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2010
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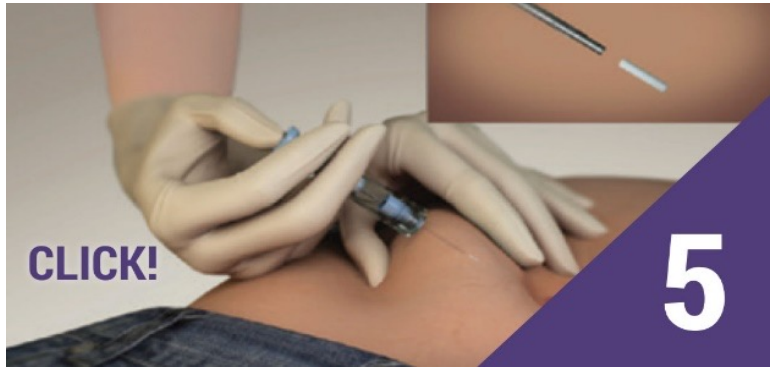
# Lec. 3: Tablet Evaluations

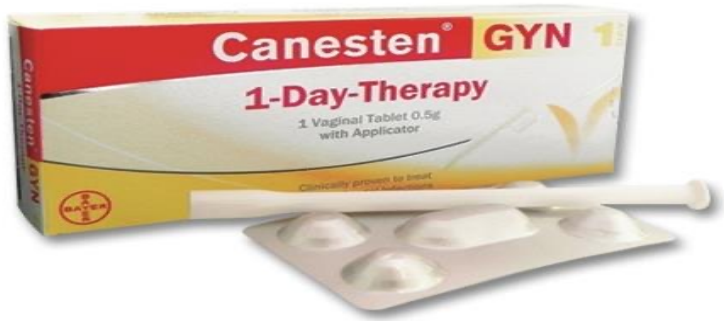
# Advantages and Disadvantages of Tablet

| Advantages | Disadvantages |
|---|---|
| Unit Dosage Form (accurate dose) | Some drugs resist compression |
| Easy to handle, store and dispense | Not ideal to hide bad taste or smell of some API |
| Easier than capsules in shipping and packaging | Difficult to formulate for drug with poor wetting properties (will be difficult for other dosage forms too) |
| Manufacturing cost is lower than most other dosage forms | Some drugs degrade if administered orally (will be difficult for other dosage forms too) |
| Their release profile is easy to control and manipulate | |

