routinely blended and granulated at the rate of 700 kg./hr. using a single model FKM600D Lodige mixer.

SUMMARY

A new approach to the preparation of effervescent granules by the fusion method has been described. The use of Littleford-Lodige mixers, both pilot plant and production models, was discussed with illustrated examples. Advantages of the procedure, which requires neither an external heat source nor a granulating solution, were presented on the basis of both development and production experience.

REFERENCE

(1) Coletta, V., and Kennon, L., *J. Pharm. Sci.*, 53, 1524(1964).

Keyphrases

Effervescent products, granular—preparation
Fusion method—effervescent products
Water of crystallization—moisture source

Evaluation of Tableting Tool Life Records

By CHARLES J. SWARTZ and JOACHIM ANSCHEL

A study of tableting tool life records, accumulated over a period of 8 years, has served to develop and define relationships between tool performance and the many operating variables that exist in routine tablet production. The effects of these numerous factors on punch and die life have led to conclusions involving techniques for extending tool usability. Outstanding among these are narrowing of working tolerances for tools and extension of product runs on individual machines rather than frequent interchange of machine and tools.

Beginning in 1959, performance records were kept at Ciba on punches and dies in use with standard tableting machines. A previous publication (1) describing all facets of a punch and die control program indicated the need for correlating these records of tool wear with many variables affecting compression. The tool life record keeping was briefly described in the same paper. These performance records have now been collected for 8 years, and the results obtained represent several billion compressions. This paper will review and evaluate the information derived from these records and attempt to define relationships which may be of practical value to research and production technologists.

Specially designed record cards for sets of punches and dies (Fig. 1) were maintained in the Pharmaceutical Manufacturing Division and reviewed jointly by Pharmacy Research and Development and Production personnel. The cards contain information on (*a*) the total number of tablets compressed with any given set of tools, (*b*) the product prepared, (*c*) the machines the tools were used with, (*d*) the type of steel, (*e*) the dies employed, and (*f*) the reasons for which the tools were eventually discarded. Cards were also kept for the tablet compressing machines with which these tools were used. The record cards further proved helpful for in-use inventory control of tools since they serve as a concise summary of available stock.

Received May 22, 1968, from the Development and Control Department, Ciba Pharmaceutical Company, Summit, NJ 07901

Accepted for publication July 25, 1968.

Presented to the Industrial Pharmaceutical Technology Section, APhA Academy of Pharmaceutical Sciences, Miami Beach meeting, May 1968.

EXAMINATION OF RECORDS

The record cards disclosed the principal reasons for termination of punch use which included damages to the tips and heads, rolled-in or burred edges, pitted faces, worn or distorted monograms, distorted or flattened bisections, undersized tip lands, and scored, pitted heads. Less frequent reasons for termination of use were distortions and eccentricities of the barrel (shank). Examination of die records showed that badly worn and scored die bores were the main reasons for rejection after use. On the other hand, carbide-lined dies outlived their usefulness principally as a result of distortion and burring of the die screw groove.

EFFECTS OF VARIABLES ON LIFE OF PUNCHES

The records show that some of the damage to tools can be attributed to normal wear, while other contributory variables are not related to regular operation. The effects of these variables will be discussed in the following section.

PUNCH RECORD CARD

1. Size ____ 6. Upper Face ____ 11. Source ____
2. Control No. ____ 7. Lower Face ____
3. Machine ____ 8. No. Uppers ____ 12. Purchase Order ____
4. Date ____ 9. No. Lowers ____ 13. Ordering Dept. ____
5. Type ____ 10. Type Steel ____

14. Inspection Notes and Comments: ____

15. Inspected by: ____ 16. Approved by: ____

17. Disposition ____

18. Date ____ 19. No. of Tablets Produced ____

20. Comments: ____

21. Approved: ____ PROD. ____ ENG. ____ PHARM.

RPH 003

Fig. 1—Punch record card.

