TABLET EVALUATION

PART 8

INDUSTRIAL PHARMACY

5TH STAGE

1ST SEMESTER

TABLET EVALUATION

To design tablets and later monitor tablet production quality, quantitative evaluations and assessments of a tablet's chemical, physical, and bioavailability properties must be made.

NON-OFFICIAL TESTS

A. General Appearance

Its visual identity and overall "elegance," essential for:

1) Consumer acceptance
2) Control of lot-to-lot uniformity
3) Monitoring trouble-free manufacturing.

THE CONTROL OF THE GENERAL APPEARANCE OF A TABLET INVOLVES:

I. Tablet's size
II. Tablet's shape
III. Tablet's color
IV. Presence or absence of an odor
V. Presence or absence of a taste
VI. Surface texture
VII. Physical flaws
VIII. Consistency
IX. Legibility of any identifying markings.

I. SIZE AND SHAPE

A compressed tablet's are determined by the tooling during the compression process.

THICKNESS OF A TABLET: is the only dimensional variable related to the process.

a) At a **constant compressive load**, tablet thickness varies with changes in die fill, with particle size distribution and packing of the particle mix being compressed, and with tablet weight.

b) while with a **constant die fill**, thickness varies with variations in compressive load.

NOTE:

Tablet thickness is consistent batch to batch or within a batch only if:

1. The tablet granulation or powder blend is adequately consistent in particle size and size distribution.
2. The punch tooling is of consistent length
3. The tablet press is clean and in good working order.

Tablet thickness should be controlled within a ±5% variation of standard value.

MEASUREMENT OF THICKNESS

A. The crown thickness of individual tablets may be measured with a micrometer

1. Permits accurate measurements
2. Provides information on the variation between tablets.

B. Other techniques involve placing 5 or 10 tablets in a holding tray (total crown thickness may be measured with a sliding caliper scale).

Adv.: 1. more rapid than a micrometer in providing an overall estimate of tablet thickness in production operations.

2. Used only if the punch and die tooling standardizes and the tablet machine is functioning properly.

Disadv.: does not as readily provide information on variability between tablets.

IMPORTANT NOTES

A. Thickness control to facilitate packaging.

Problems:

a) Difficulties in the use of unit dose and other types of packaging equipment (if the volume of the material being packaged is not consistent).

b) Variable thickness of tablets (relates to consistent fill levels of the same product container with a given number of dosage units).

B. Weight of the tablet effected by:

i. The physical dimensions of the tablet

ii. Density of the materials and their proportion.

C. The size and shape of the tablet can influence:

1. Choice of tablet machine
2. P.S. for the granulation
3. Production lot sizes
4. Packaging operations
5. Cost to produce the tablet.

D. The shape of the tablet alone can influence the choice of tablet machine used.

Ex: Shaped tablets requiring "slotted punches" must be run at slower speeds than are possible round tablets using conventional punches?

Because of the nonuniform forces involved within a tablet during compression

The more convex the tablet surface, the more likely it is to cause capping problems

Forcing the use of a slower tablet machine or one with precompression capabilities.

II. UNIQUE IDENTIFICATION MARKINGS.

Technique: unique marking on the tablet in addition to color, to aid in the rapid identification of products **(embossing , engraving, or printing)**.

Types of informational marking placed on a tablet:

a. Company name or symbol
b. Product code (e.g. National Drug Code (NDC) number)
c. Product name
d. Product potency.

III. ORGANOLEPTIC PROPERTIES.

a) **Color** (rapid identification and consumer acceptance).

Adv.: The color of a product must be uniform within a single tablet also from tablet to tablet, and from lot to lot.

Disadv.: 1- Nonuniformity ("mottling") of color can lacks esthetic appeal.

2- Consumer can recognize nonuniformity of content and general poor quality of the product.

HOW TO DISTINGUISH THE DIFFERENCE IN COLOR?

A. Eye: cannot discriminate small differences in color nor can it precisely define color.

Visual color comparisons against some color standard.

Color standards are subject to change with time

Frequent redefinition

Gradual and significant change in acceptable color.

B. Machines like:

i. Reflectance spectrophotometry
ii. Tristimulus colorimetric measurements,
iii. Microreflectance photometer (measure the color uniformity and gloss on a tablet surface).

b) Odor (indicate a stability problem)

Examples:

1. Odor of acetic acid (degrading aspirin tablets).
2. Odor of the drug (vitamins have a characteristic odor).
3. Added ingredients (flavoring agents have pleasant odors).
4. The dosage form (film-coated tablets usually have a characteristic odor).

c) **Taste** (important in consumer acceptance of chewable tablets).

