New Approach to the Fusion Method for Preparing Granular Effervescent Products

By RICHARD B. MURRAY

General methods for the preparation of effervescent granules are discussed briefly and a new adaptation of an old procedure is presented. The use of a special mixer in simplifying the initial blending, heating, and screening steps of granulations made by the fusion method is described. No external heat source is required, nor are liquids in any form used to accomplish the granulating. The instrumentation, basic formulation data, the method for monitoring the fusion process in the mixer, and the advantages of the new procedure are reported. Process data for granulation batch sizes of 60 and 300 kg. are given.

EFFERVESCENT SALTS have been known and used for about 130 years. Their popularity with the medical profession and the public has varied widely during this period. The preference for this dosage form declined markedly after reaching a peak during the early 1900's, but a significant number of ethical and proprietary products have since created or maintained considerable popularity in the market place.

Effervescent combinations consisting of a medicinal agent, a dry, nontoxic organic acid such as citric or tartaric acid, and an alkali metal carbonate or bicarbonate obviously cannot be wet granulated with aqueous solvent systems in the usual manner. With the exception of an experimental technique described by Coletta and Kennon (1) in 1964 which utilized the Wurster air-suspension apparatus, methods for preparing effervescent granules generally follow one of three approaches. The common goal of all three approaches is the introduction of just enough water to initiate a reaction between the acidic and basic components of a formulation, thereby massing it. The "wet method" utilizes a nonsolvent liquid such as alcohol, containing a small percentage of water. The "steam method" makes use of steam to add controlled amounts of water to the mixing material. The "fusion method" employs heat to liberate water of crystallization from components such as hydrous citric acid to effect moistening.

The fusion method normally presents two major production problems. The first is the need for specialized equipment such as steam-heated hot plates, ovens, or externally heated coating pans which are required to trigger the fusion process. The second problem involves the means of monitoring the progress of the fusion reaction and determining the point at which it is to be terminated.

This paper describes the use of a standard production mixer with no external heat supply for the preparation of granular effervescent salts by the fusion method. The required heat was generated solely by the resistance of the mixer contents to turbulent, high-speed mixing.

EXPERIMENTAL

Equipment—The mixer used for development studies was a Littleford-Lodige,[1] model FM100D, Fig. 1. This particular unit has a total capacity of 3.3 cu. ft. and a working capacity of 2.1 cu. ft. It has stainless steel contact parts and is equipped with a 5-hp. drive motor coupled to the plow shaft, with a variable speed drive which allows plow speed to be varied from 90 to 225 r.p.m. The mixer also has one high-speed chopper assembly powered by another 5-hp. motor. Rubbing plates were not utilized.

Carbon dioxide formed during the fusion reaction was vented by way of the liquid input tube. The optional vent pipe available for Lodige mixers, fitted with a filter boot, will also effectively relieve pressure and prevent material loss.

Instrumentation—The mixer was instrumented to measure three variables: the rotation speed of the plow shaft, the current demand of the plow drive motor, and the temperature of the mixing chamber. The factory-installed tachometer and ammeter were sufficiently accurate to measure the plow speed and electrical current demand. The mixing chamber temperature was monitored using a Simpson model 389-3L temperature tester equipped with a No. 0010 thermistor probe fixed in place at the nozzle end of the liquid input tube. Positioning the probe in this highly turbulent area of the chamber assured constant contact with the mixing materials.

Preliminary Tests—The suitability of various effervescent formulations for granulation by the fusion process was tested on a small scale using covered

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[1] Marketed by Littleford Bros., Inc., Cincinnati, Ohio.

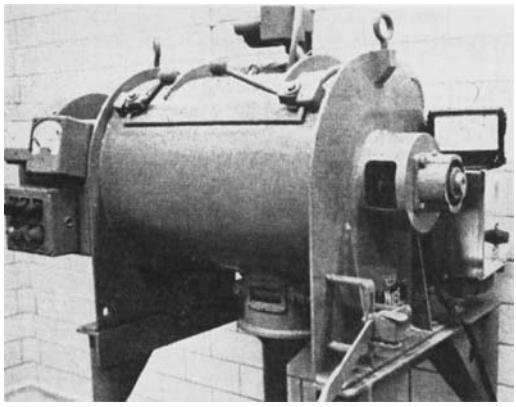

Fig. 1—Littleford-Lodige mixer, model FM100D, equipped with tachometer, ammeter, and temperature tester.

trays in a standard drying oven at 49° (120°F.). Blended ingredients were spread to a uniform depth of about 2 cm. Test blends which reached the desired degree of wetness within 1 hr. in the oven were generally suitable for scale-up and evaluation in the FM100D Lodige mixer. If a blend was slow to react, the proportion of hydrous citric acid was increased and the mixture was rechecked. Attempts to use a laboratory size M20E Lodige mixer for granulating were unsuccessful. Temperature rise sufficient to start the fusion reaction could not be attained due to the absence of a high-speed chopper and to the relatively small capacity of the mixing chamber.

