

Melt Granulation with polyethylene glycol in a Single Pot Processor

Abstract

This study compares different processing methods to prepare a melt granulation with polyethylene glycol (PEG) in a high shear mixer/One-pot processor. For melting the PEG, either the heated jacket or heated jacket supplemented with microwaves was used to supply the necessary energy. For cooling the mass after granulation, 3 methods were compared: cooling with the jacket, cooling with pressurized air and cooling with liquid nitrogen.

The results of the comparison show a significant time reduction in the process when using microwave energy for heating the product, and liquid nitrogen for cooling. No differences in granule particle size distribution could be observed.

Introduction

Melt agglomeration is a process by which agglomeration – or size enlargement by which fine particles are bound together to agglomerates or granulates – is obtained through the addition of either a molten binder liquid or a solid binder which melts during the process. Agglomerates are formed by agitation of the mixture. To obtain a stable, dry granule, a cooling to ambient temperature is necessary to solidify the binder.

Recently, the interest in melt agglomeration processes from the pharmaceutical industry has grown steadily because of the advantages the technique offers over conventional wet granulation methods:

- When the binder is added in solid form, the liquid addition step is avoided, simplifying the equipment, the process and the cleaning.
- As no liquid is added, the drying phase – often the most time-consuming step in a conventional process – is eliminated.
- When the binder used is insoluble in water, melt agglomeration may present a simple way to form sustained release formulations.

Many different procedures and equipment have been used for melt agglomeration. High shear mixers are very well suited to execute a melt agglomeration process: the high shear forces caused by the impeller rotation make it easier to obtain a uniform distribution of the molten binder, and generate enough frictional heat to assist the melting process. High shear mixers have also been shown to be suitable for melt pelletization, due to the high shearing forces, plus the bowl shape.

In a high shear mixer almost all procedures for melt agglomeration and melt pelletization use the heat supplied by the heated jacket of the bowl and/or the development of heat caused by friction to melt the binder. In production scale equipment the heating of the product using the jacket can be very time-consuming (1).

The application of an external heating source, independent from the jacket of the bowl or from the generation of friction heat, might prove to be more time-efficient.

The first part of this study investigates the possibility of using microwave energy as an external heating source to melt the binder. These trials used pilot scale equipment and compared the process with regard to process time and granule particle size, using either the heated jacket or microwaves as the energy source.

The second part of the study focuses on the cooling phase of the process, which is necessary to obtain a dry, stable granule. In many cases, this phase is the most time-consuming of the whole melt granulation process due to the limited cooling capacity of the jacket of the high shear mixer and an insulation effect of the binder itself. The aim was to shorten the cooling time by using pressurized air or liquid nitrogen to reduce the temperature of the product.

Experimental methods

Materials

The formulation used for the trials was derived from the extensive literature available on the subject (2, 3):

| | |
|---|-----|
| PEG 3000 flakes (Condea Chemie) | 23% |
| Lactose 200 Mesh (DMV, The Netherlands) | 77% |

A batch size of 20 kg was used.

Equipment

All trials were executed on a 75-L high shear mixer-dryer, equipped with vacuum, gas-assisted vacuum and microwave drying systems (ULTIMAPRO™ 75, Collette NV, Belgium), without special PTFE coating of the interior of the bowl (1).



Figure 1: One Pot processor equipped with microwaves

For the liquid nitrogen cooling trials, a special patented valve (Linde, Germany) was attached to the gas inlets of the gas-assisted vacuum drying system, connected to a supply tank of liquid nitrogen (Hoek Loos, Belgium).

The particle size of the agglomerates was determined by sieve analysis with a set of sieves with the following mesh sizes: 1000 μm , 850 μm , 500 μm , 250 μm , 150 μm , 75 μm , (Retsch, Germany). Each batch was passed through a 2000 μm sieve and three 100 g samples of each batch were shaken on a shaker (Retsch, Germany) for 10 minutes. The amount of particles on each screen was measured.

Production procedure

The standard production procedure for melt granulation can be divided into 3 main parts, regardless of the actual parameters used: heating the material, granulation/massing and cooling of the product.

Heating of the material.

This phase in the production process is necessary to increase the temperature of the product mass to the melting point of the PEG 3000 (55-58°C). The PEG 3000 needs to melt to act as binder for granulation.

Two methods for heating the product mass have been investigated: using the double jacket of the bowl, and using both double jacket and additional microwave energy.

