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BIGEL: A REVIEW

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ABSTRACT

Bigels are semisolid formulations which are made by mixing of the two phases, oleogel and hydrogel which allow to load both hydrophilic and lipophilic drugs and enhance the stability of the gel, improve permeability, increase hydration property and can also control the rate at which drug is released. Main purpose of this review article is provide a brief information on bigels their types, characteristics, method of preparation and application.

KEYWORDS: Bigels, Organogel, Oleogel, Hydrogel, Gelators, Hydrophilic and Lipophilic.

INTRODUCTION

Bi-gels, are special robust materials. These are the amalgamation of the organo-gels and hydro-gels. To describe the gels two main aspects must be remembered (i) Rheological (ii) Structural pattern.[1] Centered on rheological characteristics a product can be interpret as a gel if the macro dimensions are immutable on the analytical structure's time scale and it is acting as a solid-like product.[2] Centered on a structural standpoint, gels are the structure's comprising molecules and chains that are partially joined together by physical and chemical connexions in a liquid medium and due to which lack of fluidity arises in this network.[3] Gels are semisolid consisting typically of two elements, solid and liquid. Solid components are known as gelator and liquid components are typically called as solvents.[4] Gels are usually formed by the ensnaring of the solvent system within the 3-Dimensional frame-network of a gelling agent.[5] In accordance with the (Polarity) charge on the solvent, gels are categorized into two categories – organo-gels (non-polar) and hydro-gels (polar solvent).[6] Several different categories of Gels such as emulgels and bigels have also been extensively studied in

the literature.[7]

Organogels are obtained by the self-assembling of either lower molecular weight components[8] or polymer to entrap the solvent phase.[9] Various organogelators such as, lecithin,[10] fatty acids, oryzanol,[11] steroids, fatty alcohol, and L-lysine have been explored in the literature.[12] Different solvents such as hexane, benzene,[13] edible oils, which further include sunflower oil,[14] and cod fish liver oil, corn oil, olive oil and almond oil have been examined.[15] These oils are very beneficial to health as they have nutritional advantage, antioxidant activity and long shelf life also.16] Due to the skin moisturizing, anti-inflammatory,[17] relaxing effects and anti-aging properties, edible oils are used extensively in the topical formulations.[18] The key drawback of the organogels is that they are oily and have sticky texture which makes it difficult to extract them after they are applied on the skin and thus have less patient compliance.[19] These are used for drugs and vaccines delivery via various routes of administration in the pharma industry however very few pharmaceutical products have been studied.[20]

Hydrogels can be defined as the 3-Dimensional. Hydrophilic, polymeric structural network capable of consuming significant amount of water or biological fluids.[21] These are jelly like system in which hydrogelators are present. The neutral or synthetic agents forms a 3-Dimensional network in order to trap polar or aqueous phase.[22] The 3-D networks are made up of the homopolymers and copolymers and they are insoluble due to the physical crosslinking such as intertwine and chemical crosslinking like junctions.[23] Unlike organogels, hydrogels are non-greasy in nature. These can be easily removed from the skin after the application. They also have good spreadability, cooling effect, and better stratum corneum hydration property.[24] Hydrogels can swell in the aqueous media as they have thermodynamic compatibility.[21] These have various application in medical and pharma industries in particular, hydrogels are equivalent to the natural tissue as they have high water content and soft consistency.[25]

The system of the bigels are very distinct from another system known in the literature. Bigels can be characterised as a class of material in which two insoluble liquids, are stabilized by the colloidal particles.[26] Firstly the colloidal particles are dispersed then sluggish heating is done above the critical temperature to prepare bigels.[27] Colloidal particles travel toward the new interface which is made after separation of the both phases due to the spinodal decomposition, due to the decrease in the interfacial area caused by the bicontinous phases

the particles become entrapped as the monolayer on the interface.[28] Bigels has the goodness of both the oily and aqueous phases. There are also certain disadvantage for Bigels, such as instability at high temperature and these are not thermo-reversible.[29]

