DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 17(11), 1437-1463 (1991)

FLUIDISED-BED GRANULATION: A CHRONOLOGY

Banks, Michael* and Aulton, Michael E.**

***Pharmaceutical Research and Development, Pfizer Central Research, Sandwich, CT13 9NJ UK**

****Department of Pharmacy, Leicester Polytechnic, Leicester, LE1 9BH, UK**

ABSTRACT

This paper is a chronological survey of published work in the field of pharmaceutical fluidised-bed granulation. It begins with early experiments in the 1960s and continues to include all relevant published work up to 1990. To aid the reader find published material for further in-depth reading a cross reference to published articles on a subject basis is provided in tabular form.

INTRODUCTION

Fluidised-bed granulation is a process for producing granules in a single piece of equipment by spraying a solution (usually containing a binder) onto a fluidised bed of powders. The technique offers significant advantages over the multistage process of conventional wet granulation. The process has received considerable attention within the pharmaceutical industry since it offers controlled release opportunities in dosage form design and presents improvements in dust control within the production environment. It is now almost three decades since the process was first described for pharmaceutical application in 1960 by Wurster[1] based upon his earlier work on air suspension

*Correspondence

coating[2]. During this period the process has been investigated by numerous workers. This paper presents a chronological review of published literature of pharmaceutical relevance to provide a comprehensive reference document for the pharmaceutical formulator and process development scientist.

THE 1960s

In 1964 Scott and his fellow workers[3] published the first article on Fluidised-Bed Granulation (FBG) since Wurster's original paper in 1960. The theory and design considerations of the process were reviewed by using a fundamental engineering approach and employing mass and thermal energy balances. The basic design criteria were thus developed by analysing these balances and considering the rates of heat and mass transfer. Equations were developed from this approach and used to predict relationships among a number of the process variables. A continuous production fluidised-bed granulator (FBG) was also described for the first time. Their second report[4] extended the theoretical basis to an evaluation of the operation and performance of a 30 kg capacity pilot model designed for both continuous and batch operation. A study of the process variables of air flow rate, air temperature, liquid flow rate, residence time and composition of granulating fluid was conducted. The influence of powder feed rate, nozzle location and the ability to produce a closely controlled granule size from the continuous mode of operation were also discussed. Granule samples produced from both modes of operation were compressed and the tablets evaluated.

Later Contini and Atasoy[5] published a short review of the advantages of the fluidised-bed granulation process from a manufacturing and economic view point. The use of a 150 kg capacity model was also reported. A similar paper, but with limited technical content, was published by Wolf[6]. This included a general overview of the mixing, wetting, drying, spray drying and agglomerating operations taking place within the FBG. The essential constructional features of the granulator, including product bowl design, fluidising air plate and distribution screen features were also discussed. During this period Liske and Mobus[7] compared the fluidised-bed and wet granulation process. This was achieved by selecting various starch/lactose-based formulations so that various binders and additional materials of widely differing density could be assessed. The processing of an unnamed active ingredient in high and low concentration was also studied. The overall results indicated that materials processed by FBG produced finer, more free flowing and homogeneous granules which after

compression produced stronger and faster disintegrating tablets than materials processed by conventional wet granulation. A complete financial analysis of the cost saving over conventional wet massing was reported by Feigenbaum.[8] The analysis was based upon various capacity units (15, 30, 60, 120 kg) and yearly material through-puts in a typical manufacturing environment with all costs calculated accordingly. The author reconfirmed the great cost saving potential of the process.

THE 1970s

Published research on the process changed to a more technical approach in the 1970s with more attention being paid to the influence of the various process variables upon the quality of the final granule produced. This more systematic approach began in 1970 with a thesis by Thurn[9] investigating in detail the mixing, agglomerating and drying operations which take place in the FBG process. Results indicated that the mixing stage was particularly influenced by air flow rate and air flow volume; the distribution of a small quantity of active substance in an inert base was used as a model. Statistical analysis of the results showed the random distribution nearing theoretical homogeneity. It was also suggested that the physical properties of the raw materials such as hydrophobicity may exert a strong influence upon the mixing stage. At the granulating stage, particular attention was paid to the nozzle and it was concluded that a binary design gave a wide droplet size distribution yielding a homogeneous granule. The need for powerful binders was recommended to aid granule formation and it was suggested that the wettability of the raw materials required particular attention. It was concluded that granules displaying good flow and compression properties could be readily reproduced from this method. The drying stage was also investigated in some detail. This thesis was perhaps the stimulus for a number of more detailed research articles investigating in greater depth the individual influence of process variables upon the quality and characteristics of the final product. Several series of papers on this topic have since been published and these are presented below.

In 1971, Bank, Bezzegh and Fekete[10] reported experiments on a 300g laboratory and a 15 kg pilot scale model. The results from these experiments were used to establish the basic parameters for a more detailed study of selected parameters in a 120 kg capacity Aeromatic model. The parameters selected were quantity of binder, fluidising air flow rate and binder flow rate. The conditions for processing good quality granules were thus optimised and the granulator adapted for automatic control by using a punch card programme system. Finally it was shown that FBG granules produced tablets with more uniform

physical characteristics (i.e. weight variation, disintegration time). Ritschel[11] published a short general review on the theory and equipment design of the technique, while Kala et al[12] discussed the construction and mode of operation of a laboratory scale unit and compared FBG granulation with conventional methods. During the same period Davies and Gloor[13] published a paper describing the effects of process variables on the physical properties of the final granules. The variables investigated included binder solution addition rate, air pressure to the binary nozzle, inlet air temperature during the granulation cycle and nozzle position in relation to the air distribution grid. All the granules produced were subjected to standard tests including sieve size analysis, density and porosity determinations. This paper was followed by a further two articles by the same authors.[14,15] Initially they reported the effects of various types of binders and binder concentrations upon granule and compressed tablet properties. In the final paper a detailed study into binder dilution effects on granule properties was presented.

In 1972 Harada[16], from material balances in a fluidised bed, derived a rate equation containing a coating rate growth coefficient and an agglomeration rate coefficient. The equation was used for calculating the particle diameter distribution and median diameters. Gupte[17] presented a model which was used to explain the effect of various factors that influence final size distribution. Factors discussed were initial weight of the powder charge, spray droplet size distribution in relation to atomising air pressure, binding agent and the drying time which was specifically related to temperature. Formulae enabling scale-up to be achieved were also presented.

