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DISSOLUTION CHARACTERISTICS OF INTERACTIVE POWDER MIXTURES. PART ONE : EFFECT OF SOLUBILITY AND PARTICLE SIZE OF EXCIPIENTS.

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ABSTRACT

Interactive mixtures of fine cohesive drug powders and coarse free flowing excipients are reported to increase dissolution rates of poorly soluble drugs. However, dissolution rates are known to be affected by the solubility characteristics of the excipients as well as excipients surface characteristics after mixing with lubricant.

In this study the effects of solubility and particle size of excipients on dissolution of micronized griseofulvin from interactive powder mixtures were investigated. Quantitative assessment of dissolution from such mixtures showed that systems containing soluble excipients increased dissolution of the drug

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more efficiently than mixtures prepared using insoluble excipients. The role of the soluble excipient was more significant after mixing with magnesium stearate. Excipients of smaller particle sizes increased dissolution more efficiently than their large size counterparts. Effects of particle size were particularly significant in case of water insoluble excipients.

INTRODUCTION

Micronization of poorly soluble drugs increases the surface area available for dissolution and consequently increases the dissolution rate (I,2). However, micronized powders are cohesive in nature, a property which promotes formation of drug agglomerates and hence, reduces surface area available for dissolution. Therefore, the presence of drug agglomerates in micronized powders is expected to have a deleterious effect on the dissolution rates of poorly soluble drugs.

One of the approaches used to increase the dissolution rates of poorly soluble drugs is the formation of interactive mixtures between the fine cohesive drug powders and coarse free - flowing excipients (3,4). The coarse excipient will break - up drug agglomerates into individual particles which then become dispersed and adhere homogenously to the carrier particles (5). The result is a large surface area available for dissolution and hence, an improved dissolution rate (6).

Nystrom , et al (7,8), using interactive mixtures pointed out that solubility characteristics of excipients would have a significant effect on the dissolution rates of poorly soluble drugs. In these studies, chemically unrelated excipients were used and it was concluded that, soluble excipients would produce higher dissolution rates than insoluble

excipients. However, these reports did not discuss the extent of this effect in the presence of lubricants.

The present work investigates not only the effects of solubility of excipients used in preparation of interactive mixtures on dissolution, but also addresses the extent of this effect with respect to variations of particle size of excipients. Also effects arising from the presence of lubricants were delineated. Micronized griseofulvin was used as a model of the poorly soluble drugs.

MATERIALS

Sugar beads, 710 - 850 µm (PCI - La Plaine St - Dennis, France), Emcompress (Forum Chemicals Ltd, England), and commercial sucrose were used. Micronized griseofulvin was provided by the Arab Pharmaceutical Manufacturing Co. (Sult, Jordan). Magnesium stearate (E.Merck,West Germany) was used as lubricant. Ethylcellulose (Riedel - de Haen, West Germany), water and ethanol 96% (Riedel - de Haen, West Germany) were used in the preparation of the granulating medium.

METHODS

Coarse sugar particles, size fractions 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 min., then the wet mass was forced

TABLE I

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

Designation and particle size range.	Excipient.
CP 7I0 - 850 μm	Commercial sucrose particles, fraction size : 7I0 - 850 μm.
CP I000 - 2000 μm	Sucrose particles, fraction size : I000 - 2000 μm.
CPG 7I0 - 850 μm	Commercial sucrose particles granulated with water, fraction size: 7I0 - 850 μm.
CPG I000 - 2000 μm	Commercial sucrose particles granulated with water, fraction size: I000 - 2000 μm.
Et - CPG 7I0 - 850 μm	Commercial sucrose particles granulated with ethylcellulose fraction size: 7I0 - 850 μm.
Et - CPG I000 - 2000 μm	Commercial sucrose particles granulated with ethylcell - ulose, fraction size : I000 - 2000 μm.
Granules of Sodium Chloride.	Commercial sugar particles and 5% NaCl granulated with ethylcellulose, fraction size: 7I0 - 850 μm.

through a 2 mm sieve. The granules were oven dried at 63^{0}C until a moisture content of 0.3% was attained. Fractions between 7I0 - 850 μm and I000 - 2000 μm were separated by sieving. Emcompress mixed with 2% talc and 0.5% magnesium stearate was slugged using a Korsch - 2I6 rotary tablet press (Korsch, West Germany) into I2 mm diameter tablets . An Erweka grinder (Erweka, West Germany) was used to grind the slugged material and fraction between 7I0 - 850 μm was obtained by sieving.

In order to avoid oversaturation of surfaces of excipient particles with drug agent, the ratio of micronized griseofulvin to excipient was maintained at 3.06×10^{-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 (Erweka, West Germany) for 45 min., then magnesium stearate was added at a concentration of 0.25% and mixing continued for 20 minutes.

Dissolution studies were performed according to USP XX paddle method at 100 rpm. 500 ml of 0.9% solution of sodium chloride, containing 0.01% polysorbate 80 was used as dissolution medium. The experiments were carried out at $37 \pm 1^{\circ}C$. 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, 1000A, AMR Electron Scanning Microscope (Lietz, West Germany). Samples were prepared for examination by sputter coating with gold.

RESULTS AND DISCUSSION

Dissolution data from different interactive mixtures are presented as % dissolved - time plot and also as dissolution efficiencies. Several workers (9-13), used the dissolution efficiency concept to correlate dissolution behaviour with tablet variables and also to compare in vitro dissolution of different formulations. 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, (DE_j), assuming a first order release from the powder mix.

$$(DE_t) = \left[I + \frac{I}{A} \cdot (e^{-A} - I) \right] . I00 \quad Eq.I$$

where $A = 4.606 - \ln (I00 - f)$. f is percentage of drug in solution at time t.

$$(DE_j) = \left[I + \frac{I}{B} \cdot (e^{-B} - I) \right] . I00 \quad Eq.2$$

where $B = K_j / K_s \cdot \left[4.606 - \ln (I00 - f_s) \right]$. 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 mixture griseofulvin - sugar beads demonstrated the highest dissolution of all mixtures studied. This mixture was chosen as the standard formulation s, to express the relative dissolution efficiencies of other formulations.

To have a meaningful comparison between effects of soluble and insoluble excipients on dissolution, the study utilized excipients of comparable shape, texture, and rugosity. Sugar granules of controlled particle sizes were used as examples of the water - soluble excipients. The water solubility of the sugar granules was reduced by using alcoholic solution of ethylcellulose as a granulating agent, and theresultant material was used as one of the insoluble excipients studied. ESM photomicrographs (griseofulvin interactive mixtures prepared from soluble and insoluble excipients) are shown in Figs. (I-4). Slugged Emcompress granules were used as another type of the insoluble excipients. Attempts to reduce the extent of rugosity or indentatations ofthe surfaces of Emcompress granules to match

