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CRITICAL MANUFACTURING PARAMETERS INFLUENCING DISSOLUTION

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This brief review of selected work from the recent literature illustrates the critical influence processing conditions can have on the performance of pharmaceutical products. Topics covered include capsules, granulation and compression, inert matrices, and extrusion/spheronization.

Key Words: Manufacturing parameters; Processing conditions; Dissolution

THE EFFECTS OF processing conditions on the performance of pharmaceutical products are well known to regulatory authorities, industrial technologists, and academic researchers. The influence of processing on disintegration times of tablets was extensively investigated several decades ago. The recognition that manufacturing parameters can affect dissolution from conventional solid dosage forms and release rate from controlled release products prompted extensive studies in industry and academia. Furthermore, regulatory authorities are paying close attention to processing conditions and require specific description of the manufacturing steps, as well as identification of all critical variables that may affect performance. The days are gone when a process could be described as "mix, dry, mill, and compress in suitable equipment under appropriate conditions."

Advances in pharmaceutical technology are, to a large extent, a result of the recognition that manufacture of a quality tablet or capsule product in a reproducible manner requires a thorough knowledge of the formulation, as well as the processing conditions. This paper will focus on processing rather than formulation effects. Of course, one realizes that the two are very closely linked. Those in industrial research and development (R&D) know well, sometimes from painful experiences, that changes in the formulation can profoundly affect processing conditions, and vice versa.

There are very few "absolute" rules in the area of pharmaceutical processing. Certain parameters are critical for a given formulation or manufacturing condition, but not necessarily for others. This paper will provide a brief review of selected papers, mainly from the recent literature.

CAPSULES

Workers at Bristol-Myers (1) published an excellent investigation of the processing conditions employed in the manufacture of cefadroxil capsules. As frequently happens, the study was prompted by problems encoun-

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tered during scale-up of the manufacturing process. During development, blending of the composition with 1% magnesium stearate for periods between five and 40 minutes prior to encapsulation on a Zanasi LZ-64 machine was found satisfactory. When the process was tested in full-scale production on a Hofliger-Karg Model GFK-1500 (H&K) encapsulator, however, a severe loss of dissolution rate was noted (Figure 1). A systematic investigation was begun. It was established that manually encapsulated blends had dissolution rates similar to the capsules made on the Zanasi. Therefore, the effect of the H&K feeding mechanism was studied further. It turned out that the powder tamping process (Figure 2) was exposing some of the powder to repeated shear that led to a more complete coating of the drug particles with Mg stearate. Simulation of the powder shearing showed that under the experimental conditions a 30-second shear exposure would best reproduce the dissolution results. With the conditions thus established, the amounts of Mg stearate were then varied. Without shear, the amount of Mg stearate was not critical

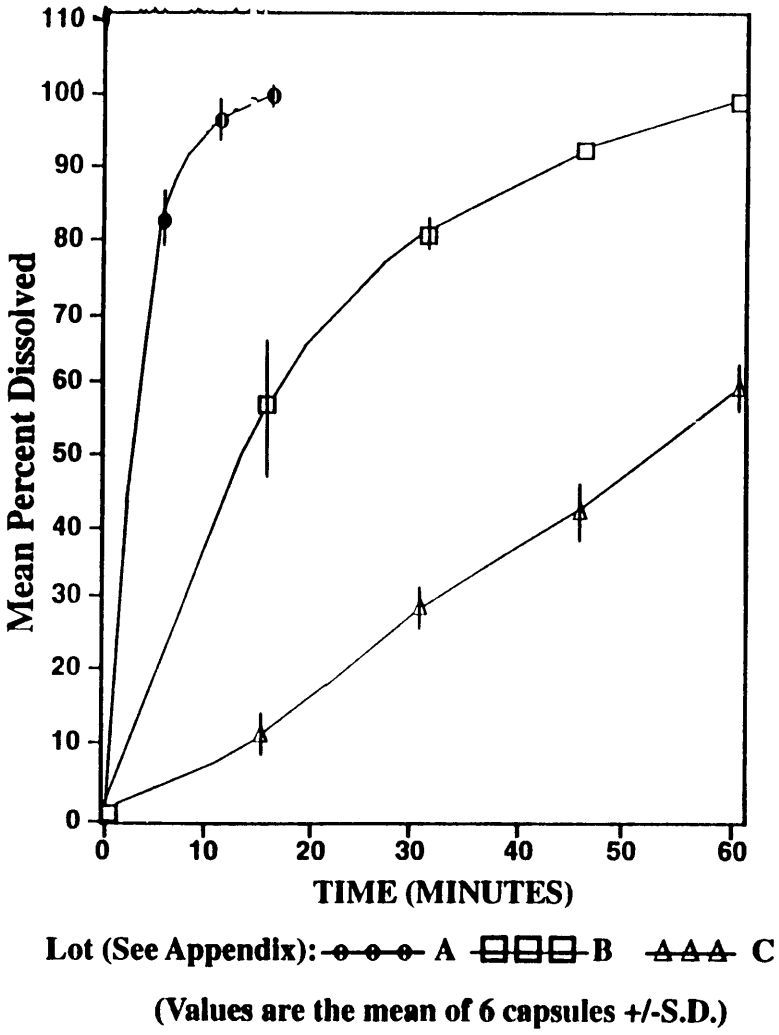

FIGURE 1. Effect of blending time and encapsulation mechanism on capsule dissolution (From Ullah I, Wiley GJ, Agharkar SN [1]; reprinted with permission of Marcel Dekker, Inc.).

