DRUGS AND THE PHARMACEUTICAL SCIENCES

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PHARMACEUTICAL POWDER COMPACTION TECHNOLOGY

SECOND EDITION

Metin Çelik

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Pharmaceutical Powder Compaction Technology

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Pharmaceutical Powder Compaction Technology

Second Edition

Metin Çelik PhD
President, Pharmaceutical Technologies International, Inc.
Belle Mead, New Jersey, U.S.A.

Research Professor of Pharmaceutical Technology
College of Pharmacy, Near East University
Lefkosia, Turkish Republic of Northern Cyprus

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healthcare

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Contents

SECTION I: THEORY OF COMPACTION

SECTION II: COMPACTION DATA ANALYSIS TECHNIQUES

SECTION III: INSTRUMENTATION AND EQUIPMENT IN COMPACTION

SECTION IV: ROLE OF COMPACTION IN THE FORMULATION AND PROCESS DEVELOPMENT OF TABLETTING

Contributors

Carl T. Allenspach Bristol-Myers Squibb, New Brunswick, New Jersey, U.S.A.

Chris Balducci Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, U.S.A.

Gerad K. Bolhuis Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Groningen, The Netherlands

Jean-Daniel Bonny Acino Pharma AG, Basel, Switzerland

Gary Bubb Specialty Measurements Incorporated, Lebanon, New Jersey, U.S.A.

Graham Buckton School of Pharmacy, University of London, London and Pharmaterials Ltd., Reading, U.K.

Metin Çelik Pharmaceutical Technologies International, Inc., Belle Mead, New Jersey, U.S.A.; and Faculty of Pharmacy, Near East University, Lefkosia, Turkish Republic of Northern Cyprus

James Cheney Celgene Corporation, Summit, New Jersey, U.S.A.

Olivia Darmuzey Novartis Pharma Stein AG, Stein, Switzerland

Hans de Waard Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Groningen, The Netherlands

Arne W. Hölzer Mölndal, Sweden

Hans Leuenberger Ifiip LLC, Institute for Innovation in Industrial Pharmacy, and CINCAP LLC, Center for Innovation in Computer-Aided Pharmaceutics, Basel, Switzerland

Michael N. Leuenberger Amificas Inc., American Institute for Innovative Computer-Aided Solutions, Oviedo, Florida, U.S.A.

Ruth Leu-Marseiler Novartis Pharma Ltd., Basel, Switzerland

Rosario LoBrutto TEVA Pharmaceuticals, Pamona, New York, U.S.A.

Susan K. Lum Patheon Inc., Whitby Development Center, Ontario, Canada

Eşay Okutgen PharmaCircle, Skillman, New Jersey, U.S.A.

Anant Paradkar Institute of Pharmaceutical Innovation, University of Bradford, Bradford, U.K.

Maxim Puchkov CINCAP LLC, Center for Innovation in Computer-Aided Pharmaceutics, Basel, Switzerland

Alan Royce Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, U.S.A.

Colleen E. Ruegger Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, U.S.A.

Hedinn Valthorsson Novartis Pharma Stein AG, Stein, Switzerland

Dong Xiang Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, U.S.A.

Peter York Institute of Pharmaceutical Innovation, University of Bradford, Bradford, U.K.

Erika A. Zannou Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, U.S.A.

Preface to the first edition

Oral administration is the dominant method of delivering drugs to the human systemic blood circulation because of its safety and simplicity. Thus, great interest has been focused within pharmaceutical science on the design of oral dosage forms with optimal therapeutic properties. The prevailing oral dosage form today is the tablet due to its elegance. Tablets of various types and biopharmaceutical properties—from conventional, disintegrating tablets, to advanced modified release systems—exist, but their common denominator is the way in which they are formed, that is, powder compaction. Physical and technological aspects of this process, from a pharmaceutical point of view, are the theme of this book.

The complexity of the compaction process—what at first sight seems to be a simple mechanical operation—was recognized early. Problems still exist in large-scale production of tablets, such as low tablet strength, capping, limited use of direct compression, and sensitivity to batch variability of starting materials. Moreover, the use of basic physical data in formulation work in order to predict tabletting behavior of particles such as compressibility (ability to reduce in volume) and compactibility (ability to cohere into compacts) is limited. Thus, tablet formulation must still be based to a large extent on empirical knowledge rather than on scientific theory.

An improved theoretical understanding of the compaction process will enable a more rational approach to the formulation of tablets. However, the investments in research on the physics of the compaction process have, in relative terms, been limited in universities and the pharmaceutical industry. In spite of this, a large number of publications on the theme of the formation of tablets by compaction exist today in the pharmaceutical literature. This literature can be broadly classified into three categories: (1) reports on specific formulations and their compactibility and on formulation solutions to compaction-related problems, (2) studies on mechanisms of and theories for the compression and the compaction of pharmaceutical powders (such studies also include articles dealing with the development and evaluation of methods for theoretical studies), and (3) evaluation, with recognized methods and theories, of the compression and compaction behavior of pharmaceutical tabletting excipients.

In the older literature, publications were focused mainly on the practical aspects of the preparation of tablets. However, since the late 1940s, articles focused on the theoretical aspects of the compaction process have been presented in the pharmaceutical scientific literature. As a consequence of the growing interest in directly compactable formulations, new excipients with improved tabletting performance have been developed and the compaction characteristics of these have been the object of scientific studies. Despite this growing literature on the physics and technology of powder compaction, the interest in bringing together the accumulated knowledge in the form of comprehensive reference works has hitherto been limited. It is thus a great pleasure for the editors of this volume to present a book on theoretical and practical aspects of the process of forming compacts by powder compression. This is, to our knowledge, the first book devoted entirely to this theme. It has been made possible by the contribution of chapters from researchers throughout Europe and North America. To achieve the high level needed, only recognized scientists, representing academia or the pharmaceutical industry, have been involved, and each contributor has been encouraged to focus on his or her field of expertise. The role of the editors has been to primarily select topics and authors for the contributions and to find a suitable structure for the book. The consequence of this is that different concepts and beliefs in the field of powder compaction are presented and discussed in the book, and we have not attempted to hide this diversity. This diversity reflects the complexity of studying and establishing theories for the handling and processing of "real" materials. Moreover, there are also different traditions with respect to the nomenclature used in the discussion on powder compaction, and this inconsistency among researchers in this respect is also reflected in this book. The editors allowed each author to use terms in accordance with his or her tradition. However, to improve the stringency in the use of the nomenclature for the future, a short list of definitions follows this preface.

During the preparation of this book, some topics within the area of pharmaceutical powder compaction have not been dealt with as separate chapters, as they are not covered extensively in the literature. Examples of such topics are energy aspects of the formation of tablets, physical instability in compacts during storage, and mathematical expressions for the tensile strength of compacts. However, these topics are discussed and references are given in some of the chapters of this book.

Although great progress in the theoretical understanding of the compaction process has been made since the late 1940s, the need for further research is obvious. It is our hope that this volume can contribute to and stimulate such intellectually challenging research.

We are very grateful to Marcel Dekker, Inc., for taking the initiative to prepare a book on pharmaceutical powder compaction technology. We express our sincere appreciation especially to Sandra Beberman and Ted Allen for pleasant cooperation during the preparation of this book, for their qualified contributions, and for their support and patience with us in our role as editors.

We are also very grateful to all contributors to this volume, for their positive attitude to share their expertise in the field of powder compaction and for the time and effort taken to write articles of high quality. Without their collaboration and contributions, the writing of this book would never have been accomplished.

Finally, we would like to thank Mrs. Eva Nises-Ahlgren for qualified administrative work in connection with the preparation of this book.

Goran Alderborn
Christer Nystrom

Preface to the second edition

In 1996, the editors of the first edition of this text, Alderborn and Nystrom,[1] were fully aware of the complexity of the compaction process and the limited, at that time, scientific theories applicable to the process. In their preface, they recognized the need for an improved theoretical understanding of compaction and compression in order to enable a more rational approach to the formulation of the solid dosage forms described as "tablets." At the same time, Alderborn and Nystrom realized the need to include information on the practical and technological aspects of compaction and compression and they largely succeeded in these endeavors, as judged by the wide acceptance of the multiauthored first edition that covered a range of theoretical and practical areas.

Even so, Alderborn and Nystrom were aware that certain topics within the area of pharmaceutical powder compaction were not dealt with as extensively as desired, due in large part to a lack of extensive coverage in 1996 when the first edition was published. It is the aim of the second edition to remedy that situation, while at the same time building on and expanding the scope of the first edition.

In Chapter 1 (*Intermolecular bonding forces: Where materials and process come together*), Buckton revisits intermolecular bonding forces, the point where materials and process come together. The stages involve an initial compression to push the particles closer together and a subsequent phase where closely packed particles no longer reduce the packing volume by simple movement around each other, but deform either by brittle fracture or by plastic flow. It is these processes of plastic flow and brittle fracture, and most usually a combination of the two, that give rise to compact formation rather than a reversible compression/decompression of the mass.

Lum shows in Chapter 2 (*Viscoelastic models*) that viscoelasticity has a tremendous effect on powder compaction and in order to produce compacts with desired properties an understanding of mechanical properties and constituent materials is needed. Problems that arise during tablet production are a consequence of viscoelasticity combined with poor interparticle bonding. The degree of interparticle bonding and bond strength is assumed to be largely governed by the magnitude of the true interparticle contact area. The amount of elastic recovery of the particles depends on the release of elastic strain during decompression and tends to disrupt interparticle bonds. This stress relaxation is a function of the viscoelasticity of the material that in turn is influenced by the speed of compression and decompression. At high compaction speeds, the internal stress after compaction is high and the propensity of the material for elastic recovery is considerably higher than at low compaction speeds.

