



Analysis of Medication Off-odors Using an Electronic Nose

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Abstract

Packaging materials have been implicated as a source for off-odors in pharmaceutical products. A new instrumentation method employing an array of conducting polymer gas sensors was used to identify the offending packaging components in the canister of a pharmaceutical inhalant. A case study is described in which tainted inhalers as well as elastomeric components of the canisters were 'sniffed' by the electronic nose. The electronic nose was able to differentiate between tainted and untainted canisters. Signal processing algorithms performed on the raw data from the sensors suggested that specific elastomeric components were responsible for the off-odor. A further experiment suggested that the propellant (Freon) extracted the odor from the elastomeric components as the medication was expelled from the canister. These data indicate that the electronic nose is a potential tool to solve odor problems in which human odor assessment is not feasible due to excess exposure to the medically active ingredient. *Chem. Senses* 22: 119–128, 1997.

Introduction

Odor complaints from medications are not uncommon (Seydell and McKnight, 1948; Grossman, 1953; Hallman and Hurst, 1953; Skouby and Zilstorff-Pedersen, 1954; Zilstorff, 1965; Erikssen *et al.*, 1975; Schiffman, 1983, 1991; Berman, 1985; Levinson and Kennedy, 1985; Physicians' Desk Reference, 1995), but many of these complaints are attributed to the odor of the drug itself or to biochemical interactions of the drug with the peripheral or central olfactory pathways. Another potential source of odor problems, however, is contamination of a pharmaceutical product due to tampering or accidental adulteration. Contaminants in medications that can potentially produce off-odors include microorganisms (D'Arcy and Woodside,

1973; Rupp *et al.*, 1977; Flaum, 1978; Frieben, 1983) and organic compounds leached from packaging material (Reepmeyer and Juhl, 1983; Airaudo *et al.*, 1990).

The purpose of the present study was to identify the source of an off-odor from a pharmaceutical inhalant. Based on the history of odor complaints, the off-odor was suspected to arise from one of the components used in packaging the drug, specifically an elastomeric component used in constructing the hand-held canister. Until recently, the most common methods used to determine the source of odorous taints were human odor assessment (Deer *et al.*, 1987; Squires *et al.*, 1991), and gas chromatography/mass spectrometry (GC/MS) in which the odor mixture is

separated into its constituent volatile components (Freeman *et al.*, 1976). However, human odor assessment of odor from a canister was not feasible in this case due to excess exposure to the biologically active ingredient. GC/MS was limited as an analytical tool for this application for two reasons. First, since the thresholds for odors are often very low (parts per billion) (Dubois, 1976), there was not enough chemical mass in a given canister to identify the offending agents. Second, lot-to-lot variations in the product precluded precise identification of the off-odor producing chemical components.

For these reasons, a new and alternative analytical approach was employed that uses an array of gas sensors and computer-based pattern-recognition algorithms to emulate the human nose. This new 'electronic nose' technology is designed to analyze, differentiate, and/or identify odors and other volatile chemicals at concentrations of parts per million to parts per billion (Gardner *et al.*, 1990; Persaud *et al.*, 1990; Shurmer, 1990; Persaud and Travers, 1991; Shurmer *et al.*, 1991, 1993, Persaud, 1992; Shurmer and Gardner, 1992; Amrani *et al.*, 1993; Gardner and Bartlett, 1994; Hatfield *et al.*, 1994; Hodgins, 1995). Volatile compounds adsorb on (and subsequently desorb from) conducting polymers which constitute the sensor array. Within seconds (to minutes) after exposure, the volatile chemicals and the polymer sensors approach an equilibrium or steady state between adsorption and desorption. The interaction of volatile compounds with the polymers leads to changes in electrical resistance which is measured relative to a predetermined reference baseline. The polymer sensors are most sensitive to the detection of polar species, and this sensitivity decreases with decreasing sample polarity.