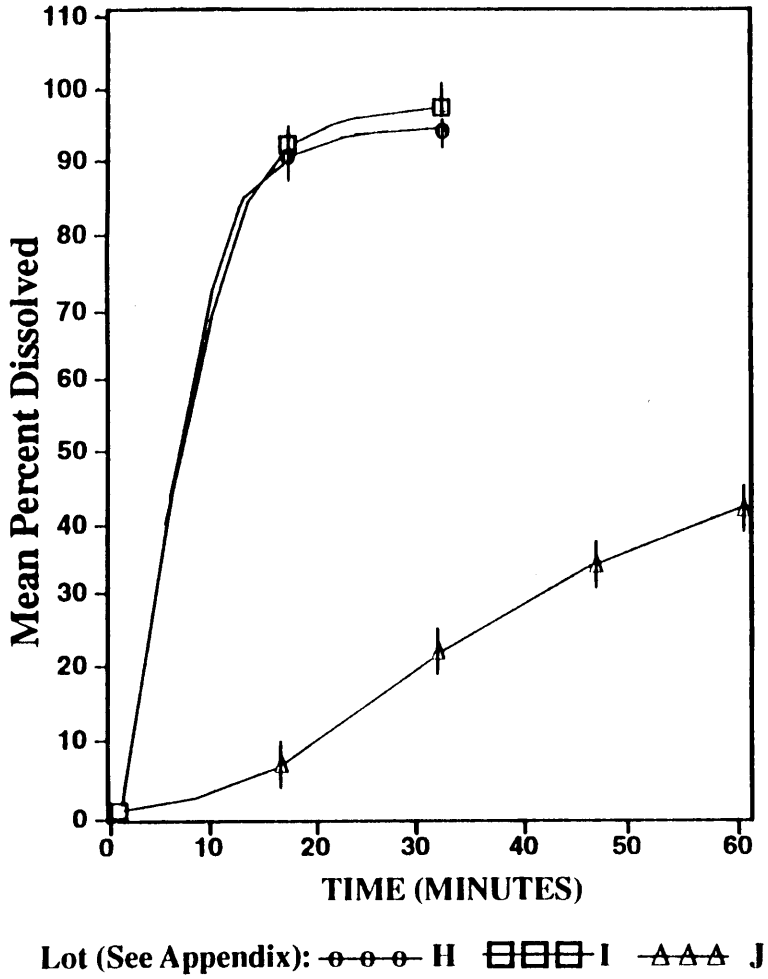

FIGURE 2. Effect of auger feeding and powder tamping on the dissolution of capsules prepared by encapsulation of an H&K machine (From Ullah I, Wiley GJ, Agharkar SN, [1]; reprinted with permission of Marcel Dekker, Inc.).

between 0.3 and 1%. With shear, however, it had to be kept below 0.6% to obtain satisfactory dissolution (Figure 3). The resulting process was successfully scaled up to batch sizes of 1100 kg.

GRANULATION AND COMPRESSION

The effect of tablet hardness on dissolution has been amply demonstrated in the literature but one can also find more complex situations. Chowhan et al. (2) prepared tablets from an experimental drug using a constant amount of microcrystalline cellulose but varying its intra- and extra-granular proportions (Figure 4). In general, dissolution decreased with increasing tablet crushing strength. When the cellulose was mostly intragranular, however, the decrease was more sensitive to the amount of residual moisture.

In a study of Naproxen tablets, Gordon (3) developed contour plots using the amount of granulating water, residual moisture content, and tablet hardness as independent variables. Hardness had no significant effect. In general, less granulating water yielded

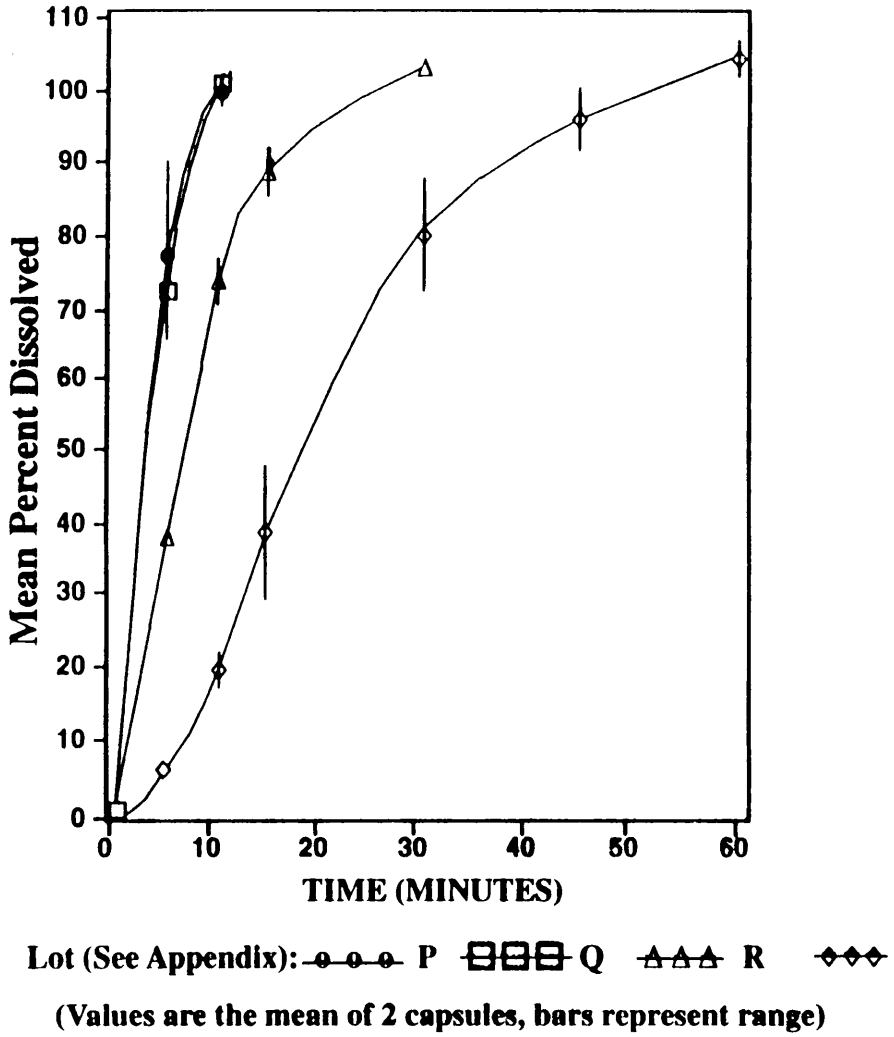

FIGURE 3. Effects of different experimental 30-second shearing on dissolution of capsule formulations containing different levels of magnesium stearate (From Ullah I, Wiley GJ, Agharkar SN [1]; reprinted with permission of Marcel Dekker, Inc.).

smaller granules resulting in faster dissolution and there was a strong interaction between the amount of granulating water and residual moisture with respect to dissolution (Figures 5, 6, and 7).

Wu and coworkers (4) were interested in the effect the solubility of drugs in the granulating liquid may have on dissolution. Zindotrine was granulated with constant volumes of fluid consisting of variable proportions of water and ethanol. Fastest dissolution was seen with tablets made with a 50/50 ratio (Figure 8). Solubility of Zindotrine is maximal in a 60% ethanol mixture. The effects are complex because the drug, partially dissolved in the granulating liquid, precipitates as finer particles upon drying. In addition, the lactose used in the formulation also has variable solubility in the granulating fluids. The processing factors may affect granule porosity.