# Types of Tablets





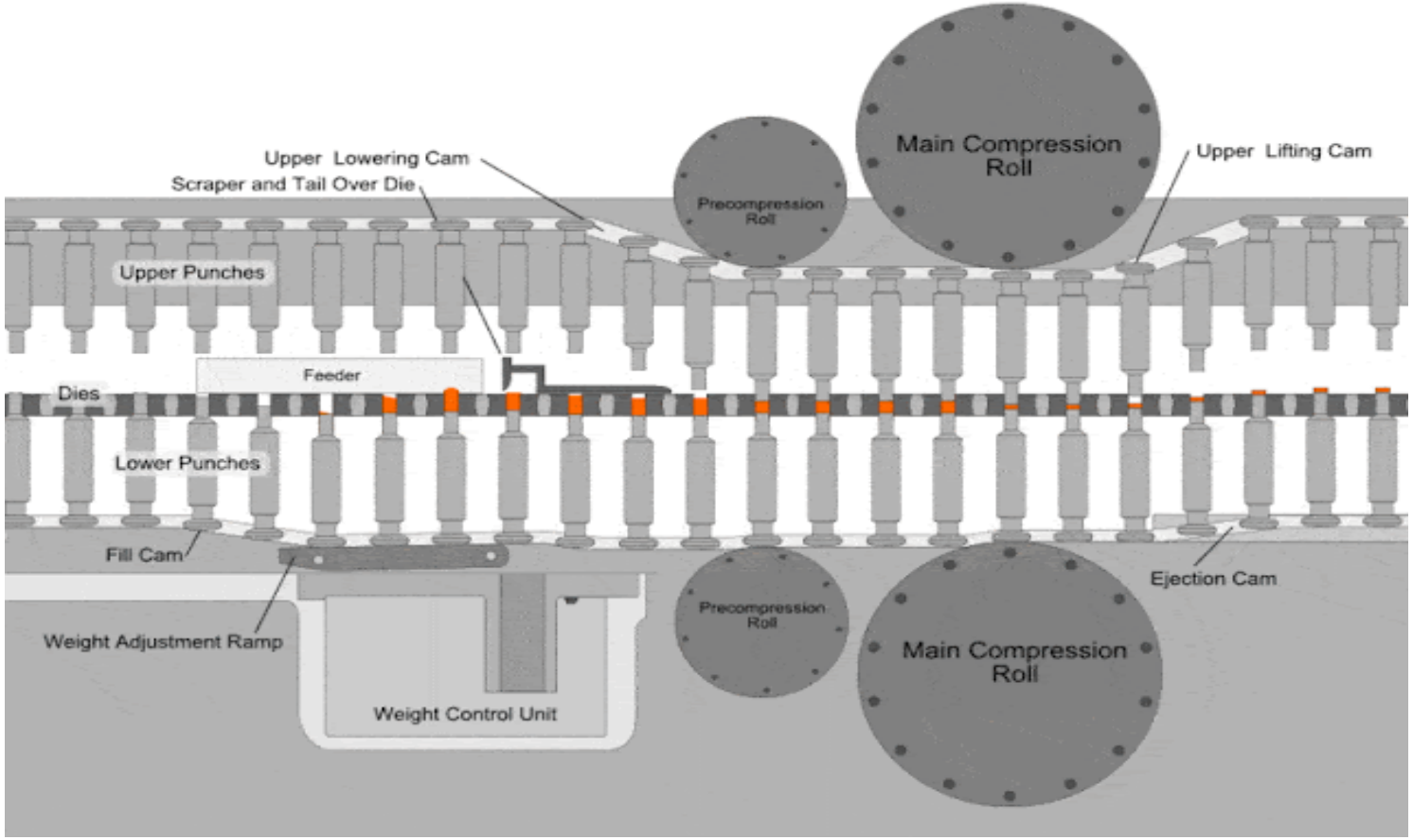


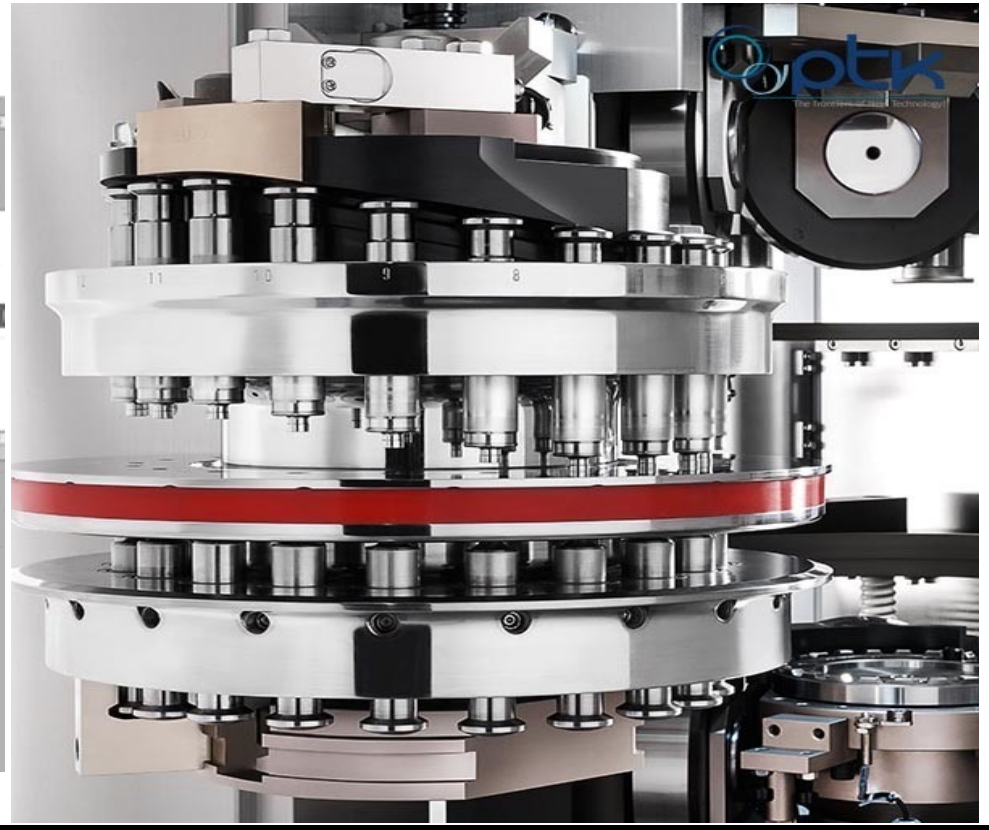

# Granulation

- Fine powder drug mostly has poor flow properties.
- Granules have better flowability and compressibility than individual ingredients.
- It ensures the consistent spread of API in the formulation.

# Compression

- Compression is the final step in the tablet formulation process.
- Requires a set of variables to be evaluated which are beyond the scope of this class.



# Tablet Ingredients

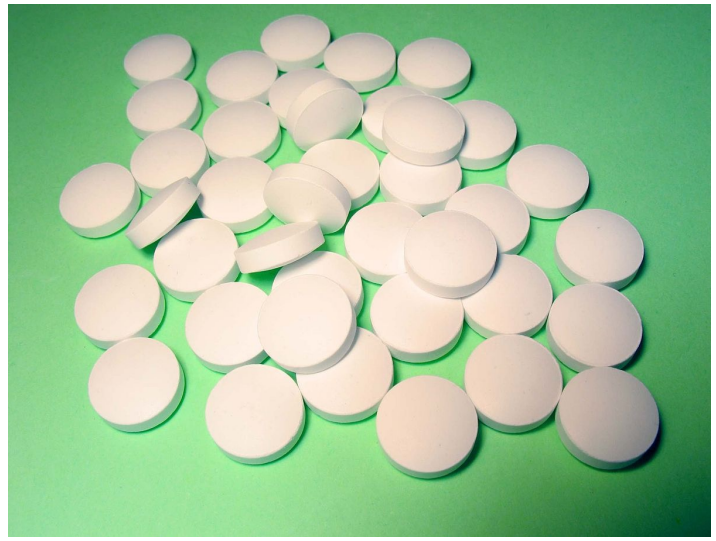
- Properties:

1. Nontoxic and legal.
2. Must be commercially available.
3. Reasonable cost.
4. Must be physiologically inert. (for excipients)
5. Must be physically and chemically stable alone and along with the other components. (not to interact with other components)
6. Free of unacceptable microbiological contaminations.
7. Must **not** alter bioavailability. (for excipients)

# Tablet Evaluation

- **General appearance**: its visual identity and overall "elegance" which is essential for:

1. Consumer acceptance.
2. Control lot-to-lot uniformity.
3. General tablet-to-tablet uniformity.
4. Monitor trouble-free manufacturing.




- The control of the general appearance of a tablet involves the measurement of a number of attributes such as the tablet's **size**, **shape**, **color**, presence or absence of an **odor**, **taste**, **surface texture**, **physical flaws**, **consistency**, and legibility of any **identifying** markings.

# Unique Identification Markings

- Print is used for rapid identification of products.
- The information included usually indicates company name, product code, and potency.
- Tablet prints **must be clear and free of flaws**.


# Organoleptic Properties (color, odor, taste, visual flaws)

- **Color** is a vital means of rapid identification and consumer acceptance.
- The color of a product must be uniform within a single tablet.
- Poor color uniformity is a problem called **Mottling** (more details on this later)**.**
- Mottling affects patient acceptance because patients will think this is a bad tablet quality and may cause some unwanted effects.

- **Odor** in a batch of tablets could indicate a stability problem.
- Such as the characteristic odor of acetic acid in degrading aspirin tablets.
- **Note**: The presence of odor may be a **characteristic** of the drug such as vitamins.

# Organoleptic Properties (color, odor, taste, visual flaws)

- **Taste** is an important property in consumer acceptance especially in chewable tablets.