Individual polymer sensors react with multiple chemical species so that detection for a single sensor element is non-specific. The electronic nose used in this study (AromaScan, 1995) contains an array of 32 different conducting-polymer sensors with different but overlapping selectivities. One constituent of an odor mixture may interact with some of the 32 sensors but not with others. The pattern of response of the sensors gives an 'odorprint' (cf. 'fingerprint') for a specific odor. Depending on the mode of operation, this array of sensors can be exposed to the odorant sample, a reference gas, or a washing gas. Various gases are drawn inside the system using an electro-pneumatic pump, a plastic tubing system and solenoid-controlled flow valves. The reference gas is generated by a series of filtering and mixing steps. First, ambient air is passed through a carbon filter to produce a stream of 'dry

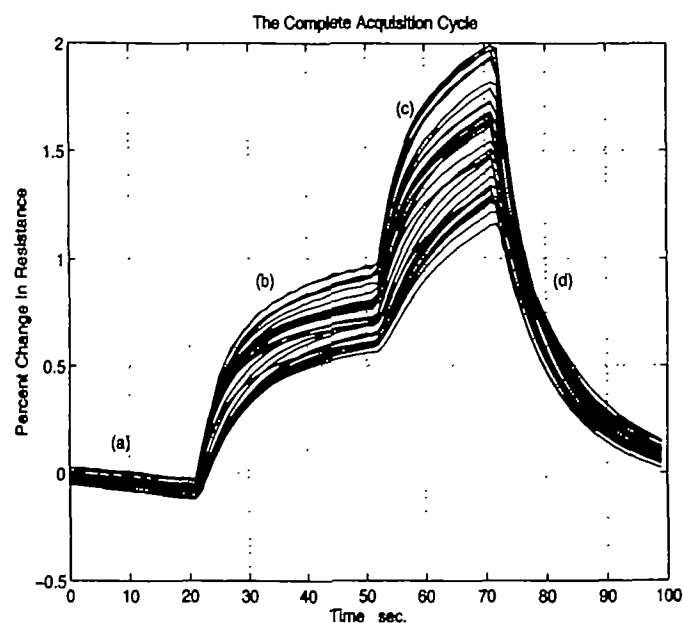


Figure 1 A complete data acquisition cycle: (a) reference phase, (b) sniffing phase, (c) washing phase, (d) transition to the next data acquisition cycle's reference phase.

air'. Next, a second stream of 'high humidity air' is generated by bubbling some of the dry air in deionized water. A stream of 'reference air' at a specified humidity is then generated by mixing the proper ratios of the high humidity air with the dry air stream. This third stream served as the reference gas in our studies. A fourth stream, the washing gas, is generated by bubbling dry air in a liquid cleansing agent. In this study, 2% n-butanol was used as the cleansing agent.

A personal computer (PC) controls the switching functions of the solenoid valves. The PC is also responsible for providing control signals to the pump, the air mixer and the temperature feedback control system. The temperature control system is used to maintain a constant temperature in the sensor compartment.

A complete data acquisition cycle consists of three phases: reference, sniffing and washing. First, the system enters a reference phase in which the sensors are flooded with the reference gas. After they approach steady-state, the odorant sample is passed over the sensors during the sniffing phase. This phase continues for seconds to minutes depending upon the dynamics of the sensors' response to the odorant molecules. The sniffing phase is terminated as the sensors approach a steady-state condition. Finally, the washing phase is performed by passing the washing gas over the sensors. During washing, the odorant molecules are

removed (desorbed) from the conducting polymers in preparation for the next data acquisition cycle.

An example data acquisition cycle is shown in Figure 1. The abscissa and the ordinate show the time and the percentage change in resistance of each sensor respectively. Figure 1 is composed of 32 different curves, each corresponding to one specific sensor. Note that the acquisition time as well as the amplitude of the curves during each phase can be different for each specific application of the electronic nose instrument. The data acquired by the electronic nose are passed through a set of pre-processing algorithms. Here, various computations are performed on the raw data, including noise reduction, scaling and data compression. The pre-processed data patterns (odorprints) are then fed into a neural-network-based, pattern-classifier system (Kermani, 1996).

Three experiments were performed here to identify the source of an unpleasant off-odor from canisters containing a respiratory pharmaceutical agent. Each canister contained a biologically active ingredient, a propellant (Freon) and other inactive ingredients. Elastomeric components used in the construction of the canisters were suspected as the source of the off-taint. Volatile aromatic compounds are generally removed from these components by an extraction process before the final assembly of the drug canister. In the first experiment, new canisters from two lots ('complaint' and 'no complaint') were compared to determine if the electronic nose could differentiate between their odors. In the second experiment, three elastomeric components were analyzed by the AromaScan instrument to determine if any of their odors matched the odor from the tainted ('complaint') canisters. In the third experiment, it was determined if the off-odor changed with repeated sprays. The results of the three experiments suggested that specific elastomeric materials were the probable source of the off-odor. The information gained from this study led to a solution for eliminating the taint problem.