Ertel et al. (5) studied the granulation of a sucrose/starch-based formulation containing 2% of the water-soluble Dyphylline. Bulk density of the granules reached a maximum value in 3–5 minutes depending on batch

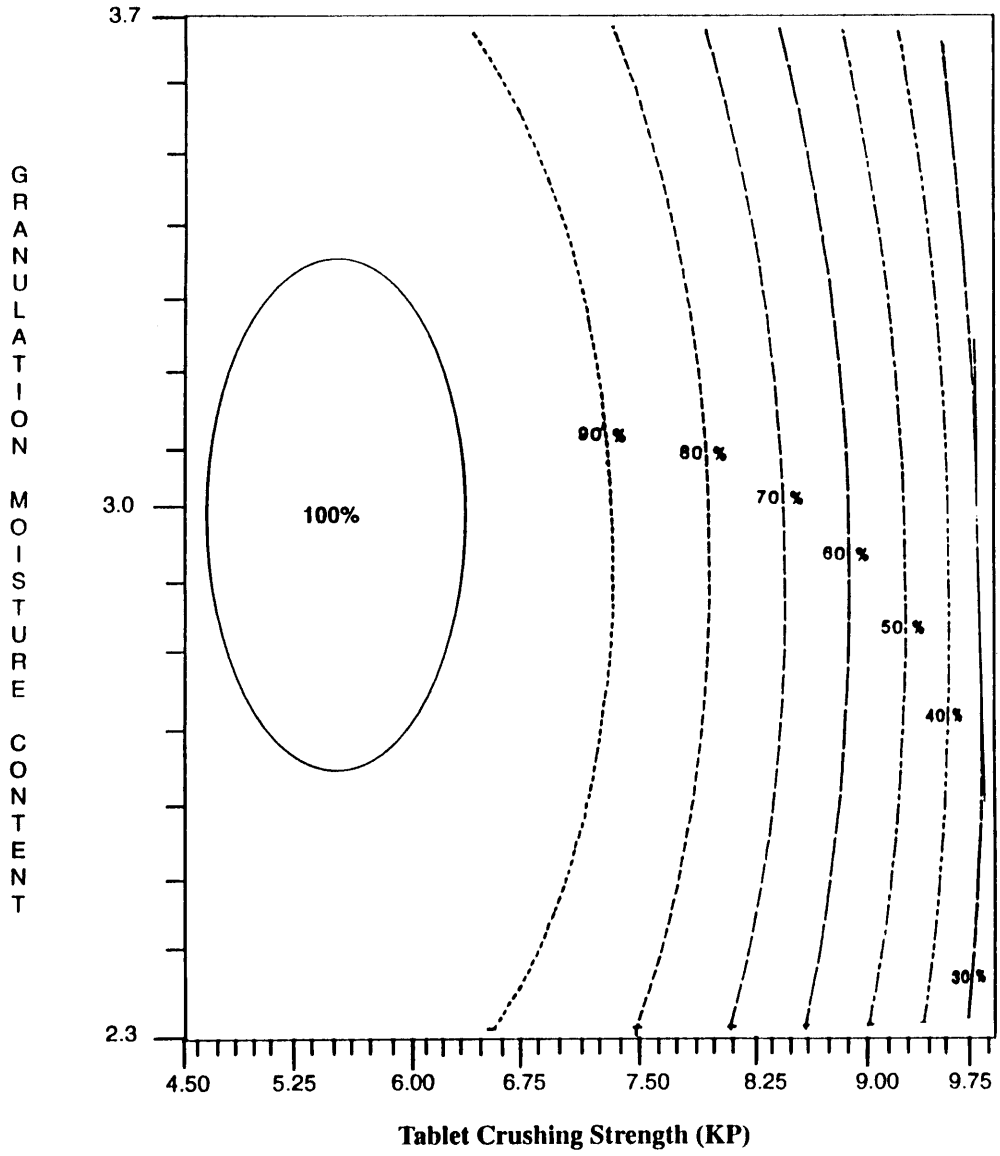

FIGURE 4. Contour plots of *in vitro* dissolution. The percentage of intragranular microcrystalline cellulose was 50% and the granulation process used 36.5% water. (From Chowhan ZT, Amaro AA [2]; reprinted with permission of Marcel Dekker, Inc.).

size and mixer type. Pore volumes reached a minimum after 8–10 minutes. Similarly, dissolution rate attained a minimum after 5–8 minutes. Tablets compressed from the granules also had a dissolution minimum (Figure 9).

Dissolution of Naproxen sodium salt tablets is fastest when they are made by direct compression. When wet granulation is employed, an exothermic reaction occurs (6), apparently involving hydration of the drug. The resulting hydrate form dissolves more slowly (Figure 10). The more granulating water is used, the more pronounced this effect becomes. Similarly, longer mixing times may cause more hydrate formation, leading to a slowdown in dissolution.

In an earlier study, Chowhan et al. (7)

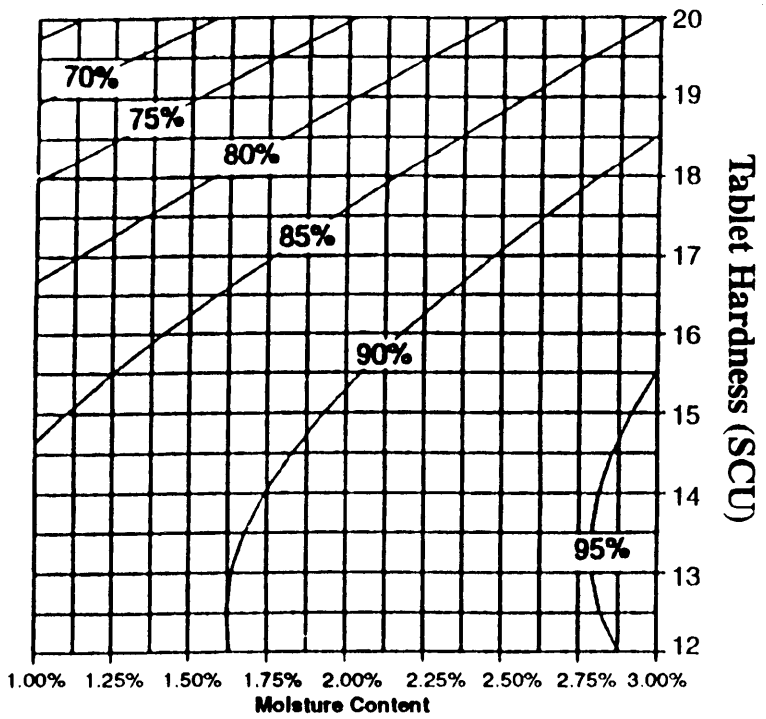

FIGURE 5. Contour surface plot for tablet dissolution with 14.0% granulating solvent (From Gordon MS [3]; reprinted with permission of Marcel Dekker, Inc.).

