Recent Advances in Techniques of Tabletting

By

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The manufacture of various dosage forms is no longer considered to be an 'art' as the existing operations are being constantly modified by the incorporation of latest techniques based on the experimental data. It has now been recognised that new and improved techniques are desirable in any manufacturing process and importance is given to quality rather than economy.

Formulation of a dosage form such as tablet can markedly affect the therapeutic efficacy of the drug and physico-chemical properties of the product if various manufacturing processes are not standardised. Parameters to be controlled include the individual and bulk particulate properties, uniform mixing of the drug with the excipients, physical properties of the granulating agent, the most suitable time and temperature conditions of drying and compression pressure. Much research work has been carried out on these parameters but the pharmaceutical manufacturers have not applied the information derived from these studies to the manufacture of tablets to a significant degree and continue to rely upon empirical formulation and processing methods.

In the field of pharmaceutical industry, physical pharmacy and biopharmaceutics have contributed immensely in the development of various dosage forms. The manufacture of these products is no longer considered to be an 'art' as the existing operations are being constantly modified by the incorporation of latest techniques based on the experimental data. It has now been recognised that new and improved techniques are desirable in any manufacturing process and importance is given to quality rather than economy. The modified formulation will necessitate the evaluation of the physico-chemical and biological properties of the product because the successful marketing of any product depends upon the clear understanding of various factors which may lead to the improvement of quality and hence the bioavailability of such dosage form.

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Particle size reduction:

In the manufacture of tablets, particle size reduction is an important step in the control of the flow properties of powders or granules, homogeneity of a mixture of powders and the absorption of medicament. The selection of a suitable comminution machine for a specific purpose has been discussed by Hiorns[1]. The dependence on material properties such as hardness was considered with reference to methods for determining the crushability and grindability. In the grinding zone of a mill, the particle-size distribution is undergoing substantial change and little is known about the flow properties of granular material under such conditions. The strength of particles varies with size, larger ones generally being weaker; but since they are irregular in shape, the direction and magnitude of the force applied to each particle can only be stated in statistical terms. Hiorns explained that since there is no theory of the comminution process that is firmly based on physical principles, the choice of equipment is usually based on experience coupled with empirical tests, depending upon properties of the feed and the extent of size reduction required.

In the pharmaceutical industry, the equipment used in comminution is almost as varied as the types of materials subjected to this process. Different types of mills are used for cutting, crushing or pulverizing with or without a measure of self-contained classification control. Probably the most commonly used mill for drug grinding is the impact mill in which large particles are split apart by the force with which they are struck by hammers or with which they strike other particles or the walls of the chambers. The large particles separated with the help of screens and collecting cyclones are subjected to further reduction.

The development of the fluid energy mill arose from the application of kinetic energy in particle size reduction. The absence of moving parts and the careful design of the grinding chamber permit grinding and classification to take place simultaneously in the absence of attritional heat. With hygeinic fittings and clean, compressed air as the fluid energy source, uncontaminated particles uniformly below 10m in size can be obtained. The importance of fluid energy mill in particle size reduction can be seen in the appearance of a pharmacopoeial requirement of a 'micronized' drug.

Process equipment for grinding with special reference to the pharmaceutical industry have been discussed by McDonald[2]. An interesting development is the mill that grinds samples under liquid nitrogen and therefore, can be used for milling certain problemetic materials.

Sieves or screens are commonly used in the classification and separation of various grades of powder but the new techniques used for the measurement of particle size are based on permeability electrical conductivity or lightscattering. Besides these, measurement of other characteristics of powders such as cohesiveness is very essential because cohesive powders do not flow easily. In general damp powders are more cohesive than dry powders and also the finer the particles in a powder, the more cohesive it is[3]. It has been observed that very fine particles form agglomerates or granules when they are shaken and they tend to block pipes, orifices and hoppers of tablet machines.

Pharmaceutical powders in the size range of 50-150 m exhibit midly cohesive characteristics and they have angle of repose between 40° and 60° when measured by any of the standard methods such as funnel, cylinder

or revolving techniques. The angle of repose is affected by the bulk density, particle size and the equipment used.

Mixing:

One of the basic requirements in solid formulations is the preparation of a uniform blend prior to final tabletting. The importance of uniform drug distribution in the final dosage form is recognised by the official compendia which require a unfiromity of various substances in all dosage units. Recently instances of excessive intertablet dose variation in commercial pharmaceutical products were brought to light and many drug recalls have occurred because of unsatisfactory drug distribution. Problems of excessive dose variation generally appear to be confined to high potency low dose drugs where a substantial portion of the weight of the final product is due to excipients employed as fillers, lubricants, disintegrators.

