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A REVIEW ON NOVEL ASPECTS OF FORMULATION AND CHALLENGES IN PHARMACEUTICAL GEL

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ABSTRACT

The goal of this study was to gather the most recent research, with a particular focus on a logical approach to topical formulation and the fundamental components of topical drug delivery systems. Topical medication applications offer the benefit of delivering the medicine directly to the site of action and working for extended periods of time. In comparison to ointments, creams, and lotions, topical gel formulations are less greasy and easier to remove from the skin, and they have better application properties and stability. The skin is one of the most extensive and easily accessible organs on the human body for topical administration, and it is the primary route of drug delivery for topical drugs. In-Situ gels are a novel approach in pharmaceutical gels. In-situ gels are a type of hydrogel that comes in the form of a solution and gels when it comes into contact with body fluids or changes in ph. pH, homogeneity, grittiness, drug content, viscosity, spreadability, extrudability, skin irritation tests, in vitro release, and in Stability are some of the factors that are used to evaluate gels. This study focuses on the categorization, formulation mechanisms, Evaluation parameters and applications of gel and in-situ gel as innovative pharmaceutical approach system.

KEYWORDS

Topical Gel, Skin, In-situ, Gel with a noval approach and Polymers.

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INTRODUCTION

Topical drug delivery techniques are becoming more common, and numerous medicines have been effectively administered this way for both local and systemic effects. Most antifungal, antibacterial, anti-inflammatory and lubricating gels have been created in recent years to administer the medication in the form of topical gels or as lubricant for surgical equipment, which are known as non-medicated gels. Gels are used to reduce

gastrointestinal discomfort, counteract the "first pass" effect, and increase medication concentration at the site of action[1]. The major route of topical medication delivery is through the skin, which is one of the most widespread and easily accessible organs on the human body for topical administration. It has the ability to penetrate deeper into the skin, allowing for greater absorption[2]. Whether the solution, ointment, or cream is intended for delivery into the eye, rectum, vaginal, or skin, it is a topical dose form. Because the skin is the biggest organ in terms of area and is easily accessible, it is commonly chosen as the site of administration for topical dose forms[3]. The advantages of topical administration over traditional dose forms are numerous. Because of the bilayer composition and structure, they are thought to be more effective and less hazardous than traditional formulations. Medication carriers that ensure adequate localization or penetration of the drug within or through the skin are being used in the formulation of topical dosage forms in order to enhance the local and limit the systemic effects, or to ensure adequate percutaneous absorption[4]. Topical formulation reduces GI irritation, prevents drug metabolism in the liver, and increases medication bioavailability. Topical treatments work directly at the site of action[5]. Gel formulations were tested for different physicochemical characteristics such as PH, Viscosity, Spreadability, stability, skin irritation, in vivo release, and antifungal activity, because gel based formulations are better percutaneously absorbed than cream and ointment[6].

Gels are a type of material that has both liquid and solid components. Gel is a two-component, cross-linked three-dimensional network made up of structural elements interspersed with an appropriate but proportionately huge volume of liquid to produce an endless rigid network structure that immobilizes the liquid continuous phase inside. Inorganic particles or organic macromolecules, usually polymers, can make up the structural components that make up the gel network[7]. Chemical or physical interactions can result in the formation of cross linkages. As a result, gels are classified as chemical or physical gel systems, respectively. Physical gels are formed by secondary intermolecular forces such as hydrogen bonding, electrostatic interactions, dipole dipole interactions, Vander Waals forces, and hydrophobic interactions, which are comparatively weaker and reversible than chemical gels[7]. The U.S.P. defines gel as a semisolid system made up of a dispersion of tiny inorganic particles or big organic molecules that is encased and interpenetrated by liquid. Gels consist of two phase system in which inorganic particles are not dissolved but only dispersed throughout the continuous phase and large organic particles are dissolved in the continuous phase, randomly coiled in the flexible chains[8.]

SKIN'S LIFE STRUCTURES[9-13]

Skin is the biggest organ of the human body and offers particular favorable circumstances over different courses, bypassing the primary pass digestion system. Skin is also a good place for directing medications to be taken. It's an enormous open door for directing medication. It allows users to order a range of different types of drug delivery systems in one place, including topical and transdermal dose shapes. Topical measurement structures are intended to be connected on skin for restricted conveyance of medications. They contrast from transdermal measurement structures, for example, patches, in the way that the medications connected topically are less inclined to be ingested into the systemic dissemination. Their activity takes place in one of the skin layers or deeper tissues beneath the surface. Differences in manufacturing structure and strategy can be important factors in determining where medication is delivered from these measurement shapes. Even from topical doses, the blood supply, which is available in the dermal layer of the skin, can cause some assimilation of medications to the systemic flow.

STRUCTURE OF GEL

The presence of a network formed by the interlinking of particles gelling agent gives a gel its rigidity. The structure of the network and the properties of gel are determined by the nature of the particles and the type of force responsible for the

linkages. Individual hydrophilic colloid particles can be made up of spherical or isometric aggregates of small molecules, or single macromolecules. The network in linear macromolecules is made up of entangled molecules, each of which has a point of contact that can be small or consist of several molecules aligned in a crystalline order. Strong primary valencies such as in silicic acid gels, to weaker hydrogen bonds and Vander waals forces may be responsible for the linkage between gelling agent particles. The fact that a slight increase in temperature frequently causes gel liquefaction indicates that these latter forces are weaker[14].

