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Parenteral thermo-sensitive organogel for schizophrenia therapy, in vitro and in vivo evaluation

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ABSTRACT

Novel biodegradable in situ forming organogel, obtained via the self-assembly of long chain fatty acid in pharmaceutical oil, was prepared and characterized. Different from traditional organogels, the use of organic solvent was avoided in this gel system, in consideration of its tissue irritation. Four kinds of fatty acids were employed as organogelators, which could successfully gel with injectable soybean oil. The gelation procedure was thermo-reversible. Phase transition temperature and time were depended on carbon chain length and concentration of gelators. Optimized formulations containing drug were then injected subcutaneously in rats for pharmacokinetic study. Results showed the steady drug release for one week with the well-controlled burst, which fitted well with the drug release mechanism of both drug diffusion and frame erosion. In vivo imaging of the organogel with fluorescence in live animals suggested that the organogel matrix was gradually absorbed and completely up-taken in nine days. Histopathological analysis of the surrounding tissues was carried out and revealed an overall good biocompatibility property of the implants over drug release period. This research demonstrates that this thermo-sensitive in situ forming organogel system represents a potentially promising platform for sustained drug delivery.
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1. Introduction

In the field of parenteral drug delivery system, biodegradable in situ forming implants have received significant research interest in the last few decades, due to the general advantage of injectable properties and avoidance of surgical removal procedure compared to pre-shaped parenteral depot systems, leading to the improved patient compliance and comfort (Kempe and Mäder, 2012). The sustained release properties enable this drug delivery system to be an option for delivery of wide categories of drugs for long term treatment. In situ forming implants exist as injectable fluid prior to administration, and form a solid or semi-solid depot at the injection site in response to external stimuli, such as light (Burkoth and Anseth, 2000), pH (Shu et al., 2001), ion (Cohen et al., 1997), temperature (Ruel-Gariepy and Leroux, 2004), and solvent exchange (Wang et al., 2012).

Up to now, only two products of in situ polymer precipitation systems (Eligard®, Atridox®) have been approved by FDA, respectively for therapy of advanced prostate cancer (Sator et al., 2003) and adult parodontitis (Steinberg and Friedman, 1999; Johnson and Stoller, 1999). This gelling system is based on the removal of water miscible organic solvent from the formulation upon administration, which may inevitably induce local tissue necrosis or inflammation due to the application of high amount of organic solvent (McHugh, 2005; Kang and Singh, 2005). In recent years, thermo-sensitive hydrogels have attracted increasing attention for local drug delivery application because of its limited toxicity (Jabarian et al., 2013; Kumar Ramadass et al., 2013). Oncogel® (ReGel® technology), a typical example of thermally-induced in situ forming polymer hydrogel for anticancer therapy, has already reached clinical phase II (Elstad and Fowers, 2009). Smart polymers with specific responses have been extensively investigated to work as a sustained drug depot and maintain a long term treatment (Lee et al., 2010). However, these smart polymers are generally water soluble, and are usually eliminated within dozens of hours from the injection site, generating a high burst and short-term drug release, which limits its application in the therapy of

Abbreviations: MA, myristic acid; PA, palmitic acid; SA, stearic acid; AA, arachidic acid; PAL, paliperidone; SD, Sprague–Dawley; Tsg, sol–gel phase transition temperature; Tgs, gel–sol phase transition temperature; tsg, sol–gel phase transition time; DSC, differential scanning calorimeter.

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certain diseases (Ruel-Gariepy et al., 2000; Chu et al., 2013; Peng et al., 2013). It seems that developing a more sustained release system with good biocompatibility remains an unsolved issue.

