

# Mixing

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أغلب الأدوية مكوّنة من أكثر من مادة، بعضها نشيط (Active ingredient) وبعضها غير نشيط (excipient).

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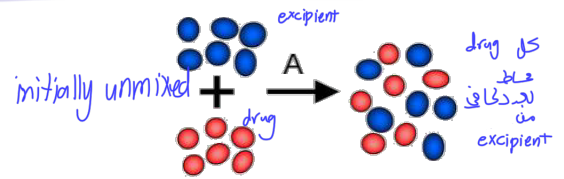
- في أدوية مثل 3 ingredients (multivitamins, mineral, active ingredient) في أدوية بسيطة مكوّنة من نشيط (active ingredient) و 1 مادة غير نشطة (excipient) مثل Normal saline (معالجة استي) ولا مواد حافظة، ال sterile products (منتجات معقمة).

\* يحتاج (Mixing) إذا أعيد powder (مسحوق) في القولبة فستكون أكثر متجانسة.

## 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.

مolecule (جزيء) molecule (جزيء)  
↓  
soln / gas (محلول / غاز)  
particle (جسيم) particle (جسيم)  
↓  
soln / gas (محلول / غاز)



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) → من اقصد ال forms (أشكال) أو مكونات (مكونات).
- Mixing of semisolids or dispersion of particles in semisolids (e.g. pastes and ointments).

# Mixing

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

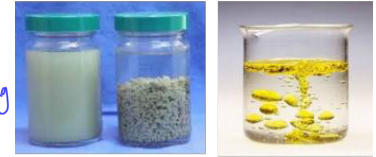
1) **Positive mixtures:** Mixtures that form spontaneously (do not need energy) and irreversibly (when formed do not tend to separate).

(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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Antimixing / segregation

## 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 of particle is the same at all positions and is proportional to the number of such particle on the total mix.

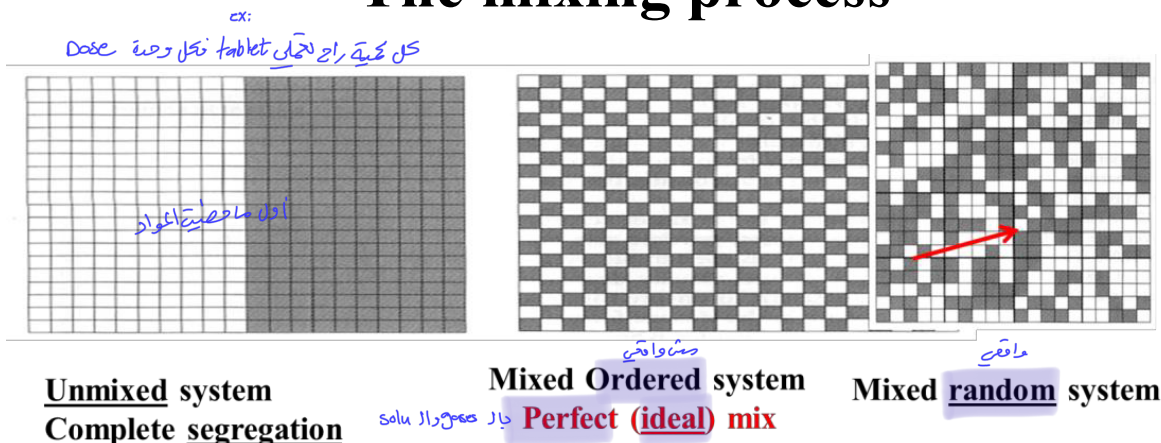
random (acceptable mixing) powder ويكون في اجزاء اعرض اجزاء ، احصائيا افضل ليجداد random



cube mixer  
powder  
random sampling

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# The mixing process



- **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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– ال particles داخل mixer بالبارية الصا vector معين 1/2 X عليها spatial orientation محدد بزمن محدد سرعة محددة .  
– دنا عمل Mixing له حصة water راجل تصير velocity انطأ ربحان الجزيئات بتغير

## 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 اسحب عينة عشان احكي واصلت mixing لحد ؟

مثلاً عني 5kg من مواد حيوي عياره 500 ، بس اوزن هاي الحبة ابي عيارها 500 بطلع وزنها 1000 منها excipient  
عشان تصير tablet

بسحب 1000mg ما يمثل Dose وحدة ، كل اتي داخل لما حبة في احتمال يكون Dose ، بوخر 1000mg و بطلع و بشوف هل عني العيار 500  
اذا طلع 500 بروج بعيد mixing و يا بزيد السرعة و time \* اذا 11 Dose 5ml بسحب 5ml و حيد

# 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.   
 *نحللها اذا طلع اذ active 75 ، لا يتكفل يرجع يعني mixing 100*
- The number of particles in scale of scrutiny depends on sample weight, particle size and particle density.

