

Mixing

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المزج: عملية ميكانيكية من أجل دمج مادتين أو أكثر في أدوية. *Active ingredient* (المكون النشط) و *excipient* (المكون المساعد).

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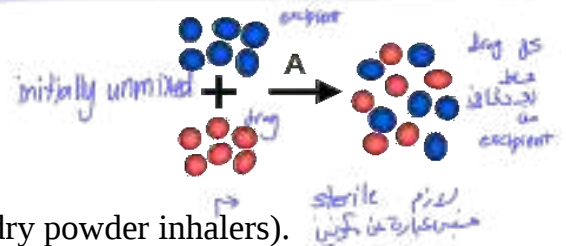
في الأدوية، المكونات هي: *active ingredient* (المكون النشط) و *excipient* (المكون المساعد). *excipient* يمكن أن يكون: *solvent* (المذيب)، *stabilizer* (مستقر)، *flavor* (نكهة)، *color* (صبغة)، *preservative* (محافظة)، *sterile products* (منتجات معقمة).

• مزج (Mixing): إذا أُخذ *powder* (مسحوق) أو *liquid* (سائل) أو *solid* (صلب) فتمزج مع *excipient* (مكون مساعد).

Mixing

- Mixing may be defined as a unit operation that aims to treat two or more components, initially in an unmixed or partially mixed state, so that each unit (particle, molecule etc.) of the components lies as nearly as possible in contact with a unit of each of the other components.

المزج: عملية ميكانيكية من أجل دمج مادتين أو أكثر في أدوية. *Active ingredient* (المكون النشط) و *excipient* (المكون المساعد).



This may be:

- Mixing of Powdered materials (e.g. tablets, capsules, dry powder inhalers).
- Mixing of miscible liquids (e.g. solutions) or immiscible (e.g. emulsions).
- Mixing of insoluble solid and liquid (e.g. Suspensions).
- Mixing of semisolids or dispersion of particles in semisolids (e.g. pastes and ointments).

Mixing

- **Types of mixtures:** How much energy is needed?

1) **Positive mixtures:** Mixtures that form spontaneously (do not need energy) and irreversibly (when formed do not tend to separate).

(e.g. gases and miscible liquids)



2) **Negative mixtures:** Mixtures that need energy input (work) to form and keep. Once the energy input is stopped they tend to separate.

(e.g. Suspensions, emulsions and creams)



3) **Neutral mixtures:** Mixtures that do not form spontaneously (i.e they need energy input) but once formed they do not tend to separate.

(e.g. Powder mixtures, pastes and ointments)



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The mixing Process

Perfect mixture: The situation in which particles of one component lay as closely as possible in contact with particles of other component.

- It is an ideal situation which is practically impossible.

Random mixture: A mixture where the probability of sampling a particular type of particle is the same at all positions and is proportional to the number of such particle on the total mix.



Random Sampling

The diagram illustrates three mixing systems using a grid of squares:

- Unmixed system:** Shows complete segregation with a clear boundary between white and black squares.
- Mixed Ordered system:** Shows a perfect (ideal) mix with alternating black and white squares in a regular pattern.
- Mixed random system:** Shows a random mix with black and white squares distributed irregularly.

Labels in Urdu:

- Unmixed system: مکمل علیحدگی (Complete segregation)
- Mixed Ordered system: مثلاً مثلاً (Perfect (ideal) mix)
- Mixed random system: عشوائی (Random)

- **Ordered system:** particles are arranged in iterative rule (repetitive pattern) (not random)
- We can consider mixing as vector quantity (spatial orientation and translational velocity of the particles)

1- particles داخل mixer بالبنية الصلبة Vector معين XYZ ، عليها spatial orientation حدد برؤس محدد سرعة حصة .
2- داخل mixing لم يثبت water ، لتغيير velocity انطا ركان ، كيميكان بتغير

The scale of scrutiny:-

- It is the weight/volume of the dosage unit that dictates how closely the mix must be examined/analyzed to ensure it contains the correct dose/concentration.

weight: tablet - capsule - grams

Volume: sus-sol-elixir

- This weight/volume is known as **the scale of scrutiny** and it is the amount of material within which the quality of mixing is important.

* The scale of scrutiny

کم اسحب عینہ عثمان احسن و صلیتہ good mixing ؟

مثلاً عنى 5 kg من مواد حيوية عيار 500 (بس اوزن هاي الحبة الى عيارها 500) بطلع وزنها 1000/500 excipient
من ٦ تحير tablet

بسبب 100mg ، ما يمثل Dose وحدة ، كل استي داخل الحبة في احتمال يكون Dose ، بوز 100mg ، دبلال وبشوف هل غني الحيار 50
إذا طبع 300 بروج بحال Mixing و يا بزيد السرعة time . + إذا 11 ال Dose 5ml ببعث 5 ml وحيد

The mixing Process

- For example, if the unit dose of tablets is 200 mg (containing 100 mg active drug) then 200 mg sample from the mix needs to be analyzed.
- The number of particles in scale of scrutiny depends on sample weight, particle size and particle density.

quality of mixing 1) Scale of scrutiny 2) Particle number 3) $\bar{L}^2$

Size reduction $\uparrow$ particles number

Number of particles of a minor active constituent present in samples taken from a 1:1000 random powder mix with different numbers of particles in the scale of scrutiny

دو minor بين سيمية او active له total

```

graph TD
    Root["|:|000"]
    Root --> Left["active"]
    Root --> Right["total"]

```

Sample number	Number of particles in scale of scrutiny		
	1000	10 000	100 000
1	1	7	108
2	0	10	91
3	1	15	116
4	2	8	105
5	0	13	84
6	1	10	93
7	1	6	113
8	2	5	92
9	0	12	104
10	1	13	90
Mean	0.9	9.9	99.6
Standard deviation	0.78	3.38	11.18
% CV	86.86	34.17	11.23
Deviation from theoretical content	±100%	±50%	±16%

Range (0-2) (5-15) (20-110)
 راجح نسبته 10 أعينيات حمراء ، أول مرة 1:1000 إلى حوالي 1:10000
 1:1000 ، ويزوج أطولها بشخص 10:10000 نفعها 1:1000

تفاوت بین این دو عبارت در این است که polylog به معنی $\log^k$ است و $\log$ به معنی $\log$ است.

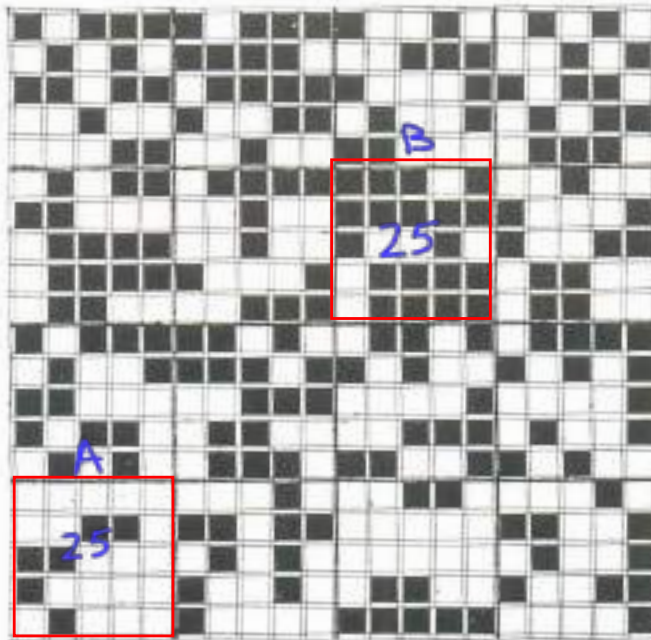
Vorteile: keine Wägen! Portals ↑ Leistung? Kosten? Wartung?

400 مربع

الابيض = الدوا

A نسبة الدوا على

B الدوا على



Theoretical percentage of white particles is 50 %

In the total 400 particles (20 * 20) the percentage of white is 51 % (= 102 % of theoretical)

If divided to 16 blocks of 25 particles (5 * 5) the percentage of white is 24-76 % (= 48 - 152 % of theoretical)

$$24\% \times 200 = 48$$

$$76\% \times 200 = 152 \text{ (over)}$$

اضافة الحينة A اعطيتي (drug 76%)

الحينة B اعطيتي (drug 24%)

$$48\% = 24\% \times 200 \quad \text{مختلر B بحين اكون ؟ مختلر}$$

$$152\% = 76\% \times 200$$

طريقة كمية الدوا على موزانة كميتر على

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The mixing Process

- Another factor to consider in mixing is the proportion of the active component in the dosage form/scale of scrutiny.



Ratio: 50 %

Total number = 400

Theoretical number of white particles = 200

200 expected

194 = A
202 = B
198 = C

A $194/200=97\%$ < 100%

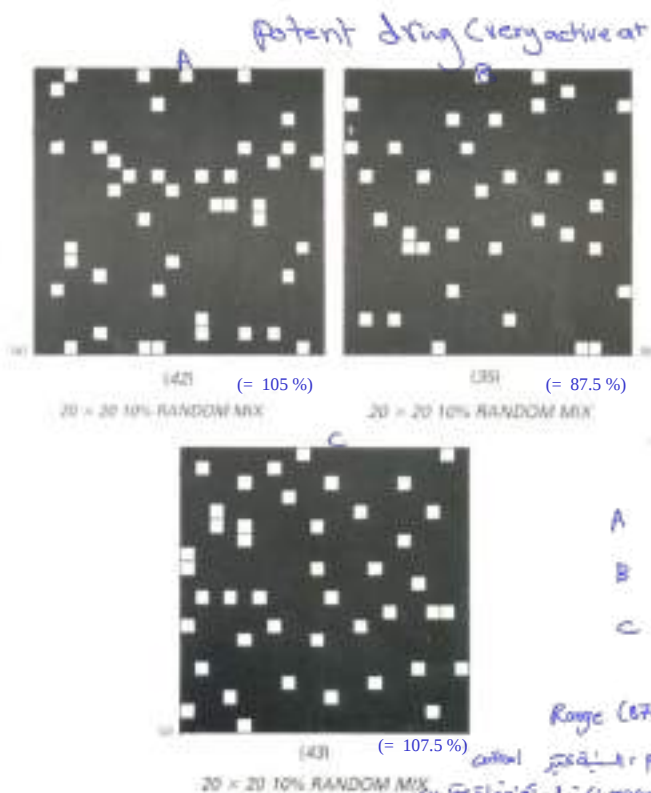
B $202/200=101\%$ > 100%

C $198/200=99\%$ < 100%

Range (97-101) يتنوع نوعاً ما
هذا يدل على أن Range
لأنه نسبة كبيرة من كمية (50%) عبارة عن drug

Fig. 10.2 Computer generated mixtures of nominal 50% active ingredients. The number of particles is not necessarily equal to the nominal 50% active ingredient concentration.

