

Mixing

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اعلب ادوية متكونة من اكتر من صاره بس في ادوية بسيطة من ادوية اكتي ومواد حافظه

sterile products (مثلاً ادوية اكتي ومواد حافظه) (Saline powder) (Vials اكتي ومواد حافظه) (Normal Saline) (ampoules اكتي ومواد حافظه) (ampoules اكتي ومواد حافظه) (ampoules اكتي ومواد حافظه) (ampoules اكتي ومواد حافظه)

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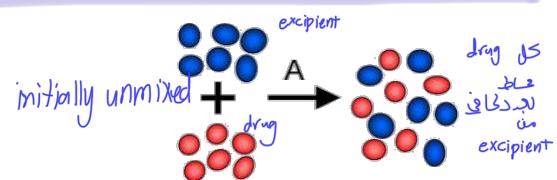
في ادوية متكونة من اكتي ومواد حافظه (30 ingredients (في الـ multivitamins minerals)) تكون مكونات ادوية المتكونة من اكتي ومواد حافظه

* بنتائج ادوية متكونة من اكتي ومواد حافظه

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.

؟ molecule جزيء particle جزيء
↓↓
solv/gas كل جزيء معاً
↓↓
solv/gas



This may be:

- 1) Mixing of Powdered materials (e.g. tablets, capsules, dry powder inhalers). سبعينه عن تكون
- 2) Mixing of miscible liquids (e.g. solutions) or immiscible (e.g. emulsions).
- 3) Mixing of insoluble solid and liquid (e.g. Suspensions). من اكتي او اعواد
- 4) Mixing of semisolids or dispersion of particles in semisolids (e.g. pastes and ointments).

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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)



shake it well before use
 (e.g. suspensions, emulsions and creams)

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. emulsifying / suspending agents, o/w + emulsifying agents base on emulsion shaking = energy for mixing)

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) movement

energy & mixing leads to
 ↓
 (semisolid) نصف سائل (solid) كثيف

energy & mixing leads to neutral
 Antimixing / segregation

= ordered

= ideal

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.



جسيم بسيار امرار
 (molecular level)

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.

المواد داخل الجهاز توزع في اجزاء اصغر من اجزاء اصغر بحسب احتمال اخذها
 random mixing

random

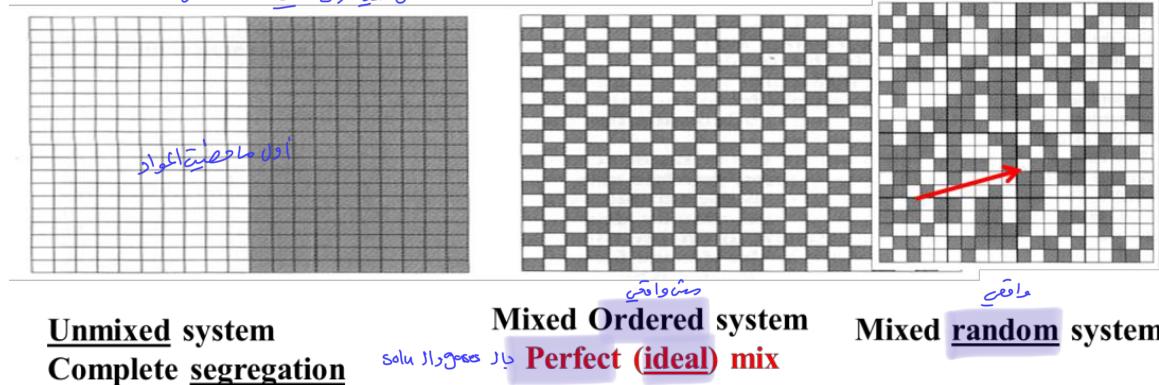


cube mixer
 random sampling leads to good mixing
 (active) drug

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The mixing process

دosis دواعی tablet کی تجویز را کیا کریں؟



- **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)

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The mixing Process

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 - granules

↳ 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

كم اسبي طينة عمان احلى ومحبطة

هذا يعني 5 kg من مهاد حيوى عياره 500 بس اوزن حمای الحبة الى عيارها 500 بطلع وزنها 1000 mg tablet 6

tablet ʃə'pl̩et̩

بسبب ما يمثل Dose وحدة كل استي داخل لماكنة في اصحاب يكون Dose ، بعده 1000mg اد بعل وبيتوف حمل عندي العيار 500 اذا طلح 300 بوجج بجيال Mixing و يابزيد الريعة time . * ادا 5ml Dose 5ml سعي 5 جمود

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. *مطحنة اداة ملحوظة برجع يعاد 75 active drug لـ 100 mg*
- The number of particles in scale of scrutiny depends on sample weight, particle size and particle density.

