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EFFECT OF PARTICLE SIZE ON DEFORMATION AND COMPACTION CHARACTERISTICS OF ASCORBIC ACID AND POTASSIUM CHLORIDE: NEAT AND GRANULATED DRUG

N. H. Shah[1,4], W. Phuapradit[1], M. Niphadkar[2], K. Iqbal[3], M. H. Infeld[1], and A. W. Malick[1]

[1] Pharmaceutical R&D, Hoffmann-La Roche Inc., 340 Kingsland St., Nutley, NJ 07110. [2] Temple University, Philadelphia, PA. [3] R. W. Johnson Pharmaceutical Research Institute, Raritan, NJ 08869. [4] To whom correspondence should be addressed.

ABSTRACT

Deformation and compaction characteristics of two soluble drugs, ascorbic acid and potassium chloride, were investigated. Five different particle size fractions of ascorbic acid with mean particle size (d_{50}) ranging from 30-300 μm and four different particle size fractions of potassium chloride with d_{50} ranging from 20-400 μm were selected in the study. The compaction behavior of the drug substances as neat drugs or as granulated drugs were evaluated on both a Carver press and an instrumented single-punch tablet press. The results clearly show that mean particle size of the drug substances plays an important role in their compactibility. Intrinsic compactibility of both drug substances was slightly improved with increased particle size. Granulations of the drugs with polyvinyl pyrrolidone significantly improved their compactibility. However, this effect was more pronounced in the drug substance with finer particle size. The Heckel plots indicate that deformation characteristics of both granulated drugs were related to their original mean particle sizes. The granulations prepared from the coarser particle size (d_{50} 250 μm to 400 μm) underwent two stages of deformation, so-called "brittle fracture" and "plastic deformation". While the granulations prepared from the finer particle size predoninantly underwent "plastic deformation". The results indicated that the plastic deformation of both granulated drugs was progressively enhanced whilst fragmentation of particles was correspondingly reduced as the particle size of the drugs was decreased. Scanning electron photomicrographs indicated that the granulation process changed the surface morphology of the drug particles imparting more "microirregularities" or "defects", thereby providing greater "interparticulate bonding" as compared with the neat drugs. Optimum

particle size range of ascorbic acid and potassium chloride for satisfactory compactibility was found to be 30-40 μm and 20-40 μm, respectively. The present study demonstrates the importance of selecting the appropriate particle size of drug for the development of tablet dosage forms.

INTRODUCTION

The integrity of a tablet is dependent on the strength and resistance of the compacted powder in withstanding external disruptive, until the tablet is administered. The purpose of compaction is to bring particle surfaces into close proximity and to enhance intermolecular forces, thereby enabling interparticulate bonding (1,2). Compactibility of powder is dependent on both the intra- and interparticulate bond strength and on the area of interparticle bonding resulting from powder compaction and decompression. Compactibility may be affected by both the physico-chemical characteristics of material under consolidation as well as tableting conditions. Important functional characteristics include the ability of particles to bond following deformation (3), particle roughness and shape (4,5), size and size distribution (6-10), moisture (11-15) and amount of elastic recovery occurring during decompression (16-18). It is generally considered that excipients which undergo rapid permanent deformation facilitate interparticle bonding and produce tablets with improved mechanical strength. Several techniques used to enhance compactibility of the excipients have been cited by Wallace et al. (19). Changes in process equipment or conditions can influence the compaction behavior of the materials as reported by Staniforth et al. (20).

The objectives of this study were: (i) to evaluate the effect of particle size of ascorbic acid and potassium chloride as the neat drugs or the granulated drugs on compactibility and deformation behavior during compaction and (ii) to establish the optimum particle size of these two water soluble drug substances for satisfactory compactibility.

MATERIALS AND METHODS

Materials

Five different particle size fractions of ascorbic acid (Hoffmann-La Roche Inc., Nutley, NJ) were used, namely granular (mean particle size, d_{50} 300 μm); fine granular (d_{50} 250 μm); USP grade (d_{50} 150 μm); fine powder (d_{50} 80 μm) and ultrafine powder (d_{50} 30 μm). Four different particle size fractions of potassium chloride were used, namely granular (d_{50} 400 μm); 60 mesh (d_{50} 250 μm); USP grade (d_{50} 80 μm) and micropulverized potassium chloride powder (d_{50} 20 μm). All grades were obtained from Mallinckrodt Specialty Chemicals Co., St. Louis, MO except the micropulverized grade was prepared by passing potassium chloride USP grade through a Micropulverizer (Hosokawa Micron International Inc., Summit, NJ) fitted with a screen plate having a diameter of 0.02 inch using hammers at medium speed. Polyvinyl pyrrolidone (PVP K30; BASF Fine Chemicals, Parsippany, NJ) and magnesium stearate (Mallinckrodt Specialty Chemicals Co., St. Louis, MO) were used as received.

