SPECIAL TOPICS

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Subject Topic 1 Introduction Date 29th - July No.

* API and Drug product
* R&D : Research and development
5th/July/2020 (slides)

Topic 2: Design of solid Dosage formulations

* Site of action : Where drug should affect
* The need for dosage forms:
  * Protection from gastric juice: e.g, we need drug to be digested not in which grashic juice exist
  * placement of drugs within body tissues: like needles
  * Optimal drug action: (controlled released ...) (sustained released)
    (طريقة توصيل الدواء للجسم)
    to choose which one of them
  * Use of desired vechicle for insoluble drugs:
    ⇒ use for drug insoluble in water, or blood so we should choose suitable way: ...

① Classified according to physical form: ← we will study ^^

② Oral Route: (slide)
- self-administered: not need to specialists in order to give the drug to patient.

③ Types of solid oral Dosage forms:-
- Delayed release tablets: (Protection from gastric juice)

• Orally disintegrating tablets: disintegrated by Mouth Salive

* Steps of drug delivery to the systemic circulation

mouth → GI needs time

* liquid drug → can affect faster but is needed to take large doses. → there is not dissolution unlike solid drug.

(Slid)

* Good formulation and TPP.

الدوا ما بكون لـ حاله معه مواد ثانية

active ingredient + inactive

Slid

* TPP: regulation from Pharmacopeia → ref. of Pharmacutical industry

* Dosage and adminstration → Dependent on drug

Typically (10 - 500 mg)

↓

active ingredient each capsulate

* overdosage: dose dumping ↑↑ drug in blood

* Clinical pharmacology: e.g: to distinguish between controlled released ---

* Solubility and drug dissolution (Notes)

* Solubility: maximum amount that can be dissolved in solvent

O → disintegration → small particle → ↑↑ A ↑ dissolution rate

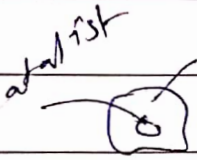
↓ size ↑ A ↑ dissolution

* Solubility and Drug Dissolution

$$\frac{dC}{dt} = \left(\frac{D \times A}{h}\right)(C_s - C_t)$$

driving force
Δ[concentration]

coeff.



redant from bulk → surface

drug from tablet → solution → Driving force
→ till reaching saturation ≡ difference in concentrat

① ↓ solubility → rate of dissolution
↳ critical.

② [C] with time

③ Surface Area → affect dissolution rate

④ ionizing materials prefere (aqueous) aq. solution

Subject 7th July 2020 Date No.

dissolution rate:
drug be out of capsulate to the surranding solution

* Partition coefficient (slid)

* lipophilicity : حب الدهون
* partition coefficient can be represented in book as log P or P (Whole drug components < active / inactive)
* bood → Lipid / → aq. or water — كيف الدواء يتوزع بين الحدود phases ?!
* ionized species not prefer organic phase

* Crystal Properties and Polymorphism (slid)

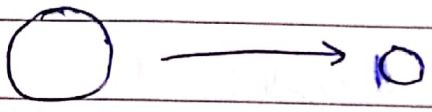
*
* to change not random crystal structure → compression, تفريغ, ...
* Stable
  metastable → barellystable chemically, physically
  → external work → تحول stable form

Stabl ↑ energy ↓
meta stable energy ↑ Higher solubility ↑ dissolution ↑

مشكلة * metastable → Stable — مشاكل بسبب ثتتر → هنا مثلا شيء التحول من meta stabe ↓ stabe — يتأثر على فعالية الدواء مع مرور الزمن

* In some properties we need it to be metable So, here we need optimization.

* Polymorphic transformations can take place during pharmaceutical processing such as particle size reduction (تصغير الحجم).



particle size reduction
we use mill (milling)
↑ energy by the mill in the particle

* Compaction and compression ↑ energy
↳ اخذ الدواء بعدها
اظهره بشكل نهائي بالتابليت

* The Seven Crystal Systems (Slid):
XRD جهاز → الاشعة → بتضرب → بعرفها → Peak حيث يكون عندنا → الزاوية
لكل زاوية بعرفها → 110 10

Title: Particle Size, Particle Morphology, and Surface area:

* apparatus used to know the shape of particle (particle / molecular level)

Particle and Capsulates?

