Melt Pelletization of a Hygroscopic Drug in a High Shear Mixer. Part 3.[1] Effects of Binder Variation

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Melt pelletization experiments with sodium valproate as a hygroscopic drug were performed in a laboratory scale high shear mixer. In the current part, the effect of altering the binder liquid properties (using different binders, varying the temperature, or adding highly dispersed silicon dioxide to the molten binder) on the pellet size, size distribution and the growth rate was studied. Three meltable binders, namely glycerol monostearate (GMS), hydrated castor oil (HCO), and polyethylene glycol (PEG), were included in the study. Two series of experiments with GMS or HCO showed a higher granule growth rate with decreasing binder viscosity. Also, increases in the granule growth rate were observed for all meltable binders tested, when the binder amount and the impeller speed were increased. Factorial designs with all three binders were performed under the same conditions. In these experiments, no correlation existed between the granule growth rate and the viscosity of the different binders. The different granule growth rate, however, was mainly attributed to the different solubility of sodium valproate in the binder liquid used. Higher solubility increased the volume of the binder liquid and, accordingly, the granule growth rate. Taking the amount of dissolved drug into account, the granule growth rates of GMS and PEG were comparable. However, HCO displayed a lower granule growth rate, which might be related to its low adhesion tension. During melt pelletization in a high shear mixer the solubility of the drug in the molten binder strongly influences the pelletization process.

Key words　　melt granulation; high shear mixer; binder properties; solubility; melt pelletization

Melt pelletization in a high shear mixer is a process used to produce pellets by agitation of a mixture of particulate solids and a meltable binder at a certain temperature, which enables the liquefying or softening of the binder. The equipment used, the process parameters, and the chosen formulation influence this process.[2]

The amount of binder was found to be important to control the granule growth.[3,4] The granulation cannot be achieved if the binder amount is too low. In contrary, an excess and/or high binder amount results in an uncontrollable granule growth. Generally, only little variation is tolerable, if the other variables are kept constant.[2] Also, changing the type of binder liquid requires adjustment of the amount of binder.

The physicochemical properties of the binder (*e.g.* viscosity or polarity) and substrate–binder interactions were found to influence the granule growth and the strength of the agglomerates. This was examined in wet granulation[5,6] as well as in melt granulation.[7,8] Binder viscosity strongly depends on the product temperature, which is in turn influenced by process variables such as jacket temperature and impeller speed. The effect of viscosity on granule growth is complex, as demonstrated by Ennis *et al.*[9] Experiments with extremely viscous binders showed an increased potential for agglomeration growth by coalescence. This was related to the increased force of dynamic pendular bridges due to the viscous contribution.[10] Consequently, the growth promoting effect of increasing viscosity dominates beyond an upper critical limit. Below that limit, decreasing binder viscosity leads to a faster granule growth.

In a previous work, it has been shown that the pelletization of sodium valproate (SV) with glycerol monostearate was successful using 1.1 to 14.1% glycerol monostearate (GMS) as a binder and by adjusting the impeller speed and massing time.[11] As seen, the appropriate binder concentration for

successful pelletization was very low. It was assumed that the high solubility of SV is associated with the low amount of binder.

In the present study, melt pelletization with three different types of binder was investigated. The binders differed in polarity and in the ability to dissolve SV. The aim was to examine the effect of the binder type on the pelletization process and to elucidate the critical binder properties in determining the granule growth. Moreover, in aiming to obtain a better understanding of how the viscosity of the binder liquid influences the process, some experiments were carried out separately.

Experimental

Materials　　The model drug, SV (Katwijk, NL), is a hygroscopic and freely water soluble substance, which takes up water at relative humidity (rh) higher than 40% at 20 °C.[12] At higher humidity it liquefies quickly. The water content of untreated SV was 0.10% measured by Karl–Fischer-titration (*n*=3).

Fine powders of GMS (Myvaplex 600P, Eastman Kodak, U.S.A.), hydrated castor oil (HCO) (Cutina HR, Henkel, Germany), and polyethylene glycol (PEG) (Lutrol E 1500, BASF AG, D-Ludwigshafen) were used as meltable binders.

Highly dispersed silicon dioxide (Aerosil 200, Degussa AG, D-Frankurt) was used to modify the viscosity of molten HCO.

