RESEARCH ARTICLE

Microstereolithography-fabricated microneedles for fluid sampling of histamine-contaminated tuna

Ryan D. Boehm¹, Panupong Jaipan², Kai-Hung Yang², Thomas N. Stewart³ and Roger J. Narayan¹,²*¹

¹ Joint Department of Biomedical Engineering, University of North Carolina and North Carolina State University, Box 7115, Raleigh NC 27695, USA
² Department of Material Science Engineering, North Carolina State University, Box 7907, Raleigh, NC 27695, USA
³ Mercury Science Inc., Raleigh, NC 27607, USA

Abstract: A custom-designed microneedle sampling system was prepared using dynamic mask microstereolithography; this sampling system was used for determination of histamine content in fresh, histamine-spiked, and spoiled tuna flesh. Lateral flow (test strip) assays were successfully utilized in the microneedle sampling system to assess histamine content. Good agreement was noted between data obtained from the microneedle sampling system and a commercially available histamine detection kit. A discrepancy was noted in the results from the microneedle sampling system and the commercially available histamine detection kit at low (negative) levels of histamine. There was an improvement in the agreement between the microneedle sampling system and the commercially available histamine detection kit at higher histamine levels. The results, which showed an improvement in the test duration and the amount of reagent needed for histamine detection, indicate the promise of printed microneedle sampling systems for histamine detection in seafood samples and other types of food testing.

Keywords: microneedles, dynamic mask microstereolithography, histamine, lateral flow, tuna

*Correspondence to: Roger J. Narayan, Joint Department of Biomedical Engineering, University of North Carolina and North Carolina State University, Box 7115, Raleigh NC 27695, USA; Email: roger_narayan@msn.com

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1. Introduction

Food poisoning is a concern when consuming fish that has been exposed to elevated temperatures for extended periods of time. Histamine fish poisoning is one of the most common types of seafood consumption-related illnesses in the United States[¹]. Histamine fish poisoning (HFP), which is sometimes referred to as scrombroid fish poisoning, is associated with mishandling of the *Scrombridae* family of fish (e.g., tuna and mahi-mahi), which have high levels of histidine in their muscles[²]. A biogenic amine known as histamine is formed during bacterial decarboxylation of histidine in the raw fish[¹–³]. Although histamine is naturally present in humans and humans possess a protective mechanism in the digestive tract to handle small amounts of consumed histamine, ingestion of tainted fish with high levels of histamine may overwhelm the protective mechanism and result in histamine intoxication, which resembles an allergic reaction[⁶,⁷]. Histamine levels that are greater than or equal to 500 mg/kg of fish tissue are noted to be toxic when ingested[⁸]; the United States Food & Drug Administration has set the acceptability limit at 50 mg/kg[⁹]. It is concerning to note that fish with unacceptable levels of histamine may not exhibit a different appearance or emit a different odor than fish that has not been compromised[⁸,¹⁰]. Furthermore, heating fish to...
normal cooking temperatures does not necessarily alter the histamine levels within the fish[1].

Due to concerns associated with histamine contamination of fish, a number of methods have been developed to screen fish flesh and ensure that it does not contain dangerous levels of histamine. Screening of histamine levels in fish may be conducted using a variety of methods, including high purity liquid chromatography (HPLC)[11], enzymatic test kits, enzyme-linked immunosorbent assays (ELISA), and lateral flow immunochromatographic test strips[12]. The lateral flow test strips are particularly useful for fieldwork since they do not require complex equipment for analysis. Lateral flow tests, sometimes referred to as dipsticks, are used in many environmental and healthcare applications (e.g., colorimetric pregnancy tests)[13]. For example, lateral flow tests have been used for botulinum neurotoxin, aflatoxin B1, and virus detection[14–17]. One such lateral flow test is the Reveal® for Histamine test kit (Neogen® Corporation, Lansing, MI, USA), which can screen for histamine in tuna and mahi-mahi; the Reveal® for Histamine test kit was used as the histamine detection mechanism in this study.

