DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 8(4), 565-578 (1982)

I. SEGREGATION OF ACTIVE CONSTITUENTS FROM TABLET FORMULATIONS DURING GRINDING: THEORETICAL CONSIDERATIONS.

by

Gary T. Greco
Food and Drug Administration
Dept. of Health and Human Services
850 Third Avenue
Brooklyn, New York 11232

ABSTRACT

The preparatory step in the analysis of active drugs in tablet dosage forms has generally consisted of the grinding or milling of a given number of the tablets into a uniformly composited powder. Since the advent of content uniformity testing (individual tablet analysis) where the compositing step is bypassed, numerous reports have cited the large percentage difference in results observed between the average composited assay value and the average assay value for the individual tablets.

This paper describes some of the factors responsible for these observed differences, as well as some of the causative events that develop during tablet grinding. Certain active constituents become separated from other tablet components during grinding because of differences in the size, shape, density, surface roughness, and resilience of their particles. At particle sizes of less than approximately 400 μm additional forces and mechanisms, namely

Van der Waals forces, electrostatic forces, adsorption, and valency forces, become significant.

INTRODUCTION

Certain drugs formulated as tablet dosage forms have been shown to undergo physical separation from other tablet components when ground or milled during the preparation of the sample for analysis. For many years, well before content uniformity tests were routinely performed on tablets, an analyst would resolve a poorly duplicated assay by directly dissolving a number of intact tablets in the appropriate medium and by performing the assay on an aliquot of the solution. Content uniformity testing, however, revealed numerous instances of ground composite samples giving values which were different from those obtained for samples prepared by direct dissolution of tablets. As a result, a considerable literature has developed in relation to this problem. Prednisolone, sodium butalbital, phenobarbital, and methocarbamol, for example, have all been reported as having demonstrated this phenomenon (1-6).

The purpose of this paper is to describe what occurs during the grinding of tablets that might cause the segregation of active constituents from other tablet components. Subsequent papers will deal with the analytical work performed on various problem dosage forms, to illustrate these phenomena and to suggest ways of dealing with some of the problems.

TABLET PREPARATION

According to the method by which they are manufactured tablets may be classified as molded tablets or compressed tablets. Molded tablets are prepared by forcing dampened powders under low pressure into die cavities, or molds, from which they are then extruded and

allowed to dry. Solidification depends upon crystal bridges built up during the drying process, and not from the result of compaction forces.

Compressed tablets are prepared by forcing dry powders into molds under high pressure. There are three general methods of manufacture for compressed tablets; wet granulation, dry granulation and direct compression. In wet granulation, a mixture of the active ingredients with a diluent and solvent is forced through a screen. The resulting granules are then dried, size reduced, blended with the remaining excipients, and finally compressed into tablet molds. In dry granulation, a mixture of active ingredients with a diluent is compressed under high pressure to form a large tablet compact, sometimes called a slug. The tablet compacts are milled and screened to form granules which are then compressed into tablet molds. In direct compression, the active ingredient is mixed with a directly compressible excipient endowed with fluidity and compressibility. No prior granulation steps are needed as in both wet and dry granulation methods (7,8).

Presently most tablets are manufactured by the compression method. The mechanism of interparticle bonding during tablet compression is not well understood, but the possibility of the formation of a liquid film at the particle surface has been suggested by thermodynamic analysis of the effects of stress distribution on melting point and solubility, and by heat transfer kinetics at the surface (9,10).

ADHESION OF TABLET COMPONENTS DURING COMPRESSION

Most solids expand on melting. Upon compression the increase in melting point is directly proportional to the rise in pressure. In tablet compressing, this relationship would indicate that

fusion can not take place, and that the pressure exerted on each particle is far from uniform.

During the compression process, particles occupying the interior of the tablet experience conditions which are different from those found at the surface. The pressure applied by the upper and lower punches of the tableting machine is directly exerted only on the superficial particles. On the other hand, particles localized in the core of the compressible mass will experience stress because transfer of this pressure through particle-to-particle contact.