The solubility of SV in the molten GMS is 55% (w/w) at 100 °C and less than 2% (w/w) in the molten PEG at 80 °C. SV is practically insoluble in HCO.

Melting　　The onset of melting of the binders was determined by differential scanning calorimetry (DSC 7, Perkin Elmer, U.S.A.). The onset of melting was 70 °C for GMS, 64 °C for HCO and 37 °C for PEG, respectively.

Viscosity　　The viscosities of the molten binders were measured using a rotation viscosimeter, Contraves Rheomat 115 (Zürich, CH) with two different cylinder systems, MS-DIN 125 and 145, depending on the viscosity of the liquid. The binder was heated for 1 h prior to the measurement and the temperature was recorded by a PT 100. The shear rate (*D*) was increased from 20 to 300 s^{-1} during 10 min. The viscosity was determined after 1 min

at $D=300\,\mathrm{s}^{-1}$.

Density of Molten Binder　The density of the molten binder was gravimetrically determined in a 100 ml volumetric flask heated in an oil bath. The expansion of the flask was taken into account.

Surface Tension　The surface tension γ_{L} of the molten binders was measured by a pendant drop method at 80 °C (PEG), 90 °C (GMS) and 100 °C (HCO). Using the drop shape analysis system DSA 10 in combination with the high temperature dosing system G 13 (Krüss GmbH, D-Hamburg), the surface tension was calculated from the shape and density of the binder drop.

Contact Angle　Compact plates of SV were prepared in a highly polished steel punch and die assembly, 12 mm in diameter, with about 15 kN compression force.

The contact angle between the molten binder and SV was measured by the sessile drop method at 80 °C (PEG), 90 °C (GMS) and 100 °C (HCO) using the drop shape analysis system DSA 10 in combination with the high temperature dosing system G 13 (Krüss GmbH, D-Hamburg). A small droplet of molten binder was placed on the plate. The geometry of the drop was analyzed optically, and based on this the contact angle was calculated.

Pelletization Equipment　A vertical axis high shear mixer with 10 l nominal volume (P 10, Diosna, Germany) was used as described previously.[11] The current of the motor and the torque to turn the impeller were monitored during the process. The product temperature and the jacket temperature were recorded by a thermoresistance probe (PT 100). All data were collected by a computer.

Pellet Production　After sieving (1000 μm), SV was preheated in the mixer at low impeller speed (250 revolutions per min (rpm)) for 10 min. The jacket temperature was adjusted according to the type of meltable binder. The amount of binder, expressed as percentage by mass of the amount of SV, was added in solid state through the lid and the massing time was started. At the same time, the impeller speed was adjusted according to the experimental plan. The mixer was loaded with 2000 *g* of the binary mixture of SV and binder.

In one series of the experiments, the binder HCO was added in molten state.

During mixing, about 100 g in-process samples were taken without interruption of the process as described previously.[11] The relative humidity in the laboratory was kept below 35% during all experiments.

Experimental Design　Binder Viscosity: Two series of experiments were carried out to examine the influence of the binder viscosity on the mean granule size and the size distribution. In the first one, 4.1% GMS was used as binder at an impeller speed 875 rpm.[11] In order to change the viscosity of the molten binder during mixing, the jacket temperature was accordingly set to be 62, 73, 82, 92 or 100 °C.

In a second series, HCO was used as meltable binder and its viscosity was altered by adding 0, 2 or 4% Aerosil to the previously molten binder. For practical reasons, the binder was added in liquid state, after heating up to 120 °C. Subsequently, the process was performed using 12% of HCO mixed with Aerosil at 100 °C and at 575 rpm impeller speed.

In both series, the massing time was adjusted in order to obtain pellets of about 1000 μm geometric mean diameter or even larger. The process was terminated when destruction of the product was observed or when the time limit of 80 or 50 min was reached. Samples were taken during the process to characterize the granule growth.

Type of the Binder: Three 2^2 factorial experiments with a center point were carried out using PEG, HCO and GMS as binders. The jacket temperature was adjusted to be 80, 90, and 100 °C for PEG, GMS, and HCO, respectively. Binder concentration was varied between 10.1 and 14.1% and the impeller speed was examined between 475 and 675 rpm (Table 1). All experiments were stopped when destruction of the product was observed or when the pellet size did not change any more. In the case of HCO, four additional runs were carried out to complete a 3^2 factorial experiment in the described parameter range (Table 1).