The parameters used for heating up the product in the first case are as follows:

| | |
|--|---------|
| Temperature of water circulating through the double jacket of bowl and lid | 60°C |
| Mixer speed | 180 rpm |

Heating of the water for circulation was started when the product was loaded into the bowl.

In the case where microwave energy was used as extra energy source to melt the binder, the same settings for temperature of the circulating water and mixer speed were used, which allows the effect of the additional energy source on the process to be evaluated. The parameters for the microwave energy were as follows:

| | |
|-----------------|---------|
| Microwave power | 2,7 kW |
| Vacuum | 90 mbar |

The reason for using vacuum during this step is due to machine restrictions. The microwave system of the equipment used for the trials has been designed for drying purposes. Because of this, the use of microwaves has been limited to a pressure range between 30 and 100 mbar. The range was defined on the one hand based on the properties of the electrical field generated by the microwaves, which has a higher risk of breakdown (or spark creation) below a pressure of 30 mbar, and on the other hand taking into consideration drying efficiency. Above a pressure of 100 mbar, the evaporation temperature of water increases and the energy supplied to the process will initially only be used to heat the water and product, and not for evaporation (4).

In both cases, granulation began when the temperature of the product reached 56°C.

Granulation.

The granulation step of the production process is intended to distribute the now molten binder evenly into the product mass and to create granules of the desired particle size. The settings for the granulation step were identical for all trials:

| | |
|---|----------------------|
| Temperature of water circulating in double jacket of bowl | Offset temp. -5°C |
| Temperature of water circulating in double jacket of lid | 60°C |
| Mixer speed | 305 rpm |
| Chopper speed | 1400 rpm |
| Granulation endpoint | 1,0 kW |

The offset temperature for the water circulating in the double jacket of the bowl indicates a regulation to keep this temperature always 5°C lower than the product temperature. The reason for selecting this offset temperature is to reduce the temperature increase of the product during granulation, caused by the energy input of the mixer, to reduce the cooling time afterwards.

As the endpoint of granulation is defined to be mixer power, time and particle size distribution were selected as variables to compare the 2 production techniques of heating using only the double jacket and heating using additional microwave energy.

Cooling

After granulation the material needs to be cooled down to solidify the molten binder and stabilize the agglomerates.

Different methods can be applied to cool the product:

- circulating cooled water through the double jacket of the bowl
- addition of dry, clean pressurized air to the bowl using the liquid spray nozzle
- addition of liquid nitrogen into the bowl via a specialized valve connected to the gas inlets of the gas-assisted vacuum drying system

For all batches, the following settings for wall temperature and mixer speed were used during cooling:

| | |
|---|--|
| Temperature of water circulating in double jacket of bowl and lid | 25°C |
| Mixer speed | 50 rpm continuous, until the product temperature reaches 50°C, then, 30 rpm 10 sec ON, 30 sec. OFF |

The pressure of the air added through the spray nozzle in the second cooling method was 4 bar. Overpressure that may be generated in the bowl because of this is evacuated through the normal overpressure valve.

For the cooling method using liquid nitrogen, the following additional settings were applied:

| | |
|--------------------------|---------|
| Vacuum | 0 mbar |
| Liquid nitrogen pressure | 3,5 bar |

Vacuum needed to be applied in the bowl to keep the pressure under control. The expansion of liquid nitrogen created a too high increase in pressure for the normal overpressure valve to evacuate. Although the setpoint for the vacuum system is 0 mbar, this pressure will never be reached because of the injection of liquid nitrogen.

Results and discussion

All results discussed below are based on at least 3 repeat batches for each production procedure.

Heating the product

On average the heating time for the batches produced using only the double jacket as energy source was 29 minutes, during which the temperature of the product was raised from 25°C to 56°C.

For the batches produced using microwaves as extra energy source, the heating time from 25°C to 56°C was reduced to an average of 14 minutes.

