

A Review : Novel Advances in Semisolid Dosage Forms & Patented Technology in Semisolid Dosage Forms

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Abstract : A recent advance in semisolid dosage form allows modified release as well as flexibility in route of administration. Recent advance of semi-solid processing has been reviewed, in particular, focusing on iron casting and product quality. Firstly, fluidity of cast iron slurry is discussed with the data of slurry viscosity and cavity filling ability. It is pointed out that process design should be done with fraction solid of slurry less than 0.3 to 0.4 and with sufficient slurry stirring. Next semi-solid casting with pressurization (SSCP) is discussed based on the author's research. Using inclined cooling plate, cast iron slurry is poured into metal mold, followed by pressurization on the cast surface. Cast sample obtained shows sound one without porosity and gives reasonable mechanical properties and solidification structure with fine globular graphite after proper heat treatment. For example, tensile strength 700 to 800 MPa with elongation value 4 % and Vickers hardness value 520 to 650 are obtained using mold preheated at 300.DEG.C.. Pressurization following the casting produces fine cementite phase in the cast sample which is disintegrated easily to form graphite particles.

Key words: semisolid dosage form: tensile strength: semi-solid casting with pressurization (SSCP).

1) INTRODUCTION^{1, 2,3}:

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.

Novel creams now a days are provided with nanoparticles and microspheres, which has an excellent emollient effect, with better spreadability, and less staining than oleaginous ointments. However both medicated and non-medicated creams provide very good emollient effects, oleaginous ointments are preferred for dry, chapped skin in an environment of low humidity because of its occlusive properties

Care should also be used in applying any drug to inflamed skin. The integrity of inflamed skin is generally compromised, resulting in increased

percutaneous migration and systemic absorption of most drugs.

2)IDEAL PROPERTIES OF NOVEL SEMISOLIDS:⁴

a) Novel ointment bases:

- i) Should absorb more water and enhance permeation.
- ii) When applied over skin,an oleaginous ointment film should formed which prevents moisture evaporation from the skin.
- iii) Should not irritate skin. Substances (e.g., hydrocarbon bases) conform an occlusive barrier on the skin that prevents.

b) Novel semisolids are safe even when applied to inflamed skin.

c) They should be odorless, easy to handle, stable and compatible with large range of drugs and should be safe.

d) Use of Novel semisolids in pediatric, geriatrics and pregnant women should be safe without causing any allergic reaction.

e) Novel semisolids should be able to extend the release pattern in a controlled manner.

f) Novel semisolid should allow its use in different routes of administration with safe, odorless, easy to handle and compatible with biological membrane.

3) NOVEL ADVANCES IN SEMISOLID DOSAGE FORMS: -

3.1) OINTMENTS^{2,5,6} :-

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.

3.2) CREAMS^{1,2,6} :-

a) Creams containing microspheres: -

Albumin microsphere containing vitamin A can be administered by using creams topically. $222 \pm 25 \mu\text{m}$ 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: -

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

c) Cream containing lipid Nanoparticles :-

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.

The development of a water-in-oil cream containing small particles of solid paraffin was studied. A high degree of occlusivity was obtained with smooth, flexible films prepared by drying aqueous dispersions of solid paraffin particles with a mean size of 200 nm

(nanoparticle dispersion). However, this nanodispersion revealed a rough texture when applied. The development of a water-in-oil cream wherein the aqueous phase was divided into small droplets solved this problem. Nanoparticles were incorporated in the aqueous phase. Hence, the oil phase in which the water droplets were dispersed served as a lubricant for nanoparticles, thereby preventing a rough feel during application.

3.3) GELS⁷⁻¹⁰: -

a) Controlled release gels: -

Drug delivery to nasal or ocular mucosa for either local 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 time.

Gelrite gels were formed in simulated tear fluid at concentrations of polymer as low as 0.1%, and it was shown that sodium was the most important gel-promoting ion in vivo. Rheology, although it may be a questionable technique for evaluating mucoadhesive properties of polymers, showed that interactions between mucin and polymers were most likely to be seen with weak gels.