Advantages of bigels as compared to organogels and hydrogels

Bigels significant characteristics are its increased constancy as compared to the emulsion (Like oil in water or water in oil), organogels, creams, emulgels, and hydrogels. Which make it an excellent carrier of the cosmeceutical and pharmaceutical agents. The formation of the extra fine colloidal dispersion can be due to the improved physicochemical stability of the bigels, which result in the preservation of the mobile phase in a 3-Dimensional network.[30] The two components do not get separated throughout storage at normal room temperature and remain stable.[31] Over time, emulsion gets destabilised and demonstrate phase separation. Thus they are stabilised by the introduction of the "emulsifier" during the preparation.[32] Bigels has both the merits of aqueous and oily phases and shows greater properties than both phases.[33] The main attributes of the bigels which make them interesting for the controlled drug delivery is the ability to deliver lipophilic (Hydrophobic) and hydrophilic drugs.[34]

Characteristics

Electronic, physical, rheological and thermal are the primary important characteristics of the bigels due to which they are used widely.[35] Effects of multiple parameter on mechanical properties of bigels are also studied in the literature.[29] Such as the material of the organogel/hydrogel, concentration of the polymer and its structure. On increasing the organogel important effects have been seen on the cohesion, firmness, adhesiveness, stickiness and viscosity of the bigels.[36] On increasing the quantity of the hydrogel increase in the hardness was observed.[19] The stickiness, firmness, spreadability of the bigels is effected by polymer concentration.[37] Bigels which contain branched polysaccharides showed high level of gel strength and also high resistance to deformation but they show poor stress relaxation properties.[38] On incorporating organogel into hydrogel (uniform mixing) the moisturizing effect was enhanced.[39] Final characteristics of bigels depend entirely on the structural distribution of both phases (organogel and hydrogel) and size of droplets of dispersed phase, both these can be studied by microscopic analysis.[29] Fraction of organogel in the formulation also determine the droplet size as on increasing the oraganogel fraction leads to formation of larger droplets.[40] But in some cases increasing the organogel content also leads to smaller droplets.[29] This unusual behaviour was due to the closer packing of the

droplets which leads to stability. Depending on the components used in the formulation the fraction of organogel can either amplify or diminishes the polydispersity.[40] Whenever it comes to drug delivery the viscosity and swelling properties are very important.[37] By using components which have high molecular weight viscosity can be enhanced.[38]

types of bigel

- **Oleogel in hydrogel.**
- **Hydrogel in oleogel.**
- **Bi-continuous bigel.**

Oleogel in hydrogel

This type of bigel is widely discussed in the literature. In this bigel the oleogel is present as dispersed phase and the hydrogel is the continuous phase (Fig. 1).[40] Various researcher have used different combination of oleogels and hydrogels for preparation of bigels such as Behera et al used Span40 and sunflower oil for oleogel and synthetic polymer such as polyvinyl alcohol for hydrogel.[34]

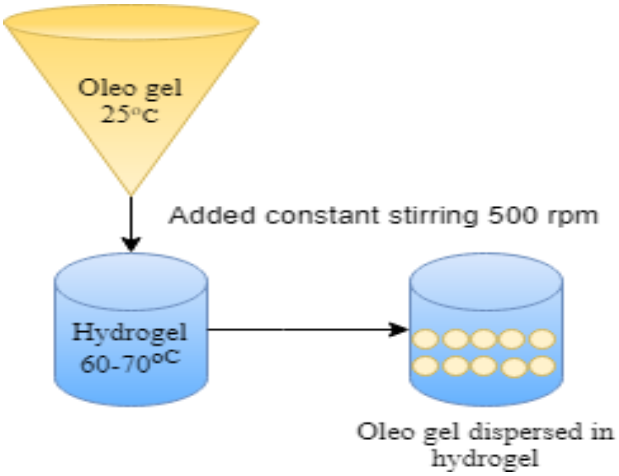

Fig. 1: Oleogel dispersed in hydrogel.

