Pharmaceutical Quality Management

QUALITY CONTROL OF SUPPOSITORIES

By:

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SUPPOSITORY:

*A **suppository** is a drug delivery system that is inserted into the rectum (rectal **suppository**), vagina (vaginal **suppository**) or urethra (urethral **suppository**), where it dissolves or melts and is absorbed into the blood stream. They are used to deliver both systemically and locally acting medications.*

Types of Suppositories:

1. **Rectal suppository:** 32 mm in length, cylindrical, have one or both end tapered.
    a) Adult rectal supp. Weight 2gm
    b) infant rectal supp.1gm
2. **Vaginal suppository:** pessaries, 5gm, usually oviform or cone shaped, weight from 3-5 gm
3. **Urethral suppository:** bougies 4 gm and 10-15 cm long for male and 6-7.5 cm long for female.

Properties of an Ideal Suppository Base:

The ideal suppository base may be described as follows:

- **i.** Melts at rectal temperature 36° C, or dissolve in rectal fluid
- **ii.** Completely non toxic, and non irritating to sensitive and inflamed tissues.
- **iii.** Compatible with a broad variety of drugs.
- **iv.** No metastable forms.
- **v.** Shrinks sufficiently on cooling to be released form the mold without the need for mold lubricants.

vi. Non- sensitizing

vii. Has a melting and emulsifying property.

viii. Water number is high (a high percentage of water can incorporated in it)

ix. It is stable on storage, dose not change odor, color, release pattern.

x. Can be manufactured by molding either by hand, compression, machine.

xi. SFI curve is sharp, in other word, the interval between melting point and solidification point is small

Type of Suppository Bases:

a) Fatty Bases.

b) Hydrophilic Suppository Bases

c) water dispersible Bases

Dose character of suppository:

- For rectal administration, one half to two or more times than the oral dose is given.
    - The correct dose of any drug depends on the rate of release from the suppository
    - Since the vehicle can change the rate of drug absorption, the amount of drug to be given in suppository dose depend on the vehicle, the chemical and physical from the drug

Quality Control Tests:

Suppository quality control includes physical and chemical aspects of the product

1. **PHYSICAL ANALYSIS**
   - **1.1. Visual examination (physical appearance)**
     - **1.1.1. Shape**
     - **1.1.2. Surface Condition**
     - **1.1.3. Color**
     - **1.1.4. Odor**
   - **1.2. Uniformity of weight**
   - **1.3. Uniformity of texture**
   - **1.4. Melting point, liquefaction time, melting and solidification time**
   - **1.5. Mechanical strength**
2. **CHEMICAL TESTING**
   - **2.1. Content uniformity testing**
   - **2.2. Dissolution testing**

❖ Physical analysis

1.1. VISUAL EXAMINATION:

- Color and the surface characteristics of the suppository are relatively easy to assess. It is important to check for the absence of fissuring, pitting, fat blooming, exudation, sedimentation, and the migration of the active

ingredients. Suppositories can be observed as an intact unit and also by splitting them longitudinally.

1.1.1 Shape

- It is advisable to check the shape of the suppository to see if it is consistent, irrespective of whether the suppository is ogive or torpedo shaped.

1.1.2. Surface condition

- The following can be checked: brilliance, dullness, mottling, cracks, dark regions, axial cavities, bursts, air bubbles, holes, etc.

1.1.3. Color

- The intensity, nature and homogeneity of the color should be verified.

1.1.4. Odor

- Verification of odor can prevent confusion when similar suppositories are being processed. A change in the odor may also be indicative of a degradation process.

1.2. WEIGHT:

- Suppositories can be weighed on an automatic balance, obtaining the weight of 10 suppositories.
- If the weight is found to be too small, it is advisable to check whether the mold is being well filled and whether there are axial cavities or air bubbles caused by badly adjusted mechanical stirring or the presence of an undesirable surfactant.
- It is also important to check that the batch of suppositories is homogeneous. If the weight is found to be too high, check that scraping has been carried out correctly, and also that the mixture is homogeneous.
- Lastly, the weight may decrease during aging when the suppositories contain volatile substances, especially if the packaging is not airtight.