Operating Variables—As machines become older, the clearances between moving parts become enlarged. These negative effects are tied to tool life performance and are reflected in the data on machine life. The primary reason for this reduction in tool life is probably centered around excessive clearances developed over years of usage. Enlarged dimensions show up most prominently in worn punch sockets, roughened cams which damage punch heads, or worn die pockets. After years of wear, the deflection of an upper punch at the die table can increase to more than double the value initially obtained in a new machine.

Other detrimental effects may result from faulty lubrication of machines as well as neglect of other machine maintenance features. Cam design as well as cam track tolerances have a direct effect on wear but these factors are more difficult to document. It should be pointed out that the cams themselves can also fail because of unusual wear but these effects will not be documented here.

Damage to punch heads is usually due to machine failures for one or more of the following reasons: (*a*) defective weight adjustment cam, (*b*) excessive ejection force, (*c*) tearing and friction resulting from lack of lubrication, (*d*) tight pressure rolls.

Shape of Punch Tips—In evaluating the reasons for failure of the numerous punches involved in the study, the most common one was "rolled-in" punch tips. This was most evident in the relatively short life of flat-beveled edge, deep concave, and modified ball-shaped tools. To overcome part of the problem with flat-beveled edge punches, the addition of a 0.005-cm. (0.002 in.) blended-in flat on the punch tip edges has been found to increase the life of the tools.

The condition of the dies employed in any compressing operation also has an important effect on punch tip life. In instances where punches are employed with worn dies, granulation is very often extruded around the edges of the punches. The constant abrasion due to powder extrusion will considerably accelerate tip wear. An insufficient or roughened die bore chamber will obviously play a large role in feathering the edges of the tips. Worn punch sockets in the upper punch guide bores also contribute to setting up the "rolled-in" problem.

Type of Steel Used—Although no definitive proof arose from an examination of the records, it can be assumed that the type of steel used and its treatment during processing can play an important role in extending tool life. The hardness, carbon content, nature of heat treatment, and inherent structural features of the steel all have a role in determining the suitability of a particular steel for certain production needs.

With one high volume product run on a 35-station machine, four groups of punches manufactured from different types of steel were evaluated. At the end of the test period, which encompassed approximately 1,900,000 compressions per punch, there was no discernible difference in the wear noted on any of the tools. All four groups displayed tip damage to about the same extent. A larger sample would have to be studied in order to obtain any meaningful results.

Storage and Care of Tooling—Rusting and pitting of tool steel is a relatively frequent occurrence if proper preventive precautions are not taken. Careful maintenance of humidity control in the tool storage area is an excellent step in this direction. Following routine use and prior to storage, the tools are cleaned ultrasonically, inspected visually, oiled down, and placed into specially constructed wooden tool boxes preventing direct contact between punches. Tools are reinspected at regular intervals by specially trained mechanics. The inspection includes selected dimensional checks in addition to hardness and visual observations for gross imperfections. If required, recommendations for rework or destruction are made at these intervals.

Effect of Granulation Characteristics—The nature of the granulation to be compressed is obviously a key variable in any evaluation of tool life. The records disclosed many examples of these effects. A tableting operation can be considered a three-component system consisting of machine, tools, and the granulation. Abrasion or corrosion by many of the chemicals involved were well established, and a few specific instances might serve to demonstrate this. In one clear illustration, it is possible to show the effects on tool life if only the conditions of manufacture of the granulation were changed. Figure 2

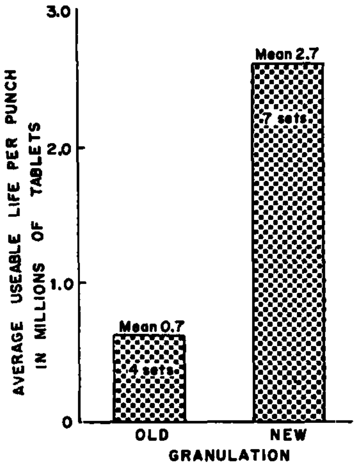

Fig. 2—Tool life associated with change in granulating procedure.

shows the average tool life before and after the modification of the granulation procedure. An almost fourfold increase in tool life resulted on the same machine under similar pressure conditions. The significant change can, therefore, be wholly attributed to modification of the granulation technique.

