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RECENT ADVANCES IN SEMISOLID DOSAGE FORM

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ABSTRACT: Pharmaceutical semisolid preparations include ointments, pastes, cream, emulsions, gels, and rigid foams. 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. Semisolids can adhere to the application surface for sufficiently long periods before they are washed off. This property helps prolong drug delivery at the application site. Novel semisolids are non-greasy since they are made up of washable water bases. Hence they cause less irritation to skin and are superior to the conventional semisolid dosage form. Now a day, novel creams are available in the market provided with nanoparticles and microspheres. Similarly, novel gels are available, including microemulsion gel, bioadhesive gel, organogel, thermosensitive sol-gel, pH-responsive complexation gel, *etc*. Oleaginous ointments are preferred for dry, chapped skin in an environment of low humidity because of its occlusive properties. A semisolid is evaluated by the following parameters such as spreadability, extrudability, viscosity measurement of pH, drug content, rheological properties, *etc*. This article reviews the recent advances of semisolids as well as its evaluation.

INTRODUCTION: Topical semisolid 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. The choice of a base for semisolid dosage forms depends on many factors. The therapeutic effect desired the nature of the active ingredient 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.

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In many cases, a compromise has to be made to achieve the required stability. For example, drugs that hydrolyze rapidly are more stable in hydrophobic bases than in water containing bases, even though they may be more effective in the letter.

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

Advantage of semi-solid dosage form:

- It is used externally
- Probability of side effect can be reduced
- Local action
- First pass gut and hepatic metabolism are avoided.

- Patient compliance is increased; the drug termination is problematic cases is facilitated as compared with other routes of drug administration.

Disadvantages of semi-solid dosage form:

- There is no dosage accuracy in this type of dosage form
- The base which is used in the semi-solid dosage form can be easily oxidized.
- If we go out after using semi-solid dosage form problems can occur.

Different Type of Semi-Solid:

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

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 a mixture of liquid and solid polyethylene glycols (macrogols) [1].

Creams: 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 the application to the skin or certain mucous membranes for protective, therapeutic, or prophylactic purposes, especially where an occlusive effect is not necessary.

Gels: 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 using suitable gelling agents.

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

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

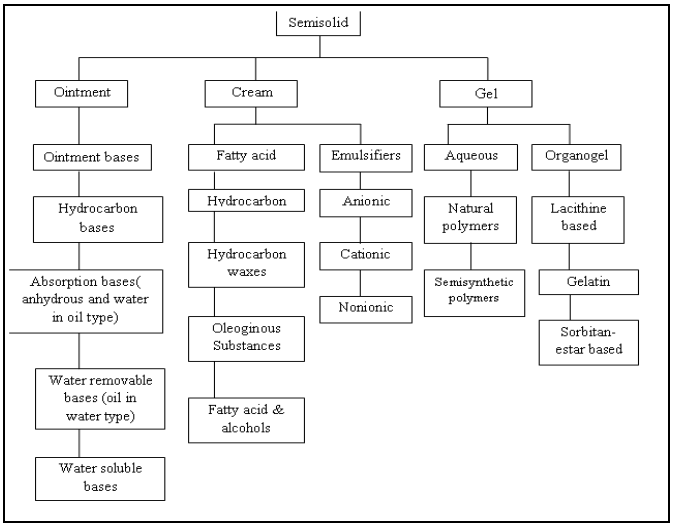

FIG. 1: BASIC RAW MATERIALS USED IN THE DEVELOPMENT OF VARIOUS SEMISOLID DOSAGE FORMS

Pastes: 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.

Poultices: A poultice is an ancient form of topical medication, also known as a cataplasma. It is a soft mass of vegetable constituents or clay, usually heated before application. Kaolin poultice BP is prepared by mixing and heating dried, heavy kaolin and boric acid with glycerin. After cooling, the aromatic substances are incorporated with stirring. The product is spread on dressing and applied hot to the skin **Fig. 1**.

Novel Advances in Semisolid Dosage Forms:
Ointment:
For Topical:
Vertical (TM): Psoriasis is a chronic skin disorder that affects 2 to 3 percent of the U.S. population. It is characterized by thick, red, scaly patches of skin and caused by an abnormally high growth rate of skin cells that form thick, dry scales (plaques). The disease is also associated with other serious conditions such as diabetes, heart disease, and obesity.

Vectical (TM) Ointment is indicated for the topical treatment of mild to moderate plaque psoriasis in patients 18 years and older [5]. Vectical (TM) Ointment is the only vitamin D3 ointment of its kind available in the United States. Vectical (TM) Ointment contains calcitriol, the naturally-occurring, the active form of vitamin D3, and is one of the only vitamin D3 products shown in clinical trials to be well-tolerated even when used on sensitive skin fold areas [2].

New Treatment for Faecal Incontinence using the Zinc-Aluminium Ointment: A randomized, double-blind trial was performed. Patients who met the inclusion criteria were randomized to receive the ointment or a placebo. All were evaluated before and 3 weeks after ointment application, using the Wexner incontinence score and the Fecal Incontinence Quality of Life (FIQL) score. The study shows that the zinc-aluminum based ointment decreases faecal incontinence significantly compared with placebo [3].