A series of six articles were published next by a group of Hungarian researchers. The first paper in 1973 by Ormós[18] reviewed the methods and techniques intended for use in quantifying granule characteristics necessary to assess granulations produced by the FBG process. The remaining five papers in this series were published with fellow workers Pataki and Csukas. Initially the effect of quantity and addition rate of granulating solution were investigated. The results were evaluated and an equation derived to calculate the average particle size of the final granules[19]. The conclusions from this led to a further study into optimising the feed rate necessary to produce a quality granulation. A correlation was given for the maximum and equilibrium liquid feed rate on the basis of the heat and liquid balances of the process[20]. The effects of several operating parameters were assessed[21], i.e. ratio of minimum bed height to

diameter of bed, degree of expansion of the fluidised bed, degree of dispersion of the granulating liquid, distance of the atomising nozzle from the air distribution plate and the type of distributor upon the physical properties of the granulates produced. Ormós, Pataki and Csukás[22] then endeavoured to provide a theoretical description of the production of granulates together with a detailed account of the log-normal distribution function and its application in classification of granule particle-size distributions. Correlations between the effect of changing process parameters on the particle size distribution parameters used to describe the resulting granulates were investigated. By the application of the log normal distribution function a calculation method was developed enabling the amount of granulating liquid and the granulation time to be optimised to produce a granule batch with good flow properties. Finally, they assessed the effects of mechanical stirring of the fluidised bed during granulation[23]. Several designs of stirrer were evaluated and it was concluded that the increased agitation eliminated channelling problems, ensured that the larger particles were in a partially fluidised state which allowed more granulating fluid to be added and decreased the porosity of the granules forming a stronger granule. A further report was published by Csukás and Ormós[24] discussing the effect of the major process parameters upon the quality of granules from a continuous fluidised bed granulator. The experimental results were subjected to mathematical interpretation enabling the limits of application of the single bed continuous operation to be outlined.

Campy et al[25] in 1974 considered that no reliable scale-up procedure had, until then, been completely elucidated and proceeded to compare the air flow rates and air pressure distribution between a 5 kg and a 30 kg capacity Glatt FBG. Static pressure measurements were made at three points in the 5 kg and 30 kg model - beneath the distribution chamber, in the expansion chamber and above the exhaust filter. For both models the outlet valve had a greater effect on the air pressure than the inlet valve, and the pressure change across the distribution plate exceeded that across the exhaust filter. The maximum reduction in pressure achieved in the expansion chamber was greater for the 30 kg model than for the 5 kg model. This was considered a factor which could result in different drying rates on scale up.

In 1975 Rouiller, Gurny and Doelker[26] assessed a 1 kg Aeromatic FBG with regard to its suitability for producing granules of acceptable and reproducible size for tableting. Starch/lactose placebo mixes were granulated with aqueous or alcoholic binder solutions. Prioux et al[27] studied the effect of

fluidising air temperature, granulating solution addition rate and atomising air pressure using a 5 kg Glatt apparatus. Continuing the work on small scale fluidised bed granulators, Johnson, Rees and Sendall[28] evaluated a 1 kg Aeromatic unit. They adopted a more mathematical approach studying the effects of fluidising air temperature, granulating solution concentration, addition rate and spray nozzle position upon final granule characteristics by means of an experiment of factorial design.

Growth of particles within the bed was examined by Shinoda et al[29] in 1976. A correlation was observed between the amount of binder solution adhering to the powder and the logarithm of the average particle size of the resultant granules. Particle growth of water soluble powders (lactose and mannitol) were observed to be faster than water insoluble powders (corn starch, crystalline cellulose). Thus indicating the importance of excipient hydrophobicity. Aulton and Banks[30] investigated this aspect further in 1977 and demonstrated a linear relationship between the cosine of the solid/liquid contact angle and granule size. The addition of a surfactant (sodium lauryl sulphate) to a model hydrophobic system was shown to improve granulation. This was related to improved powder/liquid affinity. Surfactant dissolved in the granulating solution gave slightly coarser granules with improved flow properties than when added directly to the powder mix. This was attributed to changes in spray characteristics and improved wetting by the atomised granulating solution.

Mehta et al[31] studied the influence of binder solution spray rate on granule size distribution in greater depth than had previously been reported. An explanation of the phenomena leading to experimental particle size distributions in a batch FBG was presented. Granulations made at various fluidising air velocities and granulating solution addition rates showed log normal distribution of particle size. The mean diameter was proportional to the square of the liquid flow rate but was independent of air flow rate. The standard deviation of particle size was, however, independent of both these parameters. The bioavailability in rabbits of tablets prepared by FBG and direct compression were compared with a commercially available product by Ritschel and Erni[32]. Results showed that the experimental tablets made by FBG and direct compression gave slightly higher blood levels than the commercial tablet. The use of FBG for manufacture of granules containing pesticides was described by Ormós et al[33].

Motto[34] reported that the FBG could be used to manufacture granules containing small quantities of active ingredients (e.g. hormones). This was confirmed by experimental assay showing that the final compressed product met pharmacopoeial specification. A comparable, yet more detailed, study into the fluidised-bed granulation of a microdose pharmaceutical powder was published by Crooks and Schade.[35] The effects of solvent, binder addition rate and fluidising air temperature upon the granule size and drug distribution of 5% w/w phenylbutazone in a lactose powder mix was studied. Results indicated that as granule size increased so did the homogeneity of the phenylbutazone distribution. This was explained by the increased wetting of the larger granules which could then pick up the finer drug particles. This was aided by the deaggregation of phenylbutazone agglomerates by the ball milling action of the large granules.

Kulling[36] discussed the inherent explosion risks in fluidised-bed systems involving dusts, solvents and hybrid mixtures of dusts/solvents. Safety measures were suggested, based upon results from extensive explosion tests on various machines. Explosion venting or explosion suppression were considered to be the most appropriate. Additional comment was made in a further paper[37] which included details covering location of pressure seals.

An extremely important series of papers assessing specific areas of the FBG technique in more detail was published by Schaefer and Wørts[38-42] during 1977 and 1978. Earlier Wørts[43] had discussed the theories of wet and dry granulation, reviewed the various types of granulation equipment available and indicated the great potential of FBG. Initially Schaefer and Wørts studied the effects of spray angle, nozzle height and starting materials on mean granule size and size distribution[38]. The influence of the water absorption properties of the starting materials were shown to be an important factor; the need for a complete investigation using hydrophobic material was indicated as being necessary. An estimation of droplet size of atomised binder solution was also reported[39]. This was achieved by using a droplet capture technique on a microscope slide covered with oil. Photography was used to reduce evaporation errors. The method suffers several disadvantages: it can only be applied to liquid flow rates below a certain value, reproducible sample collection is difficult, and errors due to droplet flattening and spreading can occur. They did, however, measure the influence of binder type and binder viscosity, spray angle, mass ratio (i.e. the ratio at the spray nozzle of the air-to-liquid mass), liquid flow rate and liquid nozzle orifice size upon spray droplet size and size distribution. An empirical

droplet size equation was derived which permitted an approximate prediction of the mass median diameter for the nozzle used in their experiments. These droplet size data were used later to evaluate the effects of binder solution and atomisation upon granule size and size distribution[41]. Aqueous solutions of gelatin, polyvinylpyrrolidone, sodium carboxymethylcellulose and methylcellulose were used to prepare granules. Granule size was found to be directly proportional to binder concentration and a wide distribution was observed with increased droplet size. The type of binder was shown to affect granule size and this was attributed to the influence on droplet size and granule growth. The effects of inlet air temperature and liquid flow rate on granule size and size distribution were investigated next by Schaefer and Wørts[40]. The control of the moisture content of the granules in the drying phase was also studied. Granule size was found to be inversely proportional to the difference between inlet air temperature and wet bulb temperature in the granulation phase and directly proportional to the liquid flow rate. An increase in the amount of attrition during the drying phase was observed at increased air flow rates. At a range of experimental conditions a reproducible correlation was found between the moisture content of the granule and the difference between the product and wet bulb temperature. The theoretical aspects of this technique had been reported earlier by Harbert[44] and the correlation was reported by the combined SIRA/Industrial Pharmacy project group on Fluidised Bed Drying Control of Pharmaceuticals, but was shown by Banks[45] to hold only for aqueous granulations. The final paper in the series by Schaefer and Wørts[42] examined the relationship under varying experimental conditions between quantity of binder solution and granule size and size distribution. Highest growth rates were obtained with the largest spray droplet size, fastest liquid flow rate, highest lactose content of the formulation and lowest inlet air temperature. These results were discussed and related to suggested growth mechanisms.