PROPERTIES OF GEL[15-18]

1. In a perfect world, a pharmaceutical or cosmetic gelling agent would be inert, safe, and not react with other ingredients in the formulation.
2. It should have adequate antimicrobial protection against microbial attack.
3. Gelling agent should produce a sensible solid-like nature at the time of storage which is easily broken when exposed to shear forces produced by squeezing the tube, trembling the bottle or at the application stage.
4. As the effective crosslink density of the gel increases, the apparent viscosity or gel strength increases. However, depending on the molecular interactions between the polymer and the solvent, a rise in temperature may increase or decrease apparent viscosity.
5. It should have thixotropic, greaseless, emollient, non-staining, and other properties.
6. It should be stable while in storage.
7. It should be simple to use and handle.
8. There should be no tackiness to the topical gel.
9. It should not have an impact on the drug's biological nature.
10. They exhibit the mechanical characteristics of the solid stage.
11. The ophthalmic gel has to be completely sterile.
12. The topical gel should not be abrasive.

Advantages of Topical Drug Delivery System[19]

1. Venous therapy.
2. Convenient and simple to use.
3. Prevents medication level fluctuations, as well as inter- and intra-patient variances.
4. The ability to quickly stop taking medications, as well as the ability to easily wash away any medication that has been applied.
5. The drug may be administered to a specified location with precision.
6. Enabling the use of drugs with a short biological half-life.
7. Allow for self-medication.
8. Physiological and pharmacological responses are being improved.
9. Patient compliance will improve.
10. It provides large surface area.
11. It prevents gastrointestinal irritation and first-pass effects.

Disadvantages of Topical Drug Delivery System[20]

1. Decreased penetration in the affected area.
2. The drug and/or excipients may cause skin irritation in people with contact dermatitis.
3. Some drugs have a low permeability through the skin.
4. Potential rapid appearance of bacterial resistance.
5. Allergic responses are possible.
6. It can only be used for drugs that have a very low plasma concentration to work.
7. Drugs may be denatured by an enzyme in the epidermis.
8. Larger-particle-size drugs are more difficult to absorb through the skin.
9. The gel's action is dependent on where it is applied and how effective it is.

GELS CHARACTERISTICS

Swelling

When a gelling agent is kept in contact with a liquid that solvates it, the agent absorbs a significant quantity of the liquid and the volume rises. This process is known as swelling. As the solvent enters the matrix, this process happens. Gel solvent interactions take the role of gel-gel interactions. The amount of swelling is determined by the number of

linkages formed between individual gelling agent molecules, as well as the strength of these linkages[21].

Syneresis

When standing, many gels contract spontaneously and release a fluid substance. This phenomenon is known as syneresis. As the concentration of gelling agent falls, the degree of syneresis increases. Syneresis occurs when a thermodynamically unstable gel is present. The relaxation of elastic stress that develops during the setting of the gels has been linked to the contraction mechanism. The interstitial spaces available for the solvent decreases as these stresses are relieved, forcing the liquid out[22].

Ageing

The spontaneous aggregation of colloidal systems is typically slow. This process is referred to as ageing. In gels, ageing causes the gelling ingredient to build a denser network.

Structure

The existence of a network produced by the interlinking of gelling agent particles gives a gel its stiffness. Straightening out the particle's nature and stress, and lowering the resistance to flow.

Rheology

Non-Newtonian flow behavior is characterized by a decrease in viscosity with increasing shear rate in the solutions of the gelling agents and dispersion of flocculated solid. The fragile structure of inorganic particles distributed in water is disturbed by applied shear stress, which causes inter particulate connection to break down, causing the particles to flow more freely. Similarly, when shear stress is applied to macromolecules, the molecules are aligned in the direction of Organic (single phase system) [23].

USES OF GEL[24]

As delivery systems for orally administered drugs.

Long-acting medications injected intramuscularly or implanted in the body.

To investigate genes linked to a certain disease.

Topical medicines that are administered to the skin, mucous membranes, or eyes directly.

As binders in tablet granulation, as protective colloids in suspensions, as thickeners in oral liquids, and as suppository bases.

A lubricant for catheters is a material that keeps them lubricated.

Patch testing frameworks.

Electrocardiography using a NaCl gel.

Prophylactic dental treatment using sodium fluoride and phosphoric acid gel.

Acne therapy with tretionoin gel.

CLASSIFICATION OF GELS[21-25]

Gels can be classified based on colloidal phases, nature, physical nature and rheological properties. Gels can also be classified according to the type of liquid used and its chemical composition.

On the basis of colloidal phases

They are classified into two types:

Organic (Single phase system)

Inorganic (Two phase system)

Organic (Single phase system)

These are large organic molecules that are dissolved in a continuous phase on the twisted strands. For example, carbopol and tragacanth Gel formers are bigger organic molecules that are either natural or manufactured polymers that tend to entangle with one another due to their random motion or are linked together by Vander Waals interactions.

