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Review Article

BI-GELS: A NOVEL MATERIAL FOR TRANSDERMAL DRUG DELIVERY

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ABSTRACT

Bi-gels semi solid formulation is combination of organogel and hydrogel with better application property such as pharmaceutical and cosmetics. The main objective of this review is specially focuses on application of bi-gels as drug delivery vehicles by transdermal route. It contains two different phases which are polar and nonpolar due to which, it possess some significant features such as ability to deliver the hydrophilic and hydrophobic drugs which also have improved permeability of drugs, better spreading ability, and water wash ability. Hence, bigels have both organogels and hydrogels they can enhanced hydration of stratum corneum and also had an ability to manipulate the drug release rate from the dosage from.

Keywords: Bi-gels, Hydrogels, Organogels, Transdermal drug delivery.

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INTRODUCTION

Due to high patient compliance, topical drug delivery is one of the commonly used drug delivery system. The formulation is applied over the skin, where skin is one of the largest organs in the body. Skin has several functions in the body which includes protection from microbes, thermoregulation, physical stress, and even from harmful radiation such as UV rays from sunlight. It has got good patient compliance when compared to other conventional method due to the following reason such as easiness of application, painless application, does not required trained medical staff for administration, helps in avoiding first pass metabolism, and can be applied to all types of patient regardless of age. Such merits made this particular route of administration one of the best in medical field.

Gels are semisolid formulation which is composed of two phases contain solid and liquid [1]. Solid phase contain gelling agent/gellator and liquid phase contain solvent. On the basis of polarity of the solvents gels are categories into different types organogel (Nonpolar solvent), hydrogel (Polar solvent).

Some new gels have also been reported such as emulgels and bi-gels [2]. They have good water content present in their structure providing hydration of stratum corneum. The hydrogel present in the bigel helps in proper hydration of stratum corneum, and the organogel present in the bigel helps in increased penetration.

Bi-gels are quite new as compared to other gels formulations. These are uniform semisolid dispersion system which contains that two gel phases are mixed together with the help of high shear rate and appear to visually seen as single gel phase [3].

ADVANTAGES OF BIGELS OVER ORGANOGELS AND HYDROGELS [4,5]

1. Improved stability.
2. Imparts wash ability.
3. Good patient compliance without compromising the beneficial effects of the oil.
4. They are easy to prepare.
5. Less amount of surfactant, less toxic.
6. They can accommodate both the hydrophilic and lipophilic drugs due to the presence of two phases.
7. It can easily penetrate through the skin. Hence, it is better choice for transdermal drug delivery.
8. Bi-gels are capable to regulating the delivery of active substances.
9. It is suitable carrier for iontophoretic drug delivery.

DISADVANTAGES

1. Phase separation in the absence of emulsifier.
2. Bi-gels are unstable at higher temperatures and thermo-irreversible.

TYPES OF BIGELS [6-10]

Bi-gels preparation are classified into four categories (Fig. 1).

Oleogel dispersed in hydrogel system (O/W)

This type of bi-gels contains oleogel as dispersed phase within the hydrogel as continuous phase.

Hydrogel dispered in oleo gel (W/O)

This type of bi-gels contains hydrogel as dispersed phase with in the oleogel as continuous phase.

Bicontinuous bi-gel

These bi-gel are formed when the gel formation is carried out at higher proportion of hydrogel/oleogel dispersed in lower proportion of oleogel/hydrogel phase, respectively.

Complex bi-gel

These bi-gels are prepared by adding organogel/hydrogel to an oil-in-water/water-in-oil structured emulsion.

METHOD OF PREPARATION OF BI-GELS

Preparation of hydrogel

Hydrogel is aqueous dispersion phase containing three dimensional network. Three dimensional network formed by either natural or synthetic gelling agent such as hydrogelator to immobilize the aqueous phase [11]. Important process parameters, such as shear speed and temperature, should be optimized based on the gelling behavior of the system [12]. The physical hydrogels are reversible in nature and gellation is attributed to some interaction such as Van der Waals force and hydrogen bonding. Chemical hydrogels are also called as permanent gels which are formed through covalent bonding results in the formation of cross-linked network [13] and schematic diagram of preparation of hydrogels (Fig. 2).