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تأثير Particle number على اد Scale of scrutiny quality of mixing

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

دوا Minor يعني نسبة اد active لا total

1:1000  
active total

Sample number	Number of particles in scale of scrutiny		
	1000	10 000	100 000
1	1 active : 1000	7	108
2	no active 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)	(84-116)

اح نسبة 10 عينات محصورة ، اقل مرة 1:1000 الى هواد Mixture (لا صلي يدون تعديل) ، ثاني مرة نؤخذ 10 عينات بعد ما نطحنه ونقيس النسبة 10:10000 الى هي نفسها 1:1000 ، ورجع اطحنها بنفس 100:100000 نفسا 1:1000

نحو يستخرج من السار ؟ صل عداد particle ما ازويه بحسن اد milling ؟  
نم برلونه على اد Variability د CV

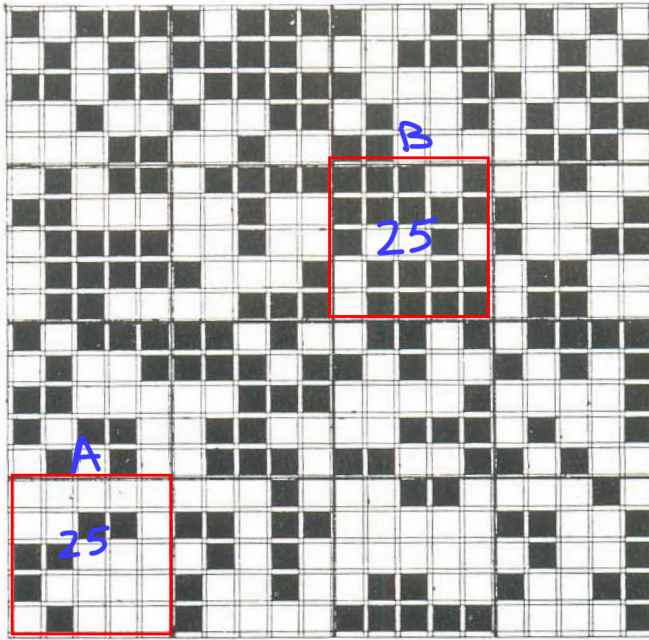
↑ Milling ↑ Particles size ↑ من صلابه او active excitant  
قلبي مع عدد اعيرين دقونه بيهم

400 مربع

الابيض ← الدوا

A نسبة الدوا على

B الدوا اقل



Theoretical percentage of white particles is 50 %

المزيج mixture يكون متفرق على 50% مثلاً دوا حيار 500 ووزن 500g  
بنظر computer معطيات معينة وهو بصرى شوا احتمال ان randomness داخل الماكينة

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

بالرسمة 51% الدوا drug

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

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

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

خطأ

لا نرمز على المختبر مكان الحبوب  
ربا وقتان غيروا حسب  
SD و CV

اضافة الحبة A اعطيت (76% drug)

الحبة B اعطيت (24% drug)

بدى اختراجه انه لا mixer كله لـ A او B كيف اكون؟ يحكى

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

ملاحة كمية الدوا اعلى ومزجته كجيرة لائق

## 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 excipient

194 = A  
202 = B  
198 = C

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

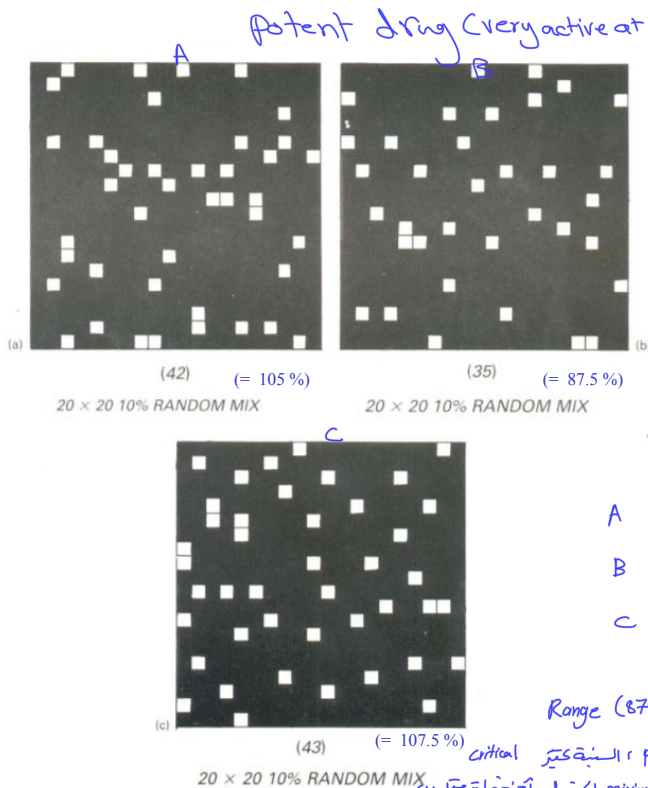
B  $202/200 = 101\%$  > 100%

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

صداها اذا Range يكون نوعاً ما مضبوط  
لأنه نسبة كبيرة من الحبة (50%) عبارة عن drug

