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Viscoelastic and thermal properties of doxycycline hyclate-loaded bleached shellac *in situ*-forming gel and –microparticle

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ABSTRACT

Bleached shellac is the aqueous insoluble natural resin lac which is interesting to be used as a matrix former for *in situ* forming gel (isg) and *in situ* forming microparticle (ism). The main aim of this research is to understand the viscoelastic and thermal properties of doxycycline hyclate (DX)-loaded bleached shellac isg and ism which were prepared into solution and emulsion, respectively using dimethyl sulfoxide (DMSO), *N*-methyl-pyrrolidone (NMP) and 2-pyrrolidone (PYR) as the solvents. The prepared isg and ism were suitable for local injection because of their newtonian or pseudoplastic flows. In the case of ism systems, the trend of viscosity was similar with isg but their viscosity was lower because of the presence of oil in the external phase. The higher intermolecular strength of polymer could delay the thermal degradation rate. In ism, the intermolecular force not only related with solvent but also stabilizer therefore the stronger bonding between solvent and glyceryl monostearate (GMS) triggered superior entanglement as system prepared with DMSO. DSC profiles also supported all these behaviors of solvent state in polymer but ism was covered by hindrance effect of oil phase. The process of preparation did not damage the compositions basically assured by thermal analysis techniques.

1. Introduction

In situ forming gel (isg) exhibits a sol-to-gel phase transition from which polymer transforms solution state into solid state or semisolid state with its convenient residence time at specific site [1]. *In situ* forming microparticles (ism) is an injectable emulsion. It comprises the drug-loaded internal phase containing polymer which is dispersed into the external phase usually oil. The emulsion is achieved by pushing two syringes coupled with a connector [2]. After contacting this emulsion with body fluid, the droplets of the internal phase were solidified and spontaneously formed into a solid matrix. However, the main obstacle was the relatively low physical stability of ism emulsion [3,4]. This research employed the isg prepared from bleached shellac as the internal phase of ism.

Shellac is the natural product from resin lac which is secreted by a parasitic insect, *Kerria lacca* [4]. The chemical structure of this material comprises a complex mixture of esters and polyesters of polyhydroxy acids. The total shellac composition is aleuritic acid, about 70 percent of homologous shellolic acid, and a small amount of free aliphatic acids [5]. The acidic structure results in its solubility depended on pH therefore shellac is practically soluble in alkaline solution. Likewise, it dissolves in some organic solvents e.g. ethanol, methanol, and partially soluble in ether, ethyl acetate and chloroform [4]. Bleached shellac is prepared by treating the dissolved polymer with sodium hypochlorite [6]. An antimicrobial agent loaded-bleached shellac system comprising *N*-methyl pyrrolidone (NMP) as solvent was formed into the isg or ism in the simulated gingival crevicular fluid when the solvent exchange and polymer precipitation occurred [7,8]. Gel formation capacity depended on the bleached shellac amount. More sustainable drug release was achieved as an amount of bleached shellac was increased. Antimicrobial agent loaded-BS system effectively inhibited *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus mutans* and *Porphyromonas gingivalis* therefore they exhibited the potential use as localized delivery systems for periodontitis treatment [7,8].

Typically the basic solvents for isg or ism are water miscible liquids including dimethyl sulfoxide (DMSO), NMP and 2-pyrrolidone (PYR). The ideal solvent for *in situ* systems needs to gain appropriate properties in terms of water affinity, viscosity, ability to dissolve the polymer and its safety [9,10]. The viscosity of solvent should be suitable to further facilitate an easy injection of formulations or good syringeability. Systems prepared with water-immiscible solvent exhibited a viscous feature leading to difficult injection which requires a warm-up step prior administration [11]. It presents a high achievement of the higher polymer and drug loading which further reduces the injection volume. However, the type and amount of solvent typically affect the viscoelastic and thermal properties of polymer solution or emulsion.

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Previously, the doxycycline hyclate (DX) loaded-*in situ* forming formulations were prepared using high loading bleached shellac as a gelling agent for periodontal healing [7,8]. Solvent effect on fluid characteristics of DX-loaded bleached shellac isg and ism formulation has been reported recently [12]. However, their viscoelastic and thermal properties influenced by used solvents (DMSO, NMP and PYR) have not been investigated. Therefore the main aim of this present research is to better understand the viscoelastic and thermal properties of DX-loaded isg and ism comprising bleached shellac as a polymer.

2. Materials and methods

2.1. Materials

Bleached shellac (Ake shellac Co. Ltd., Lumpang, Thailand) with an acid value of 70–95 mg KOH/g, loss on drying less than 3.5% and colour index of 2 was used as received. DX (Batch No. 20071121, Huashu Pharmaceutical Corporation, Shijiazhuang, China), was used as the model drug. Olive oil (Lot no. L4418R, Bertolli, Italy) was used as a medium of the external phase. Glyceryl monostearate (GMS) (PC Drug, Bangkok, Thailand) was used as an emulsion stabilizer. NMP (lot no. A0251390, Fluka, New Jersey, USA), DMSO (lot no. 453035, Fluka, Switzerland) and PYR (lot no. BCBF5715V, Fluka, Germany) were used as the solvents for bleached shellac.