Methods

Intrinsic Compaction

Intrinsic compaction of both neat drugs with different particle size fractions was evaluated on a Carver Press (Fred S. Carver Inc., Summit, NJ) at different compression forces using a 7/16 inch diameter round standard concaved punch with a 500 mg of tablet weight. Compression force applied was monitored from the dial readings of Carver Press. Prior to each compaction, die cavity and punch surface were lubricated by applying a very thin coat of magnesium stearate using a paintbrush.

Granulation Compaction

Different particle size fractions of the drug substances were granulated with 10% w/w polyvinyl pyrrolidone, then dried overnight at 50°C. The dried

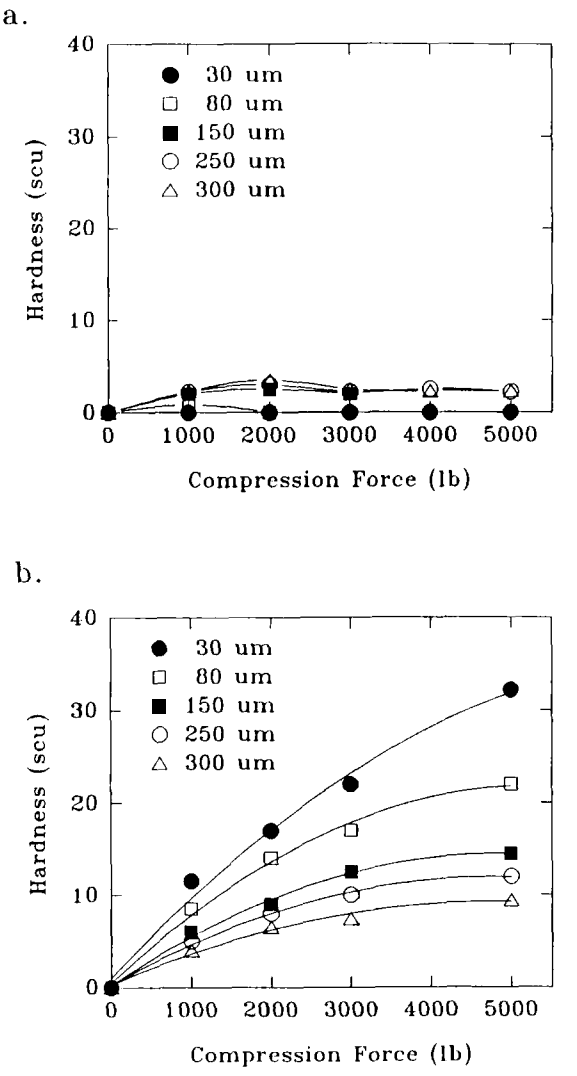

Figure 1: Effect of particle size on compaction of ascorbic acid as neat drug (a) and granulated drug (drug) evaluated on a Carver press.

granulation was sieved through a screen #20 mesh and blended with magnesium stearate for 3 minutes in a PK blender (Patterson Kelly Co., Stroudsburgh, PA). The tablets were compressed on the Carver Press or an instrumented F-Press (Manesty Machines Ltd., Liverpool, England) at different compression forces using a round standard concaved punch, with a