It is, therefore, imperative that all powder mixtures cantaining two or more components varying in shape, particle size and density should show uniformity when subjected to statistical analysis employing physical or chemical assay results obtained on samples acquired on the basis of a well designed sampling plan.

The selection of equipment for the mixing of powders depends upon the mechanism by which the particles get mixed in the large variety of mixers or blenders. In the sample tumbler blenders, the mobility of the particles takes place by the diffusion method and consequently attrition of particles will be minimal. On the other hand, impact mills and mullers tend to combine interparticulate mixing with particle size reduction through their violent scattering and shearing forces.

Several published reviews dealth with various aspects of mixing including theories of mixing, methods of sampling mixer evaluations and related statistical techniques [5, 6]. Some articles were also published on mixing operations in V-type mixers [7,8]. These studies focused their attention primarily on the rates of mixing, the operative mechanism involved and performance evaluations comparing V-mixers with other types of mixing equipment.

In 1970, Miles and Schofield [9] reviewed the many factors that must be considered when selecting a suitable solid mixer including particle size and shape, flow properties, segregation tendency, size reduction and moisture content of the materials. In view of the wide-spread use in the pharmaceutical industry of tumbling mixers such as double Cone and V-blenders, it is important to note that such equipment are likely to cause segregation with free-flowing powders having a wide size or density difference between components.

In pharmaceutical mixing operations where materials of different particle characteristics (size, shape, density etc.) are encountered, preparation of uniform blend involves not only successful mixing but also the avoidance of segregation in any subsequent handling. It is generally felt that segregation is a potentially greater problem with free-flowing materials than with poor flowing blends. This is based on one criterion for mixing i.e. powders must have independent motion or flow to mix or unmix[5]. The distribution of low dose drugs via solvent was suggested by Train[5], colourants have commonly been added to tablet granulations in this manner.

A twin-shall blender was used to investigate the blending procedures used in mixing aspirin-lactose (1:99) blends [10]. Powders having good flow were less apt to show unmixing tendencies and better blends were obtained when the amount of solvent was limited since this prevented drug migration. A vertical Cone mixer was used to mix a single active component, fenfluramine hydrochloride with a number of diluents.

An alternative process which avoids the potential problem of demixing during material transfer operations, involves the use of a fluid-bed spray granulator for carrying out mixing, granulating and drying operations without unloading the powder mix. Other studies assessed the influence of moisture and the role of mixing aids on the mixing efficiency in urinary powder systems.

Mixing problems associated with the cohesiveness of minor and major components in two component systems were investigated by Shotton and Orr [12]. A free-flowing major component such as heavy magnesium carbonate may facilitate distribution of the minor component by causing dispersion of agglomerates due to shear. Electron microscopy and other techniques were used by Travers and White [13] to show that indentations and irregularities on a crystalline diluent can act as adsorption sites for a micronised powder thus reducing segregation tendencies in a powder mix.

Granulating:

For several reasons it may be necessary to granulate powdered materials prior to tablet compression. Many of the machine problems due to dust, cross-contamination are reduced by decreasing the quantity of fine powder in the granules. Besides this, there is improvement in the flow properties and increased uniformity in weight of tablets.

It is well known that crystalline substances, in general, do not require any processing and can be compressed directly. Efforts are being made to find substances like spray-dried lactose that can be mixed with active drugs and can be compressed directly without additional processing. Out of the three methods of granulation recommended by B.P.C. i.e. dry granulations, granulation by preliminary compression and wet granulation, the last technique is still an important and commonly used process in tablet making.

The impression that if the lubricant is incorporated into the mixture of drug and other excipients, it will lose its lubricating properties, has been found to be incorrect. It has been demonstrated that tablets prepared with these internally or "self libricated" granulations exhibited not only very good physical properties but also gave a reduced disintegration time.

A number of investigations have been carried out by various research workers to reduce the numbers of steps involved in the manufacture of tablets. Many of these inventions proved to be applicable to only a few substances or to small scale operations only. Peck [14] has reviewed various methods of granulation such as wet granulation, granulation by extrusion or fusion, dry granulation, spray drying, granulation by crystallization and advantages and disadvantages of various types of granulating equipment.

