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A Review on Bigel Novel Drug Delivery System

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Abstract: *Bigels are systems that are usually formed by mixing a hydrogel and an organogel: the aqueous phase is generally made of hydrophilic biopolymer through the organic phase comprise of a gelled vegetable oil because of the presence of an organogelator. The quantity of the gelling agent in every phase, the organogel/ hydrogel percentage, and the temperature of mixing and speed of each parameter need to be considered for bigel preparation. Bigels are chiefly beneficial drug delivery systems, which have been prepared for transdermal, buccal, and vaginal routes. Analytical studies and microscopical determination are the most reported characterization techniques. Bigel's composition and distinguishing structure confer promising drug delivery aspects such as mucoadhesion, the capability to control drug release, and the probability of using both hydrophilic and lipophilic drugs in the same system.*

Keywords: Hydrogel, oleogel, bigel, organogel, organogelators.

I. INTRODUCTION

Gels are semisolid systems that consist of a solid and a liquid component in which the solid compound and gelator form a 3D network that traps the liquid phase.[1,2] The gelator is generally used at concentrations below 15% w/v which increases the surface tension, hence preventing the flow of the solvent.[3,4] According to the polarity of the liquid constituent gels are classified into hydrogels and organogels.[5] Hydrogels are gels that contain a continuous phase usually water that is the polar solvent used, whereas organogels (or oleogels) contain apolar liquids such as organic solvents or mineral or vegetable oils as their continuous phase.[6,7]

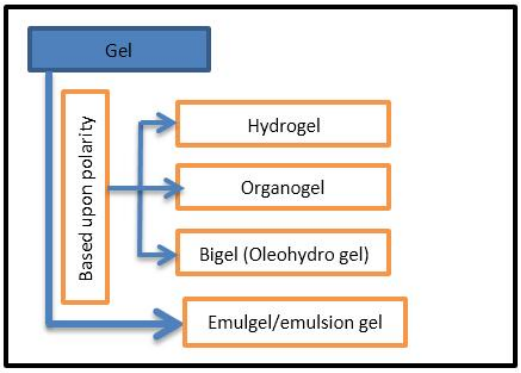

Figure 1: Types of gel

Certain new gels have also been reported such as emulgels and bigels. These formulations have good water content present in their structure which provides hydration to the stratum corneum. The hydrogel present in the bigel helps in proper hydration of the stratum corneum and the organogel present in the bigel helps in increased penetration.

Hydrogels have many advantages as a pharmaceutical formulation for topical use, such as their ease of formulation, non-oily nature, good spreadability, ability to increase stratum corneum hydration, cooling effect, and ease of removal after application because they can be rinsed with water. All these advantages are responsible for good patient compliance. However, they generally act as carriers of hydrophilic but not hydrophobic drugs and are less able to cross the stratum corneum of the skin. Organogels are also easy to formulate and their lipophilic nature means that they are capable of dissolving hydrophobic drugs and increasing their permeability through the stratum corneum. The main disadvantage of

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organogels is their oily nature, which hampers their removal from the skin after it is applied because of their stickiness and oily residues which leads to lower patient compliance.[5,8,11]

Emulgels or emulsion gels were prepared to overcome the disadvantages of hydrogels in terms of the release of hydrophobic drugs. They are biphasic systems that generally consist of a hydrophilic and lipophilic phase, which show emulsion-like behavior and the continuous phase of which is gelled. Therefore, emulgels combine the features of both emulsions and gels and can be made of either emulsion hydrogels or emulsion organogels.[9,12] Bi-gels are somewhat new as compared to other gels formulations. These are uniform semisolid dispersion system that contains two gel phases, are mixed with the help of a high shear rate, and appear as a single gel phase visually.

Some researchers differentiate between gel-filled emulsions and bulk gel emulsions depending on dispersed or continuous phases respectively gelled in the system. When only the dispersed phase is gelled, the system has a suspension-like behavior.[12] Emulgels have low structural stability due to the different mechanical properties of their two phases, which produce systems in which both phases are structured. Although they are usually called bigels or biphasic gels in the literature.[9,12] Some authors also refer to them as hybrid gels.[14]

Depending on the arrangement of the hydrogel and organogel, bigels can be classified as organogel-in-hydrogels, hydrogel-in-organogels, and bicontinuous bigels. Firstly biphasic systems the oil phase which is dispersed into the aqueous phase, is the most widely studied, whereas hydrogel-in-organogel bigels are less likely known. Bigels have also been observed as complex matrix-in-matrix structures.[8]

There are some advantages of bigels over organogels and hydrogels.[13,14]

- Enhanced stability.
- Better wash ability.
- Good patient compliance without compromising the beneficial effects of the oil.
- They are easy to formulate.
- Surfactant use in less amount, therefore it is less toxic.
- Both hydrophilic and lipophilic drugs can be incorporated due to the presence of two phases.
- Bigels can easily penetrate through the skin. Hence it is a better choice for transdermal drug delivery.
- Bigels are having the capability to regulate the delivery of active pharmaceutical substances.
- It is a good carrier for iontophoretic drug delivery.

Disadvantages of bigels are as follows:

- Phase separation occurs if an emulsifier is absent.
- Bigels are thermo-irreversible and unstable at higher temperatures.