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النوعية المطحنة ونوعية المراقبة وعدد الجسيمات

↑ Size
reduction ↑ 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

total active minor درا

1:1000
active total

النوعية المطحنة

Sample number	Number of particles in scale of scrutiny		
	1000	10 000	100 000
1	1 active : 1000	7	108
2	no active 0 excipient lots	10	91
3	1	15 <i>نحو 15٪ من 10</i>	116 <i>نحو 16٪ من 100</i>
4	2 <i>الزيادة 100٪ من 1</i>	8	105
5	0 <i>نحو 100٪ من 1</i>	13	84 <i>نحو 84٪ من 100</i>
6	1	10	93
7	1	6	113
8	2	5 <i>نحو 5٪ من 10</i>	92
9	0	12	104
10	1	13	90
Mean	0.9 <i>النوعية المطحنة</i>	9.9 <i>النوعية المطحنة</i>	99.6 <i>النوعية المطحنة</i>
Standard deviation	$SD = \sqrt{\frac{\sum (x - \bar{x})^2}{n-1}}$ 0.78	3.38	11.18
% CV	$\frac{SD}{\bar{x}} \times 100\% = 86.86$	34.17	11.23 <i>نحو 11٪ من 100</i>
Deviation from theoretical content	±100%	±50%	±16%
Range	(0-2)	(5-15)	(84-116)

نحو 10٪ من عينات مصادر ، اعلى مرارة 1:1000 (النوعية المطحنة) ، ثالث مرارة 1:10000 (النوعية المطحنة) ، اعلى مرارة 1:100000 (النوعية المطحنة) ، وبرفع اطهانها يتغير النسبة 1:1000 ، وبرفع اطهانها يتغير النسبة 1:10000 ، وبرفع اطهانها يتغير النسبة 1:100000

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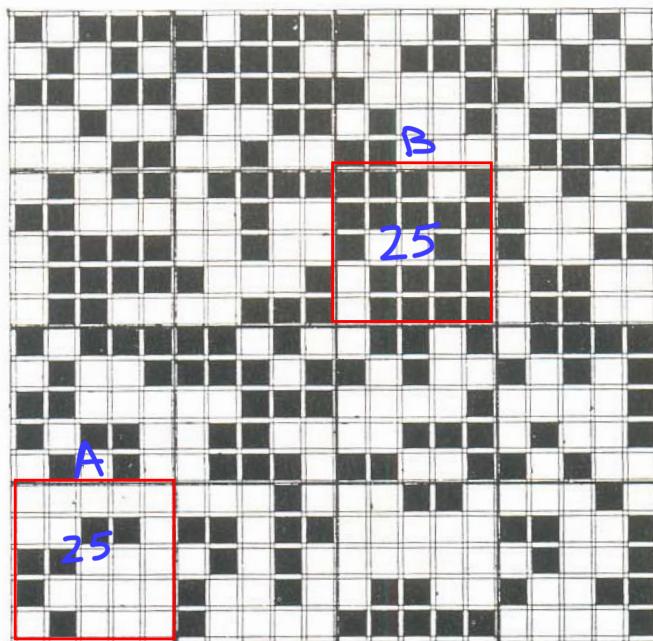
النوعية المطحنة active excipient particles ↑ Milling ↑
نحو 10٪ من عينات مصادر ، اعلى مرارة 1:1000 (النوعية المطحنة) ، ثالث مرارة 1:10000 (النوعية المطحنة) ، اعلى مرارة 1:100000 (النوعية المطحنة) ، وبرفع اطهانها يتغير النسبة 1:1000 ، وبرفع اطهانها يتغير النسبة 1:10000 ، وبرفع اطهانها يتغير النسبة 1:100000

ج ٤٠٠

الابيحن \rightarrow لدوا

أبنية الدواجن

الددا اعـلـى



Theoretical percentage of white particles is 50 %

اللهم ااربي يكون مهنياً 50% ، مهندساً 20% ، داً مهندساً 30% ، مهندساً 1000%.

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

drug ۱۱ ۵۱٪ بارجعه

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

$$24\% * 200 = 48$$

$$\frac{76}{48\%} * 200 = 152 \text{ (over)}$$

1

لدرهم على الحشر من مكان اصحاب
ربا و تنازع عندها أصحاب

أخت العينة A اعتماد (drug 76%)

(dry 24₁₀) 100% air

نی افتکن، نه الیکس mixer بکس ایف ۲ بیم ۱۱۰ ولت ۲۴°۶ برابر ۴۸٪ =

$$152\% = 67\% \times 200$$

مداده کمیه اله را اعلیٰ در درا نگیر که تر لعنه

The mixing Process

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



Fig. 32.2 Computer generated mixtures of nominal 50% active ingredient. The numbers in parentheses refer to the number of