In Chapter 3 (*Application of percolation theory and fractal geometry to tablet compaction*), Leuenberger and coauthors have updated their work in the area of percolation theory, fractal geometry, and the use of virtual R&D reality so as to allow new insights into the physics of tablet compaction and the properties of the tablets. The results attained so far are promising and should stimulate further research in this field.

Bubb addresses postcompaction data analysis techniques in Chapter 4 (*Postcompaction data analysis techniques*) using data collected from an instrumented rotary tablet press. The

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[1] *Pharmaceutical Powder Compaction Technology*, Alderborn G and Nystrom G, eds, Marcel Dekker, Inc., New York, 1996.

discussion of an individual pulse analysis is followed by an in-depth analysis of compaction and ejection profiles. Bubb is also the author of Chapter 5, titled *Tablet press instrumentation in the research and development environment*, where he makes the point that an instrumented tablet press in an R&D environment is a necessity if one wishes to have a deeper understanding of compaction principles, shorten development time, and enable easier transition from R&D machines into production equipment.

In Chapter 6 (*Advanced compaction research equipment: Compaction simulators*), compaction simulators are discussed by Ruegger and Çelik. As they point out, with the increasing use of quality by design during drug product development, the standardization of functionality tests is more important than ever to determine the design space for tablet compaction. Although less sophisticated types of equipment may be used to determine the compaction design space, the use of a compaction simulator will increase the likelihood of success for the development of a robust tablet formulation while minimizing the amount of material needed for drug product development and characterization of the formulation and the individual components.

The current state of compactibility functionality tests is reviewed in Chapter 7 (*Compactibility functionality test*) by Okutgen. As this author points out, probably the most important aspect of pharmaceutical formulation development is the selection of suitable excipients since these can profoundly influence the properties of the dosage form, especially when the drug concentration is small. This type of information and the existence of standard test methods to measure such properties are important to assure consistent quality and functioning of different excipients as well as one excipient from lot-to-lot. When the dosage form is a tablet, it is necessary to consider the assessment and comparison of the compaction behavior of the inactive ingredients, including diluents, binders, antiadherents, glidants, and lubricants. Okutgen shows that, even today, the formulator lacks both a single source of reference and the existence of a standard test method to assess and compare the compaction behavior of excipients that play a critical role in the compactibility of a powder composition.

Chapter 8 (*Compaction properties of directly compressible materials*) deals comprehensively with the compaction properties of directly compressible materials. The authors, Bolhuis and de Waard, have both updated and expanded the senior author's chapter in the first edition. They point out that in spite of enormous improvements in wet granulation techniques (high shear granulation, fluid bed granulation, extrusion granulation, continuous granulation, and all-in-one granulation), tablet production by direct compaction has increased steadily over the years because it offers economic advantages through its elimination of the wet granulation and drying steps. As a result, it requires fewer unit operations in production, which means less equipment and space, lower labor costs, less processing time, and lower energy consumption. Additionally, the elimination of the wet granulation step increases the stability of drugs that can degrade by moisture and/or heat. Another advantage of direct compaction is that the tablets generally disintegrate into primary particles rather than into granules. The increased surface area for dissolution may result in a fast drug release for some drugs and some drug products.

Lubrication issues in direct compaction is the title of Chapter 9 by Bolhuis and Hölzer. According to these authors, lubricants are commonly included in tablet formulations in order to reduce die wall friction during both compaction and ejection of the tablet. Their presence, however, may cause undesirable changes in tablet properties, such as decreased diametrical breaking strength and tablet softening.

Paradkar and York discuss crystal engineering and particle design in Chapter 10 (*Crystal engineering and particle design for the powder compaction process*). These authors note that for several decades, in addition to investing huge resources in the drug discovery process for identifying new chemical entities, pharmaceutical interests have been engaged in the engineering of drug substances to overcome challenges in drug delivery linked to their pharmaceutical properties. Particle size, shape, crystal habit, crystal form, density, and porosity are primary properties of solids; whereas flowability, compressibility, compactibility, consolidation, dust generation, and air entrapment during processing are secondary ones. Their chapter shows that it is critically important to employ efficient and effective particle design techniques with the ability to produce small, uniform particles with desired primary and secondary properties for the development of pharmaceutical products. In the area of particle engineering the approaches are focused on alteration of primary and secondary particle properties by a single step process using techniques such as spherical crystallization and crystallo-co-agglomeration. Green processes like supercritical fluid technology may well be preferred over solvent-based crystallization methods considering stringent regulatory controls and the desired control of primary and secondary drug particle characteristics.

The pharmaceutical industry, whether brand name or generic, has over the past few years been increasing its focus on developing combination products, which have been a key component of very successful lifecycle management strategies mainly due to significant advantages in both therapeutic and commercial aspects, including extension of patent coverage. Thus, Chapter 11 (*Compaction of combination products* by Allenspach and Zannou) focuses mainly on formulation options for compaction products and their impact on compaction behavior when a monolayer tablet is not feasible due to compaction properties, intended biopharmaceutical performance (e.g., dissolution/bioavailability and/or stability), and/or line extension or market differentiation. A major topic is multilayer tablet compression (bilayer being the most common) including tablet strength and layer adhesion strength measurement and prediction, formulation considerations to optimize compaction properties, and manufacturing considerations during the compression unit operation.

Balducci and a number of coauthors observe in Chapter 12 (*Quality by design and compression*) that the goal of quality by design is to define a drug product manufacturing process that is flexible enough to allow mitigation of inherent variability in the process that may arise from raw materials or equipment fluctuations. In contrast, traditional manufacturing processes are considered too rigid to account for inherent variability of the process and provide no opportunity for continual improvement. They show that when quality by design is fully implemented into the development strategy, the critical sources of process and material attribute variability can successfully be identified, measured, and understood so that they can be controlled with the appropriate control strategy. Statistical design provides an economical use of resources, especially when many process parameters exist. Also, statistical design facilitates an in-depth understanding of the process and provides strong assurances to regulatory agencies regarding superior process quality.

The final chapter (Chapter 13, *Expert systems and their use in pharmaceutical applications*) is a review that seeks to describe the current status of expert systems applicable to the development of pharmaceutical formulations and processes. Although the literature on expert systems has expanded rapidly since the time first edition was published, the author, Çelik, opines that very few expert systems have been successfully applied to pharmaceutical systems, with even fewer applied to powder compaction. Hopefully, this deficiency will be remedied in the future as more companies realize the value in developing and applying their own expert systems. Stay tuned for the third edition!

James Swarbrick
Executive Editor, Drugs and the Pharmaceutical Sciences
PharmaceuTech Inc.
Pinehurst, North Carolina, U.S.A.

1 Intermolecular bonding forces: Where materials and process come together

Graham Buckton

INTRODUCTION

The application of a compaction force to a powder will require a number of mechanisms to allow the powder bed to convert to a compressed compact—a tablet. The stages involve an initial compression to push the particles closer together and a subsequent phase where closely packed particles no longer reduce the packing volume by simple movement around each other but deform either by brittle fracture or by plastic flow. It is these processes of plastic flow and brittle fracture, and most usually a combination of the two, that give rise to compact formation, rather than a reversible compression/decompression of the mass. These concepts and the process of elastic recovery will be discussed in more detail elsewhere in this book. The processes of brittle facture and plastic flow give rise to surface contact and bond formation. The bond strength will be linked to the surface area over which bonding can occur and the type of bonding that happens (1–7).

THE COMPRESSION STAGE

Prior to the process of forming a compact, the powder bed must be compressed to consolidate the powder. The extent of volume reduction during compression will be related to a number of factors and will ultimately set up the process of compact formation (through suitable bonding). The starting properties of the powder(s) to be compacted and the way that these properties change during the early phase of the compaction process will be significant. Major contributors to this process can be expected to be particle size and shape with high surface area and surface roughness being regarded as favorable to set up the compaction process (8). That being said, the process becomes dominated by the deformation mechanism with highly fragmenting brittle materials exposing a large increase in surface area for compact formation, which will most probably override any effect of the size, surface area, and roughness of the starting materials.

Inevitably, the physical form of a material, in terms of whether it is amorphous or crystalline, and if crystalline the properties of that crystal, will affect the compression and compaction processes. Different crystal forms include salts, polymorphs, hydrates, and solvates, each of which can have different external habits (needles or prisms), melting points, and mechanical properties. While amorphous materials have a tendency to plastic deformation and crystalline to brittle fracture, it is far from being as simple as that with many materials having both brittle and plastic behaviors, and some changing their behavior as a function of strain rate (tablet machine speed). While these points will not be discussed here in any detail, it is vital to remember that the understanding of the interplay between the materials properties and the process is the cornerstone of Quality by Design. The principles of Quality by Design are that critical sources of variability in a product are identified and explained, variability is controlled by understanding the materials and the process, and product quality attributes can be accurately and reliably predicted using a design space relating to materials properties, the process, and the environmental/other factors that may be significant. In this short chapter, the nature of materials is touched upon and their interaction with atmospheric humidity mentioned in one example. In no way will the coverage be comprehensive, but it will hopefully be indicative.