Applications of bigel:

- In topical drug delivery
- It makes them interesting in the controlled delivery of active products.
- It includes the delivery of both hydrophilic and lipophilic active agents.
- Enrichment of hydration of stratum corneum results in cooling and moisturizing agent.

1.1 Types pf Bigel[15,16]

Bigels preparation is categorized into four classes:

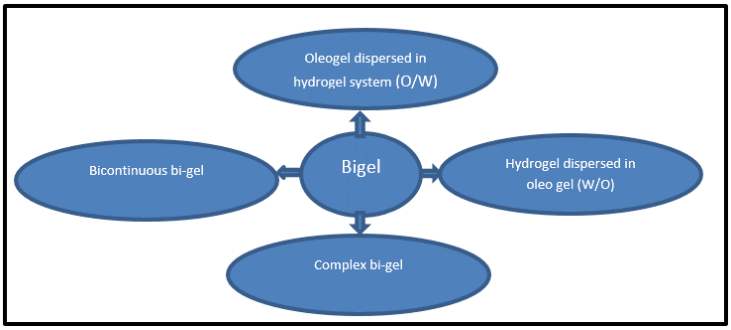

Figure 2: Types of bigel preparation

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1. Oleogel dispersed in hydrogel system (O/W): This type of bi-gels contains hydrogel as a continuous phase in which oleogel is dispersed.
2. Hydrogel dispersed in oleo gel (W/O): This type of bi-gels contains oleogel as a continuous phase and hydrogel dispersed within.
3. Bicontinuous bigel: This bigel is formulated when the gel formation is carried out at a higher proportion of hydrogel/oleogel dispersed in a lower proportion of oleogel/hydrogel phase, respectively.
4. Complex bigel: These bigels are prepared by adding organogel/hydrogel to an oil-in-water/water-in-oil structured emulsion.

A. Hydrogels

Hydrogel is a 3D network that is made of hydrophilic polymers that can take up a large volume of water or biological fluids.[23]These systems are physicochemically compatible with water and therefore it is having good water absorption, they contain hydrophilic functional groups in their polymeric chain such as amino or carboxylic groups among others, and also from the possibility of modulating their porosity and crosslinking density.[3,24,25]For making the hydrogel resistant to dissolution we can crosslink and integrate the network of hydrogel they can disintegrate and even dissolve. They contain a large proportion of water coupled with their flexibility, porosity, and rubbery consistency. Soft means that they closely resemble natural tissues which together with their biocompatibility describes why hydrogels are the most widely investigated materials for pharmaceutical and biomedical purposes. Hydrogels have numerous applications such as in hygiene products, cell culture supports, contact lenses, drug delivery systems, wound dressings, and tissue engineering.[5,23,26]

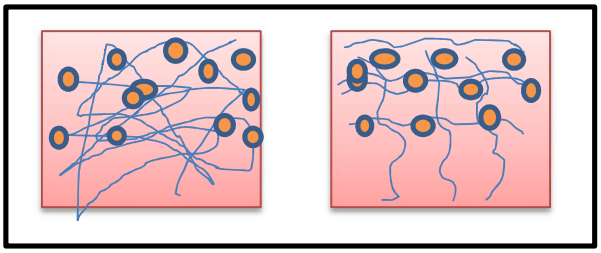
Hydrogel-forming polymers

With the help of natural and/or synthetic polymers hydrogels can be prepared. There are two main classes of natural polymers used to obtain hydrogels. i.e. 1) polysaccharides, such as starch, alginate, and agaroses (2) proteins, such as collagen and gelatin. Natural polymers are usually biodegradable and nontoxic. Though, these hydrogels which are based on natural polymers can be modified through synthetic monomers via graft copolymerization, spreading their use for the formulation of superabsorbent hydrogels. However, the biodegradability of the resulting hydrogels can be compromised here.

The preparation of hydrogels comprising synthetic polymers typically involves chemical polymerization reactions.[28] There are three polymerization techniques for obtaining hydrogels: bulk, solution, and suspension polymerization.[29] In each case, these polymerization reactions commonly include monomers, a crosslinking agent, and an initiator.

One of the main disadvantages of these polymerizations is the necessity for a purification step, involving washing the reaction product with distilled water to remove residues of the reagents used and particularly unreacted monomers which are often toxic and can later be leaked from the hydrogel.[23,28,30]

The use of nontoxic monomers is a solution for avoiding the purification process, increasing the conversion of the monomers through subsequent post-polymerization curing, and obtaining hydrogels by direct crosslinking of water-soluble preformed polymers. In this last case, both natural (e.g., polysaccharides) and synthetic [e.g., polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP)] water-soluble linear polymers can be used.[23,27]



(a) (b)

Figure 3: (a) physical cross-link and (b) chemical cross-link.

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Orange beads represent hydrophilic functional groups in the polymer chains.