Formulation and Process Data—The same basic effervescent granulation was prepared in each of the following examples to better illustrate the effects of mixer size and speed. The formulation which was granulated consisted of 50% potassium bicarbonate, 30% anhydrous citric acid, and 15% hydrous citric acid, plus small amounts of sweeteners, flavors, and water-soluble dyes.

Trial A—The model FM100D Lodige mixer was charged with 60 kg. of material. Mixing was commenced using a plow speed of 220 r.p.m. with the chopper operating. Current demand and temperature were recorded at 30-sec. intervals (see Figs. 2 and 3). As anticipated, the temperature and time relationship proved to be nearly linear throughout the process. The initiation and the progress of the fusion process were monitored by observing the drive-motor current demand. The current remained constant at 12.5 amp. for the first 4 min., then increased as the fusion reaction progressed and resistance to mixing increased. The fusion reaction apparently commenced when the temperature of the mixing material was just over 32° (90°F.). A suitable degree of wetness was reached in 8 min., at which time the current demand was 20 amp., an increase of 7.5 amp. over the initial power requirement. The temperature of the mixer contents reached 38° (101°F.).

The granulated material was immediately discharged and spread on trays for drying in forced air ovens at 49° (120°F.). The wet mass produced in the Lodige did not require wet screening. The dried granulation was passed through a No. 12 mesh stainless steel screen and, when intended for tableting, blended with a suitable lubricant.

Trial B—Sixty kilograms of the basic effervescent formulation was granulated in the FM100D Lodige mixer with the plow speed reduced to 110 r.p.m. and the chopper operating. The current demand remained constant at 8 amp. and the temperature increased to about 32° (90°F.) during the first 7 min. of mixing (Figs. 2 and 3). The fusion reaction began at this point and was terminated after 14 min. total mixing time. The final temperature was 41° (106°F) and the final current demand was 15.5 amp. The increase from initial to terminal power requirements again amounted to 7.5 amp.

Trial C—Scale-up to a production batch size was done in a model FKM600D Lodige mixer (Fig. 4). This unit has a working capacity of about 13 cu. ft. The plows are driven by a 15-hp. motor through a variable speed drive and the mixer is equipped with two high-speed chopper units individually powered with 5-hp. motors. A thermistor probe was in-

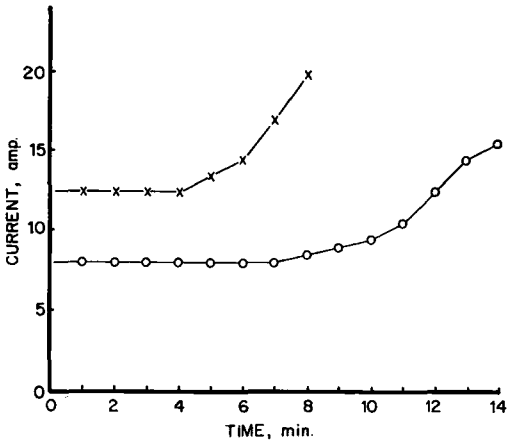

Fig. 2—Drive motor current demand during processing; FM100D Littleford-Lodige mixer. Key: plow speed X—X, 220 r.p.m.; O—O, 110 r.p.m. (separate trials).

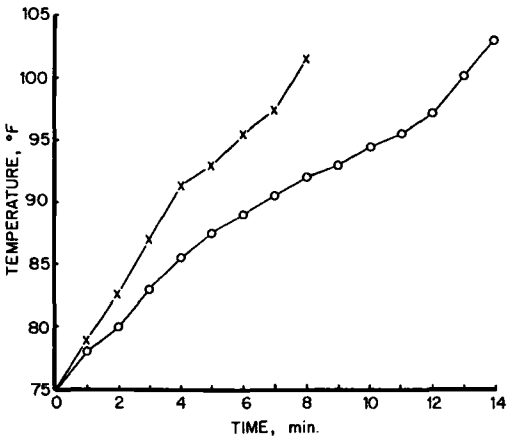

Fig. 3—Temperature of the mixer contents during processing; FM100D Littleford-Lodige mixer. Key: plow speed X—X, 220 r.p.m.; O—O, 110 r.p.m. (separate trials).