COMPACTION

Bonding surface area can be regarded as the effective surface area that is involved in the interaction between particles. It is not possible to be certain or to have a practical measurement of the actual surface area that is available during tabletting. The surface area will alter because of fracture and flow and will be influenced by the porosity of the materials. Rather than having a direct measurement, surrogate secondary properties are often correlated to tablet strength; these would include particle size, particle shape, and particle surface energy (9) along with an understanding of compaction mechanism and bond strength (8,10).

BONDING MECHANISMS

Rumpf (11) described bonding mechanisms as being of five types (Box 1).

Box 1 The Types of Bonding That Can Give Rise to Tablet Formation

1. **Solid bridges**
2. Moveable liquids
3. Non–freely moveable binders
4. **Attraction between solid particles**
5. **Mechanical interlocking**

The three that are regarded as dominant are shown in bold.

Solid bridges are formed between two particles by processes such as crystallization of amorphous portions of solid, sintering, or chemical reactions (such as salt formation between adjacent particles).

Bonding between moveable liquids is related to surface tension forces. As compaction is assisted by the presence of some moisture, this may well play a role in the process for tablets. Non–freely moveable binders would include the binders used in wet granulation processing, such as polyvinylpyrrolidone, which make powders into better compact formers.

Attractions between solid particles will be discussed further below. Mechanical interlocking can be envisaged during tabletting, by both plastic flow and brittle fracture. Further, it is probable that this assists with increasing surface area for interparticulate bonding as much as physical interlocking.

While all these binding mechanisms can be regarded as of significance, it is probable that solid bridge formation, intermolecular forces, and mechanical interlocking are dominant (12).

SOLID BRIDGES

Pilpel and York proposed that particle contact points experience such high local stresses during the compaction process that asperity melting occurs. This does not necessarily mean that the melting point of the material is reached across the sample, but rather that at extreme local pressure, the combination of local heating and pressure is sufficient to cause molecular movement, and as the pressure is released, perhaps during the compaction process as a slip of fragmentation occurs or during release of the pressure as the punch is removed, the adjacent particles return to the crystalline state and the newly formed crystalline region bridges more than one particle, most probably forming a network structure, giving the tablet great strength. Consequently, the formation of solid bridges can inevitably be viewed as a strong bonding mechanism as the bonds will have the strength of the intermolecular forces that are holding the particles together. The strength of bonds within crystals will vary from material to material depending on the forces that hold the crystal together. This is what gives rise to changes in melting points, enthalpies of fusion, and surface energies.

The crystallization of amorphous, or partially amorphous, materials to give rise to solid bridges (13–16) is very common, by both intentional use of crystallizing excipients and uncontrolled use of partially amorphous materials. A good example of intentional use is that of spray-dried lactose, which is a commercially available tabletting excipient with an amorphous content of around 15% to 20%. The amorphous content causes improved tabletting properties compared with crystalline material alone. This is due to the amorphous material adding a plastic deformation to the usual brittle fracture of crystalline lactose and the fact that the amorphous material will crystallize to form solid bridges during compaction. Sebhatu et al. (17) studied the effect of storage at 57% relative humidity on the compression properties of spray-dried lactose (Fig. 1) and found that the tensile strength of the tablets increased during the first four hours of storage. During this period the water content increased as water was absorbed into the amorphous lactose, resulting in a plasticizing effect and an increase in the mobility of the amorphous phase. The mobile amorphous material was able to flow under compression and produce stronger tablets. Storage for longer times resulted in the amorphous material crystallizing, and as such, the benefit that amorphous material can add to the compression process was lost. As crystallization had occurred, there was no change in tablet properties for any increase in storage time at 57% RH. Subsequent to this, the compacts stored for zero to four hours at 57% RH prior to compaction were exposed to 57% RH post compaction (Fig. 2) and were seen to produce stronger tablets over time, because of the amorphous material crystallizing to form solid bridges. The tablets that were produced from lactose that was crystalline prior to compaction (those stored for more than four hours at 57% RH prior to compaction) did not show postcompaction changes in properties (Fig. 2).

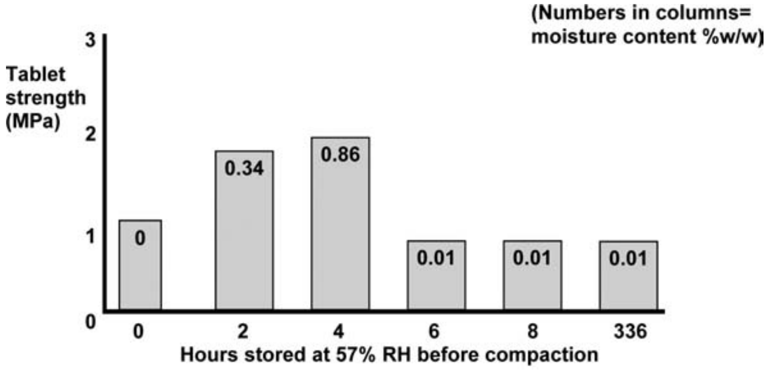

Figure 1 Effect of storage at 57% humidity.

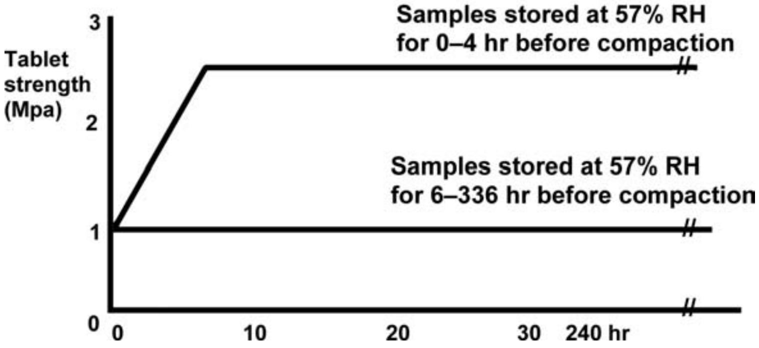

Figure 2 Schematic representation. From Ref. 17.

These data indicate that the deformation process is altered by having the mix of crystalline and amorphous (brittle and plastic materials, respectively) and that the solid bridge formation continues post compaction as the amorphous lactose converts to crystalline material, with improved tablet strength. The comments above show that it is important to understand the state of physically unstable materials prior to tabletting, for example, if amorphous lactose has crystallized, the outcome will be different and the product properties will change. Depending on drug dose, the properties of the active can also affect the tabletting behavior, and it is relatively common for processed active to be partially amorphous. For high-dose drugs, this could well be significant for the tablet strength.

The discussion around solid bridges highlights that new crystalline regions can be created during tabletting. With this in mind, it is important to realize that (to a greater or lesser extent) the polymorphic form of the drug present in the final compressed tablet can change as a consequence of compaction, either by the crystallization from the amorphous state or by solid-state transitions induced by the pressure or combination of local heat and pressure that occur. These solid-state transitions have potential significance not only for compaction properties but also for dissolution and bioavailability of poorly soluble drugs and for intellectual property infringement for compounds that have protected physical forms.

INTERFACIAL FORCES

Tablets will, to a large extent, be held together by interfacial forces, also known as long-range attractive forces. These long-range forces, which are lower energy than covalent bonding forces, are due to physical bonding on different types, all with energies usually less than around 40 kJ/mol. Long-range forces are electrical in nature and can be considered as electrostatic (which can be both attractive and repulsive depending on whether the two materials carry the opposite or the same charge, respectively), van der Waals, and hydrogen bonding. While electrostatic forces will often be induced on powders during mixing and other dry processing events, it is van der Waals and hydrogen bonding forces that are most likely to make the major contribution during tabletting.

Van der Waals forces consist of dipole, induced dipole, and dispersion forces. Many molecules have an imbalance of charge across their structure. Water is an example of such an asymmetric charge distribution, with an oxygen atom carrying a net negative charge, being balanced by two hydrogen atoms, each of which has a slight net positive charge. Most drugs are ionizable and have such an asymmetric charge distribution. Certain molecules exist with a permanent charge imbalance and can simplistically be regarded as small bar magnets. Such materials are said to have *permanent dipoles*, and interactive forces are due to attraction between the negative pole of one molecule when in reasonably close contact with the positive pole of another. These interactive forces are also termed *orientational* or *Keesome* interactions, and the molecules that take part in such interactions are regarded as polar molecules. Hydrogen-bonding interactions are a specific sort of this type of bonding, resulting from the fact that hydrogen consists of only one proton and one electron, making it very strongly electronegative. When hydrogen bonds, its electron is lost, leaving an exposed proton. This unique situation causes a strong attraction between the proton and an electronegative region from another atom. The strength of the hydrogen bond results in drastically different properties of interaction, exemplified by the fact that water has such a surprisingly high melting and boiling point (in comparison with non-hydrogen-bonded materials). Strengths of hydrogen bonds fall in the range 10 to 40 kJ/mol (18). Many excipients and active pharmaceutical ingredients are able to hydrogen bond. Examples of excipients with hydrogen bonding potential would include sugars, celluloses, and starches.

A bond between carbon and oxygen would be expected to be dipolar; however, if the molecule of carbon dioxide (not of significance for tabletting, but the easiest molecule with which to demonstrate the concept) is considered (O=C=O), it can be seen that the molecule is, in fact, totally symmetrical, the dipole on each end of the linear molecule being in perfect balance with that on the other end. Even though these molecules do not carry a permanent dipole, if they are placed in the presence of a polarized material, a dipole will be induced on the (normally symmetrical) molecule, such that interaction can occur. Such interactions are common and are termed *dipole–induced dipole* (or Debye) interactions.