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Ratio: 10 %

Total number = 400

Theoretical number of white particles = 40

perfect color
يكون هو المطلوب

A $42/40=105\%$

B $35/40=87.5\%$

C $43/40=107.5\%$

النتيجة لا potent مفرطة التباين

Range (87.5% - 107.5%)

هذا يدل على mixing مع مناسب لـ potent drug (بمقدار كبير) critical
من الصعب أن potent تتحقق بطريقة صحيحة mixing أكثر من عملية متكررة

Fig. 10.3 Computer generated mixtures of nominal 10% active ingredients. The number of particles is not necessarily equal to the nominal 10% active ingredient concentration.

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الـ potent غالباً على CNS والفرصات ضئيلة جداً

إذا potent ما نرى على طريقة mixing لـ mixer لـ mixing time

نفسه لـ potent في نفس mixing ما نرى في mixing (step of granulation)

The mixing Process

➤ The variation in component percentage between different samples taken from a mixture increases:

1. as the amount (number of particles) in scale of scrutiny decreases.
2. as the proportion of a component in mixture decreases.

لما كان 50% كانت النسبة صحيحة ومقبولة (97-101)
 لما كان 10% نسبة الموازنة زاد CV، ازترى
 potent (87-105) خطر له

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The mixing Process

➤ This indicates that:

- the **lower the percentage of active ingredient (potent drug)** in mixture, the more difficult it is to achieve an acceptably low deviation in active content.

- The more particles are present in dose (scale of scrutiny) the lower the deviation of content → The number of particles can be increased by decreasing particle size (This can be done by **milling**).

ازترى عدد د particles، بالذات في الجرعة، كثر انه د active particles، قل د inactive particles
 mixing

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Mathematical treatment of mixing process

- There will be always some variation in the composition of samples taken from random mixtures.
- The aim during formulation and processing is to minimize this variation to acceptable levels by selecting appropriate:
 - ① – scale of scrutiny
 - ② – particle size
 - ③ – mixing procedure

time ↓
speed ↑
الساعة >

acceptable random mixing = powder

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Mathematical treatment of mixing process

- For random mix, if we consider that particles are all of same size, shape and density then:

Proportion of drug in total mix $SD = \sqrt{\frac{p(1-p)}{n}}$ p: proportion of the drug
drug = component

- P is the proportion of a component in total mix
- As p increases, %CV decrease

Example:

n = 100 000, p = 0.5 ⇒ SD = 1.58×10^{-3} , %CV = 0.32%

n = 100 000, p = 0.001 ⇒ SD = 9.99×10^{-5} , %CV = 10 %

- The scale of scrutiny can be increased by increasing the amount of additives in the mixture but this will lead to a decrease in p.

دراماتيكي الميزان
الهيئة بالي الزيد

الـ Excipient = مادة غير فعالة
مادة غير فعالة
مادة غير فعالة

(↓ proportion ↑ CV) point

لا proportion ↑ CV

المزيج المستقر
الـ potent = مادة فعالة

Evaluation of degree of mixing

Needs for monitoring of mixing:

- To follow a mixing process:
 - To indicate the degree of mixing
 - To indicate when sufficient mixing has occurred and determine the suitable mixing time
- To assess the efficiency of a mixer

Sampling

- ① Scoop sampling
- ② Thief sampling

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Unit dose thief sampler

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Unit dose thief sampler is used for sampling from a container. It is a long, thin, and slightly curved tube with a red handle. The sampler is inserted into the container, and the sample is collected in the tube. The sampler is then removed from the container, and the sample is analyzed.

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Evaluation of degree of mixing

Mixing Index (M)

$$M = \frac{S_R}{S_{ACT}} \quad \text{acceptable random mixing}$$

S_R : Content standard deviation of random mixture

S_{ACT} : Content standard deviation of mixture under investigation. $\rightarrow$ كل مرة بين منية يكون على Certainty $\rightarrow$ ACT

- In some cases, it is possible to achieve an acceptable variation in content before obtaining a random mix

إذا كان في particles كل نفس size وال Flow كمية
عقول يتناسب مع بعضها بعضا لا acceptable مثل ال good-mixing

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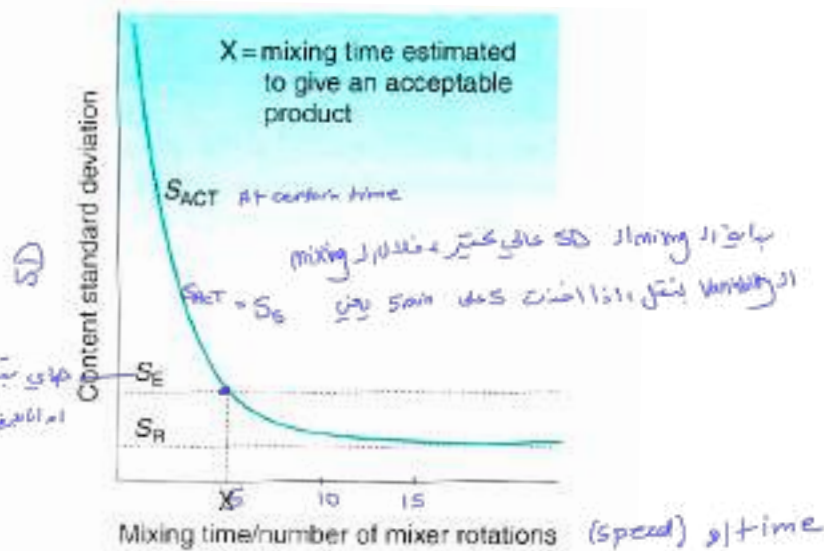


Fig. 12.4 The reduction in mixing time possible if a random mix is not required. S_{ACT} represents the content standard deviation of samples taken from the mix, S_E the estimated acceptable standard deviation and S_R the standard deviation expected from a random mix.

بدي او مقلما

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SD بال powder مازال يوجد للجزر

Mechanisms of mixing

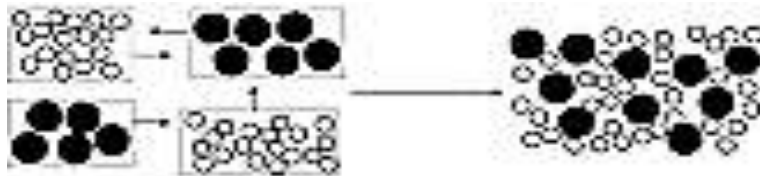
Powders

There are three main mechanisms for powder mixing:

- a) **Convection** (the transfer of large amount of particles from one part of the powder bed to another).

This may occur when a mixer blade or paddle moves through the mix.

This mechanism contributes mainly to macroscopic mixing of powders, but mixing does not occur within the group of particles moving together.



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Mechanisms of mixing

Powders

- b) **Shear** (Layer of powder flows over another layer)

This may occur when some of the material is removed (e.g. by convective mixing) causing powder bed to collapse.



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powder bed: continuous

layers

Mechanisms of mixing

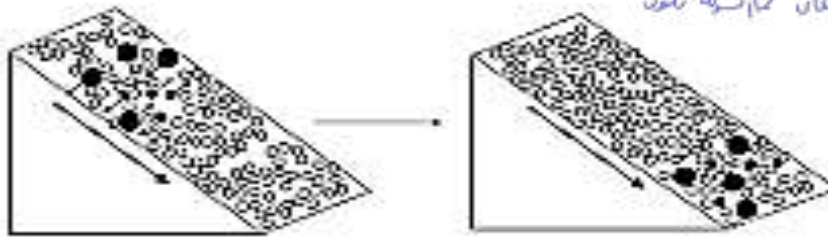
Powders

c) Diffusion (mixing of individual particles)

This mechanism is necessary to form true random mixture.

When a powder bed is forced to move or flow it will dilate (the particles become less tightly packed and the voids between them increase).

This allows particles to fall under gravity through the voids created.



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Mechanisms of mixing

Liquids

a) Bulk transport

- The movement of a large portion of the material being mixed from one position in the system to another.



b) Turbulent mixing

- The haphazard movement of molecules when forced to move in turbulent manner, which means random fluctuation of the fluid speed and movement direction, so that the fluid has different instantaneous velocities at different locations at the same time.



السرعة لكل
بالذات

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parallel surfaces & بصير في eddies بتدوروا مع بعض
ويعطوا الف واحد

Mechanisms of mixing

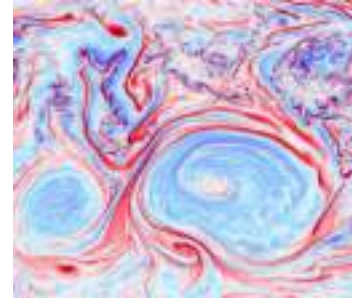
Liquids

b) Turbulent mixing

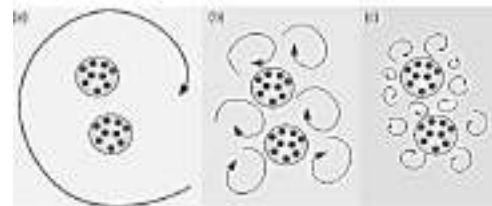
- It can be seen as a composite of different eddies (small portions of fluid moving as a unit) of various sizes.

The large ones tend to break into smaller and smaller sizes until they are no longer distinguishable. → 

- Turbulence is a highly effective mechanism for mixing.



افضل پکتر من Bulk Transport



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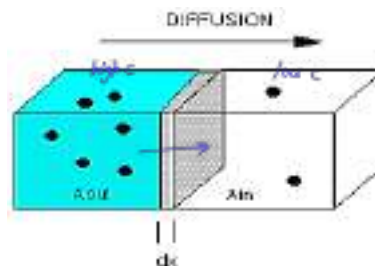
Mechanisms of mixing

Liquids

c) Molecular diffusion

- The molecular diffusion is the primary mechanism responsible for mixing at the molecular level.

- This mechanism produces well mixed liquids if there is sufficient time. *Bulk transport is slow*
- Considerable time is needed if this is the only mixing mechanism. *لا يحدث خلط جيد في البداية*



Driving force: Concentration gradient

diffusion membrane: مایه مذکوبه
 molecular diffusion: نفوذ مولکولی
 concentration: غلظت
 driving force: نیرو محرکه

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Segregation: movement of particles after mixing

Powder segregation (demixing)

- Segregation is the opposite effect to mixing, i.e. components tend to separate out (S_{ACT} increases).
- It may cause a random mixture to change to non-random or may be responsible that a random mixture never occurs.
- Segregation is more likely to occur if powder bed is subjected to vibration and when the particles have greater flowability.



