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REVIEW : ADVANCED APPOROCHES IN SEMISOLID

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ABSTRACT

A recent advance in semisolid dosage form allows modified release as well as flexibility in route of administration. Several novel drug-carrier systems have been examined that offer enhanced release, controlled release, or a stable environment for the incorporated drug. Novel semisolids are non greasy since they are made up of water washable bases. Hence they cause less irritation to skin and are superior to conventional semisolid dosage form.

Key words *control release, diffusion, skin.*

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INTRODUCTION

A transdermal patch is a medicated adhesive patch Semisolids constitute a significant proportion of pharmaceutical dosage forms They serve as carriers for drugs that are topically delivered by way of the skin, cornea, rectal tissue, nasal mucosa, vagina, buccal tissue, urethral membrane, and external ear lining, A wide range of raw materials is available for the preparation of a semisolid dosage form.

A semisolid dosage form is advantageous in terms of its easy application, rapid formulation, and ability to topically deliver a wide variety of drug molecules. 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 drug

TYPES OF CONVENTIONAL SEMISOLID DOSAGE FORMS :

OINTMENTS [(2 , 6)]:-

They are soft hydrocarbon based semisolid preparation, composed of fluid hydrocarbon meshed in a matrix of higher melting solid hydrocarbon petrolatum being a tasteless, odorless, unctuous material with a melting range. Since they are greasy nature so they stain cloths. Principle ingredients forming the system hydrocarbon and silicon oil are generally poor solvent for most drugs, seemingly setting a low limit on the drug delivery capabilities of the system.

Creams [1,2 ,6]:-

Creams are semisolid dosage forms that contain one or more drug substancesDissolved or dispersed in a suitable base, usually oil in- water emulsion or aqueous microcrystalline dispersion of long-chain fatty acids or alcohols that are water-washable and are cosmetically and aesthetically acceptable. *They are viscous semisolid emulsion system with opaque appearance as contrasted with translucent ointments. Consistency and rheological character depends on weather the cream is w/o or o/w*

Pastes [2 , 6]:- are semisolid dosage forms that contain one or more drug substances incorporated in a base with large proportions of finely dispersed solids, are intended for external application to skin, but very thick & stiff. ·Pastes are less greasy because of the absorption of the fluid hydrocarbon fraction to the particulates.

·There are two types of paste, a) Fatty pastes (eg: - zon paste) and

b) Non greasy pastes (eg: - bassorin paste is also named as tragacanth jellies since hydrophilic component of tragacanth gels in water).

Jellies[1,2,6,7]:-: are transparent, non-greasy, semisolid prepration for external applications to skin & mucous membrane.

- Gels are aqueous colloidal suspensions of the hydrated forms of insoluble medicament.
- Gels are richer in liquid than magma
- Jellies are transparent or translucent non-greasy semisolid gels.
- Some are as transparent as water itself, an aesthetically pleasing state, other are turbid, as the polymer is present in colloidal aggregates that disperse light.

Poultices [7]:-are soft, viscous wet masses of solid substances applied to skin & now outdated.

Poultice must retain heat for a considerable time because they are intended to supply warmth to inflamed parts of body.

Suppositories*:* are intended in other than oral cavity i.e., vaginal, nasal cavity. generally introduced in systemic.

Plasters[4]:- :-

Plasters are solid or semisolid masses adhere to the skin when spread upon cotton felt line or muslin as a backing material and they are mainly used to,

·Afford protection and mechanical support.

·Furnish an occlusive and macerating action.

·Bring medication into close contact with the surface of the skin.

Rigid foam[1]

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

E.g. shaving creams, whipped creams, aerosolized shaving creams.

THEORY OF SEMISOLID DOSAGE FORMS: -

HYDROPHILIC PROPERTIES :-

The water absorbing capacity of oleaginous and water-in-oil bases may be expressed in terms of the water number, defined in 1935 by Casparis and Meyer as the maximum quantity of water that is held (partly emulsified) by 100g of a base at 20^{o} C. The test consists of adding increments of water to the melted base and triturating until the mixture has cooled. When no more water is absorbed, the product is placed in a refrigerator for several hours, removed, and allowed to come to room temperature. The material is then rubbed on slab until water no larger exudes, and finally, the amount of water remaining in the base is determined.

