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DISSOLUTION CHARACTERISTICS OF INTERACTIVE POWDER MIXTURES. PART TWO: EFFECT OF SURFACE CHARACTERISTICS OF EXCIPIENTS.

E.Sallam+, H.Ibrahim, M.Takieddin,
M.Abu Shamat and T.Baghal.
Department of Pharmaceutics, Faculty of Pharmacy,
University of Jordan, Amman, and Arab Pharmaceut.
Manufacturing Co+, Sult, Jordan.

ABSTRACT

The efficiency of interactive powder mixtures as a process used to increase the dissolution rate of poorly soluble drugs is dependent on the degree and extent of dispersion of drug agglomerates into individual particles. Furthermore, the dispersion mechanism is dependent on the surface characteristics of excipient particles.

The smooth excipient particles produce interactive powder mixture with high dissolution efficiency for poorly soluble drugs. In contrast, when the excipient particulate surfaces have high rugosity, the corresponding interactive powder mixtures produce lower dissolution efficiency. The main reason is the entrapment of drug particles and agglomerates into the indentations

+ For Correspondence : Dr E.Sallam, P.O.Box 960761, Amman, Jordan.

already present on excipient particulate surfaces. When the entrapment sites are blocked with fine excipient particles the dissolution efficiency increases significantly. Therefore, surface characteristics of excipient particles should be examined carefully before formulation of solid dosage forms using interactive powder mixtures as a process for increasing the dissolution rate of poorly soluble drugs.

INRODUCTION

In earlier studies dissolution rate of poorly soluble drugs was increased by forming interactive powder mixtures (I - 3). The degree of solubility of excipients were shown to affect the dissolution rate of these drugs from their corresponding interactive mixtures (2 - 4).

The efficiency of interactive powder mixtures as a process used to increase the dissolution rate is dependent on the degree and extent of dispersion of drug agglomerates into individual particles. This is dependent on the characteristics of excipient surfaces. Many reports (5-9) indicated that porous excipient particles with high rugosity characteristics increased the uptake of drug particles and stability of these mixtures due to the entrapment of drug particles mechanically inside the cavities or porous structures. Increasing the stability of powder mixtures is advantageous, nevertheless it may have deleterious effect on dissolution rate of poorly soluble drugs. Many reports (I0-I4) showed that when drug particles were entrapped into excipient particles , the dissolution rate was reduced. However, these reports did not study the phenomenon in details with respect to the interactive powder mixtures.

The present study investigates the effect of rugosity of excipient particulate surfaces on the diss-

olution rate of poorly soluble drugs from their interactive powder mixtures.

MATERIALS

Sugar beads, 710 - 850 µm (PCI - La Plaine St - Dennis, France), Emcompress with particle size smaller than 250 µm (Forum Chemical Ltd., England), commercial sucrose and sucrose powder of particle size smaller than 150 µm were used. Micronized griseofulvin was provided by the Arab Pharmaceutical Manufacturing Co. (Sult, Jordan). Ethylcellulose (Riedel - de Haen, West Germany), water and ethanol 96% (Riedel - de Haen, West Germany) were used in the preparation of the granulating media.

METHODS

Coarse sugar particles, size fraction 710-850 µm and 1000-2000 µm, were obtained by sieve fractionation of commercial sucrose. Granules were made of sucrose particles using water and 10% ethylcellulose solution in ethanol, respectively. Table (I) lists different types of excipients used in the study and their corresponding designations. The granulation media were added gradually to the sucrose powder in a planetary mixer (Erweka Co., West Germany) until granulation was complete. Mixing with the granulating agent was carried out for 15 minutes; then wet mass was forced through a 2mm sieve. The granules were oven dried at 63^{o}C until a moisture content of 0.3% was attained. Fractions between 710-850 µm and 1000-2000 µm were separated by sieving. 1% w/w, 2% w/w, and 5% w/w of sucrose particles smaller than 150 µm were used to fill sites available for entrapment of drug agglomerates or particles on granules of FPG 710-850 µm. Mixing was done in

TABLE I

Different types of excipients and corresponding designations and particle size ranges.

Designation and particle size range	Excipient.
CP 710-850 µm	Commercial sucrose particles, fraction size : 710 - 850 µm
CP 1000-2000 µm	Sucrose particles, fraction size : 1000 - 2000 µm.
CPG 710-850 µm	Commercial sucrose particles granulated with water, fraction size: 710 - 850 µm.
CPG 1000-2000 µm	Commercial sucrose particles granulated with water, fraction size: 1000 - 2000 µm.
Et-CPG 710-850 µm	Commercial sucrose particles granulated with ethylceelulose fraction size: 710-850 µm.
Et-CPG 1000-2000 µm	Commercial sucrose partilces granulated with ethylcellulose fraction size: 1000-2000 µm.
FPG 710-850 µm	Sucrose powder of particle size smaller than 150 µm granulated with water, fraction size: 710 - 850 µm.
FPG 1000-2000 µm	Sucrose powder of particle size smaller than 150 µm granulated with water, fraction size: 1000-2000 µm.
Et-FPG 710-850 µm	Sucrose powder of particle size smaller than 150 µm granulated with ethylcellulose fraction size: 710-850 µm.
Et-FPG 1000-2000 µm	Sucrose powder of particle size smaller than 150 µm granulated with ethylcellulose fraction size: 1000-2000 µm.

a cube mixer (Erweka Co., West Germany) for I5 minutes. Excess fine sugar was removed from the mix by gentle sieving over 500 μm sieve for 20 minutes.

In order to avoid oversaturation of surfaces of excipient particles with drug agent, the ratio of micronized griseofulvin to excipient was maintained at $3.06 \times I0^{-3}$ in all experiments. In a typical run the powder mix used in a dissolution experiment was prepared by mixing griseofulvin with the excipient in a cube mixer for 45 minutes.

Dissolution studies were performed according to USP XX paddle method at I00 rpm. 500 ml of 0.9% solution of sodium chloride ,containing 0.0I% polysorbate 80 was used as dissolution medium. The experiment were carried out at $37 \pm I^{\circ}C$. 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 drug powder mixtures were done using Lietz, I000A, AMR Electron Scanning Microscope (Lietz, West Germany). Samples were prepared for examination by sputter coating with gold.

RESULTS AND DISCUSSION

The dissolution efficiency has been determined quantitatively as already described in the first part of this study (4).

The excipients which have been used in the present study exhibit different surface characteristics as indicated by ESM examination. The different excipients can be classified as follows:

I - Sugar beads. The particles are spherical with smooth and regular surfaces (Fig. I). Consequently, the dissolution profile of their interactive powder mixture is going to be considered as a reference.

2 - Coarse sugar particles (CP) 710-850 μm and 1000 - 2000 μm size fractions. The particles are either single crystals or aggregate of small crystals with large one. The surfaces are smooth with minimum indentations and cavities (Fig.2).

3 - Sugar granules (710-850 μm and 1000-2000 μm) prepared from coarse sugar particles granulated either with water (CPG) or ethylcellulose (Et-CPG). The particles are granular in shape, aggregate of crystals with minimum indentations and cavities (Fig. 4,5).

4 - Sugar granules (710-850 μm and 1000-2000 μm)prepared from fine sugar particles granulated either with water (FPG) or ethylcellulose (Et-FPG). The particles are granular in shape with porous surface and high rugosity. Cavities are present in a prominent ratio relative to the other granules (Fig.6).

5 - Emcompress powder. The particles are highly indentated with the highest rugosity among the excipients used in this study (Fig.7).

Emcompress powder and sugar granules prepared with ethylcellulose are examples of insoluble excipients. Different size fractions have been used with soluble and insoluble excipients in order to check the validity of the effect of indentations of excipient particles on the dissolution rate of poorly soluble drugs. Griseofulvin the model drug is micronized powder with cohesive nature as shown in Fig.(8).

Fig. (9) shows the dissolution efficiency of interactive powder mixtures prepared from soluble excipients having different surface characteristics. The maximum