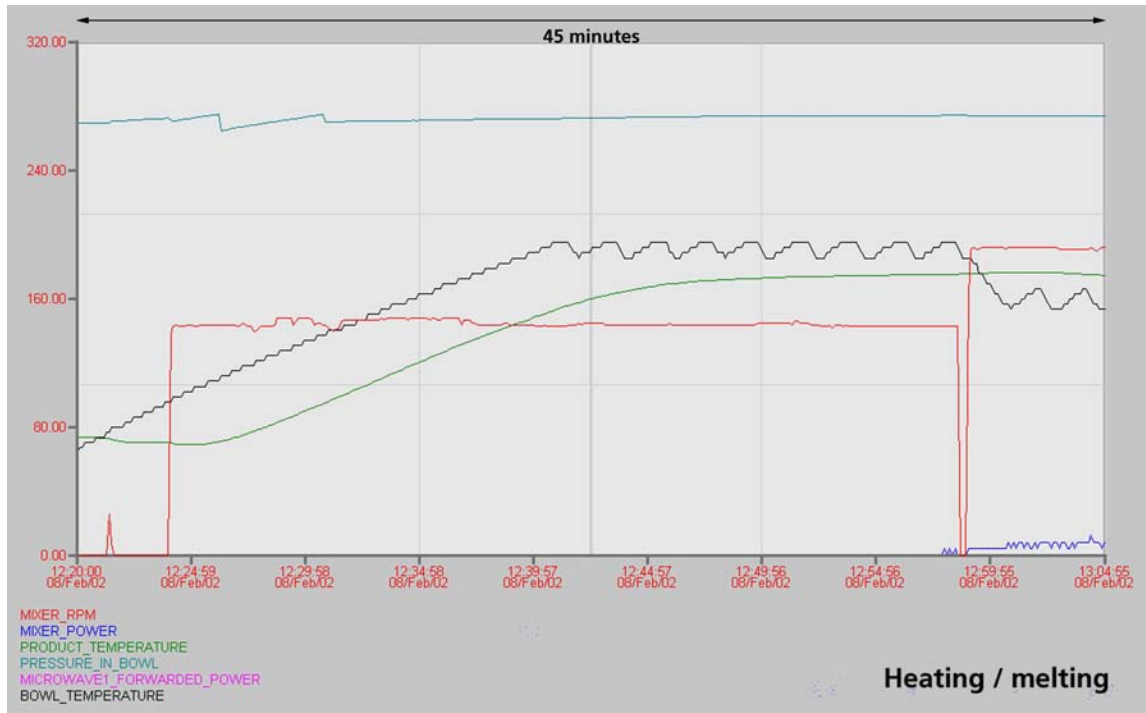


Figure 2a: graphical print-out of the heating process using only double jacket

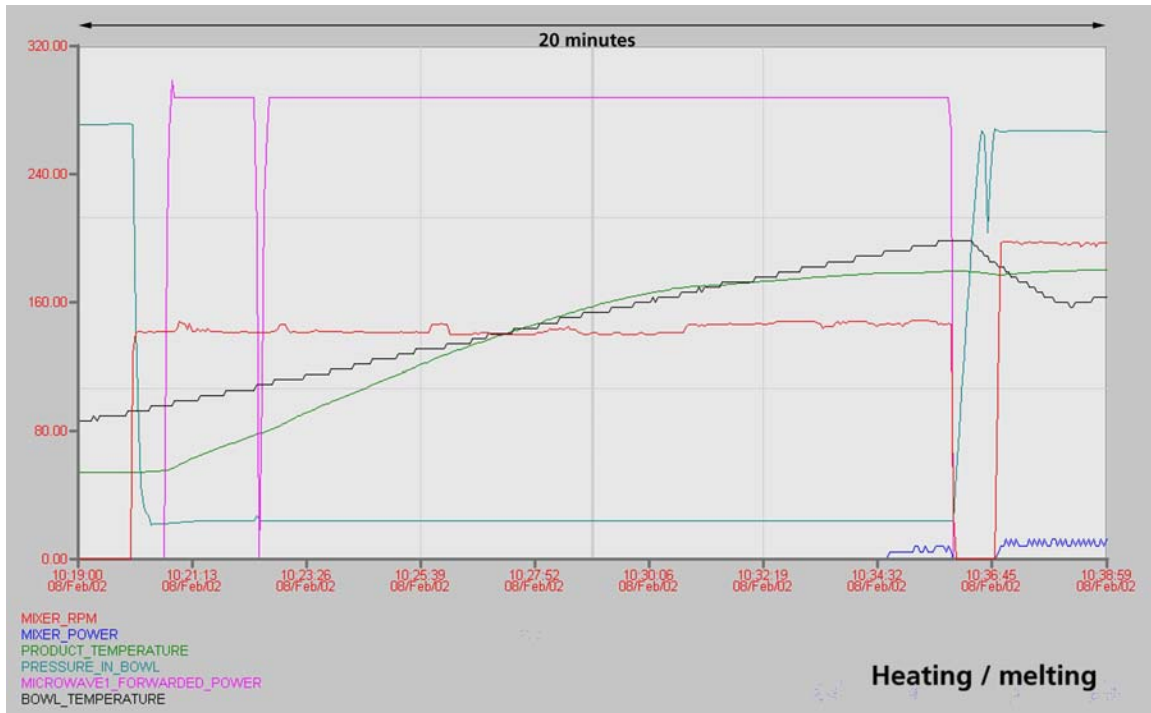


Figure 2b: graphical print-out of the heating process using microwaves

As all settings are equal for the 2 production methods, except for the use of microwaves as additional energy source (and the vacuum necessary to apply the microwaves), the significant reduction in heating time can be fully attributed to the microwaves.

Although it has not been tested, these results indicate that microwaves alone, without the use of a heated jacket, would also provide enough energy to heat and melt the binder. Omitting the heated jacket however limits the possibilities of controlling the temperature of the bowl wall, by which sticking of the product can be avoided in later steps of the process.

Another observation was made during the heating phase, related to the product movement in the bowl. When the product is heated using microwaves, it could be observed that when the temperature was raised above 50°C, a vortex was created by the product, while this movement could not be observed for the batches heated with double jacket only. The vortex movement in the product can only be created when there is enough liquid present to make the mass heavier and start agglomeration.

This observation thus indicates that when the mass is heated using microwaves, all the PEG has molten, while when the mass is heated using double jacket only, the PEG is only partially molten. The effect of this difference in melting of the PEG becomes clear during the granulation step (see below).

Granulation/massing

When only the double jacket was used to heat up the product mass, it took on average 18 minutes to reach the pre-determined endpoint of 1,0 kW.

From the power measurement of the mixer, it could be observed that during the first 7 to 8 minutes of the granulation, no increase in mixer power was taking place, and thus no agglomeration was taking place.

The batches in which microwave energy was used to heat up the mass, took only 5 minutes (on average) to reach the endpoint of 1,0 kW. For these batches, the mixer power showed a clear increase from the start of the step. Even at the end of the heating phase with microwaves, an increase in mixer power could be observed, indicating that the granulation already started before the temperature of 56°C was reached.

