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EFFECT OF PROCESSING ON RELEASE FROM AN INERT, HETEROGENEOUS MATRIX

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ABSTRACT

Matrixes containing 40% ephedrine hydrochloride and hydrogenated castor oil are prepared by two processes: (a) compression of a physical mixture and (b) compression of a congealed melt. The release from the melt matrix is slower than from the matrix prepared by compression of a physical mixture. The effect of applied pressure on the release profile is studied. For matrixes prepared by both processes as the applied pressure is increased, the release rate is slower; however, this effect is more pronounced for the physical mixture matrix. The effect of

comminution of the medicinal compound on release profile is considered. In matrixes produced by compression of a physical mixture the fastest release occurs from the finer particles suggesting a boundary layer diffusion. In matrixes produced by the melt process as the particle size is decreased, the release is slowed presumably because of an increased tortuosity and more intimate contact between the ephedrine hydrochloride and the hydrogenated castor oil, which produces mass transfer by matrix diffusion.

INTRODUCTION

A product development scientist considers formulation and the method of manufacture in designing a product. It is recognized that the milling process which controls the particle size of a medicinal compound may influence the release of the compound from a solid dosage form (1). It may be less well recognized that in preparing solid dispersions for a given formula various methods (physical blending, melting followed by congealing, and solvent deposition) may produce solids with different release characteristics.

The purpose of this study was to investigate the release of a highly water-soluble medicinal compound from inert, heterogeneous matrixes prepared by the compression at various pressures of a physical mixture and of a congealed and milled melt. The effect of particle size of the medicinal compound on the rate of

release from the matrixes prepared by the two process was also investigated.

EXPERIMENTAL

Preparation of Physical Mixture Matrix. By means of U.S. Standard Sieves ephedrine hydrochloride (Mallinckrodt, L<ot 4965-KXDZ) was separated into 20/40-, 80/100- and <200-mesh size fractions. The hydrogenated castor oil (HCO, Castorwax, NL Industrial Chemicals) satisfied the criteria of a matrix material (2). The HCO was milled and an 80/100-mesh size fraction was collected. Forty percent of the selected size fraction of the ephedrine hydrochloride and HCO were mixed in a V-blender for 10 minutes. The mixture was compressed at 7, 14, 35, 139, 244 and 348 MPa using a hydraulic press fitted with a 12.75 or a 28.575 mm flat-faced punch and die set. The cylindrical matrixes were weighed, and their thickness and diameter were measured.

Preparation of Melt Matrix. The melt was prepared by heating the HCO to 100°C in a porcelain dish and adding the ephedrine hydrochloride with stirring. The molten mass was poured onto a glass plate on which it congealed. After 24 hours the mass was comminuted, and the 60/140-mesh size fraction was collected and compressed into a matrix as previously described.

Measurement of Matrix Parameters. The methodologies have been described for the determination of solubility, diffusivity, densities and rate of release (3, 4). Values of porosity, drug

loading and tortuosity of the matrixes are given in a previous publications (5).

RESULTS AND DISCUSSION

Formulation and processing should be considered concurrently in the design and production of a product. It has been shown that the release profiles of ephedrine hydrochloride and procaine hydrochloride from compressed matrixes of hydrogenated castor oil (HCO) of the same formulation are different if prepared by compression of a physical mixture or by compression of a melt and that different diffusional equation describe the release form the matrixes prepared by compression of a melt and physical mixture (5).

Effect of Applied Pressure. A study was conducted to determine the influence of applied pressure on the release profile from a matrix containing 40% ephedrine hydrochloride and HCO. The release profiles at 25°C in terms of cumulative amount released per unit area versus square root of time are shown in Figure 1 for a physical mixture matrix compressed at 7, 14, 35, 139, 244 and 348 MPa. The slopes of the profiles decrease as the applied pressure is increased. For example, the release flux is 3.1 times faster from the matrix of a physical mixture compressed at 7 MPa than from that compressed at 348 MPa.

