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Bigels as drug delivery systems: From their components to their applications

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Bigels are systems that usually result from mixing a hydrogel and an organogel: the aqueous phase is commonly formed by a hydrophilic biopolymer, whereas the organic phase comprises a gelled vegetable oil because of the presence of an organogelator. The proportion of the corresponding gelling agent in each phase, the organogel/hydrogel ratio, and the mixing temperature and speed all need to be taken into consideration for bigel manufacturing. Bigels, which are particularly useful drug delivery systems, have already been formulated for transdermal, buccal, and vaginal routes. Mechanical assessments and microscopy are the most reported characterization techniques. As we review here, their composition and unique structure confer promising drug delivery attributes, such as mucoadhesion, the ability to control drug release, and the possibility of including both hydrophilic and lipophilic drugs in the same system.

Keywords: Hydrogel; Organogel; Organogelator; Bigel manufacturing; Bigel characterization; Drug delivery bigels

Introduction

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

Hydrogels have several advantages as pharmaceutical forms for topical use, such as their ease of preparation, 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 this translates into high acceptance by patients. 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 prepare and their lipophilic nature means that they are capable of dissolving hydrophobic drugs and increasing their permeability through the stratum corneum. The main drawback of organogels is their oily nature, which hinders their removal from the skin after application because of their stickiness and oily residues, leading to lower patient compliance.[5,8–11]

Emulgels or emulsion gels were developed to overcome the drawbacks of hydrogels in terms of the release of hydrophobic drugs. They are biphasic systems, usually comprising a hydrophilic phase and a 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 either emulsion hydrogels or emulsion organogels.[9,12]

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Golodnizky *et al.*[13] differentiate between 'gel-filled emulsions' and 'bulk gel emulsions' depending on whether the dispersed or continuous phase, respectively is gelled in the system. Lupi *et al.* state that, when only the dispersed phase is gelled, the system has a suspension-like behavior.[12] In any case, emulgels have low structural stability owing 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]

Different systems have been included under the term 'bigel' according to Shakeel *et al.*[9]: a combination of two gel strips of different polarity, a mixture of a hydrogel and an organogel, a mixture of two interpenetrated colloidal gels, and bicontinuous type gels showing phase-separated characteristics.[9] Bigels have been widely investigated over the past decade, especially for drug delivery.[9] Some of the first references to bigels (strips) in the literature date back to the 1990 s, when Hu *et al.*[15] described materials with a heterogeneous or modulated internal structure obtained by limiting the interpenetration of two gel networks. In 1999, Rhee *et al.*[16] formulated an oleo-hydrogel system that enhanced the skin permeability of ketoprofen over conventional products. In 2008, Almeida *et al.*[17] reported bigels obtained by mixing a hydrogel and different organogels with results that earmarked them as promising potential systems for topical use.[17] In 2012, Varrato *et al.* proposed that bigels could be obtained by a mechanism of aggregation through arrested demixing of binary colloidal gel mixtures, which involved manipulating interspecies interactions and resulted in the formation of a bicontinuous structure of two interpenetrating colloidal gels.[18]

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

As with emulgels, bigels have the advantages of both emulsions and gels (hydrogels and organogels in this case) and, therefore, constitute interesting candidates for topical and transdermal controlled drug delivery.[12] By combining the advantages of both hydrogels and organogels, bigels can also overcome the main drawbacks of each component.[6,8,10] Thus, these biphasic systems have better properties than either of the two gels separately.[9] Among the main benefits of bigels are their ability to carry both lipophilic and hydrophilic drugs in the same system, and the possibility of controlled drug delivery and enhanced patient compliance because of the combined properties of these systems, such as their non-oily nature.[11,19] Unlike emulsions and emulgels, bigels do not need surfactants; thus, although this could be translated into a phase separation under certain circumstances, bigels have enhanced stability compared with other formulations, such as creams and lotions. The gelation of both the aqueous and the oily phases makes it difficult for the droplets to escape the 3D network of the gel and, thus, they do not aggregate or flocculate.[1,12] Bigels also have better physicochemical stability compared with emulsions because of the formation of an extra-fine dispersion resulting from the entrapment of the mobile phases in the 3D network of the gels. Therefore, the structuring of both phases in bigels means they do not undergo phase separation when stored at room temperature for up to 6–12 months.[1,2,8] Other characteristics of bigels are their non-thermoreversibility because of destabilization at high temperatures and electrical conductivity, which has been associated with embedded water pockets caused by the presence of the hydrogel.[1,8] This conductivity could be explained by considering the bicontinuous nature of bigels and the possible presence of a percolation network in the conductive phase.

Recently, Shakeel *et al.* formulated bigels containing silica nanoparticles, thus combining both interfacial and bulk stabilization of oil–water emulsions in the same system.[20] This synergistic stabilization was achieved by the adsorption of the nanoparticles at the oil–water interface and the incorporation of polymeric gelators in both phases. Thus, these novel formulations are both bigel systems and pickering emulsion/bicontinuous jammed emulsion systems.[20] In pickering emulsions, the particles cover unconnected droplets from one of the phases dispersed within the other continuous phase, whereas, in bicontinuous jammed emulsions, the particles coat the interface of the two interpenetrating continuous fluid phases (Fig. 1). These bicontinuous particle-stabilized emulsions are called 'bijels' and can be obtained from immiscible or partially miscible liquids that undergo phase separation, resulting in a bicontinuous arrangement of the fluids. The phase separation leads the particles to accumulate on the interface until they are fully jammed.[21,22]

With this background, this review offers a comprehensive description of bigels from their components to their manufacturing and characterization methods, with a special focus on their uses as drug delivery systems.

Hydrogels

The most popular definition of a hydrogel is a 3D network made of hydrophilic polymers that is able to take up large amounts of water or biological fluids.[23] This water absorption results from these systems being physicochemically compatible with water, that their polymeric chains can contain hydrophilic functional groups, such as amino or carboxylic groups, among others; and also from the possibility of modulating their porosity and crosslinking density.[3,24,25] Although the crosslinking supports and integrates the network of hydrogels and makes them resistant to dissolution, they can disintegrate and even dissolve. The high proportion of water they contain, coupled with their porosity, flexibility, and soft and rubbery consistency, means that they closely resemble natural tissues, which, together with their biocompatibility, explains why hydrogels are some of the most widely investigated materials for biomedical and pharmaceutical purposes. Hydrogels have several applications, such as in contact lenses, hygiene products, cell culture supports, drug delivery systems, wound dressings, and tissue engineering.[5,23,26]

Hydrogel-forming polymers

Hydrogels can be prepared from natural and/or synthetic polymers.[27] Two main classes of natural polymer are used to obtain hydrogels: polysaccharides, such as starch, alginate, and agarose; and proteins, such as collagen and gelatin. Hydrogels based on

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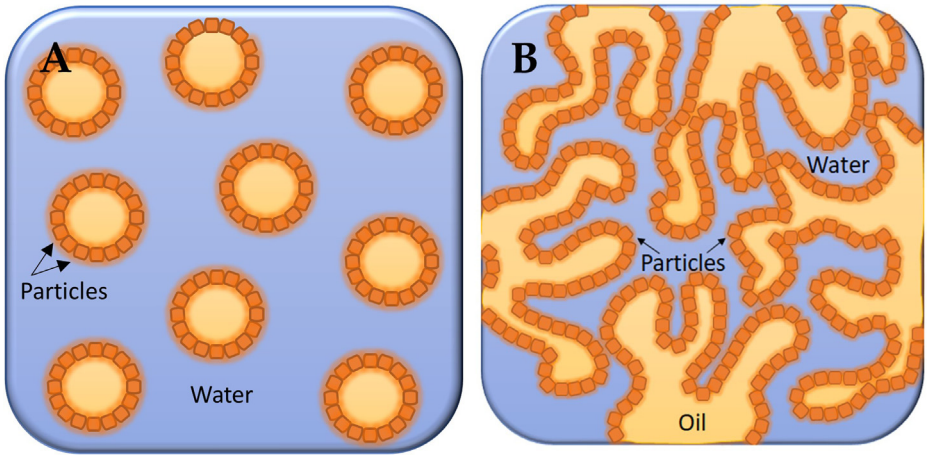

FIGURE 1
Schematics of **(a)** pickering emulsion and **(b)** bicontinuous jammed emulsion (bijel) systems.

natural polymers are usually biodegradable and nontoxic. However, the natural polymers in these hydrogels can be modified through synthetic monomers, via graft copolymerization, extending their use for the preparation of superabsorbent hydrogels, for instance. However, the biodegradability of the resulting hydrogels can be compromised in this case.

The formulation of hydrogels comprising synthetic polymers usually involves chemical polymerization reactions.[28] Three polymerization techniques for obtaining hydrogels are: bulk, solution, and suspension polymerization.[29] In each case, these polymerization reactions usually include monomers, a crosslinking agent, and an initiator. One of the main drawbacks of these polymerizations is the need for a purification step, involving washing the reaction product with distilled water to remove residues of the reagents, and especially unreacted monomers, which are often toxic and can later be leached from the hydrogel.[23,28,30]

One possible solution for avoiding the purification process is to use nontoxic monomers, increasing the conversion of the monomers through a 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] These polymers can be crosslinked to form hydrogels in different ways: by chemical reaction between the polymer chains; by ionizing radiation, which causes the formation of free radicals in the main chain that can form 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.[23] Hydrogels can also be synthesized from hydrophobic polymers that have been converted into hydrophilic polymers through reactions such as oxidation or hydrolysis, which give rise to polar groups.[31]

Based on the above, both chemical and physical hydrogels can be obtained by polymer crosslinking. Both types of hydrogel differ in the nature of the crosslink junctions that stabilize the network. In physical or reversible hydrogels, chain entanglements and/or secondary forces, such as hydrophobic, ionic, or hydrogen bonds, are established between polymer molecules, thus forming a network with transient junctions (Fig. 2a). However, the junction points in the networks of chemical or permanent hydrogels are often covalent bonds, that is, permanent junctions[32] (Fig. 2b).