One procedure that is described in many histamine detection methods is homogenization of fish flesh; most assays are performed on fluid extracts from the homogenized fish flesh. In this study, we investigated the use of a microstereolithography-prepared microneedle sampling system for detecting histamine in fish flesh. Systems containing microneedle arrays have previously been developed for sampling of analytes in transdermal blood and/or interstitial fluid[18–20]. For instance, systems containing microneedles arrays have been developed for detection of glutamate[21], glucose[22,23], and potassium ions[24]. In this study, microneedle arrays were used as a sampling mechanism for detection of histamine in fish flesh. Visible light dynamic mask microstereolithography was used to prepare customized microneedle arrays; this approach has been previously used to create microneedle arrays for drug delivery[23–28] and biosensing applications[21,29]. Reveal® for Histamine lateral flow test strips were integrated with the microneedle sampling system. Flesh from fresh, histamine-spiked, and spoiled tuna was examined with the microneedle sampling system; the results from the microneedle sampling system were compared to results from the manufacturer’s protocol that involved homogenization of tuna flesh.

2. Materials and Methods

2.1 Microneedle and Lateral Flow Test Holder

To sample the tuna flesh for histamine, arrays of microneedles were used to capture fluid from the tuna samples. A custom lateral flow test strip holder was designed to stabilize a microneedle array, allowing the sampled fluid to be washed off of the microneedle array and into a reservoir for wetting of a lateral flow test (Figure 1). Both of these components were custom designed using computer-aided design software (SolidWorks Education Edition 2014–2015, Dassault Systèmes SolidWorks Corporation, Concord, NH, USA). The microneedle arrays were composed of nine offset microneedles, which exhibited a thin pyramidal shape and a trapezoidal eyelet design to capture fluid (Figure 1A). The test strip and microneedle holder (Figure 1C) was designed with three chambers: (i) a washed sample reservoir for placement of the lateral flow test, (ii) the microneedle holder/wash chamber, and (iii) an

![Figure 1](image-url). Computer aided design schematic of the microneedle array and the custom lateral flow test holder. (A) Front, left, top, and isometric views of the microneedle design are shown clockwise from upper left position. (B) Insertion of the microneedle into the central chamber of the test strip holder following application of the microneedle array to the tuna sample. (C) Section view of the custom test strip holder showing: (1) the washed sample reservoir for the test strip, (2) the central chamber holding the microneedle array in place, and (3) the inlet port for the sample diluent. (D) The sample diluent is added to the port at site (3), where it runs through the channel to (2) the central chamber, washing the acquired sample from the microneedle array into the reservoir at site (1). The lateral flow test strip is placed into the groove at site (1) and is wetted by the microneedle array wash/diluent at the beginning of the screening test.
inlet port for the sample diluent.

The devices were fabricated using a photosensitive acrylate-based, class-IIa biocompatible polymer known by the tradename eShell 200 (Envisiontec, Ferndale, USA)\(^{30}\). This material was polymerized into the desired component geometries based on STL files, which were created using computer aided design software. A Perfactory III SXGA+ visible light dynamic mask microstereolithography system with an Enhanced Resolution Module (EnvisionTEC GmbH, Gladbeck, Germany) was utilized to fabricate the devices in an additive layer-by-layer manner. A z-direction step size of 50 µm was used to build the devices; the dynamic mask was illuminated with visible light at a lamp power of 550 mW.

Following the microstereolithography step, the devices were rinsed with isopropanol 2–3 times and dried with compressed air. The test strip holders were immersed in isopropanol for 15 minutes and sonicated in an ultrasonic bath. The parts were then removed, dried with compressed air, and hand-rinsed with isopropanol as needed to remove unpolymerized resin. Both types of devices were dried in a heated chamber at 30°C for at least 30 minutes before undergoing a post curing procedure. For post curing, the parts were loaded into an Otoflash Post Curing Light Pulsing Unit (EnvisionTEC GmbH, Gladbeck, Germany) and exposed to two sets of 2000 light pulses. This unit utilizes light pulses in the 300–700 nm spectral range at 10 Hz to polymerize residual unpolymerized material within the devices\(^{31}\). The devices were imaged with a VHX-5000 optical microscope (Keyence, Itaska, IL, USA).