Many companies utilize taste panels to judge the preference of different flavors and flavor levels in the development of a product.

A tablet's level of flaws such as:

Chips, Cracks, Contamination from foreign solid substances (e.g., hair, drops of oil, and "dirt"), Surface texture ("smooth" versus "dull")

Method of detection:

1. Visual inspection techniques 2. Electronic devices.

IV. HARDNESS AND FRIABILITY.

Tablets require a certain amount of strength, or hardness and resistance to friability.

Properties:

1. Withstand mechanical shocks of handling in manufacture, packaging, and shipping.
2. Adequate tablet hardness and resistance to powdering and friability are necessary requisites for consumer acceptance.
3. Relationship of hardness to tablet disintegration and more significantly, to the drug dissolution release rate.
4. The monitoring of tablet hardness for drug products that possess real or potential bioavailability problem or that are sensitive to altered dissolution release profiles as a function of the compressive force employed.

HARDNESS DETECTION:

A. The strength of a tablet was determined by breaking it between the second and third fingers with the thumb acting as a fulcrum.

If there was a “sharp” snap, the tablet was deemed to have acceptable strength.

Tablet hardness: (tablet crushing strength) force required to break a tablet in a diametric compression test.

Hardness test: a tablet is placed between anvils, and the crushing strength that just causes the tablet to break is recorded.

B. Several devices operating to test tablet hardness:

1. **Monsanto tester**
2. **Strong-Cobb tester**
3. **Pfizer tester**
4. **Erweka tester**
5. **Schleuniger tester**

- **The hardness of a tablet, like its thickness, is a function of the die fill and compression force:**

- **At constant die fill,** the hardness values increase and thickness decrease as additional compression force is applied.

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Tablet laminate or cap

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Destroying the integrity of the tablet.

- **At a constant compression force (fixed distance between upper and lower punches**

↓

Hardness increases with increasing die fills and decreases with lower die fills.

GENERAL NOTES

I. Tablets are harder several hours after compression than they are immediately after compression.

II. Lubricants can affect tablet hardness when they are used in too long a period.

III. Large tablets require a greater force to cause fracture and are therefore "harder" than small tablets.

IV. For a given granulation, a flat beveled tool produces a tablet harder than a deep cup tool.

V. Tablet hardness is not an absolute indicator of strength?

Since some formulations, when compressed into very hard tablets, tend to "cap" on attrition, losing their crown portions.

↓

Another measure of a tablet's strength (friability) is often measured.

VI. Tablets that tend to powder, chip, and fragment when handled

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Lack elegance and consumer acceptance, and can create excessively dirty processes in such areas of manufacturing as coating and packaging.

↓

Tablet's weight variation or content uniformity problems.

FRIABILITY

- The laboratory friability tester is known as the **Roche friabilator**.

- **Conventional compressed tablets that loss less than 0.5 to 1.0% of their weight are generally considered acceptable.**

- **Chewable tablets and most effervescent tablets** (undergo high friability weight losses) → special stack packaging.

Note: When capping is observed on friability testing (the tablet should not be considered for commercial use, regardless of the percentage of loss seen).

FRIABILITY ADDITIONAL TESTS:

Rough handling tests usually include:

1. Vibration test
2. Drop test
3. Incline plane test
4. Shipped bottled products across the country and back again to estimate the strength of the new tablet product in shipment.

These tests can be performed to **give indication of how well a tablet will hold up in its specified package and shipping container during shipment.**

OFFICIAL TESTS

A. Drug content and release.

To evaluate a tablet's potential for efficacy:

1. The amount of drug per tablet needs to be monitored from tablet to tablet and batch to batch.
2. Measure the tablet's ability to release the drug needs to be ascertained.

B. WEIGHT VARIATION.

A tablet designed to contain a specific amount of drug in a specific amount of tablet formula

Weight of tablet is measured to ensure that a tablet contains the proper amount of drug.

Test: samples of tablets (usually 10) are weighted throughout the compression process. The composite weight divided by 10.

Problem in the test: Within the sample that has an acceptable average weight, there could be tablets excessively overweight or underweight.