RHEOLOGICAL PROPERTIES [8, 9]:-

Different semisolid dosage forms exhibit different rheological properties. Semisolids do not flow at low shear stresses but undergo reversible deformation like elastic solids. When a characteristic shear stress, called the yield value or yield stress, is exceeded, they flow like liquids. Yield stresses usually are caused by structural networks extending throughout an entire system. To break such a network requires stress produce no flow but only elastic deformation. When the yield stress is exceeded, the network is partly ruptured and flow occurs.

NOVEL ADVANCES IN SEMISOLID DASAGE FORMS: -

1. OINTMENTS:-

Rectal Ointment:

it is used for the symptomatic relief against anal and peri-anal pruritus, pain and inflammation associated with hemorrhoids, anal fissure, fistulas and proctitis. Rectal ointment should be applied several times in a day according to the severity of the condition. For intrarectal, use,apply the ointment with the help of special applicator.

CREAMS[1,2 ,6]:-

a) Creams containing microspheres[16]:-

Albumin microsphere containing vitamin A can be administered by using creams topically. 222 ± 25 µm size of microsphere of vitamin A were produced by emulsion method. The in vitro and in vivo drug release of a microencapsulated and nonmicroencapsulated vitamin A cream was studied. The in vivo study in six volunteers revealed that these microspheres were able
to remain on the skin for a long period of time, and as a consequence they were able to prolong the release of vitamin A

b) Lamellar faced creams[17]:-

They are liquid paraffin in water emulsionprepared from cetrimide / fatty alcohol like mixed emulsifiers and ternary system formed by dispersing the mixed emulsifier in require quantity of water. The cationic emulsifying wax showed phenomenal swelling in water and this swelling was due to electrostatic repulsion whish can be suppressed by addition of salt and can be reduced by changing surfactant counter ion.

c) Cream containing lipid Nanoparticles[19]:-

Occlusion of cream is important criteria since it increases the penetration of topical drugs. This can be achieved by using oils and fats like liquid and semisolid paraffin in large quantities. However, such formulations have the limitations of poor cosmetic properties since they have greasy feel and glossy appearance

Gels *:*

Gels with permeation enhancers:-. skin can act as a barrier to the deeper penetration of drug molecules. With the introduction of various penetration enhancers, however, systemic drug delivery through the transdermal route has gained major footing. These chemicals, incorporated in a suitable drug-carrying semisolid vehicle, enhance the amount of drug permeation through skin. The high diffusion rates of indomethacin and diclofenac show that lecithin microemulsion gel is a suitable matrix for transdermal drug delivery.

Oleo-hydrogel systems. Oleo- hydrogel systems for localized skin have been explored successfully. Rhee et al. examined transdermal permeation using various vehicle systems to avoid systemic side effects and gastrointestinal irritation from ketoprofen upon oral administration. The researchers examined an oleo-hydrogel system that consisted of ketoprofen incorporated into an emulsion of oil and carbomer hydrogel mixture, with *N*-methylpyrrolidone as a permeation enhancer. The greater bioavailability of ketoprofen in the oleo-hydrogel system was ascribed to good drugrelease properties, higher emulsion droplet stability of the carbomer gel, and the penetration-enhancing effect of *N*methylpyrrolidone. The formulation of ketoprofen oleohydrogel that showed maximum percutaneous absorption was one that contained 3% ketoprofen, 1% carbomer, 10% *N*methylpyrrolidone, 10% oils, 8% surfactant, and water adjusted to ph

Controlled release gels[19]:-

Drug delivery to nasal or ocular mucosa for eitherlocal or systemic action suffers from many obstacles.Gel formulations with suitable rheological and mucoadhesive properties increase the contact time at the site of absorption. However, drug release from the gel must be sustained if benefits are to be gained from the prolonged contact timeH 4.6 using triethanolamine.

