Injectable long-term control-released in situ gels of hydrochloric thiothixene for the treatment of schizophrenia

Che Xin, Han Fei, Wang Yan, Wang Lihong
School of Pharmacy, Shenyang Pharmaceutical University, Shenyang 110016, China
chexin98@aliyun.com

ABSTRACT SUMMARY
A novel injectable long-term control-released in situ gel of hydrochloric thiothixene (HT) for the treatment of schizophrenia was developed based on biodegradable material polylactic acid (PLA). The results of the in vitro and in vivo studies showed the in situ gel had a long-term releasing for several weeks and a good histocompatibility without any remarkable inflammatory reactions.

INTRODUCTION
Schizophrenia is a major psychosis with unknown etiopathogenisis. HT is a commonly used drug for schizophrenia in clinic because it seldom induced side reaction of extracorticospinal tract. HT is usually given orally as doses of 5-15 mg or intramuscularly injected as small doses of 4-8 mg every 8-12 h. Because the psychotics often could not control their behaviors normally, the independent administration of antipsychotic drug based on medical order was difficult. The omissions of the administration often brought an unsatisfactory therapeutic efficacy. Therefore, a long-term sustained-released preparation that could last the drug releasing for several weeks after one administration is desired by doctors in clinic.

PLA was a widely used biodegradable material in pharmaceutics. PLA could be hydrolyzed slowly in body. The production of the hydrolyzation was lactic acid. Because the lactic acid was a common metabolic product in our body, PLA was a highly safe biomaterial with high histocompatibility and sufficient biodegradable ability.

The purpose of this study was to develop a novel injectable long-term control-released in situ gel of hydrochloric thiothixene for the treatment of schizophrenia based on biodegradable material PLA.

EXPERIMENTAL METHODS
The in situ gels were prepared by dissolving a predetermined amount of PLA in the in situ gelling solvents NMP, benzyl benzoate and triacetin, respectively.

The syringeabilities of the formulations were tested by a Stable Micro Systems TA-XT Plus Texture Analyser (Stable Micro systems, Godalming, UK) and performed using a 5 ml glass syring with 21 G needles.

In order to investigate the releasing property of HT from the PLA-based in situ gels, an in vitro drug release study was carried out by using a RX-6 dissolution test apparatus (Tianjin optical instrument factory, Tianjin, China). The release medium was 900 ml phosphate buffer solution (pH 7.40). Moreover, because the period of the dissolution test was long, sodium azide (0.02%, w/v) was added into the phosphate buffer solution in order to prevent bacterial contamination. The test temperature was set at 37°C and the paddle method was used.

The quantification of HT was performed by HPLC with C18 column. The mobile phase was methanol-water-cholamine (350:50:0.05) at a flow rate of 1.0 ml/min. The detecting wavelength was 229 nm.

Stability study was performed to investigate the influence of the storage temperature on the physical-chemical properties of the gels. The test temperatures were set at 4°C, 25°C and 40°C, respectively. The test was carried out without illumination. In order to presume the store condition a stability investigation was also performed at 4°C for at least 12 months.

24 male Wistar rats were divided into two groups. The first group was injected with HT in situ gel; the second group was injected with HT solution. The HT in situ gel and the HT solution, equivalence to 7 mg of HT, were intramuscularly injected, respectively. In in vivo study, the amount of HT in the plasma was analyzed by HPLC. Propranolol was selected as internal standard.

In histological safe study, 24 male Wistar rats were divided into two groups. The rats in Group 1 were injected 0.3 ml physiological saline and the rats in Group 2 were injected 0.3 ml in situ gels, subcutaneously. To evaluate the inflammatory reaction after injection, the comparison of the
numbers of neutrophils, eosinophils and macrophages between Group 1 and Group 2 was performed.

RESULTS AND DISCUSSION

The in situ gels were prepared by using three different solvents with different water miscibility. Briefly, NMP was used as water-miscible solvent. Moreover, triacetin and benzyl benzoate were selected as partially miscible solvent and immiscible solvent, respectively. Nine in situ gel formulations with different gelling solvents or concentrations of PLA were prepared and investigated. The properties of them, such as syringeability and drug releasing profile, were tested. The results showed that to select benzyl benzoate as the gelling solvent and choose the highest concentration of PLA (40%) (F9) could get a long sustained releasing time for more than 30 days.

Consequently, the stability study for F9 was carried out to evaluate the physical and chemical stability of the in situ gel during a period of a storage time. The results showed that it could be stored at 4°C for at least one year.

For the purpose of evaluating the efficiency and the safety of the injectable in situ gels, an in vivo evaluation was carried out. Fig. 1 showed the profiles of the plasma concentrations of HT over time after the intramuscularly injection of the two HT preparations.

Fig. 1 The plasma concentration-time curves of HT in situ gels and HT solution in rats.

As shown in Fig. 1, compared with the HT solution, the selected formulation F9 had a longer sustained release time for several weeks. Moreover, no red swelling and inflamed symptoms at the injected site were found.

Fig. 2 showed the comparisons of the numbers of eosinophils, neutrophils and macrophages in tissue samples at 1st, 7th, 14th and 28th day after the injections of in situ gel formulation (F9) and physiological saline, respectively. From Fig. 2 we could see that the amount of inflammatory cells had no obviously difference between two groups. Thus, the inflammatory response of F9 was relatively mild and comparable to that of physiological saline.

Fig. 2 The results of the histological safe evaluation.

The results of the in vivo study and histological safe evaluation showed the injectable PLA-based in situ gel was a safe and effective long-term sustained preparation.

CONCLUSION

The injectable PLA-based HT in situ gel containing 15% (w/w) HT and 45% (w/w) PLA with benzyl benzoate as gelling solvent was a suitable injectable degradable long-term sustained released drug delivery system for antipsychotic drug HT. The results of the in vitro and in vivo studies showed that it was a safe and effective long-term sustained injectable HT preparation.

REFERENCE

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