

Research Title Preparation of *in-situ* forming gels and microparticles comprising doxycycline hyclate using shellac as polymer with different solvents and study of their solvent exchange and transformation

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Abstract

As drug delivery systems, *in situ* forming gel exhibits a sol-to-gel phase transition after contact with aqueous fluid whereas *in situ* microparticle (ISM) observes transformation of emulsion droplets into the solid particles to modulate the drug release. Phase separation is the main strategy of these systems, and it undergoes the prompt changes in solubility of polymer in response to solvent exchange. This research purposed to better comprehend the behavior of solvent (e.g. Dimethyl sulfoxide (DMSO), *N*-methyl-2-pyrrolidone (NMP) and 2-pyrrolidone (PYR)) state in bleached shellac from preparation process to the entire phase separation of *in situ* forming microparticle and gel. The formulations employed the *in situ* forming gel as an internal phase of ISM, and emulsion was achieved by mixing the *in situ* forming gel with the external phase made from GMS and olive oil. In preparation process, the parameters such as pH, solubility parameter, density, interfacial tension and phase separation rate of emulsion compositions were investigated. During the phase separation, the physical characteristics were examined for the three phases according to exposure time. 1) Before (morphology of o/o emulsion and its droplet size, viscosities, viscoelasticity and thermal analysis). 2) During (transformation of sol to microparticles, solvent and drug releases, *in vitro* degradation, water diffusion rate and solvent diffusion). 3) After (texture analysis, XRD pattern and SEM

microphotograph). Bleached shellac dissolved in solvents via strongly hydrogen bonding and van der Waals forces. *In situ* forming gel using NMP as solvent could not fabricate into an emulsion because NMP was partially miscible with olive oil. The solubility parameter could be in rank of the solvent order as following: NMP > DMSO > PYR. NMP was described as the best “good solvent”. This parameter related to viscosities, viscoelasticity and thermal analysis. Additionally, PYR itself was more viscous than DMSO and NMP, respectively. There are four crucial steps of phase separation. Firstly, water flowed into the system with different rate in rank of the solvent order as following: DMSO > NMP > PYR. This water permeation decreased the solubility of bleached shellac, and it then precipitated. Secondly, solvent and drug diffused out in few minutes later. The diffusion rate of all species was presented in term of solvent applied in formulation as DMSO > NMP > PYR. PYR formula had the slowest release rate of solvent and drug because solvent itself and its systems were higher viscous. Whereas, all diffusion profiles from DMSO and NMP systems were governed by solubility parameter. Thirdly, pores were supplied with water and solvent fluxes. The size and density of pores were increased by time similarly to the release rate of solvent and drug. Bleached shellac matrices prepared using PYR as solvent eventually dissipated due to hydrolysis at ester bond which was accelerated by PYR-induced water accumulation. A higher porous structure collapsed easily and it was more likely plastic but a dense one considerably resisted to a compression and deformed elastically. Finally, the degradation of bleached shellac in aqueous condition actually started after systems completed solidification. At steady state, the total mass loss converted to PYR >> NMP > DMSO similarly to a water content pattern. PYR could gain the high amount of water and pH of doxycycline hydrochloride solution in matrix was maintained by buffer pH nearly to 7, resulting in the large hydrolysis at polyesters. However, all behaviors of solvent state in ISM was covered by hindrance effect of oil phase. The solvent had no effect on the structure of remained bleached shellac after solvent exchange. PYR was the most appropriated solvent for preparing the *in situ* forming systems because its formulations demonstrated the proper sustained drug release profiles and preferable self-degradation in physiological condition for periodontitis treatment.

Keyword : Solvent exchange, *in situ* forming gels, *in situ* forming microparticles, bleached shellac