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

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Ratio: 10 %

Total number = 400

Theoretical number of white particles = 40

perfect order  
يكون 40 ابيض

A  $42/40 = 105\%$

B  $35/40 = 87.5\%$

C  $43/40 = 107.5\%$

Range (87.5% - 107.5%)

مقادير mixing من مناسب لـ potent drug ، النسبة كتر critical  
من صيد ال potent بتحتاج لطريقة تقصى mixing الحذر في امزجته مثل القوي

Fig. 32.3 Computer generated mixtures of nominal 10% active ingredient. The numbers in parentheses refer to the number of 'white' particles in each mix, theoretically 40

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ال potent غالباً عال CNS والهرمونات فأي زيادة بتتوقف

اذا potent اولاً جاترني على طريقة mixing - نوع mixer - Mixing time

معدة ال potent لازم نضبط mixing ثاني بعد ال mixing الاول (step of granulation)

## The mixing Process

➤ The variation in component percentage between different samples taken from a mixture increases:   
 *اوضاع عينة وتغير خطأ عالي*

*متى مجال الخطأ يزيد؟  
amount*

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

*لما كان 50% كانت النسبة دقيقة ومقبولة (97-101)  
لما كان potent 10% نسبة الدوائية رار CN راح تزيد (87-105) خطر لـ potent*

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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. *في احتمال كبير رار mixing بصير high variability لانه potent موشان تغير هاي*

*الغرة و تحقق عبيس بزيادة time / اختيار Miller / ازير السرة و ادا ما ضبط رلاشي من مبرون بعمل simulation اي تحسين رار mixing*

- 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**). *is a choice*

*ازير عدد ر particles بالاتي بصير غرضه كثر انه particles من Active تلتق مع particles من inactive بصير بتحسن 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: تجتم من عند طريق

- ① – scale of scrutiny
- ② – particle size
- ③ – mixing procedure

acceptable random mixing ← powder

↓  
time  
speed > الحاجة

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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 علاقة حساب SD وعلاقة لـ proportion

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

p: proportion of the drug  
drug = component

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

Example:

مثبت

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

زاد

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

- 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.

لازم اسوف اعطى 6 اد اعتر من جانب  
عشان احسن ر potent

الـ excipient بي مافقد اعتر الجوز بيزيد  
scale of scrutiny بازي ازرا excipient الـ لما مافغير تحته بي نسبتته  
بتقل لاخر total زاد

(↓ proportion ↑ CV) potent متناقص

↓ proportion ↑ CV

# Evaluation of degree of mixing

## Needs for monitoring of mixing:

- To follow a mixing process:

هل دبلت لدرجة  
acceptable  
mixing

- To indicate the degree of mixing

- To indicate when sufficient mixing has occurred and determine the suitable mixing time

على أي زمن أو وقت، مرات زيادة mixing من لصالح mixing time

- To assess the efficiency of a mixer

في mixer رتي من mixer بى تناسب نوعية حيث من mixing لدرجة في Steps ثانية ابرهاى step 1

## Sampling

- ① Scoop sampling
- ② Thief sampling

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لنفتح بـ حسب العينة  
والمستشعر



## Unit dose thief sampler

↓

tube اسطوانى مـ حسب بالآخر مكان يتنـ بالـ powder

الاصـ للعلية manual اذا ال Continuator مـ عـ

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اذا ال Continuator مـ عـ اذا البودة صـ اـ مـ مـ (ما سـ عـ) (مـ ثـ نـ يـ حـ البودة مـ تـ عـ) يـ عـ يـ رـ