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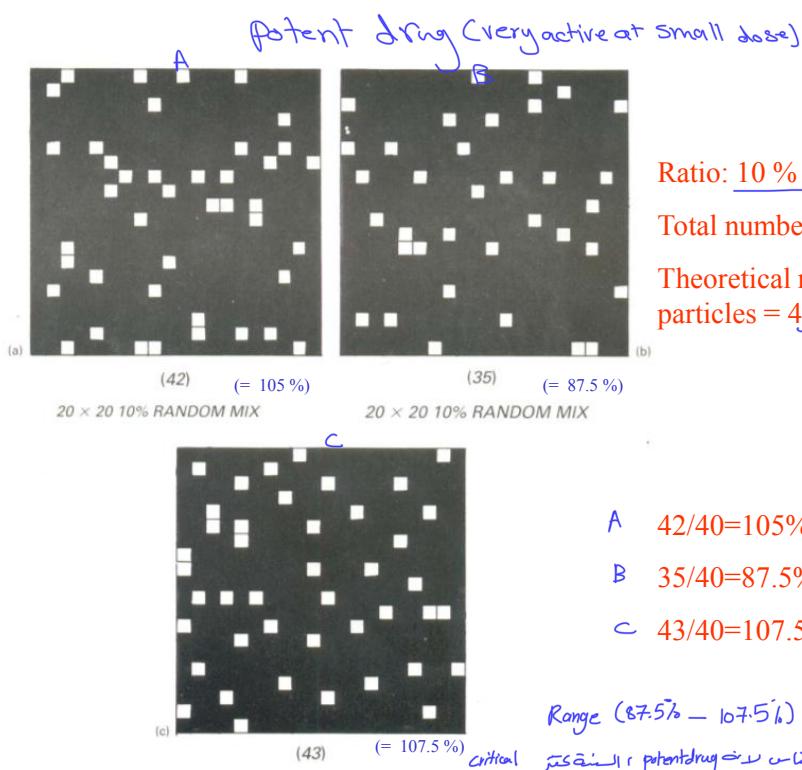


Fig. 32.3 Computer generated mixtures of nominal 10% active ingredient. The numbers in parentheses refer to the numbers in the following table.

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أ- **potent** عاليًا عال CNS والهرمونيات فاي-برادة بمحفز

اول ادعاً patent علی محدودیتی دارد، mixer یا جانشینی می‌کند.

(Step of granulation (part 1)) داول mixing خانه دار Mixing unit's Potent یار

The mixing Process

► اجتنب عالم خطأ عالي 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. \uparrow $\text{Number of particles}$ \downarrow Variability
2. as the proportion of a component in mixture decreases.

لما كان 50% كانت لدية خصائص مماثلة (101-107) حيث في 80% نسبة الدواعي ملائمة راد

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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.

mixing كبار بار / بغير الـ Miller / time
الـ granulation / درايفن من همبل بـ الـ ميلر
 - 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**).

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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

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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:

$$SD = \sqrt{\frac{p(1-p)}{n}}$$

p: proportion of the drug

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

Example:

$$\text{ن} = 100\,000, p = 0.5 \Rightarrow \text{SD} = 1.58 \times 10^{-3}, \% \text{CV} = 0.32\%$$

$$n = 100\,000, p = 0.001 \Rightarrow SD = 9.99 \times 10^{-5}, \%CV = 10\% \quad 6.12$$

- 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 .

الستي بلي ارلي
الستي بلي ارلي

بایی از ایار ۱۳۹۰ ماه تغیر مکتبه بن سنته *sent of scrutiny* بدان مقصود می‌شود.

(↓ proportion ↑ CV) patient's also have

↓ proportion ↑ CV

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

good
مقبول
acceptable
mixing

عالي زمان انواع مراقبه لصالح mixing time

steps قاسمه جهاز
step اد

Sampling

- ① • Scoop sampling
- ② • Thief sampling

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Unit dose thief sampler

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powder اسحاب محبب بارآخر عنان ينزل بار contam

الاصناف العالية اذا ال محظى manual Contaminar

اذا ال container ضيق ادالبودة متراقبه ممكن ان يتم (مايسن)

اداسع بـ Scoop

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Evaluation of degree of mixing

Mixing Index (M)

acceptable variation \rightarrow
 solid speed / time \rightarrow perfect mixing

$$M = \frac{S_R}{S_{ACT}} \quad \begin{matrix} \text{acceptable random mixing} \\ \equiv \end{matrix}$$

S_R : Content standard deviation of random mixture

S_{ACT} : Content standard deviation of mixture under investigation. \rightarrow كلمرة سبب مينة بجود عنى
Certaintime \rightarrow ACT

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

أمثلة على S_{ACT} \rightarrow Flow rate, size of particles
عامل بنتجها بحجمها، بجهة مثل \rightarrow good mixing acceptable

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✓

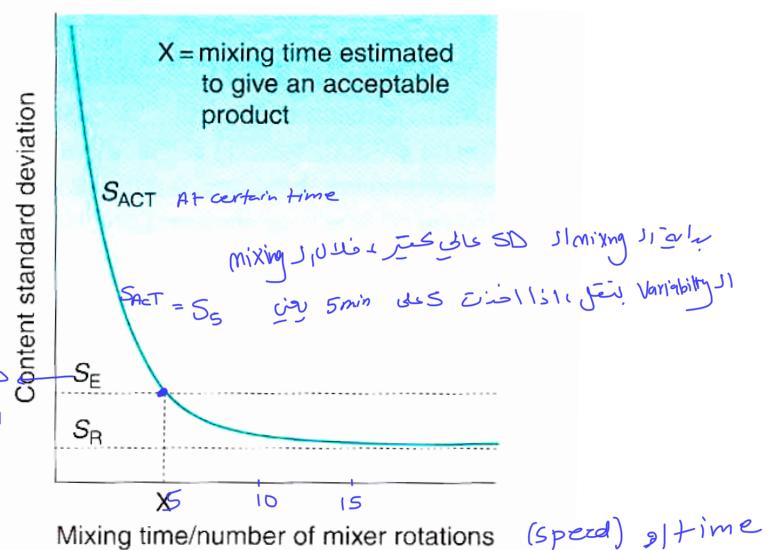


Fig. 12.4 The reduction in mixing time possible if a random mix is not required. S_{ACT} represents the content standard deviation of samples taken from the mix. S_E the estimated acceptable standard deviation and S_R the standard deviation expected from a random mix.