The release profiles at 25°C are shown in Figure 2 for a matrix of a melt of ephedrine hydrochloride and HCO compressed at

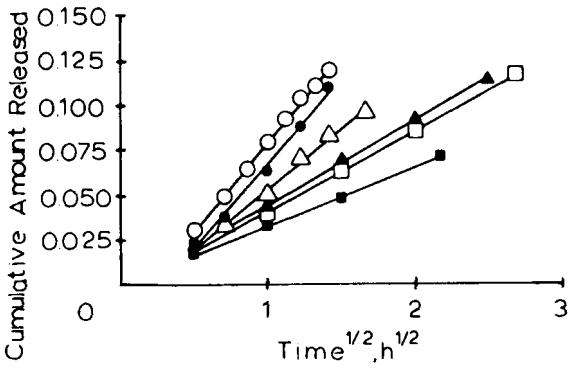

FIGURE 1

Effect of applied pressure on release profiles form a matrix prepared by compression of a physical mixture of 40% ephedrine hydrochloride and hydrogenated castor oil. Key: (○) 7; (●) 14; (△) 35; (▲) 139; (□) 244; (■) 348 MPa.

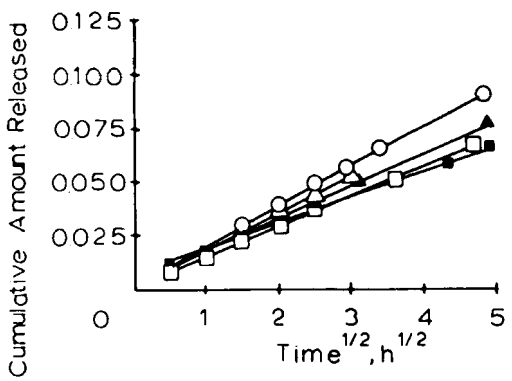

FIGURE 2

Effect of applied pressure on release profiles from a matrix prepared by a melt process. Key: same as Figure 1.

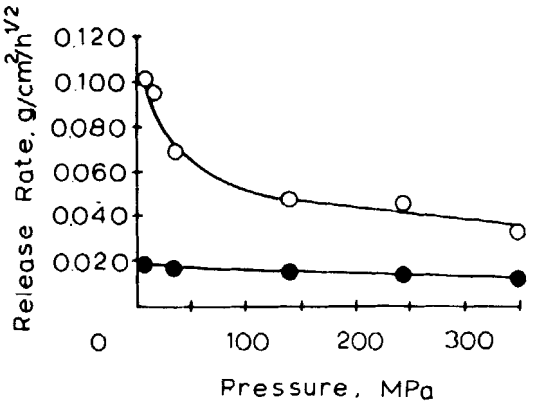

FIGURE 3

Effect of applied pressure on release flux from matrixes prepared by (○) compression of a physical mixture and (●) the melt process.

several applied pressures. The slopes of the profiles decrease as the applied pressure is increased. For example, the release flux is 1.6 times faster from the melt matrix compressed at 7 MPa than from that compressed at 349 MPa.

The release fluxes of ephedrine hydrochloride from the melt matrix and from the physical mixture matrix are shown in Figure 3. The matrixes of the physical mixture are more sensitive to the applied pressure than the melt matrix with a decrease in the release flux from 10.1×10^{-2} g/cm^2/h$^{\frac{1}{2}}$ at a pressure of 7 MPa to 3.28×10^{-2} g/cm^2/h$^{\frac{1}{2}}$ at a pressure of 348 MPa. At these same pressures the release flux from the melt matrix varies from 1.86×10^{-2} to 1.18×10^{-2} g/cm^2/h$^{\frac{1}{2}}$. Although it

