Review Article

Basic concepts of bigels

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ABSTRACT

The current learning describes the synthesis of innovative bigels as delivery matrices for controlled delivery applications. Since the past few years, many literatures are reviewed for pharmaceutical and cosmetic application focused on the controlled delivery of both lipophilic and hydrophilic active agents. Biphasic systems formed by water-based hydrogels and oil-based organogels are referred as Bigels. The bigels were prepared by mixing agar hydrogel and oleogel (stearyl alcohol) in different proportions. A deeper knowledge of the relationship between macroscopic properties and microscopic parameters seems necessary to aim at designing materials with specific rheological properties and suitable for specific uses. These formulations possess characteristics of both gels such as the cooling effect, enhancement of hydration of the stratum corneum, moisturizing effect, easily spreadable, and emollients application to the skin. The use of two gel systems in bigels can produce a synergetic effect such as enhancement of hydration of stratum corneum and drug penetration due to the presence of both water phase and oil phase. The suitability of the formulations for controlled drug release applications was thoroughly examined using microscopy, Fourier-transform infrared spectroscopy, as well as mechanical, electrical, thermal, drug release, and antimicrobial studies. At present, bigels are being widely explored as potential matrices for controlled drug delivery. In this article an attempt was made to highlight bigels and its characteristics. Nevertheless, newer therapeutic applications of bigels were also been discussed in our compilation.

Keywords: Innovative bigels, two-phase systems, hydrogels, organogels, characteristics, macroscopic properties, microscopic parameters, controlled delivery systems, applications

INTRODUCTION

We always anticipate that, incorporation of antifungal substances in a gel would may improvise sustainability of drug release and drug contact time in skin.[1-4] Gels are semi-solid matrices comprising small amounts of a solid dispersed in a relatively large amount of a liquid.[5] Gels might provide faster drug release compared to creams and ointments, regardless of water solubility of the substance. Many scientists have proposed the development of formulation by mixing hydrogels and organogels. Such formulations are regarded as Bigels. Bigels are stable, non-oily systems that combine advantages of hydrogels and oleo gels. The oil phase keeps the skin moist and nourished which prevents water loss and ensures uniform spreading of the drug substance onto the skin.[6] Due to the mixing of two phases of different nature (polar and apolar), bigels possess some interesting features such as ability to deliver hydrophilic and hydrophobic drugs, better spreadability and water washability, improved permeability of drugs, enhanced hydration of stratum corneum, and ability to manipulate the drug release rate. Bigels are interesting semisolid formulations with better properties for different applications such as cosmetics and pharmaceutical systems. The key point in this article is to have a thorough understanding of bigels and its characteristics together with the discussion on exhibiting bigel systems to relate their properties with functional constituents and different parameters.[7-9]

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DEFINITION

The gel is said to be a hydrogel or an organogel depending on the nature of the liquid component: Water in hydrogels and an organic solvent in organogold.[10] "Bigel (oleogel/hydrogel, oleohydrogel, and biphasic gels) is a semi-solid formulation that consists of two phases: Hydrogel and oleogel. Bigels, synthesized by mixing organogel (oil phase) and hydrogel (aqueous phase), have been broadly considered by several researchers, particularly for drug delivery applications." Bigels differ from emulgels because both phases are structured while in emulgels, the internal phase is a liquid.[11-14]

CLASSIFICATION

- On the basis of nature of 3-D network structures formed by gelators, gels can be classified into two categories.
  - Polymer gels: Formation occurs through cross-linking of polymer molecules.
  - Particle gels: Formation followed by aggregation of colloidal particles.
- Gels can also be classified on the basis of polarity of liquid solvent
  - Hydrogel: Formed when the liquid solvent is *polar* (Disadvantage – Difficulty in delivering drugs across stratum corneum due to less skin permeability)
  - Organogel: Formed when the liquid solvent is *non-polar.* (Disadvantage – Sticky nature makes it difficult to remove after application on skin).