Pellet Characterization　The geometric weight mean diameter (d_{gw}) and the geometric standard deviation (s_{g}), which were measured using sieve analysis, were used to determine the mean pellet size and the size distribution, respectively. Therefore, about 100 g sample was sieved using 12 analytical sieves in the range from 125 to 4000 μm on a Vibro-type sieve tower (Retsch KG, D-Haan) for 5 min on medium level.

Results and Discussion

Binder Viscosity: Changing the Jacket Temperature
In a previous part of the study, it was shown that pellets of

Table 1.　Product Temperatures Resulting from Process Variables and Type of Binder

No.	Impeller speed (rpm)	Binder concentration (%)	Product temperature (°C)		
			HCO	GMS	PEG
1	475	10.1	110	90	82
2	475	12.1	108		
3	475	14.1	109	91	82
4	575	10.1	110		
5	575	12.1	111	91	83
6	575	14.1	113		
7	675	10.1	114	91	83
8	675	12.1	113		
9	675	14.1	115	92	84

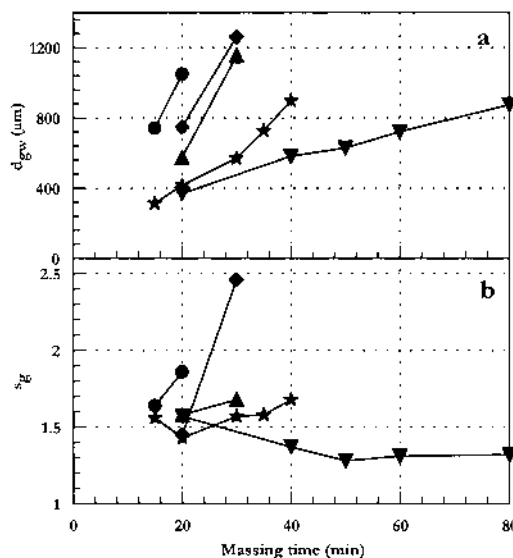Jacket temperature: 100 °C (HCO), 90 °C (GMS), 80 °C (PEG).

Fig. 1.　Effects of Massing Time and Jacket Temperature on the Mean Granule Size d_{gw} (a) and Size Distribution s_{g} (b)

Jacket Temperature: 62 °C (▼), 73 °C (★), 82 °C (▲), 92 °C (◆), 100 °C (●). Binder: 4.1% GMS; impeller speed: 875 rpm.

SV can be prepared in the high shear mixer with 4.1% GMS at an impeller speed of 875 rpm and a jacket temperature of 90 °C.[11] In the present study, it was possible to prepare pellets under the same conditions in a jacket temperature range from 62 to 100 °C. The effect of the jacket temperature on the resulting granule growth is shown in Fig. 1. The growth rate was accelerated with increasing jacket temperature.

Due to friction the product temperature was slightly higher compared to the jacket temperature. The mean product temperatures and the binder viscosities are given in Table 2. Figure 2 shows the relationship between the binder viscosity and the mean pellet size after 20 and 30 min of massing (taken from Fig. 1). For binder viscosities in the range of 50 to 250 mPa, higher viscosity resulted in a smaller geometric weight mean pellet diameter d_{gw}. The smallest pellet size distribution (s_{g}) of the in-process samples, which characterizes the most homogenous product, was found at 62 °C, followed by the experiment at 73 °C (Fig. 1b).

Binder Viscosity: Addition of Highly Dispersed Silicon

Table 2. Effect of Jacket Temperature on Product Temperature and Binder Viscosity with GMS

