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# Studies on upscaling parameters of the Gral high shear granulation process

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## Summary

Granulation of lactose in three high shear mixers of the type Gral (Gral 10, 75 and 300) is compared. An attempt is made to identify scale-up parameters. It is concluded that an equal Froude-number results in a comparable process concerning temperature and particle size distribution. A constant relative swept volume and a constant impellor tip speed appeared not to result in a comparable process. Monitoring the temperature rise during the process might be an interesting process control.

## Introduction

In the pharmaceutical industry high shear mixers are widely used for wet granulation. High speed mixers are available in different types and sizes thus being applicable in laboratory, pilot plant as well as production plant.

During the development phase, manufacturing is, by necessity, carried out using laboratory or pilot plant equipment. The process subsequently has to be transferred to large production scale for full scale manufacture. In practice this occurs often by 'trial and error'. Obviously, there is a need to approach scaling up more theoretically.

Most of the work published on granulation in high speed mixers deals with results obtained in small scale equipment (Holm et al., 1983, 1984, 1985; Jaegerskou et al., 1984; Kristensen et al., 1984; Lindberg and Johnsson, 1985; Holm, 1987; Yliruusi and Tihtonen, 1989; Schaefer et al., 1990). Much less has been published about upscaling of this wet granulation process.

As a parameter for up-scaling the relative swept volume has been applied (Schaefer et al., 1986, 1987), being the volume swept out per second by impellor and chopper divided by the volume of the mixer. The relative swept volume has been considered to relate to the work input on the material which is assumed to provide densification of the wet mass.

The use of a power curve, a technique used in the scale-up of fluid mixing impellor systems, has been applied for wet granulation (Cliff and Parker, 1990). Here, a power curve describes the relationship between the rheological properties of the wet mass and the machine parameters of the granulation equipment. By using a power curve a link was made between the consistency of

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the damp mass and the load on the main impellor.

For fluid mixing, impellor tip speed has been described as an up-scale parameter (Oldshue, 1985). An equal tip speed corresponds to the same maximum shear rate. An alternative might be a constant specific power consumption, which has been related to the relative swept volume described for wet granulation.

For the blending of powders the Froude-number has been described (Lloyd et al., 1970); $Fr = N^2D/g$, where $N$ represents the revolutions per min, $D$ the diameter of the impellor and $g$ the gravitation constant. This dimensionless number, being the ratio of the centrifugal force to the gravitational force, can be a criterion for dynamic similarity of the mixer.

The aim of this study was to determine which parameters can be used to estimate the scale-up effects of the wet granulation process.

## Experimental

### *Materials*

Lactose 200 M (DMV, Veghel, The Netherlands) was used as starting material. The geometric-weight mean diameter, $d_{gw}$, is 45 $\mu$m. A 30% w/w solution of polyvinylpyrollidone (BASF, Leverkusen, Germany) in water was used as binder solution.

### *Equipment*

Three commercially available Gral high speed mixers, Gral 10, 75 and 300 (machines Collette, Wommelgem, Belgium) were examined. The geometry of each Gral is shown in Table 1.

In the Gral 75 the rotation speed of the impellor is continuously adjustable. In the Gral 10 and 300, impellor speed can only be varied at two levels. Chopper speed in each Gral can be varied at two levels.

The levels of impellor rotation speed, and the corresponding peripheral speeds, Froude-numbers and relative swept volumes used in the present experiments are shown in Table 2. Chopper speed was chosen to be 3000 rpm in all experiments.

TABLE 1

*Geometry of the Gral 10, 75 and 300*

| Gral | 10 | 75 | 300 |
|---|---|---|---|
| Volume ($\times 10^{-3}$) (m$^3$) | 8 | 75 | 300 |
| Impellor blade angle (°) | 50 | 49 | 57 |
| Number of chopper blades | 2×2 | 2×2 | 3×2 |
| RP1 [a] | 0.40 | 0.29 | 0.30 |
| RP 2 [a] | 0.69 | 0.64 | 0.48 |
| RP 3 [a] | – | – | 0.67 |
| $D_t{}^b/D_h{}^c$ | 1.36 | 1.35 | 1.40 |
| $I_d{}^d/D_t$ ($\times 10^{-2}$) | 46.9 | 46.3 | 49.0 |
| $I_b{}^e/D_t$ ($\times 10^{-2}$) | 9.4 | 9.6 | 7.1 |

[a] RP a: relative position of chopper blade a towards cover. [b] $D_t$: diameter of bowl. [c] $D_h$: height of bowl. [d] $I_d$: diameter of impellor. [e] $I_b$: width of impellor.