Some of the polymers used in the formulation of hydrogels can interact with biological systems, including mucoadhesive polymers and stimuli-sensitive polymers.[24] Mucoadhesive polymers are natural or synthetic polymers able to adhere to a mucosa, especially to the mucus layer that covers the epithelial surface of the mucosae and the main molecules composing this layer.[33] Mucoadhesion is a complex process with a first stage of contact between the mucoadhesive polymer and the mucous membrane in which the polymer undergoes wetting, swelling, and spreading; and a second consolidation step in which physicochemical interactions (hydrophobic, hydrogen bonds, Van der Waals forces, ionic, or covalent bonds) are established between functional groups of the polymer and the mucus layer.[34–36] Mucoadhesive drug delivery systems increase the residence time at the site of administration, which can result in enhanced drug absorption and allows controlled release that could translate into easier posology and better compliance from patients.[37]

'Smart' or 'stimuli-sensitive' polymers undergo changes in their physicochemical properties and/or 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 different types of stimuli-sensitive hydrogel exist, pH-responsive hydrogels have been widely studied for targeted and controlled drug release. The networks of these hydro-

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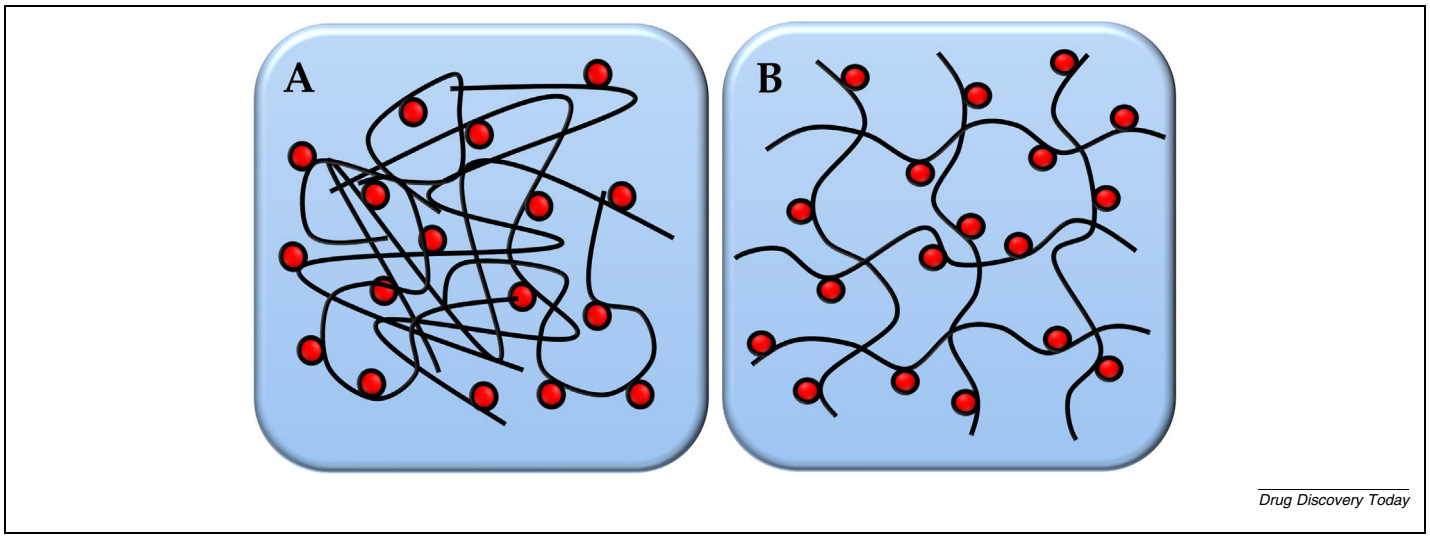

FIGURE 2

Schematics of a **(a)** physical hydrogel and **(b)** chemical hydrogel. Red beads represent hydrophilic functional groups in the polymer chains.

gels comprise pH-responsive polymers, which contain ionizable functional groups with an acidic or basic character joined to the backbone chain, meaning that these polymers are able to exchange hydrogen ions with the medium in response to variations in pH, which produces the swelling/deswelling of the hydrogel and can affect the drug release profiles.[39]

Polymers in the formulation of hydrogels for bigels

Different hydrophilic polymers have been used in the synthesis of hydrogels for the formulation of drug delivery bigels. The most frequently reported in the literature can be classified into synthetic polymers (Carbopol®), semisynthetic (hydroxypropyl methylcellulose; HPMC) and natural (alginate, gelatin, guar gum, and pectin).

Carbopol®

Carbopol®-based hydrogels are one of the most common hydrogels for obtaining bigels for drug delivery. Carbomers (or Carbopol® polymers) are synthetic high-molecular-weight acrylic polymers crosslinked with allyl sucrose or allyl pentaerythritol. They are pH sensitive and also have bioadhesive characteristics because of their ability to establish hydrogen bonds with mucin.[2,40] There are different carbomers, among which Carbopol® 940 is one of the mostly commonly used in bigels; this polymer usually requires the addition of triethanolamine as a neutralizing agent for the complete formation of the gel. These polymers have been mainly included in bigels for topical,[11,41–47] but also for vaginal[2] and buccal[48] administration.

Hydroxypropyl methylcellulose

HPMC is a non-ionic cellulose derivative the backbone of which contains methoxyl and hydroxypropoxyl groups. There are different grades of this polymer based on the degree of substitution and molecular weight, which are the parameters that condition its gelling ability.[49] This mucoadhesive polymer has been included as a hydrogel-forming polymer in bigels for vaginal administration of tenofovir[50] and for topical delivery of imiquimod,[10] diltiazem hydrochloride,[5] flurbiprofen,[51] and paracetamol.[52]

Alginate

Alginate (usually sodium alginate) is an anionic polymer obtained from brown seaweed and from bacteria from the genera *Pseudomonas* and *Azobacter*. In the presence of divalent cations, such as Ca^{2+}, this polymer forms gels with pH-dependent swelling.[25] Alginate also has mucoadhesive properties.[37] Sodium alginate hydrogel-based bigels were prepared by Martins *et al.*[14] Alginate hydrogels have also been included in the formulation of bigels for the topical delivery of immune response modifiers,[10] and antioxidant[53] and antifungal[54] drugs and for oral administration of metronidazole in the treatment of periodontal diseases.[55]

Gelatin

Gelatin is a natural proteic polymer resulting from the partial hydrolysis of animal collagen, and has mucoadhesive properties.[37,56] Bigels comprising gelatin-based hydrogels have been broadly studied using the antimicrobial drug ciprofloxacin as a model active ingredient.[6,57] Wakhet *et al.*[58] developed bigels with a gelatin-agar mixture hydrogel including metronidazole as the drug,[58] whereas Golodnizky *et al.* reported on the preparation of gelatin hydrogel-based bigels, with very promising findings for drug delivery purposes, despite being originally intended for the food industry.[13]

Guar gum

Guar gum is a mucoadhesive polysaccharide extracted from the seeds of the legume *Cyamopsis tetragonoloba*.[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.

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Pectin

Pectin is a heterogeneous polysaccharide present in the cell wall of higher plants. The carboxylic groups in pectin make this polymer mucoadhesive and pH responsive. Some of these functional groups are naturally esterified, and pectins can be classified according to their degree of esterification.[63,64] Bigels comprising pectin-based hydrogels have been formulated using both low [8,65] and high methoxyl pectins.[50]

Other hydrogelators

Other polymers, such as gum acacia,[66] chitosan,[50] hyaluronic acid,[67] sodium carboxymethylcellulose,[20,61] sterculia gum,[68] tamarind gum,[69] whey protein concentrate,[70] acrylamide,[68] Poloxamer 407,[19] PVA, PVP,[71] and sodium polyacrylate,[72] are also mentioned as hydrogelators in the bigel literature.

Organogels

According to Vintiloiu and Leroux,[4] 'organogels are semi-solid systems, in which an organic liquid phase is immobilized by a three-dimensional network composed of self-assembled, intertwined gelator fibres'.[4] These biphasic systems can be opaque or transparent and have viscoelastic properties. At low shear rates, they behave like solids and have elastic properties, but become fluid when the shear stress is so high that the physical interactions of the network are disrupted.[3,73] They also have thermodynamic and kinetic stability, which can be attributed to the opposing forces associated with the partial solubility of the organogelator in the solvent and to the low state of energy of the organogels after their fibrous structure has formed.[4,74] Another important property of these gels is their thermoreversibility. When their temperature increases above the sol-to-gel transition temperature (T_{gel}), organogels lose their solid-like structure and begin to flow because of the disruption of the physical interactions among the organogelator molecules. However, these physical interactions revert to a more stable configuration on cooling.[7,73]

Organogelators

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

Low-molecular-weight organogelators

LMWOs are organogelators with a molecular weight usually < 1 kDa.[7] Even at concentrations lower than 2%,[74] they form organogels by self-assembly through noncovalent bonds, such as hydrogen bonds or van der Waals forces; that is, physical organogels.[3] These physical interactions lead to the formation of aggregates that interweave and cause the gelation of the solvent.[4] Based on the kinetic stability of these aggregates, networks established by LMWOs can be either solid (or strong) or fluid (or weak) fiber matrices.

Solid-matrix organogels

Solid-fiber matrices are formed by temperature decreases below the limit of solubility of the organogelator, resulting in the fast and partial precipitation of the gelator in the organic solvent and the subsequent formation of aggregates through cooperative intermolecular interactions.[3,4] Based on this, solid-fiber matrix organogels are obtained by dissolving the organogelator in the heated solvent and then cooling the resulting system. When the temperature drops below this limit, the affinity between the molecules in the gelling agent and the solvent diminishes, allowing the organogelator to form aggregates as fiber-like structures by self-assembly, producing the organogel.[3,74] The remaining solvent–aggregate affinity prevents the complete phase separation of the system, thus acting as a stabilizing factor.

The networks of this type of organogel are permanent, most often crystalline, and their junction points are relatively large (pseudo)crystalline microdomains (Fig. 3a). Given their rigidity, the solid-fiber matrices undergo aggregation and alignment to form bundles; that is, higher-order structures.[3,4] These characteristics make solid-fiber matrix organogels, which are produced by most LMWOs, that are robust and resistant to deformation.[4,7] Furthermore, the usual chirality of the organogelator molecules affects the formation and stability of the solid fibers.[3,4] The presence of chiral centers in the molecules facilitates the formation of compact packing, thus conferring thermodynamic and kinetic stability on the organogels.[73]

Fluid-matrix organogels

Fluid-matrix organogels are formed from the organic solutions of surfactants. The addition of polar solvents, such as water, into these solutions causes the reorganization of the surfactant molecules into mono- or bilayer cylindrical aggregates that immobilize the solvent.[4,7] To obtain fluid-matrix organogels, the organogelator, such as lecithin, is mixed in a minimum concentration with the apolar solvent, which results in the self-assembly of the organogelator into reverse micelles. The subsequent addition of the polar solvent causes the uniaxial growth of the reverse micelles into tubular micellar aggregates. When these aggregates are long enough, they overlap to establish the 3D network and trap the apolar solvent in it[3,74] (Fig. 3b).

