AQEX PHARMA SOLUTIONS

DESIGNING OF DISSOLUTION TEST

Deo Narain Dikshit MSc .PhD

Agenda

AQEX PHARMA SOLUTIONS

01 UNDERSTANDING PROCESS

02 RELATIONSHIP OF CMA , CPP ON CQA

03 CRITICAL PROCESS PARAMETERS IN TABLE MANUFACTURING

04 WET GRANULATION.

05 INTERDEPENDENCE OF CPP , CQA AND DISSOLUTION

06 INTERPRETATIONS

Process

- Process is defined as

"A set of sequential activity which results in a out put with desired Quality Attributes "

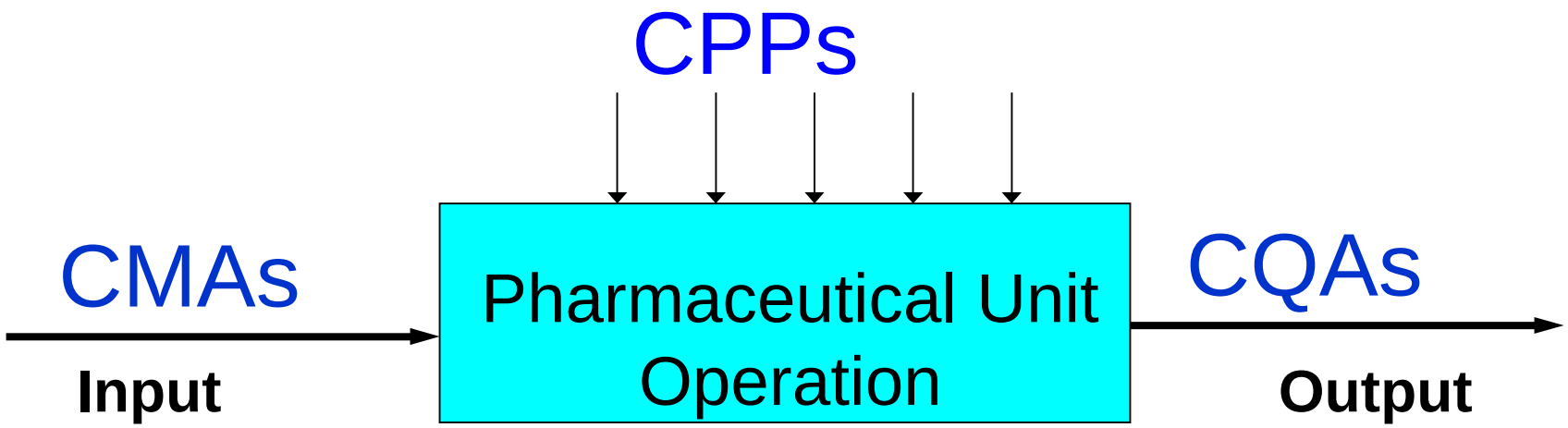
- Our understanding of Quality in Pharmaceutical production has evolved significantly over the past decade.
- The Quality-by-design initiative has proved to be a catalyst for those working in the pharmaceutical science community to reconsider the Product development based on scientific understanding of process , Critical Material Attributes , Critical Process Parameters , Relationship and inter dependence of CMA and CPP with Critical Quality Attributes of the Product at critical stages of the manufacturing

What is Critical Process Parameter

- Critical Quality Attributes (CQA)
  - A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q8)
  - Critical Process Parameter (CPP)
  - A process parameter whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8)
  - *Critical Material Attribute (CMA)**
  - *A physical, chemical, biological or microbiological property or characteristic of an **input material** that should be within an appropriate limit, range, or distribution to ensure the desired quality of output material.*

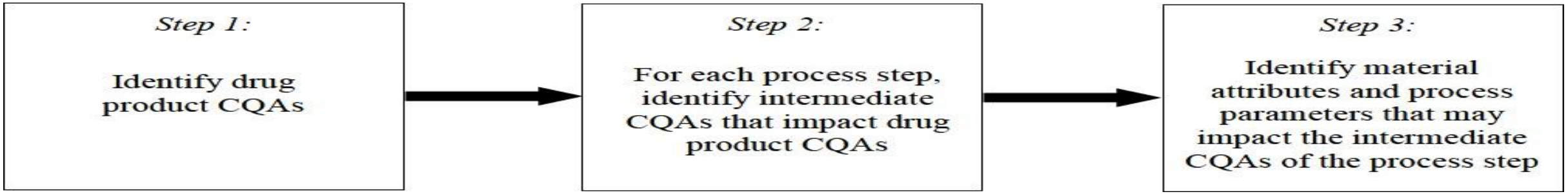
*CMA is not defined in ICH guidance, but used here for discussion purposes

Relationship between CMAs, CPPs and CQAs



$$\mathbf{CQAs = f\ (CPP_1, CPP_2, CPP_3 \ldots CMA_1, CMA_2, CMA_3 \ldots)}$$

Example Approach to Identify Material Attributes and Process Parameters



Drug Product CQAs:
Content Uniformity

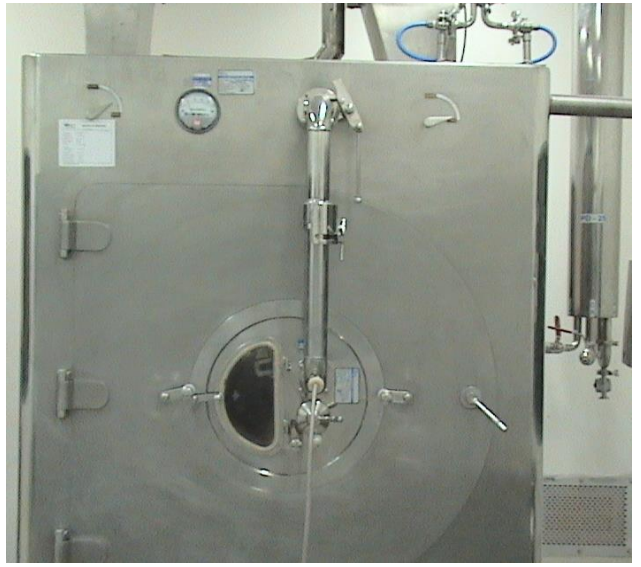
Intermediate CQAs:
Blend Uniformity

Process Variables:
1. Particle size distribution
2. Loading level
3. Number of revolutions

MANUFACTURING PROCESS FOR TABLET DOSAGE FORM

TABLET

- Granulation
- Compression
- Coating
- Blending



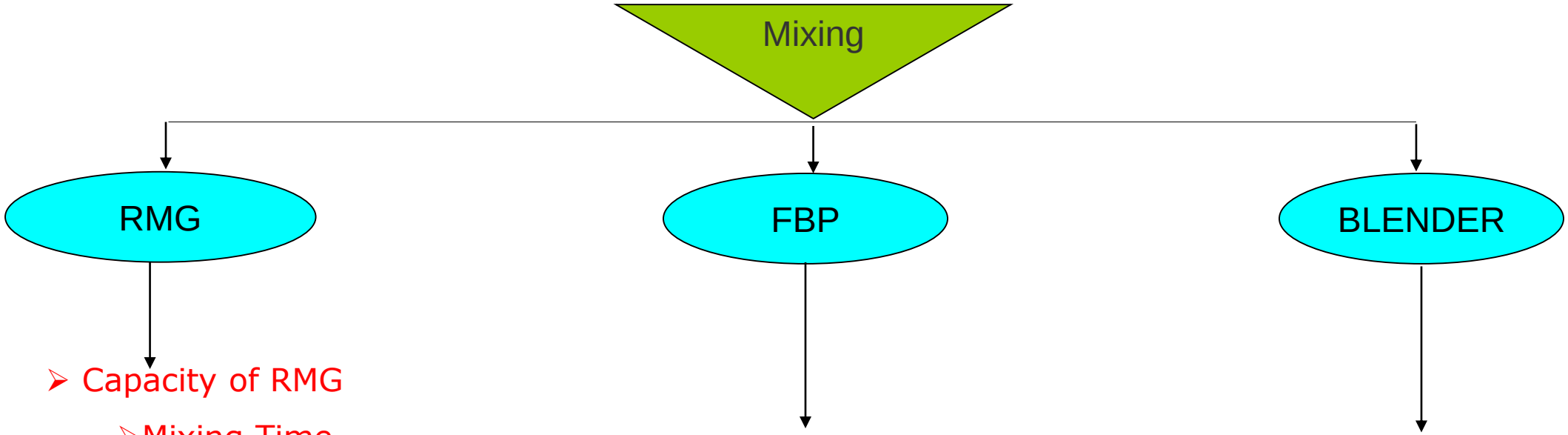
GRANULATION

Granulation is the process in which powder particles are made to adhere to form agglomerates called granules

WHY GRANULATION?

- ✓ Granules being denser than the powder occupy lesser volume per unit weight therefore they are more convenient for storage and shipment.
- ✓ For slightly hygroscopic material granulation reduce the possibility of caking. As granules can absorb more moisture yet retain their flow ability because of their size
- ✓ To prevent segregation of the constituents of the mix
- ✓ To improve the flow properties of the mix
- ✓ To change the particle size distribution so that bulk density can be improved
- ✓ To increase apparent density of the powder, Granulation can improve or modify drug release profile.