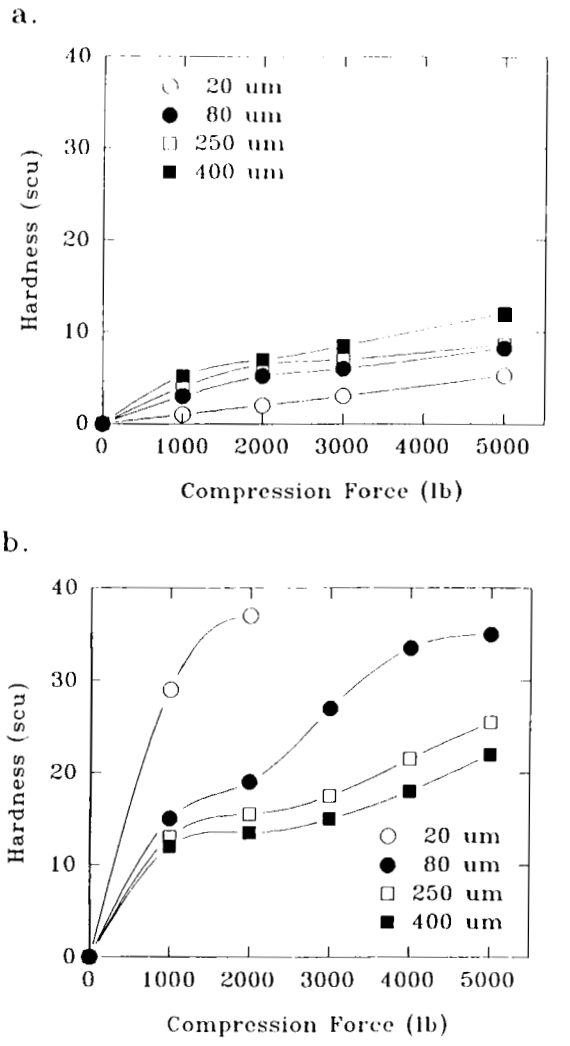

Figure 2: Effect of particle size on compaction of potassium chloride as neat drug (a) and granulated drug (b) evaluated on a Carver press.

diameter of 7/16 inch. Each tablet comprised of the drug substance 500 mg, polyvinylpyrrolidone (PVP K30) 25 mg and magnesium stearate 2 mg. Compression force applied was monitored from the dial readings when the Carver press was used, or from Rostar tablet press monitor (instrumented tablet press developed at Hoffmann-La Roche Inc.) when the F-Press was used.

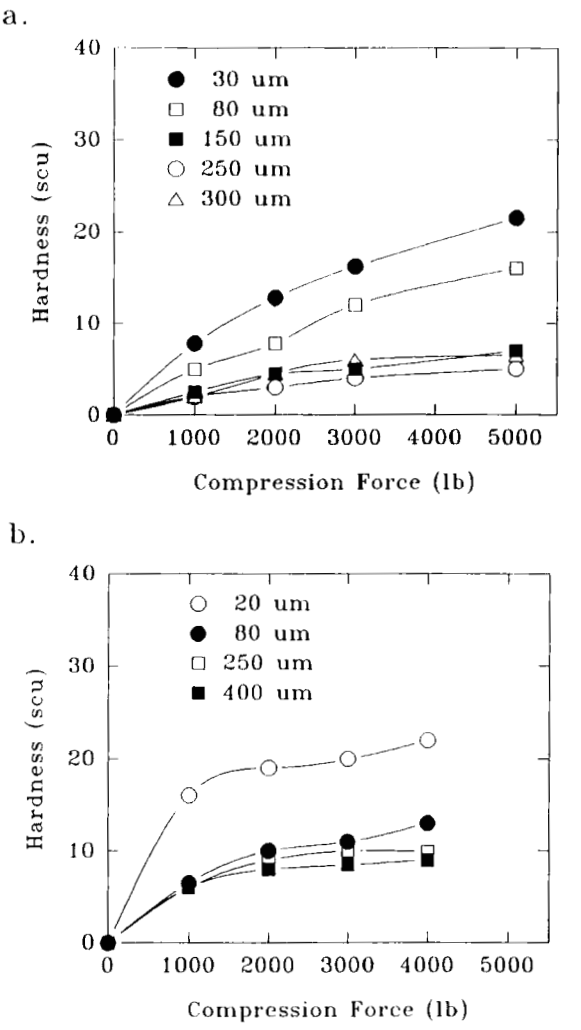

Figure 3: Effect of particle size on compaction of ascorbic acid (a) and potassium chloride (b) as the granulated drugs evaluated on an instrumented F-press.

Compactibility Determination

Hardness of tablets was measured by Hardness tester (Key International Inc., Englishtown, NJ). Compactibility was determined from the slope of the initial linear portion of the compression force-hardness profiles.