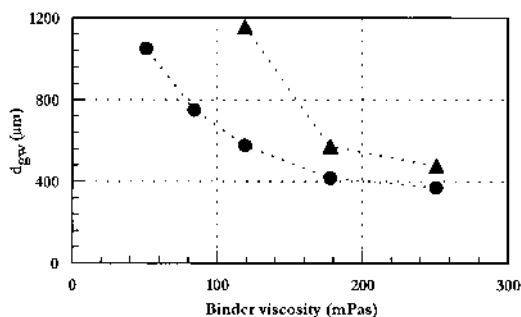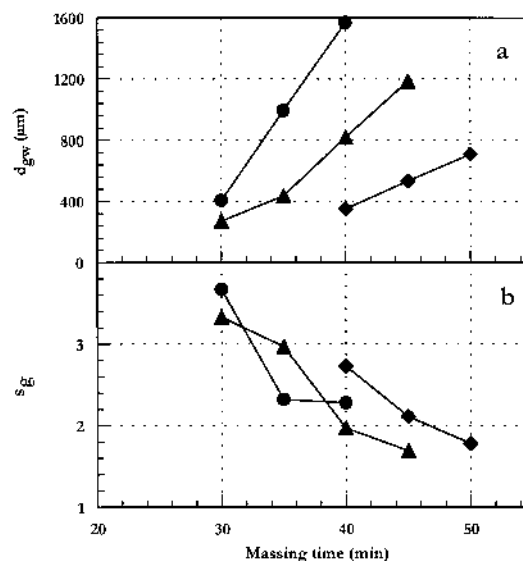| Jacket temperature (°C)	Product temperature (°C)	Binder viscosity at jacket temp. (mPa)
62	76	251
73	83	178
82	91	119
92	98	84
100	108	51

Fig. 2. Effect of Binder Viscosity during the Process on the Mean Pellet Size after 20 min (●) and after 30 min (▲)

Binder concentration: 4.1% GMS; impeller speed: 875 rpm.

Fig. 3. Effects of Massing Time and Binder Composition on the Mean Granule Size d_{gw} (a) and Size Distribution s_g(b)

Used types of binder: HCO (●), HCO+2% Aerosil (▲) and HCO+4% Aerosil (◆). Binder concentration: 12.1%; impeller speed: 575 rpm; jacket temperature: 100 °C.

Dioxide In the second experiment, the binder viscosity was increased by the addition of highly dispersed silicon dioxide (Aerosil), to examine the influence of binder viscosity without varying the jacket temperature or other process parameters that might also affect the granule growth. The effect of increasing binder viscosity on mean pellet size and pellet size distribution is shown in Fig. 3. The viscosity of molten HCO was 28 mPa at 95 °C. For technical reasons it was not possible to determine the viscosity at higher temperatures. The viscosity of the binder at 95 °C was increased to 46 or 97 mPa by the addition of 2 or 4% Aerosil, respectively. The product temperature exceeded 110 °C during the mixing process. Thus, the true values of viscosity were lower during pelletization, but this was assumed to have no influence on the ranking order.

Increasing binder viscosity delayed the granule growth as described in the previous experiment (Fig. 3a). A higher binder viscosity prolonged the time necessary to obtain pellets of a certain size. Comparing the size distribution at that point of the process, where the mean pellet size was 600 μm as estimated by linear interpolation, the distribution s_g decreased from 3.2 (0% Aerosil) to 2.5 (2% Aerosil) and finally 2.0 (4% Aerosil) (Fig. 3b).

Both experiments, using two different binders and two methods to modify their viscosity, showed a decrease in the granule growth rate, if the viscosity of the binder increased. This is contradictory to findings of other authors.[10,13] However, the influence of viscosity on the granule growth is complex.[9,10] The distribution of a high viscous binder might need more time compared to the distribution of a low viscous binder, which can cause a delay in granule growth. A higher viscosity will increase the viscous contribution to the force of dynamic pendular liquid bridges, increasing the potential of the granule growth process. In contrast, higher viscosity leads to lower surface plasticity and, consequently, a decrease in deformability of the granule. Finally, the granule growth can be slower.[3,4,14] It is the balance of the counteracting effects of the viscosity that determines the different growth rates.

3^2-Design for HCO It was possible to prepare pellets in the most 3^2 factorial design points. The only exception was the point, in which both variables were on the high level (Table 1, No. 9). Run 9 was characterized by uncontrollable granule growth; after 20 min the resulting product could be described as a powder with a few small granules, and after 25 min as powder with big lumps. During these final 5 min, the amount of fines smaller than 500 μm decreased from 49 to 36% while the amount of granules larger than 2000 μm increased from 9 to 53%. The effects of binder concentration and impeller speed on mean granule size (d_{gw}) and size distribution (s_g) are shown in Figs. 4 and 5. In general, the granule growth rate was accelerated by increasing impeller speed and also by increasing binder concentration. A compensating effect between impeller speed and binder concentration was confirmed in this study similar to previous results with SV and GMS.[11] A higher impeller speed could be compensated by a reduction in binder concentration in order to achieve pellets of a similar size after a certain massing time. In the present experiment, the granule growth was similar, if one variable kept on the high level and the other one on the low level and also if both variables kept on the intermediate level (Table 1, No. 3, 5, 7).