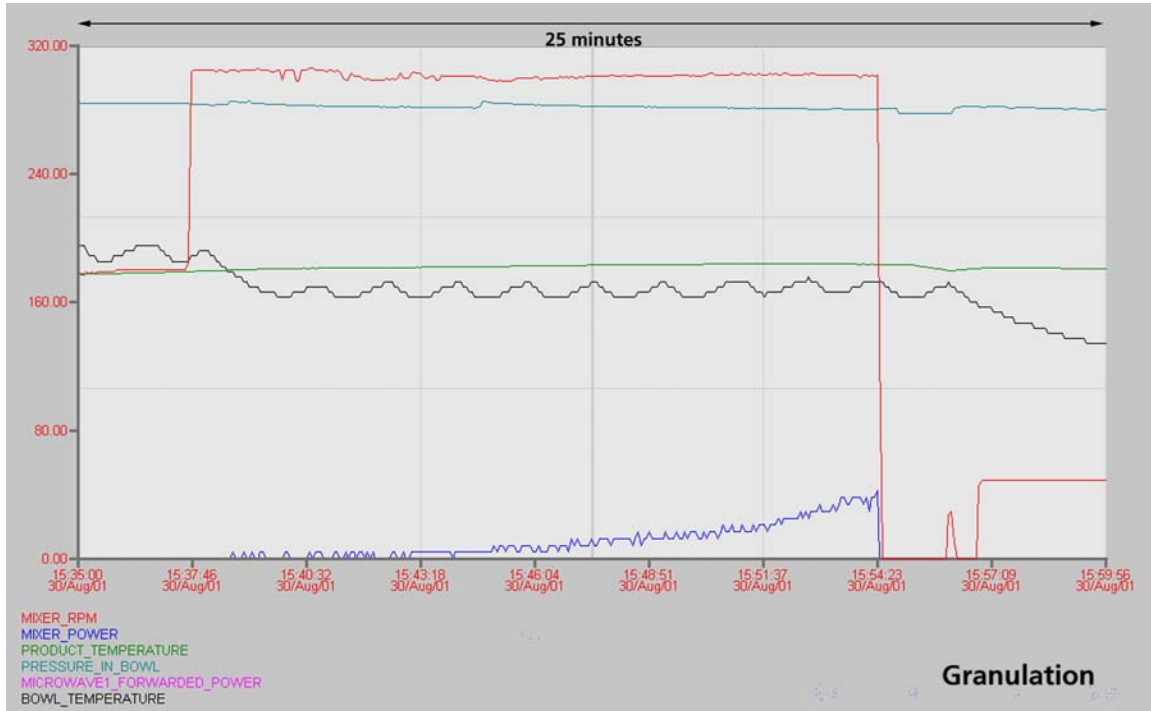


Figure 3a: graphical print-out of the granulation process using double jacket only

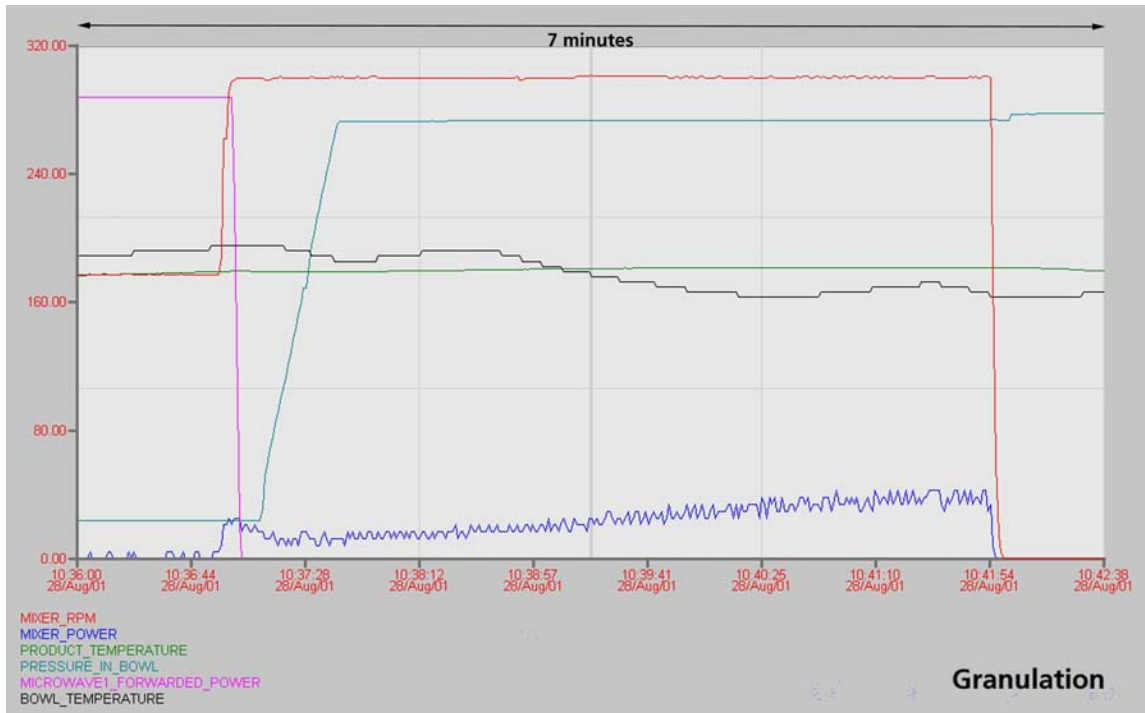


Figure 3b: graphical print-out of the granulation process after using microwaves

To make sure that the resulting granules from the 2 processes have the same characteristics, a particle size distribution was done for each batch produced.

| | Double Jacket | Double Jacket + Microwaves |
|------------|---------------|----------------------------|
| 1000 μ | 5.4% | 5.1% |
| 500 μ | 27% | 36.5% |
| 250 μ | 46.5% | 43.3% |
| 150 μ | 10.4% | 6.1% |
| 75 μ | 5.9% | 5.3% |
| < 75 μ | 4.8% | 3.7% |

Table I: particle size distribution (average of 3 batches)

From the results it is clear that the endpoint of 1,0 kW for granulation, produces similar granules for both production techniques, with the production technique using microwaves producing even slightly bigger granules notwithstanding a shorter granulation time.

