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# DEVELOPMENT OF A CLINICAL CAPSULE FORMULATION CONTAINING A MARGINALLY WATER SOLUBLE DRUG

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## ABSTRACT

A good clinical development program maximizes the clinical efficacy of a new drug product and, in addition, requires only minimal formulation changes in the transition from clinical to market image product. This study demonstrates the development design as well as the technology utilized to improve the dissolution characteristics of a marginally water soluble drug to be administered in a capsule dosage form for clinical trials. A satisfactory formulation was achieved by controlling drug particle size, selecting an appropriate diluent and incorporating a surfactant.

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## INTRODUCTION

Clinical supplies, as defined by the Pharmaceutical Manufacturers Association, "are finished dosage forms of new drug substances undergoing clinical study". A new drug substance goes through four phases of clinical testing. Phase I studies use healthy human volunteers to determine the possible drug side effects and how the body changes and eliminates the drug. The exception are those drugs which would be potentially harmful to the healthy population, such as anticancer agents or antiarrythmics. These drugs are administered to patients afflicted with the disease. If Phase I shows the drug to be safe, then Phase II commences to evaluate the efficacy of the drug in the treatment of a particular disease(s). The therapeutic dosage range and regimen are defined, additional safety data documented and more information obtained concerning the drug's effectiveness. In Phase III, extensive studies document the indications of use, safety and side effects, which are filed with the Food & Drug Administration as part of a New Drug Application. These studies involve hundreds of patients. After the product has been approved by the FDA for marketing, then Phase IV studies are conducted to substantiate any additional claims for therapeutic efficacy of drug, new dosage forms or new routes of administration.

The first step in developing a clinical formulation is to conduct a preformulation study on the drug itself. The testing results provide information on the physical and chemical properties of drug which include: physical description, microscopic examination, solubility, particle size distribution, dissolution, partition coefficient and dissociation constant (pKa), polymorphism, stability and compatibility with excipients (1). The preformulation report also provides short term stability data on a prototype capsule formula under accelerated storage conditions. This formula, used to provide Phase I clinical supplies, usually consists of drug, diluent and lubricant. Additional excipients may be required to improve drug dissolution. The extent of absorption and the resultant therapeutic effectiveness of drugs

generally depend upon the extent and rate which the drug dissolves in body fluids. If the drug is poorly soluble or hydrophobic, then it is essential to formulate a clinical product which will maximize the dissolution rate of drug. The methodology available to improve the release rate of drugs is well documented (2-4). They include particle size reduction, incorporation of water soluble excipients and wetting agents, dispersions and formation of polymorphs, and salts or complexes of the poorly soluble drug. Initial clinical testing of orally administered investigational drugs is most frequently done in hard gelatin capsules due to limited quantities of bulk drug available for experimental evaluation, ease of formulating and simplified blinding techniques. Due to the manufacture of small size batches between 100-1,000 capsules, Phase I clinical formulas are encapsulated either manually or on non-automated equipment such as a Bonapace [1].

Phase II studies utilize a double blind protocol requiring all capsules to look the same so that the patient and investigator cannot distinguish between active and placebo. Blinding of capsules is usually accomplished by making adjustments in the concentration of excipients (if there is more than one strength) and using the same size, color and shape capsule for the active and placebo. The batch sizes, at approximately 5,000-10,000 capsules, are usually encapsulated on an automated capsule filling machine such as the H&K 120 [2]. Formula or processing changes in the product used in Phase I may be required for successful encapsulation. If powder flow is a problem, then it can be improved by densification. This may be accomplished by either (1) adding a binder solution to manufacture a wet granulation and achieve a coarser particle size distribution or (2) dry compaction using a Chilsonator [3]. Dry compaction is the method of choice when the drug is unstable in water/alcohol or is adversely effected by prolonged drying at elevated temperatures.

The batch size of the requests for Phase III clinical supplies increases to 50,000-500,000 capsules, and usually requires high

speed equipment. In addition, a reference commercial product is included to evaluate comparative efficacy and justify claims. In encapsulating the reference product, the first choice is to put the capsule or tablet, intact, inside the empty capsule (with inert excipients as required) so as not to alter its bioavailability. An alternate method is to reduce the capsule or tablet to powder if its size precludes an adequate fit inside the capsule; however, additional testing is necessary to show bioequivalency. It is during this phase that the transition from clinical to market image formulation usually occurs. Therefore, it is important in clinical development to formulate a product which requires minimal formulation changes in the transition from clinical to market image product. Sometimes this transition may be significant due to the market image considerations. Examples include changing a capsule to a tablet to support dosage or bioavailability requirements, altering the tablet shape or design and increasing the tablet or capsule fill weight. In the first example, different formulation and manufacturing parameters may be required to achieve good compression characteristics. Any changes in excipients, such as binder, diluent or lubricant may effect the bioavailability of drug; therefore, bioequivalency must be determined. In the second case, a different tablet shape may alter the dissolution or compressibility profile, requiring adjustments in the formula or manufacturing procedure. Increasing the fill weight to change the drug-excipient ratio may necessitate a different size capsule or tablet. Different processing equipment, mixing time and batch sizes used in the scale-up from Phase II to III may also effect the dissolution rate of drug and subsequent bioavailability. Therefore, the necessity of scrutinizing formulation procedures for clinical products is of utmost importance.

This study describes the technology used to improve the dissolution characteristics of a poorly water soluble drug incorporated into a capsule formulation for clinical trials. This was achieved by controlling both formula and processing variables; specifying drug particle size, selecting the appropriate excipient and incorporating a surfactant.

## EXPERIMENTAL

### Materials

The drug lot used in this study was designated as A[4], a crystalline powder which is slightly soluble in water (0.8 mg/ml at 20°C). The excipients evaluated were sodium lauryl sulfate NF[5], microcrystalline cellulose NF[6], hydrous lactose NF[7] and hydrogenated vegetable oil NF[8].

### Drug Particle Size

The initial particle size of drug was 5 - 500 microns. Particle size reduction was evaluated by (1) passing drug A through a Fitzmill[9] using three different screen sizes at high speed (6400 rpm), impact forward and (2) micronizing the drug through a Gem - T Mill[10], 80 - 100 psig, at a feed rate of 100 g/hr.

### Microscopy

Photomicrographs of milled and micronized drug were obtained using a scanning electron microscope[11] to determine the relationship between drug particle size and dissolution. Each sample was dispersed onto tape which was mounted onto an aluminum stub. The entire sample was coated with approximately 125 angstrom of gold. Magnifications of 100 and 300x at 15kv were obtained for all samples; however, for the micronized sample of very small particle size, a photomicrograph was obtained at 3000x at 15kv.

### Manufacturing Procedure

A solution of sodium lauryl sulfate in water was added to milled or micronized drug through the intensifier bar of a blender[12]. The wet powder was dried in an air oven at 45 - 50°C to a loss on drying (Cenco, 90V, 10 min) of not more than 1.5% and reduced by hand through a No. 60 screen. The diluent and lubricant (prescreened through a No. 40 screen) were added with mixing in a blender. Encapsulation was carried out on a Bonapace or PD-8[13] capsule filling machine to provide 200 mg of drug per capsule.