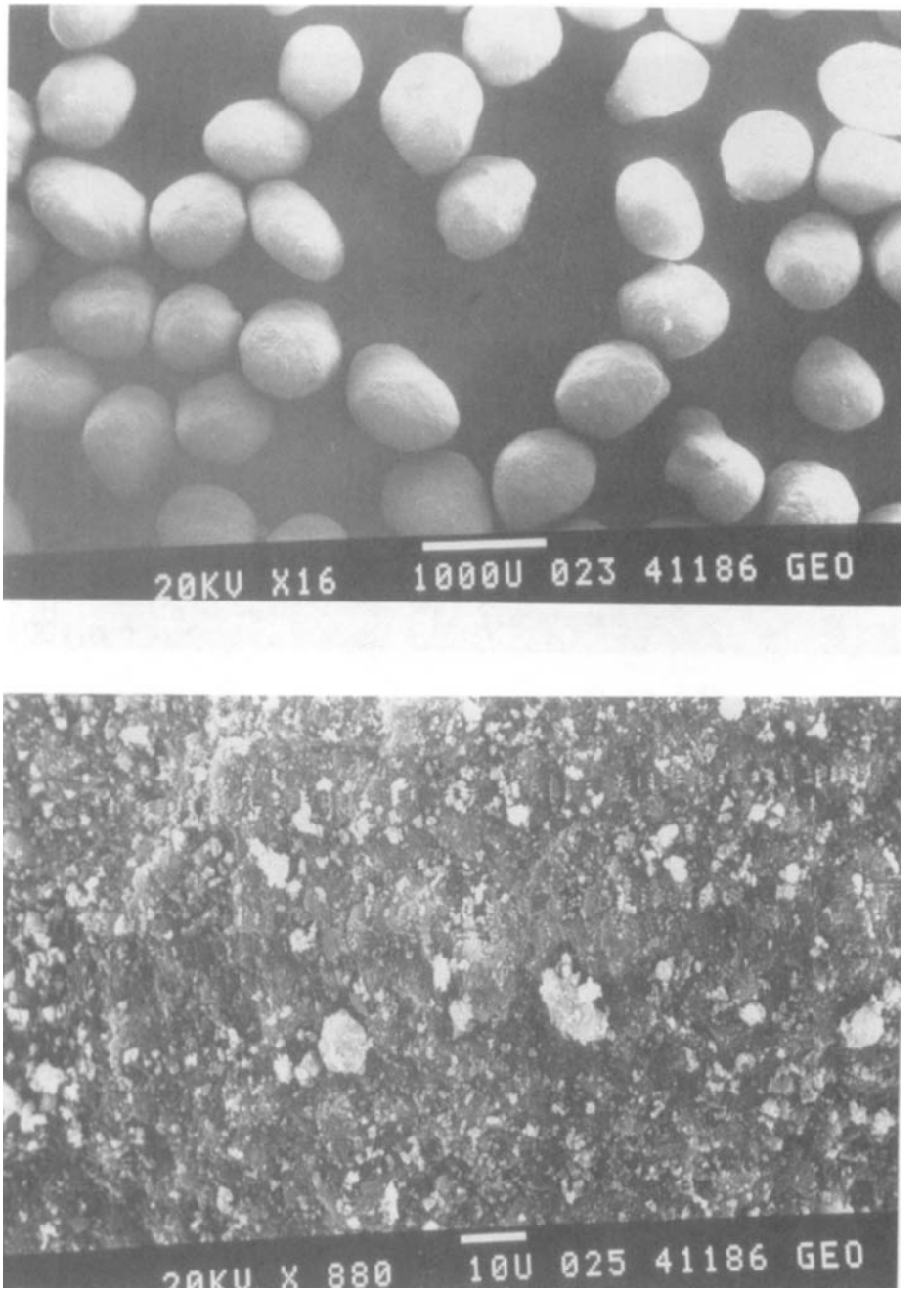
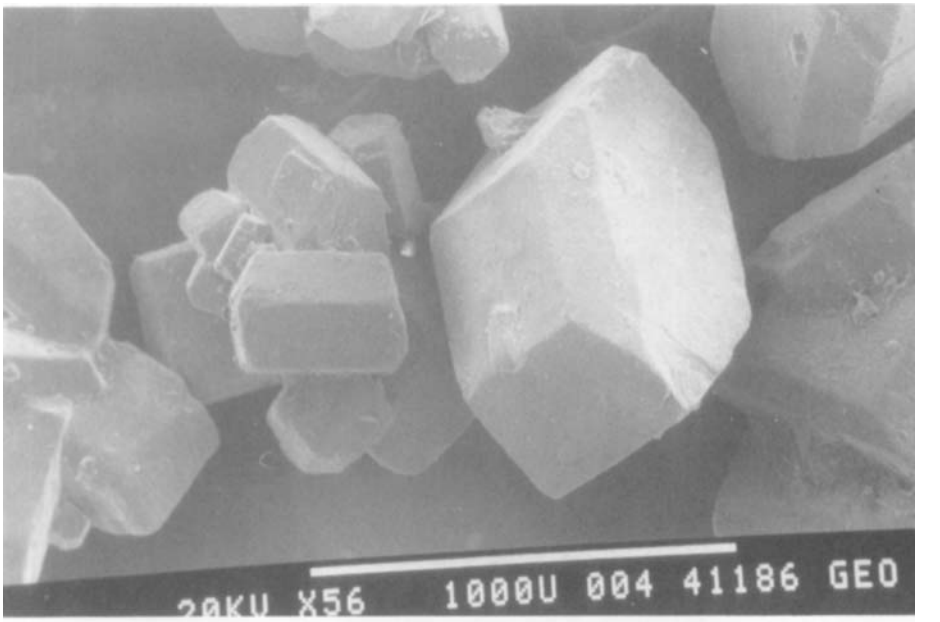
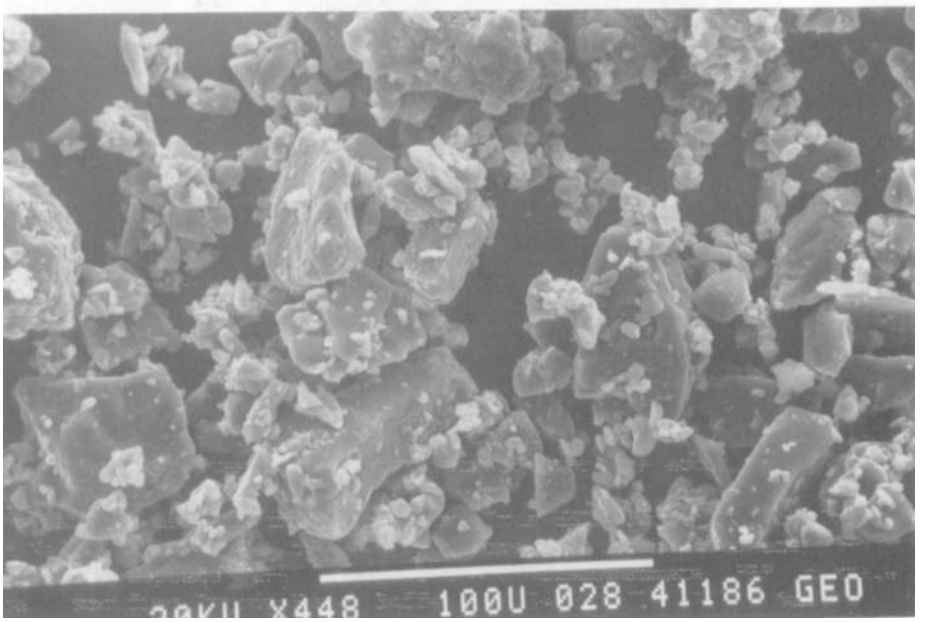


FIGURE I

ESM Photomicrographs of Sugar Beads Interactive Powder Mixture with Micronized Griseofulvin.





FIGURES 2 & 3

Fig.2 : ESM Photomicrograph of Coarse Sugar Particles (710-850 μm), Upper Photomicrograph.
Fig.3 : ESM Photomicrograph of Fine Sugar Particles, Lower Photomicrograph.

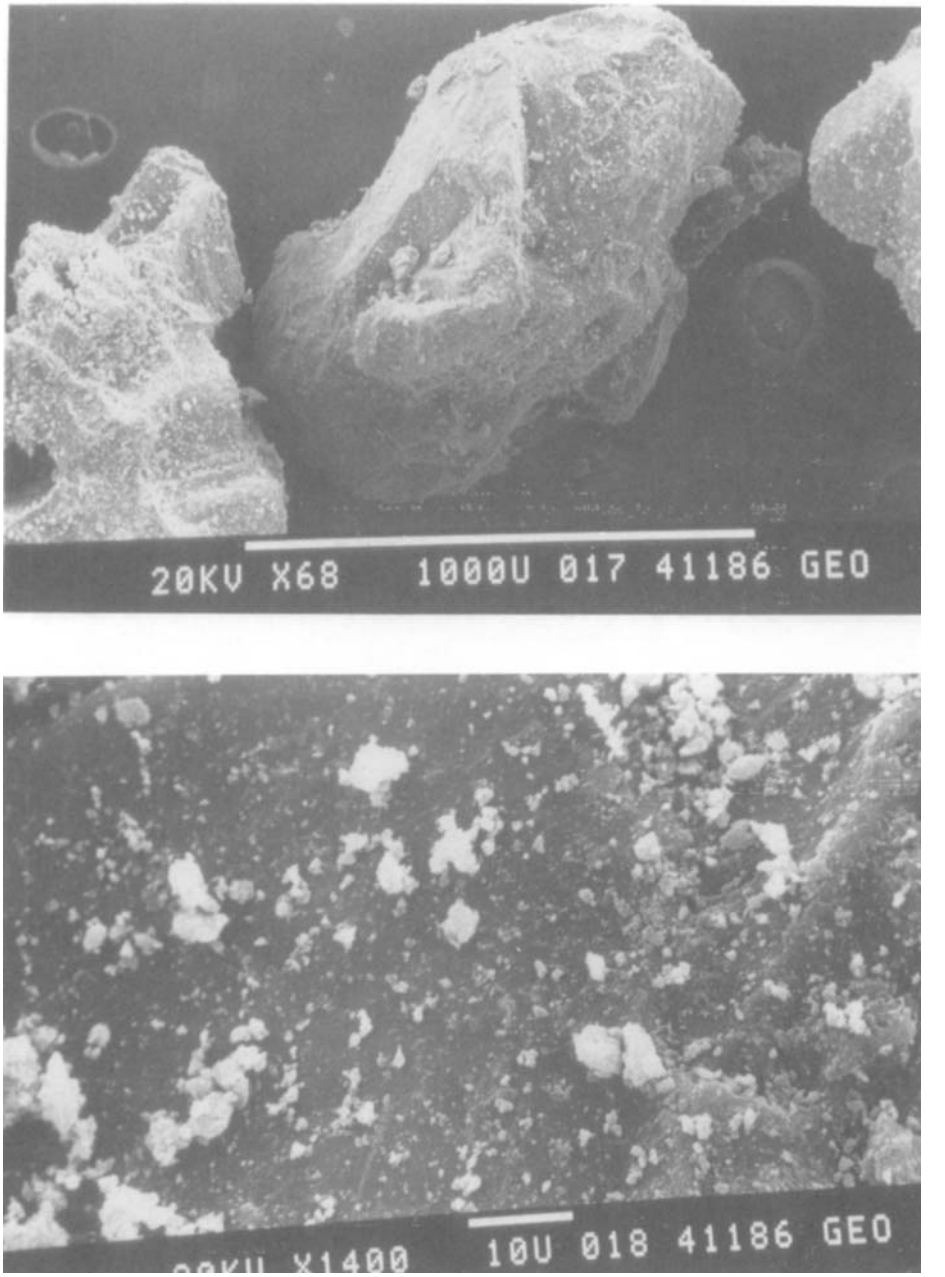


FIGURE 4

ESM Photomicrographs of CPG (710-850 µm) Interactive Powder Mixture with Micronized Griseofulvin.

