Review on Bigels: A Versatile Gel System

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Abstract- The scientific and industrial world has paid increasing attention to Bigels as a structured multiphase gel system because these solutions unite hydrogel and organoogel characteristics. A biphasic gel system consists of interweaving incompatible gel networks that produce long-lasting structures that provide enhanced strength together with controlled delivery functions and improved biocompatibility. Advanced drug delivery systems with cosmetic formulations and wound healing scaffolds and food emulsions become possible through the beneficial interaction of water-based and oil-based phases. The rheological and physicochemical properties of bigels become highly flexible through composition modification and selection of structuring agents along with gelation methods. These two-phase materials possess an advantage for sustained-release technology because they contain both water-soluble and oil-soluble agents thus serving as excellent pharmaceutical and cosmetic formulation vehicles. Their adhesive property towards skin helps bigels show great potential as drug delivery methods through the skin surface. Bigels demonstrate significance in tissue engineering among recent analyses that shows their biocompatible nature helps cells proliferate and differentiate through tunable properties. Bigels will transform numerous market sectors due to ongoing developments in material science and nanotechnology thus creating progressive solutions for pharmaceuticals, biomedicine and industrial industries.

Index Terms-Bigels, Biomedical applications, Controlled release, Drug delivery

1. INTRODUCTION

A substance is considered a gel if it behaves like a solid during experiments, has a stable structure, shows a plateau in storage modulus at low tan values between 10−3 to 102 rad/s, and doesn't flow. From a structural perspective, gels contain molecules, particles, and chains linked together in a liquid medium, causing them to lose fluidity. These semisolid formulations consist of two key components: a liquid solvent and a solid gelling agent, working together to create a 3D networked system. The classification of gels is a topic of intrigue, with two distinct categories emerging based on the nature of the 3D network structures formed by the gelators. Polymer gels, a product of polymer molecules crosslinking, offer a unique perspective into the intricacies of gel formation. On the other hand, particle gels, formed through the aggregation of colloidal particles, present an intriguing complexity to the study of gels.

The term "bigels" encapsulates the fusion of these concepts, representing a fascinating intersection of polymer and particle gels. This innovative approach not only diversifies the application potential of gels but also opens up new avenues for exploration in the realm of pharmaceutical sciences. The evolution of bigels stands as a testament to the ever-expanding horizons of gel science, offering a glimpse into a future where innovation knows no bounds.

1.1 Components of Bigels:

Bigels are a type of gel structure that is formed by mixing two immiscible gels, typically hydrogel and organogel, stabilized by the presence of surfactants or emulsifiers. These components work together to form a stable system with both oil and water phases in the structure, giving the bigel its unique properties.

Hydrogel	Organogel
Liquid solvent = polar	Liquid solvent = non polar
It is a 3D hydrophilic network which have ability to absorb huge amount of water.	It is a solid system in which organic liquid is entrapped inside thermoreversible 3D network.
Helps in hydration of stratum corneum	Enhance drug permeation through stratum corneum.
Hydrophilic in nature	Lipophilic in nature.
Generally lighter and non-greasy	Thicker often greasy
Limited skin penetration.	Better skin penetration

Soluble in water	Soluble in organic solvent
Stable in aqueous environment, may need preservatives.	Stable in non-aqueous environment, less prone to microbial growth
Example: hydrogel wound dressings, eye drops.	Example: organogel-based topical ointments, transdermal patches.

2. Bigels

Bigels are gels generated by the mixture of two gels, namely organogel and hydrogel. Since hydrogels are polar and organogels are non-polar, bigel contains both internal and exterior immobilized phases. The immobility of the exterior phase stops the motion of the internal phase, effectively eliminating the possibility of internal phase coagulation. If the bigels' exterior phase is cross-linked, a permanent bigel is formed. Hydrogel hydrates the stratum corneum, whereas organogel promotes penetration. Other benefits of bigels include easy washability, simple spreadability, good contact duration, accommodate both lipophilic and hydrophilic medications, offers regulated drug administration, good moisturizing impact on the skin, and bigels may solve the disadvantages of both.