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جود المكونات المدعى \rightarrow SD

Mechanisms of mixing

Powders

There are three main mechanisms for powder mixing:

Conveyor بدانة ال (التشغيل)
حامل بتحمل الماء a) **Convection** (the transfer of large amount of particles from one part of the powder bed to another).
التجاهز ، ماء صافى تباعن دهان الماء

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

Ball milling
الكرة طحن
طحن في وعاء
طحن ما في طحن

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.

Shearing = layering



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powder bed: container العود بار Volume

layers طبقات

Mechanisms of mixing

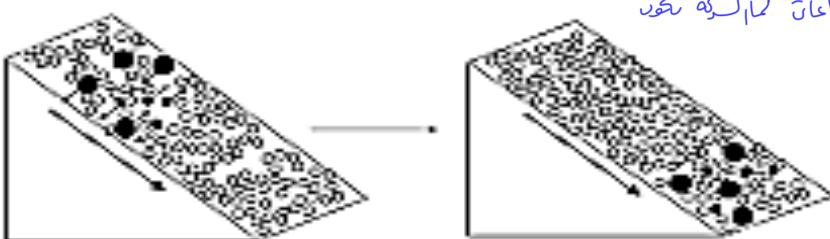
Powders

مدونات
لتحقيق
التركيز
الثابت
layers

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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ابدأ بالكرة اسفل راسها

Liquids

Mechanisms of mixing

حركة بسيطة
الاتجاهات

a) Bulk transport

→ Convection

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



b) Turbulent mixing

→ Shearing

- 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.

↑
Turbulent



الحركة اهل
النف

الحركة التي تكون في Fluctuation ، مرحلة سرقة عالقة مرحلة دفع وامانة
الحركة العوجة ما يكفي randomness دانسيي random دفعها في
عند عشوائية الون واحد

الحركة التي تكون في Fluctuation ، مرحلة سرقة عالقة مرحلة دفع وامانة
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Mechanisms of mixing

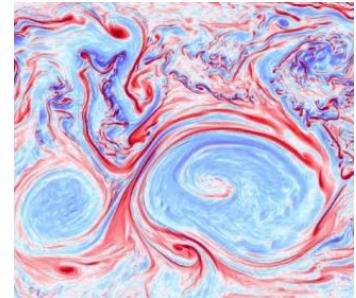
Liquids

b) Turbulent mixing

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

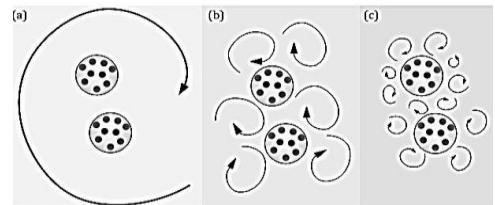
The large ones tend to break into smaller and smaller sizes until they are no longer distinguishable.

جفحة بحث دیھن یا نس \rightarrow
(good mixing)



- Turbulence is a highly effective mechanism for mixing.

Bulk Transport اخضاع بکتریون



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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.

mixing بدن

Bulk Transport بدن

shearing بدن

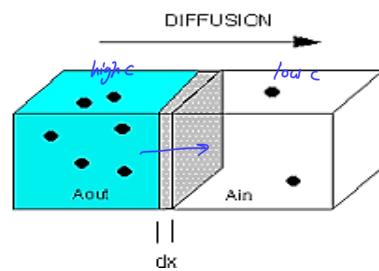
layering بدن

mixing بدن

Diffusion بدن

mixing بدن

- Considerable time is needed if this is the only mixing mechanism.



diffusion membrane بدن

mixing بدن

molecular diffusion بدن

concentration driving force بدن

gradient بدن

Driving force: Concentration gradient

driving force بدن

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). $SD \uparrow$
- It may cause a random mixture to change to non-random or may be responsible that a random mixture never occurs. mixing always goes to extremes
- Segregation is more likely to occur if powder bed is subjected to vibration and when the particles have greater flowability. \rightarrow spherical



الجنة يتمثل \downarrow \rightarrow \rightarrow small scale \rightarrow lab scale \rightarrow يعلوا

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Segregation can be due to

difference in :

- 1. Particle charge → movement, جذب جاذبية powder جذب جاذبية
- 2. Particle density مادة معدنية، مادة نuetral مادة نuetral
- 3. Particle shape شكل
- 4. Particle size and size distribution حجم حجم

