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A Review: On Scale-Up Factor Determination of Rapid Mixer Granulator

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ABSTRACT

Today the production of Pharmaceutical granules is still based on the batch concept. In the early stage of the development of a solid dosage form the batch size is small. In later stage the size of the batch produced in the pharmaceutical production may be up to 100 times larger. Thus scale-up process is an extremely important one. Unfortunately in many cases the variety of the equipment involved does not facilitate the task of scale-up. During the scale-up process the quantity of the granules may change. A change in granule size distribution, final moisture content, friability, compressibility and compactibility of the granules may strongly influence the properties of the final tablet, such as tablet hardness, tablet friability, disintegration time, dissolution rate of the active substance, and aging of the tablet. In the following sections, the scale up process is analyzed taking into mathematical considerations of scale up theory, the search for scale up invariants, the establishment of in-process control methods. This paper describes an overview of granulation, rapid mixer granulator, Scale up in the field of granulation, various approaches used for scale up determination of Rapid Mixer Granulator, process variables, methods for end point determination & analysis of granulation process.

Key words: Scale-up, rapid mixer granulator , variables, end point determination

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INTRODUCTION

Agglomeration can be defined as the size enlargement process, in which the starting material is fine particles and the final product is an aggregate in which primary particles can still be identified. The granules are held together with bonds formed by the binder used to agglomerate.
Granulation is a process of size enlargement whereby small particles are gathered into larger, permanent aggregates in which the original particles can still be identified

I. **Diagrammatic representation of mechanism of granule formation [1]**

II.

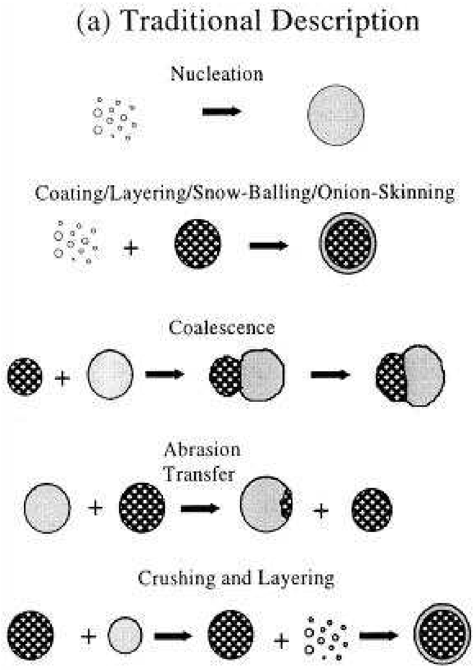

Fig. A1

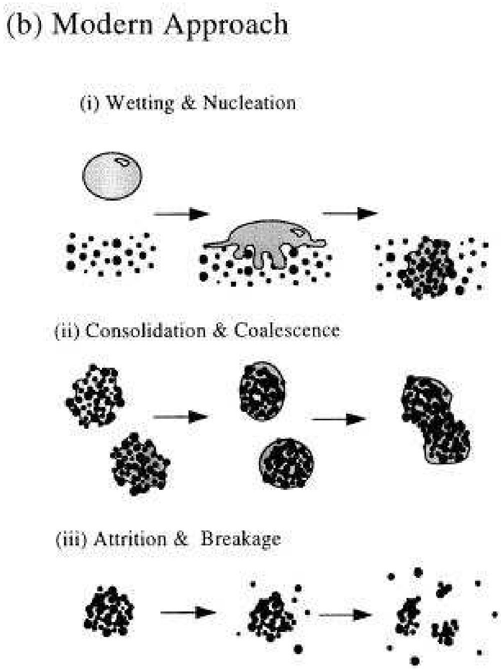

Fig.A2

The **type of bonds** formed through four transition states

- Newitt and Conway-Jones(1958) [2] introduced pendular, funicular and capillary state,
- Barlow(1968) introduced droplet state
- York and Rowe (1994) introduced "pseudo droplet state"
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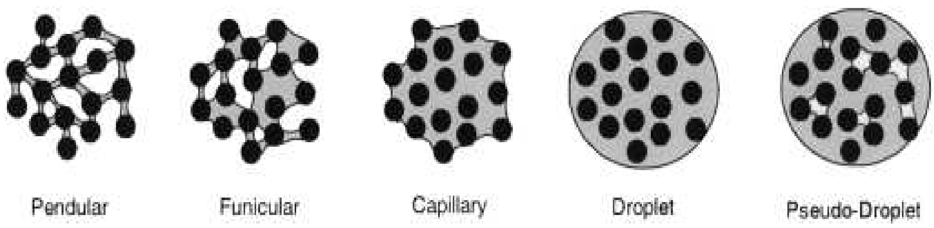

