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Dissolution characteristics of interactive powder mixtures. 4. Effects of additives on the dissolution of griseofulvin from Emcompress carrier

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Summary

Excipient particles having highly indented surfaces such as Emcompress powder, entrapped drug particles and/or agglomerates, thus hindering their dispersion into the powder mixture and reduced the surface area available for dissolution. The result was a reduction in the dissolution of griseofulvin from such interactive powder systems relative to those excipients which have smooth particulate surfaces. At pH 1.0 the dissolution efficiency of the drug showed a maximum value since effects arising from indentations were insignificant. On the other hand, at pH 7.0 Emcompress powder was insoluble and hence, indentations, with the drug particles and/or agglomerates entrapped therein, impaired the dissolution process. Filling entrapment sites with additives, e.g. calcium hydrogen phosphate dihydrate, lactose, sucrose and maize starch improved dissolution. Different mechanisms are discussed to explain the role of each filling agent in improving dissolution from the griseofulvin-Emcompress interactive mixtures.

Introduction

Several authors proposed the use of macroporous free flowing excipients with cohesive drug powders in order to produce highly homogeneous stable powder mixtures (Staniforth and Rees, 1982; Schmidt and Benke, 1985; Staniforth, 1987). The operating mechanism depends on the strong adhesion ability of fine drug particles to the active sites on the surface of coarse excipient particles. This approach was adopted to increase the dissolution rates of poorly soluble drugs (Nystrom and Westerberg, 1986; Westerberg et al., 1986; Nilsson et al., 1988). The coarse excipient particles, during the mixing process, broke up drug agglomerates into individual particles which were then dispersed homogeneously and adhered strongly to the surfaces of the excipient particles (Hersey, 1979; Egermann, 1983). The result was a large surface area available for dissolution and hence, an improved dissolution rate for poorly soluble drugs.

Excipient particles having highly indented surfaces like Emcompress powder were shown to entrap drug particles and/or agglomerates (Sal-

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lam et al., 1986, 1988; Ibrahim et al., 1988). Such effects resulted in hindering drug dispersion onto the powder mixture and reduced the surface area available for dissolution. As a result, the dissolution efficiency of poorly soluble drugs like griseofulvin was impaired. These effects were particularly significant when insoluble excipients were used (Ibrahim et al., 1988; Sallam et al., 1988). In the case of insoluble excipients, the wettability of surfaces was also reported to be dependent on their rugosities (Buckton, 1988). Filling entrapment sites with additives was suggested to improve dissolution of such systems (Sallam et al., 1988). In this study, the effects of premixing of Emcompress powder with different filling agents to block entrapment sites; on the dissolution of griseofulvin from Emcompress interactive powder mixtures were investigated.

Materials and Methods

Emcompress powder of particle size smaller than 250 μm (Forum Chemical Ltd, U.K.), Sucrose powder, Calcium hydrogen phosphate dihydrate (Merck, Germany) and Lactose (Riedel de Haen, Germany) were used. Maize starch and micronized griseofulvin were of pharmaceutical grade supplied by the Arab Pharmaceutical Manufacturing Co. Ltd (Sult, Jordan).

Emcompress powder was used as a model of excipients possessing a highly indented particulate surface. Sucrose powder (SP), calcium hydrogen phosphate dihydrate (CHPD), lactose powder (LP), maize starch (MZS) were used to fill sites available for entrapment of drug particles and/or agglomerates on Emcompress powder. Size fractions of 38–125 μm were used for all filling agents.

The cube mixer (Erweka Co., Germany), was used to prepare 5% w/w and 10% w/w premixes of Emcompress with the different filling agents. Mixing was carried out for 15 min. In order to avoid oversaturation of surfaces of excipient particles with drug agent, the ratio of micronized griseofulvin to excipient was maintained at 3×10^{-3} w/w in all experiments (Nystrom and Westerberg, 1986; Westerberg et al., 1986).

In a typical run, the powder mix used in a dissolution experiment was prepared by mixing griseofulvin with the excipient (premixed with filling agent) in a cube mixer for 45 min.

Dissolution studies were performed according to the USP XXI paddle method at 100 rpm. 500 ml of a 0.9% solution of sodium chloride, containing 0.01% w/w polysorbate 80 (Riedel-de Haen, Germany) was used as a dissolution medium.

Dissolution runs were carried out using the above mentioned dissolution medium without controlling its pH (pH approx. 7.0), and after adjusting the pH values to 1.0 and 2.9 using concentrated hydrochloric acid. Each dissolution study was done in triplicate, using 0.75 g of the powder mix. Griseofulvin concentration in solution was continuously monitored by circulating the solution into Kontron spectrophotometer (Kontron, Sweden) and measuring the absorbance at 295 nm.