All mixers were equipped with a power consumption meter, measuring the power consumption of the impellor motor.

### *Method*

The aim of the experiments was not to create an optimal process, but to study differences in mixing performance. Before addition of the binder solution, the lactose was mixed during 2 min in order to stabilize the power consumption of the impellor motor. The binder solution was added at once, during which the process was stopped. The reason of this procedure is the ease and reproducability. In experiments described in literature the binder solution is almost always added slowly (Holm et al., 1983, 1984, 1985;

TABLE 2

*Impellor speeds, peripheral speed, Froude-number and relative swept volumes*

| Gral | Rotation-speed (rpm) | Tipspeed (m s$^{-1}$) | Froude-number | Rel. swept vol. (s$^{-1}$) |
|---|---|---|---|---|
| 10 | 430 | 5.2 | 1.18 | 1.86 |
| 10 | 650 | 7.8 | 2.70 | 2.79 |
| 75 | 178 | 4.5 | 0.42 | 0.78 |
| 75 | 258 | 6.5 | 0.89 | 1.14 |
| 75 | 300 | 7.5 | 1.20 | 1.32 |
| 300 | 120 | 5.2 | 0.33 | 0.48 |
| 300 | 185 | 8.0 | 0.79 | 0.75 |

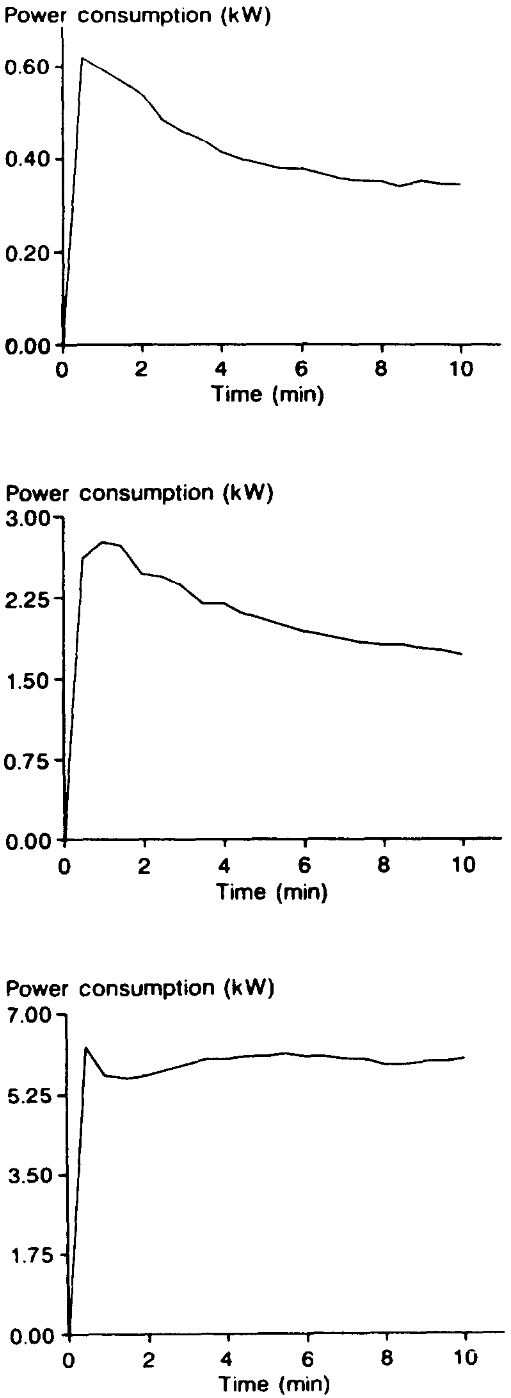

Fig. 1. Examples of power profiles during the granulation process from the Gral 10, 650 rpm (upper); Gral 75, 300 rpm (middle) and Gral 300, 185 rpm (lower).