اوا سـ بـ Scoop

# Evaluation of degree of mixing

## Mixing Index (M)

acceptable random  
solid / time speed  
perfect

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

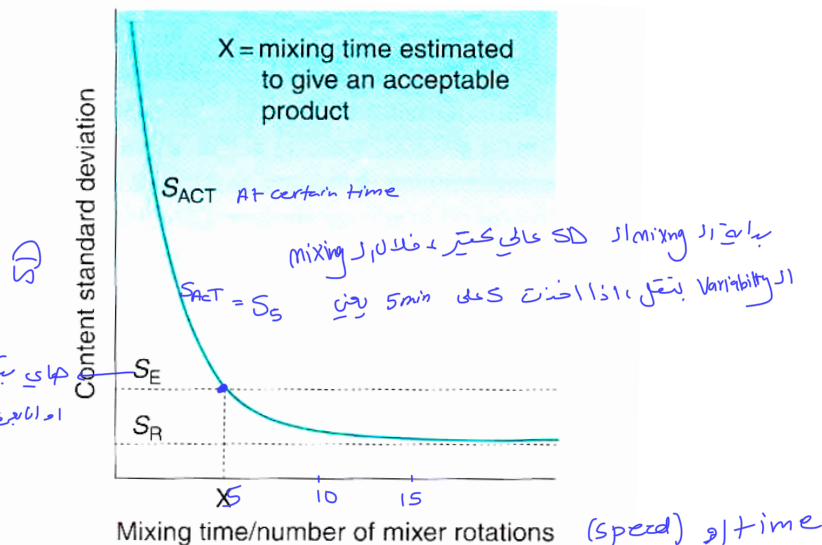
$S_R$  : Content standard deviation of random mixture

$S_{ACT}$  : Content standard deviation of mixture under investigation. →  $S_{ACT}$  = certain time

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

اذا كان او particles كل نفس size او Flow كويسه  
عطلو بتجانس ج بجمعها ، بوضو ل acceptable قبل او 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.

بي او مملها

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SD با او powder مارج بوقف للميز

# 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).   
 Conveyor حامل بنقل الاسيار  
 بداية ال mixing (التشغيل)  
 تحريك كمية كبيرة من powder من مكان لكانه دمج بداية mixing ، خط ال mixing دار exipient مشغل الجهاز ، كميات كبيرة يتحرك بكل الدقائق ، كل جهاز قياس لهي الميزة ؟ لا

This may occur when a mixer blade or paddle moves through the mix.   
 الاجزاء داخل ال mixer  
 جزء كبير بيها جزء كبير pink يعني يتنوع اجزاء كبيرة يتحرك ليس

This mechanism contributes mainly to macroscopic mixing of powders, but mixing does not occur within the group of particles moving together.   
 كل مجموعة يتحرك مافي ابيها بين الاحمر ولا اخرجوا الانيم



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# Mechanisms of mixing

## Powders

- b) **Shear** (Layer of powder flows over another layer)   
 بار milling لاكون في ٢ من قليل  
 هون مافي Shearing عالي

This may occur when some of the material is removed (e.g. by convective mixing) causing powder bed to collapse.   
 لجد ما انتقلت المواد باطل خطوة هون يتبلى نخل ال layers بيها

Shearing = layering



ال Shearing يصير بين هاي (الطبقة) الكبيرة الي يتحرك

powder bed: container الوجود بار volume

هون يكون layers

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# Mechanisms of mixing

## Powders

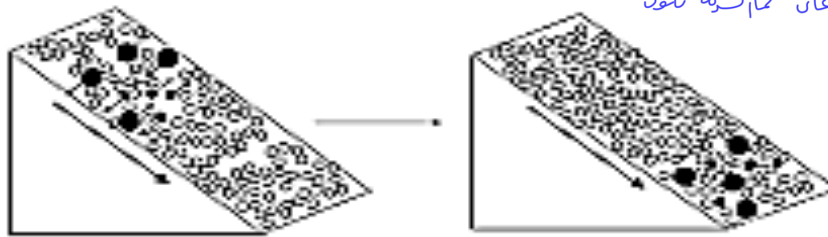
بمقدور powder بالاختلاط لازم ما اعطيهما الحزمين السائلين والاصح بين نحبها عن mixing good  
 راح سبيلش نتجرعن بسن dilate فراغات بينهم ربيص في مجال يصير diffusion لا particles مادة لمادة drug وال excipient ديوخا بين نجف

### 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.



ال particles يدخلوا بيصير دبر في فراغات لما الة تكون عالية.

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# Mechanisms of mixing

ال Flow والة اسرع راسل

## Liquids

### a) Bulk transport $\rightarrow$ Convection

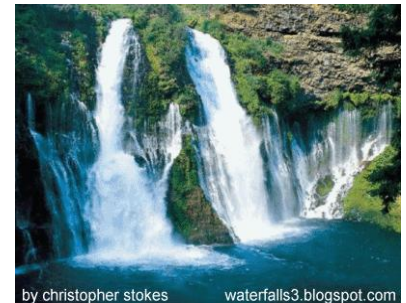
- The movement of a large portion of the material being mixed from one position in the system to another.