Advanced novel approaches

A. Physical means

1. Phonosoresis(sonophoresis)
2. Iontophoresis
3. Electrophoresis

B. Chemical means

1. Systemic Drug Delivery
2. Localized Drug Delivery

3. Localized And Systemic Drug Delivery

Phonosoresis(sonophoresis): [35]:-

It is defined as the movement of drugs through intact skin and underlying soft tissues under the influence of an ultrasonic perturbation.

It is safe and effective technique for enhancing drug administration in clinical applications when with a proper frequency, power level, and duration.

It increases drug permeation through the skin by disordering the structured lipids in the stratum corneum.

Potent chemotherapeutic agent limits the therapeutic window. This window can be expanded by controlling the drug delivery in both,space [selective to the tumor volume] and time [timing and duration of release] such that non targeted tissue are not adversely affected.

This can be achieved by developing Transdermal drug delivery with the use of ultrasound technique(US) is one of the effective and safe option to treat cancerous tissue.

Low frequency US -- less than 1 Mhz

medium -- 1-5 Mhz

high frequencies -- 5-10 Mhz

Ultrasonic waves can be carefully controlled and focused on the tumor site.

Low frequency US (20 khz) can be used in the transdermal delivery of medium and high mol.wt. proteins (including insulin, interferon and erythropoetins).

Three hours after the US treatment, the skin regained its transport resistance to insulin, indicating that no permanent damage was done by US.

Iontophoresis: [35]:-

It is basically an injection without the needle.

Mechanism:

Repulsive electromotive force using a small electrical charge applied to an iontophoretic chamber containing a similarly charged active agent and its vehicle.

One or two chambers are filled with a solution containing an active ingredient and its solvent, also called the vehicle.

The positively charged chamber, called the anode, will repel a positively charged chemical, whereas the negatively charged chamber, called the cathode, will repel a negatively charged chemical intotheskin.

This technique is highly desirable to improve the transdermal delivery of peptide and proteins .

Electrophoresis:

Here the membrane of a cell exposed to high-intensity electric field pulses(up to several hundred volts for micro- or milliseconds) can be temporarily, thus becoming highly permeable to exogenous molecules in the surrounding media.

The charged molecules were considered transporting through existing shunt routes of the skin at transdermal voltage <100 v.

When transdermal voltage was greater than 100v, the transcorneocyte pathway was also accessible to charged molecules as lipid bilayers were electroporated.

It is effective, safe, cost-effective, as well as powerfully versatile.

e.g. microchip controlled for complex drug delivery patterns

Chemical means:

1. Systemic drug delivery : **[36]:-**

The skin's large surface area1.73 m2, facilitates its use as a potential site for the application of topical dosage forms.

Advantages:

First-pass gut and hepatic metabolism is avoided.

constant drug levels in the bloodstream are maintained for longer periods of time.

side effects are decreased.

bioavailability is improved.

the dosage is smaller.

compliance is increased

Submicron emulsion vehicle system:

Conventional creams -- mean droplet size ranging from 10 to 100 µm.

They have poor penetration of drug-loaded oil droplets into deep skin layers.

Microparticles -- diameters 3-10 µm penetrate follicular ducts.

Particles >10 µm remain on the skin surface.

Particles of <3 µm are distributed randomly into hair follicles and stratum corneum.

Submicron emulsion vehicle system (SMEVS) penetrate the layers of the stratum
corneum, increasing its fluidity.18,19

It causes slow, continuous, and controlled systemic delivery of the drug.

(SMEVS) formulated by processing a medium-chain triglyceride emulsion with
high pressure homogenizer alongwith lecithin, an efficient dispersing agent, causes a drastic reduction in droplet size, usually to between 100 and 300 nm.

skin can act as a barrier to the deeper penetration of drug molecules. With the
introduction of various penetration enhancers, however, systemic drug delivery
through the transdermal route has gained major footing

2. Localized drug delivery: [37]:-

Oleo-hydrogel systems:

An oleo-hydrogel system that consisted of ketoprofen incorporated into an emulsion
of oil and carbomer hydrogel mixture, with *N*-methylpyrrolidone as a permeation
enhancer to avoid systemic side effects and gastrointestinal irritation from ketoprofen
upon oral administration.