Many reports have demonstrated that oil could act as a drug reservoir slowly releasing the drug continuously at a rate dependent upon both the intrinsic aqueous solubility of the drug and the dissolution rate of the drug particles into the tissue fluid surrounding the drug particles, which apparently generated more sustained drug release compared with aqueous medium (Chang et al., 1999; Hsu et al., 2004; Larsen et al., 2000, 2006; Tahara et al., 2012). Meanwhile, parenteral oily suspension products have been available on market for decades, such as Prolixin® Decanoate and Haldol® Decanoate. Additives including amino acid derivatives have been widely employed to modify the drug release profiles of parenteral organogels, while organic solvents were indispensably applied to maintain the formulation in a sol state (Plourde et al., 2005; Couffin-Hoarau et al., 2004; Vintiloiu and Leroux, 2008). Long chain fatty acids have received extensive attentions as biocompatible additives in pharmaceutical manufacturing system. However, they are barely reported to be utilized in the in situ forming system (Jiang et al., 2008; Mu et al., 2013). The accumulation of very long chain saturated fatty acid in various cells and organs may be involved in inflammation and oxidative stress during the pathogenesis of metabolic syndrome (Matsumori et al., 2013). Based on health concerns, in this study, myristic acid (MA), palmitic acid (PA), stearic acid (SA), arachidic acid (AA), four kinds of long chain saturated fatty acids, were the first introduce to in situ forming gel system composed of vegetable oil, conducting as thermo-sensitive organogelators.

The purpose of this research was to develop a new in situ forming implant system with sustained drug release and low toxicity. The thermo-sensitive in situ organogels, prepared with organic phase (injectable soybean oil) and organogelator (fatty acid), were performed as injectable fluids with low viscosity in vitro, and formed a semi-solid drug depot at body temperature, as shown in Fig. 1. This gelling system was merely induced by the temperature change, and was produced without the application of organic solvent and chemical cross-linking agent, thus avoiding the additional toxicity to human body. The formulation was heated and subcutaneously injected within the injectable temperature window acceptable by human body (Alonso et al., 1993; Hashmi and Davis, 2010). In this study, paliperidone (PAL), which was stable during the preparation (Kumar and Randhawa, 2013). was chosen as model drug for long-term maintenance treatment of schizophrenia. In vitro and in vivo evaluations were performed. This thermosensitive organogel system, achieving a one-week sustained drug release, provided a potential cost-effective alternative of clinic application for long-term maintenance treatment.

Fig. 1. A preheated formulation injected to 37 °C aqueous solution.

2. Materials and methods

2.1. Materials

Injectable soybean oil was purchased from Zhonghang Tieling Pharmaceuticals Co., Ltd., China. Stearic acid and palmitic acid were purchased from Beijing Yili Chemicals Co., Ltd., China. Myristic acid and arachidic acid were purchased from Tianjin Guangfu Chemical Reagents Co., Ltd., China. Paliperidone and coumarin 6 were purchased from Sigma–Aldrich, St. Louis, MO, USA. All agents applied were of the highest grade.

Sprague–Dawley (SD) male rats (200 ± 25 g) and KM mice (20 ± 2 g) were purchased from Experimental Animal Center of Jilin University, China. Male nude mice (CD1-*Foxn1*^{nu}, body weight 18 ± 2 g) were purchased from Vital River Laboratories, China. All experiments on animals were performed according to the Guidelines for Animal Experiments, Jilin University, China.

2.2. Determination of drug concentration by HPLC

Drug concentration was detected by HPLC analysis, which consisted of a Waters 1525 pump, and a UV detector set at 280 nm. The mobile phase was consisted of methanol:water:triethylamine (80:19.5:0.5 (v/v/v)), adjusted to pH 10.22 with acetic acid. The analytical column was a zorbax extend-C18 (4.6 mm × 250 mm, pore size 5 μm) (Agilent). The flow rate was set at 1 ml/min.

2.3. Preparation of in situ forming organogels

The organogel formulations were prepared by separately dissolving four fatty acids in appropriate amounts of injectable soybean oil under magnetic stirring at 60 °C. Prior to the in vitro and in vivo evaluation, certain amount of drug was added to the preheated organogel (50 °C) and shaked vigorously to form a dispersion. Drug powder was preprocessed through 100 μm aperture sieve to achieve good syringeability. Concentration of fatty acid (FA) and drug loading (DL) were determined by the formula below:

$$\text{FA Concentration (\%w/v)} = \text{weight of FA/volume of soybean oil} \times 100\% \quad (1)$$

$$\text{Drug Loading(mg/ml)} = \text{weight of drug/volume of soybean oil} \quad (2)$$

2.4. Gelation temperature and gel characterization

2.4.1. Inverse flow method

Sol–gel phase transition temperature (Tsg) and time (tsg) were determined by inverse flow method. Briefly, 0.5 ml of each formulation was gently heated in a water bath and added into the test tube. The preheated gels were then placed in the constant

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