Jaegerskou et al., 1984; Kristensen et al., 1984; Lindberg and Johnsson, 1985; Schaefer et al., 1986, 1987; Holm, 1987; Yliruusi and Tihtonen, 1989; Cliff and Parker, 1990; Schaefer and Holm, 1990). Although this may result in an optimal process there are a few reasons for the alternative chosen.

(1) For an identical procedure of adding the binder solution at a slow rate the nozzle has also to be scaled-up.

(2) Slowly adding the binder solution prolongs the process time. Because the mixing bowl could not be cooled during the process, this results in a strong temperature rise. Through this temperature rise the evaporation of water would increase considerably.

(3) During the liquid addition phase a densification of the wet mass might already occur (Jaegerskou et al., 1984; Schaefer and Holm, 1990). This densification might in a certain mixer depend on the impellor rotation speed, but might also depend on the size of the mixer. A subsequent kneading phase might thus not be comparable because of a difference in consistency of the wet mass after the liquid addition phase (i.e., different starting points).

In each experiment the rotation speed during dry mixing was at the same level as during the kneading phase. The degree of filling of the mixing bowl was kept constant at the same relative level. The load expressed as kg lactose per l of bowl volume was 0.333 kg/l.

The relative amount of binder solution was kept constant at a level corresponding to a theoretical water content of 10.0% of dry material and a content of binder in the granules of 3.0%.

Each experiment was repeated three times. During each experiment three samples of 100 g were withdrawn from the Gral 10 and 75, and six samples of 100 g from the Gral 300. Samples were taken at different massing times. The process was stopped during sampling.

The samples were tray dried for 24 h at 60°C, and subsequently pressed through a 1 mm sieve by using Frewitt equipment (Frewitt MG1–314, Fribourg, Schwitzerland). Granule-size distribution was determined twice with a Malvern 2600 particle sizer (Malvern Instruments, Worchester, U.K.) using an 18 mm beam expander, a 1000 mm range lens and a dry powder feeder.

The temperature of the mass was measured at the start of the process and during sampling using a contact thermometer. The temperature rise is expressed as $\Delta T$, describing the difference between the temperature of the wetted mass and the starting temperature.

## Results and Discussion

*Power consumption*

During each experiment the power consumption of the impellor motor was recorded. Power consumption during dry mixing was considered as baseline. The influence of sampling on the obtained record could be minimized by averaging the different curves from the same experiments.

Directly after liquid addition the slope of the power consumption curve increased strongly in each Gral (Fig. 1), due to the directly formed binder bridges between the lactose particles.

After the initial strong increase in power consumption, the curves differed in each Gral during the further process. In the Gral 10 and 75 power consumption decreased while in the Gral 300 it also decreased slightly but increased again upon further mixing. A clear explanation for the observed differences could not be given.

By integrating the power consumption curve and dividing it by the load in the mixing bowl the specific energy consumption could be calculated. It seemed that at each point of time a relation, such as suggested earlier (Schaefer et al., 1986, 1987; Lindberg and Johnsson, 1985; Holm, 1987) could be found between the relative swept volume and specific energy consumption (Fig. 2).

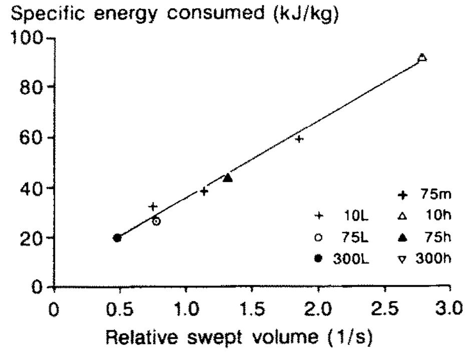


Fig. 2. Correlation between specific energy consumed after 10 min mixing time and the relative swept volume for the Gral 10, 75 and 300. L, m and h refer to the low, medium and high speed, respectively.

*Temperature*

Fig. 3 shows the temperature profiles during mixing, while Fig. 4 depicts the recorded temperatures as a function of tip speed, Froude-number and relative swept volume, respectively. The relations are shown for the situation after 10 min of mixing, but similar plots exist at other mixing times. As can be seen, an equal Froude-number results in an comparable temperature rise during the process. This applies to a smaller extent for the data of relative swept volume, while tip speed does not seem to be related to temperature effect.

