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TECHNICAL REPORT

TITLE: USP METHOD IMPROVEMENTS FOR HPLC OF LIDOCAINE AND RELATED IMPURITIES

MARKET SEGMENT: PHARMACEUTICAL

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INTRODUCTION

Lidocaine is a local anesthetic that causes loss of feeling in the skin and surrounding tissues. It is used to prevent and treat pain from some procedures and used to treat minor burns, scrapes and even insect bites. 1 Lidocaine medication is used on the skin and can also be used by mouth, nose, or throat.

The chemical structure of lidocaine (Figure 1) represents a 2-(diethylamino)-N-(2,6-dimethylphenyl)-acetamide, featuring an aromatic ring (2,6-dimethylbenzene) as a lipophilic group, an amide linkage, and a diethylamino functional group.

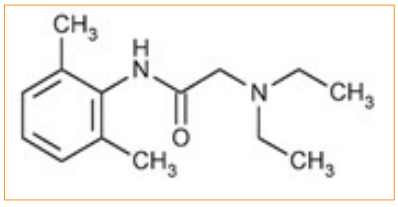

Figure 1: Lidocaine Structure

Like many small molecule pharmaceutical drugs, lidocaine can contain levels of impurities and unwanted substances that can affect its safety and efficacy. Two common impurities of lidocaine are N-(2-6 dimethylphenyl) chloroacetamine (impurity H) and 2-6 dimethylaniline (impurity A). The structure of these analytes can be seen next.

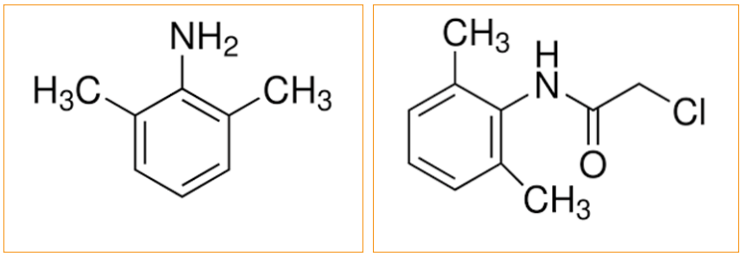

Figure 2: Common impurities from lidocaine: N-(2-6 dimethylphenyl) chloroacetamine (impurity H, right) and -2-6 dimethylaniline (impurity A, left)

KEY WORDS:

lidocaine, high pH separations, HALO 120 Å Elevate C18 column, LC-UV, USP

Mobile phase pH is an important parameter to consider when wanting to separate these analytes by high pressure liquid chromatography. At low pH, basic compounds become positively charged which allow for unwanted interactions between the silanols on the silica surface. However, under high pH conditions, basic molecules are neutral, allowing for an increase in retention (less polar) and significant improvement in chromatographic peak shape. Since lidocaine is a base, increasing the mobile phase pH is recommended to achieve good peak shape and retention. A separation of lidocaine and its impurities following the USP organic impurities method recommends running under slightly alkaline conditions (pH 8) in order to meet resolution requirements. A HALO® Elevate C18 column packed with superficially porous particles incorporates surface modified organo-silane technology for alkaline resistance resulting in excellent stability in high pH environments. As shown below, HALO® Elevate C18 (USP L1) not only has been shown to separate lidocaine and its impurities following these conditions, but the method has been further optimized to reduce run times and improve throughput.

CHANGES TO USP <621>

Use of a different column must be in the same L category, but switching from a totally porous particle (TPP) to a superficially porous particle (SPP) column is permitted. Particle size and/or length of the column may be modified, provided that the ratio of the column length (L) to the particle size (dp) remains constant or in the range between −25% to +50% of the prescribed L/dp ratio. When changing from TPP to SPP in isocratic methods, other combinations of L and dp can be used, provided that the plate number (N) is within −25% to +50%, relative to the prescribed column. The higher efficiency of superficially porous particles (SPPs) allows for the use of shorter columns without sacrificing resolution. This also allows for faster run times and increased column throughput.

EXPERIMENTAL

Columns:

1. 3.9 mm x 15 cm, 5 µm packing L1 (per USP)
   L/dp= 30,000 (for -25-50%, L/dp can be 22,500-45,000)
2. HALO 120 Å ELV C18, 4.6 x 150 mm, 2.7µm packing L1 (92274-702): L/dp= 55,555
3. HALO 120 Å ELV C18, 2.1 x 100 mm, 2.7µm packing L1 (92274-602): L/dp= 37,037

Solution A: 4.85 g/L of monobasic potassium phosphate in water. Adjust with sodium hydroxide solution to a pH of 8.0

Mobile Phase: Acetonitrile and Solution A (30:70)

Standard Solution: 0.5 µg/mL of USP Ropivacaine Related Compound A RS and 5 µg/mL each of USP Lidocaine Related Compound H RD and USP Lidocaine RS in Mobile phase