Preparation of oleogel

Oleogel is organogel phase usually made by self-assembly of either polymer or low molecular weight components to entrap the aqueous phase [14-17]. Accurately weighed quantity of organogelator such as fatty acids, fatty alcohol, lecithin, waxes, cyclodextrins steroids, and its derivatives, in predefined oil phase at a constant homogenization condition and temperature higher than melting point of the organogelator. The gellation will be formed when the temperature is brought down to room temperature 25°C [18-24].

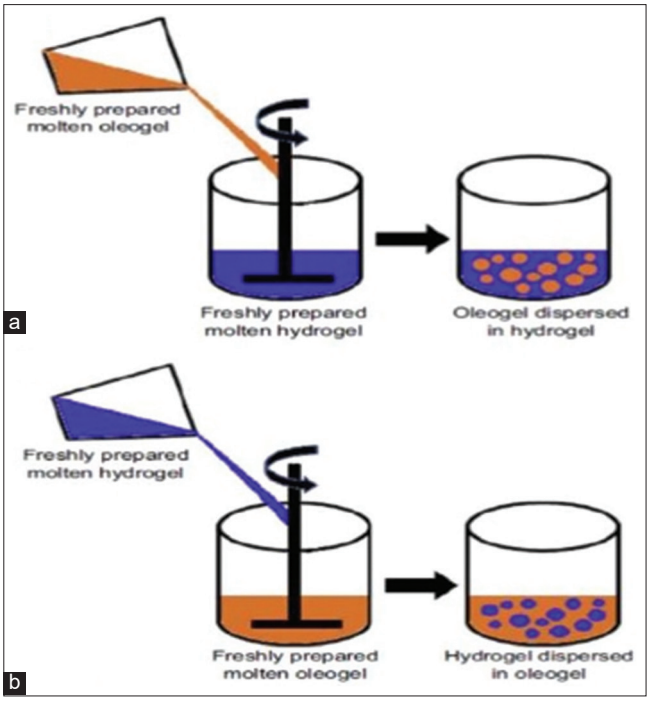

Fig. 1: Schematic diagram representing the formation of different types of bi-gels (a) oleogel dispersed in hydrogel and (b) hydrogel dispersed in oleoge

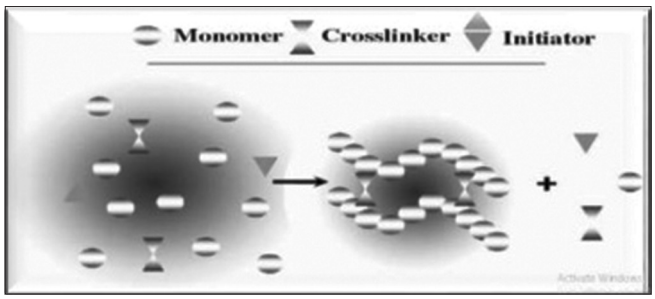

Fig. 2: Schematic diagram of preparation of hydrogel

Preparation of bi-gel

Bi-gel is prepared by mixing of hydrogel and oleogel at high shear rate without alter the characteristic properties of the both component. The homogenous mixture forms a smooth gel at particular shear speed and temperature. The stable bi-gel formation mainly depends on the composition of both the phases. Finally, gel formation checked by the tube inversion test method [25] and schematic diagram of preparation of hydrogels (Fig. 3).

CHARACTERISTICS

Bi-gels are characterized for physical, mechanical, structural, thermal, rheological, and electrical properties for their utilization in different commercial applications [26].

