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Review Article

Predictive and correlative techniques for the design, optimisation and manufacture of solid dosage forms

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Abstract

There is much interest in predicting the properties of pharmaceutical dosage forms from the properties of the raw materials they contain. Achieving this with reasonable accuracy would aid the faster development and manufacture of dosage forms. A variety of approaches to prediction or correlation of properties are reviewed. These approaches have variable accuracy, with no single technique yet able to provide an accurate prediction of the overall properties of the dosage form. However, there have been some successes in predicting trends within a formulation series based on the physicochemical and mechanical properties of raw materials, predicting process scale-up through mechanical characterisation of materials and predicting product characteristics by process monitoring. Advances in information technology have increased predictive capability and accuracy by facilitating the analysis of complex multivariate data, mapping formulation characteristics and capturing past knowledge and experience.

Introduction

The vast majority of medicinal products are presented to patients as tablets or capsules. In recent times, the pharmaceutical industry has undergone a period of great change. There is increasing pressure on pharmaceutical companies to reduce the time from drug discovery to marketed product, to reduce costs and maximise the patent life and profitability of a product. Product development scientists are required to produce robust dosage forms, which may be manufactured over a range of scales with minimal time and cost. This need has encouraged the development of predictive techniques that may have benefits in reducing the time taken to develop suitable formulation and process parameters. Prediction may also have benefits in full-scale production if the causes of product variation can be identified and controlled. Predictive techniques have been used at many stages of the product development process, including selection and optimisation of formulations, prediction of process scale-up capability, control of process end-points and predicting the properties of processed material. Prediction has been shown to offer greater control, understanding and confidence in dosage-form properties, with a corresponding increase in product quality. This review summarises the predictive techniques used, to date, in the formulation and fabrication of solid dosage forms, along with some of the precedents for predictive techniques set outside the pharmaceutical industry.

Predictive/correlative techniques

Techniques used to predict the properties of solid dosage forms can be divided into three categories: predictions based on the physicochemical properties of raw materials, the mechanical properties of raw materials or process monitoring.

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Predictions based on the physicochemical properties of raw materials

Raw-material-based predictions have used knowledge of the physicochemical properties and the molecular structure of raw materials to predict and optimise formulation properties.

Surface energy and solubility parameters Surface interactions are important in defining the properties of solid dosage forms. Adhesive and cohesive forces can be calculated from surface energy and solubility parameter values of the raw materials. The spreading coefficient (the ability of a liquid to wet a substrate) can also be derived. For a comprehensive discussion on the measurement and theory of surface energetics, the reader is referred to reviews by Buckton (1995a, b) and Hancock et al (1997). These parameters have provided an insight into the interactions between formulation components and have been used as a basis to predict blending, granulation, compression and film-coating behaviour.

- *Surface energy and blending processes*. Rowe (1988a, b) used solubility parameters to predict powder blending behaviour. In a simple binary system, the adhesive interactions of magnesium stearate and microcrystalline cellulose and their effect on tablet tensile strength were studied. The results were in agreement with the predicted behaviour (a reduction in tablet tensile strength with increasing magnesium stearate concentration). Addition of a third component (colloidal silica) also had a predictable effect (partial recovery of tensile strength) (Rowe 1988a, b, 1992).

Rowe (1989a, 1992) also studied the mixing of water-insoluble colorants (red iron oxide and carbon black) with a model formulation and found that a homogenous blend was obtained when the adhesive interactions between components were lower than the cohesive interactions within components. Ahfat et al (1997) suggested that surface-energy data was more effective at predicting blending behaviour than were solubility parameters, as surface-energy measurements account for surface heterogeneity effects, whereas the solubility parameter is an approximation based on the structure of the bulk material. However, surface energy is only one factor which influences blending, and Barra et al (1998, 2001) demonstrated the importance of including both particle-size and surface-energy effects in blend prediction.

- *Surface energy and granulation*. Rowe (1988c, 1989b, c) proposed that if the spreading coefficient of a binder over a substrate were positive, then the binder would flow, adhere to and form a film around the substrate, resulting in a strong dense granule. However, if the spreading coefficient were negative, the substrate would adhere to the binder but a binder film would not be formed around the substrate. Bonds between particles would only be formed between isolated patches of binder on the substrate, resulting in weak porous granules. Several authors have subsequently demonstrated the accuracy of these predictions (Rowe 1990; Zajic & Buckton 1990; Planinsek et al 2000).

Rowe (1990) demonstrated, during the granulation of paracetamol, that the strongest granules, and consequently tablets, were formed using binder solutions with the highest spreading coefficient. Granules prepared using binders with low spreading coefficients were more susceptible to capping on compression, indicative of lower bond strength between particles in these systems. Zajic & Buckton (1990) and Planinsek et al (2000) used a similar approach to predict the friability of granules and demonstrated that binder solutions with higher spreading coefficients produced less friable granules with improved flow properties. In addition, Planinsek et al (2000) were able to determine an optimum binder concentration based on the relative adhesive and cohesive forces of the components. The binders used had a lower cohesive force than the adhesive force between the binder and substrate.

- *Surface energy and compression*. Evidence has been provided to suggest that tablet tensile strength may be predicted from surface-energy measurements. El-Gindy & Samaha (1983) showed that for a series of plastically deforming materials, tablet tensile strength increased with an increase in surface free energy.

- *Surface energy and film coating*. Effective tablet film coating requires efficient spreading of the coating solution, and strong adhesion of the dried film to the tablet surface. Rowe (1988c) was able to predict the adhesion of a series of cellulose derivative film coats to both lactose and microcrystalline cellulose compacts using solubility parameters. Several authors have since identified limitations in using surface-energy approaches to predict film adhesion. Khan et al (2001) showed that the adhesion of hydroxypropyl methylcellulose (HPMC) films to tablets was significantly altered by the addition of polysorbate, polyethylene glycol and lactose. However, the spreading coefficient of the HPMC film-coating solutions remained largely unaffected by the addition of the additives, indicating that the spreading coefficients were not predictive of film adhesion in this case. This was possibly a result of the additives being present in concentrated form in the dried film, compared with the relatively dilute coating solution.

The pressure used to compact the tablet may also affect the predictions. Felton & McGinity (1999) suggested that film adhesion is influenced by surface roughness in addition to surface energy. A rough surface may increase the interfacial contact area between the film and the tablet substrate, resulting in a higher adhesion force, although Khan et al (2001) found there to be an increase in film adhesion at high compression pressures, where the surface should be smoother. This may have been a result of a change in substrate surface energy at high compression pressures as previously suggested by Buckton & Newton (1986).

Mechanical and physicochemical predictions from molecular structure

Several attempts have been made at predicting the physicochemical properties of materials from their molecular and crystal structure (Roberts et al 1991, 1995, 2000; Newton et

al 1993; Sheridan et al 1995; Payne et al 1996, 1999). The ability of a powder to deform and adhere during compression is critical in tablet manufacture. The need for effective and reliable prediction of mechanical properties has stimulated many publications in this area. Roberts et al (1991, 1995) and Newton et al (1993) originally used the cohesive energy density of powders to predict the tensile strength and Young's modulus of compacts prepared from a series of simple molecular solids. It was concluded that while trends could be predicted, the exact magnitude of the change could not be predicted, possibly as a result of the influence of particle size, changes in deformation mechanics with pressure and the unpredictable nature of cracks and flaws within the material.

Payne et al (1996) and Roberts et al (2000) demonstrated a more reliable molecular modelling approach for predicting mechanical properties. They used a mechanical model of the crystal structure to calculate the crystal lattice energy, from which Young's modulus could be calculated. Using this approach, it was possible to predict the Young's modulus for a series of compacts prepared from aspirin and polymorphs of primidone, carbamazepine and sulfathiazole. For this model, crystals with a high aspect ratio (needle-form crystals) introduced slight predictive errors, as these tend to have a preferred alignment within the compact, thereby altering the mechanical properties.

Molecular modelling has been developed further to predict the conformation of potential polymorphs using the crystal structure (Payne et al 1999). Potential packing structures are ranked according to their free energy; those structures with the lowest energy are the most thermodynamically stable and therefore the most likely polymorphs.

Sheridan et al (1995) predicted the physicochemical properties of compounds using molecular modelling. Three molecular orbital indices were calculated using the molecular models – electron density, frontier electron density and superdelocalisability index, which predicts the probability of a reaction occurring at a particular atomic centre of a molecule. For the series of compounds studied, superdelocalisability indices for hydrogen-bonding functional groups were found to be most predictive of the surface energy of a molecule. The fact that molecular orientation across a crystal surface may change during processing is a limitation of this approach.

Mechanical properties of the bulk material

Several techniques have been used to measure the mechanical properties of the bulk material to predict the material's processing characteristics, such as granulation, flow and compaction properties.

Mixer torque rheometry Mixer torque rheometry has been used extensively to characterise the rheological properties of wet granulations (Rowe & Sadeghnejad 1987; Parker et al 1990, 1991; Hancock et al 1994; Rowe 1996a). The torque generated during mixing is believed to be proportional to the cohesiveness of the powder (Parker et al 1990) and is typically measured as a function of the volume of binder liquid added to the powder (Hancock et al 1994).

Studies using the mixer torque rheometer have focussed on three key areas: formulation optimisation, identifying source variation in materials and scale up of granulation processes.

- *Formulation optimisation*. The effect of binder and substrate characteristics on granule properties has been studied using the mixer torque rheometer. Parker et al (1990, 1991) showed that increasing the concentration and viscosity of HPMC and polyvinylpyrrolidone (PVP) binders resulted in increased granule cohesion. However, significant differences were noted between binders at equivalent viscosity, with granules containing HPMC having a lower torque value compared with granules containing PVP binder. It was suggested this was a result of preferential absorption of HPMC onto microcrystalline cellulose particles resulting in a reduction in intra-granular viscosity (Parker et al 1990, 1991). Hancock et al (1994) assessed the granulation characteristics of hydrophilic and hydrophobic glass ballotini using mixer torque rheometry. It was found that overwetting occurred at lower liquid contents with PVP for a hydrophilic substrate and with HPMC for a hydrophobic substrate. The spreading of HPMC over a hydrophilic substrate was predicted to be greater from surface-energy data, enabling stable granules to be formed even at elevated liquid contents. The effect of substrate particle size on granule characteristics has also been demonstrated. Rowe (1995) studied the granulation of binary mixes of microcrystalline cellulose with two particle-size fractions of lactose. This showed that increasing the particle size of the lactose increased the cohesion of the granules at maximum torque, as predicted.

- *Material variation*. Parker & Rowe (1991) showed differences in the sensitivity of granulation end point and the cohesive strength of granules produced from microcrystalline cellulose obtained from three different suppliers. In addition, Rowe & Parker (1994) showed that the consistency of granules may also be affected by changing the batch of drug substance used in the formulation. It has been suggested that differences in granulation behaviour of material from different sources or batches may be a result of differences in particulate properties (Rowe & Parker 1994).

