Drug Development and Industrial Pharmacy, 22(1), 1-10 (1996)

The Past, Present, and Future of Tableting Technology

Metin Çelik

Pharmaceutical Compaction Research Laboratory & Information Center, College of Pharmacy, Rutgers University, P.O. Box 789, Piscataway, NJ 08855-0789

ABSTRACT

The evolution of tableting technology was briefly reviewed and the predictions and suggestions for the future of this field were made. The factors that would be primarily responsible for the progress in the development of the justified formulations and processes of the future were pointed out to be dependent on the successful implementation of the following concepts: universal excipient harmonization; standardized excipient functionality testing; compaction data bank; preformulation database; formulation and process expert systems; a new generation of tableting equipment; and interactive electronic reports. A case study on the use of an integrated compaction research system to evaluate the performance of customized punch displacement profiles was briefly discussed. A special emphasis was given to the first-time application (in the field of pharmaceutical technology) of a prototype interactive electronic data reporting method. Two short communication case studies were presented using the data obtained from milling and compaction studies in order to demonstrate the potential usefulness of the interactive digital data communication in the area of solid-dosage forms.

INTRODUCTION

Solid medicinal preparations in the form of tablets have been used since antiquity (1). They were called *troches* and were subsequently called *pastils* in Latin and *lozenges* in English. The most widely used solid-dosage form, however, was the pill—hence the term *pilula* was first used by the Roman encyclopedist Pliny (A.D. 23-79) in the *Encyclopedic Natural History* (A.D. 77).

The earliest reference to a dosage form resembling the tablet can be found in Arabic medical literature, in which drug particles were compressed between the ends of engraved ebony rods, the force being applied by means of a hammer. The Arabic philosopher and phy-

sician, Ibni Sina (980–1037) (also known as Avicenna, whose medical work *Quanum* was the greatest single influence on medieval medicine) prepared gold- and silver-plated pills.

The details of the tableting process as it is now known were first published in 1843 in Britain, when Thomas Brockedon was granted a patent for "shaping pills, lozenges and black lead by pressure in dies." Brockedon's original interest was in the compression of graphite powder, to produce a substitute for the natural Cumberland graphite used in lead pencils, but he soon recognized the possibilities of applying the same principle to single doses of drugs. Tablet presses were developed, and a tablet of potassium bicarbonate was soon on the commercial market.

The use of the tablets rapidly increased, especially in the United States, where the demand for large quantities of medicinal supplies during the Civil War spurred their development. Power-driven presses replaced Brockedon's hammer, and by 1874, there existed both rotary and eccentric presses that in their mode of operation were fundamentally similar to those in use at the present time. The first tablet machine to make use of a lever to obtain pressure was the Smedley compressor, invented in 1879 by Bennet L. Smedley of Philadelphia.

A monograph for *Glyceryl Trinitrate Tablets* was included in the British pharmacopeia of 1885. No other tablet monograph appeared until 1945; this, however, was due to the absence of acceptable quality control standards rather than the lack of popularity of the dosage form itself.

In 1895, an editorial in the *Pharmaceutical Journal* predicted that "tablets have had their day and will pass away to make room for something else." Despite these predictions, after a century, the pharmacopeias have hundreds of monographs for tablets, far in excess of any other dosage form.

More than 100 years ago, Bernard Proctor recognized that "pill dissolution" was a necessary prerequisite for drug absorption. Nevertheless, it was not until 1930 that pharmaceutical scientists attempted to relate in vitro testing to in vivo availability. The main criterion of the tablet maker seemed to be that the tablet should be sufficiently hard to be transported without crumbling. It is highly likely that many of those early tablets survived, unscathed, the hazards of the digestive tract.

The earliest instrumentation to control the tableting process was used in the 1930s in the form of simple mechanical or hydraulic pressure gauges fitted to some tablet machines. Modern instrumentation schemes have been almost entirely dependent on the growth of industrial electronics, developed first during the 1950s.

The first publication in this field dates, in fact, from the year 1951, and describes work done by Brake at Purdue University (2); it was followed by a series of papers from Higuchi and his coworkers (3–5). This pioneering work was made possible by the growing availability of devices such as displacement transducers, strain gauges, and linear amplifiers; today, some 40 years later, the microprocessor and microcomputer have become equally indispensable for their rapid data-processing capabilities in the same field.