When compared with conventional gel or plaster formulations,the oleo-hydrogel
system was found to be the optimal formulation because it decreased systemic
circulation ofthe drug and increased localized action.

greater bioavailability of ketoprofen was ascribed to;

good drug release properties.

higher emulsion droplet stability of the carbomer gel the penetration-enhancing effect of methylpyrrolidone. formulation of ketoprofen oleohydrogel that showed maximum percutaneous absorption was one that contained; 3% ketoprofen 1% carbomer 10% *N*methylpyrrolidone 10% oils 8% surfactant and water adjusted to pH 4.6 using riethanolamine

Volatile vehicle–antinucleant polymer systems:

Increasing the thermodynamic activity of drug molecules was found to be the most
efficient parameter for transdermal permeation of topically applied drug molecules.

This can be achieved by the volatile vehicle–antinucleant polymer system.

Enhanced permeation of sodium nonivamide acetate(an antinociceptive agent)was observed with ethanol–buffer solutions (pH 4.2) containing antinucleant polymers.

Here supersaturation (achieved by evaporation of the vehicle) for penetration
enhancement.

However supersaturated solutions are physically unstable and can result in the
crystallization of a drug upon preparation of the solution.

This effect can be controlled by antinucleant polymers such as methylcellulose,
cyclodextrin derivative (RAMEB),HPMC,PVP,SCMC(soium carboxy) and a vinylpyrrolidone/vinyl acetate copolymer (Kollidon® VA64)

These polymers are adsorbed on the hydrophobic surface of crystals, thus stabilizing
the precipitates and increasing the thermodynamic activity of the drug.Which
enhances the permeation of drug.

Sodium deoxycholate gels leave no residue after application.

Solid lipid nanoparticles:

Solid lipid nanoparticles of glyceryl behenate have been investigated as efficient
carrier systems for topical use.

provide both burst and sustained drug release.

Burst release improves the penetration of drug into the skin.

Due to presence of a solid matrix, sustained drug release is exhibited.This effect
prolong drug delivery and minimizes the irritation potential drug.

It possess the better drug penetration because close contact to the stratum corneum
and increases the amount of encapsulated drug penetrating the skin.

3.Localized and systemic drug delivery: [39]:-

Liposomes as drug carriers: Liposomes are microscopic vesicles composed of membrane-like lipid layers

Surrounding an aqueous compartment .

Phospholipids most often are used in the preparation of liposomes.Because of the amphiphilic nature of phospholipids, when they are dispersed in aqueous solutions they arrange in bilayers, with the fatty-acid tails (nonpolar) located in the membrane's interior and the polar heads pointing outward.using liposomes both lipophilic as well as hydrophilic drugs can be incorporated within the lipid bilayers and aqueous compartment, respectively. They serve as a reservoir for the prolonged release of drugs within various skin layers. They are nongreasy and nontacky, liposomal preparations.

Mechanism: [40]:-

liposomes carry a drug in dissolved form to the skin surface, and their lipid bilayer ruptures as a result of both their interaction with surface lipids and the action of bacterial flora that are present. Thus the encapsulated drug is freed, allowing it to penetrate. Small liposomes disintegrate quickly on the skin surface and may form a lipid layer that prevents the hydrophilic substance from reaching the skin.31 However, this action enhances the absorption of lipophilic substances. skin permeation was enhanced to a significantly higher degree by liposomes consisting of skin lipid composition (ceramide, cholesterol, palmitic acid, and cholesteryl sulfate) as compared with other liposomes. The enhanced permeation was attributed to the optimum solubility of these constituents with lipid layers of skin.

A study that proposed the use of topical retinoids (e.g., vitamin A) in liposome form found that nonliposomal forms are susceptible to oxidation and show irritant action as a result of the large dose of drug in the formulation.

