

EVALUATION OF SEMISOLID DOSAGE FORMS



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INTRODUCTION

- Semisolid pharmaceutical systems comprise a body of products, which when applied to the skin or accessible mucous membranes tend to alleviate or treat a pathological condition or offer protection against a harmful environment.
 - They have the property to cling to the skin or mucous membrane for a protracted period of time to exert their therapeutic effect through protection and occlusion.
 - The adhesion is due to their plastic rheological behavior which allows semisolid to retain their shape and cling as film until acted upon by an outside force.
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- Semisolid dosage forms usually are intended for localized drug delivery. In the past few years, however, these forms also have been explored for the systemic delivery of various drugs.
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- Semisolids constitute a significant proportion of pharmaceutical dosage forms.
- They can be applied topically to the skin, cornea, rectal tissue, nasal mucosa, vagina, buccal tissue, urethral membrane, and external ear lining.

DEFINITION

- Semisolid dosage forms are dermatological products of semisolid consistency which are applied to skin or mucous membrane for therapeutic or protective action or cosmetic function.
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IDEAL PROPERTIES OF SEMISOLIDS

PHYSICAL PROPERTIES

- Smooth texture
- Elegant in appearance
- Non dehydrating
- Non gritty
- Non greasy and non staining
- Non hygroscopic

PHYSIOLOGICAL PROPERTIES

- Non irritating
- Do not alter membrane / skin functioning
- Miscible with skin secretion
- Have low sensitization index

APPLICATION PROPERTIES

- Easily applicable with efficient drug release.
 - High aqueous wash ability.
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CATEGORIES OF SEMISOLID DOSAGE FORMS

- Ointments
 - Creams
 - Pastes
 - Jellies / Gels
 - Suppositories
 - Poultices
 - Plasters
 - Rigid foams
 - Glycero-gelatins
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❖ OINTMENTS

Ointments are semisolid preparations meant for external application to the skin or mucous membrane.

They usually contain a medicament or medicaments dissolved, suspended or emulsified in the base.

❖ CREAMS

Creams are viscous emulsions of semisolid consistency intended for application to the skin or mucous membrane

➤ O /W type

➤ W/O type

❖ PASTES

Pastes are the preparations contain a large amount of finely powdered solids such as starch and zinc oxide. These are generally very thick and stiff.

❖ JELLIES

These are thin transparent or translucent, non greasy preparations. They are similar to mucilages because they are prepared by using gums but they differ from mucilages in having gelly like consistency.

❖ SUPPOSITORIES

These are meant for insertion in to the body cavities other than mouth. They may be inserted in to rectum, vagina or urethra.

❖ POULTICES

These are also known as cataplasms. They are soft viscous wet masses of solid substances.

❖ PLASTERS

These are solid or semi solid masses adhere to the skin when spread up on cotton felt line or muslin as a backing material.

❖ RIGID FOAMS

These are systems in which air or some other gas is emulsified in liquid phase to the point of stiffening.

EVALUATION OF OINTMENTS



- Content uniformity of drug**
 - Penetration**
 - Rate of release of medicament**
 - Absorption of medicament in blood stream**
 - Irritant effect:**
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Content uniformity of drug

A known weight of ointment is taken and assayed for amount of the drug.

Penetration

A weighed quantity of ointment is rubbed over skin for a given period of time and unabsorbed ointment is collected and weighed.

The differences in weights represent the amount absorbed.

In Vitro Skin Penetration

- Flow through cell
 - Franz diffusion cell
- They mainly have two compartments
- 1) Donor
 - 2) Receptor

Method:

- mouse skin or human cadaver skin.
 - Placed in between the two compartments.
 - The passage of semisolid preparation through the epidermal surface to receptor compartment is measured by,
 - Detector (Flow through type)
 - Sampling (Franz diffusion cell)
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RATE OF RELEASE OF MEDICAMENT

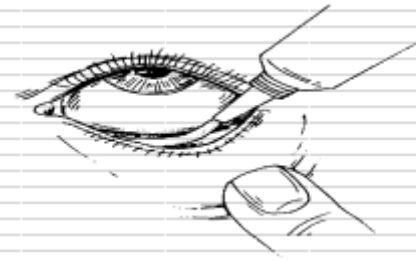
- To assess rate of release of medicament, small amount of the ointment can be placed on the surface of nutrient agar contained in a Petri dish or alternately in a small cup cut in the agar surface.