Scanning electron microscopy (ESM) photomicrographs of powders were carried out using Leitz, 1000A, AMR Electron Scanning Microscope (Leitz, Germany). Samples were prepared for examination by sputter coating with gold.

Data treatment

Dissolution data from different interactive powder mixtures were presented as % dissolved-time plots and also as dissolution efficiencies. The dissolution efficiency equations were used previously (Ibrahim, 1985) and were applied to describe quantitatively in-vitro dissolution behaviour of different interactive powder mixtures (Ibrahim et al., 1988). The following equations were used to calculate the dissolution efficiency at time t, (DE_t), and the relative dissolution efficiency of formulation (j) with respect to a standard formulation (S), (DE_j), assuming a first-order release from the powder mix.

$$(DE_t) = \left[\left(1 + \frac{1}{A} \cdot (e^{-A} - 1)\right)\right] \cdot 100 \qquad (1)$$

where $A = 4.606 - \ln(100 - f)$; f is the percentage of drug in solution at time t.

$$(DE_j) = \left[1 + \frac{1}{B} \cdot (e^{-B} - 1)\right] \cdot 100 \qquad (2)$$

where $B = K_j/K_S \cdot 4.606 - \ln(100 - f_S)$.

K_j and K_S are first-order rate constants of dissolution from the test formulation (j) and the standard formulation (S), respectively. The interactive powder mixture of griseofulvin Emcompress without filling agent was chosen as the standard formulation, to express the relative dissolution efficiencies of other formulations.

Results and Discussion

ESM examinations

Examination of ESM photomicrographs of Emcompress powder (Fig. 1) reveals that the particles are highly indented with very high rugosity surfaces, although they are free flowing particles. Griseofulvin powder is a micronized powder of cohesive nature, (Fig. 1). Examination of Fig. 2 shows that particles of calcium hydrogen phosphate dihydrate (CHPD) powder are the finest relative to the other filling agents. The apparent particle shape and size of lactose powder (LP) and sucrose powder (SP) show close similarity (Fig. 2). However, SP seems to possess more of coarse fractions. Both powders are cohesive in nature. Maize starch (MZS) exhibits regular shaped, more or less spherical particles. MZS, on the other hand, is a fine powder and lacks cohesiveness (Fig. 2).

Dissolution studies

Fig. 3 shows the dissolution profiles of griseofulvin from interactive powder mixtures of Emcompress powder at pH values of 1.0, 2.9 and 7.0. At pH 7.0, Emcompress powder is insoluble in the dissolution medium and the interactive powder mixture exhibited least dissolution. At pH 1.0, on the other hand, Emcompress powder is completely soluble; and grisoefulvin dissolution was maximum. Dissolution of the powder mix at pH 2.9 showed intermediate values.

The dissolution of griseofulvin-Emcompress interactive powder mixtures in the presence of filling agents was also shown to be pH dependent. Since Emcompress particles are soluble at pH 1.0, the adhered drug particles either entrapped or attached to the surface, were immediately exposed to the medium for the dissolution process to commence. Consequently, the dissolution efficiency at 10 minutes (DE_{10}) showed maximum values at pH 1.0 (DE_{10} range, 58.0–71.7), relative to its corresponding values at pH 2.9 (DE_{10} range, 22.6–38.8)