Fig.B

- ➢ Pendular state = particles are held together by surface tension at the solid-liquid-air interface and the hydrostatic suction pressure of the liquid bridge.
- ➢ Funicular state = continuous network of liquid interspersed with air
- ➢ Capillary state = the pore spaces in the granule are completely filled
- ➢ Droplet state = liquid completely surrounds the granule

High shear granulation (HSG)

- Extremely high shear forces compared with other granulators
- HSG is fast, efficient, reproducible method, and have modern process control capabilities
- Easy to process cohesive materials that are impossible to process in low shear mixers/fluid bed granulators

- Wet granulation (the most common) or dry granulation (modified release tablets; excipients used are: wax, low melting point materials)

Rapid Mixer Granulator [3]

Rapid Mixer Granulator is designed to achieve excellent mixing and consistent granules at lower operating cost along with higher productivity. Better mixing and closed control of granule size leads to faster tableting speeds with improved quality and least rejections.

Fig.C: Rapid mixer granulator

Technical specifications:

Models	RMG 10	RMG 25	RMG 50	RMG 100	RMG 150	RMG 250	RMG 400	RMG 600	RMG 800	RMG 1000	RMG 1200
GROSS CAPACITY Ltr	10	25	50	100	150	250	400	600	800	1000	1200
NET CAPACITY Ltr	08	20	40	80	120	200	320	480	640	800	960
MIXER MOTOR HP	1.5/2	3/5	5/7.5	7.5/10	10/15	22.5/30	35/40	40/50	50/60	60/75	75/100
GRANULATOR MOTOR HP	1/1.5	1.5/2	2/3	3/5	3/5	5/7.5	7.5/10	10/15	10/15	15/22.5	22.5/30
LENGTH mm	1600	1750	2000	2400	2400	2700	2800	2950	3100	3200	3500
WIDTH mm	650	700	1500	2100	2100	2200	2400	2500	2700	2800	3000
HEIGHT(LID CLOSED) mm	1200	1750	1750	2000	2000	2100	2150	2200	2800	3000	3000
WEIGHT (KGS)	305	400	600	1400	1600	1800	2400	3000	3500	4200	4800

Table1: showing various models of rapid mixer granulator & their technical specifications

Working Principle of rapid mixer granulator

Blending and wet massing is accomplished by high mechanical agitation by an impeller and chopper. Mixing, densification, and agglomeration of wetted materials are achieved through shearing and compaction forces exerted by the impeller. The impeller rotates on the vertical shaft at a rotational speed corresponding to a radial blade tip speed of approximately 5-15 m/s. the chopper rotates at a similar tip speed which, because of its small diameter, corresponds to a very high rotation speed in revolutions per minute (rpm)(i.e. 1500-4000 rpm). The primary function of chopper is to cuts lumps into smaller fragments and aids the bowl or sprayed onto the powder to achieve a more homogeneous liquid distribution.

The granulation is conventionally performed in the following process steps:

1. Mixing of dry material at high impeller and chopper speeds for a few minutes (approx. 2-5 min).
2. Addition of liquid binder by pouring it onto the powder, while both the impeller and chopper are running at a low speed (approx.1-2min.)
3. Wet massing with both agitators running at high speed (approx.1-5min.)
4. Wet sieving the granules.
5. Drying the granulate
6. Dry sieving of the granulate

General production design of rapid mixer granulator

The Rapid mixer Granulator is a multi-purpose processor equally suitable for high speed dispersion of dry powders, aqueous or solvent granulations,effervescent products and melt pelletization. There should be both simplicity and flexibility in plant design. User-selected process options, cleaning equipment, control systems and PAT technologies combine in a system to meet process requirements exactly. This approach ensures that qualification and validation procedures are kept to a minimum.

1. Through-the-wall configuration

Through-the-wall offers the best option in terms of cleanliness, maintenance and ATEX. By keeping the motors out of the process room, you are preventing risk of contamination coming from these difficult to clean items. Maintenance is carried out from the technical area, minimizing the need for the maintenance engineer to work in a GMP area. This makes the job easier and again reduces the risk of contamination.