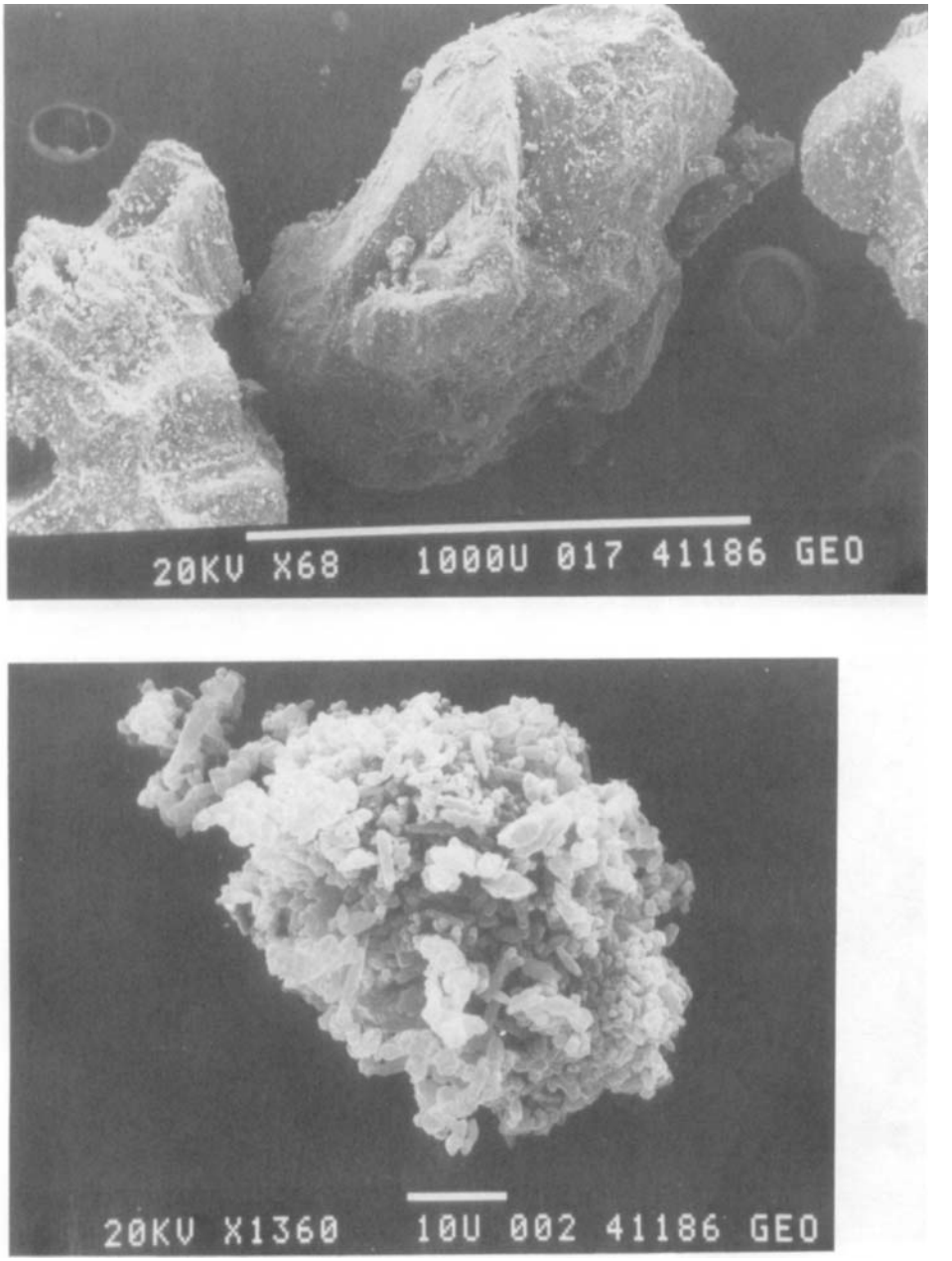


FIGURE I

ESM Photomicrographs of Interactive Powder Mixture of Griseofulvin and Sugar Granules 710 - 850 μm (017) and Micronized Griseofulvin (002).

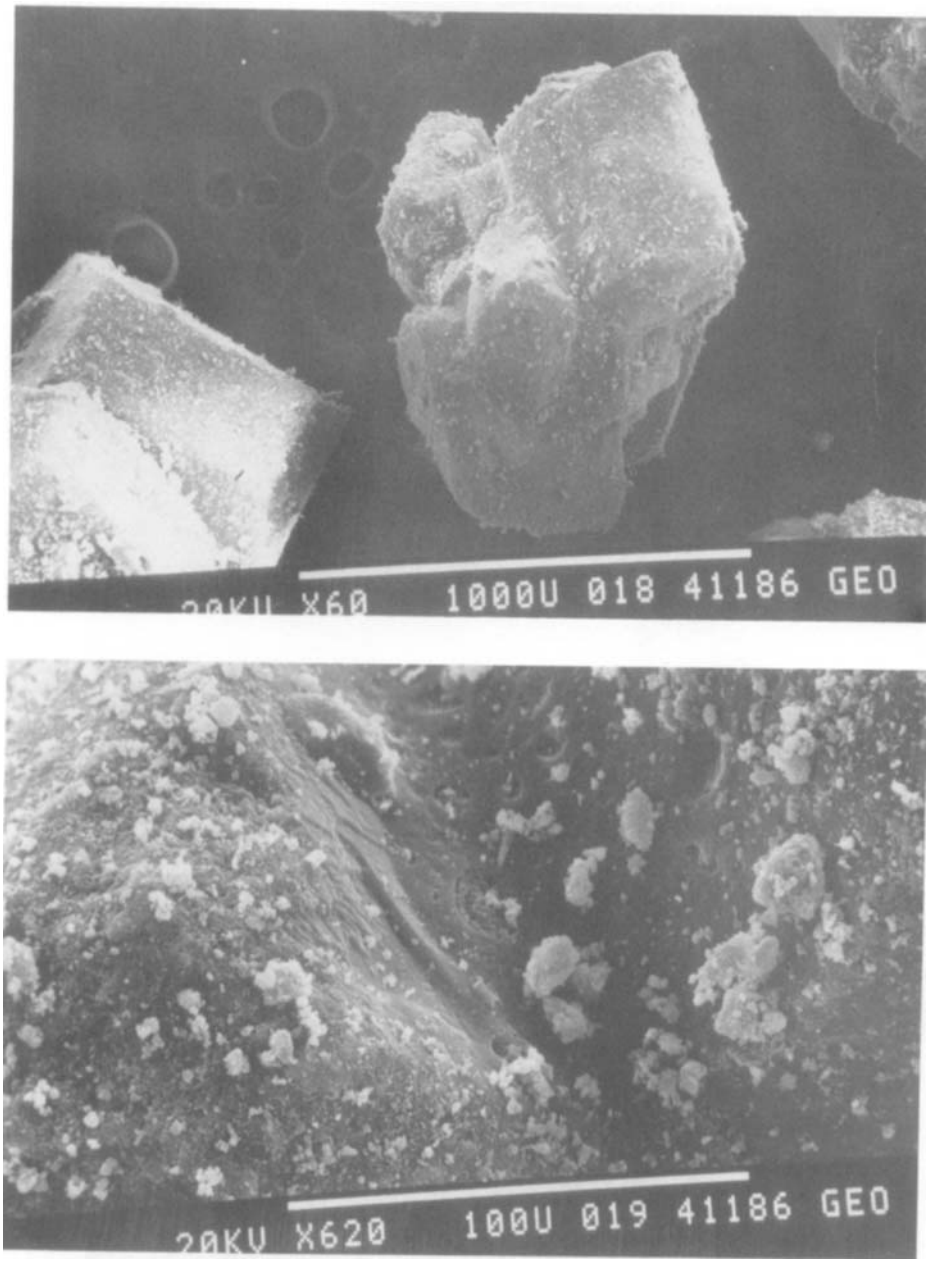


FIGURE 2

ESM Photomicrographs of Interactive Powder Mixture of Griseofulvin and Sugar Granules with Ethylcellulose 710 - 850 μm.

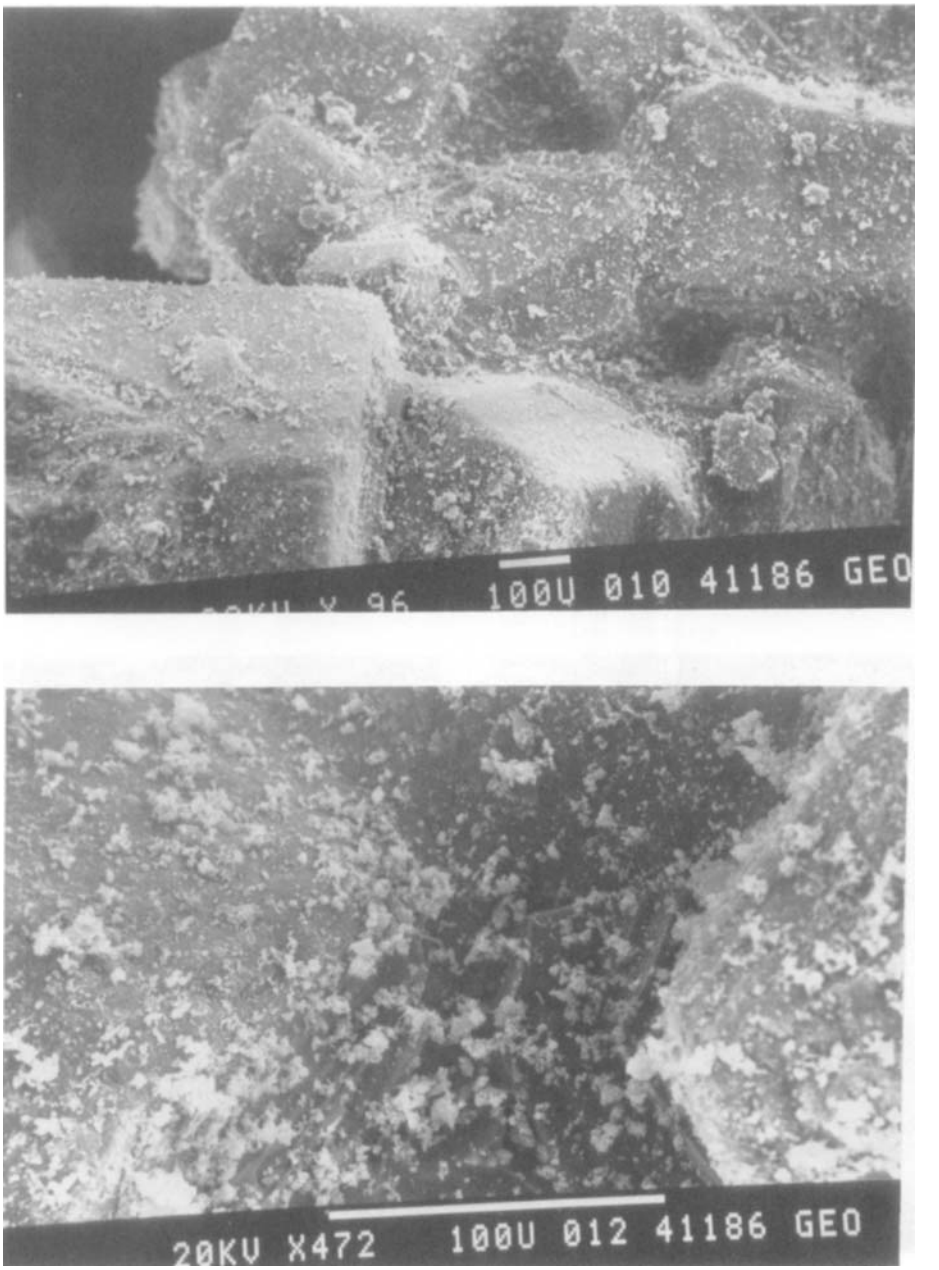
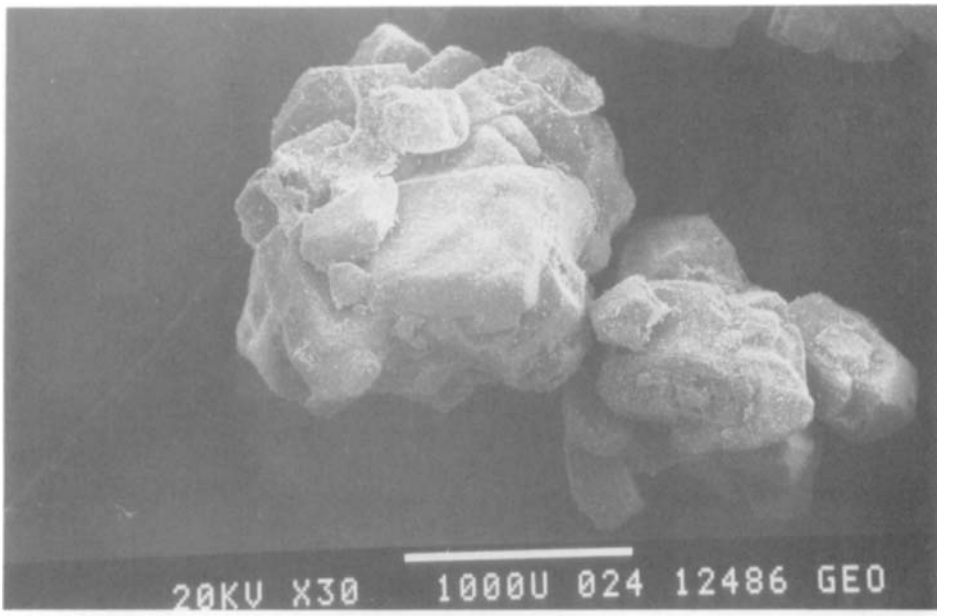