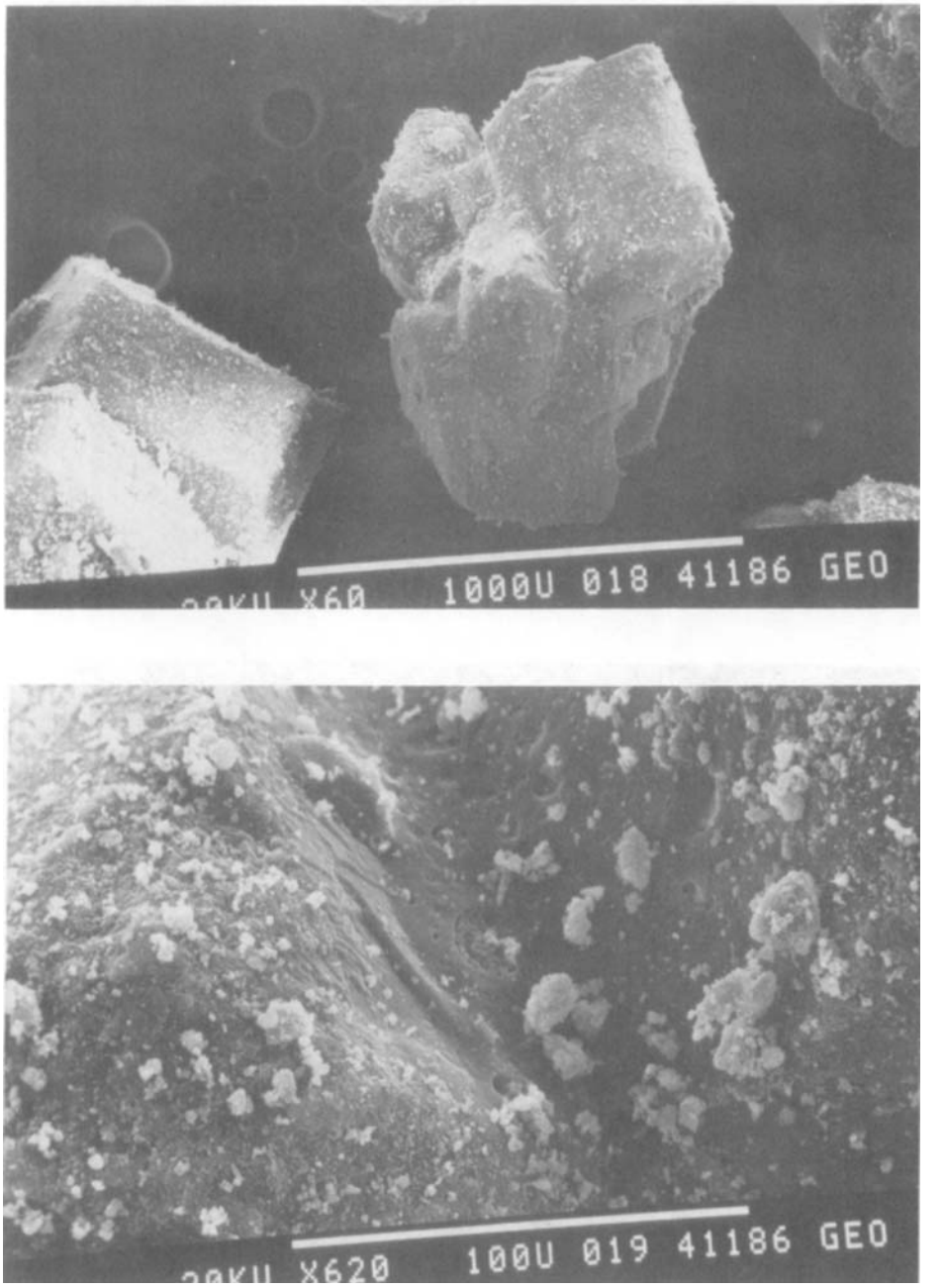


FIGURE 5

ESM Photomicrographs of Et-CPG (710-850 μm) Interactive Powder Mixture with Micronized Griseofulvin.

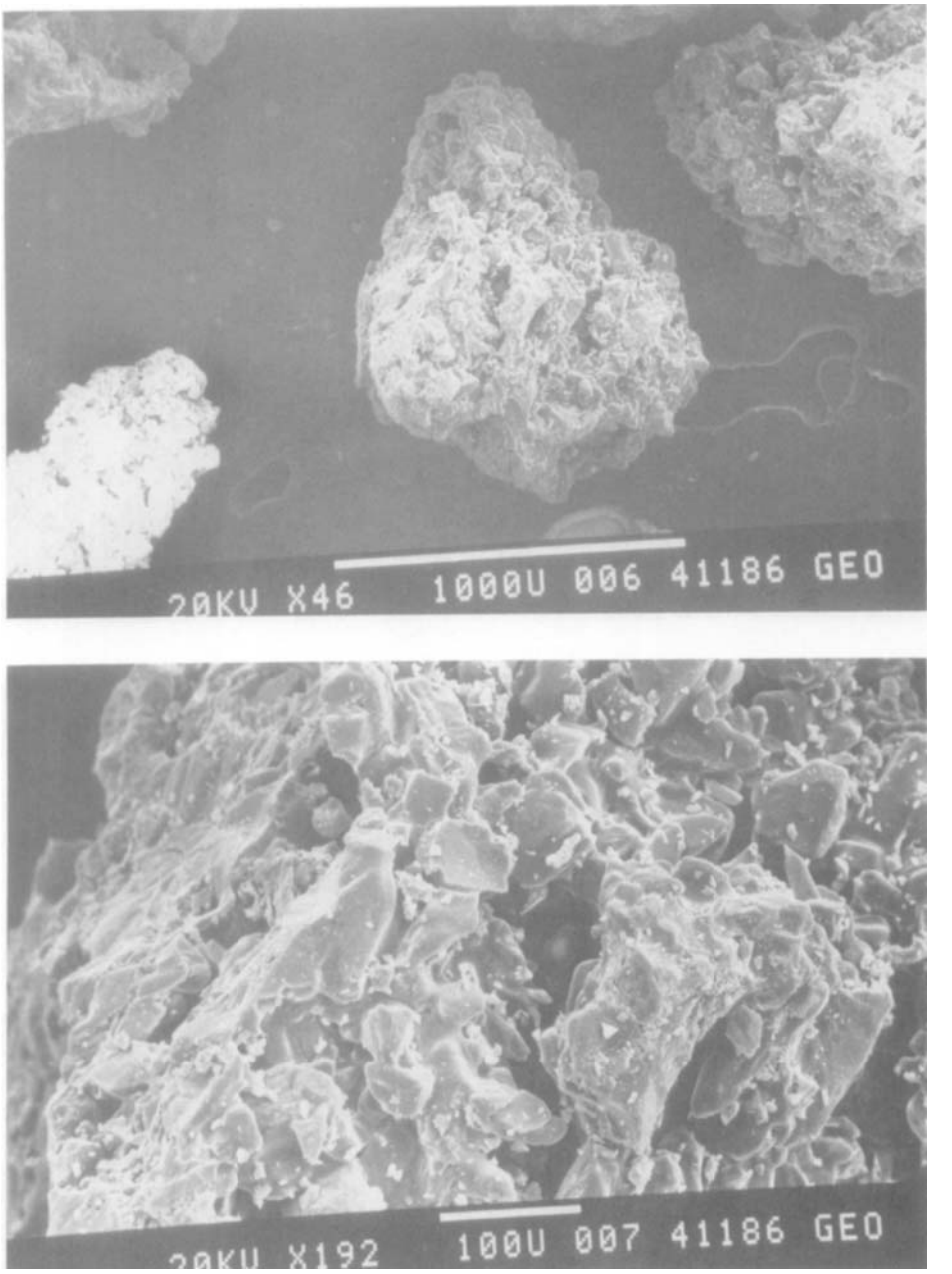


FIGURE 6

ESM Photomicrographs of FPG Particles showing the porous srtucture of particulate surfaces.