(active ingredient + excipients = tablet)

① grounding form → to increase the particle size
→ to minimize the particle size

② Compaction and compression → Soft capsules / Hard capsules

* particle size

* Milling → Excessively small particle → aggravate problem (long acicular)

* Shape affects the flow ability

Subject Date 7th July No.

* Paracetamol : مسكنات
* compactibility : بعدما يصير compression ، بتظل على بعضها
↳ porous قليلة

* shape و أحسن particle size الهدف بكون على أحسن
↓
optimization هاي العملية بتسمى

* ال بتشتغل عليه active ingrediant ال بتشتغل عليه فعالية

كيفية تصنيعه لـ منتج ← أفضل process لإنتاج

* ↓ particle size → ↑ uniform dissolution

* Poorly soluble → ↓ dissolution rate
⇒ we aim to minimize the particle size so ↑↑ dissolution rate
* felodipine → active ingrediant احد انواع ال

* Methods to determine Particle size and Shape:
* light microscopy: UV light → index معين → Reflection معين
* SEM : اعطيني ، احجم → morphology → فاكي معقد
صورة → shape
سطح بتبع بيا تركيب

* Sieve : { particle size distribution }

NOTEBOOK

% → particle → size

* Air pemeability : expose surface ← سر
* Various gas adsorption techniques:

كمية الغاز الممتص.

غاز معين (N_2) ونقيس الغاز الي صار فيه امتصاص

ضغط غاز على هاي البارتكل ← equilibrium ←

كم ضغط الي طالع ← فرق pressure ←

هي الكمية الي صار الها امتصاص على السطح

↑ P ← بشوف كم كمية الغاز الي صار الها امتصاص على السطح

8th - July - 2020 :

Bulk Powder Properties :

interparticle : particle ○ ○ particle → between Particle

intra particle : inside particle it-self → porous / → not poros

bulk density : using powder of the particle in the graduated cylinder

Total porosity : → intra
→ inter

bject 8th - July - 2020 Date No.

tapped density: powder

→ mechanical tapping till the powder doesn't move any more
↓ volume constant

* Hausner ratio: tapped and bulk ratio
tapped ≅ bulk → flowability ↑

* melting point ≥ 50°c → drying → melting problem

* Moisture → problematic / good → optimization

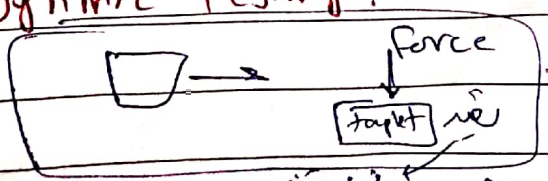
* deformation behavior → plastic / elastic → mechanical Properties

* Bio pharmaceutical Properties:
DC: direct compression

* Mechanical Properties → active / inactive
* limitations → Dynamic Testing → Tensil strength

* Quasi- Static Testing: → Tensil strength
inactive ingredient

* Dynmic Testing:



→ under the curve

Production Road

NOTEBOOK

Subject Date 12th - July No.

Exipients : (Slids) :

Exipients : (slid (80))

- are selected based on their :
- Chemical / Physical Compatibility with drug → No-rxn with the drug or separate from each other

adhesiveness → between the substances each other and with machine

(81) : diluents : أكثر المواد , liquid drug

(84) : لازم اعرف المادة الي بضيفها ↓ بساعدنا في عملية formulation

13th - July - 2020 :

Drug - excipient compatibility Study.