In a British symposium held in 1979 on "The Pharmaceutical Industry in the Year 2001," it was predicted that compressed tablets were not likely to be superseded before the year 2001. It was felt that many formulations then on the market would still be available virtually unaltered in the year 2001 and Brockedon's revolutionary invention would be with us for some time to come.

The future of tableting will depend on the parallel evolution of the tableting equipment and the knowledge of tablet formulators, as well as its evolution as a dosage form.

UNIVERSAL EXCIPIENT HARMONIZATION AND FUNCTIONALITY TESTING

One of the most important aspects of tablet product design and development has undoubtedly been the selection of suitable excipients. Early formulators had chosen mainly either traditionally known excipients or the ones with which they were experienced. The success of the selected material is sometimes just a coincidence. Neither the number of new excipients nor the number of scientists who took the challenge of trying the new excipients was satisfactory. This was partly due to their lack of knowledge about the tabletability properties, as well as other physicomechanical characteristics, of the pharmaceutical powders. In fact, there has not been much progress in this area until recently.

Pharmacopeias were the only main reference sources for the excipients for a long period. The monographs of the excipients were included both in the United States Pharmacopeia (USP) and the National Formulary (NF) until they merged in 1970. After the merger, the monographs of the excipients appeared in the NF with the exception of those materials that function as both drug and excipient (such as mannitol, talc, etc.). The *Handbook of Pharmaceutical Excipients* (6), which was first published in 1986 under the direction of the American

Pharmaceutical Association and the Pharmaceutical Society of Great Britain, became another important reference source for pharmaceutical materials. Today, many excipient suppliers are providing users with comprehensive information on their products as well.

A recent survey by Shangraw and Demarest (7) revealed a number of interesting facts about solid-dosage formulation design and development: Lactose and microcrystalline cellulose are the most preferred fillers–binders and tradition is still a very important reason for the preference (Table 1). The use of natural ingredients as binders and disintegrants is being phased out. An overall general satisfaction was observed with present pharmaceutical excipients.

A historical problem encountered by formulation scientists has always been the lack of harmonized standards for excipients. Each of the national pharmacopeias contain monographs for specifications and test methods for only a portion of the existing excipients. However, many of these standards are not unified amongst the various pharmacopeias. In 1991, the International Pharmaceutical Excipients Council (IPEC) was formed in order to develop harmonized pharmacopeial excipient standards, harmonized GMP (good manufacturing practice) guidelines, and harmonized new excipient safety evaluation guidelines (8,9). IPECs of the U.S., Europe, and Japan joined forces to coordinate activities worldwide. IPEC has now evolved into an organization with approximately 100 pharmaceutical and excipient companies as international members. Major compendia have also agreed to address the harmonization of excipient compendial processes. These efforts will undoubtedly result in safer, cheaper, more cost-effective, and more robust products in the 21st century, and will eliminate the need to produce multiple formulations due to the varying compendial standards if that dosage form is to be marketed throughout the world.

The development of simple, affordable, reproducible, universally applicable, meaningful, and realistic functionality tests for the fingerprints of tableting ingredients is highly desired by both the excipient and pharmaceutical manufacturers. However, at present, the excipients are only tested for quality, uniformity, identity, safety, and purity. Their performance fingerprints have never been required. In 1991, the USP/NF formed a special advisory panel in order to develop internationally applicable physical test methods for basic powder properties (such as density, particle size, particle shape, etc.) as well as for applied powder properties (such as fluidity, compactability, etc.). Since then, recommendations were made for particle size characterization.

The assessment of the compaction performances of the formula ingredients is an important aspect of tablet product design and development. However, there is no standard compaction test method required by the pharmacopeias. Therefore, data obtained from two or more compaction studies usually are not comparable, since, because of the inconsistent techniques employed, the equipment (i.e., type of press and tooling), the parameters monitored (i.e., compaction speed, applied force, and punch displacement), or the methods used to manipulate the compaction data (i.e., Heckel equation, work of compaction) vary widely in these studies (10,11). Recently, Çelik and Okutgen (11) optimized the parameters of tablet weight, lubrication, equipment, tooling, punch displacement profile, pressure range, as

Table 1

Reasons for Preference of Fillers-Binders

Reasons	Lactose	Starch	Microcrystalline Cellulose	Calcium Phosphate
Solubility	19	4	9	1
Cost	15	6	3	2
Tradition	21	9	18	4
Compatibility	20	7	33	3
Uniformity of supply	14	4	26	3
Compactability	17	6	46	8
Handling	8	3	11	0
Physiological inertness	8	1	16	2
Total selections	41	12	52	8

Source: Adapted from reference 7.

well as other pre-, during, and postcompaction parameters in their compaction studies, and proposed a standard compaction functionality "tabletability" testing method capable of comparing the relative tabletability features of different materials and different lots of the same material with high sensitivity. Applying this test method, the authors generated "compaction fingerprints" for a number of commonly used tableting excipients in order to establish a compaction data bank that can eventually be utilized as an informative reference source in tablet formulation studies.