These organogels comprise transient networks the junction points of which are usually simple chain entanglements. The aggregation into high-ordered structures attributed to solid-fiber matrices does not occur in the case of fluid-fiber matrices. Given these transient junctions and the fluidity of these matrices, they are also known as 'worm-like' or 'polymer-like' networks.[3,4] Other distinctive features 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. Unlike solid fibers, fluid fibers are rarely influenced by chirality because they are dynamic.[75]

Polymeric organic gelators

POGs are compounds with a molecular weight over 2 kDa and a structure that can range from linear to hyperbranched and star-shaped.[4,7] Polymeric organogelators can cause the gelation of organic solvents even at very low concentrations, although their gelation ability is lower than that of LMWOs, which are more common. However, the chemical structure of the backbone of these organogelators can be modified to tailor their gelling ability.[76,77]

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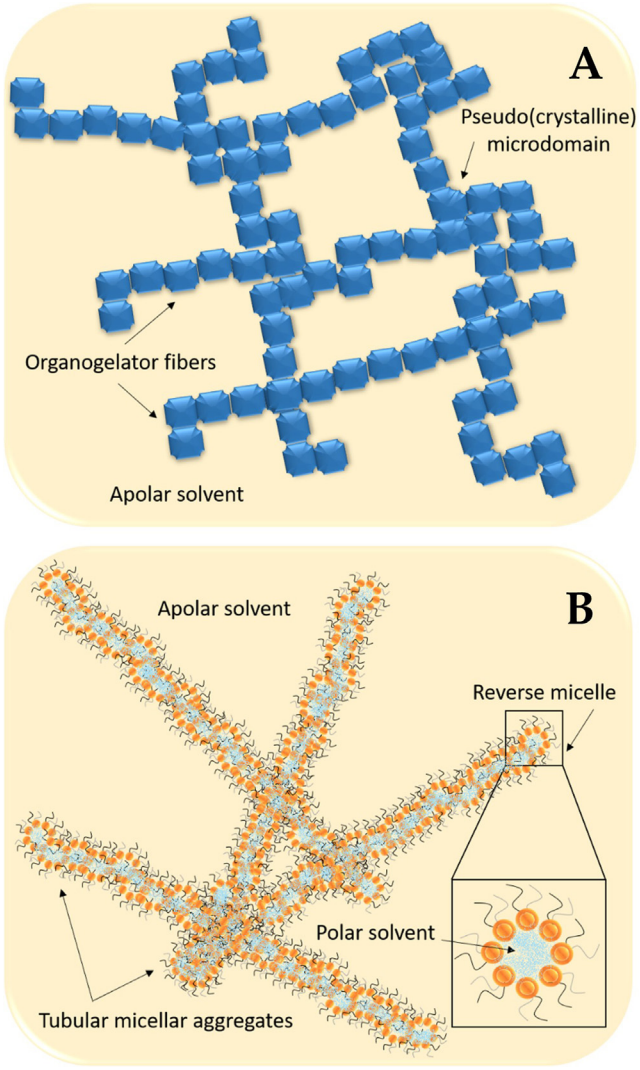

FIGURE 3
Schematics of **(a)** solid-matrix and **(b)** fluid-matrix organogels.

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. These covalent bonds irreversibly establish the network of chemical organogels. Stimuli, such as temperature, pH change, and the presence of salts or light, can trigger the formation of covalent crosslink bonds. Chemical organogels do not usually transform into the liquid phase when they are diluted or subjected to a temperature change, and their matrices are robust and resistant because the polymers often assume a helical conformation.[7,73] Supramolecular crosslinking points are required to obtain physical polymer organogels. 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. In this case, LMWOs act as gelation-causing segments and allow the self-assembly and the formation of the supramolecular polymer.[77] Thus, the gelator in polymer-based organogels can be a supramolecular crosslinkable polymer, a polymer-crosslinking agent organogelator, or a LMWO-incorporated polymeric organogelator. These conformational changes lead to the aggregation of the organogelator molecules and the formation of the 3D network that immobilizes the solvent.[7,73]

Unlike organogels formed by LMWOs, organogels based on POGs usually have lower T_{gel} and higher gel strength, which produces more rigid and stable organogels.[7,74]

Organogelators commonly used in the formulation of bigels for drug delivery

Numerous organogelators are applied in the formulation of bigels for drug delivery. The most frequently reported in the literature are described below.

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Sorbitan esters

Sorbitan monostearate (Span®60) and sorbitan monopalmitate (Span®40) are two of the most common organic gelators reported in the development of bigels for drug release.[9] These sorbitan esters are produced 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 are non-ionic surfactants that stabilize water-in-oil emulsions and are widely used as emulsifiers in pharmaceutical systems. However, their ability to immobilize organic solvents, vegetable oils among them, has also been described.[1,71,78] Sorbitan monostearate and sorbitan monopalmitate are classified as LMWOs and are two of the most important organogelators forming fluid-matrix organogels.[4,7] Although organogels based on these organogelators are usually described as fluid-matrix type, Murdan *et al.*[79] were the first to describe the organogelator properties of Span®60 and Span®40 and that they are able to form organogels either with or without the addition of water before cooling the heated organic dissolution of the organogelator, as reported by Vintiloiu and Leroux [4]. In fact, the most frequent preparation of these organogels reported in the literature is in the absence 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. Sorbitan monostearate has been widely used for the gelation of sesame oil in the formulation of bigels for topical and vaginal administration.[1,2,50,62] Bigels containing an organogel based on sorbitan monostearate as a gelling agent of soybean oil,[5,52] almond oil,[11,41] and jojoba and tea tree oils[47] have also been developed for topical drug delivery. The development of antimicrobial bigels comprising sorbitan monopalmitate-sunflower oil organogels has been widely studied by Behera *et al.*[71,80,81] This sorbitan ester has also been included as an organogelator of olive oil in antibiotic bigels.[68] Although it is less common, Span®80 has also been used in bigels for pharmaceutical use.[82]

Monoglycerides and fatty acids

Other LMWOs included in the composition of bigels are monoglycerides,[20] especially the glyceryl fatty acid ester glyceryl monostearate.[7,9] Bigels containing glyceryl monostearate as a gelator of canola oil were formulated by Golodnizky *et al.*[13] Different bigels have been developed by Lupi *et al.*[8,12,65] for cosmetic and pharmaceutical applications using olive oil as an organic solvent and glyceryl monostearate mixed with policosanol (fatty alcohols), or as a mixture of monoglycerides of fatty acids as an organogelator. Stearic acid is another organogelator commonly used in the formulation of bigels. It is an 18-carbon saturated acid obtained through the hydrolysis of animal fats or the hydrogenation of cottonseed or vegetable oil.[83] Fatty acids have been extensively used as organogelators of vegetable oils[6] and are also included among LMWOs.[7] Antimicrobial bigels containing stearic acid as an organogelator and sesame oil,[6] soybean oil,[6,58] and rice bran oil[69] as solvents have been manufactured. Bollom *et al.*[70] also used stearic acid for the gelation of soybean oil in bigels intended for the food industry.

Waxes

Waxes 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] Martins *et al.* [14] included beeswax as an organogelator of medium-chain triglycerides (Neobee®) to obtain bigels, and candelilla wax has also been used as an organogelator for the manufacture of drug delivery bigels.[72]

Lecithin

Lecithin is probably the best known natural organogelator. It is called 'the natural surfactant' and encompasses 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 ability to enhance skin permeation and their amphiphilic nature, which allows the incorporation of drugs in the aqueous and organic phase, thus enhancing the permeation of both hydrophilic and lipophilic drugs.[3,4] Scartazzini and Luisi first described the use of lecithin for the design of organogels in 1988.[74] During the early 1990 s, Jones and Kloesel formulated lecithin organogels by adding a small amount of water to a solution of lecithin in an organic solvent. Pluronic lecithin organogels (PLOs) emerged later through the addition of an aqueous solution of Pluronic F127 in place of water to a solution of lecithin in isopropyl palmitate.[7] Lecithin organogels are transparent, whereas PLOs are opaque and yellowish.[3] Bigels with soy lecithin as an organogelator have been studied by Bollom *et al.*[70] PLOs have also been used to manufacture these biphasic systems. Charyulu *et al.* prepared bigels for the topical administration of flurbiprofen containing soy lecithin, isopropyl palmitate, and Pluronic F127 to formulate the organogel.[51]

Other organogelators

Many other organogelators can be found in the bigel literature, including cetyl alcohol and 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 usually obtained from low-molecular-weight polyethylene through the method described for solid-fiber LMWO-based organogels.[74] The organogelators used in the formulation of bigels are mostly LMWOs, which might be because there is a limited number of polymer organogelators, as indicated by Suzuki and Hanabusa.[77] However, bigels have also been developed containing organogels based on Carbopol® 974P NF and polyethylene glycol (PEG)-400.[46] The use of hydrophilic colloidal silica particles as an organogelator was reported in a recent review by Shakeel *et al.*,[88] among different strategies to obtain unconventional bigels, which are explored below.