The gels were also evaluated in the chamber using porcine nasal mucosa and from the results it was found that the rate of transport of drugs through the mucosa could be controlled by the rate of release from the formulation. Furthermore, the chamber can be used to evaluate the potential toxicity of formulations.

b) Organogels: -

Sorbitan monostearate, a hydrophobic nonionic surfactant, gels a number of organic solvents such as hexadecane, isopropyl myristate, and a range of vegetable oils. Gelation is achieved by dissolving/dispersing the organogelator in hot solvent to produce an organic solution/dispersion, which, on cooling sets to the gel state. Cooling the solution/dispersion causes a decrease in the solvent-gelator affinities, such that at the gelation temperature, the surfactant molecules self-assemble into toroidal inverse vesicles. Further cooling results in the conversion of the toroids into rod-shaped tubules. is formed which immobilizes the solvent. An organogel is thus formed. Sorbitan monostearate gels are opaque, thermoreversible semisolids, and they are stable at room temperature for weeks. Such organogels are affected by the presence of additives such as the hydrophilic surfactant, polysorbate 20, which improves gel stability and alters the gel microstructure from a network of individual tubules to star-shaped "clusters" of tubules in the liquid continuous phase. Another

solid monoester in the sorbitan ester family, sorbitan monopalmitate, also gels organic solvents to give opaque, thermoreversible semisolids

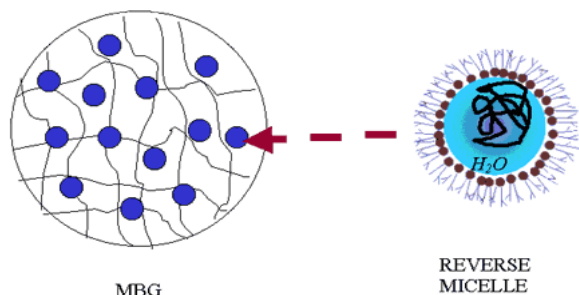


Fig: ORGANOGELS NET FORMATION

Development of novel nanobiotechnological applications

The aim of this project is to develop new enzyme-immobilized systems and their use environments favoring the desired bioconversions. As new enzyme encapsulation systems studied the organogels which are based on a matrix of a natural polymer around the nanodispersion. The obtained system is a solid-like gel. The biocatalytic reactions can occur continuously offering simplified final product isolation and a possibility of enzyme recycling. Studies focused on the use of cellulose derivatives such as the hydroxypropylmethyl cellulose, HPMC as a gelling agent. We also develop new environments for mild biocatalytic reactions. This is the case of CO₂ that can be applied to solubilized substrates with limited solubility in conventional media. The technique is considered as very suitable for bioconverting delicate products used in pharmaceuticals where the use of solvents is avoided. The organogels (MBG) Lipase-immobilization in microemulsions based organogels (MBG)

c) Extended release gels: -

TIMERx is a controlled release technology consists of an agglomerated, hydrophilic complex that, when compressed, forms a controlled-release matrix. Advantage of this system includes,

- Predictable modified release profile like zero order or first order or initial immediate release kinetics
- It can be manufactured on standard manufacturing equipment.
- Cheap.

d) Amphiphilic gels: -

Amphiphilic gels can be prepared by mixing the solid gelator like sorbitan monostearate or sorbitan monopalmitate and the liquid phase like liquid sorbitan esters or polysorbate and heating them at 60°C to form a clear isotropic sol phase, and cooling the sol phase to form an opaque semisolid at room temperature.

Amphiphilic gel microstructures consisted mainly of clusters of tubules of gelator molecules that had aggregated upon cooling of the sol phase, forming a 3D network throughout the continuous phase. The gels demonstrated thermoreversibility. Gelation temperature and viscosity increased with increasing gelator concentration, indicating a more robust gel network. At temperatures near the skin surface temperature, the gels softened considerably; this would allow topical application. This study has demonstrated the formation/preparation of stable, thermoreversible, thixotropic surfactant gels (amphiphilic gels) with suitable physical properties for topical use.

