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RESEARCH PAPER

Effects of Hydrophilic Excipients and Compression Pressure on Physical Properties and Release Behavior of Aspirin-Tableted Microcapsules

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ABSTRACT

Aspirin ethylcellulose microcapsules were tableted by compression with or without excipients (lactose or polyvinylpyrrolidone [PVP]). The effects of the amount of the excipients and microcapsule size on the crushing strength and release rate of aspirin from tableted microcapsules were investigated. Tablets without excipients had a crushing strength that was independent of the applied pressure and microcapsule size. An increase in compression pressure from 15 to 60 MPa resulted in an increase in the crushing strength of tablets containing 20% or 40% w/w lactose, but the reverse results were obtained for the tableted microcapsules containing 20% or 40% w/w PVP. Results showed that the release rate of aspirin from microcapsules containing lactose or PVP was independent of the compression pressure with the exception of tablets containing 40% w/w lactose. In vitro release profiles of aspirin from tableted microcapsules containing lactose or PVP showed that increasing the concentration of the excipients resulted in an increase in the release rate of aspirin. Values of n *were changed by the compression pressure and the added excipients.*

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INTRODUCTION

Tableting of microcapsules offers a convenient method for formulating microencapsulated drug particles into a dosage form (1,2). Acceptable tablets containing microcapsules should exhibit sufficient physical integrity to withstand handling, while maintaining a drug release profile similar to the uncompressed microcapsule. Drug release after compression of microcapsules may be faster or slower, depending on the effect of compression on the porosity and microcapsule integrity (3–6). The influence of hydrophilic excipients on tableted microcapsules has not been adequately studied (7,8). In the present study, the influence of hydrophilic excipients and compression pressure on the tablet properties and release behavior of tablets made from aspirin ethylcellulose microcapsules was investigated.

MATERIALS AND METHODS

Materials

Aspirin microcapsules containing 8% ethylcellulose (Pars Darou Pharm. Company, Iran), Lactose (Merck, Germany), and polyvinylpyrrolidone (PVP 35,000) were obtained.

Methods

Preparation of Tableted Microcapsules

Tableted microcapsules (500 mg) containing both microcapsules and excipients (lactose or PVP) were prepared by compression. Aspirin microcapsules (88–385 μm) and excipients were uniformly mixed and compressed. Compression was carried out using an infrared (IR) spectrophotometric tableting machine with a pressure gauge (Riken Seiki Co., Tokyo) under different pressures, ranging from 15 to 60 MPa, for 1 min. To determine the effect of percentages of hydrophilic excipients, two concentrations (20% and 40% w/w) of each excipient (lactose or PVP) were used. To investigate the effect of microcapsule particle size on the release rate and tablet properties of microencapsulated aspirin tablets without excipients, three particle size fractions (88–385, 385–600, or 600–1020 μm) of aspirin microcapsules were used.

Tablet Evaluation

The height and thickness of 5 tablets were measured to 10 μm using a micrometer (Mitutoyo, Japan) 1 min after ejection. The true densities of the tablet components were determined using an air comparison pycnometer. Tablet crushing strength of 5 tablets was determined from the force required to fracture the tablets on a motorized tablet hardness tester. The porosity of the tablets was calculated as described elsewhere (9).

Release Studies

The USP basket method was used for all the in vitro dissolution studies. In this method, distilled water that simulated gastric fluid (pH 1.20 without enzyme) was used as the dissolution media. The rate of stirring was 100 rpm. The tableted microcapsules were placed in 900 ml of gastric fluid and maintained at 37°C. At appropriate intervals, 5 ml of each sample were taken and filtered through a 0.45-μm Millipore filter. The dissolution media was then replenished with 5 ml of fresh dissolution fluid to maintain a constant volume. The samples were then analyzed at 275 nm by an ultraviolet-visible (UV-Vis) spectrophotometer. The mean of three determinations was used to calculate the drug release from each of the formulations.

RESULTS AND DISCUSSION

Tablet Properties of Aspirin-Tableted Microcapsules

The effects of compression pressure and particle size of microcapsules on the hardness of tableted microcapsules without excipient are shown in Table 1. It can be seen that the hardness of tablets prepared by direct compression of three different particle sizes of aspirin microcapsules was unaffected by the change of compression pressure ($P > .05$). This might be because a compression pressure above 15 MPa is so much higher that it results in that hardness. This phenomenon was also indicated for microencapsulated theophylline (8) and sodium phenobarbital (10). Table 1 also shows that increasing the microcapsule size from 85–385 μm to 600–1020 μm had no significant effect on the hardness of the tablets ($P > .05$). Porosity data confirmed that compression pressure above 15 MPa is so much higher because the porosity of the tablets was not changed by the compression pressure (Table 2). For instance, as the compression pressure was increased from 15 to 60 MPa, the porosity the of tablets was reduced from 4.76% to 2.74% for a particle size of 85–385 μm, which was not statistically significant ($P > .05$).