2.2. Preparation of isg and ism

The 30% w/w bleached shellac and 10% w/w DX were dissolved in DMSO, NMP or PYR to prepare as the isg. The formulations of isg and ism are shown in Table 1 (A). For ism preparations, their internal phases were the components of isg. The 5% w/w GMS dissolved in olive oil (external phase) was prepared at 80 °C under continuous mixing until obtaining a clear solution and converted into the milky dispersion under an ambient condition. The ism components are shown in Table 1 (B). The 1:1 the internal phase: the external phase were mixed into ism emulsion with 2 syringes coupled with a connector (Qosina, USA). The emulsification was achieved by back-and-forth movement of the syringe plungers for 50 mixing cycles for 1–2 min in 3 ml single-use syringe as previously described to prepare the ism [13,14]. However, NMP exhibited a partial miscible with olive oil; thus, generated a rapid phase separation as previous investigation [12]. Therefore DMSO and PYR could be used as the solvents to fabricate into the o/o emulsion of ism.

Table 1
Composition formula of drug free and DX-loaded isg and ism using different solvents.

(A)

Formula	Amount (%w/w)				
	Bleached shellac	DX	Solvent		
			DMSO	NMP	PYR
DMSO isg	30	–	70	–	–
NMP isg	30	–	–	70	–
PYR isg	30	–	–	–	70
DXDM isg	30	10	60	–	–
DXN isg	30	10	–	60	–
DXP isg	30	10	–	–	60

(B)

Formula	Amount (%w/w)					
	Internal phase				External phase	
	Bleached shellac	DX	Solvent		Olive oil	GMS
			DMSO	PYR		
DMSO ism	15	–	35	–	47.5	2.5
PYR ism	15	–	–	35	47.5	2.5
DXDM ism	15	5	30	–	47.5	2.5
DXP ism	15	5	–	30	47.5	2.5

2.3. Evaluations

2.3.1. Appearance viscosity and rheological behavior

The appearance viscosity and rheology of the prepared isg and ism were investigated using Brookfield DV-III Ultra programmable rheometer (Brookfield Engineering Laboratories. Inc., USA) (n = 3). The flow parameters were characterized using the exponential formula when N is an exponential constant and ŋ' is a viscosity coefficient [15].

2.3.2. Viscoelastic behavior studies

The viscoelastic properties of isg and ism were assessed using a small-amplitude oscillatory shear experiment. The dynamic rheological behaviors, including dynamic strain sweep, dynamic frequency sweep and dynamic temperature sweep were investigated with rheometer (Kinexus rheometer, model KNX 2100, Marvern, UK) using plate-and-plate geometry (CP1/50 diameter 50 mm). For each measurement, to minimize shearing during sample loading, approximately 0.56 ml of each sample was carefully loaded onto the plate using a micropipette (n = 3).

2.3.2.1. Dynamic strain sweep. A dynamic strain sweep was first performed from 0.01 to 100% at ω = 1.0 Hz before the dynamic viscoelastic measurements. The storage modulus was recorded to define the linear viscoelastic region (LVR) on which the storage modulus is independent from the strain amplitude. Selecting a strain (γ) in the serial oscillation tests which the dynamic oscillatory deformation of each sample was within the LVR.

2.3.2.2. Dynamic frequency sweep. The viscoelastic parameters (log mode), including shear storage modulus or elastic modulus (G', "solid like") and loss modulus or viscous modulus (, "liquid like") as functions of angular frequency (ω) were measured over a range of 0.1–10 rad/s at selected strain (γ) of sample series under 25 °C which the complex modulus (G^*), complex viscosity (η^*) and loss tangent ($\tan\delta$) were recorded.

2.3.2.3. Dynamic temperature sweep. The gelification temperature of the polymeric systems was investigated by monitoring the variation of the elastic and viscous moduli with the temperature in the range from 20 to 45 °C, at a fixed frequency of 1 Hz, heating rate at 50 °C/min and selected strain (γ) of sample series.

2.3.3. Thermal property studies

Thermal properties of each component, isg and ism prepared with different solvents were determined using the thermal gravimetric analysis (TGA) (Pyris TGA, PerkinElmer, USA) and differential scanning calorimetry (DSC) (Pyris Sapphire DSC, Standard 115V, Perkin Elmer instruments, Japan). TGA experiments were conducted in the temperature range from ambient temperature to 600 °C. The constant heating rate was 5 °C/min. The activation energies of crystallization or phase transformation of the samples were also measured by DSC. For solid samples, the temperature range was from an ambient temperature to 300 °C except the bleached shellac which was evaluated in the temperature range from an ambient temperature to 100 °C and −100 °C to 300 °C. For liquid samples, the temperature range was −100 °C to 100 °C. All the DSC tests were studied at a heating rate of 10 °C/min.

2.3.4. Statistical analysis

Statistical significance of the measurements was examined using the one-way analysis of variance (ANOVA) followed by the least significant