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SURFACE CHARACTERISATION OF SUCROSE AND ANTIOBIOTICS POWDER MIXES WITH RELEVANCE TO MIXING THEORIES.

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ABSTRACT

Adhesional ordered mixing is not applicable in real systems because ordered interaction between drug and excipient particles can not be achieved. In contrary, Interactive Mixture approach is more applicable because it allows the powder mixtures to be described according to the state of homogeneity achieved which is dependent on mixing variables.

Surface characteristics of powder mixture particles are important to study in order to understand the interparticulate interactions between drug and excipient particles.

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Indentations on excipient particles act as mechanical entrapment sites for drug particles which result in areas containing highly localised drug content. Consequently, the state of homogeneity of powder mixtures is possibly affected. Furthermore, the release of particles which are entrapped will be different from those held by interparticulate forces on the plain surfaces of excipient particles. This is particularly important when the excipient particles are insoluble and drug particles are poorly soluble.

INTRODUCTION

The homogeneity of a powder mix is dependent upon the association of particles of one species with another species. Until Hersey (1) introduced the concept of ordered mixing, mixing processes were defined in terms of randomisation.

The most common proposed ordered mixing is the adhesional ordered mixtures. These powder mixtures require interacting particulate systems (6), where the randomisation process is prevented by the adherence of small drug particles to large excipient particles.

Yip and Hersey (7) defined the ordered mixture as the one which has a zero standard deviation of sample concentration at all sample sizes on the bases that the sample size is greater than the size of single

ordered unit. As opposed to random mixtures where the standard deviation decreases with increasing sample size (4). Consequently, standard deviation for an ordered mixture will depend on the errors of analysis and sampling.

In order to attain a zero standard deviation for adhesional ordered mixtures an ordered adhesion of a fine drug particles of mono-sized distribution to a coarse excipient of monosized distribution is required. In practice, these conditions can not be fulfilled as indicated by Egermann (8). The conditions required for ordered mixtures are applicable in idealised systems. While the real systems are exhibiting random adhesion behaviour, wide size distribution of drug and excipient powders relative to the required monosize distribution, agglomerates in drug cohesive powder and different distribution of active sites on excipient particles. Accordingly, discussions have been developed concerning the terminology which describes powder mixtures (9-16).

The terminology "Interactive Mixtures" seems to be more applicable in practice than "Adhesional Ordered Mixtures". In this case the interactive mixture may be descibed either as incomplete when $\sigma > \sigma_R$ or complete when $\sigma = \sigma_R$. While the ordered one ($\sigma < \sigma_R$) is considered as an ideal, theoretical system because it requires an ordered adhesion which can not be fulfilled in practice (15 and 16).

The present study investigates the extent of physical interactions between drug and excipient particles. This investigation is achieved by examining the surface characteristics of particles in powder mixtures. It also correlates between these parameters and the performance of dry mixing process in terms of mixing theory.

EXPERIMENTAL

Materials

Sucrose, ampicillin trihydrate and cloxacillin sodium powders have been provided by the Jordanian Pharmaceutical Manufacturing Company (Na'or, Jordan). All materials are pharmaceutical quality currently used for preparing dry syrup formulations.

Methods

500 g of powder mixtures of sucrose (1.00-0.85 mm) and drug powder (7.5% w/w) are prepared by mixing in cube mixer (Erweka Co., West Germany) for 1 hour. In order to examine the extent of size reduction exerted on drug particles by large excipient particles, portion of powder mixture has been shaken gently and manually on 0.315 mm sieve into a collecting pan.

Scanning Electron Microscopy (ESM) of drug powder mixtures have been done by Electron Optics Unit at

Sunderland Polytechnic, Sunderland, U.K. The ESM is a Cambridge Instruments Stereoscan. Sample preparation is done by sputter coating with carbon followed by gold. Slow vacuum has been performed in order to minimise sucking off fine drug particles from the surface of sucrose particles.

The particle size distribution of ampicillin trihydrate powder before and after mixing has microscopy (Bausch and Lomb).