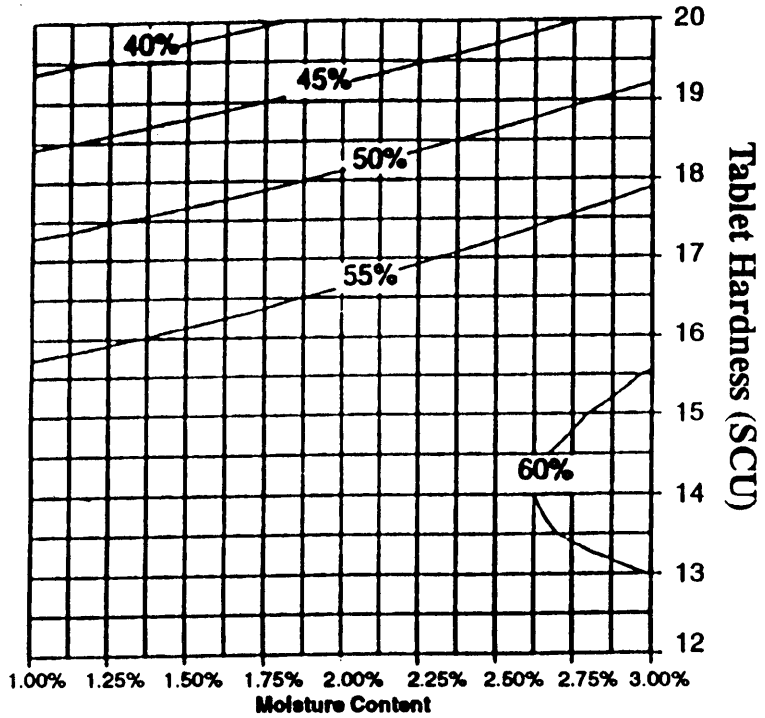

FIGURE 6. Contour surface plot for tablet dissolution with 14.875% granulating solvent (From Gordon MS [3]; reprinted with permission of Marcel Dekker, Inc.).

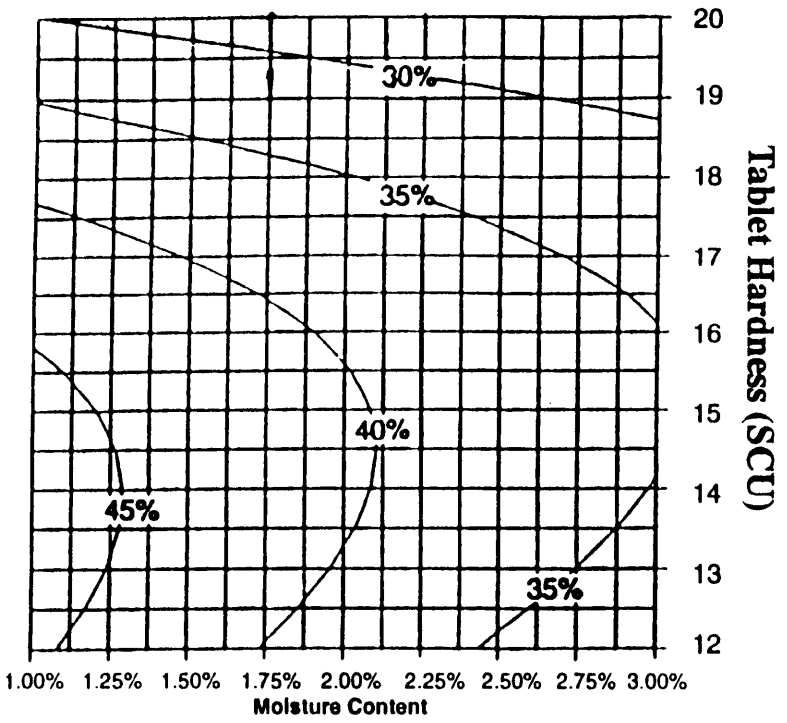

FIGURE 7. Contour surface plot for tablet dissolution with 15.75% granulating solvent (From Gordon MS [3]; reprinted with permission of Marcel Dekker, Inc.).

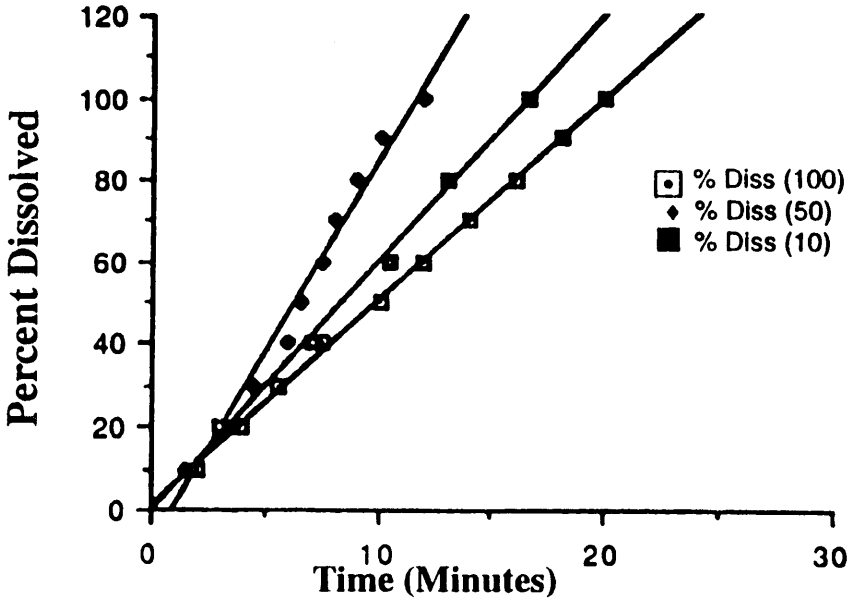

FIGURE 8. Dissolution profiles in 0.1 N HCl of tablets made with varying granulation liquids. Water and 20% ethanol are not shown to avoid graphical clutter (From Wu P, et al. [4]; reprinted with permission of Marcel Dekker, Inc.).