To make hydrogels in different ways polymers can be crosslinked by ionizing radiation and by the chemical reaction between the polymer chains; which results in the formation of free radicals in the main chain that forms crosslink junctions; or by physical interactions such as entanglements.[28] Caló and Khutoryanskiy proposed a method for synthesizing hydrogels from ready-made water-soluble polymers based on thermal treatment and microwave radiation. Hydrophobic polymers can be used to make hydrogels which can later be converted to the hydrophilic polymer through reactions such as oxidation and hydrolysis and give rise to polar groups.[31]

By polymer crosslinking, both chemical and physical hydrogels can be obtained. Both physical and chemical hydrogel differ like the crosslink junctions that stabilize the network. In physical or reversible hydrogels, chain entanglements such as hydrophobic, ionic, or hydrogen bonds are established between polymer molecules thus forming a network with transient junction.[32]

The polymers used in the formulation of hydrogels can interact with biological systems, including mucoadhesive polymers and stimuli-sensitive polymers.[24] Mucoadhesive polymers may be natural or synthetic polymers that may be able to adhere to a mucosa more specifically to the mucus layer that covers the epithelial surface of the mucosae and the main molecules composing this layer.[33] Mucoadhesion is a complex method with a first step of contact between the mucous membrane and mucoadhesive polymer in which the polymer undergoes wetting, spreading, swelling, and a second joining step in which physicochemical interactions (hydrophobic, hydrogen bonds, Van der Waals forces, ionic, or covalent bonds) are formed between polymer's functional groups and a mucus layer.[34,36]

Polymers that are smart or stimuli-sensitive undergo changes in their physicochemical properties and structural conformation in response to environmental stimuli, which can be physical (e.g., temperature), chemical (e.g., pH), and biological (e.g., glucose).[38] Although Hydrogels that are stimuli sensitive exist in different types, for controlled drug release and targeted drug delivery pH responsive hydrogels have been widely studied. Hydrogels are composed of pH-responsive polymer networks that contain ionizable functional groups which are having acidic and basic groups joined to the backbone chain, which means these polymers can able to exchange hydrogen ions with the medium in response to changes in pH, which causes the swelling or de swelling of the hydrogel and can alter the drug release profiles.[39]

Polymers used in the formulation of hydrogels for bigels:

For the bigel drug delivery system, hydrophilic polymers have been used in the synthesis of the hydrogel. These polymers are classified as:

- Alginate: Alginate (sodium alginate) is an anionic polymer that is obtained from brown seaweed and bacteria from the genera *Pseudomonas* and *Azobacter*. This polymer causes pH dependant swelling to occur with gel formation in presence of divalent cations such as Ca^{2+}. This polymer has mucoadhesive properties.[37] This polymer is included in the formulation of bigel for topical drug delivery of immune response modifiers, and antioxidant and antifungal drugs.[54,55]
- Gelatin: Gelatin is a natural proteic polymer obtained from the partial hydrolysis of animal collagen, and it has mucoadhesive properties.[37,56] Bigels composed of gelatin-based hydrogels have been broadly studied with the help of antimicrobial drug ciprofloxacin as a model active ingredient.[6,57]
- Carbopol®: The most commonly used polymer for hydrogels is carbopol for obtaining bigels drug delivery. Carbopol also called Carbomers are synthetic high-molecular-weight acrylic polymers that are crosslinked with allyl pentaerythritol or allyl sucrose. They are bioadhesive and pH-sensitive characteristics because of their ability to establish hydrogen bonds with mucin.[2,40] There are different carbomers, Carbopol® 940 is most widely used in bigels; this polymer commonly requires the additional triethanolamine as a neutralizing agent for the complete formation of the gel. For formulations such as topical, vaginal, and buccal administration these polymers are used.[11,47,48]
- Hydroxypropyl methylcellulose (HPMC): This is a non-ionic cellulose derivative that contains methoxyl and hydroxypropyl groups. Different grades of this polymer are available based on the molecular weight and degree of substitution which are the parameters that condition its gelling ability.[49] For topical delivery of imiquimod, diltiazem hydrochloride, flurbiprofen,[51] and paracetamol, the mucoadhesive polymer has been included as a hydrogel-forming polymer in bigels.
- Guar gum: This polymer is extracted from the seeds of the legume *Cyamopsis tetragonoloba it is a*

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mucoadhesive polysaccharide.[37,59] Examples of guar gum-based bigels for topical delivery of antimicrobial drugs[1,60,61] and vaginal release of tenofovir[62] can be found in the literature.

- Pectin: Pectin is a heterogeneous polysaccharide present in the cell wall of higher plants. The mucoadhesive and pH-responsive property of this polymer is due to the carboxylic group present in it. Certain functional groups are naturally esterified and pectins can be classified according to their degree of esterification.[63,64] Bigels can be prepared using low and high methoxy pectin which are pectin-based hydrogels.[8,65,50]
- Cellulose derivatives: Cellulose perhaps is the most plentiful organic compound in the world which is frequently formed by plants. Cellulose has many semi-synthetic derivatives which are comprehensively used in the pharmaceutical and cosmetic industries.
- Other hydrogelators: Polymers such as hyaluronic acid,[67] Poloxamer 407, acrylamide, Polyethene glycol, Polyamide, Acrylic acid polymer, PVA, PVP,[71], and sodium polyacrylate[72] are also stated as hydrogelators in the bigel literature.