2.2 Fish Preparation

Tuna steaks that were cut to a 1-inch thickness were used to perform histamine testing. The tuna samples were acquired from a local fresh fish market. To calibrate the microneedle testing procedure, tuna pieces were incubated overnight in histamine solutions within vacuum seal bags in a refrigerator. Pieces of tuna were trimmed to ~100 g pieces and loaded into individual vacuum seal bags. Histamine (Sigma-Aldrich Co. LLC, St. Louis, MO, USA) solutions were prepared in 1 × phosphate buffered saline (PBS) to 0.5 mg/mL and 1.0 mg/mL concentrations; 1 × PBS alone was used as a negative control. A volume of 5 mL of each of these solutions was added to individual vacuum bags containing the tuna and zip-sealed; most of the air in the bags was then removed. The tuna samples were incubated overnight with the histamine solutions in a 4°C refrigerator.

In addition, tuna samples were prepared for a time course examination, which involved placing samples in the refrigerator for up to seven days. Tuna steaks again were cut into approximately 100 g individual pieces, placed into vacuum bags, and zip sealed; in this study, the bags were not vacuumed to remove air. Five time points were used to measure the fish spoilage over the course of the seven day period. For the “Day 0” time point, a piece of tuna flesh was immediately frozen. Tuna flesh from days 1, 3, 5, and 7 were also removed from incubation in the refrigerator and frozen for histamine testing at a later time.

Lastly, a piece of spoiled tuna was examined with the microneedle sampling system procedure and the manufacturer-described procedure to obtain a comparison between the two procedures. The tuna flesh for this study was stored in a vacuum sealed bag containing 1 × PBS with the air removed by vacuum; the sample was then placed in a refrigerator overnight. The tuna flesh was originally designated as a negative control during the calibration steps described above; however, it was determined that the tuna flesh was spoiled upon acquisition from the source. This occurrence provided an opportunity to study a tuna flesh sample acquired from a commercial source in an authentic spoilage scenario.

2.3 Histamine Testing Procedure

To conduct the histamine screening, colorimetric lateral flow tests were acquired as components of Reveal\(^{®}\) for Histamine screening test kits (Neogen\(^{®}\) Corporation, Lansing, MI, USA), which provide a detection threshold of 50 ppm. For the microneedle sampling system procedure, the microneedle array was pressed into the tuna sample for 5 seconds to acquire a fluid sample. The microneedle array was then placed into the test strip holder as seen in Figure 1. With the microneedle array in place, 1000 µL of the sample diluent provided in the test kit was added to the input port of the test strip holder. This fluid flowed over the microneedle array, washing the test fluid sample into the reservoir, where one of the Reveal\(^{®}\) test strips was placed to begin the screening. The test strip was allowed to incubate in the sample fluid for 10 minutes or less before the result was determined.

To more objectively compare positive test results and negative test results, an Accuscan\(^{®}\) Gold (Neogen\(^{®}\) Corporation, Lansing, MI, USA) test strip reader
was used to optically measure the intensities of the colored test and control lines in the lateral flow strip. Each test strip has colored control and test lines that appear upon introduction of a fluid sample. The ratio of the color intensities of these lines was used to assess if a sample was positive or negative for histamine at the 50 ppm level. The Accuscan® reader provided a ratiometric readout of the lines, which was used to differentiate between a positive result and a negative result. If the ratio of the test:control lines was greater than or equal to one, the test was read as negative for histamine. If the ratio of the test:control lines was less than one, the test was read as positive for histamine. For each test lateral flow strip, three measurements were taken in short succession with the reader; the average ratio was used to determine positive versus negative for the individual strip. For the calibration studies with the 1 × PBS, 0.5 mg/mL histamine, and 1.0 mg/mL histamine solutions, nine test strips were used for each type of tuna sample. Five test strips were used for the time course study. Four test strips were used for each testing method were used in the time course study.