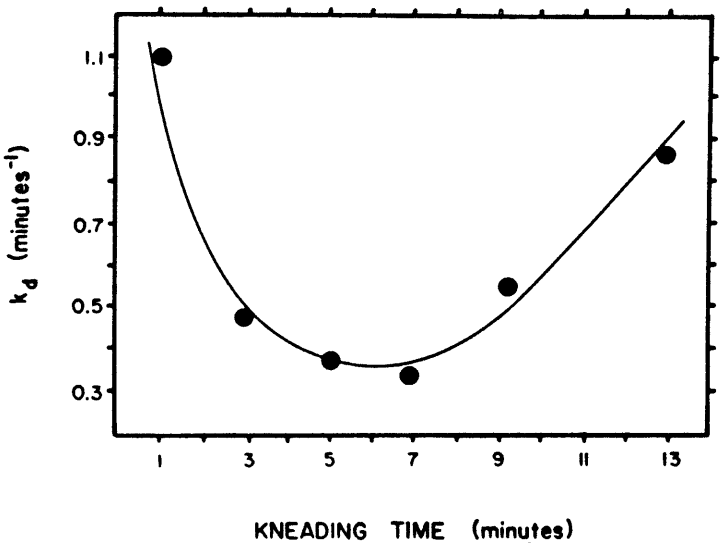

FIGURE 9. Plot of the dissolution rate of Dyphylline from tablets versus the kneading time used to prepare the granules from which the tablets were compressed. Testing was performed using a paddle rotation speed of 50 rpm (From Ertel KD, et al. [5]; reprinted with permission of Marcel Dekker, Inc.).

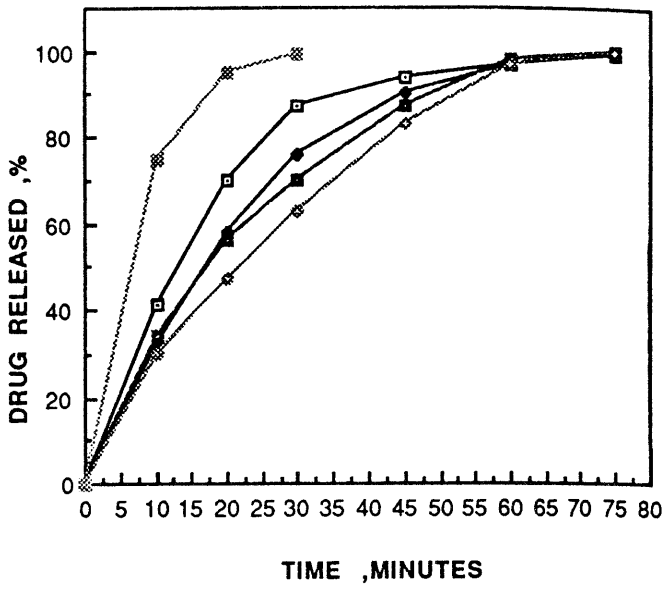

FIGURE 10. Dissolution profile of Naproxen sodium tablets. Prepared using different amount of water, ❍ dry blending, -⊡- 110 g water, -●- 125g water, -□- 150g water, and -❍- 175g water (From Bansal P, et al. [6]; reprinted with permission of Marcel Dekker, Inc.).

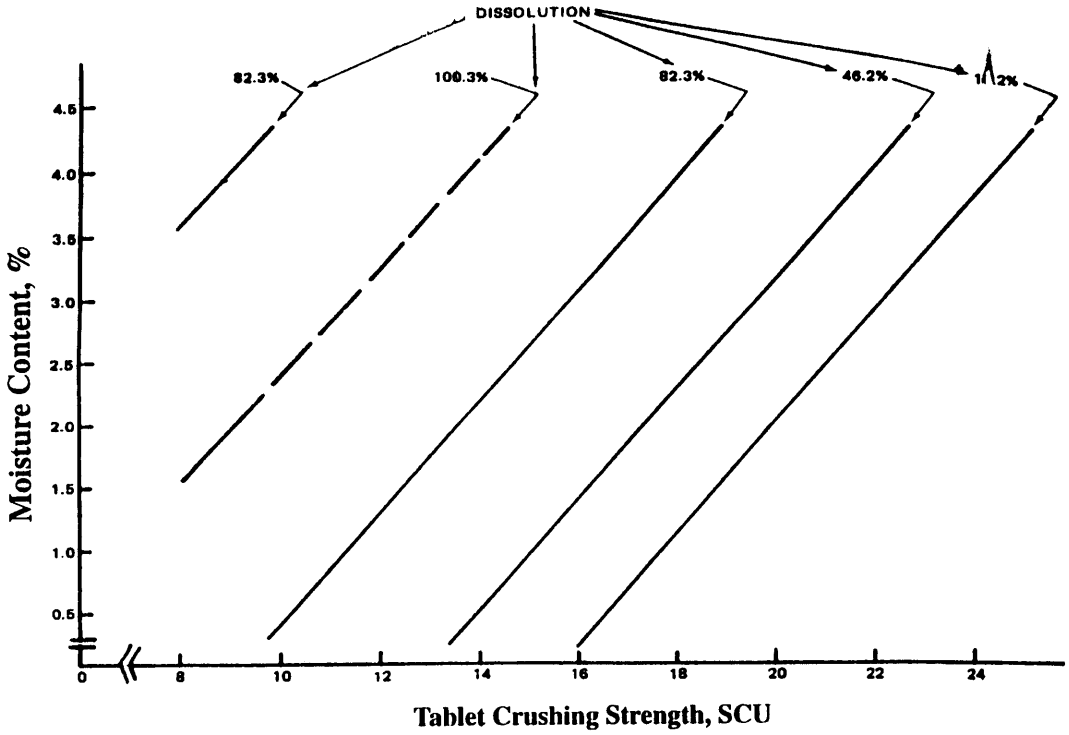

FIGURE 11. Response surface contour plots of a two-variable system, tablet crushing strength, and granulation moisture content and a response variable dissolution (at 10 minutes) (From Chowhan ZT, et al. [7]; reprinted with permission of the American Pharmaceutical Association).

developed an interesting contour plot for the dissolution behavior of ticlopidine as a function of tablet moisture content and crushing strength (Figure 11). Above a certain hardness, higher moisture content gave faster dissolution. Below that critical point there was an optimum moisture content and its value decreased with decreasing hardness.

A number of papers discuss the advantages of spray drying of drug solutions leading to amorphous forms that can result in increased dissolution rates. Takeuchi et al. (8) sprayed an aqueous ammonia solution of tolbutamide on cores of the disintegrant pregelatinized corn starch (Figure 12). The process has the advantage that relatively high drug loading ratios can be used successfully.