For ATEX, the design allows to classify the technical area as safe. This avoids the need for costly flameproof motors, making the upgrade. The frame mounting provides a standard format for the machine, allowing it to be constructed and installed using the same structure. This structure may be raised using standard modules to achieve the customer’s desired height. For some installations it is also possible to mount control panels on the structure, allowing qualification of the complete system prior to shipping, significantly reducing the installation time on site.

2. Impeller & chopper options

(a) Standard pma impeller*:* Standard impeller designed for use with the conical bowl of the PMA high shear granulator.

(b) U-shaped chopper: Standard chopper for use with the conical bowl of the PMA high shear granulator.

(c) M8 impeller: Innovative swept-back design; for improved mixing characteristics, faster processing and a more clearly defined end-point.

(d) Multi-bladed chopper: Flush mounted, multi-blade design improves binder solution dispersion and product movement at slow speeds.

3. Filtration

(a) Material filter & shroud*:* Production filtration is achieved using an easily removable material filter that can be cleaned and re-used. For vacuum and CIP applications stainless steel may be utilized.

4. Discharging

(a) Through-the-wall mill: Product can be discharged from the high shear granulator directly into a receiving container, or via a sizing mill. This breaks down the granules to produce more even sizing for subsequent processing. Through-the-wall hinge-mounted sizing mill, directly connected to the discharge port, using inflatable seals. For maintenance, cleaning and product changeovers, the seals are deflated and the mill hinged away from the port, allowing full access. The TTW mounting ensures the motor and controls are kept away from the clean process area. Pressure Shock Resistant options are available, matching the containment and safety credentials of the main machine.

(b) Concealed hinge mechanism: The cover is mounted on a concealed hinge mechanism allowing the cover tobe lifted with the minimum effort, but keeping the counterweight in the technical area. This leads to a more GMP design, reducing surfaces, making cleaning easier. On equipment supplied with the Pressure Shock Resistant design option the hinge interlocking system is power assisted to provide safe and comfortable opening to the bowl cover.

5. Loading

(a) Gravity loading: Simple open / close ports may be mounted on the cover and used to dispense product into the mixing bowl. For potent powders, split-valve technology provides full containment during loading. The PMA-Advanced™ can also be delivered with a cone loading port, allowing for the removal of the powder loading ports from the cover, but giving permanent connection to a Gravity Loading Station, but also continuous access to open the cover.

(b) Vacuum loading: Rapid loading can be achieved using vacuum technology. Aeromatic-Fielder's innovative killed-vacuum technique makes for easy operation and maintenance, and only requires a standard-sized filter**.**

6. Binder solution addition

(a) Nozzle: A range of nozzles are available to give the optimum binder liquid droplet size for an even distribution throughout the powder mass**.**

(b) Pump: The binding solution required for granulation may be pumped into the mixing bowl using a mechanical or peristaltic pump to deliver the binder liquid to the spray nozzle. Special pumps are available for the dosing of high viscosity binders.

(c) Pressure pot: Alternatively a pressure pot offers fast, high-pressure delivery of the binder solution, for excellent dispersion of liquid via the binder nozzle spray system. These systems are chosen typically for small scale, R&D-sized granulators.

7. Standard platform designs (optional)

Two standard platforms are available to integrate with the PMA-Advanced™. The "Medium" platform provides room adjacent to the bowl for the operator to carry out all filling and cleaning operations. The “XL” platform additionally provides space for other items / operators on the platform and also provides sufficient space to allow the operator interface to be mounted at the platform level. Due to the clean lines of this design the bowl/ cover area can be easily accessed using mobile steps.

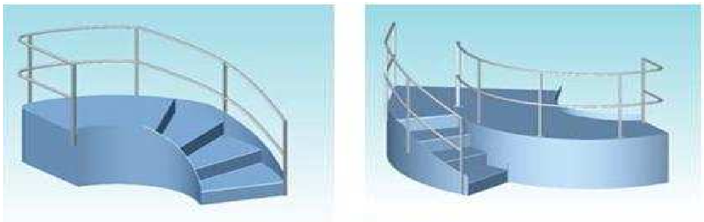

Fig D: Standard platform designs

Design of mixing chamber & impeller

The mixing chamber and the impeller are simultaneously designed to ensure the best movement of the particles inside the bowl. This movement depends on the bowl (Fig E) and impeller (Fig F) geometry. The geometry of the impeller is adapted to the bowl shape in order to improve the volume of powder swept by the mixing tool, and to decrease wall adhesion and dead zone. Moreover, the movement of the powder blend inside the bowl depends on the impeller speed. At low speed, the impeller gives the powder a bumping movement whereas at high speed, the powder is submitted to a rotational movement (Fig F).