The variation in tool life from product to product can be noted in Fig. 3. With Product A, the punch life was consistently low, ranging between 0.3 and 0.7 million compressions per tool. In this instance, the short life of the tools was found to be related to a combination of the properties of the product compressed and the deep concave shape of the punches used with carbide insert dies. The hygroscopic and acidic nature of the granulation further contributed to shortening the tool life.

Machine Variables—Punches employed for the other products showed a large variation in tool life which is not as readily explained as for Product A. Products B and E in Fig. 3 provide an interesting comparison since the nature of the granules and excipients is somewhat similar in both. One product (Product E) was compressed on the same tableting machine on a long-run basis with stops only for cleaning and maintenance. It has been the authors' experience that this practice tends to increase punch life. Frequent removal of the punches from the machine and interchange of punches with different dies will increase the wear on the tools involved (Product B).

Tool life in excess of 4 million tablets per punch (Product C with a mean of 2 million) was achieved by employing the punches with a newer tableting machine of improved design (Manesty Rotapress 55). This machine has closer tolerances on the upper punch guides. As observed by stroboscopic light, punches on this higher speed machine seem to flow more smoothly through the cam tracks. Reduced vertical travel accommodates the rotational speeds required to produce up to 5,000 tablets/min.

With an average tool life of 2.2 million compressions for Product D the extension from 1–2 million to 2–3 million in some of the later sets of tools can be attributed to the replacement of the machine heads by specially designed ones with tighter punch socket clearances. This correlates well with the performance noted above with tooling for Product C. Details of this particular modification were reported in an earlier communication (1).

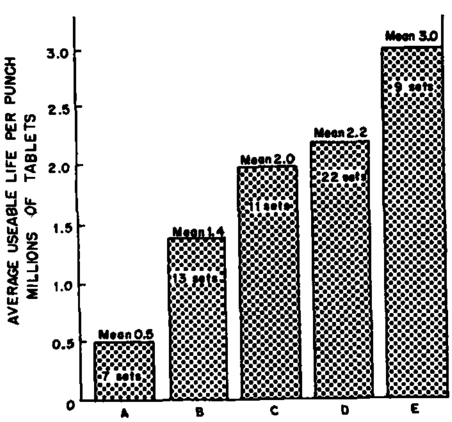

Fig. 3—Variation in average tool life for different products.

EFFECTS OF VARIABLES ON DIE LIFE

Although useful working life of dies varied considerably from product to product, it was much more consistent than that of punches within each product class. The records were not extensive enough for graphical representation, but several points of interest were noted. Die life ranged from 200 thousand to 12 million compressions per die and in all these instances dies were no longer usable when the wear rings (grooves) in the die bore became excessive. Carbide-lined dies, as expected, extended tool life by threefold or more but the effect of carbide-lined dies on punches must be weighed. As noted earlier, "rolled-in" tips were the main reason for punch failure and constant honing of the punch tips on carbide insert dies accelerates this process. The weakest portion of the carbide insert die is its supporting steel casing. The act of repeated tightening of these dies into die tables causes burring of the die screw groove as well as eventual deformation in this area leading to "popping" of the dies during running of the presses.

DISCUSSION

With many of the products studied, improvements in tool life were noted for more recent sets. There are many factors explaining these changes which have been described earlier. But as a result of the control program for incoming tools, it has been possible to consider the dimensional specifications of the punches and dies to be constants. Changes to tighter tolerances on new machines seem to be the greatest contributing factor. The smoother flow pattern of upper punch movement in newer machines must certainly aid in the extension of punch life.