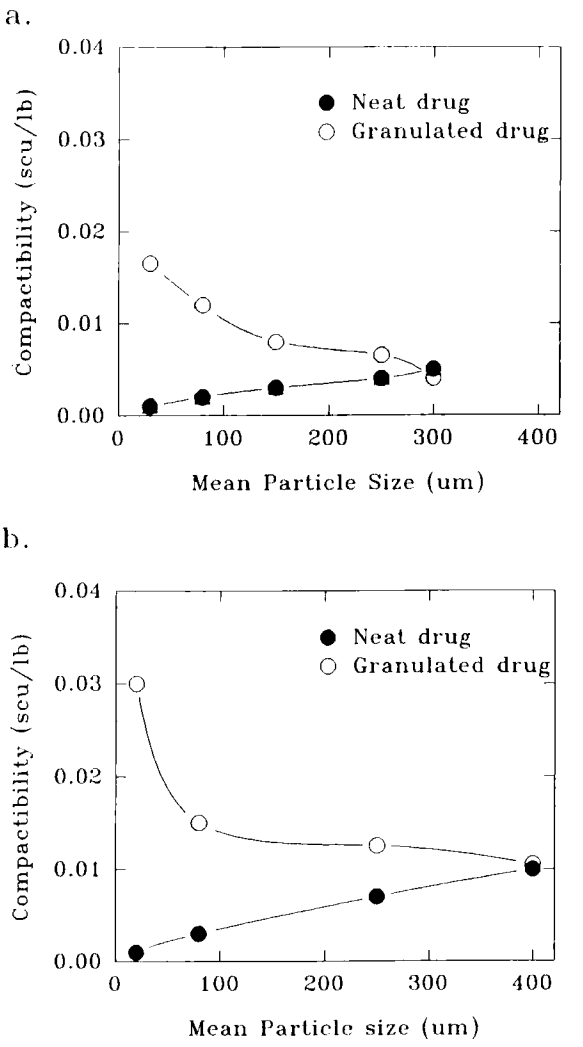

Figure 4: Relationship between the particle size and compaction of ascorbic acid (a) and potassium chloride (b) as the neat drugs and the granulated drugs evaluated on a Carver press.

RESULTS AND DISCUSSION

Intrinsic Compactibility

The compression force-hardness profiles of ascorbic acid and potassium chloride as the neat drugs using Carver Press are shown in Figures 1a and 2a,

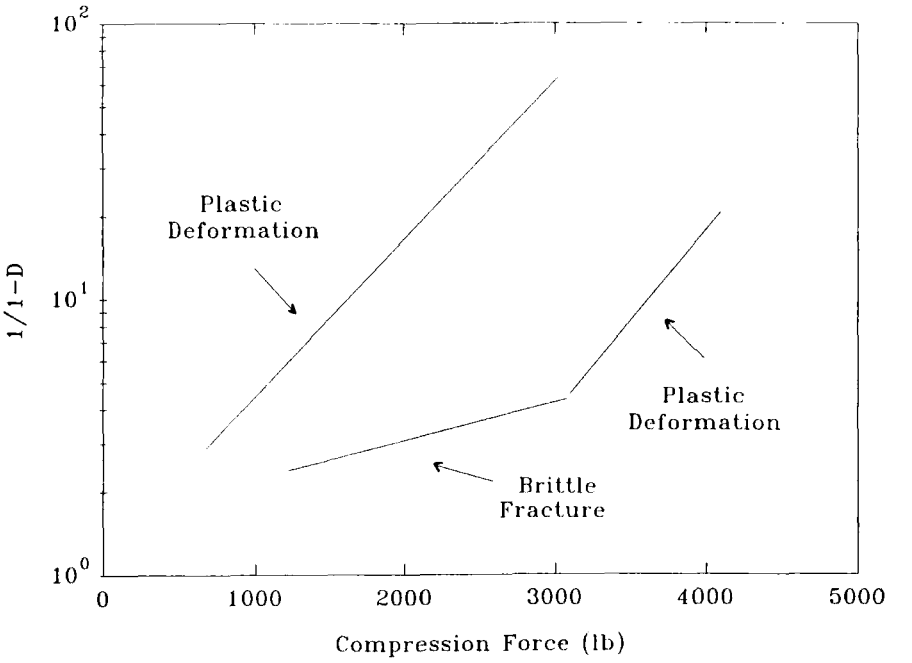

Figure 5: The Heckel plot showing the relationship between pressure and relative density of the compacted powder during compaction.

respectively. Intrinsic compactibility of both drug substances was considerably poor and was slightly improved with the increased particle size.

Granulation Compaction

Granulating the drug with the binder (PVP K30) significantly improved the compactibility of ascorbic acid and potassium chloride as shown in Figures 1b and 2b, respectively. The improved compactibility of of both granulated drugs was attributed to increased deformation of the particles due to the binding properties of PVP K30, thus resulting in adhesive attraction of the particles. However, the improvement was more pronounced when granulating both drugs having finer mean particle size. This effect was also evidently shown when the instrumented F-Press was used (Figures 3a and 3b). The finer particles of the drug provided greater surface area for the distribution of

