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EFFECT OF PRESSURE ON DISINTEGRATION OF TABLETS AND DISSOLUTION OF EPHEDRINE SULFATE

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ABSTRACT

The influence of applied pressure on the disintegration of model ephedrine sulfate tablets and the release of ephedrine sulfate is reported. Six frequently used disintegrating agents were employed with a water-soluble diluent (lactose) and with a water-insoluble diluent (dibasic calcium phosphate). Although disintegration time may be independent of pressure (dibasic calcium phosphate) or may be lengthened by increased pressures (lactose), changes in applied pressures did not significantly alter the dissolution of the water-soluble medicinal compound.

INTRODUCTION

To expedite clinical availability of a medicinal compound from a compressed tablet disintegrating agents are incorporated. By capillary action or by swelling in the presence of water the disintegrating agent applies force to and ruptures the tablet

matrix. The resulting increase in surface of the solid particles speeds dissolution of the medicinal compound.

The processes of disintegration and dissolution occur concomitantly, and in tablets composed of a water-soluble diluent the dissolution of the diluent may influence the effectiveness of the disintegrating agent. In tablets composed of a water-insoluble diluent the action of the disintegrating agent is the primary mechanism of release. The purpose of this report is to consider the effect of applied pressure on the disintegration of tablets and the release of a water-soluble medicinal compound from tablets of a water-soluble and a water-insoluble diluent with six commonly used disintegrating agents.

EXPERIMENTAL

By means of a hydraulic press fitted with a 12.7 mm punch and die set flat-faced tablets were prepared by direct compression at 35, 71, 176, 282, and 353 MPa. The formulation as given in Table I was blended in a V-blender for 15 minutes. Anhydrous lactose was selected as a water-soluble diluent: dibasic calcium phosphate U.S.P. (Emcompress™, Edward Mendell Co., Inc.) was selected as a water-insoluble diluent. The disintegrating agents were: starch N.F., pre-gelatinized starch N.F. (Starch 1500, Colorcon, Inc.), microcrystalline cellulose N.F. (Avicel™ PH 101, FMC Corp.), crospovidone N.F. (Polyplasdone™, Edward Mendell Co., Inc. and Primojel™, Generichem Corp.).

The disintegration was determined by the U.S.P. method (1). Dissolution was determined by the analytical procedure and method

TABLE I. Model Tablet Formulation

Ingredient	Mg/Tablet
Ephedrine sulfate U.S.P., 80-mesh	25.0
Diluent, 40-mesh	875.0
Disintegrating agent, 80-mesh	50.0
Talc U.S.P., 100-mesh	50.0

specified in the U.S.P. monograph (2). Individual plots of the dissolution profiles were drawn, and the time required for 90 percent of the ephedrine sulfate to dissolve ($t_{90\%}$) was evaluated.

RESULTS AND DISCUSSION

In designing a tablet containing a water-soluble medicinal compound a water-soluble or water-insoluble diluent and a suitable disintegrating agent may be selected. The effect of the pressure used to produce the tablet may effect the efficiency of a disintegrating agent depending on the solubility of the diluent. Model tablets of ephedrine sulfate were used to study the effect of pressure on disintegration and dissolution from tablets with a water-soluble lactose diluent and a water-insoluble dibasic calcium phosphate diluent and various disintegrating agents. Pressures ranged from 35 to 353 MPa which approximates the pressures used in conventional manufacturing operations.

As shown in Figure 1 for a lactose diluent with 5% disintegrating agent as the pressure is increased from 35 to 200

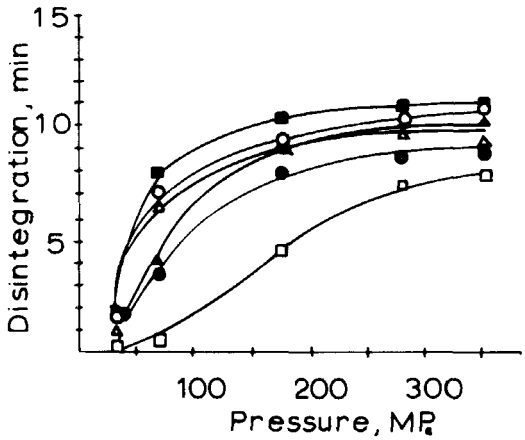

FIGURE 1

The effect of applied pressure on various disintegrating agents in an ephedrine sulfate tablet with a lactose diluent. Key: ○, Primogel; □, Polyplasdone XL; ● Explotab; ■, Avicel PH 101; △, starch, and ▲, Starch 1500.