INITIAL MIXING PARAMETERS



- Capacity of RMG
- Mixing Time
- Mixing Speed

- Capacity of FBP
- Mixing Time
- CFM OF Blower

- Capacity of Blender
- Mixing Time
- Blender RPM

DRY GRANULATION

Dry Granulation Parameters

- Sieve /Mesh size.
- Capacity of Blender
- Mixing Time
- Blender Speed (RPM)
- Roller pressure
- Screw feeder RPM
- Pressure roller speed
- % Ratio of fines and granules

ROLL COMPACTOR

WET GRANULATION

- Wet granulation is the most commonly used method of granulation in which binder solution is added to the dry mix

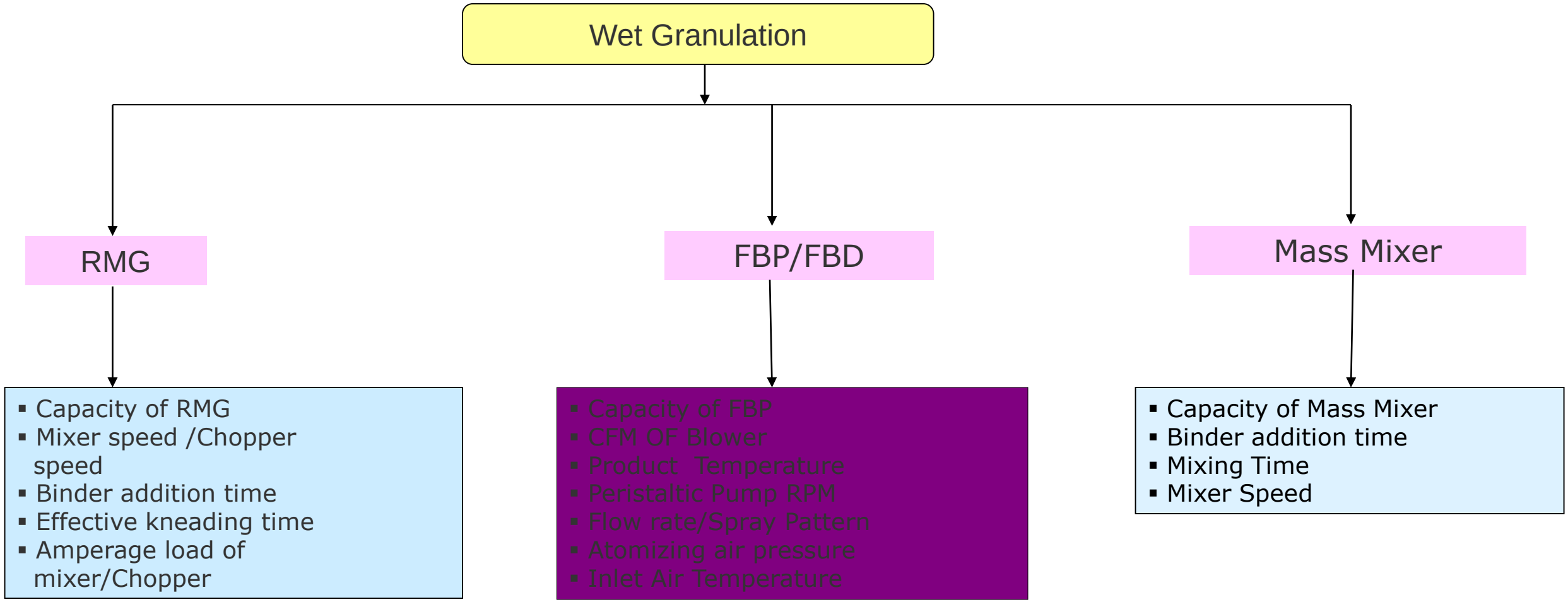
Mechanisms of Granules Formation

- **Nucleation:** Granulation starts with particle to particle contact and adhesion due to liquid bridges .Number of particles will join to form the pendular state
- **Transition:** Nuclei can grow in two possible ways Either single particles can be added to the nuclei by pendular bridges or two or more nuclei may combine the combined nuclei will be reshaped by the agitation of the bed
- **Ball Growth:** Granule growth produces large spherical granules and the mean particle size of the granulating system will increase with time and agitation

CRITICAL PARAMETERS DURING BINDER PREPARATION

- Temperature of binder solution
- Capacity of Paste kettle
- Total time taken for preparation of binder solution
- Viscosity of binder if required

WET GRANULATION PARAMETER



ONE-POT TECHNOLOGY

- **Mixing, Granulating and Drying in ONE processing vessel** In one-Pot technology mixing, granulation and drying options integrated into one processing vessel

One-Pot Processing option:

- Application of a vacuum within the bowl to dry the wet mass allows drying of pharmaceutical compounds at low temperature

ONE-POT TECHNOLOGY

- The vacuum drying process can be enhanced by the addition of a small amount of gas (Transflo™), passing through the product during the drying phase resulting in shorter drying times and lower residual moisture content of the final product
- To further enhance the drying process, microwaves should be added as an additional energy source - microwave drying is the fastest drying technique available in One-Pot processing
- Through accurate control of product temperature and absorbed / reflected microwave power, this technology is ideal for fast processing of pharmaceutical product and is the unique one-pot process allowing higher ‘Product Quality’ & direct ‘Scale Up’

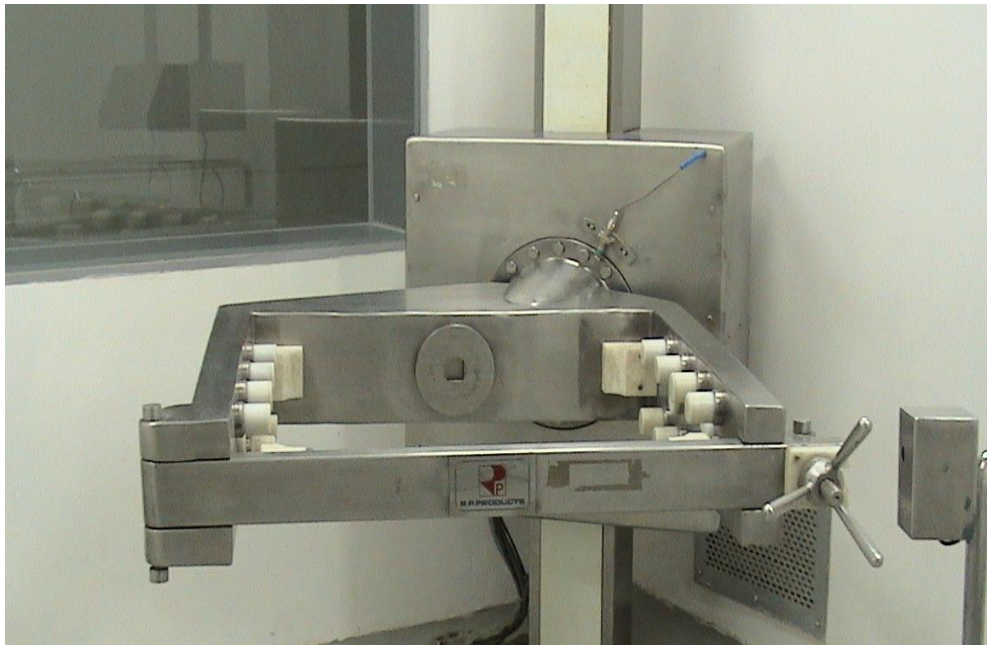
CRITICAL PARAMETERS DURING DRYING

- Inlet air temperature
- Outlet air temperature
- Bed temperature
- Exhaust flap opening /CFM
- Drying time
- LOD of granules (After complete drying)

CRITICAL PARAMETERS DURING BLENDING /MIXING

Blending/Mixing

- Type of blender/Mixer
- Capacity of Blender/Mixer
- Blender RPM
- Blending time