The mechanical properties are affected by several parameters such as oleogel/hydrogel content, polymer structure (linear or branched), and concentration of polymer. The increasing in concentration of oleogel leads to stiffness, cohesiveness, viscosity, firmness, adhesives and creep recovery of bi-gels [27]. Likewise increasing the concentration of hydrogel content leads to increase in hardness was observed. Bi-gels containing branched structured polymer as water structuring agent show higher gel strength and better resistance than liner structure polymer, but it had poor stress relaxation [28]. The water structuring agent shown profound effect such as firmness, stickiness, spread ability, stickiness, stress relaxation, and residual stress of the bi-gel system [29].

Structural properties also major factor of bi-gel stability. The structural distribution of each phase within the system and droplet size in the dispersed phase can be easily estimated by the microscopic analysis [27].

Physical properties are easily estimated after preparation of bi-gel cool down at room temperature and subjected to analysis of appearance, color, homogeneity, consistency, etc. In general, bi-gels are in white to off-white in color and viscous in nature.

Thermal properties also an important attributes of bi-gel stability for their successful commercial utilization. Thermal stability of bi-gels enhanced by increasing the oleogel phase or organo gelator concentration [6,30,31]. Thermal properties of the bi-gel are studied using the differential scanning calorimetry performed under inert N_2 gas atmosphere using aluminium crucible with pierced aluminum lid. Fifteen milligram of prepared formulation were taken and keep into aluminium crucible with pierced aluminum lid and subjected to melting and crystallization at defined temperature from 25°C to 150°C. The changes in entropy during melting were calculated using Eq. 1.

$$\Delta G=\Delta H_m-T_m\Delta S \quad (1)$$

Where, △G = Gibbs' free energy, △G is zero at the melting point of the material, though the enthalpy and the entropy of the sample increase.

The melting occurs at the point when DG of the liquid becomes lower than the solid. Electrical characterization is an important factor to quantify the different parameters of the bi-gel such as electrical conductance,

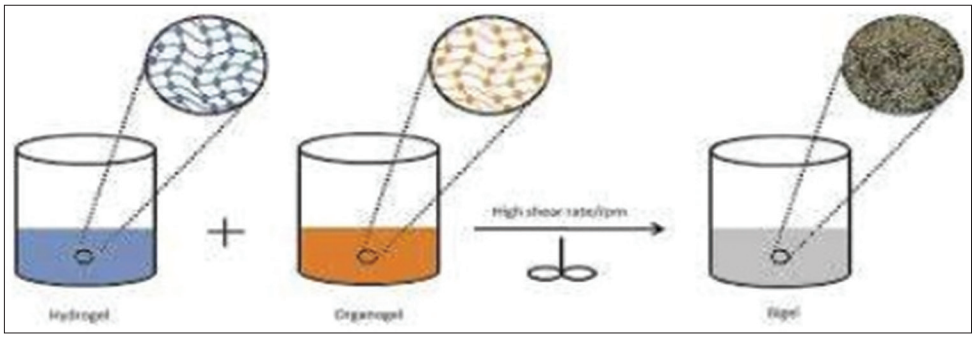

Fig. 3: Schematic diagram of preparation of bi-gel

Table 1: Different bi-gel systems in the literature are reported for drug delivery applications