- *Process scale-up*. Rowe & Parker (1994) proposed a method for predicting granulation characteristics during process scale-up, using mixer torque rheometry. Variation of wet-mass consistency at different granulation end-points is used to construct a calibration curve for the Power number (related to the flow pattern of the powder within the mixer) against the Pseudo Reynolds number, which defines the viscous forces of the mass. Both the Reynolds number and Power number are independent of the scale of mixer. Granulations are produced on progressively larger-scale equipment, by calculating the required power at

granulation end-point and the consistency of the granules is checked using the mixer torque rheometer. This methodology has subsequently been refined by including the Froude number, which corrects for the gross vortexing and fluctuations in powder bed height that occur in large-scale granulators (Landin et al 1996).

Powder flow characterisation techniques Powder flow has a strong influence on dosage-form weight uniformity. Powder flow is thought to relate to inter-particulate cohesion and friction, and most flow characterisation techniques measure these properties either directly or indirectly.

• *Angle of repose*. Free flowing powders falling onto a platform under gravitational force will form a cone of powder, as described by Train (1958). The angle between the horizontal and the slope of this cone is known as the angle of repose, with more-free-flowing powders exhibiting a lower angle.

Several authors have shown that angle of repose measurements are predictive of tablet and capsule fill-weight uniformity (Colombo et al 1978; Dahlinder et al 1982; Nyqvist & Nicklasson 1985; Tan & Newton 1990a). In contrast, other researchers have suggested that angle of repose is a poor measure of powder flow (Amidon & Houghton 1985; Fassihi & Kanfer 1986; Munoz-Ruiz et al 1993a, b; Antequera et al 1994). Angle of repose measurements may only be used for free-flowing powders (Newton 1987) and are believed to lack sufficient sensitivity and reproducibility to discriminate between broadly similar powders (Amidon & Houghton 1985). Hedge et al (1985) attempted to address these issues by measuring the angle of repose in a rotating cylinder to eliminate operator variability. However, concerns were still raised as to whether this technique was an effective measure of powder flow.

• *Compressibility index*. Several indices relate the compressibility of a powder to its flow properties (Carr's index, Hausner ratio, Kawakita equation) (Podczeck 1998). These parameters measure the changes in powder bed density on tapping: a greater increase in powder bed density is indicative of high inter-particle cohesion and poor powder flow. In addition, Varthalis & Pilpel (1976) defined the angle of internal flow from tapped density experiments.

Carr's index, Hausner ratio and the angle of internal flow have been used to predict tablet and capsule weight uniformity with varying degrees of success (Nyqvist & Nicklasson 1985; Fassihi & Kanfer 1986; Newton & Bader 1987; Tan & Newton 1990a; Munoz-Ruiz et al 1993a, b; Antequera et al 1994; Amidon & Houghton 1995; Podczeck & Newton 1999). While compressibility indices appear more predictive than angle of repose measurements (Amidon & Houghton 1995), there are several instances where the correlation with dosage-form weight uniformity has been poor (Doelker 1993; Podczeck & Newton 2000). Podczeck & Newton (2000) showed that for the addition of small quantities of magnesium stearate to powdered cellulose, Carr's index measurements lacked sufficient sensitivity to predict small changes in flow and capsule fill-weight uniformity. In addition, Doelker (1993) demonstrated that the Hausner ratio was a poor predictor of tablet weight uniformity for microcrystalline cellulose powders. It has been suggested that the variation in compressibility index measurements increases for more cohesive powders and should be used in combination with other flow characterisation techniques, as one method cannot adequately characterise all the factors that influence powder flow (Amidon & Houghton 1985).

• *Hopper measurements*. Several techniques have measured powder flow through hopper systems. These techniques include measuring the mass of powder that flows through a hopper within a defined time period and measuring the minimum hopper orifice that causes arching and blockage of powder flow (Gioia 1980).

Munoz-Ruiz et al (1993a, b) showed that mass flow rate through a hopper could be used to predict the weight uniformity of maltodextrin tablets and correlated well with compressibility index values. Antequera et al (1994), Velasco et al (1995) and Dahlinder et al (1982) found that minimum blocking aperture and mass flow rate were predictive of tablet weight uniformity. However, Doelker (1993) suggested that mass flow rate was a poor predictor of tablet weight uniformity and lacked correlation with compressibility indices. A limitation of this technique is that it is only suitable for measuring free flowing powders (Newton 1987; Antequera et al 1994).

• *Shear cells*. The rheology of powders under shear stress is used as a measure of inter-particle attractive forces and powder flow. The shear properties of powders depend upon the normal load applied to the powder bed. Powder is packed into two halves of a cylinder and consolidated at a series of normal loads under shear stress. For a detailed review of shear-cell measurements and derived indices, the reader is referred to Podczeck (1998). Shear-cell measurements are considered more reliable for measuring powder flow and for predicting weight uniformity than other flow characterisation techniques described above. The shear-cell approach is also suitable for measuring the flow of both cohesive and free-flowing powders (Amidon & Houghton 1985). Several authors have successfully used shear cell measurements to predict tablet and capsule fill-weight uniformity (Nyqvist 1982; Amidon & Houghton 1985; Nyqvist & Nicklasson 1985; Tan & Newton 1990a).

A drawback of the shear-cell approach is the wide variety of methods and shear-cell apparatus available, which can lead to variability and lack of correlation between measurements (Antequera et al 1994). For example, Ramachandruni & Hoag (2001) demonstrated that instrument and process parameters can significantly affect the results obtained. The technique is also considered to be time consuming and laborious (Velasco et al 1995).

• *Powder avalanche behaviour*. The avalanching behaviour of a powder may be used to measure its flow properties. The Aeroflow Instrument (Faure et al 1999) has been used to study this. Faure et al (1999, 2001) studied the effect of

wet-mass consistency, prior to drying, on the flow properties of the dried granules, using the Hausner ratio and avalanching behaviour. The Hausner ratio and time between avalanches of the dried granules decreased with an increase in wet-mass consistency, indicative of improved granule flow.

• *Powder rheometry*. Flow characterisation techniques have often suffered through a lack of sensitivity and high variation between measurements. Powder rheometry measures the flow, compaction and cohesion properties of powders in response to the stresses imposed by a moving rotor blade (Podczeck 1999a, b).

Podczeck (1999a, b) used powder rheometry to study the flow and packing properties of different grades of microcrystalline cellulose. Podczeck (1999b) concluded that, with appropriate methodology, the powder rheometer was able to detect small differences in the flow and packing properties of microcrystalline cellulose, which could not be detected from Carr's index measurements. Podczeck & Newton (2000) also studied the effect of small quantities of magnesium stearate on the flow properties of powdered cellulose using Carr's index, shear cell and powder rheometry measurements. Powder rheometry and shear-cell measurements predicted capsule fill-weight uniformity with greater accuracy than Carr's index measurements. Powder rheometry has an advantage over shear-cell methods in that testing is rapid and simpler to perform. Powder rheometry has also been used for the study of wet powder masses. Luukkonen et al (2001) studied the wet-massing behaviour of microcrystalline cellulose in both a powder rheometer and a mixer torque rheometer. The powder rheometer followed a similar torque pattern to mixer torque rheometry on liquid addition.

• *Mercury porosimetry*. Guerin et al (1999) attempted to develop a micro-technique using mercury porosimetry to characterise flow behaviour. They concluded that mercury porosimetry was more sensitive than tap testing and discriminated between powders with similar flow properties.

Tablet compaction and capsule filling simulation

• *Tablet machine simulation*. The tablet machine (or compaction) simulator has considerable benefits as a predictive technique as it can mimic, in real time, the compression cycle of any tablet press and provide a means for characterising the compaction properties of drugs and formulations using a small quantity of material (Celik & Marshall 1989). The perceived disadvantage of compaction simulators is that they are expensive and studies are often time consuming (Celik & Marshall 1989). For a comprehensive review on compaction simulation in tabletting research, the reader should refer to Celik & Marshall (1989) and Nokhodchi & Rubinstein (1996).

Jain (1999) reviewed some of the indices that are generated using compaction simulation to characterise a powder's compaction and compression properties. In brief, the main indices quoted are: mean yield pressure, which is the mean pressure above which a material irreversibly deforms; strain-rate sensitivity, which describes the effect of punch speed on mean yield pressure; work of compaction, which includes both the plastic compaction energy (recoverable) and elastic compaction energy (lost) during a particular compression event; the compression pressure–tablet tensile strength relationship; and elastic recovery of tablets post compression. Compaction simulators have principally been used for mechanical property characterisation, for formulation optimisation and prediction of scale-up and for prediction and selection of suitable compression settings.

During preformulation assessment of a new drug entity for oral delivery, an understanding of the material's basic mechanical properties is required. Nichols & Frampton (1998) and Garekani et al (1999) studied the effect of crystal habit on the compression properties of paracetamol. Polyhedral crystals were more compressible than plate-like crystals as a result of increased plastic deformation, as seen by a reduced mean yield pressure and an increase in tablet tensile strength. Marshall & York (1991) and Sun & Grant (2001b) showed that plate-like crystals were more compressible than prism-shaped and needle-like crystals for nitrofurantoin and L-lysine monohydrochloride, respectively. The increase in compressibility was possibly a result of greater plasticity or a closer packing structure on compression. Sun & Grant (2001a) have also studied the compaction properties of different L-lysine salts and found that tablet tensile strength decreased with increasing yield strength of the salt. However at high compaction pressures, tensile strength was determined predominantly by interparticle bonding rather than yield pressure.

Compaction simulators may also be used to study the mechanical properties of excipients. Bolhuis et al (2001) compared the compaction properties of different hydrates of calcium lactate. Calcium lactate pentahydrate was found to have low strain-rate sensitivity and a high bonding capacity, indicating its suitability as a filler in direct compression formulations. Yang et al (1996) studied the compaction properties of polyethylene oxide (PEO) polymers for controlled-release applications. PEO polymers had low yield pressures that were highly dependent on punch speed (i.e. high strain-rate sensitivity), suggesting a need to blend PEO with highly compactable excipients to manufacture tablets on a high-speed press.

Once characterised, the mechanical properties of both drugs and excipients can be used as input parameters in expert systems to predict the most suitable formulation. Characterising the basic mechanical properties of drugs and excipients may also aid in setting material specification limits. Evidence has been provided to suggest that compaction properties may vary as a function of crystallinity for microcrystalline cellulose (Suzuki & Nakagami 1999) and water content for HPMC (Malamataris & Karidas 1994; Nokhodchi et al 1996b, c) and maltodextrin (Li & Peck 1990), indicating the need for control of these materials.

Compaction simulators may be used during formulation optimisation. Asgharnejad & Storey (1996) studied the effect of process and formulation variables on the compression properties of an experimental drug using a

compaction simulator. The drug substance had a relatively high yield pressure that varied as a function of compression speed, indicating that the drug deformed by a mixture of plastic flow and brittle fracture. To improve compression properties the drug was wet granulated with plastically deforming excipients, which increased the tensile strength and reduced the capping tendency of the resultant compacts. From the compaction simulation data, the final formula was successfully predicted as suitable for scale up from a single punch to a high-speed rotary tablet press. Celik et al (1996) studied the effect of formulation variables on the compression properties of a drug substance with poor intrinsic compression properties. Stronger tablets were formed with increasing amounts of microcrystalline cellulose in the formulation, as a result of increased plastic deformation.