A Novel Wound Healing Ointment:
A Formulation of *Hypericum perforatum* oil and Sage and Oregano Essential Oils Based on Traditional Turkish Knowledge: *Hypericum perforatum* L. (Hypericaceae), olive oil (Oleaceae), *Origanum Tourn* ex L. and Salvia L. species (Lamiaceae) are used against inflammatory disorders and for healing of skin wounds in traditional Turkish medicine. A new ointment formulation was developed to provide more efficient wound healing activity. The content of the formulation was as follows; olive oil extract of flowering aerial parts of *Hypericum perforatum* L., olive oil, an equivalent mixture of *Origanum majorana* L. and *Origanum minutiflorum* Schwrd. et Davis essential oils (*Origani petroleum*), *Salvia triloba* L. essential oil [4].

Creams:
Creams Containing Microspheres: Microspheres are white powders that under a microscope show every particle to be spherical. In cosmetics, microspheres are used for: enhanced feel, optical blurring, absorption/ delivery of materials. Microspheres can alter the tactile qualities of a cosmetic like initial contact, application, after feeling, *etc*. [5]

Albumin microsphere containing vitamin A can be administered by using creams topically. 222 ± 25 μm sizes of microsphere of vitamin A were produced by emulsion method. The *in vitro* and *in vivo* drug release of a microencapsulated and non microencapsulated vitamin A was studied. The *in vivo* study in six volunteers revealed that these microspheres were able to remain on the skin for a longer period, and as a consequence, they were able to prolong the release of vitamin A [6].

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 a 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 the addition of salt and can be reduced by changing surfactant counterion [7].

A Cream Containing Liquid Nanoparticles: For enhanced penetration of topical drugs, occlusion of skin is the prime criterion. This requirement can be achieved easily by the incorporation of large quantities of fats and oils, especially liquid and

semisolid paraffin. However, such formulations have the limitations of poor cosmetics properties characterized by a greasy feel and glossy appearance [8].

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 (nanodispersion). 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 served as a lubricant for nanoparticles, thereby preventing a rough feel during application [7].

Microsphere-Based Improved Sunscreen Formulation of Ethylhexyl Methoxycinnamate: Polymethylmethacrylate (PMMA) microspheres of Ethylhexyl methoxycinnamate (EHM) were prepared by emulsion solvent evaporation method to improve its photostability and effectiveness as a sun screening agent. The PMMA microspheres of EHM were incorporated in a water-removable cream base. The incorporation of EHM loaded PMMA microsphere into cream base had greatly increased the efficacy of sunscreen formulation approximately four times [9].

Gel: The word ‘‘gel’’ is derived from ‘‘gelatin,’’ and both ‘‘gel’’ and ‘‘jelly’’ can be traced back to the Latin gelu for ‘‘frost’’ and gelare, meaning ‘‘freeze’’ or ‘‘congeal”. The USP defines gels (sometimes called jellies) as semisolid systems consisting of either suspension made up of small inorganic particles, or large organic molecules interpenetrated by a liquid. Gels are the relatively newer class of dosage forms created by entrapment of large amounts of aqueous or hydro-alcoholic liquid in a network of colloidal solid particles, which may consist of inorganic substances such as aluminum salts or organic polymers of natural or synthetic origin.

Depending upon the nature of colloidal substances and the liquid in the formulation, the gel will range in appearance from entirely clear to opaque. Most topical gels are prepared with organic polymers such as carbomers which impart an aesthetically pleasing, clear sparkling appearance to the product and are easily washed off the skin with water. Gels are two component semisolids systems rich in liquids. In a typical polar gel, a natural or synthetic polymer builds a three-dimensional matrix throughout a hydrophilic liquid. Typical polymers used include the natural gums tragacanth, carrageenan, pectin, agar, and alginic acid; semi-synthetic materials such as methylcellulose, hydroxyethyl cellulose, hydroxyl propyl methyl cellulose, and carboxymethyl cellulose; and the synthetic polymer, carbopol may be used. Certain clays such as bentonite, veegum, and laponite provided that the drug does not bind to the polymer or clay. Such gels release medicaments well; the pores allow relatively free diffusion of molecules, which are not too large.

Among the gelling agents used are:

- Synthetic macromolecules: Carbomer 934
- Cellulose derivatives: Carboxymethylcellulose, Hydroxypropylmethylcellulose

Gels are compatible with many substances and may contain penetration enhancers for anti-inflammatory and anti-nauseant medications [10].

Nanosphere Gel: Tyrosine-derived nanospheres have demonstrated potential as effective carriers for the topical delivery of lipophilic molecules. Gel formulation containing nanospheres was developed for effective skin application and enhanced permeation. Carbopol and HPMC hydrophilic gels were evaluated for dispersion of these nanospheres. Sparingly water-soluble diclofenac sodium (DS) and lipophilic Nile Red were used as model compounds. DS was used to determine the optimum polymer type, viscosity, and release properties of the gel while fluorescent Nile Red was used *in-vitro* and *in-vivo* skin distribution studies. Also, the effect of a penetration enhancer, Azone, on the skin delivery was investigated. Dispersion of Nile Red-loaded nanospheres in 1% w/v HPMC gel produced a uniform and stable dispersion with suitable rheological properties for topical application, without any short-term cellular toxicity or tissue irritation. *In-vitro* permeation studies using human cadaver skin revealed that the deposition of Nile Red via the nanosphere gel in

the upper and lower dermis was 1.4 and 1.8 fold higher, respectively than the amount of Nile Red deposited via an aqueous nanosphere formulation. *In-vivo*, the HPMC gel containing Nile Red-loaded nanospheres significantly enhanced (1.4 fold) the permeation of Nile Red to the porcine stratum corneum/epidermis compared to the aqueous Nile Red-loaded nanospheres. An additional increase (1.4 fold) of Nile Red deposition in porcine stratum corneum/epidermis was achieved by incorporation of Azone (0.2M) into the nanosphere gel formulation [11] **Fig. 2**.

