DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 11(2&3), 725-741 (1985)

RECENT ADVANCES IN GRANULATION TECHNOLOGY AND EQUIPMENT

Curt Appelgren
Taljegardsgatan 3
S-431 33 Molndal
Sweden

"Granulation" is a very common but unspecific term as used in the pharmaceutical industry. It is used to describe methods of producing granules. A more adequate term for these unit operations is "size enlargement".

When speaking of granules, we often mean a relatively coarse product with a particle size of $\sim$ 0.1 - 3.0 mm.

The following five methods can be used to produce granules:

- Dry methods
- Wet methods
- Spray-drying
- Melt forming methods
- Crystallisation methods

With dry methods, the powder mass is compacted, crushed and fractionated. Compaction may be performed with a tabletting machine or a rolling compactor. The method is very dusty and noisy.

Wet methods are the dominating size enlargement principle in the pharmaceutical industry. Wet methods are based on mixing the powder with a suitable liquid in order to produce agglomerates which are then dried to give a granular product.

Spray-drying involves breaking up a solution into drops, by means of a spray-nozzle, and allowing the drops to fall with or against a stream of gas so that the solvent evaporates. The solid particles formed are then separated from the process gas by means of a cyclone. Granules of this type usually have a low bulk density owing to high porosity.

0363-9045/85/1102-0725$3.50/0

Melt forming methods are not yet widely used in the pharmaceutical industry. The method is based on melting one or more substances, converting them into drops of desired size, by means of a spray-nozzle, and allowing the drops to fall in a cooling zone until they solidify again. This method can only be used if the substance is stable when molten and the melt has a low viscosity.

Of the crystallisation methods, fractionated crystallisation and spray crystallisation may be mentioned. Spray crystallisation involves feeding cores into a fluidised bed and coating them to the required size by spraying them with a concentrated solution of an active substance. The core may contain the same active substance as the solution or be of inert material, for example a fraction of sugar crystals.

One might ask: why convert powder into granules? Which of the following factors do we want to alter?

- The segregability of mixtures
- The flow properties
- The bulk density
- The solubility
- The binding properties
- The stickiness
- The hardness
- The friability
- The size and size distribution
- The shape

To produce non-segregating mixtures is important when the product contains several components in powder form as they usually differ in size, shape and specific weight. This can be achieved by making granules so that the composition of each granule is identical to that of the granule bulk.

Improved flow is important in subsequent processing, for example tabletting or other volume filling.

The bulk density of the granules is an important factor in connection with filling of the matrix in modern high-speed tabletting machines. It is influenced by additives as well as by the process as such.

The solubility can be altered by means of additives and binding agents. It is thus possible to reduce the solubility, which is utilised in matrix tablets, or increase the rate of dissolution by improving the wetting properties.

By means of additives and binding agents, both the binding properties and stickiness can be altered, which is important in tabletting.

The hardness and friability of the granules can be modified by means of additives or alterations to the process.

The size, size distribution and shape can be altered by modifying the process. In this review, I will concentrate on the wet processes as these are the dominating methods of producing granules for tabletting and spherical granules for coating in a fluidised bed or coating-pan, for example.

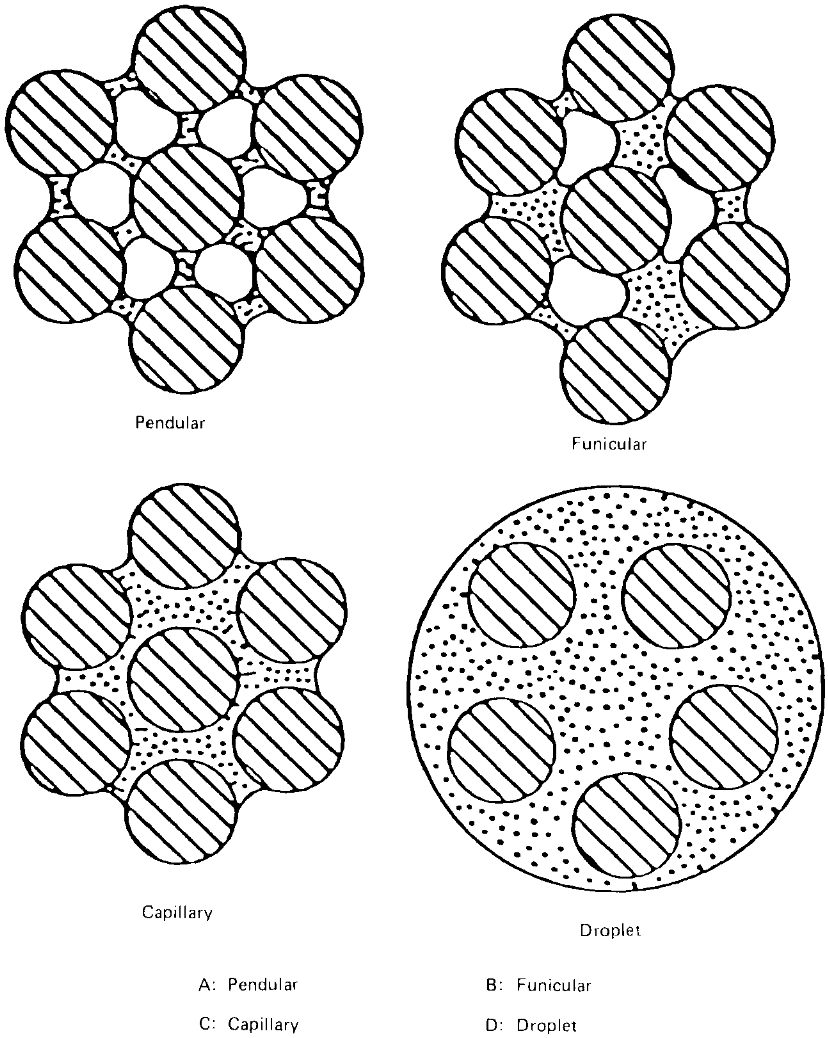
Before chosing suitable equipment for a wet size enlargement process, you have to decide what properties the granules should have.