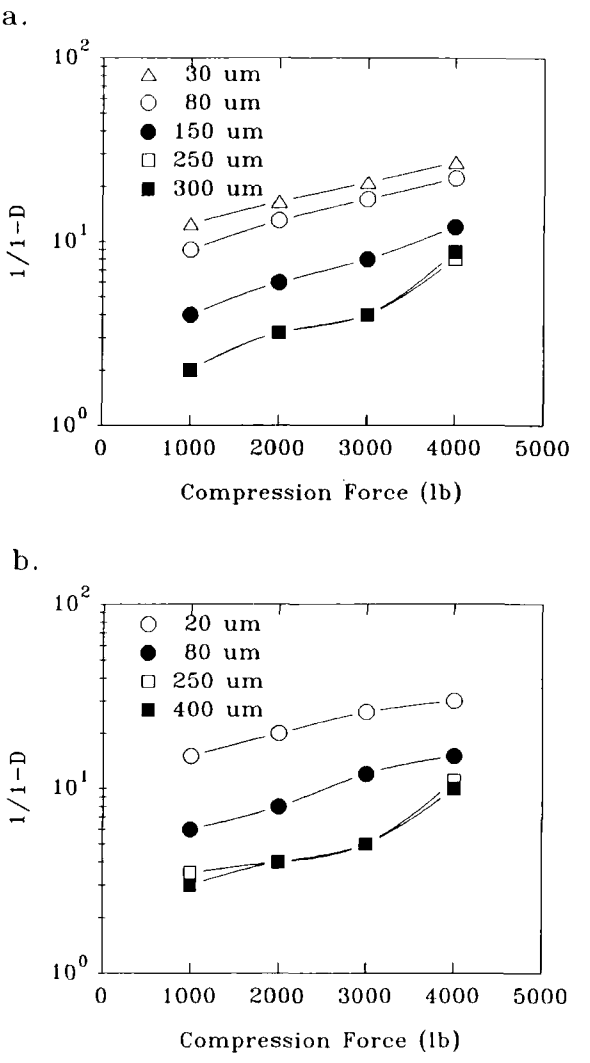

Figure 6: Effect of mean particle size on deformation behavior of ascorbic acid (a) and potassium chloride (b) as the granulated drugs during compaction evaluated on a Carver press.

PVP K30, thus enhancing interparticulate bonding. The plots of compactibility versus mean particle size of both drugs were constructed as shown in Figures 4a and 4b. The results clearly show that the effect of the original mean particle size of both drug substances plays an important role in their compactibility.

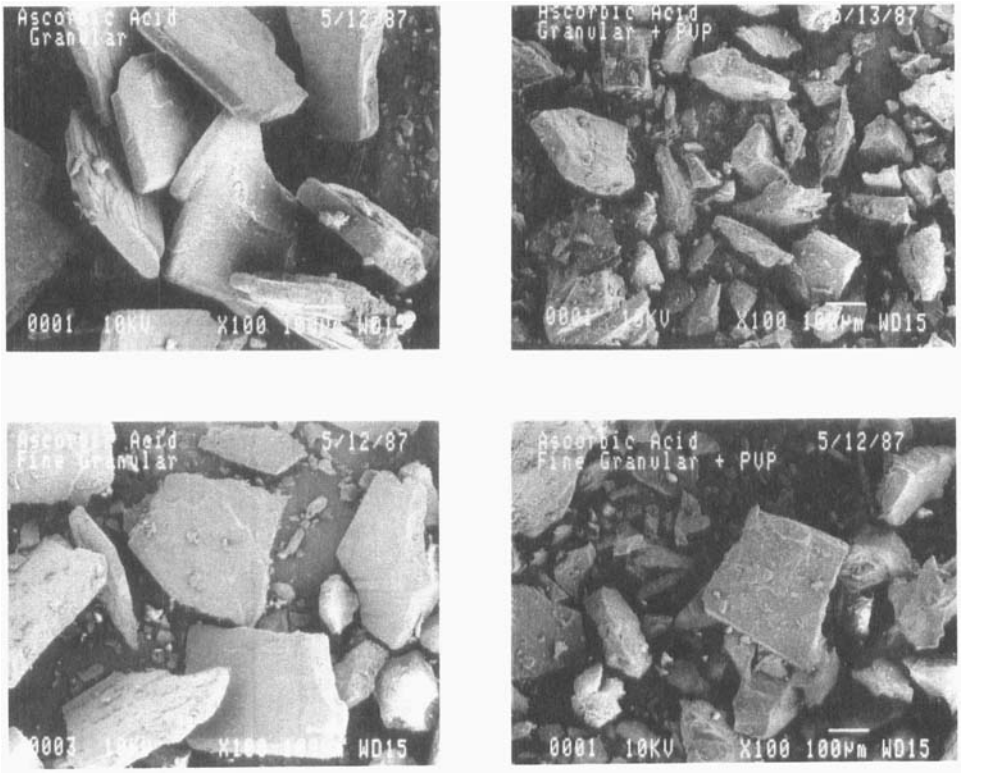

Figure 7: Scanning electron photomicrographs of ascorbic acid in the forms of: top - granular grade of neat drug (left) and granulated drug (right); bottom - fine granular grade of neat drug (left) and granulated drug (right).