The mean size of the starting material, SV, was determined as $d_{gw}=85 \mu$m. Figure 4 indicates very slow granule growth during the first 20 to 40 min, depending on the process variables. However, after a certain lag-time, the mean pellet size increased at different rates. During this lag-time, the torque to turn the impeller was significantly higher than later in the process and also higher than the torque curves yielded with other binders (Fig. 6). This might indicate a slower distribution of the molten binder in the mass.
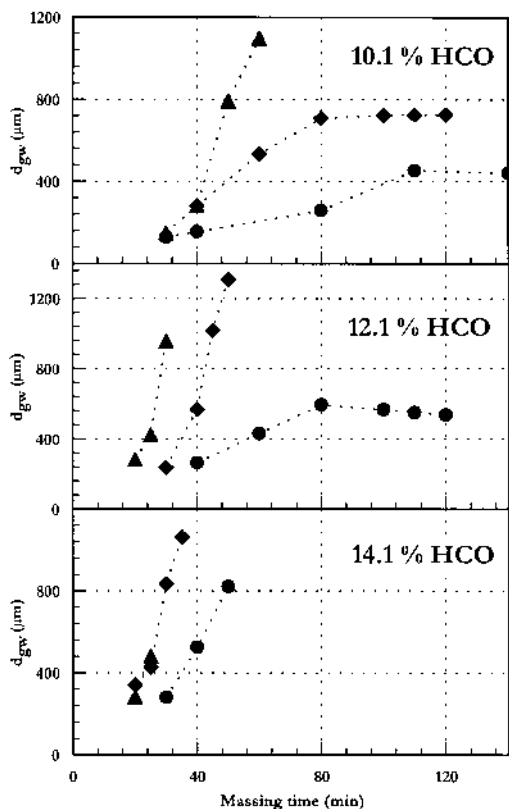
Fig. 4. Effects of Massing Time and Impeller Speed on Mean Granule Size d_{gw}

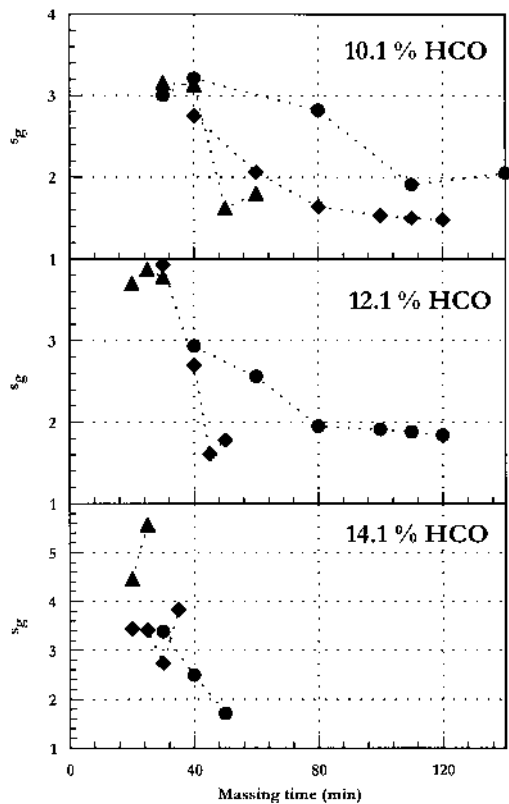Impeller speed: 475 rpm (●), 575 rpm (◆), 675 rpm (▲); jacket temperature: 100 °C.

Fig. 5. Effects of Massing Time and Impeller Speed on Granule Size Distribution s_g

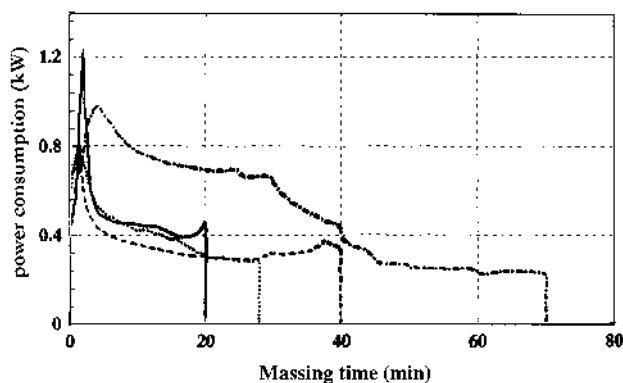Impeller speed: 475 rpm (●), 575 rpm (◆), 675 rpm (▲); jacket temperature: 100 °C.