Inorganic (Two phase system)

If the dispersed phase's partial sizes are large and form a three-dimensional structure throughout the gel, the system is made up of floccules of small particles rather than larger molecules, and the gel structure is not necessarily stable. For example, Aluminum Hydroxide Gel USP.

Based on the solvent's properties

Hydrogels (water based)

A hydrogel is a water-insoluble cross-linked polymer chain network that can appear as a colloidal gel with water as the dispersion medium. The cross-linked polymer network of hydrogel allows it to absorb large amounts of water liquids. For example, polaxamer gel, gelatin, cellulose derivatives, and bentonite magma. Hydrophilic gels, also known as hydrogels.

Hydrogels have a variety of applications.

Long-acting medication delivery systems.
Cell culture has been done with hydrogel-coated wells.
As a sensitivity detector for the environment.
Medical electrode for ECG.
Healing dressings.
Drug delivery and diagnostics in the rectal cavity.
Hydrogels, which are made up of cross-linked polymers, are utilised in medical electrodes (e.g., polyvinylpyrrolidone).

Organogels: (with a non-aqueous solvent)

Organogels are semisolid networks in which a three-dimensional (3D) network of interwoven and self-assembled gelator fibres immobilises the organic continuous phase. Organ gels are a type of gel that consists of a liquid organic phase encased in a three-dimensional cross-linked network. There are two ways that organ gel networks can develop. The first is traditional polymerization-based gel network creation. Organ gels that are "low molecular weight gelators" can, nevertheless, be made to self-assemble into gels. Plastibase (low molecular weight polyethylene mixed in mineral oil and quickly cooled), Olag (aerosol) gel, and metallic stearate dispersion in oils are only a few examples.

Xerogels

Xerogels are solid gels with a low solvent content. These are made by evaporating the solvent or freezing it, leaving the gel framework behind, which expands and can be reconstituted when it comes into contact with new fluid. Tragacanth ribbons, acacia tear-cyclodextrin, dry cellulose, and polystyrene are only a few examples.

Based on Rheological characteristics

Plastic gels

The rheogram plot shows the yield value above which the elastic gel disturbs and begins to flow in these polymer gels, indicating non-Newtonian plastic flow. They include aluminum hydroxide, and bingham bodies, which exhibit flocculated form of suspensions, e.g., aluminum hydronite.

Pseudo-plastic gels

Exhibits pseudo-plastic flow. The viscosity of these gels decreases as the rate of shear increases, but there is no yield value. The shearing action on the long chain molecules of the linear polymers produces the rheogram. E.g. Liquid dispersion of tragacanth, sodium alginate, Na CMC etc.

Thixotropic gels

Thixotropy is the reversible behaviour of some gels, which liquefy when shaken, agitated, or otherwise disturbed and then re-solidify after being left to stand. Thixotropy occurs in paints, such as lithopone in oil, which runs easily when agitated but gels when left to stand. These gels have very weak particle bonding that can be broken down by shaking. The reversible isothermal gel-sol-gel transformation will cause the resultant solution to revert back to gel when the particles collide and bind together again. In colloidal systems, nonspherical particles form a scaffold-like structure. For example, kaolin, bentonite agar etc.

Based on the laws of nature

Elastic gels

The elastic behavior of agar, pectin, Guar gum, and alginates gels is observed. At the point of junction, comparably weak interactions such as hydrogen bonds and dipole attraction are used to connect the fibrous molecules. A salt bridge of type -COO-X-COO connects two neighboring strand networks if the molecule has a free -COOH group. Carbopol and alginate are two examples.

Rigid gels

This is made up of macromolecules with main valence bonds connecting the framework. For example, in silica gel, silica acid molecules are bound together by the Si-O-Si-O bond, resulting in a polymer structure with a network of pores.

CLASSIFICATION OF GELS ON THE BASIS OF DRUG DELIVERY ARE

Controlled release gels

The DDS have developed a new form of drug, controlled release DDS, which improves the bioavailability and concentration of the drug. Controlled release is able to prevent premature degradation and maintain its concentration within therapeutic range. Gels are used as controlled drug delivery vehicles thanks to the diffusion mechanism, in which the drug is delivered via a polymer matrix system (water-insoluble matrix) or reservoir system (water-insoluble polymeric

membrane) Gels with suitable rheological and mucoadhesive properties increase the contact time at the site of absorption. However, drug release must be sustained if benefits are to be gained from the prolonged contact time. Drug delivery to the nasal or ocular mucosa for local or systemic action faces numerous challenges[20].

Extended Release Gels

It's a controlled-release technique composed of an agglomerated, hydrophilic compound squeezed within a controlled-release matrix. A covering of xanthan and locust bean gums (two polysaccharides) and dextrose surrounds the pharmaceutical core. In the presence of water, interactions between matrix components produce a tight gel, while the inner core remains a mess. The drug is trapped in the pores of the gel, causing the tablet to expand and degrade as it travels through the digestive system of the patient. The medication can then gradually "back-diffuse" out of the gel matrix until it erodes and the bulk of the drug is liberated. The most significant element influencing the rate of release is the gel matrix's characteristics.