Note: (USP)/(NF) provides limits for the permissible variations in the weights of individual tablets (expressed as a percentage of the average weight of sample).

The USP variation test

Weight 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average.

(The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and no tablet differs by more than 2 times the percentage limit).

Table: Weight Variation Tolerances for Uncoated Tablets

Average Weight of Tablets (mg)	Maximum Percentage Difference allowed
130 or less	10
130-324	7.5
More than 324	5

The weight variation test method determine drug content uniformity of tablets if:

i. All Tablets (90 to 95%) active ingredient.
ii. Uniformity of the drug distribution in the granulation or powder in tablets made were perfect.

Ex: Aspirin tablets (90% or more active ingredient)

±5% weight variation is close to define true potency and content uniformity (95 to 105% of the label strength)

(if the average tablet weight is close to the theoretic average weight).

Important note: **1.** The weight variation test is clearly not sufficient to assure uniform potency of tablets of moderate- or low-dose drug **(excipients make up the bulk of the tablet weight).**

2. The potency of tablets is expressed in terms of grams, mg, or micrograms (for some potent drugs) of drug per tablet and is given as the label strength of the product.

Official compendia or other standards provide an acceptable potency range around the label potency.

i. For highly potent, low-dose drugs such as digitoxin (not less than 90% and not more than 110%).

ii. For most of larger-dose drugs in tablet form (not less than 95% and not more than 105%).

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 powder mixture or granulation during the various manufacturing processes
3. Tablet weight variation.

Note:

i. **The weight cannot be used as a potency indicator** (except when the active ingredient is 90 to 95% of the total tablet weight).

ii. **In tablets with smaller dosages**, good weight variation does not ensure good content uniformity, (large weight variation precludes good content uniformity).

Test

To assure uniform potency for tablets of low-dose drugs, a content uniformity test is applied.

a) 30 tablets are randomly selected for the sample
b) At least 10 of them are assayed individually (9 of 10 tablets must contain not less than 85% or more than 115% of the labeled drug content).
c) (10^{th} tablet may not contain less than 75% or more than 125% of the labeled content).
d) If these condition are not met, the tablets remaining from the 30 must be assayed individually, and none may fall outside of the 85 to 115% range.

PURITY

The purity of official tablets is assured by utilizing raw materials, (both active drug and excipients)

meet official or other rigid specifications.

Extraneous substances present in a raw material or a drug that are not specifically allowed by compendial specifications or well-defined manufacturer's specifications may render the product unacceptable for pharmaceutical use.

These extraneous substances:

1. Toxic on acute or long-term use
2. unpredictable or deleterious effect on product stability or efficacy.

Certain well-defined **impurities** often appear in the specification of **raw materials or drug substances**, or if they are the **product of unavoidable decomposition of the drug**, they may be listed with an upper tolerance limit.

Ex:

Aspirin tab as specified by the USP may contain no more than 0.15% of free salicylic acid relative to the amount of aspirin present.

C. DISINTEGRATION.

For most tablets, the first important step toward solution is breakdown of the tablet into smaller particles or granules, a process known as disintegration.

The time that it takes a tablet to disintegrate is measured in a device described in the USP/NF.

Q/ Research has established that one should not automatically expect a correlation between disintegration and dissolution?

Since the dissolution of a drug from the fragmented tablet control the appearance of the drug in the blood

Disintegration is a (guide for an optimum tablet formula) and (as an in-process control test to ensure lot-to-lot uniformity).

COMPONENT OF DISINTEGRATION APPARATUS:

The USP device to test disintegration:

1) uses 6 glass tubes that are 3 inches long, open at the top
2) and held against a 10-mesh screen (2mm opening) at the bottom end of the basket rack assembly.

Important note:

To be in compliance with the USP standards, the tablets must disintegrate, and all particles must pass through the 10-mesh screen in time specified.

If any residue remains, it must have a soft mass with no palpably firm core.

Disintegration times is running for (uncoated tab., plain-coated tab., enteric coated tab., buccal tab., and sublingual tab.).

i. **Uncoated USP tablets** (disintegration time 5 min (aspirin tablets)), but majority of the tablets have a maximum disintegration time of 30 min.

ii. **Enteric coated tablets** are not to disintegrate after 1 hr in simulated gastric fluid. The same tablets are then tested in simulated intestinal fluid and are to disintegrate in 2 hrs plus the time specified in the monograph.

