Topical semi-solid dosage forms

Definition

Topical semi-solid dosage forms are normally presented in the form of creams, gels, ointments, or pastes. They contain one or more active ingredients dissolved or uniformly dispersed in a suitable base and any suitable excipients such as emulsifiers, viscosity-increasing agents, antimicrobial agents, antioxidants, or stabilizing agents. Preparations susceptible to the growth of microorganisms should contain a suitable antimicrobial agent in an appropriate concentration unless the preparations themselves have adequate antimicrobial properties. Assurance must be provided through product development studies that such excipients do not adversely affect either the stability of the final product or the availability of the active ingredient(s) at the site of action; there must be no incompatibility between any of the components of the dosage form.

The choice of a base for semi-solid dosage forms depends on many factors: the therapeutic effect desired, the nature of the active ingredient(s) to be incorporated, the availability of the active ingredient(s) at the site of action, the shelf-life of the finished product, and the environmental conditions in which the product is intended to be administered. In many cases, a compromise has to be made in order to achieve the required stability. For example, drugs that hydrolyse rapidly are more stable in hydrophobic bases than in water-containing bases, even though they may be more effective in the latter.

The base should neither irritate nor sensitize the skin, nor should it delay wound healing. It should be smooth, inert, odourless, physically and chemically stable, and compatible with both the skin and the active ingredient(s) to be incorporated. It should normally be of such a consistency that it spreads and softens easily when stress is applied.

It may be necessary for a topical semi-solid dosage form to be sterile, for example, when it is intended for use on large open wounds or severely injured skin.

Manufacture

The manufacturing processes should meet the requirements of Good Manufacturing Practice. The following information is intended to provide very broad guidelines concerning the main steps to be followed during production, indicating those that are the most important.

Throughout manufacturing, certain procedures should be validated and monitored by carrying out appropriate in-process controls. They should be designed to guarantee the effectiveness of each stage of production. Appropriate limits should be set for the particle size of the active ingredient(s), which should be controlled during production. Particular care should be paid to environmental conditions, especially with respect to microbial and cross-contamination.[1]

[1] *Warning:* Semi-solid dosage forms should not be diluted. If a dilution is nevertheless necessary, this requires special attention; the same type of base should be used in order to obtain a homogeneous mixture.

Packaging must be adequate to protect topical semi-solid dosage forms from light, moisture, and damage due to handling and transportation. The use of flexible tubes of suitable metal or plastic is preferred. Preparations for nasal, aural, vaginal, or rectal use should be supplied in containers adapted for appropriate delivery of the product to the site of application, or should be supplied with a suitable applicator.

Organoleptic inspection

Evidence of physical instability is demonstrated by:

- a noticeable change in consistency, such as excessive "bleeding" (separation of excessive amounts of liquid) or formation of agglomerates and grittiness;

- discoloration;

- emulsion breakdown;

- crystal growth;

- shrinking due to evaporation of water; or

- evidence of microbial growth.

A noticeable change in odour is also a sign of instability.

Sterility

Preparations required to be sterile should comply with 3.2 Test for sterility.

Uniform consistency

Topical semi-solid dosage forms should be of uniform consistency. When a sample is rubbed on the back of the hand, no solid

components should be noticed.

Containers

The container material should not adversely affect the quality of the preparation or allow diffusion of any kind into or across the material of the container into the preparation. The container should be fitted with a closure that minimizes microbial contamination and is equipped with a device that reveals whether the container has ever been opened.

Labelling

Every pharmaceutical preparation must comply with the labelling requirements established under Good Manufacturing Practice.

The label should include:

(1) the name of the pharmaceutical product;

(2) the name(s) of the active ingredient(s); INNs should be used wherever possible;

(3) the amount of the active ingredient(s) in a specified quantity of suitable base or vehicle, and the quantity of preparation in the container;

(4) the batch (lot) number assigned by the manufacturer;

(5) the expiry date and, when required, the date of manufacture;

(6) any special storage conditions or handling precautions that may be necessary;

(7) directions for use, warnings, and precautions that may be necessary;

(8) the name and address of the manufacturer or the person responsible for placing the product on the market;

(9) the name and quantity of antimicrobial agent incorporated in the preparation; and

(10) if applicable, the statement that the preparation is "sterile".