The wet size enlargement process involves moistening a powder with a suitable liquid until agglomerates are formed. The different stages were described by Newitt and Conway Jones as long ago as in 1958.

The mass is normally moistened until it lies between the funicular and capillary state, so that agglomerates are formed. When the granules are to be tabletted, a binding agent is usually included in the solution, for example polyvinyl pyrrolidone, gelatin or a cellulose derivative, in order to improve the binding properties during tabletting. If a powder is soluble in water, some of it will dissolve during moistening.

During subsequent drying of the agglomerates, the liquid will evaporate and firm bridges will form between the particles so that granules are formed. The following three types of bridges can be distinguished:

- Binding agent bridges
- Crystalline bridges
- A mixture of the two



Particle-particle bonding mechanisms in the presence of liquids

Figure A

The reason why a wet method is often used to produce granules is that the substances included in the powder mixture do not bind together sufficiently well to produce a tablet during compression. By moistening the powder with a liquid in which the binding agent is dissolved, granules with better binding properties can be obtained.

The liquid bridges play a decisive role in holding the powder particles together in the agglomerate. The distribution of the liquid between the powder particles determines how evenly the binding agent bridges are distributed. The binding agent must thus create binding bridges which cement the particles together within the granule as well as giving the granule a surface which enables it to bind with other granules during compression. It is thus clear that it is pure binding agent bridges we want as the powder substances themselves were not able to bind together when compressed.

Unfortunately, the binding bridges often contain loosely recrystallised substance, which has a negative influence on the hardness, friability and binding properties of the granules.

As it is important that the liquid is homogeneously distributed, it is obvious that the drying stage and the rate of drying must be precisely controlled in order to prevent migration of the binding agent to the surface of the granule, when the solvent evaporates. In systems where the powder component dissolves in the granulation fluid, slow drying may also lead to crystal formation.

In other words, a wet size enlargement process consists not only of a wet mixing stage but also a drying stage.

There are two main methods of distributing a liquid in a powder:

- methods using shearing forces and
- methods using atomisation of the liquid.

The oldest method based on pure shearing-force distribution of the liquid is that using the pestle and mortar. As we all know, the powder is placed in the mortar and the liquid added in portions and mixed into the powder by pressing the mass between the pestle and the wall of the mortar.

The motorised and industrialised equivalent of the pestle and mortar is the planetary mixer. The pestle is here replaced by a wing but the method is still based on using shearing forces to distribute the liquid.

The following machines can also be assigned to the group based on shearing-force distribution:

- The JH-mixer
- The ribbon mixer
- The zig-zag mixer

A modification of mixers based on shearing-force mixing is the so-called intensive mixer, which may be said to be a second-generation planetary mixer. The only difference is that intensive mixers produce a certain quantity of shearing force in the mass in a shorter time. The following are examples of mixers in this group:

- Fiedler
- Diosna
- Eirich
- Colletts

But there are many others. They have certain geometric differences which may lead to differences in efficiency.

This trend towards producing a certain amount of shearing force in a shorter time has accentuated the problem of over-moistening of products where the powder dissolves in the granulation fluid. The operator may not be able to stop the process in time, with over-moistening as a result.