Methods

Experiment 1

The purpose of this experiment was to determine if the electronic nose could differentiate between tainted and untainted canisters. Two sets of five canisters each were presented to the AromaScan electronic nose. These two sets were the following: (1) pharmaceutical inhalant from a

tainted lot that had never been sprayed, and (2) pharmaceutical inhalant from an untainted lot that had never been sprayed. Many complaints of off-odor had been received from the tainted lot; no complaints had been received from the untainted lot. The method of presentation of the odor from the canisters to the electronic nose was designed so that the operator of the equipment was never exposed to the medicine inside the canister. A single canister was placed into a 1 liter Tedlar® bag (SKC, Inc., 863 Valley View Road, Eighty Four, PA, USA) and sealed using special-purpose air-tight clips (also from SKC). Once the bag was securely sealed, it was inflated using the reference air provided by the AromaScan system. The contents of the canister were then released into the sealed Tedlar bag filled with reference air using a series of three pulses. The exhaust port of the AromaScan instrument was placed in a hood and directed to the outside environment to avoid any contamination of the laboratory environment. Each canister was sampled using a single sniff cycle, and a new bag was used for each of the 10 canisters.

The odor samples were presented to the electronic nose in an alternating order, i.e. tainted (A), untainted (B). This sequence was repeated five times. For each data acquisition cycle, the sensors were first exposed to reference air for ~7 min (reference phase) to produce a baseline. Time traces of the 32 conducting polymer sensors were then acquired for 5 min (sniffing phase). Following each sniffing phase, the sensors were purged by the washing agent (2% butanol) for 5 min (washing phase). These phase durations were found heuristically to be sufficient for establishing the baseline, sniffing the samples and washing the sensors respectively. A sampling interval of 10 s was selected for all phases, resulting in 30 data points per sniffing phase.

Experiment 2

The purpose of this experiment was to determine if the off-odor from the tainted canisters matched the odor of one of the three types of elastomeric packaging components used in the manufacture of the canisters. Tainted canisters containing the pharmaceutical inhalant and three types of elastomeric packaging components were presented to the AromaScan electronic nose.

The elastomeric component samples were prepared using the same types of bags and clips described in experiment 1. Each bag contained 18.5 g of a given component type. The Tedlar bags were then inflated using the reference air provided by the AromaScan system. Bags were left to

equilibrate for 2 h to generate a stable headspace. The tainted canister sample was prepared in the same way as in experiment 1. Again, extreme care was taken not to expose the operator of the electronic nose to the medicine contained inside the canister.

The inhalant and the packaging component odor samples were presented to the electronic nose in a sequential manner, i.e. elastomer 1, elastomer 2, elastomer 3 and tainted spray. This sequence was repeated three times (three data acquisition cycles), thus providing three complete data sets for each odorant sample. After each data acquisition cycle, the corresponding Tedlar bag was refilled with reference air to provide a sufficient volume of gas in the headspace for the next acquisition cycle. After each refilling of the Tedlar bags, their contents were allowed to equilibrate for 2 h.

Experiment 3

The purpose of this experiment was to determine if the Freon propellant's ability to extract odorous compounds from the canister components played a role in determining the nature of the unpleasant odor. If Freon was playing a role, then the concentration of the off-odor from the canisters would be expected to change with multiple successive sprays. The following experiment was designed to answer this question. Three sets of five canisters each were presented to the AromaScan electronic nose. These three sets were the following: (1) canisters from a tainted lot which were sprayed twice into an exhaust hood before insertion into Tedlar bags; (2) canisters from a tainted lot which were sprayed 10 times into an exhaust hood before insertion into Tedlar bags; and (3) canisters from a tainted lot which were sprayed 50 times into an exhaust hood before insertion into Tedlar bags. The presentation of the odor from the canisters to the electronic nose was identical to that described in experiment 1.

Data from sensors used for processing

Polymer sensors have been shown to be sensitive to polar molecules such as water. Thus, humidity has a prominent effect (external noise) on the response of polymer sensors. In order to reduce the effect of humidity on the response of the sensors, the humidity of the reference gas must match that of the odorant samples being tested. From a practical standpoint, however, a slight difference is always present between the humidity of the reference gas and that of the odorant sample. In this study, the response due to the residual humidity difference was found to be remarkably