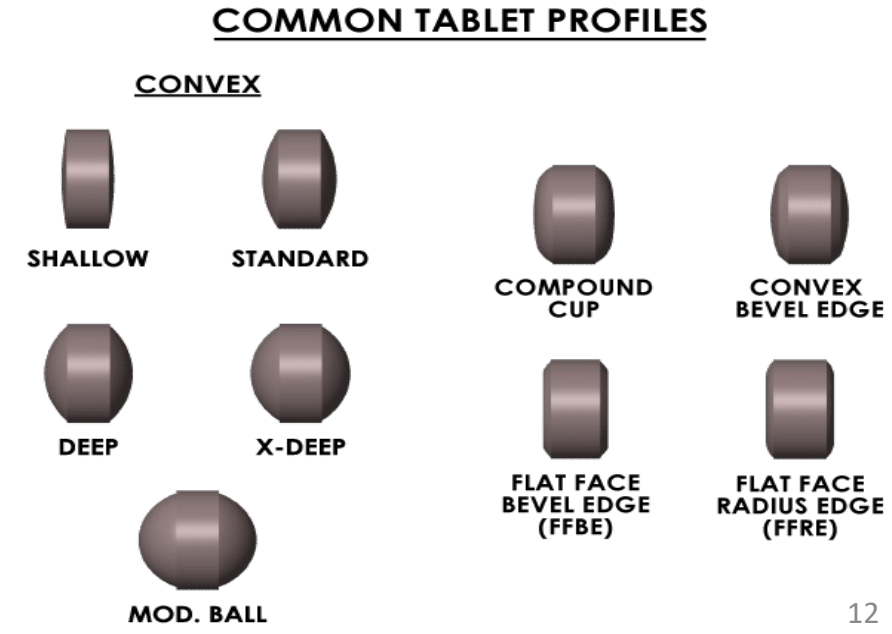
- **Tablet visual flaws:**
- Chips, cracks, contamination from foreign bodies (for example: hair, oil drops, and dirt).
- Surface texture ("smooth" versus "rough").
- Appearance ("shiny" versus "dull").
- These flaws will affect **patient acceptance** and may indicate a **formulation problem**.

# Size and Shape

- Tablet shape and diameter are determined by die shape. (**fixed**)
- Tablet thickness is the **only** dimensional variable related to the process.
- Tablet thickness can be **changed** during the process.
- The thickness should be consistent from batch to batch (indicate good manufacturing):
- **If it was not consistent:**

1. This may indicate a content uniformity problem.
2. Affect patient acceptance of the dosage form.
3. This may result in **packaging** problems.

- Tablet **shape** variation will also result in the same problem above.

# Size and Shape

- Tablet thickness is measured using a micrometer caliper (vernier caliper).
- Thickness variation should not be more than ± 5%.
  - If more than that it will indicate a poor manufacturing technique.
- It also will lead to **packaging problems** since the package is designed for a certain thickness and an increase in that thickness will lead the tablet to not fit in the packaging.

# Tablet Hardness (Non-Official)

- Tablets must withstand **mechanical strength** during manufacturing, packaging, shipping, and handling.
- Tablets require some hardness and resistance to withstand reasonable abuse when in the hands of the consumer such as bouncing about in a woman's purse in a partially filled medication bottle.
- Tablet hardness is related to disintegration time (hard tablets **may** undergo slow disintegration).
- Tablet hardness can be varied with 1) die fill and 2) compression force. In addition to the **amount of binder** added
  - At a constant die fill, hardness values increase, and thickness decreases as additional compression force is applied (to a certain limit).

# Tablet Hardness (Non-Official)

- Hardness can change also with variable die fill when the compression force is constant, hardness increases with increased die fill and decreases with lower die fills.

- Intact and uniform tablets are an important requirement for patient acceptance.
- **The tablet hardness test** is the force required to **break the tablet** in a **diametric compression test** (it is called tablet crushing strength).
- The test can be done by **Monsanto** or **Pfizer** hardness tester.
- https://youtu.be/q7PFpwa_hg4

# Tablet Friability (USP official test)

- Tablet **hardness** is not an absolute indicator of good tablets since some formulations tend to "cap" on attrition, losing their crown portions when compressed into very hard tablets. ➔ we need a friability test
- Another measure of a tablet's strength is its friability.
- **A friability test** is performed to ensure the tablet stays intact under mechanical pressure during shipping and handling.
- Tablets that tend to powder, chip, and fragment when handled, **lack elegance and consumer acceptance**.

# Tablet Friability

- The laboratory friability tester is known as the **Roche friabilator**.
- It revolves at 25 rpm, dropping the tablets a distance of six inches with each revolution.
- **Test limit**: Conventional compressed good tablets are expected to lose **less than** 1% of their weight.

# Drug Content and Release

- A physically sound tablet may not produce the desired effects.
- To evaluate a tablet's potential for efficacy, the amount of drug per tablet must be monitored from tablet to tablet and batch to batch, and a measure of the tablet's ability to release the drug must be ascertained. ➔ other tests are needed!
- Other tests for tablet Evaluation: (Official USP tests)

1. **Weight variation test.**
2. **Content uniformity test.**
3. **Disintegration test.**
4. **Dissolution test**.

# Weight variation (USP official test)

- The weight of the tablet is routinely measured to help ensure that a tablet contains the proper amount of the drug. (more details will be in the lab)
- Tablet-to-tablet weight must be within the USP weight variation limit.

**Factors that lead to weight variation can be:**

- Poor flow of tablet formulation.
- Poor machine setup. (more on that at the end of the lecture).

# Weight Variation

1. The weight variation test is a good indicator of content uniformity **in a case** where the active ingredients represent a good percentage of tablet weight.
   - Such as the **Aspirin tablet**, the acetylsalicylic acid represents about **90%** of the tablet's weight.➔ Here, the weight variation test is an important test for content uniformity.
2. **On the other hand**, a weight variation test is of limited importance in very potent drugs where the effective dose is very small.
   - For example, **digoxin tablet** contains less than **1%** API.

| Average weight of Tablets (mg) | Maximum Percentage Difference Allowed |
|---|---|
| 130 or less | ±10 % |
| 130- 324 | ±7.5 % |
| More than 324 | ±5 % |

# Content Uniformity Test (USP official test)

- It is performed **to** ensure the variation of active pharmaceutical ingredients is within the limit.
- At least the contents of 9 of 10 tablets must be within 85%-115% of the theoretical drug contents and only one tablet is allowed to be within 75%-125%.
- **Three** factors can directly contribute to content uniformity problems in tablets"

1. Nonuniform distribution of the drug substance throughout the powder mixture or granulation,
2. Segregation of the powder mixture or granulation during the various manufacturing processes.
3. Tablet weight variation.

