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Pharmaceutical Sciences **Review Article……!!!**

SCALEUP FACTORS WITH AN INDUSTRIAL PERSPECTIVE

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KEYWORDS:

Scaleup factor, statistics, unit operations, product development, critical process parameters, critical quality attributes.

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ABSTRACT

The objective of this review article is to study how scaleup factors are utilized in technology transfer of pharmaceutical products. This review article is to discuss the various aspects for utilization of scaleup factors of different unit operations for technology transfer process in pharmaceutical industry, importance of scaleup factors in technology transfer, reasons for using scaleup factors , methodology and facts. The use of mathematical considerations of scale up theory, the search for scale up invariants, the establishment of in-process control methods are one of the keys in development of a robust product. Usage of scientific approach to change any process not only saves the risk of failure but also reduces costing of a trial batch which was to be executed for studying the effects of various process parameters.

INTRODUCTION:

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, scaleup process is an extremely important one. A change in granule size distribution, final moisture content, friability, compressibility and compactability 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.

SCALE-UP BASICS:

According to the modeling theory, two processes may be considered similar if there is a

GEOMETRICAL SIMILARITY:

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.

KINEMATIC SIMILARITY:

Two geometrically similar systems are called kinematically similar if they have the same ratio of velocities between corresponding system points.

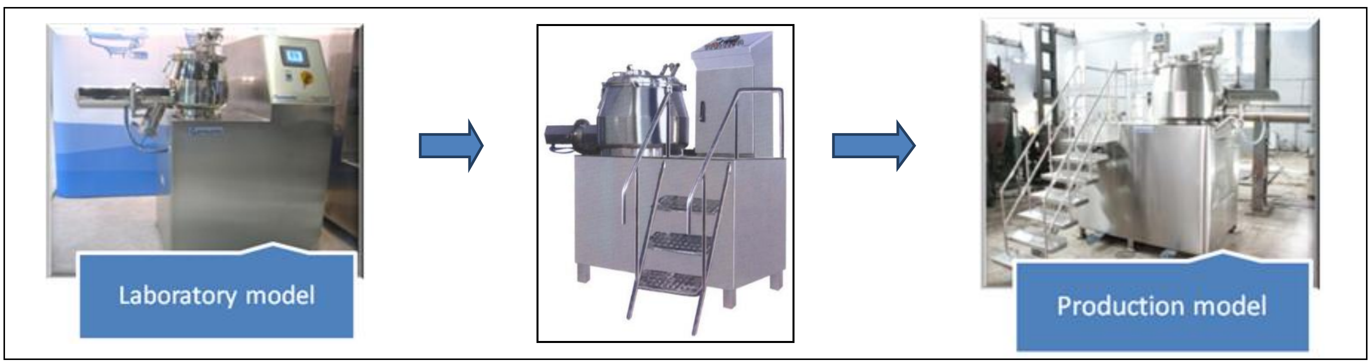
DYNAMIC SIMILARITY:

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 MODELS FOR ALL UNIT OPERATIONS

RMG	Fill Ratio (H/D Ratio) Impeller tip speed Newton's Power number for torque
Multi mill / Quadro co-mill	• Tip speed
Blender	Froude number No of rotations
FBD/FBP/ Wurster	Base plate ratio Occupancy/ gun nozzle size Tip speed
Compression	Dwell time Blend residence time in feeder
Auto Coater	Brim volume for occupancy Spray rate * Pan dia/ Batch size Spray rate/Air flow rate ratio

RMG



Granulation is the most crucial step in Oral solid dosage form formulation process and when developing from lab scale to industrial scale many aspects are taken into consideration.