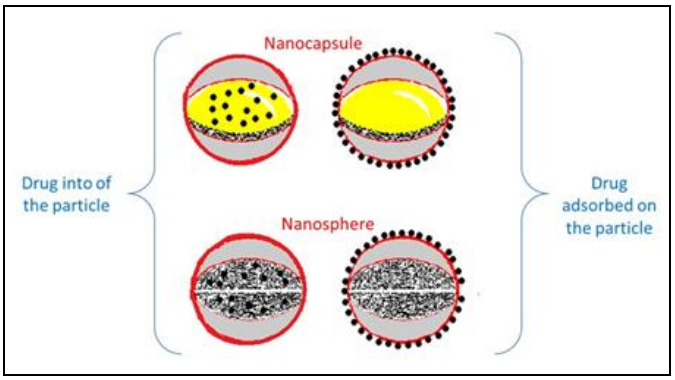

FIG. 2: NANOSPHERE FORMATION

Controlled Release Gel: Drug delivery to nasal or ocular mucosa for either local or systemic action faces many obstacles – these routes are protected by effective mechanisms. 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 the 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.

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 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. The gels were also evaluated in the Ussing chamber using porcine nasal mucosa. The rate of transport of drugs through the mucosa could be controlled by the rate of release from the formulation. Furthermore, the Using chamber could be used to evaluate the potential toxicity of formulations [12, 13].

Organogels: Sorbitan monostearate, a hydrophobic nonionic surfactant, gels several organic solvents such as hexadecane, isopropyl myristate, and a range of vegetable oils. Gelation is achieved by dissolving/dispersing the organogelator in the 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. Once formed, the tubules associate with others and a three-dimensional network are 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 continuous liquid phase.

Another solid monoester in the sorbitan ester family, sorbitan monopalmitate, also gels organic solvents to give opaque, thermoreversible semisolids. Like sorbitan monostearate gels, the microstructure of the palmitate gels comprises an interconnected network of rod-like tubules. Unlike the stearate gels, however, the addition of small amounts of a polysorbate monoester causes a large increase in tubular length instead of the clustering effect seen in stearate gels. The sorbitan stearate and palmitate organogels may have potential applications as delivery vehicles for drugs and antigens **Fig. 3**.

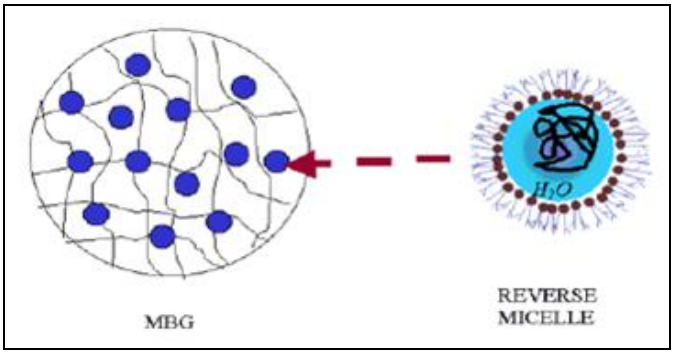

FIG. 3: ORGANOGELS NET FORMATION

Sustained Release Gels: A gel formulation formed by incorporating technical doramectin into a 10% hydroxypropyl methylcellulose aqueous solution was used to subcutaneously inject steers at varying dosages. Doramectin serum concentration of steers receiving 600 µg (AI)/kg body weight declined from 21.9 ppb at 0.5 weeks to below detectable at 8 wk postinjection. The 1,200 µg (AI)/kg injection resulted in serum concentrations of 29.1 ppb at 0.5 wk and declined to 0.5 ppb at 8 weeks postinjection. Both the 600 and 1,200 µg (AI)/kg injections provided 100% inhibition of index of fecundity (IF) in adult lone star ticks, *Amblyomma americanum* L. (Acari: Ixodidae) through week 8, after which inhibition declined to 79.4 and 45.3%, respectively, during the 12th-week post-treatment [14].

P407 gel content can affect drug release rates. The inorganic salts and PEG 400 commonly included in the formulation of P407 gels can also change the rate at which a drug is released. Lidocaine was selected as a model drug because, although widely used in the treatment of pain, its use is limited by the short duration of its effects. The use of P407 gels prolongs the residence time of the lidocaine at the injection site, sustains drug release, and increases therapeutic efficacy. Release studies were performed in a diffusion system. During the release, data followed the Higuchi square root law time kinetic (r>0.98). The increased polymer concentration in the gel increases viscosity and reduces lidocaine release rates and diffusion coefficients *via* extended gel dissolution time and prolonged drug diffusion through the gel matrix. Lidocaine release rates and diffusion coefficients increased in gels composed of NaCl or PEG 400 aqueous solution. Because these additives are hydrophilic, they reduce gel dissolution time, thereby accelerating drug diffusion [15].