Several authors have attempted to predict the optimum formula for binary mixtures from a knowledge of the compaction properties of individual components. Vachon & Chulia (1999) successfully used a linear plot of net work of compression normalised to powder volume against compact strength of individual components, to predict the tensile strength of both binary and ternary mixtures. However, the compaction properties of mixtures may not always be linearly related to the compaction properties of the individual components. van Veen et al (2000) attempted to predict the tensile strength of sodium chloride and pregelatinised starch compacts from the compaction properties of the individual components. The tensile strength of the tablets was lower than predicted. This was attributed to non-linear behaviour of the two materials in combination.

Capping (the cracking of tablets on decompression) is a potential problem in tablet manufacture. Sugimori & Kawashima (1997) developed a method for predicting the capping tendency of tablets by correlating the residual die wall pressure (measured using a strain gauge) with the axial crushing strength of a cylindrical compact. Capping occurred when the residual die wall pressure exceeded the tablet crushing strength. Equations were developed to predict suitable tablet components and tablet shapes to reduce capping tendency.

Compaction simulators may also be used to study and optimise the pre-processing of materials during product formulation. Omelczuk et al (1997) studied the effect of micronisation on the compaction properties of an investigational drug. Micronised drug produced stronger tablets than unmicronised, possibly as a result of an increase in surface area and surface energy. The increase in tensile strength was observed in formulated compacts with a 65% drug loading, but there was little difference in tablet tensile strength between micronised and unmicronised drug in formulated compacts at 30% drug loading. Suihko et al (2000) assessed the effect of molecularly dispersing and physically blending tolbutamide and hydroxypropyl-β-cyclodextrin on compression properties of the mixture. Molecularly dispersed material showed reduced elastic and plastic deformation, suggesting a more rigid crystal structure.

Several authors (Garr & Rubinstein 1991; Marshall et al 1993; Nokhodchi et al 1996a; Lahrhib et al 1997) have studied the effect of varying compression settings on the compaction properties of materials in an attempt to predict suitable compression settings during manufacture. The key variables during compression are pressure and speed. Pre-compression can also be used on high-speed presses. All of these variables can be studied on a compaction simulator.

For plastically deforming materials such as HPMC and polyethylene glycol, there is increased resistance to deformation at higher punch speeds, due to a disproportionate increase in elastic energy (Nokhodchi et al 1996a; Lahrhib et al 1997). In extreme cases (e.g. paracetamol and ibuprofen), higher punch speeds can lead to capping and lamination (Garr & Rubinstein 1991; Marshall et al 1993). The addition of plastically deforming microcrystalline cellulose or brittle di-calcium phosphate reduced the capping tendency of paracetamol compacts (Garr & Rubinstein 1991). Pre-compression is often used for materials that undergo a high degree of elastic deformation or capping and is believed to remove air from the powder bed, preventing it from expanding during compression, or to increase the dwell time allowing for greater plastic deformation (Bateman et al 1990). Pre-compression has been shown to increase the tensile strength of ibuprofen and paracetamol compacts (Bateman et al 1990; Ruegger & Celik 2000). Optimum settings were achieved when the pre-compression pressure was lower than the main compression pressure, due to a reduction in elastic energy. Akande et al (1998) studied the effect of lag time and dwell time during pre-compression and main compression on the strength of paracetamol/microcrystalline cellulose tablets. Generally, an increase in dwell time resulted in the formation of stronger tablets, while the lag time between pre and main compression had little effect. All these studies show that compaction simulation may be useful in predicting behaviour of formulations and suitable process parameters for tablet manufacture.

• *Capsule filling simulation*. Capsule machines may be categorised according to the filling method used (tamp or dosator) and whether they are continuous or intermittent. All of these machines rely on the formation of a loosely packed plug of material of consistent weight and volume that is dosed into the capsule shell (Jones 2001). Several attempts have been made to produce a capsule filling machine simulator to predict the performance of capsule formulations on a range of filling machines during process scale up (Jolliffe et al 1982; Britten & Barnett 1991; Britten et al 1995; Heda et al 1999). However, this has not been as successful or received as much attention as compaction simulators. In contrast to tablet compaction simulators, capsule-filling-machine simulators have tried to model more parts of the capsule-filling process (powder-bed preparation as well as plug formation), increasing the complexity of the equipment.

Tan & Newton (1990b, c, d) studied the effects of compression settings on powder plug properties, using an mG2 dosator filling machine simulator. In capsule filling, the minimum compression setting should be used to assist plug retention within the dosator nozzle, as compression may

affect both weight uniformity and the drug release profile. Tan & Newton (1990b) calculated the minimum compression requirements for powder retention within a dosator nozzle for a range of powders. The magnitude of compression was found to be both particle-size and material dependent. Calculated stress requirements for powder retention were generally too low to measure, although the filling performance of the powders supported the theoretical values. Tan & Newton (1990c) subsequently found that for microcrystalline cellulose, calcium carbonate and starch 1500, powder was retained and the most reproducible fill weights were achieved when no compression was applied. Increasing compression resulted in an increase in coating of the dosator wall and a reduction in weight uniformity. Tan & Newton (1990d) found that the coating of the dosator wall resulted in significantly lower plug densities than predicted.

Using a modified compaction simulator with punches to match size-1 tamping pins, a long die to simulate the length of a capsule plug and a speed to simulate tamping speed, Heda et al (1999) simulated powder plug formation. For a coherent plug to be formed, it is necessary for force to be transmitted throughout the powder plug. Heda et al (1999) demonstrated that force transmission and thus plug integrity were dependent on the length of plug and the material used.

Process monitoring

Process monitoring techniques involve measuring changes in either process parameters or the physicochemical properties of the material during processing and predicting the properties of the final product.

Near infrared spectroscopy Near infrared (NIR) spectroscopy measures the absorbance of near infrared radiation (700–2500 nm) (Martens & Martens 1992) by molecules, resulting from the vibration of intermolecular bonds. In the NIR region absorbance is low, enabling analysis of most drugs and excipients without prior sample preparation. In addition, both the chemical and physical environment of the bond affects the absorption of NIR radiation, enabling the monitoring and prediction of both chemical and physical changes in solid dosage forms. The application of NIR in solid dosage form processes is becoming increasingly widespread. For reviews on the use of NIR spectroscopy in the pharmaceutical industry, refer to Morisseau & Rhodes (1995) and Blanco et al (1998b).

NIR has found both qualitative and quantitative applications in the pharmaceutical industry, due to being a rapid, non-destructive method of analysis. For quantitative applications, the spectral output is calibrated against a reference technique using multivariate statistical analysis. Advances in instrumentation allow NIR analysis to be performed either at-line, or through the use of fibre optic probes in-line. This has particular advantages in process monitoring and prediction of process end-point, as current information on the process can be gathered in real-time, allowing operators to respond to changes in the process immediately.

NIR has been applied at all stages of solid dosage form manufacture including raw material analysis, blending, granulation, compression and film coating. Candolfi et al (1999) used NIR to identify a range of excipients commonly used in tablet manufacture, providing a rapid method for identifying materials without using conventional time consuming analytical techniques. NIR is also sensitive to physical changes such as changes in particle size, which has allowed both the median and cumulative particle size of a range of excipients to be measured prior to manufacture (Frake et al 1998; O'Neil et al 1999).

During blending operations it is necessary to obtain a homogenous mix without segregation. There is a need for reliable models to predict process end-point, which may vary between different blend compositions, and between multiple runs of identical blends (El-Hagrasy et al 2001). Several authors have described either at-line (Wargo & Drennen 1996) or in-line (Hailey et al 1996; Sekulic et al 1998; El-Hagrasy et al 2001) NIR systems for qualitatively predicting mixing end-point. These systems typically measure the variation in NIR spectra in both the time and wavelength domains and the blend is considered to be homogenous when the spectra converge to constant variance. NIR is also suitable for quantitatively measuring the concentration of components within powder blends. Patel et al (2000) described a quantitative approach for identifying two different polymorphs of sulfamethoxazole within both binary and multi-component powder blends, which is difficult to achieve using conventional analytical techniques.

NIR is suitable for monitoring and predicting the end-points of granulation and drying operations, as it is sensitive to changes in both particle size and the distribution of water. Rantanen et al (1998, 2000) qualitatively predicted granulation end-points for a range of different formulations, with an associated error of 0.2%. As a result of its sensitivity to changes in chemical composition, Rasanen et al (2001) used NIR to study polymorphic conversion of anhydrous theophylline to theophylline monohydrate during wet granulation. NIR was able to detect polymorphic conversion in a faster, more flexible and more controlled manner than with conventional analytical techniques. Frake et al (1997) described a system for the qualitative in-line monitoring of a fluid bed drying process, which requires tight process control to ensure consistency of the output material. An increase in absorbance was seen with time resulting from an increase in granule particle size. By monitoring changes in the spectral peaks associated with water it was possible to measure the gradual decline in water content with time. Morris et al (2000) applied NIR for accurate end-point prediction in a fast drying process, where end point was more critical than conventional drying processes.

NIR has been used during tablet compaction to predict the effect of compression pressure on tablet hardness (Kirsch & Drennen 1995; Morriseau & Rhodes 1995; 1997; Chen et al 2001). An increase in compression pressure and tablet hardness is typically characterised by greater NIR absorbance (Morriseau & Rhodes 1997). One of the problems associated with NIR is calibration and validation

of models as slight variation in spectral peaks can invalidate a model. Kirsch & Drennen (1999) developed a refined tablet hardness model, which reduced the spectra to a slope and intercept, averaging out the influence of individual spectral features. This model was found to be a reliable predictor of tablet hardness.

During the film coating of tablets, the thickness of the applied coat is important, particularly for controlled-release coatings, where it can influence drug release rate. Many methods of measuring film thickness are time consuming and indirect, such as measuring the weight gain of samples of tablets as the process proceeds. Kirsch & Drennen (1996) and Andersson et al (1999) have demonstrated the capability of NIR for predicting film-coat thickness and process end-point to a low limit of quantification (0.1–0.2 mm). NIR has also displayed great potential in predicting the properties of the final dosage form. In addition to tablet hardness and film-coat thickness, NIR has been used to predict the dissolution rate of dosage forms (Kirsch & Drennen 1995), drug content (Blanco et al 1998a, 2000; Chen et al 2001) and quantifying the decomposition of acetylsalicylic acid into salicylic acid in aspirin tablets (Drennen & Lodder 1990). Many models can be combined and a series of tablet properties can be predicted from a single spectrum (Kirsch & Drennen 1995). With faster acquisition times it may be possible to measure these properties on every tablet in-line, in contrast to many of the destructive techniques currently used, which rely on representative sampling.