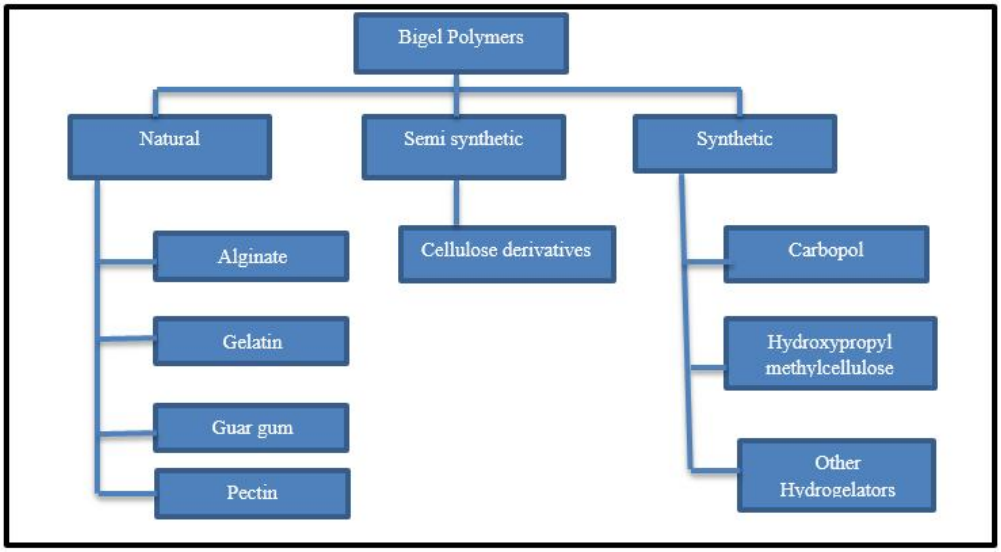

Figure 4: Classification of bigel polymers

B. Organogels

Organogels are described as semi-solid systems in which an organic liquid phase is immobilized by a three-dimensional network composed of self-assembled, inter-twined gelator fibres'.[4] These are called biphasic systems that may be opaque or transparent and have viscoelastic properties. They behave like solids and have viscoelastic properties at lower shear rates. But at higher shear rates they become fluid due to physical interactions of the network being disrupted.[3,73] They also have kinetic stability and thermodynamic stability, which can be attributed to the opposing forces associated with the partial solubility of the organogelator in the solvent, and when the energy state is low the organogels after their fibrous structure has formed.[4,74] Thermo reversibility is another important property of these gels. Due to the disruption of physical interaction among the organogelator molecules, organogels lose their solid-like structure and begin to flow.

Organogelators:

Depending on the molecular weight of gelling agent, organogelators are classified as either low-molecular-weight organogelators (LMWOs) or polymeric organic gelators (POGs).

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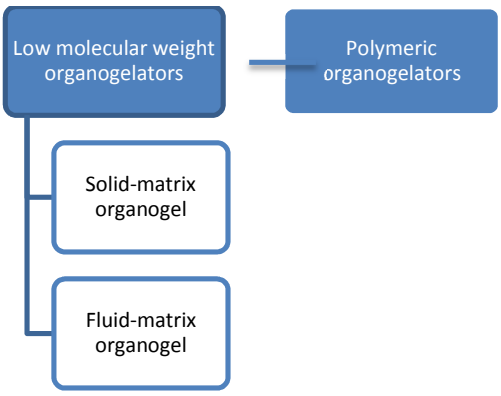

Figure 5: Types of organogelators

Low-molecular-weight organogelators

These organogelators are having molecular weight usually < 1 k Da.[7] At concentrations lower than 2%,[74] they form organogels through non-covalent bonds by self-assembling, such as van der Waals forces or hydrogen bonds; that is, physical organogels. They form aggregates due to physical interactions that interweave and cause the gelation of the solvent.[4] Due to the kinetic stability of these aggregates, they form networks by LMWOs that can be either solid (or strong) or fluid (or weak) fiber matrices.

Solid-matrix organogels

When the temperature decreases below the solubility limit of the organogelator, Solid-fiber matrices are formed which results in the fast and partial precipitation of the gelator in the organic solvent and the successive formation of aggregates by cooperative intermolecular interactions.[3,4] Depending upon this phenomenon, solid-fiber matrix organogels are formed by dissolving the organogelator in the hot solvent and then cooling down the system. When the temperature drops below this limit, the affinity between the molecules in the gelling agent and the solvent diminishes, and aggregates of organogelators formed by self-assembly and look like a fiber structure producing the organogel.[3,74] Complete phase separation of the system can be prevented by remaining solvent aggregate affinity thus acting as a stabilizing factor.

The networks of solid-matrix organogel are permanent, frequently crystalline, relatively large junction points (pseudo) crystalline microdomains. Aggregation of solid-fiber matrices occurs and it aligns to form bundles; that is higher-order structures. These characteristics make solid-fiber matrix organogels which are produced by most LMWOs that are robust and resistant to deformation.[4,7] Chirality of the organogelator molecules affects the formation and stability of the solid fibers. The thermodynamic and kinetic stability of organogels and compact packing is due to the presence of chiral centers in the molecule.