The selection of equipment is controlled by the method by which the granulating fluid is added to the mixture of dry powders. The two basic type of equipments such as vertical shaft with sigma blade and horizontal shaft mixers are still commonly used. It has been found that better distribution can be achieved by spraying the granulating fluid in the dry powders rather than pouring. This development has led to the design of a fluid-bed granulator. Although this apparatus was fabricated for the coating of tablets but it has given promising results for formulation of granules with adhesive materials. Thus the fluid-bed equipment not only prepares the granules but also is used to dry the granules.

Another invention which has been patented [15] is regarding the vapour phase granulating system. The granulating solution is passed through a trunion of the rotating drum where it condenses on the moving solid particles and initiate the formation of agglomerates. The heated jacket on the outside of the drum or the Chamber assists to remove the excess moisture to a desired level. Thus the blending granulation and drying processes are carried out in one step only. In order to overcome the limitation imposed by this process to the use of vapour of the granulating fluid, some modification have been incorporated in this process by programming the rate of addition of the granulating agent and rate of removal of the excess solvent by combined temperature and vacuum control system. Authomation of this process has resulted in the batch-to batch unfformity, reduced cross-contamination and reduction in material handling.

The preparation of granules, according to another invention, untilises spray congealing. In this method a melt or hot slurry of selected materials is sprayed into an air-cooled chamber to form particles of predetermined size range. This method has limited applications for granulation but it probably could be a useful method for taste masking, affording protection to unstable drugs and preparation of sustained release products.

In a modified method, [16] granulation can be undertaken in a [16] inch coating pan. The pan provided with extra heaters so that pan contents can be raised to 60°. After the addition of a disintegrant, 4% polyethylene glycol (PEG) 6000 is incorporated. The whole mass is tumbled and heated for 5 minutes. The molten PEG acts as a binder and spreads itself over the powder. After thorough mixing, the mas is allowed to cool while the pan is kept rotating. During cooling, PEG solidifies to produce granules. The resulting granules are free flowing but may require the inclusion of a glidant. The whole granulation process takes about 15–20 minutes with minimum handling and with the use of a single piece of equipment.

Solid spherical, free flowing granules with low friability can be prepared by spheronization of extruded pellets [17] of wet granulated materials. Equipment basically consists of a horizontal spinning plate at the base of a stationary cylinder. The controlling factors in the granulation are degree of wetting, solvent content, temperature, plasticity, adhesive properties of wet mass, extruder speed, extruder screen size and spheronizer speed. These factors consequently affect the tablets hardness and dissolution rate.

Although it has been claimed that a disadvantage of wet granulation is that crystal growth (e.g. of micronized material) cannot be reliably eliminated, it is also possible that dry granulations have an adverse effect on the dissolution behaviour of a substance due to agglomeration. In the dry granulation, usually powder mix is compacted in heavy duty tablet making machines but roll-type compacting machines have been used to form a variety of compacts which are comminuted suitably and compressed on a standard rotary tablet press.

Drying:

Drying of solids is a unit operation which has received little theoretical or practical consideration even in pharmaceutical technology despite its importance in processes such as the manufacture of tablet granulation.

Drying of granulation has traditional be performed by tray drying and the factors involved have been classified as a dynamic balance between the rate of moisture movement from inside the solid to the surface and the evaporation of moisture from the surface [18]. It has been shown that the drying rate is controlled by the film thickness of the vapour above the bed and there is no difference fundamentally between the heat balances involved in fluidised drying and those involved in tray drying. In countercurrent rotary dryers, the rate determining step is diffusion of moisture in the granule.

Fluidization occurs between an incipient fluidizing velocity and is limited at the higher and by an entrainment velocity beyond which conveyance takes place. The linear velocity of the air in the bed is different from that in the ducts. The velocity between particles in the free cross section i.e. in the ducts is denoted as superficial velocity.

In a mixture of two particle sizes it was shown that when one fraction is abundant, there is a tendency for accumulation of the course fraction above the distributor.

The temperature of the material being dried is frequently uniform through the bed except for a small range immediately above the distributor. It is not possible to obtain a countercurrent arrangement of the streams of the material and drying medium in a fluid bed dryer. Therefore, one would not expect that the drying mechanism reported in counter-current drying would apply to fluid-bed drying.

During drying there is some classification of the material in the dryer; fine particles are dried faster and become less dense and less dry but denser large particles show some accumulation tendencies in the lower central area. Unlike counter-current rotary drying, fluid-bed drying cannot be accounted for by water diffusion inside the granules as the rate limiting step.

In high speed compression, it is important to take into account the propertion of residual moisture in the granulation. Optimum quantities of residual moisture depend upon the physical and chemical characteristics of the particular solids. In order to produce granules with relatively simple control of residual moisture, a rotary vacuum system has been developed [19] with instrumentation capable of precise determination of drying rates. By plotting drying rate dw/de versus time, it can be seen that rate of drying is fast as the temperature increases.