NIR has additional applications during the filling of gelatin capsules. The moisture content of a capsule can influence drug release as well as processing characteristics. If the moisture content is too low, the capsules become brittle and may fracture; if the moisture content is too high, the capsule shells soften and become sticky. Buice et al (1995) and Berntsson et al (1997) demonstrated the on-line use of NIR to predict the moisture content of gelatin capsules. Herkert et al (2001) used NIR in combination with automated visual inspection equipment as a 100% identity check for capsules within a blister pack on a packaging line. The system identified and rejected every faulty capsule on the line, thus offering greater assurance of product quality.

Acoustic monitoring Acoustic monitoring involves detecting and analysing the sound signals emitted by a particular process or system, the frequency of which are generally higher than those that can be detected by the human ear. Acoustic monitoring employs the use of a series of sensors fitted around the system of interest. Processes that emit acoustic signals include mixing, grinding, fluidisation and compaction, thus this technique has potential use in monitoring these processes.

Whitaker et al (2000) used acoustic emission to determine the end-point of a high-shear granulation process and to predict the flow, particle size and compression properties of the resultant granules. These studies showed a clear correlation between the acoustic signals generated on addition of different binder volumes, and particle size and flow properties post granulation. When the granules were subjected to further milling and blending with lubricants, the correlations between the acoustic signals during granulation and particle size, flow and compaction properties were less significant. Tsujimoto et al (2000) used acoustic emission to predict process end-point in a fluidised bed dryer. An acoustic emission sensor was calibrated using various fluidisation conditions with spherical granules. Using the acoustic calibration model it was possible to predict the onset of unstable fluidisation and bed collapse resulting from excess moisture.

Several authors have used acoustic emission techniques to monitor the deformation and compaction characteristics of materials (Waring et al 1987; Wong et al 1991; Hakanen & Laine 1993, 1995). Wong et al (1991) demonstrated a difference between the deformation mechanics of single crystals of lactose monohydrate and anhydrous lactose using acoustic emission and micro-indentation tests. Anhydrous lactose crystals were mechanically weaker than lactose monohydrate crystals and emitted acoustic signals with lower amplitude. Assuming single crystals were representative of the bulk material, acoustic emission could be used to predict the compaction properties of materials. Waring et al (1987) and Hakanen & Laine (1993, 1995) studied the compaction properties of lactose, sodium chloride, microcrystalline cellulose and paracetamol. Quantitatively analysing the acoustic peaks associated with particle rearrangement, compression and decompression may enable the deformation mechanism and capping tendency of materials to be predicted.

Monitoring changes in process parameters Historically, the torque, power, or current drawn by the impeller blade of a granulator has been used to measure and predict granulation end-point. The variation and gradual increase in power consumption is attributed to the evolution of strength within the wet granule mass (Leuenberger 1982; Faure et al 2001). Power consumption has been studied extensively for monitoring granulation end-point and predicting granule characteristics (Stamm & Paris 1985; Ritala et al 1988; Elbers et al 1992; Kopcha et al 1992). A limitation of this approach is that it does not take into account the gradual increase in granule diameter as the process proceeds. Ohike et al (1999) and Talu et al (2001) used a stress probe inserted into the granulation chamber, to correlate the stress fluctuations generated during granulation with changes in granule diameter, thus offering a more reliable approach for predicting granulation end-point.

Imaging systems Watano (2001) described a novel imaging system for controlling granulation growth and identifying the process end-point in fluid bed and high-shear granulators. The system consisted of an image probe, which collected real-time images of the granules within the granulator, and a fuzzy logic control system. The control system enabled accurate control of binder volume and flow rate to ensure the desired mean granule diameter was achieved.

Artificial intelligence (in-silico formulation)

Many of the approaches detailed in this review so far have attempted to predict the properties of a dosage form using a single physicochemical or mechanical measure of the formulation constituents. The success of these approaches has often been limited by the fact that dosage-form properties are dictated by a complex set of physicochemical and mechanical properties, and processing conditions. Advances in information technology have been used to manage complex multivariate information, to map processes and formulation characteristics and to capture and retain formulation experience and expertise. This had led to a significant increase in predictive power and capability.

Artificial neural networks

Artificial neural networks (ANNs) are predictive tools that mimic the learning behaviour of the human brain to recognise patterns and correlations in non-linear datasets. The multivariate nature of formulations can make ANNs a useful approach. The neurons in an ANN are arranged in a network architecture that may vary depending on the problem being modelled. The ANN typically consists of an input layer and output layer interconnected through one or more hidden layers, which perform the mapping functions. The weights of the various connections are modified through a process of training. The most common form of training used for formulation systems is supervised back propagation training, which adjusts the weights of the connections between neurons by back propagation of errors to bring the predicted output closer to the experimental output. Once trained, the ANN can predict the outcome of a set of formulation or process variables on product performance and vice-versa (Hussain et al 1994; Rowe 1996b; Takayama et al 1999; Agatonovic-Krustin & Beresford 2000).

During product development, ANNs have been used primarily for formulation and process optimisation. Several authors have used ANNs to predict the effect of process and formulation variables, such as lubricant type, compression pressure and the duration of lubricant mixing on the crushing strength and disintegration time of tablets (Turkoglu et al 1995; Bourquin et al 1998a, b, c; Rocksloh et al 1999). ANNs have also proved beneficial in the optimisation of drug release rate from controlled-release formulations, which are particularly complex in terms of the number of interacting factors which influence drug release (Hussain et al 1994; Bozic et al 1997; Wu et al 2000).

In addition to optimising the properties of the final dosage form, ANNs have proved useful in optimising the properties of process intermediates. Murtoniemi et al (1994) and Watano et al (1997) used an ANN to predict the effect of process variables on the size, friability, density and shape of granules produced in a fluid bed dryer. ANNs may also be used as early as the preformulation stage to predict the properties of materials. Ebube et al (2000) used an ANN in preformulation to predict the water uptake, glass transition temperature and viscosity of a range of polymers and their blends.

Genetic algorithms are another artificial intelligence technique, which may be used in product formulation. The genetic algorithm begins by assessing a range of parent solutions in terms of how well they fit a specified problem. The successive generations of solutions are formed either by random change (mutation) or by combining fragments of earlier solutions (reproduction). As in natural evolution, only the best solutions to a problem will survive. The use of genetic algorithms in product formulation has been less widespread than ANN. However, genetic algorithms may be more effective than ANNs in finding solutions for certain problems. Turkoglu et al (1999) predicted the effect of formulation and process variables on tablets produced using a roll compaction process. These studies suggested that the predictions generated using genetic algorithms were more accurate than ANNs in this instance.

Expert systems

Expert systems are computer-based programmes, which retain and capture the knowledge and experience of experts within a defined area. The use of an expert system as a predictive tool is less obvious than some of the techniques discussed previously, though experts, by their very nature, attempt to predict and anticipate the outcome of their decisions and actions. Expert systems consist of a user interface, a knowledge base, which captures and retains expert knowledge, and an inference engine, which consults the knowledge base to draw conclusions and potential solutions to the current problem. Knowledge for expert systems may be acquired through interviews with experts, extensive literature reviews or, more recently, through neuro-fuzzy logic technology which generates rules based on previous studies (Rowe & Colbourn 2000). The effectiveness and span of application of an expert system is controlled by the amount and validity of the data within the knowledge base.

The inference engine typically operates using either rule-based induction or case-based reasoning. Rule-based induction uses a series of rules to link pieces of information together, for instance if the system recognises a certain condition (e.g. the drug is poorly soluble), then it will propose an appropriate action (use a soluble filler) based on the knowledge within the expert system. This process can be refined further by imposing certain conditions (e.g. select an alternative filler if the drug is incompatible with certain soluble fillers) (Rowe 1993a, b). In case-based reasoning, the expert system recognises certain situations and recalls previous solutions to similar problems. The solution is either used directly, or adapted to account for differences between the current and previous problems (Keen 1993; Aamodt & Plaza 1994).

Expert systems are commonly used in tablet and capsule formulation to predict the type and quantity of excipients based on the properties of a drug substance (Ramani et al 1992; Rowe 1993a, b; Bateman et al 1996; Lai et al 1996). The user inputs the relevant physicochemical and mechanical properties of the drug substance along with the product specification. The system will predict the type and quantity of excipients required to meet the product speci-

fication, using the knowledge base and inference engine for a number of suggested formulations. The formulator will test the conformance of the predicted formulations with the product specification and feed the information back to the expert system, further modifying the formulation if necessary. Ramani et al (1992) suggested that the use of an expert system to predict formulations led to a 35% reduction in drug development time.

Additional applications for expert systems within the pharmaceutical industry have included selection of pharmaceutical mixers based on the flow, strength, size/shape and segregation propensity of particles (Lai 1988), identification and solution of film coating defects during tabletting (Rowe & Upjohn 1993a, b) and diagnosis and solution of breakdown causes for high-speed rotary tablet presses (Murray 1989).

Precedents outside the pharmaceutical industry

It has been suggested that the pharmaceutical industry is conservative in the implementation of new technology compared with other industries, as a result of the stringent regulatory control imposed on the development and manufacture of pharmaceuticals. While the truth of this statement is hard to verify objectively, there are several predictive technologies employed in other industries, which have not yet been widely adopted for pharmaceutical formulations.

Predictive process control

Predictive process control has successfully been applied in the food and chemical industries for controlling evaporation, drying, coating, distillation and polymerisation reactions and can be viewed as a combination of process monitoring and artificial intelligence (Braatz et al 1992; Dutton 1997; Krishnan & Hoo 1999; Voorakaranam & Joseph 1999). In a simple process, the output may vary linearly with a single variable, allowing the operator to adjust and control the process in response to changes in the variable. In practice, this situation rarely occurs and the process output is often related to a multiplicity of non-linear, interacting variables. Process control is therefore reliant upon the operator's experience in estimating when the process is likely to fluctuate out of specification. Tools such as statistical process control may assist process monitoring, but this is retrospective and there may be a substantial lag time between the process deviating away from specification and the operator's ability to respond, leading to a lack of process control. Predictive control monitors the process through a range of sensors (may be NIR, acoustics, temperature, pressure, moisture) and anticipates problems based on a well-defined process model. The process control software predicts if the process is about to deviate out of specification and modifies the variables immediately, ensuring that the process remains within specification (Dutton 1997). The process model, which is central in predictive process control, can be developed using either multivariate calibration methods (Voorakaranam & Joseph 1999) or ANNs (Gurumoorthy & Kosanovich 1998). However, there is a trade off between model robustness and sensitivity compared with the speed of response. Predictive control has resulted in significant improvements in product quality, process yield, waste reduction and minimisation of process down-time (Dutton 1997).