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

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

***In-situ* Gel of Azithromycin:** Gelation of pectin caused by divalent cations, especially calcium ions, has been applied to develop an ophthalmic formulation of azithromycin. Rapid elimination of drug on installation into *cul de sac* would be minimal with *in-situ* gelling ophthalmic solution leading to increased precorneal contact time and prolonged drug delivery. In the formulation development studies pectin was used in different concentrations (1-5% w/v), and different proportions of the hydrocolloids hydroxypropyl methylcellulose and sodium carboxymethyl cellulose of different grades of viscosity were used. The primary criteria for formulation optimization were gelling capacity and rheological behavior. Also, formulations were evaluated for pH, and antimicrobial efficacy and drug release. The clarity, pH, gelation in simulated tear fluid, and rheological properties of the optimized formulations were satisfactory. The formulations inhibited the growth of *Staphylococcus aureus* effectively in a cup–plate method and were proved to be safe and nonirritant on rabbit eyes. The results indicate that pectin based *in-situ* gels can be successfully used to prolong the duration of action of azithromycin.

Sol-gel phase transition on the eye surface can be triggered by a change in temperature, pH, or ionic strength. Carbopol 940 and Poloxamers are used as the gelling agents in pH triggered and temperature sensitive *in-situ* gelling systems, respectively for sustaining the drug delivery. Ion activated sol-gel transition, also known as osmotically induced gelation, occurs on the ocular surface due to the ions. in the tear fluid resulted in a change in electrolyte composition [4]. Gelrite® (gellan gum) in ophthalmic formulations, which gels upon installation in the eye due to the presence of cation has shown prolonged precorneal contact time in

humans. Sodium alginate has been used as the gelling agent in sustained release ocular formulations of ofloxacin and gatifloxacin. Pectins also gel in the presence of divalent cations and *in-situ* gelling of pectin mediated by calcium ions in the lacrimal fluid has been reported in a US patent. Also *in-situ* gelling of pectin has been used to sustain drug delivery from formulations (*e.g*., acetaminophen, theophylline and cimetidine) [16].

***In-situ* Gel of Metoprolol Tartrate:** An intranasal in situ gel with increased nasal residence time to improve the bioavailability of metoprolol tartrate. The *in-situ* gel systems containing carbopol, hydroxypropylmethylcellulose K4M, and K15M in different concentrations were prepared. The samples were characterized by viscosity, rheological behavior, gelation behavior, gel strength, and mucoadhesion. The formulations F10 (0.4% w/vcarbopol, 1% w/v hydroxypropyl methylcellulose K15M) and F13 (0.3% w/v carbopol, 1% w/v hydroxypropyl methylcellulose K15M) showed gel strength of 40.33 ± 0.47 and 43.00 ± 1.41, respectively, and mucoadhesion strength $31.48 \pm 0.14 \times 10^3$ and $32.12 \pm 0.05 \times 10^3$ dyne/cm^2, respectively. *In-vitro* release profiles showed an initial burst followed by slow release. F10 and F13 released 88.08 ± 0.98 and 91.18 ± 1.09% drug in 8 h. The R^2 value for F10 (0.9953) and F13 (0.9942) was maximum for Higuchi, showing mixed order kinetics while n value obtained on treatment with Korsemayer Pappas equation were near to 0.5, suggesting release by fickian diffusion mechanism. The nasal permeability of formulations F10 and F13 were found to be 0.057 and 0.063 cm/s, respectively. Histopathological examination revealed slight degeneration of nasal epithelium with increased vascularity by F10 but no inflammation by formulation F13. Thus, a pH-triggered *in-situ* gel system containing low concentration (0.3% w/v) of carbopol demonstrated the sustained release of metoprolol tartrate without any destructive effect on the mucosa [17].

Amphiphilic Gels: Amphiphilic gels can 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 (amphiphilogels) with suitable physical properties for topical use.

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 to 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 is hydrophilic gels, or hydrogels, usually made of hydrophilic polymers, which under certain conditions and polymer concentration, jellify. 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.

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 confirmation of the solvent was found to influence the molecular interactions associated with the formation of ethylcellulose gel networks.

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 bio adhesion by a modified tensiometry test.

Mucoadhesive Nasal Gels: Venlafaxine Hydrochloride, were prepared using polymers like carbopol 934 and sodium alginate and characterized in terms of viscosity, texture profile analysis, *ex-vivo* drug permeation profiles, and histopathological studies. The results show that values of viscosity, hardness, and adhesiveness increase while those of cohesiveness decrease with a corresponding increase in the concentration of the polymers.

Ex-vivo drug permeation profiles showed that formulation containing 5% sodium alginate provided a better-controlled release of the drug than the other formulations throughout 12 h. Mucoadhesive nasal gel of venlafaxine hydrochloride is a novel dosage form which delivers the drug directly into the systemic circulation and provides controlled release of the drug [18].

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. 4**.