Fluid-matrix organogels

With the help of organic solutions of surfactants fluid-matrix organogel formed. Reorganization of the surfactant molecules occurs into mono or bilayer cylindrical aggregates by the addition of polar solvents, such as water, into these solutions. For obtaining fluid-matrix organogels, the organogelator, such as lecithin, is mixed in a lower concentration with the apolar solvent, which results in the self-assembly of the organogelator into reverse micelles. Uniaxial growth of the revere micelles into tubular micellar aggregates form by subsequent addition of the polar solvent. When these aggregates are long enough, they overlap to establish the 3D network and trap the apolar solvent in it.[3,74]

These organogels are composed of transient networks the junction points of which are generally simple chain entanglements. The aggregation turns in high-ordered structures which are attributed to solid fiber matrices do not occur in the case of fluid-fiber matrices. It Gives transient junctions and the fluidity to these matrices, they are also known as 'worm-like' or 'polymer-like' networks. Other functions of this type of organogel are the continuous breaking and recombination of the network chains and the dynamic exchange of organogelator molecules between the aggregates and the bulk liquid. Fluid fibers are affected by chirality unlike solid fiber because they are dynamic.[75]

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Polymeric Organic Gelators

The molecular weight of polymeric organic gelators is over 2 k Da and a structure of this range from linear to hyper-branched and star-shaped. . At a very low concentration of Polymeric organogelators can cause the gelation of organic solvents. These polymers are having lower gelation ability than that of LMWOs. However, Organogelators can be modified to tailor their gelling ability by chemical changes in the structure.[74,76]

POGs can result in physical or chemical organogels depending on whether the networks are induced by weak interchain interactions, such as hydrogen bonds or van der Waals forces, or actual chemical bonds (i.e., covalent bonds), respectively. A network of chemical organogels establishes irreversibly by covalent bonds. Stimuli, such as pH change, temperature, and presence of salts or light, can cause the formation of covalent crosslink bonds. Chemical organogels do not transform into the liquid phase when they are thinned or subjected to changes in temperature, and their matrices are robust and resistant because the polymers often assume a helical conformation.[7,73]

To obtain physical polymer organogel supramolecular crosslinking points are required. These can be achieved by conformational changes in the polymer backbone, usually resulting in a helical structure, by adding crosslinking agents or incorporating LMWOs into the polymers.[77]

Organogelators commonly used in the formulation of bigels for drug delivery: Abundant organogelators are used in the preparation of bigels for drug delivery. The most commonly reported organogelators in the literature are described below.

Sorbitan Esters

Sorbitan monopalmitate (Span®40) and sorbitan monostearate (Span®60) are two of the most frequent organic gelators reported in the formulation of bigels for drug release. These sorbitan esters are formed by the esterification of dehydrated sorbitol and fatty acids,[78] which are stearic acid in the case of Span®60 and palmitic acid in the case of Span®40.[71] Both of these esters are nonionic surfactants which stabilizes water-in-oil emulsions and are widely used as emulsifiers in pharmaceutical systems. Both of these esters such as sorbitan monostearate and sorbitan monopalmitate are classified as LMWOs and are the most important organogelators forming fluid-matrix organogels. Organogels are called fluid-matrix types which are usually based on these organogelators.

The most common preparation of these organogels reported in the literature is without the use of water, simply by dissolving the organogelator in the solvent at high temperatures until it is melted, then leaving the system to cool once it is homogeneous.

For the preparation of topical and vaginal bigel sorbitan monostearate has been widely used for the gelation of sesame oil in the formulation. Sorbitan monostearate used as a gelling agent of almond oil, jojoba oil, soybean oil, and tea tree oils, has also been developed for topical drug delivery. Antimicrobial bigels are composed of sorbitan monopalmitate sunflower oil organogels. This sorbitan ester has also been included as an organogelator of olive oil in antibiotic bigels.[68]

Monoglycerides and Fatty Acids

Other LMWOs included in the preparation of bigels are mono-glycerides, particularly the glyceryl fatty acid ester glyceryl monostearate.[7,9] Glyceryl monostearate is used as a gelator of canola oil in bigels. For cosmetic and pharmaceutical applications different bigels have been developed using olive oil as an organic solvent and glyceryl monostearate mixed with policosanol (fatty alcohols), or as a mono-glycerides mixture of fatty acids as an organogelator. Stearic acid is also used as an organogelator in the preparation of bigels. Monoglycerides and fatty acids are 18-carbon saturated acids obtained by the hydrolysis of animal fats or the hydrogenation of cottonseed or vegetable oil. For vegetable oils, fatty acids are mostly used as organogelators and are also included among LMWOs. Stearic acid is used for the gelation of soybean oil in bigels which are intended for the food industry.

Waxes

These are natural molecules that have organogelling properties and are classified as LMWOs.[7,84] Bigels for the topical administration of imiquimod or coenzyme Q10 using beeswax for the gelation of fish oil have been studied by Rehman *et al*[10,43,44] which includes beeswax as an organogelator of medium-chain triglycerides (Neobee®) to get bigels, and for the manufacturing of bigel drug delivery candelilla wax has also been used as an organogelator.[72]

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Lecithin

Among other organogelator lecithin is probably well known natural organogelator. It is called a natural surfactant and it includes the richest group of phospholipids in biological systems, mostly from soybean and egg yolk.[7,85] Lecithin forms fluid-matrix organogels that are widely studied for topical drug delivery because of their facility to improve skin permeation and their amphiphilic nature, which allows to incorporate of drugs in the organic phase and also in an aqueous phase, consequently improving permeation of both hydrophilic as well as lipophilic drugs. In 1988 Scartazzini and Luisi first described the design of organogels by the use of lecithin.[74] Jones and Kloesel during the early 1990s, formulated lecithin organogels by adding a small volume of water to a solution of lecithin in an organic solvent. The addition of an aqueous solution of Pluronic F127 in place of water to a solution of lecithin in isopropyl palmitate gives rise to the formation of Pluronic lecithin organogels (PLOs). PLoS are opaque and yellowish whereas Lecithin organogels are transparent.[3] For the manufacture of biphasic systems PLOs are used. Charyulu *et al*. prepared bigels for the topical administration of flurbiprofen containing soy lecithin, isopropyl palmitate, and Pluronic F127 to formulate the organogel.