Amphiphilic Gels

Amphiphilic gels are made by combining a solid gelator, such as sorbitan monostearate or sorbitan monopalmitate, with a liquid phase, such as liquid sorbitan esters or polysorbate, and heating them both at 60°C to form a clear isotropic sol phase, then cooling the sol phase to form an opaque semisolid at room temperature.

Hydrophilic Gels

The internal phase of hydrophilic gels is made up of a polymer that forms a three-dimensional net-like structure that holds the liquid vehicle in place as the external phase. Intermolecular forces bind the solvent molecules to a polymeric net, reducing their mobility and resulting in a structured system with increased viscosity[26].

Non-Aqueous Gels

Propylene glycol dicaprylate/dicaprate was used to successfully manufacture ethylcellulose as a non-aqueous gel. The novel non-aqueous gel had rheological profiles that matched those of a physically cross-linked three-dimensional gel network, as well as mechanical properties that made it suitable for use as a vehicle for topical drug delivery. The molecular interactions associated with the formation of ethylcellulose gel networks were found to be influenced by the solvent's conformation. The gel matrices had viscoelastic, yield stress, and thixotropic properties. With increased polymeric chain length and polymer concentrations, rheological and mechanical properties trended upwards significantly. We've found some excellent linear correlations[27].

Bio adhesive Gels

Bio adhesive gels were developed for insulin delivery through the nose. The toxicity of four absorption enhancers, saponins, sodium deoxycholate, ethylenediamine tetra-acetic acid (EDTA), and lecithin, was investigated using a nasal perfusion test. 4000 Iu/dl insulin, 2% or 4% low and medium molecular weight chitosan, and lecithin or EDTA were used in the gels. A membrane-less diffusion technique and a modified tensiometry test were used to investigate drug release and bio adhesion. In diabetic rats, the optimized gel was given nasally. An insulin enzyme immunoassay kit was used to measure blood insulin levels, while glucose oxidase technique kits were used to measure serum glucose[28].

Reversible Sol-Gel hydrogels with thermo sensitive properties

They are polymeric solutions that go through a reversible sol to gel transformation under the influence of environmental factors such as temperature and pH, resulting in the development of in-situ hydrogels.

Complication Gels

Oral insulin administration systems are designed to keep the sensitive medicine safe from proteolytic breakdown in the stomach and upper small intestine. The insulin was shielded from proteolytic breakdown by remaining in the gel. The complexes dissociated in the basic and neutral intestinal environments, causing rapid gel swelling and insulin release. Strong dose-dependent hypoglycemic effects were seen in both healthy and diabetic rats within 2 hours of administration of the insulin-containing polymers. These effects lasted up to 8 hours after the drug was given.

GEL WITH A NOVAL APPROACH

Hydrogel

Hydrogels are water-immobilized gel systems made up of insoluble polymers. Hydrogels are made up of water and a hydrophilic but non-water soluble polymeric material. The dry polymer swells and absorbs liquid when it is exposed to water. Chemical or physical forces are used to crosslink the polymer strands. Hydrogels can be classified according on the kind of polymer used and/or the cross-linking method[29]. Hydrogels are three-dimensional structures with polymeric networks that can absorb and hold large amounts of water and biological fluids, causing them to swell[30].

Hydrogels are classified as follows

Preformed Hydrogels

Are described as simple viscous solutions that do not change after being administered.

In-situ gels

Are solutions or suspensions that gel after arriving at a specific location as a result of physicochemical changes. Due to several advantages such as increased patient compliance and lower drug administration frequency, the in-situ gelling system has become one of the most popular new drug delivery methods. The phrase 'in-situ' comes from the Latin and meaning 'in place.

In-situ gel formation is triggered by a variety of factors, including pH changes, temperature changes, and solvent exchange. Due to the presence of bio adhesive nature of polymers, the gel formed by the insitu gelling system floats over stomach contents, resulting in a prolonged gastric retention time. In-situ gels are formulations that are in the form of a solution before being administered to the body, but then gelate to form a gel afterward. Oral, nasal, ophthalmic, vaginal, injectable, intraperitoneal, and rectal routes are all possible ways to administer in-situ gelling systems[31].

Advantages of in-situ gelling system[32]

It shows increased gastric retention with slow drug release compared to those who were given fast-release drugs.

In-situ gels demonstrate patient compliance and simplicity of administration.

It reduces the number of times you have to take a dose.

It has fewer side effects than other pharmacological dosage forms.

Acting directly on the specified place, it demonstrates local activity and site specificity.

Disadvantages of in-situ gelling system[33]

As a result of storage issues, it degrades.

Chemical degradation makes it more prone to stability issues.

It needs a large amount of fluids.

The classification of in situ gels is as follows[34]

Based on the gelation mechanism:

a) Electrical current sensitive gel
b) Gel with a pH Sensitive pH
c) Thermo sensitive gel
d) Enzyme sensitive gel
e) Ion trigger or the presence of ions

Depending on the administration route

a) Ocular delivery using in situ formed polymeric systems
b) Oral administration of in situ developing polymeric systems
c) Nasal medication delivery with in-situ formation
d) Injectable drug delivery systems that develop in situ
e) Rectal and vaginal delivery using in situ forming polymeric systems

In this study, in situ gels were prepared employing an ion trigger mechanism and a variety of polymers such as gellan gum and sodium alginate.