A lot of effort has been devoted to developing different types of probes for detection of the end-point. Marc Donsmarck will describe a dėvice of this kind to us later on, so I will not go into it here. Let us instead see what happens when the mass is exposed to shearing forces and why certain masses give rise to more or less uncontrolable processes.

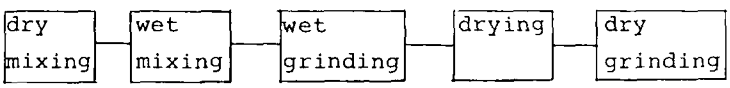
Part of the energy delivered to the mixer is converted into thermal energy, leading to a temperature rise in the mass. As the solubility is usually temperature-dependent, this introduces a complicating factor in systems where the powder is soluble in the granulation fluid.

One way to reduce the shearing force needed to distribute the liquid in the powder is to add the granulation fluid by spraying. Some authors claim that it is better to add the fluid by spraying, while others have found that this is not the case. The conclusion probably depends on which formulation is studied.

Combination of shearing forces and atomisation of the fluid in the mixing stage is employed in, for example,

- The Nauta mixer and
- The P-K mixer

Reports on whether the intensive mixer requires more or less granulation fluid are also contradictory. This is in all probability also due to differences in the formulations studied - that is, in the solubility of the powder in the fluid. When the quantity of fluid is reduced, the content of crystalline bridges increases.



In addition to the wet mixing operation, a line for granule production also includes at least one drying stage. Wet grinding is also often necessary before drying.

In addition, dry grinding is very often necessary after the drying stage in order to break up cakes formed during drying. Dry grinding is dusty and reduces the yield.

I must emphasise once again that the choice of drying process is very important in order not to impair the final product. A slow drying process may undo all your efforts to distribute the granulation fluid homogeneously, and hence achieve homogeneous distribution of binding bridges, owing to chromotographic effects. A slow drying process may also lead to crystal growth. This is described very well in a publication by Pietsch in "Drugs made in Germany", 13 58 1970.

The properties of mixers based mainly on the shearing-force principle may be summarised as follows:

- The process can be controlled if the powder is insoluble or only sparingly soluble in the granulation fluid

- They are not suitable for powders that are soluble in the granulation fluid or when crystal bridges are undesirable
- It is an advantage to apply the granulation fluid by spraying
- Those with batchwise operation are large and clumsy and energy-demanding as the whole mass is processed at once

The other principle, based on atomising the fluid and coating the particles, has many similarities with an over-moistened coating process where the moisture content is so high that the particles adhere to form agglomerates. Fluid bed granulation is the most obvious example but pan, drum and plate granulation also belong to this group.

Fluid bed granulation methods have been studied more scientifically than methods employing shearing forces. Detailed descriptions of this technique have been published by Thurn, Ormos, Wørtz and Schafer, among other authors. This method creates almost exclusively binding agent bridges between the particles in the granules.

It has also been found that spray granulation gives tablet granules with superior tabletting properties, probably due to the very low content of crystal bridges compared to the intensive mixer method, and favourable drying, which helps to ensure homogeneous distribution of binding agent bridges in the granules.

The disadvantages of the method are as follows:

- Low capacity
- Gives granules with a low bulk density
- Requires more granulation fluid
- Requires a filter in the fluid bed as the initial material is a powder

Various pieces of equipment have been developed to reduce these disadvantages, for example the Glatt Rotogranulator, utilising a combination of fluid bed and marumerizer technique, but the same problems remain, with addition of sticking to the walls. Another variation is the Japanese CF granulator.

In addition to the above-described batchwise operating wet mixers, a number of continuously operating mixers have been developed.

Unfortunately, the more conservative parts of the pharmaceutical industry tend to have unjustified prejudices against these mixers, such as that they require large products or cannot be used for GMP reasons, which is quite wrong.

A continuously operating mixer may very well be used in a batch-wise granulation process. The argument that large products are necessary is also pure ignorance since the batch size depends on the capacity of the continuous mixer per unit time and the operating time. It is quite feasible to process batches down to one kilo with a continuous mixer.

A major advantage is that it is possible to test full-scale production conditions with batches of only four or five kilos. The time can then be scaled up from 10 seconds to 10 minutes, in other words 60 times, which corresponds to a batch of 240 - 300 kilos.

As regards the problem of meeting GMP requirements, this objection is completely unfounded.

