BENEFITS OF SINGLE-POT SOLUTIONS FOR THE PRODUCTION OF PHARMACEUTICAL GRANULES

As illustrated by granules for vitamin C and effervescent tablets

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Summary

Pharmaceutical products such as ordinary or effervescent tablets are manufactured from powdery raw materials. Among other things, these bulk materials tend to show inadequate rheological properties (when used as bulk materials). This results in poor flow behaviour, inadequate amenability to dosing, poor solubility kinetics, segregation, and potential health and safety problems due to the build-up of dust (e.g. dust exposure for systems operators, problems in terms of explosion control).

In order to ensure reliable production of pharmaceuticals at optimal and reproducible quality levels, the raw materials are processed into granules.

Various methods may be used to manufacture granules, which often involve more than one system (granulator, dryer, and other equipment downstream). The resulting transport between items of equipment can lead, among other things, to extra costs in terms of personnel, the risk of product damage, and additional space requirements at production facilities. Sometimes the methods are highly energy-intensive (e.g. fluid bed dryers) and associated with elaborate explosion control concepts.

One compact and economical solution is the production of granules with the single-pot system associated with the horizontal vacuum shovel dryer. This makes it possible to implement the various process steps involved in granulation in a single piece of equipment. The system favours gentle handling of the product concerned and enables energy-efficient mixing and drying to be performed as quickly as possible.

The use of this single-pot system for the granulation of pharmaceutical bulk materials is described in what follows, along with an outline of the principles of granulation and particularly wet granulation. By way of illustration, the manufacture of vitamin C granules and granules used in effervescent tablets is also portrayed.

Contents

1. Introduction

Most medicines are administered orally. Common delivery forms include ordinary tablets, effervescent tablets, or sachets to be taken directly [1]. Optimal tabletting at high cycle rates requires raw materials to have impeccable rheological properties when in bulk material form (e.g. flow behaviour and amenability to dosing). This is made possible through the manufacture of granules.

As regards granulation, there are various important steps integral to the process, such as mixing, liquid addition, accretion of granules, and drying. For the implementation of such complex processes, it is desirable, from the user's perspective, to use the most compact and economical equipment possible.

The following description, which uses two different applications by way of illustration, outlines the manufacture of granules by means of wet granulation as part of a so-called single-pot solution. The two applications concerned, i.e. effervescent tablets and vitamin C granules, are both very common delivery forms. They differ in terms of their manufacture, but both lend themselves to implementation within the compact and economical system.

2. Principles of granulation

Powdered raw materials for pharmaceutical formulations may show inadequate flow properties due to small particle sizes (with mean primary particle sizes often below 100 µm). This results in the formation of unstable secondary agglomerates e.g. through Van der Waals forces. The associated undesirable side effects include material sticking to walls and the formation of bridges, which make dosing more difficult and the system harder to clean, among other things. For this reason, granulation is used to optimise the properties of raw materials. [1]

Granules show optimised particle size distribution and bulk densities, which help avoid dust or excess size. An individual granule consists of several powder particles. For pharmaceutical applications, the range of particle sizes for granules is between 0.05 and 2 mm [1].

Other benefits associated with granulation are [2]:

- Avoidance of segregation effects thanks to stable mixtures
- Dust-free transport and simple dosing thanks to improved flow properties
- Improved properties in terms of tablet compression
- Targeted release of active ingredients, including by modifying granulation
- Optimal solubility, e.g. by avoiding clumping during dissolution
- Improved stability for storage purposes by reducing the surface area of the product
- Precise reproducibility, minimising differences between batches

Essentially, the granulation process can be divided into the following individual steps:

1. Mixing
2. Granule accretion
3. Drying
4. Next steps (e.g. sieving, addition of flow additives)

2.1 Mixing

Prior to granulation, the components need to be homogenised quickly using a method that can be readily reproduced.

The fastest possible way to achieve optimal mixing quality in real conditions is through so-called random mixing.