In-situ gel formation is mediated by the following mechanisms

In-situ gels are hydrogels that are liquids at room temperature but gel when exposed to body fluids or when the pH changes. Various polymers are used in in-situ gelling systems, which transform from solution to gel owing to changes in physicochemical characteristics. When a low viscosity solution comes into touch with bodily fluids, changes in polymer confirmation occur, and a viscous gel with a density lower than stomach fluid forms.

In-situ gelling system approaches: There are following types of in-situ gelling system approaches.

System that is thermally triggered (Temperature-induced in-situ gelling system)

The most widely used systems in in-situ gelling formulations are temperature induced systems. External heat, other than body temperature, is not required to cause gelation in these systems. Temperature-induced systems can be divided into three categories. They are some of them.

Type that is thermo sensitive in a negative way

Type that is positively thermosensitive.

Type that can be reversed in temperature[35].

Temperature responsive polymers or thermo responsive polymers are used in temperature induced gelling systems because they exhibit a drastic and discontinuous change in their physical properties with temperature. This type of polymer falls into the category of stimuli responsive materials, which change their properties in response to changes in the environment. At high or low temperatures, these polymers show a miscibility gap, with an upper or lower critical solution temperature. The upper critical solution temperature range is 0-100C. The solution is liquid at room temperature, but it transforms into gel when it reaches the body fluid due to exposure to body temperature. Because the solution is in liquid form, the hydrogen bonding between polymer and water causes abrupt changes at lower critical solution temperatures, resulting in the formation of gel[36].

pH-activated systems

The formation of a gel is caused by a change in pH in this system. PH sensitive or pH responsive polymers are utilized in this method. Polyelectrolytes are pH sensitive polymers with acidic or alkaline ionisable functional groups. The polyelectrolytes in the formulation cause an increase in external pH, which causes the hydrogel to swell, resulting in the formation of in-situ gel. Polymers with anionic groups are suitable for pH-triggered systems. Cellulose acetate phthalate (CAP), carbomer and its derivatives, polyethylene glycol (PEG), pseudo latexes, and poly methacrilic acid (PMC) are only a few examples.

Biomaterials' Physical Changes

Swelling

In the production of in-situ gel, swelling is a sort of physical technique. The polymers that surround the polymer ingest the fluids present in the external environment and expand from inside to outside, progressively releasing the medication in this method.

Diffusion

Diffusion is a sort of physical technique utilised in the production of in-situ gels. Solvent diffuses out of the polymer solution into the surrounding tissues in this method, resulting in the development of a precipitate or solidification of the polymer matrix. N-methyl pyrrolidone is the most widely utilised polymer in the diffusion method to in-situ gelling system development (NMP)[39].

Induced chemical systems

Chemical reactions are used in this method to create an in-situ gel. Ionic cross linking, enzymatic cross linking, and photo polymerization are all used to create insitu gels.

Cross-linking of ions

Ion sensitive polymers are used in this method. In the presence of ions such as Na+, K+, Ca2+, and Mg2+, ion sensitive polymers cause gelation. To form a gel, ion sensitive polymers go through a phase transition.

Cross-linking by enzymes

The most practical method for forming an in-situ gelling system is enzymatic cross linking. In this method, the gel is created by cross-linking with enzymes found in the body fluids.

Photo polymerization

Electromagnetic radiations are employed in this method to create an in-situ gel[37]. Polymers with polymerisable functional groups that dissociate in the presence of light initiators such as acrylates or other polymers that have long wavelength ultraviolet and visible wavelengths are the best candidates for photo polymerisation. Because short wavelengths are biologically harmful, they aren't used. Ketones like 2, 2-dimethoxy-2-phenyl acetophenone are used as the initiator for ultraviolet photo polymerization in this method. Visible light

systems include camphorquinone and ethyl eosin initiators[38].

Applications

Drug delivery methods for oral use

In-situ drug delivery systems are also being developed to deliver drugs through oral route. The new system is designed to make it easier for patients to take their medication in the same way as they would have done before, by using oral route or intravenous route. Example,

Clotrimazole an antimicrobial drug

Paracetamol an anti-inflammatory drug

Systems for delivering ophthalmic drugs

In the management of intraocular tension in glaucoma, ophthalmic medication delivery methods are used. Due to the significant draining of tear fluids from the eye, conventional dose forms have poor bioavailability, resulting in fast drug clearance. Ophthalmic medication delivery methods are utilised to improve bioavailability issues. In the development of ophthalmic in-situ gelling systems, a variety of natural polymers are utilized. Example,

Ofloxacin an antimicrobial drug

Levofloxacin is available as an in-situ ophthalmic gel.

Ciprofloxacin is available as an in-situ ophthalmic gel[39].

Drug delivery methods that are injectable

Injectable drug delivery methods are also manufactured as in-situ gels, which have gotten a lot of attention in the recent decade because of the benefits of not requiring a surgical procedure and patient compliance. Injectable in-situ gels are made of synthetic polymers and block copolymers. Example,

Bupivacaine an anti-inflammatory drug.