راجع السلايد (87) Testing → توفر الوقت لتجريب المواد

(88) stabl , not stabl → degradation

(89) 1:1 → most ~~no~~ common ratio

(90) Filler : using a lot of quantity of it (38 - 40%)

%	level 1	level 2

represent category
~~represent~~ ↓
chemical structure مادة بتمثل مجموعة من نفس

Q(91) Samples may be exposed in open pans or sealed in bottles / vials to mimic product packaging →

in order to sudy the degradation

mimic product packaging

a/c

*(Q1) Samples may be exposed in open pans or sealed in bottles/vials to mimic product packaging →
in order to sudy the degradation
mimic product packaging

NOTE: Drug-excipient compatibility study:
- need time sufficiently
- consume a lot of materials

↓

Feasible (time)

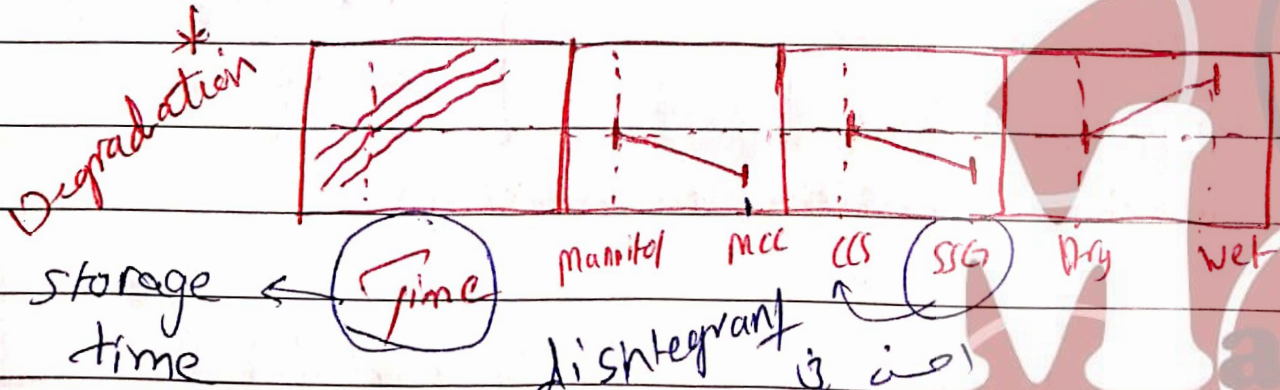
↓

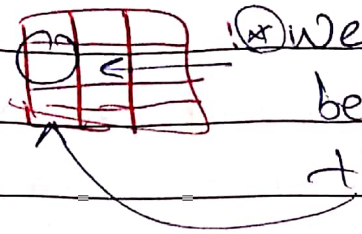
Model formulation approach

* (Q1): degradation → DSC

* (Q2): 75% RH: Relative humidity

* (Q4) * Filler 2. surfactant, Binder and lubricant did not show significance:
they didn't affect the stability



(95) * Table  (*) We study two factors between filler 1 and time for an example

* Mannoitol/CCS → affect the degradation
TRY to avoid ↵
↓
save stability of the drug

* Interaction profiles: * How different excipients react with the drug
↓
و النوع الي بدي أضيفه

15th / July / 2020.

* (97): formulations: drug + excipient. etc
active inegredient

(*) mechanical treatment for powder except mixing
(*) Direct compression (DC) consist of 3 steps:
① weigh the active inegredent and excipient and seiving → particle size
② blending
③ compression of tablet

(*) (99): Drug which are sensitive to moisture.
↓
Drug + water → degradation

Subject Date 15 July No.

* powder → granules

(100) * adhesive = binder → fluid, wetting, forces → but → drying

كيف اضمن انه الجزيئات الملتصقة ما ترجع مثل ما كانت، تظل على طريقة granules

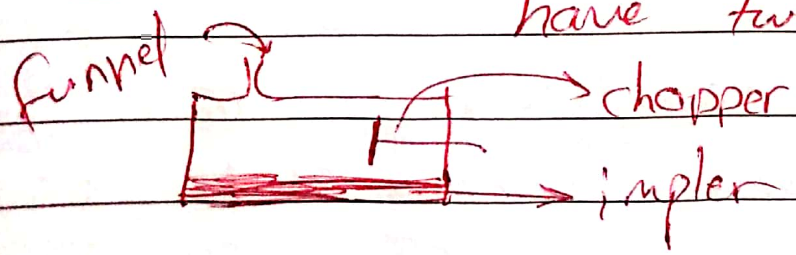
* ماضي اي شي يعتمد على طبيعة excipient في
* process ال يعتمد على النوع ← طبيعة مادة وخصائصها للدوا
اللي بدي اختارها