1.3. MELTING RANGE TEST:

- **Macromelting range:** *measures the time it takes for the entire suppository to melt when immersed in a constant temperature (37ºC) water bath. The apparatus used for measuring the melting range of the entire suppository is a USP tablet disintegration apparatus*
- **Micromelting range:** *is the melting range measured in capillary tubes for the fat base only.*

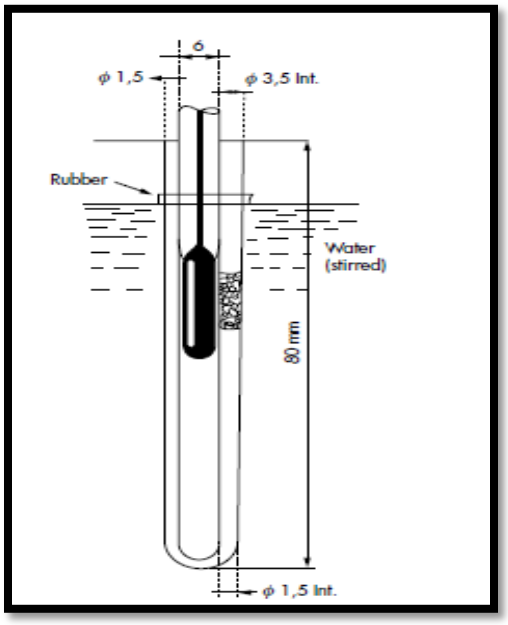
Melting range (melting point, melting zone, Micromelting):

- Melting range or melting zone is the term often preferred by some rather than melting point. Many suppository bases and medicated suppositories are mixtures, and so do not have a precise melting point. Routinely, though, we continue to call the physical phenomenon obtained under rigorous conditions the melting point.
- The release rate of the suppository is related to its melting point; it is therefore critical that this test be evaluated using a non-destructive method. A number of different techniques are used to study melting behavior, including the open capillary tube, the U-tube, and the drop point methods In general, the melting point should be equal to or less than 37°C. A non-destructive method must be used because if the suppository is melted before a measurement is made, the suppository constituents may be transformed into a metastable state

Melting point determination:

- The use of a U-shaped capillary tube to determine melting point provides precise information for excipient control and consistency in production for those suppositories containing soluble active principles. This method is not suitable when the suppositories have a high powder content, which prevents

the fat from sliding inside the capillary tube to give the end-point determination. The melting point can also be determined by placing a small-diameter wire into the mold containing the suppository melt before the form solidifies. The form is then immersed in water, held by the wire, and the temperature of the liquid is raised slowly (about 1◦C every 2–3 minutes) until the suppository slips off the wire; this is the melting point of the suppository.



- **Liquefaction time:**
  - Liquefaction testing provides information on the behavior of a suppository when subjected to a maximum temperature of 37°C. The test commonly used is Krowczynski's method, which measures the time required for a suppository to liquefy under pressures similar to those found in the rectum (approximately 30 g) in the presence of water at 37°C. In general, liquefaction should take no longer than about 30 minutes.
  - For Krowczynski's method, the apparatus consists of a 16 mm diameter glass tube, 235 mm long with an approximately 6 mm diameter reduction at

the base. One end is blocked with a small rubber stopper to facilitate cleaning after use. A thermostat graduated in tenths of a centigrade is used. The tube and thermometer are held in place by means of a large rubber stopper with two holes in a 225mm long tube with a 50mm diameter, fitted with lateral tubes to allow the water at 37˚C from a constant-temperature water bath to circulate.