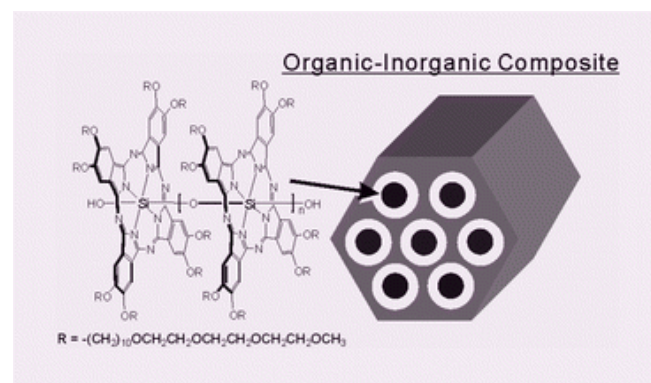


Fig: AMPHIPHILIC GEL STRUCTURE

e) Hydrophilic gels: -

Hydrophilic gels are bicoherent systems composed of the internal phase made of a polymer producing a coherent three-dimensional net-like structure, which fixes the liquid vehicle as the external phase. Intermolecular forces bind the molecules of the solvent to a polymeric net, thus decreasing the mobility of these molecules and producing a structured system with increased viscosity. The physical and chemical bonds binding the particles of the internal phase provide a relatively stable structure, which can originate by swelling of solid polymers, or by decreasing the solubility of the polymer in a solution. An important group of gels used in pharmacy are hydrophilic gels, or hydrogels, usually made of hydrophilic polymers, which under certain conditions and polymer concentration, jelly. Attention of pharmaceutical research now concentrates primarily on hydrophilic gels, as this dosage form seems to be prospective for the development of modern drugs based on systems with prolonged and controlled release of active ingredients.

f) Non aqueous gels: - Ethylcellulose was successfully formulated as a nonaqueous gel with propylene glycol dicaprylate/dicaprate. The novel nonaqueous gel exhibited rheological profiles corresponding to a physically cross-linked three dimensional gel network, with suitable mechanical characteristics for use as a

vehicle for topical drug delivery. Molecular conformation of the solvent was found to influence the molecular interactions associated with formation of ethylcellulose gel networks.

g) Bioadhesive Gels : - Chitosan bioadhesive gel was formulated for nasal delivery of insulin. A nasal perfusion test was carried out to study the toxicity of four absorption enhancers like saponin, sodium deoxycholate, ethylenediamine tetra-Acetic Acid (EDTA) and lecithin. The gels contained 4000 Iu/dl insulin, 2 or 4% of low and medium molecular weight of chitosan, and lecithin or EDTA. Drug release was studied by a membraneless diffusion method and bioadhesion by a modified tensiometry test

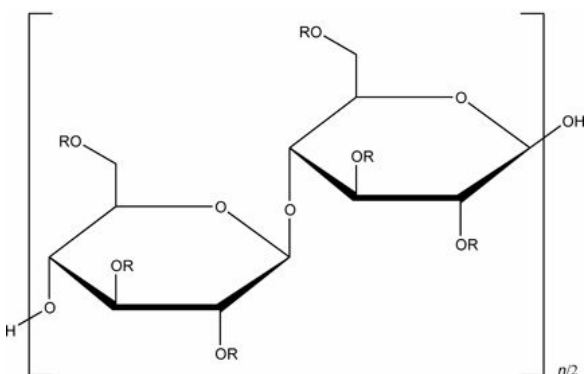


Fig: STRUCTURE OF POLYSACCHARIDES [CHITOSAN]

h) Thermosensitive sol-gel reversible hydrogel:

They are the aqueous polymeric solutions which undergo reversible sol to gel transformation under the influence of environmental conditions like temperature and pH which results in in situ hydrogel formation.

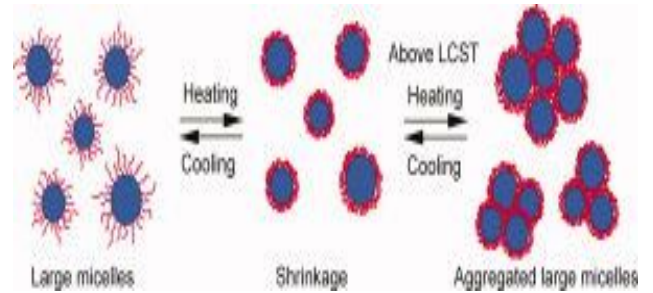


Fig: SOL-GEL FORMATION METHOD

Advantages of thermosensitive sol-gel reversible hydrogels over conventional hydrogels are,

- a) It is easy to mix pharmaceutical solution rather than semisolids
- b) Biocompatibility with biological systems
- c) Convenient to administer
- d) The pharmaceutical and biomedical uses of such sol-gel transition include solubilization of low-molecular-weight hydrophobic drugs
- e) Release can be in a controlled fashion.
- f) Helps to deliver labile biomacromolecule such as proteins and genes.
- g) Immobilization of cells
- h) And tissue engineering .

i) Complexation gels : - The goal of oral insulin delivery devices is to protect the sensitive drug from proteolytic degradation in the stomach and upper portion of the small intestine. In this work, the use of pH-responsive, poly (methacrylic-g-ethylene glycol) hydrogels as oral delivery vehicles for insulin were evaluated.