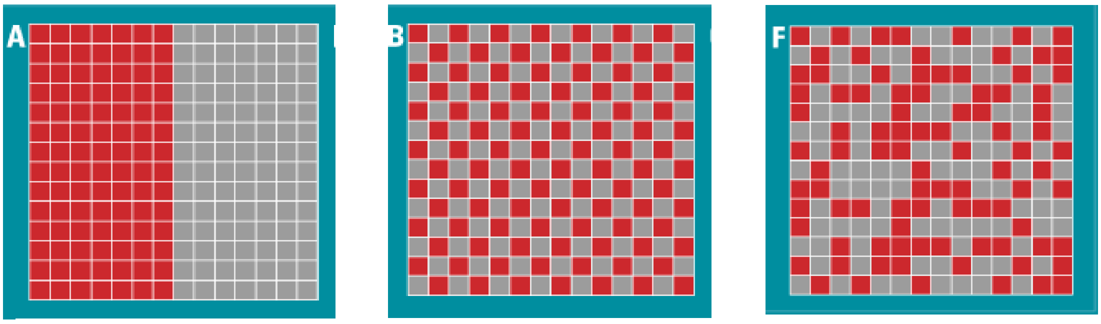

Fig. 1: A schematic representation of mixing quality: A - after filling, B - maximum theoretical homogeneity, F - random mixing, maximum homogeneity in real conditions

Even the modified application of mechanical energy can promote a significant degree of stability within the mixture. Finer particles of components rub into the surface of larger particles and are pressed into the surface pores. There is generally no significant destruction of particles in the 100-200 µm size range during the mixing process [4].

The use of a horizontal mixer from the so-called shovel or ploughshare mixer class, on which the single-pot system described below is based, is mainly associated with universal applicability, gentle movement of the product involved, and the particularly fast rate at which optimal mixing quality is achieved.

Fig. 2: Horizontal mixer: Lödige Ploughshare® Mixer [4]

Mixers with a horizontal mixing shaft and mixing tools transfer the product to a mechanically generated fluid bed. For the purposes of this dynamic state, the mixing shaft speed must ensure, for the particles, a particle movement with a Froude number greater than 1 (preferably 3-7). This means loosening the product bed sufficiently to ensure the statistically predominant contact between the particle surfaces is significantly reduced and that movement of the particles can be generated right across the entire mixing vessel.

At the same time, the mix product is thrown in waves by the shovels from right to left and then back. Transport in axial direction determines the time needed to achieve the best possible mixing quality.

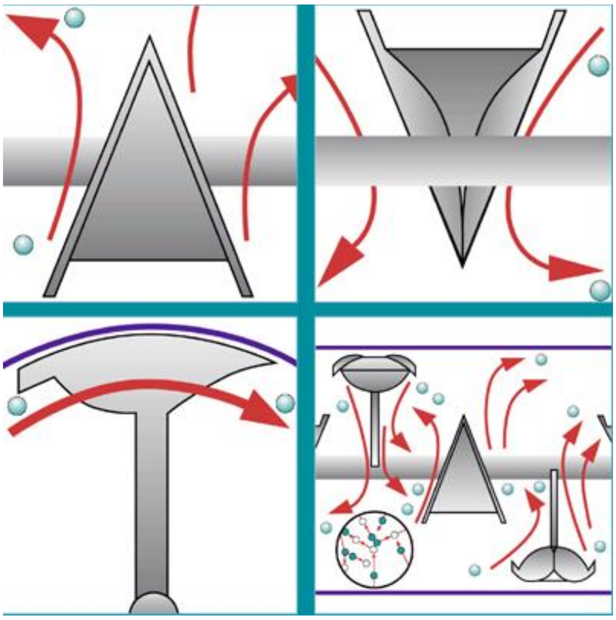

Fig. 3: Schematic representation of product movement in the horizontal mixer [4]

2.2 Granule accretion

Typically, granulation occurs through the constant binding of particles via a bridge. Various processes can be used for the agglomeration/granulation of powders [2]. The accretion-type granulation dealt with here can be achieved in two different ways. For pharmaceutical applications, these are generally:

- Wet granulation through the addition of liquid, which may also contain an additional binding agent (e.g. spray drying, spray agglomeration, mixing-type granulation), and then drying, and
- Dry granulation through mechanical compacting of the powder mixture, e.g. in a roller compacter. [1].