Flow: تدفق
Cup: كوب
Tablet: قرص
Mixing: مزج
Vibration: اهتزاز
Segregation: فصل
Spherical: كروي

Scaling up: التوسع
Lab scale: مقياس المختبر
Scale: مقياس

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Segregation can be due to difference in :

- Particle charge
- Particle density
- Particle shape
- Particle size and size distribution

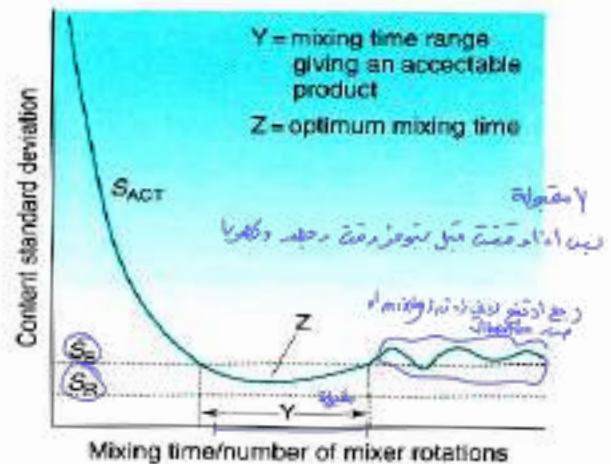


Fig. 12.5 Possible effect of extended mixing time on the content standard deviation of samples taken from a mix prone to segregation. S_{ACT} represents the content standard deviation of samples taken from the mix. S_e the estimated acceptable standard deviation and S_R the standard deviation expected from a random mix.

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Powder segregation (demixing)

Factors affecting segregation:

1. Particle size large-small-moderate

Percolation segregation

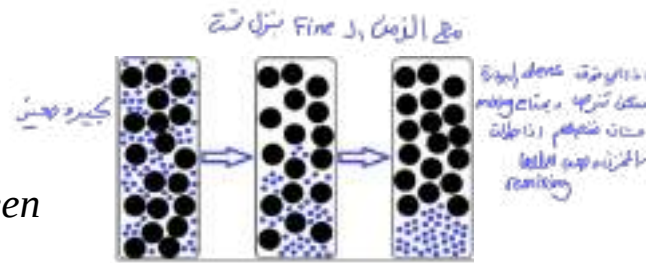
(small particles tend to fall through voids between large particles)

Trajectory segregation

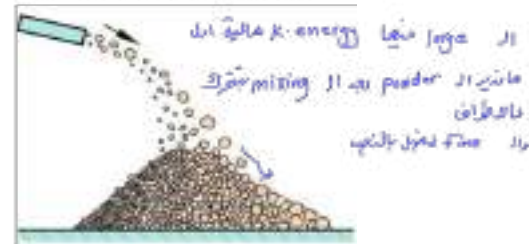
(large particles tend to have greater kinetic energy)

Elutriation segregation (dusting out)

(Air-blown small particles sediment and form a layer over coarse particles)

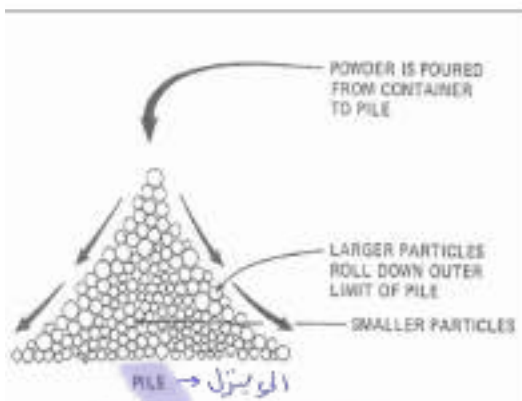


Percolation segregation:

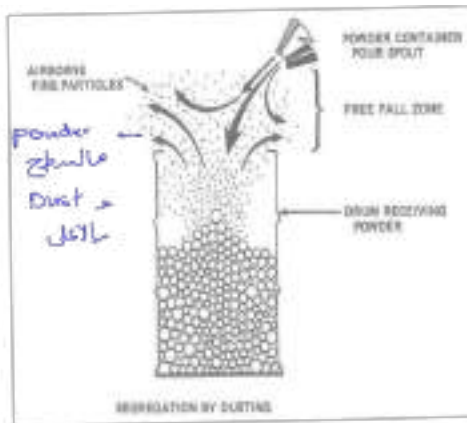


Trajectory segregation

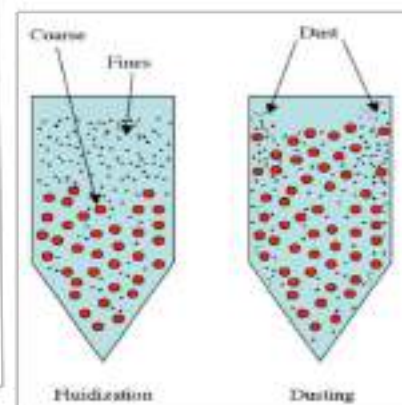
29



Trajectory segregation



(Elutriation)



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Powder segregation (demixing)

Factors affecting segregation:

$$D = \frac{\text{mass}}{\text{volume}}$$

2. Particle density light — heavy

Segregation occurs due to density differences.

لديهم لما اعمل milling اعمل one size عنان له volume
لعمل مثابة عالي يختلف الـ mass داخل حد الـ volume

3. Particle shape

Spherical particles are easier to be mixed but also to segregate than irregular or needle shaped particles.

الاجل spherical لانه ممتاز للكمس بين الحبيبات الـ mixing
رغم segregation من بداية الـ mixing

من حبيبات الـ shape ؟ crystallization

Approaches to solve the problem of segregation

1. Selection of particular size fractions to achieve drug and excipients of the same particle size range.

اعمل الـ size fraction (1)
 اعمل الـ size fraction (2) granulation

2. Milling of the components so that their size becomes small and same.

استعمل solvent
سرعة التبريد
مركبات مختلفة

3. Controlled crystallization during production of drug or excipient to give particles of particular size or shape.

4. Selection of excipients which have similar density to the drug.

اختار excipient الـ density متساوية لـ drug الـ density

Approaches to solve the problem of segregation

- size • 5. Granulation of powder mixture.
- 6. Reduce the extent to which the powder mass is subjected to vibration or movement after mixing. ارتداد movement رال
Vibration
- 7. Using equipments where several processes can be carried out without transferring the mix. نستخدم اجهزة يمكن العمل على عدة خطوات
بدون نقل من جهاز الى جهاز
(two in one - three in one)
- 8. Production of an ordered mix.

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Case (عليه اشكاه تنصيب مشكلة ويحلها)

① إذا المشكلة size يايجل milling يصغر ويختار كله نفس size أو يمشيرون طريقه Granulation

② Density (أنداء) صبه Density و drug تختار Density أو excipient

③ Shape يتحكم بالبرصة التي بتعدلي أو shape الوهر أو compaction يتحكم بالشكل أو العنبريد أو solvent

④ إذا في movement يمشي، وروح الى نفس movement. استنتجته براني انفس ال compaction أو العنبريد لأحداً للتأكلية الغير استمر العنبريد / aggrigate -

⑤ natural part

Ordered mixing

- It is termed also **adhesive** or **interactive** mixing.
- In this case, very small particles may become adsorbed onto the active sites of large particles.

اسماء, ordered mixing

- This minimizes the segregation between small (adsorbed) particles and large (carrier) particles.

a small (adsorbed) particles and

- Ordered mixing is most likely to occur when the adsorbed particles are very small so that the adsorption force is higher than the gravitational force trying to separate the components.

→ بعد حبس في ارضه 1 potent drug بطريقة متعارة لكي لا يخطا بال Dose بال متعارة 6 dry powder inhaler (sterin) - منها انش
لايسن excipient - انش processes 1 dry powder inhaler 1 Drug 6 Polysaccharide (safe carrier)

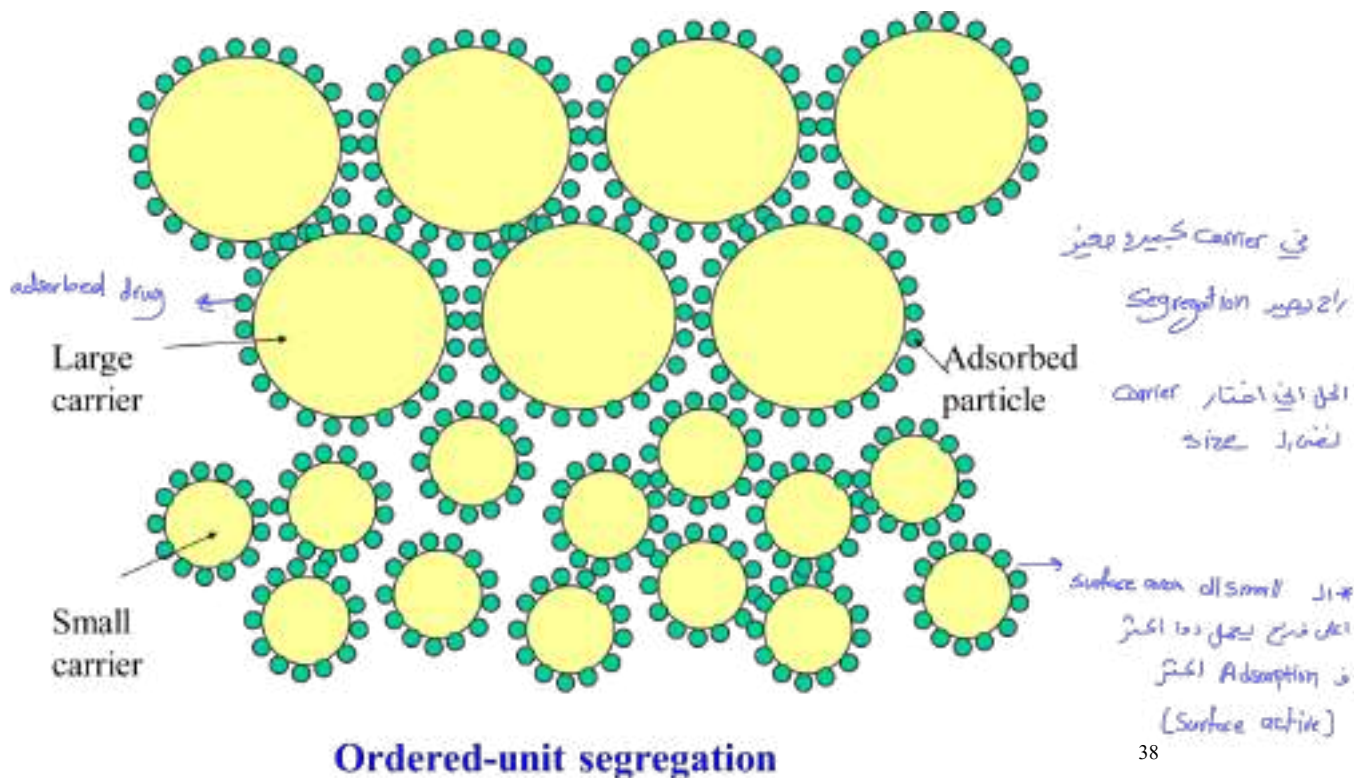
Segregation in ordered mixes

Ordered unit segregation

احترق Carrier كبيره في راج كبيره Segregation زكاد particle اذية

- The carrier particles vary in size. →
الى لحداد drug
- In this case segregation occurs within the carrier particles according to size.
- The small particles have higher specific surface area than the large and so higher content of adsorbed material.
راج يكون في احتلاله بكمية ادا الحرجية