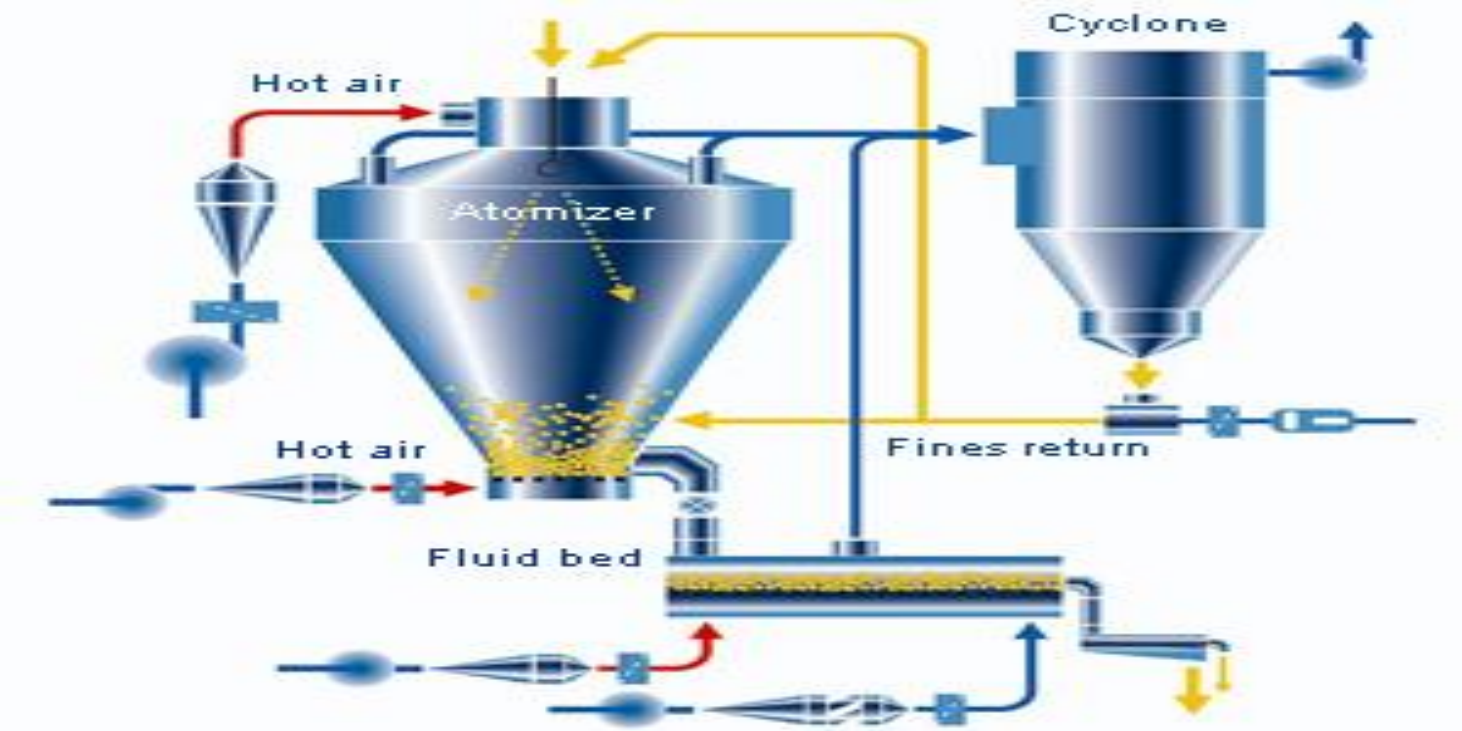


CRITICAL PARAMETERS DURING COMPRESSION

- Speed of machine
- Compression force
- Type of Feeder
- Feeder speed
- Tablet weight
- Tablet thickness
- Tablet hardness
- Tablet DT
- Tablet friability
- Tablet diameter/shape

Spray Drying Process

- Spray drying is a very fast method of drying due to the very large surface area created by the atomization of the liquid feed. As a consequence, high heat transfer coefficients are generated and the fast stabilisation of the feed at moderate temperatures makes this method very attractive for heat sensitive materials.



SPRAY DRYING PROCESSOR

Spray Drying Process

There are four basic stages of the spray drying technique:

1.Atomization: A liquid feed stock is atomized into droplets via either a nozzle or a rotary atomizer. Nozzles use pressure or compressed gas to atomize the feed while a rotary atomiser use a wheel rotating at high speed.

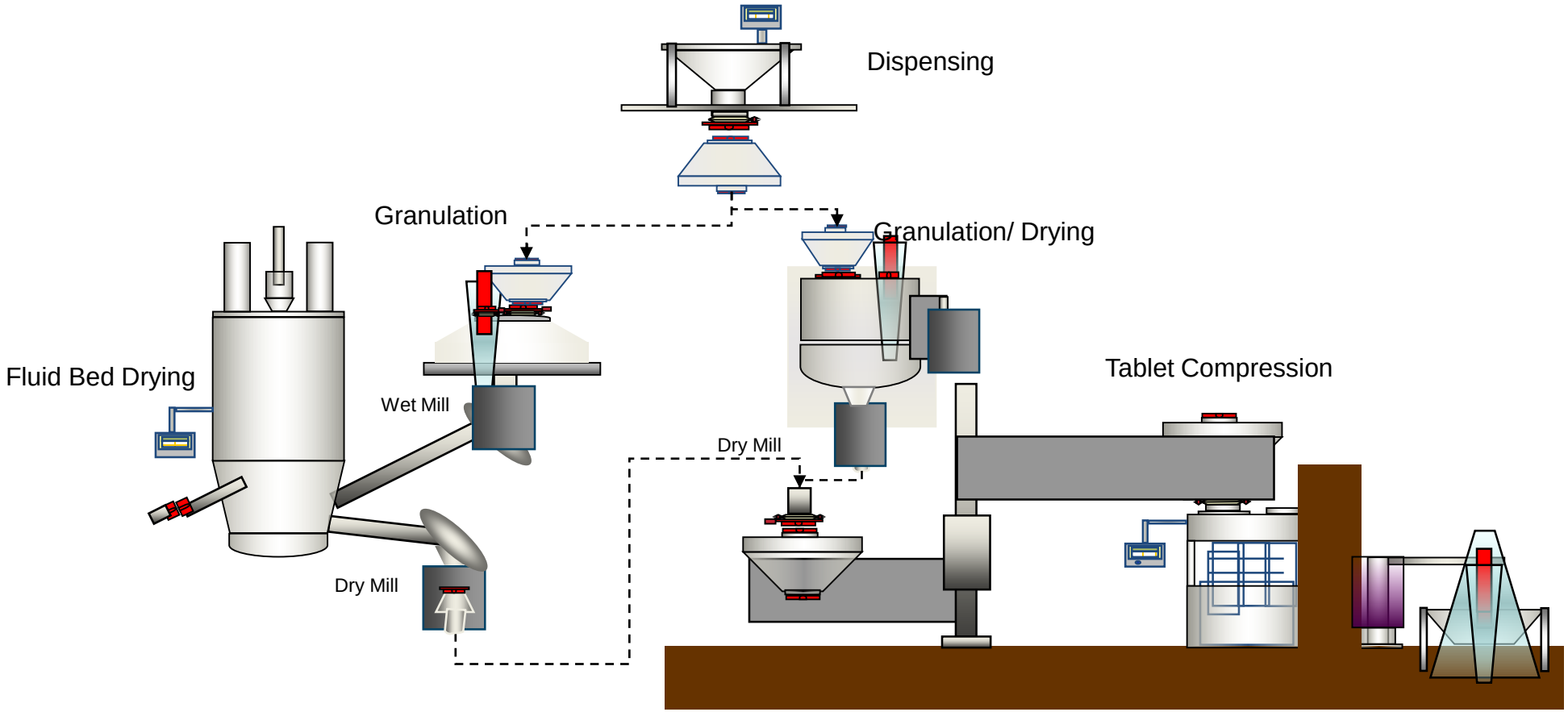
2.Drying: Heated process gas (air or nitrogen) is brought into contact with the atomized feed using a gas disperser – leading to evaporation.

3.Particle formation: As the liquid rapidly evaporates from the droplet, a particle forms and falls to the bottom of the chamber.

4.Recovery: The powder is recovered from the exhaust gases using a cyclone or bag filter. The whole process generally takes no more than a few seconds.

SOLID DOSAGE PROCESSING: CONTAINED MATERIALS HANDLING

Containment is the area separation from Product to Personal/ Environmental area by a barrier to prevent contamination from one area into the other.



CRITICAL PARAMETERS DURING COATING

- Inlet air temperature
- Outlet / exhaust air temperature
- Bed Temperature
- PAN RPM
- Pump RPM /Flow rate /Spray Pattern
- Atomizing air pressure
- Spray Gun Distance to the Bed
- Weight gain / % Weight build up

TYPES OF TABLETS

- Plain/Uncoated
- Coated
- Press coated and multilayered
- Sustained release
- Effervescent
- Gelatin Coated
- Dispersible / Chewable
- Buccal /Sublingual
- Multiple Kits

MANUFACTURING PROCESS FOR SOFTGEL DOSAGE FORM

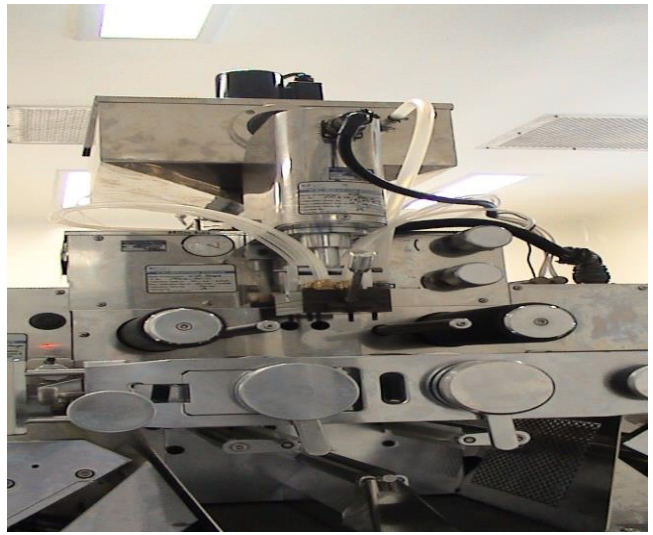
SOFTGEL

Gelmass Prep.