RESULTS AND DISCUSSIONS

Surface Characterisation of Sucrose Particles:

ESM photomicrographs of sucrose particles are shown in Figures (1,2&5). Although the particles are chosen to exhibit a very close size distribution (1.00-0.85 mm fraction), the surface area of individual particles varies significantly. This is because most of the particles donot show plain surfaces. In contrary they show indentations or clusters of small sucrose crystals which result in variations in surface area between individual particles. Furthermore, the active sites present on the sucrose particles which are responsible for adhesion between sucrose and drug particles are expected to vary between individual sucrose particles. All these variations will not allow adhesional ordered mixtures to be achieved in real systems.

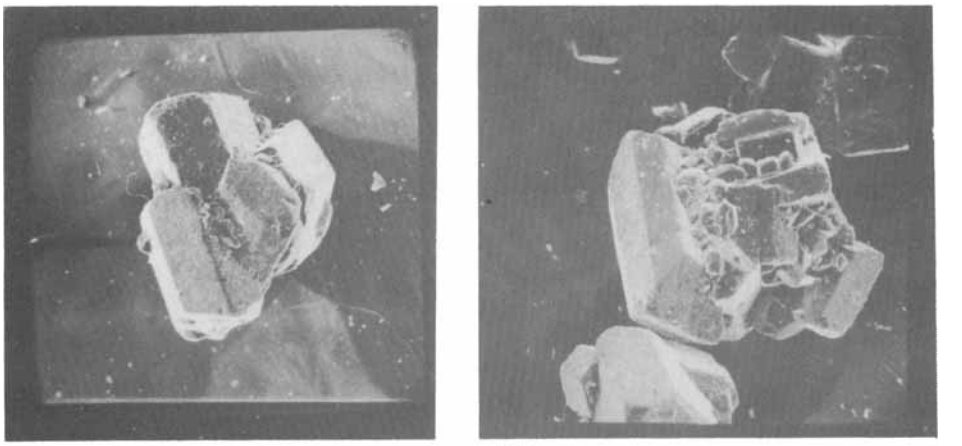

Fig.1,ESM Photomicrographs of sucrose particles(1.00-0.85 mm) showing variations in surface area and degree of indentations.

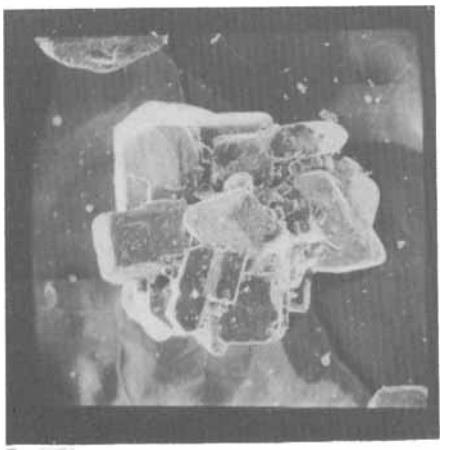

Fig.2,ESM Photomicrographs of sucrose particles showing indentations.

As shown in Fig .3 the presence of fine sugar particles will be adhered to the surface of larger sucrose particles. This phenomenon may well affect the interparticulate adhesion and the location of drug particles on the larger sucrose particles.

Ampicillin T.H and Sucrose Powder Mixture

ESM photomicrographs of ampicillin trihydrate and sucrose powder mixture are shown in (Fig .4&5).

Indentations on sucrose particles act as mechanical entrapment sites for drug particles. As a result, drug particles are entrapped in these indentations allowing presence of areas on sucrose surfaces having more localised drug content (Fig .4&5). The plain surfaces of sucrose particles will be having less drug content as shown in Fig .5a. It is also possible that the adherence sites within the indentations are stronger than other sites which strengthen the mechanical entrapment of drug particles.

The presence of identations and adherence sites on sucrose particles is random in nature. Therefore, the distribution of drug particles on sucrose particles is expected to be following random pattern. This means that the homogeneity required for adhesional ordered mixing will not be achieved in real systems. In contrary, the "Interactive Mixtures" approach is more

Fig.3,ESM Photomicrographs of sucrose particles showing fine sugar particles adhered to the surface of coarse particles.