PREFORMULATION DATABASE, FORMULATION AND PROCESS EXPERT SYSTEMS

Physicochemical particulate properties (including particle density, size, shape, and distribution; crystal density, habit, order/disorder state, hardness, and hygroscopicity) and mechanical properties (including elasticity, plasticity, and brittleness) dictate how formulations will behave during tablet processing and ultimately perform as a drug delivery system. Therefore, preformulation is the first step in the rational development of all dosage forms. Since the number of tableting excipients is limited (although it may be a large number), it is highly feasible to establish a preformulation database by generating information on the above properties of the excipients and the most commonly used drug substances. The information contained in such a database can then form the foundation of a formulation and process expert system.

It is quite common in formulation development studies that the formulation scientist has the precise knowledge of the active ingredients that are to be compacted into a tablet form and yet still needs to know which excipients to select, and their proportions. At this stage, a knowledge-based formulation and process expert system can be helpful to the scientist in selecting suitable excipients using information accumulated in the database. The outcome may heavily depend on the desired dissolution, disintegration, and mechanical properties of the final tablets as specified by the scientist.

Another case where such an expert system could facilitate tablet formulation studies is in the determination of the optimum manufacturing conditions. For example, the parameters of the compaction force and speed become highly critical when time-dependent materials are involved in the formulation. In this case, higher applied forces may not necessarily mean higher tablet strength, and higher compaction speeds may cause some tableting problems, such as capping.

When compared to the human experts, the expert systems have the following advantages: the knowledge of an expert system is permanent and can be easily transferable; the decision process is consistent (therefore, it is predictable) and can easily be documented. Despite these advantages, the formulation and process expert systems are not intended to take the place of the formulation scientists. They must be considered as vital tools to be used by the formulators for a rapid, cost-effective and scientific development of a dosage form as well as for training unexperienced scientists.

CONVENTIONAL AND NONCONVENTIONAL TABLET PRESSES

The fundamentals of the operations of many existing "conventional" rotary presses are still essentially similar to those that were in use several decades ago, although today's presses are faster, have better instrumentation, and comply with GMP regulations. Despite the rapid rate of production, most modern machines are still not satisfactory due to their inability to accommodate the variation in the properties of the feedstock and to adapt quickly to the changing characteristics of the material being compressed (12).

The technology is available for the development of innovative "nonconventional" tablet presses if alternative operation modes are needed. Table 2 lists some of the current and desired features of both existing and innovative tablet presses.

In most of the available rotary presses, the principle of powder filling is volumetric. As the formulation flows from the hopper through the feeders into the dies, there might be variation in the fill weight of the formulations with poor flow characteristics. This could lead

Table 2

Features of the Current "Conventional" and Future "Nonconventional" Presses

Conventional Tablet Presses	Nonconventional Tablet Presses
Volumetric fill	Weight fill option
Constant punch separation	Constant applied pressure option
Rigid cam design	Flexible actuator design

to content uniformity problems as well as variation in tablet hardness. The ultimate solution to the former problem would be the design and development of a press that would have an option for weight fill, or, at least, possess a better powder-feeding mechanism. In fact, a new-generation tablet press with a different powder-filling mechanism and compaction cycle has recently been developed by an Italian manufacturer (13). The novelty of this press resides in the sideways filling of the die with the formulation at the center of the rotating die table and piped to the dies through special holes. The centrifugal force generated by the turret rotation causes the dies to fill.

Most of the existing rotary presses move the upper and lower punches through a rigid cam. When the punches reach the fixed-compression rollers and start to enter the die, the compaction load is exerted on the powder until a preset distance between the two punches is attained. This constant punch separation governs the magnitude of the load applied. Depending on the physicomechanical properties of the material being compacted, any weight variation within the die can cause an increase or decrease in the amount of load applied, resulting in a variation in the thickness and strength of the tablet, which may possibly cause some posttableting problems such as inconsistent disintegration, dissolution, and bioavailability profiles.