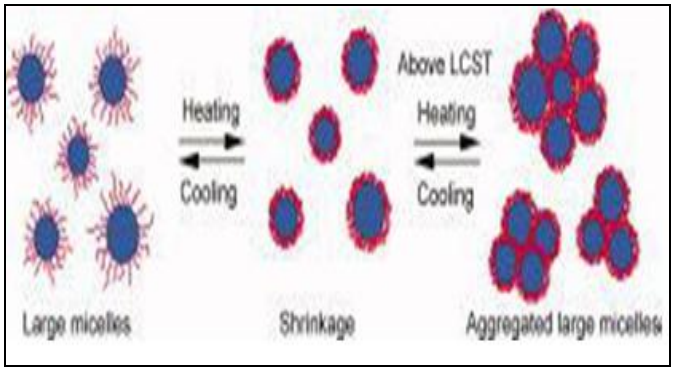

FIG. 4: THERMO SENSITIVE SOL-GEL REVERSIBLE HYDROGEL

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. The release can be in a controlled fashion.

f. Helps to deliver labile biomacromolecules such as proteins and genes.

g. Immobilization of cells

h. And tissue engineering

N-Methyl-2-pyrrolidone (NMP) is the lactam of 4-methylaminobutyric acid. It is colorless with the high boiling point, low viscosity, low toxicity, and good biocompatibility [19]. It is a water-miscible organic solvent used as a good solvent for sparingly soluble drugs in water. The effects of N-methyl-2-pyrrolidone on the thermosensitive properties of aqueous ethylene oxide-propylene oxide block copolymer (Lutrol R F127) system. Due to the aqueous solubility enhancement and biocompatibility, N-methyl-2-pyrrolidone is an interesting solubilizer for the poorly water-soluble drugs to be incorporated in the Lutrol R F127 system. Effect of N-methyl-2-pyrrolidone on physicochemical properties of Lutrol R F127 system was investigated using appearance, pH, gelation, gel melting temperature, and rheology. T

he antimicrobial activity of the thermosensitive N-methyl-2-pyrrolidone gel was also tested. Lower N-methyl-2-pyrrolidone amount (≤30% w/w) could shift the sol-gel transition to a lower temperature, but the gel-sol transition was shifted to a higher temperature. Higher n-methyl-2-pyrrolidone (≥40% w/w) could shift both sol-gel and gel-sol transitions of the system to a lower temperature. The amount of N-methyl-2-pyrrolidone >60% w/w could reverse the phase of the LutrolR F127 system to non-newtonian flow at 4° and Newtonian flow at

high temperature. Aqueous LutrolR F127 system containing N-methyl-2-pyrrolidone exhibited anti-microbial activities against *Staphylococcus aureus, Escherichia coli* and *Candida albicans* with the N-methyl-2-pyrrolidone in a dose-dependent manner [20].

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. 5**.

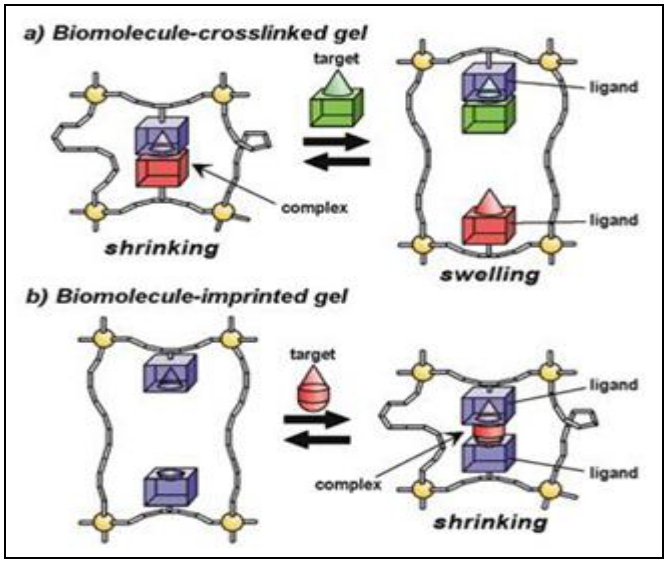

FIG. 5: COMPLEXATION GEL CROSSLINKAGE PATTERN

Insulin was loaded into polymeric microspheres and administered orally to healthy and diabetic Wistar rats. In the acidic environment of the stomach, the gels were unswollen due to the formation of intermolecular polymer complexes. The insulin remained in the gel and was protected from proteolytic degradation. In the basic and neutral environments of the intestine, the complexes dissociated which resulted in rapid gel swelling and insulin release. Within 2 h of administration of the insulin-containing polymers, strong dose-dependent hypoglycemic effects were observed in both healthy and diabetic rats. These effects lasted for up to 8 h following administration [21].

Microemulsion Gel System: Topical micro-emulsion systems for the antiacne agent, nadifloxacin were designed and developed to overcome the problems associated with the cutaneous delivery due to poor water solubility. The potential of a microemulsion system for topical delivery of NDFX is to improved and maximized therapeutic efficacy is achieved not only by enhancing its solubility but also the cutaneous penetration as compared to conventional topical preparation. The traditional way of preparation of microemulsion was to dissolve the drug in oils followed by micro emulsification; this method can be applied for most of the drugs, such as triptolide aceclofenac and diclofenac diethylamine [9]. In this study, due to the higher solubility of NDFX in surfactants than that in oils, another approach was adopted to dissolve poorly water‐soluble drugs into o/w microemulsion, which firstly involved the dissolution of the drug in a hydrocarbon chain of surfactants followed by micro emulsification [22].