As the settings for the granulation step are identical for both production techniques, the difference in duration of the granulation step must be related to the method of heating up the mass, and thus melting the PEG.

Considering the fact that the work was done using PEG flakes, the explanation is most likely as follows:

Microwaves have the property of penetrating into the material exposed to them (except in case of reflecting materials), where they are (partially) absorbed, causing the material to

heat. When the PEG flakes are exposed to microwaves, they are heated by the microwaves throughout the flake, and thus the flakes melt homogeneously. Heating by the double jacket relies on conductive heat transfer, meaning that the flakes will start to melt on the outside, while the inside remains solid until the conductive heat transfer reaches it as well.

When the granulation phase is started, the PEG flakes in the batches produced using microwaves are most likely molten, while the PEG flakes in the batches produced using only double jacket have only melted on the outside, while the inside is still solid or only partially molten. The temperature detected by the temperature probe is in both cases the same, as it only measures the surface temperature of the granules/particles. In the second case, the PEG flakes need to be molten further to be able to granulate the product, explaining the longer granulation time and the absence of mixer power rise at the start of the granulation phase.

The explanation above is also corroborated by the observations made at the end of the heating phase (see above): the batches produced with microwaves already have the vortex movement, only present when enough liquid is available, while in the batches produced using only the double jacket this movement cannot be observed at this point.

Cooling

All different cooling techniques have been tested for batches produced with both heating mechanisms. No difference could be observed in the results for the cooling times between batches heated with the different techniques, thus the results presented are the average of all batches cooled with that particular technique.

When only the jacket was used for cooling down the melt granulate, it could be observed that on average 70 min. were needed to bring the temperature from approx. 56°C to 25°C. When pressurized air at 6 bar was added to this cooling technique, the cooling time could be reduced to an average of 50 minutes, which constitutes a significant decrease in cooling time.

However, even when pressurized air is used, the cooling phase still remains the most time-consuming step of the process, with the risk of influencing the granulate properties (mainly shape and particle size distribution).

For the batches cooled with liquid nitrogen, the cooling phase was stopped when the temperature probe indicated 40°C. The reason for this was the observation that cooling of the product with liquid nitrogen happens so fast that the reaction time of the temperature probe in the test equipment was not fast enough: while the temperature probe of the test equipment still showed 40°C, measurement with an external temperature probe indicated that the actual product temperature was already approx. 25°C. Because this observation was shown to be repeatable in 3 batches, it was decided to take the indicated endpoint of 40°C as endpoint for the cooling step.

The time needed for cooling the product down to 40°C indicated product temperature (= 25°C actual product temperature) was 12 minutes on average.

From these results it is clear that liquid nitrogen cooling is by far the fastest method of cooling a melt granulate, but that a fast reaction temperature probe is necessary to control the process accurately.

As the supply lines between the liquid nitrogen tank and the special valve in the test rig were not traced, it can be expected that the nitrogen entering into the bowl is a mixture of liquid and gas nitrogen. The supply lines are in contact with room temperature, causing the temperature of the nitrogen to increase slightly during transport from the tank to the bowl. When traced lines are used, the nitrogen that reaches the bowl is all liquid and an even better cooling effect can be expected.