Solvents in organogels for bigel synthesis

Alkanes with more than five carbons, such as hexane, cyclohexane, and alkene squalene, were the most common of the first organic solvents intended for the formulation of organogels. The toxicity of most of the organic solvents that tend to be included in drug delivery organogel formulations hindered their progress in the clinical field, leading to the use of more biocom-

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patible and biodegradable organic solvents and organogelators to achieve pharmaceutical and environmental acceptability. Mineral and vegetable oils, such as sunflower oil and soybean oil, or even more biocompatible solvents, such as medium-chain triglycerides and isopropyl myristate, are now more frequent in newer drug delivery systems. Polar solvents, such as water, ethanol, or PEG, can also be included in organogels as cosolvents.[7] 'Ethylene glycol, propylene glycol, glycerol and PEG 400 are the most common solvents used in the preparation of organogels' according to Yapar *et al.*[46] Nevertheless, the main organic solvents found in the formulation of bigels are vegetable oils. Sunflower oil, sesame oil, fish oil, soybean oil, olive oil, and almond oil appear most frequently in the literature of these systems,[9] among which sesame oil, fish oil, and olive oil are the most common, according to Andonova *et al.*[11]

Sunflower oil

Sunflower oil, derived from sunflowers (*Helianthus annuus* L.)[89] has benefits when administered orally and topically and has been widely used for the formulation of antimicrobial drug delivery bigels by Behera *et al.*,[66,71,80,81] and in antioxidant bigels by Miliani-Martínez *et al.*[72]

Sesame oil

Sesame oil is a high-quality vegetable oil obtained from the seeds of *Sesamum indicum* L.[90] It is recognized as having antioxidant, anti-inflammatory, antiviral, antibacterial, and antifungal properties, and, thus, is widely used in pharmaceutical systems.[1] Bigels containing sesame oil as the organic solvent have been formulated for topical[1,2] and vaginal administration of drugs.[50,62]

Fish oil

Fish oil is usually obtained from cold-water fish, such as herring, mackerel, sardine, trout, or salmon.[91] Fish oil contains two main omega-3 polyunsaturated fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[92] Its anti-inflammatory effect and potential to improve skin permeation make this oil suitable for inclusion in bigels for transdermal drug delivery.[10,43]

Soybean oil

Soybean oil derives from the seeds of *Glycine* max. The high polyunsaturated fatty acid content lowers serum cholesterol levels, 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]. Bigels containing soybean oil as a solvent were also manufactured by Bollom *et al.*[70]

Olive oil

Olive oil originates from the fruit of the olive tree (*Olea europaea* L.).[94,95] The best known fatty acid in olive oil is oleic acid, which is used as an excipient in topical formulations, in which it can enhance the percutaneous absorption of drugs. Another important component of this oil is oleocantal, which has analgesic and anti-inflammatory activity.[96] Olive oil exhibits antiaging, anti-inflammatory, and anti-neoplastic properties and has been widely studied for use in cosmetic and topical pharmaceutical bigels.[8,12,65] It has also been used as an organic solvent in bigels intended for gastrointestinal drug delivery.[68]

Almond oil

Almond oil is mostly obtained from sweet almonds (*Prunus dulcis*) and is commonly used in cosmetics. This organic solvent has been studied for its biomedical application, such as the prevention of cardiovascular disease.[97,98] Bigels containing almond oil as an organic solvent were formulated by Andonova *et al.*[11,41]

Other solvents

Other organic solvents that have also been investigated in the formulation of bigels for drug delivery are canola oil,[13] jojoba oil and tea tree oil,[47] linseed oil,[55] palm oil,[67] rice bran oil,[69,99] liquid paraffin,[19,20],isopropyl palmitate,[9] caprylic/capric triglyceride (Tegosoft® CT),[48] and PEG 400.[46]

Bigel manufacture

The manufacture of bigels includes the separate preparation of the hydrogel and the organogel and their subsequent mixing (Fig. 4). This second step can be done by incorporating the organogel into the hydrogel[2] or vice versa.[71] Overall, two variants of this process can be distinguished: 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.[9] The settlement of the structure for individual gels has been described in the literature for 24 h at both room temperature[10] and at 4 °C,[1] and for bigels at room temperature[53] and at 4 °C,[8] 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]

The preparation of the individual gels has been described in both cases as an easy process.[5] The gelling agent and the rest of the components of each gel, such as preservatives for the hydrogel and antioxidants for the oleogel,[55,65] are dissolved, dispersed, or mixed with the solvent. Different concentrations of gelling agents, mixing temperatures, and mixing speeds have been reported to obtain both organogels and hydrogels (Table 1). Given that organogels are commonly prepared with heat contribution, the mixture of their components is usually allowed to cool to room temperature to achieve the actual formation of the organogel before it is blended with the hydrogel.[44] This cooling step is sometimes also performed in hydrogels that have been obtained at high temperature.[60] Recently, Yapar *et al.*[46] proposed a novel technique to prepare organogels for their inclusion in bigels. This methodology comprised a first step of high-speed homogenization of the organogel components and a second step of microwave rather than conventional heating. After microirradiation, the organogel turned transparent, as did the bigel containing it. The authors demonstrated that microwave exposure did not affect either the amount or the antioxidant activity of the drug contained in the organogel in the final bigels. According to these results, this could represent a new method to obtain organogels for drug delivery bigels and offers the advantages of lower preparation time and energy consumption, as reported by the authors. Singh and Kumar used gamma radiation-induced crosslinking to obtain both the hydrogel and the final bigels for the formulation of these drug delivery systems.[68]

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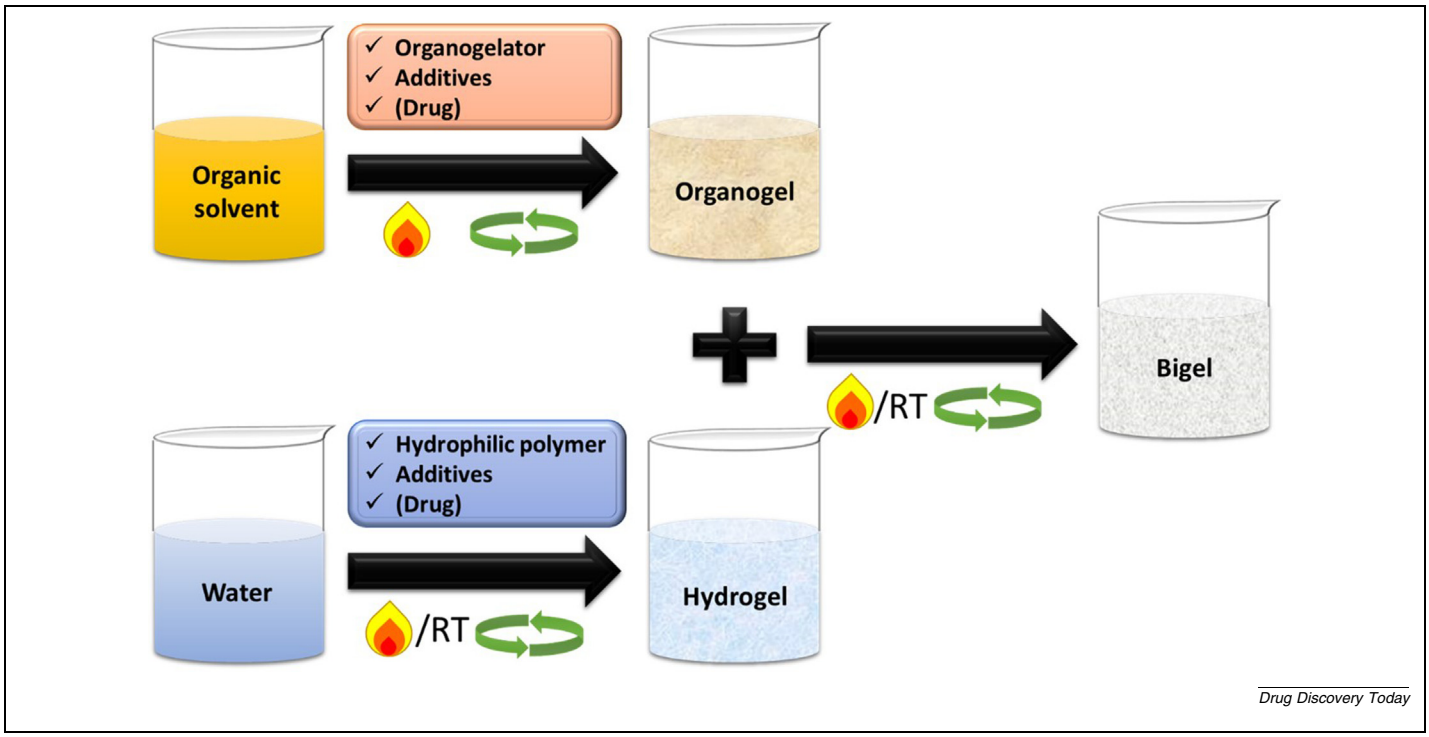

FIGURE 4

Schematic of bigel preparation. The formation of the organogel usually requires heating, whereas the hydrogel and bigel can be prepared both with heating and at room temperature (RT).

For drug-loaded bigels, the active ingredient can be included in the organogel and/or in the hydrogel. For instance, bigels from ciprofloxacin-loaded organogels were formulated by Singh *et al*.,[1] tenofovir-based bigels with the drug incorporated in the hydrogel were developed by Martín-Illana *et al*.,[50] and a bigel from a coenzyme Q10-hydrogel and a coenzyme Q10-organogel was prepared by Zulfakar *et al*.[43]

The process of mixing the prepared organogel and hydrogel (i.e., the synthesis of the bigel) is also conditioned by variables such as the proportion of each gel, the mixing temperature, and the mixing speed.[9] The most commonly used conditions for the preparation of the bigels are shown in Table 2. Although bigels are most frequently prepared with a greater proportion of hydrogel, there are also cases that use a greater amount of organogel than hydrogel, such as those prepared by Bollom *et al*..[70] Golodnizky *et al*. differentiate between bigels obtained by mixing both gels at room temperature and bigels resulting from mixing both phases in liquid state.[13] They highlight the presence of an emulsifier that stabilizes the oil–water interface, which allows the control of the emulsion properties of the bigel in the second method.

As expected, all the processing parameters, such as those mentioned in Tables 1 and 2, can influence the final properties of the bigels. For example, the organogel/hydrogel ratio conditions the release of the drug from the system; thus, small ratios are associated with a faster release of the drug and large ratios with a more controlled release.[72] The structure and proportion of polymer in the hydrogel are other variables that allow the tuning of the drug release profile of bigels.[9]

Although bigels are usually manufactured by mixing the previously obtained organogel and hydrogel as explained above, Kawano *et al*. formulated organo/hydro hybrid gels by including the corresponding gelling agents in a bicontinuous microemulsion.[100] The organogel comprised 12-hydroxystearic acid and toluene, whereas the hydrogel was based on acrylamides. These novel hybrid gels achieved by double gelation of bicontinuous microemulsions could be considered another type of bigel with interesting potential as drug delivery systems. Shakeel *et al*.[88] described the development of unconventional bigels using various strategies, such as adding different gelling agents to the organogel or hydrogel, the use of emulsion hydrogel or emulsion organogel instead of the corresponding gel, as in the bigels for cosmetic use developed by Lupi *et al*.[12] and for the food industry by Bollom *et al*.,[70] respectively, and the aforementioned interfacial stabilization with silica nanoparticles.