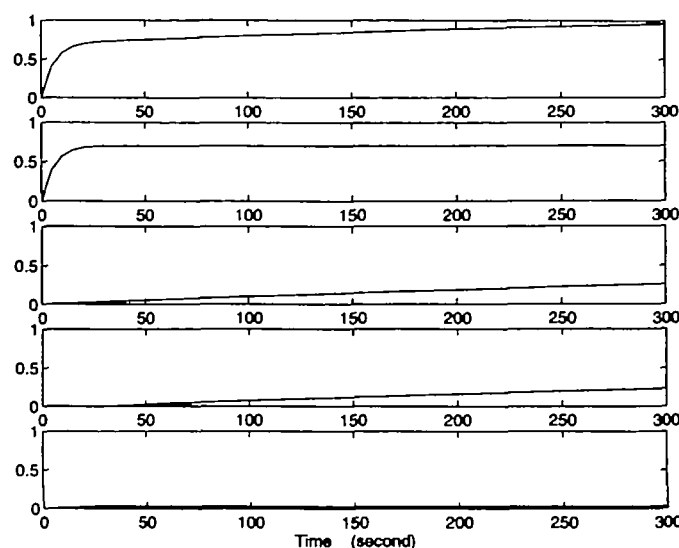


Figure 2 Removing the effect of humidity: (a) a hypothetical sensor waveform response to an odorant sample containing water vapor, (b) the same sensor's response to water vapor alone, (c) the same sensor's response to the odorant alone, (d) results after applying the bias removal procedure – R_{new} , (e) difference between sensor's response to the odorant and R_{new} .

faster (settling time ~ 30 s) than that of the odorant samples under test (settling time > 5 min). Therefore, we were able to remove the effect of the residual humidity difference by zeroing the first 30 s of the sniffing phase, and adjusting the successive sample points correspondingly.

Figure 2(a) illustrates a hypothetical waveform from one of the 32 polymer sensors. The response is composed of two parts: (1) the humidity difference between the reference gas and the sample, and (2) the volatile odorous compounds in the sample. Figure 2(b) shows a typical humidity response—it reaches a steady state at ~ 30 s. Figure 2(c) represents the odor response, which is smaller and much slower than that of the humidity. Adding Figures 2(b) and 2(c) generates the total response in Figure 2(a). The humidity portion of the sensor response can be removed by ignoring the first 30 s of the response. To accomplish this, the sensor response was shifted downward so that the sample at $t = 30$ s was set to a value of zero [$R_{new}(30) = 0$]. The sensor values at $t = 0, 10$ and 20 s were also set to zero [$R_{new}(0) = R_{new}(10) = R_{new}(20) = 0$]. All the other points were shifted by the formula:

$$R_{new}(10*k) = R_{old}(10*k) - R_{old}(30), \text{ for } k = 4, 29$$

The resulting waveform for R_{new} is shown in Figure 2(d). The error in this approach is analyzed in Figure 2(e). Here, Figure 2(d) is subtracted from the true odor signal in Figure