Deformation Behavior

The Heckel equation was derived to interpret density-pressure relationships in compaction testing (21).

$$\ln [V_p/V_p - V_\alpha] = KP + A \quad \text{(Eqn. 1)}$$

$$\ln [1/1 - D] = KP + A \quad \text{(Eqn. 2)}$$

where V_p is the volume of the compacted powder at a specified compression force, V_α is the volume of the compacted powder with porosity approaching

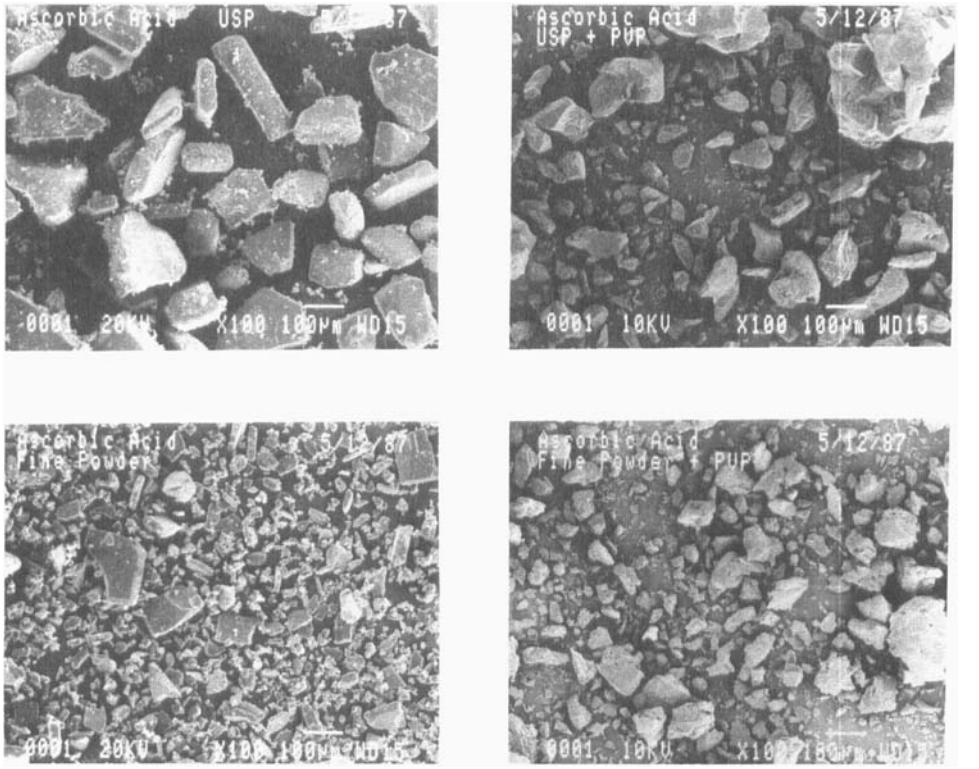

Figure 8: Scanning electron photomicrographs of ascorbic acid in the forms of: top - USP grade of neat drug (left) and granulated drug (right); bottom - fine powder of neat drug (left) and granulated drug (right).

zero, D is the relative density of the compact at pressure P, which equals to V_a/V_p, P is the compression force, K and A are constants. The values of K and A are determined graphically from slope and intercept, respectively from the linear portion of the plots of ln [1/1-D] vs P as shown in Figure 5. The K value is characteristic of the deformation behavior of the material under compaction. The A value is a measure of densification due to slippage and rearrangement of particles and depends mainly on their size, shape and hardness.