ex: Syrup + Flavoring agent

### b) Turbulent mixing $\rightarrow$ 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.



اللة الى بالة

by christopher stokes waterfalls3.blogspot.com

الفة منه يكون في Fluctuation ، مرة سرعة عالية مرة واحدة  
 اللة المودة مراح لعل randomness دانسي random دناخل شيد  
 نصل عاد random عن لة ال haphazard movement سرعة علوانج بنفس اللة

parallel surfaces 24 بصير في eddies بتدخولوا في  
 عبطوا لون واحد

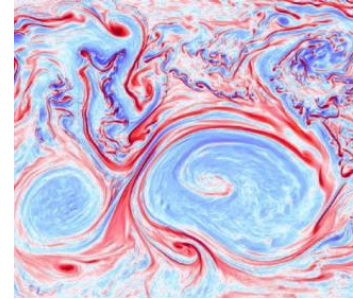
# Mechanisms of mixing

## 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.

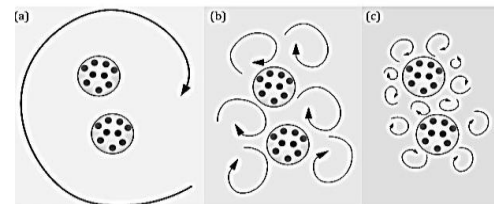
The large ones tend to break into smaller and smaller sizes until they are no longer distinguishable.



- Turbulence is a highly effective mechanism for mixing.

Bulk Transport من اخضر بكتير من

سجدا بيكف وديسر تيانس →  
(good mixing)



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# Mechanisms of mixing

## Liquids

### c) (Molecular) diffusion

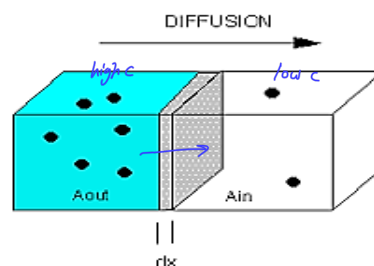
- The molecular diffusion is the primary mechanism responsible for mixing at the molecular level.

- This mechanism produces well mixed liquids if there is sufficient time.

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

بصير mixing بدون  
shearing راد Bulk Transport و  
layering ولا تريك ، بس يوزد وقتة طوي

تحتاج دمنة  
لل mixing



بار mixing مافي diffusion membrane  
بس بصير mixing لانه في molecular diffusion  
مناطعة الحارة معة اذا تريكها ملاجاتها يكتف  
driving force واد  
(concentration gradient)

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Driving force : Concentration gradient

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  
مادي يكون ال  
cups مادي بين اعين ال  
مادي بين اعين ال  
milling مادي بين اعين ال  
Flow مادي بين اعين ال

اي اتي راح بسبب movement بعد mixing  
Vibration مادي بين اعين ال  
مكان لكان بعينه ثانية

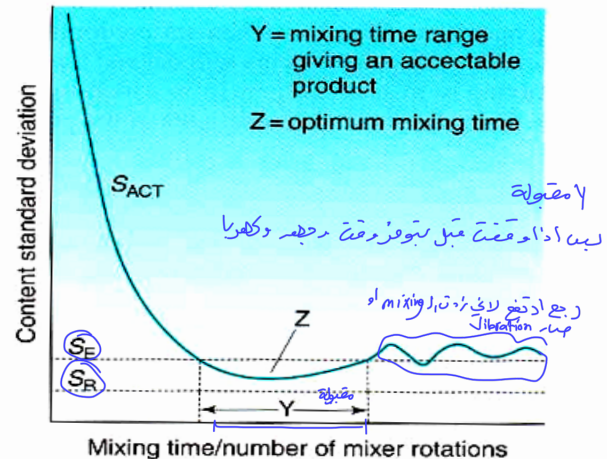
scaling up

small scale  
الاحصنة بتتبع lab scale مادي بين اعين ال  
احصنة شائعة

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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

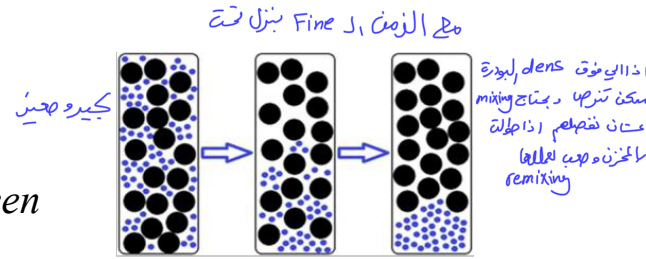
(small particles tend to fall through voids between large particles)

### Trajectory segregation

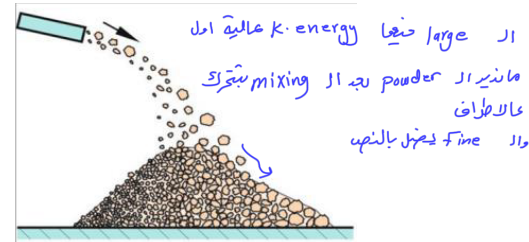
(large particles tend to have greater kinetic energy)