Submicron Emulsion Vehicle System Containing Solid Lipid Nanoparticle: Conventional creams have a mean droplet size ranging from 10 to 100 μm. Such formulations have demonstrated poor penetration of drug-loaded oil droplets into deep skin layers. It has been reported that microparticles with diameters ranging from 3 to 10 μm selectively penetrate follicular ducts, whereas particles >10 μm remain on the skin surface, and those < 3 μm are distributed randomly into hair follicles and stratum corneum. Taking these constraints into consideration, researchers have developed the submicron emulsion vehicle system (SMEVS) for improving drug permeation. The submicron lipid particles of a SMEVS penetrate the layers of the stratum corneum, increasing its fluidity and leading to the disruption of barrier continuity. Significant hydration of the stratum corneum, assisted by gap formation, permits the penetration of submicron emulsion particles by forming a drug depot in the skin.

The result is slow, continuous, and controlled systemic delivery of the drug. A SMEVS can be formulated by processing a medium-chain triglyceride emulsion with a high-pressure homogenizer. In addition, the presence of lecithin, an efficient dispersing agent, causes a drastic reduction in droplet size, usually to between 100 and 300 nm. Such a system is highly valuable for the transport of hydrophobic drugs, which are incorporated into the oil phase of submicron emulsions and thereby improve penetration of the

stratum corneum. Studies of SMEVSs have shown effective transdermal Delivery of Diazepam and Various Steroidal and Nonsteroidal Anti-Inflammatory Agents [23].

Sustained release becomes important with active ingredients that are irritating at high concentrations or supplying the skin over a prolonged period 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 kinetics throughout 24 h. Within the first 6 h retinol, SLN displayed controlled release. After longer periods (12–24 h) the release rate increased and even exceeded the release rate of comparable nanoemulsions. Pure SLN dispersions are characterized by low viscosity. In contrast to membranous vesicles, SLN can also be stably incorporated in convenient topical dosage forms like hydrogels or creams. In the Franz diffusion cell, these preparations showed a controlled release over 12-18 h. Similar to SLN dispersions, an increase in release rate over a 24-h period was found. A good correlation between polymorphic transitions and increased drug release was observed [24].

Evaluation:

Evaluation of Cream:

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

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

Biological testing: This is particularly essential for products containing antiseptics, hormones, vitamins, *etc*.

Phase separation: The rate and degree of phase separation in an emulsion can be easily determined by keeping a certain amount in a graduated cylinder and measuring the volume of separated phase after definite time intervals. The phase separation may result from creaming or coalescence of globules. The phase separation test can be accelerated by centrifugation at low/moderate speeds. One can at best expect a mixture of creamed and coalesced particles and in such a situation it may be difficult to make correct interpretations.

Globule Size: Growth in the globule size after the preparation of an emulsion is an indication of its physical instability. The globule size is measured by microscopic methods or by electronic devices such as colter counter. In either of these two techniques, the original product has to be suitably diluted before estimation. The dilution may introduce errors because of incomplete deflocculation or new patterns of flocculation.

Rheological Properties: The rheological characteristics of an emulsion system depend upon globule size, emulsifier, and its concentration, phase volume ration, *etc*. Use of a heliapath attachment with Brookfield viscometer helps in detection of creaming tendency, and hence it is advisable to study rheological properties over extended periods, which can help in the prediction of their long term behavior. Many emulsion show change in consistency with time, which follows a linear relationship when plotted on a log-log scale over several tenfold time intervals.

Effect of Thermal Stresses: It is usual to evaluate thaw stability of an emulsion by subjecting it too high and low temperatures in alternating cycles. The samples are first exposed to 60 ºC for a few hours and then to 0 to 40 ºC. Such exposures are repeated several times, and emulsion stability assessed after each cycle.

Evaluation of gel: Drug content: 1 gm of the gel was accurately weighed in a 50 ml of the volumetric flask to which 20 ml purified water was added with continuous shaking. Volume was adjusted with a mixture of 10% methanol in water. Plain bases were also treated in a similar manner for blank determination. The absorbance of the solution with the blank was measured at 360nm using UV-spectrophotometer.

Homogeneity of Drug Content: For homogeneity of drug contents, six tubes were taken randomly and assayed for the drug content as stated above. Studies were performed in triplicate, and mean values were used for the analysis of data.

Measurement of pH: The pHs of carbopol gels of TN were determined by digital pH meter. One gram of gel was dissolved in 100 ml of distilled water and stored at 4 °C for two hours. The measurement of the pH of each formulation was in triplicate, and the average values are presented.

Viscosity: Brookfield synchrolectric viscometer model RVT attached with spindle D was used for the determination of viscosity. Gels were filled in jar and spindle was lowered perpendicularly taking care that spindle does not touch the bottom of the jar. The spindle was rotated in the gel at increasing shear rates 0.5, 1, 2.5, and 5 rpm. At each speed, the corresponding dial reading was noted. The reverse reading was also noted and the average was taken for these two readings. The viscosity of the gel was obtained by the multiplication of the dial readings with the factors given in the Brookfield viscometer catalogs.

Spreadability: A modified apparatus consisting of two glass slides containing gel in between with the lower slide fixed to a wooden plate and the upper one attached to a balance by a hook was used to determine spreadability.