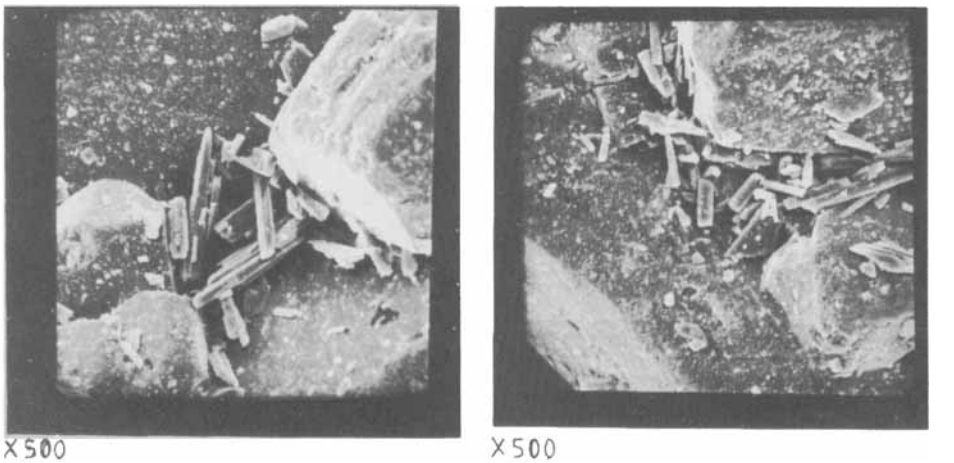

Fig.4, ESM Photomicrographs of ampicillin trihydrate and sucrose powder mixture showing entrapped drug particles.

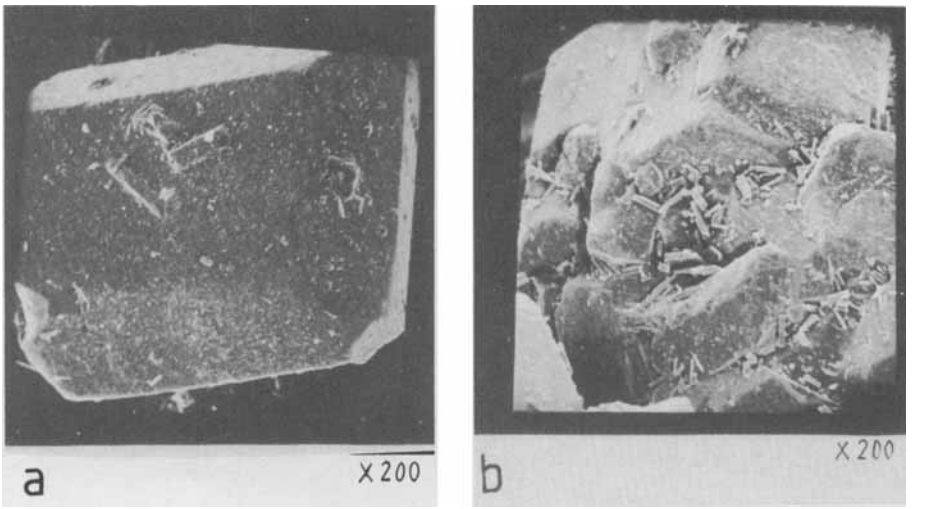

Fig.5, ESM Photomicrographs of ampicillin trihydrate and sucrose powder mixtures showing difference in drug content between plain surfaces (a) and indentated surfaces (b).

applicable to describe the state of homogeneity achieved by this type of powder mixtures.

On examining the photomicrographs (Fig. 6) of ampicillin trihydrate particles before and after dry mixing, it is clear that the particle size has been reduced significantly. Ampicillin trihydrate particles are broken into smaller particles as a direct effect of the milling action induced by large sucrose particles. The degree of size reduction will be dependent on the time of mixing, nature of drug powder and, particle size and weight of excipient particles.