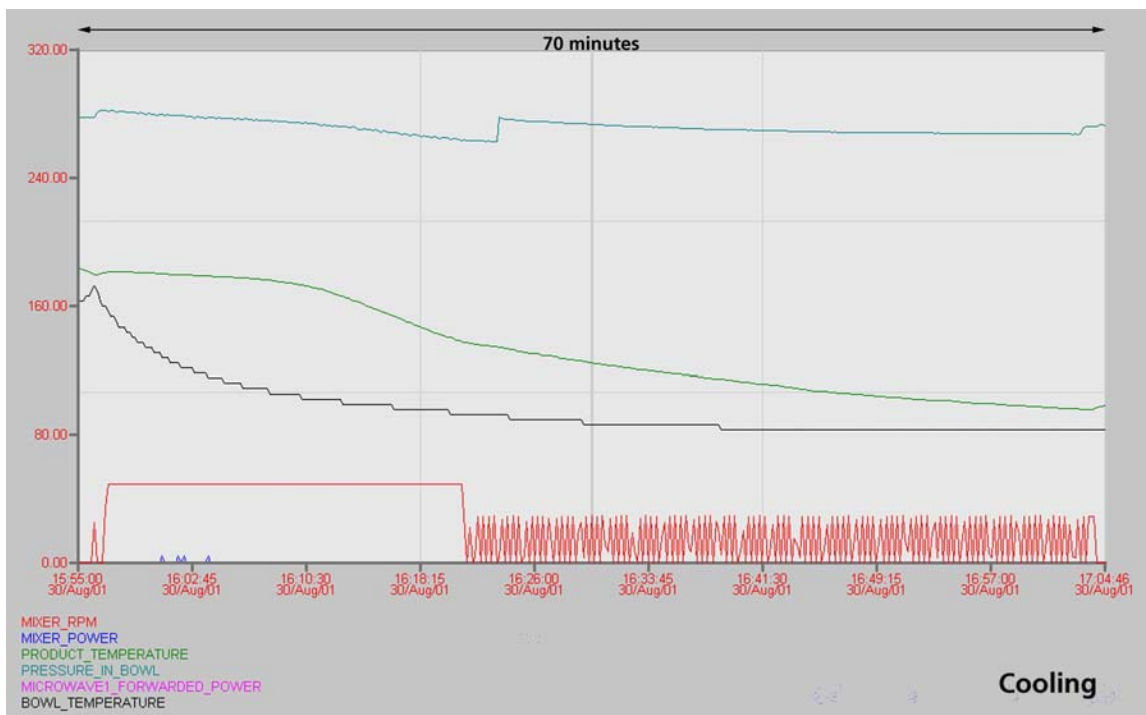


Figure 4a: graphical print-out of the cooling step using double jacket only



Figure 4b: graphical print-out of the cooling step using double jacket + pressurized air

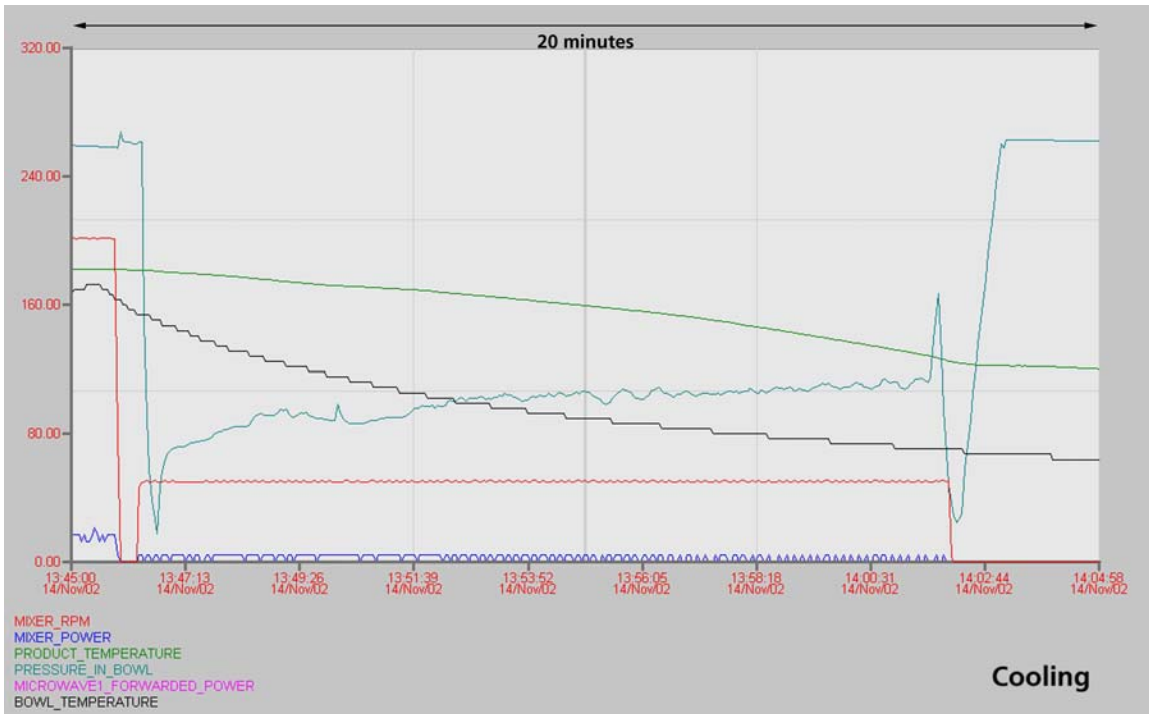


Figure 4c: graphical print-out of the cooling step using liquid nitrogen

Overview

An overview of the results of the study on process time can be found in the table below.