Table 1

Effects of Compression Pressure and Microcapsule Size on the Crushing Strength (kP) of Tablets Containing Aspirin Microcapsules Without Excipients

	Compression Pressure (MPa)			
Microcapsule Size (μm)	15	30	45	60
85–385	9.14 ± 0.15	9.33 ± 0.18	9.11 ± 0.61	8.59 ± 0.49
385–600	9.38 ± 0.30	9.13 ± 0.52	9.43 ± 0.52	9.25 ± 0.32
600–1020	9.28 ± 0.32	9.41 ± 0.34	9.73 ± 0.47	9.47 ± 0.31

Figure 1 shows the effects of compression pressure and excipients on the crushing strengths of tableted microcapsules. From Fig. 1, it can be seen that an increase in compression pressure from 15 to 60 MPa resulted in an increase in the crushing strength of tablets containing 20% or 40% w/w lactose. On the other hand, the crushing strength of tableted microcapsules containing 20% or 40% w/w PVP decreased with an increase in compression pressure from 15 or 30 to 60 MPa (Fig. 1). The crushing strength of tablets containing PVP was higher than that of tablets with or without lactose at low pressures (15 and 30 MPa), whereas the hardness of tablets containing lactose was higher than that of tablets with or without PVP at higher pressures (45 and 60 MPa). This implies that the excipient and compression pressure play an important role in the tableting formulations of aspirin microcapsules (Table 3).

Release Behavior of Aspirin from Tableted Microcapsules

The effect of pressure on the release rate of aspirin from tableted microcapsules containing 0%, 20%, and 40% w/w lactose or PVP was investigated. The results showed that the release rate of aspirin from tableted microcapsules was not affected significantly by the compression pressure, with the exception of tablets containing 40% w/w lactose. Figure 2 shows that an increase in compression pressure from 15 to 60 MPa resulted in a reduction in the release rate of aspirin from tableted microcapsules containing 40% w/w lactose. In comparison, the release of aspirin from tableted microcapsules without excipients at pH 1.2 is shown in Fig. 3. The tab-

Table 2

Effects of Compression Pressure and Microcapsule Size on the Porosity (%) of Tablets Containing Aspirin Microcapsules Without Excipients

	Compression Pressure (MPa)			
Microcapsule Size (μm)	15	30	45	60
85–385	4.76	4.27	3.80	2.74
385–600	4.50	4.57	4.56	4.24
600–1020	5.55	4.64	4.67	4.48

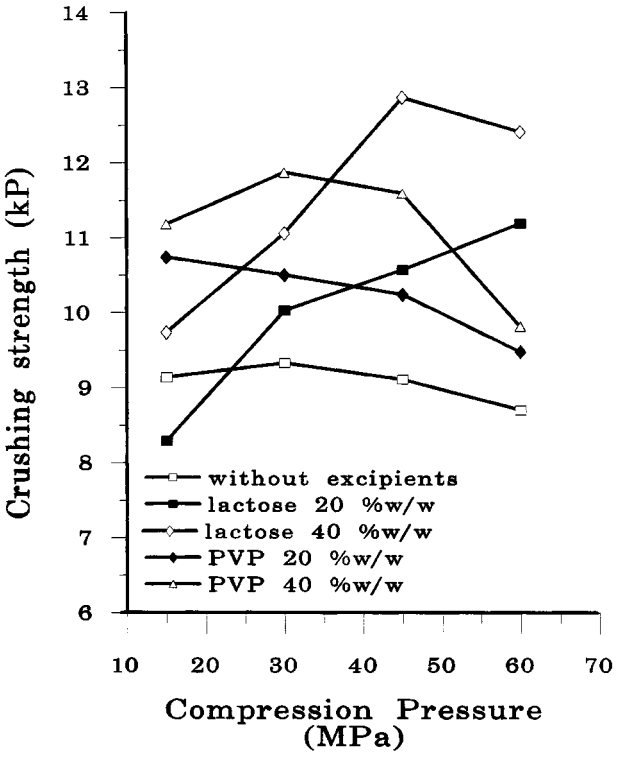

Figure 1. The effects of compression pressure and type of excipient on the crushing strength of tableted aspirin microcapsules.