مثلاً: هل سيتم fluid ولا كان binder يعني fluid
هل سيتم wet granulation ولا dry granulation ؟
هل هو sensitive لل moisture ولا
مش sensitive ؟

كل ماي العوامل تساعد اختار
سؤال ان من يسأل كيف ؟
عندي ماضي الدوا ← معلومة / معلومة / معلومة ؟ نوع ال granulation* المناسب

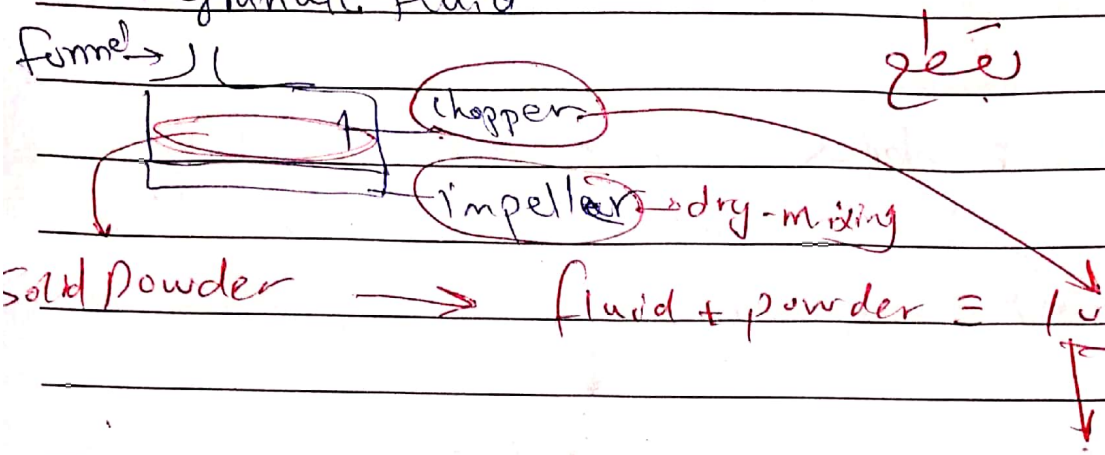
* (101) : * Planetary mixers:
مزيج ناعم + لا يؤثر ب shear كلي

(102) * closed vessels that normally have two agitators:



Subject Date 15th July No.

→ granule fluid



Solid Powder → fluid + powder = lumps

homogenous mixing

(103) spraying + fluidization = homogenous mixing

(104) : Disintegration times were greater for tablets produced from the denser granulates:

denser granulates → more time to disintegrate

→ high shear mixer

disintegration time ↓ = immediate release

→ low density

↑ disintegration ↓ disintegration

immediate release

extended released drug

(108) : Technology transfer to manufacturing Sites:

lab scale → manufacturing scale

Subject Tablet formulation Date 22th July No.

Design

NOTE

(112) Content Uniformity ≡ wet granulation for tablet

(114) The last decision to choose design we should ask about:
- class's drug
- dose
- segregation
- flow property
- sensitivity → moisture, heat

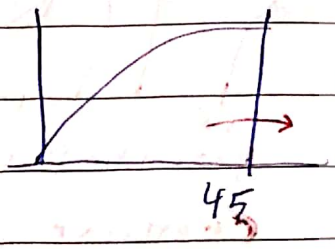
(116) Not releasing ≡ NOT dissolving ≡ NOT to reach citing action

API

release

+ excipient
* manufacturing

(118) → We care about rate of transfer mass



(119) too much lubrication ≡ Dissolution

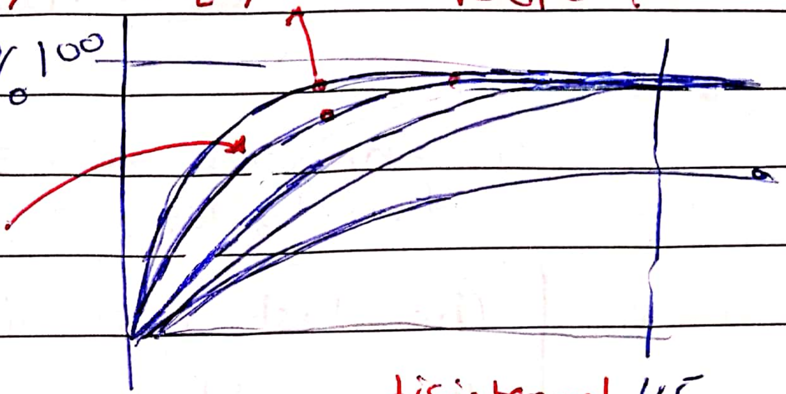
رقم سلايد

NOTE:

(122) لانه نفكر بطريقة ريح لانه اسرع واحد هو خيارنا!! اعتيادية

↓

بنفكر بطريقة منطقية بالنسبة لل excipient



disintegrant more expensive than fillers

71/25/4 → optimal

45/45/10 ✗

هاد اسرع واحد

↓

كان تقريبا الهم نفس التأثير

(125) $69.3 \geq 0.59 * D_{50} + 2.25 * hardness$ المعادلة

فقط لمثال المطروح

للظروف المخصوصة في المثال مش معادلة عامة لكل الحالات

Date No.

127

130

Residual ≡ difference between actual and predicted

Caliper ≡ measure thickness

Subject: Process operations and scalability of dosage form — Date — No.

Slide #3:

Stage	Typical...	reason
Registration	. . . .	from FDA guidance

→ from FDA, we know the number

(#4)

* CQA: critical quality attribute

(#5) (Root cause analysis) differes from (pFMEA)

deviation تدور على الاسباب ليه ما يصير عنا — تقلل من الاشياء الي Risk بندور عليها

↑ رقم RPN → بعطي priority لازالة unite — Risk ↓ مثلا

(#6)

unit	CQA	CPP
Roller compaction	Degradants	

CQA → الاشياء بفحصها

CPP → (نقدر اتحكم فيهم بالعملية)

→ cpp اذا ما قدرت اتحكم ب

→ فتحات , ناتجة عن degradation للدواء

→ process parameter الي ممكن تأثر على Roller speed

* High degradation → من الحرارة و الرطوبة اكثر تأثير

Scanned with CamScanner

Subject Video 1 (A) Date No.

Tablet manufacturing Process part A:

Different ways of manufacturing Tablets:

1. Direct compression
2. Dry granulation
3. wet granulation

* Wet granulation method:

Raw materials warehouse

Active ingredients:

Inactive ingredients.

* Dispensing room:

(بيهيأ أجزا المواد)

* Stainless steel double jacketed kettle
  Use to make strach paste

* contain strach paste and pouring past in beaker

* Ribbon type mixer: Use for mixing the active and inactive ingredients and addition of starch paste

* fluidised bed dryer

Subject (A) Date No.

Hot air is moving from lower side and moving up.
* granules are transfered in this bed for drying
* Contain granules (Diagram b)

* Tray drier:
Previous material is shifted in the drier for drying
Hot air moves parallel to these trays and material get dried.

* Oscillating granulator:
It move to and fro for making granules of required size

* Cone Mixer: It is used for final mixing use for mixing active and in active ingredients

* Dry granulation:
by this process first dummy or slug is formed which then chrushed by crusher machine and then pass through seive of different required size

* Direct compression:
In this method powder is mixed and transfered

directly in compression machine for making tablets

By all three processes:
Wet granulation
Dry granulation
Direct granulation
granules are shifted for the compression

* Tablet compression machine
Is use to compress the material and give shape to granules and fine powder into tablets

* Hopper
* Feed frame
* upper punch

* Tablets coating:
tablets are put in this coating pan and spraying gun sprinkle the coating material on tablets and tablets get coated

* polishing on tablets:
tablets are put in his pan with some polishing material and tablets are get polished

Subject (B) Date No.

* Blister packing machine:
Used for tablets blister packing

* Tablets are automatically filled in these cavities in which they are covered, sealed with Aluminium and PVC sheet.

* Printing on tablets blister strips and expiry and manufacturing date.

* Packing:

* Storage of tablets:

Subject Video #3 Date No.

Which tableting process is right for you?