Liposomal encapsulation allowed a large portion of the applied dose in enclosed form to be released in small amounts for prolonged periods, thus reducing local irritation In addition, the enclosed drug was found to be less susceptible to the risk of deactivation by oxidation. Other drugs that yielded better results with liposomal formulations include methyl nicotinate, hydrocortisone, minoxidil, lidocaine, dibucaine, interferons, methotrexate. Solutions and aqueous gels are two of the most common forms in which liposomes are applied to skin. The choice of hydrophilic polymers that minimally influence the stability as well as the rate of penetration of liposome-entrapped substances into the skin is a crucial factor in their efficient functioning. E.g. Aqueous gels of carboxymethylcellulose were found not to influence the stability of the hydrogenated soya lecithincholesterol liposomes and appeared to be convenient vehicles for liposome formulations as compared with xanthan gum. 34 Ethanol has been used widely as a skin permeation enhancer, but only in small concentrations.

A novel system, ethosomes, is composed of phospholipids, ethanol, and water with sufficiently high concentrations of ethanol. 35 E.g. increased minoxidil penetration into deeper skin layers was observed. Drug release from liposomes dependent on the size and multilamellarity of the liposome itself. Release rate is faster in unilmellar than in multilamellar. The release can be also dependant on the kind of drug: the release of cations is slower than that of anions

NOVEL ADVANCES IN SEMISOLID APPLICATIONS: -

1. NASAL [28, 29]: -

Numerous drug substances can be prepared as nasal solutions or suspensions to be administered either as drops or sprays gels, jellies or ointments. Some drugs are sufficiently volatile they can be carried into the nose through an inhaler.

a) Introduction: Drug delivery to nasal mucosa for either local or systemic action faces obstacles like cilia, mucus. These routes are protected by effective mechanisms.

Nasal drug administration has been routinely used for administration of drugs for the upper respiratory tract, like adrenergic agents, and is now also being used as a viable alternative for the delivery of many systemic therapeutic agents. A number of dosage forms are common and include solutions, suspensions and gels.

Nasal gels are semisolid preparations prepared for nasal application and can be for either local or systemic use, in a water soluble or water miscible vehicle where as Nasal ointments are prepared from either water miscible/soluble or oleaginous bases.

b) Advantage, Application and uses: The advantages of nasal delivery include,

(1) Lower doses,
(2) Rapid local therapeutic effect,
(3) Rapid systemic therapeutic blood levels,
(4) rapid onset of pharmacological activity, and
(5) Few side effects.

In addition to the nasal decongestants, saline and other routine locally acting drugs, nasal administration is being investigated for the delivery of insulin, vaccines, number of poly peptides and proteins, progesterone, metoclopramide, propranolol (for migraine headaches), dihydroergotamine, desmopressin, atropine, vitamin B12 , antihistamines, anti-obesity agents, narcotic analgesics like Butorphanol tartarate (analgesic), cyanocobalamin (haematopoeitic), narfaralin acetate (treat endometriosis), nicotine (adjunct in smoking cessation) and a host of other agents.

An example of drug that shows effectiveness upon administration as a nasal gel, as compared to an oral tablet, is vitamin B12, where clinical studies showed a six fold increase in maximum blood levels, a doubling of speed in entering the bloodstream, and a 2.5 fold increase in measurable vitamin B12 in the blood 48 hours after administration. Similar results have been reported in other studies.

c) Risk associated with nasal semisolids: The risk of patient-to-patient contamination is very high with nasally administered products; patients should be advised that a nasal product is for ONE PATIENT ONLY.

d) Formulation aspect: In addition to the active drugs, nasal preparations contain a number of excipients, including vehicles, buffers, preservatives, tonicity adjusting agents, gelling agents and possibly antioxidants. Important in the formulation process is the use of ingredients that are nonirritating and compatible with the nose as discussed within each category. In general, the same excipients used in ophthalmic formulations can also be used in nasal formulations.

It was possible to control the release of uncharged drug substances by including surfactants that form micelles in the gel. This release depended on lipophilic interactions between the drug and the polymer and/or the micelles. Controlled-release formulations of charged drugs could be designed by mixing the drugs with oppositely charged surfactants in certain ratios. In this way, vesicles in which the drug and surfactant constituted the bilayer formed spontaneously. The vesicle formation was affected by the presence of polymer, and very small vesicles that gave a slow release rate were formed when a lipophilically modified polymer was used.