As the particle size of drug powder decreases the state of homogeneity of powder mixtures increases accor-

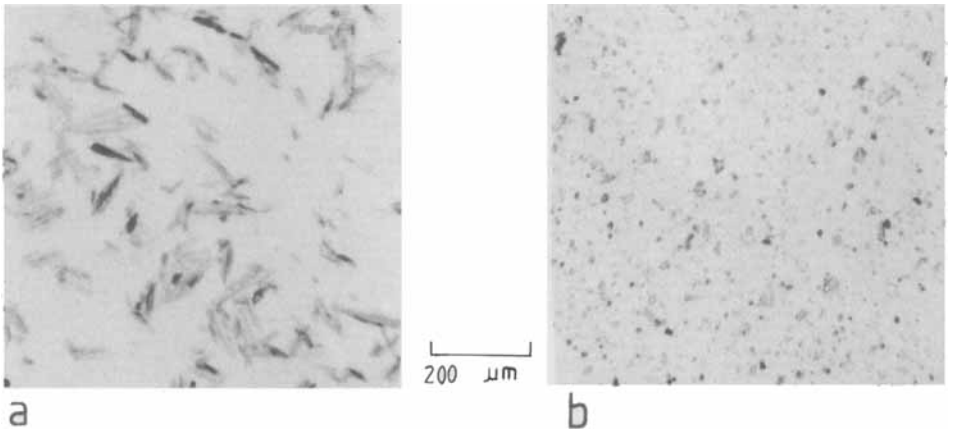

Fig.6, Photomicrographs of ampicillin trihydrate particles before (a) and after mixing(b).

ding to random mixing theory. Moreover, the adhesional interaction between drug particles and excipient particles increases. However, there are two draw backs which may affect the state of homogeneity of powder mixtures. Firstly, by decreasing the particle size of drug particles, the surface area increases and consequently it may saturate the active sites on the surface of excipient particles particularly when the concentration of drug is relatively high. This may leave free drug particles in the system which promotes segregation. Secondly, the cohesiveness of drug particles may increase which results in appearance of drug agglomerates (Fig. 7) in the powder mixture. Presence of agglomerates in the system produces skewed distributions as indicated in many studies (17-20).

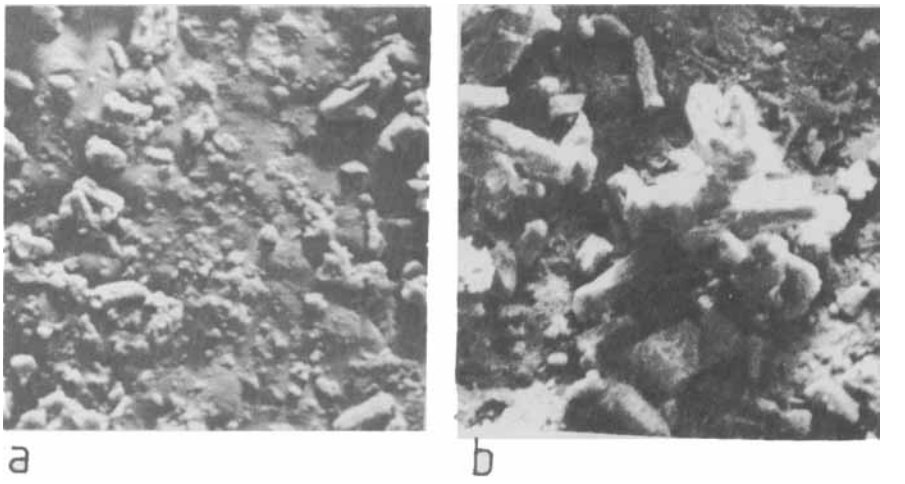

Fig.7, ESM Photomicrographs of ampicillin trihydrate showing size reduction after mixing (a) and presence of drug agglomerates (b).

It is interesting to point out that ampicillin trihydrate particles which are entrapped into the indentations of sucrose particles are showing the least degree of size reduction. Their particle size is kept almost the same as their original particle size before mixing. The indentations act as a mechanical protection for entrapped particles against milling action exerted by large sucrose particles.