Variables Affecting Granulation Process:

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

I. SCALE UP FACTOR FOR RMG

1) GEOMETRIC SIMILARITY

FILL RATIO: is defined as the ratio of Bed height and RMG Diameter (H/D ratio)

H/D Ratio(Constant fill ratio) = Powder bed height (cm)/(RMG bowl diameter (m) x 100)

Powder Bed height (cm) = (Dry mix volume (L) x 1000) / Total volume of RMG (L)

Total Volume of RMG = ¼ π D^2

Bed height (cm) = Dry mix volume (L) X 1000 / ¼ π D^2 X 10000

Bed height (cm) = 4 X Dry mix volume (L) X 1000 / π D^2 X 10000

RMG Bowl diameter = Available from equipment manual or qualification document

Where ,

D = Diameter of RMG bowl in meter

π = 3.14

2) KINETIC SIMILARITY

TIP SPEED:

RPM to be scaled down and scaled up according to **Tip speed: 2*(π)*R*N**

Or Distance travelled by impeller tip to be kept constant

V= D x 3.14 x N

N = mixing tool speed (Impeller)

D = tool diameter

The tip speed represents the **linear velocity at the tip of the impeller**. Tip speed is responsible for the movement within the bowl and is related to the shear forces imparted by the impeller.

3) DYNAMIC SIMILARITY

A).NEWTON'S POWER NUMBER CAN BE USED TO SCALE TORQUE:

$$Ne_P = P / (\rho R^5 N^3)$$

P = Power consumption by the impeller blade = **Torque* (2* π *N)**

N = Impeller RPM

R = Impeller Radius

ρ = Wet mass density of granules (**Method to determine ρ need to be finalized**)

Newton's power number relates the drag force acting on a unit area of the impeller and the inertial stress.

B). RELATIVE SWEPT VOLUME (RSV)

RSV = Volume of Material Swept per Second / Volume of the Bowl

This parameter is calculated as the volume swept by the blades per unit time vs. the bowl capacity. It is related to the work or energy imparted on the wet mass during the granulation.

$$\text{Impeller swept volume} = \frac{\text{Impeller height (m)}}{\text{Bed height (cm)/100}}$$

FROUDE- NUMBER

Tip Speed High Comparability: Tip speed scale up according to Froude- Number

Fr = N^2 x D/g

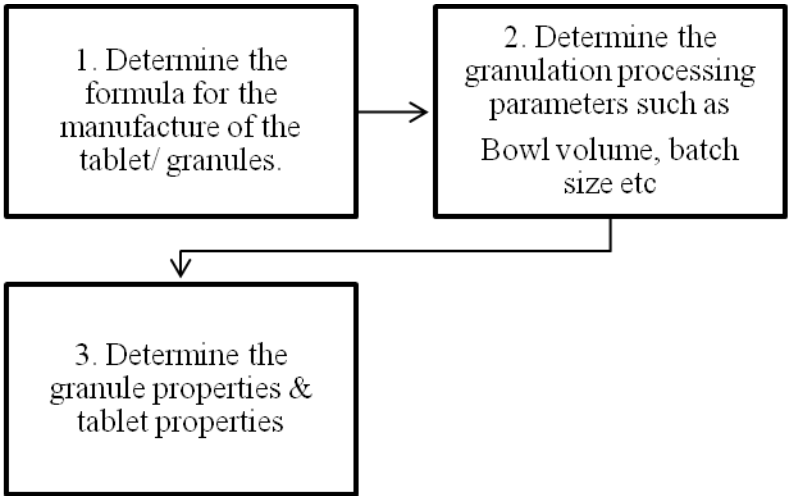
N = tool speed (Impeller)

D = tool diameter

g = gravity acceleration

The Froude number is the **ratio of the centrifugal accelerationto gravitational constant**, and relates to the compaction forces experienced by the wet mass owing to centrifugal and centripetal forces generated by the plow.

Stepwise Scale Up Determination Of Rapid Mixer Granulator



II. SCALEUP FACTOR FOR BLENDER

Conta blender

1) GEOMETRIC SIMILARITY: Keeping the ratio of all lengths constant (constant fill ratio)

2) DYNAMIC SIMILARITY: maintaining constant forces

- **Froude Number**

Froude Number : $\frac{N^2 R}{g}$

Where,

N - Rotation RPM

R –Vessel Radius

g – Gravitation Constant

3) KINEMATIC SIMILARITY: maintaining a consistent number of revolutions (rpm × minutes)

50 L Blender : 15 RPM*10 minutes: 150 revolution

250 L Blender : 10 rpm* 15 minutes : 150 revolution

To Keep Froude Number same from Demo to Exhibit to Commercial scale, we have to change the variable i.e Rotation RPM