FIGURE 3

ESM Photomicrographs of Interactive Powder Mixture of Griseofulvin and Sugar Granules I000 - 2000 μm.



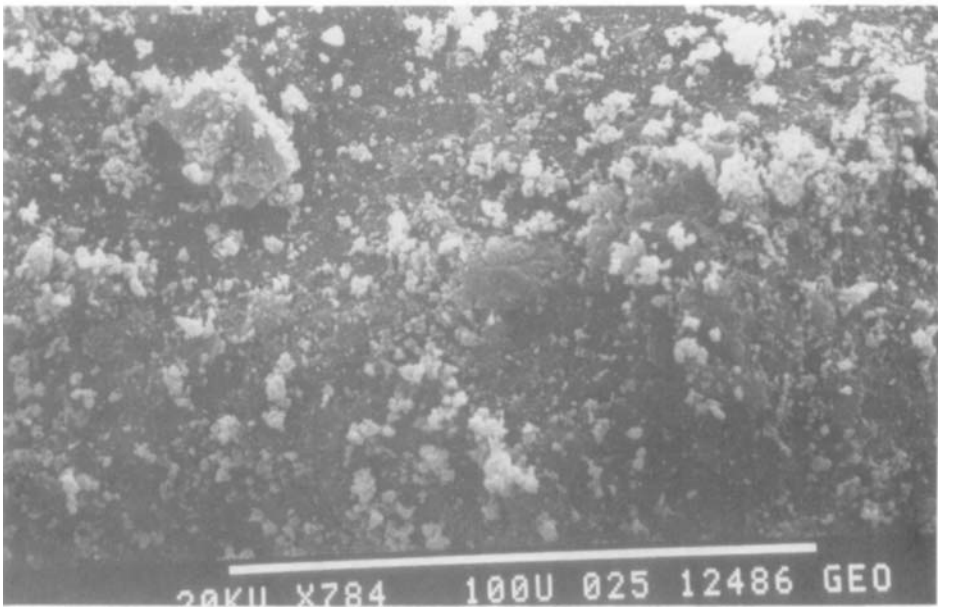


FIGURE 4

ESM Photomicrographs of Interactive Powder Mixture of Griseofulvin and Sugar Granules with Ethylcellulose I000 - 2000 μm.

those of other granules were of limited success. The material showed the highest rugosity among the granules used in the study (Fig.5).

Examination of Figs. 6 and 7 indicate that interactive mixtures containing soluble excipients significcantly improved the dissolution of drug compared to the pure drug alone or to mixtures containing insoluble excipients. The observed effect could be attributed to the high solubility of the excipient particles which dissolved fast enough exposing the drug particles to the wetting effects of the medium and consequently dissolution. The maximum dissolution attained by the use of sugar beads could be explained in light of the fact that the beads are spherical in shape and have smooth regular surfaces relative to other excipients as shown in the ESM photomicrographs of Fig. (8). Therefore; drug particles and drug agglomerates were dispersed into the dissolution medium from such water - soluble smooth surfaces with sufficient ease to achieve the highest dissolution rate among different systems studied.

ESM examination of the ethylcellulose - treated granules showed that ethylcellulose covered the sucrose particles constituting the granules (Fig.2). Furthermore, microscopical examination of thegranules during dissolution revealed that the vehicle penetrated the granules only through holes in the coat (Fig.9), thus retarding the dissolution of the excipient core. This effect was further demonstrated in a separate experiment using sugar granules containing 5% sodium chloride and granulated with ethylcellulose. Granules of the latter were allowed to dissolve in a 0.I% silver nitrate solution and particles were photographed. Fig.(I0) shows deposits of silver chloride particles forming in places where chloride ions migrate out of holes in the

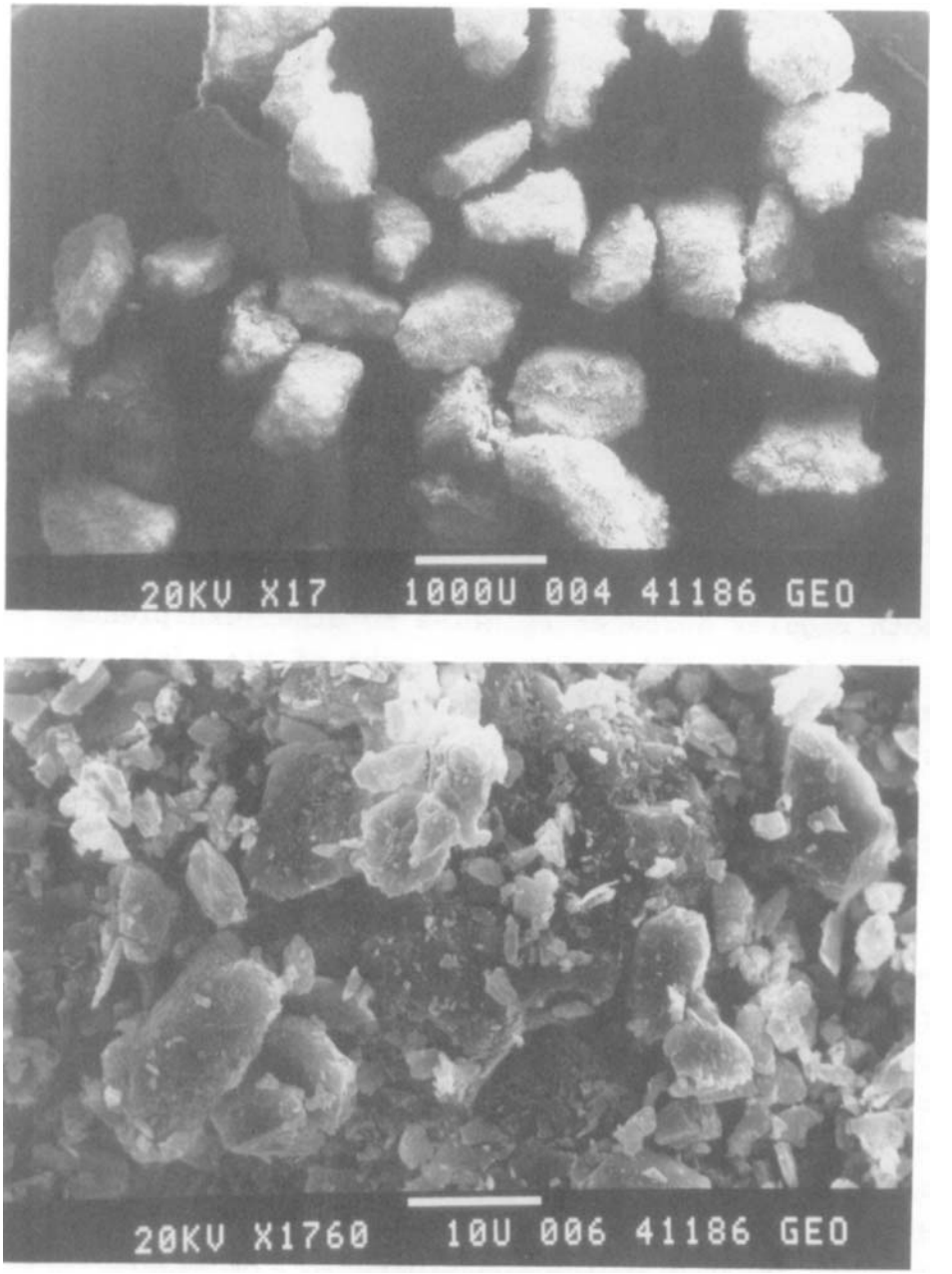


FIGURE 5

ESM Photomicrographs of Interactive Powder Mixture of Griseofulvin and Slugged Ecompress Particles 710-850 μm.