### Elutriation segregation (dusting out) →

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

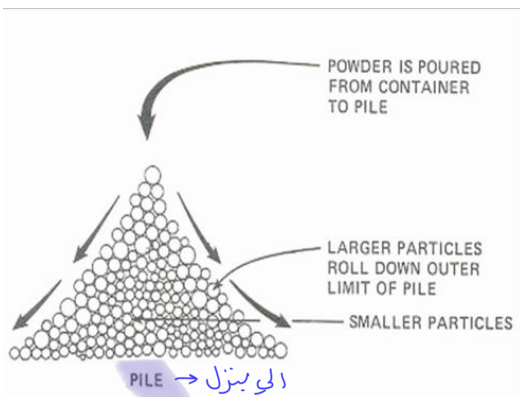


Percolation segregation:

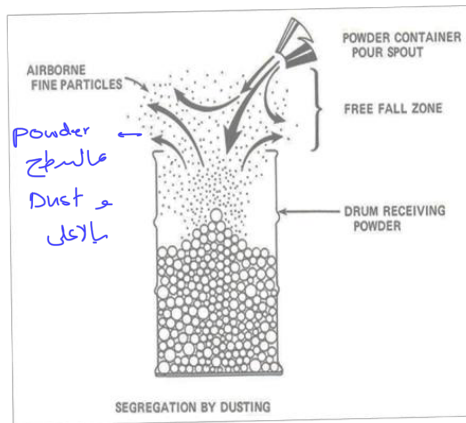


Trajectory segregation

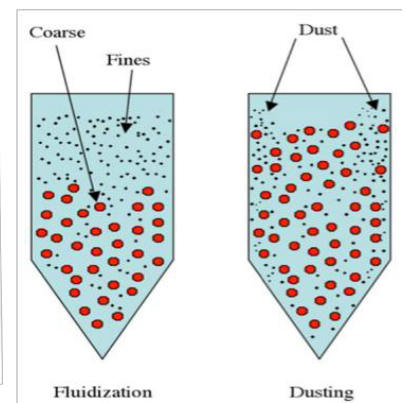
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Trajectory segregation



(Elutriation)



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# Powder segregation (demixing)

## Factors affecting segregation:

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

Factor  
Segregation  
لأنه ينتج عن  
D

### 2. Particle density light — heavy

Segregation occurs due to density differences.

لأنه لما اعمل milling اوح one size عنان Volume  
يعزل ثابتة الى يختلف الـ mass داخل مادة Volume

### 3. Particle shape

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

من سهل يتحرك

الاميل spherical لأنه ممتاز للكمين بين المسكة الـ flow  
يعزل Segregation من بداية الـ mixing

من يتحكم بالـ shape ؟ خلال Crystallization<sup>31</sup>

Size  
Size  
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.  
اعمل milling واختار الـ Fraction المناسبة  
اعمل الـ size  
اعمل الـ size
2. Milling of the components so that their size becomes small and same.
3. Controlled crystallization during production of drug or excipient to give particles of particular size or shape.  
بحكم الـ solvent  
طريقة سرعة التبريد  
طريقة سرعة التبريد  
اذا المسكة  
الـ shape
4. Selection of excipients which have similar density to the drug.

بختار الـ excipient الـ density من جهة الـ drug 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.   
 أقل ال movement راد   
 Vibration
- 7. Using equipments where several processes can be carried out without transferring the mix.   
 بتستخدم اجهزة بتعمل الحرك من خطوة مرة واحدة عن   
 ما يصل انقل من جهاز لجهاز   
 (two in one three in one -)
- 8. Production of an ordered mix.

تعمل راد potent inhaler

Case   
 ( عليه اسئلة بتجيب منك في الامتحان )

- 33 اذا المسئلة
- ① Size ياجل milling بهضرو بخار كله نفس ال size اربط عن طريق Granulation
  - ② Density (اندر) حسب Density ال drug بخار Density ال excipient
  - ③ Shape يتحكم بالرجلة الى بتجدر ال shape الى ال (crystallization) يتحكم بالتبريد او التبريد او solvent
  - ④ اذا في movement بتوقف ال ليس الى بعد movement بتوقفه جاني اخذ ال vibration ال طريقة الاصل لكن مكلفة الخانتهم اجهزة dual in one
  - ⑤ ordered mix