If the medicament is bactericidal the agar plate is previously seeded with a suitable organism like *s.aureus*. After a suitable period of incubation, the zone of inhibition is measured and correlated with the rate of release.

- Another method for finding out release rate is to smear internal surface of test tubes with thin layers of ointment, fill the tubes with saline/serum and after a gap of time estimating the amount of drug present in the serum/saline.

ABSORPTION OF MEDICAMENT INTO BLOOD STREAM

- The diadermatic ointment should be evaluated for the rate of absorption of drug into the blood stream. This test can be run in-vivo only.
 - Definite amount of ointments should be rubbed through the skin. Under standard conditions and medicaments are estimated in the blood plasma or urine.
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IRRITANT EFFECT

- In general no ointment should possess irritant effect on the skin or mucous membranes the tests for irritancy can be carried out on the skin and eyes of rabbits or the skin of human beings.
 - The irritant effect can also be judged to a certain extent by injecting the ointment into thigh muscles and under the abdominal skin of rats. Reaction are noted at intervals of 24,48,72 and 96 hours. Lesions on cornea, iris, conjunctiva are used for judging the irritancy to the eyes. Presence of patches on the skin within 2 weeks indicate irritancy to pressing skin.
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DRAIZE TEST

□ Draize skin irritation test:

- A known amount of test substance is introduced under a one square inch gauge patch,
 - The patch is applied to skin of 12 albino rabbits, (6 with intact skin) and (6 with abraded skin),
 - The patch is secured in place with adhesive tape and the entire trunk of the animal is wrapped with an impervious material for a 24 hour period,
 - After 24 hours the patches are removed and resulting reaction is evaluated for erythema and edema formation.
 - The reaction is again scored at the end of 72 hours and the two readings are averaged.
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CONCLUSION FROM DRAIZE TEST

CATEGORY DRAIZE	CODE	SKIN REACTION
Mild	MLD	Well defined erythema and slight edema (edges of area well defined by definite raising)
Moderate	MOD	Moderate to severe erythema and moderate edema (area raised approximately 1 mm)
Severe	SEV	Severe erythema (beet redness to slight eschar formation (injuries in depth) and severe edema (raised more than the 1 mm and extending beyond area of exposure.

DRAIZE EYE IRRITATION TEST

- ❑ A known amount of test material is placed in one eye of each of 6 albino rabbits the other eye remains untreated, serving as a control.
 - ❑ The eyes are not washed after instillation and are examined at 24,48 and 72 hours for ocular reaction.
 - ❑ The test is considered positive if ulceration, opacity of the cornea , inflammation of the iris, swelling of the conjunctiva occurs.
 - ❑ A substance is an eye irritant if,
 - 4 of six rabbits score positive
 - it is considered a non irritant if none or only one of the 6 animals exhibit irritation.
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CONSISTENCY TEST

□ PENETROMETRY:

❖ PROCEDURE:

Preparation of test sample: 3 methods (A,B,C)

- A: Carefully and completely fill three containers without forming air bubbles. Level if necessary to obtain a flat surface.
- B: Apply a suitable shear to the samples for 5 min carefully and completely fill three containers without forming air bubbles. Level if necessary to obtain a flat surface.
- C: melt 3 samples carefully and completely fill three containers without forming air bubbles. Level if necessary to obtain a flat surface.

CAUTION: Store the samples at $25 \pm 0.5^{\circ}\text{C}$ for 24 hours unless otherwise prescribed.

Determination Of Penetration :

Place the test sample on the basis of the penetrometer. Verify that its surface is perpendicular to the vertical axis of the penetrating object. Bring the temperature of the penetrating object to $25 \pm 0.5^{\circ}\text{C}$ and then adjust its position such that its tip just touches the surface of the sample . Release the penetrating object and hold it free for 5 sec. clam the penetrating object and measure the depth of penetration. Repeat the test with 2 remaining containers.

RESULT:

The penetration is expressed in terms of mm as the arithmetic mean of the three measurements. If any of the individual results differ from the mean by more than 3%, repeat the test and express the results of the 6 measurements as the mean

EVALUATION OF CREAMS



As these products are used widely and for various parts of the body, stringent evaluation and quality control is essential. Appearance spread ability, wash ability.

❖ Rheology

Rheology is very important as these creams are marketed in tubes or containers. The rheology or viscosity should remain constant. As these products are normally non-Newtonian in nature, the viscosity can be measured using viscometers used for such liquids.