The $\Delta T$ values obtained might be somewhat lower than the temperature rise seen in practice, since the wetted mass is cooled due to opening of the bowl during sampling. Cooling will depend on size and construction of the mixer. Therefore, comparison of $\Delta T$ values is subject to some uncertainty.

*Particle size distribution*

Particle size distributions were followed during the process. A fixed pattern of granule growth appeared to exist which seems to be independent

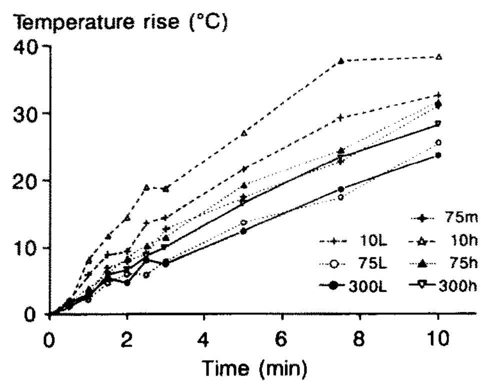


Fig. 3. Effect of massing time on temperature rise of the moist mass during mixing in the Gral 10, 75 and 300. Symbols as in Fig 2.

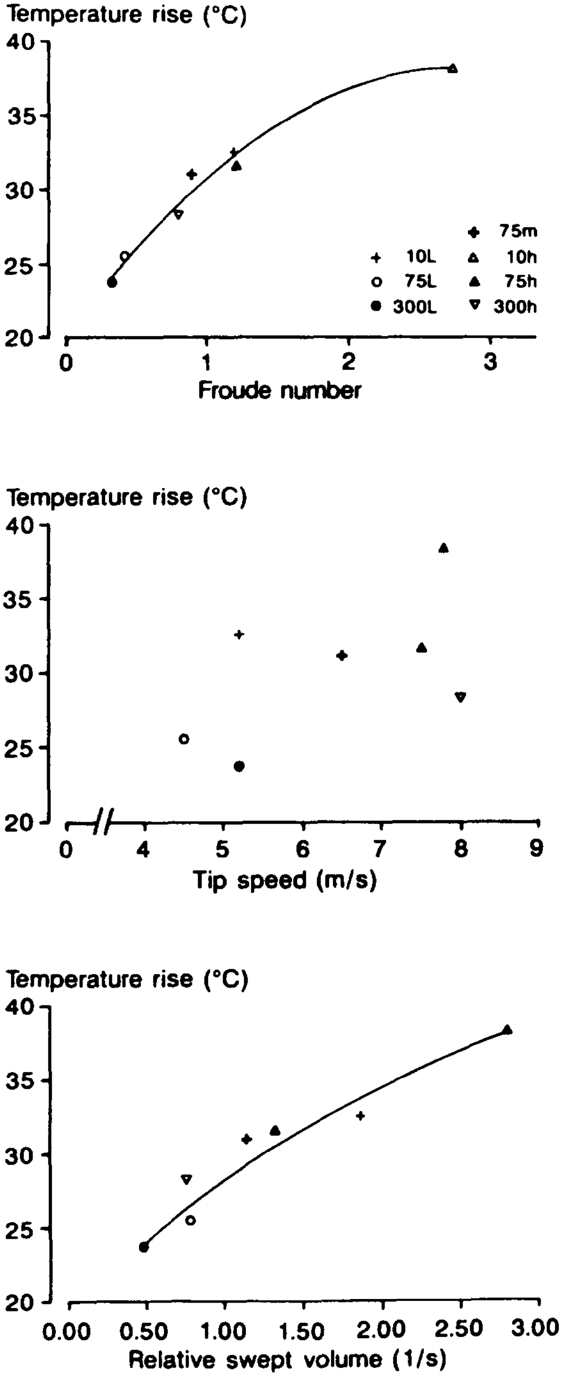


Fig. 4. The temperature after 10 min mixing as a function of the Froude-number (upper), impellor tip speed (middle) and the relative swept volume (lower). Symbols as in Fig. 2.