London–van der Waals forces are termed dispersion forces. These are interactions between molecules that do not have a charge imbalance and the ability to have an induced dipole either. Essentially, these are interactions between nonpolar materials. These dispersion forces occur between all materials, and thus, even though the interaction forces are weak, they make a very significant contribution to the overall interaction between two molecules. Dispersive forces are extremely complex to describe but can be considered in a simplistic fashion by considering the fact that the electrons that spin around two neighboring nonpolarized atoms will inevitably not remain equally spaced and consequently result in local imbalances in charge, which leads to transient induced dipoles. These induced dipoles and the forces that result from them will constantly be changing, and obviously, the magnitude of these interactions is small compared with the permanent and induced dipole situations described above. As stated above, dispersion forces are complicated interactions; examples of their properties include their long range (in the order of 10 nm, which is significantly longer than the bond length), nonadditivity (because neighboring molecules exert an influence on two interacting molecules), and the fact that the interactions can obviously be attractive or repulsive (but in practice are considered to be attractive over long distances). A typical strength for van der Waals bonding would be 1 kJ/mol.

It follows then that the total van der Waals force acting between two molecules can be considered as the sum of the three contributing types of forces, that is, dipole-dipole (orientation, or Keesome), dipole–induced dipole (Debye or induced), and induced dipole–induced dipole (London dispersion) forces (19–22).

THE EFFECT OF LUBRICANT ON TABLET BONDING

As essentially every compressed tablet has a lubricant as part of the formulation, and as it is known that the presence of lubricant can affect tablet strength (as well as dissolution rate, etc.), it is worth considering the effect of the lubricant. Magnesium stearate is the most commonly used and investigated lubricant for tablets, but its complexity presents problems in gaining a full understanding of its influence. The British Pharmacopoeia describes magnesium stearate as "a mixture of magnesium salts of different fatty acids," so there is an understanding that this is not a chemically pure material. It is known that different polymorphic forms, different hydrate levels, and different sizes and shapes of the particles all have an effect on the properties of magnesium stearate (23). It is therefore not surprising that materials from different vendors and even lots from the same vendor can have different behaviors in products. That said, there are a number of publications on magnesium stearate and its effects in tablets that do highlight general trends. It is clear that magnesium stearate will be used as small particle size material and will be mixed (for critical duration with respect to the effect) just prior to tabletting, such that magnesium stearate will be positioned between particles and between the particles and the die wall. It is therefore to be expected that the interfacial bonding that has been described above will be altered by the presence of this excipient between two other particles. Indeed, it has been shown (3,24,25) that increasing the amount of magnesium stearate in a powder mix results in the remaining strength of a compact falling to essentially a plateau level (3). It has been argued that the plateau level that is obtained provides information on the contribution of the solid bridge formation in a compaction process on the basis that the process of fracture (or presumably plastic flow, as a number of the materials studied were not brittle) will penetrate the lubricant covering of the particles and override their contribution to the bonding process.

CHEMICAL IMAGING IN TABLETS

Advances in chemical imaging have provided a way to better understand the compaction process. A number of methods now exist including Terahertz spectroscopy, which is good for studies around density differences in tablets, showing defects and potential for lamination. More regular use comes from near infrared (NIR) and/or Raman spectroscopy. These methods can be complimentary as NIR provides information about water and its distribution and binding energy, often to some extent masking other effects, and Raman does not detect a signal for water; hence, together, they can provide a lot of information about what is in a tablet and where it is distributed, which in turn can shed light on how the compaction process may have progressed. A chemical image is constructed by measuring spectra in each defined region (often 1 μm x 1 μm) of a sample and then repeating until an entire area is mapped. By knowing the characteristic peaks for each component in the formulation, it is possible to do analysis of each μm square and see which component(s) is (are) present in that region. In Figure 3, a map of a sample is shown, and the upper plot shows the distribution of the active, and the bottom plot, one of the excipients. It can be seen that the regions where the active has high intensity (black), the excipient is absent, and vice versa. This method can be used to show how different batches of the same product differ and explain what has happened during the processing to cause this (mixing failure, compaction differences, etc.). Equally, as different polymorphic forms and amorphous forms have different spectra, it is possible to use this approach to see what changes have happened to materials during the tabletting process and to see if these are the same in each batch. Understanding this helps control batch-to-batch variability in tablet properties, stability, and dissolution; it also helps to ensure that physical-form patents are not being infringed. As the spectra are taken on each individual small area, the resolution and detection sensitivity is very high indeed—such that individual particles can be indentified and their properties (polymorphic form/amorphous content) studied in the formulation.

CONCLUSIONS

Tablets are held together predominantly by solid bridges and interfacial forces of attraction, which can be hydrogen bonding or the range of van der Waals interactions. Solid bridges are caused by the material properties and the compaction process, and will be prone to give different tablet strengths as factors such as the amorphous content change (equally likely to be true with changes in polymorphic form, hydrates and particle size, surface area, and roughness). The interfacial forces can act over ranges much longer than a simple bond, and the strength of these will be related to the nature of the materials that are compressed and the surface area over which bonding can take place, which is also linked to the materials properties and the processing used.

Materials can and will change their form during compaction, and these form changes will alter tablet bonding and the subsequent tablet properties—chemical stability and dissolution included. There are techniques available that allow tablets to be studied and the properties to be understood.

The interplay between input materials properties, which must be very well understood, and critical parameters controlled, the processes used to make the tablets and the measured properties of the tablets that are produced, especially by techniques such as chemical imaging,

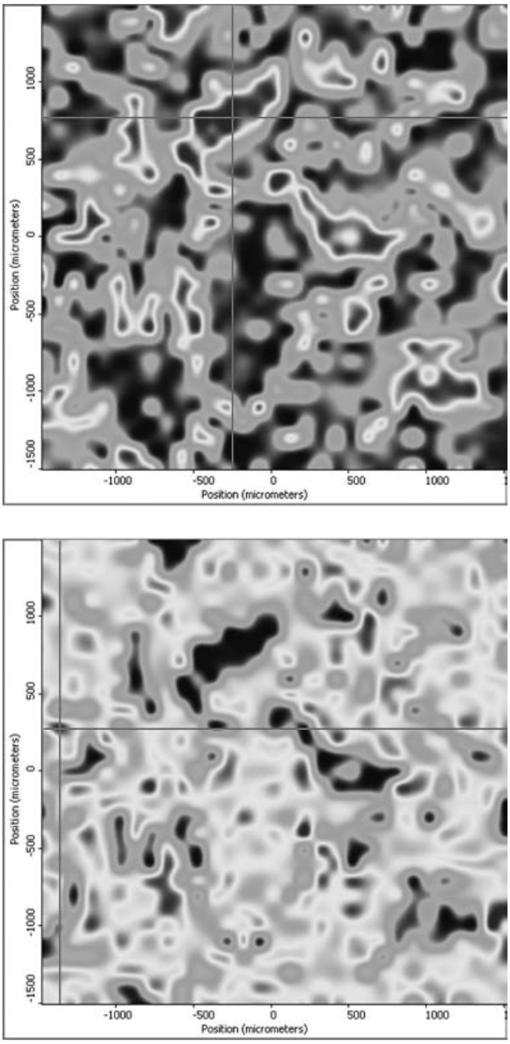

Figure 3 Raman maps of a tablet showing the distribution of the active (*top*) and excipient (*bottom*). Black, high intensity; white, low intensity.

provides the basis for Quality by Design and the guarantee that uniformly high-quality product can be produced with an established design space.

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2 Viscoelastic models

Susan K. Lum

INTRODUCTION

> S.G. the director of production at XYZ Pharmaceuticals looked more harassed than usual today. He had been raked over the coals for allowing 9 out of 17 1200 kg scale lots from a recent commercial campaign fail acceptable quality level (AQL) inspection due to fractured tablets with the majority of defects being capping, lamination or hairline cracks. The coating operator and production managers were reporting in again, "sorry but it's the same problem as before, sometimes it works and sometimes it doesn't, this pan has loads of split tablets." How did it get to this point? The press was overhauled and many mechanical issues that could have led to tablet breakage, like the bottom punch seals, were fixed. The tablet pan speed in coating was slowed to a crawl to reduce stress on the tablets. All operator and engineering shifts were trained and retrained to make sure the tablets were compressed to meet specification. There were only so many engineering controls to be done—it was filed this way.

Pharmaceutical formulation development difficulties often arise during scale-up since significant increase in production and local strain rates occur. Such cases are commonly encountered in technical transfer since there is limited understanding regarding the effect of process variables on material properties at either the pilot or commercial scale. Technical difficulties can sometimes be managed with extreme engineering controls, but often the root cause is the formulation. A tablet is only as robust as the components that form it. Often these materials form differently under different compression speeds. This strain rate sensitivity has lead to other well publicized manufacturing cases like the FDA-triggered recall in 2005 of all lots of a controlled-release tablet made by a large multinational (1). It was found that the tablets could split apart. This deficiency could cause patients to receive a portion of the tablets that lack any active ingredient or, alternatively, a portion that contained the active without the intended controlled-release effect. Clearly, the materials chosen, the formulation, and processing together defined the boundary of failure. How could these known risks have been better managed?