### Dissolution Studies

Dissolution testing of the capsules was carried out using the USP XX Dissolution Apparatus II[14]. Each capsule was placed inside a spiral wire and transferred into a glass dissolution vessel

TABLE 1

Effect Of Milling On Particle Size Of Drug A

| Process | Size Range (Microns)[a] |
|---|---|
| Unmilled Drug | 5 - 500 |
| Fitzmill | |
| 0.012" 8% open area | 3 - 100 |
| 0.020" 24% open area | 5 - 120 |
| 0.024" 24% open area | 5 - 200 |
| Micronization | 1 - 15 |

[a]Determined by Scanning Electron Microscope



containing 900 ml of distilled water. Temperature of the dissolution medium was 37 ± 0.2°C. Paddle speed was 50 rpm unless otherwise indicated. At appropriate time intervals, samples were withdrawn and the absorbance measured spectrophotometrically to determine the percent of drug dissolved.

## RESULTS AND DISCUSSION

### Drug Particle Size

Table I shows the effect of the Fitzmill and Gem - T Mill on the particle size of drug A. Photomicrographs of the unmilled and milled/micronized samples are shown in Figures 1-5. In the Fitzmill evaluation, drug passed through a 0.012" 8% open area round hole screen gave the smallest average particle size and narrowest range. Satisfactory dissolution was achieved when 200 mg of the fitzmilled drug (3-100 microns) was formulated into a capsule (Figure 6). This study showed that particle size reduction resulted in increased drug surface area and in a faster dissolution rate. However, results of validation studies in our manufacturing facility indicated that reduction through this screen size was not

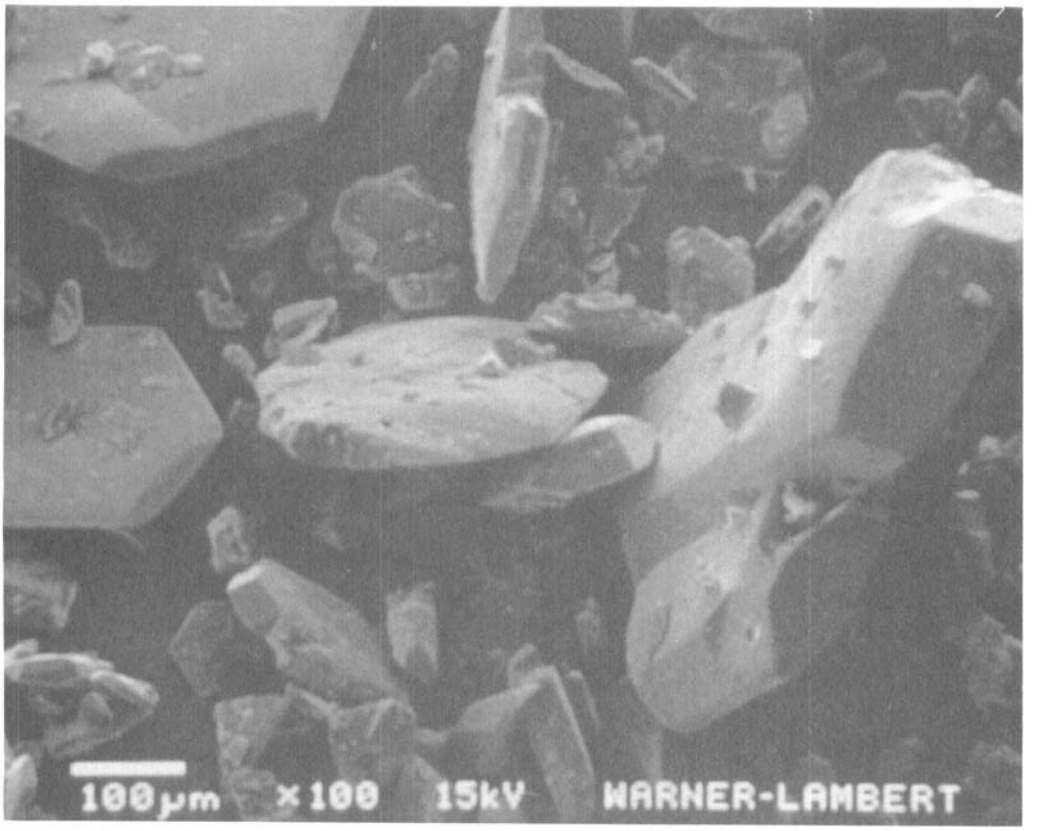


FIGURE 1
Fitzmilled drug, 5-500 microns (100x)

feasible in large scale production due to heat build up and ultimate clogging on the screen. The dissolution rate of drug with a particle size range of 5 - 120 microns (0.020" screen) was the most comparable to the drug with particles between 3 - 100 microns (Figure 6). Micronization was also evaluated because it reduces materials to a particle size within a very narrow range and tends to be more reproducible from batch to batch. The particle size of micronized drug A ranged between 1 and 15 microns. The dissolution rate of micronized drugs can actually decrease due to the greater cohesive forces, related to increased surface area, which exist

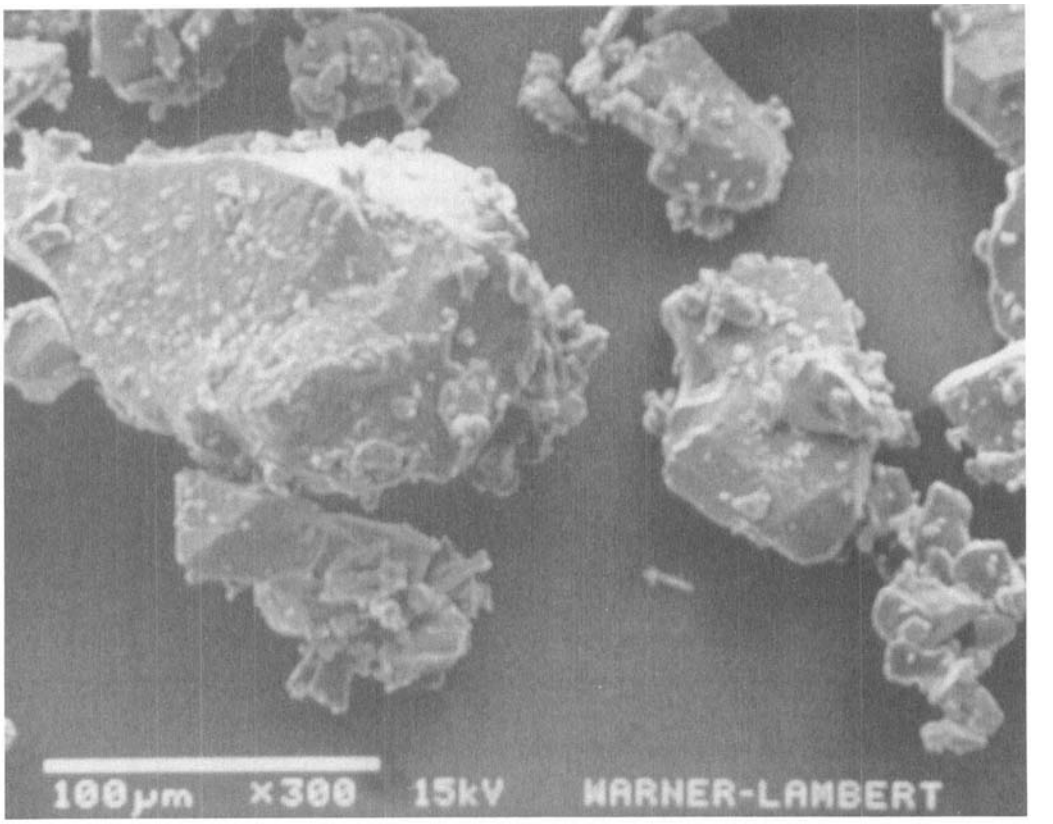


**FIGURE 2**
Fitzmilled drug, 5-200 microns (300x)

between the particles thus producing a larger effective particle size. A static charge may cause the fine drug particles to dissolve at a slower rate. Micronization of drug A produced statically bound particles; deagglomeration was achieved by incorporating a surface active agent, sodium lauryl sulfate at a level of 1% based upon drug content. The dissolution profile of micronized drug was compared to fitzmilled drug (5 - 120 microns) with both formulations containing surfactant (Figure 7). The percent of drug that dissolved at the end of 60 minutes was equivalent for both lots, but micronized drug was significantly