The choice of method will depend on the raw materials, the application field, and the properties required of the final product. Other important parameters also need to be considered, such as processing time, product temperature stress, etc. Aspects such as particle size as well as the surface structure of the basic material and, for example, the shearing forces within the process have a decisive influence on the binding strength between the particles. [1]

The granulation method adopted in the single-pot approach is the wet granulation described below.

2.3 Wet granulation

Once the recipe components have been combined and pre-mixed, the granulation liquid is poured in. The liquid medium is added to the powder mixture, which has been pre-mixed in the device. The liquid starts to work on parts of the surface of the primary powder particles and binds several particles together to create secondary agglomerates. With many products, water is sufficient to bring about binding, provided the product mixture or one of the powder components is soluble in water. In order to improve binding properties, the granulation solution may contain additional binding agents, which increase the binding effect and improve the solidity of the dried granulated matter. [2]

During the subsequent drying process, these liquid bridges, with some solid content, become solid bridges. The durability of these bridges depends primarily on the solubility of the product in the liquid. It is possible, to a limited extent, to control the solidity and the initial compacting of the particles through the amount of liquid added [2]. The amount of granulation liquid required depends on the mixing system, the specific machinery used, and the product properties of the raw materials used.

During the first granulation phase, a high-performance mixer is needed to facilitate a fast and even distribution of the liquid for granulation purposes. The quality of the granules depends considerably on a fast and impeccable distribution of liquid at the start [3].

A chopper can be added to the mixer to support the process of liquid distribution. This also intensifies the compacting of the granules and optimises the particle size distribution, with finer particles being worked into the wet surfaces of the larger agglomerates and any excessive accretion of granules being limited through deagglomeration. [3]

The input of the liquid is followed by the granulation phase. The liquid is distributed further, and there is more contact involving the wet particles. Any granulation effect here is limited to the moisture on the surface of the particles. The finished, wet granulated matter is mostly sticky in consistency.

The optimal end-point, for granulation purposes, correlates in most cases with recurrent delivery of power from the mixer drive, whereby the power measured can be defined as a reproducible end-point for granulation in a production device.

Fig. 4: Wet granulated matter following discharge

Granulation through the addition of liquid can be precisely controlled in batch processes with the help of typical granulation curves associated with the power consumption for the mixing shaft and/or the product temperature.

Besides the most commonly adopted accretion-type granulation, granules are occasionally manufactured from a paste. This generally achieves a rather more uneven type of granulated matter as regards particle size and distribution. The product twice undergoes a so-called toughening phase, which requires a great deal of drive power: once to manufacture the paste and a second time starting from the paste created.

This process may be chosen if process management would otherwise fail.

2.4 Drying

In the drying phase, the added liquid is removed from the granules once more to ensure the intermediate or final product will be stable during storage.

During the course of drying, the soft wet granules start to harden. Among other things, this helps ensure the material shows optimal compressibility.

The structure of the granules should remain unchanged during drying, and any fractures or abrasion are to be avoided. An optimal way to achieve this is to use a fluid bed. Assuming the agglomerates are sufficiently stable, drying may also be performed in a system with mechanically generated motion, such as in a horizontal mixer/dryer.

The drying step takes up the most time of the entire process. Optimisation can be achieved by selecting suitable process parameters, such as using a vacuum in the drying chamber. The vacuum expels the vapours from the dryer at maximum speed.

The boiling point for the liquid to be evaporated is also reduced and the product temperature lowered at the same time, which can have a positive impact on temperature sensitive active ingredients.

2.5 Next steps

The drying process is followed by sieving. During granulation, a certain amount of oversize is produced which has to be removed before loading the tablet press. This can be done with a forced sieving, e.g. in a sieve mill, since the oversized grain is a qualitatively perfect, homogeneous product that can be further processed in a suitable particle size without restriction. [3]

Before compression in tablet presses, lubricants or flow aids are added to the final granulate. In the vast majority of cases, this is magnesium stearate. The mixing task in this step is simple, so the addition can be done in a simple mixer, e.g. a free-fall mixer, or take place directly during transfer into the tablet press. Excessive mixing should be avoided, as the lubricant would no longer be efficiently available at the contact surfaces for the desired effect in the press due to its incorporation into the structured surface of the granules.

