Background review of breath analysis using electronic noses and mass spectrometers. Why it is important to do (obesity)? What diseases it diagnose? What volatile compounds are normally present? a history of breath analysis devices and methods. How does it perform? What gases is involved and their concentration? What are the available commercial devices right now for breath analysis and how much they cost? Are there any hand held devices available for breath analysis?

Literature Review Breath Analysis Harvard Referring

Human body emits odours from different parts of the body. The emitted odour generally contains various types of volatile compounds. These emitted compounds varies from individual to individual depending upon sex, age, physiological status and probably genetic background (Shirasu and Touhara, 2011). The volatile compounds can serve as useful biomarkers which can be indicative of the physiological status (normal or abnormal) of an individual and can also provide information about the progression of a particular disease or therapy treatment. Therefore it is useful to analyze these compounds. Major sources of odour in the body particularly include breath, sweat, skin, urine etc (Shirasu and Touhara, 2011).

Out of these sources breath has been known to be a useful physiological specimen from Hippocrates times (known to be as the father of medicine) (Adams, 1994) but it has not found much clinical significance. Modern breath analysis started in the year 1971 when Nobel prize winner Linus Pauling separated the components of breath by gas chromatography (Pauling et al., 1971) which indicated that “human breath is a complex gas comprising of more than 200 volatile organic compounds generally in picomolar concentrations” (Koc-Rauchenwald et al., 2011). Breath analysis offers unique advantages as it is rapid, simple and non-invasive (Dubowski, 1974) and often can be repeated easily. It is an indicator of the arterial blood concentration of compounds because of passive diffusion taking place in the lungs and therefore evades the use of arterial blood collection (Manolis, 1983). Breath analysis is simple because its composition is not as complex as that of urine or blood and can be applied to a wide range compounds (Francesco et al., 2005). More than 3500 VOCs have been identified in the exhaled breath so far and the list continues to grow (Risby and Solga, 2006).

Majority of the gases in the breath are a mixture of nitrogen, oxygen, CO_2, H_2O (Miekisch et al., 2004). The remaining fraction has thousands of trace volatile organic compounds (VOCs) whose concentrations varies from parts per million (ppm) to parts per trillion (ppt) by volume.

The below mentioned tables lists some of the molecules present in the breath alongwith their concentration (Risby and Solga, 2006).

Concentration (v/v)	Molecule
Percentage (%)	Oxygen, water, carbon dioxide
Parts-per-million (ppm)	Acetone,carbon monoxide,methane, hydrogen
Parts-per-billion (ppb)	Formaldehyde,acetaldehyde,isoprene,1-pentane,ethane, ethylene, other hydrocarbons, nitric oxide, ammonia, methylamine etc.

VOCs which are common to human metabolism are quite few and basically include isoprene, acetone, methanol, ethane etc. These are useful for clinical diagnosis as they are products of core metabolic processes (Mukhopadhyay, 2004). The volatile compounds present in the breath can be either endogenous or exogenous in origin.

Endogenous compounds are those which are produced within the body. These mainly include inorganic gases such as NO and CO) and VOCs such as isoprene, ethane, pentane, acetone. It can also include some non volatile substances such as isoprostanes, peroxynitrite, or cytokines (Miekisch et al., 2004). Tests for endogenous compounds can provide information regarding disease state. Exogenous compounds are those which are inhaled from the environment or are produced upon ingestion of food or derived from compounds after smoking (Cao and Duan, 2006). These include for example halogenated organic compounds and basically indicate recent exposure to drugs or environmental pollutants (Pleil and Lindstrom, 1997).

Analysis of the exhaled breath has been used for the identification of various diseases such as oxidative stress, lung diseases, metabolic disorders, gastroenteric disorders etc. (Cao and Duan, 2006). Oxidative stress involves damage to the cells caused due to the chemical reaction taking place between reactive oxygen species and oxidative agents. Oxidative stress has been found in disease states like lipid peroxidation, bronchiectasis etc. Clinical studies have shown strong correlation between high peroxidase activity and exhalation of hydrocarbons (Aghdassi and Allard, 2000). Exhaled ethane and n-pentane are the markers used to monitor oxidative damage in the body (Miekisch et al., 2004). H_2O_2 has also been used as a biomarker (Horvath et al., 2001).Various lung diseases like asthma, constructive pulmonary disease, interstitial lung disease, adult respiratory distress syndrome can be diagnosed by examination of breath components. In case of asthma patients high concentration of nitric oxide has been detected (Kharitonov et al., 1996). Some researchers have also examined markers for lung cancer such as monomethylated alkanes and C_4 to C_{20} alkanes in breath.

Various metabolic disorders can also be detected by examining breath such as diabetes. Acetone has been found to be increased in patients with diabetes mellitus (Henderson et al., 1952). Gastroenteric disorders such as carbohydrate malabsorption are being detected by measuring breath hydrogen (Perman, 1991). *H.pylori* infection can also be detected (Brown and Peura, 1993). Renal diseases diagnosis is also possible with the help of breath analysis. Volatile organic amines have been found in the breath of renal patients.

Breath Analysis is mostly done with the help of mass spectrometry in conjunction with or without gas chromatography. GC-MS (gas chromatography-Mass spectrometry) analysis allows traditional ionization sources to be used. Ionization results in the fragmentation of the analyte and the resulting spectrum are specific to the compound. New breath biomarkers can be identified by studying chromatographic retention data and mass spectral data (Risby and Solga, 2006).

In addition to breath analysis breath profiling can be done with the help of soft ionization alongwith mass spectrometry. Two other techniques such as Atmospheric pressure ionization mass spectrometry (API-MS) or selected ion flow tube mass spectrometry (SIFT-MS) are used for direct breath analysis (Smith and Spanel, 2005). There are other techniques such as Fourier transform infrared spectroscopy (FTIR).

Breath analysis is also done using electronic noses. Electronic noses produce a chemical fingerprint of the gaseous sample with the help of chemical sensors. The fingerprint can be matched with reference database using a pattern matching algorithm. This method does give a list of the compounds but indicates the similarity percent (Francesco et al., 2005)

There are a number of commercial devices available in the market used for the analysis of breath which has been approved by the Food and Drug Administration (U.S.A). Most of these devices are portable and are hand held. These devices are used in various analysis using different technique. One of the devices known as EC50 ToxCO + costs around $1950 and is used for detecting carbon monoxide poisoning. This device is manufactured by Bedfont Scientific Ltd., Rochester UK. It is based on the technique of electrochemical gas and sensor technology. Another device known by the trade name NIOX MINO manufactured by Aerocrine AB (Solona, Sweden) uses electrochemical sensor and is used for asthma and airway inflammation. The cost of this device is $2500.

Alcohawk Precision Digital Alcohol Detector is based on semiconductor oxide sensor used to check for alcohol intoxication and is manufactured by Q3 Innovations. It costs around $68.55 (Mashir et al., 2011). Some other devices are EMMA Emergency Capnometer (based on Infrared gas analysis), Micro H_2(electrochemical gas sensor based).

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