Schepky[46] published in 1978 a general review of the fluidised-bed granulation process. The paper provided background on the development of the technique, the effect of process variables on the final granulation and comments on scale-up aspects. Control and automation of the process was also discussed in addition to safety aspects. Simon[47] provided a more in-depth review of the methods used to reduce the effects of an explosion in a fluidised bed. Three methods were described - the use of explosion relief flaps, installation of a suppression system (activated by pressure sensors which trigger off special extinguishers and close off relief flaps) and use of inert gases to facilitate fluidisation. Aspects of pollution control were also discussed.

Using an experiment of factorial design Aulton and Banks[48] investigated the effect of seven process variables on the particle size and flow properties of the resulting granules. Five of the seven variables investigated had a significant effect on granule quality. These were concentration of granulating solution, spray nozzle set-up, atomising air pressure, fluidising air velocity and fluidising air temperature. The tabletting characteristics of selected batches representing poor, intermediate and good granules were assessed. There was little difference in the crushing strength/compression force profile between the three types of granules. However, at high compaction pressures the 'poor' granule batch gave a wider tablet weight variation than the other two. A technique for studying the distribution of binder within fluidised-bed granules involving the binding of fluorescein isothiocyanate to PVP was later described by Aulton, Banks and Davies[49]. The resulting complex was used as a binder during FBG. The granules produced were observed under light excitement and this enabled the distribution of the fluorescent PVP within the granules to be assessed.

A second major series of articles was published in 1979 by the group of Hungarian researchers led by Ormós. In the first paper Ormós and Pataki[50] studied the granule formation of five different raw materials (possessing widely different water solubilities and wettabilities), granulated using an aqueous gelatin solution in a laboratory FBG. The largest granule growth was found when the raw material was readily soluble in the granulating solution. Less pronounced growth occurred when the raw material was insoluble, although readily wettable, in the granulating solution. The smallest size increase was noted with the non-soluble, non-wettable material. These results were then used to verify a previously developed calculation method[22] enabling the quantity of granulating fluid and processing time to be optimised in order to achieve a good granule. The effects of initial particle size and size distribution of raw material on the physical characteristics of the final granule was also studied[51]. This was achieved by using glass beads of various size fractions and gelatin as the binder. Different rates of granule growth were achieved depending on the initial particle size. The growth rate decreased as the proportion of granulating solution increased. The smaller size fractions produced stronger granules than the larger size fractions although this difference became less pronounced at higher binder levels. Ormós, Pataki and Stefko[52] characterised four binders (sodium carboxymethylcellulose, PVP, sugar and ammonium nitrate) in aqueous solution by measuring viscosity and surface tension at various concentrations and temperatures. Their studies then related these characteristics to atomisation and adhesive properties and then to

granule formation in a fluidised bed. Each binder was shown to possess a narrow optimum concentration range. The effects of the relative amounts of each binder applied at the optimum concentration on the physical characteristics of granules in a fluidised bed were then reported.[53] Growth rates and granule strength were found to be different with different binders. The particle size distribution of granules produced from each binder was approximated by a log normal distribution function. Ormos[54] demonstrated that the average particle size and the amount of the product fraction (as functions of the relative quantity of granulating solution) could be calculated from limited experimental results if the data were analysed using the log normal distribution function. The linear approximation of the log normal distribution function parameters was shown to adequately describe the changes of the average particle size of granules and the process of granule formation. This was followed by a study[55] on the bed expansion of fluidised heterodisperse granule masses produced in a fluidised bed. Based on experimental results, equations were formulated for the minimum fluidisation velocity and the bed expansion. Measured and calculated values were compared to show the validity of the correlations. The optimum volume of granulating solution for a given addition rate, was elucidated. The effect of granulating solution volume and addition rate on the granule size and size distribution during batch FBG was investigated by Ormós and Pataki[56]. It was concluded that the optimum volume of granulating solution at a given feed rate should be determined first followed by the optimisation of the feed rate. Granulating solution addition rates slightly above the equilibrium feed rate determined from the heat balance were found to be best. Ormós, Machacs and Pataki[57] concluded this series of papers by studying the type and rotation speed of three mechanical agitators within the fluidised bed on granule formation. Two model systems were selected for this study representing a material soluble and a material insoluble in the granulating fluid. Results showed that with increasing rotation speed, the average particle size of granules, the particle size distribution and the upper limit of porosity decrease, the relative amount of the product fraction and the extent of wetting increase and the strength of the granules improves. The trend and extent of the changes were dependent upon the physical characteristics of the raw materials to be granulated. No significant difference was observed between the designs of agitator used.

Aulton and Banks[58] examined the effect that the wettability of the powder mix had on the process of granule growth in a fluidised bed. They granulated mixtures of various ratios of salicylic acid (hydrophobic) and lactose (hydrophilic) and quantified a relationship between the cosine of the contact

angle and the mean size of granule produced. Droplet size had previously been shown to be an important factor yet difficult to measure. Aulton and Banks[59] demonstrated the use of laser light scattering (employing a Malvern ST1800 particle and droplet size analyser) to quantify droplet size distributions of atomised solutions containing binder. The effects of adding surfactant to the characteristics of the spray were also determined.

THE 1980s

Gorodnichev, El-Banna and Andreev[60,61], using a 2^4 factorial design protocol, studied the effect of atomising air pressure, binder concentration, fludising air temperature and fluidising air velocity on an aminophenazone/methylcellulose formulation. Granule compression studies with a single punch and a hydraulic press showed that the batch prepared using a high atomising air pressure, high methylcellulose binder concentration (3%), low fluidising air temperature (40°C) and velocity produced the optimum quality of tablets. This granule batch also required the least work of compression during compaction. The same authors[62] then used these conditions to study granule growth by monitoring granule size distribution with increased binder addition. Granule growth curves indicated that the granule process consisted of a primary agglomeration phase (nucleation) and a secondary agglomeration phase of the smaller granules into coaser granules. An empirical kinetic relationship was presented to describe the possible mechanism of granule growth. In 1981 Ceschel, Cottini and Gibellini[63] described the transfer of a conventional wet-massed/tray-dried process to a fluidised-bed granulation process. Initially the process was developed at a laboratory scale (0.5 kg) then scaled-up through pilot scale (10 kg) to a production scale (approximately 100 kg). The successful transfer was achieved by quantifying the effect of process and product variables at each scale on granule characteristics. From this knowledge the key variables were adjusted to ensure that the final granule size distribution, bulk density and moisture content characteristics met previously defined limits. The limits of these granule parameters were selected from traditional wet-massed granule batches which exhibited optimum compression properties. Aulton and Banks[64] used a torque-arm mixer to assess the flow properties of a large number of granulations which had been prepared in a fluidised bed under a wide range of operating conditions. The results from this test correlated well with the results of other, more conventional tests - such as, flow through an orifice, angle of repose and Hausner ratio.