Mode: LC

Detector: UV 230 nm

Column Temperature: 30°C

Flow Rate: 1 mL/min. (4.6mm), 0.4 mL/min. (2.1mm)

Injection Volume: 20 µL (4.6mm), 3.4 µL (2.1mm)

RESULTS

A separation of lidocaine and two impurities is performed on a HALO 120 Å Elevate C18 column using purified standards. (Figure 3) Resolution value NLT 1.5 of impurities is achieved under recommended USP conditions using a 4.6 x 150 mm column dimension. Running lidocaine under alkaline conditions allows for good peak symmetry and retention. (compared to low pH conditions)

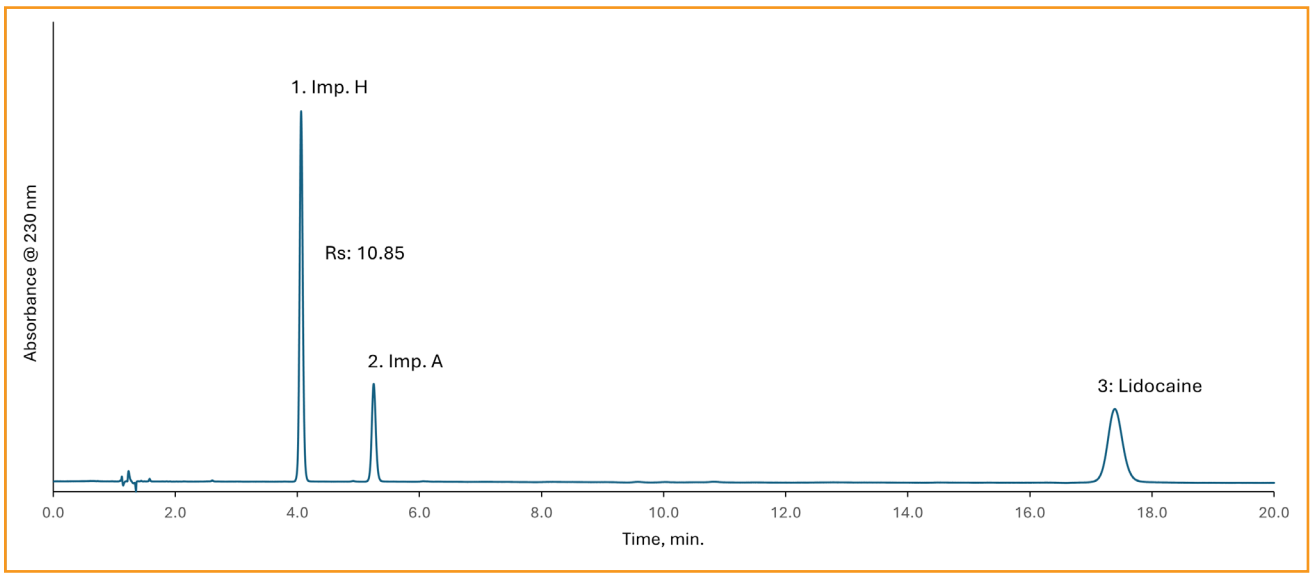

Figure 3. Separation of Lidocaine and its Impurities following USP method

Over the years silica particle manufacturing along with instrument technology has greatly improved, allowing many USP methods to be further improved upon. This includes speeding up the analysis time and decreasing solvent waste. For example, moving to a 2.1 x 100 mm column dimension allows for a significant reduction in flow rate and separation run time. In fact, the same lidocaine separation on a smaller column dimension allows for half the run time along with a ~150% solvent savings while still achieving the resolution specification between two impurities. (Figure 4)