Another important specialized drying operation is spray drying. Spray dried slurries of aluminium silicate or magnesium carbonate with various types of binders to produce fine-particle aggregates in the size range of

10-80 m. Lactose has also been spray dried from an aqueous solution.

Dose variation in tablets generally arises either as a result of tablet weight variation or because the drug is heterogeneously distributed throughout the tablet mass. It has been shown [20] that larger granules contained a disproportionately high concentration of drug at the expense of the smaller granules. However, they gave no experimental details of either the massing condition or the drying conditions. Such variables have been shown to effect both the physical properties of granules prepared by a wet granulation process [21] and also the migration of soluble constituents to the periphery of such granules during the drying stage. It has also been demonstrated that the planetary mixer is more efficient in its distribution hinder solution throughout the mass than the **other mixer.**

When infrared radiation [22] is used to dry a mixed bed composed of Kaolin granules massed with salt solution, solute migration can deplete the bottom layer of granules so that it contains barely one quarter of the initial salt concentration. This depletion has been found to be much greater than that recurring when a similar bed is dried by convection drying. The augmented solute migration in the drying of fixed beds by infrared readiation is due to vapour diffusion and condensation.

Compression:

A number of new tablet machines have been designed but the fundamental mechanical unit remains the same, the latter consists of a steel die cavity in which two punches meet from opposite sides thereby compressing the granules or suitably prepared powder into tablets or slugs.

Several improvements in the rotary tablet machines have been reported but none of these represents a radical change in the compressing equipment. A modified rotary machine has been described in which compression rollers are mounted obliquely and not perpendicular to the die table. It was claimed that this arrangement reduces the rate of compaction, increases the dwell time and minimises wear of the punches and compression rollers.

An interesting technique has been used to compress formulations with a strong tendency to adhere to the punches and dies. At one compression station of a two station machine, a pharmaceutical lubricant composition was compressed at high pressure to clean and lubricate the press tooling. The problematic tablet composition was compressed at the second station.

It has been demonstrated that rotation of the die substantially decreases the friction during compaction and ejection of compacts. For example, during compaction in a lubricated stationary die, 20% of the applied stress was consumed by die wall friction compared to 2% if the die was rotated. Some tablet machines can be fitted with an attachment which rotates the punches during compaction. These devices will help to facilitate compaction of certain pharmaceutical formulations which are difficult to compress.

Strain measurement techniques are now widely used to instrument tablet machines in pharmaceutical research, development and production operations. Strain gauges fixed to the components of the tablet machine, detect the forces which are then monitored on a dual beam oscilloscope. The observations can be made permanent by photographing the displays with an oscilloscope camera. Knoechel **et al** [23] found that instrumented rotary tablet machine could be used to compare lubricants, lubricant concentrations, to compare flow properties of granulations at preselected force levels. In addition to demonstrating the contribution of induced feeding to reduced weight variability the instrumentation assists in detection of press or tool malfunction more rapidly than by other means. It becomes apparent that instrumentation of tablet machines serves primarily although not solely as a development tool in scientific formulation.

The study of crystalline and spray-dried lactose which differ in their compression characteristics revealed that particle re-arrangement is more essential in the consolidation of small lactose particles than of large ones. The 75 – 104m size fraction was most resistant to deformation. It has also been noted that with small particle-size fractions, spray-dried material produced less die wall friction and the large size fractions of the spray-dried lactose studied were predominantly crystalline and, therefore, possessed similar properties to crystalline lactose. There was a tendency for tablet strength to increase with a reduction in particle size.

From density measurements at different tabletting pressures, it was concluded that microcrystalline cellulose behaves more like a granular material than a powder. Physical and chemical effects of moisture have been noted on the flow of material in the die and on compaction. It has been shown barium sulphate compacts were strongest when pressed under high vacuum. Water vapour reduced the shear strength by decreasing the interparticulate adhesion and liquid bridges produced no increase in strength. At high humidity an improved consolidation increased the strength of compacts.

Rees and Shotton[24] using crystalline sodium chloride and three liquids, water, decahydronaphthalene and light liquid paraffin demonstrated that during compression, the force lost to the die wall increased due to cumulative contamination of the die, such losses were much less with water than with other liquids and this was attributed to boundary lubricant properties of water.