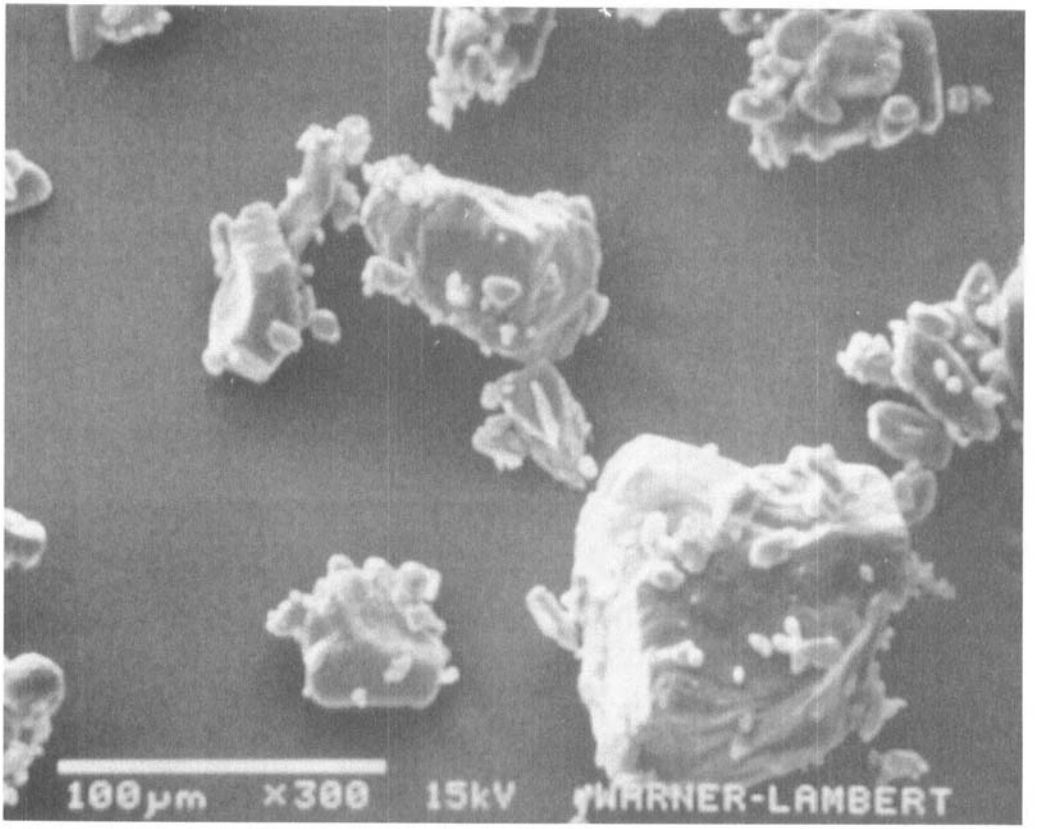


**FIGURE 3**

Fitzmilled drug, 5-120 microns (300x)

slower in the first 30 minutes. Micronization was not as effective as the Fitzmill in increasing drug dissolution. One possible explanation is that the increased cohesion of particles was not completely eliminated even with the incorporation of surfactant. The micronized drug particles required at least 30 minutes to disperse in the dissolution fluid before achieving a release rate comparable to fitzmilled material.

Diluent

Formulations A - D were manufactured to evaluate the effect of lactose, microcrystalline cellulose and various ratios of

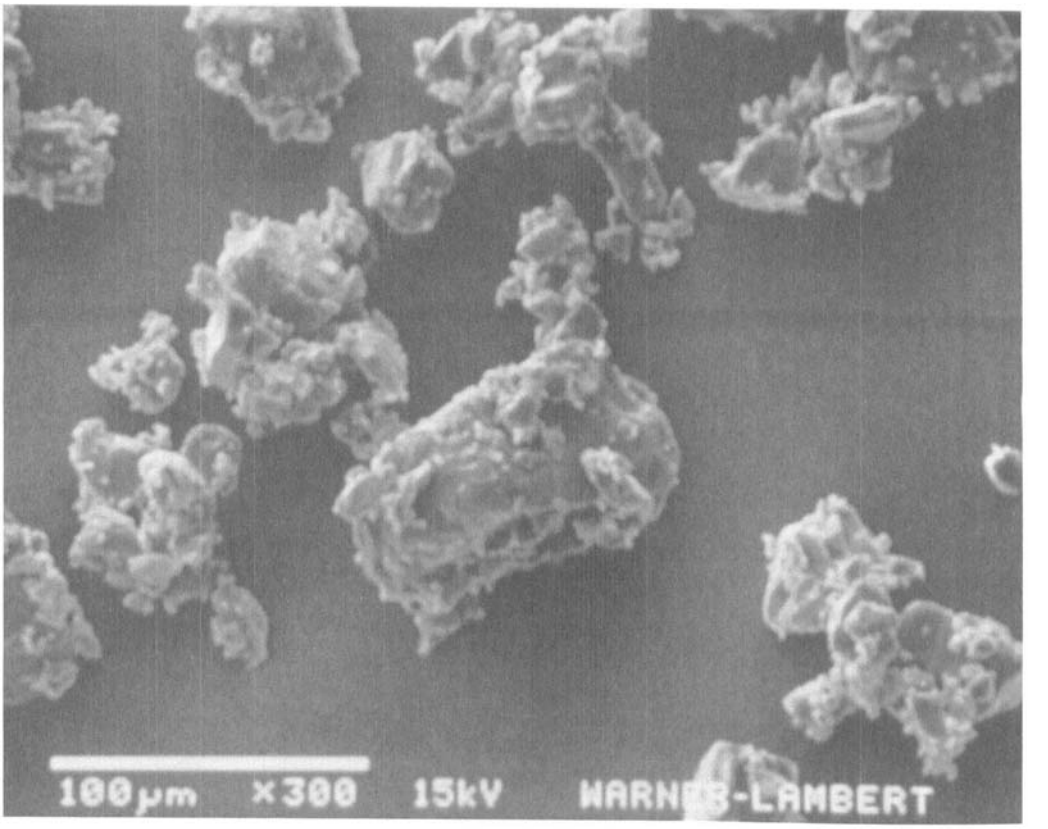


**FIGURE 4**

Fitzmilled drug, 3-100 microns (300x)

microcrystalline cellulose and lactose on the dissolution of fitzmilled drug (3 - 100 microns). The formula compositions are shown in Table II. The excipient choice in many capsule formulations containing a hydrophobic drug is usually a water soluble excipient, such as lactose. It tends to overcome the hydrophobic properties of drug by producing a more hydrophilic composition. Figure 8 shows that the drug release rate from formula A was found to be 64 and 73% at the end of 30 and 60 minutes, respectively. During dissolution testing, mounding observed at the vessel apex revealed a relatively dense settling.

