SEMISOLIDS

Lecture 11

Pharmaceutical Semisolid Preparations

Including several types like ointments, creams, gels, pastes and rigid foams.

Properties: Cling to the surface of application for reasonable duration of time before they are washed or worn off. This adhesion is **due to their plastic rheological behavior which retain their shape and cling as a film.**

- **Ointments** are composed of fluid hydrocarbons meshed in a matrix of higher melting solid hydrocarbons. While most ointments are based on mineral oil and petrolatum, there are alternative types. Polyethylene glycol can be incorporated into mineral oil to yield a plastic matrix e.g. Plastibase.
- Most ointments are prepared by melting components together. Drugs or other components are added in the fluidized state.
- If the solids are insoluble and to be suspended, the system is put through a milling process (a colloid mill, homogenizer or ultrasonic mixer) so that the solids are fully dispersed.
- **Creams** are semisolid emulsion systems with opaque appearance. Their consistency and rheologic character depend on whether the emulsion is a w/o or o/w type and on the nature of the solids in the internal phase.

- **Gels** are semisolid systems in which a liquid phase is constrained within a three-dimensional polymeric matrix in which a high degree of physical or sometimes chemical cross-linking has been introduced.
- The polymers used to prepare gels include the natural gums (tragacanth, pectin, agar and alginic acid), synthetic and semisynthetic materials such as methylcellulose, hydroxyethylcellulose, carboxymethylcellulose and Carbopol.
- **Pastes** are basically ointments into which a high percentage of insoluble solids has been added. They are valuable as protective barriers on the skin such as treating diaper rash.
- Pastes are prepared by incorporating a solid directly into a congealed system by levigation with a portion of the base to form a paste-like mass. The reminder of the base is added with continuous levigation until the solids are uniformly dispersed in the vehicle.

- **Foams** are pressurized dosage form containing one or more active ingredients that upon valve actuation emit a fine dispersion of liquid and/or solid material in gaseous medium. Foams are generally easier to apply, less dense and spread more easily than other topical dosage forms, e.g. aerosolized shaving creams.

Note: The bulk of semisolid preparations are applied to the skin where they serve as:

- Vehicles for topically applied drugs
- Emollients
- Protectives

- A lesser portion of topical semisolid dosage forms are applied to mucous membranes such as rectal tissue, buccal tissue, vaginal mucosa, nasal mucosa, external ear lining and cornea.

Formulation of semisolid dosage forms

Raw Materials

- The raw materials are available for skin use> oral use > parenteral use.

The difference in the number of materials available for each route is due to the:

- Type of absorption barrier.
- The environment surrounding absorption sites.

E.g.: Isopropyl myristate and butyl stearate may be used topically without toxic effects, yet these esters may not be used orally because hydrolysis of the esters by digestive enzymes yields poorly tolerated alcohols. The absence of comparable hydrolytic enzymes on the skin surface makes these compounds satisfactory for dermatologic medication.

Examples of raw materials used in semisolids:

Oils, Fats, Emollients, Emulsifiers, Waxes, Cellulose derivatives, Humectants, Lanolin derivatives and Water absorption bases.

In advance of any formulation, the following tests must be carried out:

- Physical and chemical incompatibilities
- Stability at alkaline and acidic pH
- Sensitivity to oxidation, moisture and light
- Solubility in various solvents
- Most suitable base for stability of drug and for its absorption
- Compatibility with container

Raw materials

A) Hydrocarbons (Petrolatum and Mineral oil)

1. Petrolatum

Complex mixture of H.C. (aliphatic, cyclic, unsaturated, branched substances) obtained from petroleum.

- Widely use, has broad chemical and physical specifications in the USP like wide density and melting point.

- Petrolatum has 2 types: (determined by dipping and withdrawing index finger slowly in petrolatum sample):

long fiber (forms transparent continuous film) used as occlusive dressing.

short fiber (ruptures easily and does not exhibit film).

2. Mineral oil

Obtained from petroleum at a particular viscosity and specific gravity ranges.

- Preferred in semisolids at low viscosity (**less tacky and greasy**)

B) Hydrocarbon waxes

- **Uses:** In creams and ointments
- **Benefits:** increase viscosity of mineral oil to prevent its separation from an ointment.

- Types:

1- Natural (Paraffin wax): obtained from petroleum and has a variety of M.P. 35-70°C.

2- Synthetic (synchrowaxes): used in conjugation with or replace the natural waxes to exhibit thermoplastic and occlusive properties (moisturizing the skin) without inelegant properties of natural one.