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Segregation in ordered mixes

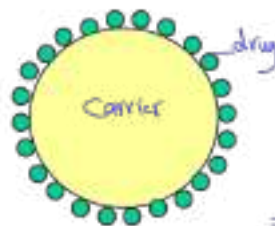
استر يزلج اش

Displacement segregation

- There is competition for the active sites on the carrier.
- This occurs when a component is added to an ordered mixture that competes with the adsorbed material for the site on the carrier and displaces it

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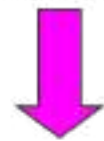
ordered mix



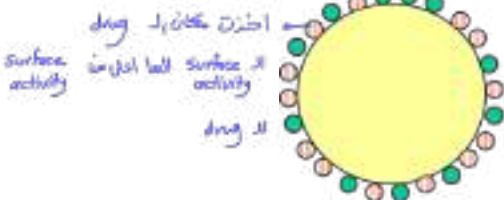
Competing particle

Adsorbed particle

Carrier



large



Segregation due to size difference due to displacement

largesize + small drug

Displacement segregation

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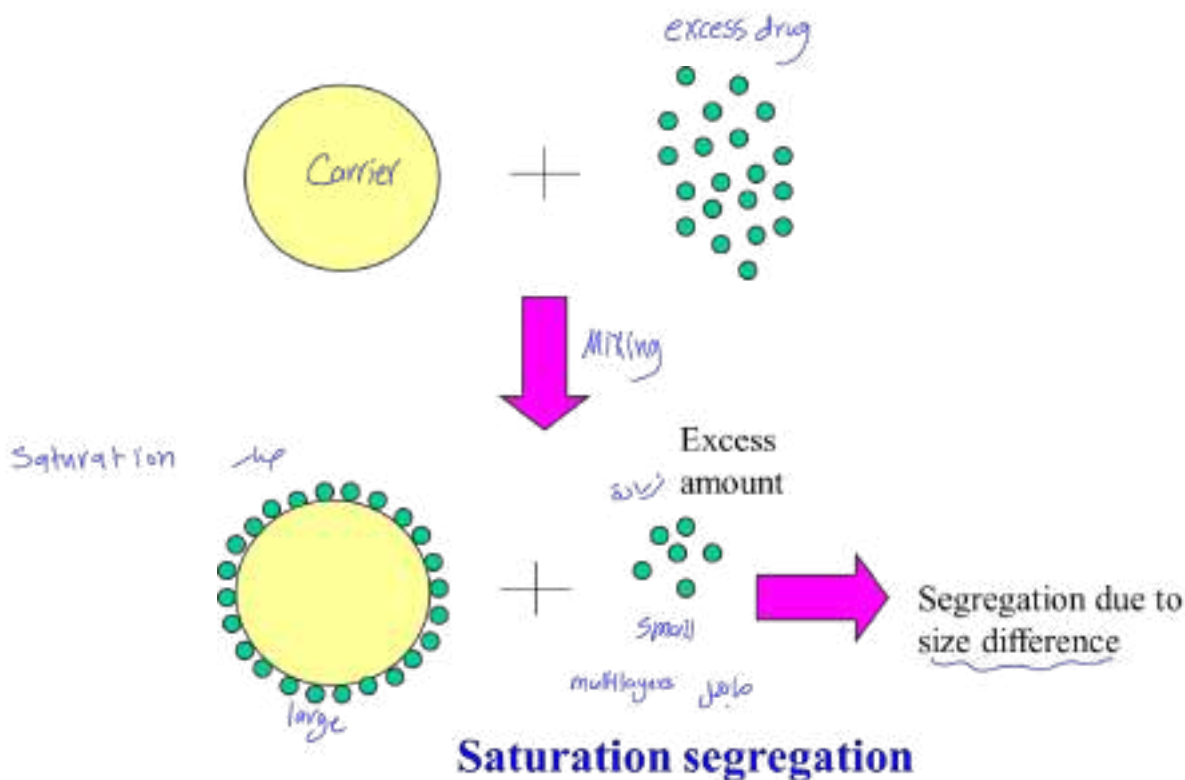
Segregation in ordered mixes

Saturation segregation

drug
Carrier

- There are insufficient carrier particles
- If the added amount of small-sized material is higher than the capacity of the carrier particles then the excess amount will be free (not adsorbed) and it segregate due to size difference.

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Practical considerations in Powder mixing

مختبري 3 مواد
A - B - C

إذا كان الدواء هو A
فإننا نبدأ بـ A
ثم نضيف B
ثم نضيف C
وهذا هو الخلط المتتالي
الذي يضمن توزيعاً متساوياً
للمكونات في الخليط النهائي

When mixing formulations where the proportion of active drug is low, a more even distribution may be obtained by building up the amount of material in the mixture sequentially (geometric dilution).

توزيع متساو للمكونات
بالتسوية

The volume of powder mixture in the mixer should be appropriate. Both overfilling and underfilling may reduce mixing efficiency.

الكمية المناسبة للمزج
overfilling, underfilling

The mixer should produce the mixing mechanism appropriate for the formulation:

- Potent drugs: diffusion is necessary
- Cohesive material: shear mixing

Solid: convection - shearing - particle diffusion
Liquid: Bulk movement - hyerling - molecular diffusion

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Practical considerations in Powder mixing

1. In order to determine suitable mixing time, the mixing process should be checked by removing and analyzing representative samples after different mixing intervals.

مختبري 3 مواد
A - B - C
Geometric mixing
mixing time
SP, near

2. Static charges may be generated during mixing that result in reduction in diffusive mixing.

charge
powder
Moisture
static charge

3. This is enhanced by low humidity in atmosphere. The mixer should be suitably earthed to dissipate the static charge.

الجهاز يكون مربوط بالأرض لتفريغ الشحنات الكهربية

4. Vibrations may cause segregation in normal mixes and dislodging of adsorbed particles in ordered mixes.

vibration
dislodging
particles
carrier
drug

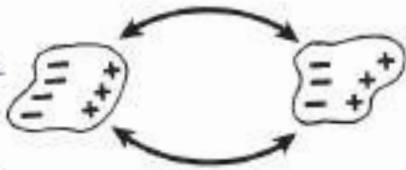
44



التيه (charge) متساوية

NEUTRAL PARTICLE (electrical charge evenly distributed over particle)

high surface energy (مرفوعة)

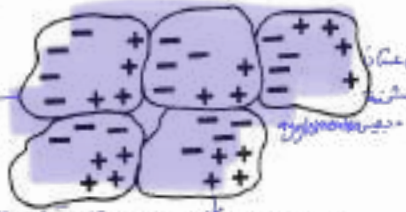


Condition dry processing

PROCESSING AND/OR DRY PARTICLE MOVEMENT CAUSES POLARIZATION OF FINE PARTICLES (static electric forces)

سبب الـ processing او الـ dry condition الـ fine particles تتكون شحنات

agglomeration
عشان يعادل الـ charge



particle (polarization) متساوية

POLARIZATION CAUSES AGGLOMERATION OF FINE PARTICLES (electrical charges induced by one particle on another van der Waals forces)

عند الـ particle (polarization) متساوية الـ energy يعطي الشحنات المتماثلة ويجذبها

Figure 22 Effect of electrical forces on fine particles.

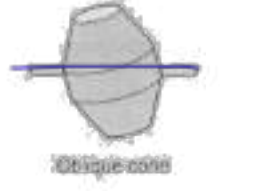
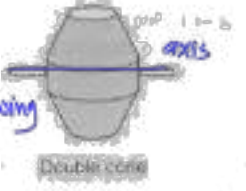
لـ small particle و لـ large particle سبب static charge

Powder mixing equipment

① Tumbling mixers

Convection: Bulk movement from left to the right / Top. bottom

- Mixing containers are mounted so that they can rotate about an axis.
- Commonly used for mixing of free flowing powders and are not suitable for cohesive powders.
- Commonly used for mixing granules with lubricant, glidant and external disintegrant.



oblique الـ axis
الـ axis
الـ axis

الـ axis
الـ axis
الـ axis

cohesive
الـ axis
الـ axis

الـ axis
الـ axis

الـ axis
الـ axis

الـ axis
الـ axis

الـ axis
الـ axis

عشوائية ①

agitation bar ②

③ يكون في مال mixer baffles على ذلك نالسا نعلي

Oblique ①

نعلي ان particles تختلج ببعض

regular movement

وسرع انه يختلج ببعضها وتغير الحركة

بالم Randomness

ان powder تختلج فيها ويرجع فبالتغير الحركة randomness

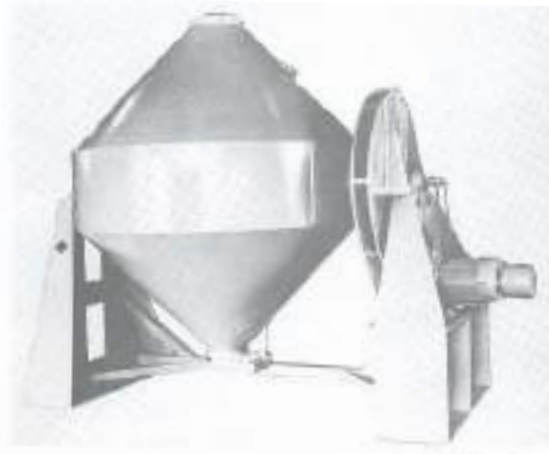


Figure 16. "Twist-and-breaker." (Courtesy of Peterson-Keller Company, Division of H&MCO Corporation, 3440 Stoneleigh, Minneapolis.)



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Figure 18. "Star" oblique-type mixer. (Courtesy: Goss Jersey.)



Figure 19. "V-shaped" blender with agitator mixing assembly. (Courtesy: Goss, Middletown, New Jersey.)

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Powder mixing equipment

Tumbling mixers

- The shear mechanism occurs because of velocity gradient produced while diffusion occur through voids produced during powder flow.
- The addition of prongs, baffles or rotating bars helps convective mixing.
- Care about segregation is necessary.