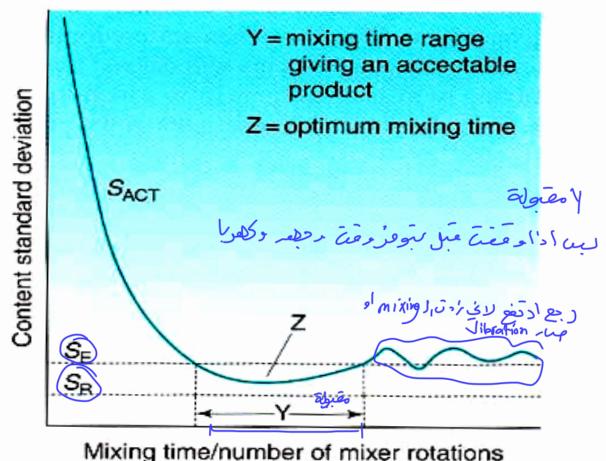


Fig. 12.5 Possible effect of extended mixing time on the content standard deviation of samples taken from a mix prone to segregation. S_{ACT} represents the content standard deviation of samples taken from the mix, S_E the estimated acceptable standard deviation and S_R the standard deviation expected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

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Powder segregation (demixing)

Factors affecting segregation:

1. Particle size (large - small - moderate)

Percolation segregation

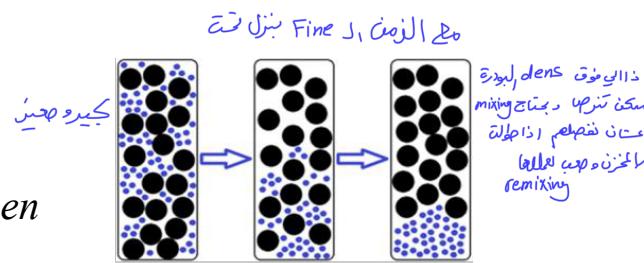
(small particles tend to fall through voids between large particles)

Trajectory segregation

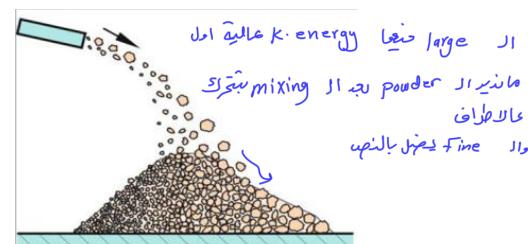
(large particles tend to have greater kinetic energy)

Elutriation segregation (dusting out) → زائلة

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

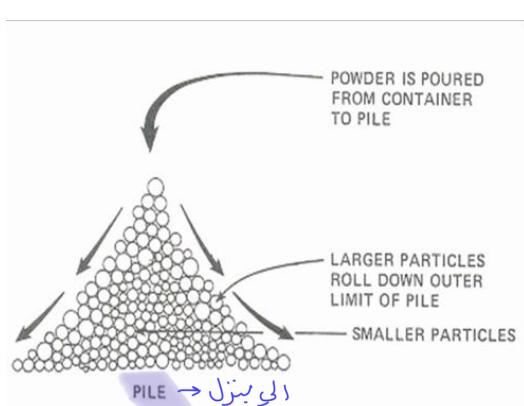


Percolation segregation:

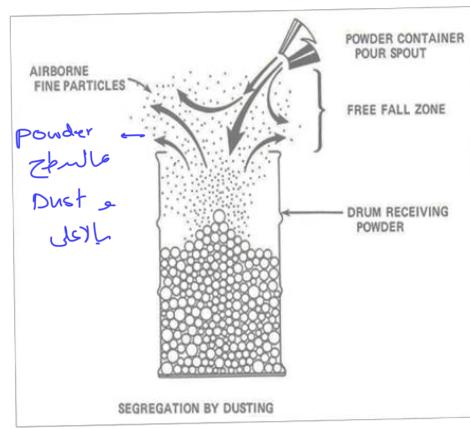


Trajectory segregation

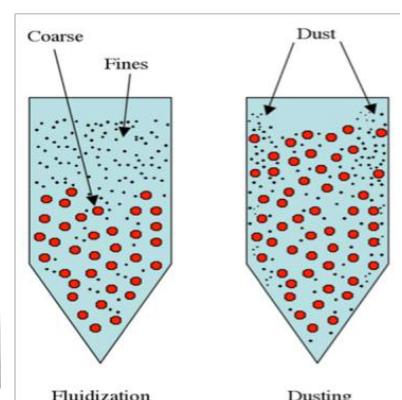
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Trajectory segregation



(Elutriation)



Dusting

Powder segregation (demixing)

Factors affecting segregation:

$$D = \frac{mass}{\nabla}$$

2. Particle density light — heavy

لدرهم لما اعل one size لادخ milling عمان, Volume

النصل ثابت ، الى يختلف ال mass داخل هاد volume

Segregation occurs due to density differences.