Braatz et al (1997) controlled a substrate coating process, using predictive process control. A predictive controlled process was able to reduce variance in substrate thickness by as much as 80% compared with manual process control in combination with process monitoring. Voorakaranam & Joseph (1999) applied predictive process control during the manufacture of fibre–resin composites for the aerospace industry. The use of fibre–resin complexes is often limited as the process is expensive due to poor control and high product wastage. Predictive process control significantly improved process control, reducing product wastage and costs. Krishnan & Hoo (1999) used predictive process control during the scale-up of a chemical batch reactor process, and showed that it was possible to develop reliable predictive models over a range of process scales. The only published use of predictive process control in pharmaceutical manufacturing appears to be in the synthesis of drug substances, and the fermentation of penicillin (Gurumoorthy & Kosanovich 1998; Krishnan & Hoo 1999).

Computer simulation

Increases in computational power have seen greater use of computer simulations for predicting powder flow and deformation properties in the ceramics, food and metallurgy industries. One of the most widely used computer simulation approaches is finite element analysis (FEA). FEA simulates the compaction process by dividing the powder bed into a series of discrete elements. The stress–strain behaviour within each individual element on compression is calculated using a defined constitutive model, which may include elastic, plastic and viscoelastic deformation (Aydin et al 1996). The computer simulation sums the stress–strain behaviour of all the individual elements and the simulated behaviour is believed to represent the real powder undergoing compaction. The predictive accuracy of the simulation is dependent on the constitutive model used, and Jin & Cristescu (1998) suggested that general models to simulate powder materials are still in the development stage. However, FEA has been used to describe mechanical behaviour and structure during compaction, unloading and ejection along with the friction generated at the powder die-wall interface (Mori et al 1999).

Aydin et al (1996) predicted the density distributions within ceramic compacts and demonstrated an excellent agreement between observed and predicted values. It can be envisaged that FEA could be used as a design tool to calculate the density distribution of pharmaceutical tablets, correlating the density distribution with tablet disintegration and drug release rates. Mori et al (1999) used FEA to predict the fracture of metal compacts on ejection. Fracture is initiated in compacts above a critical tensile stress by differing amounts of elastic recovery during ejection. Stress–strain distributions were calculated using FEA during unloading, using a model of the powder

between punches during compression and ejection. Using the correct constitutive model for pharmaceutical powders it may be possible to predict which compacts, and under which conditions, will cap and laminate on ejection.

A criticism of FEA is that it often assumes that particles exist entirely as spheres, which is frequently not the case with pharmaceutical materials. Smith & Midha (1997) used an alternative approach termed random sphere construction (RSC), which constructs irregular particles from a series of overlapping spheres. During powder metallurgy processes particle packing is critical, as a low density prior to compaction could result in a structurally weak compact being produced. Smith & Midha (1997) suggested that RSC could be used on-line to predict packing densities from particle morphology during powder metallurgy processes. In addition, Tamura et al (1998) demonstrated that computer simulation could be used to predict and model, simultaneously, flow and compaction of powder within a die.

A potential problem with using computer simulation for pharmaceutical systems is that they are often multi-component in nature, thus complicating the selection of an appropriate constitutive model.

Conclusions and the future of predictive techniques

The predictive techniques described in this review can be divided into three broad categories: firstly, theoretical predictions based on the physicochemical properties of raw materials (surface energy and molecular modelling); secondly, predictions relating to the mechanical properties of the bulk material (mixer torque rheometry, flow characterisation, compaction simulation); and thirdly, process monitoring techniques which monitor changes in process and material characteristics in-process to predict the properties of dosage forms or intermediates (NIR, acoustics, imaging systems).

Historically, attempts were made to predict the properties of a dosage form or an intermediate using a single univariate parameter (e.g. predicting granule properties based purely on the surface energy of the substrate and binder). In reality, the science of prediction is far more complex and the outcome may be related to an array of interacting parameters. Advances in information technology have provided a platform for developing artificial intelligence systems and software capable of analysing complex datasets. Artificial intelligence has led to a marked increase in predictive accuracy on both the effect of formulation constituents and process parameters on the properties of solid dosage forms. A criticism of artificial intelligence is that all predictive techniques require some degree of training, where predictive accuracy is influenced by over- or under-training and the reliability is hampered by limitations such as an incomplete understanding of all the factors affecting a model. However, increases in computational power and understanding have seen rapid advances in predictive technology and this trend appears to be continuing.

The development of techniques capable of measuring the mechanical properties of small quantities of material, such as flow characterisation techniques, mixer torque rheometry and compaction simulators, has enabled predictions on the processing characteristics of materials to be made and validated on a small scale, bringing significant advances in the prediction of process scale-up capability. Process monitoring techniques have enabled process end-points and the properties of dosage forms to be controlled and

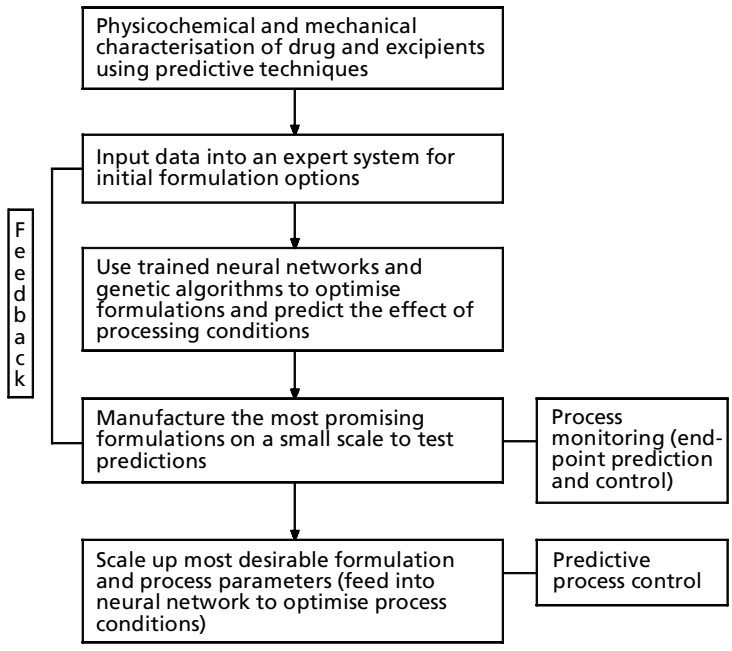

Figure 1 Flow diagram of a suggested product development cycle incorporating predictive techniques.

predicted with greater accuracy. The techniques described in this review in isolation have proved beneficial in predictive science. However, significant gains are attainable within solid dosage form development, if these techniques are used together as a complete battery of predictive techniques. Figure 1 outlines how the predictive techniques already in use can cover a wide range of formulation design and manufacture processes.

Techniques which have not yet been widely adopted in pharmaceutical formulation and manufacture are computational simulations of processes, computer-aided dosage-form design and predictive control of manufacturing processes. It is feasible that virtual product development may become possible if existing techniques can be integrated and further developed, resulting in substantial reductions in development time and costs associated with the use of large quantities of expensive drug substance. Experimentation will still be essential to provide validation of predictions and the development of models. The skills base of formulation science may change to accommodate this, further incorporating material sciences, chemical engineering, advanced statistics and computer programming, in addition to an understanding of the application of these techniques to pharmaceutical sciences.

References

Aamodt, A., Plaza, E. (1994) Case-based reasoning: foundational issues, methodological variations, and system approaches. *AI. Comm.* **7**: 39–59

Agatonovic-Krustin, S., Beresford, R. (2000) Basic concepts of artificial neural network (ANN) modelling and its application in pharmaceutical research. *J. Pharm. Biomed. Anal.* **22**: 717–727

Ahfat, N. M., Buckton, G., Burrows, R., Ticehurst, M. D. (1997) Predicting mixing performance using surface energy measurements. *Int. J. Pharmaceutics* **156**: 89–95

Akande, O. F., Ford, J. L., Rowe, P. H., Rubinstein, M. H. (1998) The effects of lag time and dwell time on the compaction properties of 1:1 paracetamol/microcrystalline cellulose tablets prepared by pre-compression and main compression. *J. Pharm. Pharmacol.* **50**: 19–28

Amidon, G. E., Houghton, M. E. (1985) Powder flow testing in preformulation and formulation development. *Pharm. Manuf.* **2**: 20–31

Amidon, G. E., Houghton, M. E. (1995) The effect of moisture on the mechanical and powder flow properties of microcrystalline cellulose. *Pharm. Res.* **12**: 923–929

Andersson, M., Josefson, M., Langkilde, F. W., Wahlund, K. G. (1999) Monitoring of a film coating process for tablets using near infrared reflectance spectrometry. *J. Pharm. Biomed. Anal.* **20**: 27–37

Antequera, M. V. V., Munoz-Ruiz, A., Mondero-Perales, M. C., Munoz-Munoz, N., Jimenez-Castellanos Ballesteros, M. R. (1994) Evaluation of an adequate method of estimating flowability according to powder characteristics. *Int. J. Pharmaceutics* **103**: 155–161

Asgharnejad, M., Storey, D. E. (1996) Application of a compaction simulator to the design of a high dose tablet formulation. Part I. *Drug Dev. Ind. Pharm.* **22**: 967–975

Aydin, I., Briscoe, B. J., Sanliturk, K. Y. (1996) The internal form of compacted ceramic components: a comparison of a finite element modelling with experiment. *Powder Technol.* **89**: 239–254

Barra, J., Lescure, F., Falson-Rieg, F., Doelker, E. (1998) Can the organisation of a binary mix be predicted from the surface energy, cohesion parameter and particle size of its components? *Pharm. Res.* **15**: 1727–1736

Barra, J., Bustmante, P., Doelker, E. (2001) Use of the solubility parameter and surface energy concepts in the formulation of solid dosage forms. *STP Pharma. Sci.* **9**: 293–305

Bateman, S. D., Rubinstein, M. H., Thacker, H. S. (1990) Pre- and main compression in tabletting. *Pharm. Technol. Int.* **2**: 30–36

Bateman, S. D., Verlin, J., Russo, M., Guillot, M., Laughlin, S. M. (1996) The development and validation of a capsule formulation knowledge based system. *Pharm. Technol.* **20**: 174–184

Berntsson, O., Zackrisson, G., Ostling, G. (1997) Determination of moisture in hard gelatin capsules using near infrared spectroscopy: applications to at-line process control of pharmaceuticals. *J. Pharm. Biomed. Anal.* **15**: 895–900

Blanco, M., Coello, J., Iturriaga, H., Maspoch, S., Serrano, D. (1998a) Near infrared analytical control of pharmaceuticals. A single calibration model from mixed phase to coated tablets. *Analyst* **123**: 2307–2312

Blanco, M., Coello, J., Iturriaga, H., Maspoch, S., de la Pezuela, C. (1998b) Near infrared spectroscopy in the pharmaceutical industry. *Analyst* **123**: 135R–150R

Blanco, M., Eustaquio, A., Gonzalez, J. M., Serrano, D. (2000) Identification and quantitation assays of intact tablets of two related pharmaceutical preparations by reflectance near-infrared spectroscopy. *J. Pharm. Biomed. Anal.* **22**: 139–148