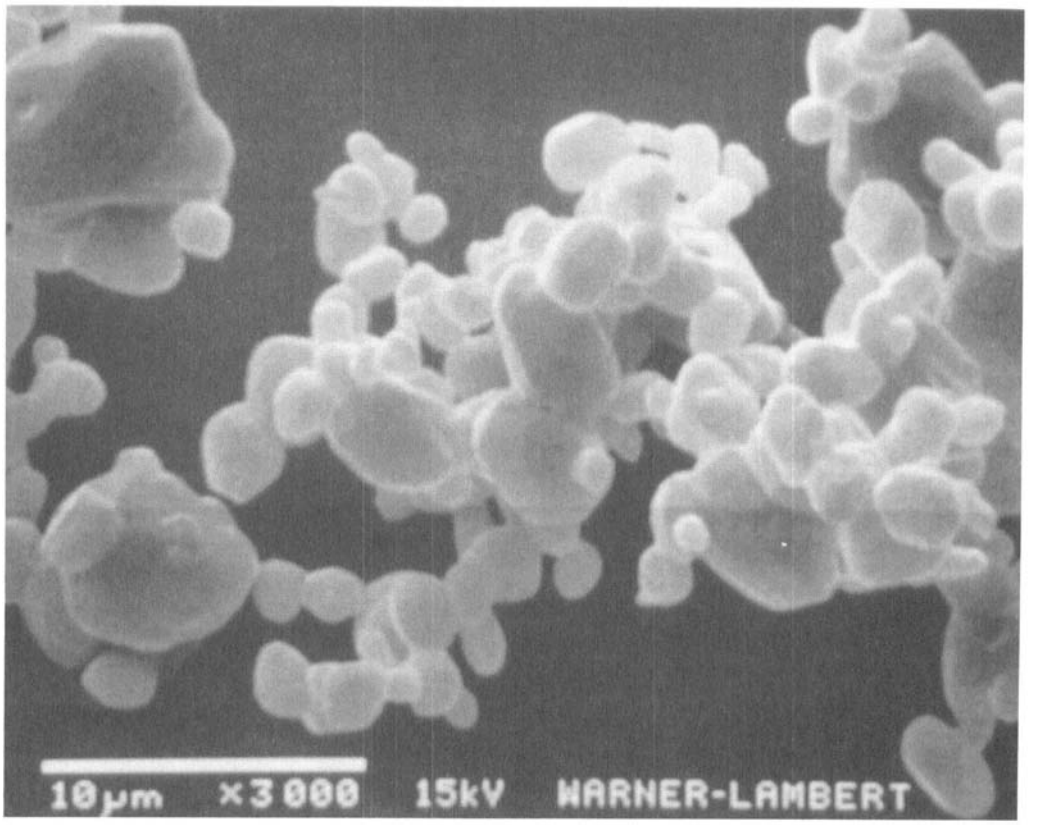


**FIGURE 5**

Micronized drug, 1 - 15 microns

This was surmised to be partially lactose which affected the solvent properties of the dissolution medium. The lactose may have entrapped the active ingredient releasing it through a diffusion mechanism and causing the drug to dissolve at a slower rate. Microcrystalline cellulose is water insoluble and its good wicking action gives it the ability to pull water into the powder bed through capillary action. Figure 8 shows that formula D containing 100% microcrystalline cellulose gave the fastest dissolution (96%) at the end of 30 minutes. There was more particle dispersion and less mounding, presumably providing for more surface contact of