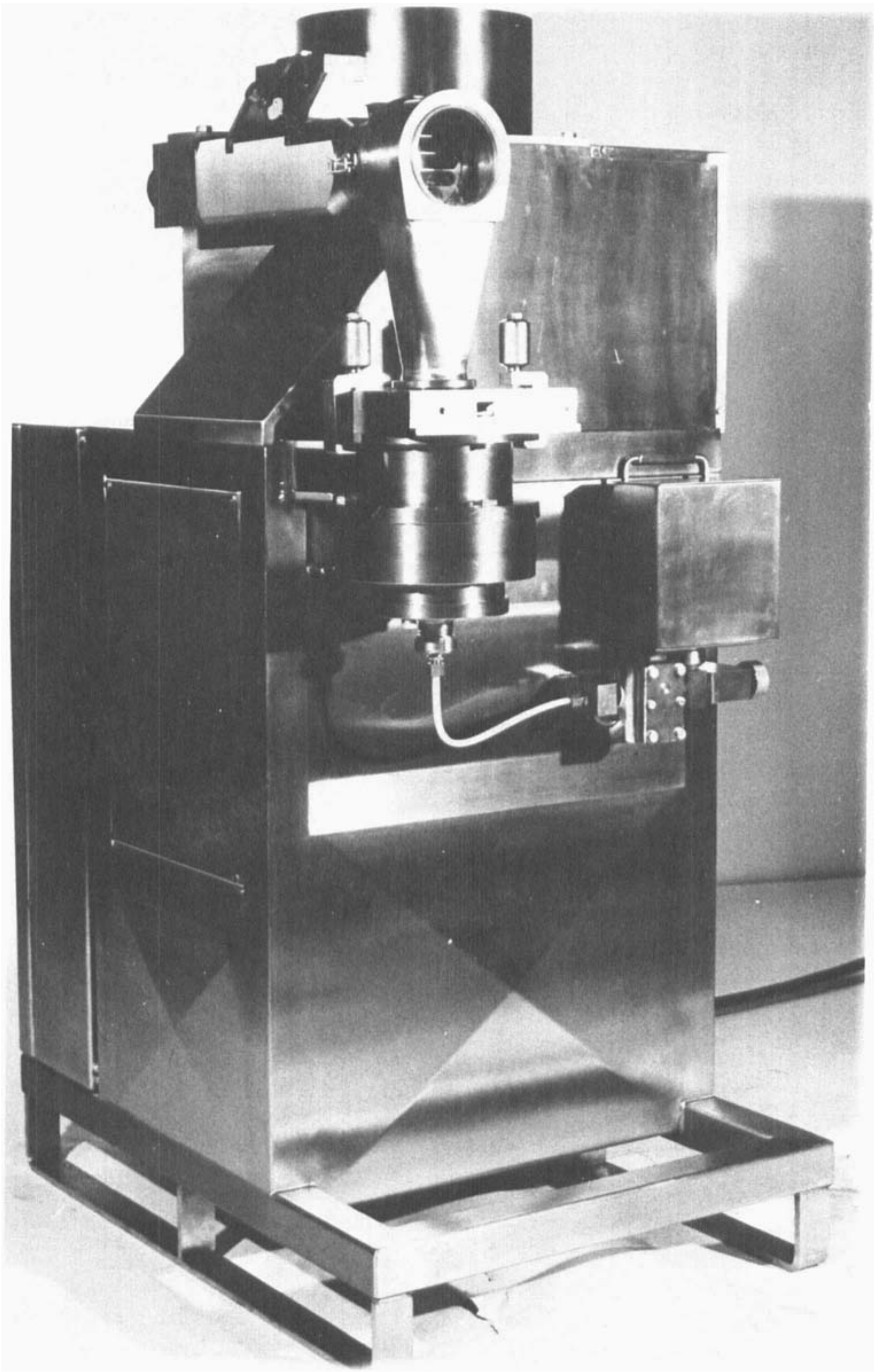
The Shugi mixer, the Funke Flow Jet mixer and the NICA instantaneous mixer are examples of such continuous mixers.

The basic principle of these mixers is that a stream of powder and a stream of liquid meet and are instantaneously mixed before leaving the mixer. They remain in the mixer for only a fraction of a second.