Gould and Tan (9) were interested in the effects of reprocessing and recompression. They studied wet-granulated tablets of a soluble drug in a microcrystalline cellulose ma-

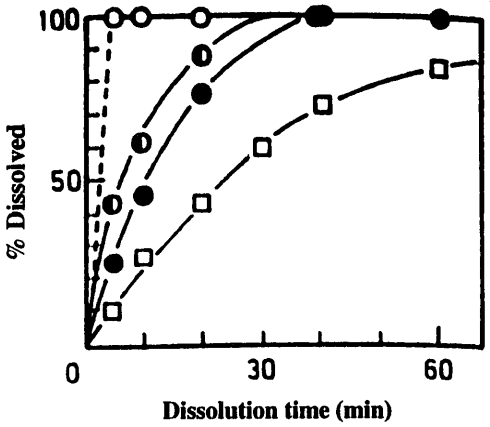

FIGURE 12. Effect of drug content on the spray-dried particle on the drug release rate from the tablet prepared from the spray-dried particles. Drugs: PCS ○, 1:1; ◐ 2:1; ● 5.1. □, powdered tolbutamide (From Takeuchi H, Handa T, Kawashima Y [8]; reprinted with permission of the Royal Pharmaceutical Society of London).

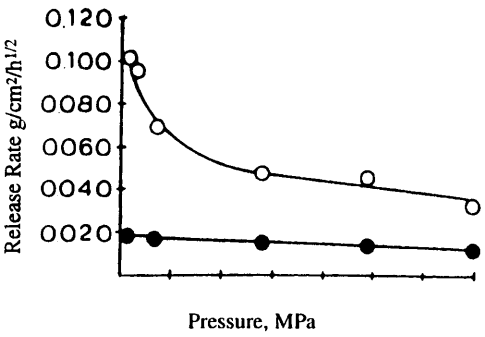

FIGURE 13. Effect of applied pressure on release flux from matrixes prepared by (○) compression of a physical mixture and (●) the melt process (From Foster TP, Parrott EL [10]; reprinted with permission of Marcel Dekker, Inc.).

trix. Recompression resulted in reduced dissolution rate, in concert with prolonged disintegration time. When one of the modern "super" disintegrants, for example, Explotab, Ac-Di-Sol, or Polyphasdone XL, was used extragranularly, however, recompression led to faster dissolution. Apparently, remilling and the resulting better overall dispersion overcame the influence of slower disintegration. Explotab was also effective intragranularly.

INERT MATRICES

Foster and Parrott (10) prepared Ephedrine and Procaine tablets in a matrix of hydrogenated castor oil. In general, release was faster when the ingredients were compressed as a simple physical mixture than when they were melted and cooled. Release rates for both kinds of tablets were slower at higher compression pressures but the rate change was more sensitive to pressure changes for the physical mixture process (Figure 13). Apparently, the higher porosity resulting from the physical mixture process was affected to a larger extent.

Researchers at the University of Belfast (11) studied ibuprofen microspheres prepared from cetostearyl alcohol melt-water emulsions. Cooling times from 65 degrees C to room temperature were varied between two and 100 minutes. Significant effects on average particle size and release rate were noted (Figure 14). Granules made by faster cooling were more porous and had a less smooth surface as seen by scanning electron microscopy.

Down et al. (12) found that enteric coating of tablets may contain microscopic holes in the area of the engravings and the holes can profoundly affect dissolution (Figure 15). Acetylsalicylic acid tablets were prepared with and without engravings and coated with a cellulose acetate phthalate/polyvinyl acetate phthalate enteric coat. The authors thought that during the coating process air bubbles may accumulate in the area around the engravings as they are partially protected from tablet-to-tablet abrasion. The bubbles then collapse during drying, giving rise to pinholes. During the first part of the dissolution test for enteric-coated tablets, performed in acid, some liquid may have migrated into the cores causing the disintegrant to swell and lose its functionality. Subsequently, in the neutral buffer, disintegration was slow and dissolution failed the United States Pharmacopeia (USP) release test. Dissolution was not reduced when plain-faced tablets were tested or when the acid part of the test was omitted.

Li and Peck (13) studied the processing conditions for coating Potassium chloride tablets with an aqueous polyethylene glycol-silicone elastomer mixture. The cores were coated in a side-vented coating pan or in a Wurster-type fluid bed column. In general, the column provided faster release rates than the pan. Apparently, there was less tablet-to-tablet contact and less shearing effect in the column resulting in a more porous coat. Processing conditions generating a more porous coat, for example, faster spray rate, lower temperature, or more concentrated coating mixture also provided faster release rates.

EXTRUSION/SPHERONIZATION

Zhang and coworkers (14) at the Philadelphia College of Pharmacy and Science made acetaminophen beads in a coating pan and by