Because of the above-mentioned drawbacks, this enforced scientists and researchers to look for other systems with better properties and so to overcome such complications, many scientists have proposed a unique and interesting formulation by mixing hydrogels and organogels called as bigel. Since hydrogels are polar and organogels are non-polar, bigels may be regarded as emulsions having both internal and external immobilized phases.[15,16]

CHARACTERISTICS

- Mechanical, structural, thermal, physical, rheological, and electrical properties of bigels are of prime importance for their utilization in different commercial applications
- Bigel has been stated to represent different type of systems such as,
  - Formulation produced from a combination/mixture of organogel and hydrogel
  - System formed by joining two different gel strips
  - System produced from a mixture of two colloidal gels interpenetrated through particular interactions
  - Gelled system developed by sequential covalent or combination of non-covalent and covalent interactions
  - Phase separated bicontinuous gels

- Out of all these bigels produced by mixing hydrogel and organogel have been mainly investigated by many researchers for cosmetics and pharmaceutical applications.

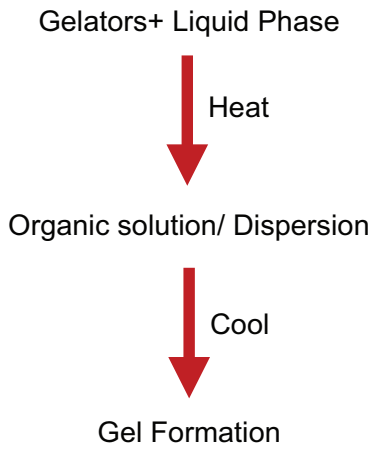
SYNTHESIS METHOD

Hydrogel preparation

- Using ionizing radiation to generate main – chain free radicals which can recombine as cross-link junctions
- Linking polymer chains through chemical reaction
- Physical interactions such as entanglements, electrostatics, and crystalline formation.
- Various technologies adopted in hydrogel formation. They are
  - Bulk polymerization
  - Free radical polymerization
  - Solution polymerization
  - Suspension polymerization.

Organogel preparation

- Stearic acid was dissolved in soybean oil at 70°C. Then, the hot solutions were incubated at room temperature for 30 min to allow the formation of organogel
- Drug-loaded formulations were prepared similarly. Drug was dissolved in the molten organogel for preparing the drug loaded organogel.



Bigels preparation

- Bigels under this category are prepared by mixing organogels and hydrogels, in different proportions with continuous stirring at high shear rate/rpm for a particular period of time to get a homogenous system. The important parameter for the preparation of Bigels is the temperature maintained during mixing
- The bigels were prepared by mixing accurately weighed organogel and gelatin-agar mixture. Molten organogel (70°C) served as the internal phase. Molten organogel was added dropwise to the gelatin-agar mixture (70°C, 300 rpm) and homogenized for 10 min. Drug-loaded bigel was prepared using drug-loaded organogel [Figure 1].

CHARACTERIZATION TECHNIQUES

- Mechanical characterization
- Physical characterization

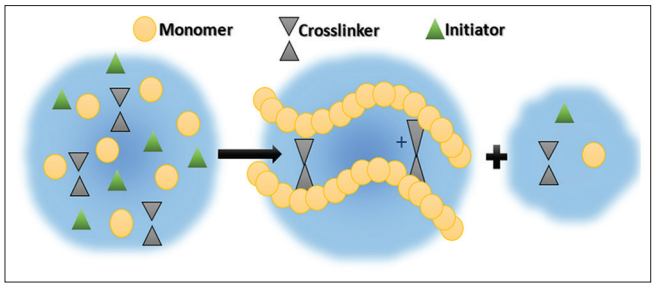


Figure 1: Schematic diagram of hydrogel preparation

- Structural characterization
  i. Microscopy
  ii. Fourier transform infrared (FTIR)
  iii. X-ray diffraction (XRD)
- Thermal characterization.

Mechanical characterization

- Organoleptic evaluation
- Firmness
- Hardness
- Cohesiveness
- Adhesiveness
- Stickiness
- Gel strength
- Stability studies

Physical characterization

- Viscosity of bigel systems as a function of
  i. Shear rate, shear history, and time
  ii. Swelling behavior of bigel systems.
- Shear thinning behavior
  i. Enhanced transdermal of bigel formulation is absorption essential
  ii. Easy spreadability
  iii. Reducing the amount of bigel required.