Fig. 6. Effect of Type of Binder on the Power Consumption during Massing

Binder: 6.1% GMS (----), 10.1% GMS (——), 10.1% PEG (····), 10.1% HCO (–·–·–). Impeller speed: 675 rpm.

It was remarkable that in three cases (Table 1, No. 1, 2 and 4) the mean pellet size was constant for at least 30 min at the end of the process. As the pellet size distribution did not change during this time, the product seems to be unaffected by the rotating impeller. No destruction phase was observed. Thus, the destruction may only dominate, if the pellets exceed a certain critical size,[15] which was not the case in these runs. All other runs resulted in a destruction of the product next to the formation of lumps at prolonged massing. The mean sizes of the broken pellets after destruction had started are not shown, because the values were biased.

Type of Binder In all melt granulation experiments with the three binders the adhesion to the mixer wall was below 5% due to a Fluor ethylene propylene (FEP)-liner on the surface of the mixer bowl and the impeller blades.[16] This is a prerequisite when the binders are to be compared, as adhesion was found to render the process irreproducible in previous experiments. In these experiments, the formation of lumps and the resulting mean granule size depended on the amount of mass sticking to the wall in the early phase of the process.

The granule growth observed in the three 2^2 factorial experiments with PEG, GMS and HCO is presented in Fig. 7. The evolution of the pellet size distribution is shown in Fig. 8. Distinct differences in the growth rate between the three binders were observed.

The experiment with GMS as binder liquid displayed the fastest granule growth. Massing times longer than shown in Fig. 7 led to destruction of the pellets in all runs.[16] When both variables were on the high level (Table 1, No. 9), uncontrollable growth was observed. Thus, pellets could not be produced opposed to the same run with HCO acting as binder. In contrast to HCO, however, it was possible to prepare pellets with a mean size of about 1000 μm within 25 min in all other cases. GMS as binder was more sensitive to the changes of impeller speed and binder concentration compared to HCO.

All five experiments carried out with PEG as binder liquid resulted in pellets. Granule growth was homogenous, and the required time to prepare pellets of a certain size was between the necessary time for GMS and HCO experiments. At prolonged massing time the process entered the destruction phase with formation of lumps and fines, except for one ex-
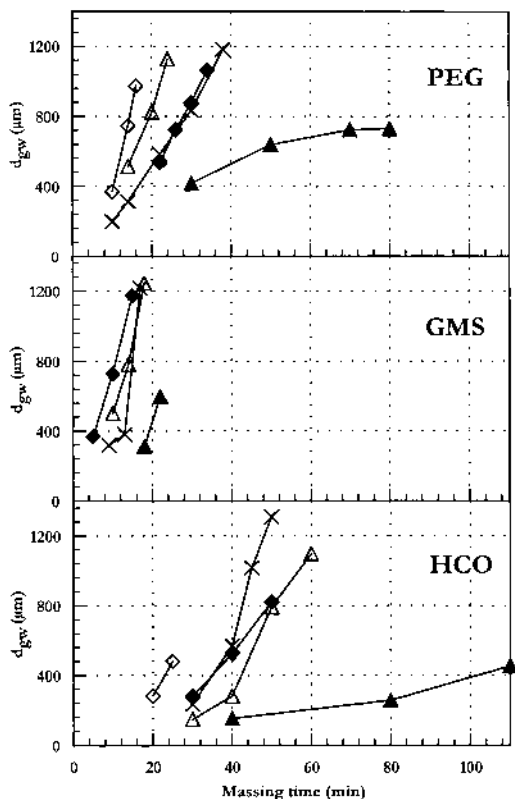
Fig. 7. Effects of Binder Concentration and Impeller Speed on the Mean Granule Size d_{gw} in Experiments with PEG, GMS and HCO as Binder Liquid