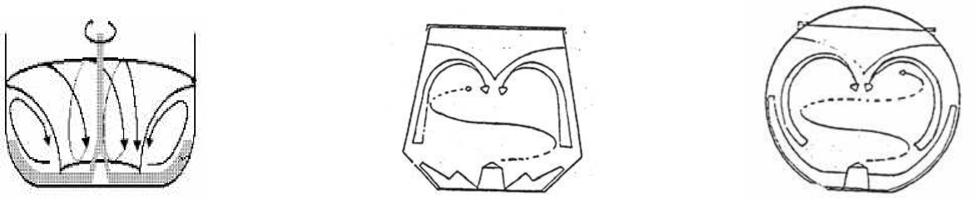

Fig E: High-shear mixer-granulators with different mixing chamber design [4]

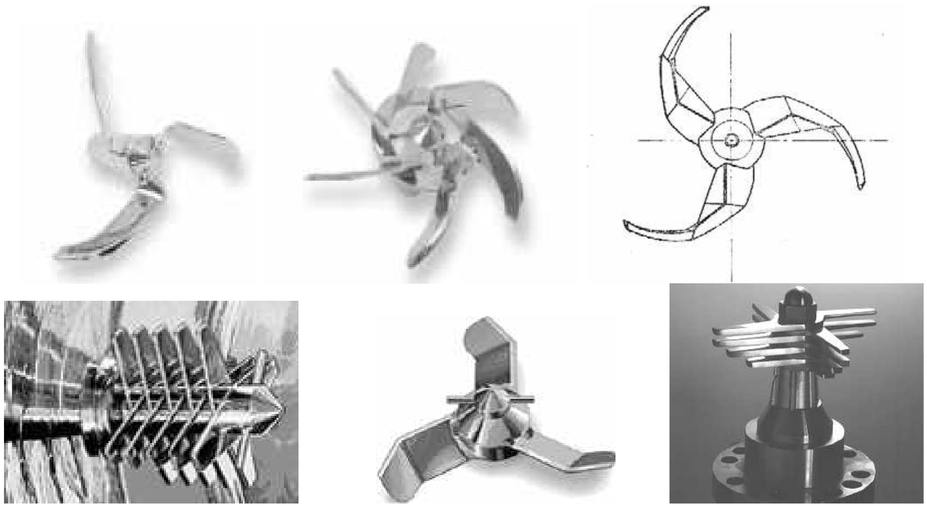

Fig F: Examples of impellers and choppers shapes [5-7]

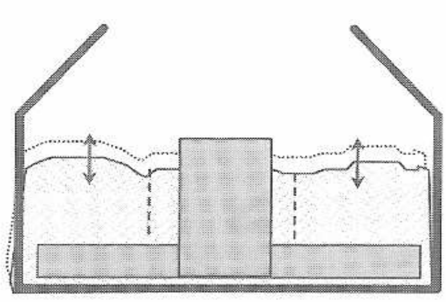

Fig G1

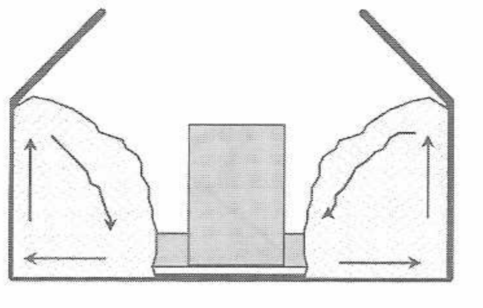

Fig G2

Flow regimes in Fielder™ mixer granulators: bumping at low speed (G1) and ropingat high speed (G2) [6]

The presence of a chopper in the bowl is also required to break coarser agglomerates and control granules distribution. [7-8]. As for the impeller, the geometry and rate of the chopper differ from one apparatus to another (Fig F). Therefore, the chopper is likely to disturb the flow pattern of the mass depending on its design and running speed. The rotation speed, the size and the shape of the mixing tools are likely to have an influence on the powder bed temperature. Holm (1987) [9], Kristensen *et al.* (1987) [10] and Schaefer *et al.* (1986, 1987) [11-12] showed that the energy consumed in a high shear mixer was converted into heat in the moist mass. This phenomenon has to be taken into account as it may induce problems when working on thermosensitive products. [7-8].The shaft in the bowl can be either vertical (FigH1) or horizontal (FigH2). When the shaft is vertical, the influence of gravity forces on the powder bed is higher.