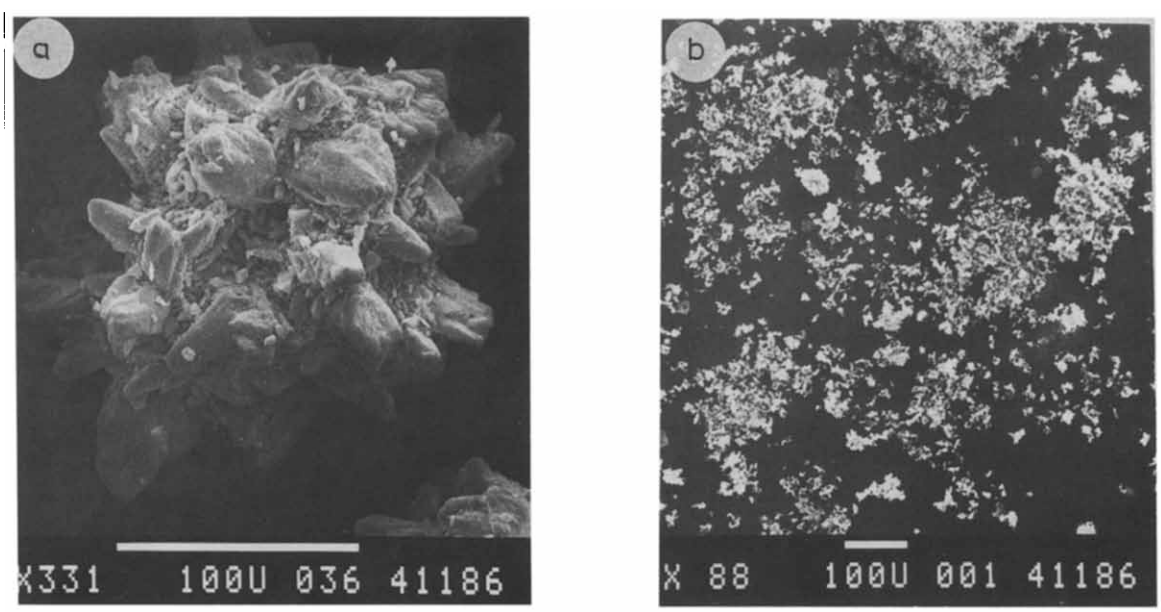

Fig. 1. ESM photomicrographs of Emcompress powder (a) and griseofulvin powder (b).