Bolhuis, G. K., Eissens, A. C., Zoestbergen, E. (2001) DC calcium lactate, a new filler-binder for direct compaction of tablets. *Int. J. Pharmaceutics* **221**: 77–86

Bourquin, J., Scmidli, H., van Hoogevest, P., Leuenberger, H. (1998a) Comparison of artificial neural networks (ANN) with classical modelling techniques using different experimental designs and data from a galenical study on a solid dosage form. *Eur. J. Pharm. Sci.* **6**: 287–300

Bourquin, J., Scmidli, H., van Hoogevest, P., Leuenberger, H. (1998b) Advantages of artificial neural networks (ANN) as alternative modelling technique for data sets showing non-linear relationships using data from a galenical study on solid dosage form. *Eur. J. Pharm. Sci.* **7**: 5–16

Bourquin, J., Scmidli, H., van Hoogevest, P., Leuenberger, H. (1998c) Pitfalls of artificial neural networks (ANN) modelling technique for data sets containing outlier measurements using a study on mixture properties of a direct compressed dosage form. *Eur. J. Pharm. Sci.* **7**: 17–28

Bozic, D. Z., Vrecer, F., Kozjek, F. (1997) Optimisation of diclofenac sodium dissolution from sustained release formulations using an artificial neural network. *Eur. J. Pharm. Sci.* **5**: 163–169

Braatz, R. D., Tyler, M. L., Morari, M., Pranckh, F. R., Sator, L. (1992) Identification and cross-directional control of coating processes. *AICHE Journal* **38**: 1329–1339

Britten, J. R., Barnett, M. I. (1991) Development and validation of a capsule filling machine simulator. *Int. J. Pharmaceutics* **71**: R5–R8

Britten, J. R., Barnett, M. I., Armstrong, N. A. (1995) Construction of an intermittent motion capsule filling machine simulator. *Pharm. Res.* **12**: 196–200

Buckton, G. (1995a) Surface characterization: understanding sources of variation in the production and use of pharmaceuticals. *J. Pharm. Pharmacol.* **47**: 265–275

Buckton, G. (1995b) *Interfacial phenomena in drug delivery and targetting*. 1st edn, Harwood Academic, Amsterdam

Buckton, G., Newton, J. M. (1986) Assessment of the wettability of powders by the use of compressed powder disks. *Powder Technol.* **46**: 201–208

Buice, R. G., Gold, T. B., Lodder, R. A., Digenis, G. A. (1995)

Determination of moisture in intact gelatin capsules by near infrared spectrophotometry. *Pharm. Res.* **12**: 161–163

Candolfi, A., De Maesschalck, R., Massart, D. L., Hailey, P. A., Harrington, A. C. E. (1999) Identification of pharmaceutical excipients usign NIR spectroscopy and SIMCA. *J. Pharm. Biomed. Anal.* **19**: 923–935

Celik, M., Marshall, K. (1989) Use of a compaction simulator in tabletting research. *Drug Dev. Ind. Pharm.* **15**: 759–800

Celik, M., Ong, J. T. H., Chowhan, Z. T., Samuel, G. J. (1996) Compaction simulator studies of a new drug substance: effect of particle size and shape, and its binary mixtures with microcrystalline cellulose. *Pharm. Dev. Technol.* **1**: 119–126

Chen, Y., Thosar, S. S., Forbess, R. A., Kemper, M. S., Rubinovitz, R. L., Shukla, A. J. (2001) Prediction of drug content and hardness of intact tablets using artificial neural network and near infrared spectroscopy. *Drug Dev. Ind. Pharm.* **27**: 623–631

Colombo, P., Conte, U., Caramella, C., La-Manna, A., Catellani, P. L. (1978) Drug content uniformity of directly compressed tablets in relation to the physical characteristics of diluents. *Boll. Chim. Farm.* **117**: 711–720

Dahlinder, L. E., Johansson, M., Sjogren, J. (1982) Comparison of methods for evaluation of flow properties of powders and granules. *Drug Dev. Ind. Pharm.* **8**: 455–461

Doelker, E. (1993) Comparative compaction properties of various microcrystalline cellulose types and generic products. *Drug Dev. Ind. Pharm.* **19**: 2399–2471

Drennen, J. K., Lodder, R. A. (1990) Non destructive near infrared analysis of intact tablets for determination of degradation products. *J. Pharm. Sci.* **79**: 622–627

Dutton, R. (1997) A connoisseur of predictive control. *Chem. Eng.* **641**: 24–26

Ebube, N. K., Owusu-Ababio, G., Adeyeye, C. M. (2000) Pre-formulation studies and characterisation of the physicochemical properties of amorphous polymers using artificial neural networks. *Int. J. Pharmaceutics* **196**: 27–35

Elbers, J. A. C., Bakkenes, H. W., Fokkens, J. G. (1992) Effect of amount and composition of granulation liquid on mixing, extrusion and spheronisation. *Drug Dev. Ind. Pharm.* **18**: 501–517

El-Gindy, N. A., Samaha, M. W. (1983) Tensile strength of some pharmaceutical compacts and their relation to surface free energy. *Int. J. Pharmaceutics* **13**: 35–46

El-Hagrasy, A. S., Morris, H. R., D'Amico, F., Lodder, R. A., Drennen, J. K. (2001) Near-infrared spectroscopy and imaging for the monitoring of powder blend homogeneity. *J. Pharm. Sci.* **90**: 1298–1307

Fassihi, A. R., Kanfer, I. (1986) Effect of compressibility and powder flow properties on tablet weight variation. *Drug Dev. Ind. Pharm.* **12**: 1947–1966

Faure, A., Grimsey, I. M., Rowe, R. C., York, P., Cliff, M. J. (1999) Process control in a high shear mixer-granulator using wet mass consistency: the effect of formulation variables. *J. Pharm. Sci.* **88**: 191–195

Faure, A., York, P., Rowe, R. C. (2001) Process control and scale-up of pharmaceutical wet granulation processes: a review. *Eur. J. Pharm. Biopharm.* **52**: 269–277

Felton, L. A., McGinity, J. W. (1999) Adhesion of polymeric films to pharmaceutical solids. *Eur. J. Pharm. Biopharm.* **47**: 3–14

Frake, P., Greenhalgh, D., Grierson, S. M., Hempenstall, J. M., Rudd, D. R. (1997) Process control and end point determination of a fluid bed granulation by application of near infrared spectroscopy. *Int. J. Pharmaceutics* **151**: 75–80

Frake, P., Gill, I., Luscombe, C. N., Rudd, D. R., Waterhouse, J., Jayasooriya, U. A. (1998) Near infrared mass median particle size determination of lactose monohydrate, evaluating several chemometric approaches. *Analyst* **123**: 2043–2046

Garekani, H. A., Ford, J. L., Rubinstein, M. H., Rajabi-Siahboomi, A. R. (1999) Formation and compression characteristics of prismatic polyhedral and thin plate-like crystals of paracetamol. *Int. J. Pharmaceutics* **187**: 77–89

Garr, J. S. M., Rubinstein, M. H. (1991) An investigation into the capping of paracetamol at increasing speeds of compression. *Int. J. Pharmaceutics* **72**: 117–122

Gioia, A. (1980) Intrinsic flowability: a new technology for powder-flowability classification. *Pharm. Technol.* **4**: 65–68

Guerin, E., Tchoreloff, P., Leclerc, B., Tanguy, D., Deleuil, M., Couarraze, G. (1999) Rheological characterisation of pharmaceutical powders using tap testing, shear cell and mercury porosimeter. *Int. J. Pharmaceutics* **189**: 91–103

Gurumoorthy, A., Kosanovich, K. A. (1998) Improving the prediction capability of radial basis function networks. *Ind. Eng. Chem. Res.* **37**: 3956–3970

Hailey, P. A., Doherty, P., Tapsell, P., Oliver, T., Aldridge, P. K. (1996) Automated system for on-line monitoring of powder blending processes using near infrared spectroscopy Part I. System development and control. *J. Pharm. Biomed. Anal.* **14**: 551–559

Hakanen, A., Laine, E. (1993) Acoustic emission during powder compaction and its frequency spectral analysis. *Drug Dev. Ind. Pharm.* **19**: 2539–2560

Hakanen, A. Laine, E. (1995) Acoustic characterisation of a microcrystalline cellulose powder during and after its compression. *Drug Dev. Ind. Pharm.* **21**: 1573–1582

Hancock, B. C., York, P., Rowe, R. C. (1994) An assessment of substrate–binder interactions in model wet masses. 1: Mixer torque rheometry. *Int. J. Pharmaceutics* **102**: 167–176

Hancock, B. C., York, P., Rowe, R. C. (1997) The use of solubility parameters in pharmaceutical dosage form design. *Int. J. Pharmaceutics* **148**: 1–21

Heda, P. K., Muller, F. X., Augsburger, L. L. (1999) Capsule filling machine simulation. I. Low-force powder compression physics relevant to plug formation. *Pharm. Dev. Technol.* **4**: 209–219

Hedge, R. P., Rheingold, J. L., Welch, S., Rhodes, C. T. (1985) Studies of powder flow using a recording powder flowmeter and measurement of the dynamic angle of repose. *J. Pharm. Sci.* **74**: 11–15

Herkert, T., Prinz, H., Kovar, K. A. (2001) One hundred percent online identity check of pharmaceutical products by near infrared spectroscopy on the packaging line. *Eur. J. Pharm. Biopharm.* **51**: 9–16

Hussain, A. S., Shivanand, P., Johnson, R. D. (1994) Application of artificial neural computing in pharmaceutical product development. *Drug Dev. Ind. Pharm.* **20**: 1739–1752

Jain, S. (1999) Mechanical properties of powders for compaction and tabletting: an overview. *Pharm. Sci. Technol. Today* **2**: 20–31

Jin, J., Cristescu, N. D. (1998) A constitutive model for powder materials. *J. Eng. Mat. Technol.* **120**: 97–104

Jolliffe, I. G., Newton, J. M., Cooper, D. (1982) The design and use of an instrumented mG2 capsule filling machine simulator. *J. Pharm. Pharmacol.* **34**: 230–235

Jones, B. E. (2001) The filling of powders into two piece hard capsules. *Int. J. Pharmaceutics* **227**: 5–26

Keen, M. J. R. (1993) Successful applications of case based reasoning. *DTI Manuf. Intell. News* **14**: 10–12

Khan, H., Fell, J. T., Macleod, G. S. (2001) The influence of additives on the spreading coefficient and adhesion of a film coating formulation to a model tablet surface. *Int. J. Pharmaceutics* **227**: 113–119

Kirsch, J. D., Drennen, J. K. (1995) Determination of film coated parameters by near infrared spectroscopy. *J. Pharm. Biomed. Anal.* **13**: 1273–1281

Kirsch, J. D., Drennen, J. K. (1996) Near infrared spectroscopic monitoring of the film coating process. *Pharm. Res.* **13**: 234–237

Kirsch, J. D., Drennen, J. K. (1999) Nondestructive tablet hardness testing by near infrared spectroscopy: a new and robust spectral best fit algorithm. *J. Pharm. Biomed. Anal.* **19**: 351–362