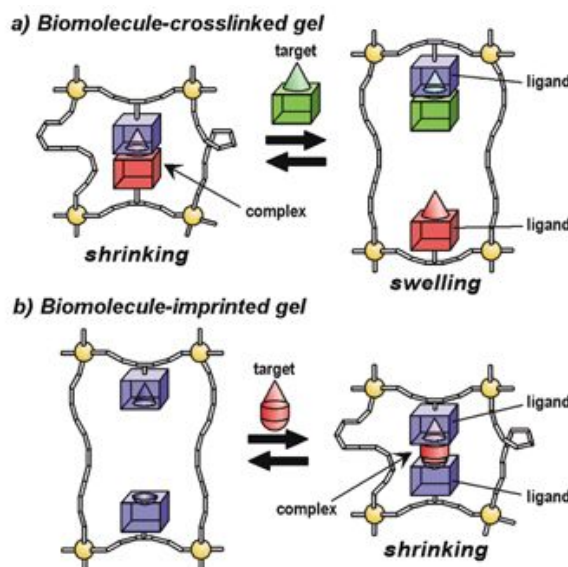


Fig: COMPLEXATION GEL CROSSLINKAGE PATTERN

4) NOVEL ADVANCES IN SEMISOLID APPLICATIONS¹¹⁻¹⁶ :-

4.1 NASAL :-

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:

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.

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.

The attributes of a vehicle for nasal semisolids include:

(1) **pH generally in the range of 5.5-7.5**, (Phosphate buffer systems are widely used and are generally compatible with most nasal medications).

(2) **Mild buffer capacity**,

(3) **Isotonic**, (The preferred agents for adjusting the tonicity of nasal solutions include sodium chloride, boric acid and dextrose. Severely hypertonic solutions should be avoided, since the nasal ciliary movement may slow or even stop. Nasal fluid is isotonic with 0.9% sodium chloride solution).

(4) **Not modify the normal mucus viscosity**, (A strongly hypertonic product, however, may result in a slight "drying" effect and thickening of the mucous and hypotonic product affect on the efficiency of the cilia in mucous and particulate removal).

(5) **Compatible with normal ciliary motion and ionic constituents of nasal secretions**,

(6) **Compatible with active ingredient**,

(7) **Stable**, (Stability is largely influenced by pH, temperature, light, oxidation and other factors. In addition to proper formulation, proper packaging is essential. Occasionally, antioxidants may be required for selected active drug ingredients).

(8) **Sterile**, (Nasal preparations should be sterile. Sterility is conveniently achieved through sterile filtration dry heat, steam under pressure {autoclaving} and gas sterilization {ethylene oxide}).

4.2 SKIN^{10,17,18} :-

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.