Solving such formulation problems begins with an understanding of the factors contributing to tablet quality. As it will be described in depth in subsequent chapters of this text, the compaction of powders is a complex process. Powder densification consists of sequential and concurrent processes where particles are brought into intimate contact, interparticulate bonds are formed, and dimensional changes occur as a result of stress redistribution. Time-dependent phenomena inherent in these processes govern the ultimate quality of the compact produced. Permanent densification occurs when stress exceeds the elastic strain limit of a given material. The extent of this nonrecoverable deformation depends on the time in which the applied stress exceeds this material yield stress. Thus, intrinsic tablet strength is a sum of the following:

1. Permanent interparticulate bonds formed intrinsically during compaction. High plasticity or irreversible deformation drives the formation of permanent particle to particle contact zones.
2. Reversible or recoverable, elastic deformation. Highly elastic material stores mechanical energy during compaction but will release it again once the stress is removed. This bounce-back is often seen as cracking, capping, or lamination during the unloading phase of the compression cycle or upon ejection.

3. Fracture toughness determines the extent to which interparticulate contact regions fracture or are crushed during compaction with time.
4. Time-dependent recovery.

It is viscoelastic theory that serves to quantify this time dependence of material properties. This provides a description of the relationship between the strain rate or the time component of the material undergoing viscoelastic deformation, the stress or the force component required to produce that strain rate, and the effect.

Empirical evidence has shown that tablet strength and durability in downstream processing are a function of both the materials as well as the processing of these materials. The rate at which compacts are formed determines the final tablet strength and viability (2–14). With the advent of modern processes, the high speed of compaction accentuates the time-dependent component of material behavior. This complexity is reflected in large-scale manufacturing of tablets where problems of low tablet strength, capping, and sensitivity to material batch variability exist and can be quite costly. Improving the theoretical understanding of the compaction process would enable a more rational approach to the formulation of tablets (15).

Problems that arise during tablet production are a consequence of viscoelasticity combined with poor interparticle bonding. The degree of interparticle bonding and bond strength is assumed to be largely governed by the magnitude of the true interparticle contact area. The amount of elastic recovery of the particles depends on the release of elastic strain during decompression and tends to disrupt interparticle bonds. This stress relaxation is a function of the viscoelasticity of the material, which in turn is influenced by the speed of compression and decompression. At high compaction speeds, the internal stress after compaction is high and the propensity of the material for elastic recovery is considerably higher than at low compaction speeds.

The concept and much of the theory for time-dependent materials properties originates in engineering sciences with the study of materials such as metals, soils, and ceramics. By applying information from these other areas to the field of solid pharmaceutics, the compaction process may be distilled into mechanical models with mathematical terms. Applied viscoelastic theory predicts the behavior of these models under stress. The behavior may be simplified by considering the bulk powder mass as a continuum or by considering a large number of individual particles in an aggregate blend on the basis of the behavior of an average single particle.

VISCOELASTIC RHEOLOGY

Viscoelastic substances are materials whose behavior lies between that of perfectly elastic solids and that of perfectly viscous fluids. Macromolecular pharmaceuticals, polymeric materials, glasses, and even concrete are considered to be viscoelastic materials; the increased use of these materials has brought with it the need to ascertain their mechanical behavior under a variety of conditions of stress, temperature, and flow (16).

The behavior of a viscoelastic material can often be described by a mechanical model whose behavior, under a specific regimen of tests, closely resembles that of the material in question. This model may then be used to predict the behavior of the material under different test conditions. Such models have traditionally been visualized as systems of springs and dashpots; the springs provide purely elastic behavior, and the dashpots purely viscous behavior in the Newtonian sense (Fig. 1). Such basic elements of springs and dashpots are useful rheological analogs for stress and strain.

Stress, σ, as shear, tensile, or compressive, describes surface forces acting perpendicularly while strain, ε, describes the local deformation in relation to original dimensions. Under

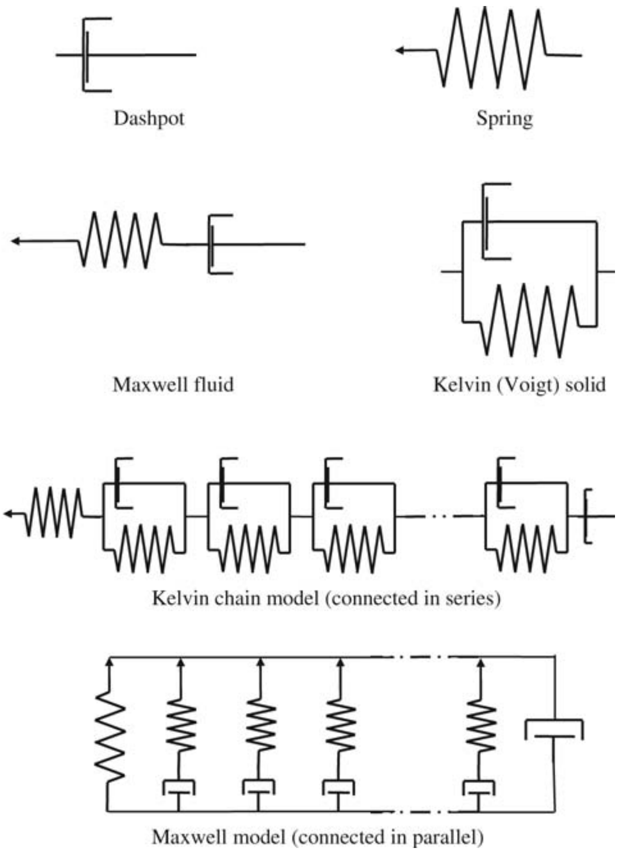


Figure 1 Elements in viscoelastic models.

uniaxial loading, the behavior of materials commonly used in tabletting is history dependent, and past compressions can affect present densification.

Elasticity

A spring represents linear elastic behavior. An ideal helicoidal spring element would be perfectly linear and massless. When a force is applied, the length of the spring increases to a certain dimension, and when the force is removed, the spring returns to its original state. Hooke's law states that the stress is proportional to the strain.

$$\sigma(t) = E\varepsilon(t) \tag{1}$$

where E is the modulus of elasticity with dimension (force/length^2). The spring has a creep function $H(t-\tau)/E$ and a relaxation function $EH(t-\tau)$. Powders, in compression, are constrained by the die wall upon dilation once a load is removed.

Viscosity

A dashpot or piston moving in a cylinder filled with a viscous fluid represents viscous behavior. The dashpot as an ideal viscous element extends at a rate proportional to the force applied according to Newton's law. Stress is proportional to the strain rate.

$$\dot{\varepsilon}\ (t) = \frac{\sigma(t)}{\eta} \tag{2}$$

where $\dot{\varepsilon} = \partial\varepsilon/\partial t$ is the rate of strain and η is the viscosity coefficient with dimension (force × time × length^{-2}). With dashpots, the greater the speed or rate of strain, the greater the resistance; since there is no restoring force, a dashpot remains extended upon load removal.

COMPOSITE VISCOELASTIC MODELS

Maxwell Model

Different combinations of springs and dashpots afford flexibility in portraying different responses. The Maxwell body is a combination of a spring and a dashpot in series. In series, the strain in each element is additive.

$$\varepsilon = \varepsilon_\mathrm{s} + \varepsilon_\mathrm{d} \tag{3}$$

where subscript s refers to the elastic spring and d, the viscous dashpot. Differentiating allows the insertion of the differentiating elastic equation (1) to give

$$\dot{\varepsilon} = \dot{\varepsilon}_\mathrm{s} + \dot{\varepsilon}_\mathrm{d} = \frac{\dot{\sigma}}{\kappa} + \frac{\dot{\sigma}}{\eta} \tag{4}$$

$$\sigma + p_1\dot{\sigma} = q_1\dot{\varepsilon} \tag{5}$$

where κ is Young's modulus of elasticity, η, viscosity, and the hybrid constitutive parameters correspond to

$$p_1 = \frac{\eta}{\kappa} q_1 = \eta \tag{6}$$

Kelvin–Voigt Model

The Kelvin body is a combination of a spring and a dashpot in parallel. With elements in parallel, the stress of each element is additive.

$$\sigma = \sigma_\mathrm{s} + \sigma_\mathrm{d} \tag{7}$$

and

$$\sigma = \kappa\varepsilon + \eta\,\dot{\varepsilon} = q_0\varepsilon + q_1\dot{\varepsilon} \tag{8}$$

The stress in the Kelvin element is related both to the elongation of the spring and to the rate of deformation of the dashpot.

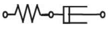
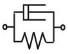
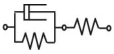
Generalized Models

Linear Viscoelasticity

Many materials, notably polymers, exhibit time-dependent behavior in their relationships between stress and strain. The common features of a three-parameter or standard solid viscoelastic behavior include an initial elastic response to an applied or eliminated stress, a delayed elastic response, and often a permanent strain that is acquired through the action of creep.