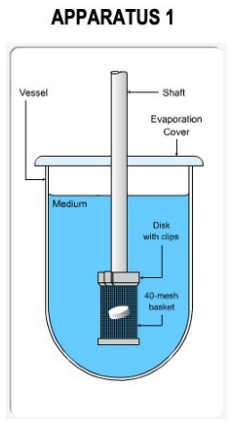
# Disintegration Test (USP official test)

- **The disintegration process** is the process of tablet breakdown into smaller particles or granules.
- To test if the tablet is able to disintegrate inside the body within a reasonable time we need a disintegration test. ➔
- The disintegration test can be performed using the USP disintegration apparatus.
- **Test Limit**:
  - Generally, tablet disintegration time is below 30 minutes.
  - **An enteric-coated** tablet is required to stay intact at **least for one hour** in the apparatus.

# Dissolution Test (USP official test)

- Is required to make sure that the tablet material after disintegration is able to go into the solution at an appropriate rate.
  - The drug in solution means it is ready for absorption.
- This means that dissolution testing will give us an **idea about formulation efficacy and bioavailability**.
- The easiest way to test that is using the simulation apparatus which is called the **USP dissolution apparatus.** (more on that in the lab).



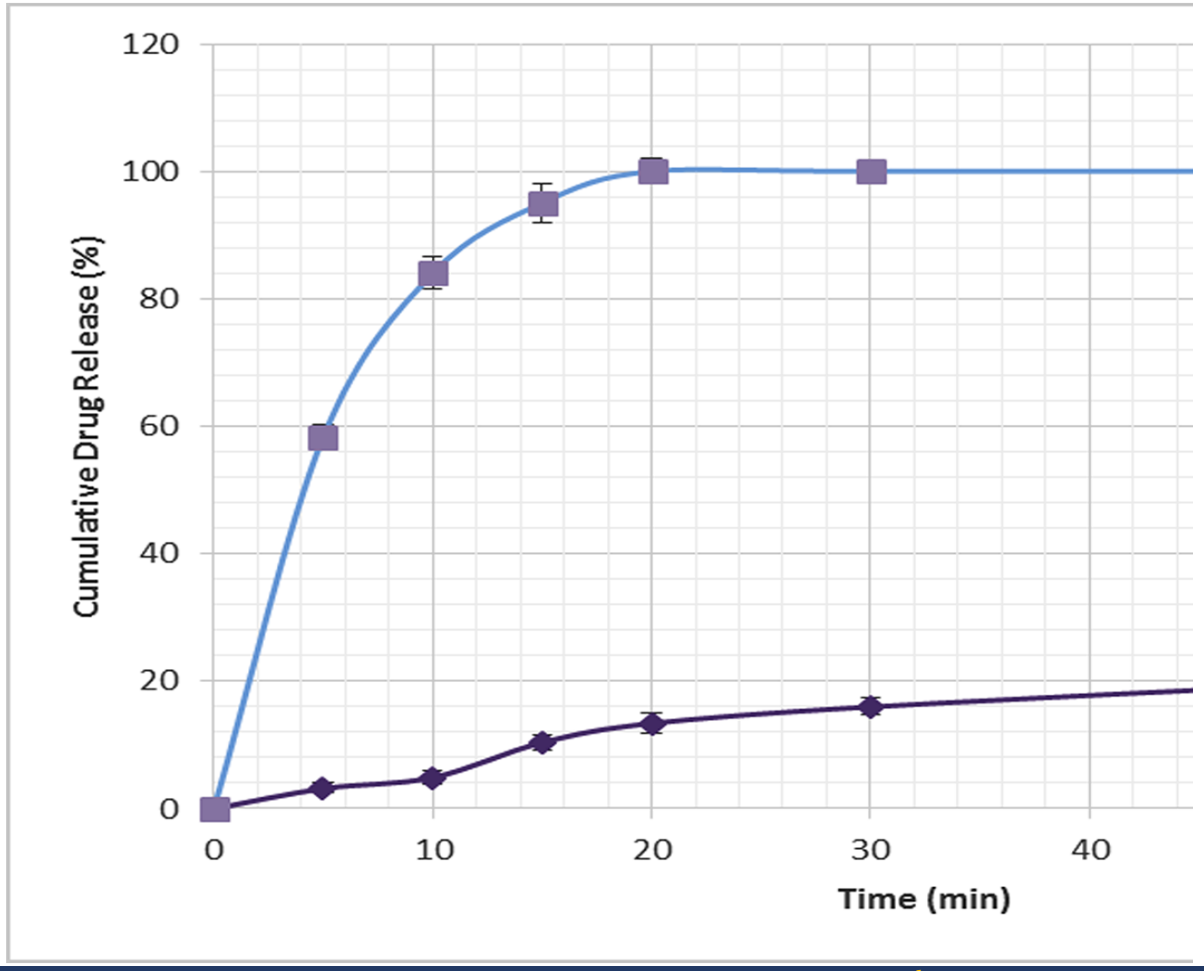


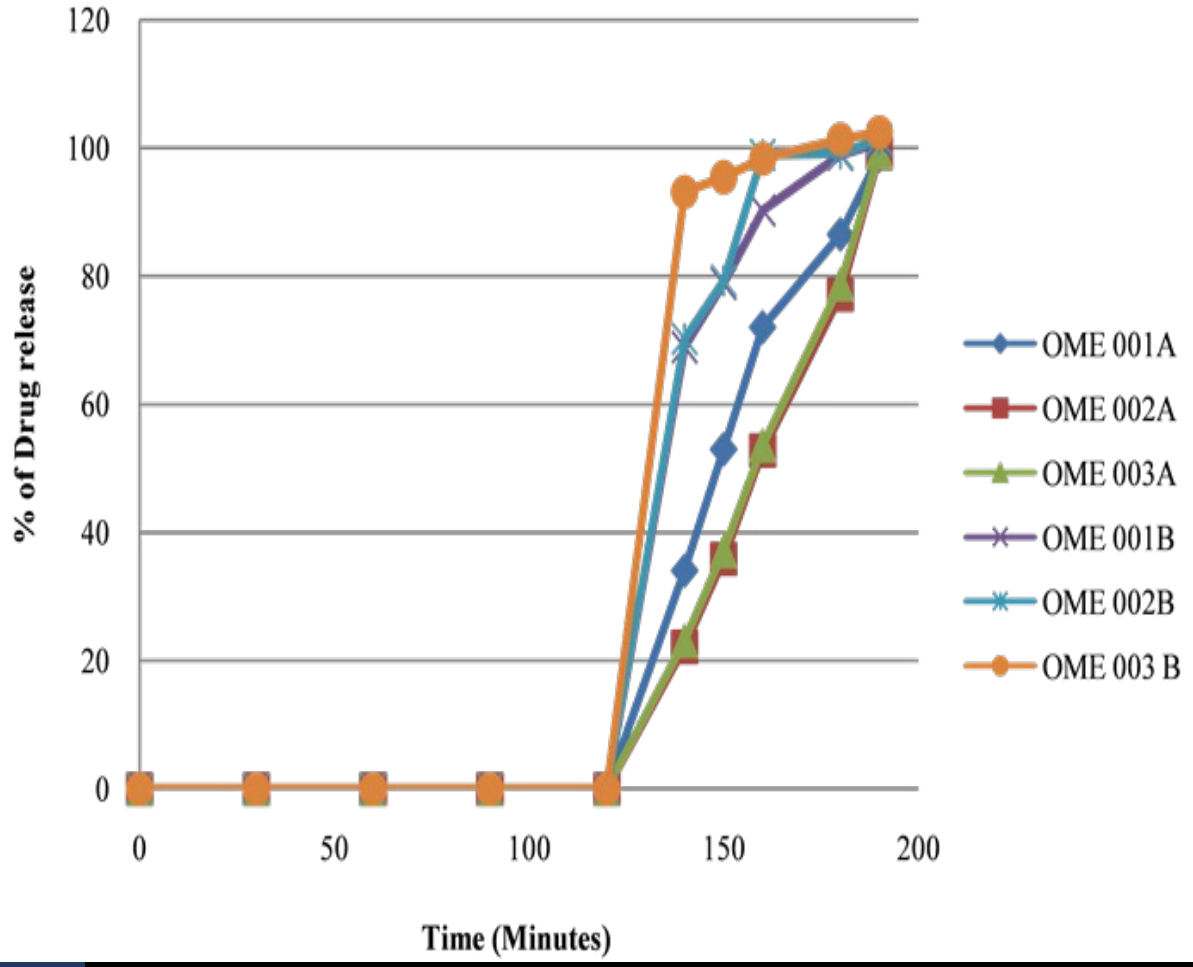
# Importance of Dissolution Testing

1. It guides formulation and product development toward **product optimization**.
   - Dissolution studies in the early stages of a product's development allow **differentiation** between formulations and correlations identified with in **vivo bioavailability data**.
2. Manufacturing may be monitored by dissolution testing as a component of the **overall quality assurance** program.
3. Consistent in vitro dissolution testing ensures **bioequivalence** from batch to batch.
4. It is a **requirement for regulatory approval** of marketing for products registered with the FDA and regulatory agencies of other countries.

# Dissolution

- Dissolution results is plotted as a release % vs time.