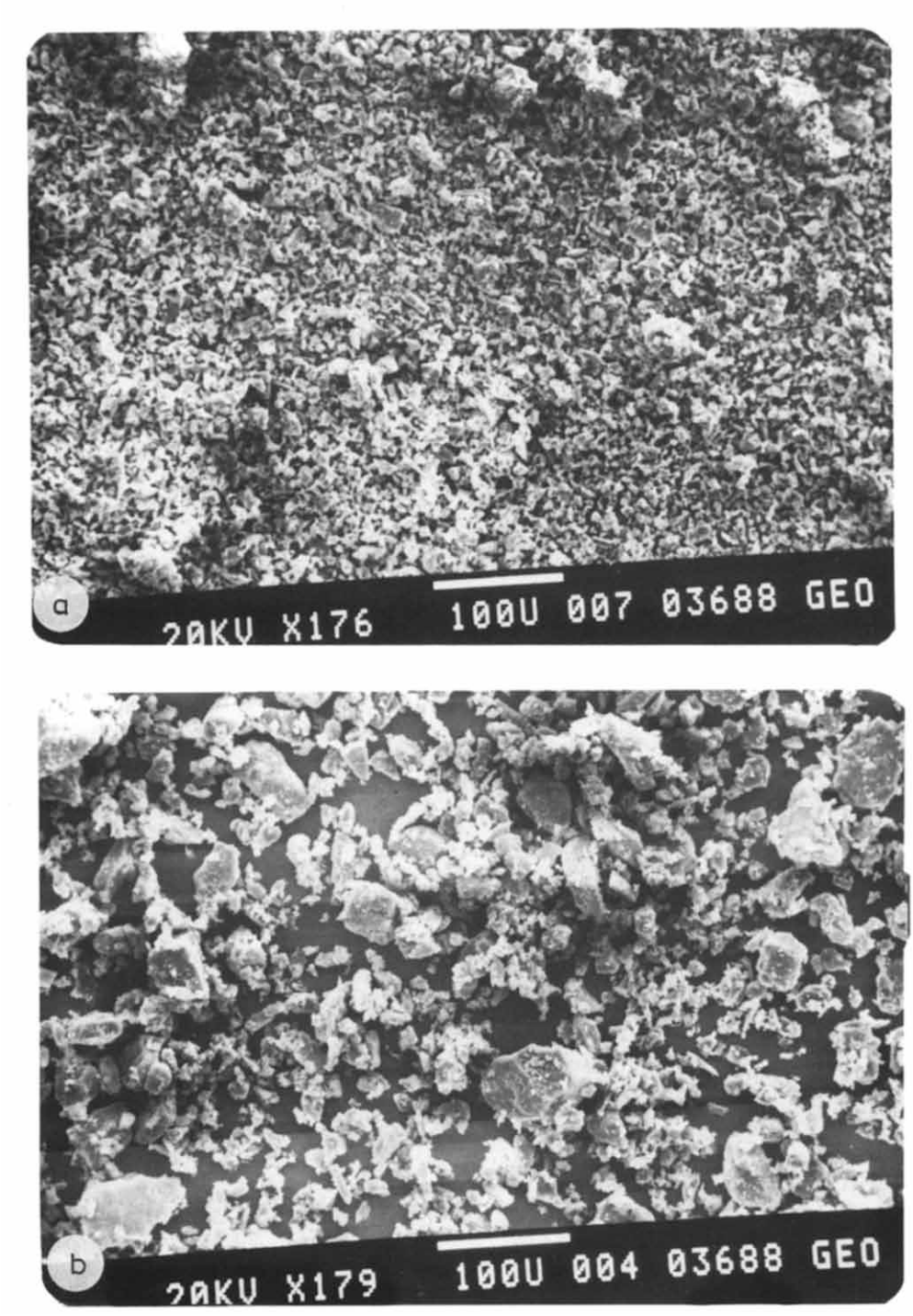

Fig. 2. ESM photomicrographs of calcium hydrogen phosphate (a, ×176), lactose (b, ×179), sucrose (c, ×172) and maize starch (d, ×1720).

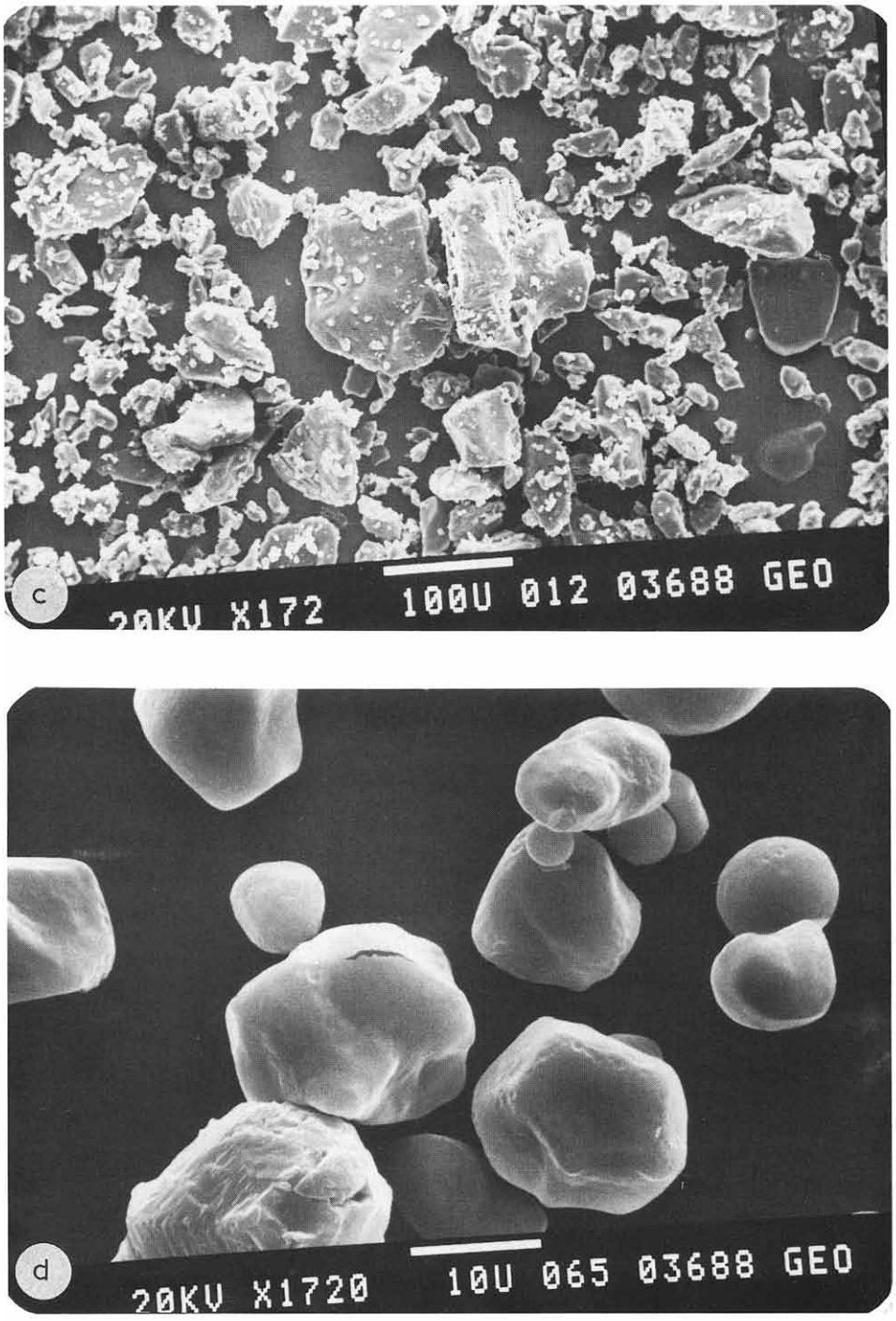

Fig. 2 (c,d).