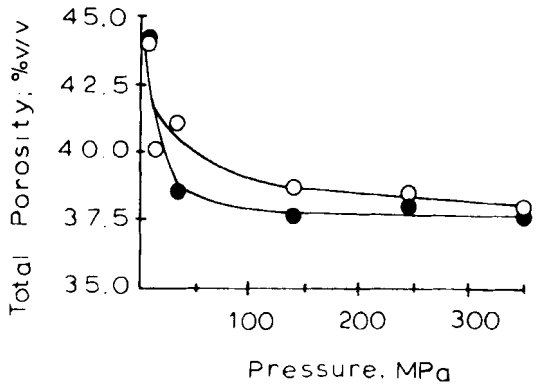

FIGURE 4

Effect of applied pressure on the total porosity of matrixes prepared by (○) compression of a physical mixture and (●) the melt process.

appears as if there is little change in the slopes for the melt matrixes, high coefficients of determination (>0.9905) indicate a significant difference at the different applied pressures.

To determine why the physical mixture matrixes are more sensitive to applied pressure than the melt matrixes, the matrix parameters (solubility, diffusivity, drug loading, tortuosity) need to be examined. The solubility and diffusivity of ephedrine hydrochloride are not affected by the applied pressure or the processing and remain constant. The total porosity of the matrix at different pressures is shown in Figure 4 (5). For the physical mixture matrixes there is a statistical difference (two sided t-test, $P = 0.01$) between the porosity of the matrixes

compressed at 7, 14 and 35 MPa when compared to the porosity of the matrix compressed at 348 MPa. There is no significant difference in the porosities of the melt matrixes compressed at 14, 35, 139, 244 and 348 MPa. Thus, a change of applied pressure is more apt to change the total porosity of the physical mixture matrixes than that of the melt matrixes. This may contribute somewhat to the decrease of release from the physical mixture matrixes as the applied pressure is increased.

The drug loading may affect the release of a drug from a matrix. In the melt matrix the drug loading was not significantly different at 14, 35, 139, 244 and 328 MPa. In the physical mixture matrixes the drug loadings for matrixes compressed at 7, 14 and 35 MPa were significantly different from the drug loadings of the matrixes compressed at a higher pressure. Drug loading in the physical mixture matrixes is more dependent on the applied pressure than the melt matrixes.

An increase in the drug loading would be expected to produce an increase in release. As shown in Table 1, an increase in applied pressure causes an increase in drug loading; however, the observed data show a decreased release with the slightly larger drug loading caused by the increased applied pressure. If the modified Lee model for an inert, heterogeneous matrix (6) (see Appendix) is utilized to describe the release, the small change of total porosity and drug loading with different applied

TABLE 1
Release Rate and Drug Loading for 40% Ephedrine Hydrochloride Matrix Compressed at Various Applied Pressures

Applied Pressure, MPa	Physical Mixture Matrixes		Melt Matrixes	
	Drug Loading, g/cm^3	Release Rate, $g/cm^2/h^{1/2}$	Drug Loading, g/cm^3	Release Rate, $g/cm^2/h^{1/2}$
7	0.380	0.101	0.392	0.0186
14	0.406	0.0963	-	-
35	0.400	0.0688	0.417	0.0170
139	0.416	0.0473	0.423	0.0154
244	0.417	0.0454	0.421	0.0139
328	0.421	0.0328	0.422	0.0118

pressure would tend to cause no net change of the amount released because the increase of total porosity would be nullified by the decreased of drug loading.

As total porosity and drug loading have no major effect on release, the tortuosity of a matrix may be significant. During compression the particles may undergo plastic deformation. The HCO being more malleable than the ephedrine hydrochloride would deform more readily into the pores and crevices on the surface of the ephedrine hydrochloride particles. As the HCO becomes more defined about the ephedrine hydrochloride particles, the diffusional pathlength becomes more tortuous, and the release is slowed.

As the applied pressure is increased, the points of contact at the asperities of the particles will be under high pressure

and temperature, which cause the HCO to melt and flow into the small fissures and pores of the medicinal compound further producing a more tortuous pathlength.