Oil phase	Organogelator	Hydrogelator	Drug incorporated
Corn oil	DIMODAN® monoglyceride	K-carrageenan	β-carotene [1]
Sweet almond oil	Span 65	Alginate	Cetavlon® [3]
Sunflower oil	Sorbitan monopalmitate (Span 40)	Guar gum, Acacia gum, Xanthan gum	Metronidazole [35]
Sunflower oil	Mixture of span 80 and tween 80	Guar gum, Acacia gum	Metronidazole [36]
Sunflower oil	Sorbitan monopalmitate (Span 40)	Sodium alginate, Sodium carboxy methyl cellulose, Maltodextrin, Starch.	Metronidazole. L.Palatrum (Lp299v) [31]
Sunflower oil	Sorbitan monopalmitate (Span 40)	Polyvinylpyrrolidone Poly (vinyl alcohol)	Metronidazole [28]
Sunflower oil	Sorbitan monopalmitate (Span 40)	Gelatin, Whey protein	Metronodazole [37]
Soyabean oil	Sorbitan monosterate (Span 60), Cetyl alcohol, Lecithin pluronic	Hydroxypropylmethyl cellulose	Diltiazem HCL [38]
Fish oil	Beeswax	Sodium alginate, Hydroxy propyl methyl cellulose	Imiquimode [27]
Sesame oil	Sorbitan monosterate (Span 60)	Gelatin	Ciprofloxacin [39]
Sesame oil (or) soyabean oil	Steric acid	Gelatin	Ciprofloxacin [40-42]
Sesame oil	Sorbitan monosterate (Span 60)	Guargum	Metronidazole [40]
Sesame oil	Sorbitan monosterate (Span 60)	Carbopol	Metronidazole [27]
Sesame oil	Sorbitan monosterate (Span 60)	Guargum	Ciprofloxacin [8]
Soyabean oil	Steric acid	Mixture of agar and gelatin	Metronidazole [43]
Rice bran oil	Stearly alcohol	Agarw	Ciprofloaxacin HCl [5]
Fish oil	Bees wax	Carbopol	Imiquimod [41]
Alomond oil	Sorbitan monosterate (Span 60)	Carbopol	Ketoprofen [44]
Isopropyl palmitate	Mixture of soya lecithin and pluronic	Hydroxy propyl methyl cellulose	Flubiprofen [45,46]
TegoSoft® CT (Caprylic/capric triglycerides)	Compritol® (Liquid excipient of glycerylbehenate).	Carbopol	Ibuprofen [47]
Rice bran oil	Steric acid	Tamarind gum	Moxifloxacin [48]
Liquid paraffin	Polyethylene	Poloxamer 407	Ciclopirox olamine and terbinafine HCl [49]
Oleogel	Polyethylene	Carbopol	NSAIDS [50]
-	Sorbitan monostearate (Span®60) and polysorbate 60	Chitosan, HPMC	Tenofovir [51]

electrical resistance, and impedance, these parameter are directly associated with the efficacy of the controlled drug delivery. Electric conductance is key parameter for the phase inversion phenomenon during production, mixing, processing, and handling of multiphase systems [32-34]. Therefore, electric property of bi-gel analyzed by electrical conductivity analysis. The electric profile measured using computer-controlled impedance analyzer. The measured data within the range of (0.1 Hz–1 MHz) at room temperature. It helps to understand the transport behavior under influence of current and microstructural arrangement of the system [9]. The O/W shows conductivity behavior due to higher ions present in water phase, whereas W/O shows insulative behaviors approximately zero electric conductivity [33].

Rheological properties such as viscosity and swelling behavior of bi-gel are also important factors to be consider for the drug delivery. Higher viscosity system containing higher molecular weight-branched chain polymer and higher concentration of organogellator. Higher the concentration of hydrogel results to decreases the viscosity of the bi-gel system [35].

APPLICATIONS

In recent years, numerous bi-gel systems has been proposed particularly in the drug delivery. Most of these bi-gel systems are used as a carries for the controlled drug delivery of active ingredients for topical and transdermal application. Different bi-gel systems are reported in the literature for control drug delivery, as reported in Table 1.

CONCLUSION

In recent times, different bi-gel systems have been produced and modified according to the needs of different applications of drug delivery. This present review represents the importance of characteristics, different types of bi-gel system and its preparation, advantages of bi-gel system, and its application in drug delivery. Moreover, utilization of this system in pharmaceutical field has also been discussed.

FUTURE PROSPECTIVE

Bi-gels are emerging class of material, and therefore, extensive analysis of this system is required for commercial application. In this review, detailed discussion of different important parameters, such as storage of bi-gels and mixing speed, mixing temperature, addition of appropriate amount of organogelator and hydrogelator, and organogel/hydrogel ratio, are required for the preparation of bi-gel [52-57]. For future prospective, further investigation is required in this area to prepare a system with characteristic properties together with enhanced the drug delivery and release rate. Moreover, along with the pharmaceutical application, bi-gel system preparation is becoming a most emerging trend in the cosmetic and food applications.

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