Binder concentration: 10.1% (▲, △), 12.1% (×), 14.1% (◆, ◇); impeller speed: 475 rpm (▲, ◆), 575 rpm (×), 675 rpm (△, ◇).
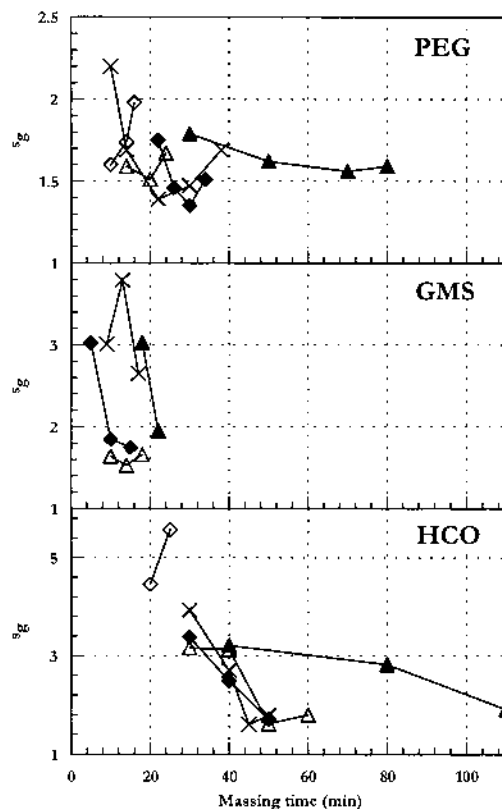

Fig. 8. Effects of Binder Concentration and Impeller Speed on the Granule Size Distribution s_g in Experiments with PEG, GMS and HCO as Binder Liquid

Binder concentration: 10.1% (▲, △), 12.1% (×), 14.1% (◆, ◇); impeller speed: 475 rpm (▲, ◆), 575 rpm (×), 675 rpm (△, ◇).

periment, where both variables were on the low level; there, granule growth was extremely delayed at the end of the process and the final mean size remained small ($<800\,\mu$m).

Granule Growth and Binder Properties The differences in granule growth observed with the three different binders might be related to differences in the viscosity as explained above. The viscosities of the binders are given in Table 3. PEG displayed the highest viscosity among the pure binders tested. According to the results above, this should have led to the slowest granule growth. However, HCO exhibited even slower granule growth. HCO and GMS had nearly the same viscosity, but differed strongly in granule growth rate. Therefore, these distinctly different granulation properties could not be attributed to viscosity alone.

A higher amount of the binder was shown to increase granule growth. The binder concentration was calculated based on the mass. Due to different densities of the molten binders (Table 3), different binder volumes were used. This has to be taken into account when different binders are compared, because the binder volume influences the liquid saturation during granulation. Consequently, the volume of the molten binder is assumed to be more important than its mass. The product temperature during massing was only slightly higher than the jacket temperature in case of GMS and PEG; in the experiments with HCO it exceeded the jacket temperature by 10 to 13 °C. The true values for density and viscosity during pelletization were assumed to be lower during these processes. The granule growth in similar process conditions (with the exception of the jacket temperature) with the differ-
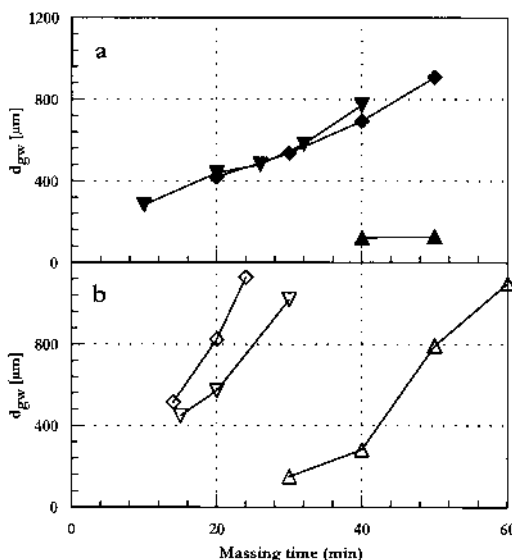
Fig. 9. Effects of Type of Binder and Binder Concentration on the Mean Pellet Size d_{gw}

Binder: GMS (▼, ▽), HCO (▲, △), PEG (◆, ◇); binder concentration: 6.1% (▲, ◆), 6.5% (▼), 10.1% (△, ◇), 9.8% (▽); impeller speed: 675 rpm.

ent binders was compared. HCO was found to cause the slowest growth rate, although the binder volume was the highest due to the lowest density (Table 3). Hence, the volume of the pure binder did not primarily control the growth rate, and other factors, which control growth kinetics, should