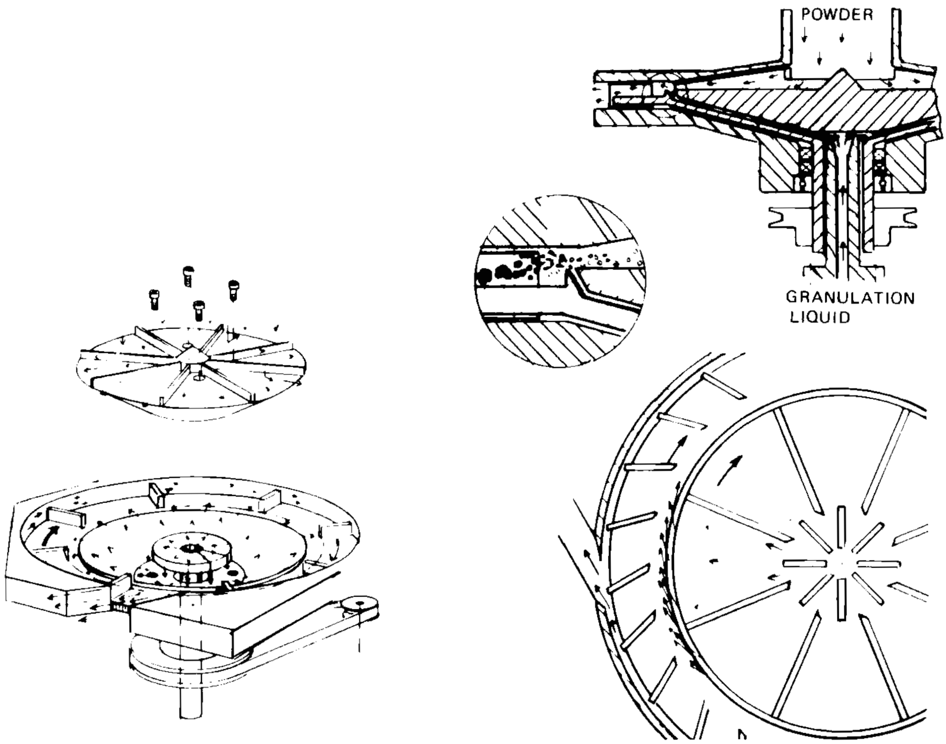
In the Shugi mixer a jet of liquid is mixed with a stream of powder and the resulting mass meets rapidly rotating blades as it falls through the mixer under the force of gravity.

In the Funke Flow Jet, the powder is thrown at right angles against a liquid film on the wall of a cone. The moistened powder mixture is then instantaneously mixed before being ejected from the mixer.

The NICA instantaneous mixer (enclosure 1) makes full use of the possibility of creating an optimal contact surface between the liquid and powder. The liquid is pumped in from below and is forced up between the two plates forming the turbine-wheel, which rotate at over 2000 rpm (enclosure 2). In the slit between the plates, the liquid is broken down to a fine mist. The powder, which is added by



Enclosure 1



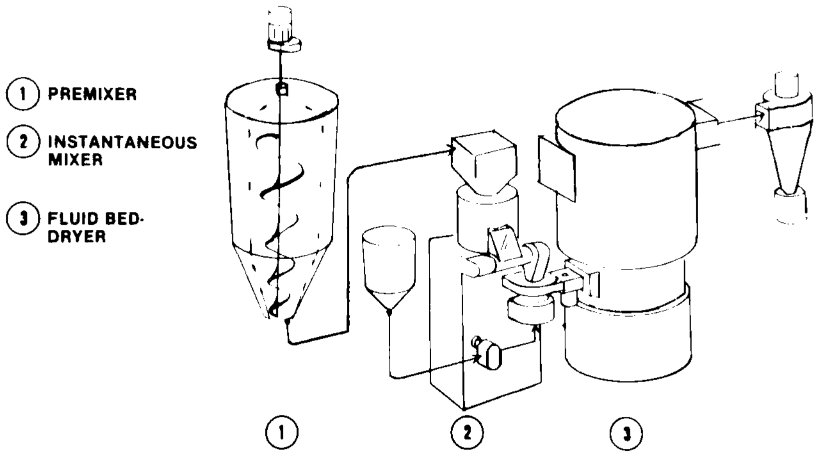
Enclosure 2

means of a screw feeder from above, is broken down into its primary particles before it meets the liquid mist. This creates an optimal contact surface between powder and liquid. The mixing then takes place in the outer zone, before the mass is ejected. The thoroughness of mixing depends on the load on the machine. The load can be regulated by altering the outlet area or input of powder and liquid. Increased load increases the bulk density of the granules.

A granulation line including a NICA instantaneous mixer may have the following layout (enclosure 3):

The powder may be pre-mixed in, for example, a srew-mixer. The dry-mixed powder is taken from the bottom of the premixer and transported to the hopper of the instantaneous mixer by means of a vaccum feeder. The vaccum feeder is regulated by a powder level gauge in the hopper. The mixer is coupled direct to a fluid bed drier. When the granules are dry, the drier is

PRODUCTION LINE FOR GRANULATION



Enclosure 3

emptied and the mixer automatically starts and blows in the next batch.