Paclitaxel was developed as an injectable in-situ gel in albino mice with subcutaneously implanted EMT-6 tumours[40].

Drug delivery techniques via the nose

The nasal route of medication delivery is the most often used because it offers numerous benefits, including patient compliance, avoidance of first-pass metabolism, and high levels of absorption and transport of chemicals[41].

Drug delivery methods for the rectal and vaginal areas

Rectal and vaginal methods are also used to deliver in-situ gels. Acetaminophen, an anti-inflammatory medication, was created as a rectal in-situ gel utilising synthetic polymers polycarbophil and poloxamer F188 and poloxamer 407, resulting in an in-situ gelling liquid suppository that is regarded an excellent technique for increasing bioavailability. Example, a. Itraconazole is an anti-inflammatory medication that comes in the form of a vaginal in-situ gel[42].

PREPARATION OF GELS[43]

Gels are generally manufactured on an industrial scale at room temperature. However, only a few polymers require specific treatment before being processed. The following procedures can be used to make gels:

Temperature variations

Flocculation

Chemicals reaction

Temperature variations

When thermal changes are applied to dissolved polymers (lipophilic colloids), gelatin is formed. Many hydrogen formers are more soluble in hot than cold water and gelation takes place if the temperature is reduced, then cooling of a concentrated hot solution will produce a gel.

For example, gelatin, sodium oleate agar, guar gummed, cellulose derivatives, and so forth. Some materials, such as cellulose ether, have their water solubility due to hydrogen bonding with the water. The hydrogen bonding in these solutions will be disrupted, resulting in decreased solubility and gelation. As a result, this technique cannot be used to make gels in a broad sense.

Flocculation

Gelation is a form of precipitation which is produced by adding just enough salt to produce age state, but inadequate to bring about complete precipitation. It is essential to ensure quick mixing to avoid local high concentration of precipitant in order to avoid over-mixing.

For example, Ethyl cellulose and polystyrene solutions in benzene can be gelled by quickly

mixing with a non-solvent such as petroleum ether. Coagulation occurs when salts are added to a hydrophobic solution; nevertheless, gelation is uncommon. The flocculation technique produces Thixotropic gels. High concentrations of electrolytes impact hydrophilic colloids like gelatin, proteins, and acacia only when the effect is to "salt out" the colloidal, and gelation does not occur.

Chemicals reaction

In this method the solute and solvent interact chemically in this process, resulting in the formation of a gel.

For example, an aluminum hydroxide gel can be made by combining an aluminium salt and sodium carbonate in an aqueous solution and increasing the concentration of reactants to generate a gel structure. PVA, cyanoacrylates with glycidol ether (Glycidol), toluene diisocyanates (TDI), and methane diphenyl isocyanine (MDI) are a few other examples of chemical reactions that cross-link polymeric chains.

GELLING AGENTS UTILISED IN PHARMACEUTICAL FORMULATIONS ARE

Pharmaceutical Gel Formulation Considerations[45]

Vehicle/solvent selection

Co-solvents may be used to enhance the solubility of the therapeutic agent in the dosage form and/or to improve drug permeation across the skin. The co-solvent can be alcohol, glycerol, PG, PG or PEG 400.

Buffers are used

In aqueous and hydroalcoholic-based gels, buffers may be used to regulate the pH of the formulation. In hydroalcoholic-based vehicles, buffer salt solubility is decreased. For example, Phosphate, citrate, and so on.

Preservatives: Certain preservatives work along with the hydrophilic polymers used to make gels, lowering the amount of free (antimicrobially active) preservative in the mix. As a result, the initial concentration of these preservatives should be increased to compensate for this. For example, Parabens, phenolic, and other similar substances.

Antioxidants: It could be used in the formulation to improve the chemical stability of oxidatively degradable therapeutics. Its selection is based on the nature of the gel preparation vehicle. Because most gels are aqueous, water-soluble antioxidants are commonly used. Examples include sodium metabisulphite, sodium formaldehyde sulfoxylate, and others.

Sweetening agents/flavors: Flavors and sweetening agents are only used in gels that are intended to be consumed through the mouth (E.g., for the treatment of infection, inflammation, ulceration, etc.).

E.g., sweeteners: Sucrose, liquid glucose, glycerol, sorbitol, saccharin sodium, aspartame, and other sweeteners are all examples.

E.g. Flavors include butterscotch, peach, vanilla, wintergreen mint, cherry, mint, anise, citrus flavors, and raspberry.

Topical Drug Delivery: Factors to Consider[46-49]

Physiological variables

Drug physicochemical characteristics

Formulation ingredients and interactions

Physiological variables

Physiological variables primarily affect skin characteristics such as thickness, moisture, and hair follicle density. Individual differences in these qualities can be significant, depending on age, gender, race, anatomical location, overall health, and environmental conditions such as temperature and humidity. The rate-limiting step for topical drug delivery should be in the formulation rather than the biological barrier, to minimise the effects of such physiological variability.

Drug physicochemical characteristics

The ease of diffusion via the topical carrier, as well as penetration through the skin or mucosal surfaces, is nearly always influenced by the drug's physicochemical characteristics. The molecule size as indicated by the molecular weight, the partition coefficient between the vehicle and the skin, the melting point, stability, and chemical functionality, which impact ionisation potential, binding affinity, and drug solubility in the vehicle, are all important properties.