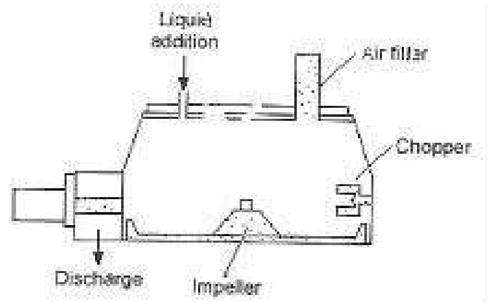

Fig H1 Vertical shaft

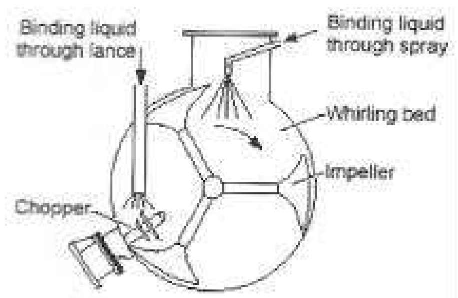

Fig H2 horizontal shaft [6]

Different granulation processes

1. Single-pot process
2. Multiphase process

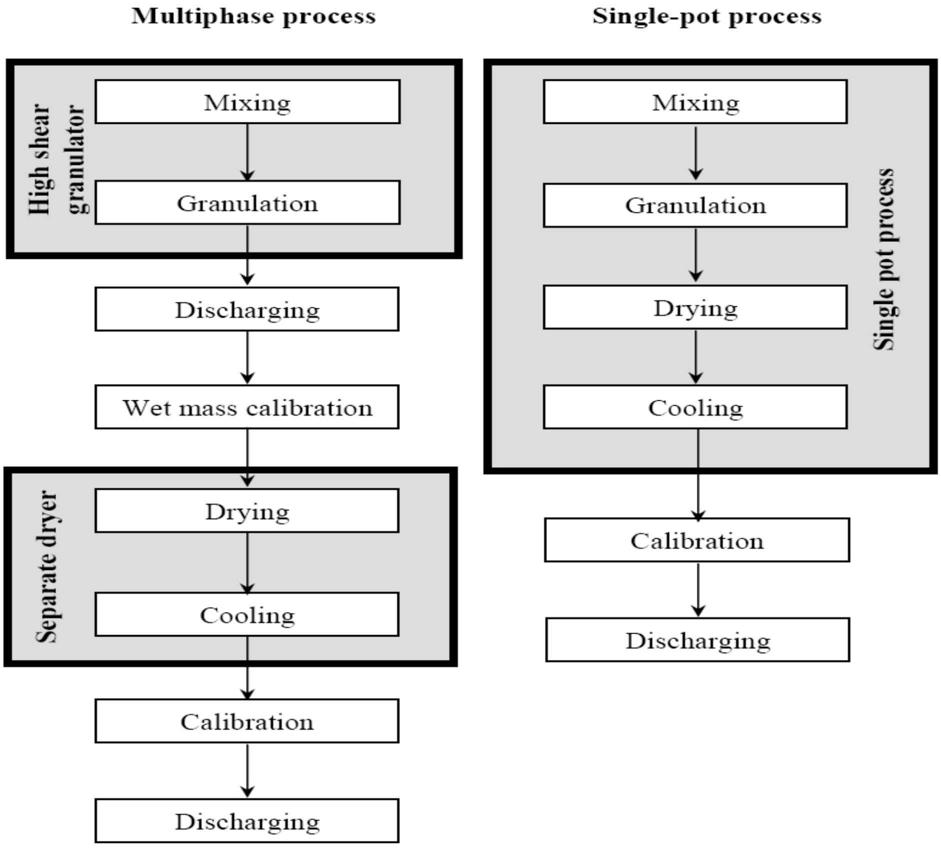

Fig I:Granulating process: multiphase process vs single pot process

Scale up in the field of granulation

According to the modeling theory, two processes may be considered similar if there is a geometrical, kinematic and dynamic similarity [13] (principle of similitude) [14-19]

- Two systems are called geometrically similar if they have the same ratio of characteristic linear dimensions. For example, two cylindrical mixing vessels are geometrically similar if they have the same ratio of height to diameter.
- Two geometrically similar systems are called kinematically similar if they have the same ratio of velocities between corresponding system points.
- Two kinematically similar systems are dynamically similar when they have the same ratio of forces between corresponding points. Dynamic similitude for wet granulation would imply that the wet mass flow patterns in the bowl are similar.