MPa the disintegration time is lengthened; and thereafter, further increases in pressure to 350 MPa cause essentially no change in disintegration. In the model tablets Polyplasdone XL ranks as the fastest disintegrating agent and Avicel as the slowest, and Explotab, Primogel, starch, and Starch 1500 are approximately equal intermediates.

As shown in Figure 2 for a dibasic calcium phosphate diluent with 5% disintegrating agent there is no significant increase in disintegration time as the pressure is increased from 35 to 275 MPa. There is no apparent difference in the effectiveness of Primogel, Explotab, starch, Starch 1500 and Polyplasdone XL as a useful disintegrating agent with this insoluble diluent. It may be questionable if Avicel is a disintegrating agent, but

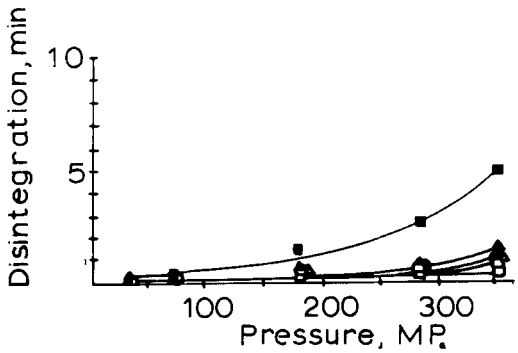

FIGURE 2

The effect of applied pressure on various disintegrating agents in an ephedrine sulfate tablet with a dibasic calcium phospahte diluent. Key: same as Figure

regardless of classification the disintegration of tablets containing Avicel was not significantly lengthened (5 minutes) from the clinical viewpoint as the pressure was increased.

In comparing the effect of a disintegrating agent in a tablet with a lactose diluent to one with a dibasic calcium phosphate diluent the disintegrating agent is less sensitive to changes of applied pressure and functions faster with the insoluble diluent. With the water-soluble diluent disintegration and dissolution occur simultaneously. It may be that the dissolution of the lactose is a more rapid process than the swelling or wicking process of disintegration; and consequently, the disintegrating agent is not in contact with and is not exerting force throughout the tablet matrix. The next result is a longer disintegration time. With an insoluble diluent dissolution does not occur, and the disintegrating agent is always in contact with the tablet matrix and is continually exerting force to rupture the tablet.

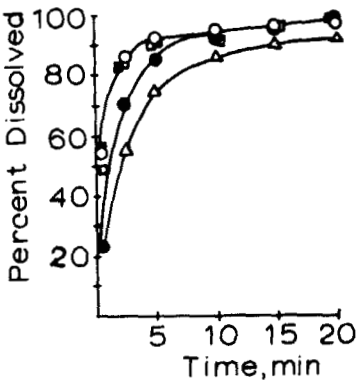

FIGURE 3

The influence of applied pressure on the dissolution of ephedrine sulfate from a tablet with a dibasic calcium phosphate diluent with 5% starch. Key: ○, 35; ●, 70; △, 175; □, 280; and ■, 380 MP_a.

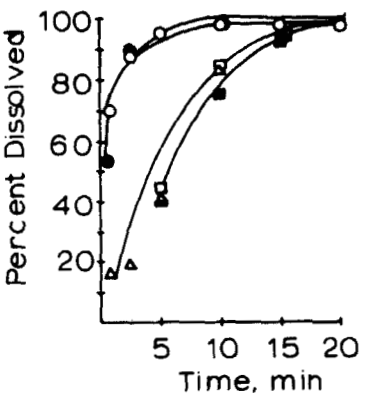

FIGURE 4

The influence of applied pressure on the dissolution of ephedrine sulfate from a tablet with a lactose diluent with 5% starch. Key: same as Figure 3.