3. Particle shape

Spherical particles are easier to be mixed but also to segregate than irregular or needle shaped particles. جفاف حبيبات مكعبات؛ لذا هي أسلوب

31 Crystallization چی چیز ؟ shape من بینم با

الحجم
size

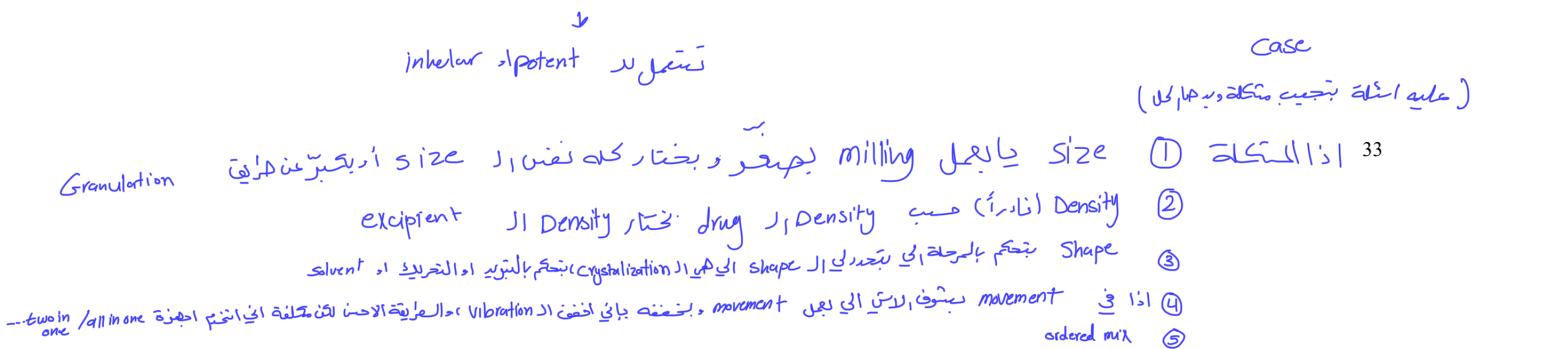
Approaches to solve the problem of segregation

1. Selection of particular size fractions to achieve drug and excipients of the same particle size range. اصل اتاي اعل② granulation
اصل اتاي اعلFraction
اصل اتاي اعلmilling
2. Milling of the components so that there size becomes small and same.
نحکممیکرو میکرو
نحکممیکرو میکرو
نحکممیکرو میکرو
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.

drug SI Density \times excipient density \times excipient \times 1000

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.
 ↓
 اقلال او راد
 vibration
- 7. Using equipments where several processes can be carried out without transferring the mix.
 ↓
 (two in one
 three in one -)
 (مالا خل اتفع من حفاز لفاز)
- 8. Production of an ordered mix.



Ordered mixing

adhesive interaction في بين عل

الاصطفاف عالي

بطيف

potent

① ↗

② ↗

③ ↗

دو منجم

غير عرض

excipient

④ Direct compression

Dry powder inhaler
Dry antibiotic

ordered mixing اسال

- It is termed also **adhesive** or **interactive** mixing.

- In this case, very small particles may become adsorbed onto the active sites of large particles.

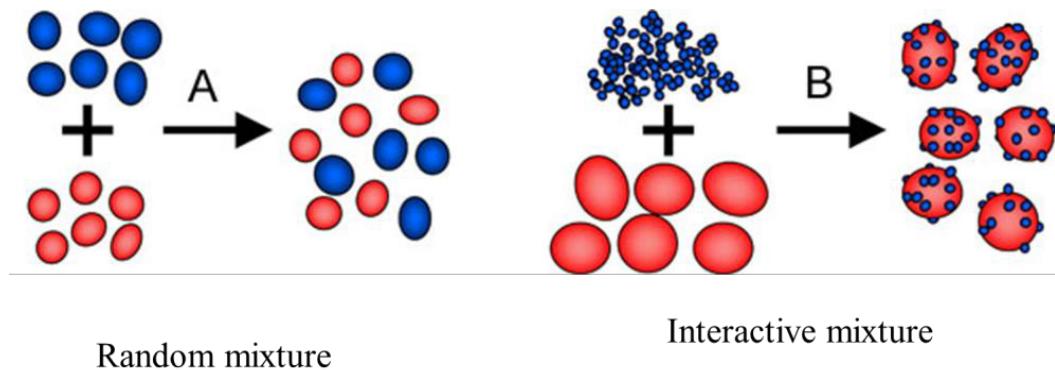
- This minimizes the segregation between small (adsorbed) particles and large (carrier) particles.

surface activity
Carrier دار Drug بين ادا ordering adsorption
لدرهم في فوج من ادا
ای اتی باز عال

- 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.

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بعد حبصي ادا اوزع د جاريفه مسازه دا ادا خطبار بعد بع ملائمه
steril dry powder
inhaler
(safe carrier) Polysaccharide Drug في potent ← Dry powder inhaler دا processes excipient
ما يسكن ادا اوزع د جاريفه مسازه دا ادا خطبار بعد بع ملائمه



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Application of ordered mixing

نحو ترتيب المكونات بمعنى فـ drug > carrier

1. Dry antibiotic formulations (fine antibiotic powder is blended with and adsorbed onto the surface of large sucrose or sorbitol particles.)
2. Dry powder inhaler formulations
3. Direct compression formulations
4. Formulation of potent drugs