3. Implementation of wet granulation in the single-pot system

Wet granulation can be implemented via various processes, such as the oldest wet granulation concept, which combined a mixer with a rack-based drying cabinet. This system required a certain amount of labour to transport things to and from the dryer. After drying, an additional manual and labour-intensive step was needed for the forced sieving that was required.

Production facilities often use a vertical high-shear mixer and a fluid bed dryer for implementation purposes. With this process, it is also necessary to transport the granulated matter for drying into the separate fluid bed dryer. Besides transport via containers, transport here is also possible via a direct line to the fluid bed dryer.

In both cases, separate systems are required for granulation and drying. Potential implications include additional space requirements, elaborate explosion control concepts, and possible damage to the sensitive goods for drying during transport. These drawbacks are avoided with the single-pot solution.

Besides the method described below, the single-pot solution may be implemented using a fluid bed dryer.

Here, pneumatic mixing is performed following filling with the fluidising agent. Separation may occur here if particle sizes and individual particle weights are not homogeneous. With particle sizes <100 µm, extreme levels of channel formation in the product bed can also often occur at the start of fluidisation, and only regular turbulence is achievable. The spraying process during liquid addition for granulation purposes, by means of dual-material nozzles, is far more sensitive than in a mixer. It is a case of striking a fine balance for the addition speed, ensuring successful bonding of individual particles without excessive wetting and clump formation. As soon as wetting becomes excessive, the process is disrupted and the fluid bed breaks up unless the operator reacts. The total spray volume is limited by the active spray mist surface at the nozzles. Another complicating factor is how any monitoring that the nozzles are functioning correctly, with the desired spray mist, will only prove inadequate.

The air used for turbulence also serves as an energy source for drying purposes. However, the energy input this way is mostly higher than required to evaporate the sprayed solution, which results in higher energy expenditure.

In the case of single-pot granulation in the horizontal vacuum shovel dryer, all process steps – i.e. mixing of powder, wet granulation, and drying – take place in a single device with a horizontal mixing shaft.

If the device has a double casing, it can accommodate drying of the product, with an energy input, following granulation. This means there is no need to transfer the product to another device, which saves time and space and also avoids potential product faults due to stress endured by the still sensitive material for drying.

Ideally, there will also be the option to conduct the drying process in a vacuum. The resulting lowering of the boiling point reduces the temperature stress on the product and accelerates the extraction of any vapours generated. This helps ensure efficient and gentle drying, including for sensitive products.

The challenge with the all-in-one solution is how the product makes different demands of the system in the respective process steps (mixing, granulation, drying). This particularly applies to the input of mechanical energy.

Successful granulation requires a great deal of energy, in order to achieve an even distribution of liquid and facilitate optimal granule accretion.

During drying, by contrast, the product needs to be moved gently so the granules created, which are still wet and not yet stable, are not damaged through abrasion or fracture.

Fig. 5: Horizontal single-pot device for production purposes [4]

The granulation in the single-pot system depicted here is taking place in a horizontal shovel dryer. This combines the benefits of the drying process with the technical possibilities offered by a horizontal Ploughshare® Mixer. Beyond producing mixtures with an excellent mixing accuracy, the mixing elements also provide essential support for the drying process by carrying out a steady exchange between product and heat transfer surface. This ensures a very effective heat transfer into the product.

Compared to alternative vertically arranged drying systems, the horizontal dryer has a significantly higher available heat exchange surface, which also leads to shorter drying times.

Benefits / Drawbacks:

+ everything in one enclosed system
+ compact and economical equipment
+ short processing times
+ energy-efficient process compared with, for example, fluid bed spray agglomeration
- not suitable for all products (stability of granules)

The application examples described below show, by way of illustration, how granulation can be achieved with the single-pot solution using the Lödige DRUVATHERM® VT shovel dryer.

3.1 Application example based on granulated matter for effervescent tablets

Granules for effervescent tablets are designed to deliver the desired effervescence effect when they are subsequently dissolved in water and release CO_2.

As water is used in the manufacture of granules, it is important that drying takes places as quickly as possible in the granulation process so the full 'effervescence reaction' does not occur as early as the granulation stage.

The main elements of effervescent tablets are fillers and excipients, binding agents, components for triggering the 'effervescence reaction', and, of course, active ingredients (e.g. vitamins, analgesic agents, and the like).

