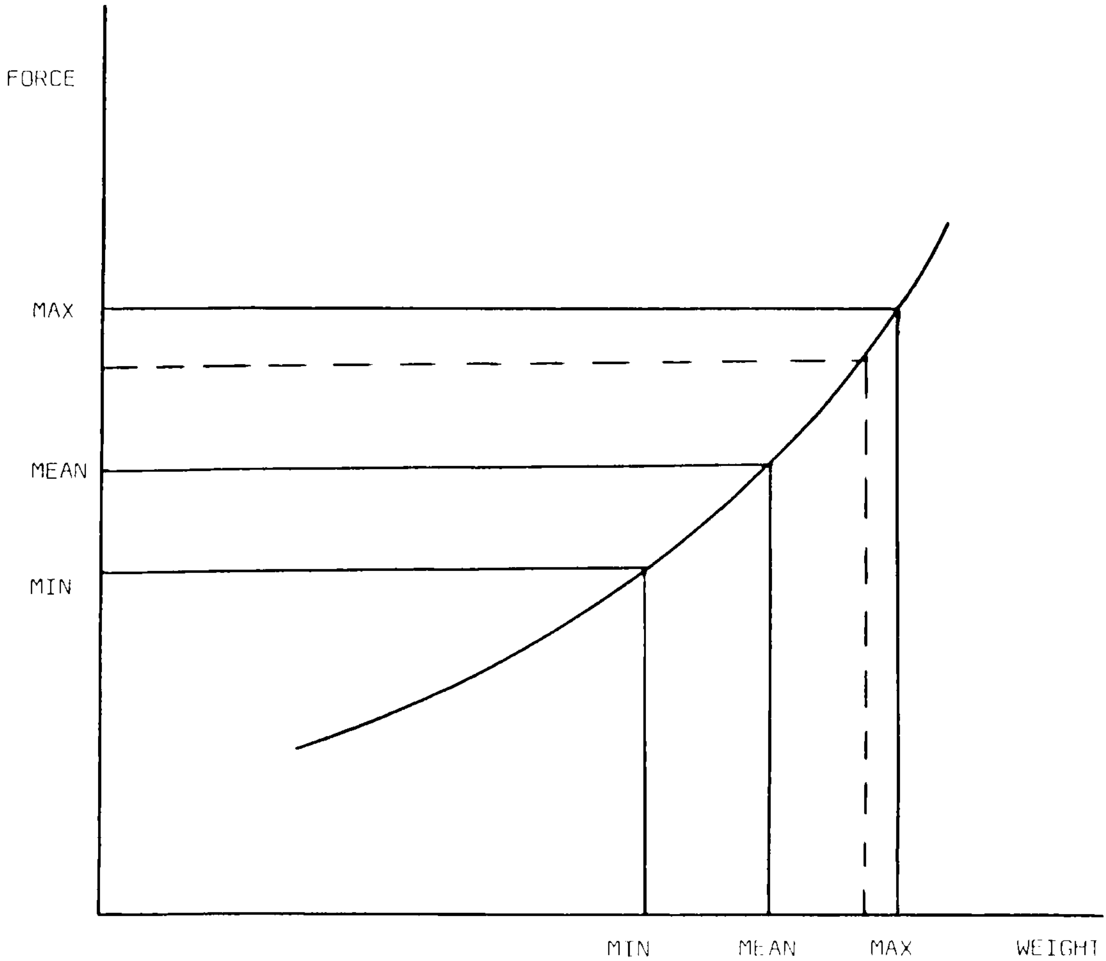
Maximum and minimum force values were then set manually into the force monitoring system which, due to the relatively unsophisticated electronic controls involved, consisted of symetrical limits round the target mean force



ASSUMED LINEAR COMPACTION FORCE-TABLET WEIGHT RELATIONSHIP

Figure 1.

value. Figure 1. demonstrates that such symetry assumes that the relationship between force applied and tablet weight variation is a linear function. Although such linearity may be approximated at small changes of tablet weight, in fact, the relationship between applied force and tablet weight is complex depending upon the characteristics of the material being compressed - in particular its packing characteristics. In general, the force: weight relationship is curvilinear as demonstrated in Figure 2. Thus, establishing an arithmetic deviation about a target force results in a tighter control of upper tablet weight than necessary.



TYPICAL COMPACTION FORCE-TABLET WEIGHT RELATIONSHIP

Figure 2.

In their simplest form such force : weight monitoring devices could be connected to cut out switches (or audible/visible signals) such that if either the upper or lower limiting values were exceeded the operator was alerted and manual adjustments made to tablet weight. To avoid such operator intervention Servo-motors were added to the weight adjusting screw to alter its position by a fixed depth. Thus, when the machine reached a force at either of the pre-set extremes, the volume of the die cavity was adjusted by a fixed increment upwards or downwards. Several devices provided for multiple incremental steps to be taken at these action limits to bring the tablet weight within the operating range.