Scale-up and monitoring of the wet granulation process

Dimensionless Groups

Because the behavior of the wet granulation process cannot yet be described adequately by mathematical equations, the dimensionless groups have to be determined by a dimensional analysis. For this reason the following idealized behavior of the granulation process in the high-speed mixer is assumed:

- The particles are fluidized.
- The interacting particles have similar physical properties.

- There is only a short-range particle–particle interaction.
- There is no system property equivalent to viscosity, i.e., (1) there are no long-range particle–particle interactions and (2) the viscosity of the dispersion medium air is negligible.

According to Buckingham's theorem, the following dimensionless groups can be identified:

$\pi_1 = \frac{P}{r^5\omega^3\rho}$	Power number
$\pi_2 = \frac{qt}{V\rho}$	Specific amount of granulation liquid
$\pi_3 = \frac{V}{V^*}$	Fraction of volume loaded with particles
$\pi_4 = \frac{r\omega^2}{g}$	Froude number (centrifugal/gravitational energy)
$\pi_5 = \frac{r}{d}$	Geometric number (ratio of characteristic lengths)

Where,
P = Power consumption, r = Radius of the rotating blade (first characteristic length of the mixer) ω = Angular velocity, ρ = Specific density of the particles, q = Mass (kg) of granulating liquid added per unit time, t = Process time, V =Volume loaded with particles, V* =Total volume of the vessel (mixer unit), g = Gravitational acceleration, d = Diameter of the vessel (second characteristic length of the mixer)

In principle the following scale-up equation can be established:

$$\pi_1 = a(\pi_2)^b \cdot (\pi_3)^c \cdot (\pi_4)^d \cdot (\pi_5)^e \quad \text{.......................} \ (4)$$

It may not be the primary goal to know exactly the empirical parameters *a, b, c, d, e* of the process. The ultimate goal would be to identify scale-up invariant

Scale up invariables

- The granulation process can be easily monitored by determination of the power consumption. [19-22]
- Usable granulates can be produced only within the plateau region $S_3 – S_4$.
- The power consumption profile as defined by the parameters S_3, S_4, S_5 is independent of the batch size.
- The amount of granulating liquid is linearly dependent on the batch size.
- The rate of addition of the granulating liquid was enhanced in proportion to the larger batch size.

Different processes occurring in each phase of the power consumption curve are
a) Particles are wetted ,(b) Nucleation (c) Plateau (d) Torque/power consumption increases again (e) Suspension

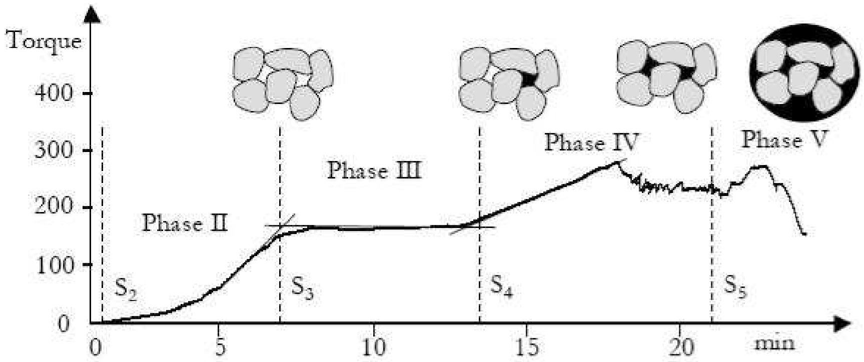

Fig J: Division of power consumption curve

The correct amount of granulating liquid per amount of particles to be granulated is a scale-up invariable [19-22] & the first derivative of the power consumption curve is a scale-up invariant. It can be used as an in-process control & for a fine tuning of the correct amount of granulating liquid.