Thus, the disintegration is more rapid with an insoluble excipient than with a soluble diluent. With the model tablets studied the disintegration is approximately 6-7 times faster with the insoluble dibasic calcium phosphate than with the soluble lactose.

Although a rapid disintegration is associated with the desired properties of a compressed tablet, the dissolution profile is a more critical parameter. A typical dissolution profile is shown in Figure 3 for the dissolution of ephedrine sulfate from a tablet with a dibasic calcium phosphate diluent with 5% starch as a disintegrating agent. From similar plots for all formulations the time required for 90% of the ephedrine sulfate to dissolve ($t_{90\%}$) was determined. There is a slight difference in the dissolution profiles at the five applied pressures shown in Figure 3; however, at 10 minutes more than 80 percent of the ephedrine sulfate has been dissolved. From the clinical viewpoint with this rapid a dissolution variations in normally used pressures to manufacture tablets would not significantly change dissolution.

A dissolution profile is shown in Figure 4 for the dissolution of ephedrine sulfate from a tablet with a lactose diluent with 5% starch as a disintegrating agent. As the pressure is increased, there is a slowing of dissolution; however, at 10 minutes more than 75 percent of the ephedrine sulfate has been dissolved. In the tablets investigated increases in pressure slowed dissolution in the initial 10 minute period; however, this effect was insignificant for the dibasic calcium phosphate diluent and minor for the lactose diluent.

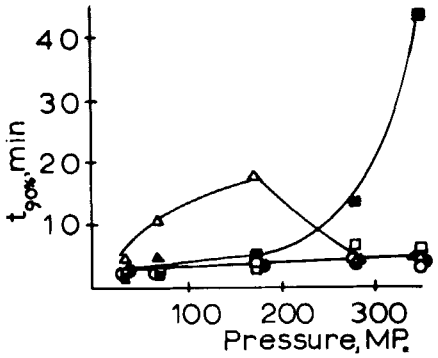

FIGURE 5

Time required for 90% of ephedrine sulfate to dissolve from tablets with a dibasic calcium phosphate diluent and various disintegrating agents. Key: ○ , Primogel; □ , Polyplasdone XL; ● , Explotab; ■ , Avicel PH 101; △ , starch; and ▲ , Starch 1500.

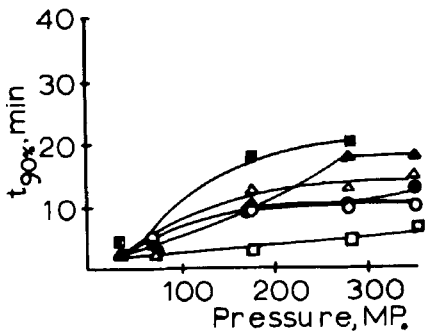

FIGURE 6

Time required for 90% of ephedrine sulfate to dissolve from tablets with a lactose diluent and various disintegrating agents. Key: same as Figure 5.

In Figure 5 the $t_{90\%}$ of ephedrine sulfate from tablets of dibasic calcium phosphate is plotted against pressure. The release of ephedrine sulfate from dibasic calcium phosphate tablets with Primogel, Explotab, polyplasdone XL, and Starch 1500 is independent of pressure. With Avicel at 350 MPa the $t_{90\%}$ is increased. It may be that at the higher pressure the porosity and capillary pore size are reduced to the extent that the "wicking" of water into the tablet is markedly reduced, and consequently dissolution is slowed.

In Figure 6 the $t_{90\%}$ of ephedrine sulfate from tablets of lactose is plotted against pressure. The release of ephedrine sulfate from lactose tablet is slightly slowed as the pressure is increased. The tablet containing Avicel is most sensitive to pressure changes.

CONCLUSION

Disintegration time may be independent of applied pressure with insoluble diluents (dibasic calcium phosphate with a disintegrating agent) or disintegration time may be lengthened as applied pressure is increased with soluble diluents (lactose with a disintegrating agent). Changes in applied pressure did not significantly alter the dissolution of a water-soluble medicinal compound (ephedrine sulfate).

ACKNOWLEDGEMENTS

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REFERENCES

1. "The United States Pharmacopeia," 21st rev., Mack Publishing Co., Easton, PA, 1985, p. 1242.

2. ibid., p. 374.