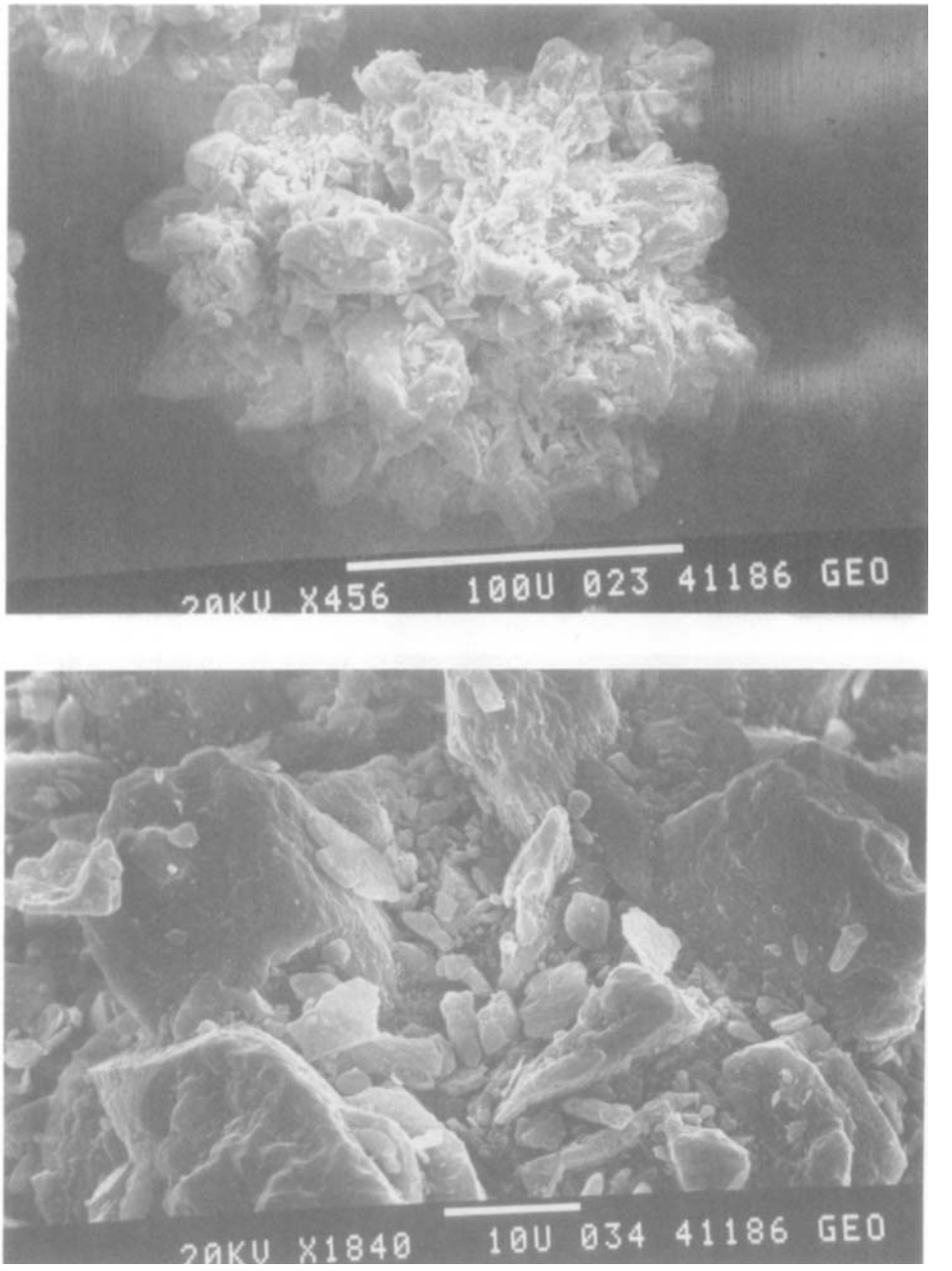


FIGURE 7

ESM Photomicrographs of Emcompress and Micronized Griseofulvin Interactive Powder Mixture showing highly Indentated surface where Drug Particles would be entrapped.

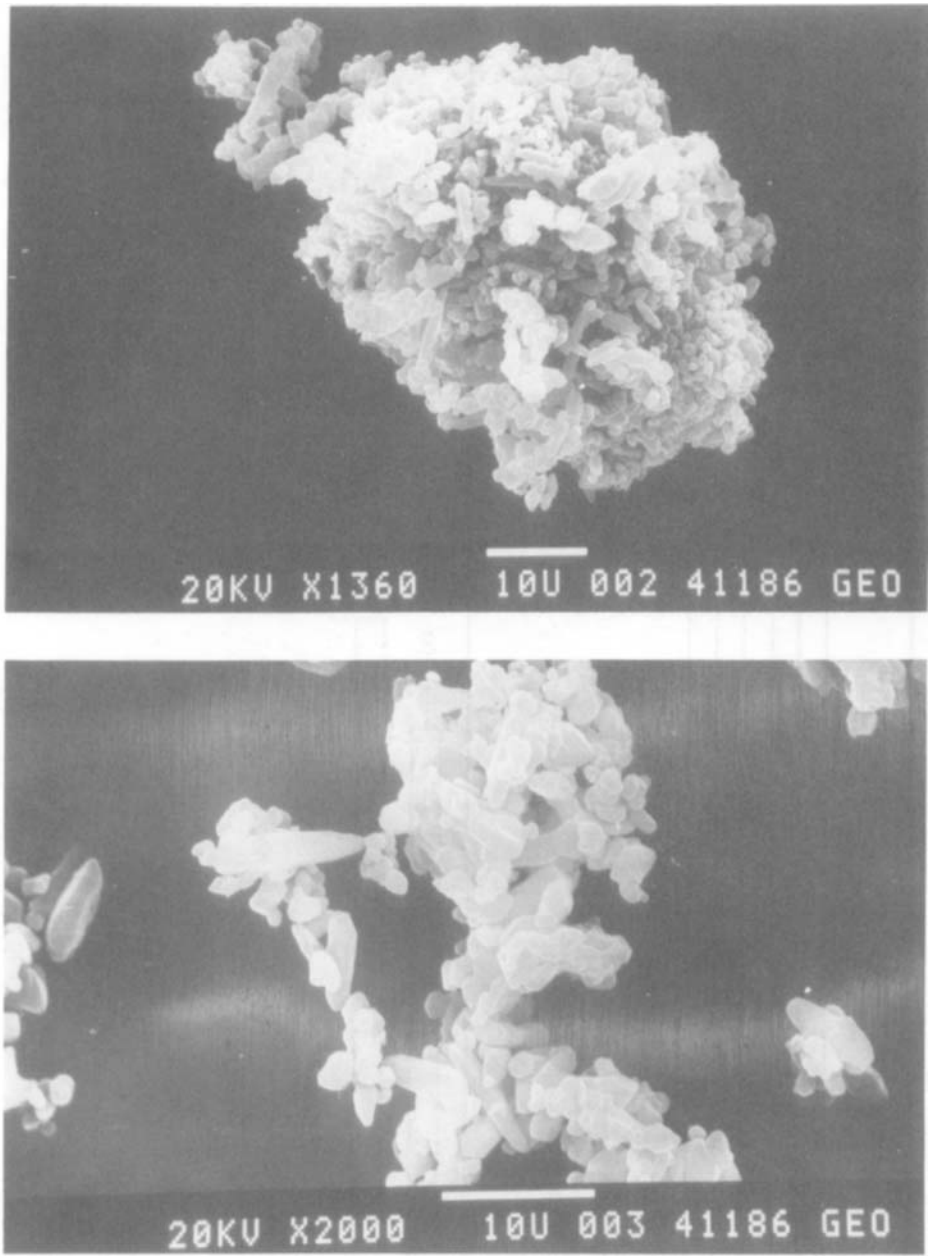


FIGURE 8

ESM Photomicrographs of Micronized Griseofulvin Powder showing the cohesive nature of this powder.