The modified Lee equation was used to calculate the tortuosities of melt matrixes (5). The tortuosity for the melt matrixes compressed at 7, 35, 139, 244 and 348 MPa are 3.0, 3.2, 3.5, 3.8 and 4.5, respectively. As expected the calculated tortuosity is increased as the applied pressure is increased.

Using the Higuchi equation with a mass transfer coefficient (7) (see Appendix) to calculate the tortuosities of the physical mixture matrixes by fitting the best calculated release profiles to the observed data, the tortuosities determined in this manner for the physical mixture matrixes compressed at 14, 35, 244 and 348 MPa are 0.8, 0.9, 1.3, 1.5 and 2.6, respectively (5).

Although the release mechanism may be different and the explicit values questionable, the trend is evident that the tortuosity of the melt matrix at a given applied pressure is greater than that of the physical mixture matrix, and consequently, a slower release occurs from the melt matrix as was observed. The high porosities of 12.5, 6.4 and 7.9% in physical mixture matrixes compressed at 7, 14 and 35 MPa permit a rapid penetration of the dissolution medium into the matrix, and a linear relationship is observed for the plot of cumulative amount released per unit area versus time. Thus, at high porosity (low applied pressure) the mechanism of release is not the same as at

pressures exceeding 35 MPa at which the release profile shows a square-root-of-time dependency.

Effect of Particle Size. The operation of milling and its production of smaller particles of a medicinal compound may affect the release of the compound from a matrix. Using 20/40-, 80/100- and <200-mesh size fractions of ephedrine hydrochloride in a 40% matrix with HCO prepared by compression of physical mixture, it has been reported that the particle size has little or no effect on total porosity (5). Similarly it was found that the drug loading did not significantly change if the applied pressure were sufficient to produce a small air porosity.

Release of ephedrine hydrochloride from matrixes compressed from physical mixtures of the three particle sizes was slowest from the matrix prepared with the largest particles. A faster release from matrixes prepared with finer particles suggests the release is controlled by a boundary layer diffusion (8). As the particle size becomes smaller, the tortuosity decreases as illustrated in Table 2. As the particle size is decreased, the specific surface area is increased and the tortuosity is decreased; therefore, a faster release would be anticipated.

Using the same three size fractions a matrix containing 40% ephedrine hydrochloride was prepared by a melt process. The release from a matrix prepared by the melt process for a given size fraction of ephedrine hydrochloride was slower than from a

TABLE 2

Effect of Particle Size of Ephedrine Hydrochloride on Caluclated Tortuosity and Time Required for 50% of Ephedrine Hydrochloride To Dissolve from Matrixes Prepared by Compression of a Melt and by Compression of a Physical Mixture

Mesh Size Fraction, passed/retained	Physical Mixture Matrix		Melt Matrix	
	$t_{50\%}$, h	τ	$t_{50\%}$, h	τ
20/40	2.9	1.9	1.9	1.0
80/100	0.7	0.4	10.6	2.9
passed 200	1.2	1.0	16.9	3.7

matrix prepared by compression of a physical mixture as shown in Table 2. In matrixes prepared by the melt process as the particle size is decreased, the tortuosity is increased. Apparently the slower release from a matrix prepared by the melt process results from the greater tortuosity and more intimate contact between the ephedrine hydrochloride and HCO, which produces a mass transfer by matrix diffusion.

CONCLUSION

It is demonstrated that processing (applied pressure, comminution, method) may influence the release of a highly water-soluble medicinal compound from an inert, heterogeneous matrix. For a given fomulation and applied pressure the release rate or flux is slower from a matrix prepared by a melt process than from a matrix prepared by compression of a physical mixture.

Although the release rate from a matrix is slowed as the applied pressure is increased for both matrixes, the matrix prepared by compression of a physical mixture is more sensitive to applied pressure than a matrix prepared by the melt process. For the matrix prepared by compression of a physical mixture the release was faster as the particle size of the ephedrine hydrochloride was decreased. For the matrix prepared by a melt process, the release was slowed as the particle size of the ephedrine hydrochloride was decreased.