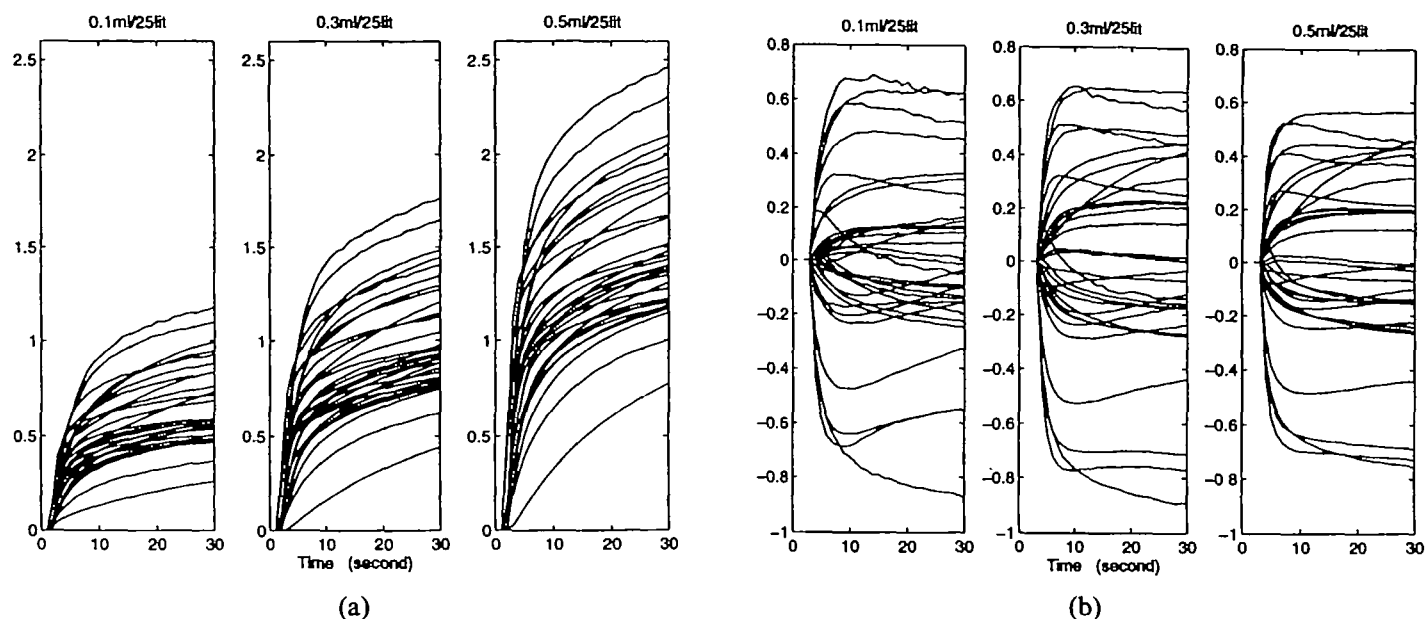


Figure 3 Minimizing concentration effects: (a) sensor response to three different fragrance concentrations, (b) scaled sensor responses.

2(c) to illustrate the accuracy. The large difference between the kinetics of the humidity and odor response in the case of these experiments is purely fortuitous. There are cases, e.g. perfumes (Kermani, 1996), in which both the odor and humidity responses follow similar kinetics, which makes it more difficult to overcome the effect of humidity.

Immediately after removing the effects of humidity, the data were scaled to decrease the dependence of the sensor output signals on concentration differences. Since precise control of odor concentration is difficult to achieve in any electronic nose experiment, the following equation was applied to each sensor's output:

$$R_{\text{scaled}}(10*k) = R_{\text{new}}(10*k)/R_{\text{avg}}(10*k), \text{ for } k = 4, 29$$

where $R_{\text{avg}}(10*k)$ is the average value of R_{new} at time $10*k$ over all 32 sensors. The outcome of this procedure is illustrated in Figure 3. In this example, we exposed the AromaScan sensor array to an odorant with three different, precisely controlled concentrations. For illustrative purposes, the odorant selected was a popular fragrance and the sampling period was reduced to 1 s, an appropriate choice for this class of odorant. In Figure 3(a), the raw data patterns are shown for 0.1, 0.3 and 0.5 ml of the fragrance deposited into 25 l Tedlar bags. Note that an increasing concentration of odorant produces a progressively larger sensor response. In Figure 3(b), the data have been scaled to reduce the differences due to concentration effects. Note

that all three cases now produce a similar pattern of response.

Results

Experiment 1

Figure 4 depicts the time-patterns acquired in the sniffing phase of experiment 1 for three repetitions of a single tainted canister. Figure 5 represents the time-patterns for three repetitions of a single untainted canister. All three repetitions of the sniffing cycle for a given canister are shown to illustrate the degree of repeatability of the response. Even though the canisters deliver a metered dose of medication, the response amplitudes vary over the three repetitions due to changes in odorant concentration and sensor sensitivity. The concentration changes were probably due to (i) differing amounts of reference air being added to the bags (repetition-to-repetition headspace volume variations), and (ii) adsorption of some of the volatile odorant molecules on the interior surface of the Tedlar bags. The patterns are composed of 32 different curves, each corresponding to one specific sensor. For each curve, there are 30 individual time points which, given the sampling interval of 10 s, span the 5 min sniffing phase. Considering the amplitude of the time-patterns shown in Figures 4 and 5, one can conclude that the odors of the tainted and untainted canisters have relatively similar intensities.

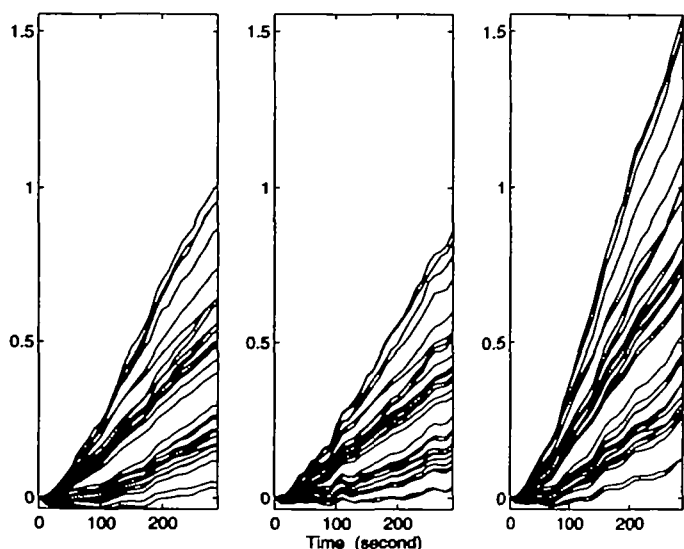


Figure 4 Three typical 'sniffing phase' response profiles from a single tainted canister.