Using a compaction simulator, Rubinstein and others (14) mimicked the action of a rotary machine using both compression to a constant force and to a constant thickness. Ibuprofen tablets compacted to a constant force within pharmacopeial weight variation limits exhibited consistent tensile strength and disintegration times, even when tablet weight varied from 460 mg to 540 mg. On the contrary, when the tablets were made under constant thickness conditions (to mimick the rotary presses), significant variations were observed in both the thickness and the disintegration times of the resulting tablets.

The conventional rotary presses are generally capable of applying both a pre- and a main compaction load. However, the flexibility of altering the type of punch profiles is limited, since these machines have a rigid cam design, i.e., the punches follow the same path regardless of the material being compacted. If a tablet production press could have a programmable flexible actuator design (similar to that of the ICRS), it would allow the users to customize the punch profiles for a given formulation without any need to modify the formulation to run on a specific tablet press. As suggested by Driscoll and others (15), such a press would be able to make tablets under both displacement (for constant punch separation) and load control (for constant applied force) using single- or double-ended sawtooth, sine wave, and other profiles. The following case study is an example to show the effects of punch profile on the mechanical properties of the tablets.

Tablets from a directly compressible formulation consisting of ibuprofen (67.5%), microcrystalline cellulose (30%), talc (2%), and magnesium stearate (0.5%) were made employing the ICRS fitted with a 10.3 mm, round, flat-faced, BB tooling using the displacement (double-ended sawtooth and sine wave) and load (single-ended) punch profiles (Figure 1). The magnitude of the applied load, the effective contact time, and the area under force versus time profiles were kept constant. It was observed that the tablets made using the load profile exhibited almost twice the strength when compared to those made under the displacement profiles, suggesting that production types of presses with customized profiles would indeed be useful in eliminating many common tabletability problems. In fact, such machines can also be programmed to run using many other combinations between the pre- and main compaction events by altering the ratio, magnitude, and duration of the pre- and main compaction forces as well as including a

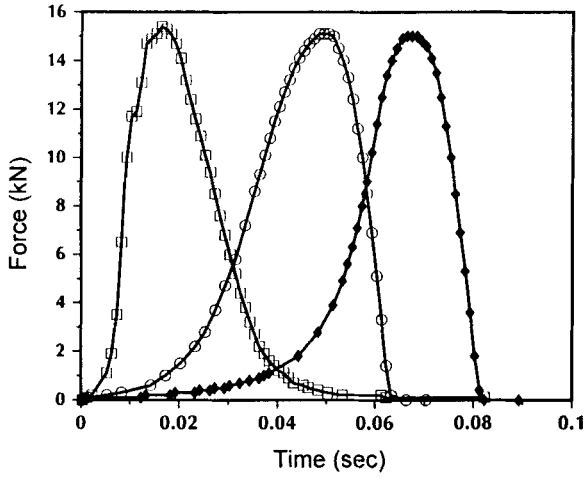

Figure 1. Force versus time profiles for the ibuprofen tablets made using various punch profiles: load controlled (□); displacement-controlled sine wave (○) and displacement-controlled sawtooth (◆).

Effective contact time, msec	(□) 61	(○) 61	(◆) 74
Area under curve (F-t), kN/sec	(□) 0.32	(○) 0.39	(◆) 0.34
Crushing force values, N	(□) 64	(○) 30	(◆) 39

bridging force (a residual force that would remain between the pre- and main compaction events).

INTERACTIVE ELECTRONIC REPORT

A growing number of scientists, especially in the field of physics, are using the Internet to directly disseminate their papers to each other as part of a more flexible system that is expected to progressively replace print journals (16). The National Science Foundation has recently funded a theoretical physicist at Los Alamos National Laboratory in the amount of $1 million to develop software for electronic printing, and to expand this concept into physics and other areas of science. Software will be developed to provide such features as links to citations, images, and data, as well as a mechanism for commentary by readers. Over 25,000 users worldwide are already archiving 45,000 electronic transactions per day. However, researchers in the area of pharmaceutical sciences, as well as many other fields, are not yet posting their research findings in the form of digital prints to the Internet or an electronic journal. Utilization of digital scientific information in this field, for example, for determining the physicochemical and mechanical properties of powders, as well as the optimum manufacturing process conditions of a product, could undoubtedly have a profound effect on the design and rapid development of a satisfactory pharmaceutical dosage form.