Thus, during routine operation, the individual forces exerted during any given turret revolution were measured and the machine permitted to continue to produce tablets until an extreme value was reached. Only at this point was action taken and then by a fixed increment of change in die volume. In consequence, if the increment of change was too small, tablet weight "hovered" around either the maximum or minimum setting. Alternatively, if the increment of change of the die volume was too great then extreme fluctuation between maximum and minimum force (and weight) occurred.

Continuous Force Monitoring

Systems introduced more recently are based upon the principle of monitoring the mean force taken from individual compaction events during a turret revolution and comparing this with a pre-set mean target force obtained from initial calibration. On setting up the machine, tablet weights are varied to establish the unique relationship between force and weight for the particular formulation being compressed.

The mean target force is then determined and inputted into the monitor. As routine production proceeds actual mean force values are compared with the target mean force and automatic, proportional, adjustments made to the weight adjusting screw. In consequence, tablet weight varies closely around a target mean. Extreme deviations from mean force (and hence mean weight) thus reflect "rogue" tablets and pre-set limits for such events can be established from the calibration curve. Tablets formed beyond these limits are rejected by special gating systems at the ejection port.

Weight Measurement with Feedback

Since force monitors can operate at very high speeds they are useful to remove "rogue" tablets and to provide a permanent record (if required) of each and every compaction event. It will be appreciated, however, the that monitoring of compaction force is only a secondary measurement of tablet weight. Thus, drifts in force (whether upwards or downwards) may not reflect changes in tablet weight for the reasons given above (i.e. changes in the physical properties of the formulation). In consequence, it is preferable, in addition to force monitoring, to control tablet weight variation by actual weight measurement.

For most tablet formulations, weighing each and every tablet is unnecessary since reproducibility of volumetric die fill will be acceptable over short periods of time. Thus, by diverting tablets to a weighing station at frequent intervals, measuring their mean weight and standard deviation, trends in tablet weight change can be monitored and appropriate, automatic, adjustment carried out.

The data so acquired is a permanent record of Quality Assurance and obviates the need for further quality control weight measurement as a post production activity.

In its simplest form weight interception consists of physically removing samples from the machine to a computerised weighing system (Such a system is operated by Roche (UK) using a Commodore 8032 micro computer and printer linked to individual Sartorius balances with Telmos weight watcher interfaces in each cubicle. The operator extracts samples every fifteen minutes making machine adjustments as appropriate).

The Manesty micro PW system links tablet weighing systems directly to compaction machines such that operator involvement is not necessary. Samples of tablets are removed automatically at pre-set intervals and transferred to an automatic balance. If weight correction is required, the new press operating force is computed and the die volume adjusted automatically until the new force is achieved.

A similar approach is offered by Hata and Kikusui.

Information Obtained

A variety of data can be generated for exception reporting or as a total record of batch production. Table 1 lists the type of data that may be presented. Although, conventionally, such data are abstracted in hard copy forming part of the batch manufacturing records since it is acquired electronically it can be stored as such and displayed, as required, using VDU's.

ADDITIONAL DATA

Several other items of "information" can be transmitted electronically to a central console in order to provide both management information as well as operator alerts. Examples of such data are presented in Table 2.

PRE AND POST COMPACTION MONITORS

Efficient tabletting will depend upon a uniform, constant, feed of the bulk solid formulation. The height of powder in feed hoppers can be monitored, simply, by inserting capacitance monitors at appropriate positions in powder streams with audible/visual warnings in the case of potential "run-out", "bridging" etc.

Since the number of acceptable tablets emerging from such automated presses is monitored it is possible to install automated systems of product capture. Thus uniform quantities of bulk tablets can be collected for subsequent packaging operations.

Table 1

Typical Data from Force : Weight Monitors

Product Name

Product Code

Lot Number

Operator

Date

Number of hours of machine operation

Number of acceptable tablets

Number of reject tablets

Acceptable tablets per hour

Number of machine adjustment

Percentage rejects

Target Weight, Mean and standard deviation

Individual tablet weights, mean and standard deviation

Highest/Lowest tablet weights

Times of sampling.

Table 2

Additional data from Compaction Machine monitors

Status of hopper fill

Rotation of pressure rolls

Lubrication status

Safety interlock operations (eg. Casing)

Punch Sticking

Hata, for example, provide an automatically controlled container auto-changer which fills uniform quantities of bulk tablets into bins from a belt conveyor situated at the discharge point of the tablet press.

It should be remembered, however, that these automatic systems do not exert control over the visual appearance of compacts emerging from machines. Thus, insidious oil leakage or overt contamination (eg. "black specs") may pass undetected in operator free compaction processes. Recently, Kanebo have introduced a tablet inspection machine whereby the surface and edge appearance of tablets is compared with a standard visual image and tablets deviating from normality rejected.

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