The application of fluidised beds to granulation, drying and spray coating were discussed by Story[65]. Possible granule growth mechanisms during granulation and the effect of granulation control parameters were presented. In summary it was concluded that fluidised-bed granulation is a convenient method for controlling granule growth since the growth regions can be separated by a suitable choice of process condition. A low growth rate in the transition period is thought to be advantageous from a production viewpoint since it results in good reproducibility. The termination of liquid addition during the transition growth phase was also recommended.

El-Arini[66], using a lactose/starch placebo formulation investigated the effects of binder type (gelatin and PVP), binder concentration and rate of spraying on granule characteristics. A 2^3 factorial design was employed in this study. Particle size, particle size distribution, percentage of fines, flowability and granule crushing strength were measured to determine the influence of these variables on the granule growth. The statistically significant effects on these granule properties were found to be as follows. The largest granules were produced using gelatin rather than PVP sprayed at the higher spray rate. Lowest mean size and greatest proportion of fines were produced by using PVP, at a low concentration and at a low spray rate.

Aulton and Banks[67] suggested that the benefits of fluidised-bed granulation had not been fully exploited by the Pharmaceutical Industry due to problems encountered when transferring existing formulations to the process. These problems were attributed to the shortage of fundamental information. The authors considered available published data in terms of apparatus, process and product parameters. It was concluded that most of the work had been carried out to quantify the effect of process variables (e.g. fluidising air temperature/velocity/ humidity and atomisation variables). Whilst certain product parameters (e.g. type, quantity, concentration of binder) had received attention, there had been little effort to investigate the effect of the physico-chemical properties of the starting materials. The growth mechanism and granule structure were subsequently investigated by Banks[68] and Aulton and Banks[69] in 1982 in a number of model powder systems. This was achieved by using sieve analysis, scanning electron microscopy, a fluorescent labelling technique to monitor binder distribution, and a solvent extraction procedure which left a network of binder. Close examination of the data enabled a growth mechanism to be proposed for lactose and modifications to this were discussed for the other materials investigated. Based upon the changes occurring in the microenvironment during powder/droplet collision the factors which

significantly influence granule formation were identified. Aulton[70] explained how it is possible to control the process of fluidised bed granulation once the influence of individual process, apparatus and formulation parameters was understood. Although the number of parameters affecting the process is large, the process is controllable and reproducible.

Ragnarsson and Sjögren[71] compared granulation of a high dose drug (with methylcellulose as binder) in a fluidised bed and in a planetary mixer. The planetary mixer gave denser granules with a broader particle size distribution. Granules from a fluidised-bed granulation process had a narrower size distribution and good flow properties. Upon compression these granules gave stronger tablets and as the amount of binder in the formulation increased so did the tablet strength. Lower strength tablets were obtained from the granules prepared in the planetary mixer and the tablet strength did not improve as the binder concentration increased. It was concluded that the distribution of binder in the granule is as important as its concentration since fluidised-bed processed granules gave stronger tablets than granules prepared using a planetary mixer. Gamlen et al[72] obtained similar results when comparing the processing of paracetamol with hydrolysed gelatin in a fluidised-bed and a planetary mixer. These authors studied granule structure in greater detail by employing a solvent extraction technique and scanning electron microscopy. Small but significant differences were observed in both granules and tablets from each process. Binder distribution was unexpectedly less uniform in fluidised-bed granulated granules than in the wet-massed granules. This could be attributed to the authors' difficulty in fluidising the paracetamol formulation. The FBG granules contained surface patches of binder and were more porous than wet-massed granules. On compression the FBG granules formed tablets of improved tensile strength and improved disintegration/dissolution characteristics. Gamlen and Greer[73] then presented some of the problems associated with fluidised-bed granulation based on their experience with processing of paracetamol and from theoretical considerations. Problems were discussed under formulation and process variables, starting material properties and product characteristics. Materials with a mean particle size greater than 50 micrometers, a low susceptibility to electrostatic charging, and reasonable wetting by water or other acceptable granulating solvents were those likely to make suitable candidates

for fluidised-bed granulationAulton[74] discussed the importance of the wetting stage during fluidised-bed granulation in greater detail. This was divided into powder wettability and the wetting power of the granulating liquid. Processing of model hydrophobic, hydrophilic and mixed systems were used to illustrate these aspects. Methods to quantify the degree of wetting were also described.

Veillard et al[75] (1982) used model soluble and insoluble formulations to study the influence of the granulation method on the characteristics of the granules produced. Granulation was carried out on four pieces of equipment; a fluidised-bed granulator, a planetary mixer, a high speed granulator and an extruder. Fluidised-bed granulation produced the most porous granules. Granules formed from the soluble formulation were always more compact, less porous and stronger than the insoluble formulation. Compressibility of the granules were also measured. A rotary fluidised-bed granulator was compared with a standard fluidised bed granulation unit by Jäger and Bauer[76]. The rotary unit consisted of a fluidised-bed bowl fitted with a rotor disc; granulating fluid was added tangentially. A lactose/starch formulation containing 1% butabarbital and granulated with PVP was processed under comparable conditions in both units. The rotary fluidised-bed unit used high spray rates and needed less processing time and used less energy. Granules from this unit were more spherical with higher density, improved flow properties and lower granule friability than the material produced from the standard FBG. There was however little difference in tablet properties when the granules from each unit were compressed under identical conditions. Thiel and Nguyen[77] studied the fluidised-bed granulation of a 0.1% ordered mix of micronised salicylic acid with lactose as a method of reducing segregation in such mixes. The ordered units were stable when fluidised with no significant losses of micronised salicylic acid during the agitation of processing.

Meshali, El-Banna and El-Sabbagh[78] in 1983 employed a factorial design experiment to assess the effect of binder concentration, binder addition rate, atomising air pressure, fluidising air temperature and velocity on a sulphadiazine formulation granulated with methylcellulose. Binder concentration affected mean granule diameter, bulk density, flow and granule friability. Fluidising air velocity rather surprisingly only affected granule flow properties. The other three variables all had significant affects on mean granule size, flow rate and granule friability. Based upon these results the authors suggested the conditions needed in order to produce granules with a low particle size, high flow rate and acceptable friability. These were obtained using low binder concentration with high values of the other four variables evaluated. Unfortunately, the study did not continue to correlate the granule compression properties with tablet quality. A study describing the use of fluidised-bed granulation to coat flufenamic acid with acrylic resins was reported by Meshali, El-Sabbagh and Foda[79].

Kocova, El-Arini and Polderman[80] studied the physical properties of tablets compressed from granules prepared in a fluidised bed granulator. Tablet

pore diameter, crushing strength and disintegration parameters were measured. The influence of surfactant addition, granule moisture content and lubrication concentration were determined on a starch/lactose placebo formulation. Additions of 1% sodium lauryl sulphate (via the granulating solution) gave granules with good disintegration properties. On compression these granules gave tablets with inferior mechanical strength to those without surfactant. Tablets with surfactant also disintegrated to the original particles whilst those without surfactant disintegrated to agglomerates.