Çelik (17) has recently developed a prototype interactive electronic report (IER) on milling in order to compare the performances of Quadro-Comil Models 193 and 197 milling equipment. The IER has two essential components: a software program and data files. The former component of the prototype IER allows the reader to select any combination of the following parameters of milling in order to examine the comparative data: mill type (two models); impeller shape (two types); screen opening (three sizes); milling speed (three levels). The reader has the option to evaluate the results statistically or graphically using either percentage frequency vs. particle size (as bar or line) or cumulative under percent vs. particle size plots. The data can also be presented in the tabular form, which can be exported as ASCII data, if desired. It is also possible to import data in order to integrate the literature (or the reader's own) data with those reported in the IER. Figure 2 shows a printout of the screen from the above report. In this example, using cumulative under percent plots, one examines the effects of screen size and speed of impeller rotation on the particle size distribution of sodium chloride. In this case, the mill (Model 193) is attached with a compressive impeller. The results show that the effect of speed is insignificant when a screen with small holes (045 R031-37 has an opening of approximately 0.114 mm) is employed. However, when a screen with larger holes (094 R037-41 has an opening of approximately 0.238 mm) is used, the particle size distribution of sodium chloride is significantly affected by the speed of impeller rotation. The full IER of this case study will soon be available both in the form of a traditional publication and, for interested readers, on digital floppy disks. The readers of this article are strongly encouraged to contact and collaborate with the author in order to widen the application of this new interactive electronic data sharing technique in pharmaceutical solid technology.

As mentioned earlier, one of the problems associated with the utilization of compaction data in the literature is that there is no universal standard data evaluation method. This problem can be eliminated or minimized, if the results are presented in an interactive digital form. In fact, compaction data are quite suitable for an application of the IER on tableting studies. This is demonstrated with the following case study in which the compaction properties of anhydrous and dihydrate forms of dicalcium phosphate (Emcompress, Mendell) were compared.

In this case study, the materials used were internally lubricated with 0.5% (w/w) magnesium stearate prior to tableting. A predetermined amount of each sample (corresponding to 0.25 cc absolute volume of that material) was compacted employing an integrated compaction research system (ICRS), which was fitted with a 10.3 mm round, flat-faced, standard BB tooling, over a wide range of applied pressures and at a constant punch velocity of 100 mm/sec. The monitored parameters of compaction were the forces on and the displacements of the upper and lower punches. The methods used to analyze the data were described elsewhere (18).

Figure 3 compares the crushing force versus applied force profiles of the two forms of dicalcium phosphate. The anhydrous form of dicalcium phosphate produced stronger tablets than those of its dihydrate form. Figure 4, which presents the percentage porosity (E %) versus mean applied pressure plots for the compacts tested, shows that the dihydrate form of this material is highly