Table 3

Effects of Compression Pressure and Type of Excipient on the Porosity of Tableted Microcapsules

	Compression Pressure (MPa)			
Composition (%)	15	30	45	60
MCP	4.76	4.27	3.80	2.74
MCP + lactose 20%	7.27	6.42	6.26	6.08
MCP + lactose 40%	8.71	6.78	6.22	6.14
MCP + PVP 20%	3.50	3.86	4.52	4.68
MCP + PVP 40%	1.84	1.54	2.32	2.34

leted microcapsules became an insoluble ethylcellulose matrix because all tablets did not disintegrate or change their shape and size during the course of release. This phenomenon resulted in a slower release rate for tableted microcapsules than for untableted microcapsules that were homogeneously dispersed in dissolution medium, leading to rapid release.

Lin showed that the release rate of theophylline from tableted microcapsules containing lactose was independent of the applied pressure (8). The present study showed that, when the amount of lactose was 40% w/w, the release rate of aspirin was dependent on the applied pressure. Lin also showed that when theophylline microcapsules (425–850 μm) were tableted without excipient, the release rate of theophylline increased with an increase

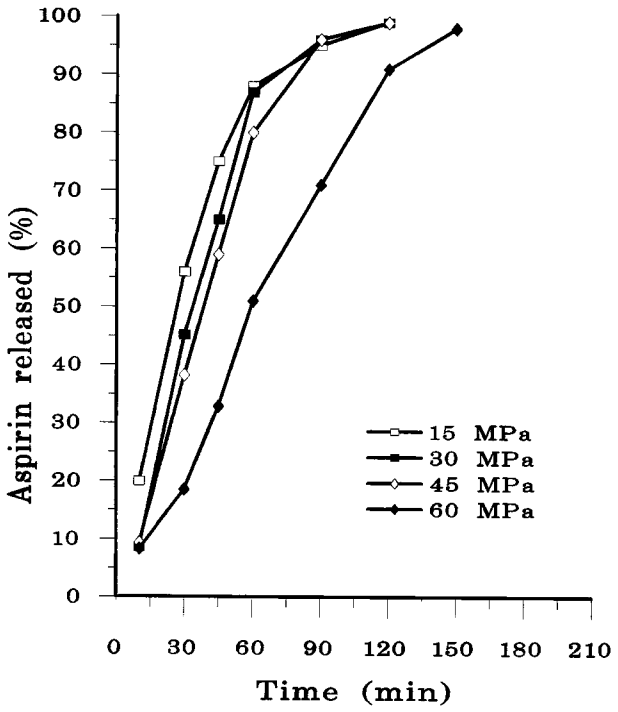

Figure 2. The effect of compression pressure on the release rate of tableted aspirin microcapsules containing 40% w/w lactose.

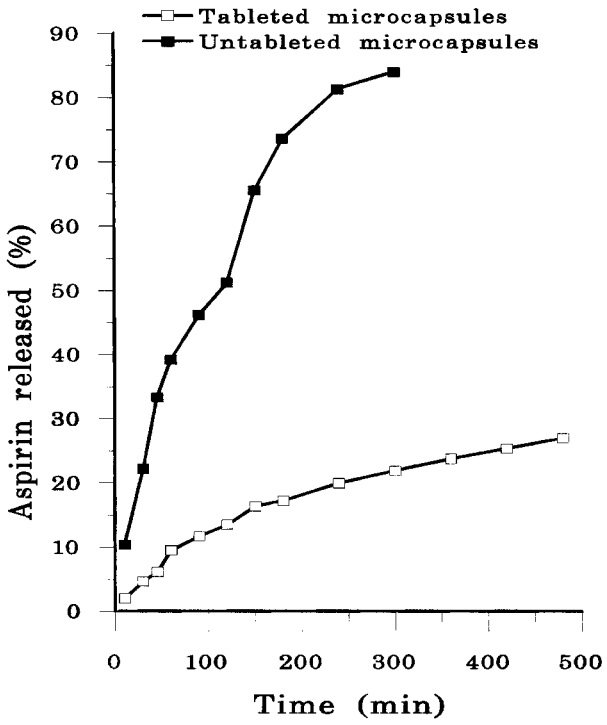

Figure 3. The release rates of aspirin from tableted and untableted microcapsules without excipients.

in compression pressure. This might be due to the less-compact nature of the tablet made by 150 kg/cm^2 pressure compared with that made by 350 kg/cm^2 pressure (8). However, the release of the drug from microcapsules compressed by a pressure of 450 kg/cm^2 is faster than that of tablets compressed by 250 or 350 kg/cm^2 pressure (8). This corresponding increase in release may be explained by the breakage of the wall and microcapsule during the higher compression pressure.