Table 3. Properties of Binders at Given Temperatures

Binder	Viscosity (mPa)	Density (g/ml) at 100 °C	Surface tension (mN/m)	Contact angle against SV (°)	Adhesion tension (mN/m)	Solubility of SV (%)
HCO	24 (100 °C)	0.8894	27.8 (100 °C)	52.7 (100 °C)	16.8	0
PEG	43 (80 °C)	1.062	36.1[a] (80 °C)	55.7[a] (80 °C)	20.3	<2
GMS	22 (87 °C)	0.9005	—[b]	—[b]	—[b]	55
GMS solution[c]	143 (87 °C)	0.9345	25.2 (90 °C)	37.2 (90 °C)	20.0	

a) PEG was saturated with SV.   *b*) Not determined.   *c*) GMS saturated with SV.

be considered.

A third difference was the solubility of the drug in each of the three molten binders (Table 3). Danjo *et al.*[17] found the solubility to be a dominant factor in wet granulation experiments, especially concerning the mean granule size. They assumed the dissolved substances to act as a second binder, building up solid bridges after drying. Hence, it may be more appropriate to consider the GMS saturated with SV, called GMS-solution, as binder liquid, because of the enormous solubility of SV in molten GMS. In case of PEG, the small amount of dissolved SV was neglected. The properties of the GMS-solution are given in Table 3. The viscosity of the solution was much higher than that of pure GMS. Consequently, when the three binders are compared on the basis of the viscosity, the granule growth became slower with decreasing binder viscosity. This is in contradiction of the experiments mentioned above and could not be confirmed by findings in literature. It should be mentioned that the critical limit for viscosity, above which a further increase leads to an increased potential for granule growth,[10] was not reached. The experiments described above with a variation in jacket temperature showed a deceleration of granule growth with a further increase in viscosity. For this reason, other factors must be responsible for the observed differences in granule growth.

The volume of the GMS-solution is higher than the volume of the molten GMS alone. Therefore, the total amount of binder in the GMS-experiments was recalculated. The mass of dissolved SV was added to the total mass of binder and subtracted from the mass of solid drug. Because only slight differences were obtained in the case of PEG, no correction was carried out.

The effect of the type of binder on granule growth is shown in Fig. 9. The total binder concentration was about 6% in Fig. 9a and about 10% in Fig 9b. In both cases, a higher binder concentration led to an accelerated granule growth. Only slight differences in growth kinetic were noticed between the experiments with 6.1% PEG and 4.1% GMS (=6.5% GMS-solution), and with 10.1% PEG and 6.1% GMS (=9.8% GMS-solution), whereas the experiments with HCO as binder showed a markedly slower granule growth with corresponding binder concentrations.

Several authors investigated the effects of binder characteristics in relation to different substrates (wetting properties) on the strength of agglomerates during granulation using glass beads[5] or excipients such as lactose and sucrose.[17] They found the work of immersion or adhesion tension, both defined as the product of the surface tension of the binder and the cosinus of the contact angle between binder and powder, to determine the agglomerate strength. The authors concluded that a high adhesion tension is favourable in granula-

tion because of the higher agglomerate strength it provoked. The calculated adhesion tension for the melt granulation experiments is given in Table 3. The values differed only slightly between PEG and GMS, but they were lower in case of HCO. This may help to explain the deviant granule growth kinetics of HCO shown in Fig. 9. The low adhesion tension of HCO may hinder the fast distribution of the molten binder in the powder during granulation. This prolongs the lag time until granule growth occurs (Fig. 7). Later, a lower granule strength due to the lower adhesion tension results in less resistance to the movement in the mixer (Fig. 6), resulting finally in a smaller granule size.

Conclusion

Binder viscosity was found to be a crucial factor influencing the granule growth kinetics in a melt pelletization process of sodium valproate. This was proven in experiments using GMS or HCO, respectively, as binder liquid. The same was assumed for PEG, which has been investigated extensively in other melt pelletization experiments.[10,18] However, viscosity cannot be used to explain the differences in the granule growth between the various types of binders tested. Binder volume as a single factor could not explain the differences either. The factors which were found to have the strongest influence on granule growth were the solubility of SV in the binder liquid and the wetting properties of binder. It was found to be important to take the amount of dissolved drug into consideration and to calculate the total binder concentration in order to compare granulation properties of different binder liquids.

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