Use of power consumption method in dosage form design

The interpretation of the power consumption method can be very important for an optimal selection of the type of granulating liquid. In order to calculate similar amounts of granulating liquid in different compositions, it is necessary to introduce a dimensionless amount of granulating liquid π. This amount π can be defined as degree of saturation of the interparticulate void space between the solid materials:

$$\pi = \frac{S - S_2}{S_5 - S_2}$$

Where,
S = Amount of granulating liquid (in liters)
S_2= Amount of granulating liquid (in liters) necessary, which corresponds to a moisture equilibrium at approx. 100% relative humidity
S_5 = Complete saturation of interparticulate void space before a slurry is formed (amount in liters)

Power consumption is used as an analytical tool to define S values for different compositions. Thus the granule formation and granule size distribution of a binary mixture of excipients are analyzed as a function of the dimensionless amount of granulating liquid π.[19-22]

Theoretical approaches to scale-up of a high-shear granulation

1. Rayleigh method (dimensional analysis) [23]: method for producing dimensionless numbers that completely describe the process. Dimensionless numbers most commonly used to describe wet granulation process are Newton, Froude and Reynolds:

Newton (power) number (Np = $\Delta P / (\rho\, n^3\, d^5)$, which relates the drag force acting on a unit area of the impeller and the inertial stress, represents a measure of power requirement to overcome friction in fluid flow in a stirred reactor.

Froude Number [24]($Fr = n^2 d / g$) has been described for powder blending and was suggested as a criterion for dynamic similarity and a scale-up parameter in wet granulation.[25]
Reynolds numbers ($Re = d^2 n \rho / \eta$) relate the inertial force to the viscous force [26]. They are frequently used to describe mixing processes and viscous flow [27].

2. Constant impeller tip speed — same shear rate, an alternative to constant power in relative swept volume (Tip speed = π ND/t where, N= rpm of the impeller, D is the diameter of the impeller, & t= is the time) [28]

3. Relative swept volume [29] — work input on the material which is assumed to provide densification

4. Mixer torque rheometry [29] — rheological properties of wet mass

Variables affecting granulation process:

Table 2: showing variables affecting wet granulation

Process variable	Product variable	Apparatus variable
Impeller/chopper rotation speed	Amount of liquid binder	Size & shape of mixing chamber
Load of the mixer	Characteristic of liquid binder a)Surface tension b)Viscosity c)Adhesiveness	Size & shape of impellor
Liquid flow rate/liquid addition method Wet massing time & temperature	Characteristic of feed material a)Particle size & distribution b)Particle specific surface area c)Solubility in the liquid binder d)Wettability e)Packing properties	Size & shape of chopper

Endpoint Determination
The formulator can define endpoint as a target particle size mean or distribution, or in terms of granulate viscosity or density. [30]

- **Benefits of Mixer instrumentation:**
  1. Machine Troubleshooting
     - detect worn-out gears and pulleys
     - identify mixing and binder irregularities
  2. Formulation Fingerprints
     - batch record becomes a batch and mix ID
  3. Batch Reproducibility
     - use end point to achieve consistency
  4. Process Optimization

- raw material evaluation
- ideal end point determination

5. Use of experimental design to minimize the effort
6. Process Scale-Up
    - move the end-point value along the scale-up path

Mixer Measurements

1. Traditional Methods

a) Power Consumption [31-35]: Power consumption of the mixer motor for end-point determination and scale-up is widely used because the measurement is economical, does not require extensive mixer modifications and is well correlated with granule growth. Intragranular porosity also shows some correlation with power consumption. Normalized work of granulation (power profile integrated over time) can accurately determine endpoints and is correlated well with properties of granulates.

b) Impeller Torque [36-40]: Direct torque measurement requires installation of strain gauges on the impeller shaft or on the coupling between the motor and impeller shaft. Since the shaft is rotating, a device called a slip ring is used to transmit the signal to the stationary data acquisition system.

c) Torque Rheometer [41-44]: A torque rheometer provides an off-line measurement of torque required to rotate the blades of the device and can be used to assess rheological properties of the granulation. It has been extensively used for endpoint determination. The torque values obtained have been termed a “measure of wet mass consistency”

d) Reaction Torque: As the impeller shaft rotates, the motor tries to rotate in the opposite direction, but does not because it is bolted in place. The tensions in the stationary motor base can be measured by a reaction torque transducer.

e) Other Possibilities: When agglomeration is progressing very rapidly, neither power consumption nor torque on the impeller may be sensitive enough to adequately reflect material changes. Some investigators feel that other measurements, such as torque or force on the impeller blades, may be better suited to monitor such events. There are other ideas floating around—for example, use of neural networks to describe and predict the behavior of the wet granulation [45] or control of the endpoint by a rapid image processing system [46]. A technique for measuring tensile strength of granules, in addition to power consumption measurement, to facilitate optimal endpoint determination, has been described by Betz, Bürgin and Leuenberger. Powder flow patterns in wet granulation can be studied using positron emission particle tracking. [47]