Encapsulation

Drying

Medicament



CRITICAL PARAMETERS DURING GELMASS PREPRATION

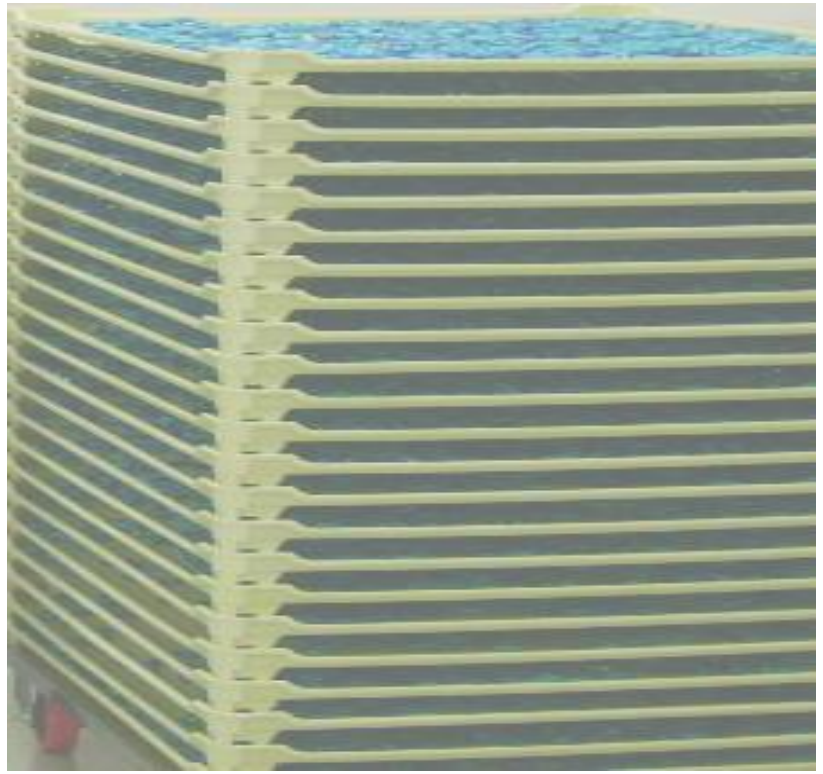
- Reactor Capacity
- Mixer Speed (RPM)
- Hot Water Temperature
- Vacuum
- Mixing Time
- Temperature of Gelatin Storage Vessel

CRITICAL PARAMETERS DURING ENCAPSULATION

- Die Size
- Machine Speed (Die roll RPM)
- Gelatin Ribbon thickness
- Drum Cooling air Temperature
- Capsule Sealing / wedge Temperature
- Spreader Box Temperature
- Gravity Feed Pipes Temperature
- Die Roll Pressure
- Environmental Monitoring (Temp. & RH)

CRITICAL PARAMETERS DURING DRYING

- Temperature and RH are critical parameters during drying of soft gelatin capsule.
- For drying of Soft gelatin capsule specially designed drying area is being used in which temperature in maintained below 25ºC and % RH NMT 30%



Control Strategy

- The control strategy is designed to ensure that a product of required quality will be produced consistently. The elements of the control strategy -how in-process controls and the controls of input materials (drug substance and excipients), intermediates (in-process materials), container closure system, and drug products contribute to the final product quality.
- These controls should be based on product, formulation, and process understanding and should include, at a minimum, control of the critical process parameters and material attributes.

Control Strategy

- Process and product understanding and identify sources of variability. Sources of variability that can have an impact on product quality should be identified, appropriately understood, and subsequently controlled.
- Understanding sources of variability and their impact on downstream processes or processing, in-process materials, and drug product quality can provide an opportunity to shift controls upstream and minimize the need for end-product testing.

MOISTURE, HARDNESS, DISINTEGRATION AND DISSOLUTION INTERRELATIONSHIPS IN COMPRESSED TABLETS

- The physical effects of moisture in the tablet manufacturing processes such as mixing, granulation, drying, flow into the die, compression and ejection from the die have been reviewed tp understand the Adverse effects on tablet hardness were reported as a result of aging tablets i n conditions of high humidity**.**
- **The effect of storage at specified** temperature and humidity on properties of directly compressible tablet formulations indicated that the evaluation o f tablet hardness was not a reliable measure of physical aging of tablets.

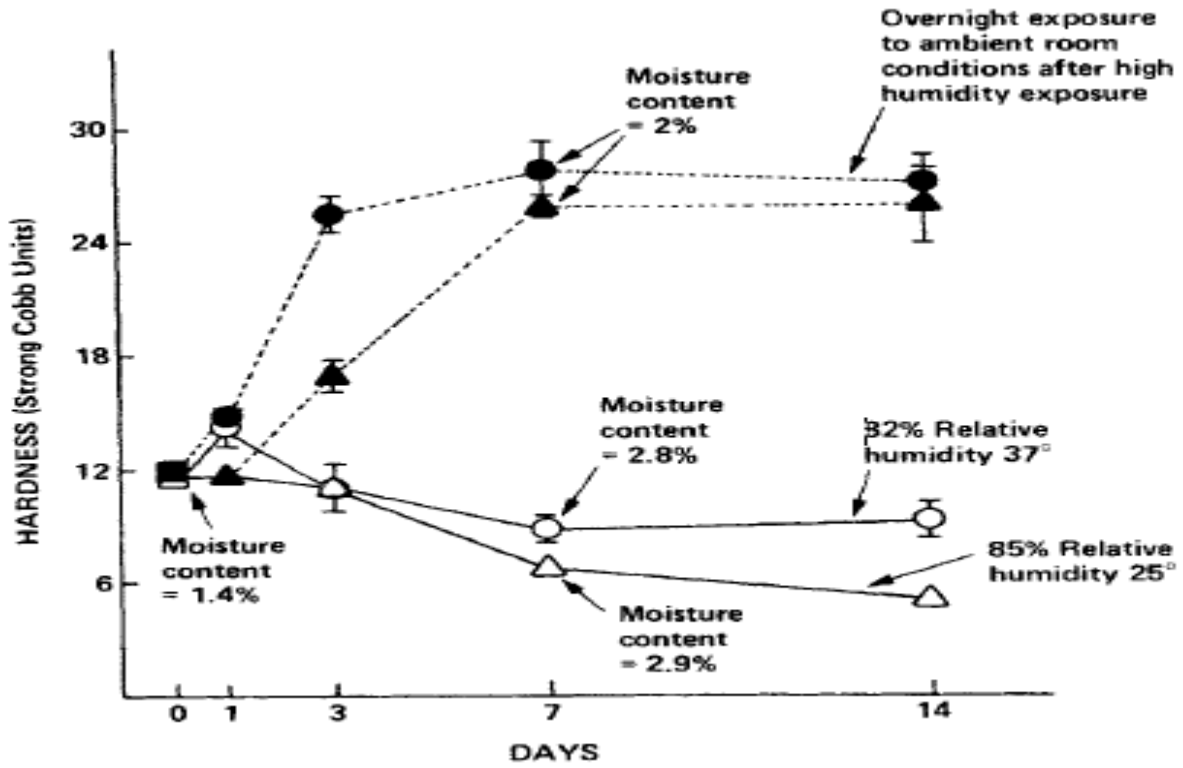
MOISTURE, HARDNESS, DISINTEGRATION AND DISSOLUTION INTERRELATIONSHIPS IN COMPRESSED TABLETS

- The moisture content of the granulation at the time of compression plays an unusually important role in the hardness increase phenomenon of compressed tablets.
- Two types of phenomena relating moisture content of the granulation at the time of compression -to tablet hardness and invitro dissolution observed-

1. The tablet compressed with high moisture content had increase in moisture content on storage due to drug and excipient combinations in a formulation and their physical properties , such as aque us solubility , crystalline property and hygroscopicity
2. The second phenomenon, interrelating moisture,hardness, and in vi tro dissolution, occurred in tablets compressed from granulations with low moisture content . These tablets did not increase in hardness on storage.

Increase of Hardness on storage at high Humidity and high Temperature

- The In-vitro dissolution of the drug was strongly dependent on initial hardness.



Effect of Moisture on DT

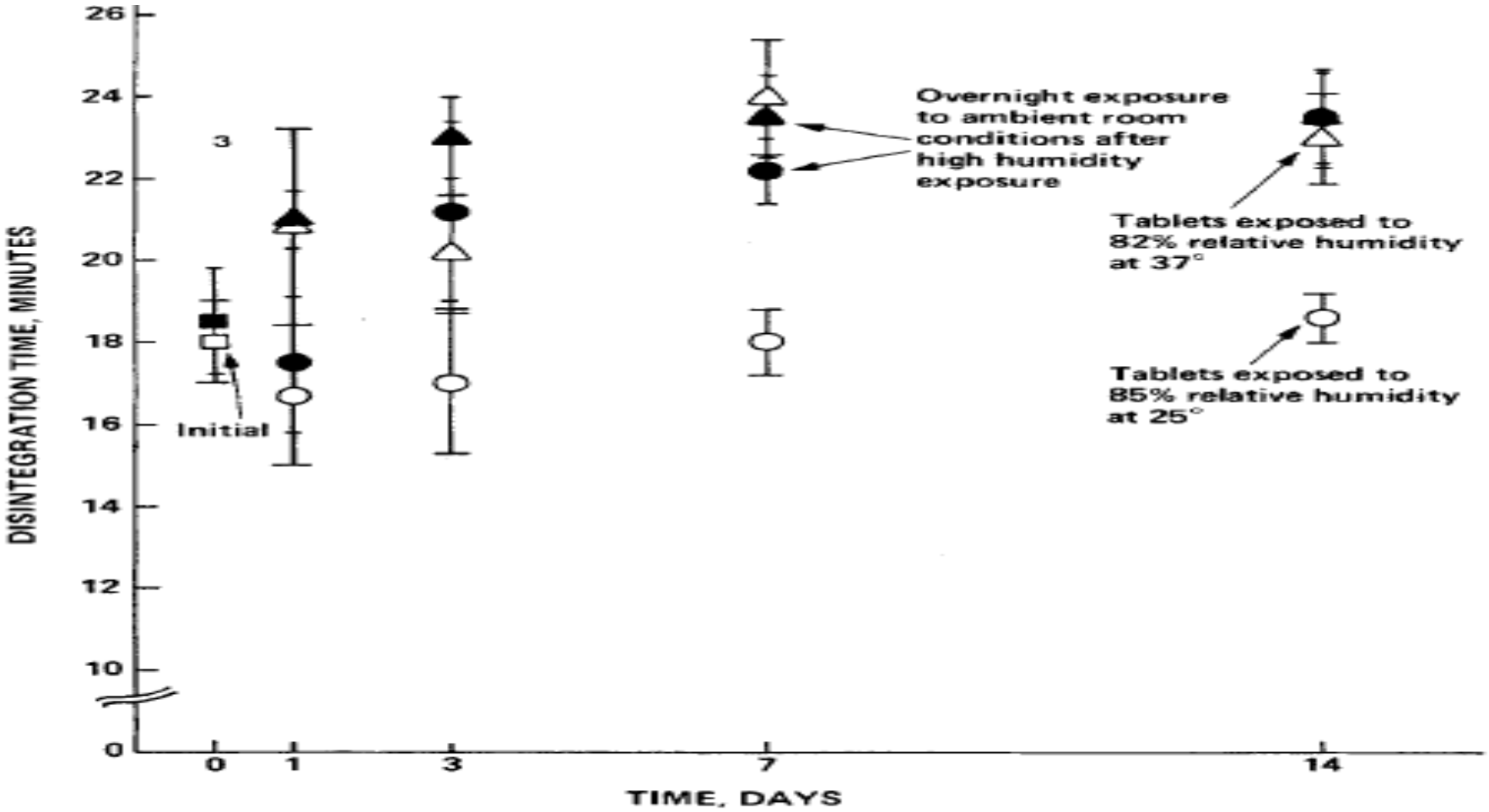


FIGURE 3:

Effect of storage on disintegration time of tablets prepared from granulation of Formulation A with low moisture content.

