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COMMUNICATION

Mechanisms of Drug Release from Matrices Prepared with Aqueous Dispersion of Ethylcellulose

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ABSTRACT

The objective of this study was to investigate the mechanism of acetaminophen (APAP) release from tablets prepared by the wet granulation method using an aqueous polymeric dispersion (Surelease) as a granulating agent. Tablets compressed from granules containing 10% w/w acetaminophen and 13.44% w/w total solids from Surelease released only 52.4% w/w drug after 120 min of dissolution testing, while controlled tablets without Surelease released 94.1% w/w drug. In order to prepare control tablets of 6.8 Kp hardness value, the upper compressional force recorded was 15.87 kN while tablets containing 13.44% w/w of total solids from Surelease had a recorded force of 6.28 kN. The drug release from tablets prepared with Surelease as a granulating liquid followed the diffusion-controlled model for an inert porous matrix.

INTRODUCTION

The physical properties of drug–binder combinations actually determine the physical properties and the compression characteristics of the resulting tablets.

The problem of capping during compression of paracetamol has been the subject of many studies. El-Gindy et al. (1) concluded that the physical properties of the drug–binder combinations actually determine the compression characteristics of the resulting tablets and can be used to solve many problems such as capping. Krycer et al. (2) found that addition of excipient to acetaminophen is necessary to modify its plastic and elastic characteristics, and to avoid lamination and capping. Bangudu et al. (3) studied the effects of moisture and stearic acid addition on the plastoelasticity and tableting characteristics of acetaminophen–microcrystalline cellulose mixtures. They found that tablets laminated when

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they contained less than 25% cellulose and when the ratio of elastic recovery to stress relaxation measured at 20 kN over a compression/decompression/ejection cycle of 2 min was greater than 9. Garr et al. (4) studied the effects of speeds of compression on the capping tendencies of acetaminophen. They found that the relatively high increases in elastic energy appear to be a more important factor than air entrapment in the capping tendency of acetaminophen compacts. However, incorporation of dibasic calcium phosphate dihydrate and microcrystalline cellulose into acetaminophen gave greater resistance to capping and produced tablets with higher tensile strength.

Ethylcellulose has been successfully used for many years to sustain the release rate of drugs. Porter (5), Klinger et a. (6), Marini et al. (7), Bodmeier et al. (8), and Lindstedt et al. (9) found that ethylcellulose provided control over drug release. Ghaly and Rivera (10), in recent work, studied the effect of total solids from Surelease on the compressibility characteristics of acetaminophen granules prepared with Surelease as granulating liquid.

The main objective of this work was to investigate the mechanism of acetaminophen release from tablets compacted of granules prepared with Surelease as granulating liquid.

The kinetics of drug release from inert porous matrix as described by Higuchi (11) can be expressed as follows:

$$Q = [D\varepsilon/\tau(2A - \varepsilon C_s)C_s t]^{1/2} \quad (1)$$

where Q is the amount of drug released per unit surface area, D is the diffusion coefficient of the drug, τ is the tortuosity factor, ε is the total porosity of the matrix after the drug has been extracted, A is the amount of the drug in the matrix, C_s is the solubility of the drug, and t is the time.

Higuchi's equation could be approximated by plotting the percent of drug released versus square root of time:

$$Q = Kt^{1/2} \quad (2)$$

Taking the logarithm of both sides of equation, one can obtain:

$$\text{Log } Q = \text{Log } K + 0.5 \log t \quad (3)$$

A straight line with slope of 0.5 should be obtained from a plot of log Q versus log t, if the drug release followed the square root of time equation described by Higuchi.

MATERIALS AND METHODS

Materials

Surelease (25% total solids) aqueous dispersion was generously supplied by Colorcon Ltd., and was used as granulating liquid.

Acetaminophen was used as a drug model in this study and was supplied by Warner Lambert Incorporation, P.R. Lactose Fast Flo (Foremost Ltd., Baraboo, WI) was selected as diluent, and magnesium stearate (Ruger Chemical Co., Inc.) was used as lubricant.

Preparation of Granules

The wet granulation method was chosen for preparation of the granules. A blend of powder containing 10% w/w acetaminophen and 90% w/w Lactose Fast Flow was granulated with Surelease dispersion in a planetary mixer (Hobart MFG Co., model 1414996) until the mixture achieved a suitable consistency. The granules were wet milled and dried in a hot air conventional oven at 40°C over 15 hr. In order to achieve granules with a high level of total solids from Surelease, a second and a third granulation were performed to a known weight portion of granules from the first granulation, using the procedure described above. The dried granulation was dry milled and lubricated with 0.5% w/w magnesium stearate.