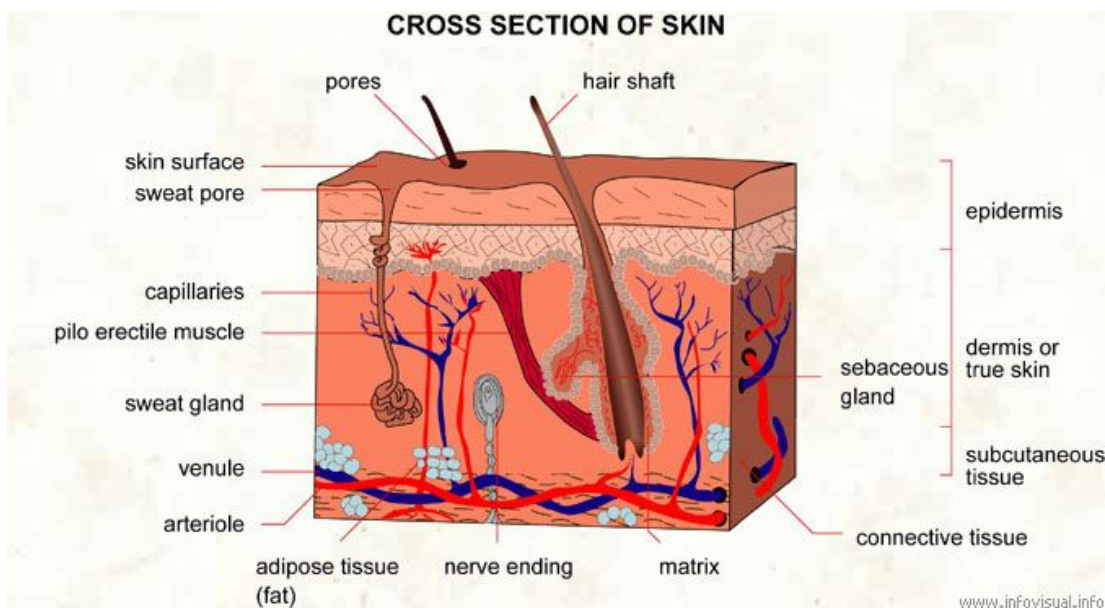


Fig: CROSS SECTION OF SKIN

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 antiseptics of skin and mucous membranes that include wounds, burns, ulcers and abscesses. **Avalon NF skin cream** is a combination of Neomycin and Fluocinolone acetonide that is used for topical application.

The company also offers anti-hemorrhoid ointment for hemorrhoid patients. Betamethasone 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^{19,20} :-

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, fluometholone, 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 petrolatum 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

f) Packaging and labeling:

Package in sterile, collapsible ophthalmic ointment tubes. For the eye. Keep out of reach of children. Use only as directed. Prevent contaminating the tip of the tube and gel; avoid contact with the eyelids or surrounding areas.

4.4 RECTAL :-

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

e) Packaging and labeling: rectal semisolids are packed in special perforated plastic tip for product to be administered into anus to treat inflammation, pain associated with hemorrhoids.

Fast-response needle probes for instant readings in tissue, semisolids, and liquids. Also for very small specimens, powders and materials. Needle tip is sealed to ensure only stainless steel contacts specimen. Max. Temp. 200°C. 5 ft. lead. Smallest microprobes give fastest reading. Short probes are easier to insert and last longer.

4.5 VAGINAL²¹ :-

Development of an ideal vaginal formulation with desired characteristics in terms of safety, efficacy, patient compliance, aesthetics, acceptability to regulatory authorities, and cost requires a careful and meaningful selection of the active ingredients and excipients.

a) Introduction: The vagina has been explored as a favorable site for the local and systemic delivery of drugs used for the treatment of female-specific conditions. Vaginal preparation are used as creams (like foams) and ointment gels

b) Vaginal administration: Vagina is an effective route for drug administration intended mainly for local action, but systemic effects of some drugs also can be attained.

Several formulations are available for intravaginal therapy. These include tablets, hard and soft gelatin

capsules, creams, suppositories, pessaries, foams, ointments, gels, films, tampons, vaginal rings, and douches

c) Advantages, applications and uses: The major advantages of this route include

- (1) Accessibility and large surface area,
- (2) Good blood supply,
- (3) The ability to bypass first-pass liver metabolism,
- (4) Prolongs the residence time
- (5) And permeability to large molecular weight drugs, such as peptides and proteins.

Among the delivery systems proposed for this route intravaginal gels, have been found to be potential vaginal drug delivery systems. The bioadhesives used in the formulation of gels play a key role in the release of the drug through the attachment to the vaginal mucosa, where the drug diffuses from the gel to the mucus.

Vaginal administration of drugs is mainly used for the treatment of local infections such as vaginitis, bacterial vaginosis, candidiasis, and other infections

Microbicides, these agents and formulations are also potential vaginal contraceptives are used in treatment of vulvovaginal infection, vaginitis, anti-infective (Clotrimazole, miconazole, clindamycin, sulfonamide), Endometrial atrophy dienesterol, progesterone are used and Contraceptive like nonoxynol-9, octoxynol are also used

d) Formulation Vaginal semisolids: Depending on the characteristics of the dosage form, excipients with different functionalities are used. All excipients present in a vaginal formulation may not be inert and therefore exhibit specific activities, which may affect the primary activity of the active molecule. Recent studies have shown that some excipients possess activities against sexually transmitted pathogens.

The ingredients normally used as excipients and possessing potent antimicrobial activities include benzalkonium chloride, sodium dodecyl sulfate/sodium lauryl sulfate, carrageenan, cellulose acetate phthalate (CAP), and undecylenic acid.