بسرعة بار
baffles

أجزاء من ميسر diffusion
لما تتحرك الحبيبات فتحدث
مقاومة بالاحتكاك بين الحبيبات
التي تنتج دوائر في جدار particles
تبدأها مع دوائر
على السطح ما تستمر
بالحركة بتدويرها في اتجاه

يحدث Segregation



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Fore Segregation
↓
المقاومة
↓
تبدأها مع دوائر

كيف ازبداد shear mixing ؟

بال different velocity / تغير الاتجاه / انا liquid تغير edies
اي استي راجع Velocity gradient randomness في حركة الحبيبات

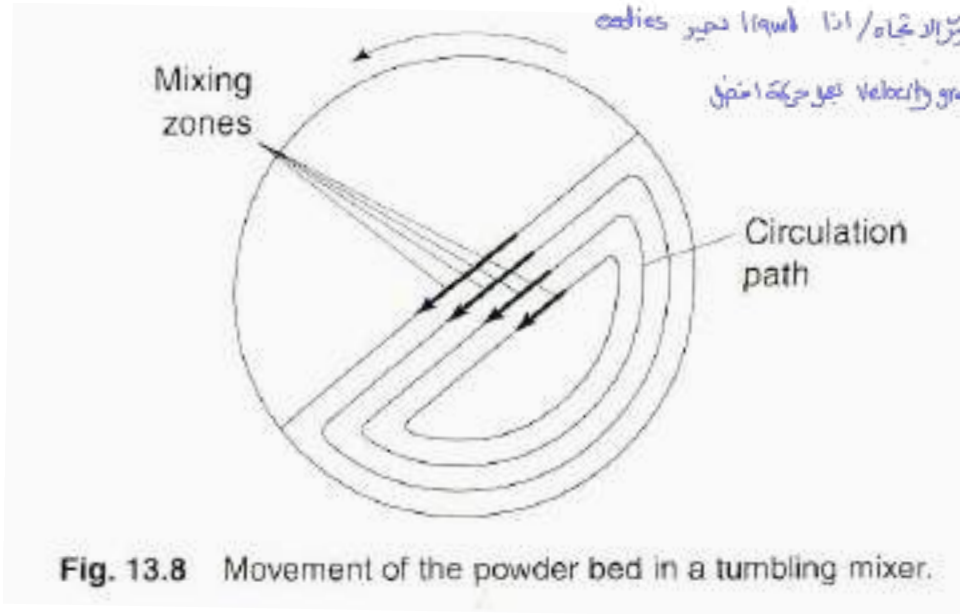


Fig. 13.8 Movement of the powder bed in a tumbling mixer.

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Powder mixing equipment

Tumbling mixers

- Capacity ranges from 50 g to 100 kg.
- The material typically occupies 1/2 to 2/3 of the mixer volume.
- The mixing efficiency depends on speed of rotation. Speed of rotation should be suitable:
 - Very high speed will cause the powder to be held on the mixer walls by centrifugal force.
 - Very low speed will generate insufficient bed expansion and little shear mixing.

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Table 9 Effect of Powder Fill on Blending Time of Double-Cone Blenders^a

Volume percent of blender filled with powder charge	Approximate blend time (minutes) in production-size blenders
50	10
65	14
70	18
75	24
80 ^b	40 ^b

^aBlending done in double-cone blenders and times measured to obtain comparable blends.

^bUniform blend not attainable with this fill level.

Source: Sweitzer, G. R., Blending and Drying Efficiency Double Cone vs. V-Shape, GEMCO, Newark, New Jersey.

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Powder mixing equipment

معدات غير عن الـ tumbler العادية

Tumbling mixers

①
Convection tumbling
②
processing
تخلطها

- **Intermediate bulk containers (IBCs)** are containers used both as mixing bowl and to either feed the hopper of a tablet or capsule machine or as the hopper itself.

توصلها على ماكينة ثانية

تلف حوالي
up
down

- **The Turbula shaker mixer (WAB, Switzerland)** is a more sophisticated form of tumbling mixer that uses inversional motion in addition to the rotational motion leading to more efficient mixing.

الميزة انها فيها حركتين من بس Convection (up-down) / فيها rotation كان

Inversion (up-down)

(inversion)
كل رتي فوق كانوا بس up-down

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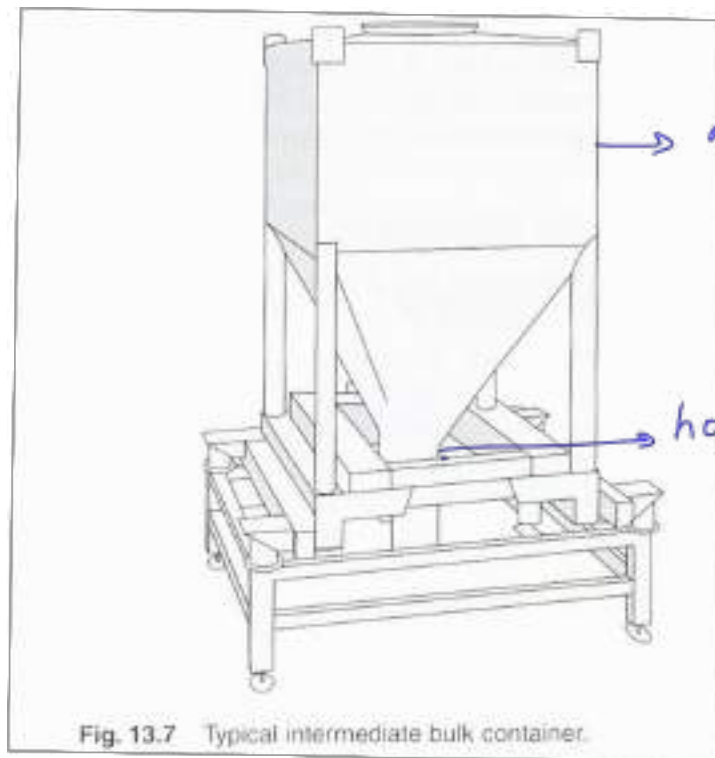


Fig. 13.7 Typical intermediate bulk container.

①
لعمل فيه mixing

②
hopper - hover (مستوية)
يكن
ما - بركبه على ماكينة الثانية
لعمل فيه mixing (للعبئة)

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Powder mixing equipment

High speed mixer granulators

- They are used both for mixing and granulation. ① اولاً ② لاحقاً two in one
- It contains centrally mounted impeller blade that rotate at high speed throwing the material towards the mixing bowl.

- The side-mounted chopper blade helps in granulation.
- Care if material fractures easily. → إذا قابلية للتكسر

- Not normally used for blending lubricants. →

استخدم high speed إذا powder رطوبته زي كمانى ما عذرة granulation
 احسن lubricant أو Stearate بدل Flow احسن بين مشكلة
 إذا overmixing. فلي ال powder يحير hydrophobic دار solubility بتقل

55

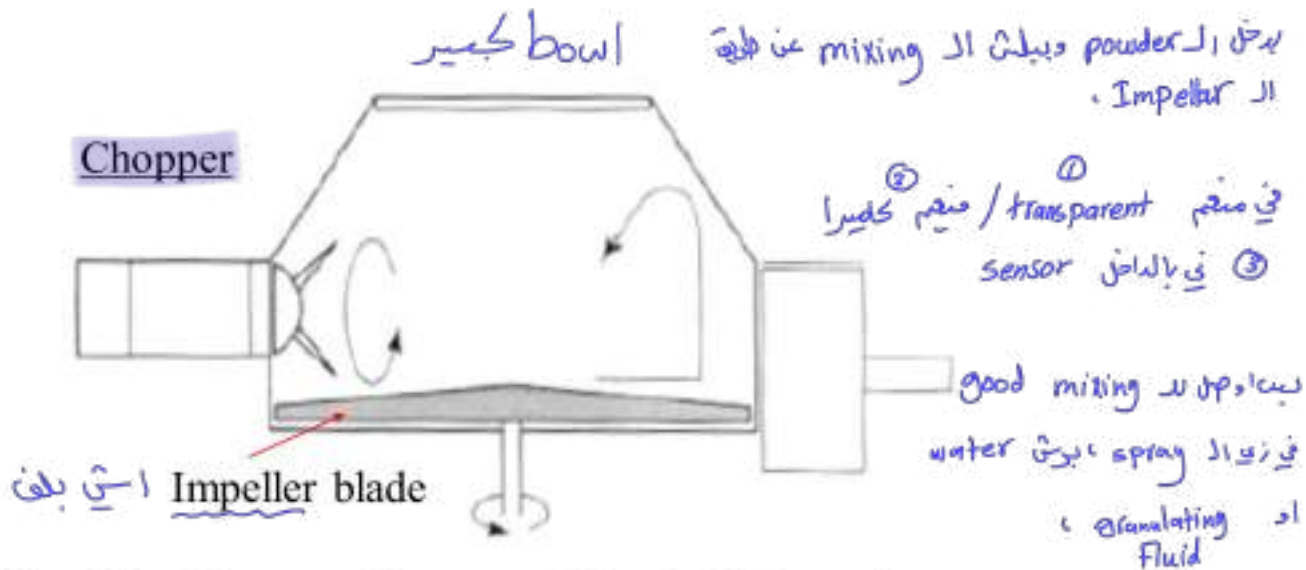


Fig. 13.9 Diagrammatic representation of a high-speed mixer-granulator.

الخطوات

- ① mixing
- ② spraying
- ③ chopping
- ④ drying

والجهاز ببلت ليحير ويحل wet mass
 ال sensor اذا مكانه وصل ال texture
 المناسب من الجنية وصارت متساكة ، ببلت يفتخل
 الجهاز كى chopper بقطعا Small granules
 ليحير ليحل drying ال granules

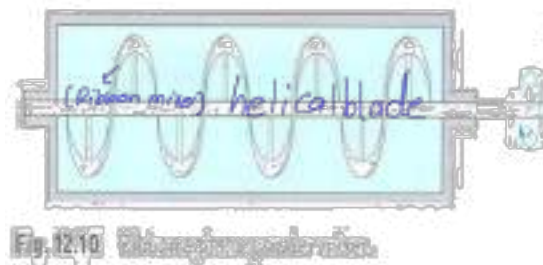
Powder mixing equipment

Agitator mixers

- These types of mixers depend on the motion of a blade or paddle though the product, and hence the main mixing mechanism is convection.

- There are three main designs of agitator mixers:

- Ribbon mixer
- Planetary (Orbital) mixer
- Nautamixer



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Powder mixing equipment

Ribbon mixers

- Mixing is achieved by the rotation of helical blades in a cylindrical tank.

Advantages

- Suitable for mixing of poorly flowing materials.
- Segregation is less likely to occur than in tumbling mixer

Disadvantages

- Dead spots are difficult to eliminate.
- The shearing action caused by movement of the blades may be insufficient to break up drug aggregates.