Control Preparation

Control formulations were prepared by mixing 10% w/w acetaminophen with 90% w/w Lactose Fast Flow in a planetary mixer for 10 min. Magnesium stearate (0.5% w/w) lubricant was added to the blend.

Preparation of Compressed Tablets

The different formulations were compacted into tablets using a Korsch EKO single-punch instrumented tablet press, equipped with 12/32-in. flat-face punches. Target tablet weight was 450 mg ± 5%. The target hardnes varied between 6.7 and 7.0 Kp.

Release Studies

The release of acetaminophen from the different tablets was measured in 900 ml distilled water at 37° ± 0.5°C using a rotating basket apparatus (Hanson Re-

search, Model SR2, USA) at a speed of 50 rpm. Samples of 10 ml were withdrawn at different time intervals and replaced with 10 ml of distilled water at room temperature. The drug concentration was determined by measuring the absorbance of the samples in a Beckman DU-650 UV spectrophotometer at a wavelength of 244 nm.

RESULTS AND DISCUSSION

Figure 1 shows the particle size distribution of the different granule formulations after dry milling. The increase in total solids (from Surelease) enhanced the uniformity of granule size. For the granules containing 13.4% w/w total solids (from Surelease), more than 60% of them were approximately 1500 μm in size. Granules containing 4.2% w/w and 9.36% w/w solids were 1500 μm in size for 40.6% and 49% (total granules), respectively.

The drug release from tablets granulated with Surelease decreased as the level of total solids increased in the formulations (Fig. 2). Control tablets released 100% of the drug at 180 min of dissolution testing while tablets containing 4.21%, 9.36%, and 13.41% total Surelease solids released only 77.4%, 70.3%, and 61.8% of drug, respectively. The tableted granules remained intact during and after dissolution while control tablets disintegrated immediately after 180 min of dissolution testing. The ANOVA one-way analysis and a pair multiple test showed significant differences among different formulas.

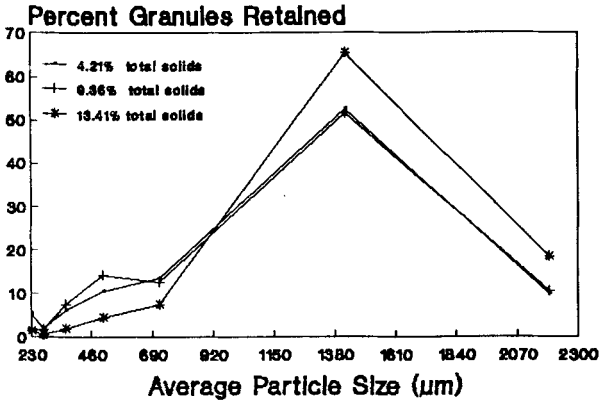

Figure 1. Particle size distribution of granules containing different levels of Surelease total solids.

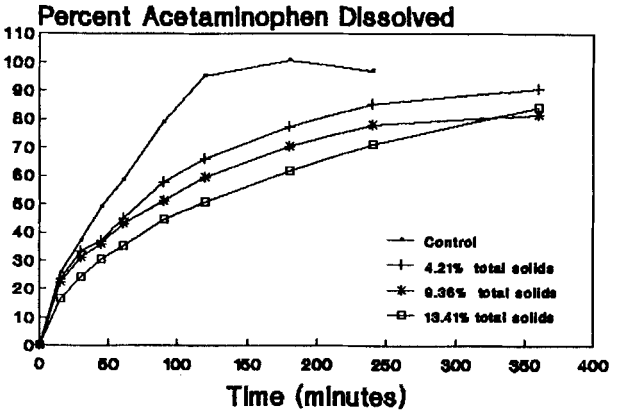

Figure 2. Percent acetaminophen dissolved from tablets containing different Surelease total solids.

Figure 3 shows the scanning photomicrographs of the surfaces of control tablet (a); tablets containing 13.41% total solids (b) before and after dissolution testing at magnification of ×600. It is apparent that the surface of tablets containing 13.41% total solids has fewer pores and channels than control tablets. The reduction in channels and pores would be consistent with the dissolution data that showed a decrease in drug release rate from tablets containing 13.41% total solids. After dissolution testing, the surface of tablets containing 13.41% total solids showed many large pores due to leaching of drug from within the matrix (c). As is depicted in Fig. 4, the percent drug release from tablets containing 13.41% total solids from Surelease and compacted at compressional forces of 1.932, 2.879, 6.276, and 18.025 kN were essentially the same. These data demonstrated that drug release from tablets containing 13.41% total solids was independent of the compressional force applied.