Effect of Moisture and Hardness on In-vitro dissolution

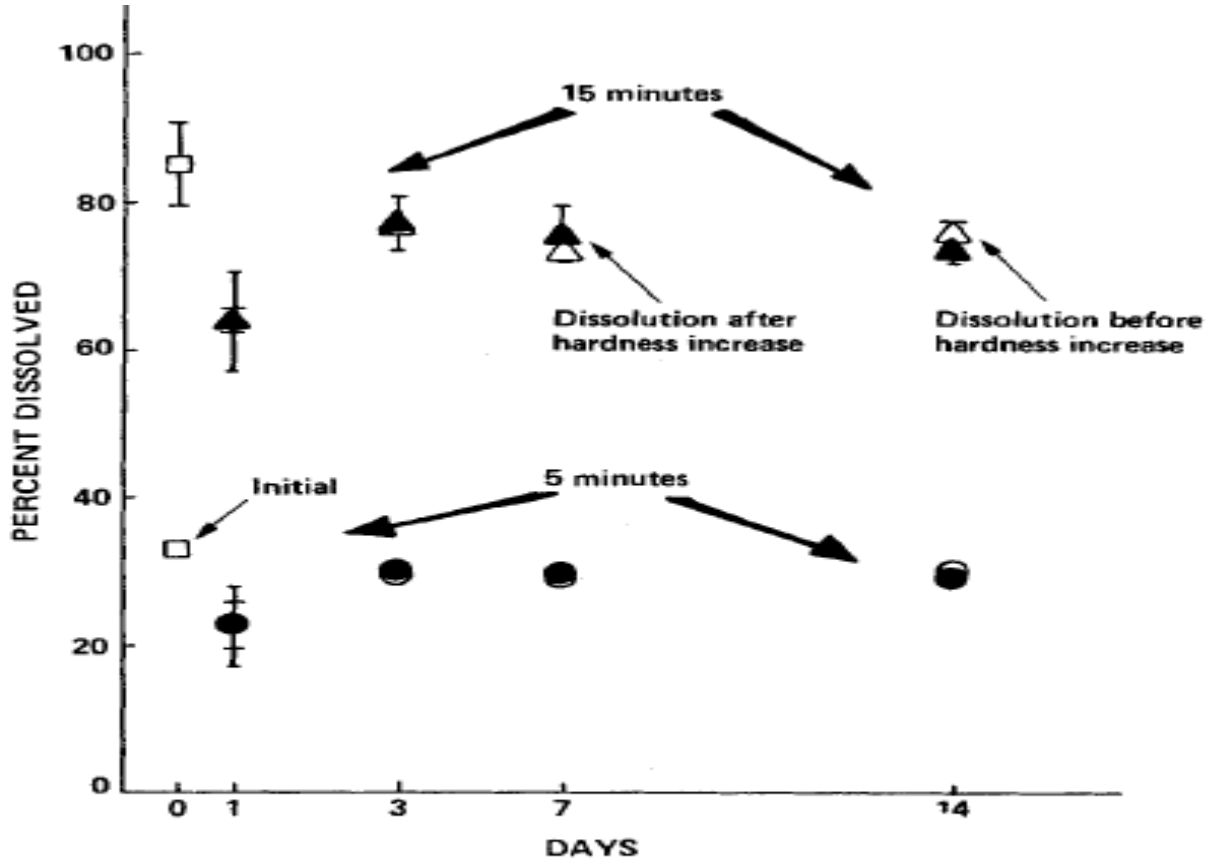


FIGURE 4:

Effect of storage on in vitro dissolution of naproxen in tablets prepared from Formulation A granulation with low moisture content.

Granulation at high sheer velocity in RMG

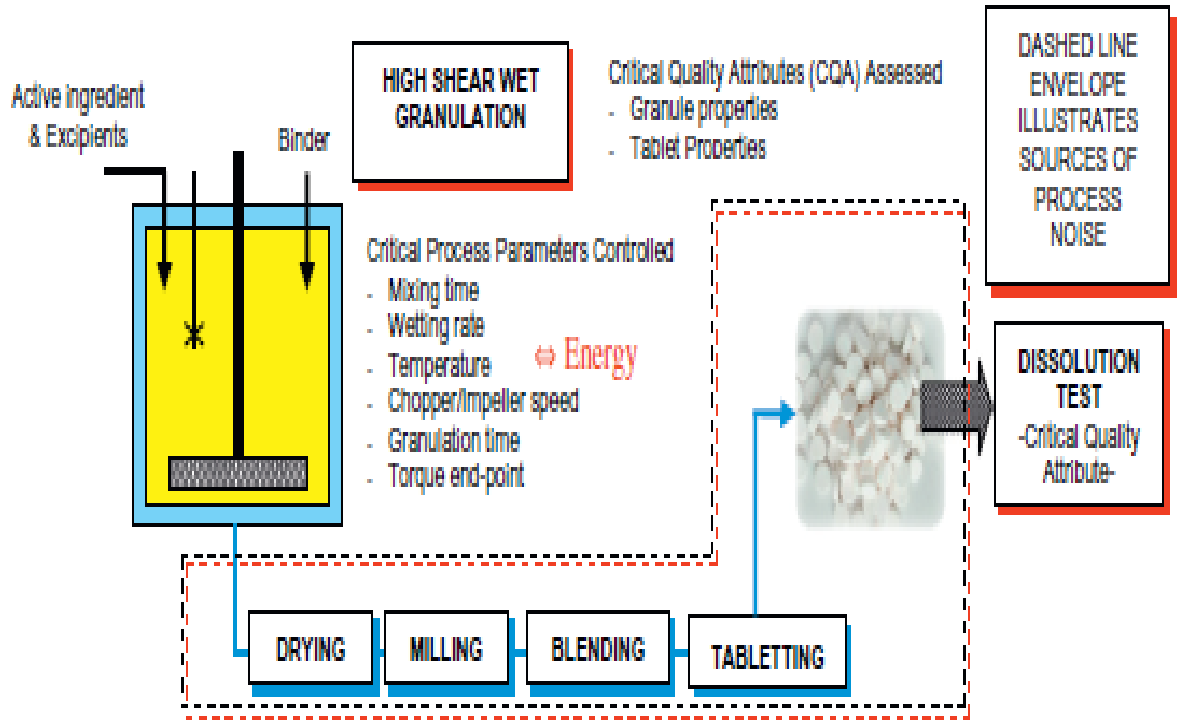


Fig. 1. Typical pharmaceutical granulation and tabletting process illustrating the critical process parameters, critical quality attributes and processes which contribute to process noise.

-

The CPP of Wet Granulation in RMG -

-Impeller speed

– Wetting rate

– Granulation time

– Jacket temperature

-

In addition granule particle size was controlled using two different milling techniques which facilitated the ability to assess the contribution of this parameter to the background noise of the overall process.