Bases uses for preparation of vaginal semisolids are of water washable type

e) Packaging and labeling: vaginal semisolids are packed in collapsible tube and Keep out of reach of children. Use only as directed

4.6 ORAL²²:-

Drug delivery through the oral route has been the most common method in the pharmaceutical applications of hydrogels. In peroral administration, hydrogels can deliver drugs to four major specific sites; mouth, stomach, small intestine and colon. By controlling their swelling properties or bioadhesive characteristics in the presence of a biological fluid, hydrogels can be a

useful device for releasing drugs in a controlled manner at these desired sites.

Oral anesthetic gel for the temporary relief of occasional minor irritation and pain associated with minor dental procedures; minor irritation of the mouth and gums caused by dentures or orthodontic appliances like sore mouth, gum and throat; minor injury of the mouth and gums; canker sores or stomatitis.

5)PATENTED TECHNOLOGIES IN SEMISOLIDS^{23,24}:-

5.1 DELIVERY OF MONOCLONAL ANTIBODY USING SEMISOLID DOSAGE FORM :-

Lysostaphin was formulated into a hydrophilic cream that forms an emulsion with the secretions of the nasal mucosa, and aqueous formulations were made containing the mucoadhesive polymers polystyrene sulfonate and chitosan. Intranasal pharmacokinetics of the drugs was measured in mice and cotton rats. Lysostaphin formulated in the cream increased nasal retention of the drug as compared to lysostaphin in saline drops. Furthermore, the levels of lysostaphin in the nose after instillation of cream are still above the minimum bactericidal concentration for most bacterial strains. The liquid polymer formulations also resulted in prolonged retention of antibody in the nose, with higher levels as compared to antibody in saline drops. The results demonstrate that cream and polymer delivery systems significantly decrease the clearance rate of lysostaphin from the nose, thereby enhancing their therapeutic potential for eradicating *S. aureus* nasal colonization.

5.2 TOPICAL DELIVERY OF VITAMIN A :-

Burst release as well as sustained release of vitamin A can be obtained by using SLN suspensions. For dermal application burst release and sustain release are taken into consideration. Burst release can be useful to improve the penetration of a drug. Sustained release becomes important with active ingredients that are irritating at high concentrations or to supply the skin over a prolonged period of time with a drug.

Glyceryl behenate SLN were loaded with vitamin A and the release profiles were studied. Franz diffusion cells were used to assess the release kinetic over a period of 24 h. Within the first few hours SLN displayed controlled release. After longer periods of time, the release rate increased and even exceeded the release rate of comparable nanoemulsions. Pure SLN dispersions were characterized by low viscosity.

5.3 DELIVERY OF EPIDERMAL GROWTH FACTOR BY TOPICAL ROUTE :-

The study investigating the effect of a topical Recombinant human epidermal growth factor (rhEGF) ointment on the rate of wound healing and skin re-

epithelialization in a rat full thickness wound model, to verify whether or not the rhEGF treatment affects both myofibroblast proliferation and collagen synthesis in the dermis was carried out when rhEGF was applied topically from the result it was found that, there was significantly enhanced wound closure. A histological examination concluded that the rhEGF treatment increased the number of proliferating nuclear antigen immunoreactive cells in the epidermis layer. In addition, the immunoreactive area of alpha-smooth muscle actin and the expression of prolyl 4-hydroxylase were significantly higher than those of the control group. Overall, a topical treatment of rhEGF ointment promotes wound healing by increasing the rate of epidermal proliferation and accelerating the level of wound contraction related to myofibroblast proliferation and collagen deposition.

5.4 TOPICAL MEDICATIONS FOR OROFACIAL NEUROPATHIC PAIN :-

There are an ever-increasing number of agents that can be used to help patients with neuropathic-based oral and perioral pain problems. A clear advancement in the delivery of such medications is the development of a vehicle-carrier agent (pluronic lecithin organogel) that can penetrate the mucosa and cutaneous tissues and carry the active medication with it to the treatment site. The major problem underlying these treatment strategies is that except for patient testimony and a few studies, there are limited empirical data on the efficacy of most of these new formulations, and additional research is clearly needed. Because of their rapid onset and low side-effect profile, topical medications offer a distinct advantage over systemic administration for those orofacial disorders that are regional, near the surface and chronic and that demonstrate some response such as pain relief to topical or subcutaneous anesthetics.