Blender Lubrication Process

$$r_2 = \frac{(V^{1/3} \times F_{headspace})_1 \; r_1}{(V^{1/3} \times F_{headspace})_2}$$

V = Blender volume
$F_{headspace}$ = (100 – Fill level % (occupancy))
r = number of revolutions

Number of revolutions = blender speed x blending time

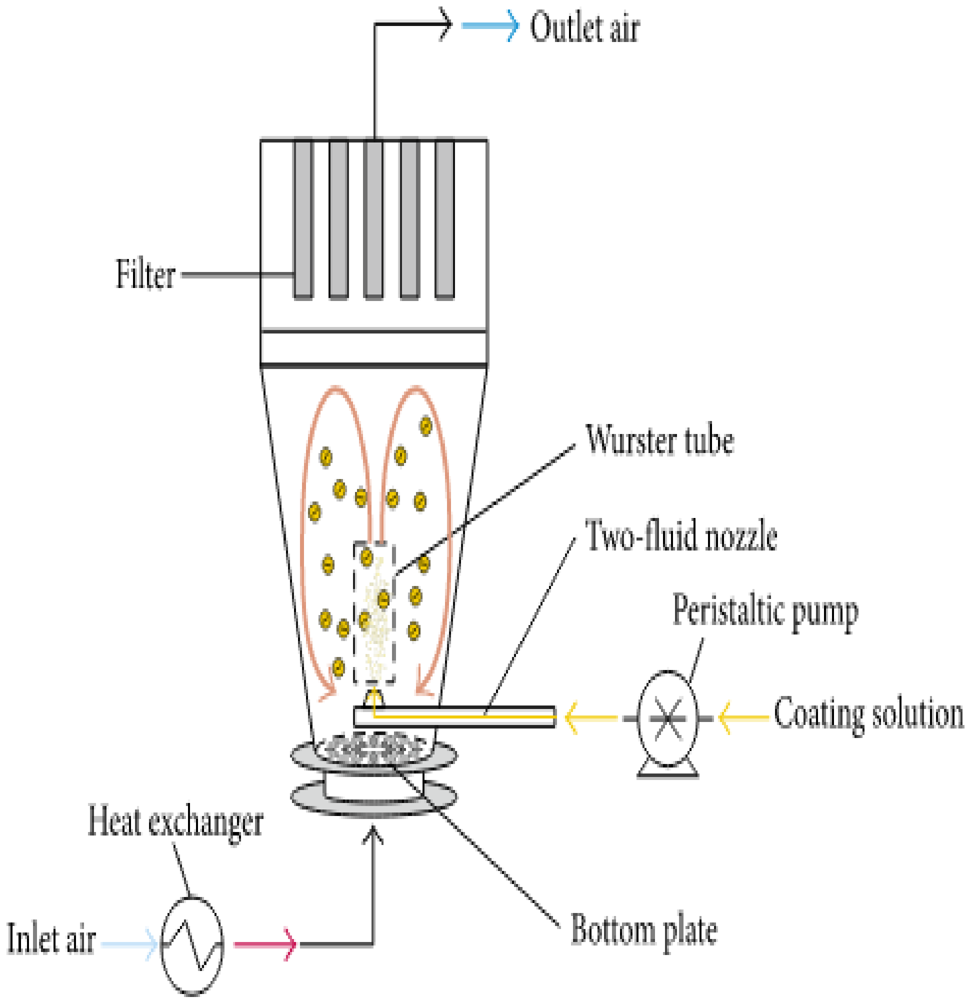
Example: To find blender speed for 1500 L blender from 200 L Blender (For Lubrication)
V_1 = Volume of small scale blender = 200 L, V_2 = Volume of large scale blender = 1500 L
Occupancy in small scale blender = 56%, Occupancy in large scale blender = 60 %
Time for smaller scale = 3 min
Blender speed for smaller scale = 10 RPM
Total revolution for small scale = 10 x 3 = 30
Blender speed for larger scale = 5 RPM
Time for larger scale = ?