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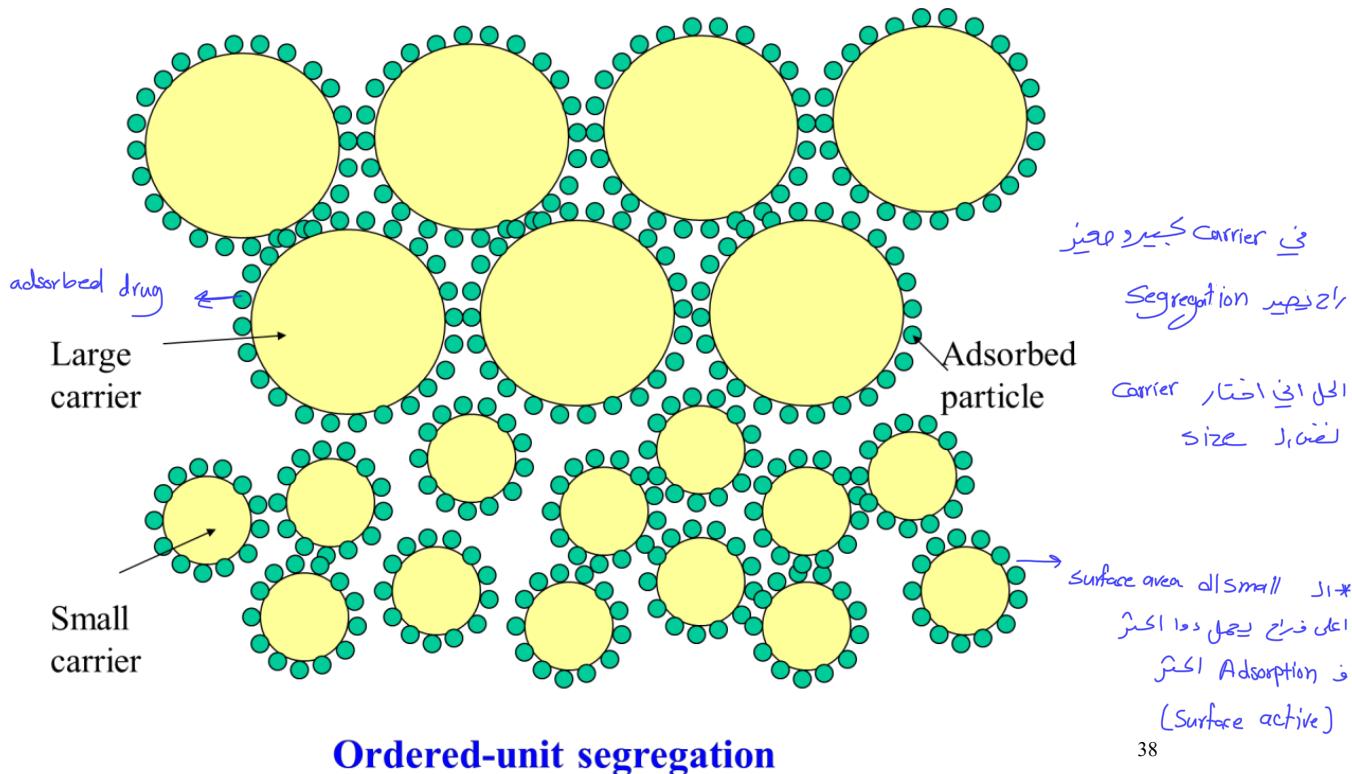
Segregation in ordered mixes

Ordered unit segregation

اصناف احتارة كبيرة وصغرى راح ت segregate carrier particle

- The carrier particles vary in size. → احتارة احتار
- 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. راح يكون في اختلاف بكمية لدرا المترجدة