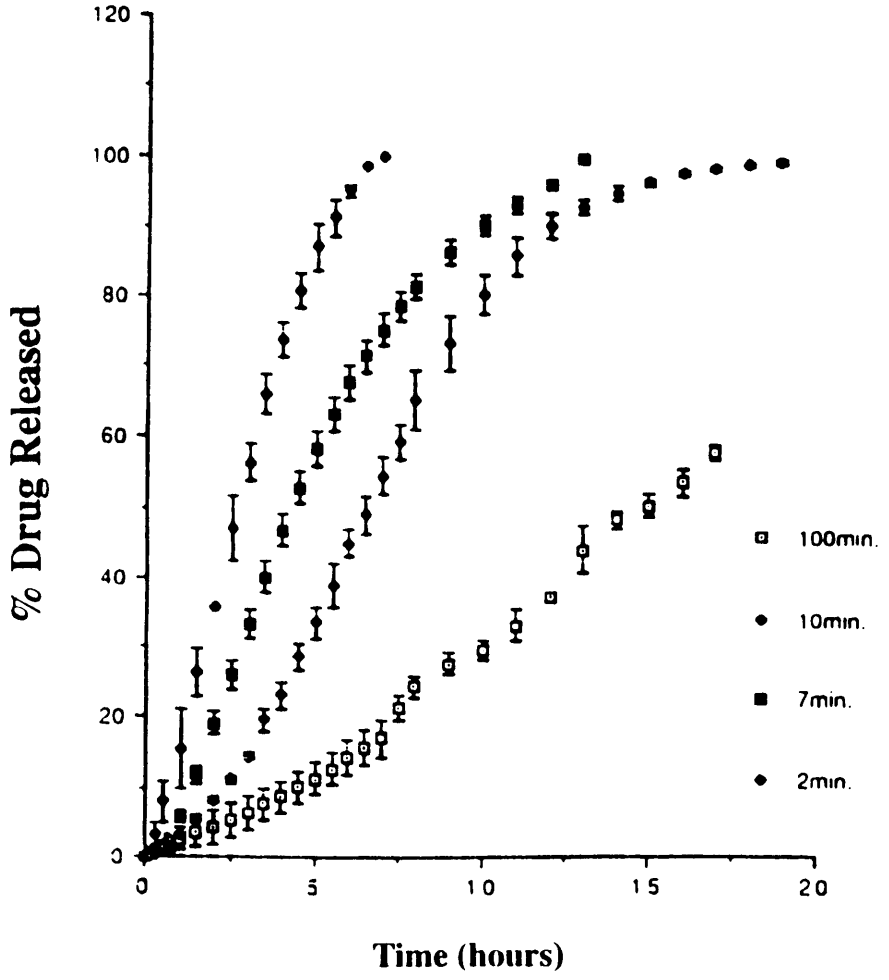

FIGURE 14. Effect of cooling time on the release of ibuprofen from cetostearyl alcohol pellets prepared at a stirring rate of 600 rpm. Error bars are ±SD of mean values (From Al-Kassas RS, Gilligan CA, Po ALW [11]; reprinted with permission of Elsevier Science BV).

marumerization. The pan-made beads disintegrated during dissolution testing and gave significantly faster dissolution. The extruded/marumerized beads held together as an inert porous matrix and the dissolution kinetics followed the square root of time relationship, indicating a mechanism of pore-diffusion control.

Subsequently (15), the beads were coated with an aqueous ethylcellulose dispersion. At identical levels of coating, pan-made beads always dissolved faster than marumerized beads. The marumerized beads held together and followed the square root of time relationship between coating levels of 2% and 10% (Figure 16). The pan-made beads disintegrated with 2% coating. At 4% coating, the tensile strength of the coating was apparently strong enough to withstand the disintegration force and the mechanism changed to pore-diffusion control (Figure 17). Heavier coating of both kinds of beads changed the mechanism to one of membrane-diffusion control, leading to a dissolution function linear with time (zero-order kinetics). The change occurred at about 12% for the extruded/maru-

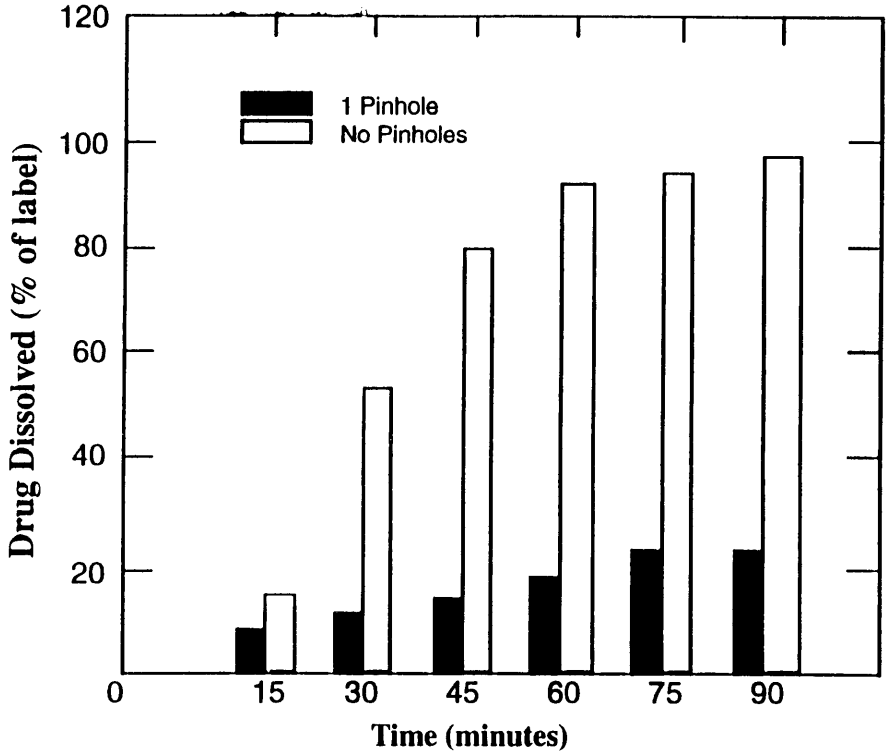

FIGURE 15. Graph showing dissolution values as a function of time, comparing tablets with a single pinhole punctured in the enteric coat and control tablets containing only natural defects in the enteric coat (From Down GRB, et al. [12]; reprinted with permission of Marcel Dekker, Inc.).

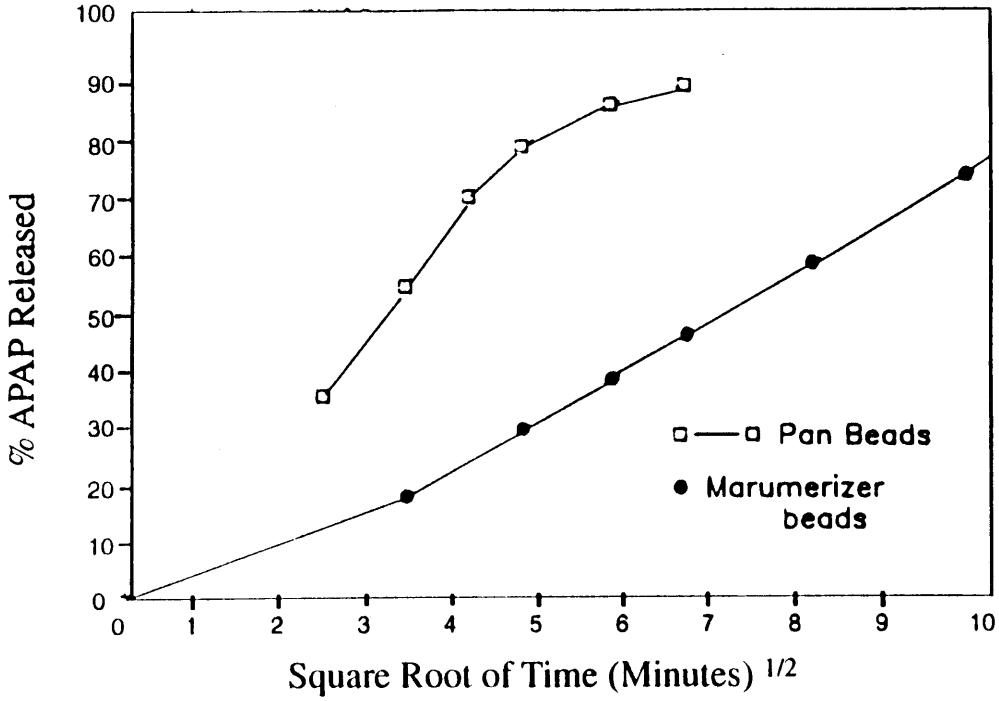

FIGURE 16. Dissolution of APAP from beads with 2% coating level of Aquacoat in terms of the square root of time model (From Zhang G, et al. [15]; reprinted with permission of Marcel Dekker, Inc.).