A summary of some basic arrays of these viscous and elastic elements that make physical sense is depicted in Table 1 (17). Simple two-parameter models such as the Maxwell or Kelvin–Voigt elements, as mentioned above, are composed of either serial or parallel connections, respectively. When in series, the entire elongation of the model is equal to the sum of the elongations of its components. When in parallel, the elongation of both elemental parts is equal at any time. Stress is then proportional to both the elongation of the spring and the rate of deformation of the dashpot. These simple models illustrate the principle central to the study of

Table 1 Rheological Models with Variable Parameters Used to Describe Viscoelastic Material Behavior

Designation	Elements	Differential equation	Creep function	Relaxation function
1 parameter (Hooke)		$\sigma = E\varepsilon$	$\frac{1}{E}$	E
2 parameter (Maxwell)		$\frac{\dot{\sigma}}{E} + \frac{\sigma}{\eta} = \dot{\varepsilon}$	$\frac{1}{E} + \frac{t}{\eta}$	$Ee^{-\frac{tE}{\eta}}$
2 parameter (Kelvin–Voigt)		$\sigma = E\varepsilon + \eta\dot{\varepsilon}$	$\frac{1}{E}\left(1 - e^{-\frac{tE}{\eta}}\right)$	$E + \eta\delta(t)$
3 parameter (standard)		$\sigma(E_1 + E_2) + \dot{\sigma}\eta$ $= E_1E_2\varepsilon + E_1\eta\dot{\varepsilon}$	$\frac{1}{E_1} + \frac{1}{E_2}\left(1 - e^{-\frac{tE_2}{\eta}}\right)$	$E_1e^{-\frac{t(E_1+E_2)}{\eta}} +$ $\frac{E_1E_2}{E_1 + E_2}\left(1 - e^{-\frac{t(E_1+E_2)}{\eta}}\right)$
4-parameter solid		$\sigma(E_1 + E_2) + \dot{\sigma}\eta_1\eta_2$ $= E_1E_2\varepsilon + \eta_1\eta_2\ddot{\varepsilon}$ $+ (E_1\eta_2 + E_2\eta_1)\dot{\varepsilon}$	$\frac{1}{E_1}\left(1 - e^{-\frac{tE_1}{\eta_1}}\right) +$ $\frac{1}{E_2}\left(1 - e^{-\frac{tE_2}{\eta_2}}\right)$	$\frac{E_1E_2}{E_1 + E_2} + \frac{\eta_1\eta_2}{\eta_1 + \eta_2}\delta(t) -$ $\left(\frac{E_1E_2}{E_1+E_2} - \frac{E_1\eta_2+E_2\eta_1}{\eta_1 + \eta_2} + \left(\frac{1}{E_1+E_2}\right)\frac{\eta_1\eta_2}{(\eta_1+\eta_2)^2}\right)e^{-\frac{t(E_1+E_2)}{\eta_1+\eta_2}}$

Source: From Ref. 17.

linear viscoelasticity. Each model is described by a linear differential equation with constant coefficients of the type (16)

$$\sigma + p_1\dot{\sigma} + p_2\ddot{\sigma} + \cdots = q_0\varepsilon + q_1\dot{\varepsilon} + \cdots \tag{9}$$

or

$$\left(\sum_0^m p_k\frac{d^k}{dt^k}\right)\sigma = \left(\sum_0^n q_k\frac{d^k}{dt^k}\right)\varepsilon \tag{10}$$

Since the equation can be divided by a constant without changing its meaning, p_0 is always set to unity. In the viscoelastic regime, elastic deformation depends directly on stress, whereas viscous internal stress depends on the rate of deformation.

Solutions to the above constitutive equation for a linear viscoelastic material form an important part of the theory of viscoelasticity. The nonzero coefficients dictate the type of behavior displayed by the model. For instance, if $q_0 = 0$, the model displays fluid flow; otherwise, it behaves as a solid. If $n = m$, the model shows an initial elastic response to an applied stress; if $n = m + 1$, this response is absent.

Although the behavior of some solids approaches Hooke's law at infinitesimal strains and the behavior of some liquids approach Newton's law at infinitesimal strain rates, these are mere ideals. Most materials show characteristics between the two. Viscoelastic behavior is hallmarked by creep, stress relaxation, and stress-strain hysteresis. Viscoelastic materials dissipate energy during deformation and consequently recover some of the deformation it has undergone. Although Kelvin–Voigt and Maxwell models are often used to describe viscoelastic behavior, these models are extremely simplified. The Kelvin–Voigt model may represent creep of a viscoelastic material but fails to represent the stress relaxation. The Maxwell model may present the stress relaxation of a viscoelastic material but fails to register the creep behavior. A response closer to the behavior of a real viscoelastic material with time dependence comes from more complex combinations.

Simple Maxwell or Kelvin models are limited and cannot describe material properties with high strain rates or over long periods of time. More complex combinations in series or in parallel have been used in generalized models to overcome these limitations. It is possible to generalize spring and dashpot models into more complicated forms using an arbitrary number of Maxwell units in parallel or Voigt units in series. The physical microconstants, which are assigned to each elastic or viscous element in the array, form the basis for the hybrid coefficients, p_k and q_k, in the constitutive equation for the mechanical model.

Whereas simple models are inadequate representations of real viscoelastic behavior, a three-parameter, standard, model consisting of two springs and a dashpot has successfully portrayed real material behavior (18,19). A standard model may be thus employed in the extension of the description of particle contact to the viscoelastic case. Linear viscoelastic relationships are valid for small strains and assume the principle of superposition holds (19) a stress history.

$$\sigma(\tau) = \sigma_1(\tau) + \sigma_2(\tau), \tau \ni (\tau_0, t) \tag{11}$$

corresponds to a strain history of

$$\varepsilon(\tau) = \varepsilon_1(\tau) + \varepsilon_2(\tau) \tag{12}$$

Materials often exhibit linear behavior at low stresses and nonlinear viscoelastic behavior at high stresses. The stress-strain relations for a linear viscoelastic material are commonly expressed as a relaxation function, $\Psi(t)$. This function, as deduced above from a standard spring-dashpot model, expresses the stress response to a step change in strain.

In operational form, this standard model (Fig. 2) appears as

$$E_1\eta\dot{\varepsilon} + E_1E_2\varepsilon = \sigma(E_1 + E_2) + \eta\dot{\sigma} \tag{13}$$

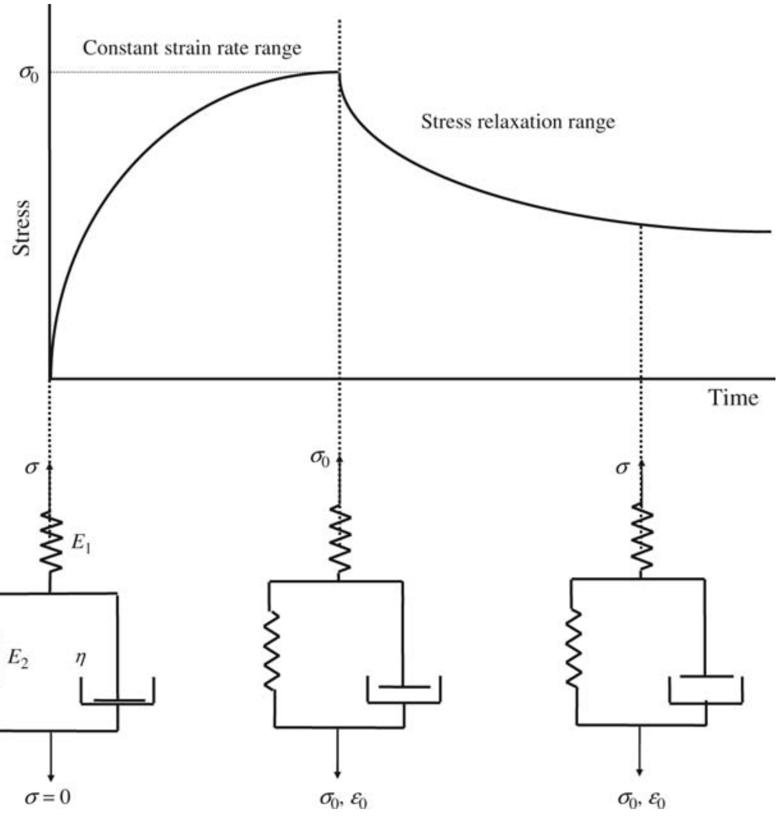


Figure 2 Illustration of the stress-time relation in association with a standard three-parameter rheological model.

By integrating over a strain history $\varepsilon(t)$

$$\therefore\ \sigma(t) = \varepsilon(t)\frac{E_1E_2}{E_1 + E_2} + \frac{E_1^2}{E_1 + E_2}\int_0^t e^{-\frac{(t-\tau)(E_1+\ E_2)}{\eta}}\ \dot{\varepsilon}\ (\tau)d\tau \tag{14}$$

Wherein the creep function is

$$\phi(t) = \frac{1}{E_1} + \frac{1}{E_2}\left(1 - e^{-\frac{tE_2}{\eta}}\right) \tag{15}$$

and the relaxation function

$$\Psi(t) = E_1e^{-\frac{t(E_1+E_2)}{\eta}} + \frac{E_1E_2}{E_1 + E_2}\left(1 - e^{-\frac{t(E_1+\ E_2)}{\eta}}\right) \tag{16}$$

Simplified three-dimensional form for viscoelastic constitutive description. When a problem has more than one stress component, then a generalization of the viscoelastic law to the three-dimensional form may be needed (16). If a viscoelastic material is isotropic, a hydrostatic stress must produce a dilatation and no distortion. The stress and strain are related by the differential equation

$$\sigma + p_1\dot{\sigma} + p_2\ddot{\sigma}\ + \cdots = q_0\varepsilon + q_1\dot{\varepsilon} + \cdots \tag{9}$$

$$\left(\sum_0^m p_k\frac{d^k}{dt^k}\right)\sigma = \left(\sum_0^n q_k\frac{d^k}{dt^k}\right)\varepsilon \tag{10}$$

or shorter by

$$P''\sigma = Q''\varepsilon \tag{17}$$

On the other hand, if shear is present, then the shear strain coupled with isotropy of the material requires that

$$\left(\sum_0^{m'} p_k'\frac{d^k}{dt^k}\right)\hat{\sigma} = \left(\sum_0^{n'} q_k'\frac{d^k}{dt^k}\right)\hat{\varepsilon} \tag{18}$$

or

$$P'\hat{\sigma} = Q'\hat{\varepsilon} \tag{19}$$

where $\hat{\sigma}$ and $\hat{\varepsilon}$ correspond to the components of the stress and strain deviators.