For the calibration studies and the spoiled fish study, the protocol described by the Reveal® for histamine test kits was used to validate the findings of the microneedle sampling system procedure. Briefly, the procedure involved acquiring a 10 g piece of tuna flesh, blending the tuna flesh in a food prep blender until it was homogenized, and adding 190 mL of deionized water to the blended sample. The sample was then hand-shaken for 20 seconds and allowed to rest for 5 minutes; the shaking and resting sequence was then repeated. Immediately prior to sampling the blended fluid, the container was shaken; the tuna sample was allowed to settle in the suspension and 100 µL of fluid was removed. This 100 µL sample was added to a bottle containing sample diluent and then mixed. 200 µL of fluid was removed from the sample diluent bottle provided in the test kit; this fluid was added to a small sample cup, which contained a lateral flow test strip. The lateral flow test strip was allowed to develop in the solution for at least 5 minutes and then evaluated with the Accuscan® reader. A positive result from the Accuscan® reader indicated that the sample contained greater than 50 ppm of histamine.

3. Results and Discussion

3.1 Microneedle and Test Holder Fabrication

The microstereolithography process was successful in creating (a) the microneedle arrays for sample acquisition from the tuna samples, (b) the microneedle holder, and (c) the lateral flow test holder. As seen in Figure 2A–C, the microneedles were arranged in staggered 3 × 3 rows in each microneedle sampling system. The trapezoidal eyelet extending from the microneedle base toward the microneedle tip served as a capture point for fluid from the tuna sample. The microneedles had heights of 1150 µm and base widths of 950 µm. Figure 2B–C show the insertion of the microneedle array into a piece of tuna and the indentation left in the tuna sample upon removal of the microneedle array.

As illustrated in Figure 1B–D, following insertion of the microneedle array into the tuna sample, the microneedle array was inserted into the central chamber of the test strip and microneedle array holder. Once in place, a lateral flow test strip was placed on the washed sample reservoir and 1000 µL of sample diluent from the Reveal® kit was added to the inlet port chamber of the device. The diluent traveled through the inlet channel, washed over the microneedles that were used to sample the tuna flesh, and entered the chamber holding the lateral flow test strip. Figure 2F shows an example of a completed test that followed this procedure. The lateral flow strip is shown to extend vertically out from the reservoir chamber, having been exposed to the diluent that flowed over the microneedles located in the central chamber. The lateral flow test strip in Figure 2F shows a positive histamine reading; a pink control band is observed in the upper portion and a more faintly pink test band is observed in the central portion. A ratio of the test: control line color intensity below 1 is indicative of a positive reading.

3.2 Comparison of Testing Methods with Histamine-Spiked Tuna Samples

For calibration of the microneedle sampling system procedure with the tuna flesh, pieces of tuna were incubated overnight in solutions of 1 × PBS (negative control), 0.5 mg/mL histamine, and 1.0 mg/mL histamine. The microneedle sampling system procedure was used to obtain fluid from the tuna sample. The same tuna sample was then evaluated using the manufacturer-described procedure (i.e., the procedure described in the Reveal® for Histamine kit). Comparisons between the data acquired from both testing methods for each solution type were made using a difference of the means with a 95% confidence interval.
The following formulas were used to compare results from the tuna samples and establish the difference of means confidence interval:

\[
C.I.\text{Upper} = (M_1 - M_2) + (t_{0.95})(S_{M_1-M_2}) \\
C.I.\text{Lower} = (M_1 - M_2) - (t_{0.95})(S_{M_1-M_2})
\]