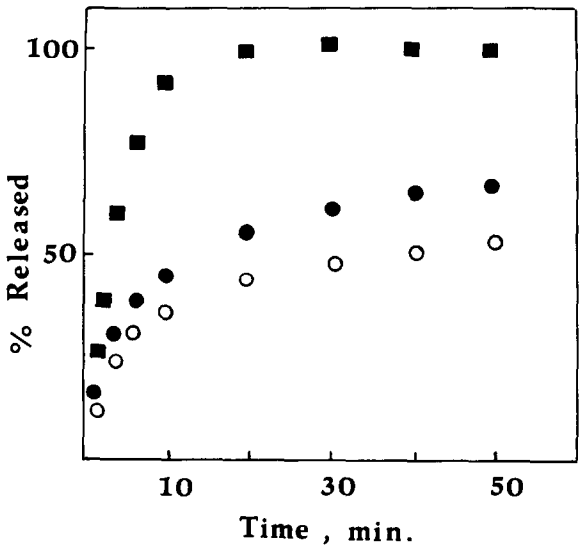

Fig. 3. Dissolution profiles of griseofulvin from interactive powder mixtures of Emcompress at pH 1.0 (■), pH 2.9 (●) and pH 7.0 (○).

and pH 7.0 (DE_{10} range 19.2–34.4) at the 10% level of the four filling agents.

At pH 7.0 Emcompress powder is insoluble and hence, indentations, with drug particles and/or agglomerates entrapped therein, caused a significant reduction in the dissolution efficiency. Furthermore, Emcompress powder is dense (2.873 g/cm^3), thus during the course of the dissolution run, particles are sedimented and accumulated together to form a cone settled at the center of the bottom of the dissolution vessel. The formation of this cone caused further hindrance to the dissolution of drug particles. At pH 2.9, on the other hand, Emcompress powder is partially soluble, therefore DE_{10} values of most mixtures are higher than corresponding DE_{10} values at pH 7.0 as shown in Table 1.

Analysis of data shows that, at pH values where the excipient is freely soluble, the solubility of filling agents only plays a minor role in influencing the dissolution of the drug. The degree of dispersion of drug particles on the surfaces of excipient particles is considered more important. It is significant to know that, all powder mixtures prepared with filling agents produced higher dissolution efficiency than Emcompress powder alone. This finding indicates that better degree of

TABLE 1

Dissolution efficiency at 10 min (DE_{10}) for griseofulvin-Emcompress interactive powder mixtures at different pH

% w/w of filling agents	pH 2.9	pH 7.0
0%	24.9	19.2
5% CHPD	29.3	25.6
10% CHPD	38.8	34.3
5% LP	31.6	29.3
10% LP	34.5	33.4
5% SP	24.9	22.7
10% SP	26.1	29.2
5% MZS	22.6	21.3
10% MZS	29.2	27.4

CPHD, calcium hydrogen phosphate dihydrate; LP, lactose powder; MZS, maize starch; SP, sucrose powder.

dispersion of drug particles was attained. Two different mechanisms are proposed to explain the findings depending on the type of filling agents. In the case of CHPD, LP and SP, where the particles are fine, cohesive and characterized by interacting with Emcompress particles; the mechanism is mainly dependent on direct filling of the entrapment sites (Fig. 4).

At 10% w/w filling agent, CHPD powder mixture produced a higher DE_{10} value than either LP or SP powder mixtures (71.2% for CHPD compared to less than 65% for LP and SP). This behaviour is attributed to the higher filling capacity of CHPD relative to either LP or SP. Higher filling capacity of CHPD suggests higher interaction with Emcompress powder. The other mechanism, is operating with the particles which are noncohesive and noninteracting with Emcompress particles like MZS. Such properties of the filling agent would not allow proper filling of entrapment sites (Fig. 5a). Furthermore, presence of MZS would allow interaction between agent and drug particles thus promoting dispersion of the drug on larger surface area (Fig. 5b). As a result, powder mixtures containing MZS, at pH 1.0, exhibited higher (DE_j) values (35.7 and 38.1 for 5% w/w and 10% w/w, respectively) than powder mixtures containing Emcompress powder alone ((DE_j) = 34.5; the value of the standard formula-