Storage

Topical semi-solid dosage forms should be kept in well-closed containers. The preparation should maintain its pharmaceutical integrity throughout shelf-life when stored at the temperature indicated on the label; the temperature should normally not exceed 25 °C. Special storage recommendations or limitations are indicated in individual monographs.

Requirements for specific types of topical semi-solid dosage forms

Creams

Definition

Creams are homogeneous, semi-solid preparations consisting of opaque emulsion systems. Their consistency and rheological properties depend on the type of emulsion, either water-in-oil (w/o) or oil-in-water (o/w), and on the nature of the solids in the internal phase. Creams are intended for application to the skin or certain mucous membranes for protective, therapeutic, or prophylactic purposes, especially where an occlusive effect is not necessary. The term "cream" is most frequently used to describe soft, cosmetically acceptable types of preparations.

Generally, o/w creams are prepared at an elevated temperature and then cooled down to room temperature in order for the internal phase to solidify. The semi-solid form of a w/o cream is attributable to the character of the external phase.

Hydrophobic creams (w/o)

Hydrophobic creams are usually anhydrous and absorb only small amounts of water. They contain w/o emulsifying agents such as wool fat, sorbitan esters, and monoglycerides.

Hydrophilic creams (o/w)

Hydrophilic creams contain bases that are miscible with water. They also contain o/w emulsifying agents such as sodium or triethanolamine soaps, sulfated fatty alcohols, and polysorbates combined, if necessary, with w/o emulsifying agents. These creams are essentially miscible with skin secretions.

Gels

Definition

Gels are usually homogeneous, clear, semi-solid preparations consisting of a liquid phase within a three-dimensional polymeric

matrix with physical or sometimes chemical cross-linkage by means of suitable gelling agents.

Gels are applied to the skin or certain mucous membranes for protective, therapeutic, or prophylactic purposes.

Hydrophobic gels

Hydrophobic gel (oleogel) bases usually consist of liquid paraffin with polyethylene or fatty oils gelled with colloidal silica or aluminium or zinc soaps.

Hydrophilic gels

Hydrophilic gel (hydrogel) bases usually consist of water, glycerol, or propylene glycol gelled with suitable agents such as tragacanth, starch, cellulose derivatives, carboxyvinyl polymers, and magnesium aluminium silicates.

Ointments[1]

Definition

Ointments are homogeneous, semi-solid preparations intended for external application to the skin or mucous membranes. They are used as emollients or for the application of active ingredients to the skin for protective, therapeutic, or prophylactic purposes and where a degree of occlusion is desired.

Ointments are formulated using hydrophobic, hydrophilic, or water-emulsifying bases to provide preparations that are immiscible, miscible, or emulsifiable with skin secretions. They can also be derived from hydrocarbon (fatty), absorption, water-removable, or water-soluble bases.

[1] Ophthalmic ointments are described in the separate monograph for ophthalmic preparations.

Hydrophobic ointments

Hydrophobic (lipophilic) ointments are usually anhydrous and can absorb only small amounts of water. Typical bases used for their formulation are water-insoluble hydrocarbons such as hard, soft, and liquid paraffin, vegetable oil, animal fats, waxes, synthetic glycerides, and polyalkylsiloxanes.

Water-emulsifying ointments

Water-emulsifying ointments can absorb large amounts of water. They typically consist of a hydrophobic fatty base in which a w/o agent, such as wool fat, wool alcohols, sorbitan esters, monoglycerides, or fatty alcohols can be incorporated to render them hydrophilic. They may also be w/o emulsions that allow additional quantities of aqueous solutions to be incorporated. Such ointments are used especially when formulating aqueous liquids or solutions.

Hydrophilic ointments

Hydrophilic ointment bases are miscible with water. The bases are usually mixtures of liquid and solid polyethylene glycols (macrogols).

Pastes

Definition

Pastes are homogeneous, semi-solid preparations containing high concentrations of insoluble powdered substances (usually not less than 20%) dispersed in a suitable base. The pastes are usually less greasy, more absorptive, and stiffer in consistency than ointments because of the large quantity of powdered ingredients present. Some pastes consist of a single phase, such as hydrated pectin, and others consist of a thick, rigid material that does not flow at body temperature. The pastes should adhere well to the skin. In many cases they form a protective film that controls the evaporation of water.