# Dissolution Testing

- The goal of **in vitro** dissolution testing is to **provide a reasonable prediction** of or correlation with the product's **in vivo** bioavailability.
- **BCS System** (Biopharmaceutics Classification System):
- The system relates combinations of a **drug's solubility (high or low)** and its **intestinal permeability** (high or low) as a possible basis for predicting the likelihood of achieving a successful in vivo–in vitro correlation (IVIVC).
- Using this system, drugs are placed into one of four categories as follows:

| | |
|---|---|
| I<br>High Solubility and High Permeability | II<br>Low Solubility and High Permeability |
| III<br>High Solubility and Low Permeability | IV<br>Low Solubility and Low Permeability |

# How Results of Dissolution Test are Interpreted

- **For Category I** (High Solubility; High Permeability): an IVIVC may be expected if the dissolution rate is slower than the rate of gastric emptying
  - **Gastric emptying is the rate-limiting** step here because the drug has good solubility and permeability (no problems).
- **For Category II** (Low Solubility; High Permeability): dissolution may be the rate-limiting step for absorption, and an IVIVC may be expected from dissolution test.
- **For Category III** (High Solubility; Low Permeability): permeability is the rate-controlling step, and only a limited IVIVC may be possible after dissolution test.
- **For Category IV** (Low Solubility; Low Permeability): significant problems are likely for oral drug delivery (Dissolution may not give a good indication)

# Processing Problems

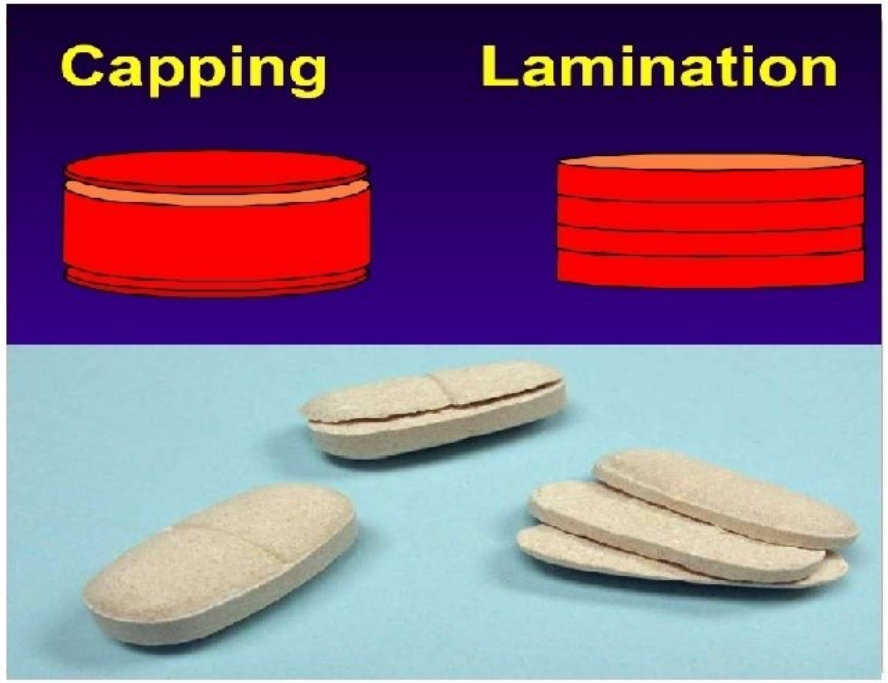
# Processing Problems

- A final tablet formulation can undergo several problems after they being compressed even after packaging, shipping, storing, and patient handling.
- Three types of problems:

1. **Problems Related to tablet processing and manufacturing.**
2. **Problems related to excipient.**
3. **Combination of both.**

# Problems Related to Tablet Processing

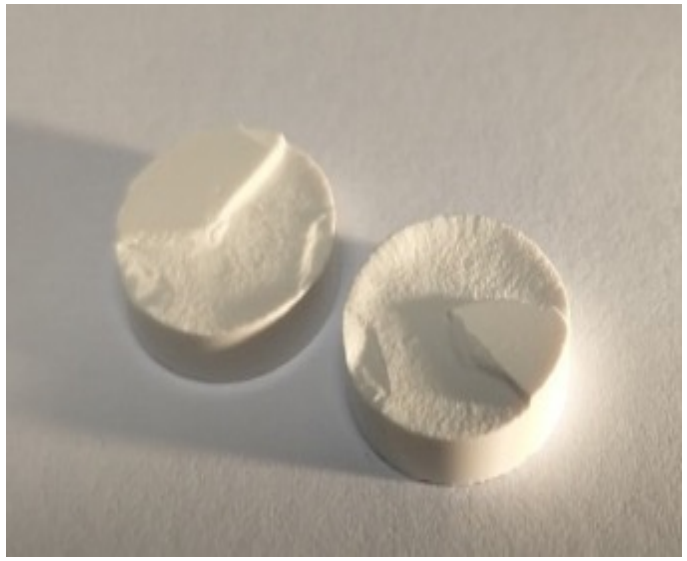
- **Capping and Lamination**
- **Capping:** Partial or complete separation of tablet top or bottom crown from the main body of the tablet.
- **Lamination:** Complete separation of the tablet into two or more distinct layers.
- These processing problems are readily apparent **immediately** after compression.
- These also may happen **later** (after hours or even days). ➔
  - This is easily diagnosed during a **friability test**.



# Problems Related to Tablet Processing

- **Causes of capping and lamination:**

1. In the past, the problem was attributed to air entrapment in the granular material that is released after compression.
2. However, research has shown that capping and lamination are due to the deformational properties of the formulation during and immediately after compression. (see next slide). This is the main reason for this problem.
3. The choice of excipient especially the **binder** may be a reason for this problem.
4. Too dry granules produce a tablet that tends to cap or laminate for lack of cohesion.
5. Incorrect compression machine setup (secondary reason).



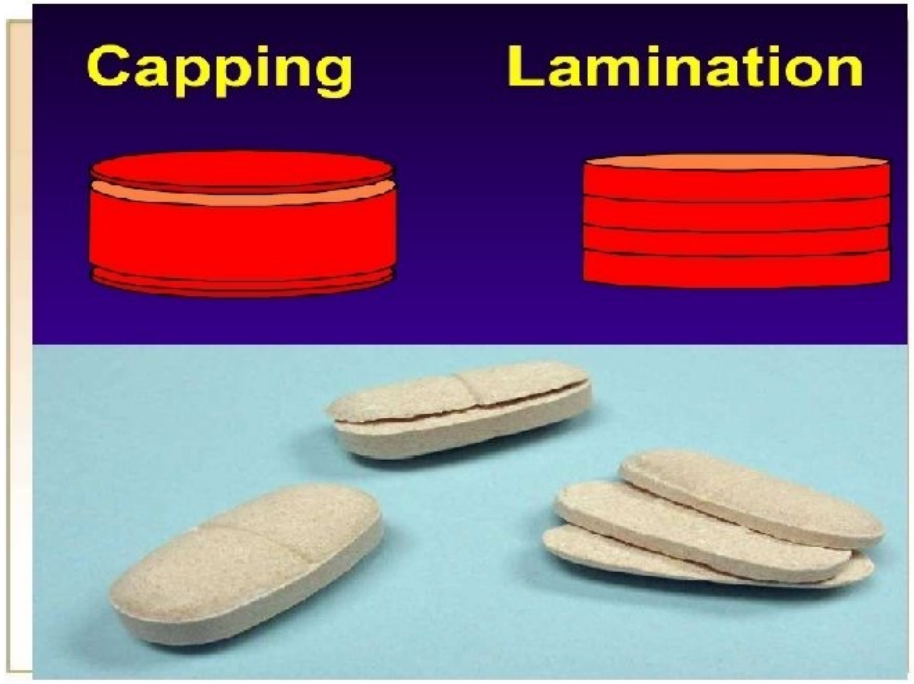
# Causes of Capping and Lamination

Deformational changes (reason 2 from the previous slide):

- During compaction particles undergo plastic deformation to produce die wall pressure **greater than what can be relieved by the elastic recovery** when punch pressure is removed.
- This will **initiate a crack** that will cause fracture upon decompression.
  - As the compact is ejected, the die-wall pressure falls to zero. The emerging portion of the compact expands while the confined portion cannot, **thus** concentrating shear stresses at the edge of the die and causing a break to develop.
- Tablets that do not fracture have the **ability to relieve** the shear stresses developed.
- This stress relaxation is **time-dependent**; therefore, the occurrence of tablet fracture is also time-dependent.➔ it may happen later on time.