Granulation at high sheer velocity in RMG

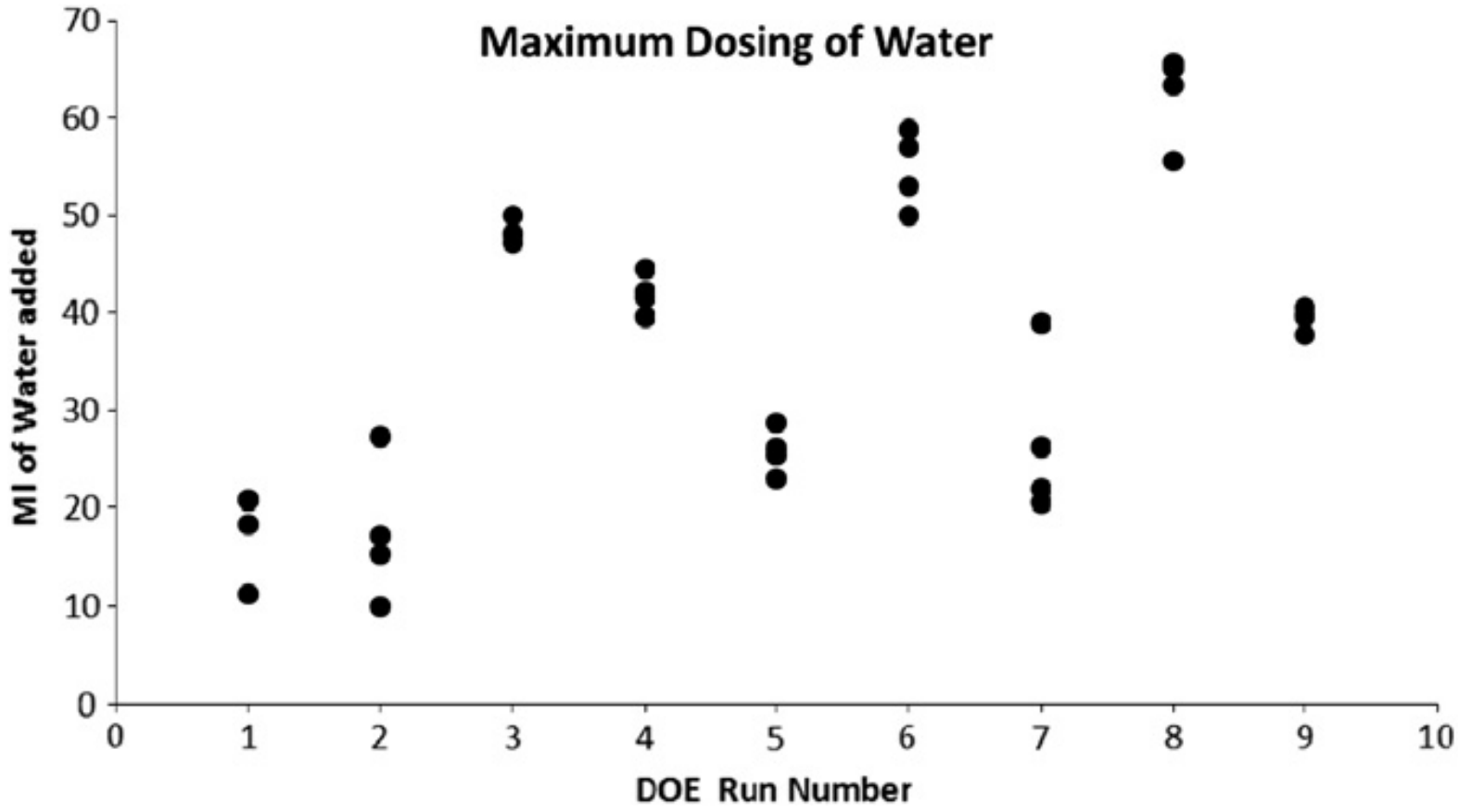
According to the International Pharmaceutical Federation (FIP) the dissolution requirements for modified-release formulations should consist of at least three points:-

1. The first limit is specified to prevent ‘‘dose dumping’’ and therefore should be set after a testing interval of 1–2 h or corresponding to a dissolved amount of 20–30% of labelled drug substance.

2. The second limit should define the dissolution pattern and thus be set around 50% release of labelled drug substance.

3. The final limit is specified to ensure (almost) quantitative drug release, which is generally understood as >80%.

Granulation at high sheer velocity in RMG &FBP - The dependence on rate of Binder Addition –Top spray



Granulation at high sheer velocity in RMG &FBP - The Process Interaction and effect of the Equipment Mechanism

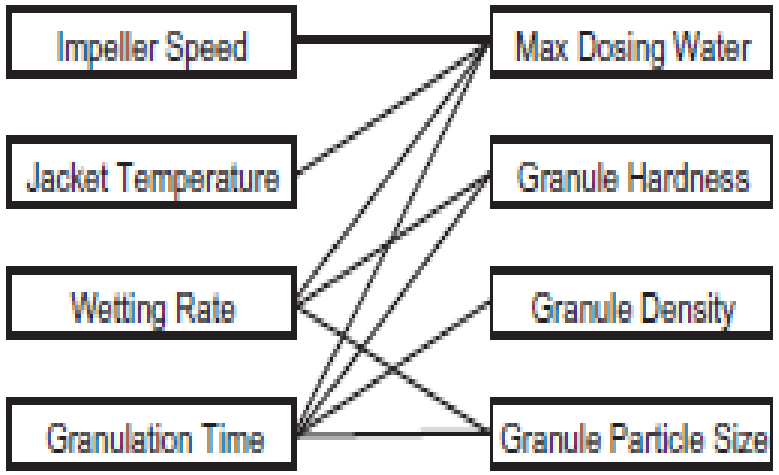


Fig. 5. Process interactions occurring at a statistically significant level (90% confidence).

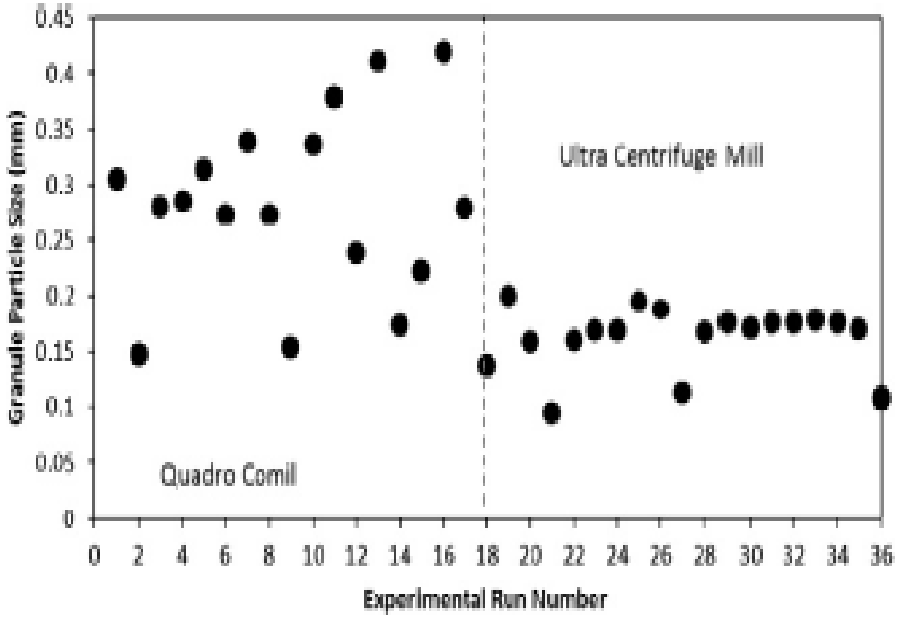
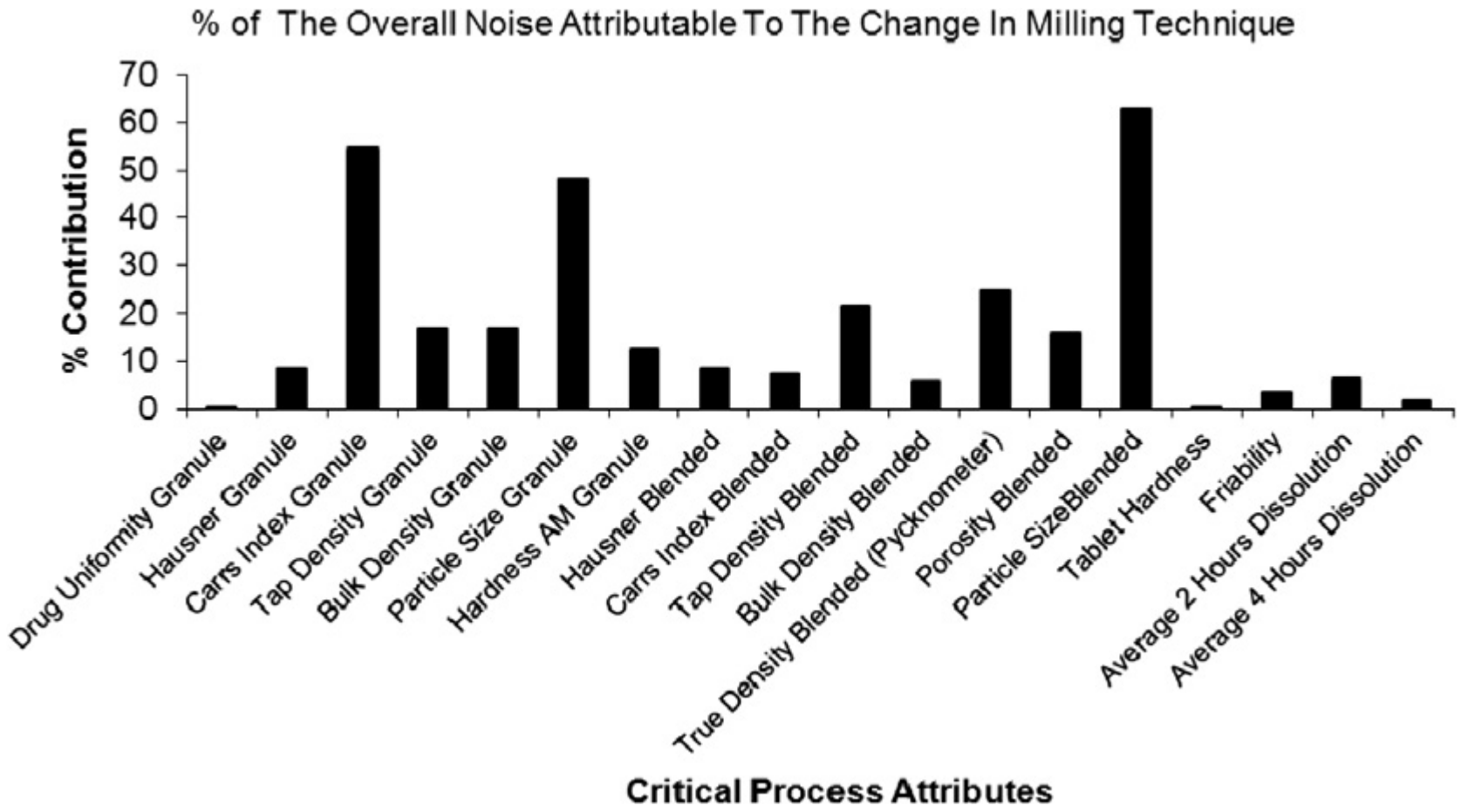


Fig. 6. Particle size distribution for the granules produce from the two different mills.