الافضل المفضل يكون في استدارة صحن
زاوية الزاوية (Dead spot) مانع من الخلط
فقدان التفتيح وبقايا Contamination

الافضل المفضل يكون في استدارة صحن
زاوية الزاوية (Dead spot) مانع من الخلط
فقدان التفتيح وبقايا Contamination

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إذا المادة lumpy متكتلة لازم افطارها في سائجة اصنعت

Powder mixing equipment

planetary mixers

- The rotational path of paddle is similar to that of a planet.
- It is used:
 - for mixing powders and semisolids
 - Wet massing (granulation) (Kneader)



Fig. 12.11 Planetary mixer for powders and semi-solids.

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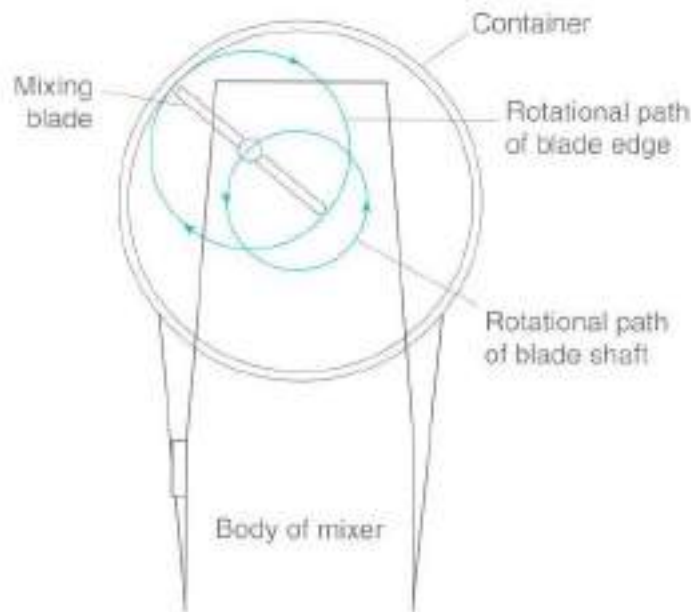


Fig. 12.12 Planetary mixer – top view showing path of paddle.

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Powder mixing equipment

Nautamixer

- It consists of a conical vessel that contains inside a helical conveyor that conveys the material up to near the top where it cascades back into the mass.
- This mixer combines convective, shear and diffusion mixing

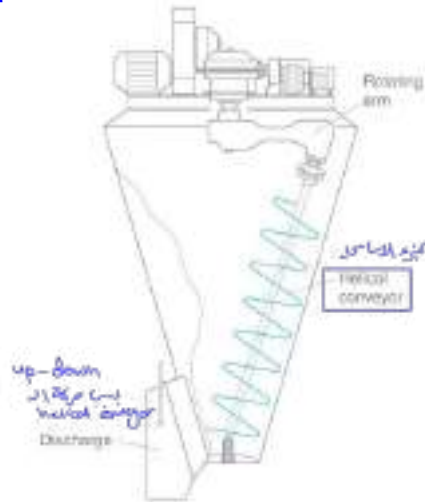
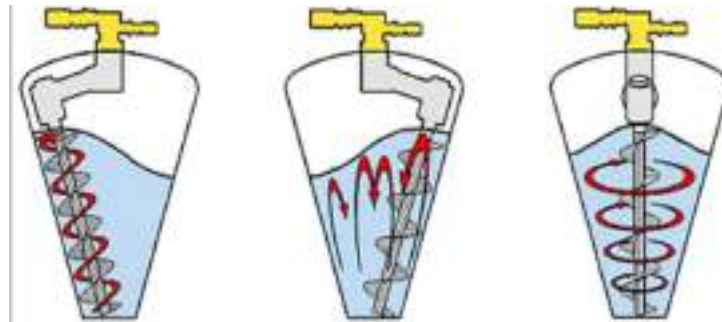


Fig. 12.13 Nautamixer (courtesy of Nautamixer Ltd.)



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Nautamixer



62

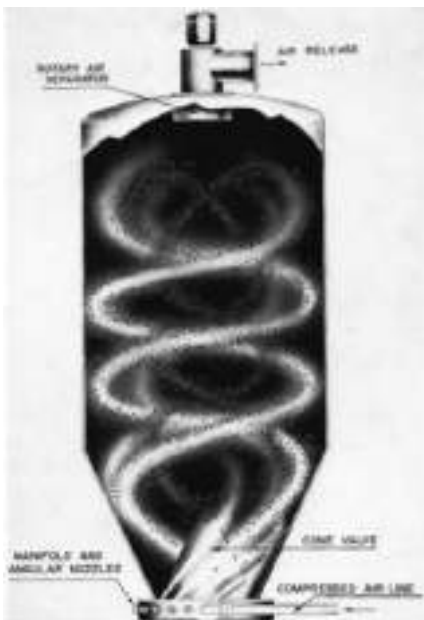
Powder mixing equipment

Fluidized bed mixers

- The fluidized bed equipment is used mainly in:
 - Drying
 - Granulation
 - Coating
- However it can be used for mixing of powders before granulation.
- Blown air fluidized and mixes the powder.
- Fluidization is very efficient mixing process.
- Diffusion of particles occur.

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Fluidized bed mixers



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Powder mixing equipment

Continuous mixers

Continuous Feeding
Continuous discharge

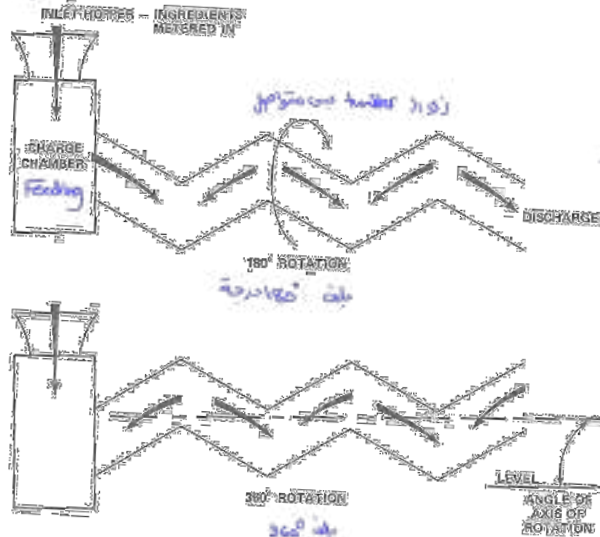


Figure 11 Schematic of "Zig Zag" continuous mixer. Courtesy of Farnsworth-Kelly Company, Division of Harsco Corporation, East Stroudsburg, Pennsylvania.



Figure 12 The "Zig Zag" continuous mixer. Courtesy of Farnsworth-Kelly Company, Division of Harsco Corporation, East Stroudsburg, Pennsylvania.

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Scale-up of powder mixing

المختلطة باليد اسمها lab scale و pilot scale mixer

مختلطة المصنع اسمها production scale و المختلطة المختبر اسمها lab scale و المختلطة المختبر اسمها pilot scale

- The extent of mixing achieved at a small laboratory scale during development work may not necessarily be mirrored when the same formulation is mixed at a full production scale, even if the same mixer design is used for both.
- Often, mixing efficiency and the extent of mixing is improved on scale-up owing to increased shear forces.
- This is likely to be beneficial in most cases, although when blending lubricants care is needed to avoid overlubrication.

معظم المختلطة المختبر اسمها lab scale و المختلطة المختبر اسمها pilot scale و المختلطة المختبر اسمها production scale

المختلطة المختبر اسمها lab scale و المختلطة المختبر اسمها pilot scale و المختلطة المختبر اسمها production scale

المختلطة المختبر اسمها lab scale و المختلطة المختبر اسمها pilot scale و المختلطة المختبر اسمها production scale

المختلطة المختبر اسمها lab scale و المختلطة المختبر اسمها pilot scale و المختلطة المختبر اسمها production scale

large scale = production scale

Scale-up of powder mixing

- The optimum mixing time and conditions should therefore be established and validated at a production scale, so that the appropriate degree of mixing is obtained without segregation, overlubrication or damage to component particles.

- Minimum and maximum mixing times** that give a satisfactory product should be determined if appropriate, so that the 'robustness' of the mixing process is established.

إذا دققت عند **minimum** ببطيء **acceptable**
maximum بجهلك احسن **mixing**
 درجة لهم بزيادة SD

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Types of mixers used for (liquids and suspensions) كوسيلة لـ Flow

Propeller (Impeller) mixers

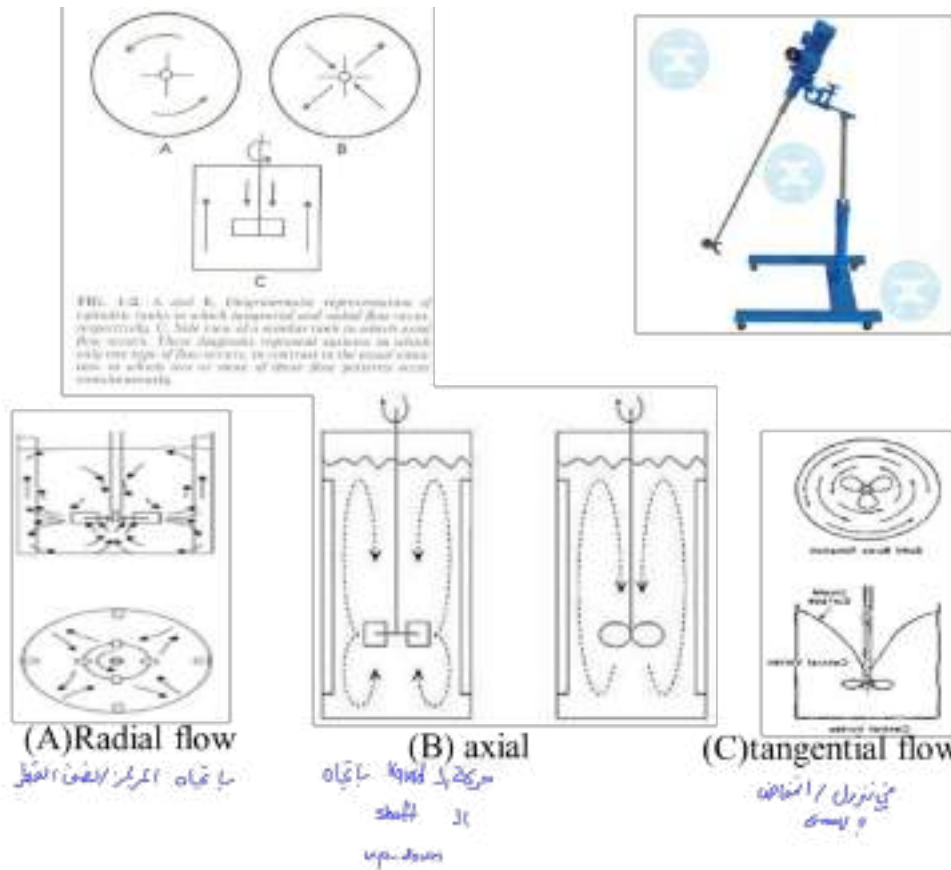
- Three basic types of flow may be produced: radial, axial and tangential.
- Angled** blades cause fluid to circulate in both an axial and a radial direction.