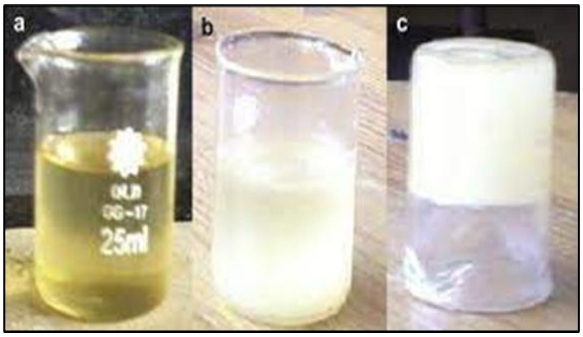


Fig 1: - Bigels

2.1 Advantages of bigels

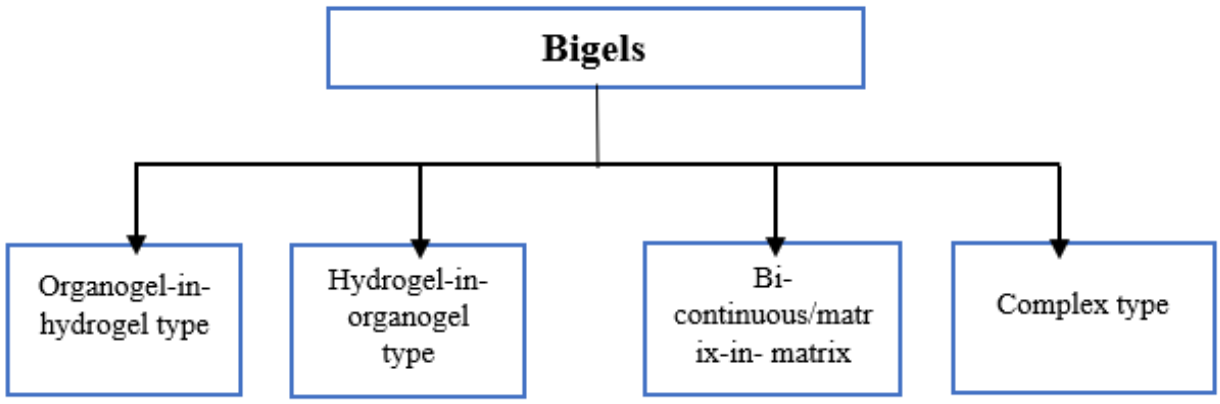
- Bigels helps in enhanced hydration of stratum corneum.
- Bigels will accommodate both lipophilic and hydrophilic drugs.
- Bigels provide controlled drug delivery.
- Bigels gives good moisturizing effect to the skin.
- Bigels provide good spreadability.
- Bigels provide good washability.

Bigels offer the ability to manipulate consistency and drug release rate by varying phase proportions and structure, ensuring good stability at room temperature for 6-12 months due to extra-fine dispersion. They overcome disadvantages of hydrogels, oily residues, and organogels, such as limited lipophilic barrier crossing and low patient compliance.

2.2 Disadvantages of bigels

- Bigels can be destabilized at high temperature.
- Developing bigels is a complex formulation process.
- Bigels may prone to phase separation.
- Complexity of formulation and the need for specialized ingredient can make bigels more expensive.

2.3 Classification of bigels



2.3.1 Organogel-in-hydrogel type

It is a system which contains organogel as a dispersed phase and hydrogel as continuous phase. Different researchers have reported this type of bigel by considering different hydrogel systems having different hydrogelators like gelatin-agar mixture, guar gum, xanthan gum & acacia gum, gelatin, whey protein, pectin, starch, sodium alginate, sodium carboxy methyl cellulose, hydroxyl propyl-methylcellulose, polyvinyl alcohol and polyvinyl pyrrolidone, carbopol. Together with these hydrogels, different organogel systems were also considered to prepare bigels. Investigated olive oil as a solvent and mixture of glyceryl stearate and policosanol as organogelator, sorbitan monopalmitate-sunflower oil based organogels were studied by Behera et al. sorbitan monostearate and sesame oil were used to prepare organogels by Singh et al. span 60, cetyl alcohol and lecithin-pluronic as organogelators and soya-bean oil as a solvent were investigated by Ibrahim et al., soya-bean oil-stearic acid based organogel.