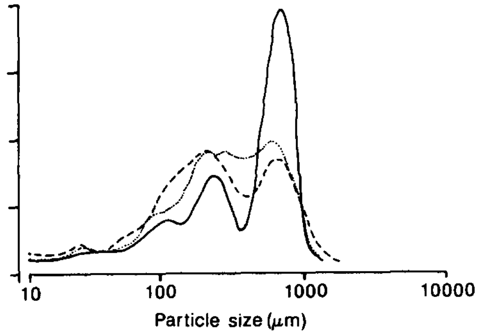


Fig. 5. An example of the particle size distributions appearing after 0.5 min (dotted line), 1.5 min (dashed line) and 5 min, respectively (Gral 75, 258 rpm).

of the type of mixer. This pattern involved three distinct distributions, i.e., three peaks could be distinguished. An example of these phenomena is shown in Fig. 5. After the appearance of the last distribution, no further changes occurred during further kneading. The rate at which this pattern was followed depended on the impellor rotation speed and type of Gral.

The cause of these distributions can be considered as an agglomeration of particles during the process. The first peak might represent the fines while the second and third peak represent the built up of the granulate. The cause of these particle size distributions may, however, also be influenced by the sieving process.

The alterations in particle size distributions during the process can be depicted very well by plotting three sieve fractions, namely, $< 113$ $\mu$m,

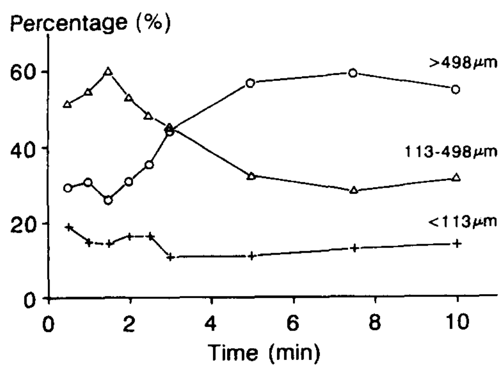


Fig. 6. An example of the three sieve fractions as a function of the process time (Gral 75, 258 rpm).

113–498 μm and > 498 μm against process time. Fig. 6 shows an example.

The time after which no change in particle size distribution occurred (i.e., end point) is plotted in Fig. 7 against tip speed, Froude-number and relative swept volume. It appeared that only a constant Froude-number results in a comparable process time.

Table 3 shows temperature rise until the point of time after which no change in particle size distribution occurred (i.e., end point) for each experiment. It appeared that the temperature rise after which the end point was obtained was practically the same in each experiment.

It has been shown in an earlier publication (Holm et al., 1985) that the consumed energy is converted completely into heat of the moist mass. Regarding Table 3, the end point might be reached on the input of a certain amount of energy. In Table 3 the specific energy consumption of the impellor motor until the end point is shown. It appeared that this specific energy consumption in the same Gral was independent on impellor rotation speed. In a larger Gral the specific energy consumption was lower, however. An explanation for these differences might be:

(1) Temperature rise is caused by total energy input of both impellor and chopper. The energy consumption of the chopper motor could not be calculated, because of the slight variations with regard to the energy consumption during dry mixing. Therefore, Table 3 only shows the specific energy consumption of the impellor motor. In literature an effect of the chopper on temperature is shown (Lindberg and Johnsson, 1985; Schaefer et al., 1986; Yliruusi and Tihtonen, 1989). The relative chopper size in the used mixers increases from Gral 10 to Gral 300. This might result in a relatively increased contribution to energy input of the chopper in a larger Gral, through which the energy input of the impellor might be lower. However, it was found in further experiments that the chopper had no significant influence on temperature.

(2) Energy consumption is calculated from the power consumption of the motor. A certain amount of this energy is lost to the motor itself. Since a larger Gral has a larger motor, energy