Formulation ingredients and interactions

The impact of vehicle formulation on the drug as well as the application site is evident. Drug diffusion, thermodynamic activity, stability, and degree of ionisation of weakly acidic or basic drugs are all included in the effect on the drug. The effect on the application site is linked to chemical changes in the barrier property caused by simultaneous uptake of formulation components and physical occlusion. These processes encourage skin hydration or changes that help drugs penetrate deeper into the skin. The consistency and viscosity of the vehicle are also influenced by the formulation factor, which determines the vehicle's adhesion and retention properties. These characteristics were crucial in ensuring vehicle retention at the application site for effective drug delivery.

The Formulated Gels' Evaluation Parameters[50,51]

Measurement of pH

A digital pH meter was used to check the pH of different gel formulations. 1gram of gel was dissolved in 100mL of distilled water and left to sit for 2 hours. Calculate the average values after measuring pH three times in triplicate.

Drug content

1g of the gel was mixed with 100ml of a suitable solvent. Filter the stock solution to remove any impurities. Then, using appropriate dilutions prepare aliquots of various concentrations and measure the absorbance. The equation was derived from a linear regression analysis of the calibration curve and was used to calculate drug content.

Viscosity study

A Brookfield Viscometer was used to measure the viscosity of the prepared gel. The gels were rotated at three different speeds: 0.3, 0.6, and 1.5 rotations per minute. The dial reading for each speed was recorded. The gel's viscosity was calculated by multiplying the dial reading by a factor found in the Brookfield Viscometer catalogues.

Spreadability

It indicates the size of the area over which the gel spreads easily when applied to the skin or affected part. The therapeutic potency is also influenced by the value spread. Spreadability is the time it takes two slides to slip away from a gel that is placed in between them under the influence of a certain load in seconds. The better the spreadability, the less time it takes to separate two slides. The spreadability is calculated using the formula below:

Spreadability (S) = M × L / T

Where,

M denotes a weight attached to the upper slide.

L is the length of the glass slides.

T stands for the time it took to separate the slides.

Extrudability study

After being placed in the container, the formulations are filled into collapsible tubes. The weight in gm. required to extrude a 0.5cm ribbon of gel in 10 seconds is used to determine extrudability.

Skin irritation study

Guinea pigs (400-500g; either sex) were used in the skin irritation study. The animals were fed conventional animal feed and provided access to fresh water at all times. The animals were cared for in a typical manner. The back of my head was shaved. At 1, 2, 3, 4, 5, 6, 7, and 8 hours, five ml of each sample was taken and replaced with a fresh dissolving media of equal volume. The samples were then analysed for drug content using phosphate buffer as guinea pigs, with a 4cm blank area marked on both sides, one side serving as control and the other as test. The gel was applied twice a day (500mg/guinea pig) for seven days, and the site was observed for any sensitivity and reaction. It was given a grade of,

No response

Patchy erythema

Erythema that is minor but confluent or modest but patchy.

Erythema severe, with or without edema

***In-vitro* Diffusion studies**

It may be done in a Franz diffusion cell to investigate gel dissolution via a cellophane membrane. A cellophane membrane was used to hold 0.5g of gel sample. Diffusion experiments were carried out at 37°C with 250mL of phosphate buffer (pH 7.4) as the dissolving media. At 1, 2, 3, 4, 5, 6, 7, and 8 hours, five millilitres of each sample were removed and replaced with an equivalent volume of new dissolving media. The

samples were then tested for drug content using phosphate buffer as a control.

***In-vivo* studies**

Three sets of six male Wistar albino rats were utilised to study carrageenan-induced rat paw edema. The samples are

For the test formulation.

Use a commercial sample (Reference).

For the sake of maintaining control.

Calculate the volume of the test animal's unilateral hind paw. Rubbed 100mg of preparation on each paw twice at 1 and 2 hours prior to carrageenan administration. They were imprisoned in cages with copography meshes. Subcutaneously inject 0.1ml of 1 percent w/v carrageenan into the paw. The volume of the hind paw was measured every hour for 5 hours. To do so, use a mercury plethysmometer. Calculate the inhibition percentage.

Stability

Freeze-thaw cycling was used to test the stability of all of the gel formulations. Syneresis was seen by exposing the product to temperatures of 4°C for 1 month, 25°C for 1 month, and finally 40°C for 1 month. After that, the gel is subjected to room temperature and the separation of liquid exudate is observed.

Homogeneity

All produced gels were visually inspected for homogeneity after being placed in the container. They were examined for the existence of aggregates and their appearance.

Grittiness

All of the formulations were examined under a light microscope for the presence of any significant particle matter. As a result, the gel preparation clearly meets the criteria of being devoid of specific matter and grittiness, as required in any topical medication.