The operator pairs P'' and Q'', and P' and Q', which describe the viscoelastic material, are entirely independent of each other. To each pair, the relation stated in equation (15) or (16) is applicable for a standard three element model. These operator pairs for different rheological models are also summarized in Table 2.

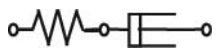
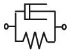
UNIAXIAL CONFIGURATION

In uniaxial tension, there is only one stress, σ_x and strain has three components, the axial strain ε_x and the lateral contractions $\varepsilon_y = \varepsilon_z$. As the operators are assumed linear and time invariant, the commutative properties yield

$$(P''Q' + 2Q''P')\sigma_x = 3Q''Q'\varepsilon_x \tag{20}$$

$$(P''Q' - Q''P')\sigma_x = 3Q''Q'\varepsilon_y \tag{21}$$

Table 2 Viscoelastic Models with Variable Parameters: Generalized

Model	Name	Differential equation inequalities	Creep compliance $\Phi(t)$	Relaxation modulus $\Psi(t)$	Complex compliance, real $G_1{}'(\omega)$	Complex compliance, imaginary $G_2''(\omega)$
	Elastic solid	$\sigma = q_0\varepsilon$	$\frac{1}{q_0}$	q_0	$\frac{1}{q_0}$	0
	Viscous fluid	$\sigma = q_1\dot{\varepsilon}$	$\frac{t}{q_1}$	$q_1\delta(t)$	0	$-\frac{1}{q_1\omega}$
	Kelvin solid	$\sigma = q_0\varepsilon + q_1\dot{\varepsilon}$ $\sigma = E\varepsilon + \eta\dot{\varepsilon}$	$\frac{1}{q_0}(1 - e^{-\lambda t}), \lambda = \frac{q_0}{q_1}$	$q_0 + q_1\delta(t)$	$\frac{q_0}{{q_0}^2+q_1^2\omega^2}$	$-\frac{q_1\omega}{{q_0}^2+q_1^2\omega^2}$
	3-parameter solid	$\sigma + p_1\dot{\sigma} = q_0\varepsilon + q_1\dot{\varepsilon}$ $q_1 > p_1 q_0$ $\sigma(E_1 + E_2) + \dot{\sigma}\eta = E_1 E_2\varepsilon + E_1\eta\dot{\varepsilon}$	$\frac{p_1}{q_1}e^{-\lambda t} + \frac{1}{q_0}\left(1 - e^{-\lambda t}\right)$ $\lambda = \frac{q_0}{q_1}$	$\frac{q_1}{p_1}e^{-\frac{t}{p_1}} + q_0\left(1 - e^{-\frac{t}{p_1}}\right)$	$\frac{q_0+p_1 q_1\omega^2}{{q_0}^2+q_1^2\omega^2}$	$-\frac{(q_1-q_0 p_1)\omega}{{q_0}^2+q_1^2\omega^2}$

Source: From Ref. 16.

for applied uniaxial stress. By analogy,

$$(Q''P' + 2P''Q')\varepsilon_x = 3P''P'\sigma_x \tag{22}$$

$$(Q''P' - P''Q')\varepsilon_x = 3P''P'\sigma_y \tag{23}$$

follows for applied uniaxial strain (in stress relaxation experiments).

Equations (20) to (23) serve as the viscoelastic equivalent of a complete statement of Hooke's law for uniaxial tension. Interpretation requires special choices for the operators. While shear deformation may be rather large, the change of volume measured by e is always very limited. It seems therefore, reasonable to neglect the latter completely and to assume $e = 0$. This corresponds to $P'' = 0$ and $Q'' = 1$. The constitutive equations for uniaxial stress in tension are then

$$2P'\sigma_x = 3Q'\varepsilon_x \quad \text{and} \quad -P'\sigma_x = 3Q'\varepsilon_y \tag{24}$$

and for applied uniaxial strain,

$$2Q'\varepsilon_x = 3P'\sigma_x \quad \text{and} \quad -Q'\varepsilon_x = 3P'\sigma_y \tag{25}$$

Elastic Parameters as a Limiting Case

In a viscoelastic body, all of the stresses, strains, and displacements occurring under load are time dependent. The elastic solid is then a limiting case of a viscoelastic material. The moduli of the springs of the rheological model do not correspond simply to Young's modulus as time, temperature and stress dependence are overt considerations. If, for example, one considers a material tested in tension, the plot of the compliance would show that the ratio $\varepsilon_x/-\varepsilon_y$ varies with time. This time dependence indicates that the concept of Poisson ratios, etc., is not very meaningful for a viscoelastic material (16, p. 178).

The linear elastic law (Hooke's law) would render the four operators (eqs. 24 and 25) as multiplicative constants and the formulation of the stress deviation as

$$\sigma_x = \frac{E}{(1+\nu)(1-2\nu)}[(1-\nu)\varepsilon_x + \nu(\varepsilon_y + \varepsilon_z)] \tag{26}$$

The differential operators P and Q can be replaced by polynomials $\wp(s)$ and $\vartheta(s)$ in considering an elastic body; hence,

$$\wp''(s)\overline{\sigma} = \vartheta''(s)\overline{\varepsilon} \tag{27}$$

$$\wp'(s)\overline{\overline{\sigma}} = \vartheta'(s)\overline{\overline{\varepsilon}} \tag{28}$$

where $\overline{\sigma}$ and $\overline{\varepsilon}$ are the Laplace transforms of the time-dependent stresses and strains.

These algebraic relations define the limits of their elastic counterparts if

$$3K \to \frac{\vartheta''(s)}{\wp''(s)}, \quad 2G \to \frac{\vartheta'(s)}{\wp'(s)} \tag{29}$$

$$E \to \frac{3\vartheta'\vartheta''}{2\wp'\vartheta'' + \vartheta'\wp''}, \quad \nu \to \frac{\wp'\vartheta'' - \vartheta'\wp''}{2\wp'\vartheta'' + \vartheta'\wp''} \tag{30}$$

For a standard (three-parameter material), a reduced or effective modulus $E_R(t, \tau)$ offers estimates of an instantaneous $E_R(\tau_0, \tau_0)$ and an asymptotic modulus $E_R(\infty, \tau)$ (18).

$$E(\tau_0, \tau_0) = \frac{1}{E_1}, \quad E(\infty, \tau_0) = \frac{E_1 E_2}{E_1 + E_2} \tag{31}$$

STRESS RELAXATION AND CREEP COMPLIANCE

As delineated in Table 2, the differential equations for the standard models are often used in materials description. The primary advantage in these models lies in the relatively few material constants needed to describe many experimental curves; they confer the ability to easily predict the results of one mechanical test from the results of another without explicit knowledge of the constitutive equations from continuum mechanics or structure.

Two standard tests applied to viscoelastic materials are that of creep and stress relaxation. Ideally, in a creep experiment, an instantaneous step increase in stress is applied to the material. Strain is then time dependent and proportional to σ_0. Likewise, ideally in a stress relaxation experiment an instantaneous step increase in strain is imposed on a sample. This means applying at $t = 0$ whatever stress is needed to achieve the desired ε_0, holding the strain constant, and monitoring the stress. The resultant experimental data may be linearized according to equation (1) (18).

$$\sigma(t) = \sigma_0 \Psi(t) \tag{32}$$

where $\Psi(t)$ is the relaxation modulus that decreases monotonically to a horizontal asymptote. To solve for $\Psi(t)$, one lets $\varepsilon = H(t)$, the Heaviside function, so $\bar{\varepsilon}(s) = 1/s$; solution then involves the LaPlace transform. The relaxation modulus is the product of an elastic response and a relaxation function expressing the time-dependence of mechanical response.

PRACTICAL APPLICATION

The application of viscoelastic modeling in pharmaceutics relies on these concepts developed originally in the fields of materials engineering and metallurgy. Building on the rheological models designed to mimic materials behavior is a step in the process to quantify observed time-dependent materials behavior.

By assuming that the energy input or work of compression correlates with the tablet forming properties of materials, force displacement measurements have been used to examine the deformation process (44). Force displacement curves are obtained from the accurate measurements of both the upper and lower punch force and displacements.

The greater area under the force-displacement curve may indicate a greater amount of energy throughput in the tabletting process. A larger energy consumption is not necessarily indicative of a better, stronger tablet. The inability to specifically allocate energy use amongst competing processes mutes the usefulness of this measurement. The resolution of the energy usage during compaction is again, as alluded above, quite difficult. The energy used may be attributed to a number of concurrent processes including internal friction, die wall friction, fracture, bonding, heating, bonding, melting, as well as plastic or viscoelastic deformation.

Upadrashta et al. (20), for example, examined the compaction characteristic of various viscosity grades of ethylcellulose using force-displacement, ejected Heckel analysis and work calculations from instrumented press test data, after accounting for machine deformation. The investigation served to provide a qualitative rank ordering of the grades of the polymer with the degree of compactibility. The better material tablet properties depended on the molecular weight of the polymer and were attributed to the elastic nature of the polymer and the elastic component of the performed work.