- The ratio of the diameter of propeller to that of the vessel is 1:10 - 1:20 and it typically rotates at speeds of 1 - 20 rps.

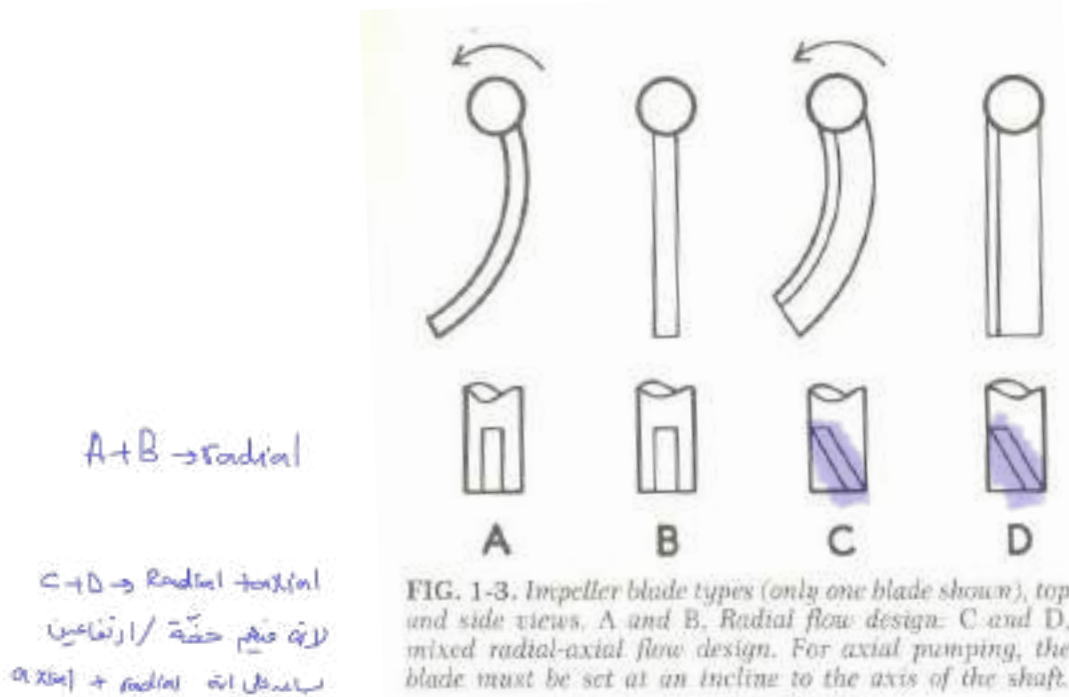
في turbine مختلف من propeller انه قاعدة دعليك blades
 Impeller Impeller

68

في helical



69



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Types of mixers used for liquids and suspensions

Propeller (Impeller) mixers

- A vortex forms when the centrifugal force imparted to the liquid by the propeller blades causes it to back up around the sides of vessel and create a depression at the shaft.

→ لما ينفش المحرك في مخرج لوراب
يغير تدرج الضغط وارتفاع السائل
↓
Depression



Depression

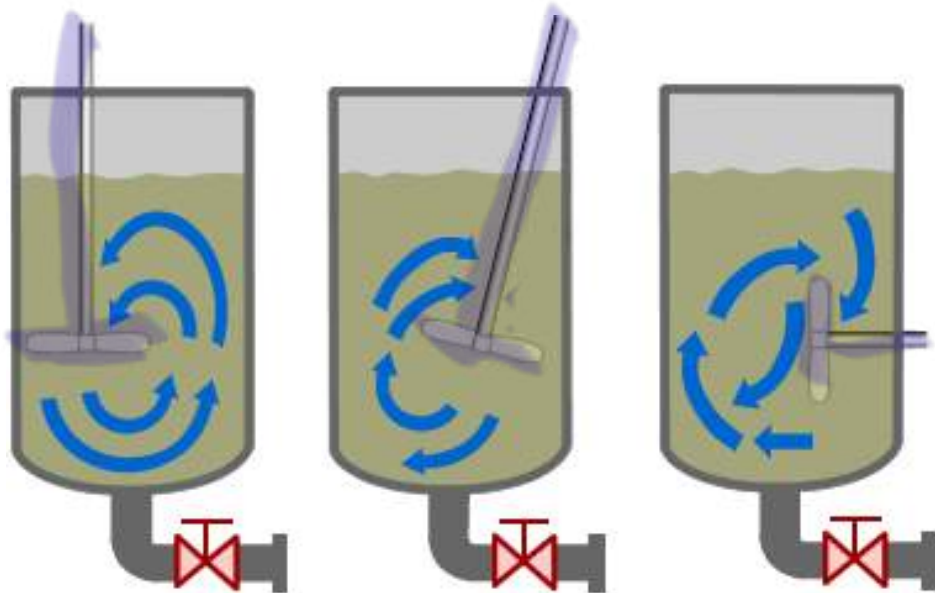
- An off-center mounting of propeller and vertical baffles discourage the formation of vortex.
- Propellers are more efficient when they run at high speed in liquids with low viscosity.

• جهاز الدفع الدوار
Propeller
ماتكون بالنهاية

مواضع الدوار (Chamber)
بغير الدوار في وسط ميعا وارتفاع الضغط
مطلوب

↓
Speed عالية مكان ما يفسر Vortex
↓
Viscosity

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Pumping, من الدوار

لجهاز الدوار 1 Propeller

بالنهاية، ما لازم تكون يمكن ال Pumping

72

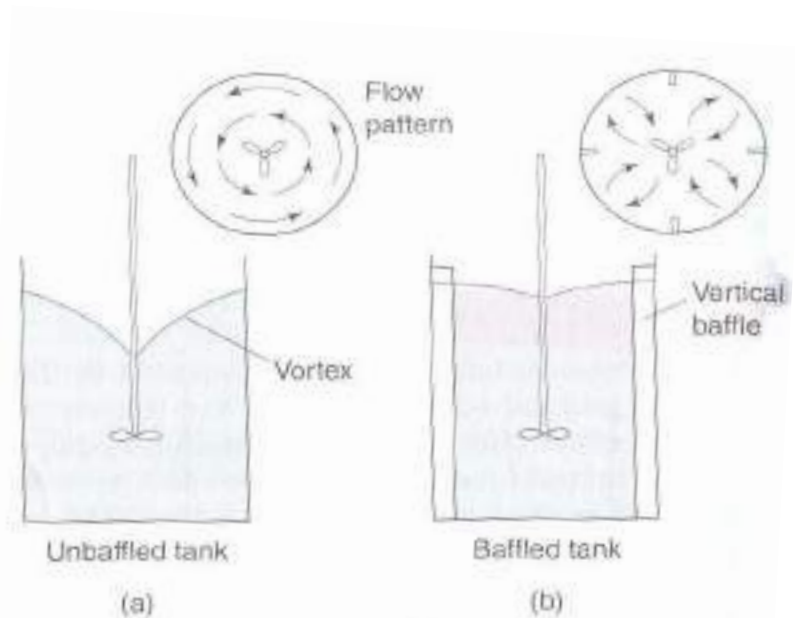


Fig. 13.13 Propeller mixer with (a) un baffled tank and (b) baffled tank.

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Types of mixers used for liquids and suspensions

Paddle mixers مراة جاتة Gate - anchor

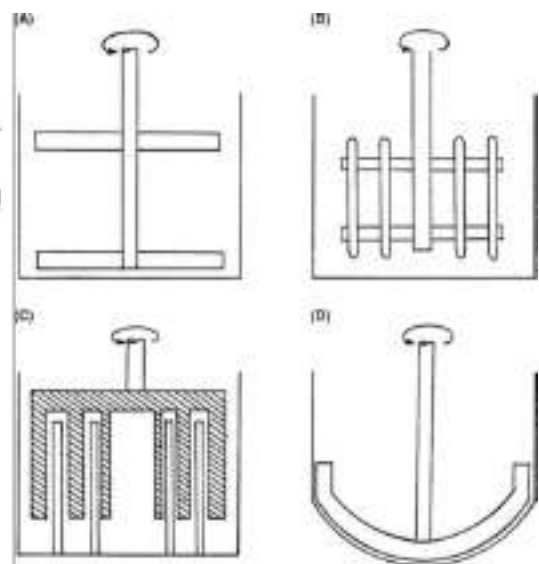
- The mixing element is large in relation to the vessel and rotates at low speeds (10–100 rpm).

high viscosity
+ low speed
ال Propeller (الحسن)

Paddle mixers

كبير المراة
turbine
propeller

مراة جزء كبير من الحاوية / ان شرايف



شكلازي مراة السنية

Types of mixers used for liquids and suspensions

Turbine mixers

- Turbine mixers may be used for more viscous liquids than those mixed by propeller.
- The impeller has four flat blades surrounded by perforated inner and outer diffuser ring.
- The rotating impeller draws the liquid into the mixer head and forces the liquids through the perforations
- They can produce stable emulsions.

المكان المناسب
في shear العالي

high viscosity
high shear

75

high viscosity

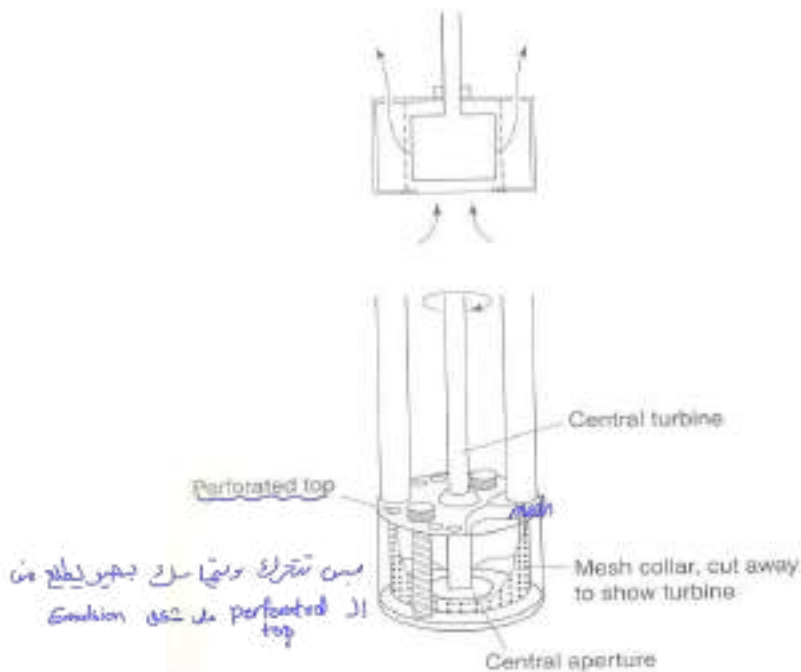


Fig. 13.14 Turbine mixer.