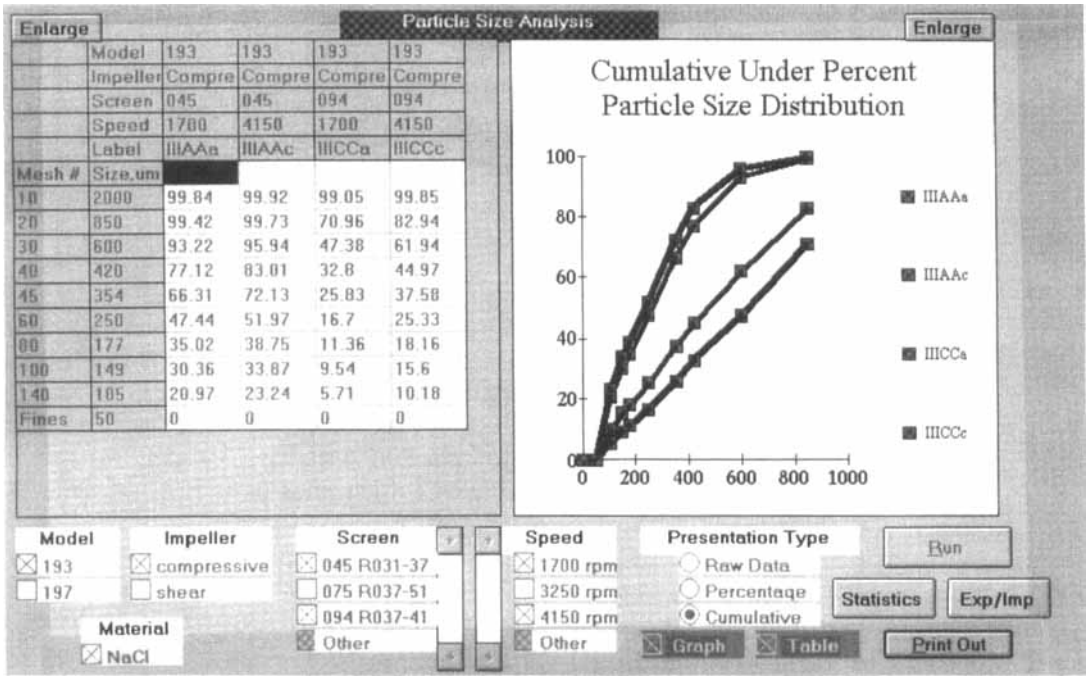

Figure 2. A typical display from the interactive electronic report on the comparison of two models of Quadro-Comil milling equipment.

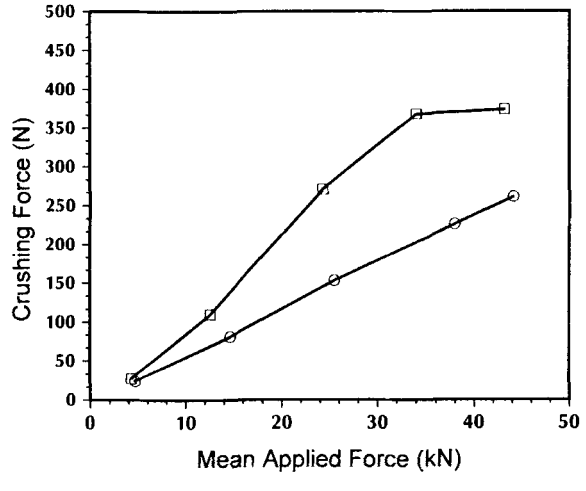

Figure 3. Crushing force versus mean applied load plots for the anhydrous (□) and dihydrate forms (○) of dicalcium phosphate compacts made at a constant punch velocity of 100 mm/sec.

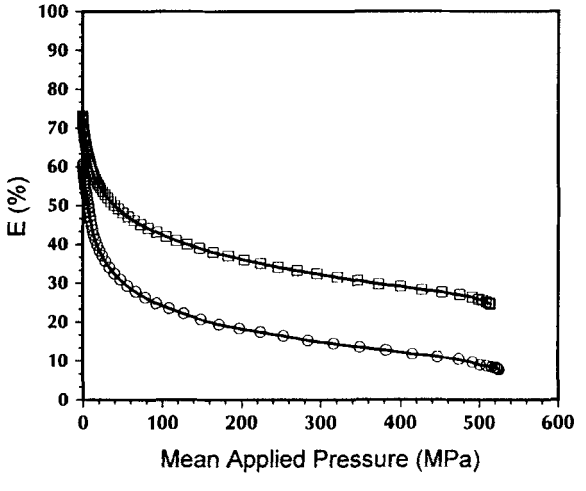

Figure 4. Percentage porosity versus mean applied pressure plots for the anhydrous (□) and dihydrate forms (○) of dicalcium phosphate compacts made at a constant punch velocity of 100 mm/sec.

compressible when compared to its anhydrous form, suggesting that higher compressibility does not necessarily mean higher strength. Tablets possessing higher strength usually absorb more energy during compaction. This is further evidenced by the data presented in the plots of total work of compaction (TWC) vs. pressure (Figure 5) in which compacts of the anhydrous form of dicalcium phosphate exhibited more energy utilization when compared to the compacts of its dihydrate form.

The way that the data were presented and interpreted in this case study is commonly encountered in the literature, although, the interpretation was deliberately kept brief here, as the purpose of this article was not to predict the compaction behavior of different forms of dicalcium phosphate, but to discuss a potential application of the IER using the data obtained from this study. The discussion below lists some of the advantages of presenting the above data in the form of the IER.

First, the method of presenting tablet strength using crushing force vs. applied force profiles has some limitations when the results of two different studies are to be compared, especially when tooling with different sizes are employed. The data can be normalized by using crushing strength versus applied pressure plots. Since the dimensions of the tooling were given, it is possible to convert the x-axis data (applied force values) to pressure. However, it is not possible to convert the y-axis data (crushing force values) to crushing strength as the thickness and the diameter of the individual tablets were not given. If the data were available in the form of IER, it would be easy to import the thickness and diameter values to make the necessary conversions.