The 'effervescence reaction' is triggered by a reaction involving organic acids (e.g. malic, tartaric, and citric acid) and sodium or potassium carbonate or their bicarbonates. On contact with water, the components react to the respective salts of the acids and duly release water and CO_2, with the latter prompting the sparkling 'effervescence effect'. [2]

Example of a reaction:

Bicarbonate + citric acid → citrate + water + carbon dioxide

$3NaHCO_{3(aq)} + C_6H_8O_{7(aq)} \rightarrow Na_3C_6H_5O_{7(aq)} + 3H_20_{(l)} + 3CO_{2(g)}$

A small amount of water, compared with other wet granulation processes, is added to the mixed powder as an initiator. This water starts the acid-base reaction and releases further water in the process. The product becomes wetter and wetter, and the mobility of the product changes too, including as a result of the stickiness that develops. The water added and particularly the water generated in the process itself lead to a very even granulation of the mixture, with the granule size gradually increasing [3].

The reaction would run run further and would eventually use too much of the reactants, resulting in a poor sparkling effect. As a result, the tablet would no longer have any effervescence effect available for later. It is always essential therefore to calculate the effervescent component in the recipe in such a way that granulation can continue to run until the desired end-point and there is still enough reaction material for the application when the reaction is stopped. This stopping of the reaction must be both quick and reliable. [3]

When this process is implemented in the mechanical generator, a certain amount of water is present. This means a vacuum needs to be created at the same time, besides the introduction of drying energy via the double casing, in order to remove as fast as possible the free water on the surface of particles that is driving the reaction (and thereby virtually generating itself) and take it out of the reaction.

As the product cools through the evaporation of the water, this in turn inhibits the acid-base reaction.

Drying then occurs, until a state is reached where stability for storage purposes is achieved, based on a water content of < 1%. This process has been used successfully since 1984 on a scale involving batches of around 1000 kg, in a production setting, on horizontal mixers/dryers. Fig. 5 shows one such single-pot apparatus, by way of illustration, with a gross volume of 3000 L, which is ready for installation in a production facility subject to GMP requirements.

The manufacturing process for effervescent granules provides an example of how a good product can only be achieved if full advantage is taken of the potential variability offered by a device. In this case, the highest possible drive speeds for the mixing shaft and chopper are used in the first mixing step in the machine in order to ensure the mixture is homogeneous. At the same time, the components within the mixture rub into each other to create a stable mixture.

Liquid addition then occurs in accordance with the same parameters. The use of a nozzle is not necessary as the turbulence of the particles in the mixing area is sufficient for distribution purposes.

Once liquid addition is complete, the drives continue to operate at high speed for a short time. Then the speed of both drives is reduced, for granulation purposes, to allow the particles to roll away and increase in size.

At the start of the drying phase, the drive speed for the mixer is reduced again and the chopper shut down completely in order to preserve as fully as possible the particle structure generated.

Initially, the mixing shaft is kept at a low speed for discharge. The mixing shaft speed is only increased and the chopper switched back on for the discharge of any residue.

Fig. 6 shows the unfolding of a single-pot process with the curves for the quality-related process values from the documentation for a classic single-pot granulation.