Cloxacillin Sodium and Sucrose Powder Mixtures:

Cloxacillin sodium particles are spherical in shape constituted of aggregates of tiny particles(Fig.8) and highly soluble in water. While ampicillin trihydrate particles are prismatic in shape and less soluble

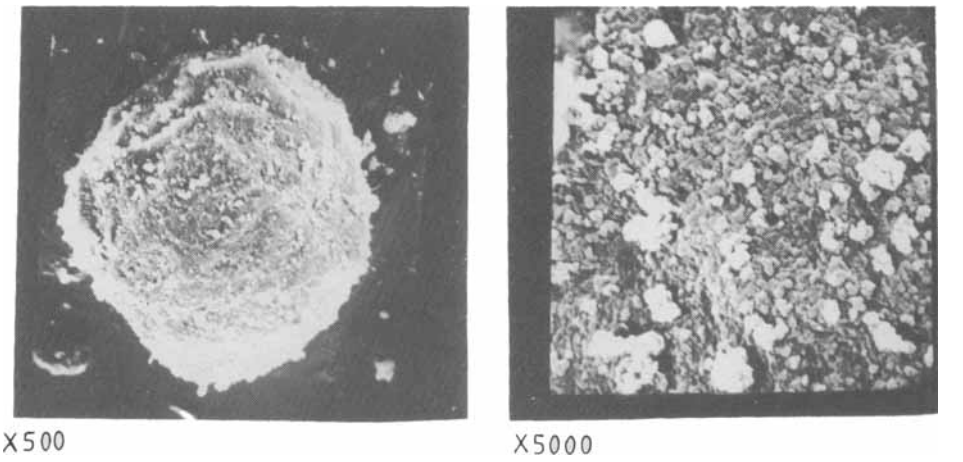

Fig.8, ESM Photomicrographs of cloxacillin sodium particles showing spherical shape. Spheres are aggregates of tiny particles.

in water. Thus, cloxacillin sodium particles are expected to behave differently from ampicillin trihydrate particles when mixed with sucrose particles.

Part of cloxacillin sodium powder dissolves in moisture layer already adsorbed on sucrose surfaces, and forms sticky layer. Subsequently, it coats sucrose particles on longer time of mixing. This coating will produce a higher state of homogeneity. However, the random stickness of spherical particles of drug and the presence of indentations with highly localised drug content on sucrose particles indicate that the theoretical quality of adhesional ordered mixing can not be achieved although coating is more or less complete as shown in Fig.9

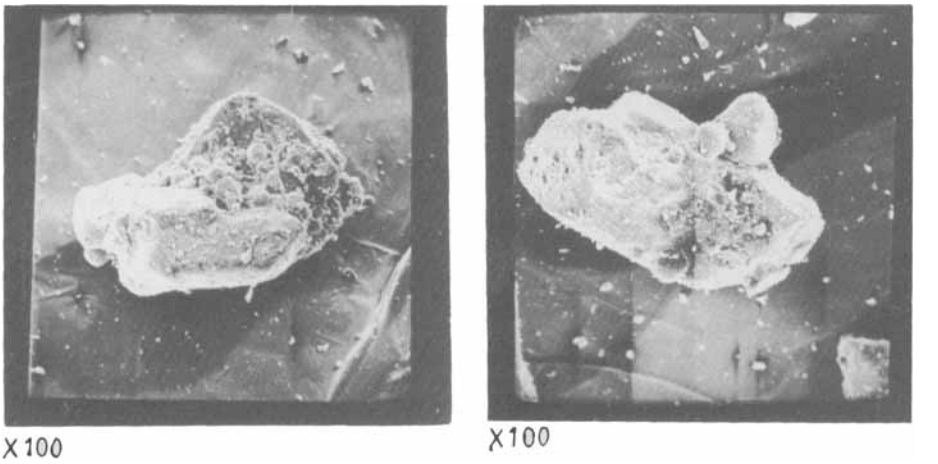

Fig.9, ESM Photomicrographs of cloxacillin sodium and sucrose powder mixture showing variation in drug content per sucrose particle.

Effect of Mechanical Entrapment on Dissolution of Drug Particles:

Indentations on excipient particles act as mechanical entrapment sites for drug particles. In case of insoluble excipients and poorly soluble drugs, the entrapped particles may exhibit slower dissolution rate than those particles held by interparticulate forces on the plain surfaces of excipient particles. The possible reasons can be summarised as follows:

1- Entrapped drug particles are showing the least size reduction because they are mechanically protected from milling mechanism exerted on by the coarse excipient particles. Accordingly, these particles are larger in size than the free unentrapped drug particles (Fig.4).