Characterization of bigels for drug delivery

Various studies have focused on drug release bigels, the most frequent of which are described below.

Preliminary characterization

Once they have been obtained, the formation of the bigels is usually confirmed by the tube inversion test.[2,11,41,47,71] This is the most common method for proving gelation and involves turning a test tube or vial with the sample in it and checking whether it flows under its own weight.[101] If the sample does not flow, a correct bigel is considered to have formed (Fig. 5). Sagiri *et al*. verified the stability of their bigels by determining the leaching of

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the internal phase of the system after 1 h at room temperature using filter paper.[6] They also quantified the oil leakage after the compression of the bigels and after soaking in water for 1 h at 37 °C.[6] Singh and Kumar determined the optimum composition of the bigels they prepared according to the oil leaching from the systems at 37 °C for 1 h,[68] and Kanoujia *et al*. observed that the higher the proportion of the organogel, the greater the range of oil leaching from the bigels.[47]

Several properties of the systems, such as homogeneity, color, smoothness, and pH, are evaluated after the bigels have been obtained.[2,11] Bigels are usually described as milky white systems, a feature that has been attributed to the dispersion of the light from the interface of both phases of the system. They are generally opaque and have a smooth texture.[1,19,51,58] The pH of bigels for pharmaceutical purposes has frequently been reported as being between 5.0 and 7.0, thus assuring physiological tolerance and safe application to the skin.[1,2,5,11,47] Bigels for vaginal administration with pH values between 4.0 and 4.9, consistent with the natural vaginal pH, can also be found in the literature.[67]

Studies on mechanical properties

Mechanical properties are probably the most-studied characteristics of bigels. Here, we review several determinations examined with different equipment. The viscometric analysis of bigels was performed using a viscometer, pointing to a non-Newtonian shear-thinning flow, characterized by a reduction in the viscosity of the system with an increase in the shear rate (the speed at which bigels flow) and increased consistency at a low shear rate. This behavior is desirable for semisolid topical dosage forms because they are easier to apply and have maximum area coverage such that a lower amount of the formulation is needed. The viscosity of bigels has been observed to be higher when the proportion of the organogel increases.

The mechanical properties of these systems have also been studied with a mechanical tester. Stress relaxation data have shown the viscoelastic fluid nature of bigels, indicating that the greater the amount of organogel in the bigel, the lower the stress relaxation and the higher the solid behavior of the system (elastic nature). Other properties, such as firmness, cohesiveness, stickiness, adhesiveness, and resistance to flow, can be enhanced when the proportion of the organogel increases, whereas others, such as spreadability and creep recovery, diminish.[1,2,10,53] Mechanical testing has also been used to perform cyclic creep studies, showing that the viscosity of bigels decreases with each cycle, although they maintain the gel structure and their elastic component so that the gel-to-sol transition does not occur.[58]

The non-Newtonian pseudoplastic flow or shear-thinning behavior of bigels has also been determined by rheological studies. Various rheological models for predicting the rheological behavior of these formulations were proposed by Lupi *et al*.[65] Based on rheological measurements, Rehman *et al*.[10,44] indicated that the greater the proportion of the hydrogel in the bigel, the higher the rigidity of its structure and the more viscous it becomes, which could be attributed to the gain in hydrogen bonds in the polymer chain network of these gels.[10,44] In work by Martins *et al*.,[14] the rheological analysis showed that the increase in the proportion of organogel/hydrogel can lead to a lower structuration and integrity of the system and subsequent lower shear stress values as the shear rate increases, as previously mentioned, although a certain amount of organogel is needed for an optimum viscoelastic behavior of the bigel. However, a greater proportion of organogelator gave rise to higher shear stress in this study. Mazurkeviciute *et al*. also reported that the consistency of their bigels decreased and became weakly structured when their oleogel content was increased, probably because of the flow of the droplets,[19] whereas a rise in consistency and strong structuration of the bigel with the organogel content was found by Lupi *et al*. using rheometric measurements.[8] Fig. 6 provides an example of bigels with greater consistency because of the structuration of the oil phase in an organogel structure and the higher proportion of the organogel than the hydrogel in the bigel system. However, the authors found that the rheological properties of the hydrogel have more influence on the characteristics of the bigel than do the properties of the organogel, although the consistency and degree of structuration increase when there are greater amounts of both organogelator and gelling agent in the hydrogel.[65] The same behavior was observed by Yapar *et al*. for bigels containing Carbopol® 974P NF as organogelator and gelling agent in the hydrogel.[46] The polymer included in the hydrogel also affects the rheological properties of the bigel, as confirmed by Behera *et al*.[66] According to Mao *et al*.,[102] 'bigels containing branched polysac-

TABLE 1

Most frequent parameters used in the preparation of organogels and hydrogels for the manufacture of bigels.

Parameter	Organogel	Hydrogel
Gelling agent concentration in gel (% w/w)	2 [72]	Up to 3 [1,2,45–47,50,53,60,62,66,72,8,10,11,13,14,41,43,44]
	3 [14,46]	3–20 [52,65,70,80]
	4 [46]	20 [6,57]
	5 [65]	25 [70]
	6 [14]	
	10–20 [10,43,44,53,66,70,71]	
	15 [1,2,10,11,41,47,60]	
	25 [13,68]	
	50 [8]	
Mixing temperature (°C)	50 [71]	RT [1,8,72,10,11,14,41,43,44,46,70]
	55–65 [45]	37 [45]
	60 [2,11,41,52,53,66]	60 [2]
	70 [1,6,10,43,44,47,55,68]	65 [52]
	80 [14]	70 [1,6,13,57,60,66]
	85 [8,65,72]	
	90 [13]	
	95 [70]	
Mixing speed (rpm)	100 [11,41,53]	100 [66]
	200 [8,65,72]	300 [53,72]
	300 [10,43,44,55]	400 [11,41]
	500 [1,2,6,47,52,60]	500 [2,8,10,52,65]
		500 + 1000[a] [43,44]
		600 [57]
		1000 [1,60]
		8000 [46]

[a] The second agitation step at 1000 rpm is performed after the addition of triethanolamine.

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TABLE 2

Most frequently used conditions in the preparation of bigels.

Organogel/hydrogel proportion	Mixing temperature (°C)	Mixing speed (rpm)
1/99 [14]	Room temperature [8,10,14,42,44,55,65,72]	50 [46]
5/95 [14,68,72]		100[a] [68]
10/90 [8,10,14,44,47,68]	50 [71]	500 [2,11,41,47,52]
15/85 [47,68]	50–55 [45]	600 [14,57,72]
20/80 [8,14,41,47,68]	60 [2,53,66]	800 [10,42–44,55]
25/75 [47,68]	60–70 [52]	1000 [1,6,60]
30/70 [10,41,44,47,51]	70 [1,47,57]	1200 [8,65]
40/60 [8,41]		6000 [53]
50/50 [10,14,42–45,53]		12 000 [66,71]
		16 000 [13]
		23 000 [70]

[a] Followed by gamma radiation exposure.

charides had higher gel strength than those containing linear polysaccharides'. Golodnizky *et al.* showed that the viscoelastic properties of bigels can also be influenced by the hydrophilic–lipophilic balance (HLB) value of the surfactants in the system.[13] They found that the lower the HLB of the sucrose esters, the higher the solid-like behavior of the bigels obtained because of the different arrangement of the surfactants according to their HLB. Their rheological measurements allowed them to confirm that the gelation process of their bigels was mainly determined by the gelation of the oil phase and not influenced by the HLB value owing to the presence of the different surfactants.

The texture of bigels has also been analyzed to study some of the other mechanical properties previously mentioned, such as firmness, hardness, adhesiveness, and spreadability.[10,44,47] Through texture analysis, Martins *et al.* observed that the higher the proportion of the organogel in the bigel, the lower the firmness and adhesivity and the easier the spreadability of the formulation.[14] Kanoujia *et al.* obtained lower hardness but higher adhesivity and spreadability values by increasing the proportion of the organogel in the bigels.[47] Golodnizky *et al.* found that the HLB value of the sucrose esters included in the bigels as surfactants also affected the texture of the system, proving once again the influence of the interface content on the properties of bigels.[13] The lower the HLB of the sucrose ester, the higher the hardness and the poorer the spreadability of the bigel, because the emulsifier is mainly available in the bulk oil phase rather than in the oil–water interface, thus enhancing the structuration of the oil phase.