Hydrogel in oleogel

In this type of bigel the hydrogel act as the dispersing phase and oleogel act as the continuous phase (Fig. 2). Researcher such as Lupi and Patel et al. formed bigels from polysaccharides based hydrogel and fumed silica with sunflower oil oleogel.[41]

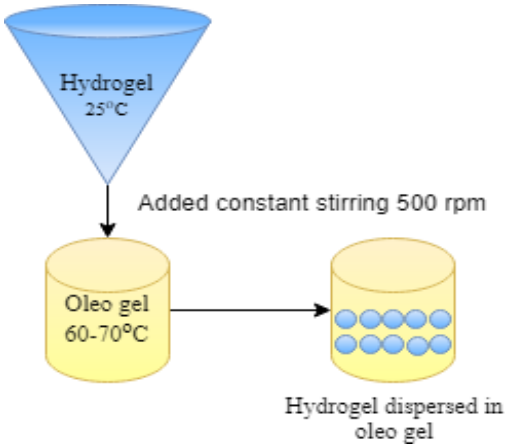

Fig. 2: Hydrogel dispersed in oleogel.

Bi-continuous bigel

In this type of bigel the high concentration of oleogel and hydrogel is dispersed within lower concentration of oleogel and hydrogel. Singh et al. formed bi-continuous gel by span60 and sesame oil based organogel and guar gum based hydrogel.[29]

METHOD OF PREPARATION

Both the gels (i.e Oleogel and hydrogel) are prepared separately and then mixed together by constant stirring at 500rpm to form bigel. Temperature is one of the most significant factor during the mixing period. High temperature of 60-70^{o}C is advised because at this temperature both the gels are in liquid state which allow the researcher to easily prepare homogenous formulation.[37,42]

Preparation of oleogel

Preparation of oleogel is done by weighing specific amount of organogelator and mixing it in predefined oil at a specific temperature which is higher than the melting point of the organogelator. The stirring is done at 500 rpm and it is left undisturbed to cool down after the temperature reaches 25^{o}C Oleogel is formed.[4]

Table 1: Different types of organogelators preparation of hydrogel.

Types of organogelators	Properties of organogelator	Example
4-tert-Butyl-1-Aryl Cyclohexanol Derivative Organogelators.	Solid at room temperature and less solubility in aprotic solvents.	Cyclohexane, benzene and carbon tetrachloride.
Polymer Organogelators	Gel prepared by these organogelator have low gel-sol transition	L-lysine, polyalkylene, PEG and polycarbonate

	temperature and high gel strength.	
Gemini Gelators	These have very high property for immobilizing aprotic	N-ε-lauroyl-L-lysine ethyl ester
	solvents	
Low molecular weight organogelators	These can immobilize high amount of aprotic solvent at very low concentration	Fatty acids and n- alkanes.

Preparation of hydrogel is done by weighing and mixing specific amount of hydrophilic gelling agent in distilled water at 60-70^{o}C and stirring is done at 500rpm.[7]

Table 2: Different types of hydrogelators.

Hydrogelators	Properties	Example
Polymeric gelling agents	Soluble in both water and alcohol and is mild acidic in nature.	Carbomer 934P, carbomer 940 and carbomer 941.
Cellulose based gelling agents	These can form gels at low temperature.	Hydroxypropyl cellulose (HPC), Hydroxypropyl methylcellulose (HPMC) hydroxyethyl cellulose (HEC) and carboxymethyl cellulose.
Natural gelling agents	Highly soluble in cold or hot water, give high viscosity at lower concentration and provide stability.	Xanthan gum, guar gum, pectin, gelatin and gellan gum.