The drier is not completely emptied between batches, however. Part of the material remains in the drier so that the mass thrown in from the mixer is set in motion immediately. The fluid bed drier is thus already operating when the mixer starts and fills it. This method of operation makes it possible to fluidise masses that are impossible to fluidise with conventional fluid bed technique.

The cycle time per batch is 10-30 minutes, depending on whether an organic solvent or water is used. Owing to the short cycle time, an aqueous granulation fluid can be used in most cases, which is an advantage from the explosion point of view. With such a process, the drying process can be optimised so as to minimise the drying time, and hence the risk of formation of crystal bridges, thereby producing a product with as good binding properties as are achieved by fluid bed granulation.

By warming the granulation solution, the product can be given the maximum permitted temperature when it enters the drier. The drier's heating battery is controlled by the bed temperature, so that the optimal product temperature is maintained. The temperature of the material entering the drier naturally influences the drying time, owing to the exponential appearance of the partial pressure versus temperature curve.

With such a process, the fluid bed does not need a filter as practically all the mass thrown into the fluidised bed from the mixer has a particle size exceeding 50 microns. These large particles are very efficiently separated in the cyclone separator and the material collected in the separator can be recovered and mixed in the final mixing stage. Such a production line is very easy to clean as the parts in contact with the product are smooth metal surfaces. Another advantage is that the individual items of equipment are small compared to those used with conventional technique. For example, a fluid bed drier for batches of 250-300 kilos is no larger than a conventional 60 kilo fluid bed drier. Another advantage is that high initial gas velocities in order to start the fluidisation can be avoided.

Excessive gas velocities used initially cause unnecessary attrition of the granules and produce powder. It also frequently happens that the operator forgets to reduce the gas flow when fluidisation has started. This also leads to poor heat utilisation.

Other types of driers may of course be used, for example drying cabinets, which have the disadvantage of long drying times, microwave driers or infra-red belt driers. Let us now move on from tablet granules.

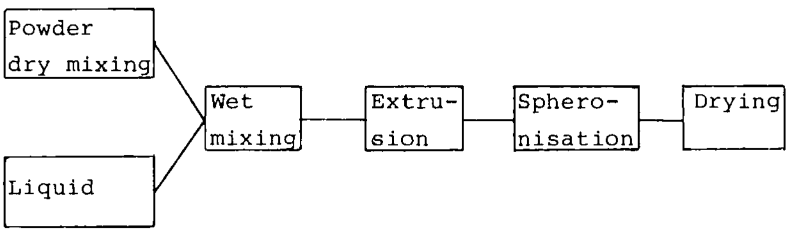
During the last 10 years, interest in spherical granules with a particle size of 0.5 - 1.5 mm has increased, owing to increased interest in controlled release products based on the multiple unit dosage principle. The most common methods are:

- tumbling agglomeration and
- marumerizer technique.

The most commonly used items of equipment for tumbling agglomeration are drums, inclined discs, cones, pans and bowl and plate granulators. The principles of this method have been well described by Newitt and Conway Jones. A fine powder is continuously fed into the pan and the granulation fluid is sprayed onto the rotating powder mass. Agglomerates are built up and when they reach a certain size they fall over the edge into a drier.

By starting from cores, the capacity can be increased and a more even particle distribution can be achieved. This technique is used in the production of non pareil seeds, where sugar crystals are rounded off by coating them with a sugar-starch mixture. The technique is very similar to sugar-coating.

The other method, based on the so-called marumerizer principle, comprises the following steps (enclosure 4):