2. SKIN [7, 30, 31]: -

Delivery of drugs to the skin is an effective and targeted therapy for local dermatological disorders.

a) Introduction: Topical gel formulations provide a suitable delivery system for drugs because they are less greasy and can be easily removed from the skin.

Topical dermatologic products are intended for localized action on one or more layers of the skin (e.g., sunscreens, keratolytic agents, local anesthetics, antiseptics and anti-inflammatory agents).Although some medication from these topical products may unintentionally reach systemic circulation, it is usually in sub-therapeutic concentrations, and does not produce effects of any major concern except possibly in special situations, such as the pregnant or nursing patient.

b) Advantage, application and uses: This route of drug delivery has gained popularity because,

(1) Provides a largest surface area
(2) It avoids first-pass effects, gastrointestinal irritation,
(3) And metabolic degradation associated with oral administration.

Galentic also manufactures zinc oxide ointment (5% and 25%), anti-hemorrhoid ointment, tiabendazole ointment, hydrocortisone and urea cream, fluocinole ointment, salicylic acid ointment,

dexamethasone acetate and clotrimazole cream, griseofulvin ointment, white petroleum jelly (sterile or non-sterile), diclofenac diethylammonium oleum lini methyl salicylate and menthol gel (rubigel), nystatin cream / ointment, salicylic acid and precipitated sulphur ointment, fucidic acid cream, aciclovir cream and diclofenac gel. viable epidermal or dermal sites (such as local anesthetics or anti-inflammatory agents) may also occasionally include a vasoconstrictor, such as epinephrine, in the formulation to retard systemic uptake of the drugs and, thereby, prolong its local effect.

Rubigel ointment is used to reduce backache, joint pains, sprains and muscle cramp, as well as offering faster penetration of active medication thereby providing faster onset of pain relief; **versept cream** is used for cleansing and antisepsis of skin and mucous membranes that include wounds, burns, ulcers and abcesses. **Avalon NF skin cream** is a combination of Neomyci and Fluocinolone acetonide that is used for topical application.

The company also offers anti-hemorrhoid ointment for hemorrhoid patients. Betamethosone valerate ointment is used for anti-inflammatory effect; phenylephrine HCL ointment reduces bleeding and swelling, and relieves itching and discomfort by tightening the blood vessels. Lidocaine HCL local anesthetic ointment provides fast, effective and lasting pain relief.

3. OPHTHALMIC [28, 31-32]: -

The present invention relates to novel ophthalmic pharmaceutical compositions comprising an inflammation-treating amount of a 4-aminoquinoline compound, derivative, isomers, or chemical salts, and methods for using these compositions for the treatment of ocular inflammatory conditions by topical administration directly to the eye.

a) Introduction: In ocular drug delivery, many physiological constraints prevent a successful drug delivery to the eye due to its protective mechanisms. Drug loss occur via,

(1)Less capacity of cualdy sac (up to 7.5µlit)

(2)Dilution of drug due to lachrymal secretion.

(3)Nasolachrymal drainage

So formulation is administration by increasing the viscosity of dosage form in order to achieve increase in contact time with corneal membrane. This can be achieved by use of ophthalmic semisolids

b) Ophthalmic administration: Ophthalmic semisolid compounds are useful for preventing and treating ocular inflammation by application of the compositions to the eye prior to, during and after an inflammatory disorder, especially inflammation of the outer and middle coats of the eye, such as dry eye, conjunctivitis, scleritis, keratitis, and uveitis.

c) Application and uses: Galentic supplies a wide range of eye ointments for a variety of ophthalmic infections. The product range includes aciclovir eye ointment, chloramphenicol ophthalmic ointment, gentamicin sulphate ophthalmic ointment, hydrocortisone acetate ophthalmic ointment, tetracycline hydrochloride ophthalmic eye ointment USP 1%, netracycline eye ointment (oxytetracycline eye ointment), oxytetracycline hydrochloride and hydrocortisone ophthalmic eye ointment, triosporin antibiotic eye ointment and sulphacetamide sodium ophthalmic ointment.