Preparation of bigel

Bigels are prepared by adding the oleogel in hydrogel which is maintained at 60-70^{o}C and constant stirring. Mixing is done until homogenous mixture is obtained (Fig. 3). Smooth gel is formed when left undisturbed and temperature decreases.[29]

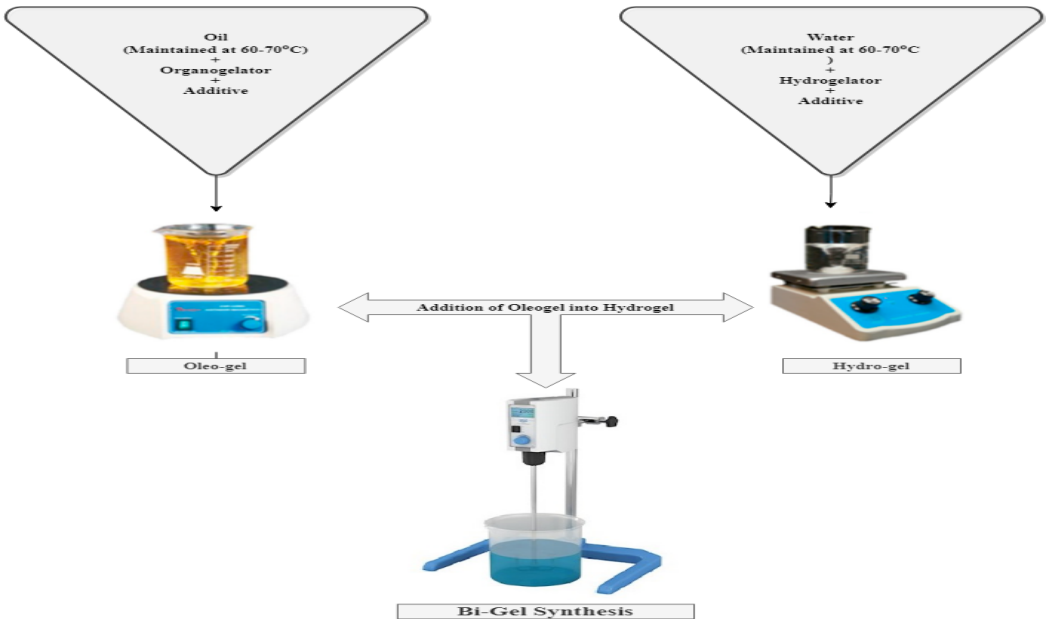

Fig. 3: Systematic representation of preparation of bigel.

Characterization

Organoleptic evaluation

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.[43] Bigel which contains high concentration of oleogel have high intensity of white colour and high spreading also.

Determination of pH

Digital pH meter were used to evaluate the pH of the formulation.[44]

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.[45]

Percentage Spreading = [(Di-Df)/Di] × 100

Extrudability

Ointment tube was taken and specific amount of gel was loaded into it. Extrudability of the gel was measured by calculating the length of the gel ribbon which was extruded from the ointment tube after uniform pressure was applied.[46] Extrudability is masured in (cm/s).

Extrudability = Distance travelled by gel in cm / 10 s

Thermal analysis

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^{o}C till 70^{o}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^{o}C as they became unstable and phase separation occurs.[7]

Drug content determination

Phosphate buffer was used to dissolve the drug incorporated bigel and kept undisturbed for at least 48h so that complete drug leaching occur. Then the dispersion which contain drug was filtered using Whatmann filter paper. The obtained solution was diluted properly and the absorbance was checked by using UV spectrophotometer at maximum wavelength of drug.[47]

***In vitro* drug release**

Dialysis membrane (HIMEDIA® LA 330-5MT) was used to check the in vitro release of the drug from the gels and was performed by using modified Franz diffusion apparatus.[48] In the donor compartment, specific amount of drug loaded sample was placed and the phosphate containing chamber (receptor chamber) was held at 32 ±0.5^{o}C. Sample of 1 ml was taken every hour and was replaced with fresh buffer system and process was continued for 7 hours. The data which was obtained was further analysed by zero-order, first-order, Korsmeyer-Peppas model and Higuchi equation.[49]

Accelerated stability studies

Freeze-thaw (F-T) thermocycles were performed (20min of freezing at 20^{o}C and 20min of thawing at 70^{o}C) 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 gives the long-term stability predictions.[50]