If the entrapped drug particles are agglomerates, they will not be efficiently broken down and consequently, individual drug particles will not be dispersed into the powder mixture. In both cases dissolution rate will be affected. Moreover, in case of soluble excipient particles the entrapped drug agglomerates may be causing lower dissolution rate than that expected.

2- The dissolution medium will not be easily wetting the interior areas of indentations where some drug particles or agglomerates are entrapped. It is therefore possible that, the imperfect contact between the dissolution medium and entrapped drug particles or agglomerates becomes more pronounced after mixing with lubricant. In this case, the lubricant e.g. magnesium stearate forms a hydrophobic coat which hinders the penetration of dissolution medium to the entrapped drug particles or agglomerates.

Table 1, shows results of ethinyloestradiol 10 ug tablets, a batch which has been prepared using cohesive drug powder, large lactose (79% w/w), starch (20% w/w) and magnesium stearate (1% w/w). The tablets have been prepared by direct compression after further mixing of powder mixture with magnesium stearate for 20 minutes in rotating jar.

Large lactose particles (Fig.10) exhibit surface characteristics similar to sucrose particles, i.e. the

Table 1. Summary of experimental data of ethinyloestradiol 10 µg tablets based on single assays of 50 tablets (21).

	Range	Mean	Coefficient of variation	Target value
µg/Tablet	6.9-9.6	8.0	6.9	10
µg/g Tablet	139-180	155	6.3	200

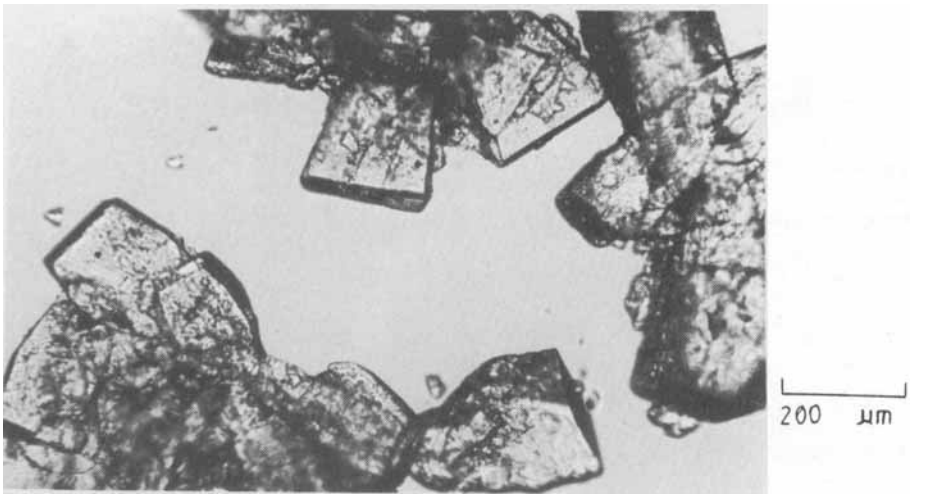

Fig.10 Photomicrograph of Large Lactose Particles.

presence of indentations which will be acting as mechanical entrapment sites for drug particles or agglomerates.

The extraction procedure uses 60% v/v aqueous methanol which is not enough to dissolve large lactose particles. As a result, the entrapped drug particles

or agglomerates will not be easily extracted as highlighted before. Consequently, the mean drug content of 50 tablets is lower than the target value as indicated in Table 1.

The results in µg/Tablet give an indication of variation in tablets that occurs. The data in µg/g tablet give an indication of variation in tablet mass; that is, it is independent of variation in tablet weight.

CONCLUSION

In conclusion, ordered mixing is not applicable because ordered interaction between drug and excipient particles can not be achieved. In contrary, Interactive Mixtures approach is more applicable because it allows the powder mixes to be described either as incomplete ($\sigma > \sigma_R$) or complete ($\sigma = \sigma_R$) according to the state of homogeneity attained.

Indentations on excipient particles act as mechanical entrapment sites for drug particles, thus areas with more localised drug content are obtained which may affect the state of homogeneity of powder mixtures. In addition, the release of particles which are entrapped will be different from those held by interparticulate forces particularly when the excipient particles are insoluble and drug particles are poorly soluble.

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