It was found that tablets containing lactose showed slower release than tablets containing PVP. For instance, the effect of lactose or PVP on the release rate of aspirin microcapsules compressed at 15 MPa is shown in Fig. 4. The same pattern was observed at the other compression pressures for tablets containing 40% w/w lactose or PVP. It can be concluded that aspirin microcapsules compressed at higher pressures showed slower release than those compressed at lower pressures; this indicates the good binding ability of lactose.

Figure 4 also shows that an increase in amount of lactose or PVP resulted in an increase in the release rate of aspirin. This shows that both excipients can alter the release of aspirin from the tableted microcapsules.

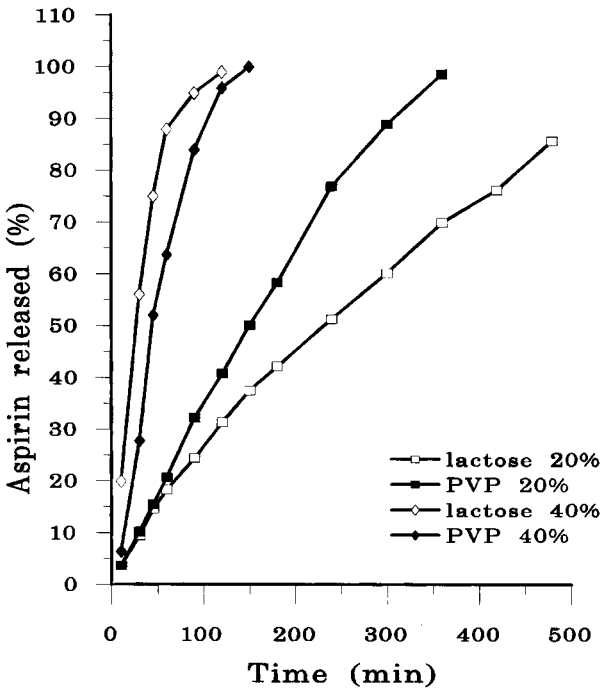

Figure 4. The effects of the type and concentration of excipient on the release rate of aspirin from microcapsules tableted at a compression pressure of 15MPa.

Korsemeyer et al. (11) used a simple empirical equation to describe general solute behavior from controlled-release polymeric matrices:

$$Q = Kt^n \quad (1)$$

where Q is the fractional release of the drug, t is the release time, K is a constant incorporating structural and geometrical characteristics of the release device, and n is the release exponent indicative of the release mechanism. When n approximates 0.5, a Fickian/diffusion-controlled release is implied, with $0.5 < n < 1$ indicating non-Fickian transport, and $n = 1$ for zero-order release. When the value of n approaches 1, phenomenologically one can conclude that the release is approaching zero order (11).

Comparing n values obtained based on Eq. 1 for different tablets showed that there was little difference between the n value obtained for untableted microcapsules ($n = 0.566$) and compressed microcapsules ($n = 0.576$) with the same microcapsule size (85–385 μm) compressed at 15 MPa, indicating the mechanism of release was diffusion. When lactose or PVP (20% w/w) was added to the tablets containing microcapsules that were compressed at 15 MPa, the values of n were 0.786 or 0.851, respectively, indicating both diffusion and erosion.

The effect of compression pressure on n value was also investigated. The results showed that, as the compression pressure was increased from 15 to 60 MPa, the n value was reduced from 0.786 to 0.642. This indicates that, with an increase in compression pressure, the mechanism of release from the tablets changes from diffusion and erosion to diffusion. The same pattern was observed for tablets containing 20% w/w PVP. Different patterns were observed for the matrices containing 40% w/w lactose or PVP. It can be concluded that the amount of hydrophilic excipients and compression pressure can alter the mechanism of release.

In conclusion, the results obtained in this study confirmed that the compression pressure and the use of lactose or PVP in the formulation of aspirin microcapsules could alter the mechanical properties and release rate of tableted aspirin microcapsules.

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