2.3.2 Hydrogel-in-organogel type

It can be defined as the system in which hydrogel phase is distributed within the continuous phase.

Second type of bigel (hydrogel-in-organogel) is the system in which hydrogel phase is distributed within the continuous matrix of organogel. This type of bigels is prepared by mixing locust bean gum-carrageenan based hydrogel and sunflower oilfumed silica based organogel at several organogel-hydrogel ratios. Hydrogel-in- organogel type morphology of bigels was confirmed by the results of confocal microscopy.

2.3.3 Bi-continuous/ matrix in matrix type

It can be regarded as a system with complex structure in which it is difficult to identify the dispersed and continuous phase. Third type of bigel can be regarded as a system with complex structure in which it is difficult to identify the dispersed and continuous phase. Bigels made by mixing cosmetic system (O/W) with organogels having monoglycerides of fatty acids as organogelator and olive oil as a solvent, with increasing fraction of organogel. At the maximum fraction of organogel, results revealed the presence of a complex matrix-in-matrix structure.

2.3.4 Complex bigel

It is type of structured material composed of two different phases that are mixed together.

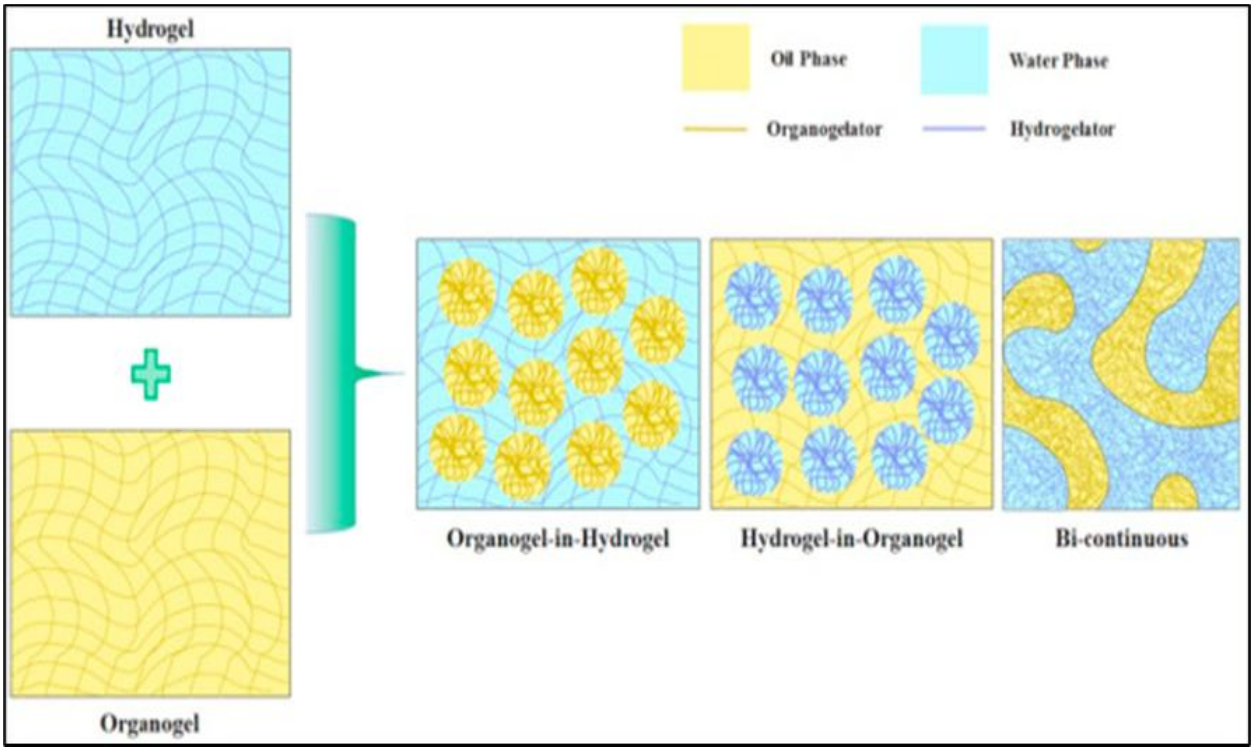


Fig 2: - Types of bigel

2.4 Preparation of bigels

2.4.1 Preparation of hydrogel:

In hydrogel, dispersion phase is aqueous system which is formed by mixing the suitable polar gelling agent in water. Based on gelling behavior there are certain parameters which are to be optimized like speed, temperature etc. Hydrogel are formed by the physical or chemical crosslinking using ionization radiation. The interaction like Van der Waals forces and hydrogen bonding are present in hydrogel therefore they are reversible in nature.

There are different techniques that is used in the hydrogel formation are as follows:

1.Bulk polymerization
2. Free radical polymerization
3. Solution polymerization
4. Suspension polymerization

2.4.2 Preparation of oleogel:

In oleogel, the dispersion phase is oil phase. Oleogel is prepared by dissolving accurate amount of olegogelator in nonpolar solvent at a definite conditions like temperature is to be maintained at higher than the melting point of the olegogelator. The gel formation will start occurring at room temperature(25℃). Oleo gel is also called organogel. The oil phase can be an organic solvent (e.g., benzene, hexane) or vegetable oils such as castor oil. Similar to hydrogels, these are also formed by weak Van der Waals forces or hydrogen bonding.

2.4.3 Preparation of bigel:

Bigels are prepared by combining hydrogel and oleogel at high shear rate, retaining the characteristic properties of both the components. The homogenous mixture forms a smooth gel by applying a definite shear speed and temperature. The mixture either forms a gel or shows phase separation on cooling to room temperature. The formation of a stable bigel is dependent on the composition of both the phases. The gel formation is checked by tube inversion test.

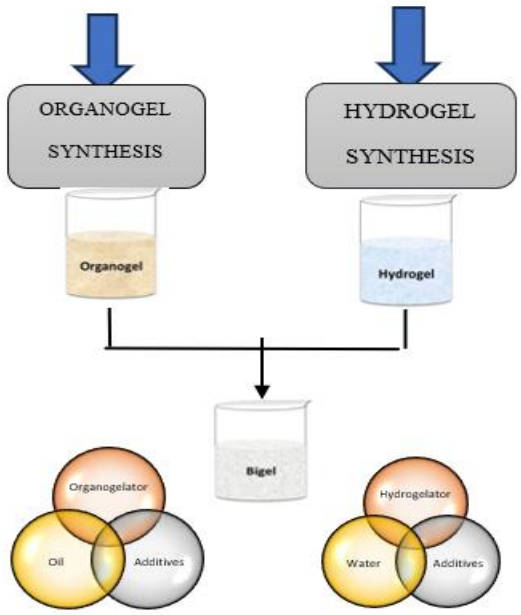


Fig 3:- Preparation of bigel

2.5 Different types of organogelator used:

Types of organogelators	Properties of organogelator	Examples
4-tert-Butyl-1-Aryl Cyclohexanol Derivative Organogelators.	Solid at room temperature and less solubility in aprotic solvent.	Cyclohexane, benzene and carbon tetrachloride.
Polymer Organogelators	Gel pre pared by this organogelator have low gel-sol transition temperature and high gel strength.	L-lysine, polyalkylene, PEG and polycarbonate
Gemini Gelators	These have very high property for immobilizing aprotic solvents.	N-ε-lauroyl-L-lysine ethyl ester
Low molecular weight organogelators	These can immobilize high amount of aprotic solvent at very low concentration.	Fatty acids and n- alkanes.

2.6 Different type of hydrogelator used:

Types of hydrogelators	Properties of hydrogelator	Examples
Polymeric gelling agent	Soluble in both water and alcohol and is mild acidic in nature.	Carbomer 934P, carbomer 940 and carbomer 941.
Cellulose based gelling agent	These can form gel at low temperature.	Hydroxypropyl cellulose (HPC), Hydroxypropyl methylcellulose (HPMC) hydroxyethyl cellulose (HEC) and carboxymethyl cellulose.