2. Emerging Technologies

a) Acoustic. Applicability of piezo-electric acoustic emission sensors to endpoint determination has been studied since the beginning of this century. The technique is very promising, especially since it is non-invasive, sensitive and relatively inexpensive. Granulation process signatures obtained with an acoustic transducer can be used to monitor changes in particle size, flow and compression properties [48-49] *b) Near-Infrared (NIR).* Use of a refractive NIR moisture sensor for endpoint determination of wet granulation has been described by several authors [50-51]. There are technological challenges associated with this approach, as the sensor can only measure the amount of water at the powder surface.

c) FBRM. Focused beam reflectance measurement (FBRM) is a particle-size determination technique based on a laser beam focusing in the vicinity of a sapphire window of a probe [52-53]. The beam follows a circular path at speeds of up to 6 m/s. When it intersects with the edge of a particle passing by the window surface, an optical collector records a backscatter signal. The time interval of the signal multiplied by the beam speed represents a chord length between two points on the edge of a particle. The chord length distribution (CLD) can be recalculated to represent either a number or volume-weighted particle size distribution. In many cases, CLD measurements are adequate to monitor dynamic changes in process parameters related to particle size and shape, concentration and rheology of fluid suspensions.

Analysis of granulation process:
Kinetic analysis of granulation process is provided with population balance modeling [54] Proposed model is an extraction of general population balance equation, PBE [54] with the assumptions that the granulator is well mixed, batch system and the only process active inside is coalescence. The discretized population balance gives a mathematical description for the change in the number of particles in size interval *i* (*N*i) with time progress:

$$\frac{dN_i}{dt} = N_{i-1}\sum_{j-1}^{i-1}(2^{j-i+1}\beta_{i-1,j}N_j) + \frac{1}{2}\beta_{i-1,i-1}N_{i-1}^2 - N_i\sum_{j-1}^{i-1}(2^{j-i}\beta_{i,j}N_j) - N_i\sum_{j-i}^{i_{max}}\beta_{i,j}N_j \qquad (1)$$

Where, *i* and *j* are the size intervals of the colliding particles. Miscellaneous empirical and theoretical expressions for coalescence kernel, βi, j have been brought and used in literature. In this paper, the size independent kernel, SIK model [55]

$$\beta = \beta_0 = const. \qquad (2)$$

was assumed.

Stepwise scale up determination of rapid mixer granulator (56-57)

1. Determine the formula for the manufacture of the tablet/ granules.
2. Determine the granulation processing parameters such as
   - Bowl volume (L),
   - Bowl diameter (m),
   - Batch size (kg),
   - Bowl volume/powder weight ratio,
   - Impeller speed (rpm)
   - Scale of manufacture (for eg. Scale of manufacture for RMG 10 is 1x while for RMG 300 is 30x

- Impeller tip velocity (m/sec) [formula, V =πnd; where n is the revolution per second & d is the diameter of the bowl] To attain the same impellor tip velocity, impellor speed was adjusted.
- The impellor tip speed of all scale up mixers was kept equal to that of the lowest scale mixer (RMG 10) for which tip speed was optimized by trial & error method.
- Chopper speed (rpm); it remains same for all the batches.
- Granulating fluid volume (L) [the theoretical volume of granulating fluid for any scale was calculated by using volume used for lowest scale multiplied by the scale of manufacture.
- Granulation time (min) [the theoretical granulation time was determined by using ratios of the impellor speeds multiplied by the time used for the lowest scale.

3. Determine the granule properties & tablet properties such as
   - ➢ Granule properties
   - Percent loss on drying
   - Granule size distribution (final blend)
   - Geometric mean diameter
   - Standard deviation
   - Bulk & tap density
   - Percent compressibility (carr's index)
   - ➢ Tablet properties
   - Weight variation
   - Hardness
   - Friability
   - Disintegration
   - Dissolution
   - Blend uniformity
   - Tablet assay
   - Content uniformity

CONCLUSION

The engineering design of various scales of rapid mixer granulator is geometrically similar. The three important factors that should be considered in scaling up a rapid mixer granulation process are: a) the impeller speed should be adjusted to keep the tip speed constant. b) The volume of granulating fluid should be linearly scaled –up based on batch size. C) The granulation time should be adjusted based on the ratio of the impellor speed from one scale to next. Good in-process controls & the use of engineering models &/or scaling factors are essential for successful scale-up.

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