Other organogelators

Various other organogelators can be found in the bigel literature, including stearyl alcohol,[9],12-hydroxystearic acid,[72] polyethylene,[19] and fumed silica.[55,86] Fatty alcohols and 12-hydroxystearic acid are LMWOs,[84,87] and polyethylene organogels are frequently obtained from low-molecular-weight polyethylene by the process described for solid-fiber LMWO based organogels.[74] The organogelators used in the preparation of bigels are mostly LMWOs, which may be because there is a limited number of polymer or ganogelators.

However, bigels have also been prepared that contain organogels based on Carbopol® 974P NF and polyethylene glycol (PEG)-400. The use of hydrophilic colloidal silica particles as an organogelator was reported in a recent review by Shakeel *et al.*[88]

Solvents in organogels for bigel synthesis

Solvents used for the formulation of organogels are five carbon atoms containing alkanes such as hexane, cyclohexane, and squalene (alkene). Many organic solvents have toxicity issues that hindered their progress in the clinical field, therefore we use more biocompatible and biodegradable organic solvents and organogelators to attain pharmaceutical and environmental acceptability. In newer drug delivery systems mineral oils and vegetable oils such as soybean oil and sunflower oil or even more biocompatible solvents such as triglycerides medium-chain and isopropyl myristate are used. Co-solvents used in organogel are water, ethanol, and PEG. In bigel preparation most commonly used solvents are PEG 400, ethylene glycol, and glycerol propylene glycol.[46] Vegetable oil is the main organic solvent used in the preparation of bigels. Oils like fish oil, soybean oil, almond oil, and olive oil repeatedly appear in the literature on these systems.

Fish oil

Fish oil is frequently obtained from cold water fishes such as sardine, trout herring, mackerel, or salmon.[91] Fish oil contains eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as two main omega-3 polyunsaturated fatty acids: Fish oil is having anti-inflammatory activity and the potential to enhance skin permeation makes this oil suitable for bigels preparation for transdermal drug delivery.[10,43]

Soybean oil

Glycine max seeds are the source of soybean oil. It lowers serum cholesterol levels due to the high content of polyunsaturated fatty acids thus reducing the risk of potential cardiovascular disease.[93] Soybean oil has been incorporated in bigels for the release of ciprofloxacin,[6] metronidazole,[58] diltiazem hydrochloride,[5] and paracetamol[52].

Olive oil

Olive oil is usually obtained from the fruit of the olive tree (*Olea europaea* L.).[94,95] Olive oil contains the best-known fatty that is oleic acid, which is used as an excipient in topical preparations, and can improve the percutaneous absorption of drugs. Oleocantal is another important component of this oil which has anti-inflammatory and analgesic properties. Olive oil has numerous activities such as anti-aging, anti-inflammatory, and anti-neoplastic properties and it is also used

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in cosmetic and topical pharmaceutical bigels.[8,12,65] It has been used as an organic solvent in bigels intended for gastrointestinal drug delivery.[68]

Almond oil

Sweet almonds (*Prunus dul- cis*) are used to obtain almond oil and are commonly used in cosmetics. Almond oil is used as an organic solvent and has many biomedical applications, such as the prevention of cardiovascular disease.[97,98]

Other solvents: Jojoba oil, tea tree oil, canola oil, palm oil,[67] rice bran oil,[19,20,69,99] isopropyl palmitate, liquid paraffin, caprylic/capric triglyceride (Tegosoft® CT),[48] and PEG 400,[46]have also been investigated in the formulation of bigel for drug delivery.

II. BIGEL PREPARATION

The preparation method of bigels includes the separate preparation of the hydrogel and organogel and mixing of both of these gels.[2,71] There are two processes of preparation of bigels, one in which the individual gels are independently prepared and stored before mixing, and another in which the gels are mixed and the previously formed bigel is allowed to settle. The individual gels are allowed for the settlement of the structure of individual gels for a period of 24 h at both room temperature[10] and at 4 °C,[1] and for bigels at room temperature[53] and 4 °C, although there are also references to bigels obtained by allowing the individual gels to settle at 25 °C for 24 h and the final bigels at 5 ± 2 °C.[43,44] Important process parameters, such as shear speed and temperature, should be optimized based on the gelling behavior of the system.