Uveitis is an inflammation of the uvea, the middle layer of tissue behind the white of the eye. The cause of uveitis is poorly understood, but a variety of systemic diseases are associated with it. Uveitis has been treated by various classes of compounds including steroids and nonsteroidal anti-inflammatory agents such as dexamethasone, flurometholone, prednisolone, indomethacin, aspirin, flubiprofen and diclofenac.

d) Risks of ophthalmic semisolids: Visual disturbances, including blurred vision

e) Formulation ophthalmic semisolids: The ophthalmic pharmaceutical composition of the invention includes one or more additional ophthalmic pharmaceutical compositions including buffers, surfactants, stabilizers, preservatives, ophthalmic wetting agents, and ophthalmic diluting agents. Semisolid ophthalmic vehicle contain soft petrolatum.

Absorption and water soluble bases generally are used for preparation of ophthalmic semisolids are

Mineral oil is added to petrolactum to lower its fusion point (but its addition increases chance of separation and to avoid this Ozokerite, Ceresin, Micro crystalline wax in small quantity are added
White petrolatum (white petroleum jelly, white soft paraffin) is a white-colored, translucent, soft, unctuous mass that is inert, odorless and tasteless. It is a mixture of semisolid saturated hydrocarbons obtained from petroleum.
It is practically insoluble in ethanol, glycerin and water but is soluble in chloroform and most fixed and volatile oils. Heating above its melting range (about 70°C) for extended times should be avoided, but it can be sterilized by dry heat

4 .RECTAL [16, 28, 35] : -

Rectal tissues are much thicker than other gastro intestinal epithelial tissue. Bioavailability of this route depends upon pH of environment, lipid solubility of drug.

a) Introduction: rectal preparation includes Ointment, creams; gels are used for application to perianal area. Preanal area is the skin immediately surrounding anus. Substance applied rectally may be absorbs by diffusion into circulation via network of three hemorrhoid arteries (superior inferior and middle hemorrhoid artery)

b) Rectal administration: previously this route was use for bowel evacuation. But now a day's rectal route is widely use for administration of drugs like paracetamol, aspirin, indomethacin, theophyllin, barbiturates, chlorpromazine and several other anticonvulsant agents

c) Advantage, application and uses: several advantages of using rectal semisolids are
(1)Large surface area
(2)The ability to bypass first-pass liver metabolism,
(3)Prolongs the residence time
(4)And permeability to large molecular weight drugs, such as peptides and proteins. **(insulin gels administered deep rectally)**
Rectal preparation are used to treat anorectal pruritis, inflammation (hydrocortisone), discomfort with hemorrhoids (hydrocortisone), pain (pramoxine hydrochloride) Astringent (for example ZnO), protectants and lubricants (coca-butter, lanolin)

d) Risks of Rectal semisolids: less frequent risk with rectal administration of drug include skin rash, dizziness, pain, headache, abdominal pain, nervousness, diarrhea, feeling unsteady or clumsy, and wheezing

Evaluation of semisolids :