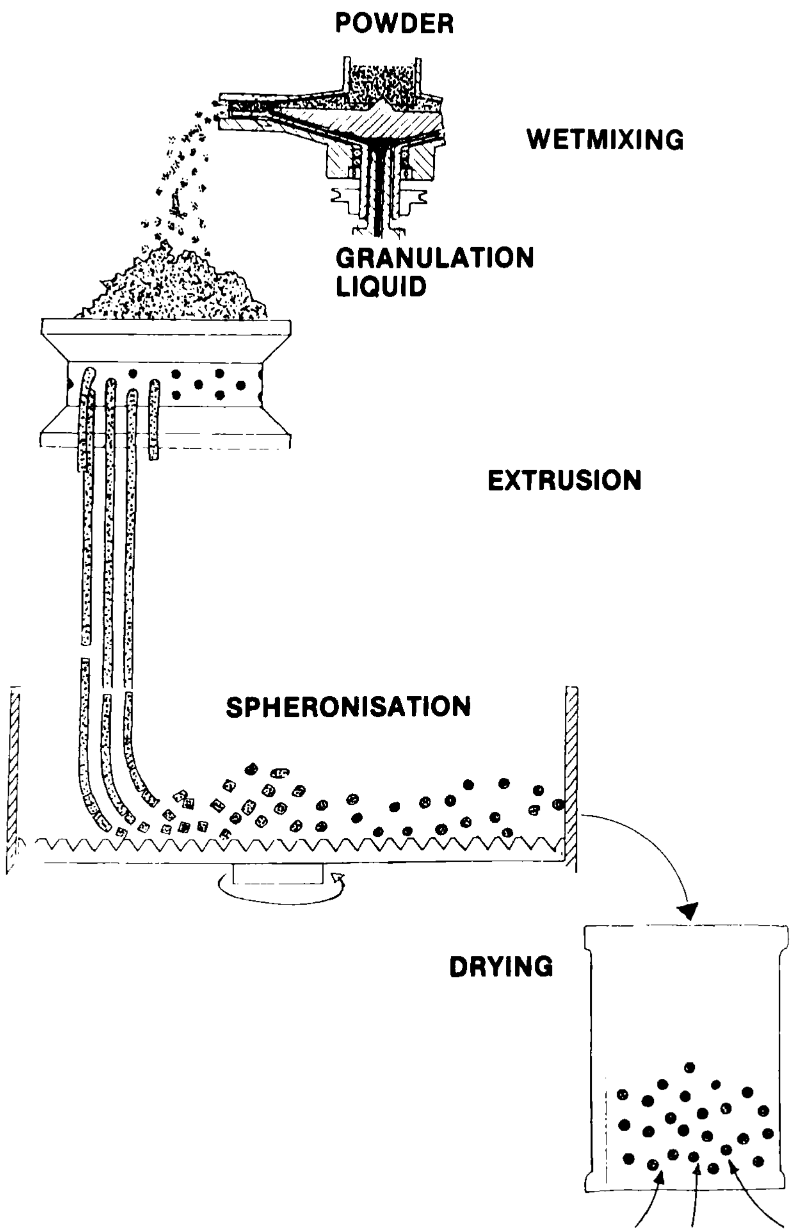


As water is normally used as the granulation fluid and the powder substances are generally more or less soluble in water, the system is very sensitive. The critical variables in this type of process are:

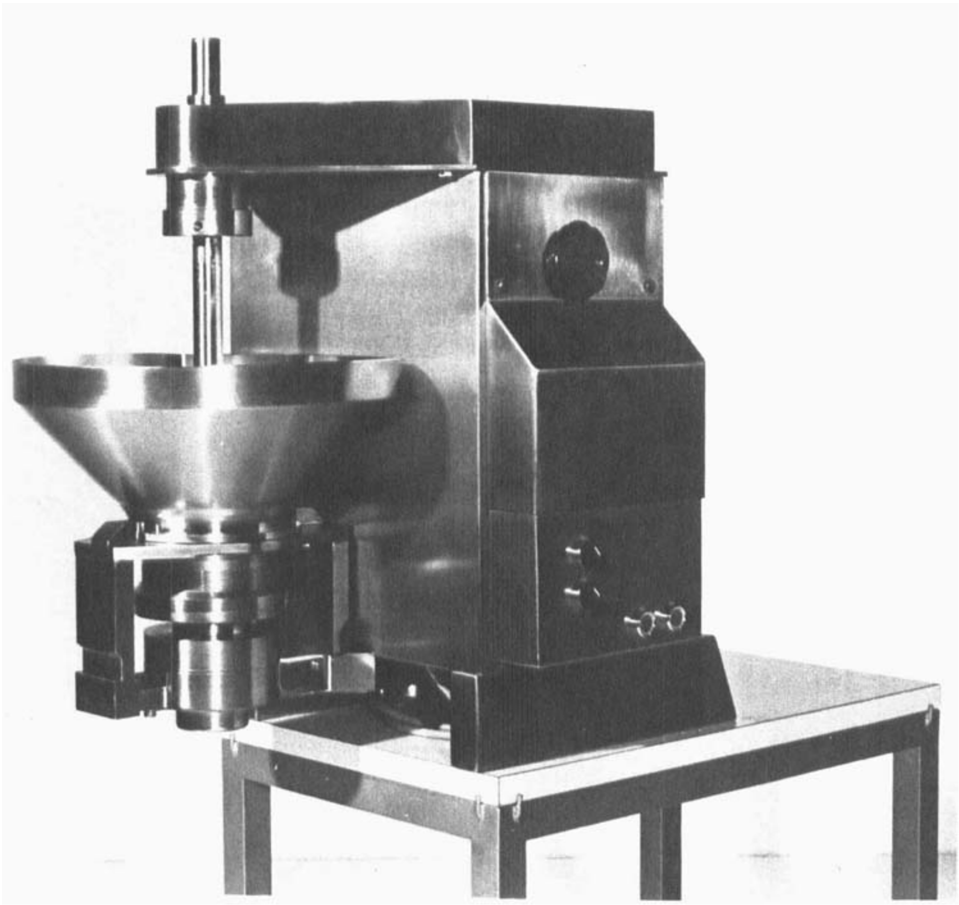
- the water content,
- the peripheral velocity of the spheronisation plate and
- the cycle time.