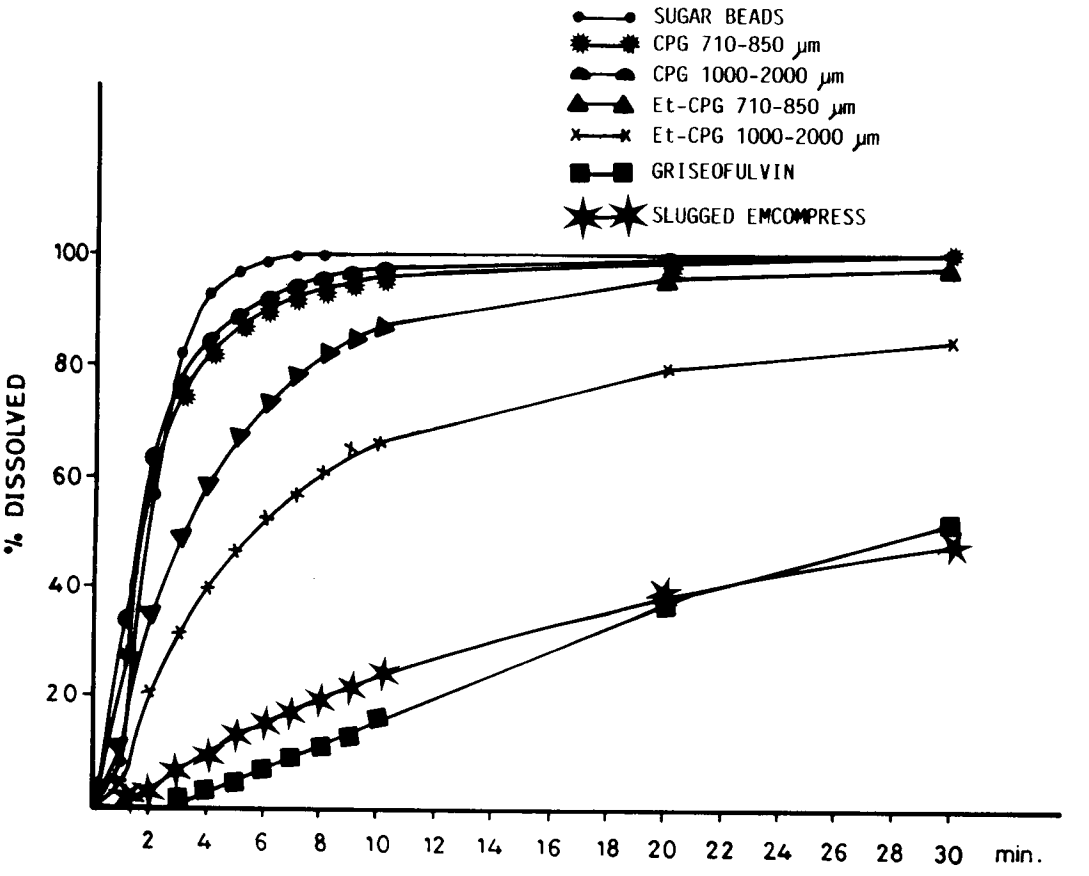


FIGURE 6

Dissolution Profiles of Griseofulvin from Interactive Powder Mixtures prepared from Soluble and Insoluble Excipients.

surface. Therefore; it is reasonable to conclude that the dissolution of griseofulvin from interactive mixtures containing ethylcellulose - treated granules were limited by the rates at which the sugar core disappeared and the ethylcellulose coat collapsed.

It is apparent from Figs. (6) and (7) that interactive mixtures containing slugged Emcompress did not improve the dissolution of griseofulvin

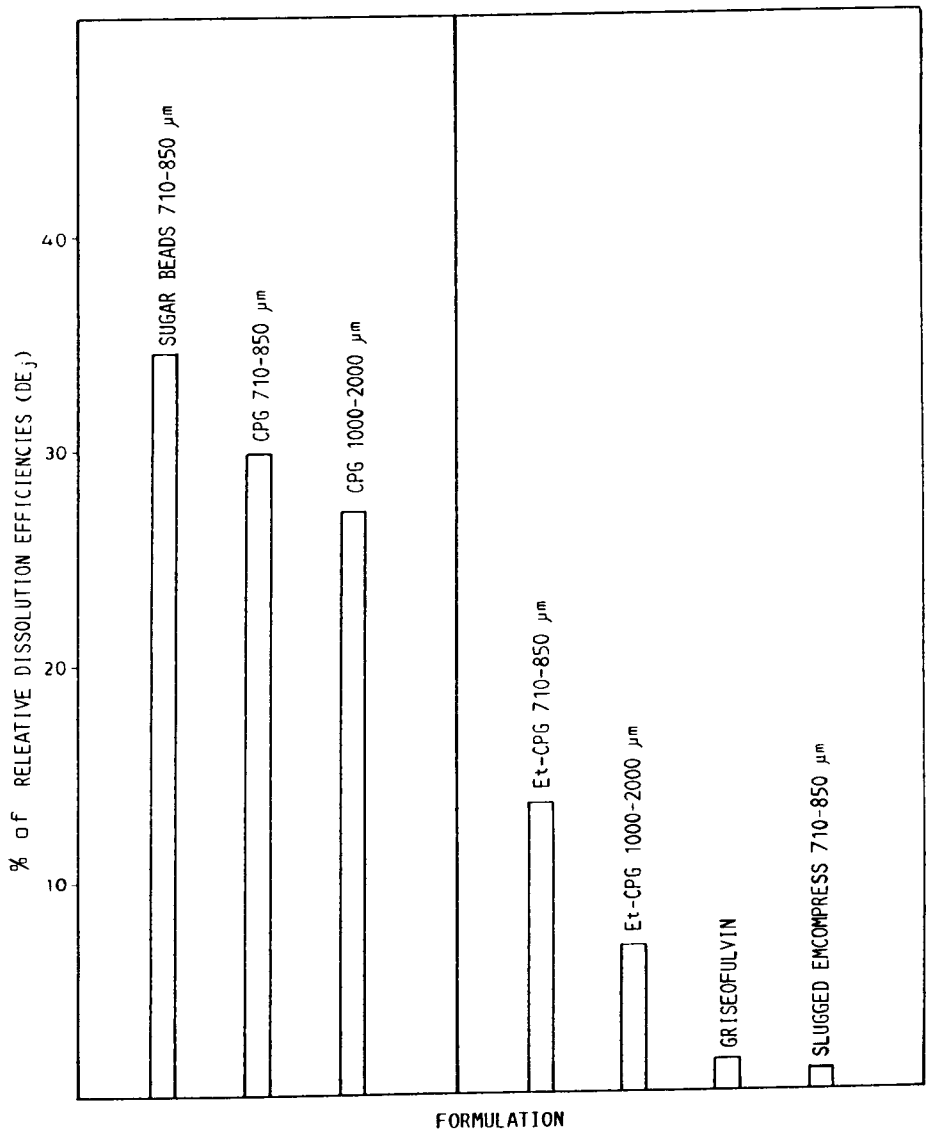


FIGURE 7

A Comparison of Relative Dissolution Efficiencies of Griseofulvin from different Interactive Powder Mixtures.