The upper and lower limits of the confidence interval were calculated using Equations 3.1 and 3.2, with \(M_1\) and \(M_2\) representing the means of the microneedle sampling system procedure and manufacturer-described procedure Accuscan™ reading ratios, respectively. The \(t_{0.95}\) value is the \(t\)-table value at 95% confidence level. The \(S_{M_1-M_2}\) represents the standard deviation for the difference of means; it was calculated by use of Equation 3.3. In this equation, \(S_1^2\) and \(S_2^2\) are the variance and \(n_1\) and \(n_2\) as the number of samples for the microneedle sampling system procedure and the manufacturer-described procedure measurements, respectively. Upon calculating the confidence intervals, if the range of the interval spans both positive and negative values, no statistical difference exists between the two means within the indicated level of confidence.

Using this method, the confidence intervals comparing the difference of means for the microneedle sampling system procedure and the manufacturer-described procedure were compared. For the negative control with PBS, the 95% C.I. range was calculated to be \(-0.14 \geq S_{M_1-M_2} \geq -10.76\), with a difference of means of \(-5.45\). Based on this calculation, a slight statistical difference was noted between the test methods for PBS. When examining the 0.5 mg/mL test comparison, the 95% C.I. range was \(-3.96 \geq S_{M_1-M_2} \geq -4.21\), with a difference of means of \(-0.13\). Looking at the 1.0 mg/mL values, the 95% C.I. spanned...
0.52 ≥ \( S_{M_1 - M_2} \) ≥ 0.01, with a difference of means of 0.25. For the nine samples tested using each method in this comparison, no statistical difference was observed at a 95% confidence level between the microneedle sampling system procedure results and the manufacturer-described procedure results. Although a difference between the microneedle sampling system procedure results and the manufacturer-described procedure results was noted for the PBS-incubated samples, the histamine-spiked samples showed comparable results for the microneedle sampling system procedure and the manufacturer-described procedure. Figure 3 shows the mean values of Accuscan\textsuperscript{®} ratio readings for each type of sample. A decrease in the relative differences between the ratios of the microneedle sampling system procedure results and the manufacturer-described procedure results was noted as the sample type changed from PBS-spiked to histamine-spiked.

**Figure 3.** Graph of the mean (± S.E.M.) of the Accuscan\textsuperscript{®} reader test:control ratio data for histamine-spiked tuna samples acquired through the microneedle sampling system procedure and the manufacturer-described procedure. For comparisons marked with “*”, no statistical difference was noted between the results from the microneedle sampling system procedure and the manufacturer-described procedure when looking at the difference of means 95% confidence intervals for \( n = 9 \) of each test type.

### 3.3 Testing of Tuna from Time Course and Spoiled Samples

In addition to the histamine-spiked tuna samples that were used to compare the microneedle sampling system procedure and the manufacturer-described procedure, tuna samples that were left in a refrigerator for seven days were tested using both procedures. Figure 4 shows the test:control ratio values and standard error of the mean values for each set of measurements at Day 0 – Day 7 time points. Large differences were noted between results from the microneedle sampling system procedure and results from the manufacturer-described procedure for Day 0 – Day 3. These results from both procedures were well into the negative ratio values; although a large discrepancy in the results from the two procedures was noted, both procedures showed that the samples were negative for histamine at the 50 ppm threshold. The Day 5 results showed a dip in the ratio readings. Both procedures detected increasing levels of histamine; however, both procedures showed that the samples were negative for histamine at the 50 ppm threshold. A substantial dip in the microneedle sampling system procedure results was noted at Day 5. At the Day 7 time point, the decrease in readings for both test procedures continued. Using the confidence interval comparison method described previously, no difference between the results from the two test methods was noted at Day 7. The results remained negative at the 50 ppm histamine detection level at all time points over the 7-day time course.

**Figure 4.** Graph of the mean (± S.E.M.) of the Accuscan\textsuperscript{®} reader test:control ratio data for tuna samples over the refrigerated 7-day time course. Color intensity ratios acquired through the microneedle sampling system procedure and the manufacturer-described procedure were compared. For comparison marked with “*”, no statistical difference was noted between the microneedle sampling system procedure and the manufacturer-described procedure when looking at the difference of means 95% confidence intervals for \( n = 5 \) of each test type.

