Characteristics of the Stability in Local Anesthetic Lipospheres

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ABSTRACT SUMMARY

Local anesthetic drug, Tetracaine (TTC) was encapsulated in a novel liposphere formulation which leads to a rapid onset time and a longer duration of anesthetic effect. 5% TTC was successfully encapsulated in the liposphere with a particle size approximately 200nm and encapsulation efficiency higher than 98%. However, this novel TTC liposphere suffered from the TTC stability problems which generated unknown impurities. How to identify this compound and to improve the TTC stability in liposphere as well as the In Vivo efficacy test will be presented in this paper.

INTRODUCTION

Tetracaine (TTC), an ester-type local anesthetic drug, has shown the strongest anesthetic effect in several investigations of percutaneous study. A liposphere formulation was designed to encapsulate TTC which leads to a rapid onset time and a longer duration of anesthetic effect. Liposphere, a lipid-based carrier, composes a hydrophobic oil core embedded inside a phospholipid layer. This formulation has suitable particle size and excellent encapsulation efficiency. In vitro and In vivo tests were all shown superior properties to commercial TTC gel. However, this formulation suffered from the TTC stability problem and generated impurities which was not listed in the USP of TTC impurity profiles. Furthermore, this impurity affected the long-term stability of TTC in liposphere dramatically. Therefore, we have used MS/MS to analyze this impurity and figure out it was an oxidized compound. In this study, we will demonstrate the analytical result of this oxidized impurity and also study various formulations to overcome the stability issue.

EXPERIMENTAL METHODS

Composition of lipospheres included phosphatidylcholine, unsaturated and saturated fatty acid and TTC. 5% TTC was dissolved in oil phase and mixed with phospholipid solution. The concentration of TTC and encapsulation efficiency (EE) were determined by HPLC. Particle size of liposphere was measured by a light scattering particle analyzer. Impurity were collected from the HPLC fractions and further analyzed by a MS/MS. In vivo efficacy study was performed by using von Frey filament test. The response ratio, reactive animals over total animals, represents the ratio of anesthetic efficacy.

RESULTS AND DISCUSSION

The following figure was shown the impurity identified from MS/MS. Figure a and b represented TTC and impurity respectively. The molecular weight of impurity was 281.7 which was 16 larger

![Figure](image-url)
than TTC 265.7. This evidence indicated that the impurity is TTC n-oxide.

In order to overcome this impurity problem, various formulations were developed and have shown on the following table. The result indicated that adding Vitamin E did not inhibit the TTC n-oxide formation. On the contrary, BHT was shown the effective inhibition up to 50%.

The following figure demonstrated the In vivo anesthetic effect of both TTC lipospheres. Results were shown that the efficacy of TTC liposphere was superior to TTC gel (AMETOP) and has also shown that both TTC lipospheres provided shorter onset time comparing to commercial TTC gel. The formulation including the BHT did not affect the anesthetic ability of TTC but enhance the stability of long term storage.

**CONCLUSION**

This study has improved the stability of TTC in a liposphere formulation design. By using anit-oxidant, TTC n-oxide was gradually reduced and also prolong the long term stability (data not shown). This study has also shown the potential commercialization of this novel TTC liposphere in terms of shorter onset time and enhanced anesthetic efficacy.

**REFERENCES**


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