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Guar gum and sesame oil based novel bigels for controlled drug delivery

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ABSTRACT

Bigels are novel semi-solid formulations which have been drawing attention of many research scientists due to their numerous advantages over the conventional gels. The objective of this study was to develop and characterize novel bigels by mixing guar gum hydrogel and sorbitan monostearate-sesame oil based organogel for controlled drug delivery applications. The confocal microscopy suggested the existence of both aqueous and oil phases together as bigel. Micro-scale deformation (viscometric) analysis in conjugation with macro-scale deformation studies suggested shear-thinning and viscoelastic nature of the bigels. Thermal study suggested an increase in thermal stability with the increase in organogel proportion in the bigels. The developed bigels were biocompatible in nature. The *in vitro* drug release study showed that the release of ciprofloxacin (lipophilic drug) increased with a decrease in the organogel content. Further analysis showed that the drug release from all the bigels followed zero order diffusion kinetics which is desirable for a controlled release system. The drug loaded gels showed good antimicrobial efficiency against *Bacillus subtilis*. In conclusion, the developed bigels may be tried as matrices for topical drug delivery.

1. Introduction

Gels are semi-solid substances in which a liquid phase is entrapped within a three dimensional network forming a supramolecular architecture [1]. They are broadly classified into hydrogels (if the liquid component is polar) and organogels (if the liquid component is apolar) [2]. Bigels are novel semi-solid formulations prepared by mixing two gels at a high shear rate [3]. The bigels can either be a mixture of two colloidal gels (identical or different types) separated through different specific interactions [4,5] or can be a mixture of an aqueous gel (hydrogel) and an oleogel (organogel) [6,7]. Bigels differ from emulsions, creams and emulgels as they do not require surfactants or emulsifiers [8]. Bigels do not show demixing of the two phases on storage at room-temperature for a period of up to 6–12 months [4]. They are stabilized by entrapment of the mobile phases via a three-dimensional gel network resulting in an extra-fine dispersion. Bigels are electrically conductive in nature (irrespective of the composition). This has been ascribed to the presence of pockets of water present in the bigels which allow electrical conduction [6].

As a pharmaceutical formulation, bigels possess many advantages over other semi-solid systems that include the synergistic effect of both gels, ease of preparation, absence of surfactants related toxicity and possible delivery of both lipophilic and hydrophilic drugs. As no extensive study has been carried out so far, bigel systems may suffer from some drawbacks like phase separation due to absence of emulsifier. Also, they are not thermoreversible as they may get destabilized at higher temperatures [3]. The concept of bigels is relatively new. Very little literature is available for the use of bigels in the field of drug delivery. Almeida et al. (2008) claimed the first report on bigels by mixing hydrogel and oleogels. They evaluated bigels based on stability, mechanical properties and moisturizing effect [6]. Varrato and Michele et al. (2012) reported the formation of self-assembled bigels by arrested demixing in binary colloidal mixtures [5]. Again in 2014, the authors reported aggregation dynamics, structure and mechanical properties of colloidal bigels [4]. In 2013, Ibrahim et al. prepared different bigel system by mixing hydrogels and organogels in different proportions. They reported a comparative study of the organogels, hydrogels and bigels for the transdermal delivery of diltiazem hydrochloride [7]. Though bigels have shown great promises as

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delivery matrices for topical application, there is a need for extensive study of the properties and possible applications of the bigels.

Guar gum is a natural polymer extracted from *Cyamopsis tetragonoloba* [9]. It consists of high-molecular-weight polysaccharides composed of galactomannans which are linear chains of (1,4)-linked-β-D-mannopyranose backbone with branch points at their 6-positions linked to α-D-galactose residues as side chains [10]. It is approved by Food and Drug Administration (USA) to be used as emulsifier, thickener and stabilizer in food, pharmaceutical and cosmetic products [9]. In recent years, scientists have used guar gum as a rate controlling agent for controlled delivery of bioactive molecules [11–14]. Sorbitan monostearate (SMS) is a non-ionic surfactant used as an emulsifier in pharmaceuticals and cosmetic formulations [15]. It is also been used as an organogelator to form organogel with a number of organic solvents including vegetable oils (e.g. sunflower oil, soybean oil, olive oil, and cottonseed oil) [16]. Since ancient times, sesame oil has been used extensively in a variety of pharmaceutical products due to its anti-inflammatory, anti-viral, anti-fungal and anti-bacterial properties [17]. It slows down the ageing process of the skin due to its high antioxidant property. The antioxidant property is associated with its major fatty acid components: sesamol and sesamolin [18].