Natural gelling agent	Highly soluble in cold or hot water, give high viscosity at lower concentration and provide stability.	Xanthan gum, guar gum, pectin, gelatin.

2.7 Characterization techniques

Different important parameters like, distribution of aqueous and organic phases within gels, average droplet size of dispersed phase, phase inversion, thermal stability, viscoelasticity, flow behaviour, antimicrobial efficiency and drug release rate can be investigated by utilizing different techniques.

2.7.1 Organoleptic characterization: -

After the formulation part is done, bigels is kept undisturbed until it cools down to room temperature. After this they are evaluated for various parameters such as uniformity, colour, pH, viscosity, segregation of phases. Bigel which contains high concentration of oleo gel have high intensity of white colour and high spreading also.

2.7.2 Mechanical characterization: -

Different mechanical properties of bigels, like viscosity are studied by different methods by viscometer, rheometer. Cone and plate viscometer are used to determine and record the viscosity of the bigels. The measurement is usually performed at standard room temperature (i.e. 25℃) with a shear rate varying from 20 to 100 s-1. Ostwald-de-Waele power law is used to measure and calculate data. This law is used to represent the non-Newtonian fluids viscosity profiles. $\tau = K.\gamma n$ (τ-shear stress, γ-shear rate, K-flow consistency coefficient and n-rate index) Interpenetrating network of the aqueous and organic phases result in the synergistic impact on the rheological characteristic of the bigels. If the hydrogel ratio is more than 50% in the formulation than organogel, bigel formation will not occur.

2.7.3 Spreadability: -

By putting 0.1g of gel between two glass slides of same dimensions (i.e. 25mm, 1mm or 75mm), the spreadability of the formulation was determined. Specific weights of 10g, 20g, 50g or 100g were subsequently loaded on the upper glass slide for 60 seconds. Before and after positioning of each weight the initial and final diameters of spreading were noted. Percentage Spreading = [(Di-Df)/Di] × 100

2.7.4 Microscopy: -

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.

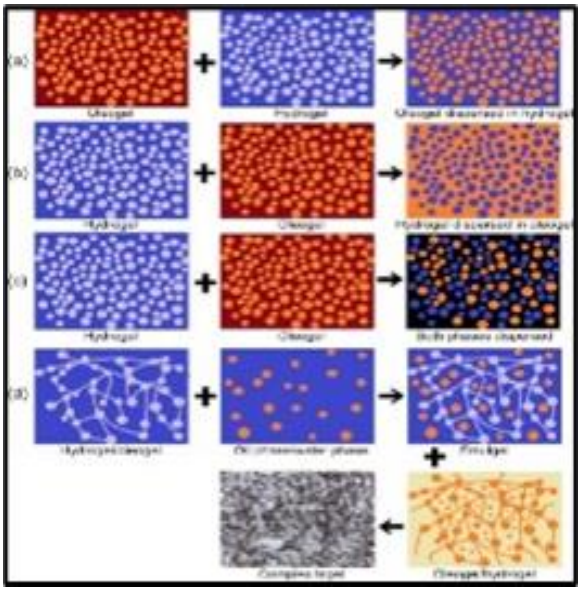


Fig 4: - Microscopic arrangement of different type of bigel

2.7.5 Thermal Characterization: -

Falling ball method was used to determine the gel-sol transition temperature of organogels (Tgs). A metal ball weighing around 250mg was firmly kept on the surface of the organogel. Thermometer was inserted into the gel and the gel was heated at a specific rate so that the rise in temperature per minute will be gradually increasing by 1℃ till 70° C. The point where

the ball began to move through the gel was reported as gel-sol transition temperature (Tgs). In cases of bigel this method can't be used above 50℃ as they became unstable and phase separation occurs.

2.7.6 In vitro release study: -

Franz's diffusion cell is used to perform in vitro release study. The volume required for dissolution, pH of dissolution media, temperature, and stirring speed is selected accordingly. The study is performed for a predefined time period.