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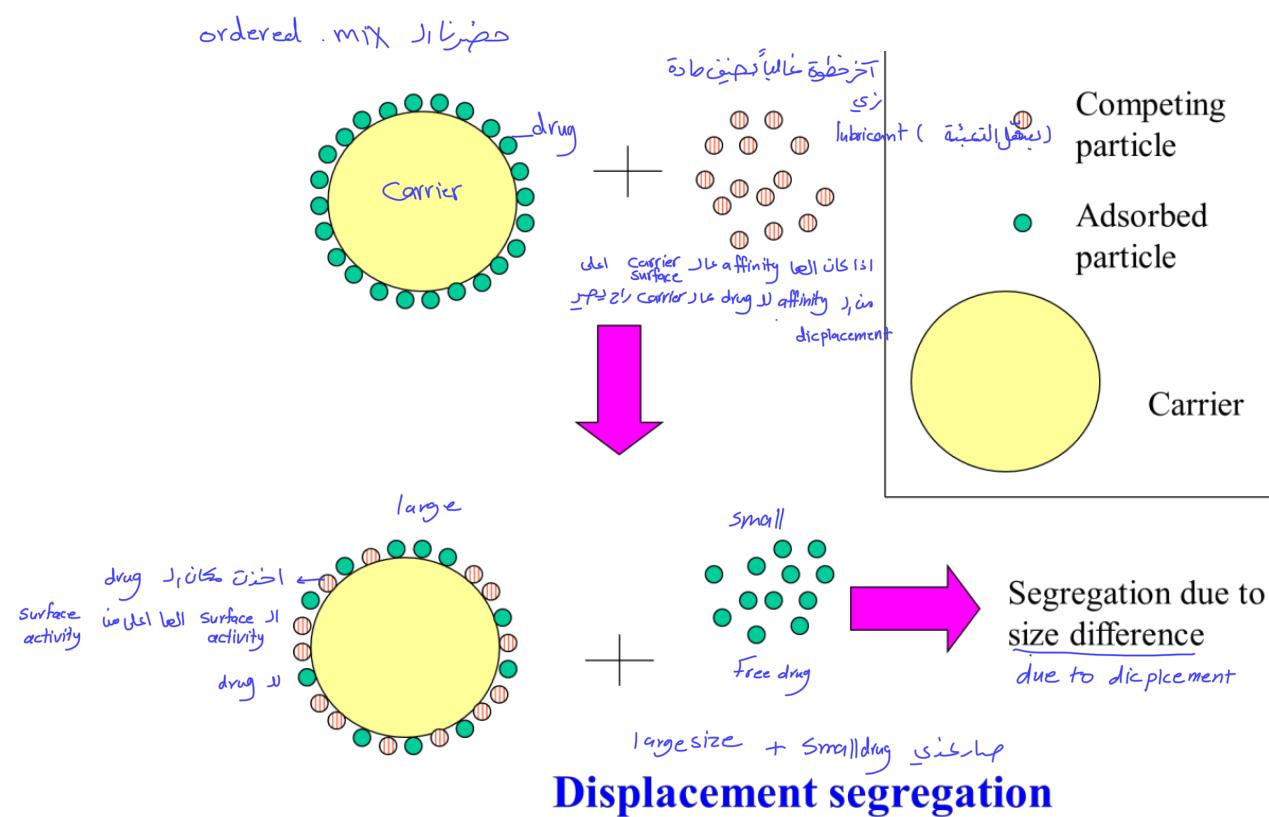
Segregation in ordered mixes

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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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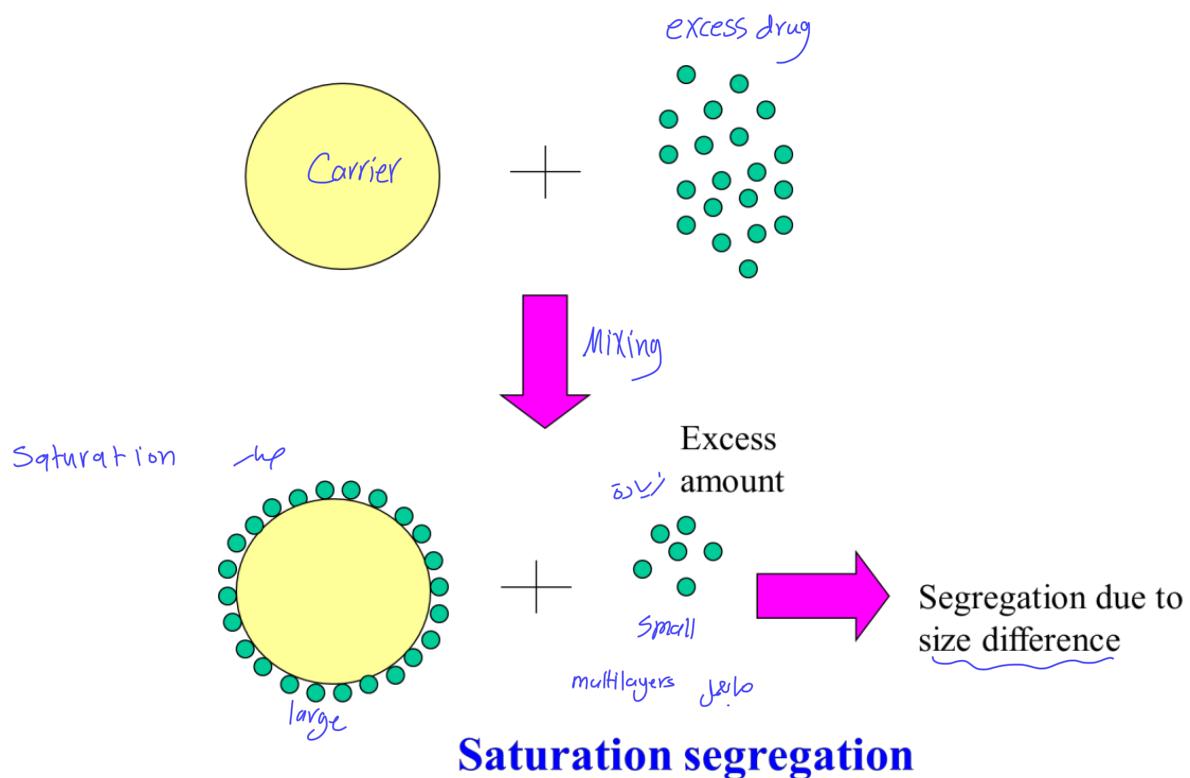
Segregation in ordered mixes

Saturation segregation

drug *Néle Jihed*
carrier S_1, S_2

- 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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