STRESS RELAXATION METHODS

The ability of a material to relieve stress under pressure has also been used to characterize the consolidation mechanism of materials. One of the first observations recognizing the role of viscoelasticity in tablet compaction was reported by Rees and Rue (21). Their empirical experiments with starches and celluloses displayed stress relaxation; time-dependent change of the load occurred when the tabletting machine was halted at its lowest point. David and

Augsberger (2) also loaded tablets in a static manner using constant stress or strain. By applying rudimentary mechanical models to the load-displacement profiles for the entire compact, they showed that various agents and excipients were neither ideally elastic, nor ideally viscous, or plastic materials.

Rippie and coworkers (9,22–24) advanced these observations with important macromolecular tabletting materials on a rotary machine. A time shift between the load maxima and displacement maxima during dynamic compression was attributed to the properties of the compacting substance. In the decompression and the post compression phases of rotary tabletting, the load versus time curves were found from radial and axial load measurements while the displacement versus time functions were deduced from the rotary geometry. By assuming that the expansion volume upon decompression was purely an elastic process and the deformation itself, purely viscoelastic, three dimensional viscoelastic models with many elements in series were adjusted to conform to the compression profile of the entire tablet. Arithmetic evaluation of the mechanical model fit resolved the stress strain relation in standard form. The resultant hybrid parameters, p_k and q_k, thus determined on the whole compact, were found to relate to the maximum compression load.

In attempting to correlate the calculated hybrid parameters with the observed behavior of the directly compactible powders examined, it was noted that the elastic parameters were indicative of the degree of interparticulate bonding. Lamination was more likely with the presence of high residual die stresses and large negative terminal elastic parameters.

The aforementioned negative viscoelastic parameters elude a physical explanation (17). While it is easier to calculate these hybrid parameters rather than the microconstants associated with each element of the mechanical model, neither should be negative in a real solution. In a four-parameter model, for example, up to four solutions for a microconstant may be obtained from regression decomposition; their physical validity must be tested to determine the real solution. The numerical stability of the regression fitting method should be addressed.

Moreover, the direct application of rheological models to the entire compact inherently assumes the tablet to be a continuum. The mathematical development of the mechanical models in materials engineering is valid for fully dense, homogeneous, isotropic materials. Rippie and coworkers (24) have acknowledged that their calculated parameters cannot be considered true material constants. The "negativity" of the elastic constants was then suggested to be a consequence of the internal structure of the compact; the internal stresses arising from internal fracturing or bond breaking during expansion processes are transmitted to the die and "overshadows the punch stress reduction from the particulate strain" (24, p. 711).

Consideration of the powder as a continuum also means ignoring the voids between the particles. It would be difficult to envision when these interparticulate pores are not important. At the beginning of compaction, these pores contribute to particle and internal structure rearrangements. In the latter stages of compaction, the porous network of the tablet is progressively established and beyond a critical point, the pore network bears load.

The physical basis for their calculated parameters must be deduced by quasi-inference. The viscous parameters calculated, for example, must be interpreted in the context of "extent of flow within the compact, rather than viscosity" (24, p. 711). The predictive capability of this model form is hampered by the absence of physical analogy.

CREEP COMPLIANCE METHODS

As an alternative to stress relaxation experiments, creep testing may be performed where the change in strain is monitored as a function of step changes in stress. Staniforth and Patel (25) tested both starch and microcrystalline cellulose in a tensile tester at 14 kN/min held at three constant loads. Like Rippie and coworkers, they attempted to apply a rheological model directly to the powder compaction data. The presence of pores and void spaces within the compact, as discussed previously, precludes the extracted parameters from representing physically real material properties. In this case, no attempt was made to calculate hybrid parameters from the assumed eight-parameter Voigt–Maxwell fluid model; instead, the compliance curve was examined and dissected qualitatively into portions that were interpreted as representing just the elastic or the plastic contributions. The mathematical description of the creep function in an eight-parameter model of the form

$$\Phi(t) = \frac{1}{E_1} + \sum_{i=2}^{k} \left(\frac{1}{E_i} \left(1 - e^{-\left(\frac{E_i}{\eta_i}\right)t} \right) \right) + \frac{t}{\eta_1} \tag{33}$$

shows that the intercept of the compliance curve is related to the elastic contribution. This elastic term, however, is a complex function of each of the four springs comprising this rheological model. The simple subtraction of the intercept from the compliance curve cannot provide a quantitative measure of the plastic contribution alone to deformation. The time-dependent elastic recovery of the material is a factor that is neglected by this analysis.

Malamataris et al. (26,27) also used creep experiments performed on a tensile tester for starch, Emcompress and paracetamol to ascertain a more fundamental measure of tabletability. In attempting to apply a Maxwell rheological form directly to the entire compact, viscoplastic deformation was assumed. The subsequent decomposition of the creep compliance curve as interpreted by the authors has several contradictions. While the reciprocal slope of the compliance curve for a Maxwell fluid should provide an apparent viscosity, the shape of the experimental curve is clearly parabolic. The assumption of a Maxwell form is inappropriate; a higher order rheological model would be more suited to the curvature of the observed data. With a three-parameter model, the reciprocal of the slope of the linear portion of the curve would be a measure of the complex modulus (defined in Table 1 as $E_1E_2/E_1 + E_2$). Apparent viscosity, η, cannot be used interchangeably as a measure of the extent of the elastic retardation as assumed in their analysis. Their derived values quantifying the elastic recovery to plastic compression are therefore in error.

The primary advance in the work of Malamataris and coworkers (26–28) is in recognizing the effect of pore structure on the derived apparent material properties. Tablets were made at different packing fractions, the rheological model applied, and the material properties calculated from curves extrapolated to describe a fully dense or zero porosity compact. Nevertheless, rheological model concepts were formulated for homogeneous constituent materials; the direct application to porous whole tablets has not been validated.

Celik and Aulton (29) quantified time-dependent deformation by creep analysis of microindentation data. Test data in the linear viscoelastic region were deconvolved to derive viscoelastic parameters of compacts for higher order rheological models, consisting of a Maxwell unit in series with several Voigt units. Elastic compliance, contributions of the retarded elastic region to the total compliance and residual shear viscosities (in the region of nonrecoverable viscous flow) were explicitly derived from creep compliance spherical indentation experiments.

PARTICLE-BASED MODELS

Numerical simulation is commonly used in soil mechanics and metallurgy for the determination of stress distribution under complex loadings. Typical studies include that by Williamson et al. (30), which describes the densification of tin cylindrical particles in uniaxial hot pressing. A general particle level continuum model based on input of elastic properties from long and shear wave velocity test data and tensile yield data from Swinkels et al. (31) was used to provide full stress and strain fields within the particles. This model assumed an unequal sized particle distribution, elastic perfectly plastic behavior, a von Mises yield condition and power law creep without boundary diffusion. Mesh refinement along the surface of the particle served to smooth the predicted curves. The reports by Lu and Shi (32), Nolan and Kavanagh (33), or Yen and Chaki (34) exemplifies dynamic numerical Monte Carlo simulations for the isostatic pressing of a random packed green compact.

The constitutive models supplied by Wang (35) and Sinka (36) provide other examples of a finite element simulation of uniaxial compression under closed die conditions. In this case, densification conditions were confined to frictionless interaction and negligible elastic recovery due to the lateral constraints of the die walls. Likewise, Mueller (37) created numerical constructs using sequential packing models for monosized spheres with different mean packing densities. Die wall effects were included as periodic boundary conditions but the final outcome was highly dependent on the assumption of the diameter aspect ratio and the assigned coordinate system. In general, a realistic construct consists of explicit relations between stress and strain agreeing with macroscopic observations at various strain rate conditions. Correlations between macroscopic and microscopic parameters are also required.

Continuum models assume that the granular media behaves as a homogeneous medium. Although there are many simulations using continuum models, these models use equivalent flow properties derived experimentally and they cannot represent local effects. Continuum calculations are mathematically complex and yield results that sometimes differ by up to an order of magnitude from experimental values (38).

Finite element simulations are conceptually simpler but rely heavily on computing power in simulating systems. This approach involves the application of Newtonian dynamical equations to a system of impacting particles, which includes keeping track of all forces and moments at each step and integrating the equations to obtain the new state of the system. A statistical distribution is often assumed to determine the state of the particles. This statistical approach eliminates the need for some force calculations and integration routines, but it affords little flexibility. Three dimensional calculations of particle impaction are nontrivial as changes in velocity are nonplanar. The definition of the vertices of the element make up contributes to the wide variability in eventual outcomes.

Micromechanical models are also used in powder metallurgy to determine stress and density distributions during compaction, but these approaches are not so familiar in pharmaceutical powder technology. As a consequence, the few examples of models for compaction have often been directly derived from soil mechanics or metallurgy. Duncan-Hewitt and Weatherly (39), for example, adapted their model from powder metallurgy.

Particle deformation modeling, in contrast to continuum mechanical treatments, describes the response of powder compacts during densification as a framework of linked particles. The linked framework connects the centers of particles through interparticle contacts. The behavior of each link is then based on the unit problem for the interaction between individual spheres; any two contact particles form a link and carries the force that would be transmitted form one particle to another through that contact. By dealing with individual particles, it becomes possible to predict the evolution of different packings from different particle material properties. This approach bridges the gap between unit models on the level of individual particles and the continuum behavior of very large packings of particles.

The physical basis for particle based models has been experimentally verified by a number of investigators. Jagota and Dawson (40,41) validated the Voronoi cell model by comparing particle model predictions with experimental data for the packing of sintered monosized glass spheres. They proposed a truss structure to represent powder morphology based on a micromechanical framework of linked particles with local as well as global descriptions that were suited for high porosity cases. Li and Funckenbusch (42) made actual