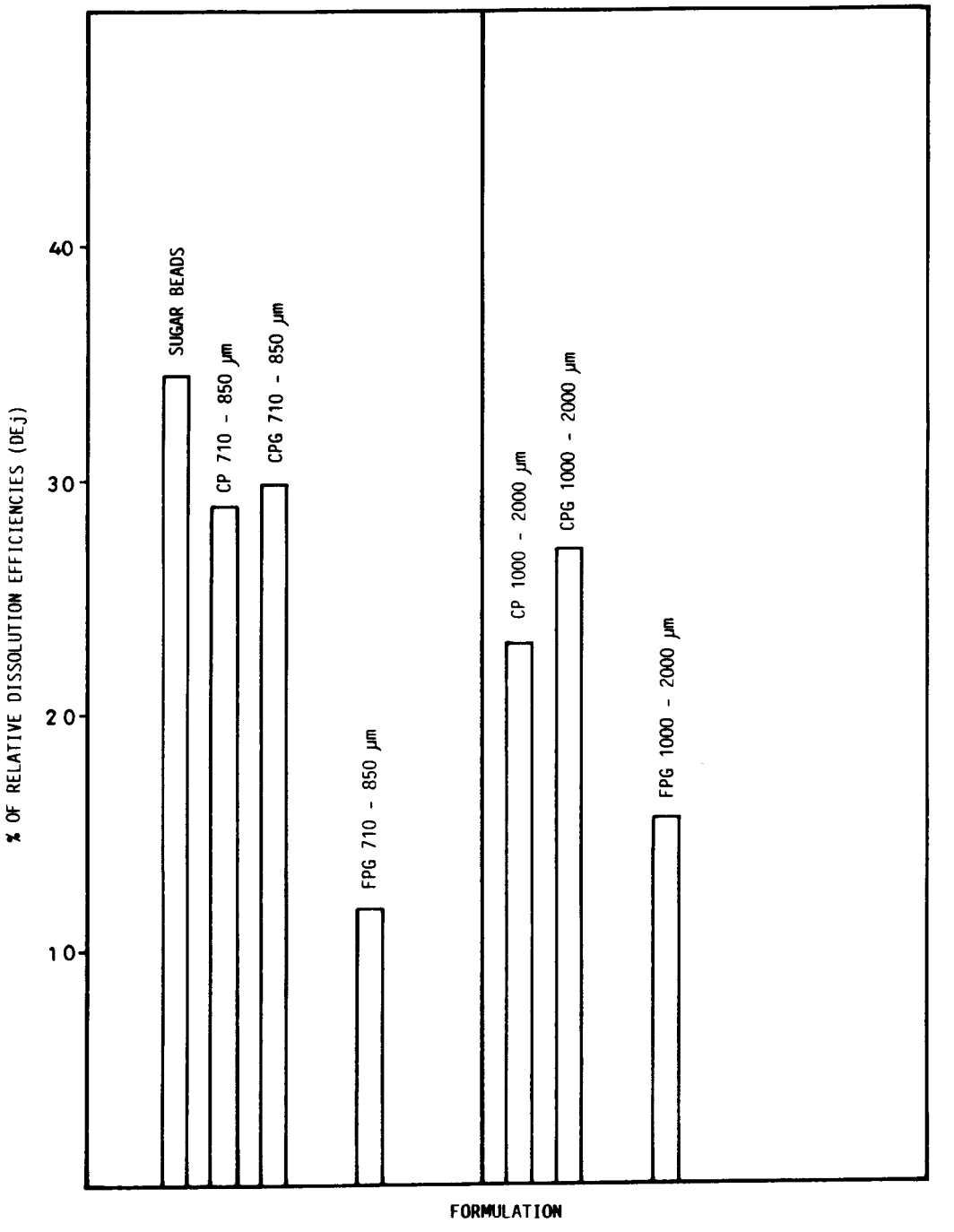


FIGURE 9

A Comparison of Relative Dissolution Efficiencies of Griseofulvin Interactive Powder Mixtures showing the effect of Indentations of Soluble Excipients.

dissolution efficiency is obtained from mixture prepared with sugar beads where the particles have smooth regular surfaces (Fig.I). Drug particles will be dispersed evenly on the surfaces and easily exposed to the dissolution medium. The result is a high dissolution efficiency.

Dissolution efficiency of mixtures prepared from either CP or CPG particles is less than that corresponding to sugar beads. This is because, CP and CPG particles have surfaces with some degree of indentation and presence of cavities as shown in Fig.(4). Indentated areas on particulate surfaces exhibit stronger adsorption sites, forces and hence , more drug particles are localised in these areas as shown in Fig. (I0).

The least dissolution efficiencies among soluble excipients have been produced by interactive powder mixtures containing FPG excipients. FPG particles show surfaces with high rugosity and presence of cavities. Fig. (II) shows drug particles accumulated and highly localised in small area on FPG particle. Presence of drug agglomerates and undispersed large number of particles localised in small areas on particulate surfaces will decrease the surface area of drug particles available for dissolution and hence, reduces the dissolution efficiency. Stereomicroscopical examination of FPG interactive powder mixture after dissolving in dissolution medium shows some of drug agglomerates still existing undispersed (Fig.I2). The number of undispersed drug agglomerates is much higher in case of FPG powder mixtures than with CP or CPG powder mixtures.
The presence of indentations or cavities on particulate surfaces will entrap drug particles and agglomerates which will be protected mechanically from dispersion in the due course of mixing.

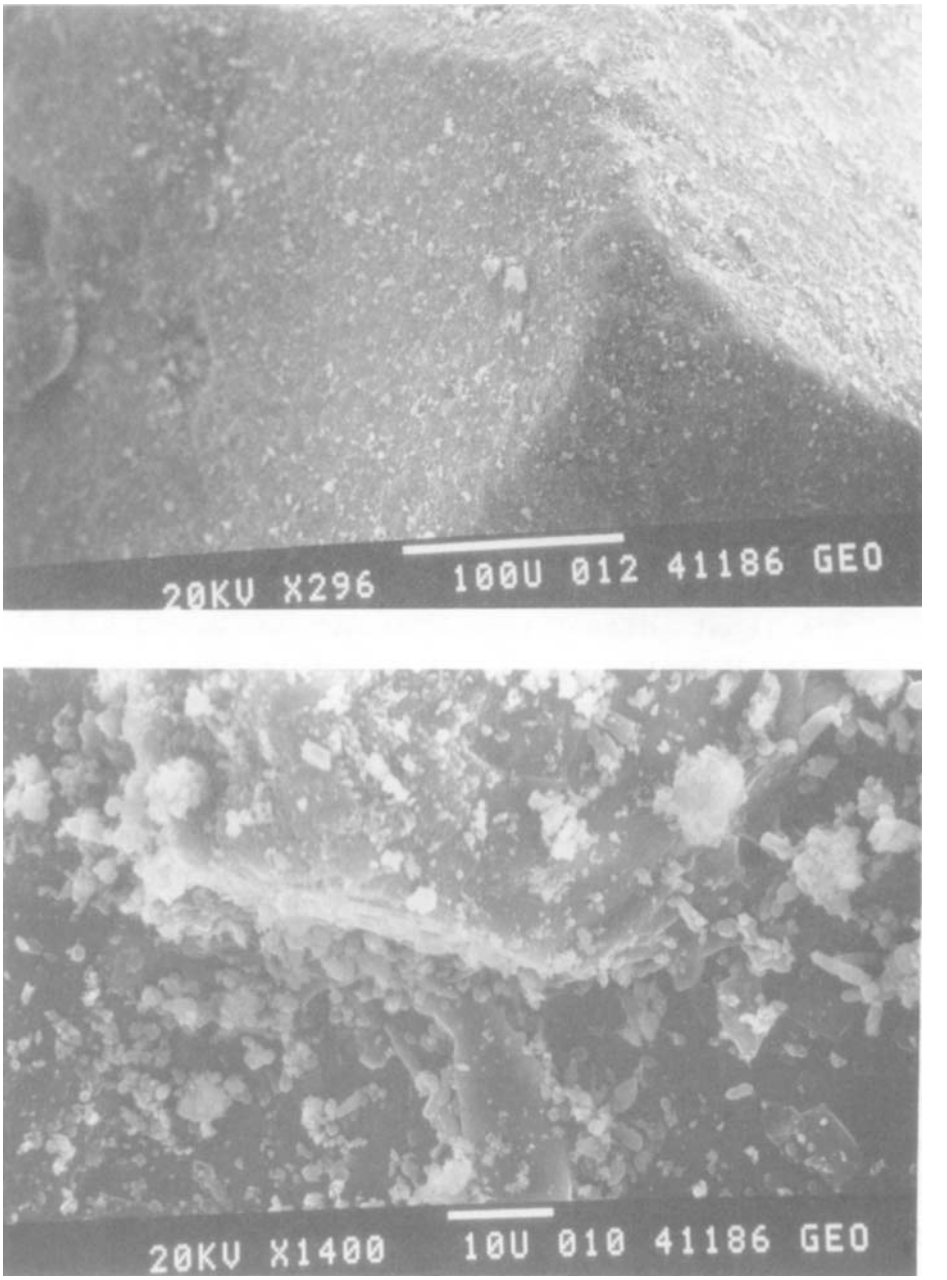


FIGURE IO

ESM Photomicrographs of CP(7I0-850 µm) Interactive Powder Mixture with Micronized Griseofulvin. Indentated Area shows more localized drug particles than plain surfaces.