$$r_2 = \frac{(200)^{1/3} \times (100 - \%\ Occupancy) \times 30}{(1500)^{1/3} \times (100 - \%\ occupancy)} = \frac{5.84 \times (100 - 56) \times 30}{11.44 \times (100 - 60)}$$

r_2 = Number of revolutions = 13.03 ~ 13
Number of revolution = 5 rpm x Min
13 = 5 rpm x time (min)
Time required for lubrication = 2.6 min ~ 3 min

III. SCALEUP FACTOR FOR FBP/WURSTER

Fluid-bed processes are used in manufacturing controlled-release products, and the process variables that should be optimized in the scale-up of fluid-bed processes are examined. Such variables include the spray rate, the pressure of the atomization air, the temperature of the inlet air, the volume of the fluidization air, the batch size, and the type of equipment that is used. Because such parameters can easily alter the end performance of the controlled-release product, they should be carefully investigated during the scaleup operation.



Wurster Coater

Scaleup Factor For Bottom Spray Coating

Approximate scale-up factors for Wurster fluid-bed processors using bottom-spray coating

Wurster Column Size (in.)	Partition Length (in.)	Batch Size (kg)*	Volumetric Capacity (L)	Spray Rate Scale-Up Factor	Process Time (min)
9	12	8	9.4	1.0	27
12	15	18	21	1.78	34
18	24	64	75	4.00	54
32	30	257	300	12.64	68
46	36	612	700	26.12	79

*Bulk density of the product is 0.85 g/cm

Approximate scale-up factors for granulators using top-spray coating.			
Unit Volume (L)	**Screen Diameter (mm)**	**Spray Rate Scale-Up Factor**	**Run Time Factor**
1.75	100	0.21	0.38
4.50	150	0.47	0.44
22	220	1.0	1.00
45	350	2.5	0.82
100	500	5.2	0.87
215	730	11.0	0.89
420	900	16.7	1.14
670	1000	20.7	1.47
1020	1 150	27.3	1.70
1560	1250	32.3	2.20
2200	1750	63.3	1.58
3000	1740	62.6	2.18

If fill ratio of the equipment remain same in all scale , then In any scale the Air Velocity should remain same:Air Velocity (Feet/Min) = Air Flow (Cubic Feet / Min) / Base Plate Area (Square Feet)

Spray rate of Scale B Batch (gm/min)(Q2) = (Q1 x A2)/A1		Air flow of Scale B Batch (CFM)(Q2) = (Q1 x A2) / A1	
Q1 =	Spray rate of Scale A Batch (gm/min)	Q1 =	Air flow of Scale A Batch (CFM)
A2 =	Base plate area at Scale 2	A2 =	Base plate area at Scale 2
A1 =	Base plate area at Scale 1	A1 =	Base plate area at Scale 1

Example:

Factor = Base plate area of FBC 1300C (cm^2) / Base plate area of FBC 125 (cm^2)

$$= \frac{10265}{1964} = 5.22$$

IV.SCALEUP FACTOR FOR COMPRESSION

Compression Machine

Compression machine speed determination based on Dwell Time:

$$DT = \frac{PHF \times 60{,}000}{\pi \times PCD \times N}$$

Where, PHF (Punch Head Flat) = 12.7 mm for B tooling & 18.23 mm for D tooling

N = No. of rotations per minute of turret

π = 3.14

PCD = Pitch circle Diameter of Turret (mm), DT (msec) = Dwell time in mili seconds

Example: To find turret rpm of large scale batch from lower scale batch. (Sejong 51 station from CTX – 26) Pinch head flat = 12.7 mm, PCD_1 = 370 mm = CTX 26, PCD_2 = 739 mm = Sejong 51

N_1 = 20 RPMN_2 = ?

$$\frac{PHF_1 \times 60{,}000}{\pi \times PCD_1 \times N_1} = \frac{PHF_2 \times 60{,}000}{\pi \times PCD_2 \times N_2}$$

$$N_2 = \frac{PHF_2 \times PCD_1 \times N_1}{PHF_1 \times PCD_2}$$

$$= \frac{12.7 \times 370 \times 20}{12.7 \times 739}$$

$$N_2 = 10.01 \text{ RPM}$$

By maintaining fill depth we can achieve desired Tablet weight, Thickness & hardness in any scale

Fill Depth (h) = 4 m / (π x D^2 x d)