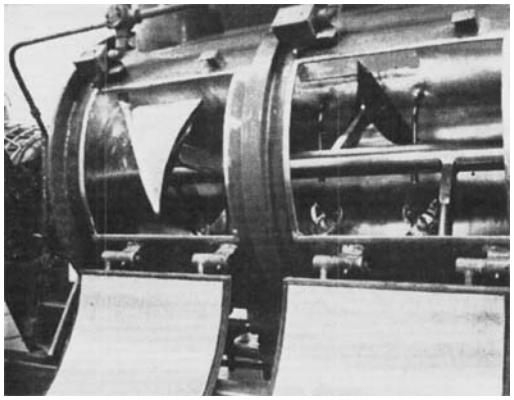

Fig. 4—Littleford-Lodige mixer, model FKM600D, showing plows, chopper heads, and liquid input tubes.

stalled at the end of one liquid input tube extending into the mixing chamber.

The mixer was charged with 300 kg. of the same effervescent formulation which was used in the preceding trials. Mixing was initiated with both chopper units operating. Plow speed was adjusted to 110 r.p.m. and the drive-motor current demand was recorded at regular intervals. The temperature in the mixer was also recorded throughout the run (Figs. 5 and 6). As noted in experiments using the FM100D Lodige mixer, the temperature and time relationship was relatively linear. The fusion reaction began after the material had mixed for 10 min. as indicated by the increase in the current required.

The granulation developed the desired consistency after 13 min., at which time the temperature was 42° (109°F.) and the drive-motor current demand had reached 32 amp. The granulation was then discharged from the mixer, spread on trays, allowed to cool to room temperature to slow the fusion reaction, and dried.

DISCUSSION

These data illustrate an interesting difference in the power requirement between the FM100D and FKM600D Lodige mixers during the granulating cycle. The current demand of the smaller unit was constant until the fusion reaction began to take place. With the large mixer, however, current demand at the beginning of the the cycle was high, then dropped gradually until the fusion reaction caused a return to the initial level. No attempt has been made to investigate this observation, but it is surmised that changes in interparticular friction due to attrition, increasing mix homogeneity, and free moisture level may be involved.

The most critical decision to be made during the preparation of effervescent granules by the fusion method, regardless of the system being utilized, is the determination of the point at which to terminate the massing reaction. Human judgment must still be relied upon, but operator experience is less important when the Lodige mixer is used for the processing. The onset and extent of the reaction can be monitored by observation of the variation in current required by the mixer. A terminal amperage which yields granulations having the desired characteristics can be established using information from a number of trial batches. This value, however, will be a valid indication of the reaction state of the granulation only if other factors which affect drive-motor current demand are held constant. These factors include plow speed, batch size, and product composition.

The terminal temperature and the total mix time have been observed to vary significantly from batch to batch. Therefore, these were not considered to be dependable indicators of the extent of the fusion reaction.

Empirical decisions can still be made by the operator if he questions the condition of a particular batch. He may discharge and examine small quantities of material from the mixer while it continues in operation.

The Lodige mixer combines into one operation the blending of raw materials and the heating to initiate the fusion reaction. Wet screening of the mass is often eliminated. Since the mixer is equally suited to the preparation of standard wet granulations and dry blends, it need not remain idle when production of effervescent products is not underway. Although the method described in this paper is strictly a batch operation, effervescent formulations have been

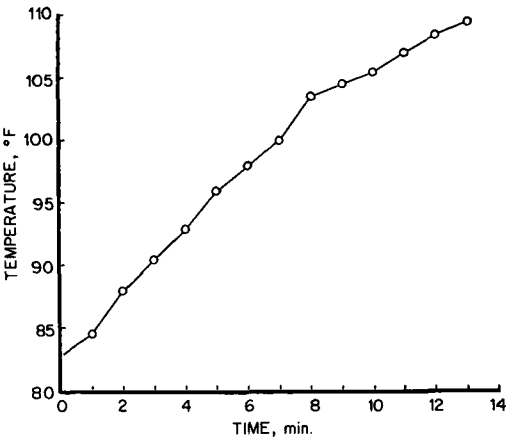

Fig. 5—Temperature of the mixer contents during processing; FKM600D Littleford-Lodige mixer.

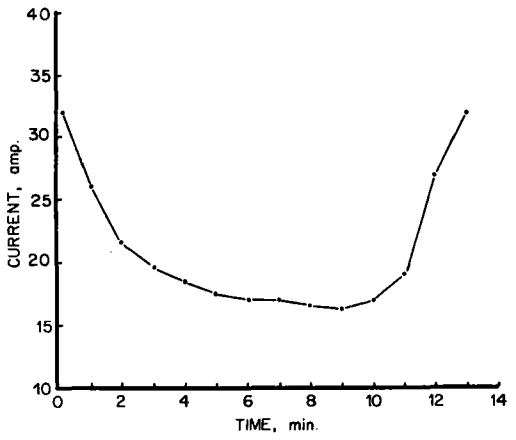

Fig. 6—Drive motor current demand during processing; FKM600D Littleford-Lodige mixer.

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.

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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.