A detailed investigation into the effects of using different grades of PVP and gelatin binder on granulation of three sieve fractions of lactose was reported by Georgakopoulos et al[81]. Gelatin produced larger granules than PVP. Increasing the molecular weight of PVP or the bloom strength of gelatin resulted in a decrease in granule friability and an increase in particle size and porosity. Similar increases in tablet tensile strength were noted when the granules were compressed to a fixed apparent density. Jäger and Bauer[82] in 1984 also studied the effects of polymer blends from different molecular weights of PVP on granule properties. A rotating fluidised-bed granulator was used. The binder blends were composed of various ratios of PVP K90, K25, K17 and K12. Granule size significantly increased as the proportion of high molecular weight PVP (K90) increased in the binder blend. The various binder blends had little effect upon tablet friability and crushing strength although tablet disintegration time increased as the level of K90 increased. It was concluded that granule and tablet properties could be optimised by application of appropriate blends of various molecular weight grades of PVP. Hajdu and Ormós[83] studied the effects of granulating solution feed rate, granulating solution concentration and feed rate of raw materials in a continuously operated FBG. The average particle size and porosity of granules increased with increasing granulating liquid feed rate and concentration. As the feed rate of raw material increased, the average granule diameter and porosity decreased.

Another study employing a 2^4 factorial design was described by Paschos, Gonthier and Jeannin[84]. The four variables studied were atomising air pressure, fluidising air temperature, drying time and binder addition rate. Larger granules with enhanced flow properties were obtained as the binder addition rate increased. Smaller granules were produced as the atomising air pressure increased. Fluidising air temperature had no effect. This is not surprising since the two temperatures selected were too high (90°C and 110°C) and too similar to be discriminatory. Factorial design was also used by Devay, Uderszky and Rácz[85] to study the effect of two effervescent tablet formulation

factors (ratio of citric acid/sodium bicarbonate and PVP concentration) and two process factors (fluidising air temperature and velocity) on an effervescent formulation. The ratio of citric acid/sodium bicarbonate did not affect granule size but as expected did reduce final tablet disintegration time. The other three factors all affected granule size but only the quantity of binder affected tablet disintegration time. Italian workers led by Crimella[86] used a starch/lactose formulation with PVP as binder to compare three wet granulation processes (planetary mixer, high-speed Diosna and fluidised-bed granulation) and two drying procedures (tray and fluidised bed). FBG yielded granules with the lowest apparent density and lowest angle of repose. On compression these granules produced the strongest tablets.

Higashide[87] in 1985 considered the distribution of a model drug (5-fluorouracil) in various particle size fractions. The model drug was included in a lactose/starch formulation granulated with hydroxypropylcellulose as binder. Granulation was carried out in a Uni-Glatt FBG, a Wurster column and an unspecified pneumatic transport system. A higher concentration of drug was found in the larger granules than found in the small granules. The ratio of exipients in the various size fractions were also measured and the weight per cent of starch was bigger in the larger granules than in the smaller granules. The mechanics of the granulation process were used to explain the experimental results.

This paper was followed by two publications containing information on scale-up aspects. In the first, after initially reviewing the formulation and processing factors affecting granule formation, Gore et al[88] considered the relationships among the various processing parameters through four scale-up stages. These stages ranged in batch size from 16 kg to 680kg. The authors found that for successful processing from laboratory scale to production scale, fluidising air temperature increased from 40-50°C to 80-90°C, the binder addition rate increased by a factor of 16 and the total process time increased by 230%. The shear in the production scale units was considered to be greater than in the laboratory size unit and therefore growth required less wetting. Granule and tabletting data from the four units were compared and it was shown that minor changes in particle size distribution of granules had little effect upon compressibility. Increased disintegration times were noted in tablets from the larger production units although this was considered insignificant as dissolution profiles were unchanged. The steps necessary to control the key factors in a production FBG process and the problems experienced were defined. Finally the authors compared granulation in a planetary mixer, high-speed mixer and in a FBG.

The high-speed granulator gave granules with the highest bulk density followed by the planetary mixer then the FBG. The FBG gave more spherical granules with a higher intergranular porosity. The differences in granule structure were studied in greater detail using scanning electron microscopy. Granules from the FBG yielded tablets exhibiting greater compressibility, lower friability and shorter disintegration times than those obtained from the planetary and high speed mixers. These results were attributed to differences in granule structure.

In a fluidised-bed technology review, Jones[89] considered spraying methods, scale-up and processing variables. The choice of spraying methods were discussed and included two granulation techniques (top spray and rotating disc) followed by three coating methods (top, bottom and tangential spraying). Scale-up predictions in a FBG were considered. Critical moisture content in the bowl (the point at which growth becomes uncontrollable) was thought to be the key area since this point is typically lower in production units due to differences in relative bed load. It was suggested that conditions which offer the shortest process time should be used in production units provided that the product performs well in laboratory tests. High inlet temperatures are also recommended since this will enable the maximum spray rate to be employed and also reduce the effect of variation in drying capacity resulting from changing ambient dew point. Spray rate should be based upon an increase in fluidising air volume and not on the size of batch that can be accommodated in the larger production units. The significant role of climatic conditions on the process was also discussed especially in geographic locations where humidity varies throughout the year.

In 1986 Alkan and Yuksel[90] evaluated the effect of increasing the quantity of PVP binder in a starch/lactose formulation from 2 to 16% w/w. The PVP was added as a 7.5%w/w ethanolic solution. As expected the granule size increased and the granule friability decreased with increased level of binder. The change in granule size was however more evident with the lower concentrations of binder. The narrowest granule size distribution was obtained at a 6% w/w level of binder. This value was thought to be the critical concentration at which granule properties change and was attributed to a change in the mechanism of granule formation. It was suggested that below 6% growth predominantly occurred by nucleation whilst at higher concentration growth proceeded by direct agglomeration of the primary nuclei particles. The effect of three binder concentrations (5, 10 and 15% w/w) and three types of binder (gelatin, acacia and PVP) on granulation of sulphadiazine powder in a FBG and using conventional wet massing was reported by Nouh[91]. Granule properties of each batch were characterised and showed that, as would be

expected, granule size increased as binder concentration increased. Smaller granules were obtained from the FBG than were obtained by conventional wet massing. Both gelatin and acacia gave larger granules than PVP in the FBG. Surprisingly tablets compressed from granules processed in the FBG had longer disintegration times and higher friability than those from conventional wet granulation. A comparison of the processing of a chloralhydrate formulation by FBG and dry granulation (compaction) was studied by Desmolin[92]. As little difference in the quality of the final product was found both methods were considered to be equivalent. Jinot et al[93] studied the effect of including various ratios of water-soluble (lactose, mannitol and disodium carbonate) and water-absorbent (cross-linked PVP and wheat starch) excipients on the FBG of a dicalcium phosphate formulation. The influence of each excipient was studied by analysing the particle size distribution of the granules produced. Lactose, mannitol and wheat starch increased the coarser sieve fraction and reduced the finer fraction sizes. Disodium carbonate increased both fractions whilst cross-linked PVP reduced the finer sieve fraction. As none of the batches met the desired particle size distribution the authors then determined [94] which operating conditions needed to be controlled to achieve this predetermined distribution. Increases in atomising air pressure and addition rate of granulating solution appeared to meet their objectives.