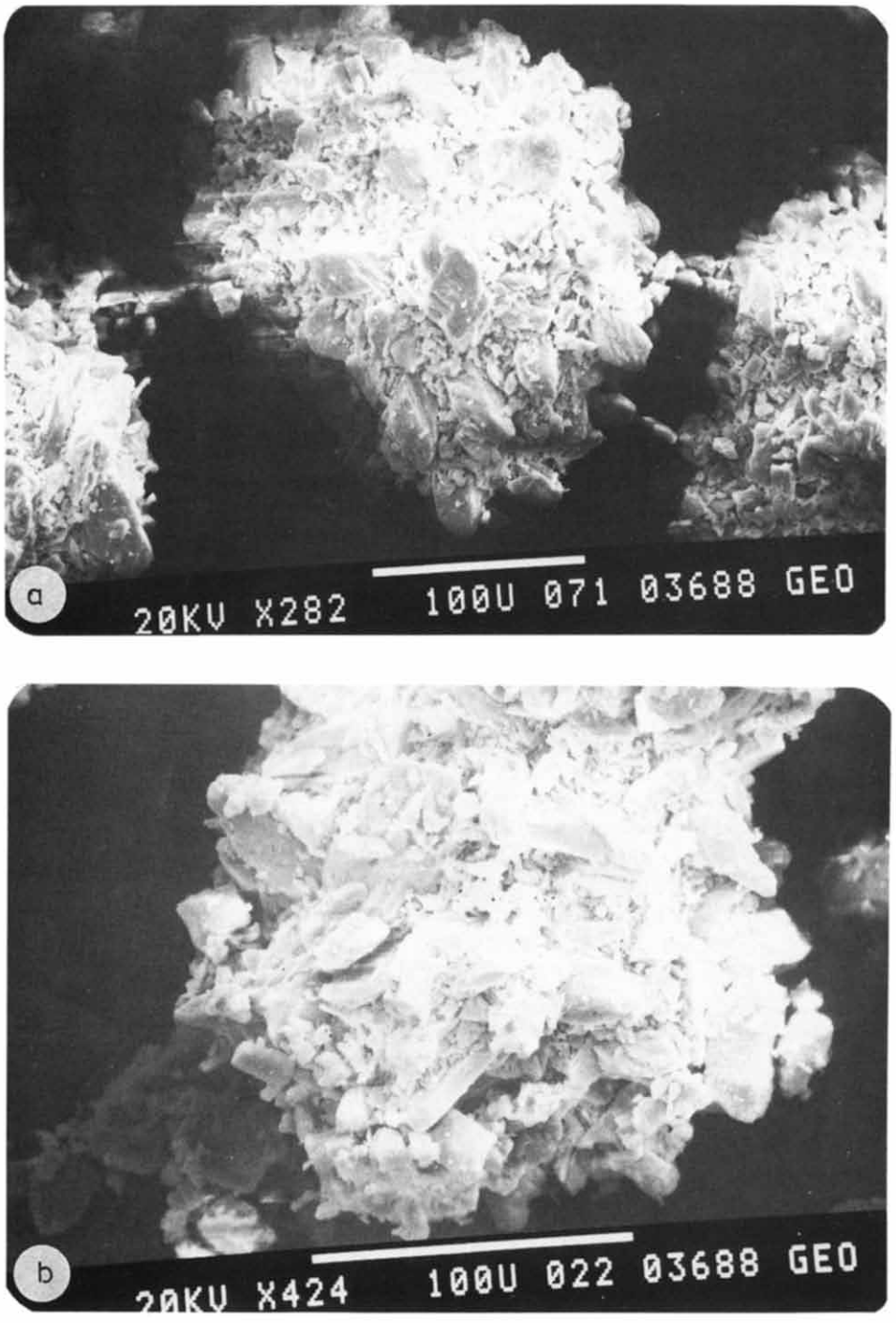

Fig. 4. ESM photomicrographs of Emcompress and griseofulvin interactive powder mixtures. Emcompress was premixed with 10% w/w calcium hydrogen phosphate dihydrate (a), lactose (b) and sucrose (c).

Fig. 4 (c).

tion). In an earlier study (Soebagyo and Stewart, 1985), the presence of starch in prednisolone interactive powder mixtures produced a mixed system of prednisolone-granule and prednisolone-starch particle adhesion units. These authors also reported presence of separated starch aggregates with drug particles. In the current study, this phenomenon was also observed. Few starch particles were located on Emcompress particles and griseofulvin-starch interactive or adhesion units (Fig. 5b) were also formed. Further, a number of separated griseofulvin-starch aggregates were observed (Fig. 5c).