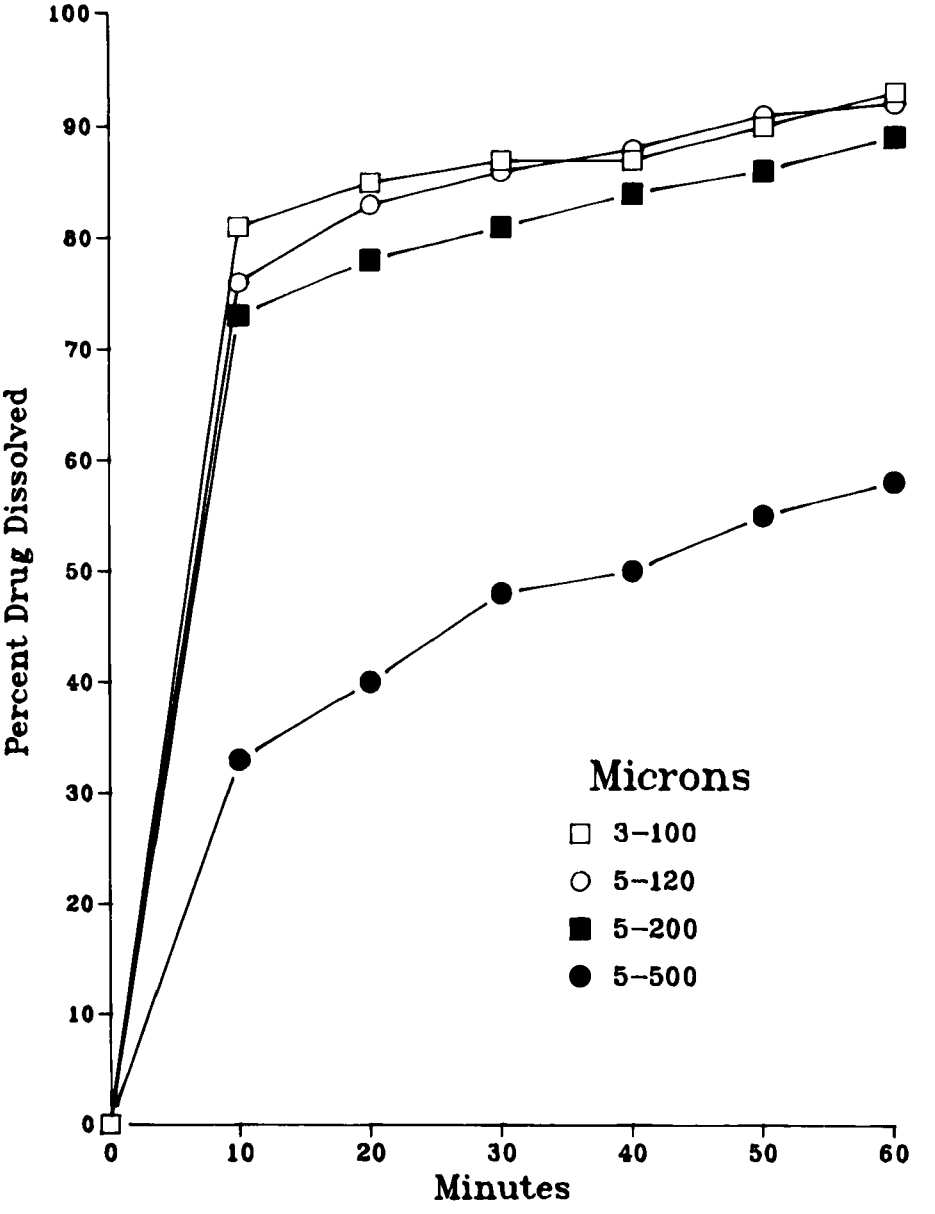


**FIGURE 6**
**Effect Of Particle Size On Dissolution**

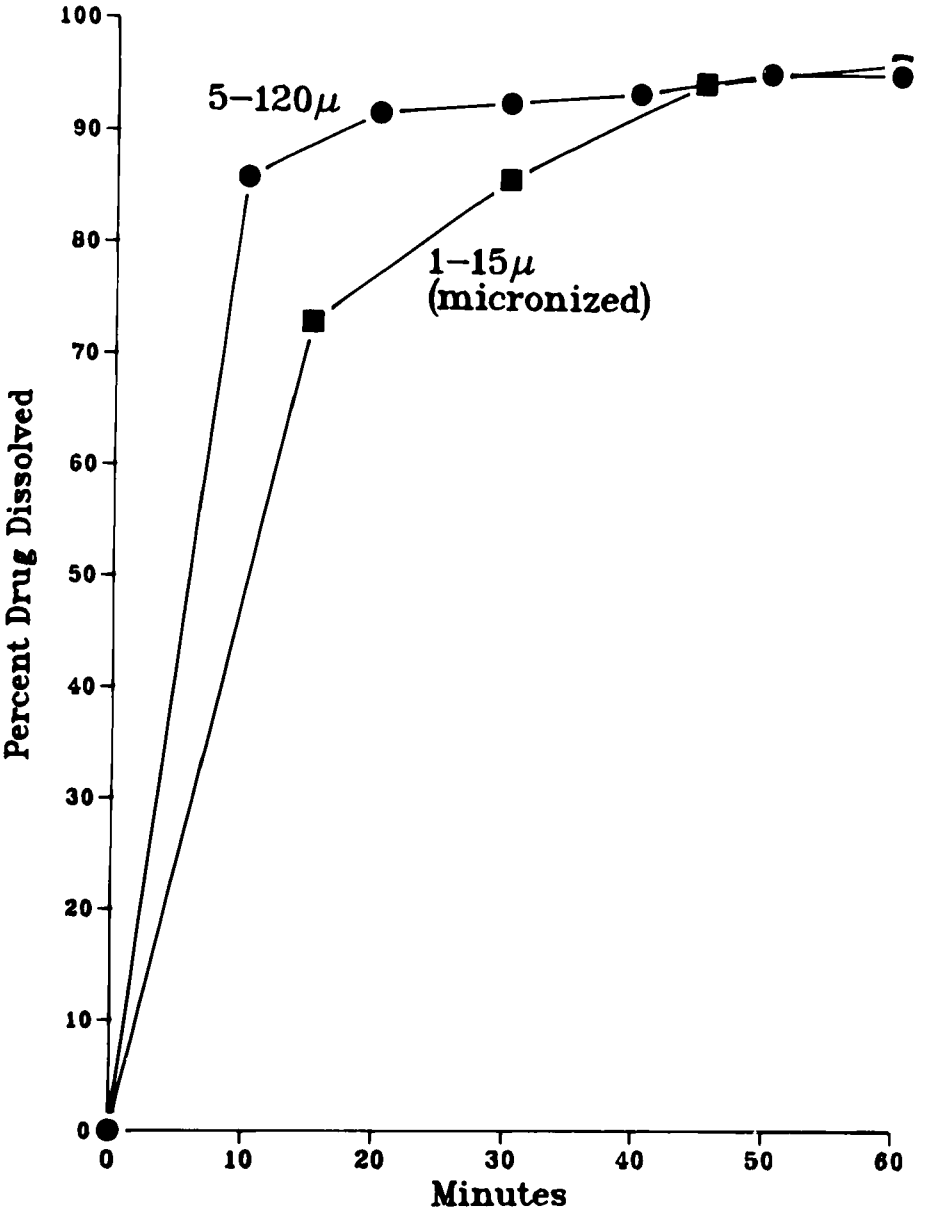


**FIGURE 7**
**Effect Of Particle Size On Dissolution**

Table 2

Diluent Formulations

| Formula | Diluent Concentrations |
|---|---|
| A | 100% lactose |
| B | 67:33 lactose - MCC* |
| C | 40:60 lactose - MCC |
| D | 100% MCC |

*Microcrystalline cellulose

drug with the dissolution medium. The low bulk density of microcrystalline cellulose made it more dispersible which provided for increased exposure of drug to the dissolution fluid. The diluent selection was further evaluated by varying the paddle speed in the dissolution test. Formulation differences were clarified by the proximity of the 50 and 75 RPM curves to each other in Figures 9 - 11. There was a significant difference between the two curves for formula A which gave poor dissolution results at the slower paddle speed (Figure 9). Formulas C and D showed closer dissolution values at both 50 and 75 RPM in Figures 10 and 11.

Surfactant

One aspect of the slow dissolution of drug A was its poor wettability. This was confirmed by physically observing both significant mounding at the vessel apex and film formation on the media surface during dissolution testing. Adsorption of air by the surface of the dissolution medium caused the drug powder to partially float. The total surface and the amount of air adsorbed increased with the extent of dispersion. Therefore, the surface area available to the dissolution fluid decreased as did the dissolution rate. The incorporation of a surfactant will increase the rate at which the solvent penetrates the solid mass, thereby