Rheologic measurements are utilized to characterize the ease of pouring from a bottle, squeezing from a tube or other deformable container, maintaining product shape in a jar or after extrusion rubbing the product onto and into the skin and pumping the product from mixing and storage to filling equipment.

□ Sensitivity

As various types of ingredients are used with occasional use of antiseptics hormones etc. there is a possibility of sensitization or photosensitization of the skin. This should be tested before hand. This test is normally done by patch test on and can be either open or occlusive. The test sample is applied along with a standard market product at different places and effect is compared after a period of time.

EVALUATION OF SUPPOSITORIES

- Appearance
- Uniformity of weight test
- Melting rang test
- Liquefaction test
- Breaking test
- Dissolution test



Appearance

- The suppository when cut longitudinally and examined with the naked eye the internal and external surfaces of the suppository should be uniform in appearance.
 - Compliance with the standard indicates satisfactory subdivision and dispersion of suspended material.
 - Surface appearance and colour can be verified usually to assess absence of fissuring, absence of pitting, absence of exudation, absence of migration of the active ingredients
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Uniformity of weight test

- To perform this 20 suppositories are weighed and average weight is calculated.
 - Then each suppository is weighed individually and weight noted.
 - No suppository should deviate from the average weight by more than 5% except that two should not deviate by more than 7.5%.
 - The weight variation may result if some cavities are under filled and other are overfilled.
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Melting Range Test

- This test is also called the macro melting range test and is a measure of the time it takes for the entire suppository to melt when immersed in a constant-temperature (37°C) water bath.
 - In contrast, the micro melting range test in the melting range measured in capillary tubes for the fat base only. The apparatus commonly used for measuring the melting range of the entire suppository is a USP Tablet Disintegration Apparatus.
 - The suppository is completely immersed in the constant water bath, and the time for the entire suppository to melt or disperse in the surrounding water is measured.
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- The in vitro drug release pattern is measured by using the same melting range apparatus. If the volume of the water surrounding the suppository is known, then by measuring aliquots of the water for drug content at various intervals within the melting period, a time-versus-drug content curve (in vitro drug release pattern) can be plotted.
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Liquefaction or Softening Time Tests of Rectal Suppositories.

- ❑ A Modification of the method developed by Krowczynski is another useful test of finished suppositories. It consists of a U-tube partially submerged in a constant-temperature water bath.
- ❑ A constriction on one side holds the suppository in place in the tube. A glass rod is placed on top of the suppository, and the time for the rod to pass through to the constriction is recorded as the softening time.
- ❑ This can be carried out at various temperatures from 35.5 to 37°C, as a quality control check and can also be studied as a measure of physical stability over time. A water bath with both cooling and heating elements should be used to assure control with 0.1°C.

Breaking test

- ❑ Brittleness of suppositories is a problem for which various solutions have already been described. The breaking test is designed as a method for measuring the fragility or brittleness of suppositories.
 - ❑ The apparatus used for the test consists of a double-wall chamber in which the test suppository is placed. Water at 37°C is pumped through the double walls of the chamber, and the suppository contained in the dry inner chamber, supports a disc to which a rod is attached.
 - ❑ The other end of the rod consists of another disc to which weights are applied. The test is conducted by placing 600 g on the platform.
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- At 1-min intervals, 200-g weights are added, and the weight at which the suppository collapses is the breaking point, or the force that determines the fragility or brittleness characteristics of the suppository.
 - Differently shaped suppositories have different breaking points. The desired breaking point of each of these variously shaped suppositories is established as the level that withstands the break forces caused by various types of handling i.e., production, packaging etc.
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Dissolution Testing

- ❑ Testing for the rate of in vitro release of drug substances from suppositories has always posed a difficult problem, owing to melting deformation, and dispersion in the dissolution medium. Early testing was carried out by simple placement in a beaker containing a medium.
 - ❑ In an effort to control the variation in mass or medium interface, various means have been employed, including a wire mesh basket, or a membrane, to separate the sample chamber from the reservoir.
 - ❑ Samples sealed in dialysis tubing or natural membranes have also been studied. Flow cell apparatus have been used, holding the sample in place with cotton, wire screening and most recently with glass beads.
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CONCLUSION

- ❖ Most of the semisolid preparations are applied to the skin or mucous membranes such as rectal, urethral, vaginal, nasal mucosa and cornea. So, semisolid preparations must be evaluated.