While the testing of time course samples remained negative, a spoiled piece of tuna was identified during the study. As described earlier, pieces of tuna that were incubated in PBS overnight under refrigerated conditions were meant to serve as negative controls during the histamine-spiking tests. However, one of the pieces of tuna that was tested in this manner returned a positive result for histamine. It was determined that the tuna sample was spoiled upon acquisition from the local fresh market. This spoiled tuna sample provided an opportunity to compare the mi-
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croneedle sampling system procedure and the manufacturer-described procedure. The positive results were initially detected using the microneedle procedure; four independent test strips were used to assess that particular piece of tuna. Upon obtaining these unexpected positive results, the histamine detection procedure outlined by the commercial Reveal® test kits was used to assess whether or not the tuna contained histamine. Four independent test strips were conducted on the tuna sample, which indicated that the tuna sample was spoiled and contained levels of histamine above the 50 ppm threshold. Figure 5 shows the mean color intensity ratios of the two test methods acquired from the Accuscan® reader. Using the difference of means calculation with a 95% C.I., no statistical difference was observed between the two test methods. The 95% C.I. for the difference of means for these samples was $-0.008 \leq S_{M_1-M_2} \leq 0.028$. It is interesting to note that the microneedle sampling system procedure was successfully able to detect histamine contamination in a tuna sample that had unexpectedly spoiled.

![Figure 5. Graph of the mean (± S.E.M.) of the Accuscan® reader test:control ratio data for the spoiled tuna sample. Color intensity ratios acquired through the microneedle sampling system procedure and the manufacturer-described procedure were compared. In a comparison of the difference of means 95% confidence intervals for $n = 4$ of each test type, no statistical difference was noted between the microneedle sampling system procedure and the manufacturer-described procedure.](image.png)

Other benefits of the microneedle sampling system procedure were noted throughout the course of the study. The amount of sample diluent used to process a sample was lower for the microneedle sampling system procedure than for the commercially available histamine detection kit procedure. The commercially available histamine detection kit provides sample diluent bottles containing 7 mL of solution to be used with each test strip. On the other hand, the microneedle sampling system utilizes only 1 mL of solution. In addition, the amount of time required to perform the microneedle sampling system procedure was much lower than the time required to perform the commercially available histamine detection kit procedure. The commercially available histamine detection kit procedure involves weighing 10 g of the sample, homogenization of the sample, addition of water, mixing, dilution, and use of the lateral flow test strip assay. On the other hand, the microneedle sampling system procedure involved application of the microneedle array to the sample for a few seconds, placement of the microneedle array into the sample holder, pipetting 1 mL of diluent into the holder, and use of the lateral flow test strip assay. The homogenization step associated with the commercially available histamine detection kit procedure added ten or more minutes of preparation time per sample. The microneedle sampling system procedure does not involve homogenization of the sample or cleaning of the homogenizer/blender between samples. The microneedle sampling system can be implemented as a single-use disposable unit, which minimizes the time needed for histamine detection.

4. Conclusion

A custom-designed microneedle sampling system was designed and used for determination of histamine content in fresh, histamine-spiked, and spoiled tuna samples. Lateral flow test strip assays were successfully integrated with the microneedle sampling system for determining histamine levels in tuna samples. Good agreement was noted between the microneedle sampling system procedure and the procedure outlined in a commercially available histamine detection kit. A discrepancy between the results from the microneedle sampling system procedure and the commercial procedure was noted at low (negative) levels of histamine; at higher histamine levels, an improvement in the statistical agreement between the procedures was noted. The microneedle sampling system procedure showed an improvement in the amount of time needed and the amount of reagent needed to screen for histamine in tuna samples. As such, the microneedle sampling system shows promise for future food testing studies.

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