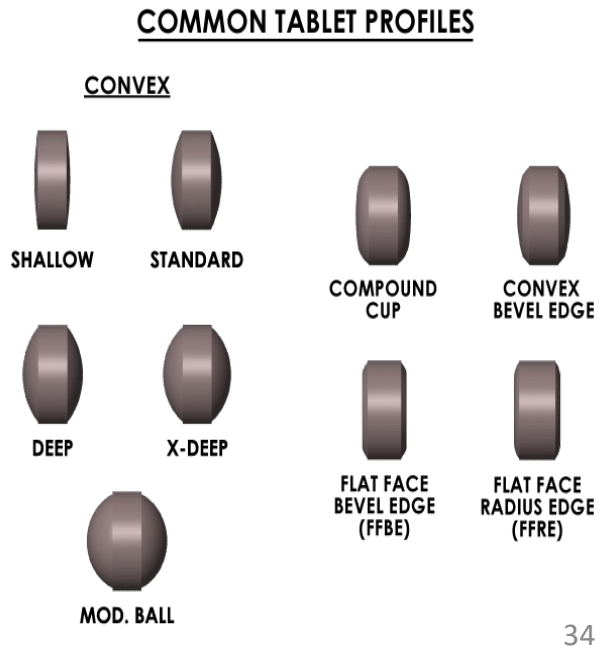
# Problems Related to Tablet Processing

- **Note: In addition to the previous reasons, lamination can also result from the following:**
- It can also result from **over compression** in which strong force will result in particles flattening and not binding correctly with each other.
- If the tablet is **too thick** this will **not** allow the particles to be compressed and bind with each other correctly.
- ➔ we have 7 possible reasons for capping and lamination and **reason 2** is the most probable (important) one



# Solution for Capping and Lamination:

1. **Slow down** the compression speed and decrease the main compression pressure in order to allow air to escape and decrease the relaxation pressure.
2. Use the **precompression step** in which the tablet is compressed with light force to pre-form the tablet before main compression.
3. Make sure you are using the **right excipients**.
4. Using **another tablet shape** may resolve the problem for example the **flat-end** tablet has a lower tendency to fracture.
   - A deep concave punch produces a tablet that cap. Because the curved part of such tablets expands radially while the body of the tablet cannot.
5. **Avoid over-drying of granules**. Excipients such as polyethylene glycol 4000, and methylcellulose can help to maintain a proper moisture level.



# Problems Related to Tablet Processing

- **Cracking**:
- The appearance of small cracks on the tablet surface (top or bottom) rarely appears on the sides.

1. This is due to the rapid expansion of the tablet after compression.
2. Also, poor granulation (dry) and working in a cold environment.

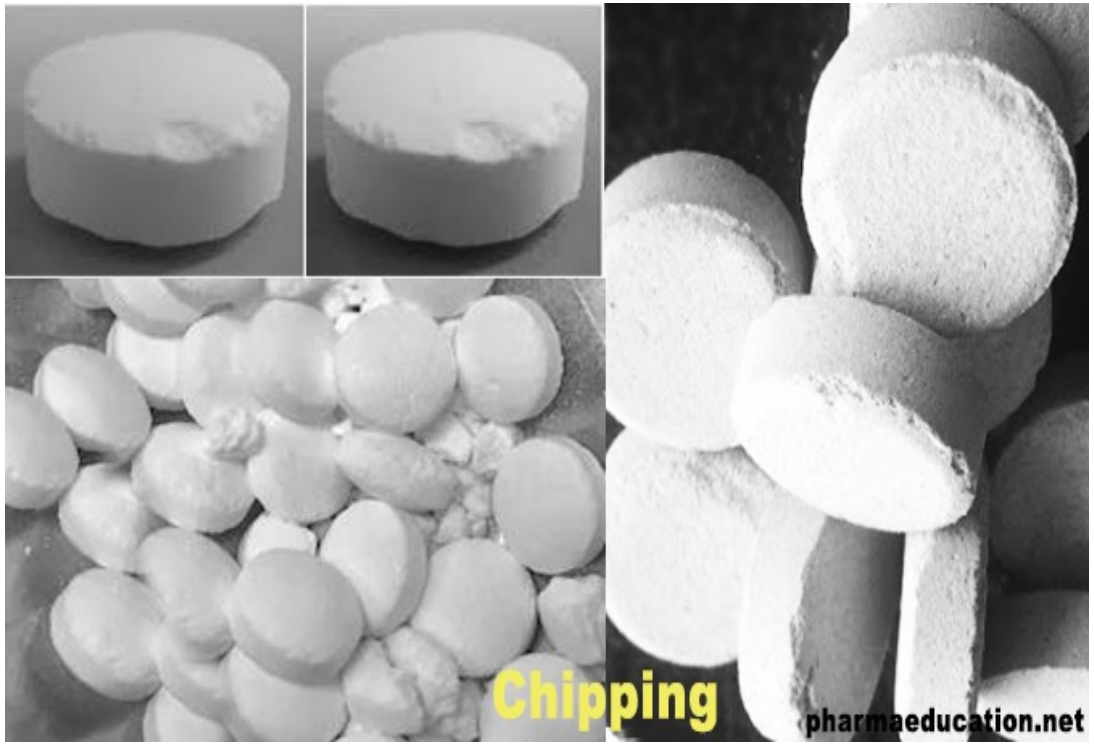
- **The solution** is to improve tablet formulation and adjust the amount of **binder** used in granulation.

# Problems Related to Excipients

- **Chipping**:
- Breaking **edges** of the tablet after compression or during shipping and handling.

1. The cause could be **poor particle flow** due to **insufficient lubrication** in which tablets are sticking in the machine.
2. It could be a poor formulation setup in which insufficient drying.

- The **solution** is to adjust the amount of **lubricant** and tablet formulation.



# Problems Related to Excipients

- **Sticking:**
- Tablet material **sticking to the die wall or punch** faces (tablet is still intact tablet).
- Serious sticking can cause chipping.
- The cause could be:
  1. **Too much moisture**,
  2. **Inadequate lubricant** and/or
  3. **Too much binder**.
  4. In addition, **low melting point excipients** such as stearic acid (lubricant) may soften if the temperature gets too high during the compression process which may cause sticking.