Plots of square root of time versus percent drug dissolved from tablets containing approximately 13.4% total solids from Surelease and different drug levels gave a linear relationship (Fig. 5). Also plots of log percent drug dissolved versus log time for the same tablets exhibited a linear relationship with a slope of approximately 0.5, as is shown in Fig. 6. The mechanism of drug release of tablets compacted from granules of acetaminophen and Lactose Fast Flo granulated with Surelease appears to follow Higuchi's diffusion model for an inert porous matrix. In addition, the drug release from these matrices was not affected by the applied compressional force, which would be constant with a matrix release mechanism.

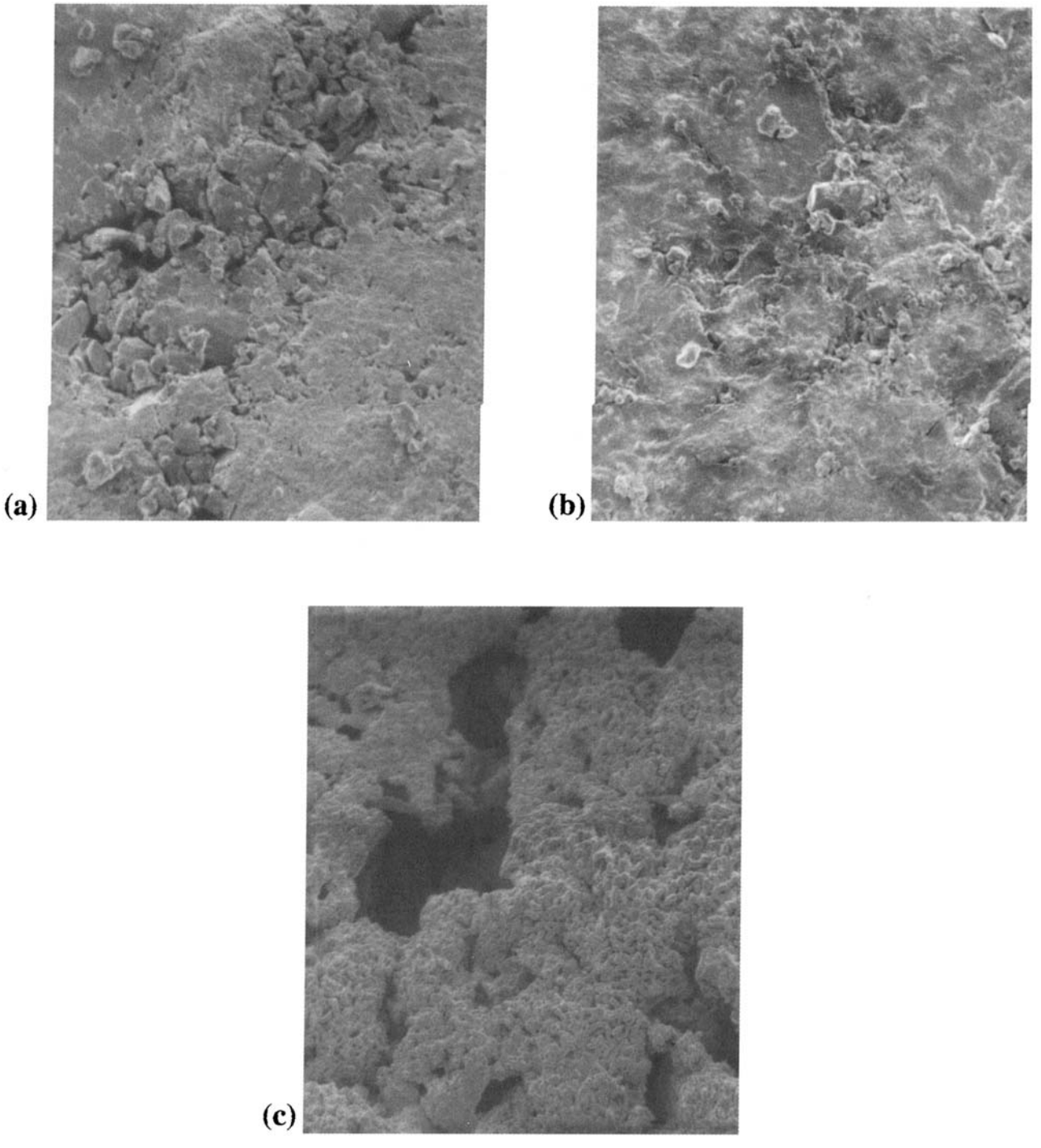

Figure 3. Scanning electron photomicrographs for: (a) control tablets, (b) tablets containing 13.41% Surelease total solids before dissolution, and (c) after dissolution.