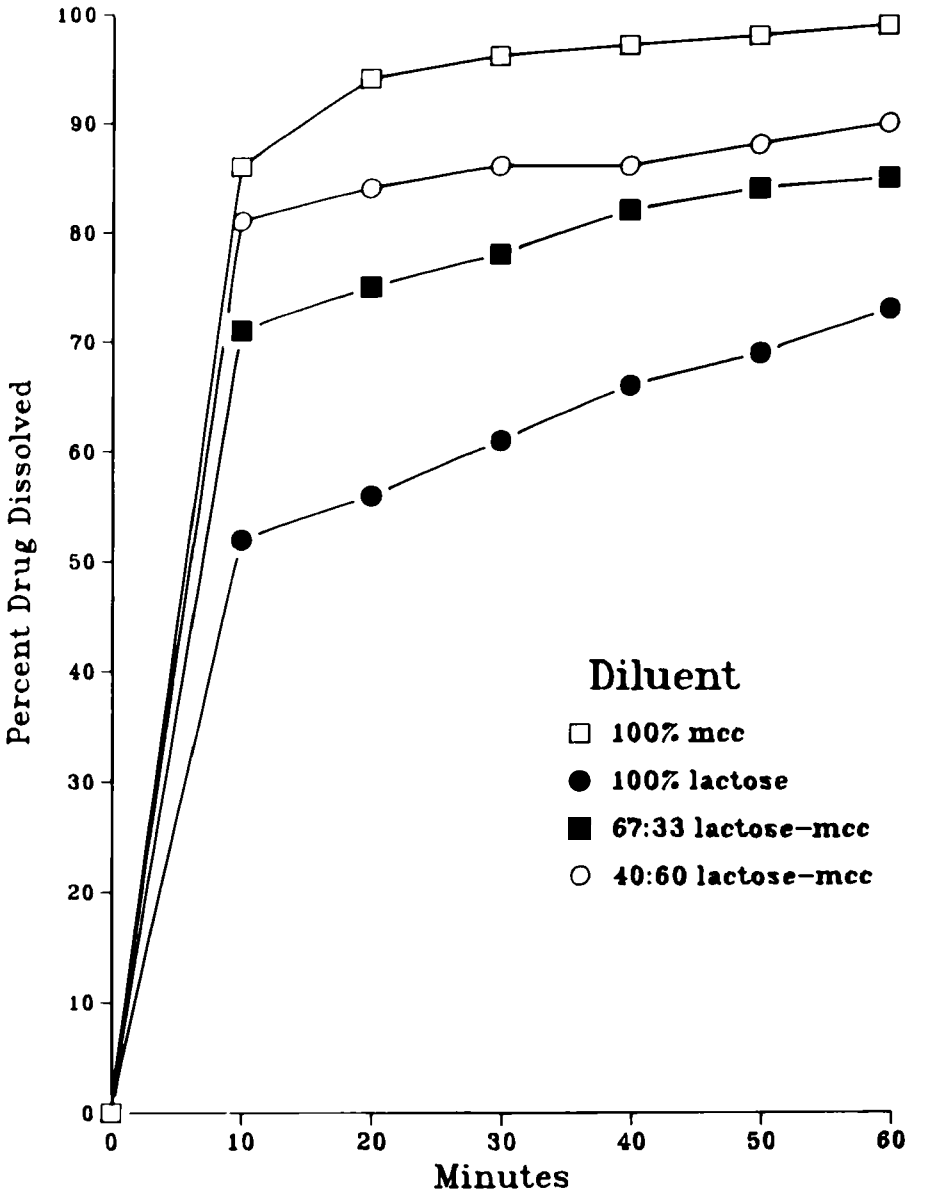


FIGURE 8
Effect Of Diluent On Dissolution

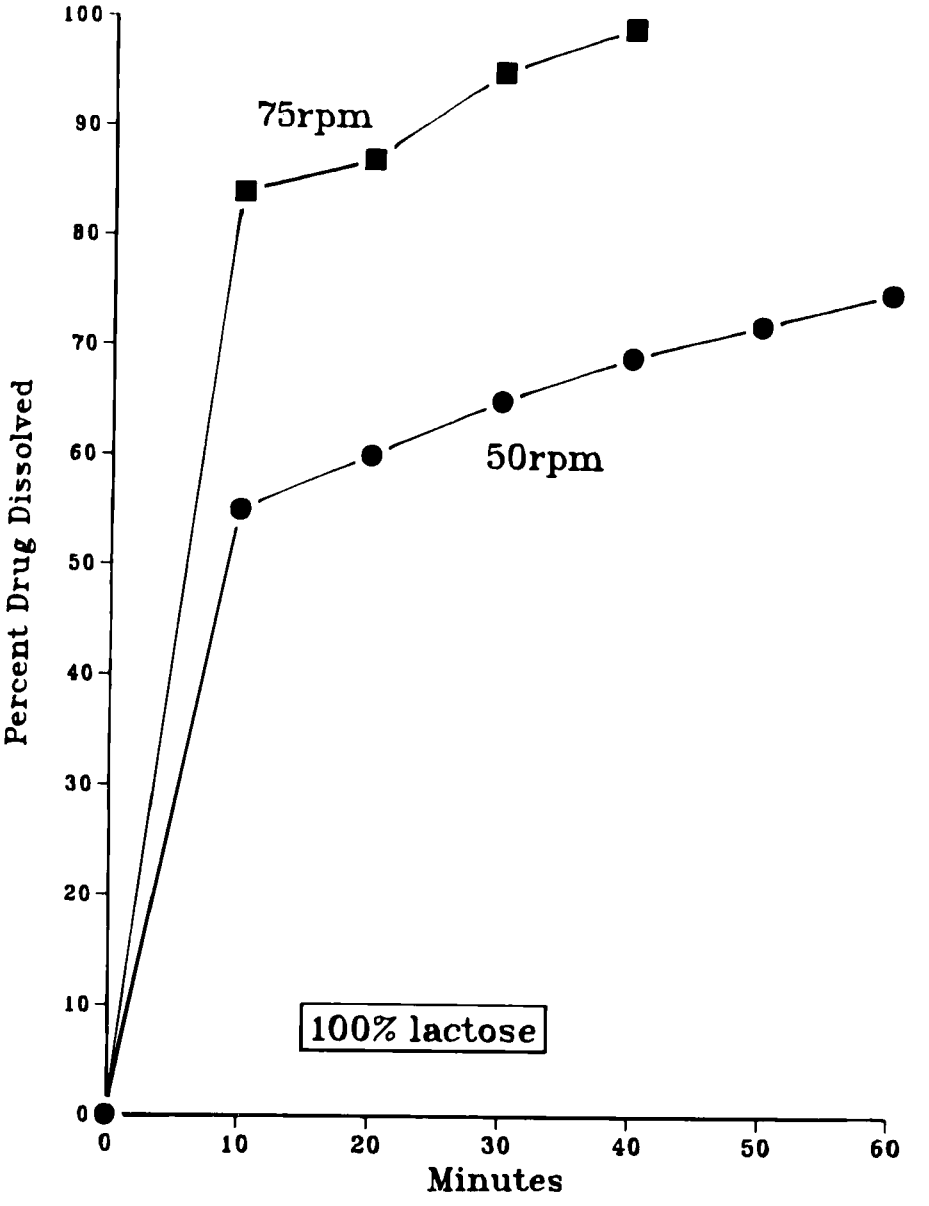


FIGURE 9
Effect Of Paddle Speed On Dissolution

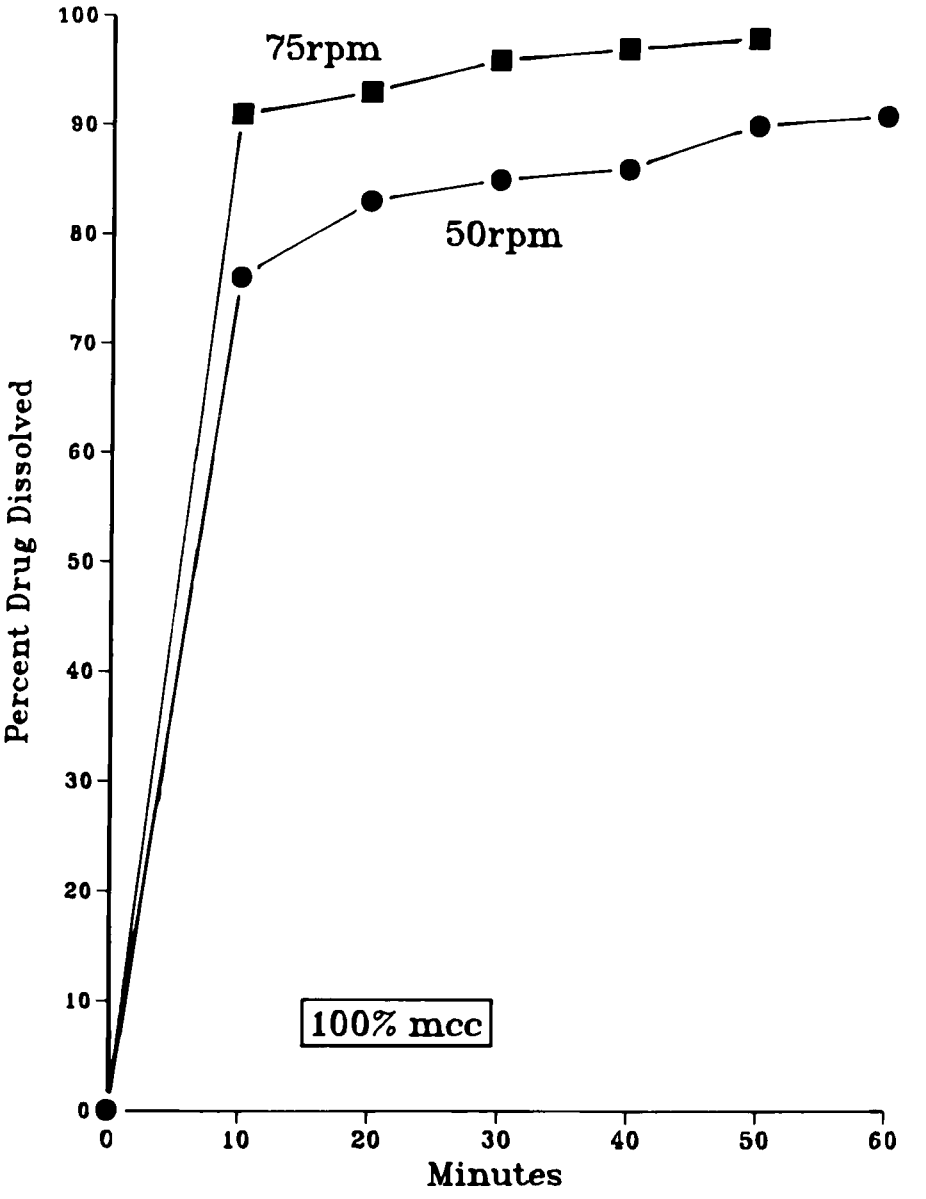


FIGURE 10
Effect Of Paddle Speed On Dissolution

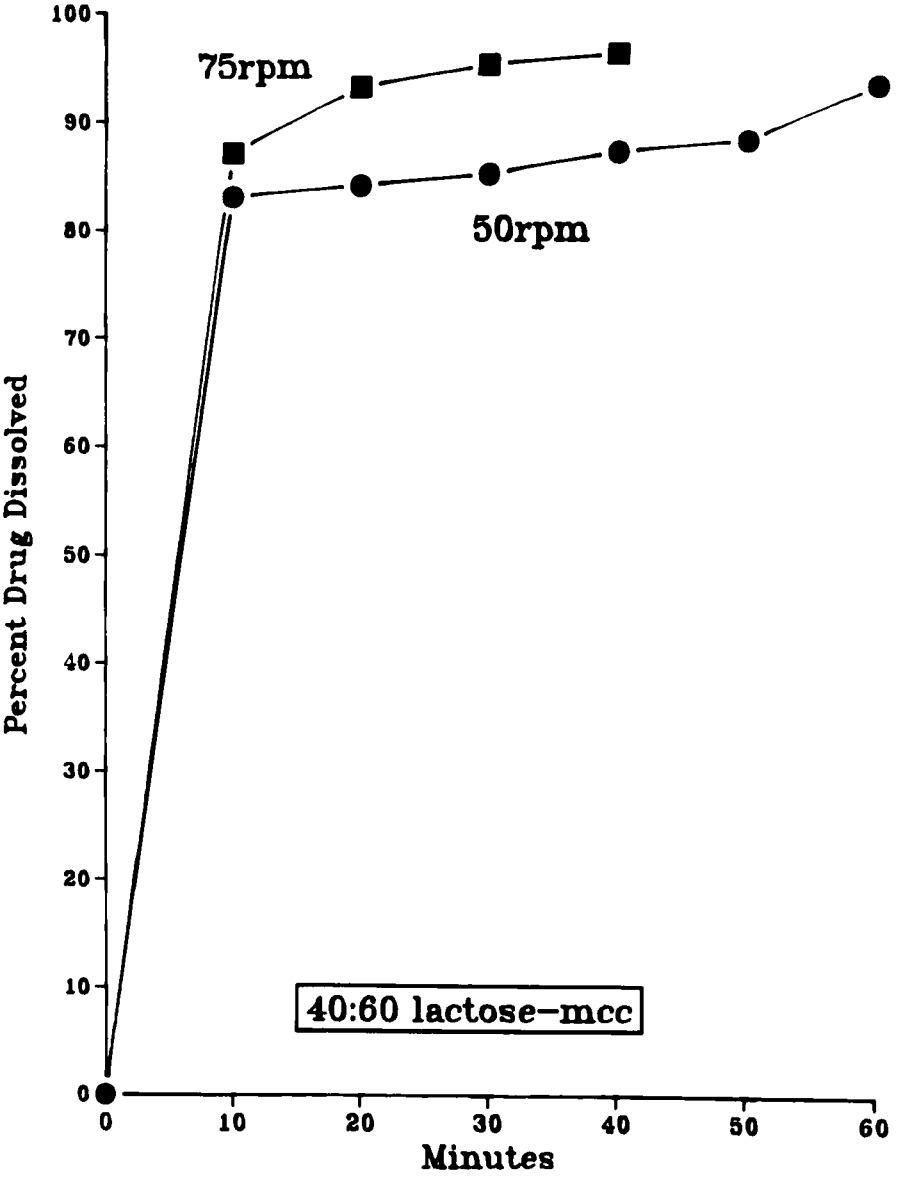


**FIGURE 11**
**Effect Of Paddle Speed On Dissolution**

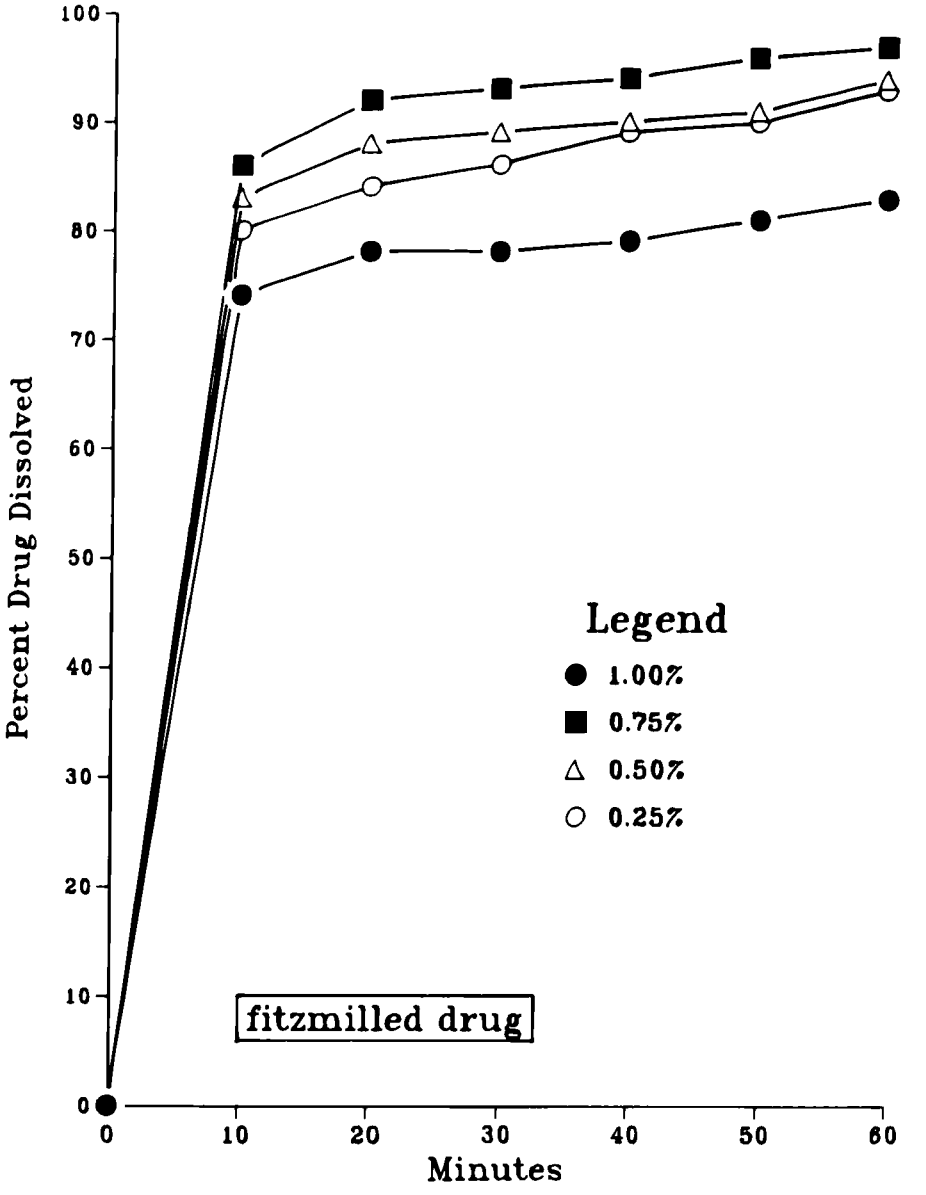


FIGURE 12
Effect Of Surfactant Level On Dissolution

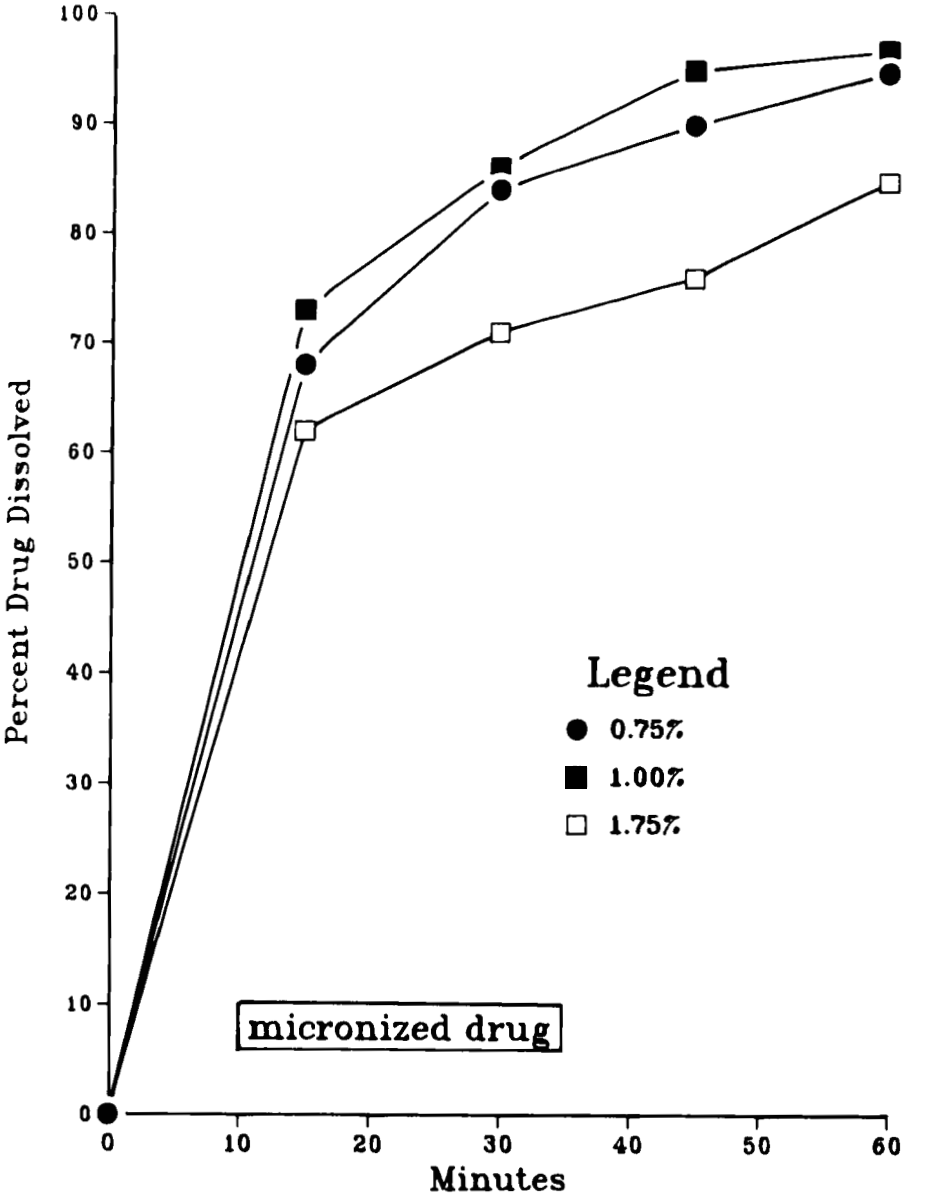


FIGURE 13
Effect Of Surfactant Level On Dissolution

increasing its effective surface area and ultimately the dissolution rate. Historically, polysorbate 80 has been the surfactant of choice for improving the wettability of hydrophobic drugs in our capsule formulations. However, Chafetz et al. (5) found that denaturation of the inner surface of the capsule, caused from the formation of formaldehyde from polysorbate 80 autoxidation, created a film around the powder mass. This phenomenon caused a decrease in the release rate of drug, in vitro. Therefore, an anionic surface active agent, sodium lauryl sulfate was selected to determine its effect on improving the wettability of drug. Different concentrations of surfactant (based upon drug content) were added to both fitzmilled and micronized drug. The addition of 0.25% increments of sodium lauryl sulfate to the fitzmilled drug increased