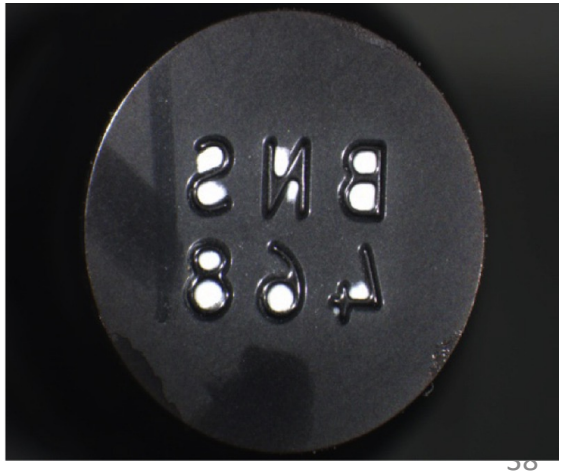
- The solution is to properly formulate tablet granules and adjust the amount of lubricant in the formulation.

# Problems Related to Excipients

- **Picking**:
- A **small portion** of the tablet surface sticks to the punch faces.
- Mostly occurs with tablets with imprints, especially with letters like B, O, and A.
- The **solution** is to:

1. Adjust the amount of lubricant and properly dry the granules.
2. Also, lettering should be designed as large as possible.



# Problems Related to Excipients

- **Mottling:**

1. **Unequal** distribution of color on a tablet.
   - It can happen when using a drug that has a color that differs from the color of excipients or a drug whose degradation products are colored.
   - It also can happen due to improper use of dyes.

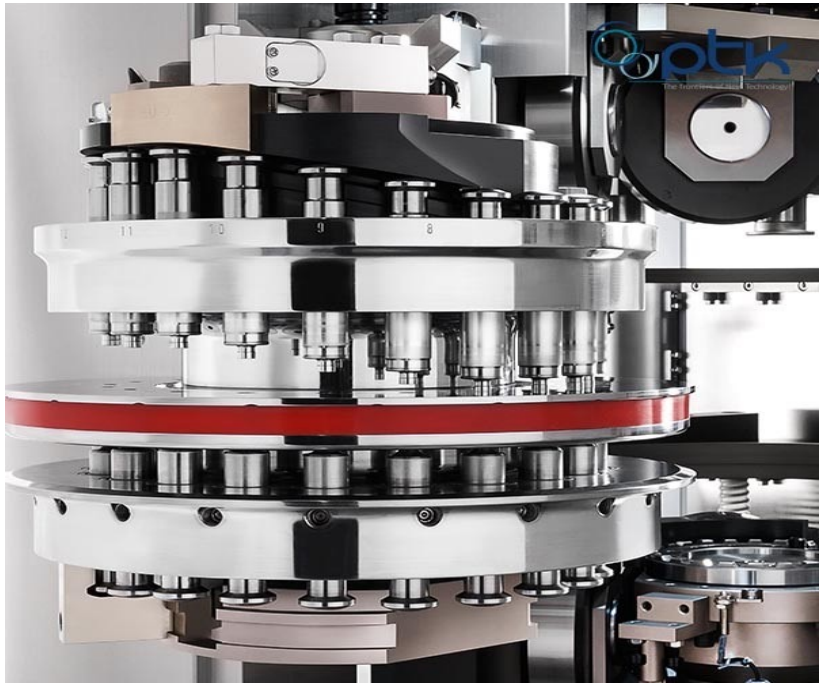
- Generally, this problem occurs when using a colorant material.
- To solve this:

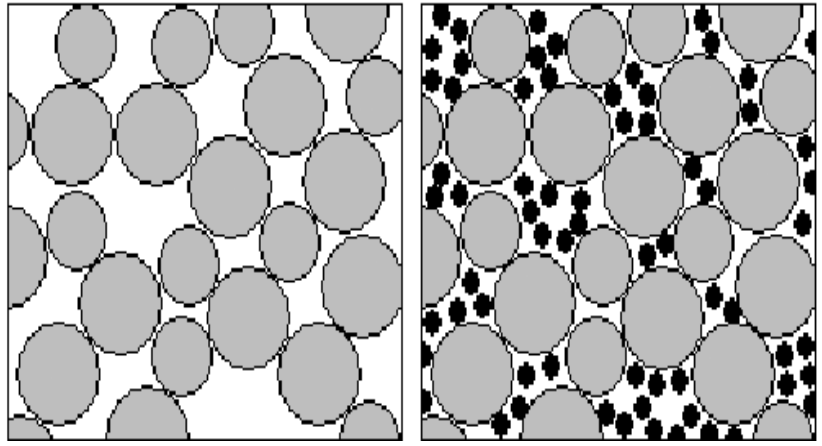
1. **Mix the dye well** during granulation and/or
2. **Change the solvent system for the dye.**
3. Make sure that the **dye is sieved** before adding to the mixture so no big chunk is present in the dye powder.

# Other Problems

- **Weight variation**:
- Tablets have different weights that are outside USP limits for weight variation.
- **Causes:**
- **A- Die Filling problems** occur when:

1. There is a variation in the lower punch length by a few thousandths of an inch. This will cause die filling to be different and lead to weight variation problems.
2. There is a **variation in granule size** and size distribution of granules. Non-homogenous granules will affect how **void spaces** between particles are filled.





# Weight Variation

**B- Poor flow**:

- Insufficient **lubricant** and glidant.
- Poor design of the hooper.

**C- Poor Mixing**:

- This may cause lubricant and glidant not to be thoroughly distributed.

- Solution: Proper formulation, tooling, and control program will minimize the weight variation problem.

# Other Problems

- **Double impression**:
- Occurs in tablet with **print** or score line.
- **Causes**: The **punch rotates** slightly when compressing the tablet which might result in an unclear print or line.
- Note: This problem is more common with machines that use pre-compression.
- The solution is to control the compression process and maintain the machine.

# Other Problems

- **Uneven breakage**:
- Tablets don't break evenly.
- The **causes** are:

1. **coarse granules** and
2. **improper mixing**.

- The **solution** is to mix well and reduce the size of granules.

# Other Problems

- **The disintegration time is too long.**
- Tablets take a relatively long time to disintegrate.
- The **causes** can be due to:
  1. Using an **excessive amount of binder.**
  2. High compression pressure, or
  3. Insufficient **disintegrant**.
- The solution is to adjust tablet formulation and use the proper amount of excipients.