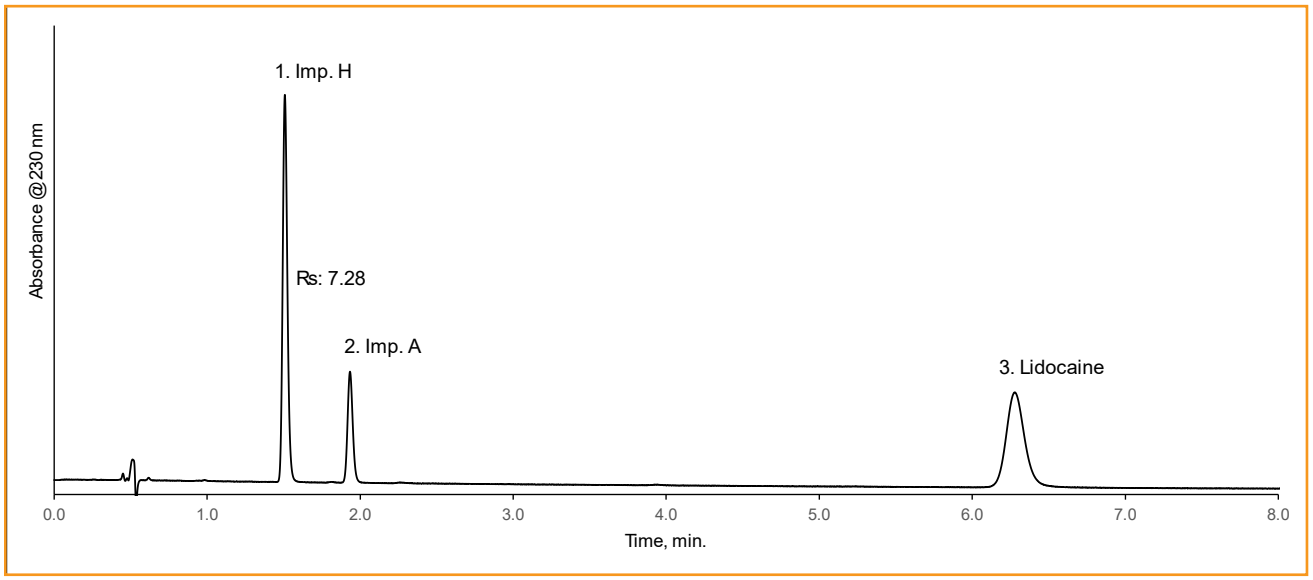

Figure 4. Separation Improvements on a 2.1 x 100 mm column

After purified standards were monitored, a sample of lidocaine hydrochloride oral topical solution USP 2% was analyzed to look for sample matrix effects using the smaller ID, shorter length column. Inactive ingredients were observed including methyl and propylparaben without any peak coelution/ interferences.

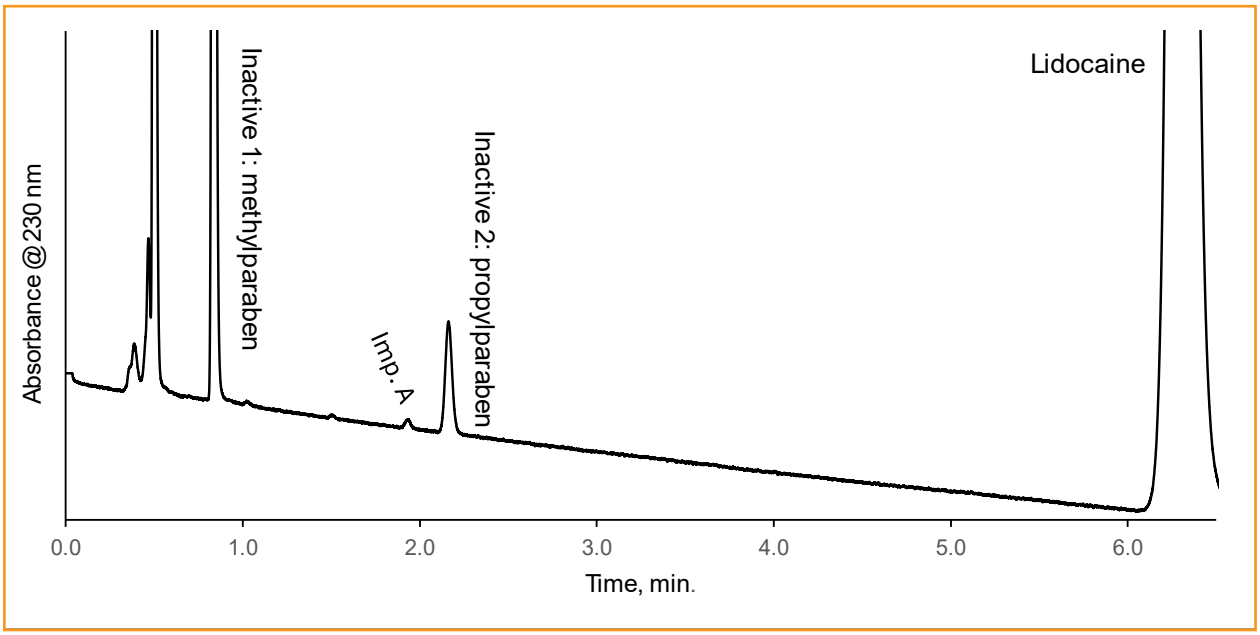

Figure 5. Lidocaine Hydrochloride Oral Topical Solution USP 2% using a HALO® Elevate C18, 2.7 µm, 2.1 x 100 mm column

CONCLUSION:

USP methods are a great way to start method development of an analyte of interest using a validated method with already determined column and mobile phase conditions. However, with the new USP guidelines in place these methods can be modified and modernized to increase sample throughput and reduce solvent consumption. There are several ways to achieve these benefits such as reducing column internal diameter, length, and even the particle size. Switching from a fully porous silica particle to a superficially porous particle is also a great way to increase column efficiencies without requiring higher pressures.

REFERENCES:

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