The main drawbacks of aggregate formation are; firstly the tendency of these aggregates to segregate and secondly reduction of the dissolution efficiency particularly at high pH values where Emcompress powder is insoluble (Table 1).

The data in Table 1 also suggest that premixing of Emcompress powder with filling agents increases the dissolution efficiency, in the following order; 10% w/w > 5% w/w > Emcompress alone.

Although CHPD has lower solubility at high pH, it produced comparable dissolution efficiency to that of lactose at a concentration of 10% w/w and pH 7.0 (Table 1). This behaviour could be attributed to the higher filling/dissolution improving capacity of CHPD than lactose, and the finer nature of its particles as already discussed before. At lower concentration (5% w/w), the filling is incomplete and hence, the solubility of lactose was an advantage which resulted in higher dissolution efficiency at pH 7.0 ($DE_{10} = 25.6$ and 29.3 for CHPD and LP respectively; Table 1).

As shown in Table 1, LP powder mixtures exhibited higher dissolution efficiencies than SP powder mixtures. LP has more fine particles than SP (Fig. 2), and from the ESM photomicrographs of their powder mixtures, it is not likely that there is significant difference with respect to the extent of filling. Thus it is possible that, at the entrapment sites sucrose dissolves, forming more viscous microenvironment around adhered drug particles thus creating higher resisting environment for dis-