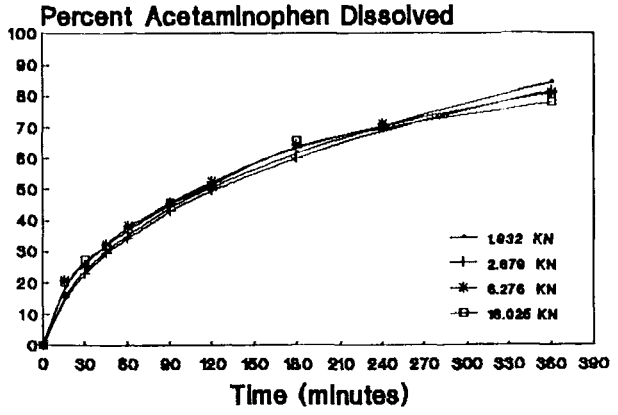

Figure 4. Percent acetaminophen dissolved from tablets containing 13.41% Surelease total solids compressed at different compressional force.

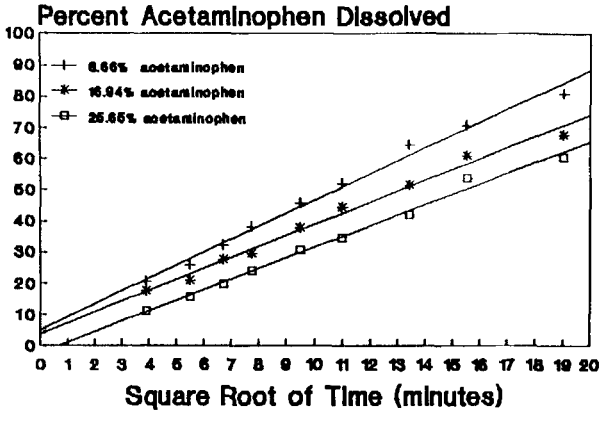

Figure 5. Square root of time plots for tablets containing different levels of drug.

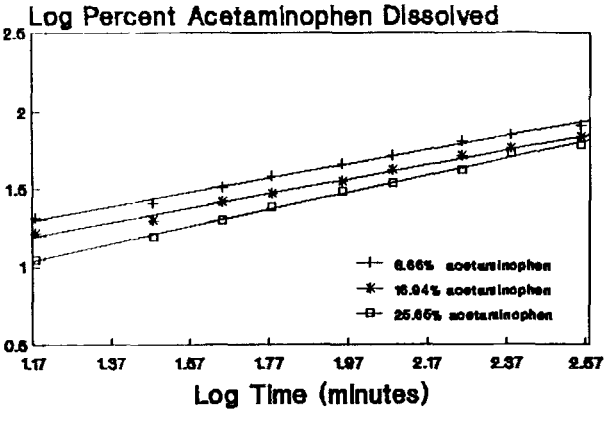

Figure 6. Log percent acetaminophen dissolved versus log time for tablets containing different levels of drug.

CONCLUSIONS

It was possible, through the manipulation of the amount of Surelease used as granulating liquid, to control the release of water-soluble drug and to create an inert porous matrix. In addition, Surelease enhanced significantly the compaction characteristics of acetaminophen and prevented capping of the tablets.

ACKNOWLEDGMENT

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REFERENCES

1. M. W. El-Gindy, M. W. Samaha, and H. A. El-Maradny, Drug Dev. Ind. Pharm., 14, 977 (1988).
2. I. Krycer, D. G. Pope, and J. A. Hersey, J. Pharm. Pharmacol., 34, 802 (1982).
3. A. B. Bangudu and N. Pilpil, J. Pharm. Pharmacol., 37, 289 (1985).
4. J. S. Garr and M. H. Rubinstein, Int. J. Pharm., 72, 117 (1991).
5. S. C. Porter, Drug Dev. Ind. Pharm., 15, 1495 (1989).
6. G. H. Klinger, E. S. Ghaly, S. C. Porter, and J. B. Schwartz, Drug Dev. Ind. Pharm., 16, 1473 (1990).
7. J. O. Marini, R. W. Mendes, J. S. Rekhi, and S. S. Jambhekar, Drug Dev. Ind. Pharm., 17, 865 (1991).
8. R. Bodmeir, H. Shen, P. Tyle, and P. Jarosz, J. Controlled Release, 15, 65 (1991).
9. B. Lindstedt, M. Sjoberg, and J. Hjatstam, Int. J. Pharm., 67, 21 (1991).
10. E. S. Ghaly and N. Rivera, Drug Dev. Ind. Pharm., in press.
11. T. Higuchi, J. Pharm. Sci., 1963, p. 1145.