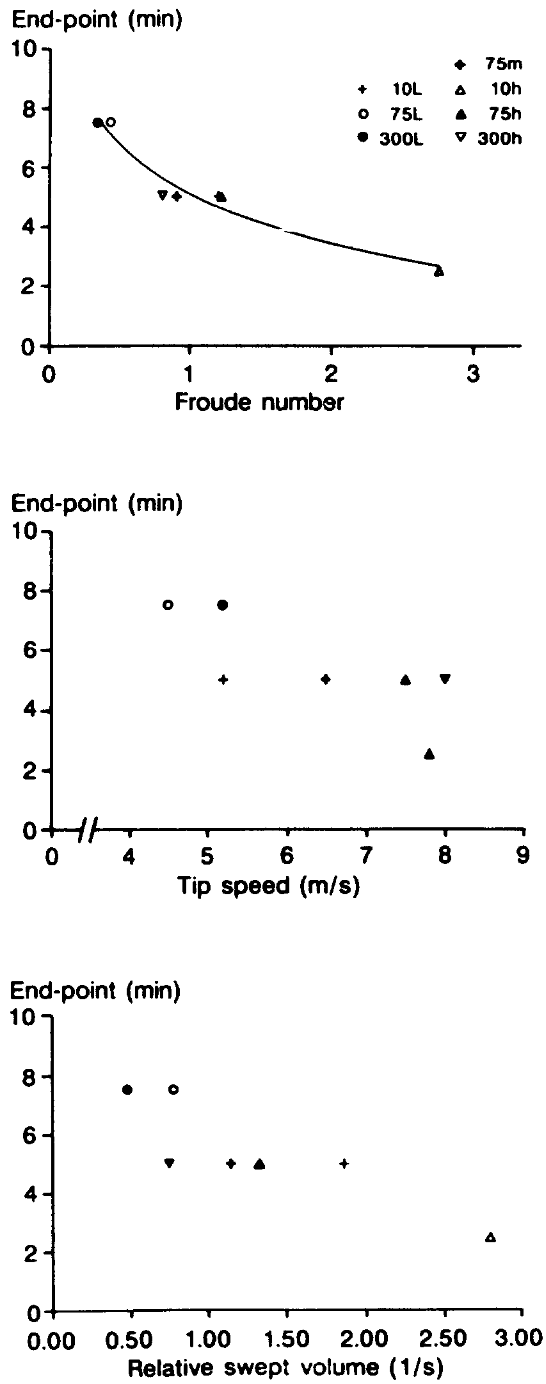


Fig. 7. End point as a function of the Froude-number (upper), impellor tip speed (middle) and relative swept volume (lower). Symbols as in Fig. 2.

TABLE 3

*End point, temperature rise and specific energy consumed at end point*

| Gral | 10 | 10 | 75 | 75 | 75 | 300 | 300 |
|---|---|---|---|---|---|---|---|
| Impellor rotation speed (rpm) | 430 | 650 | 178 | 258 | 300 | 120 | 185 |
| Mixing time (min) | 2.5 | 5.0 | 7.5 | 5.0 | 5.0 | 7.5 | 5.0 |
| Temperature increment (°C) | 21.5 | 18.9 | 17.4 | 17.4 | 19.2 | 18.6 | 16.4 |
| Specific energy consumed (kJ/kg) | 34.5 | 28.3 | 20.2 | 20.0 | 24.4 | 14.6 | 15.7 |

losses due to the motor will be less. The differences between the mixers concerning real energy input into the moist mass might thus be less than shown in Table 3. Regarding the results shown in Fig. 2, the energy appears to be directly related to relative swept volume, indicating that differences in engine efficiency are negligible.

(3) Energy conversion into heat and spreading of the binder solution and densification of the moist mass might be done more effectively in a larger Gral due to heavier mass.

The peripheral tip speed and relative swept volume, which is related to the specific energy consumption (Fig. 2), are thus not usable as upscale parameters. In contrast, the Froude-number seems to be a parameter usable for scaling up of the granulation process. An explanation for this must be found in the underlying mechanism. The Froude-number is related to the centrifugal force. This force pushes the particles against the wall of the bowl. The centripetal force (force of equal strength but opposite direction of the centrifugal force) is the wall pushing back to prevent particles from going through the wall. Both forces create a zone of compaction along the wall of the bowl responsible for producing dense granules. As a consequence of the acceleration force and resistance of the bowl (constituting a couple) the densified mass starts to spin around its axis, producing spherical granules.

## Conclusion

It is shown that the three Grals are not geometrically similar and that the power consumption curves differ in each Gral. From the experiments it appeared that the granulation process can be scaled-up by keeping the Froude-number constant. A constant relative swept volume and a constant tip speed did not result in a comparable process. Since granule growth is related with temperature, it makes sense to monitor the temperature during the process.

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