Second, although percentage porosity plots are commonly used to measure the ability of a material to reduce in volume as a function of applied pressure (Figure 4), another common way of utilizing the porosity data is the use of Heckel plots ([ln (1/E)] vs. applied pressure), which give more information about the densification properties and deformation mechanisms of the materials tested (Figure 6). The author does not usually present both methods in the same article even though no extra measurement is needed to obtain both plots. Using the IER method, both plots can be obtained almost instantly. In addition, the reader can have the option to determine the linearity of different parts (initial densification portion, high pressure range, unloading zone, etc.) of the Heckel plots.

Third, the rank-order TWC versus pressure profiles do not always correlate with the rank order of crushing force/strength versus pressure plots (19). However, when the TWC values are plotted as a function of percentage porosity (Figure 7), more meaningful data interpretation is possible, since the latter plots allow direct analysis of how much energy is needed to reduce the porosity of a compact to a known level. For example, the compacts of the anhydrous form of dicalcium phosphate required much more energy to attain, such as a 25% porosity level, and exhibited higher strength than those of the dihydrate form (Figures 3 and 7).

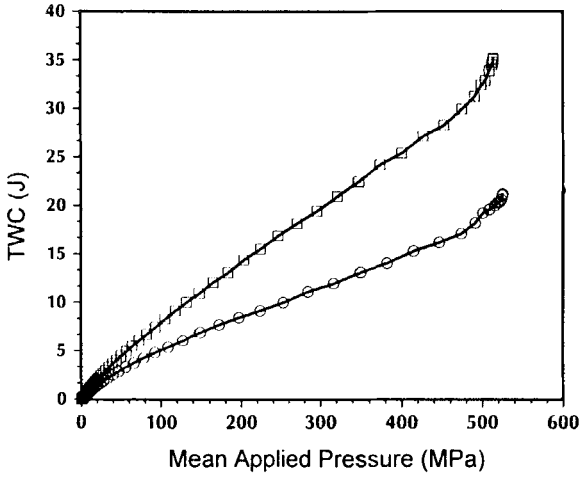

Figure 5. Total work of compaction versus mean applied pressure plots for the compacts of anhydrous (□) and dihydrate forms (○) of dicalcium phosphate made at a constant punch velocity of 100 mm/sec.

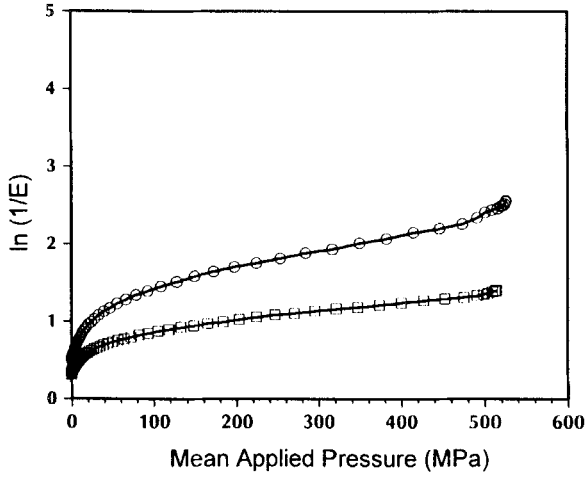

Figure 6. Heckel plots for the compacts of anhydrous (□) and dihydrate forms (○) of dicalcium phosphate made at a constant punch velocity of 100 mm/sec.

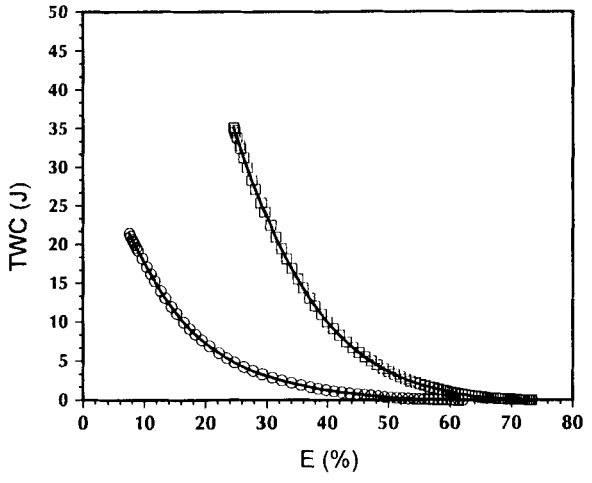

Figure 7. Total work of compaction versus percentage porosity plots for the compacts of anhydrous (□) and dihydrate forms (○) of dicalcium phosphate made at a constant punch velocity of 100 mm/sec.