Because of the extremely high pressures produced in the mass interior due to the irregular shapes of the particles, particle-to-particle contact only occurs at a few points. The pressure is different on each side of the axis of the particle; whereas one surface point is being compressed the opposite surface point is under a tension or negative pressure. In this negative pressure area, if the compound expands on melting, its melting point will be lowered when the point pressure on the opposite side of the particle is increased. Since all particles should occupy both high and low pressure areas during tablet compression, then there will be a reduction in melting point at some portion of the surface of each particle, whether the material expands or contracts on melting.

The mechanical energy of compression is convertible to thermal energy. The heat generated in this manner can be transferred from the outer surface to the interior of the particle. The rate of heat conduction is dependent on the specific heat and thermal conductivity characteristics of the solid, and on the geometry of its particles. As a result there is the formation of

localized high-temperature areas, or "hot spots", on the surface of the particles. If the temperature of the hot spots equals the reduced melting points of the substance being compressed, surface fusion will occur (9,11,12).

GRINDING OF TABLETS

When a material is ground or milled, the resulting particles have a variety of sizes. Extremely fine particles are produced upon "attrition", which is the mechanism of fracture whereby a force is applied parallel to the surface of the solid as when using a mortar and pestle. A force that is applied perpendicular to the surface of a solid, which also occurs in mortar and pestle grinding, causes "fragmentation", i.e., the formation of two or more large fragments.

When a force is applied on tablets with a mortar and pestle, the weakest flaw in the tablet determines its strength to fracture and controls the number of particles produced by the fracture. Since the particles have irregular shapes the force is initially applied to their highest points, resulting in localized high stresses and high temperatures in the particulate material. When the applied force is greater than the elastic limit, the particle fractures. As the material fractures, the points of applied force shift and stress waves emanate from these fractures. The energy released by the stress waves will also lead to new high stress areas and, ultimately, to further cracks or fractures (13,14).

Due to the high pressure evolved from compression during tablet manufacturing, some particles will undergo extensive plastic deformations, frequently without any surface fusion. Furthermore, gaps are often produced in the structure of a tablet as the result of particles merely undergoing elastic deformations which brings about

changes in particle shape without fusion when the compression stress is removed (15). These gaps are possible flaws in the tablet structure (13). A second possible flaw in tablets is the weakly held liquid film contact between the particles caused by compression. During initial milling these internal weaknesses may fracture first, giving particles whose sizes resemble the original ones prior to compression. As milling progresses, new cracks are formed that propagate through the deformed particles and produce fracture. With continued milling the particle size distribution will have a narrower range and a finer mean.

The goal of milling is to form cracks that will propagate through the particles and produce fractures in these particles that will prevent the formation of particles whose sizes are close to those found before tablet compression. The reason for this is to prevent any given compound from having one predominant size of particles.

CAUSES OF SEPARATIONS OR SEGREGATIONS

In the use of any mixing apparatus there is a tendency for particles to segregate. Whenever a material is free flowing, contains particles with two or more different physical or chemical properties which are allowed to move as independent entities, then segregation will occur (16-18). There are various forces and mechanisms which when exerted on a given particle system will have a strong tendency to segregate particles (19).

The forces and mechanisms which can act simultaneously on a particle system are:

I. Large Particle Sizes (Larger than 400 micrometers)

When particle systems contain particles of different sizes, two main mechanisms of segregation can occur, "trajectory segregation"

and"percolation". Trajectory segregation occurs when particles are projected horizontally, the distance they travel being proportional to the square of the particle diameter (20). Because larger particles will have to travel a longer distance than smaller ones, size segregation will ensue.

Percolation occurs when differently sized particles in particle systems are disturbed. Due to gravitational force, each particle competes for the void spaces created by the disturbance (21,22). The probability that a particle will fall into a void space is determined by the size of the particle. The smaller the particle in comparison to the other particles in the system, the greater the number of void spaces it can occupy, and thus the greater the probability that the smaller particles will move downwards if the difference in size among the particles is small, the segregation probability is less (20,23-26).