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Types of mixers used for liquids and suspensions

Air jet mixers *high speed with pressurized air*

- These mixers utilize jets of air or some other gases. $N_2 - CO_2$
- The liquid must be of low viscosity, **non-foaming**, unreactive with the gas employed and reasonably nonvolatile.

الغازات المستخدمة في الخلط
gas used for mixing
الخليط الناتج من الخلط
mixture produced by mixing

الغازات المستخدمة في الخلط CO_2 / N_2

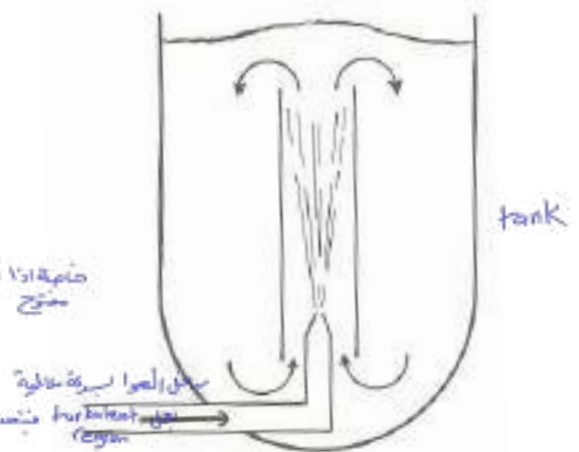


FIG. 1-8. Vertical tank with centrally located air jet and draft tube. Bubbles confined within the draft tube rise, inducing an upward fluid flow in the tube. This flow tends to circulate fluid in the tank, drawing it into the turbulent region in the vicinity of the jet.

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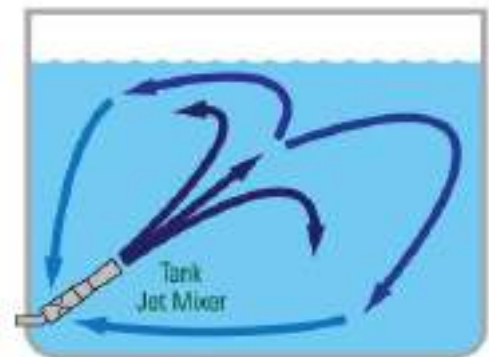
Types of mixers used for liquids and suspensions

Fluid jet mixers

الغازات المستخدمة في الخلط / pumping by

- When liquids are to be pumped into a tank for mixing, the power required for pumping is often used to accomplish the mixing.
- The fluids are pumped through a nozzle arranged to permit good circulation of the material through the tank.
- It is also possible to pump the liquid from the tank through the jet into the tank.

الغازات المستخدمة في الخلط / pumping by
الغازات المستخدمة في الخلط / pumping by
الغازات المستخدمة في الخلط / pumping by



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Types of mixers used for liquids and suspensions

Inline mixers (Continuous mixing)

powder
liquid

- In this case, mobile, miscible components are fed through an inline mixer designed to create turbulence in a flowing fluid stream.
- It can be accomplished essentially in two ways: in a tube (pipe) through which the fluids flow, or in a chamber in which a considerable amount of hold up and recirculation occur.
- Controlling the feeding rate of raw materials is necessary to ensure uniform mixtures.

للاهم نتأكد انه ما يفيض chock Feeding
دلا بطور بال discharge

79

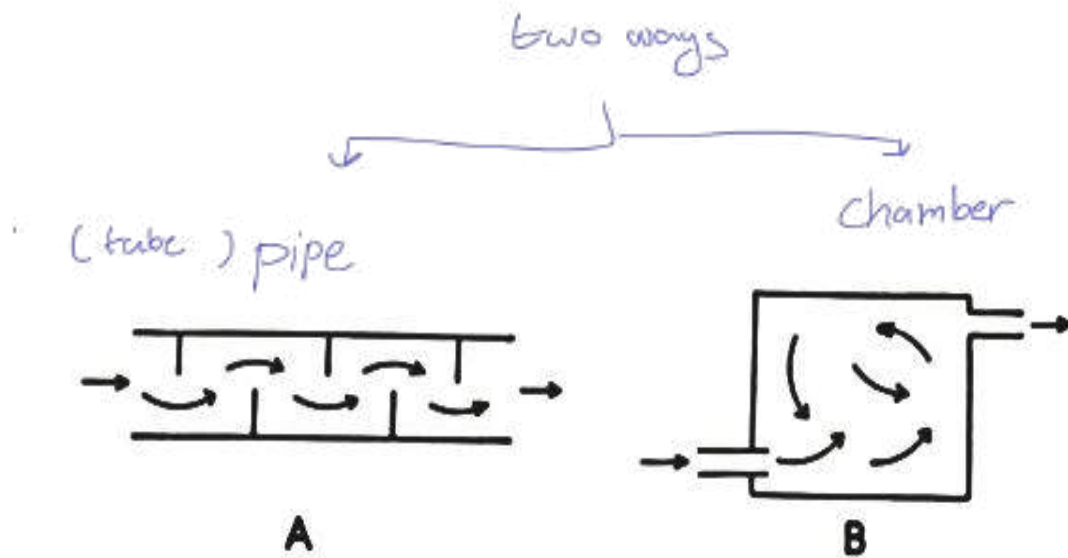


FIG. 1-5. Continuous fluids mixing devices. A, Baffled pipe mixer; B, mixing chamber with flow induced recirculation.

الفرق بين ال Pipe وال Chamber ؟

ال pipe فيه Baffle يعمل الحركة موجهة ، راجح تحبها ال liquid فيه وترجع خبثها ال random
baffles

اما ال chamber فيه recirculation راجح يطلع المادة ال ما يفيض good mixing / في holding gap يعني ال liquid يعمل فترة قبل ما يطلع

Done

Types of mixers used for liquids and suspensions

- On an industrial scale, solutions are prepared in large mixing vessels with ports for mechanical stirrers.

- When heat is desired, thermostatically controlled mixing tanks may be used.



FIGURE 13.1 Large-scale pharmaceutical mixing vessels.
(Courtesy of Schering Laboratories.)

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Mixing of semisolids

- Semisolids, unlike liquids and powders, do not flow easily.
- The suitable mixers must have rotating elements with narrow clearances between them selves and the mixing vessel to avoid dead spots

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Types of mixers for semisolids

- 1) Planetary mixers
 - 2) Sigma blade mixer
 - 3) Vessels (tanks) with counter-rotating mixing bars
- It is very difficult using primary mixers to completely disperse powder particles in a semisolid base so that they are invisible to the eye.
 - The mix is usually subjected to the further action of a roller mill or colloid mill, so as to 'rub out' these particles by the intense shear generated by rollers or cones set with a very small clearance between them.

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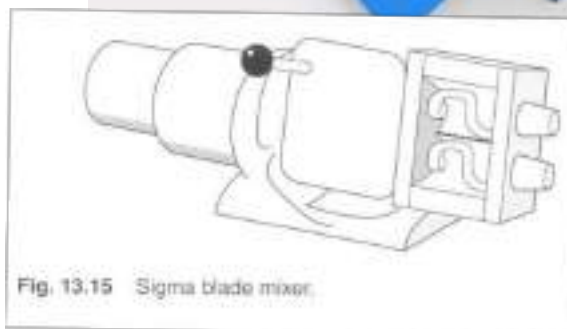
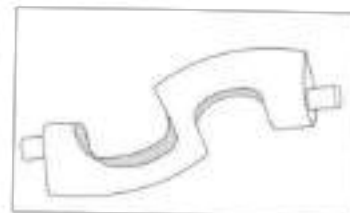


Fig. 13.15 Sigma blade mixer.



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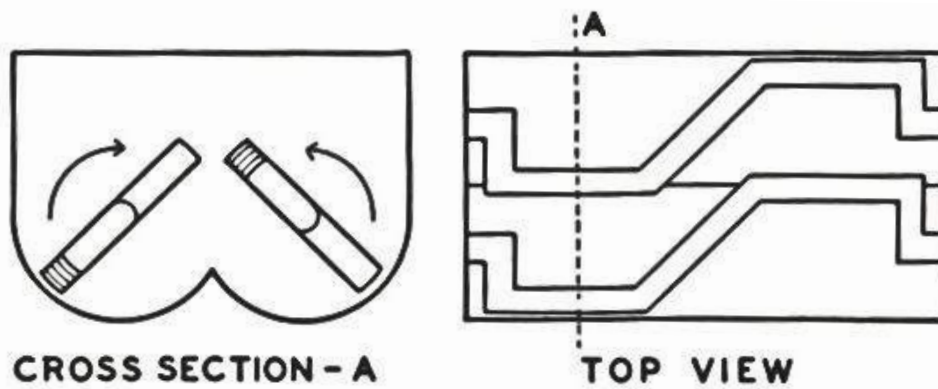


FIG. 1-8. Schematic drawing of a top-loading sigma-blade mixer with overlapping blades. The top view shows the relationship of the counter rotating blades to the overall geometry of the mixer.

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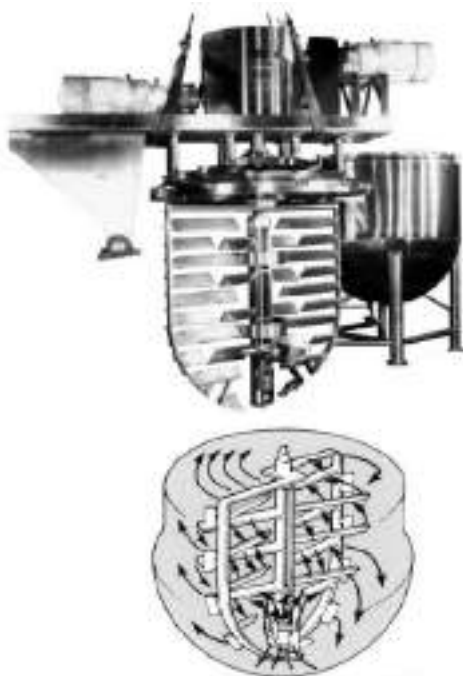


Fig. 5 Large-scale manufacturing unit (Tri-mix Turbochear) with counter-rotating mixing bars. (Courtesy of Lee Industries, Inc., Philipsburg, Pennsylvania.)



Stainless steel tank, which has counter sweep agitation and a built-in homogenizer.

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