In a comprehensive paper published in 1987, Rowley[95] described the scale-up factors in adapting a conventional wet granulation process to FBG. After review of the existing wet granulation process it was recommended that FBG feasibility studies should be carried out at a 15kg scale to study and determine the key processing parameters (eg spray rate, atomising air pressure and fluidising air temperature). Once these parameters have been identified and retested, scale-up should proceed to an intermediate scale of approximately 60-100kg provided that the final production scale is in excess of 200kg. The author indicated that premix times used for 15-60kg should be appropriate for larger bowl sizes. Spray rates cannot always be directly increased on scale-up and caution should be exercised. Spray angle of atomised granulating solution can cause problems, whilst bowl charge size should be accurate since under or over filling can also be detrimental. The duration and frequency of shaking the filter bag can be critical. A practical example, including experimental data, of such a scale-up programme was presented. It was finally concluded that most formulations can be processed using a FBG provided that a thorough review, a carefully planned feasibility study and an intermediate scale up procedure are carried out.

An excellent paper reviewing pharmaceutical wet granulation was published by Kristensen and Schaefer[96]. Initially the fundamental mechanisms of granule growth were presented. A comprehensive discussion of published data covering granulation methods and equipment, granulation variables and end point control was also presented. It is interesting to note that the authors indicate that no end-point control method for granulations in the FBG has yet been devised. Hontz[97] investigated the effects of inlet air temperature, binder (PVP) concentration, binder solution concentration and microcrystalline cellulose concentration upon granule and tablet properties using an experiment of factorial design. Binder and microcrystalline cellulose concentration were found to have a significant effect upon granule tabletting properties. Alkan and Ulusoy[98] reported again a comparative study examining the addition of binder (PVP) either as solution or as a dry powder. They found a larger mean granule size when the dry binder was granulated with ethanol in a FBG. However, those granules produced by the addition or an alcoholic solution of PVP were less friable and more free flowing.

In 1988, Huang and Kono[99] developed a mathematical coalescence model for batch fluidised bed granulators. This model was based on assessments of surface crater and liquid bridge formation in colliding granules. These, in turn, depended on granule porosity and voidage saturation. Wan and Lim[100] studied the effect of incorporating PVP as a binder on fluidised bed granulation of lactose. They were able to produce almost monosized granules with a low PVP concentration, a slow spray rate or small volume of PVP solution, and with a large feed load. Of the variables studied, the concentration of PVP binder exerted the greatest influence on size and properties of the granules. In the following year they[101] studied further the mode of addition of PVP on the properties of lactose granules and starch granules. The PVP was added either externally (in the form of a spray) or internally (as a powder). They found that the addition of internal PVP enhanced the yield of granules larger than 355 μm whilst these larger granules were less in evidence when the binder was added externally. In a subsequent paper [102] compression properties of these FBG granules were examined. Olsen[103], in a review of batch fluidised bed processing equipment relevant to the pharmaceutical industry, described fluidised-bed granulators and suggested variations that can be built into customised equipment to meet the requirements of particular products. The article also describes other design considerations, including, GMP features, safety, product handling and process control. The effects of the bag-shaking

TABLE 1 : Subject Index of Published Articles

REVIEW ARTICLES	INFLUENCE OF RAW MATERIALS	APPARATUS PARAMETERS
General Aspects of FBG 5, 6, 11, 12, 43, 45, 65, 67, 68, 88, 89, 96.	**Starting Material Type** 7, 38, 40, 42, 50, 51, 68, 73, 74, 75, 81, 93.	**Safety & Environmental** 36, 37, 46, 47, 103.
GROWTH MECHANISMS / MODELS	**Wettability of Starting Materials** 9, 29, 30, 46, 58, 68, 74, 80.	**Fluidised Bed Granulator Design** 3, 4, 21, 23, 24, 57, 76, 89, 103, 104.
Studies of Pharmaceutical Systems 3, 16, 22, 31, 42, 49, 55, 62, 68, 69, 87, 90, 99, 105-111[1].	**Binder Type** 4, 7, 9, 14, 26, 39, 46, 52, 53, 54, 55, 66, 81, 82, 91, 98.	**Nozzle Design & Position** 4, 9, 15, 21, 27, 28, 38, 39, 48, 68.

Notes

1. Whilst this review has been limited to studies of pharmaceutical systems, there are a number of important studies from chemical engineering sources which relate to fundamental growth mechanisms of granules during fluidised bed granulation (refs. 105-111). These are worthy of note ; their findings can be extrapolated to pharmaceutical systems.

TABLE 1 (cont) : Subject Index of Published Articles

PROCESSING PARAMETERS			END PRODUCT PROPERTIES [2]
Fluidising Air Flow Rate 4, 10, 21, 25, 48, 60, 61, 68, 78. **Fluidising (Inlet) Air Temperature** 4, 15, 27, 28, 40, 42, 48, 60, 61, 63, 68, 78, 84, 97. **Binder Concentration (and thus Viscosity) and Quantity** 7, 10, 14, 15, 19, 20, 28, 29, 39, 41, 42, 46, 48, 52, 53, 61, 63, 66, 68, 71, 78, 82, 83, 85, 90, 91, 97, 100, 101. **Granulating Solution : Liquid Flow Rate to Atomiser** 4, 10, 13, 19, 20, 26, 27, 28, 31, 39, 40, 42, 56, 63, 66, 68, 78, 83, 84, 94, 100.	**Granulating Solution : Total Volume** 19, 20, 35, 54, 56, 100. **Granulating Solution : Temperature** 9, 48, 63, 68. **Atomizing Air Pressure** 9, 15, 17, 21, 27, 38, 40, 41, 48, 60, 61, 63, 68, 78, 84. **Droplet Size** 9, 39, 40, 41, 42, 59, 68, 89. **Bed Load** 17, 21, 26, 42, 99, 101. **Bed Expansion** 21, 55.	**Moisture within Bed and Granules** 3, 89. **Process Time** 4, 9, 17, 40, 84. **Comparison of FBG with other Granulation Techniques** 71, 72, 75, 86, 87, 91, 92. **Continuous FBG Processing** 83. **Control and Automation** 38, 46, 68, 70. **Scale-Up** 8, 17, 25, 46, 63, 88, 89, 95.	**Granule Structure : Distribution of Binder within the Granules** 9, 72, 98. **Drug Content Uniformity : Distribution of Low-Dose Active** 1, 9, 34, 35, 76, 77, 87. **Evaluation of Tablets Compressed from Fluidised Bed Granules** 7, 9, 10, 14, 30, 32, 48, 60, 61, 63, 68, 71, 72, 75, 76, 80, 81, 82, 85, 86, 91, 97, 102, 104.

Notes

2. Many of the articles quoted in this review assess the quality of the granules produced by FBG by means of tests such as granule particle size, size distribution, flowability, bulk and granule density, friability and porosity. These properties are therefore not categorised in this table.

cycle on granulations in a FBG process was described by Rowley[104]. The article indicated that the particle size distribution of the finished granulation could be improved if the shake time and the coresponding interval between bag shakes are optimised.