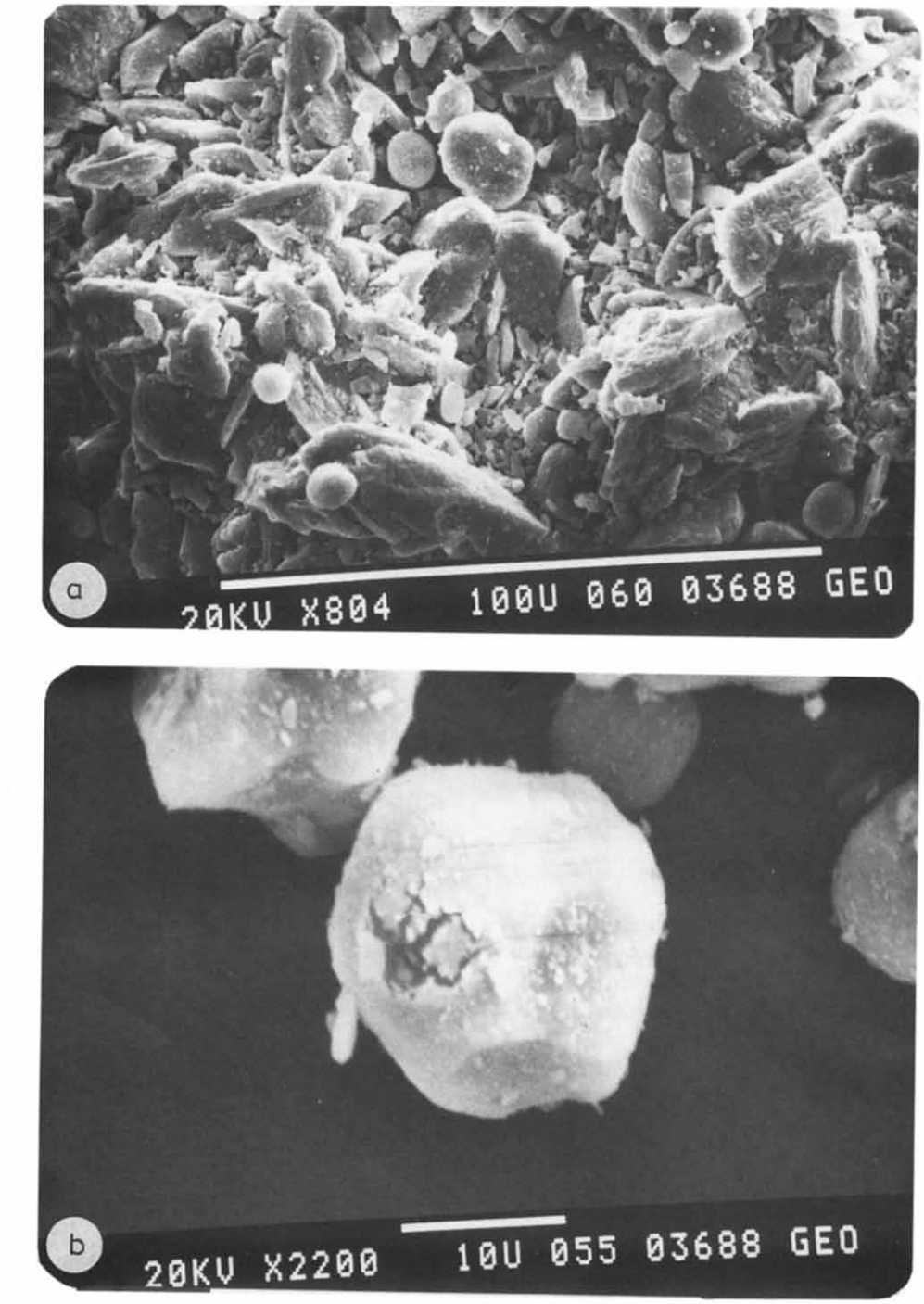

Fig. 5. ESM photomicrographs of Emcompress and griseofulvin interactive powder mixture. Emcompress was premixed with 10% w/w maize starch (a). Griseofulvin particles adhered to maize starch grains during mixing with Emcompress (b). Aggregates of maize starch grains and drug particles (c).

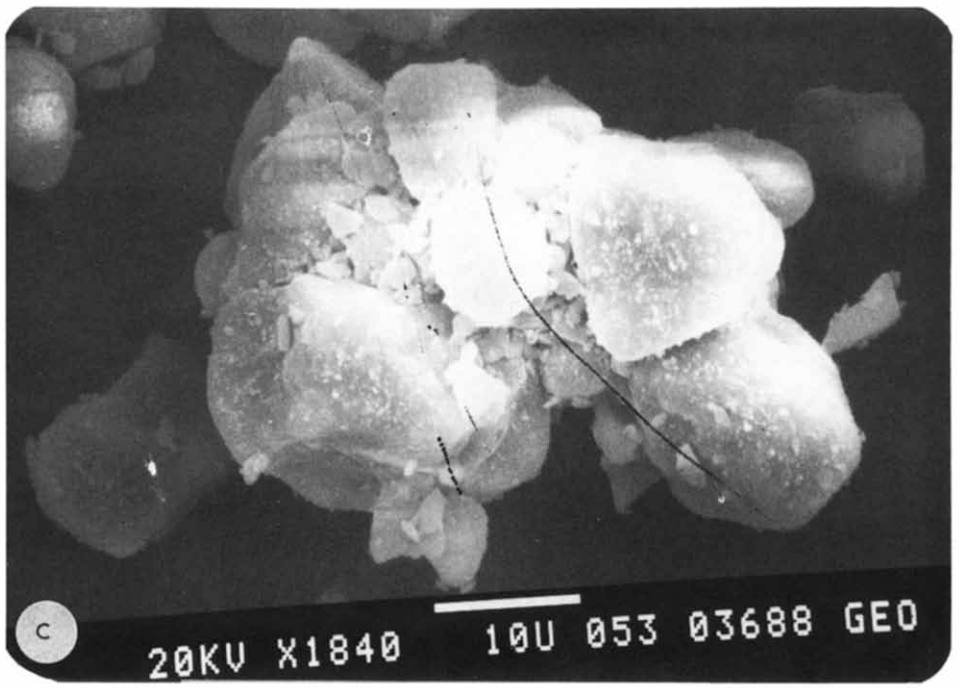

Fig. 5 (c).

solution and a lowering in the dissolution efficiency. However, further studies are required to investigate this effect.

Conclusion

The pH of the dissolution medium plays a major role in the dissolution of griseofulvin from Emcompress interactive powder mixtures. At pH 1.0 Emcompress powder is soluble, and dissolution is maximum. The solubility of the filling agents does not significantly affect the dissolution at pH 1.0, since it is overshadowed by the high solubility of Emcompress powder at that pH.

At pH 7.0 Emcompress powder is insoluble and hence, indentations with entrapped drug particles and/or agglomerates reduced the dissolution efficiency. Premixing of Emcompress powder with filling agents increased the dissolution efficiency in accordance with the amount added in the following order, 10% w/w > 5% w/w > Emcompress alone.

Maize starch seemed not to interact with Emcompress powder and hence, the filling capacity was minimum. However, with systems containing MZS dissolution efficiency increased due to the formation of presumably an additional interactive powder mixture composed of drug particles and starch granules, thus creating higher surface area available for dissolution. Formation of separated aggregates with drug particles produced lower dissolution efficiency at high pH where Emcompress powder is insoluble.

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