C) Oleaginous substances

Vegetable oils (almond oil, sesame oil and olive oil)

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Problem: contain trace metal contaminants that catalyze oxidation reactions

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Solution : use of antioxidants (butylated hydroxyanisole, butylated hydroxy toluene and salts of EDTA)

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Problem: drug compatibility or dermal sensitivity

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Solution: Isolation and synthesis of pure chemical entities present in vegetable oils for better control on quality of an emulsion and release of a drug from a base

D) Fatty acids and alcohols

1. Stearic acid

Uses: As an emulsifier in water-removable creams to develop a certain consistency and to give a matt effect on the skin.

2. Stearyl alcohol and cetyl alcohol (palmityl alcohol)

Uses: As auxiliary emulsifiers and emollients in creams

- Stearyl alcohol produces a firm cream that may be softened with cetyl alcohol.

E) Emulsifiers

Water soluble soaps used for (o/w emulsions)

The viscosity of the cream or ointment prevents the coalescence of the emulsified phase and helps to stabilize the emulsion.

Additional substances added to achieve stability:

- Cetyl alcohol and glyceryl monostearate tends to stabilize the o/w emulsion. The interfacial film formed around the dispersed phase globules is solid, thereby making the emulsified preparation more rigid.

- Polyvalent ions (magnesium, calcium and aluminium) tend to stabilize w/o emulsions by cross-linking with the polar groups of fatty materials.

- The combination of SAA with an auxiliary emulsifier is referred to as a mixed emulsifier system, e.g. triethanolamine stearate soap combined with cetyl alcohol for o/w emulsion. Beeswax and divalent calcium ions for w/o emulsion. Maximum stability of an emulsion occurs when a complex interfacial film is formed.

- The soap-type emulsion may be unstable in the presence of acidic substances. Cationic or nonionic emulsifiers are preferable for drugs requiring an acidic pH.

- The nonionic emulsifiers are employed for both o/w or w/o emulsified semisolids because they are compatible with many drug substances. In addition, they are versatile and used with strongly acidic salts or with strong electrolytes.

- Recently used emulsifiers (lactic acids with fatty acids) like acyl lactylates.

These acyl lactylates are claimed to be mild and non irritating to the skin and eyes to produce an emollient feel to the skin and to serve as O/W or W/O emulsifiers.

- To achieve adequate stability in creams in which the oil content exceeds 10%, it is recommended to use of a co-emulsifier. The HLB system should be utilized to calculate the ratio between the two emulsifiers for the lipid being used.

- One of the important non-ionic emulsifiers is: Promulgens (mixture of fatty alcohol and their ethoxylates). They differ in melting point and in consistency of the emulsions that they form.

- Types of Promulgens are:

1. Type D (forms creams since they are thicker in consistency).
2. Type G (forms liquid emulsions).

- Both types are not subjected to hydrolysis since having no ester linkage.
- Both are Compatible with SLS (anionic surfactant) and quaternary ammonium compounds (cationic surfactant)

F) Polyols

Glycerine, Propylene glycol, Sorbitol 70%, Low M.wt. PEG are used as humectants in creams.

The choice of a humecatant is based on:

1. Its rate of moisture exchange.
2. Its effect on the texture and viscosity of the preparation.

These materials:

- Prevent the cream from drying out and prevent the formation of a crust when the cream is packaged in a jar.
- Improve consistency and rub-out qualities of cream when applied to skin so permit spread of cream without rolling.

Misuse: tackiness due to increase humectant content

Notes:

1- **PG and PEG** are sometimes used in combination with glycerine due to their lesser ability to absorb moisture than glycerine.

2- **Sorbitol 70%** is more hygroscopic than glycerine thus used in a lower conc. 3% as compared to 10% for glycerine.

Insoluble Powders

I. Insoluble drugs must be uniformly dispersed throughout the vehicle to ensure homogeneity of the product. **(P.S.74 Microns -200 mesh size are impalpable and avoid grittiness).**

Adv. of Milling a drug to a finely divided state: provides more surface area for contact with the dermal site and increases the rate of dissolution of poorly soluble substances.

Some powders do not disperse uniformly but tends to aggregate in the base. This may be due to the electrically charged surface condition of the particles after milling.

Aggregation of particles becomes a problem for those that are 5 microns or smaller in size.

Many drug substances used in topical preparations like **(Prednisolone, Flurocortisone acetate)** exist in several polymorphic states **thus having varying amounts of free energy or thermodynamic activity.** The activity and availability of drug related to its thermodynamic activity, thus choosing the proper crystalline form for use in semisolid is important.

Following the incorporation of a drug into the semisolid preparation, the maintenance of the selected polymorph form in the semisolid is also important. The components of the vehicle and method of preparation of semisolids affect the stability of polymorphic form.