Microscopic techniques

Various microscopic techniques have been used for the study of bigels. Andonova *et al.*[11] observed bigels based on Carbopol® hydrogel and sorbitan monostearate/almond oil organogel under optical microscopy and reported droplets of the organogel dispersed in the hydrogel.[11] They noted that the mixing of both gels and, therefore, the microstructure of these bigels, became non-homogeneous when the amount of organogel was increased. They additionally used this microscopic technique to study the stability of the formulations.[41] Bigels were also observed under optical microscopy by Ibrahim *et al.*[5] Fig. 7a shows an example of bigels observed under optical microscopy. Phase-contrast optical microscopy was used by Lupi *et al.* to examine bigels (Fig. 7b).[8,12] They reported 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

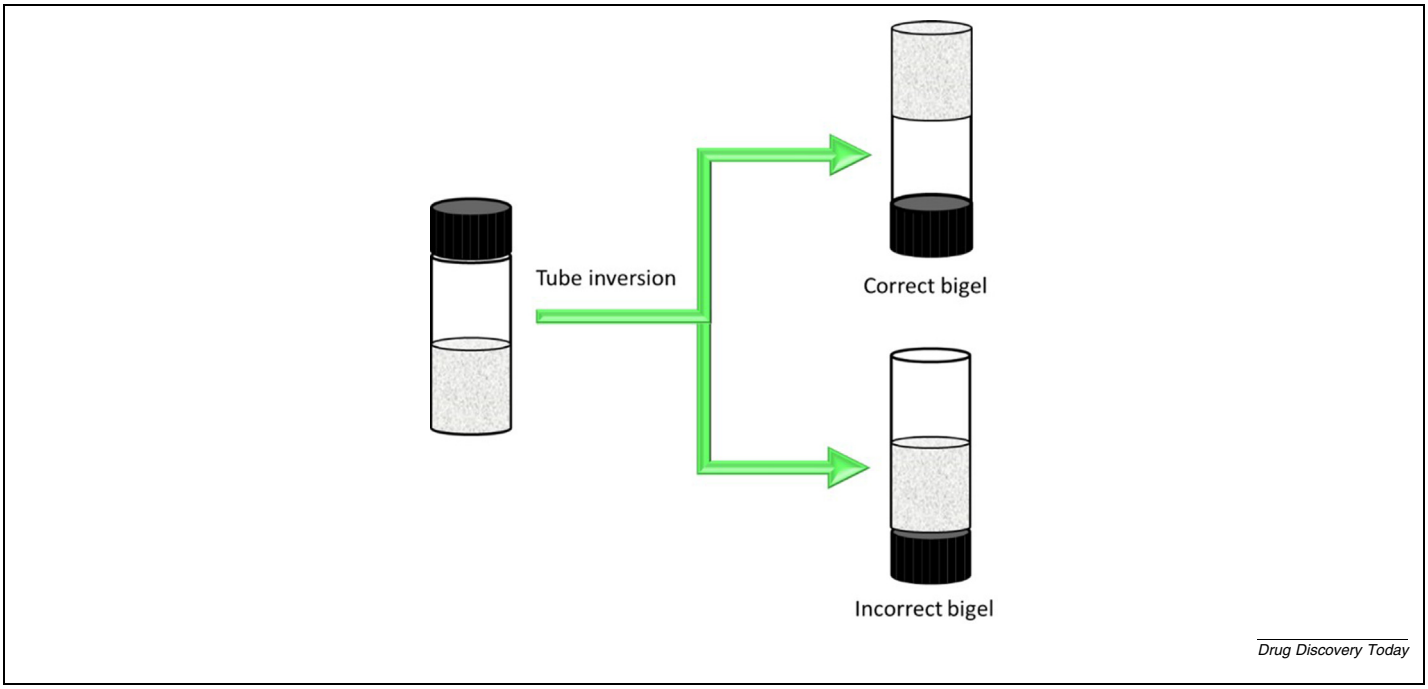

FIGURE 5

Schematic of the tube inversion test for confirming the formation of bigels.

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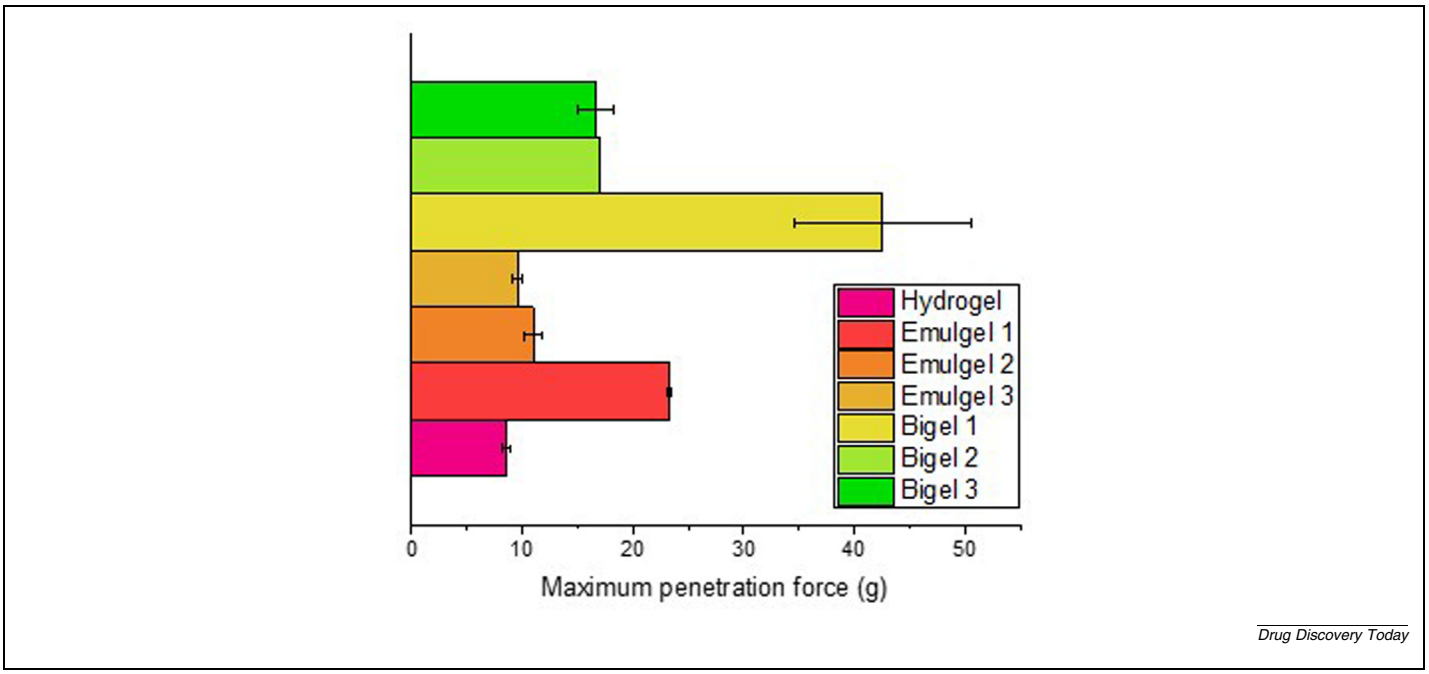

FIGURE 6

Consistency of a 1% w/w guar gum hydrogel and the emulgels and bigels composed from this hydrogel, sesame oil, and sorbitan monostearate in the absence and presence of Tween®60 respectively. The proportion of the oil phase decreases from systems 1 to 3 (1 > 2 > 3).

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.[8,12] This direct correlation between the concentration of the oleogel in the bigel and the droplet size observed by optical microscopy has also been established by other authors.[19] Images of tymoquinone-loaded bigels under a stereo microscope were taken by Yapar *et al.*,[46] who reported that the systems were strangely transparent and had a smooth surface. Polarized microscopy was used by Miliani-Martínez *et al.* to study the structure of vitamin E-loaded bigels, showing crystals surrounding the oil droplets at the interface of the bigels, which were attributed to the presence of the drug (Fig. 7c).[72] Similarly, Rehman *et al.* observed bigels under polarized microscopy and reported that the individual components of the formulation could be distinguished.[10] Different structures (bigels or emulgels) were attributed to systems comprising gelatin hydrogel and sesame/soybean oil in the presence and absence of stearic acid respectively, using bright-field microscopy (Fig. 7d)[6]; dispersion of the droplets in the organogel in a continuous matrix of hydrogel was also noted.[58] The same effect was observed by Singh and Kumar in bright microscopic images of bigels comprising sorbitan monopalmitate/olive oil organogel and sterculia gum/polyacrylamide hydrogel.[68] Bright-field microscopy allowed Martins *et al.* to establish differences in bigel microstructure according to both the proportion of the organogelator and the organogel/hydrogel ratio in the system.[14] A more heterogeneous globular gelled structure was observed by increasing this ratio.

Using confocal microscopy, Lupi *et al.* again observed that the structure of the bigels changed from an oil-in-water pattern to matrix-in-matrix when the dispersed phase volume fraction exceeded a certain value.[65] They attributed a nonspherical shape to some of the particles, especially at the highest proportion of the dispersed phase.[65] Singh *et al.* observed the microstructure and particle size distribution of the dispersed droplets by confocal laser scanning microscopy using specific fluorescent dyes for both phases.[1] They observed the appearance of spherical droplets, the size of which decreased in this case as the amount of the organogel in the system was increased, and the microstructural organization of both phases according to the distribution of the dyes. The size distribution narrowed, and the average droplet size decreased as the proportion of the organogel increased.[1] Golodnizky *et al.* determined the influence of the HLB of the surfactants in the bigels on their microstructure through confocal laser microscopy.[13] The higher the HLB of the sucrose ester and the lower its molecular weight, the greater the size of the oil droplets in the microstructure. This behavior was attributed to the faster diffusion of the smaller surfactant toward the oil–water interface, whereas the larger surfactants remained mainly in the oil phase rather than the interface, giving rise to smaller droplets in the bigel microstructure. Confocal laser microscopy allowed the classification of guar gum hydrogel and sorbitan monostearate/sesame oil organogel-based biphasic systems showing different structures as bigels or emulgels depending on the presence or absence of Tween®60, respectively; this was similar to the behavior previously observed for other formulations in the presence and absence of stearic acid (Fig. 7e).[62]

Fluorescence microscopy is another type of microscopy applied in the study of bigels and has been used to confirm the formation of organogel-in-hydrogel structures and determine the droplet size in these systems[47,66,71] (Fig. 7f) and 3D digital microscopy.[53] The surface microstructure of dried and freeze-dried bigels has been studied with field emission SEM (FESEM),[58] SEM,[50] and cryo-SEM (Fig. 7g).[68,86] Finally, Singh and Kumar

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studied their bigel formulation under atomic force microscopy and related the surface roughness to the mucoadhesion ability of the system.[68]

Fourier transform infrared spectroscopy

Fourier transform infrared spectroscopy (FTIR) is a spectroscopic technique that has been widely used for the determination of molecular interactions between the hydrogel and the organogel. 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 also enabled Ilomuanya *et al*. to discover the importance of hydrogen bonding in the structure of their bigels.[67] Both the concentration of the polymer in the hydrogel and the proportion of the gels have proven to influence the FTIR spectrum of the bigels.[44,71] Interactions or compatibility between the drug and the bigel have also been studied by using this spectroscopic method.[11,47,60,61,67]

Thermal analysis

Thermal analysis, mainly differential scanning calorimetry (DSC), is useful to establish the 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 melting point of bigels can be determined through the drop-ball method using a melting point apparatus. This point tends to be higher when the proportion of the organogel increases, because of the higher molecular order of the solid compounds, which are richer in this gel. The thermal stability of the bigels is enhanced by increasing the proportion of the organogel.[1,2] This behavior was also observed by Kanoujia *et al*. through DSC.[47] Ilomuanya *et al*. used DSC to study the structure of their bigels and determine the drug–excipient compatibility.[67] This thermal analysis enabled Yapar *et al*. to confirm the total dissolution of the drug thymoquinone in the organogel phase of their systems.[46]