CONCLUDING PARAGRAPH

Considerable amounts of published data are now available to the pharmaceutical formulator and process development scientist following three decades of research into the process of fluidised bed granulation. This has resulted in a greater understanding of the inter-relationships between the apparatus, process and material variables and, more importantly, the availability of information on the fundamental mechanics of the process. It is believed that this information should eliminate many of the problems originally encountered by the pharmaceutical industry when implementing the technique in the early 1970s. To aid the reader find published material for further indepth reading, a cross reference to the published articles on a subject basis is provided in Table 1.

BIBLIOGRAPHY

1. Wurster, D.E., J. Am. Pharm. Ass. (Sci. Edn.), 49, 82 (1960).

2. Wurster, D.E. J. Am. Pharm. Ass. (Sci. Edn.), 48 (8), 451-454 (1959).

3. Scott, M.W., Lieberman, H.A., Rankell, A.S. and Battista, J.V. J. Pharm. Sci., 53 (3), 314-319 (1964).

4. Rankell, A.S., Scott, M.W., Lieberman, H.A., Chow, F.S. and Battista, J.V. J. Pharm. Sci., 53 (3), 320 (1964).

5. Contini, S. and Atasoy, K. Pharm. Ind., 28, 144-146 (1966).

6. Wolf, G. Drugs Made in Germany, 11, 172-180 (1968).

7. Liske, T. and Mobus, W. Drugs made in Germany, 11 (4), 182-189 (1968).

8. Feigenbaum, L. Labo-Pharma-Problemes et Techniques, 177,62-67 (1969).

9. Thurn, U. Dissertation No. 4511, Eidgenossischen Technischen, Hochschule, Zurich (1970).

10. Bank, A., Bezzegh, D. and Fekette, P. Proc. 2nd. Conf. Appl. Phys. Chem., 2, 687-92. (1971).

11. Ritschel, W.A. Pharm. Ind., 33 (10), 685-9 (1971).

12. Kala, H., Dittgen, M. and Moldenhauer, H. Pharmazie, 26 (11), 664-675 (1971).

13. Davies, W.L. and Gloor, W.T. J. Pharm. Sci., 60 (12), 1869 - 1874 (1971)..

14. Davies, W.L. and Gloor, W.T. J. Pharm Sci., 61 (4), 618-622 (1972) .

15. Davies, W.L. and Gloor, W.T. J. Pharm Sci., 62 (1), 170-172. (1973).

16. Harada, K. Kagaku Kogaku, 36 (11), 1237-43 (1972).

17. Gupte, A.R. Pharm. Ind., 35, 17-20 (1973).

18. Ormós, Z. Hung. J. Ind. Chem., 1, 207-228 (1973).

19. Ormós, Z., Pataki, K. and Csukás, B. Hung. J. Ind. Chem., 1, 307-328 (1973).

20. Ormós, Z., Pataki, K. and Csukás, B. Hung. J. Ind. Chem., 1, 463-474 (1973).

21. Ormós, Z., Pataki, K. and Csukás, B. Hung. J. Ind. Chem., 1, 475-492 (1973).

22. Ormós, Z., Pataki, K. and Csukás, B. Hung. J. Ind. Chem., 3, 193-216 (1975).

23. Ormós, Z., Pataki, K. and Csukás, B. Hung. J. Ind. Chem., 3, 631-646 (1975).

24. Csukás, B. and Ormós, Z. Int. Congr. Chem. Eng., Chem. Equip. Des. Autom., Proc. 5th, D, D4.22 (1975).

25. Campy, D., Eaves, T., Grudzinski, E.M. and Worthington, H.E.C. J. Pharm. Pharmac., 26: Suppl. 76P (1974).

26. Rouiller, M., Gurny, R. and Doelker, E. Act. Pharm. Technol., 21 (2), 129-138 (1975).

27. Prioux, P., Lefort Des Ylouses, D., Seiller, M. and Duchene, D. J. Pharm. Belg., 30 (2), 132-146 (1975).

28. Johnson, M.C.R., Rees, J.E. and Sendall, F. J. Pharm. Pharmac.,27: Suppl. 80P. (1975).

29. Shinoda, A., Nasu, T., Furikawa, M., Sakashita, S., Uesugi, K., Miyake, Y. and Toyoshima, S. Yakuzaigaku, 36 (2), 83-88 (1976).

30. Aulton, M.E., Banks, M. and Smith, D.K. J. Pharm. Pharmac. 29, Suppl. 59P (1977).

31. Mehta, A., Adams, K. and Zoglio, M.A. J. Pharm. Sci., 66 (10), 1462-146 (1977).

32. Ritschel, W.A. and Erni, W. J. Pharm. Sci., 66 (10), 1438-1441 (1977).

33. Ormós, Z., Pataki, K., Csukás, B., Dencs, B. Proc. Conf. Appl. Chem. Unit Oper. Processes 3rd, 595-598 (1977).

34. Motto, D. Boll. Chim. Farm., 116, 307-313 (1977).

35. Crooks, M.J. and Schade, H.W. Powd. Tech., 19, 103-108 (1978).

36. Kulling, W. Pharm. Ind. 39, 631-636 (1977).

37. Kulling, W. Pharm. Ind. 39, 831-834 (1977).

38. Schaefer, T. and Wørts, O. Arch. Pharm. Chem. Sci. Ed., 5, 51-60 (1977).

39. Schaefer, T. and Wørts, O. Arch. Pharm. Chem. Sci. Ed., 5, 178-193 (1977).

40. Schaefer, T. and Wørts, O. Arch. Pharm. Chem. Sci. Ed., 6, 1-13 (1978).

41. Schaefer, T. and Wørts, O. Arch. Pharm. Chem. Sci. Ed., 6, 14-25 (1978).

42. Schaefer, T. and Wørts, O. Arch. Pharm. Chem. Sci. Ed., 6, 69-82 (1978).

43. Wørts, O. Pharm. Int., 6, 12-15 (1972).

44. Harbert, F.C. Mfg. Chem. and Aerosol News, 45 (1), 23-25 (1974).

45. Banks, M., Scherer Award Paper, submitted 1974, (unpublished).

46. Schepky, G. Acta Pharm. Technol. 24(3), 185-212 (1978).

47. Simon, E.J. Mfg. Chem. and Aerosol News, 49 (1), 23-32 (1978).

48. Aulton, M.E., Banks, M., Mfg. Chem. and Aerosol News 12, 50-56 (1978).

49. Aulton, M.E., Banks, M., Davies, I. ab I. Drug Dev. and Ind. Pharm. 4 (6), 537-539 (1978).

50. Ormós, Z., Pataki, K. Hung. J. Indust. Chem., 7, 89-103 (1979).

51. Ormós, Z., Pataki, K. Hung. J. Indust. Chem., 7, 105-117 (1979).

52. Ormós, Z., Pataki, K., Stefko, B. Hung. J. Indust. Chem., 7, 131-140 (1979).

53. Ormós, Z., Pataki, K., Stefko, B. Hung. J. Indust. Chem., 7, 141-151 (1979).

54. Ormós, Z. Hung. J. Ind. Chem., 7, 153-163 (1979).

55. Ormós, Z. Hung. J. Ind. Chem., 7, 221-235 (1979).

56. Ormós, Z., Pataki, K. Hung. J. Indust. Chem., 7, 237-24 (1979).

57. Ormós, Z., Machacs, M., Pataki, K. Hung. J. Ind. Chem., 7, 341-350 (1979).

58. Aulton, M.E., and Banks, M. Proc. Int. Conf. Powder Technology in Pharmacy, Powder Advisory Centre, Basel, Switzerland (June 1979).