D. DISSOLUTION.

Since disintegration test offers no assurance that the resultant particle will release the drug in solution at an appropriate rate

Dissolution tests and test specifications have now developed for nearly all tablet products.

Important note:

A. **The rate of drug absorption** for **acidic drug moieties** (absorbed high in the GI tract) is determined by (rate of drug dissolution from tablet).

If the product objective (high peak blood levels for drug)

Obtaining rapid drug dissolution from tablet is critically important.

The rate of dissolution may be directly related to:

1. Efficacy of the tablet product
2. Bioavailability differences between formulations.

B. The most **direct assessment of a drug's release** from various tablet formulations or products is **accomplished through in vivo bioavailability measurements.**

Disadvantages of in-vivo studies:

1. Length of time needed to plan, conduct and interpret study.
2. Highly skilled personnel required for human studies.
3. Low precession and high variability of measurement.
4. High cost of studies.
5. Use of human in 'nonessential' studies.
6. Correlation exist between diseased patients and the healthy humans in the test.

C. In vitro dissolution tests have been extensively studied, developed, and **used as an indirect measurement of drug availability**

(in preliminary assessments of formulation factors and manufacturing methods that are likely to influence bioavailability).

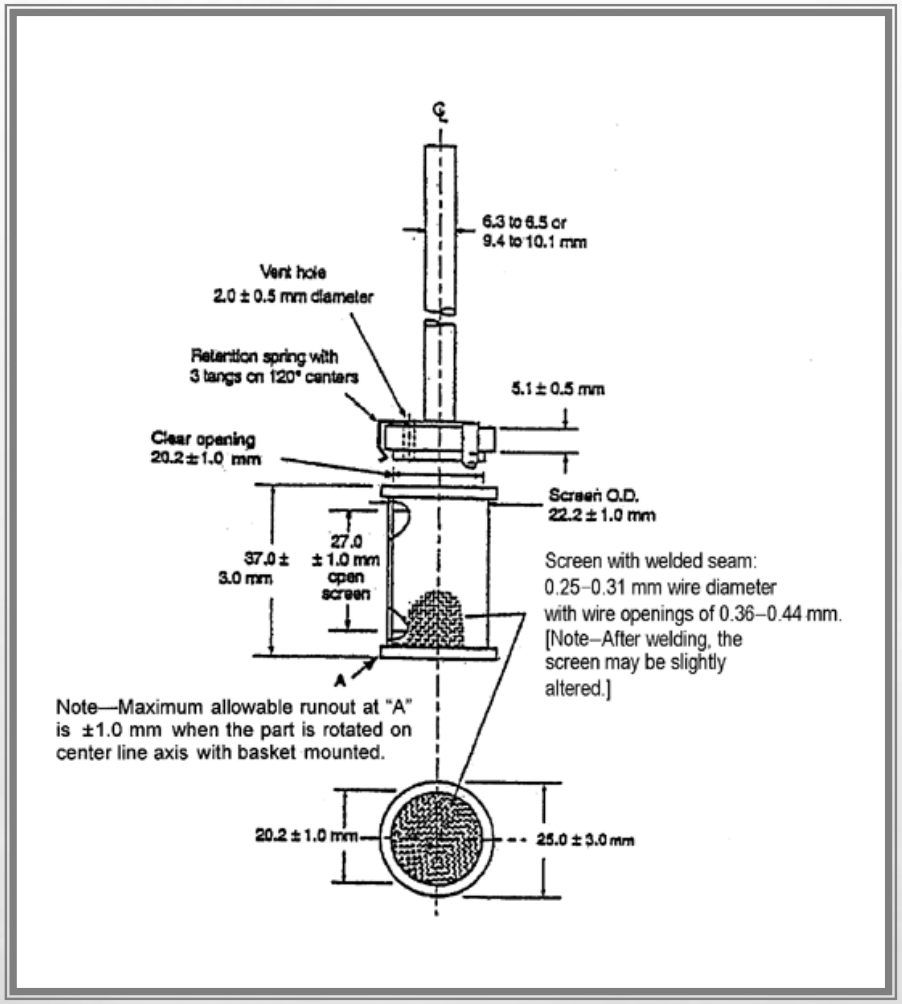
Two objectives in the development of in vitro dissolution tests are to show:

1) The release of the drug from tablet is as close as possible to 100%
2) The rate of drug release is uniform batch to batch and is the same as the release rate from those batches proven to be bioavailable and clinically effective.