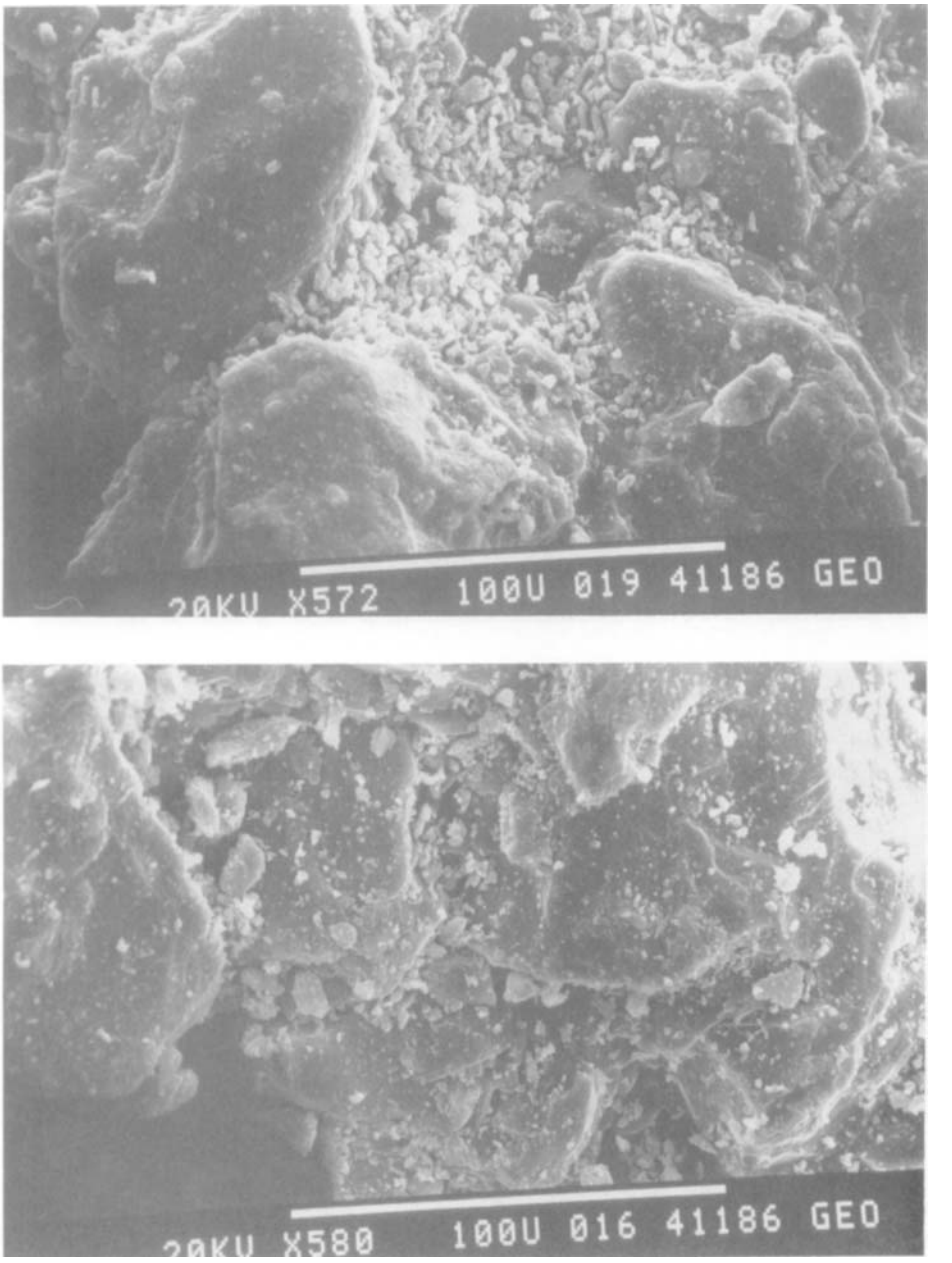


FIGURE II

ESM Photomicrographs of FPG (710-850 μm) Interactive Powder Mixture with Micronized Griseofulvin showing areas with accumulated drug particles.

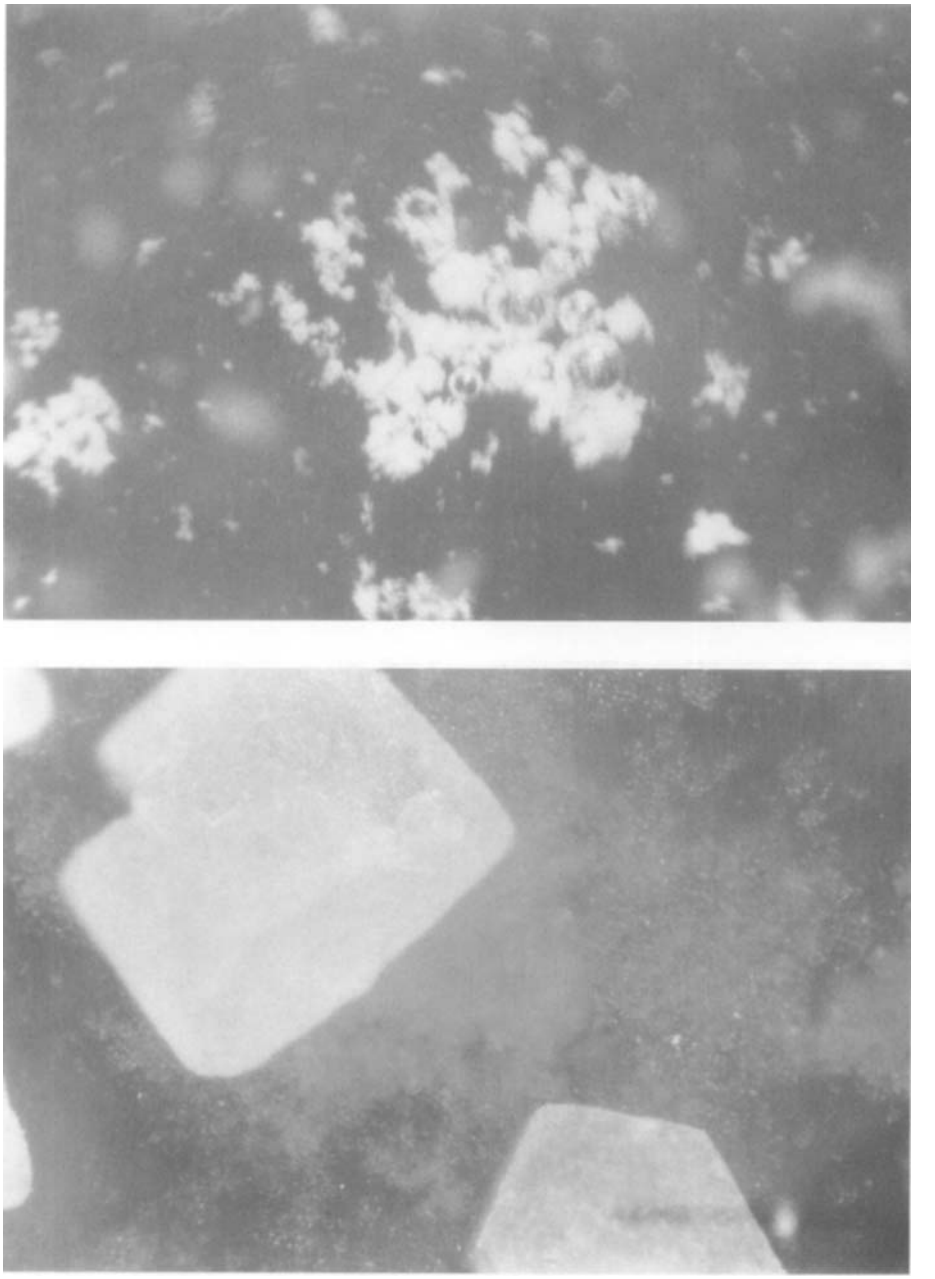


FIGURE I2

Stereomicroscopical Examination of FPG (710-850 μm) Interactive Powder Mixture after dissolving in dissolution medium showing presence of drug agglomerates (Upper Photomicrograph). CP Interactive Powder Mixture (Lower Photomicrograph) shows drug particles dispersed in dissolution medium.

When sugar granules have been prepared using alcoholic ethylcellulose as a binding agent, the surfaces are rendered hydrophobic without losing the particulate shape and rugosity. The same phenomenon is observed as shown in Fig. (I3). However, the relative reduction in dissolution efficiency is higher because the granules are less soluble (4).

When the rugosity is high, dissolution efficiency decreases. Emcompress powder exhibits the highest rugosity produces the least dissolution efficiency, although it has the smallest particle size, i.e. the highest surface area.

Fig. (I4) shows the dissolution profiles of Et-FPG (710-850 μm) and Emcompress interactive powder mixtures during 30 minutes of dissolution process. There are two phases of dissolution which are explained as follows :

I - The first 6 minutes, both mixtures exhibit similar dissolution performance. This phase is probably due to the dissolution of drug particles which are not entrapped into indentations of excipient particles.

2 - The dissolution profiles after 6 minutes show significant decrease in the dissolution performance of Emcompress interactive powder mixture, although it has the higher surface area. In this phase the higher rugosity of Emcompress powder in addition to being insoluble excipient, hinder to a higher extent the wettability of entrapped drug particles. Consequently, the dissolution efficiency of Emcompress powder mixture is less than its corresponding produced by Et-FPG interactive powder mixture.