Where,

m = Tablet weight

π = 3.14

D = Tablet Diameter/ length

d = Density of mass

V.SCALEUP FACTOR FOR PAN COATING

Tablet Coating machine

- **Occupancy:** Needs to be calculated based on Brim volume* of pan
- **Spray rate:** (Spray rate * Pan dia/ Batch size) to be kept constant across scale
- **Air flow rate**: Drying capacity (CFM / Spray rate) to be kept constant across scale
- Consistency in baffle design across scale
- Differential air pressure of bowl to be maintained

Scale Up of Pan Speed:

- Calculate linear velocity of tablets in lab scale
- Calculate the pan speed required to attain the equivalent linear velocity in large scale
- Thus the dwell time of tablet in the spray zone at large scale will be equivalent to that used in the small scale
- Thus the strategies used in small scale can be fully utilized.

Small scale	Large Scale
• Pan Diameter: 60 cm • RPM: 5 to 20 • Pan circumference: 2 π r =188.4 cm • Peripheral pan speed (distance in 1sec) at 10 rpm:2 π r N= 31.27cm/sec • RPM kept: 10	• Pan diameter: 150 cm • RPM: 2 to 11 • Pan circumference=2 π r =471 cm • Peripheral pan speed at 10 rpm= 2 π rN =75.36cm/sec 75.36 cm in 1 sec at 10 rpm 31.27 cm in 1 sec at rpm =31.27 X 10/75.36 = 4.14 rpm

Scale up of Spray Rate:

S2 = (S1 X 2 V2)/ V1

S2: Spray rate to be used in production.

S1: Spray rate to used in lab scale

V2: Inlet air CFM in production (600 in SBA)

V1: Inlet air CFM in lab (100 in Neocota)

Keeping % pan load constant, inlet CFM in proportion to pan load, Pan speed as calculated.

Pan design constant…

Brim Volume = Volume of Cylindrical Part (till brim) + Volume of Conical Part (till brim)
Volume of Cylindrical Part = L/2 * (θ*R2 - AG) A = Opening Radius = D/2
G = 2* Sqrt(R2 - A2)
R = Pan Radius
L = Cylindrical length
θ = 2* ArcCOS (A/R)
Volume of Conical Part = [2*H/(R-A)] * Integration[x^2*acos(A/x) - A*sqrt(x^2-A^2)] dX (Lower Limt= A, Upper Limit= R)
H = Taper depth
Use following link to integrate: X = Variable to be integrated from
A to R

CALCULATION FOR COATING PARAMETERS FOR SCALE UP STAGE

PARAMETER	SCALE UP EQUATION
Batch size	Batch size (L)= $\frac{\text{Batch size (S)}}{\text{Volume (S)}}$ x Volume (L) L = large coating pan , S= small coating pan.
Pan speed	Pan speed (L)= $\frac{\text{Pan diameter (S)}}{\text{Pan diameter (L)}}$ x Pans peed (S)
Spray rate/gun	Spray rate (L)= $\frac{\text{Gun spacing (L)}}{\text{Gun spacing (S)}}$ x Spray rate (S)/Gun
Spray time	Spray time (L)= Spray time (S) x $\frac{\text{Batch size (L)}}{\text{Batch size (S)}}$ X $\frac{\text{Spray Zone (S)}}{\text{Spray zone (L)}}$
Air flow	Airflow= $\frac{\text{Total spray rate (L)}}{\text{Total spray rate (S)}}$ X Air flow (S)

CONCLUSIONS

The traditional process of pharmaceutical product development involves a long journey of many experiments, observations, challenges, and resolutions before the drug reaches the global market. Most available dosage forms, such as tablets, capsules, powders, granules, lozenges, and suppositories, are solid dosage forms containing both the mixture of drugs and excipients. The large-scale production of solid dosage forms requires well proven and documented formulae for production. Dry powder blending and mixing is a crucial step in the manufacturing of many pharmaceutical products, particularly tablets and capsules, that directly have an impact on the uniformity of content. Nowadays, many of the pharmaceutical processes have shifted from a trial and error design approach towards quality by design approaches for scaling up. QbD involves identifying the critical process parameters and critical product attributes that significantly affect the desired characteristics of the final product.

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