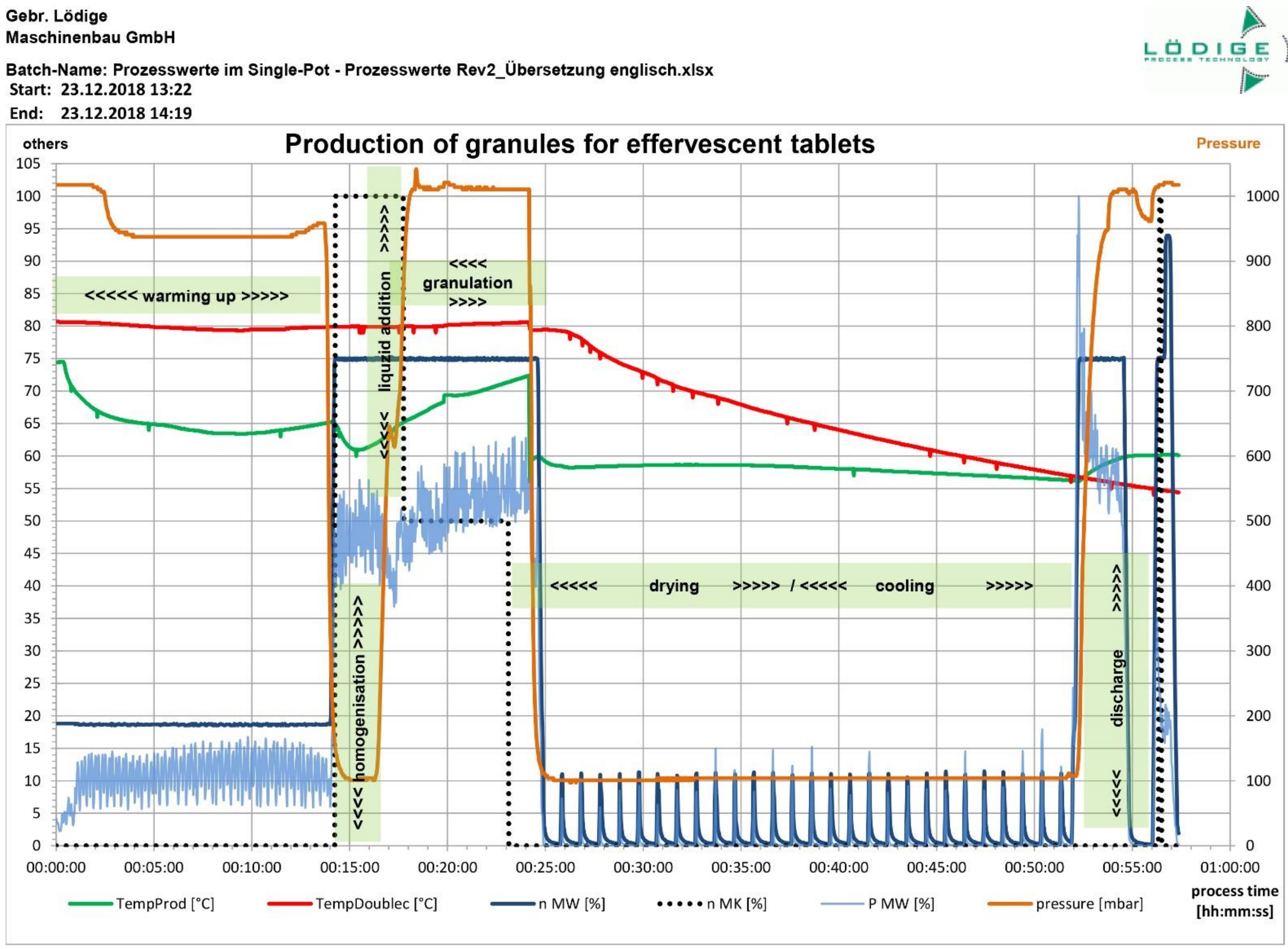

Fig. 6: Curve showing the process values in a classic process [4] - Legend: TempProd: product temperature, TempDoublec: double casing temperature, n MW: mixer speed, n MK: chopper speed, P MW: mixer drive power, pressure: pressure in mixer/dryer

3.2 Application example based on vitamin C granulated matter

The granulation of vitamin C powder essentially follows the basic granulation approach described in section **2.**

Apart from the tabletting agent (lubricant), all components are mixed together and wet granulation takes place to achieve a stable mixture in the form of granules.

After filling with the components, the process begins with dry mixing.

Liquid addition takes place, with liquid added to the moving product bed. The mixer and chopper drives run at 100% speed to ensure immediate fine distribution of the liquid. Addition occurs over a period of 2-5 minutes to make optimal use of the distribution efficiency associated with the chopper.

The granulation step is performed, with the drive speeds already being reduced. The mixer drive in this phase should favour granulation through rolling in order to slowly increase the size of the particles. Also in this phase, the chopper helps with compacting and helps limit the particle size distribution.

If drying is initiated in a vacuum, the chopper is shut down completely and only switched on at intervals at a low speed. The mixer drive can still be slowed down.

Once drying is complete, the product can be discharged. If discharge takes place via a forced sieving arrangement, loading of the sieve must be managed in a way that avoids blockages.