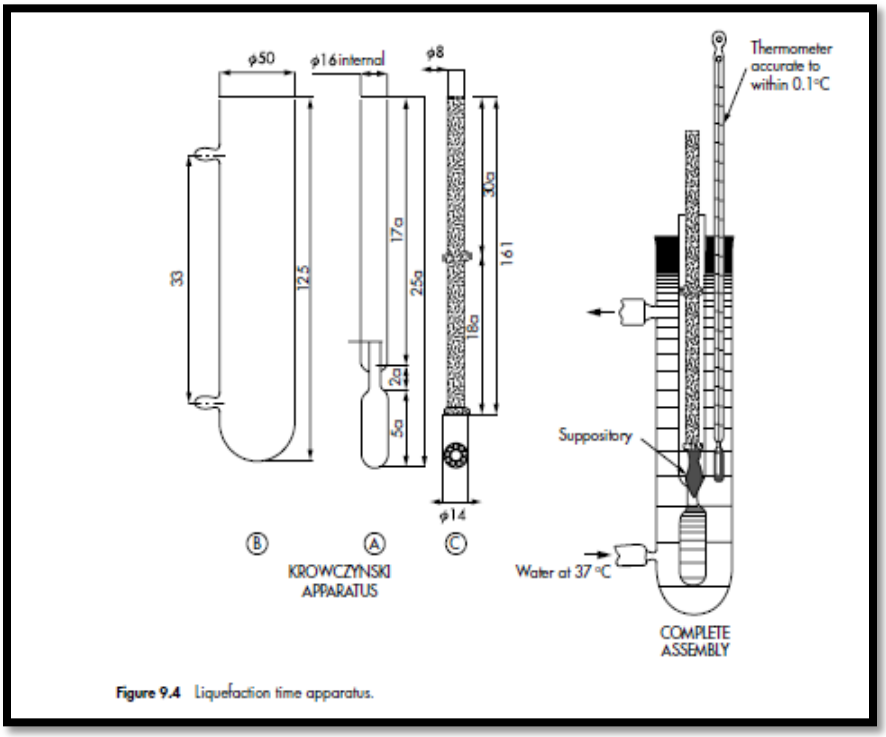


Figure 9.4 Liquefaction time apparatus.

Suppository penetration test

- A suppository penetration test can be used to determine the temperature at which the suppository becomes sufficiently soft for a penetrating rod to drop through its length. The apparatus used is shown in Figure. The temperature is adjusted to that required for the test, generally about 37˚C. The suppository is placed in the device and the penetration rod gently moved into place. The device holding the suppository and penetration rod is lowered into the constant temperature bath and a stopwatch is started. When the penetration rod drops through the softened suppository the time is recorded.

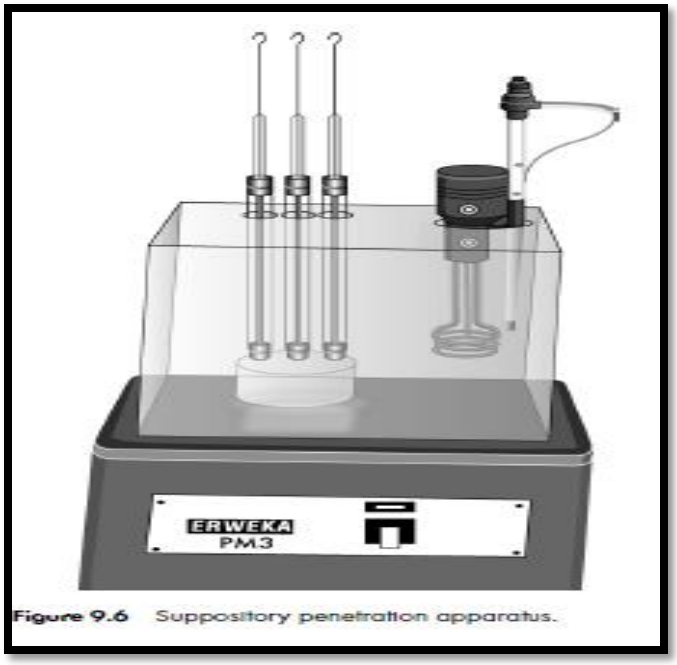


Figure 9.6 Suppository penetration apparatus.