Rehman *et al*. studied 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] They reported a higher thermal stability in the bigels when the proportion of organogel was increased.[10] DTG and TGA were also used by Singh and Kumar for the characterization of bigels.[68]

An interesting finding was obtained from the thermal analysis of bigels comprising a gelatin-based hydrogel and a glycerol monostearate/canola oil organogel. DSC and TGA results indicated the melting, evaporation, and decomposition temperatures of the bigel components, and the diffusion of the polymer from the hydrogel to the oil–water interface, thus modifying the stability of the system.[13]

Stability studies

Given that biphasic systems tend to undergo destabilization, bigels are usually 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 confirmed the stability of the bigels formulated by Ilomuanya *et al*.[67] Kanoujia *et al*. demonstrated the stability of their bigels through an accelerated stability test 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 changes in organoleptic characteristics, pH, or drug content.[47] Singh *et al*. also tested the accelerated stability of bigels 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.[1,2] They carried out intermediate stability studies according to the guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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 through drug release and antimicrobial studies The systems containing a higher proportion of the organogel were more stable, which was attributed to the structure of the organogelator, and the drug and antimicrobial efficacy remained stable in all cases.[1,2] Andonova *et al*. also studied the intermediate stability of bigels following ICH guidelines, and analyzed whether the bigels underwent color changes, phase separation, and syneresis.[41] The stability of bigels comprising a Poloxamer 407 hydrogel and a polyethylene organogel was tested for 6 months at 25 °C/60 %RH and 40 °C/75% RH by Mazurkeviciute *et al*., who found a decrease in the consistency of the systems and phase separation at higher temperature and humidity conditions.[19] The stability of bigels was also tested at 5 °C for 6 months with fish oil-based, which showed no significant changes in color or pH, although a slight loss was observed in the fatty acid content of the oil[10]; and at room temperature for 12 months with bigels containing alginate and almond oil, in which no phase separation or microbial growth were observed.[53]

Another stability study reported in the literature is an accelerated photostability test in ketoprofen-loaded bigels and the subsequent quantification of nondegraded drug in the system.[11] Finally, the physical stability of bigels can also be determined through the centrifuge stability tests to determine the sedimentation or coalescence of the internal phase in oil-in-water systems.[72]

Other tests

Other tests have been reported in the literature on bigels, including particularly ^{1}H self-diffusion NMR,[12] X-ray diffraction,[1,14,58] electrical property studies,[8,12,58,60] and swelling of fresh[58,68] and freeze-dried bigels.[50,62] Given that the topic of this review is drug delivery bigels, mention should also be made of tests such as bio/mucoadhesion,[50,62,67,68] *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,[1,2,19,53,66,67], and *in vivo* studies.[5,11,41,42,44,67] Bigels tend to swell less when the proportion of the organogel is increased in the system because of its lipophilic character. This behavior was observed both for bigels[68] and freeze-dried bigels.[62] Bigel swelling can also be influenced by the pH of the medium owing to the ionic nature of the polymers.[50,68] In terms of drug release, both the presence[68] and greater proportion of the organogel in the bigel[2,62] cause the release to be more controlled. As in the case of swelling, drug

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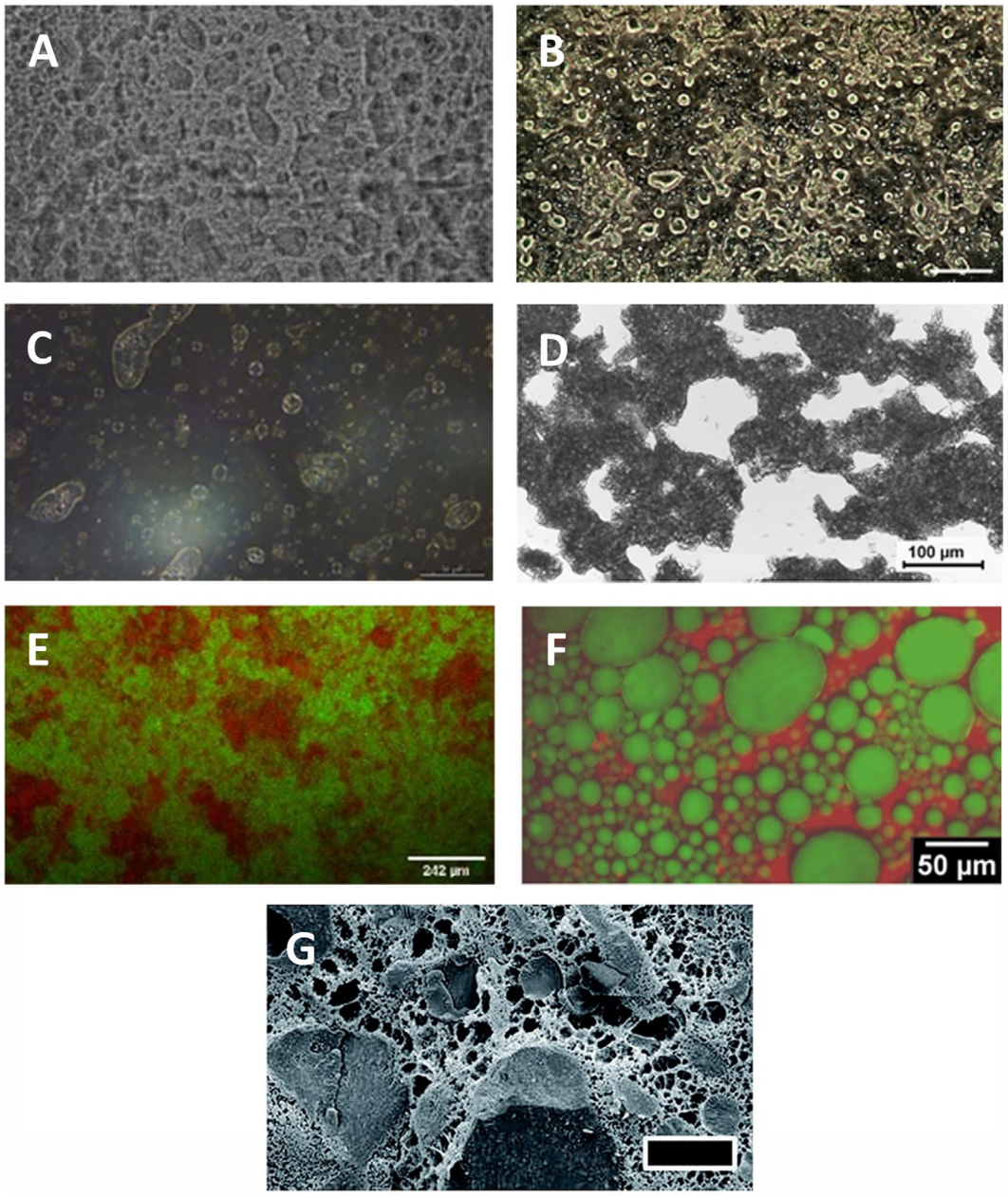

FIGURE 7

Bigel microstructure under different microscope techniques: **(a)** optical,[5] **(b)** phase contrast,[8] **(c)** polarized,[72] **(d)** bright field,[6] **(e)** confocal laser,[70] **(f)** fluorescence,[66] and **(g)** cryo-SEM.[86] Reprinted from [5] (a), [8] (b), [72] (c), [6] (d), [70] (e), [66] (f) and [86] (g).

delivery from bigels can also vary according to the pH of the medium.[50,68]

Bigels in drug delivery

Bigels have been described as promising candidates for food and controlled drug delivery.[8,103] Some of their properties, such as their good spreadability and their cooling effect, give them excellent potential for transdermal administration.[9] In cosmetics, Lupi *et al*. developed bigels from a typical oil-in-water cosmetic emulgel containing hyperthermal water with different oils and essential oils among others, to which was added an extra virgin olive oil-based organogel.[12] They performed an in-depth study of the disposition of both phases in the bigel using a variety of techniques.[12] In regard to drug delivery, most of the bigels reported in the literature have an organogel-in-hydrogel structure and are intended for the topical administration of drugs, which can be released in a controlled manner because of the structuring of the phases in the system.[8] Some of the characteristics of bigels that make them so interesting as drug delivery systems are shown in Fig. 8. Various drugs have been included in

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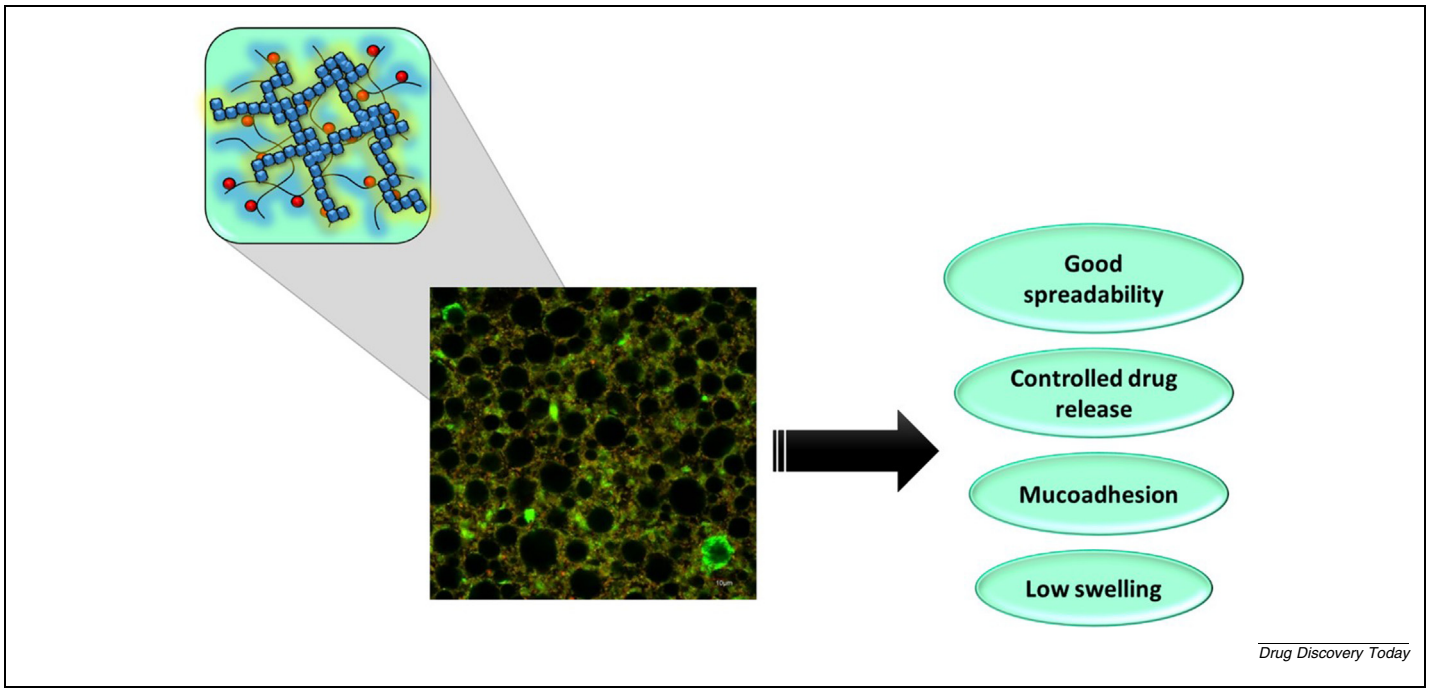