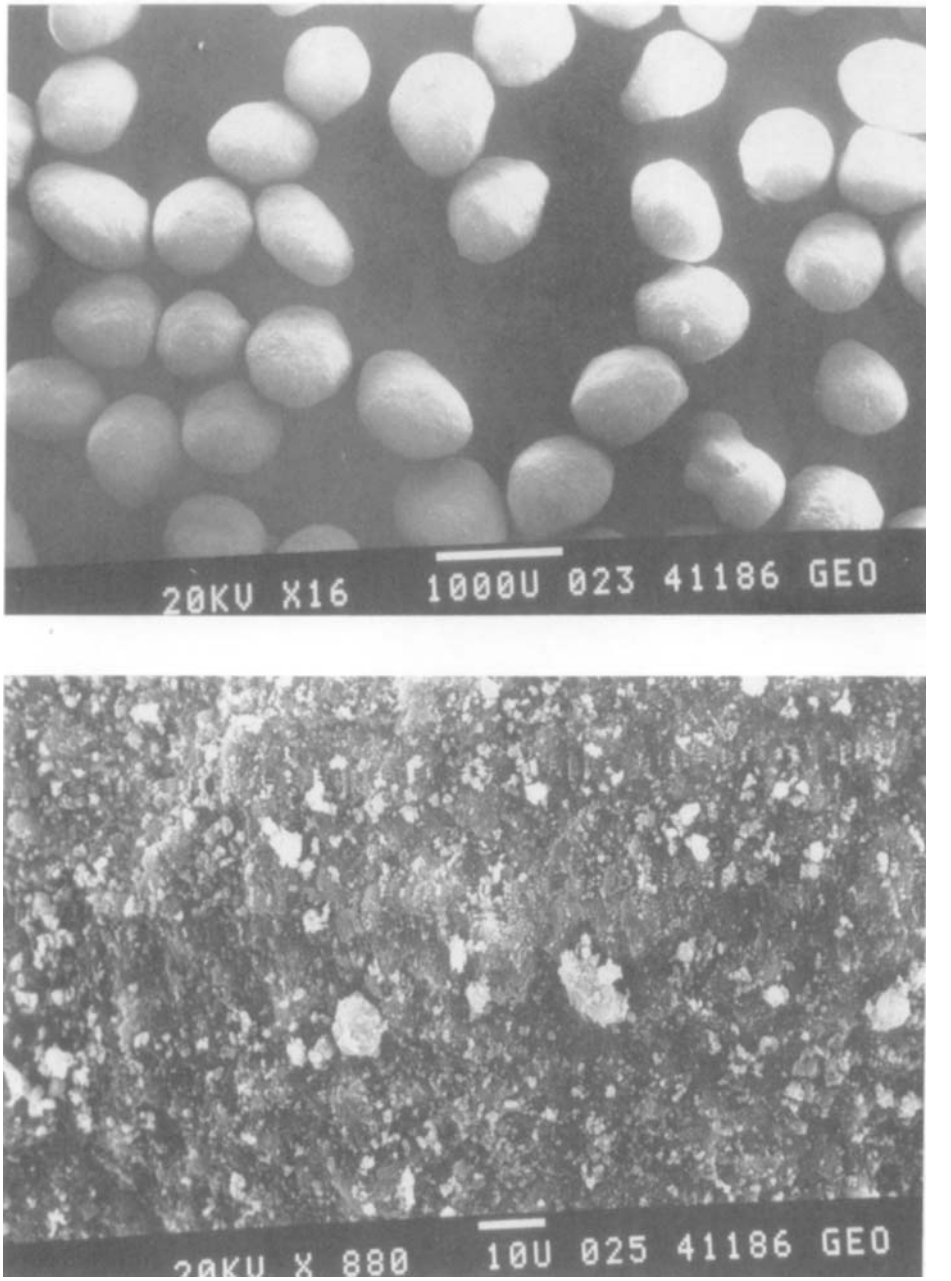


FIGURE 8

ESM Photomicrographs of Interactive Powder Mixture of Griseofulvin and Sugar Beads 710 - 850 μm.

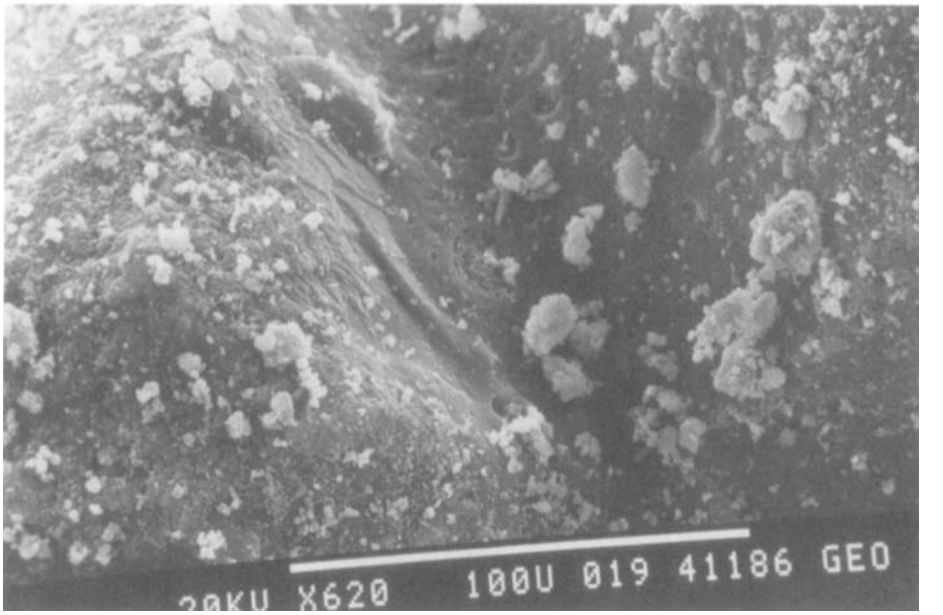


FIGURE 9

ESM Photomicrograph of Ethylcellulose - Treated Granules showing holes in the hydrophobic coat.

to an appreciable extent. The solubility and the high degree of rugosity exhibited by slugged Emcompress particles explain the observed smaller relative dissolution efficiency compared to those with ethylcellulose treated excipients. It is also possible that fine hydrophobic particles abraded from the excipients granules adhered to the drug particles rendering their wettebility and dissolution more difficult.

The findings forwarded so far, characterized from those of previous report (I4), show that the extent of solubility of the excipients plays very important role in determining the degree of improvement of dissolution of poorly soluble drugs by the interactive mixture