The drug aliquot is collected at different time points, filtered through a 0.45 mm millipore filter, and is assayed using UV-Visible spectrophotometer or HPLC.

2.7.7 Accelerated stability studies: -

Freeze-thaw (F-T) thermocycles were performed (20min of freezing at 20℃ and 20min of thawing at 70oC) to gel the accelerated stability data. This method was performed in 5 different cycles and after each cycle the bigels were analysed for colour change, viscosity, phase segregation and homogeneity. These studies give the long-term stability predictions.

2.7.8 Fourier transform infrared (FTIR): -

This spectroscopy is used to assess the functional groups which are present in the bigel formulation. Mostly all the functional groups of the molecules absorb infrared radiation in a range of 4000 and 1500 cm-1. The spectrum was recorded in this specific range and it is used to determine the lipophilic and hydrophilic existence of the mixture. In a range of 3300 to 3200 cm-1 a large hump is usually observed which is due to the intra and intermolecular hydrogen bonds inside the hydrogel.

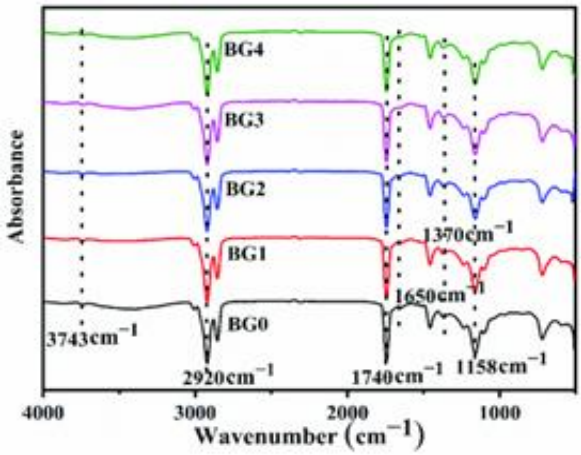


Fig 5:- FTIR characterization of bigel

Table 1. Different Bigel Systems in the literature are reported for drug delivery applications: -

Organogelator	Hydrogelator	Drug Incorporated
DIMODAN® monoglyceride	K-carrageenan	β-carotene
Span 65	Alginate	Cetavlon®
Sorbitan monopalmitate (Span40)	Sodium alginate,Sodium carboxy methyl cellulose, Maltodextrin, Starch.	Metronidazole L.Palatrum (Lp299v)
Sorbitan monostearate(Span 60), Cetyl alcohol, Lecithin pluronic	Hydroxypropylmethylcellulose	Diltiazem HCL
Beeswax	Sodium alginate, Hydroxy propylmethyl cellulose	Imiquimode
Stearic acid	Gelatin	Ciprofloxacin
Stearic acid	Mixture of agar and gelatin	Metronidazole
Stearyl alcohol	Stearly alcohol	Ciprofloaxacin HCl
Bees wax	Carbopol	Imiquimod
Sorbitan monostearate (Span 60)	Carbopol	Ketoprofen
Mixture of soya lecithin and pluronic	Hydroxy propyl methyl cellulose	Flubiprofen
Compritol® (Liquid excipient of glycerylbehenate).	Carbopol	Ibuprofen
Stearic acid	Tamarind gum	Moxifloxacin
Polyethylene	Poloxamer 407	Ciclopirox olamine and terbinafine HCl
Polyethylene	Carbopol	NSAIDS
Span 60 and Polysorbate 60	Chitosan, HPMC	Tenofovir

3 FUTURE PERSPECTIVES

Bigel is quite a new concept, research in this novel system are largely conducted over the past few years. Due to the widespread application of the bigels in the food, pharmaceuticals and cosmetics industry, bigels have become increasingly important in the recent 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. Use of a drug in aqueous as well as oil phase in the same formulation in bigel preparation for drug delivery becomes preferable. Although other characteristics of bigels such as their microstructure and mechanical properties are deeply evaluated, still there is a long way to go.

4 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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