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Short communication

Design and in vitro characterization of *in situ* forming prolonged release implant formulations of a narcotic antagonist drug

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Introduction

Addiction to alcohol and opioids is one of the leading health issues. Alcohol is thought to cause 3.6% of deaths globally, while opioids account for 76% of drug use disorder deaths. By binding competitively to these receptors, opioid antagonists prevent alcohol and psychotropic drugs from activating on the μ, κ, and δ opioid receptor sites. When given orally, this group of active pharmacological compounds has a low bioavailability due to the significant first-pass metabolism causing fluctuations in plasma concentrations. Oral tablets have also been linked to increased rates of early treatment failure. Due to all these factors, creating a dosage form that bypasses the liver, maintains a consistent plasma concentration, and relieves patients of the burden of medicine administration would be ideal. This study aimed to develop a narcotic antagonist drug (XTZ) containing in situ forming gel systems satisfying all requirements based on a gelling mechanism by solvent exchange by employing biodegradable polymers and different solvents. Controlled drug release with a low burst release over a month were the primary targets for optimal in situ forming gel formulation.

Materials and methods

Poly(D,L-lactide) (Mn 18 000 – 28 000) (PDLL), poly(D,L-lactide-co-glycolide) 50:50 (Mn 38 000 – 54 000), poly(D,L-lactide-co-glycolide) 85:15 (Mw 190 000 – 240 000), poly(ethylene glycol) dimethyl ether (Mn = 250) (PEG250DME), benzyl alcohol, ethyl heptanoate, N-methyl pyrrolidone (NMP), polyethylene glycol 400 (PEG400), stearic acid, hydroxypropyl cellulose (Mw = 100 000), poly(ethylene glycol) 4000 (PEG4000) were obtained from Sigma Aldrich (Germany), and dimethyl sulfoxide (DMSO) was obtained from Isolab (Germany).

High-performance liquid chromatographic (HPLC) and ultraviolet (UV) spectrophotometric methods were developed and validated for the quantification of the drug.

The solubility of the active substance in various solvents (PEG250DME, DMSO, PEG400, ethyl heptanoate, N-methyl pyrrolidone, and benzyl alcohol) was determined for formulation studies. After deciding the solvent in which the drug has maximum solubility, in situ forming gel formulations (Table 1) were prepared with different polymer types.

Table 1. Ingredients in in situ forming gel formulations

% w/w	F12-1	F12-2	F12-3	F12-4	F12-5	F12-6
XTZ	21.28	20.20	19.61	18.69	19.05	18.18
PDLL	10.64	15.15	9.80	14.02	20	9.09
Benzyl alcohol	68.07	64.64	70.59	67.28	60.96	72.73

In vitro drug release testing of the formulations was carried out, and the effects of stearic acid, PEG4000, and HPC on the burst drug release from the formulations were investigated. In vitro drug release, viscosity (Bağcı et al., 2020), injectability, solvent exchange, polymer degradation (Kamali et al., 2018), SEM analysis (Phaechamud et al., 2017), and stability (-20±5ºC and 5±3ºC) analyses were performed for in vitro characterization of the optimum formulation. Differential Thermal Analysis (DTA), Thermogravimetric Analysis

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(TGA), and Fourier Transform Infrared Spectrophotometer (FT-IR) analyses were performed to examine the interaction between the drug and polymer.

Results and discussion

Formulations in which the drug is completely dissolved have been successfully developed using 10-20% PDLL (18 000 - 28 000) and benzyl alcohol. In vitro drug release profiles showed that F12-2 formulation was successfully released the drug for a month and at a rate close to that of the target profile (Di = 59 mg, kr^o = 0.426 mg/h), which was formed by the pharmacokinetic parameters of the drug (Fig. 1). When the drug release from the optimum formulation was evaluated regarding release kinetics, the Higuchi model (r^2= 0.9979; MSC=7.6; AIC=102.4) was the best-fitted model indicating that the release occurred by diffusion mechanism. Addition of stearic acid, PEG4000, and HPC with the aim of increasing viscosity and hydrophobicity, or creating a plasticizer effect did not yield any results or reduce the burst release. Therefore, the F12-2 formulation was chosen as the optimum formulation.

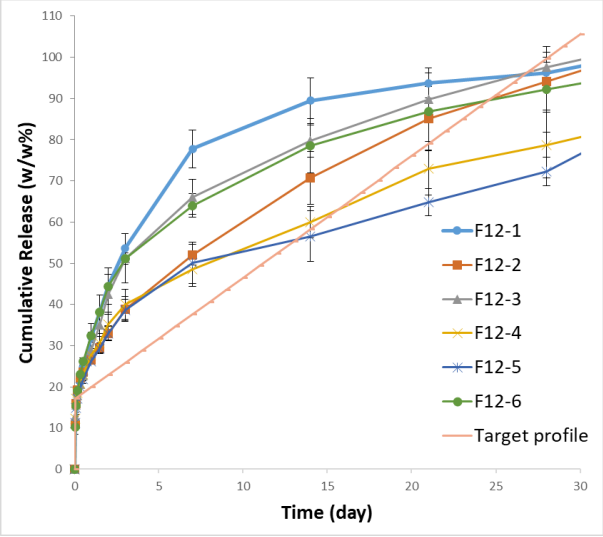

Fig. 1. Drug release from formulations and target profile

The viscosity of the optimum formulation was 239 cP at 50 rpm; the syringeability was 13.7 ± 0.45 N. When the migration of benzyl alcohol from the formulation into the release medium was examined, it was seen that 72.03 w/w% of it rapidly migrated to the in vitro release medium within 4 hours. The polymer degradation in the release medium was about 2.32 w/w% at the end of 28 days.

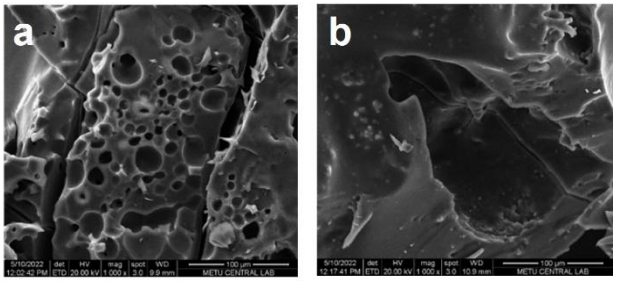

Fig. 2. Cross-section SEM images of in situ forming gels a) day 2, b) day 35

When SEM images were examined, it was observed that a sponge-like porous structure was formed (Fig. 2). During the three-month stability studies, the amount of drug, the polymer degradation, the viscosity, the injectability, and the thermal properties of the formulation were examined and the formulation was found to be more stable at -20±5ºC.

Conclusion

XTZ is part of the multifaceted treatment of alcohol and opioid addiction, including psychosocial support. In treating opioid addiction, it is crucial to develop appropriate dosage forms so that patients are not burdened with the responsibility of taking drugs. In this study, an in situ forming implant dosage form was successfully developed that could provide effective plasma concentration for 28 days by administering subcutaneously.

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