Extrudability: A simple method was adopted for determination of extrudability in terms of weight in grams required to extrude a 0.5 cm ribbon of gel in 10 seconds from the collapsible tube

Evaluation of Ointments:

Penetration: For assessing the penetration, some very simple experiments have been suggested. Weighed quantities of the ointments are rubbed over definite areas of the skin for a given length of time. After that the unabsorbed ointment is collected from the skin and weighed. The difference between the two weights roughly represents the amount absorbed. Rate of release of medicaments to assess the rate of release of a medicament small amount of the ointment can be placed on the surface of nutrient agar contained in a petri dish or alternately in a small cup cut in the agar surface. If the medicament is bactericidal, the agar plate is previously seeded with a suitable organism like *S. aureus*. After a suitable period of incubation, the zero of inhibition is measured and correlated with the rate of release. Another method for finding out release rate is to smear the internal surface of test tubes with thin layers of ointment, fill the tubes with saline or serum and after a gap of time estimating the amount of drug present in the serum/saline.

Absorption of medicaments into the bloodstream. The diadermatic ointments should be evaluated for the rate of absorption of the drug into the bloodstream. This test can be in vivo only. Definite amounts of ointments should be rubbed the skin under standard conditions and medicaments estimated in the blood plasma or urine.

Irritant Effect: In general, no ointment should possess an irritant effect on the skin or the skin or mucous membranes. The tests for irritancy can be carried out on the skin and eyes of rabbits or the skin in rats. Reactions are noted at intervals of 24, 48, 72, and 96 h. Lesions on the cornea, iris, conjunctiva are used for judging the irritancy to the eyes. Presence of patches on the skin within 2 weeks indicates irritancy to skin.

Evaluation of Paste:

Abrasiveness: The teeth were mechanically brushed with pastes or powders, and then the effects were studied by observation, mechanical or other means. An abrasive character normally depended on the particle size.

Particle Size: This can be determined by microscopic study of the particles or other means.

Cleansing Property: This is studied by measuring the change in the reflectance character of a lacquer coating on a polyester film caused by brushing with a tooth cleanser (paste or power). Also, an *in vivo* test has been suggested in which teeth were brushed for 2 weeks, and condition of teeth was assessed before and after use with the help of photographs.

Consistency: It is important that the product, paste, should maintain the consistency to enable the product press out from the container. Study of viscosity is essential for these powders from the container.

The pH of the Product: pH of the dispersion of 10% of the product in water is determined by pH meter.

Foaming Character: This test is especially required for foam-forming toothpaste or toothpastes or tooth powders. Especially amount of product can be mixed with a specific amount of and water to be shaken. The foam thus formed studies for its nature, stability, and washability.

Limit Test for Arsenic and Lead: This is very important, as these are highly toxic metals. Specific tests are there to estimate these two metals. However, if the raw materials are tested for the limit of these two metals, products may not have an excess of such metals. Volatile matters and moisture A specific amount of the product required to be taken in a dish and drying is to be done till constant weight. Loss of weighing will indicate the percentage of moisture and volatile matters. Effect of special ingredients Special tests should be done for the special ingredients if any like antiseptic, enzymes, etc. For each one special and specific test is to be done [25].

***In-vitro* Release Study:** The release of an API from semisolid dosage forms is an important quality control tool. The drug released from a semisolid dosage form in which the drug is completely dissolved is described by the Higuchi diffusion equation.

Plexiglas Flow-Through Cells: Plexiglas cells have been developed for studies of *in vitro* drug release from semisolid dosage forms. The system consists of a base plate supporting a plate containing a sample reservoir. A receptor-fluid reservoir is placed above it, and a semipermeable membrane is supported between the receptor-fluid reservoir and sample reservoir. The receptor-fluid reservoir is divided into two equal sections, one carrying the inlet and the other carrying the outlet for the receptor fluid. A solid Plexiglas block seals the top of the receptor- fluid reservoir.

The entire cell is immersed in a constant temperature water bath. The system is automated and computer controlled by connecting it to a pump for the receptor fluid, a medium splitter, and a fraction collector. This instrument is especially useful for measuring the effect of variables such as membrane type, the flow rate of a receptor fluid, and temperature upon release rates.

Insertion Cell: An insertion cell, whose dimensions permit the cell to be used with the compendia flow-through cell, has been devised. It is easier to use and does not require the removal of air bubbles from the membrane–liquid interface, a common problem with the use of Franz-diffusion cells. The upper section of the insertion cell consists of an oblong Plexiglas block with a 9-mm circle cut out of it. The middle section consists of a matching oblong Plexiglas block with a similar 9-mm circle cut out of it, which acts as the sample holder. The lower component is a solid Plexiglas block. All three sections are screwed together. A membrane is placed between the upper section and the sample-holder section. A stainless steel spring supports the insertion cell (for the turbulent-flow mode), and a layer of glass beads in the conical section of the flow-through cell supports the insertion cell (for the laminar flow mode). The insertion cell is positioned 10 mm from the conical section of the flow-through cell when it is used with the spring support. The entire assembly is automated in the same way as for the Plexiglas flow-through cell. To study the effect of the flow of receptor fluid on drug release, it is recommended that the insertion cell be used in a downward orientation.