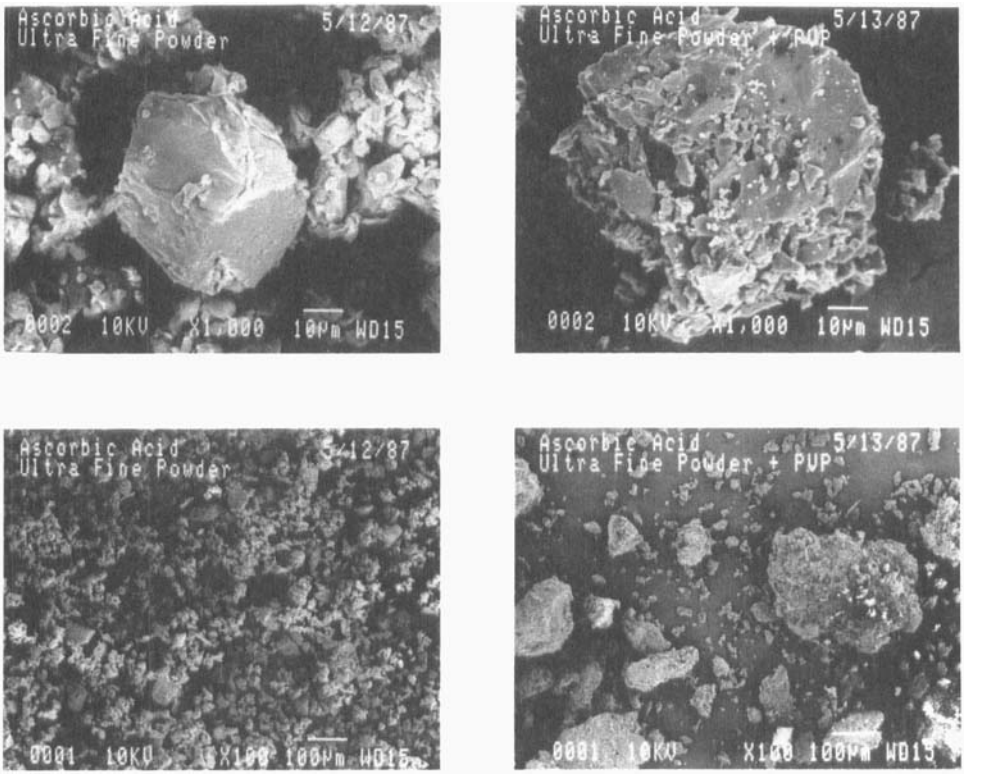

Figure 9: Scanning electron photomicrographs of ultra fine grade of ascorbic acid in the forms of neat drug (left) and granulated drug (right).

The Heckel plot can be used to distinguish the deformation behavior of the powdered materials. Hersey and Rees (22) distinguished two types of powder behavior by relating the constant K to the yield pressure of a material by:

$$K = 1/P\gamma \qquad \text{(Eqn. 3)}$$

where $P\gamma$ is the mean yield pressure. Materials with a high yield pressure are classified as "brittle fracturing", whereas materials with a low yield pressure are classified as "plastic deforming materials". In order to understand the mechanism of deformation under compression, the Heckel plots of both drugs

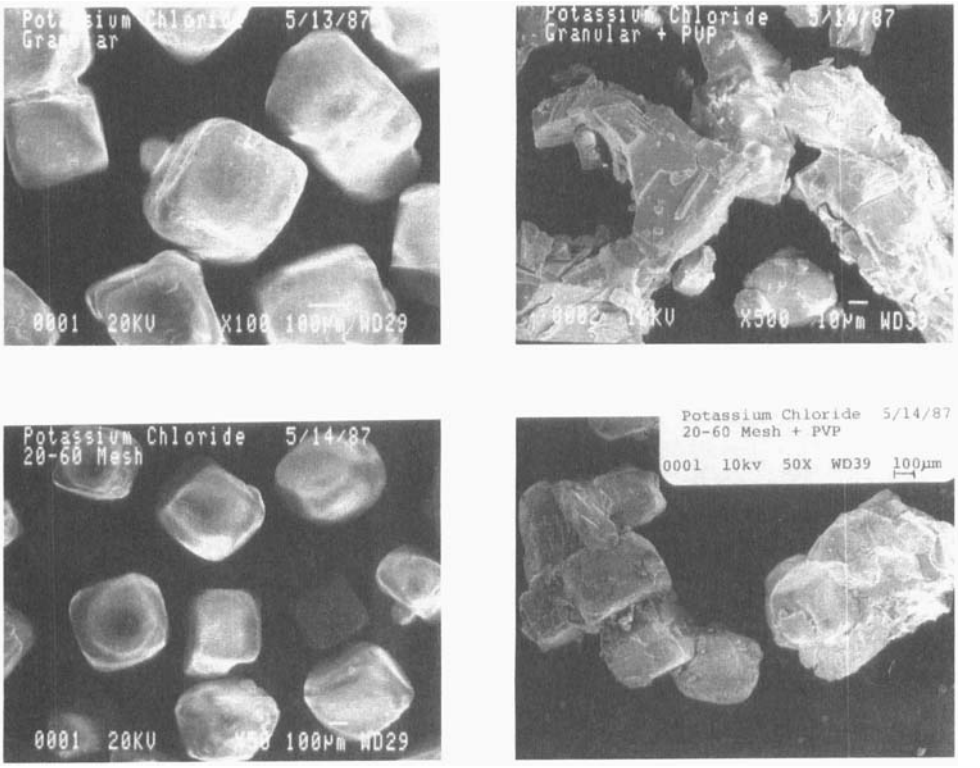

Figure 10: Scanning electron photomicrographs of potassium chloride in the forms of: top - granular grade of neat drug (left) and granulated drug (right); bottom - 60 mesh grade of neat drug (left) and granulated drug (right).

were constructed as shown in Figures 6a and 6b. The results indicate that the granulations prepared from coarser particle size of both drugs (d_{50} 250 to 400 μm) underwent two stages of deformation process, so-called "brittle fracture" and "plastic deformation", indicated by a significant increase in slope of the curve at the compression force greater than 3000 lb.