## Ordered mixing

ما بتجيب على كل شي

في interaction بين ال drug و excipient بحيث عمل adhesive

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

ال اساس ال ordered mixing

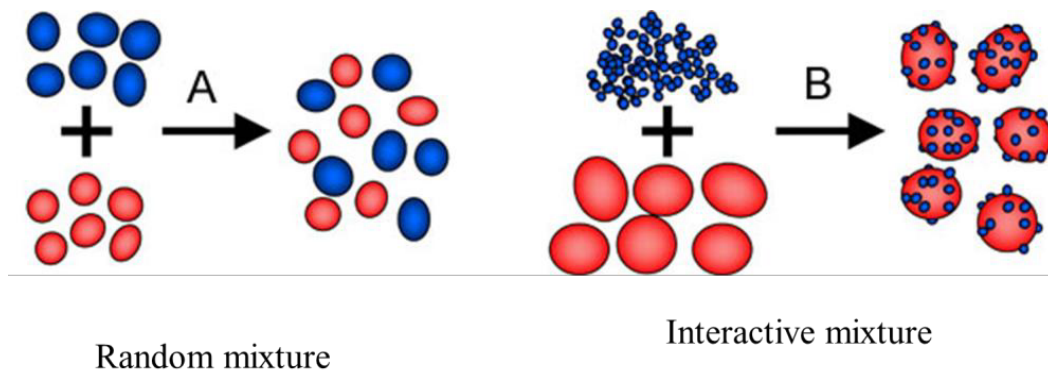
- This minimizes the segregation between small (adsorbed) particles and large (carrier) particles.

Surface activity   
 لازم في قوة من ال drug و Carrier   
 affinity بين ال drug و Carrier   
 adsorption بتأثر ال ordering

- 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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\* بعمل حبيبي ابي اذرع ال potent drug بطريقة متساوية لان ال خطأ بال Dose بال مشكلة 6 و dry powder ال sterile رينها اصل   
 inhaler   
 مايتن excipient راتل processes ال Dry powder inhaler < potent في ال Drug و Polysaccharide (safe carrier)



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## Application of ordered mixing

نزي شراب الابطال يكون في drug و 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 نزي البادول
4. Formulation of potent drugs



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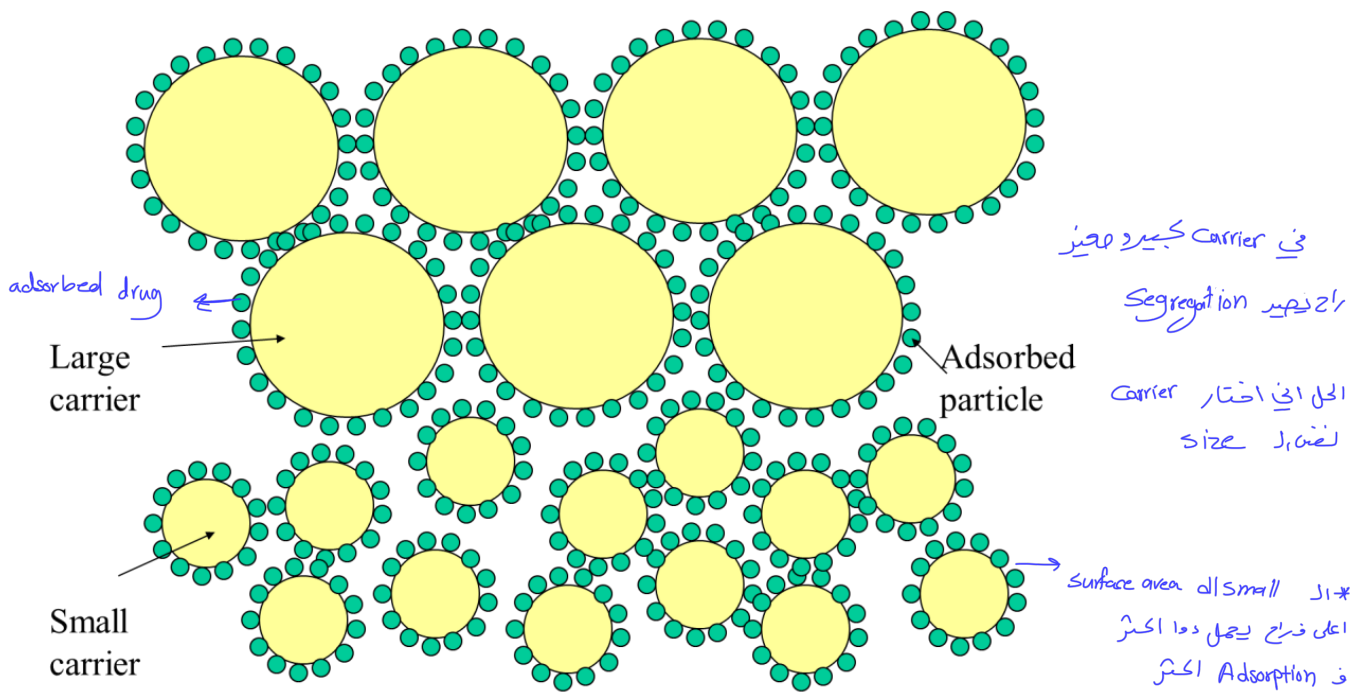
# Segregation in ordered mixes