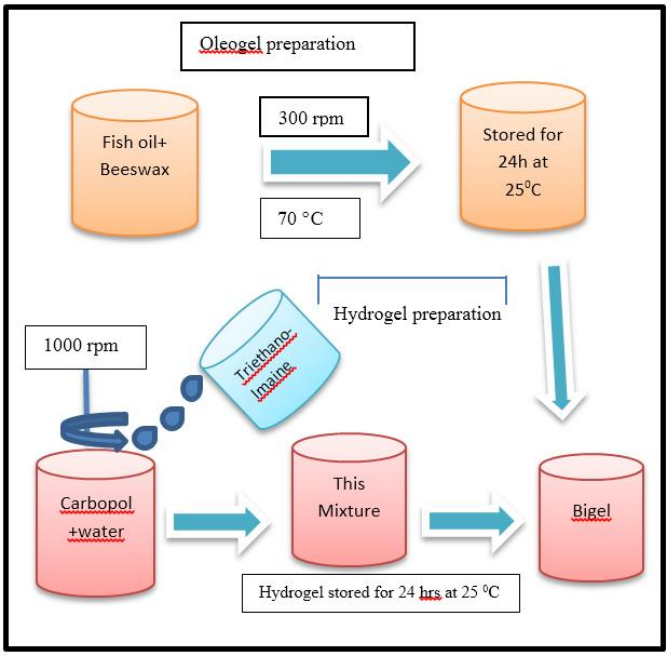

Figure 6: Bigel preparation

Different concentrations of gelling agents, mixing temperatures, and mixing speeds have been reported to obtain both organogels and hydrogels (Table 1). Organogels are usually prepared with heat contribution, after that the mixture is allowed to cool down at room temperature to get the actual formation of the organogel before it is blended with the hydrogel.[44] This cooling step is also included in hydrogel preparation which is obtained at high temperature. The novel technique to prepare organogels for their inclusion in bigels is two step process. The first step of high-speed homogenization of the organogel components and a second step includes microwave irradiation rather than conventional heating. Organogel turned transparent after micro-irradiation, as did the bigel containing it. Exposure to microwave radiation did not affect either drug's amount or the antioxidant activity contained in the organogel in the final bigels.

As expected, all the process parameters, such as those mentioned in Tables 1 and 2, can affect the final properties of the bigels. For example, the organogel/hydrogel ratio controls the release of the drug from the system; thus, a small amount

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of drug is used in case of fast release of the drug, and a large amount is associated with a more controlled release.[72] The structure and amount of polymer in the hydrogel and other variables that controls drug release profile of bigels.

Table 1: Parameters involved in the preparation of organogel and hydrogel for bigel manufacturing.

Parameter	Organogel	Hydrogel
Gelling agent concentration in gel (% w/w)	2	Up to 3
	3	3-20
	4	20
	5	25
	6	
Mixing speed (rpm)	100	100
	200	300
	300	400
Temperature (°C)	55-65	37
	60	60
	70	65
	80	70

III. BIGEL CONFIRMATION STUDIES

Various studies have focused on drug release bigels.

Preliminary Characterization

The tube inversion technique is the confirmation test for checking whether the bigel is formed or not.[2,11,41,47,71] This is the most certainly used gelation technique that involves turning a test tube or vial with a sample present in it and checking whether it flows under its weight.[101] A good bigel is formed if the sample does not flow. The stability of bigels is determined by leaching of the internal phase of the system after 1 h at room temperature using filter paper. They also quantified the oil leakage after the compression of the bigels and after soaking in water for 1 h at 37 °C.

Once the bigel is formed numerous properties such as homogeneity, smoothness, pH, and color have been evaluated.[2,11] It is commonly described as a milky white system, a feature that has been attributed to the dispersion of the light from the interface of both phases of the system. They are opaque and generally have a smooth texture.[1,19,51,58] Bigels have a pH between 5 to 7 thus assuring physiological tolerance and safe application to the skin.[1,2,5,11,47] Bigels for vaginal use are usually having pH in the range of 4.0 and 4.9, constant with the natural vaginal pH also found in the literature.[67]

Microscopical Studies

The microscopic techniques are used to study the stability of the formulations. Bigels are observed under optical microscopy, phase contrast optical microscopy is also used. It is reported that the formation of organogel-in-hydrogel bigels with interconnections among organogel particles, and a more complex matrix-in-matrix microstructure of the systems (in which each phase appears to be entrapped inside the other) when the proportion of the organogel increased. This microscopic study allowed a higher particle size to be attributed to batches containing a higher proportion of the organogel. Fluorescence microscopy is also used to study bigel formulation. This microscopy is used to confirm the formation of organogel-in-hydrogel structures and the determination of droplet size is also done and 3D digital microscopy.[53] The surface microstructure of dried and freeze-dried bigels has been studied with field emission SEM (FESEM).

Table 2: Most frequent conditions in the preparation of bigels.

Organogel/hydrogel Proportion	Mixing temperature(^{0}C)	Mixing speed(rpm)
1/99	Room Temperature	50
5/95		100
10/90	50	500

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15/85	50-55	600
20/80	800	
25/75	1000	
30/70	1200	
40/60	6000	

Fourier Transform Infrared Spectroscopy

To determine molecular interactions Fourier transform infrared spectroscopy (FTIR) is a spectroscopic technique that has been widely used. Using FTIR, Andonova *et al*. studied physical mixtures of the Carbopol® hydrogel and an almond oil organogel and concluded that no chemical interactions occurred in the bigels developed.[41] FTIR enabled us to determine the importance of hydrogen bonding in the structure of bigels.[67] Both the amount of the gel and the concentration of the polymer in the hydrogel affect the FTIR spectrum of the bigels.[44,71] The compatibility studies between the drug and the bigel have also been studied by using this spectroscopic technique.