The segregation rate in binary particle systems is dependent on the ratio of the volumes of the two particle sizes. Hence in a binary system, the number of particles of each particle size will play a major role in determining the rate of segregation. If the volume of one component is held constant while the volume of the other is varied, there will be a linear relationship between the particle volume ratio and the segregation rate (21,27). Partly this is caused by the greater number of void spaces created by the larger volume of the larger particles, which increases the probability of smaller particles slipping between three larger particles touching on a triangular grid. There is also a greater number of void spaces in the shape of a four sided grid formed by four larger particles (28). Consequently, if smaller particles can slip through the triangular and square grids produced by the larger particles, the segregation rate will increase (29).

There is little tendency toward segregation of particles that differ solely in density, unless the density differences are extremely large (19). There is , however, a nonlinear interaction between size and density. If the larger particles are more dense than the smaller particles, the segregation rate is lower at the higher particulate volume ratios. When the smaller particles become more dense, the segregation rate increases in a nonlinear fashion as the particulate volume ratios increase. The general effect is that density has a more pronounced effect on segregation rate as the size differences of the particles increase (30).

Particle shape also has an influence on the behavior of a particle within a particle system. A small change in particle shape can produce a substantial change in particle behavior in the system (31). In one study, to eliminate size differences between two types of particles, particle volumes were kept constant and only the shapes were changed. When sharp-cornered or angular particles were mixed with spherical ones in a Lucite cylinder, the sharp-cornered particles migrated to the surface of the bed and downward, with the flat surface of the particle oriented against the side walls of the container. This behavior was only observed with angular particles (32). For mixtures of single and paired spherical particles, the pairing of the small particles led to a decrease in segregation, whereas the pairing of the large particles resulted in increased segregation. These behaviors are consistent with the percolation phenomenon described above.

As the surface roughness of a rotating particle increases, so does the rotational momentum transfer between the particles involved in a collision (33). Rotating aggregates will tend to break apart

TABLE 1. RELATIONSHIP BETWEEN PARTICLE SIZE AND MECHANISMS OR FORCES FOR SEGREGATION (37,38)

Particle Size Diameter	Mechanism	Force
$\geq$ 400 μm	Trajectory segregation, percolation	Translational momentum transmissions, rotational momentum transmissions, centrifugal forces, gravitational forces
$\leq$ 400 μm	None	Van der Waal's forces, electrostatic forces, adsorption
$\leq$ nm Range	None	Valency forces

because of the centrifugal forces, thus aiding the mixing process (34). However, particles with differing degrees of surface roughness will experience different momentum transmissions during collision, and will, as a result, acquire segregational tendencies (35).

Resilience or elasticity of the particles involved in a collision will determine the momentum transfer; therefore otherwise identical particles with differing elasticity characteristics will experience different momentum transfers and the possibility of segregation exists (34).

II. Fine Particle Sizes (Less than 400 micrometers)

When a solid particle is reduced in size to a degree that makes the effect of its surface properties significantly different from those of the original particle, the powder can be said to have been

TABLE 2. EFFECT OF PHYSICAL AND SURFACE PROPERTIES OF PARTICLES ON SEGREGATION.

Physical Property Relevant to Segregation	Degree of Segregational Tendency	Surface Properties Revelant to Segregation
Particle size	Greatest	
Particle shape	Great	
Particle density	Little*	
Particle roughness, particle resilience	Intermediate	Electrostatic forces
	Little	Van der Waal's forces, adsorption
	Very Little	Valency forces

*Density has a more pronounced effect on segregation as the size difference among particles increases.

reduced to a very fine level (36). The particle size at which surface effects become significant varies from substance to substance (37). In very fine powders, the individual masses of the particles are small and the forces present on the surface of the particles, to be discussed below, are relatively large in comparison with the inertial forces. The particles therefore no longer behave as separate entities but are now affected by each other (38). The effect that one particle has on another greatly depends on the characteristics of their surfaces and on the existing interfacial conditions.