FIGURE 8

Properties of bigels relating to aspects of their composition and structure that make them appealing as drug delivery systems.

bigels, including antimicrobials, such as metronidazole,[2,55,58,60,61,66,71] ciprofloxacin,[1,6] and moxifloxacin[68]; antiretrovirals, such as tenofovir[50,62] and a combination of tenofovir and maraviroc[67]; antifungals, such as ciclopirox olamine and terbinafine hydrochloride[19]; drugs for acne treatment, such as isotretinoin[47]; immune response modifiers, such as imiquimod[10,42,44]; pain reliever drugs, such as paracetamol;[52] anti-inflammatory drugs, such as ketoprofen,[11] ibuprofen,[48] and diclofenac diethylamine[45]; calcium channel blockers, such as diltiazem hydrochloride[5]; and antioxidants, such as coenzyme Q10,[43] 1,4 naphthoquinones,[53] vitamin E,[72] and thymoquinone.[46] Some examples of these bigels formulated for drug delivery are described below.

Bigels containing imiquimod as the drug with a polymer hydrogel and beeswax/fish oil oleogel have been widely investigated by Rehman *et al*. for the treatment of skin diseases, such as skin cancer.[10,42,44] They first formulated these bigels with sodium alginate or HPMC as the polymer of the hydrogel. The resulting systems displayed pseudoplastic behavior and easy spreadability that made them a good option for skin application. These bigels also revealed greater *in vitro* cumulative drug permeation than the corresponding hydrogels, which was attributed to the addition of fish oil, particularly to its omega-3 fatty acids.[10] Once they had demonstrated the suitability of imiquimod/fish oil bigels as topical or transdermal drug delivery vehicles, the research group redeveloped these bigels, this time with Carbopol® 940 as the hydrogel-forming polymer. The aim of this work was to reduce the inflammation caused as a side effect of the drug through its controlled release from bigels containing fish oil as an anti-inflammatory agent. The bigels formulated exhibited lower *ex vivo* cumulative drug permeation and more controlled release compared with a commercial imiquimod cream; neither did the bigels induce the severe inflammation observed with the commercial product. These promising results were explained by the controlled release of the drug from these systems or the presence of the two anti-inflammatory fish-oil fatty acids, one of which showed molecular interaction with imiquimod, thus supporting the aforementioned synergistic effect.[42] Subsequently, Rehman *et al*. reported that fish oil could act as a suppressor of the proinflammatory cytokines upregulated by imiquimod as an inductor of IL-10. These findings explain why the combination of imiquimod and fish oil in these bigels not only reduced the inflammatory side effects induced by this drug, but also improved its antitumor effectiveness.[44]

Nanosystem-based bigels have also been developed for drug delivery. Andonova *et al*. prepared ketoprofen-loaded nanoparticles based on poly(vinyl acetate) and other polymers, and selected those offering the highest values of drug photoprotection for their inclusion in bigel systems comprising a Carbopol® 940 hydrogel and a sorbitan monostearate/almond oil organogel.[11] A bigel with ketoprofen loaded in poly(vinyl acetate) and hydroxypropyl cellulose-based nanocarriers exhibited more controlled release and higher photostability of the drug than a bigel containing free ketoprofen, and produced interesting results in terms of its antinociceptive, anti-inflammatory, and antihyperalgesic activities. Hamed *et al*. formulated bigels containing a Carbopol® 971P-based hydrogel and an oleic acid-based organogel, with glyceryl behenate as an organogelator, for the topical administration of diclofenac diethylamine.[45] They incorporated the drug into the organogel in its free form, and as a drug-loaded nanoemulsion and drug-loaded gold nanorods in a nanoemulsion. The rheological properties of the bigels were influenced by the form in which the drug was included. Bigels containing the drug combined with the nanorods showed the

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slowest rate of drug release and the greatest *ex vivo* skin permeation.

Although most of the drug delivery bigels found in the literature are for topical administration through the skin, bigels for vaginal drug release have also been developed. Singh *et al*. formulated systems comprising Carbopol® 934 hydrogel and sorbitan monostearate/sesame oil organogel for the vaginal administration of drugs, specifically for the treatment of bacterial vaginosis with metronidazole.[2] Fluorescence microscopy revealed the microstructures of an oil-in-water type of emulsion gel, and a biocompatibility study showed no significant differences in the viability of HaCaT cells compared with the controls. Most of the batches released the drug in a controlled way through a diffusion mechanism, one even following a Fickian release behavior, and all showed good antimicrobial efficiency against *Escherichia coli* compared with a commercial metronidazole gel. Tenofovir-loaded freeze-dried bigels have been formulated as novel drug delivery dosage forms by mixing a guar gum-based hydrogel and a sorbitan monostearate/sesame oil organogel in different proportions and in the presence and absence of Tween®60. Confocal laser micrographs revealed the formation of emulgels when the systems did not contain Tween®60, whereas the presence of this surfactant, especially at the higher proportion of the organogel, gave rise to a more complex microstructure that was identified as a bigel structure. This formulation also showed a low degree of swelling and the greatest controlled release of the drug, as well as the longest bioadhesion time in simulated vaginal fluid compared with the other batches. All these results, along with the absence of cytotoxicity observed in three human cell lines, positioned these freeze-dried bigels as an interesting option for the prevention of the sexual transmission of HIV in women.[62] The dosage form that showed the best results was then modified by changing the polymer in the hydrogel for chitosan, HPMC, or pectin in different concentrations. The purpose was to obtain pH-sensitive formulations for a vaginal controlled release of tenofovir that was faster in the presence of semen. The batch containing 3 %w/w of pectin in the hydrogel exhibited the best mechanical properties and excellent *ex vivo* mucoadhesiveness, in addition to pH-dependent swelling and drug delivery, with a controlled release of tenofovir in simulated vaginal fluid and the fastest release in the presence of simulated seminal fluid of all the batches formulated. These findings point to a smart dosage form that would give women greater protection against HIV during sexual intercourse, when they would be particularly exposed to the virus.[50] Leveraging one of the main advantages of bigels, Ilomuanya *et al*. subsequently developed mucoadhesive bigels containing a hyaluronic acid hydrogel and surfactants/palm oil organogel for the vaginal administration of tenofovir and maraviroc.[67] The entry inhibitor was included in the organogel and the reverse transcriptase inhibitor in the hydrogel. All the formulations had good organoleptic properties and most allowed a zero level of HIV infectivity in TZM-bI cells at a concentration of 0.1 mg/ml. The bigel with the lowest organogel/hydrogel ratio showed the best results in terms of mucoadhesion, cell viability, and safety against vaginal and rectal epithelium, thus representing an interesting tool for long-term pre-exposure prophylaxis of HIV.

In recent years, drug delivery bigels have been formulated for buccal administration. In 2018, ibuprofen-loaded bigels were proposed by Hamed *et al*. for the treatment of periodontitis.[48] Subsequently, Wróblewska *et al*. developed bigels based on a sodium alginate hydrogel and a fumed silica/linseed oil organogel for the local administration of metronidazole in periodontal diseases.[55] Bigel systems showed higher *ex vivo* mucoadhesion than the commercial product and the corresponding hydrogels and organogels. *In vitro*, the drug was released for several hours by Fickian diffusion, and the antibacterial activity of these systems was similar to that of the commercial product. The *ex vivo* permeation test attributed a high initial permeability rate to the bigel formulation, which would result in fast therapeutic action, and the lowest drug retention in the mucosa of all the tested systems, which would imply less risk of local cytotoxicity.[55]

Concluding remarks and future perspectives

The concept of bigels is relatively new, and research in this area has been largely conducted over the past 10 years. The study of the components of bigels (hydrogels and organogels) and of some of their combinations, such as emulsions, as dosage forms in themselves is already well advanced, which facilitates the preparation and characterization of bigels. Research in other fields, such as cosmetics and food technology, has also served as useful tools for the manufacture of, and insight into, drug delivery bigels. The result of mixing two types of gel and their arrangement in bigels makes these biphasic systems appealing for pharmaceutical purposes. Although most of the drug-release bigels developed are intended for administration through the skin, other routes of administration have already been suggested. Buccal and vaginal bigels have emerged as alternative options, thus increasing the potential applications of these dosage forms as drug delivery systems. Nevertheless, although some bigel characteristics, such as their microstructure and mechanical properties, are widely investigated, there is still a long way to go in this field. Some of their most promising features, namely the possibility of including drugs in both the aqueous and oily phases of the same formulation, have recently begun to be exploited in the preparation of bigels for drug delivery. This could represent major advances in the management of diseases such as HIV infection, in which the combination of different drugs is vital, various sexually transmitted diseases that are often concurrent such as genital herpes and AIDS, and sexually transmitted diseases and contraception with the same drug delivery system.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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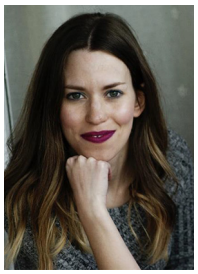

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