Kopcha, M., Roland, E., Bubb, G., Vadino, W. A. (1992) Monitoring the granulation process in a high shear mixer/granulator: an evaluation of three approaches to instrumentation. *Drug Dev. Ind. Pharm.* **18**: 1945–1968

Krishnan, A., Hoo, K. A. (1999) A multiscale model predicitive control strategy. *Ind. Eng. Chem. Res.* **38**: 1973–1986

Lahrhrib, H., Wells, J. I., Rubinstein, M. H. (1997) Compressing polyethylene glycols: the effect of compression pressure and speed. *Int. J. Pharmaceutics* **147**: 199–205

Lai, F. K. Y. (1988) A prototype expert system for selecting pharmaceutical powder mixers. *Pharm. Technol.* **12**: 22–31

Lai, S., Podczeck, F., Newton, J. M., Daumesnil, R. (1996) An expert system to aid the development of capsule formulations. *Pharm. Technol. Eur.* **8**: 60–68

Landin, M., York, P., Cliff, M. J., Rowe, R. C., Wigmore, A. J. (1996) Scale-up of a pharmaceutical granulation in fixed bowl mixer-granulators. *Int. J. Pharmaceutics* **133**: 127–131

Lau, H. Y. K., Mak, K. L. (1999) A unified framework for the development of automated manufacturing systems supervisory software for the pharmaceutical industry. *Int. J. Computer Integrated Manuf.* **12**: 193–210

Leuenberger, H. (1982) Granulation: new techniques. *Pharm. Acta Helv.* **57**: 73–82

Li, L. C., Peck, G. E. (1990) The effect of moisture content on the compression properties of maltodextrins. *J. Pharm. Pharmacol.* **42**: 272–275

Luukkonen, P., Schaefer, T., Podczeck, F., Newton, J. M., Hellen, L., Yliruusi, J. (2001) Characterization of microcrystalline cellulose and silicified microcrystalline cellulose wet masses using a powder rheometer. *Eur. J. Pharm. Sci.* **13**: 143–149

Malamataris, S., Karidas, T. (1994) Effect of particle size and sorbed moisture on the tensile strength of some tableted hydroxypropyl methyl cellulose (HPMC) polymers. *Int. J. Pharmaceutics* **104**: 115–123

Marshall, P. V., York, P. (1991) Compaction properties of nitrofurantoin samples crystallised from different solvents. *Int. J. Pharmaceutics* **67**: 59–65

Marshall, P. V., York, P., Maclaine, J. Q. (1993) An investigation into the effect of punch velocity on the compaction properties of ibuprofen. *Powder Technol.* **74**: 171–177

Martens, H., Martens, M. (1992) NIR spectroscopy – applied philosophy. In: Hildrum, K. I., Isaksson, T., Naes, T., Tandberg, A. (eds) *Near infrared spectroscopy – bridging the gap between data analysis and applications.* 1st edn, Ellis Horwood Ltd, Chichester, pp 1–18

Mori, K. I., Sato, Y., Shiomi, M., Osakada, K. (1999) Prediction of fracture generated by elastic recoveries of tools in multi-level powder compaction using finite element simulation. *Int. J. Mach. Tools Manuf.* **39**: 1031–1045

Morris, K. R., Stowell, J. G., Byrn, S. R., Placette, A. W., Davis, T. D., Peck, G. E. (2000) Accelerated fluid bed drying using NIR monitoring and phenomenological modeling. *Drug Dev. Ind. Pharm.* **26**: 985–988

Morisseau, K. M., Rhodes, C. T. (1995) Pharmaceutical uses of near infrared spectroscopy. *Drug Dev. Ind. Pharm.* **21**: 1071–1090

Morisseau, K. M., Rhodes, C. T. (1997) Near infrared spectroscopy as a non destructive alternative to conventional tablet hardness testing. *Pharm. Res.* **14**: 108–111

Munoz-Ruiz, A., Mondero-Perales, M. C., Antequera, M. V. V., Jimenez-Castellanos, M. R. (1993a) Physical and rheological properties of raw materials. *STP Pharma. Sci.* **3**: 307–312

Munoz-Ruiz, A., Mondero-Perales, M. C., Antequera, M. V. V., Villar, T. P., Munoz-Munoz, N., Jimenez-Castellanos, M. R. (1993b) Rheology and compression characteristics of lactose based direct compression excipients. *Int. J. Pharmaceutics* **95**: 201–207

Murray, F. J. (1989) The application of expert systems to pharmaceutical processing equipment. *Pharm. Technol.* **13**: 100–110

Murtoniemi, E., Yliruusi, J., Kinnunen, P., Merkku, P., Leiviska, K. (1994) The advantages by the use of artificial neural networks in modelling the fluidised bed granulation process. *Int. J. Pharmaceutics* **108**: 155–164

Newton, J. M. (1987) Filling of hard gelatin capsules. *STP Pharm. Pratiques* **3**: 880–885

Newton, J. M., Bader, F. (1987) The angle of internal flow as an indicator of filling and drug release properties of capsule formulations. *J. Pharm. Pharmacol.* **39**: 164–168

Newton, J. M., Mashadi, A. B., Podczeck, F. (1993) The mechanical properties of an homologous series of benzoic acid esters. *Eur. J. Pharm. Biopharm.* **39**: 153–157

Nichols, G., Frampton, C. S. (1998) Physicochemical characterisation of the orthorhombic form of paracetamol crystallised from solution. *J. Pharm. Sci.* **87**: 684–693

Nokhodchi, A., Rubinstein, M. H. (1996) Compaction simulators in tableting research. *Pharm. Technol.* **20**: 6–67

Nokhodchi, A., Ford, J. L., Rowe, P. H., Rubinstein, M. H. (1996a) The effects of compression rate and force on the compaction properties of different viscosity grades of hydroxypropylmethylcellulose 2208. *Int. J. Pharmaceutics* **129**: 21–31

Nokhodchi, A., Ford, J. L., Rowe, P. H., Rubinstein, M. H. (1996b) Influence of moisture content on the consolidation properties of hydroxypropyl methyl cellulose K4M (HPMC 2208). *J. Pharm. Pharmacol.* **48**: 1116–1121

Nokhodchi, A., Ford, J. L., Rowe, P. H., Rubinstein, M. H. (1996c) Effect of moisture on the Heckel and energy analysis of hydroxypropyl methyl cellulose 2208 (HPMC K4M). *J. Pharm. Pharmacol.* **48**: 1122–1127

Nyqvist, H. (1982) Prediction of weight variation in tablet production from shear cell measurements. *Acta Pharm. Suec.* **19**: 413–420

Nyqvist, H., Nicklasson, M. (1985) Flow properties of compressible lactose containing small quantities of drug substances. *Drug Dev. Ind. Pharm.* **11**: 745–759

Ohike, A., Ashihara, K., Ibuki, R. (1999) Granulation monitoring by fast fourier transform technique. *Chem. Pharm. Bull.* **47**: 1734–1739

Omelczuk, M. O., Wang, C. C., Pope, D. G. (1997) Influence of micronisation on the compaction properties of an investigational drug using tablet index analysis. *Eur. J. Pharm. Biopharm.* **43**: 95–100

O'Neil, A. J., Jee, R. D., Moffat, A. C. (1999) Measurement of the cumulative particle size distribution of microcrystalline cellulose using near infrared reflectance spectroscopy. *Analyst* **124**: 33–36

Parker, M. D., Rowe, R. C. (1991) Source variation in the wet massing (granulation) of some microcrystalline celluloses. *Powder Technol.* **65**: 273–281

Parker, M. D., York, P., Rowe, R. C. (1990) Binder–substrate interactions in wet granulation. 1: The effect of binder characteristics. *Int. J. Pharmaceutics* **64**: 207–216

Parker, M. D., York, P., Rowe, R. C. (1991) Binder–substrate interactions in wet granulation. 2: The effect of binder molecular weight. *Int. J. Pharmaceutics* **72**: 243–249

Patel, A. D., Luner, P. E., Kemper, M. S. (2000) Quantitative analysis of polymorphs in binary and multi-component powder mixtures by near infrared reflectance spectroscopy. *Int. J. Pharmaceutics* **206**: 63–74

Payne, R. S., Roberts, R. J., Rowe, R. C., McPartlin, M., Bashall, A. (1996) The mechanical properties of two forms of primidone predicted from their crystal structures. *Int. J. Pharmaceutics* **145**: 165–173

Payne, R. S., Roberts, R. J., Rowe, R. C., Docherty, R. (1999) Examples of successful crystal structure prediction: polymorphs of primidone and progesterone. *Int. J. Pharmaceutics* **177**: 231–245

Planinsek, O., Pisek, R., Trojak, A., Srcic, S. (2000) The utilisation of surface free energy parameters for the selection of a suitable binder in fluidised bed granulation. *Int. J. Pharmaceutics* **207**: 77–88

Podczeck, F. (1998) *Particle–particle adhesion in pharmaceutical powder handling*. 1st edn, Imperial College Press, London

Podczeck, F. (1999a) Rheological studies of the physical properties of powders used in capsule filling – Part I. *Pharm. Technol. Int.* **11**: 16–24

Podczeck, F. (1999b) Rheological studies of the physical properties of powders used in capsule filling – Part II. *Pharm. Technol. Int.* **11**: 34–42

Podczeck, F., Newton, J. M. (1999) Powder filling into hard gelatin capsules on a tamp filling machine. *Int. J. Pharmaceutics* **185**: 237–254

Podczeck, F., Newton, J. M. (2000) Powder and capsule filling properties of lubricated granulated cellulose powder. *Eur. J. Pharm. Biopharm.* **50**: 373–377

Ramachandruni, H., Hoag, S. W. (2001) Design and validation of an annular shear cell for pharmaceutical powder testing. *J. Pharm. Sci.* **90**: 531–540

Ramani, K. V., Patel, M. R., Patel, S. K. (1992) An expert system for drug preformulation in a pharmaceutical company. *Interfaces* **22**: 101–108

Rantanen, J., Lehtola, S., Ramet, P., Mannermaa, J. P., Yliruusi, J. (1998) On-line monitoring of moisture content in an instrumented fluidized bed dryer with a multi-channel NIR moisture sensor. *Powder Technol.* **99**: 163–170

Rantanen, J., Rasanen, E., Tenhunen, J., Kansakoski, M., Mannermaa, J. P., Yliruusi, J. (2000) In-line moisture measurement during granulation with a four wavelength near infrared sensor: an evaluation of particle size and binder effects. *Eur. J. Pharm. Biopharm.* **50**: 271–276

Rasanen, E., Rantanen, J., Jorgensen, A., Karajalainen, M., Paakkari, T., Yliruusi, J. (2001) Novel identification of pseudopolymorphic changes of theophylline during wet granulation using near infrared spectroscopy. *J. Pharm. Sci.* **90**: 389–396