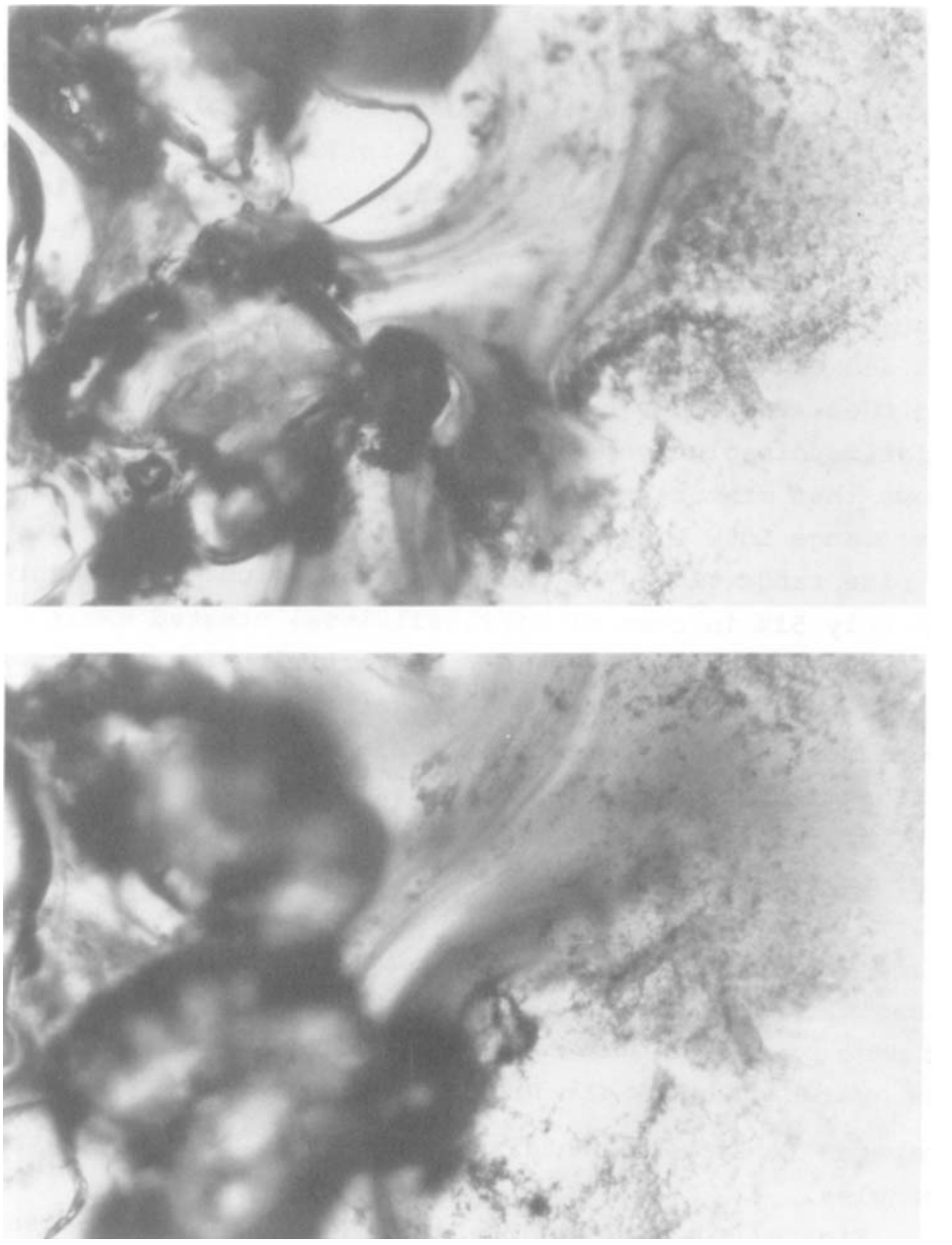


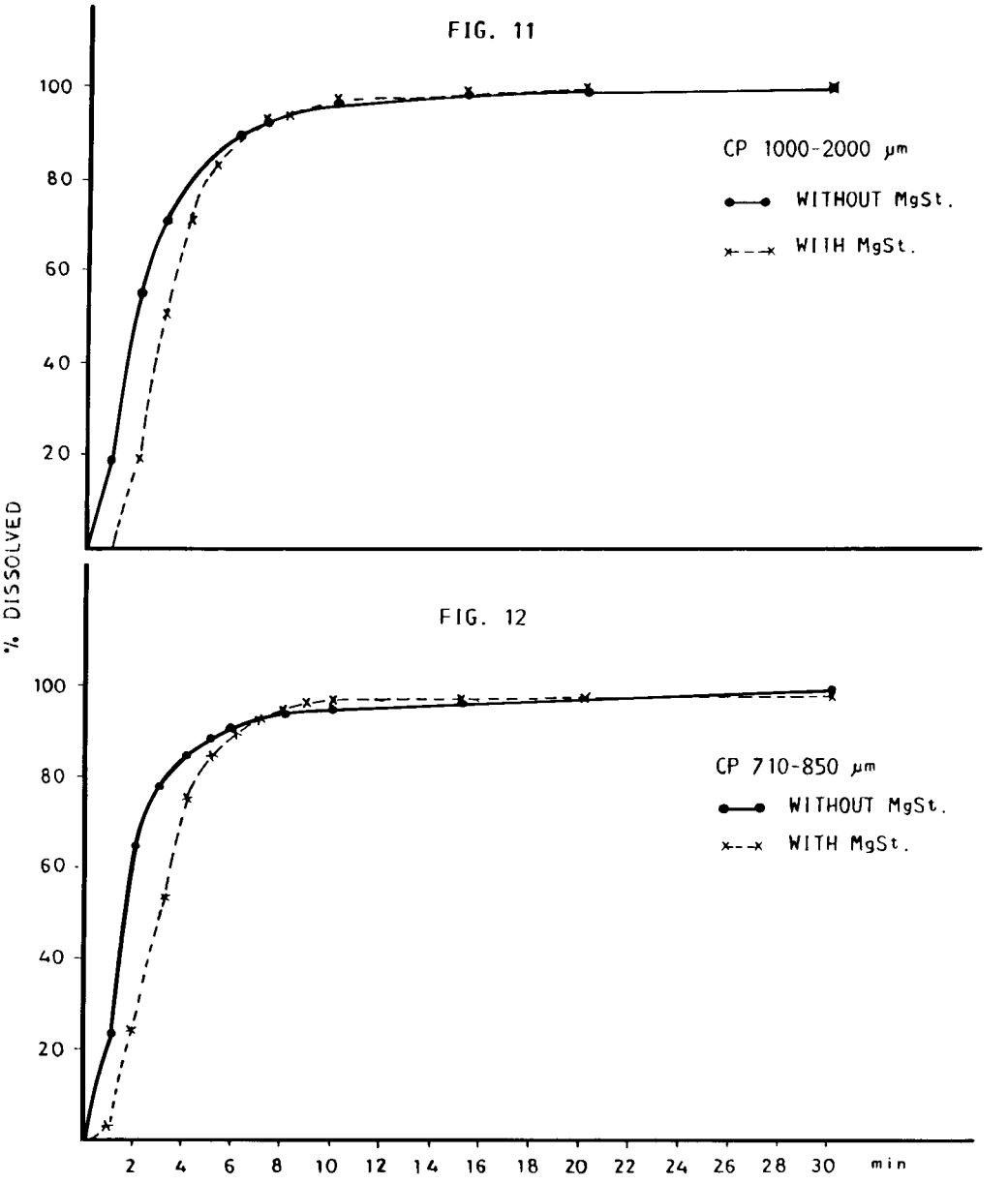
FIGURE I0

Photomicrographs of Sugar Granules containing 5% Na Cl and granulated with Ethylcellulose in 0.I% Ag NO_3 solution.

approach. The effects of particle size of excipients on dissolution of griseofulvin from the interactive mixtures studied canbe deduced from Figs. (6) and (7). The role of the particle size in influencing dissolution was quite apparent in case of insoluble excipients. In I0 minutes dissolution time, systems containing soluble excipients released 96% of the drug, whereas systems containing ethylcellulose - treated excipients released 87% and 66% of thedrug for size fractions 7I0 - 850 μm and I000 - 2000 μm, respectively. Comparison of the relative dissolution efficiencies depicted in Fig.(7) shows that mixtures containing excipient particles of size range I000 - 2000 μm were 9I% oftheir counterparts of size range 7I0 - 850 μm in case of soluble excipients, and only 5I% in case of ethylcellulose- treated excipients.

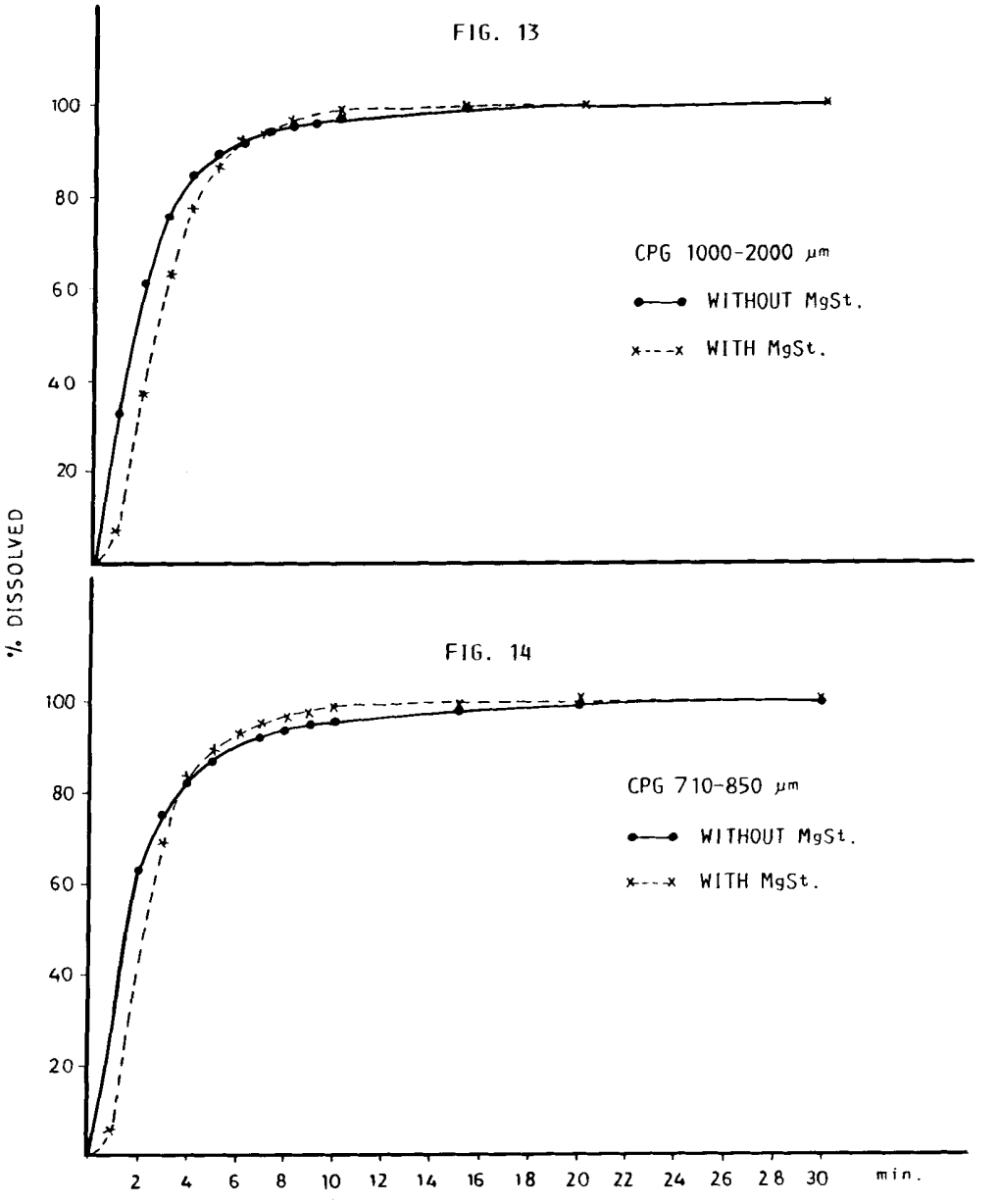
The observed effects of the particle size on dissolution could be interpreted in light of the fact that, the number of excipient particles available for interaction with drug particles increase with the decrease of particle size of the excipient. This effect would minimize the possibility of the drug being deposited in multilayers on the excipient and also would provide the means of having a large surface area available for dissolution. While the same conditions would be existing in case of the soluble excipients, apparently the effect was overshadowed by the high solubility of the excipient compared to systems containing ethylcellulose - treated granules.

Figs. (II - I7) and Table (2) show effects on dissolution arising from mixing different griseofulvin interactive mixtures with a fixed concentration of magnesium stearate for a fixed mixing time. Lerk, et al (I5), studied the interaction of excipients with lubricants during mixing. The authors found that the



FIGURES 11 & 12

Dissolution Profiles of Griseofulvin from Interactive Powder Mixtures showing effects of Mg Stearate using Soluble Excipients.



FIGURES 13 & 14

Dissolution Profiles of Griseofulvin from Interactive Powder Mixtures showing effects of Mg Stearate using Soluble Excipients.