If the hypothesis is true, i.e. the drug particles entrapped into indentations show slower dissolution efficiency, then by filling the sites of entrapment

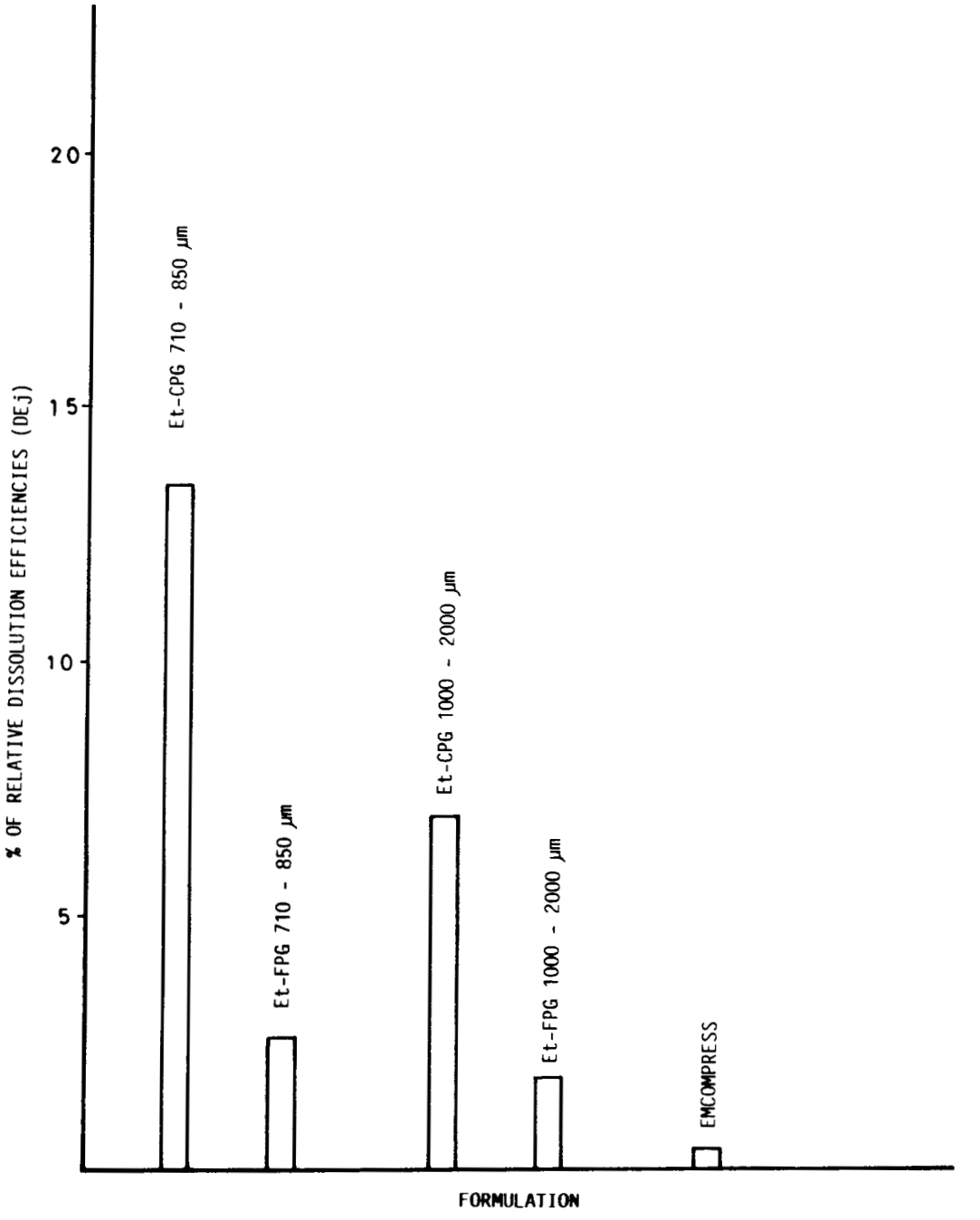


FIGURE I3

A Comparison of Relative Dissolution Efficiencies of Griseofulvin Interactive Powder Mixtures showing the Effect of Indentations of Insoluble Excipients.

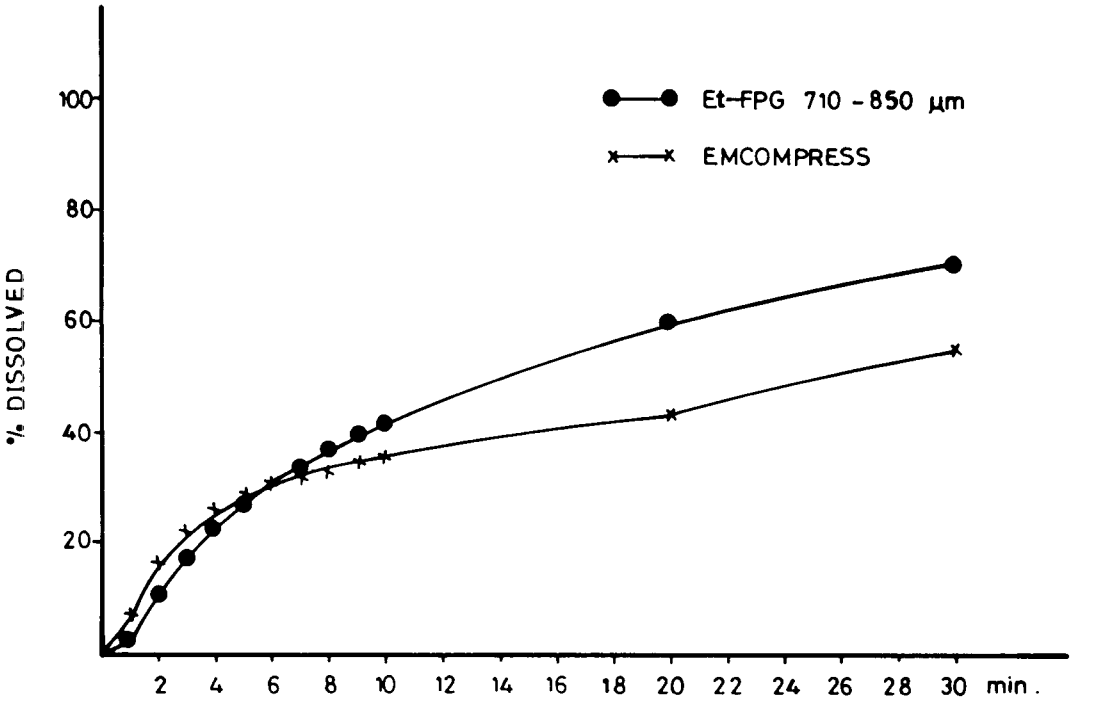


FIGURE I4

Dissolution Profiles of Griseofulvin from Interactive Powder Mixtures of Et-FPG (710 - 850 µm) and Emcompress.

with fine particles the dissolution efficiency will be expected to increase. When FPG particles are mixed with either 1%, 2% or 5% fine sugar particles, the dissolution efficiency increases significantly as shown in Fig. (15). The maximum dissolution efficiency is produced by powder mixture where FPG particles are mixed with 5% fine sugar. The main mechanism is that fine sugar particles (fig.3) are blocking the cavities and pores, i.e. the entrapment sites on FPG particulate surfaces as shown in Figs. 16 and 17. Thus, the drug particles and/or drug agglomerates will be exposed to a less number of entrapment sites and hence, better

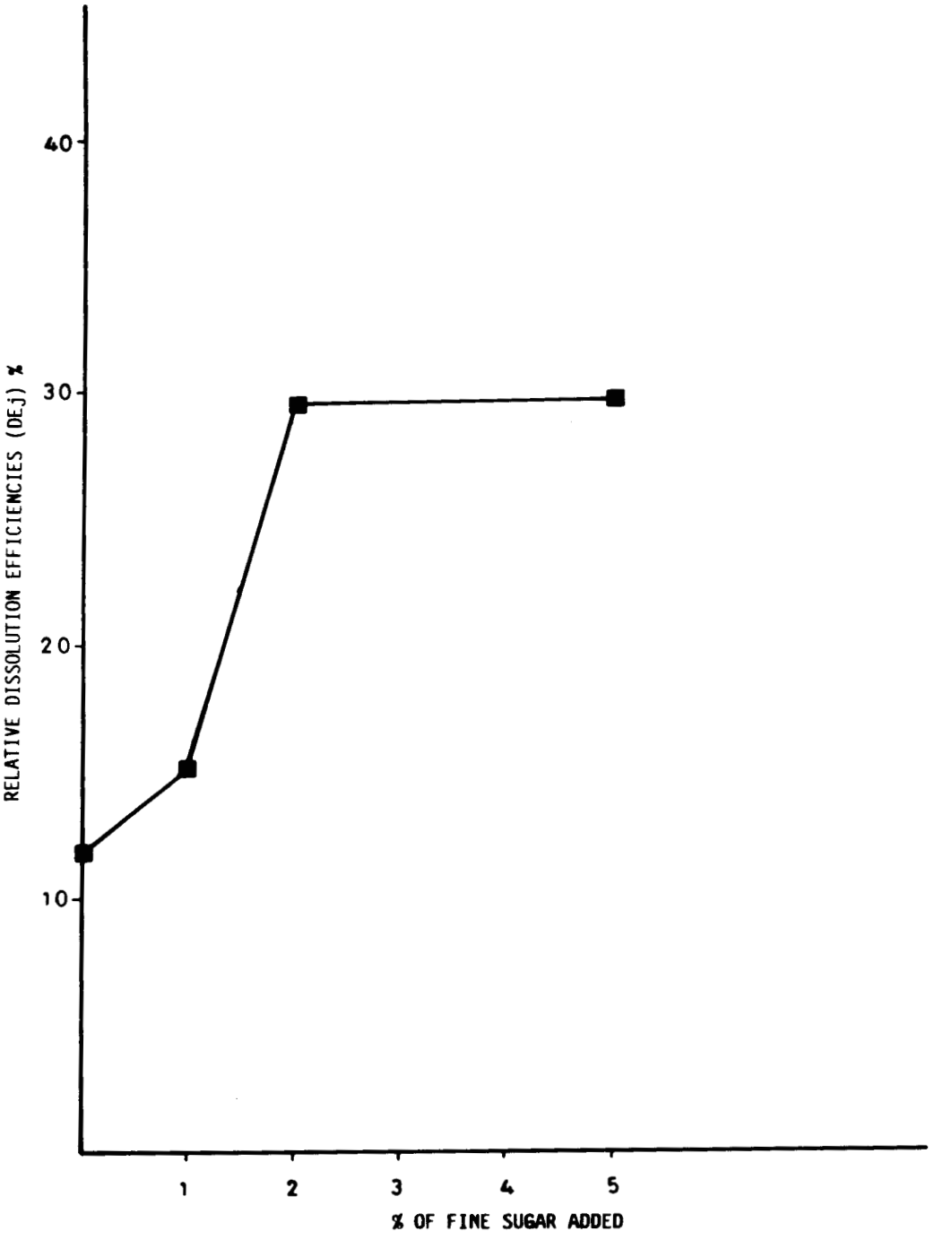


FIGURE I5
The relative Dissolution Efficiencies of FPG Interactive Powder Mixtures after Primary Mixing with Fine Sugar Particles.