59. Aulton, M.E., Banks, M. J. Pharm. Pharmac. 31, Suppl. 102P. (1979)

60. Gorodnichev, V.I., El-Banna, H.M., Andreev, B.V. Pharm. Chem. J. (USSR) 14(10), 72-77 (1980).

61. Gorodnichev, V.I., El-Banna, H.M., Andreev, B.V. Pharmazie 36(4), 270-273. (1981)

62. Andreev, B.V., Gorodnichev, V.I. Minina, S.A, El-Banna, H.M. Pharm. Ind. 42(12), 1304-1306 (1980).

63. Ceschel, G.C., Cottini, F., Gibellini, M. Il Farmaco Ed. Prat. 36 (6), 281-293. (1981).

64. Aulton, M.E., Banks, M. Proc. Int. Conf. Pharm. Tech. and Prod. Mfr, Powder Advisory Centre/APGI, Paris, (December 1981)

65. Story, M.J. Int. J. Pharm. Tech. & Prod. Mfr. 2(4), 19-23 (1981).

66. Kocova El-Arini, S. Pharm. Ind. 43(7), 674-679 (1981).

67. Aulton, M.E., Banks, M. Int. J. Pharm Tech. & Prod. Mfr. 2(4), 24-29 (1981).

68. Banks, M. Ph. D. Thesis, C.N.A.A. (Leicester Polytechnic). (1981).

69. Aulton, M.E., Banks, M. Proc. Brit. Pharm. Technol. Conf., Solid Dosage Research Unit, London, p362 (April 1982).

70. Aulton, M.E. Proc. Interphex Conference, Brighton, Paper 2a - 3 (May 1982).

71. Ragnarsson, G, Sjogren, J. Int. J. Pharmaceut. 12, 163-171 (1982).

72. Gamlen, M.J., Seager, H., Warrack, J.K. Int. J. Pharm. Tech. & Prod. Mfr. 3(4), 108-114 (1982).

73. Gamlen, M.J., Greer, W. Fluid. Technol. Pharm. Manuf. Int. Conf. Paper 2. (1982).

74. Aulton, M.E. Fluid. Technol. Pharm. Manuf. Int. Conf. Paper 3, Powder Advisory Centre, London (1982).

75. Veillard, M., Bentejac, R., Puisieux, F., Duchene, D. Int. J. Pharm. Tech. & Prod. Mfr. 3(4) 100-107 (1982).

76. Jäger, K-F., Bauer, K.H. Drugs Made in Germany 25(2), 61-65 (1982).

77. Thiel, W. J. and Nguyen, L.T. J. Pharm. Pharmacol. 34 692-699 (1982).

78. Meshali, M., El-Banna, H.M., El-Sabbagh, H. Pharmazie 38(5), 323-325 (1983).

79. Meshali, M., El-Sabbagh, H., Foda, A. Acta Pharm. Technol. 29(3), 217-219 (1983).

80. Kocova El Arini, S., Polderman, J. Drugs Made in Germany 26(4) 205-211 (1983).

81. Georgakopoulos, P.P., Malamataris, S., Dolamidis, G., Pharmazie 38(4), 240-243 (1983).

82. Jäger, K-F., Bauer, K.H. Acta Pharmaceutica Technologica 30(1), 85-92 (1984).

83. Hajdu, R., Ormos, Z. Hung. J. Ind. Chem. 12, 425-430 (1983).

84 Paschos, S., Gonthier, Y., Jeannin, C. Int. J. Pharm. Tech and Prod. Mfr. 5(4), 13-17 (1984).

85. Devay, A., Uderszky, J., Rácz, I. Acta Pharmaceutica Technologica 30(3), 239-242 (1984).

86. Crimella, T., Delucchi, F., Gallazzi, A., Kauten, G., Iamartino, P., Maccario, G., Pedrani, M., Rizzo, D., Boll. Chim. Farm. 123(5) 210-222 (1984).

87. Higashide, F., Miki, Y., Nozawa, Y., Ishibashi, K., Pharm. Ind. 47(11), 1202-1205 (1985).

88. Gore, A.Y., McFarland, D.W., Batuyios, N.H., Pharm. Technol. 9(9), 114-122 (1985).

89. Jones, D.M. Pharm. Technol. 9(4), 50-62 (1985).

90. Alkan, M.H., Yuksel, A. Drug Dev. and Indust. Pharm. 12(10), 1529-1543 (1986).

91. Nouh, A.T.I. Pharm. Ind. 48(6), 670-673 (1986).

92. Desmolin, H. S.T.P. Pharma. 2, 863-866 (1986).

93. Jinot, J-C., Piquet, E., Bessot, C., Guyot, J-C. S.T.P. Pharma 2(13), 126-131 (1986)

94. Jinot, J-C., Piquet, E., Bessot, C., Guyot, J-C. S.T.P. Pharma 2(14), 196-201 (1986).

95. Rowley, F.A. Pharm. Technol. 11(7), 76-79 (1987).

96. Kristensen, H.G., Schaefer, T., Drug Dev. and Indust. Pharm. 13 (4&5), 803-872 (1987).

97. Hontz, J. "Assessment of selected formulation and processing variables in fluid bed granulation", PhD thesis, University of Maryland in Baltimore. (1987) (See Dissertation Abs. Int. 48 (6), 1655-B (1987)).

98. Alkan, H., Ulusoy, A. Doga Tu J. Med. and Pharm., 11(1), 1-7 (1987).

99. Huang, Ching-Chung, Kono, H.O. Powder Technology 55, 35- 49 (1988).

100. Wan, L.S.C. and Lim, K.S. S.T.P. Pharma, 4 (7) 560-571(1988).

101. Wan, L.S.C. and Lim, K.S. S.T.P. Pharma 5 (4), 244-250 (1989).

102. Wan, L.S.C. and Lim, K.S. S.T.P. Pharma 5(8/9), 530-536 (1989).

103. Olsen, K.W. Pharm.Technol. 13(1), 34 - 46 (1989).

104. Rowley, F.A. Pharm. Technol. 13(9), 78-82 (1989).

105. Smith, P.G. A study of fluidised-bed graunulation. PhD thesis, University of London. (1980).

106. Oliver, R. Fluidised-bed granulation. PhD thesis, Heriot-Watt University. (1982).

107. Smith, P.G. and Nienow, A.W. Chem. Eng. Sci., 38(8), 1223-1231 (1983).

108. Smith, P.G. and Nienow, A.W. Chem. Eng. Sci., 38(8), 1233- 1240 (1983).

109. Maroglou, A. Fluidised-bed granulation. PhD. thesis, University of Aston in Birmingham (1985).

110. Maroglou, A. and Nienow, A.W. Powder Metallurgy, 29(4),291-195 (1986).

111. Waldie, B., Wilkinson, D. & Zachra, L. Chem. Eng. Sci. 42(4), 653-665 (1987).