Ritala, M., Holm, P., Schaefer, T., Kristensen, H. G. (1988) Influence of liquid bonding strength on power consumption during granulation in a high shear mixer. *Drug Dev. Ind. Pharm.* **14**: 1041–1060

Roberts, R. J., Rowe, R. C., York, P. (1991) The relationship between Young's modulus of organic solids and their molecular structure. *Powder Technol.* **65**: 139–146

Roberts, R. J., Rowe, R. C., York, P. (1995) The relationship between the fracture properties, tensile strength and critical stress intensity factor of organic solids and their molecular structure. *Int. J. Pharmaceutics* **125**: 157–162

Roberts, R. J., Payne, R. S., Rowe, R. C. (2000) Mechanical property predictions for polymorphs of sulphathiazole and carbamazepine. *Eur. J. Pharm. Sci.* **9**: 277–283

Rocksloh, K., Rapp, F. R., Abu Abed, S., Muller, W., Reher, M., Gauglitz, G., Schmidt, P. C. (1999) Optimisation of crushing strength and disintegration time of a high-dose plant extract tablet by neural networks. *Drug Dev. Ind. Pharm.* **25**: 1015–1025

Rowe, R. C. (1988a) Interactions in the ternary powder system microcrystalline cellulose, magnesium stearate and colloidal silica – a solubility parameter approach. *Int. J. Pharmaceutics* **45**: 259–261

Rowe, R. C. (1988b) The interaction of lubricants with microcrystalline cellulose and anhydrous lactose – a solubility parameter approach. *Int. J. Pharmaceutics* **41**: 223–226

Rowe, R. C. (1988c) Binder–substrate interactions in tablets: a theoretical approach based on solubility parameters. *Acta Pharm. Technol.* **34**: 144–146

Rowe, R. C. (1989a) Interactions in coloured powders and tablet formulations: a theoretical approach based on solubility parameters. *Int. J. Pharmaceutics* **53**: 47–51

Rowe, R. C. (1989b) Binder–substrate interactions in granulation: a theoretical approach based on surface free energy and polarity. *Int. J. Pharmaceutics* **52**: 149–154

Rowe, R. C. (1989c) Surface free energy and polarity effects in the granulation of a model system. *Int. J. Pharmaceutics* **53**: 75–78

Rowe, R. C. (1990) Correlation between predicted binder spreading coefficients and measured granule and tablet properties in the granulation of paracetamol. *Int. J. Pharmaceutics* **58**: 209–213

Rowe, R. C. (1992) Interactions in powders and granules – a reappraisal. *Int. J. Pharmaceutics* **79**: 257–261

Rowe, R. C. (1993a) Applying neural computing to product formulation. *Manuf. Chem.* **67**: 21–23

Rowe, R. C. (1993b) An expert system for the formulation of pharmaceutical tablets. *DTI Manuf. Intell. News* **14**: 13–15

Rowe, R. C. (1995) The rheological properties of lactose/microcrystalline cellulose/water mixes: measurement using mixer torque rheometry. *Pharm. Sci.* **1**: 547–549

Rowe, R. C. (1996a) Mixer torque rheometry – further advances. *Pharm. Technol. Eur.* **8**: 38–48

Rowe, R. C. (1996b) Applying neural computing to product formulation. *Manuf. Chem.* **67**: 21–23

Rowe, R. C., Colbourn, E. A. (2000) Generating rules for tablet formulation. *Pharm. Technol. Int.* **12**: 24–27

Rowe, R. C., Parker, M. D. (1994) Mixer torque rheometry – an update. *Pharm. Technol. Eur.* **6**: 27–34

Rowe, R. C., Sadeghnejad, G. R. (1987) The rheology of microcrystalline cellulose powder/water mixes – measurement using a mixer torque rheometer. *Int. J. Pharmaceutics* **38**: 227–229

Rowe, R. C., Upjohn, N. G. (1993a) An expert system for the identification and solution of film coating defects. *Pharm. Technol. Int.* **5**: 34–38

Rowe, R. C., Upjohn, N. G. (1993b) Formulating pharmaceuticals using expert systems. *Pharm. Technol. Int.* **5**: 46–52

Ruegger, C. E., Celik, M. (2000) The influence of varying precompaction and main compaction profile parameters on the mechanical strength of compacts. *Pharm. Dev. Technol.* **5**: 495–505

Sekulic, S. S., Wakeman, J., Doherty, P., Hailey, P. A. (1998) Automated system for the on-line monitoring of powder blending processes using near infrared spectroscopy Part II. Qualitative approaches to blend evaluation. *J. Pharm. Biomed. Anal.* **17**: 1285–1309

Sheridan, P. L., Buckton, G., Storey, D. E. (1995) The use of molecular orbital indices to predict the surface properties of pharmaceutical powders. *Int. J. Pharmaceutics* **125**: 141–149

Smith, L. N., Midha, P. S. (1997) Computer simulation of morphology and packing behaviour of irregular particles, for predicting apparent powder densities. *Comp. Mat. Sci.* **7**: 377–383

Stamm, A., Paris, L. (1985) Influence of technological factors on the optimal granulation liquid requirement measured by power consumption. *Drug Dev. Ind. Pharm.* **11**: 333–360

Sugimori, K. I., Kawashima, Y. (1997) A new practical index to predict capping occurring during the tableting process. *Eur. J. Pharm. Biopharm.* **44**: 323–326

Suihko, E., Poso, A., Korhonen, O., Gynther, J., Ketolainen, J., Paronen, P. (2000) Deformation behaviours of tolbutamide, hydroxypropyl-beta-cyclodextrin and their dispersions. *Pharm. Res.* **17**: 942–948

Sun, C., Grant, D. J. W. (2001a) Compaction properties of L-Lysine salts. *Pharm. Res.* **18**: 281–286

Sun, C., Grant, D. J. W. (2001b) Influence of crystal shape on the tabletting performance of L-Lysine monohydrochloride dihydrate. *J. Pharm. Sci.* **90**: 569–579

Suzuki, T., Nakagami, H. (1999) Effect of crystallinity of microcrystalline cellulose on the compactibility and dissolution of tablets. *Eur. J. Pharm. Biopharm.* **47**: 225–230

Takayama, K., Fujikawa, M., Nagai, T. (1999) Artificial neural networks as a novel method to optimise pharmaceutical formulations. *Pharm. Res.* **16**: 1–6

Talu, I., Tardos, G. I., van Ommen, J. R. (2001) Use of stress fluctuations to monitor wet granulation of powders. *Powder Technol.* **117**: 149–162

Tamura, S., Aizawa, T., Mitsuno, T., Kihara, J. (1998) Steel powder compaction and forming analysis. *Int. J. Powder Mettal.* **34**: 50–59

Tan, S. B., Newton, J. M. (1990a) Powder flowability as an indicator of capsule filling performance. *Int. J. Pharmaceutics* **61**: 145–155

Tan, S. B., Newton, J. M. (1990b) Minimum compression stress requirements for arching and powder retention within a dosator nozzle during capsule filling. *Int. J. Pharmaceutics* **63**: 275–280

Tan, S. B., Newton, J. M. (1990c) Influence of compression setting ratio on capsule fill weight and weight variability. *Int. J. Pharmaceutics* **66**: 273–282

Tan, S. B., Newton, J. M. (1990d) Observed and expected powder plug densities obtained by a capsule dosator nozzle system. *Int. J. Pharmaceutics* **66**: 283–288

Train, D. (1958) Some aspects of the property of angle of repose of powders. *J. Pharm. Pharmacol.* **10**: 127T–135T

Tsujimoto, H., Yokoyama, T., Huang, C. C., Sekiguchi, I. (2000) Monitoring particle fluidisation in a fluidised bed granulator with an acoustic emission sensor. *Powder Technol.* **113**: 88–96

Turkoglu, M., Ozarslan, R., Sakr, A. (1995) Artificial neural network analysis of direct compression tabletting study. *Eur. J. Pharm. Biopharm.* **41**: 315–322

Turkoglu, M., Aydin, I., Murray, M., Sakr, A. (1999) Modelling of roller-compaction process using neural networks and genetic algorithms. *Eur. J. Pharm. Biopharm.* **48**: 239–245

Vachon, M. G., Chulia, D. (1999) The use of energy indices in estimating powder compaction functionality of mixtures in pharmaceutical tableting. *Int. J. Pharmaceutics* **177**: 183–200

van-Veen, B., van der Voort Maarschalk, K., Bolhuis, G. K., Zuurman, K., Frijlink, H. W. (2000) Tensile strength of tablets containing two materials with a different compaction behaviour. *Int. J. Pharmaceutics* **203**: 71–79

Varthalis, S., Pilpel, N. (1976) Anomalies in some properties of powder mixtures. *J. Pharm. Pharmacol.* **28**: 415–419

Velasco, A. M. V., Munoz-Ruiz, A., Mondero-Perales, M. C., Jimenez-Castellanos Ballesteros, M. R. (1995) Flow studies on maltodextrins as directly compressible vehicles. *Drug Dev. Ind. Pharm.* **21**: 1235–1243

Voorakaranam, S., Jospeh, B. (1999) Model predictive inferential control with application to a composites manufacturing process. *Ind. Eng. Chem. Res.* **38**: 433–450

Wargo, D. J., Drennen, J. K. (1996) Near infrared characterisation of pharmaceutical powder blends. *J. Pharm. Biomed. Anal.* **14**: 1415–1423

Waring, M. J., Rubinstein, M. H., Howard, J. R. (1987) Acoustic emission of pharmaceutical materials during compression. *Int. J. Pharm.* **36**: 29–36

Watano, S. (2001) Direct control of wet granulation processes by image processing system. *Powder Technol.* **117**: 163–172

Watano, S., Takashima, H., Miyanami, K. (1997) Scale-up of agitation fluidised bed granulation by neural network. *Chem. Pharm. Bull.* **45**: 1193–1197

Whitaker, M., Baker, G. R., Westrup, J., Goulding, P. A., Rudd, D. R., Belchamber, R. M., Collins, M. P. (2000) Application of acoustic emission to the monitoring and end point determination of a high shear granulation process. *Int. J. Pharmaceutics* **205**: 79–91

Wong, D. Y. T., Waring, M. J., Wright, P., Aulton, M. E. (1991) Elucidation of the compressive deformation mechanism of lactose monohydrate and anhydrous lactose single crystals by mechanical strength and acoustic emission analysis. *Int. J. Pharmaceutics* **72**: 233–241

Wu, T., Pan, W., Chen, J., Zhang, R. (2000) Formulation optimisation technique based on artificial neural network in salbutamol sulphate osmotic pump tablets. *Drug Dev. Ind. Pharm.* **26**: 211–215

Yang, L., Venkatesh, G., Fassihi, R. (1996) Characterization of compressibility and compactibility of poly(ethylene oxide) polymers for modified release application by compaction simulator. *J. Pharm. Sci.* **85**: 1085–1090

Zajic, L. Buckton, G. (1990) The use of surface energy values to predict the optimum binder selection for granulations. *Int. J. Pharmaceutics* **59**: 155–164