NOTE:

- Since 1970, the United States Pharmacopeia and National Formulary have provided procedures for dissolution testing.
- They determine compliance with the limits on dissolution as specified in the individual monograph for a tablet (or capsule). The USPXX/NFXV, supplement 3, specifies that either of two apparatus be used for determining dissolution rates.

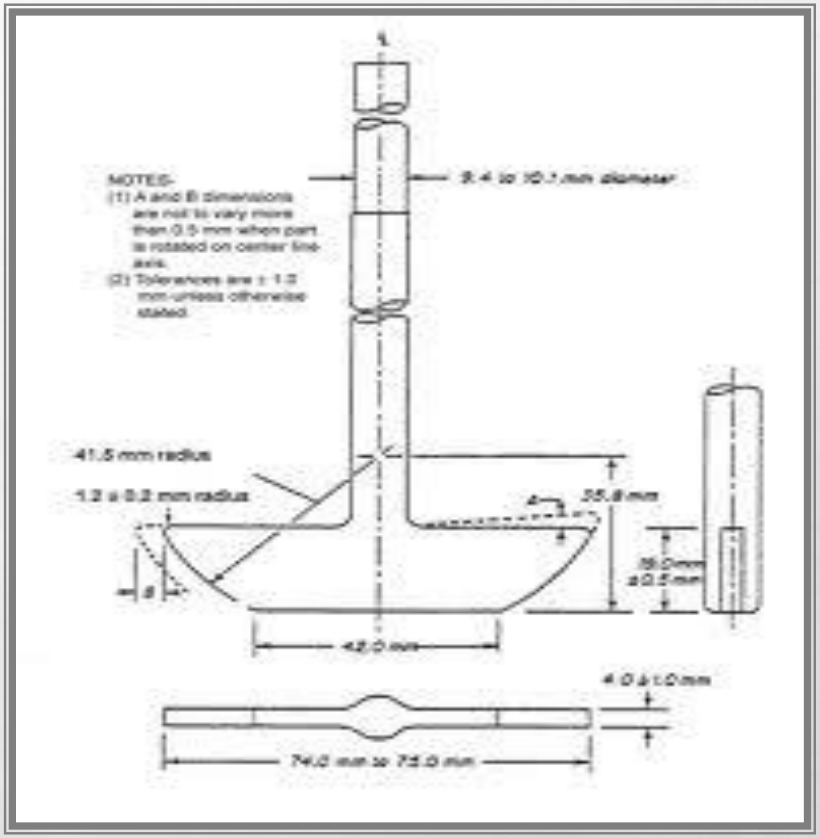
APPARATUS 1


6.3 to 6.5 or
9.4 to 10.1 mm
Vent hole
2.0 ± 0.5 mm diameter
Retention spring with
3 tangs on 120° centers
5.1 ± 0.5 mm
Clear opening
20.2 ± 1.0 mm
Screen O.D.
22.2 ± 1.0 mm
37.0 ±
3.0 mm
27.0
± 1.0 mm
open
screen
Screen with welded seam:
0.25–0.31 mm wire diameter
with wire openings of 0.36–0.44 mm.
[Note–After welding, the
screen may be slightly
altered.]
A
Note—Maximum allowable runout at "A"
is ±1.0 mm when the part is rotated on
center line axis with basket mounted.
20.2 ± 1.0 mm
25.0 ± 3.0 mm


RC-6D 溶出度测试仪

APPARATUS 2


ERWEKA
ERWEKA


NOTES-
(1) A and B dimensions are not to vary more than 0.5 mm when part is rotated on center line-axis.
(2) Tolerances are ± 1.0 mm unless otherwise stated.
9.4 to 10.1 mm diameter
41.5 mm radius
1.2 ± 0.2 mm radius
35.8 mm
42.0 mm
4.0 ± 1.0 mm
74.0 mm to 78.0 mm

IMPORTANT NOTE

Industrial pharmacists test their formulations for dissolution.

Their results are plotted as concentration versus time.

Values for $t_{50\%}$, $t_{90\%}$, and the percentage dissolved in 30 min are used as guides.

- **The value for $t_{50\%}$ is the length of time required for 50% of the drug to go into solution.**
- **A value for $t_{90\%}$ of 30 min is an excellent goal since a common dissolution tolerance in USP/NF is not less than 75% dissolved in 45 min.**