Other advantages of the potential application of the IER to the compaction studies include the following flexibilities to the reader: examination of data by the use of many other user-selected compaction equations (for example, F-D curves, power of compaction, Kawakita equation, etc.); selection of alternative parameters of compaction data evaluation method (for example, instead of total work of compaction, the reader can select net work of compaction, elastic energy, work done on the lower punch, etc.); examination of even very "busy" plots (by omitting some curves temporarily contrary to hard copy where the curves are omitted permanently for the sake of clarity); rapid and easy utilization of the data in formulation studies by exporting/importing the data; and establishment of preformulation and compaction data banks. The use of IERs will also force the authors to include complete information (such as punch deformation data, the measurements of weight, thickness, diameter, etc., of the individual tablets) for a comprehensive evaluation of their data by the readers. This will not only discipline the workers to report their data more completely, but will also help with the implementation of somewhat standardized reports on compaction studies.

CONCLUSIONS

The pharmaceutical industry is entering the 21st century, which will be a new era that is far more scientific, technologic, and sophisticated than anyone would have imagined just a quarter of a century ago. However, the continued success in the field of solid-dosage forms and other areas of pharmaceutical science will depend entirely on how fast pharmaceutical scientists will adapt to the rapidly changing technology.

It is not difficult to predict that, in the 21st century, trial-and-error formulation development will be a part of history. Pharmaceutical scientists will enjoy the availability of the harmonized and fingerprinted (in terms of functionality testing) excipients, and formulations will be developed utilizing databases (preformulation and compaction data banks, etc.) and expert systems (formulation and processes). The highly likely development of a new-generation tablet press with better powder-feeding mechanisms and formulation-customized load applications will minimize and/or eliminate many tableting problems such as capping, weight and hardness variations, etc. Scientific communication will be very rapid and comprehensive because of the future implementation of the electronic presentations/publications of the scientific data.

Finally, the future of tableting will depend on organizational restructuring, intense competition, and shifting of corporate values, as well as on the tablet's evolution as a dosage form.

REFERENCES

1. G. B. Griffenhagen, Pharm. Technol., 4(3), 45 (1980).
2. E. F. Brake, M.S. Thesis, Purdue University, West Lafayette, IN (1951).
3. T. Higuchi, E. Nelson, and L. W. Busse, J. Pharm. Assoc. Sci. Ed., 41, 93 (1952).
4. T. Higuchi, E. Nelson, and L. W. Busse, J. Pharm. Assoc. Sci. Ed., 43, 344 (1954).
5. E. Nelson, J. Am. Pharm. Assoc. Sci. Ed., 44, 494 (1955).
6. Handbook of Pharmaceutical Excipients, published by the American Pharmaceutical Association and the Pharmaceutical Society of Great Britain (1986).
7. R. F. Shangraw and D. A. Demarest, Pharm. Technol., 17(1), 32 (1993).
8. Louis Blecher, Pharm. Technol., 15(6), 54 (1991).
9. Louis Blecher, Pharm. Technol., 17(2), 38 (1993).
10. M. Çelik, Drug Dev. & Ind. Pharm., 18, 767 (1992).
11. M. Çelik and E. Okutgen, Drug Dev. & Ind. Pharm., 19, 2309 (1993).
12. M. H. Rubinstein, Pharm. Technol. Int., 4, 28 (1992).
13. P. L. Catellani, P. Santi, E. Gasperini, S. Ciceri, G.

Dondi, and P. Colombo, Int. J. Pharmaceutics, 88, 285 (1992).
14. M. H. Rubinstein, S. D. Bateman, and H. S. Thacker, Pharm. Technol. Int., 15, 150 (1991).
15. C. E. Driscoll, E. Okutgen, and M. Çelik, Pharm. Research, 11(10), S132 (1994).
16. Franklin Hoke, The Scientists, 9(7), 3 (1995).
17. Metin Çelik, Tableting Technology in the Year 2001, 5th Annual Symposium on the Solid Dosage Technology of the PCRL&IC, Piscataway, NJ (1995).
18. M. Çelik and K. Marshall, Drug Dev. & Ind. Pharm., 15, 759 (1989).
19. M. Çelik and L. Maganti, Drug Dev. & Ind. Pharm., 20(20), 3151 (1994).