Modified USP Type II Dissolution Apparatus: A USP Type II dissolution apparatus was modified for studying the *in vitro* release of phenol from the ointment. It comprised a 200-mL vessel, 2.5 ×1.5 cm paddle, and an Enhancer diffusion cell (Van Kel, Cary, NC) composed entirely of PTFE. Filled cells were placed in the bottom of the vessels, and the paddles were lowered to 1 cm above the sample surface. Fifty milliliters of high-performance liquid chromatography–grade filtered water, degassed and pre-warmed to 37 ºC, was used as the dissolution medium. The system was found to yield reproducible results with good reliability in the data generated [26].

Instrumental Analysis:

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.

Analysis of Gel using FT-NIR Transmission Spectroscopy: Transmission Fourier transforms near-infrared (FT-NIR) spectroscopy for quantitative analysis of an active ingredient in a 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 means a squared error of calibration was 0.0775%. The percent relative standard deviation for multiple measurements was 0.10%. The results prove that FT-NIR can be a good alternative to other more time-consuming means of analysis for these types of formulations.

Topical formulations, such as gels, creams, and ointments, represent a small but significant overall fraction of marketed pharmaceutical products. Most of these formulations present analytical challenges to those who must develop methods to test them. Typically, test procedures for these products require tedious extractions and difficult sample preparation procedures. Fourier transform near-infrared (FT-NIR) spectroscopy is an analytical technique that has gained popularity in recent years for analyzing raw materials, intermediate products, and finished dosage forms. Among the finished products that have been most often analyzed using NIR spectroscopy are tablets, capsules, and lyophilized materials.

Analysis of Multiplexed 2DE Gels: 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. One such technological jump in 2DE has been the introduction of multiplexed gel-staining methods. Samples are visualized using different fluorescent stains (such as the Cy2, Cy3, and Cy5 stains commonly used) and run on the same physical two-dimensional gel. Multiple images are then produced, allowing the analysis of each sample to be performed [27].

Packaging of Novel Semisolids: Most semisolid products are manufactured 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 becomes 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.

Because it is chemically inert, impermeable, strong, and rigid, glass has FDA clearance and is the ideal container for most drug products. With the proper closure system, it provides an excellent barrier to practically every element except light. Opaque jars are used to protect light-sensitive products and are available as porcelain white or dark green or amber. Commercially available empty ointment jars vary in size from 0.5 ounces to 1 pound.

The specific FDA regulation about drug products states that "Container closures and another 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 the product in the final container in which it is marketed. This includes stability testing of the filled container at room temperature, *e.g.* 20 ºC as well as under accelerated stability testing condition, *e.g.* 40-50 ºC. Ointment jars are made up of clear or opaque glass or plastic. Some are colored green, amber or blue. Opaque jars are used for light sensitive products, are porcelain white, dark green or amber. Commercially available empty ointment jars vary in size from about 0.5 ounce to 1 pound. In commercial manufacture and packaging of topical

products, the jars and tubes are first tested for compatibility and stability for the intended product. This includes stability testing of filled containers. Tubes use to package topical pharmaceutical products are gaining in popularity since they are light in weight, relatively inexpensive, convenient for use, compatible with most formulative component and provide protection against external contamination. Ointment tubes are made of aluminum or plastic. When the ointment is used for ophthalmic, rectal, vaginal or nasal application, they are packed with special applicator tips. The multiple dose tube used for pharmaceutical has conventional continuous thread closure. Single dose tube may be prepared with a tera way tip. Meter dose, temper evident and child resistant closures are also available. Standard size of empty tubes has a capacity of 1.5, 2, 3.5, 5, 15, 30, 45, 60 and 120 gm. 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 [28].

Plastic containers used for emulsion systems must be thoroughly evaluated for physical and chemical changes in the emulsion as well as for physical changes in the container. Product–plastic interactions may be divided into five categories: permeation, leaching, sorption, chemical reaction, and alteration in the physical properties of the plastics or products [29, 30]. For adequate protection of the product, container evaluation during the development stage of the product is imperative the protocols and standard for tests to demonstrate resin equivalence are found in the USP/ NF and include three categories of tests for chemical and spectral characteristics and moisture barrier. [7] Some examples of plastics include high- or low-density polyethylene (HDPE or LDPE) or a blend of each, polypropylene (PP), polyethylene terephthalate (PET), and various plastic/foil/paper laminates, sometimes 10 layers thick [31]. Each of these plastics has its characteristics and advantages that make it conducive to the packaging of semisolid products. For example, LDPE is soft and resilient and provides a good moisture barrier. HDPE provides a superior moisture barrier but is less resilient. PP has a high level of heat resistance, and PET offers transparency and a high degree of product chemical compatibility. Thus, plastics and plastic laminates are generally preferred over metal tubes for packaging of pharmaceutical and cosmetic products [29].

CONCLUSION: The main advantages of novel semisolid dosage forms are non-greasy since they are made up of water washable bases, easy application, rapid formulation, and ability to topically deliver a wide variety of drug molecules. Now a days, greater efforts has been made for achieving controlled release formulations by using different carrier systems, eliminating the cosmetically unfavorable qualities of the conventional semisolid dosage forms. Appropriate excipient selection and safety evaluation are important in the development of semisolid dosage form.

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CONFLICT OF INTEREST: Nil

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