A series of computations were then performed in order to represent the similarity of the odor profiles of each canister type in a simple, pictorial diagram. First, humidity effects were removed and concentration responses were reduced for each data point at a specific time in the time-pattern of each sensor response, as described in Figures 2 and 3. These procedures have been shown to effectively cancel both the humidity contributions and the scaling effect of concentration (Kermani, 1996). This is necessary since the amount of odorous compounds released from a canister varies with repeated sprays.

Next, the scaled patterns were delivered to an order-reduction unit in which the dimension of the patterns was reduced from 960 (30 time points \times 32 sensors) to two. This was done to compress the data so that it could be represented pictorially and visualized more easily. This data compression procedure also simplified the training of the neural network and improved its generalization properties. The data reduction was performed as follows.

First, four approximately equal time slices were constructed using a windowing procedure (Kermani, 1996). These four time slices characterize the dynamics of the sensor signals as follows: period 1, early onset; period 2, rapid change; period 3, slow change; and period 4, steady state. These four time slices proved adequate to capture the signal dynamics in the experiments of this investigation.

Next, the time slices of the patterns were separately integrated with respect to time. The integration procedure reduced the dimension of each time period to 32 (one

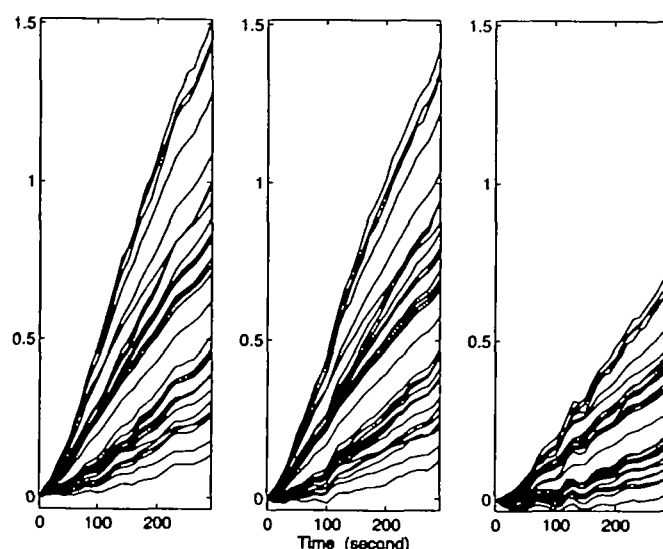


Figure 5 Three typical 'sniffing phase' response profiles from a single untainted canister.

number for each sensor). Note that the integration operation, in general, can result in loss of important information that may be hidden in a data set. However, independent studies (Kermani, 1996) showed that this problem does not occur in many electronic nose applications due to the high degree of point-to-point correlation in each sensor signal.

Finally, by incorporating a Karhunen–Loève expansion (KLE) (Chen and Huo, 1991; Fukunaga, 1992; Bigun, 1993; Burl, 1993; Grother, 1993), the number of variables was further reduced from 128 (4 time slices \times 32 points per time slice) to 4 (4 time slices \times 1 point per time slice). The KLE was performed independently on each of the time slices, reducing its size from 32 to only one data point. The patterns were not forced to shrink to one point; rather, this reduction was automatically achieved by setting a low threshold (0.01) in KLE computations (Kermani, 1996). The one-dimensional reduced data was found to be adequate to account for 99% of the variance.

In order to visualize the results, only two of the four time slices were used—the ones corresponding to the slow-change and steady-state periods. These two time slices were selected because their replicate correlation coefficients were greater when compared to the early-onset and rapid-change periods. The average correlation coefficients among three repetitions for the four time-slice periods were 0.33, 0.46, 0.68 and 0.78 respectively.