It is therefore important to establish the limits of variation for these variables in order to control the process as precisely as possible. The following factors are of decisive importance for the success of this type of process:

- that the water is homogeneously distributed in the powder - in other words, an efficient mixer,
- that the extruder does not create a water gradient during extrusion,
- that the extrudate has a plastic consistency without being too viscous, in other words, the mass should be plastic but not elastic and
- that the granules are emptied direct into the fluid bed drier so as to prevent formation of agglomerates, which would otherwise have to be broken up after drying, with surface damage as a result.


POWDER
WETMIXING
GRANULATION
LIQUID
EXTRUSION
SPHERONISATION
DRYING

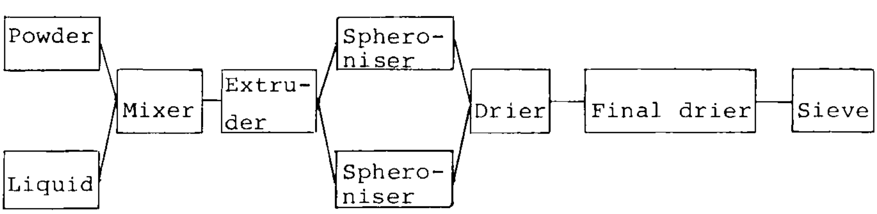
Enclosure 4



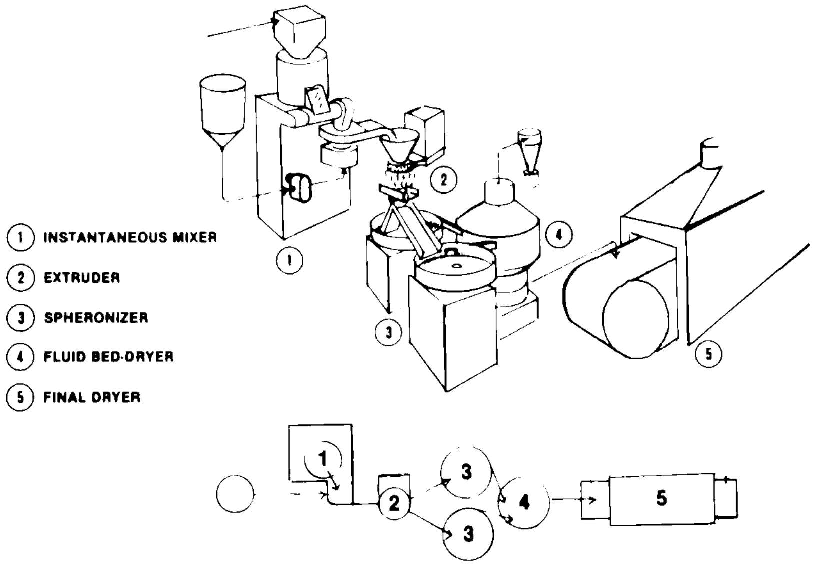
Enclosure 5

It is a great advantage if the same extruder is used on a laboratory scale as in full-scale production as this facilitates scaling-up (enclosure 5). The extruder must then have a minimal deadspace, so that the batches of each formulation produced in a laboratory spheroniser do not need to be too big, while at the same time having a sufficiently high capacity for full-scale production.

A full-scale line with a capacity of 125-150 kilos of dry granules per hour could have the following layout (enclosure 6):



PRODUCTION LINE FOR SPHERONISED GRANULATE



Enclosure 6

The instantaneous mixer and the extruder have the same capacity and operate continuously. This is important in order to standardise these two critical operations. The spheronisers are fed alternately. The cycle time for a 10 kilo batch of wet mass in the spheroniser is 3-4 minutes.

The drier placed after the spheronisers operates according to the back-mixer principle and dries the product so that the granules do not adhere to form agglomerates which have to be broken down after drying, leading to surface damage. The final drying process can be performed in several ways - with a drying cabinet, a microwave drier, a continuous fluid bed drier or an infra-red belt drier.

In conclusion, I would like to recommend C.E. Capes's "PARTICLE SIZE ENLARGEMENT, Handbook of Powder Technology", published in 1980, which covers the subject of size enlargement very well and contains many useful references.