Armstrong and Griffiths[25] observed that water acts as a lubricant and therefore, facilitates consolidation but they claimed that the effect is most significant with materials of low water solubility. Although moisture slighly increased the strength of the phenacetin and acetaminophen (paracetamol) compacts the opposite effect occurred with dextrose.

Livingstone reviewed the advantages and techniques of preparing tablets by direct compression. He advocated that crystalline material should be used as far as possible to render non-compressible materials compressible. Evidently, this approach to formulation depends upon the co-operation between chemical and pharmaceutical scientists, and has not been adopted by the pharmaceutical industry.

Formulation:

In a tabletting formulation, the selection of a number of ingredients and their concentration is based upon the compromise which will provide a product with optional biological properties under standardized processing conditions. Each of these ingredients should not only contribute essential processing requirements but also

support the therapeutic activity of the drug and pharmacopoeial and manufacturer's quality standards.

Although excipients can influence the pharmacological activity of the medicaments, they should not possess any biological activity in the concentrations used in the formulation. Relatively a few excipients of chemically unique nature have found their way into tablet compositions. Nevertheless, the search goes on in the effort to overcome deficiencies within existing materials or for economic reasons.

A number of research publications has appeared on the comparative evaluation of starches and other similar substances in tablet formulations. It has been shown[26] that tablets made with barley starch were superior to rice, wheat, potato and arrowroot starches in giving the lowest disintegration time and highest release.

Cassava and Yam starches have been evaluated[27,28] and found to compare favourably with the potato starch as a disintegrant and a binder.

Starch sodium glycolate was investigated as a disintegrant[29]. It was found to be better than other starches, alginic acid and microcrystalline cellulose. In another study[30] carboxymethyl starch was found superior to corn, wheat, potato and rice starches. Each of these disintegrants have been found to have a pronounced effect upon the relationship between compressional pressure and dissolution efficacy[31]. Besides being a disintegrant, a compressible starch has been found to be a good vehicle in aspirin tablets[32].

It has been shown[33] that hydroxypropylcellulose could be a useful binder in direct compression tablets when properly combined with potato starch and lactose. Aspirin tablets made by the dry method had good properties when microcrystalline cellulose, carboxymethyl cellulose, ethyl cellulose, carboxymethyl starch, anhydrous lactose, polyvinyl pyrrolidone, dextrose, silartex and crystalline lactose binders were used[34]. It has also been shown[35] that hydrolysed gelatin or water or both together produced paracetamol or phenacetin mixtures with satisfactory compression characteristics.

A method for the rapid evaluation of the effect of excipients on colour fading was suggested. It involved the use of a faedometer to accelerate light induced fading followed by spectrophotometeric evaluation[36].

Conclusion:

Most of the information on techniques of tabletting is available from publications by Little and Mitchell,[37] King[38] and Miller[39] and a number of research papers and other publications[40]. Schools of Pharmacy of the University of London and Wisconsin are credited with the pioneer work which has provided the impetus towards the investigation of the fundamentals of tabletting. Significant contribution to the advancement of tablet technology has been made in the establishment of the quantitative date concerning relationship of tablet properties tc compression force, the measurement of lubricant efficiency, the evaluation of bonding strength. Inspite of these developments, pharmaceutical manufacturers have not made use of the information derived from these studies to a significant degree and continue to rely upon empirical formulation and processing methods.

It is, therefore, the duty of the development pharmacist to apply the results obtained on isolated parameters of complex systems of tabletting to various processes involved in the manufacture of tablets.

APPENDIX

TABLETS

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents (U.S.P.).

Tablets are compact products containing a medicament or mixture of medicaments in mouled or compact forms. (B.P.C.).

These are circular discs either flat or biconvex, oval, oblong, cylindrical triangular etc.

TYPES OF TABLETS

A. **Moulded Tablets:**

i. Hypodermic tablets
ii. Dispensing tablets.

B. **Compressed Tablets**

i. Single Compressed Tablets.
ii. Multiple Compressed Tablets.
iii. Chewable Tablets.
iv. Lozenge Tablets.
v. Buccal or Sublingual Tablets
vi. Effervescent Tablets.
vii. Delayed and/or Sustained-action Tablets
viii Sugar-coated Tablets.
ix. Chocolate-coated Tablets.
x. Enteric-Coated Tablets.
xi. Film-Coated Tablets.

COMPRESSED TABLETS

Ingredients:

a. Medicaments
b. Excipients
Excipients may function as:-
i. Diluents
ii. Binders
iii. Disintegrators
iv. Lubricants
v. Colouring agents.
vi. Flavouring agent

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(Continued on page 40)