the dissolution rate, with 0.75% producing the most satisfactory results at the end of 30 minutes (Figure 12). A 1% level caused a significant decrease in dissolution. One possible explanation for this occurrence was that the critical micelle concentration of sodium lauryl sulfate had been exceeded. At concentrations above the CMC, excess surfactant was not adsorbed at the interfacial surface, but remained in the liquid where these molecules aggregated to form micelles. This resulted in an increase in the percentage of undissolved drug. The same effect was recorded with micronized drug A. The incorporation of 1% sodium lauryl sulfate improved the dissolution when compared to 0.75%; the addition of 1.5% surfactant caused a significant decrease in the release rate of drug (Figure 13).

## CONCLUSION

A capsule formulation containing a marginally water soluble drug was successfully developed for clinical investigation. This was achieved by appropriate selection of diluent, particle size reduction of active ingredient and incorporation of a surfactant to increase the wettability of drug. The low bulk density of the diluent, microcrystalline cellulose made it more dispersible which increased the exposure of drug surface to the dissolution medium.

Drug reduced through a Fitzmill, 0.020" (#000) round hole screen, impact forward, high speed (6400 rpm) produced a particle size of less than 120 microns with good dissolution results. There was no benefit in micronizing the drug to improve its release rate. A level of 0.75% (based upon drug content) surfactant, sodium lauryl sulfate was found to be optimum for maximizing drug dissolution. The results achieved with this formulation screening process should make the the transition from clinical to market image product more effective.

## FOOTNOTES

[1]Model BB315, Dott. Bonapace & C., Milano, Italy.

[2]Robert Bosch GmBH, Produktbereich Hofliger+Karg, Waiblingen, Germany.

[3]Fitzmill Chilsonator[R], Fitzpatrick Co, Elmhurst, ILL.

[4]Parke-Davis Experimental Lot 43732.

[5]Henkel Corp., Hoboken, NJ.

[6]AVICEL pH 101, FMC Corp., Newark, DEL.

[7]B.V. Hollandsche Melksuikerfabriek, Uitgeest, Holland.

[8]STEROTEX HM, Capital City Products Co., Columbus, OH.

[9]Model D Comminuting Machine, W.J. Fitzpatrick Co., Chicago, ILL.

[10]Gem T Research Model Type 1047, Plastomer Products Div., Newtown, PA.

[11]Model 1200B, Amray, Bedford, MA.

[12]Liquid-Solids Blender, Patterson-Kelly Co., East Stroudsburg, PA.

[13]Capsugel, Greenwood, SC.

[14]Model 72RL-115, Hanson Research Corp., Northridge, CA.

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4. P. Finholt, in "Dissolution Technology", L.J. Leeson and J.T. Carstensen, eds., Washington, DC, 1974, p. 106.

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