## Ordered unit segregation

احتراق Carrier كبير و هين راح نصير Segregation زياد على particle العادية

- The carrier particles vary in size. →  
التي تحمل 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.  
راح يكون في اختلاف بكمية ادوا الموجودة

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Ordered-unit segregation

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# Segregation in ordered mixes

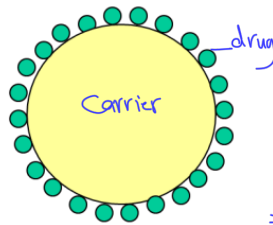
استي يزيح استي

## 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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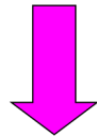
حضرنا ال ordered mix



آخر حطوة غالباً تبين مادة

لي (ببطل التعبئة) lubricant

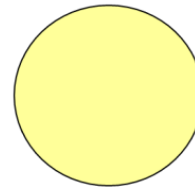
إذا كان ال affinity عال carrier surface  
من ال affinity ل drug عال carrier راح يزيح displacement



Competing particle

● Adsorbed particle

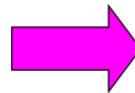
Carrier



large

small

Segregation due to size difference  
due to displacement



large size + small drug

## Displacement segregation

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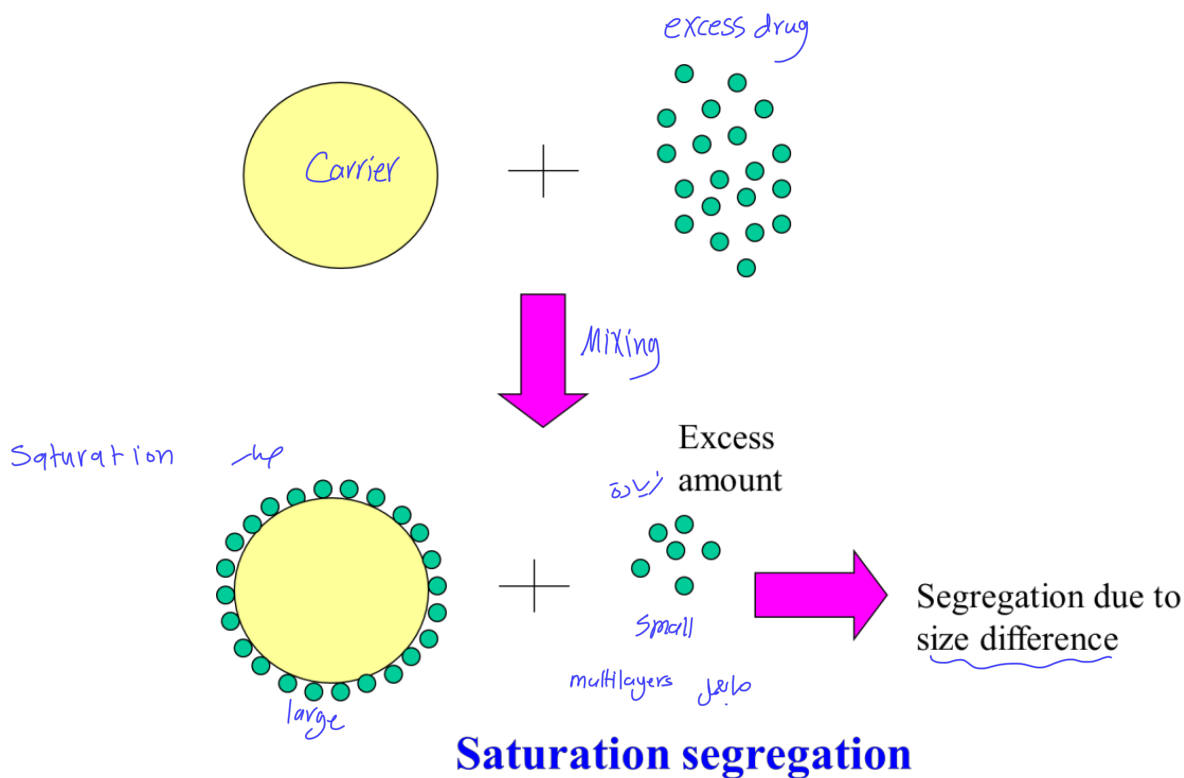
# Segregation in ordered mixes

## Saturation segregation

دواء  
carrier مع

- 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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