Ciprofloxacin (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid) is a synthetic broad spectrum fluoroquinolone anti-bacterial drug. It is widely used in the treatment of mild to moderate urinary, skin, gastrointestinal, abdomen, eye and respiratory tract infections caused by Gram positive and Gram negative bacteria [19–21]. There are a number of semi-solid formulations available in the market for topical application of ciprofloxacin [22]. Besides that, different research groups have chosen ciprofloxacin as a model drug for studying controlled delivery applications [23–26]. Hence, it was chosen as the model drug to study the *in vitro* drug release kinetics from the bigels.

In this work, we report the preparation of sesame oil-guar gum-sorbitan monostearate bigels of varying compositions, its physico-chemical characterization and drug delivery application. The stable bigels were characterized by confocal microscopy, viscosity, mechanical analysis, differential scanning calorimetry and cytocompatibility study. Ciprofloxacin loaded bigels were checked for their *in vitro* release behavior and antimicrobial efficiency studies.

2. Materials and methods

2.1. Materials

Guar gum (Merck, India), sorbitan monostearate (Loba Chemie Pvt. Ltd.), sesame oil (Tilsona®, Recon Oil Industries Pvt Ltd, India) and microbial culture of *Bacillus subtilis* (National Collection of Industrial Microorganism, India) were used in this study. Ciprofloxacin was provided as a gift by Aristo Pharmaceuticals Pvt Ltd, India and was used as received. Ciprofloxacin ophthalmic ointment (CIPLOX®) was purchased from Cipla, India. Nutrient agar, propyl paraben, Dulbecco modified Eagle's medium (DMEM), Fetal Bovine serum (FBS), 0.25% trypsin-EDTA and MTT were procured from Himedia laboratories Pvt. Ltd, India. HaCaT cell line was kindly provided by Dr. T.K. Maiti, IIT Kharagpur, India.

3. Methods

3.1. Preparation of bigels

3.1.1. Preparation of the hydrogel

1 g of guar gum was added to 90 g of water (70 °C), kept under stirring (1000 rpm) using an overhead stirrer until a smooth transparent mixture was obtained. The weight of the solution was made to 100 g using warm water. The hot mixture was then allowed to cool down to room-temperature (25 °C) for 2 h. Guar gum, being a natural polymer, is prone to bacterial attack, hence propyl paraben (0.02% w/w) was added to the water as a preservative before the addition of guar gum [27].

Table 1
Compositions of the bigels (20 g).

Formulations	Hydrogel (g)	Organogel (g)	Ciprofloxacin (g)
GG1	17.78	2.22	–
GG1C	17.78	2.16	0.06
GG2	16	4	–
GG2C	16	3.94	0.06
CG3	14.55	5.45	–
GG3C	14.55	5.39	0.06
GG4	13.33	6.67	–
GG4C	13.33	6.61	0.06

3.1.2. Preparation of the organogel

Accurately weighed sorbitan monostearate (15% w/w) was added in sesame oil (70 °C), kept under stirring (500 rpm) using an overhead stirrer. The hot transparent mixture converts into organogel when cooled to room-temperature [28]. Ciprofloxacin loaded organogel was prepared in the similar manner. The amount of ciprofloxacin added to the organogel was such that the final concentration of the drug in the prepared bigels was 0.3% w/w.

3.1.3. Preparation of the bigel

The prepared hydrogel and organogel were kept overnight (~24 h) at 4 °C before use. The apolar phase (organogel, 70 °C) was slowly incorporated into the aqueous phase (hydrogel, 70 °C), kept on stirring (1000 rpm) using an overhead stirrer [6]. The stirring was continued until a homogenous mixture was obtained. The compositions of the prepared bigels have been tabulated in Table 1.

The prepared bigels were checked for presence of physical instability such as bleeding (separation of liquid), grittiness, discoloration, breakdown, crystal growth, shrinking due to evaporation of water, microbial growth and change in odour or pH. The pH of the bigels was determined using a pH meter (EI instruments, 132E) at room-temperature at regular intervals. The amorphous nature of the bigels was checked by X-Ray Diffraction studies (PW3040, Philips Analytical ltd., Holland) in the range of 5° 2θ–50° 2θ at a scanning rate of 2° 2θ/min [28].

3.2. Stability studies

Biphasic formulations usually undergo destabilization. The stability of the prepared bigels and ciprofloxacin loaded bigels was tested by thermocycling and intermediate stability studies. The stable formulations were selected for further analysis.

3.2.1. Accelerated stability study by freeze–thaw thermocycling method

The bigels were passed through five cycles of freeze-thaw thermocycling. Each cycle consisted of 15 min of freezing (−20 °C) followed by 15 min of thawing (70 °C). At the end of five cycles, the bigels were checked for any visible, physical and organoleptic changes [29]. The stability of ciprofloxacin was checked after each freeze-thaw cycle of the ciprofloxacin loaded bigels. ~1 g of the sample was collected after each cycle and the drug release was performed for 1 h through the pre-activated dialysis membrane using modified Franz's diffusion cell. The releasate was analysed spectroscopically in the UV region (200–400 nm) [30].