Structural characterization

I. Microscopy
   - The simplest characterization technique to investigate the morphology of bigels as microscopic analysis
   - Many researchers have reported microscopic techniques to analyze the structural features of bigels.

II. FTIR
   - To identify the functional groups and to understand the chemical interactions between the bigel components
   - FTIR has been reported for many bigel systems, by operating FTIR spectrophotometer in attenuated total reflectance mode with a particular range of wavenumber.

III. XRD
   - XRD analysis can be performed for the bigel systems to understand the nature of the structure (i.e., amorphous or crystalline)
   - Researchers have reported the XRD analysis of various bigel systems using X-ray diffractometer equipped with Cu Kα as the X-ray radiation source.

Thermal characterization

- Thermal characterization can be defined as the analysis of physical properties of a system as a function of temperature/time under particular conditions using suitable experimental technique.[17,18]
- It can be studied by different techniques such as differential scanning calorimetry, dynamic rheological method, and thermogravimetric analysis.

APPLICATIONS

- Topical drug delivery
- It makes them interesting for controlled delivery of active products
- Include delivery of both hydrophilic and lipophilic active agents
- Enrichment of hydration of stratum corneum results in cooling and moisturizing agent
- Easily spreadable
- Water washability on application into the skin
- Improvement of permeability of drugs through skin
- Ability to manipulate the consistency and drug release rate by varying the proportion and structure of each phase.

Applications along with research insights

- Applications of Bigel systems have been proposed particularly in the field of drug delivery and cosmetics. Controlled delivery of different drugs together with metronidazole, ciprofloxacin, tenofovir, or diltiazem hydrochloride using bigel systems has been reported
- So far, applications of bigels are concerned and based on it, the research studies are conducted by the researchers as follows:
  - Sagiri *et al*., bigels exhibited lower drug release as compared to emulsion gel which was attributed to the structuration and aggregation of internal phase (oil phase) resulted in reduced permeability and lower dissolution of drugs
  - Satapathy *et al*. also reported the highest drug release from hydrogel followed by emulsion gel and then bigel which was associated with the conductivity and swelling behavior of formulations
  - Ibrahim *et al*. reported similar results of higher drug release rate from hydrogel as compared to bigels with the help of permeability studies of diltiazem hydrochloride using abdominal skin of rabbits. In contrary, higher drug release rate from bigels has also been reported as compared to hydrogel which was linked with the existence of fatty acids in fish oil
- (Drug release rate from bigels can be manipulated by varying the polymer fraction, the organogel content or the backbone structure of polymer chains [linear or branched]).
  - Recently, Andonova *et al*. reported the delivery of ketoprofen incorporated into the polymer carriers which

were basically embedded within the bigel formulation. Results revealed that the prepared formulation provided better drug photostability and controlled release together with an effective and safer formulation for dermal application.

- Therefore, future studies should be focused on the development of bigel systems having better drug release ability in addition to the excellent mechanical properties. Moreover, the utilization of bigel systems in food applications has not been explored yet, which can be an interesting field of research for further studies. In future, along with pharmaceutical and cosmetics applications, bigel formulations can be prepared and analyzed for food applications.[19-21]

CONCLUSION

In recent years, bigels are gaining importance due to its widespread applications in food, pharmaceuticals, and cosmetic industry. So far, researchers have explored the bigel systems mainly for controlled drug delivery for topical applications. These systems have been explored in academic research, but commercial products are still not established.

Moreover, oleogel and bigel formulations can prove to be suitable vehicles for local delivery of water-insoluble drugs. By comparing the mechanical properties of these three types of gels, the results provide valuable guidance for the future development of local semisolid formulations for periodontitis.

Therefore, further research needs to be conducted to address the potential issues such as stability, toxicity, and bioequivalence of bigels to establish them as ideal controlled delivery vehicles for topical applications.

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