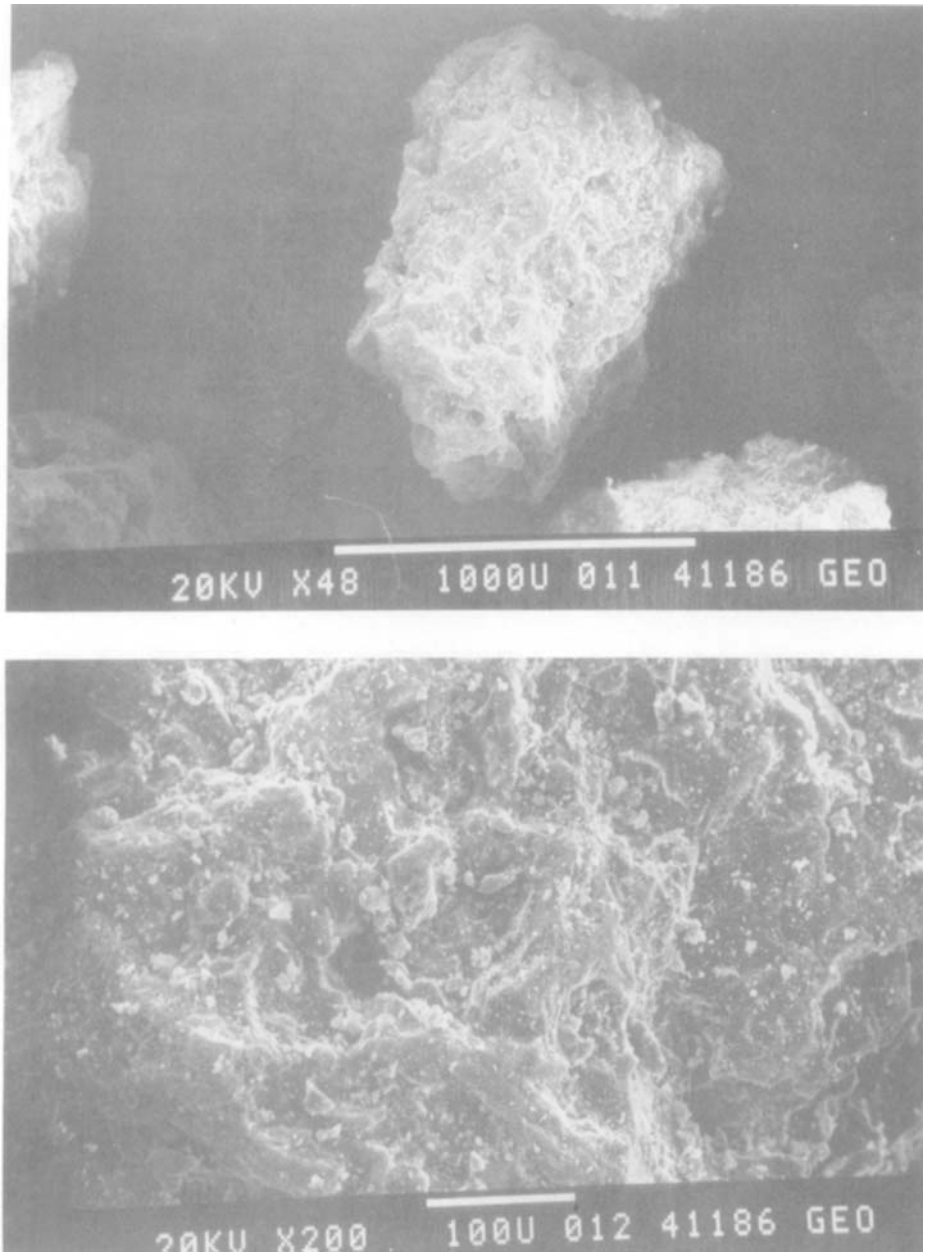


FIGURE I6

ESM Photomicrographs showing Fine Sugar Particles are blocking the cavities on FPG (710-850 μm) Particulate Surfaces after mixing with 2% w/w Fine Sugar Particles and then with Micronized Griseofulvin.

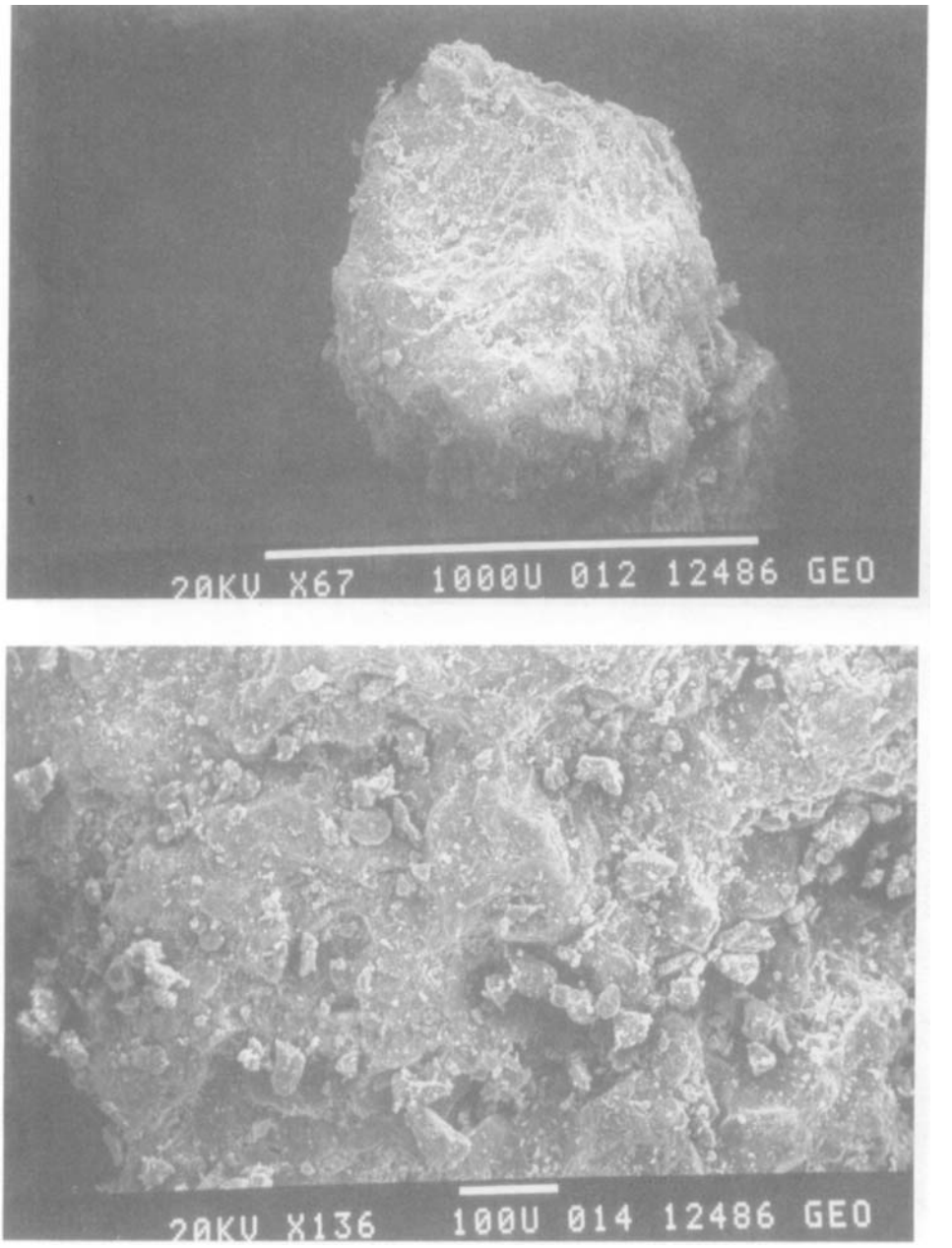


FIGURE I7

ESM Photomicrographs showing Fine Sugar Particles are blocking the cavities on FPG (7I0-850 μm) Particulate Surfaces after mixing with 5% w/w Fine Sugar Particles and then with Micronized Griseofulvin.

dispersion is obtained during mixing process. The end result is a higher surface area available for dissolution and consequently, dissolution efficiency increases.

CONCLUSION

Excipient particles having highly porous or indentated surfaces entrap drug particles and agglomerates hindering their dispersion into the powder mixture and hence, reducing the surface area available for dissolution. The result is a reduction in the dissolution efficiency of poorly soluble drugs from interactive powder mixtures. Filling entrapment sites with fine excipient particles results in increasing the dissolution efficiency. In contrast, the smoother excipient particles produce higher dissolution efficiency for the same interactive powder mixtures.

In conclusion, surface characteristics of excipient particles should be examined carefully before formulation of solid dosage forms using interactive powder mixtures as a process to improve the dissolution rate of poorly soluble drugs.

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