Particularly at high compression forces, brittle fracture of these aggregates may create many new surfaces for bonding and producing harder tablets. While the granulations prepared from finer particle size of both drugs

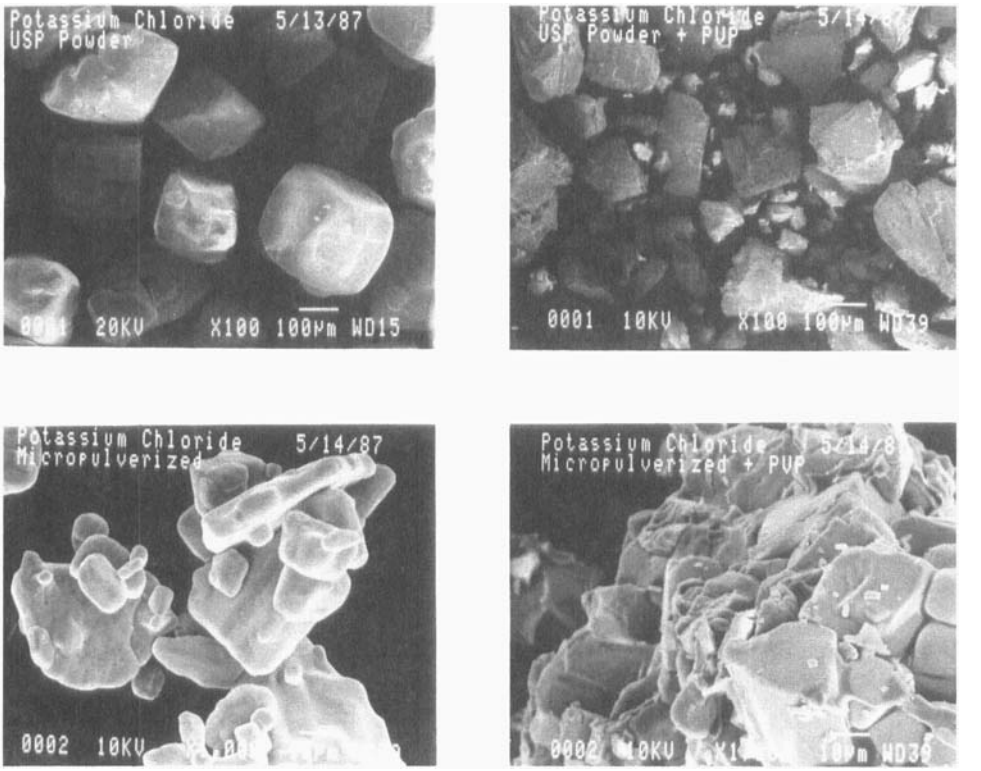

Figure 11: Scanning electron photomicrographs of potassium chloride in the forms of: top - USP grade of neat drug (left) and granulated drug (right); bottom - micropulverized grade of neat drug (left) and granulated drug (right).

(d_{50} 150 μm or below for ascorbic acid; d_{50} 80 μm or below for potassium chloride) predominantly underwent only "plastic deformation", indicated by the linearity of the Heckel plots. The results indicate that the plastic deformation of both granulated drugs was progressively enhanced whilst fragmentation of particles was correspondingly reduced as the particle size of the drugs was decreased. The results demonstrate that the greater area under the curve of the Heckel plot was associated with the finer particle size of the drugs. This implies that the area under the curve could be indicative of the compactibility of the materials.

Scanning Electron Micrographs

Scanning electron photomicrographs can adequately distinguish the differences in surface morphology between the neat drugs and the granulated drugs as shown in Figures 7-11. Surface of the neat drug, particulary potassium chloride was much smoother, in contrast with the granulated drug which had more "microirregularities" or "defects" on the surface. The poor intrinsic compactibility of the drug substances may be due to the smoothness of surface of drug particle, therefore providing fewer interparticle bonding sites. Wet granulation of these two water soluble drugs with PVP K30 resulted in aggregation between PVP K30 and the drug particles. These may contribute to the surface microirregularities which provided more adhesive contact points or interparticle bonding sites, thus improving the compactibility. These effects were more pronounced in the granulation of the drugs with finer particle size. The results indicate that differences in deformation and compaction properties of both granulated drugs could also be a reflection of changes in surface morphology of the drug particles.

CONCLUSIONS

The results clearly show that the particle size of ascorbic acid and potassiun chloride plays an important role in their compactibility. Optimum particle size range of ascorbic acid and potassium chloride for satisfactory compactibility was found to be 30-40 μm and 20-40 μm, respectively. The present study clearly demonstrates the importance of selecting the appropriate particle size of drug for the development of tablet dosage forms.

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