Table No.1: Gel forming substance[44]

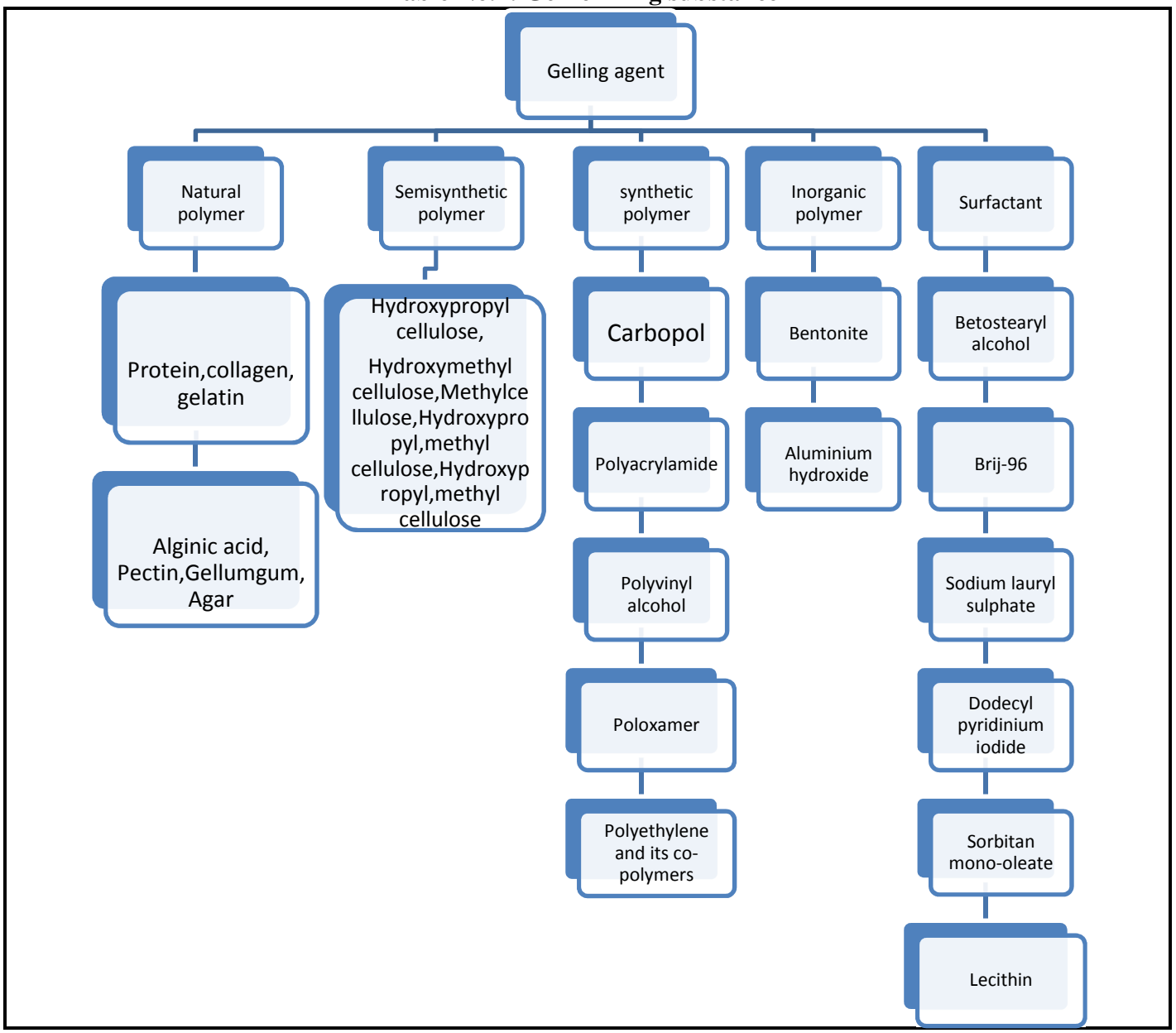

Table No.2: Examples of some marketed Gel

S.No	Route and Application	Proprietary	Active ingredients	Gelling agent
1	Vaginal: acidity restoration and maintenance	Aci-Gel	Acetic acid	Tragacanth, acacia
2	Acne Vulgaris	Desquam-X Gel	Benzoyl peroxide	Carbomer 940
3	Antipruritic	Termovate Gel	Clobetasol	Carbomer 934
4	Hematologic (nasal)	Nascobal	Cyanocobalamin	Methyl cellulose
5	Anti-inflammatory; antipruritic	Tropicort Gel	Desoximetasone supplement	Carbomer 940
6	Progesterone	Crinone Gel	Progesterone	Carbomer
7	Dermatologic	Regranex Gel	Becaplermin	Na CMC

CONCLUSION

Gels are becoming more popular as a result of their increased stability and ability to provide controlled release over other semisolid preparations such as creams, ointments, pastes, and so on. The gel formulation can provide better absorption characteristics and increase bioavailability of the drug they say. A thorough examination into the gel formulation's stability properties over a long period of time may open the door to its therapeutic usage in patients. The primary benefit of topical drug delivery is that it allows for the accumulation of high local drug concentrations within the tissue and its vicinity for enhanced drug action. This is especially useful when drugs with a short biological half-life and a narrow therapeutic window are administered via this route. The report also provides the better information regarding to the formulation and evaluation parameters of the novel herbal gel for anti-inflammation activity. Clinical data indicates that topical gel is a safe and effective therapy option for skin disorders.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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