Tableting tools are manufactured in accordance with precise specifications and are readily damaged by improper handling. Machine operator carelessness or lack of experience can contribute to a considerable reduction in tool life. On the other hand, better lubricants and improvements in tablet formulation technology have increased the life span of tableting tools.

Keeping and reviewing of tool life records can lead to considerable savings in time and money in tablet manufacture. Under optimum conditions, life records of controlled tableting tools can show the maximum life expectancy of the equipment. When tool life is below these expected standards, reasons can usually be determined from the knowledge gained rather than just intuition. Benefits derived from the program have been substantial, and as a consequence, it will be continued as a valuable control procedure.

REFERENCE

(1) Swartz, C. J., Weinstein, S., Windheuser, J., and Cooper, J., *J. Pharm. Sci.*, 51, 1181(1962).

Keyphrases

Tableting tool life records—evaluation
Punches—variables affecting wear
Dies—variables affecting wear
Record card—punches

Notes

Effect of Paralyzation with Dimethyltubocurarine on Cortical After-Discharge Duration

By ROBERT N. STRAW

Paralyzation with dimethyltubocurarine iodide increased the duration of cortical after-discharge in a manner similar to that previously reported for gallamine triethiodide. The after-discharge duration was determined from EEG records obtained from cats fitted with electrodes.

PARALYZATION WITH gallamine triethiodide, but not with decamethionium bromide or succinylcholine chloride, increases the duration of cortical after-discharge (1–3). The purpose of this investigation was to examine the effects of paralyzation with dimethyltubocurarine iodide on after-discharge duration.

METHODS

Five adult cats of both sexes were used in these experiments. Stainless steel screw electrodes were threaded into the skull under sodium pentobarbital anesthesia as previously described (1, 3). Preliminary trials to determine the threshold for a bilateral cortical after-discharge began after a 2-week recovery period. Each cat was stimulated with a 5-sec. train of 1-msec., monophasic square wave pulses at 50 p.p.s. (delivered from a Grass S-4 stimulator *via* a Grass SIU-4B stimulus isolation unit and Grass CCU-1A constant current unit) starting from 2.5 ma. and with increments of 2.5 ma. At least 5 min. elapsed between stimuli. The threshold was redetermined 2 days later starting with a current 5 ma. below the previously determined threshold. The threshold value obtained at this second trial was then used in each experimental trial. Throughout all experimental trials the cats, restrained only by the confines of their cage, were stimulated once on every other day.

Received April 24, 1968, from the Department of Pharmacology, The Upjohn Company, Kalamazoo, MI 49001
Accepted for publication June 25, 1968.
The author wishes to acknowledge the technical assistance of Mr R. E. Williams.

The medial ectosylvian gyrus was chosen as the cortical area to be stimulated since, according to Garner and French (4), it has a relatively low seizure threshold. In addition, a generalized clonic overt seizure always accompanies the bilateral after-discharge elicited by stimulation of this area (5).

The stereotaxic coordinates (6) of the bipolar stimulating electrodes were $A = 10$; $L = 16$; $A = 2$; $L = 14$. Bipolar EEG recordings were made from both the stimulated site and the contralateral homologous area. In addition, EEG recordings were made from the posterior lateral and posterior sigmoidal gyri. All EEG recordings were made on a Grass model III electroencephalograph.

In the paralyzation experiments, the animals were given dimethyltubocurarine iodide (1 mg./kg.) intravenously. This dose was selected because it produces apparent total neuromuscular blockade of sufficient duration to conduct a trial under complete paralysis. Artificial respiration (Harvard pump set at 16 strokes/min.) was immediately started, the tidal volume being based on the animals' weights.

The after-discharge duration was determined from the EEG record. Analyses were performed on the data using a randomized complete block analysis of variance or by use of a Student's t comparison (7). For all tests, $p < 0.05$ was selected as the significant probability.