Contless tablets and pills are being produced worldwide at this four successful tablet production, the following parameters have to be observed above all the compression force of the taplet punch is crucial lower compression force above a required minimum value allow higher production speed and reduce the wear of the punches, thus saving costs from maintenance and repair,
during compression the tablet can sticks to the punches and walls of the die, this can be reduced to a certain degree by using lubricants for example after compression the final tablets are characterized by their friability and hardness

Friability: describes the amount of loss of surface material from compressed tablet during handling, low friability is need to keep the tablet weight constant especially for coating processes, during packaging, coating or transport the tablets need sufficient hardness to prevent breaking, All of this has to be checked during the final characterization

these parameters and others determine the right method for tablet compression, the three most common manufacturing processes are:

1. direct compression
2. wet granulation
3. Roller compaction ≡ dry granulation.

direct compression: Is the easiest and most cost efficient process

API and functional excipients - such as filler binder or lubricant are mixed in the screw mixer, the pre-mixed powder is then compressed directly with a tablet press.

The advantages of direct compression:
- low cost
- fast and efficient → production and it for sensitive API's → works with water and heat

However, it may be difficult for low dosage due to weak content uniformity also the pre-mixed powders need good flowability to ensure a perfect fill of the cavities of the press and to avoid →

arching, bridging or rathole in during compression good flow property, can speed up the process the flow properties are measured by the angle of repose.

* A small angle indicates good flow ability if the pre-mixed powder has insufficient flow properties indicated by a high angle of repose

a wet granulation process needs to be applied!

* Wet granulation:

It produces larger and rougher particles or granules, this increases the flow properties by decreasing the particle surface and reduces the amount of dust.

granulation can be done with a wet or dry manufacturing process, for both, first step is milling and mixing all required components.

for wet granulation, a suitable granulating fluid like water binder solution or organic solvent is added to the pre-mixed powder this is then granulated with a low or high shear mixing tool to creat a wet mass.

Afterwards, the wet granules are milled

* Dried in drying oven and sift to the final particle size.
Functional excipients such as lubricants or disintegrates are only added now by blending not before as in direct compression.
After this step, the product is ready for compression.

The pros of wet granulation:

(Pros)

good distribution of API → due to good content uniformity
suitable for many excipients

(Cons)

unsuitable for sensitive APIs
not suitable for heat sensitive water
many process steps
↳ It is very costly

* Roller compaction

the process of roller compaction also called dry granulation increases flowability but has some specific characteristics for roller compaction:
one possibility to pre-mix the excipients only without the API. this premix can then

be compressed with slugs or by roller compaction. After that, it is ground to granules without the use of a fluid. Since, the API only needs to be added now.

pros

Suitable for sensitive APIs
good distribution of API
↓
due to content uniformity

Cons

more process steps → costly
specialized equipment needed

excipients
↓
roller compaction
↓
grinding to granules
↓
Sieving
↓
Mixing with API

Subject Date No.

Final Steps:

All three processes, direct compression, wet granulation and roller compaction lead to the compression of the prepared powders or granules into tablets by a rotary tablet press, whatever process for tablet manufacturing our customers choose, we can provide them with appropriate high quality excipients, as well as in-depth application expertise

bject موضوع: 2.9

Date No.

Blending, compression, And coating ·scale-up.

#6 slide:

critical process parameters

CPP	
	→ attribut get affected

lube: lubricant

Throughout batch طول الباتش

CU : Content uniformity

#8

وصل لـ homogenity

#2: homogenity in solid mixture تقاس

CV%:

CV ↑ less homogenous ↓↓CV more homogenous

S ↑ بيتأثر بـ mean ↓S في تغير في sample conc.

↳ homogenous ↑

Subject Video Unique Mixer Date No.

Solid blenders

Unique Mixers offers a wide range of standard and customized equipments.

Liquid Agitators
Solid Blenders
High viscosity Mixers
process Equipments

Solid Blenders :

* Fluidization Mixers
* Batch Plough Share Mixer
* Chopper Assembly

* Plough share Mixer with choppers
* continuous Plough Share Mixer
* Twin Shaft Paddle Mixer with chopper
* Convective Blenders
* Ribbon Blender
* Paddle Blender
* Paddle Blender with screw Discharge
* Ribbon Paddle Blender with choppers

* V blender (with intensifier Bar)
* Double Cone lender
* V blender (GMP)