The results are illustrated in Figure 6. In this figure, the abscissa and the ordinate represent the significant

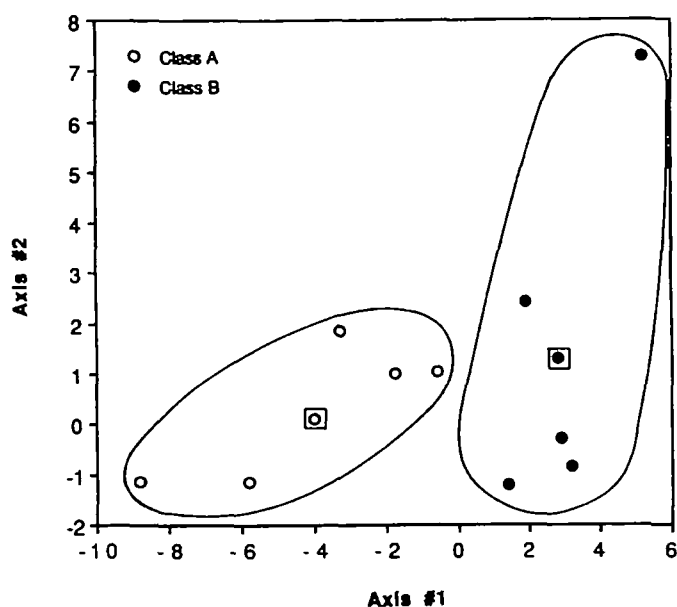


Figure 6 Comparison of odor characteristics: five tainted canisters (p), and five untainted canisters (P).

eigenvectors corresponding to the third and the fourth time slices, respectively. One can define these unitless axes, labeled axis 1 and axis 2, as the base vectors of the reduced-order data. The open circles in the figure represent the odor quality of five tainted canisters. The dark circles represent the odor quality of the five untainted canisters. Ellipse-shaped contours have been inserted around the two odorant classes to enhance visualization. The centroid of each class is displayed as a square around the appropriate symbol. There is no overlap between the odor quality of canisters from a tainted and an untainted lot which suggests that they have different odors.

Experiment 2

Time-patterns for the three elastomeric components and a tainted canister were processed using the concentration cancellation technique, bias removal and data compression by KLE as described in experiment 1. The results are shown in Figure 7. As in experiment 1, two dimensions were found to be adequate to account for 99% of the variance. The four odorant classes (elastomer 1, elastomer 2, elastomer 3 and tainted spray) are displayed in Figure 7. Elastomer 1 is represented by pluses, elastomer 2 by asterisks, elastomer 3 by crosses and tainted spray by circles. Each class is enclosed in an ellipse-shaped contour. Note the tight grouping of elastomers 1 and 3 with the tainted spray. The close proximity of the tainted spray to elastomers 1 and 3 indicates that the odor from the tainted canister was very similar to that of

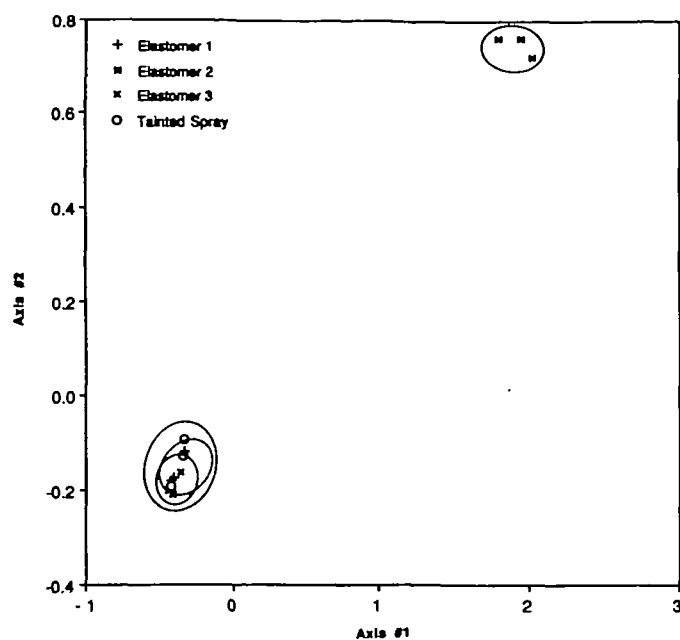


Figure 7 Comparison of odor characteristics of a tainted canister and three elastomeric components.