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APPENDIX

Diffusional Models. Paul and McSpadden (7) derived a model for matrixes in which the release is governed by diffusion through the matrix and boundary layer by (a) employing the assumptions of Higuchi (9, 10) and (b) introducing a mass transfer coefficient representing the resistance within the boundary diffusion layer. The cumulative amount released per unit area is:

$$Q = (A - 0.5C_s)\left\{\left[\left(\frac{D}{\alpha}\right)^2 + \frac{2DC_s t}{A - 0.5C_s}\right]^{\frac{1}{2}} - \frac{D}{\alpha}\right\} + 0.5C_s\left\{\frac{(D/\alpha)^2}{\left[\left(\frac{D}{\alpha}\right)^2 + \frac{2DC_s t}{A - 0.5C_s}\right]^{\frac{1}{2}}} - \frac{D}{\alpha}\right\} \quad \text{(Eq. 1)}$$

According to Cussler (11) the mass transfer coefficient equals D/h. The mass transfer coefficient relates the mass transferred to the concentration difference between the matrix surface and the bulk solution and the interfacial area. This modification and the correction for a heterogeneous matrix transforms Eq. 2 to:

$$Q = (A - 0.5\varepsilon C_s)\left\{\left[\left(\frac{h}{\tau}\right)^2 + \frac{2D\varepsilon C_s t}{A - 0.5\varepsilon C_s}\right]^{\frac{1}{2}} - \frac{h}{\tau}\right\} \qquad \text{(Eq. 2)}$$

$$+ 0.5\varepsilon C_s \left\{\frac{(h/\tau)^2}{\left[\left(\frac{h}{\tau}\right)^2 + \frac{2D\varepsilon C_s t}{A - 0.5\, C\varepsilon_s}\right]^{\frac{1}{2}}} - \frac{h}{\tau}\right\}$$

All terms but the tortuosity may be experimentally measured so that the tortuosity may then be calculated.

Lee (6) derived a diffusional model for release form a homogeneous matrix applicable for all values of A and C_s:

$$Q = \frac{1 + H}{(3H)^{\frac{1}{2}}}\left[C_m (Dt)^{\frac{1}{2}}\right] \qquad \text{(Eq. 3)}$$

where:

$$H = 5\left(\frac{A}{C_m}\right) - 4 + \left[\left(\frac{A}{C_m}\right)^2 - 1\right]^{\frac{1}{2}} \qquad \text{(Eq. 4)}$$

In a heterogeneous matrix diffusion occurs solely in the space previously occupied by the medicinal compound and air. The insertion of C_s for C_m introduces this consideration. To compensate for the increased diffusional pathlength in a

heterogeneous matrix, the diffusivity is divided by the tortuosity. Thus,

$$Q = \frac{1 + H}{(3H)^{\frac{1}{2}}} \left[\varepsilon C_s \left(\frac{Dt}{\tau} \right)^{\frac{1}{2}}\right] \qquad \text{(Eq. 5)}$$

where:

$$H = 5 \left(\frac{A}{\varepsilon C_s} \right) - 4 + \left[\left(\frac{A}{\varepsilon C_s} \right)^2 - 1 \right]^{\frac{1}{2}} \qquad \text{(Eq. 6)}$$

All terms but tortuosity may be experimentally measured so subsequently the tortuosity may be calculated.

Glossary.

A = drug loading, g/mL

C_m = solubility of medicinal compound in matrix, g/mL

C_s = solubility of medicinal compound, g/mL

D = diffusivity of medicinal compound, cm^2/s

h = thickness of diffusion layer, cm

t = time, s

ε = porosity of matrix, dimensionless

τ = tortuosity of matrix, dimensionless

Q = cumulative amount released per unit area

α = mass transfer coefficient, cm/s