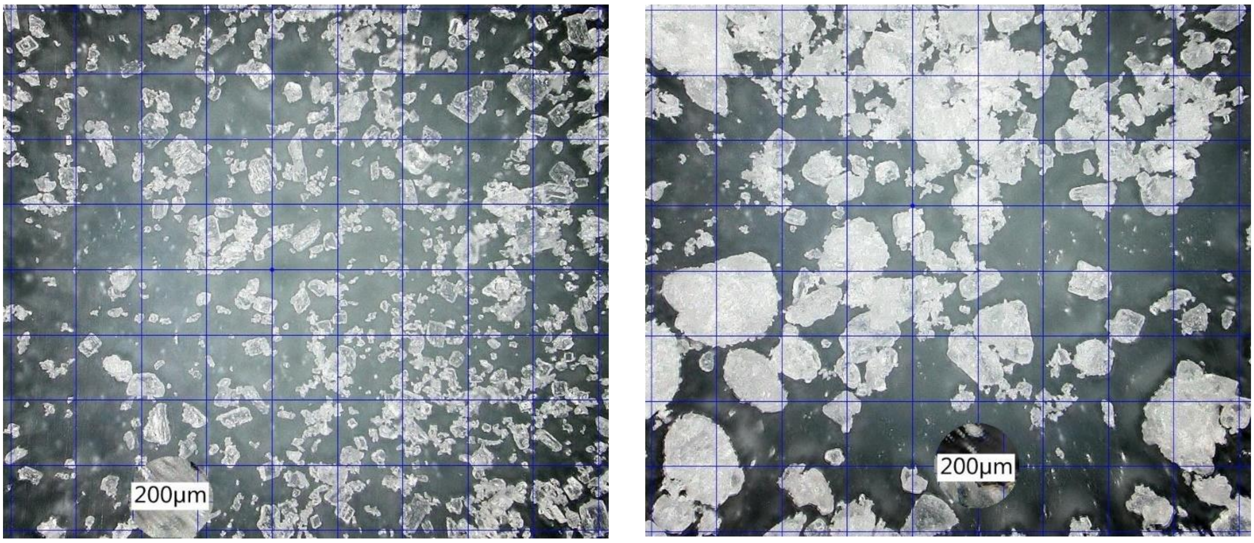

Fig. 7: Vitamin C particles under a digital microscope, left before granulation, right thereafter [4]

Fig. 7 shows images, with a digital microscope, of vitamin C as raw material in powder form and as dried granulated matter after sieving with a 1.5 mm sieve.

Fig. 8 shows similar granulated matter in a fill bag following discharge and sieving with a 1.5 mm sieve.

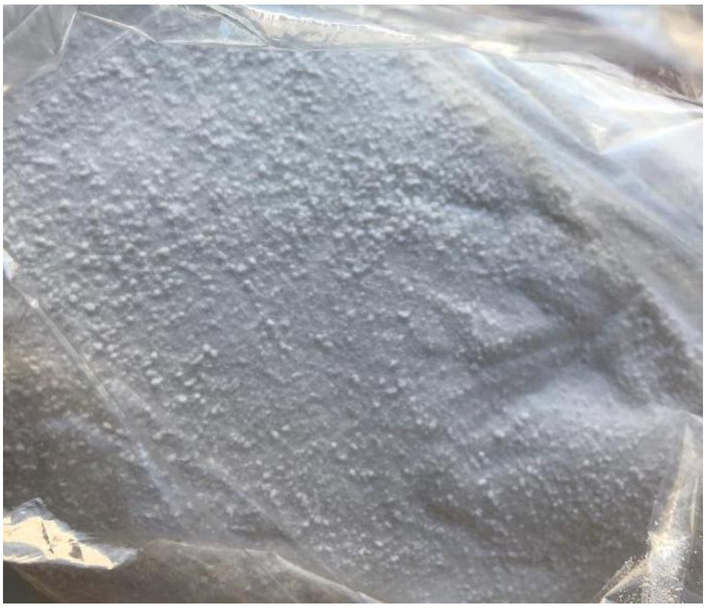

Fig. 8: Dried granulated matter after forced sieving through a 1.5 mm sieve [4]

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