The Process Interaction and effect of the Equipment Mechanism

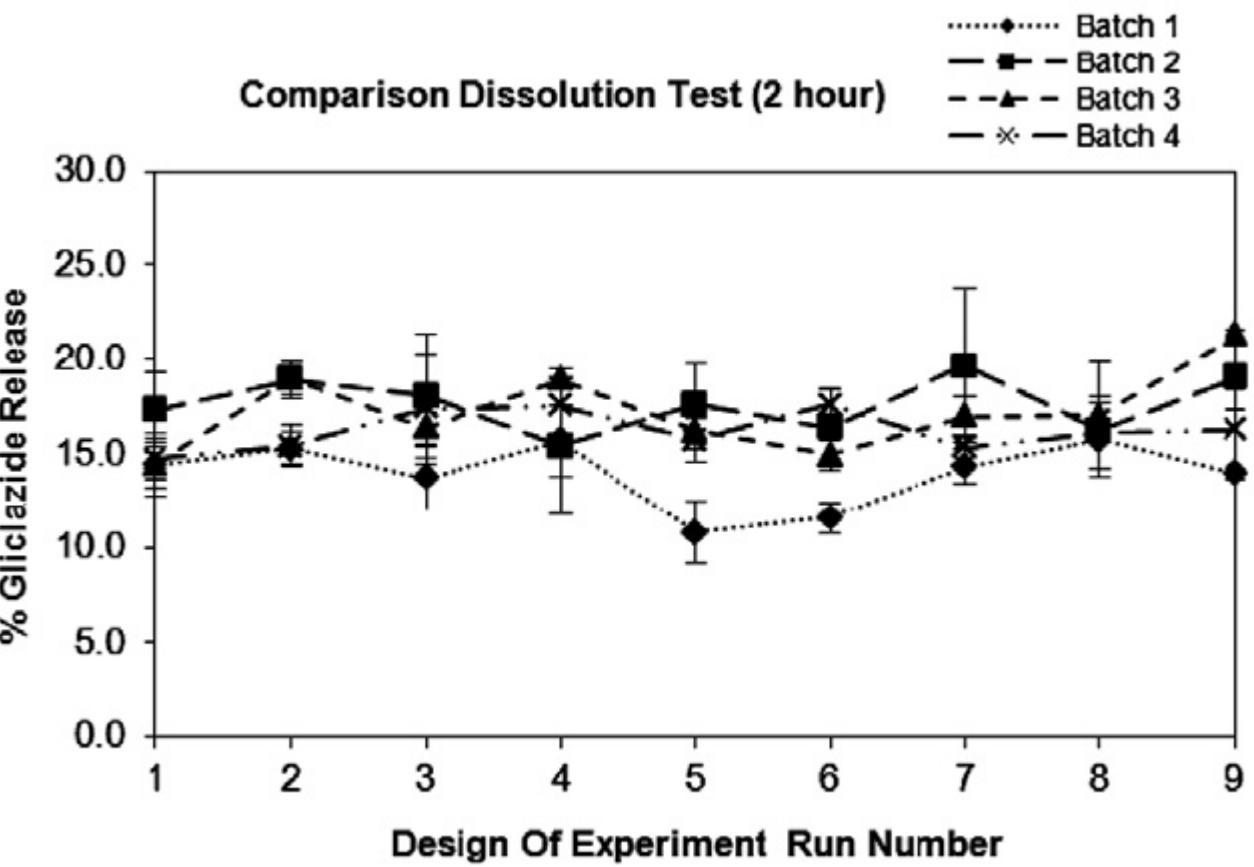


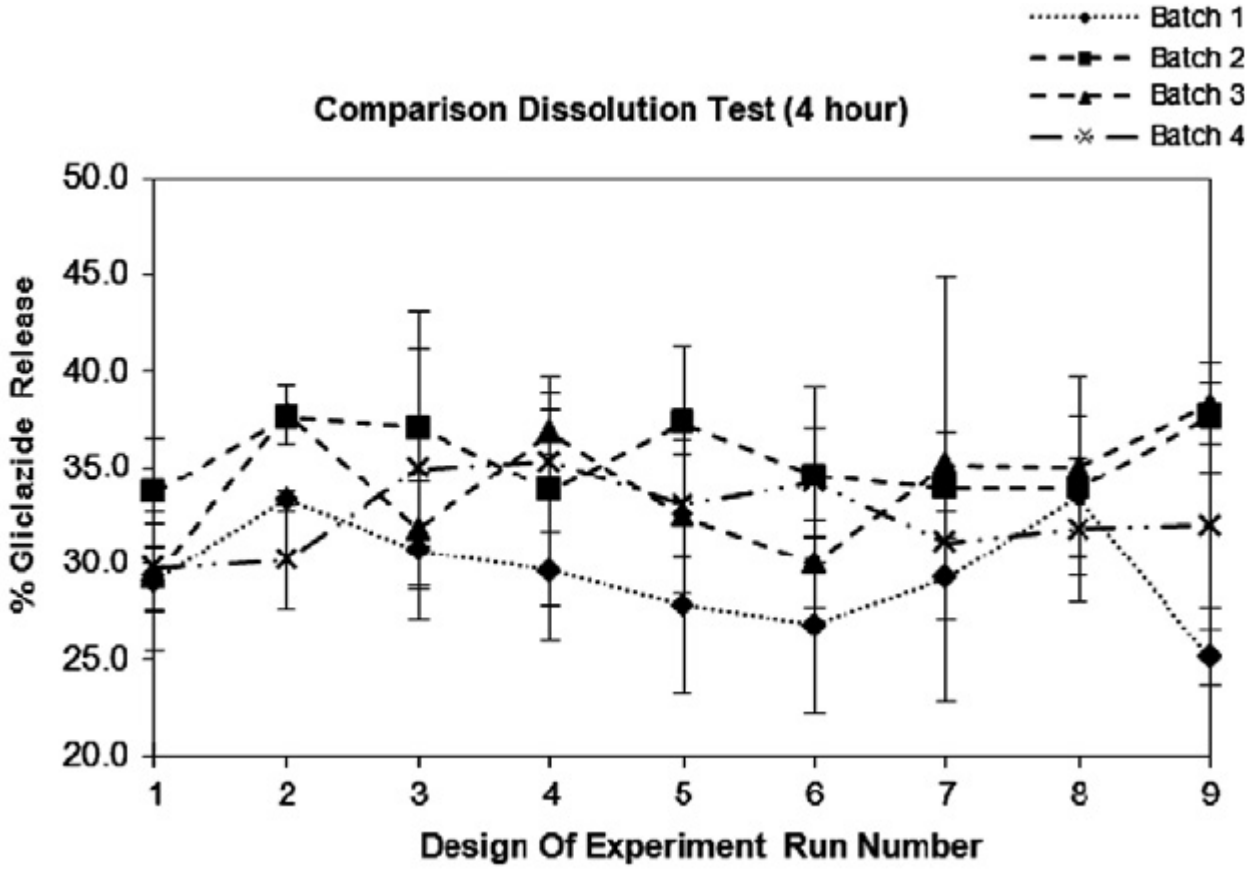
The Process Interaction and effect of the Equipment Mechanism- Interdependence of CPP and Dissolution and CQA

–The CQA Granules Density , Hardness and PSD of Granules was impacted by -
- Impeller speed
– Granulation time
– Wetting rate
– Granulation time

1. By inference from the analysis of the critical quality attributes for the granules the important factors for dissolution are granule hardness, density and particle size.
2. As wetting rate is associated with the 4 h dissolution it could be also be deduced that particle size is increasingly important with respect to dissolution over extended time periods.

Granulation at high sheer velocity in RMG &FBP - The Controlled Drug Release variations on time interval





Granulation at high sheer velocity in RMG &FBP - The Controlled Drug Release variations on time interval

❖When examining the effectiveness of the overall production system an obvious check point is the critical quality parameter of dissolution which was obtained at both 2 and 4 h.

❖ The dissolution values shown in Fig. are in general consistent with the low active pharmaceutical ingredient (API) release values encountered with a controlled release system of a poorly water soluble drug.

❖The results indicated a high degree of variability between repeat runs which is less common.

The noise is present in multivariate systems and will cause variability in the production outcome . Another possible cause for this variability in dissolution may have been the use of impeller torque as a granulation endpoint.

Conclusion

1. The Critical Quality Attributes which affect the Dissolution were granule density, granule hardness and granule particle size.

2. The Critical Process parameters with most influence on the tablet dissolution were linked to granule density granule hardness and granule particle size also

PROCESS CONSIDERATIONS IN REDUCING TABLET FRIABILITY AND THEIR EFFECT ON IN VITRO DISSOLUTION

- The Granulations containing lower moisture contents required higher compression and ejection forces to manufacture a tablet at a given hardness, although this did not influence friability.
- Increased tablet hardness (and to a lesser extent decreased tablet thickness) decreased the tablet friability of he larger tablet. An increase in the quantity of granulating fluid increased the granulation particle size and slightly improved compactibility without significantly affecting friability.
- Tablet dissolution increased as the quantity of granulating fluid was decreased.
- There was a strong interaction, with respect to dissolution, between moisture content and the amount of granulating fluid.