FIG. 15

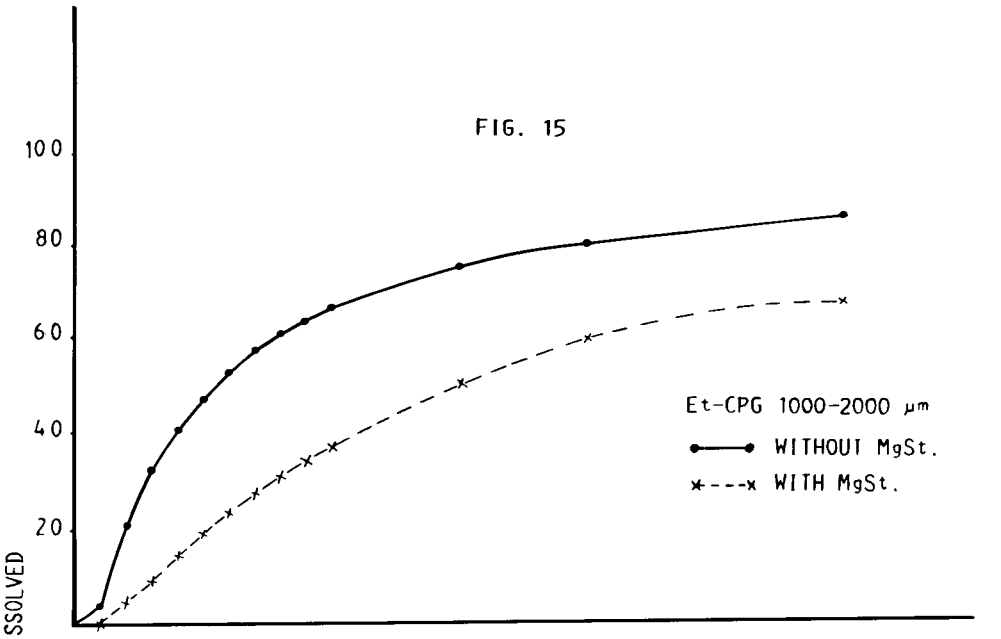
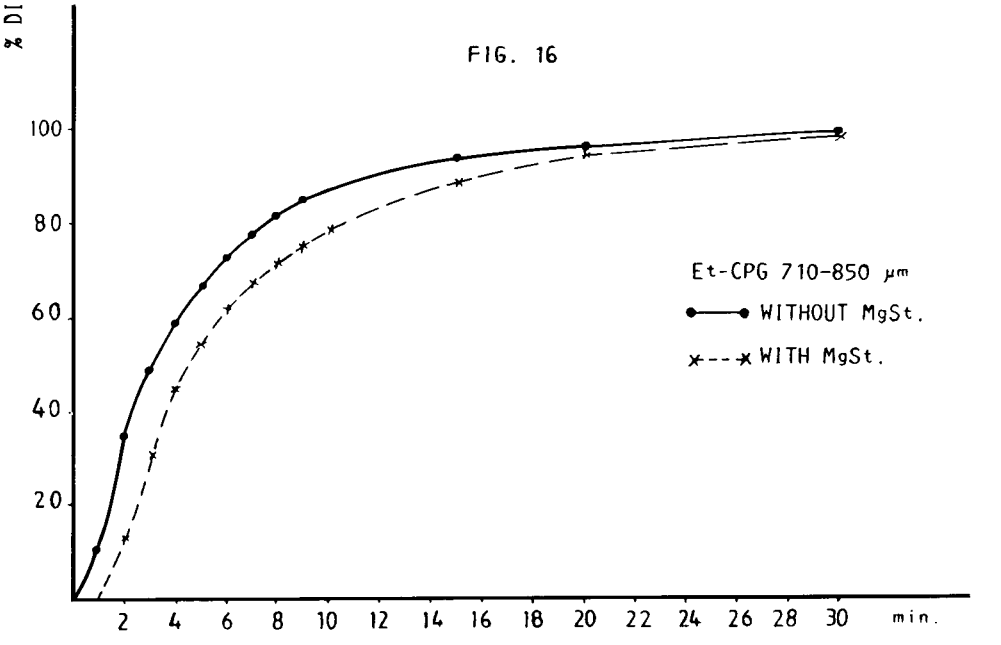


FIG. 16



FIGURES 15 & 16

Dissolution Profiles of Griseofulvin from Interactive Powder Mixures showing effects of Mg Stearate using Insoluble Excipients.

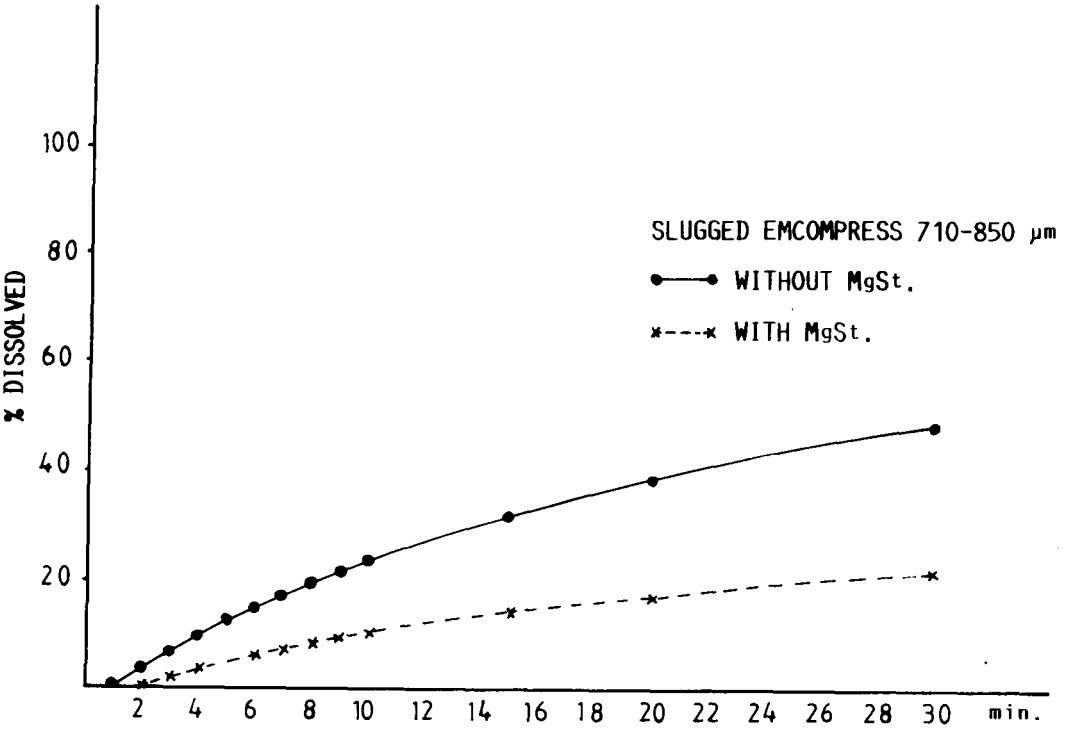


FIGURE I7

Dissolution Profiles of Griseofulvin from Interactive Powder Mixtures showing Effects of Magnesium Stearate (Insoluble Excipients).

dissolution rate of sodium chloride, which served as a soluble excipient, was decreased by increasing lubricant concentration and mixing time. Their results were interpreted as due to the formation of a hydrophobic film around the excipient particles (I5,I6). The current study shows that the presence of the lubricant reduced the dissolution of griseofulvin from systems containing either soluble or insoluble excipients. As can be judged from Table (2), the extent of reductions in the dissolution efficiencies of griseofulvin from mixtures containing soluble excipients were insignificant after 5 minutes dissolution. The data also suggest that the lubricant

TABLE 2

Relative percentage reduction in dissolution efficiency (DE_t), due to mixing with magnesium stearate.

Excipient	$\frac{(DE_t) - (DE_t)_{Mg\ St}}{(DE_t)} \times 100$				
t , minute.	I	2	3	4	5
I - Soluble Excipients					
CP 710 - 850 μm	88	66	37	15	5
CP 1000 - 2000 μm	92	68	33	14	5
CPG 710 - 850 μm	82	40	9	-	-
CPG 1000 - 2000 μm	80	60	23	11	5
II - Insoluble Excipients					
Et-CPG 710 - 850 μm	93	62	40	28	22
Et-CPG 1000 - 2000 μm	90	79	72	66	63
Slugged Ecompress (710 - 850 μm)	100	67	63	59	58

succeeded in hindering solvent penetration into the excipient core and hence the dispersion of the drug particles in the dissolution medium for a period of 2 to 3 minutes. However, this effect arising from partial coating of the drug particles with the lubricant disappeared fast. On the other hand, mixtures containing insoluble excipients showed a substantial reduction in dissolution at times greater than 5 minutes. With mixtures containing ethylcellulose - treated excipients, solvent penetration of the excipient core through pin-

hole in the surface and the collapse of the ethylcellulose coat were rendered more difficult by the presence of the lubricant. This effect is evident from the large values of the relative percentage reduction in dissolution efficiencies at 5 minutes as shown in Table (2).

Coarse sugar particles are mainly single crystals with minimum irregularities relative to granules (Fig.I8). It is conceivable that these crystals would have a continuous film of lubricant around the particles when mixed with magnesium stearate. The coarse particle granules,on the other hand, are formed of aggregates of smaller particles. At magnesium stearate concentration of 0.25%, the continuous film of lubricant would not probably be formed around the granules. Microscopical examination reveals presence of discontinuous film or batches of lubricant particles in case of granules while more or less a continuous shell of lubricant particles was formed around coarse particles (Fig. I9). This behaviour probably explains the higher extent of reduction in dissolution due to lubricant shown by coarse particles relative to sugar granules having the same size range.

The two size fractions of the soluble excipient (sugar coarse particles) did not show a significant difference in dissolution, probably because magnesium stearate at a concentration of 0.25% coated both size fractions in a similar fashion. In case of sugar granules on the other hand, the smaller size fraction gave small reduction in dissolution efficiency because of its high surface area.