At the surface of a fine particle, four significant forces may be present: Van der Waal's, electrostatic, adsorption, and valency

(37). When the size of the particles of a substance are small enough so that their thermal and mechanical forces become of the same order of magnitude as their van der Waal's forces, the latter can play a prominent role in the association of particles into larger masses (39).

Since most organic solids have low dielectric constants and they do not dissipate the electrical charges produced by the mechanical displacement of their electrons, electrostatic charge accumulation occurs on their particles upon grinding or mixing. Due to aggregation, the powder will first acquire a fluffy appearance followed by "balling-up" and ultimately "caking" (37,40). The high pressures generated by the grinding on a mortar and pestle can lead to solid-to-solid interaction among the components of a tablet through the formation of additional adsorption sites. Adsorptions will occur upon charge transfer or donor-acceptor type of interactions. Each combination of grinding systems and tablet formulation will have its own individual characteristics (39,41,42).

Valency forces generally occur at the surface of those particles having a surface area of less than 400 m^2g^{-1}. The breakage of the valency bonds in the crystal structures during grinding will change the chemical properties of the particles. For example when the surface area of graphite was reduced to about 600 m^2g^{-1}, cyanogen, formed by the reaction of ambient nitrogen with the broken valency bonds in the graphite, was detected by its characteristic odor. Therefore, reducing the particle size of a solid to a very fine level can result in the formation of impurities upon chemical changes introduced into the solid by the grinding process (37).

CONCLUSION

Both segregation and mixing of particles occur simultaneously during grinding or blending (43). The end product of mixing is not

a fully randomized mixture, but rather a mixture where the population of particles of each component is segregated in a particular manner, dependent not only on its inherent physical characteristics and surface effects, but also on the grinding system and the tablet formulation. Where materials of different particle characteristics are blended, an understanding of the causes of segregation can be of value in the preparation of a more uniform blend. Table 1 indicates the forces and mechanisms that come into play in particle segregation. Table 2 shows the relative effects of the properties of particles on their tendency to segregate.

ACKNOWLEDGEMENT

The author wishes to thank Cesar A. Lau-Cam, Ph.D., Science Advisor, Food and Drug Administration, New York Regional Laboratory, and Professor of Pharmacognosy, St. John's University, College of Pharmacy and Allied Health Professions, Jamaica, New York, for his invaluable assistance in the preparation of this paper.

REFERENCES

1. M.L. Dow, J.F. Brower, and P.E. Flinn, Laboratory Information Bulletin No. 1965, Aug. 10th, 1-7 (1976), FDA-DHHS, Rockville, MD 20857.

2. E.L. Gunderson, L.A. Roberts, and D.J. Smith, Laboratory Information Bulletin No. 549, June 27th, 1-3 (1967), FDA-DHHS, Rockville, MD 20857.

3. T.J. Farrell, Laboratory Information Bulletin No. 530, May 24th, 1-3 (1967), FDA-DHHS, Rockville, MD 20857.

4. C.C. Douglas, Laboratory Information Bulletin No. 535, June 13th 1 (1967), FDA-DHHS, Rockville, MD 20857.

5. B.A.Goldwitz and M.J. Finkelson, Laboratory Information Bulletin No. 2061, April 29th, 1-5 (1977), FDA-DHHS, Rockville, MD 20857.