- **Melting and solidification time:**
  - There is a relationship between melting and solidification that is important to characterize. The release of the active ingredient from the vehicle is related to the melting point of the vehicle and the solubility of the drug in the vehicle. Suppositories undergo three changes in phase during their "life." First, they are melted and then solidified; upon administration, they are again melted. An understanding of these factors and their relationships is critical for evaluating the bioavailability of the final suppository formulation. The higher the melting point, the later the drug effects appear. If too high, the drug effect does not appear.
  - The European Pharmacopoeia also describes a procedure that involves heating the material, then allowing it to cool slowly while stirring. The temperature is recorded at 1 minute intervals. The cooling curve normally passes through a minimum, which indicates a supercooled melt. Heat is liberated during crystallization and the temperature–time curve rises. The maximum temperature in this phase is the solidification temperature.

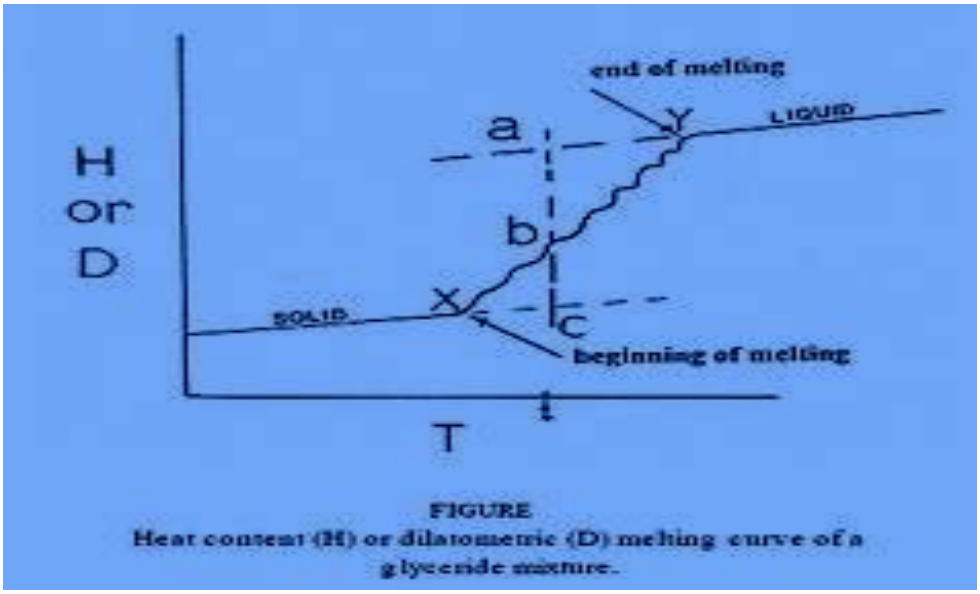


FIGURE
Heat content (H) or dilatometric (D) melting curve of a glyceride mixture.

1.4. MECHANICAL STRENGTH/CRUSHING TEST:

- Suppositories can be classified as brittle or elastic by evaluating the mechanical force required to break them. Tests are used that measure the mass (in kilograms) that a suppository can bear without breaking. A good result is at least 1.8– 2 kg pressure. In the example laboratory set-up shown in Figure, the suppository is positioned in an upright position and increasing weights are placed on it until it loses its structure and collapses. The purpose of the test is to verify that the suppository can be transported under normal conditions, and administered to the patient.


Figure 9.7 Mechanical strength/breaking apparatus.