5.5 FOAM DRUG DELIVERY :-

Pharmaceutical foams are pressurized dosage forms containing one or more active ingredients that, upon valve actuation, emit a fine dispersion of liquid and/or solid materials in a gaseous medium. Foam formulations are,

- a) Generally easier to apply,
- b) Less dense,
- c) Spread more easily than other topical dosage forms.



Fig: FOAM DRUG DELIVERY

Foams may be formulated in various ways to provide emollient or drying functions to the skin, depending on the formulation constituents. Therefore, this delivery technology should be a useful addition to the spectrum of formulations available for topical use; however, as yet, only a few are commercially available. Probably the most convincing argument for the use of foams is ease of use by the patient, and consumer acceptance. Most foam dosage forms used in dermatology to date have incorporated corticosteroids, although some products have also been used to deliver antiseptics, antifungal agents, anti-inflammatory agents, local anesthetic agents, skin emollients, and protectants.

6) CHEMICAL TESTS :-

Chemical tests to be performed include,

- a) Chemical potency test
- b) Content uniformity test
- c) pH measurement

6.1 IN-VITRO RELEASE PROFILE TEST ²⁵ :-

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.

6.2 INSTRUMENTAL ANALYSIS

1. ANALYSIS OF PHARMACEUTICAL CREAMS USING UV SPECTROPHOTOMETRY :-

Solid-phase extraction (SPE) using C-18, diol and ion-exchange sorbents followed by UV spectrophotometric (conventional and derivative mode) assay was applied to the analysis of basic, acidic and neutral drugs commercially available in creams. A representative set of drugs (promethazine, chlorhexidine, benzydamine, ketoprofen, ibuprofen, fentiazac, piroxicam, fluorouracil, crotamiton and hydrocortisone acetate) was selected, and for each drug the appropriate SPE conditions (adsorption, washing and elution) were investigated to obtain a practical and reliable sample clean-up.

2. MODIFIED USP TYPE II DISSOLUTION APPARATUS :-

Dissolution apparatus is modified for studying the in vitro release of phenol from ointment. It comprised a 200-mL vessel, 2.5 * 1.5 cm paddle, and an Enhancer diffusion cell (VanKel, Cary, NC). The cell contained an adjustable-capacity sample reservoir, a washer for controlling the exposure of the surface area, and an open screw-on cap to secure the washer and membrane over the sample reservoir. The water bath was maintained at 37 C. Filled cells were placed in the bottom of the vessels, and the paddles were lowered to

1 cm above the sample surface. 50 ml of high-performance liquid chromatography-grade filtered water, degassed and prewarmed to 37 °C, was used as the dissolution medium.

3. ANALYSIS OF GEL USING FT-NIR TRANSMISSION SPECTROSCOPY :-

Transmission Fourier transform near- infrared (FT-NIR) spectroscopy was used for quantitative analysis of an active ingredient in translucent gel formulation. Gels were prepared using Carbopol 980 with 0%, 1%, 2%, 4%, 6%, and 8% ketoprofen and analyzed with an FT-NIR spectrophotometer operated in the transmission mode. The correlation coefficient of the calibration was 0.9996, and the root mean squared error of calibration was 0.0775%. The percent relative standard deviation for multiple measurements was 0.10%.

The requirements and expectations of 2DE increase, new technologies emerge in a bid to more accurately capture the sometimes small, but significant, changes occurring in proteomics experiments. Therefore a proteomics researcher requires software that is extremely sensitive and still maintains his confidence in the analysis.

7. PACKAGING OF NOVEL SEMISOLIDS :-

Semisolid products are manufacture by heating and are filled into the container while cooling still in the liquid state. It is important to established optimum pour point, the best temperature for filling and set or congealing point, the temperature at which the product become immobile in the container.

Topical dermatological products are packed in either jar or tubes whereas ophthalmic, nasal, vaginal and rectal semisolid products are almost always packed in tubes.

The specific FDA regulation pertaining to drug products state that,

“Container closures and other component part of drug packages, to be suitable for that intended use must not be reactive, additive or absorptive to the extent that identity, strength, quality or purity of drug will be affected.”

All drug product containers and closures must be approved by stability testing of product in the final container in which it is marketed. This includes stability testing of filled container at room temperature e.g. 20 °C as well as under accelerated stability testing condition e.g. 40 - 50 °C.

Ointment, creams and gels are most frequently packed in 5, 15 and 30 gm tubes. Ophthalmic ointments typically are packed in small aluminum or collapsible plastic tubes holding 3.5 gm of ointment .

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