6. G.T. Greco, Laboratory Information Bulletin No. 2429, June 30th 1-5 (1980), FDA-DHHS, Rockville, MD 20857.

7. M.A. Zoglio, H.E. Huber, G. Koehne, P.L. Chan, and J.T. Carstensen, J. Pharm. Sci., 65, 1205 (1976).

8. A.B. Selkirk and D. Ganderton, J. Pharm. Pharmacol, 22, 865 (1970).

9. A.S. Rankell and T. Higuchi, J. Pharm. Sci., 57, 574 (1968).

10. E.W. Seugling, Pharm. Technol., 4, 27 (1980).

11. E.N. Heistand and C.B. Peot, J. Pharm. Sci., 63, 605 (July 1974).

12. S.C. Porter, Pharm. Technol. 4, 67 (March 1980).

13. E.L. Parrott, J. Pharm. Sci., 63, 813 (1974).

14. G. Steiner, M. Patel, and J.T. Carstensen, J. Pharm. Sci., 63, 1395 (1974).

15. A. Ritter and H.B. Sucker, Pharm. Technol., 4, 57 (March 1980).

16. J.C. Samyn and K.S. Murthy, J. Pharm. Sci., 63, 370 (1974).

17. E. Shotton and N.A. Orr, J. Pharm. Pharmacol., 23, 260S (1971).

18. J.T. Carstensen, J. Pharm. Sci., 63, 1494 (1974).

19. H. Campbell and W.C. Bauer, Chem. Eng., 73, 179 (1966).

20. J.C. Williams, Pharma Int., Eng. Ed., 6,5 (1972).

21. J.L. Olsen and E.G. Rippie, J. Pharm. Sci., 53, 147 (1964).

22. C.H. Chou, J.R. Johnson, and E.G. Rippie, J. Pharm. Sci., 66, 104 (1977).

23. D.N. Travers and R.C. White, J. Pharm. Pharmacol., 23, 260S-261S (1971).

24. M.C.R. Johnson, J. Pharm. Pharmacol., 25, 162P (1973).

25. D.E. Fonner, G.S. Banker, and J. Swarbrick, J. Pharm. Sci., 55, 576 (1966).

26. M.C.R. Johnson, J. Pharm. Pharmacol., 31, 273 (1979).

27. J.A. Hersey, P. Cook, M. Smyth, E.A. Bishop, and E.A. Clarke, J. Pharm. Sci., 63 408 (1974).

28. D. Train, J. Am. Pharm. Assoc., Sci. Ed., 49, 265 (1960).

29. T.M. Jones, J. Pharm. Sci., 57, 2015 (1968).

30. E.G. Rippie, J.L. Olsen, and M.D. Faiman, J. Pharm. Sci., 53, 1360 (1964).

31. A.F. Asker, K.M. Saied, and M.M. Abdel-Khalek, Pharmazie, 30 181 (1975).

32. E.G. Rippie, M.D. Faiman, and M.K. Pramoda, J. Pharm. Sci., 56, 1523 (1967).

33. E. Nelson, J. Am. Pharm. Assoc., Sci, Ed., 44, 435 (1955).

34 L. Lachman, H.A. Lieberman, and J.C. Kanig, The Theory and Practice of Industrial Pharmacy, Lea and Febiger, Philadelphia,PA. p. 95 (1970).

35. R.H. Hammer, J.L. Templeton, and H.L. Panzik, J. Pharm. Sci., 63 1960 (1974).

36. M.J. Groves, Pharm. Technol. 4, 81(May 1980).

37. E.A. Smith, J. Soc. Cosmet. Chem., 21, 563 (1970).

38 P.J. Lloyd, P.L.M. Yeung, and D.C. Freshwater, J. Soc. Cosmet. Chem., 21, 205 (1970).

39. E.N. Hiestand, J. Pharm. Sci., 55, 1325 (1966).

40. C.C. Yeung and J.A. Hersey, J. Pharm. Sci., 68, 721 (1979).

41. J.L. Lach and M. Burnstein, J. Pharm. Sci., 54, 1730 (1965).

42. T. Mizutani and A. Mizutani, J. Pharm. Sci., 67, 1102 (1978).

43. M.D. Faiman and E.G. Rippie, J. Pharm. Sci., 54, 719 (1965).