PHYSICAL TESTS [1,]: -

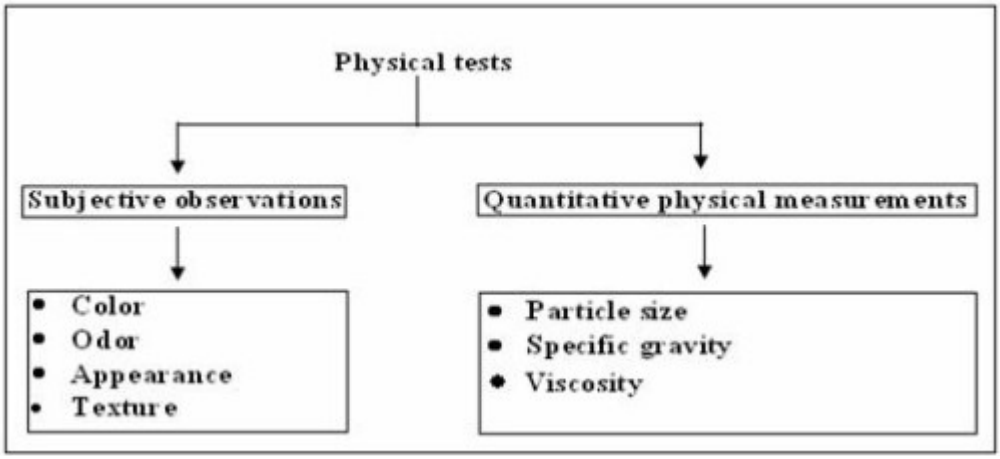

Fig : Physical tests

Viscosity measurement is done with the help of Brook-field viscometer, Cone and plate viscometer and Penetrometer – for consistency measurement.
Texture analysis:- Stable micro systems have launched a new Q.C. device – Texture analyzerwhich is used to detect,

a) Ointment flow characteristic
b) Ointment consistency
c) Gel strength [12]: - Gels have gained wide acceptance as semisolid dosage forms. It has been postulated that the strength rather than the viscosity of a gel layer plays a major role in

determining the amount of drug release from hydrophilic matrices. Recent advances have occurred in the development of an optimal apparatus to characterize gel strength. One proposed apparatus consists of a sample holder placed on an electronic microbalance connected to a computer. A probe is lowered into the sample by means of a motor equipped with a speed transformer, and the force required to penetrate the gel is measured. The increase in force with time is a function of the mechanical resistance of the sample to the penetration of the probe. Because the lowering speed is known, the displacement covered by the probe as a function of time is calculated and used to compute the gel-strength parameter or mechanical resistanceof the gel system.

d) Flavour release [49]: -A theory of flavour release from gelatin-sucrose gels has been developed based on combined interfacial mass and heat transport. The driving force for flavour release is shown to depend on the bulk melting temperature of the gel, which depends on the gelatin and sucrose concentrations. For gels possessing melting points below the mouth temperature, the driving force for flavour release is the rate at which heat can diffuse into the gels matrix and initiate melting. For harder gels with melting points above mouth temperature the diffusion of sucrose from the surface of the gel into the adjacent saliva phase is the rate limiting step for flavour release, because this lowers the melting temperature of the surface layer. The theoretical model gives good agreement with in vitro release experiments using gelatin gels containing sucrose and dye.

e) Sachet or Tube extrusion force measurement: -*Stable micro systems* have launched a new Q.C. device that quantifies the force required to extrude the contents from either tube or sachet style packaging. This device allows manufacturers to tests the force required to extrude the content of a sachet or tube at regular intervals over a long period of time, throughout its shelf life and adopt formulation accordingly.

CHEMICAL TESTS [1]: -

Chemical tests to be performed include,

a.Chemical potency test

b.Content uniformity test

c.pH measurement

IN-VITRO RELEASE PROFILE TEST [2, 12]: -

The principal in vitro technique for studying skin penetration involves use of some variety of a *diffusion cell* like Franz cell and Flow through cell in which animal or human skin is fastened to a holder and the passage of compounds from the epidermal surface to a fluid bath is measured.

Hairless rats were sacrificed by an overdose of halothane anesthesia. The skin from the dorsal surface was excised, and the adherent fat and subcutaneous tissue were removed. The skin was mounted on Franz diffusion cells with the epidermis facing the donor compartment. The skin permeation studies were performed by the procedure as described under “release studies.”

For the skin retention studies, the donor cell was removed, and the excess formulation was removed from the surface of the skin using a cotton swab. The skin was then washed with 50% ethanol: water and blotted dry with lint-free absorbent wipes. The entire dosing area (0.636 cm^2) was collected with a biopsy punch. The epidermis was separated from the dermis, and the tissues were minced using a dissection blade. Where applicable, the stratum corneum (SC) was stripped 20 times using breathable medical tape and the stripped skin was used to conduct permeation and skin retention experiments. Active drug content of epidermis and dermis was extracted using a previously reported method. Briefly, the samples were homogenized and boiled for 10 minutes in solvent (xM). The samples were then centrifuged and the supernatant was collected for analysis of drug by HPLC. The experiments were repeated at least 3 times using the skins from different rats.

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