Thermal Analysis

Mainly differential scanning calorimetry (DSC), is used to evaluate temperatures at which the water molecules of the bigel evaporate, the organogel melts, and undergoes gelation because of the melting and solidification/crystallization of the organogelator, respectively.[44,57] The drop-ball method is used to check the melting point of bigels can be determined. When the concentration of the organogel increases, because of the higher molecular order of the solid compounds which are richer in this gel this point tends to be higher. The thermal stability of the bigels is increased by increasing the proportion of the organogel. The decomposition temperature of the bigel components and the weight loss of the system by heating using differential thermogravimetry (DTG) and thermogravimetric analysis (TGA), respectively.[10] The thermal stability is higher in bigels when the organogel proportion is increased.

IV. IN-VIVO BIOAVAILABILITY STUDY

Protocol for in-vivo study should be approved by Institutional Animal Ethics Committee. Male Wister rats weighing 240-270 gms were taken and randomly divided into three test groups of nine animals each. One group was used as control which received oral drug suspension and the other two groups. One test group received prepared gel applied topically while in the other test groups plain gel of drug was applied topically. The animal in the control group was fasted overnight and administered with 7.2mg/kg of drug suspension in distilled water. The rats in test groups were anesthetized and hair from the abdominal area was removed using an electrical clipper and drug-loaded gel (an equivalent amount containing 7.2mg/kg of drug) was applied. Serial blood sampling (0.5ml) was done from the retro-orbital vein at the time intervals of 0.5,1,2,4,6,8,10,12 and 24 hours after administration.

Plasma was separated by centrifugation at 3000 rpm, 4ºC, for 15 min and 4ml methanol was added to 200 µl plasma samples for deprotienation and extraction of the drug. The mixture was then vortexed for 2 min, followed by centrifugation for 5 min at 3,200 rpm. The organic layer was separated and filtered using a 0.2- µm membrane syringe filter. About 20 µl of the filtrate was injected into the HPLC for estimation of drug concentration.

V. STABILITY STUDIES

Usually, biphasic systems tend to undergo destabilization bigels and are subjected to stability studies. Some of the conditions applied in these studies are detailed below.

Three-month stability studies performed at 25 °C ± 2 °C/ 65 ± 5% RH and 40 °C ± 2 °C/ 75 ± 5% RH confirmes the stability of the bigels.[67] The second condition for bigel is an accelerated stability test which is based on the freeze–thaw method and a long-term stability study at 30 °C ± 2 °C/ 65 ± 5% RH for 3 months without any significant variations in organoleptic characteristics, drug content or pH.[47] Bigels were also tested by the accelerated stability through the freeze–thaw thermocycling method, and evaluated visual and organoleptic changes and the stability of drug-loaded bigels by drug release and antimicrobial efficiency tests. The condition for intermediate stability study is (ICH) (30 ± 2 °C/65 ± 5% RH for 6 months), looking for physical changes, such as phase separation in the bigels, and again for drug instability

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through drug release and antimicrobial studies The systems containing a higher amount of the organogel were considered more stable, which was attributed to the structure of the organogelator, and the drug and antimicrobial efficacy remained stable in all cases. Another condition for checking the stability of bigels was also tested at 5 °C for 6 months with fish oil-based, which showed no significant alteration in color or pH, although a slight loss of fatty acid occur in oil; and no phase separation or microbial growth was observed in case of bigels kept at room temperature for 12 months.

Other Tests

In the literature other tests are also reported on bigels which are as follows: ^{1}H self-diffusion electrical property studies,[8,12,58,60] NMR,[12] X-ray diffraction and swelling of fresh[58,68] and freeze-dried bigels.[50,62] *In vitro*[5,10,43] and *ex vivo* skin permeation,[42,44,45,47] *in vitro* cytocompatibility,[6,44,67,71] *in vitro* drug release,[2,11,45,47,60,71] skin drug content analysis and *ex vivo* retention studies,[43,47] *in vitro* pharmacological activity.

VI. FUTURE PERSPECTIVES

Bigel is quite a new concept, research in this novel system are largely conducted over the past few years. The component of bigels (hydrogels and organogels) are studied well and certain combinations such as emulsions, and dosage forms themselves enables the formulation and characterization of bigels. Research in other areas such as cosmetics and food technology served as useful tools for the formulation of bigel drug delivery systems. Although many bigels have been prepared for the transdermal delivery system. Although other characteristics of bigels such as their microstructure and mechanical properties are deeply evaluated, still there is a long way to go. Use of a drug in aqueous as well as oil phase in the same formulation in bigel preparation for drug delivery becomes preferable. The concept of bigel is the major advancement in the management of diseases which is sexually contraception with the same drug delivery system.

VII. CONCLUSION

In recent years, various bigel systems have been produced particularly in drug delivery. Most of these bigel systems are used as a carrier for controlled drug delivery of active ingredients for topical application. Bigels have good spreadability and no pieces of evidence of phase separation as we see in the case of emulsion. Bigel is also having high stability and its preparation is very easy. We can use hydrophilic as well as a lipophilic drugs in the bigel formulation.

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