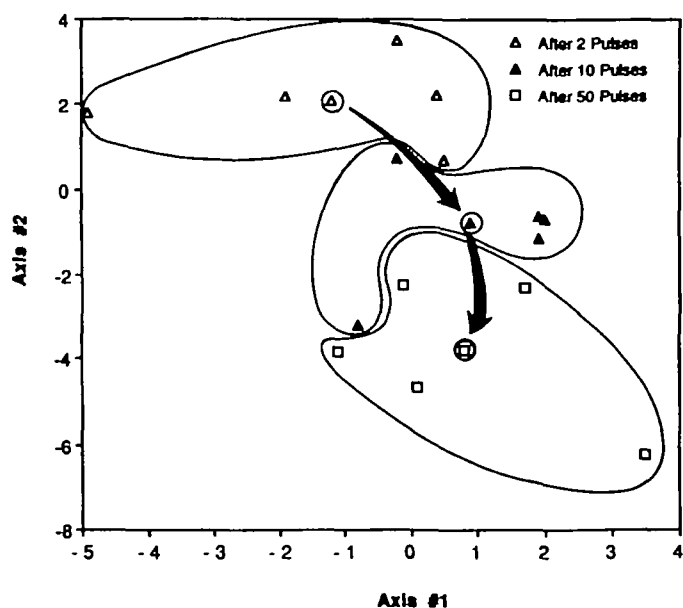


Figure 8 Comparison of lingering odor characteristics of tainted canisters after clearing them with spray releases: after two initializing pulses, after 10 initializing pulses, and after 50 initializing pulses.

elastomeric components 1 and 3. The clear separation of the classes tainted spray and elastomer 2 suggests that the tainted spray and elastomeric component 2 have different odor qualities.

Experiment 3

Time-patterns for the tainted canisters (which were sprayed

for a varying numbers of pulses before testing) were also processed using the concentration cancellation technique, bias removal and data compression by KLE as described in experiment 1. The results are given in Figure 8. The open triangles represent the odor quality of five canisters from a tainted lot from which two pulses of odorant had previously been released. The solid triangles represent the odor quality of five canisters from a tainted lot from which 10 pulses of odorant had previously been released. The squares represent the odor quality of five canisters from a tainted lot from which 50 pulses of odorant had previously been released. Note that each class has been encircled by a contour to enhance visualization. Note also that the contours have been drawn arbitrarily to highlight the cluster locations. The centroid of each class is indicated by a circle around its corresponding symbol. The bold arrows illustrate the changing nature of the classes. The results indicate that the odor from the canisters changes as they are sprayed more times.

General discussion

The main findings of the three experiments are the following. The electronic nose can differentiate between odors from tainted and untainted canisters (Figure 6). This means that the signals from the sensors, when normalized and submitted to data compression, have acceptable repeatability. Next, the patterns of the tainted spray appeared to be closest to the elastomeric components 1 and 3, but significantly different from elastomeric component 2 (Figure 7). Therefore, elastomeric component 2 was eliminated as a source of the odor taint, and elastomeric components 1 and 3 were a potential source. In addition, the patterns of elastomeric components 1 and 3 are very similar.

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After completion of the experiment, we learned that the elastomeric materials used for components 1 and 3 were identical. Finally, repeated spraying of tainted canisters shifted their odor profile (Figure 8). This was found to give further support for elastomeric components 1 and 3 as the odor source for the reasons described as follows.

The similarity of the odors of elastomeric components 1 and 3, and the tainted canisters, suggested that the elastomeric components used in construction of the tainted canisters had not been properly extracted with Freon. It is probable that the Freon used as propellant in the pharmaceutical preparation extracted odors from the canister's elastomeric components 1 and 3 causing the off-odor. The construction of the canister permits the drug and propellant to come into contact with elastomeric components 1 and 3 as they are expelled. The fact that the odor changed with repeated spraying suggests that the offending compounds may have been extracted by the Freon during storage, and subsequently released as the medication was expelled from the canister. Leaching of compounds from elastomeric materials in drug formulations has been described previously. Constituents of rubber (elastomeric) closures, including 2-mercaptobenzothiazole (Reepmeyer and Juhl, 1983; Airaudo *et al.*, 1990) and 2-mercaptobenzo-thiazole disulfide and 2-mercaptobenzimidazole (MBI) (Airaudo *et al.*, 1990), have previously been shown to leach into drug preparations.

The use of the electronic nose (AromaScan, 1995) helped identify the offending canister components responsible for the off-odor of a pharmaceutical inhalant and permitted remediation of the problem. The electronic nose was especially helpful in this application since a human odor panel could not be exposed to the drug and the mass of the volatile compounds responsible for the odor was too small to be detected by GC/MS.

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