1.5. DISINTEGRATION TEST/MACRO-MELTING RANGE OF SUPPOSITORIES

- **Apparatus and Conditions**
  - Disintegration apparatus used with previously described procedure.
  - Apparatus is maintained at 36-37°C as the immersion fluid.
  - Disintegration is considered to be achieved when
    - ✓ The components of the suppositories have separated, e.g. melted fatty substances have collected on the surface of the liquid, insoluble powders have fallen to the bottom and soluble components have dissolved or are distributed in one or more of the ways.
    - ✓ There is softening of the test sample, usually accompanied by an appreciable change of shape without complete separation of the components. The softening process is such that a solid core no longer exists when pressure is applied with a glass rod.
- **Acceptance Criteria**
  - Unless otherwise stated in the individual monograph, for each of the three suppositories
  - examine the state of the sample after 30 minutes for fat based suppositories and rectal capsules
  - and after 60 minutes for water soluble suppositories

❖ Chemical Testing

2.1 DISSOLUTION TESTING:

- One of the most important quality control tools available for *in vitro assessment is dissolution* testing. Dissolution testing is often required for suppositories to test for hardening and polymorphic transitions of active ingredients and suppository bases
- unlike for tablets and capsule dosage forms, there are not enough dissolution testing methods or validations for suppositories. This can be partly attributable to the immiscibility of some of the suppository vehicles in water. If the drug is immiscible in an aqueous dissolution fluid then it may require a partitioning step; unfortunately this involves extra time, which alters the dissolution rate calculation. If a filtration step is involved in dissolution testing, the filtration membrane may introduce an erroneous result between actual and obtained results as it may clog. Variations in density between the suppository and the receiving fluid must also be considered.

Dissolution testing Apparatus

- Dissolution testing methods include the paddle method, basket method, membrane diffusion method/dialysis method, and the continuous flow/bead method.
- The melting suppositories with the paddle method showed fat floating rapidly to the surface of the fluid instead of staying below the water surface.
- With the basket method, the surfactant produced small droplets of the fat that were dispersed into the medium almost immediately. Some of the fat particles also blocked the basket mesh. When a surfactant was not used, the basket served as the container for all the melted fat.

- In the flow-through cell, the two suppository compositions behaved differently. The surfactant makes the fat more sensitive to agitation. A deformation of the suppository is seen as a fast release of small droplets of fat when the surfactant is incorporated.
- With the dissolving suppositories, the paddle method at 50 rpm and the flow-through method at 16 mL/min produced the same dissolution profiles with and without surfactant.

- **Acceptance Criteria:**

Table 1. USP Acceptance Criteria

Stage	Number units	Acceptance Criteria
S1	6	Each unit is not less than Q* +5%
S2	6	Average of the 12 (S1+S2) units is ≥ Q and no uni is less than Q–15%
S3	12	Average of 24 (S1+S2+S3) units is ≥ Q and not more than 2 units are less than Q–15% and no unit is less than Q–25%

*Q is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content.

2.2. CONTENT UNIFORMITY TESTING

- In order to ensure content uniformity, individual suppositories must be analyzed to provide information on dose-to-dose uniformity.
- Content uniformity tests can be used to optimize production techniques and sampling methods.
- Content uniformity is important not only between suppositories, but also within suppositories in the event that a suppository is halved for administration.

- Assay 10 units individually as directed in the *Assay in the individual monograph, unless* otherwise specified in the *Procedure for content uniformity"*
- Limit A (if the average of the limits specified in the potency definition in the individual monograph is 100.0% or less) – Unless otherwise specified in the individual monograph, the requirements for dosage uniformity are met if the amount of the drug substance in each of the 10 dosage units as determined from the Content Uniformity method lies within the range of 85.0% to 115.0% of the label claim, and the RSD is less than or equal to 6.0%.
- If 1 unit is outside the range of 85.0% to 115.0% of label claim, and no unit is outside the range of 75.0% to 125.0% of label claim, or if the relative standard deviation is greater than 6.0%, or if both conditions prevail, test 20 additional units. The requirements are met if not more than 1 unit of the 30 is outside the range of 85.0% to 115.0% of label claim, and no unit is outside the range of 75.0% to 125.0% of label claim and the RSD of the 30 dosage units does not exceed 7.8%.