The Process Variables and CQA

TABLE 1 - The Formulation Variables and the Levels Evaluated in this Investigation

Variable	Levels Investigated		
Quantity of granulating fluid	14.00%	14.875%	15.75%
Granulation moisture content	1.0%	2.0%	3.0%
Tablet hardness	12 SCU	16 SCU	20 SCU

Tablet Hardness - Tablet hardness was determined immediately after compression, using a motorized hardness tester **Fifteen tablets were tested for each batch and** the mean and standard deviation were calculated. Hardness was measured in SCU **(1.4 SCU = 1 kilopond = 9.8 newtons**

Relationship in CPP and Process Performance

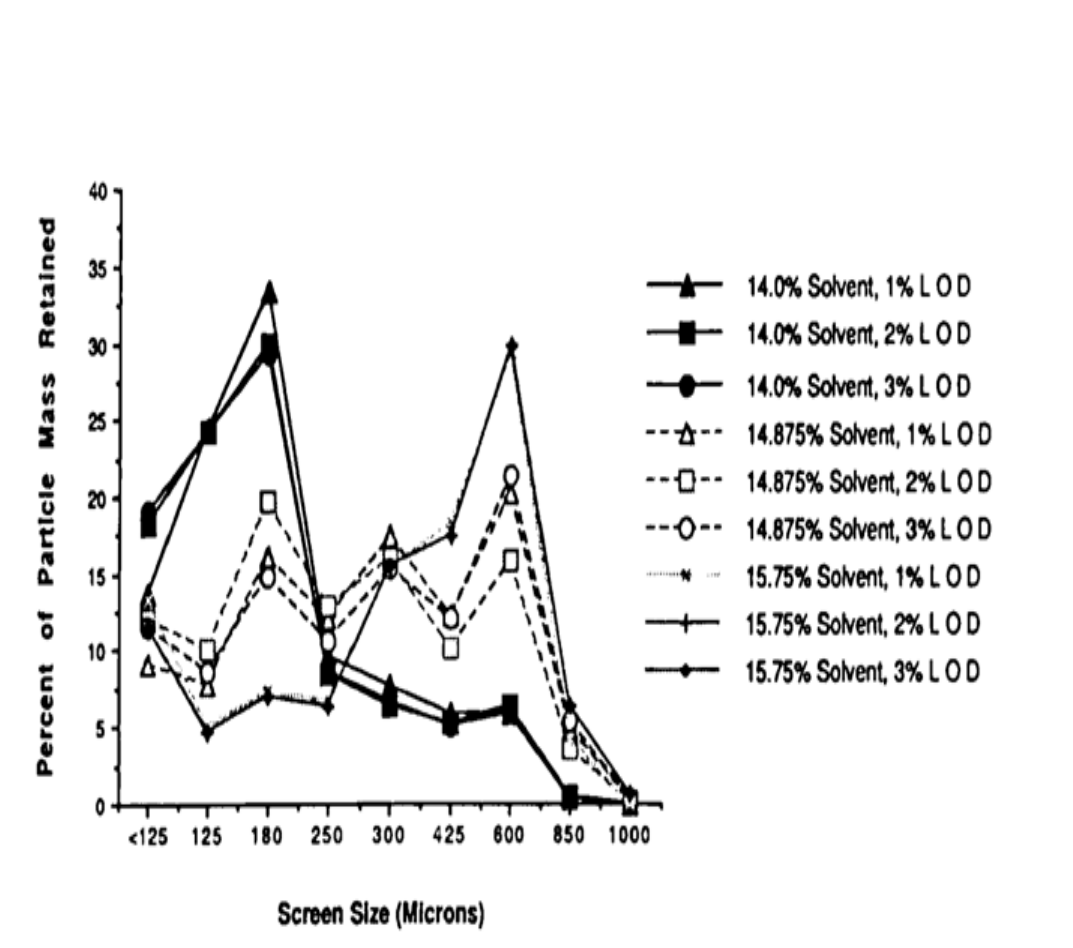
TABLE 4 - Bulk and Tapped Density of the Granulation, and the Calculated Percent Compressibility, at Different Levels of Granulating Fluid

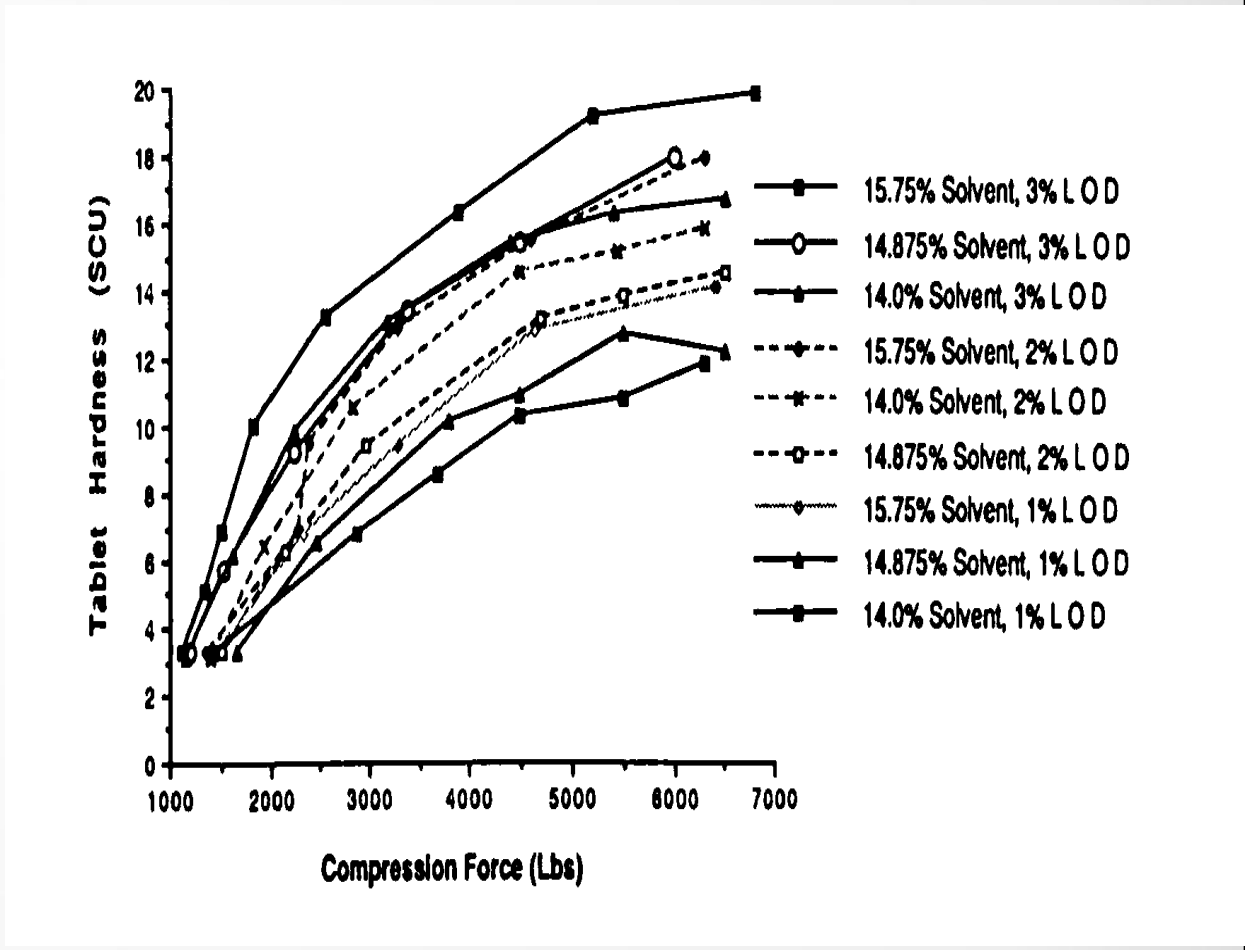
Granulating Fluid (%w/w)	Bulk Density ± SD (gm/cc)	Tapped Density ± SD (gm/cc)	% Compressibility
14.000	0.626 ± 0.027	0.710 ± 0.010	11.8
14.875	0.658 ± 0.003	0.777 ± 0.008	15.3
15.750	0.655 ± 0.006	0.785 ± 0.017	16.6

The relationship between granulating fluid quantity and tablet friability and dissolution will be discussed later. The table **demonstrates that the granulation tapped** density and the percent compressibility tend to increase as the amount of granulating fluid is increased.

This indicates that, within the range studied in this investigation, the flow properties of the granulation improved as the quantity of granulating fluid decreased.

Interdependence of Screen size , PSD , LOD and Hardness





Interdependence of CPP , Variables and Dissolution

Amount of Magnesium Stearate (%)	Tablet Strength (mg)	Granulation Moisture Content (%)	Tablet Hardness ± SD (SCU)	Tablet Weight ± SD (mg)	Tablet Friability (Avg.)	% Dissolved ± SD (Avg. of Six Tablets)		
						10 min	20 min	30 min
0.4	250	2.0	12.3 ± 0.4[a]	379 ± 1	0.21	51 ± 7	94 ± 2	99 ± 0
0.2	250	3.0	12.1 ± 0.5	387 ± 2	0.30	68 ± 10	98 ± 1	99 ± 0
0.4	250	3.0	12.2 ± 0.5	381 ± 1	0.25	53 ± 4	97 ± 1	100 ± 0
0.4	250	3.0	15.3 ± 0.7[b]	381 ± 1	0.21	50 ± 3	93 ± 2	99 ± 0
0.4	500	2.0	12.4 ± 0.3	762 ± 2	6 broken	N.A.[c]	N.A.	N.A.

AQEX PHARMA SOLUTIONS

"Value Creation by Passion"

THANK YOU

CONTACT US
+(91) 9805325654 , 9318810790

www.aqexpharmasolutions.com
Deo.dikshit@aqexpharmasolutions.com