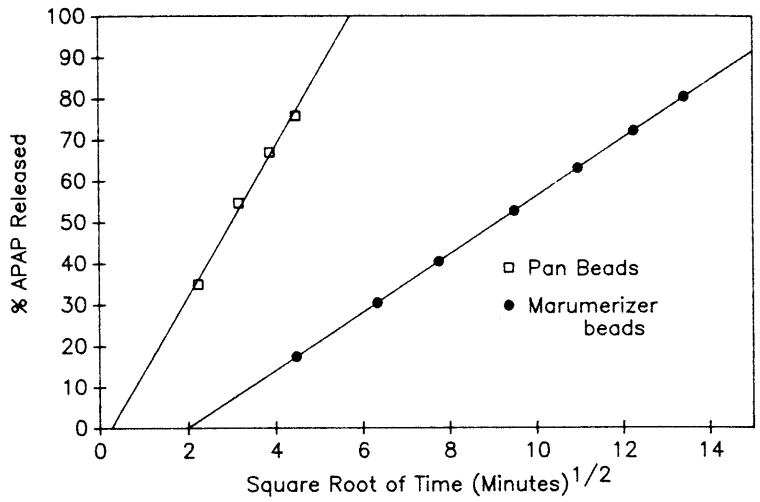

FIGURE 17. Dissolution of APAP from beads with 4% coating of Aquacoat in terms of the square root of time model (From Zhang G, et al. [15]; reprinted with permission of Marcel Dekker, Inc.).

merized beads (Figure 18) but only at 18–20% for pan-made beads (Figure 19). Calculations based on bead size and density were in line with the observed changes of dissolution mechanism.

In conclusion, this brief review of selected work from the recent literature has illustrated the critical influence processing conditions can have on the performance of pharmaceutical products.

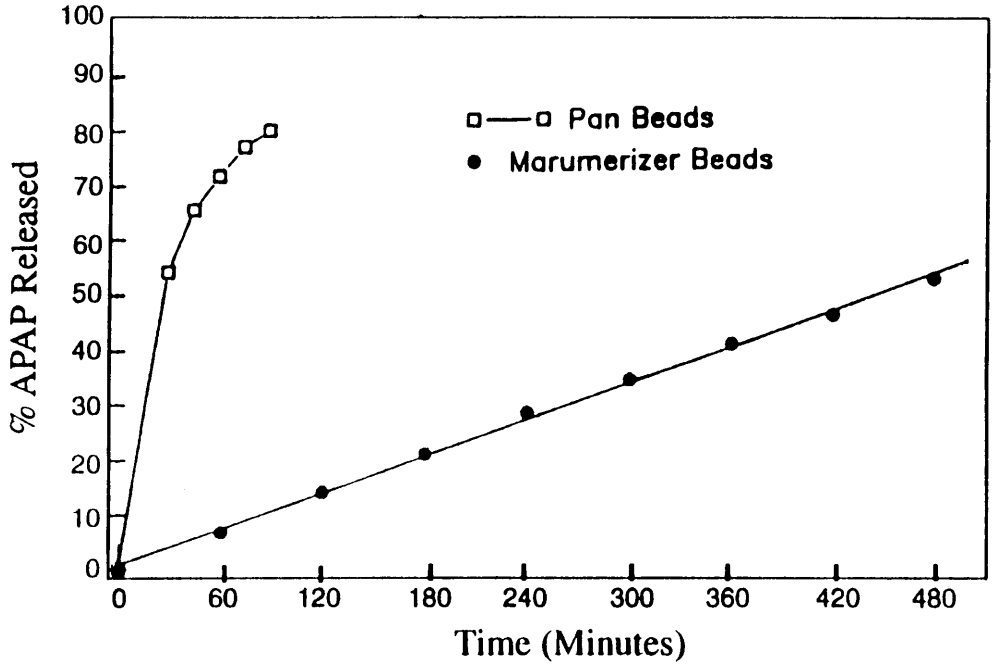

FIGURE 18. Dissolution of APAP from beads with 12% coating level of Aquacoat (From Zhang G, et al. [15]; reprinted with permission of Marcel Dekker, Inc.).

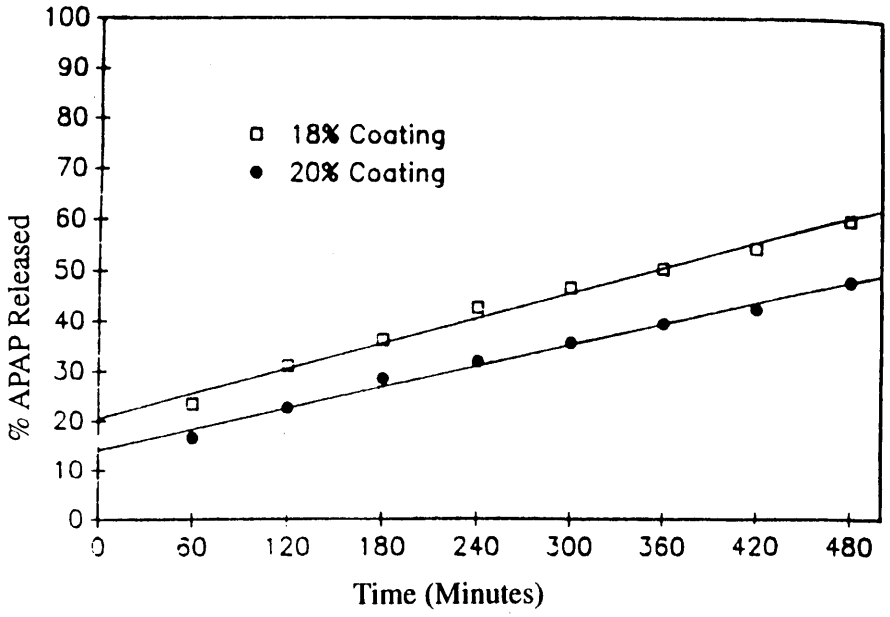

FIGURE 19. Dissolution of APAP from pan beads with the Aquacoat coating (From Zhang G, et al. [15]; reprinted with permission of Marcel Dekker, Inc.).

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