| Step | Microwaves | | | Jacket | | |
|----------------------------------|-------------------|--------------|-----------------|---------------|--------------|-----------------|
| <i>Heating</i> | 14 min. | | | 29 min. | | |
| <i>Granulation</i> | 5 min. | | | 18 min. | | |
| <i>Cooling</i> | Jacket only | Jacket + air | Liquid nitrogen | Jacket only | Jacket + air | Liquid nitrogen |
| | 70 min. | 50 min. | 12 min. | 70 min. | 50 min. | 12 min. |
| <i>Total Average time</i> | 89 min. | 69 min. | 31 min. | 117 min. | 97 min. | 59 min. |

Table II: summary of process times

The results show clearly that the use of microwaves for heating and melting the product mass, and liquid nitrogen for cooling the melt granulate present very significant time savings in the production of PEG based melt granulations. Production time is reduced 4 times compared to the conventional technique of using the double jacket of the granulator for heating and cooling of a melt granulation.

Conclusions

A one-pot processor equipped with microwaves has been shown to be very advantageous in the production of melt agglomerates based on PEG. Heating/melting of the product takes only half as long using microwaves compared to the traditional production method using only the double jacket, while the reduction in granulation time is even more (3,6 times). The production time (not including cooling) can thus be reduced by a factor of 2,5.

However, the cooling phase remains the most time-consuming step on which the method of heating has no effect.

The experiments using liquid nitrogen as cooling medium, offer however a solution to this problem. Using liquid nitrogen, the cooling time can be drastically reduced with a factor of 6,5 compared to the traditional cooling technique using the double jacket. With the availability of the special valve, the addition of liquid nitrogen to the one pot processor poses no problems, making this system excellent equipment for producing melt granulations.

Using both microwave heating and liquid nitrogen cooling, a pharmaceutical manufacturer will be able to increase his production capacity 4 times. The additional investments costs for the microwave heating and liquid nitrogen cooling systems are clearly lower then the investment required for the conventional technique capable of producing the same output (4 high shear mixers with heated jacket).

References

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SIDEBAR

Microwave technology for One-Pot processors

Microwaves are a form of electromagnetic energy with frequencies between 300 MHz and 300 GHz. In the electromagnetic spectrum they fall between radio waves and optical waves. For domestic, scientific, medical and industrial purposes two frequencies are allocated that do not interfere with communications frequencies: 915 MHz and 2450 MHz. The most common frequency in the pharmaceutical industry is 2450 MHz, because of the advantages this frequency offers in conjunction with vacuum (1,2).

The use of microwaves in a One-Pot Processor is directed by the properties the different materials of the system have when exposed to microwaves: reflection, transparency or absorption.

Microwaves are reflected off metals, which they do not heat. For this reason metals are used as conduits for microwaves (wave-guides) and as walls for a microwave oven. As pharmaceutical equipment is manufactured from stainless steel, the vacuum chamber acts as confinement for the microwaves by reflecting them back into the chamber. Another effect of the reflection of microwaves in the metal bowl of a one pot processor – much the same as in a domestic microwave oven – is that the microwave energy is distributed homogeneously into the bowl cavity, even though there are only 1 or a few entry points for the microwaves (3).

Many materials are transparent to microwaves and do not heat either, for example quartz glass and PTFE. In pharmaceutical equipment, the processing area (or product contact zone) needs to be clearly and tightly separated from the technical area, where the microwave generator and waveguides are located. To allow the microwaves to enter the bowl, while keeping the processing and technical zones separated, a window needs to be present which is transparent for microwaves. In most cases Teflon or quartz glass are used for these microwave windows (3).

For the drying process the most important property of microwaves however is absorption of microwaves by the materials, as materials that absorb microwaves are heated. Given the characteristics of the materials commonly used in pharmaceutical production, microwave energy is very well suited for drying of pharmaceutical formulations. The most frequently used granulation liquids (water, alcohol...) have much higher loss factors (the parameter that indicates the amount of microwave energy absorbed by a material) than the other standard ingredients for a wet granulation (lactose, cornstarch...), leading to higher absorption of microwave energy and thus preferential heating of the liquids (3).

References:

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