Droplet size distribution

One of the crucial parameter for the absorption of the drug from gels is distribution of droplet size. Small size of droplets gives us larger area of interfacial surface which leads to increase in the absorption of the drug and provide excellent stability. ImageJ software can be used to analyse the droplet size distribution.[51]

Formula used to calculate[52] SPAN = (D90-D10)/D50

Optical microscopy

Different types of microscopic techniques, including confocal microscopy, scanning electron microscope (cryo-SEM) and transmission electron microscope are used to study the mutual disposition of oleogel and hydrogel within the bigels. Fluorescent dyes are incorporated into both phases to identify oleogel and hydrogel.[41,53]

Fourier transform infrared (FTIR)

This spectroscopy is used to assess the functional groups which are present in the bigel formulation.[54] 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.[55] 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.

Mechanical properties

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.[56] The measurement is usually performed at standard room temperature (i.e 25^{o}C) 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 then bigel formation will not occur.[41]

Electric conductivity

To comprehend the conductivity profiles, the electrical property of the bigels are evaluated. A computer-controlled impedance analyser can be used to calculate the electrical profiles of the bigel.[53] The data is measured at room temperature in a specific frequency range. The influence of the current on the conductivity of the formulation helps us to understand their transport behaviour. Due to the ions which are present in the water phase, the bigels containing higher fraction of hydrogel exhibits greater conductivity.[57]

Photostability study

Photostability studies are conducted to assess the stability profile of the bigels in the presence of light. This further helps us in determining the type of packaging which will be used for the final product (i.e Primary or secondary packaging). These studies are performed in compliance with ICH Q1B guideline. Four different conditions are used for the testing of the product, i.e first- wrapped in an aluminium foil, second- packing in cardboard box, third- keeping it in container having label and last- label free container. After exposure is done to specific amount of light the formulation is evaluated for various parameters like pH, impurities, assay and appearance.[58]

Applications

Delivery of the drug is a specific procedure in which the release of the active pharmaceutical ingredient (API) to a specific site is done to achieve a specific therapeutic response.[59] Largest human organ is skin which provide protection against micro-organisms, heat, chemical and other toxins.[60] So, it is not easy to achieve drug delivery through the skin as very limited number of active agents have the properties which are required to cross the skin barrier. Transdermal delivery for the controlled release of the drug by skin has been thoroughly investigated. Some parameters which influence the permeation of the drug through the skin are blood flow at the site of application. Permeability of skin and physicochemical properties of the drugs used.[61]

Table 3: Different organic and aqueous phases.

Organic phase	Aqueous phase	Application	Reference
Cholesterol-span 60- based oleogel	Carbopol 934- hydrogel	Moisturizing effect	[30]
Almond oil-span 60- oleogel	Carbopol 940 in ethanol and purified water	Moisturizing topical effect	[62]
Sesame oil-span60- oleogel-	Carbopol 934-	Bacterial vaginosis	[36]

metronidazole	hydrogel		
Sesame oil- span 60- oleogel	Cabopol 934-hydrogel	Intophoretic delivery of drug	[63]
Sunflower oil-span 40-oleogel	Polyvinyl alcohol-hydrogel	Controlled delivery system	[37]
Fish oil-oleogel	Carbopol 934/940-hydrogel	Enhanced antitumor activity	[55]
Sesame oil-stearic acid-oleogel	Gelatin-hydrogel	In-vitro release of drug (ciprofloxacin)	[64]
Organogel with policoosanol	LM-pectin-hydrogel	Cosmetics and pharmaceutical	[40]
Span 40-sunflower oil	Natural gum-hydrogel	Controlled release of drug	[65]
Stearyl alcohol oleogel	Agar hydrogel	Controlled release of drug	[43]
Bovine serum albumin	Gelatin	Drug delivery and tissue engineering	[33]

CONCLUSION

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 ability of loading both hydrophilic and lipophilic active agents increases the patient compliance. These system have been studied, but no commercial goods have been developed. As these were first developed in 2008 with a vision to overcome the various problems like phase separation of emulgels and also increase the loading capacity drug.

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