The particle size of the water - insoluble excipient was more crucial in influencing effects of lubricant on dissolution. After 5 minutes dissolution, Et-CPG 7I0 -

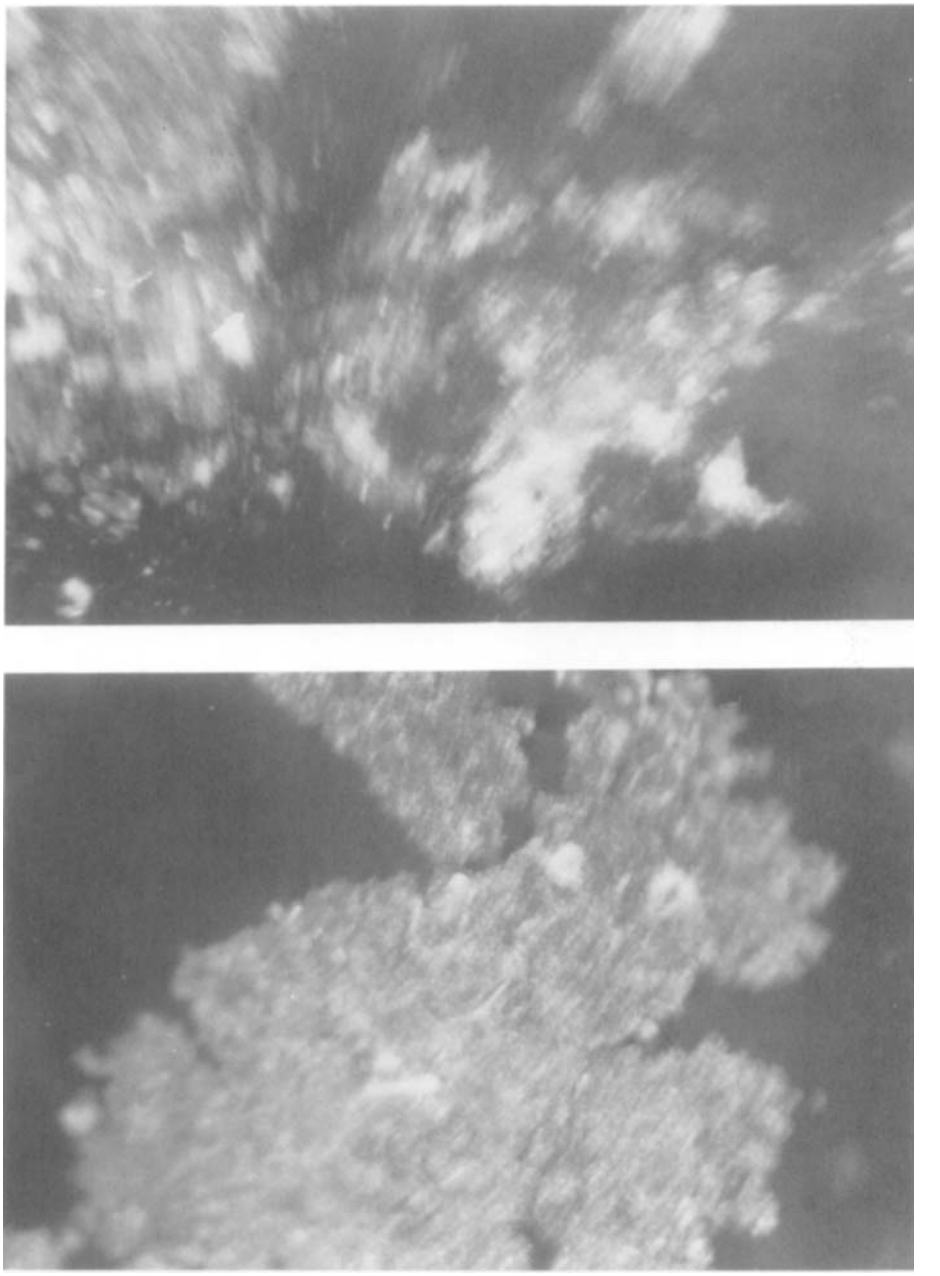


FIGURE I8

ESM Photomicrographs of Interactive Powder Mixture of Griseofulvin and Sugar Particles 710 - 850 μm.

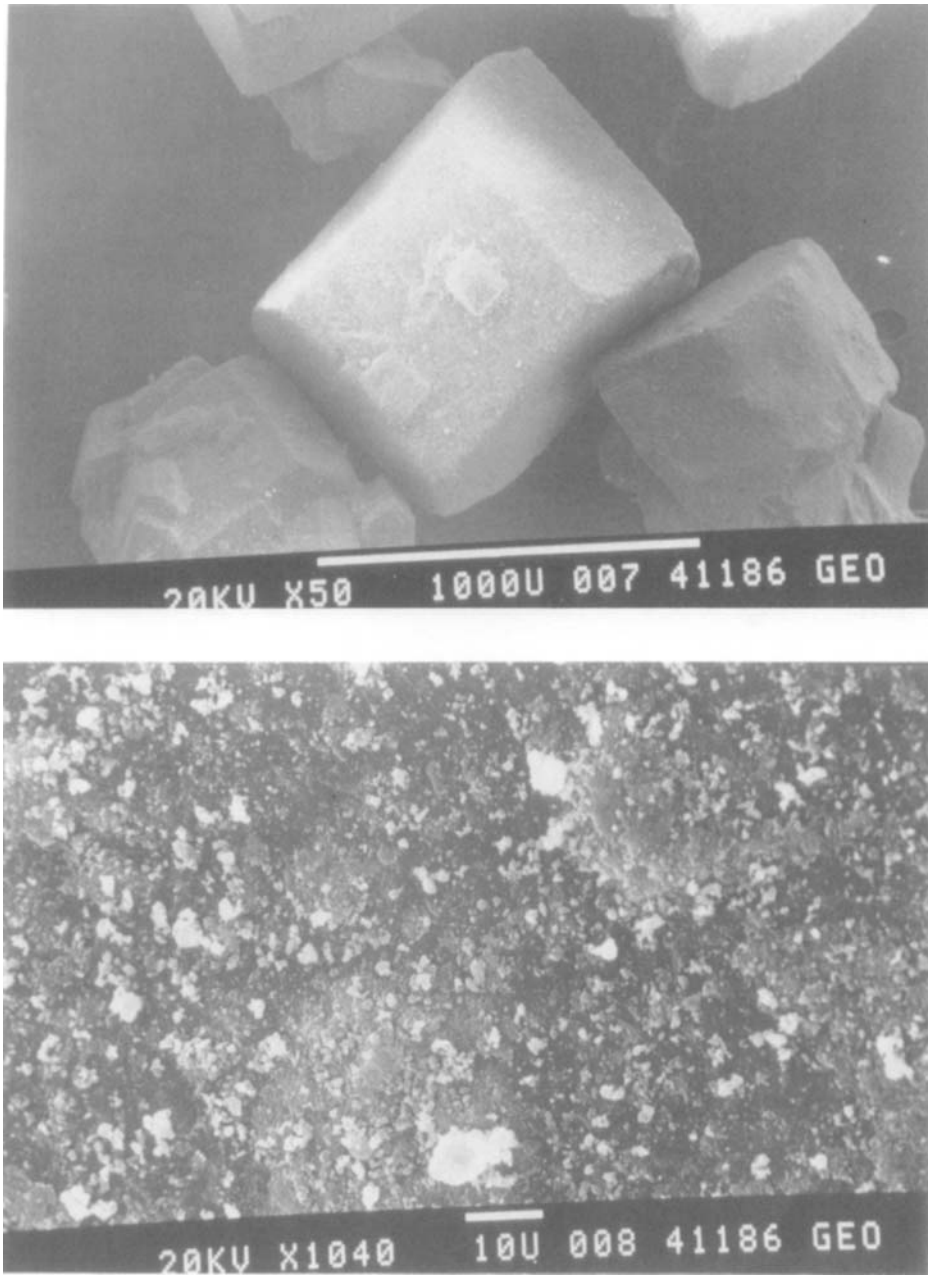


FIGURE I9

Photomicrographs showing coverage of Sugar Particles and Suagr Granules with Magnesium Stearate. Partially Coated Granule (Upper Photomicrograph) and Completely Coated Particle (lower Photomicrograph).

850 µm showed 22% relative percentage reduction in dissolution efficiency; meanwhile, the larger particle size Et - CPG I000 - 2000 µm showed a value of 63%. This effect could be probably related to large surface area of the smaller size fraction and its relationship to the presence of holes in the ethylcellulose coat.

CONCLUSION

Improvement of dissolution of griseofulvin was achieved by the use of interactive powder mixtures where excipients were soluble and insoluble granules made to have comparable shape, texture and rugosity. It was demonstrated that the degree of solubility of the excipient was of prime importance in controlling the extent of improvement in dissolution. Furthermore, the mechanism of dissolution of the water - soluble or partly soluble excipient particles plays a significant role in determining the goodness of dissolution of the poorly soluble drug. The latter effect became even more significant after mixing with lubricant. Particle size of excipients affected dissolution of the model drug in more or less the expected manner. Excipients of smaller particle size generally improved dissolution of drug agent better than excipients of large size fractions.

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