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A review: Solvent Depletion Approach in Volatile Organic Compounds in Low AET Extractable and Leachable Analysis

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Abstract
The identification of volatile organic compounds (VOCs) through a preliminary extractable study and the attribution to the contact component from which they originate is one of the essential requirements of the E&L study. Polar to mid-polar VOCs demonstrate low detector sensitivity compounds compared to non-polar VOCs due to their solubility in polar solvents that restrict them from transit into headspace. Most pharmaceutical and biological formulations are aqueous; therefore, the identification of potential volatile leachable compounds becomes more challenging when the estimated Analytical Evaluation Threshold (AET) for an E&L study is at a sub-ppb level. This review article emphasises various approaches used to enhance detector sensitivity and highlights the benefits of the solvent depletion approach. Changing the phase ratio and partition coefficient are two conventional methods used to improve detector sensitivity, but they are often found to be insufficient for achieving the sub-ppb level. The introduction of hydrate-forming inorganic salts, such as Sodium sulphate anhydrous and magnesium sulphate anhydrous, which are primarily used as drying agents, played a key role in enhancing the detector sensitivity of polar to semi-polar volatile compounds by depleting the aqueous portion from the sample solution and making them freely available to the headspace for detection.

Keywords: Solvent Depletion, AET, Extractable & Leachable, Volatile organic compound, Head Space

Introduction
From drug product manufacturing to administration to patients, pharmaceutical products come in contact with multiple container closure systems (CCS) made of different materials. During contact with drug products, packaging material may release species in the form of organic compounds (Volatile, Semi-volatile and Non-volatile Compounds) and inorganic compounds (metals). Therefore, detailed compatibility studies on these materials used in CCS may be required to ensure that product quality remains consistent and that no safety concern is triggered due to product/material incompatibility, especially when the administration method associated with a particular dosage or form is of high concern [1, 2]. In this article, the focus remains only on volatile organic compound analysis. The instrumentation employed in this study includes gas chromatography headspace-mass spectrometry (GC-MS).

Are All VOCs Hazardous to Health? Are Acetonitrile, Benzene, Isopropyl Alcohol, Toluene, and Methyl Alcohol all VOCs the same? Are they hazardous? The answer is NO and YES! No, they are not the same because each one is chemically different. YES, However, some of them are the same because they are hazardous if ingested, inhaled, or to a lesser degree if absorbed through the skin [3].

For example
- Acetonitrile can cause fatal cyanide poisoning
- Benzene has been linked with a higher risk of cancer
- Methanol severely irritates skin, eyes, and mucous membranes
- Toluene toxicity leads to instant deaths and permanent lung and kidney damage [4-7]

Challenges Associated with Voc Analysis

- Volatile compounds differ in molecular weight, polarity, and volatility, hence demonstrating variable sensitivity to the detector.
- Most of the pharmaceutical and biological formulations are aqueous, providing affinity to challenge polar and semipolar VOC, which create a challenge for detection at low levels.
- Large volume parenteral requires VOCs detection at low-level AET
- Low volume of sample availability due to their cost, usage, and route of administration; therefore, phase ratio is not feasible
- Loss of VOCs during sample concentration steps due to low boiling point, i.e. Evaporation; therefore, the liquid-liquid extraction approach is not feasible.

Conventional Approach for Enhancing Sensitivity

Changing the phase ratio (Change in Vial Size/Sample)

The phase ratio (β) is defined as the relative volume of the headspace compared to the volume of the sample in the sample vial, where Vs = volume of sample phase and Vg = volume of gas phase. Lower values for β (i.e., larger sample size) will yield higher responses for volatile compounds. However, decreasing the β value will not always produce an increase in response needed to improve sensitivity.

β (Phase Ratio) = Vg/Vs

When β is decreased by increasing the sample size, compounds with high partition coefficient (K) values partition less into the headspace compared to compounds with low K values, and yield correspondingly minor changes in Cg. Samples that contain compounds with high K values need to be optimised to provide the lowest K value before changes are made in the phase ratio [8].

Changing the partition coefficient (Introduction of Inorganic Salt)

Headspace results are optimal when the analytes are chemically able to escape the sample and move into the headspace. This measure is known as the partition coefficient (K), which is a temperature-dependent expression of the sample concentration (CS) and the gas phase concentration (C_G). This comparison is depicted in Figure 1. In liquid samples, solvent adjustments or the addition of non-volatile salts may be essential to affect K. In solid samples, sometimes a small amount of solvent can assist in creating more favourable K values in an analysis[8]

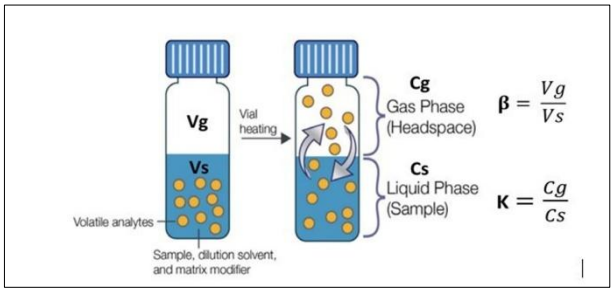

Fig 1: The partition coefficient (K) and the phase ratio(β) in the headspace vial

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The mechanism involves an inorganic Salt in an Aqueous Solution

Step 1 - Breaking the attraction forces holding the lattice together to free the ions in the sample

Step 2 -Forming new forces of attraction between free ions and water molecules and making dissolved polar volatile compounds free from weak attraction forces.

Step 3- Now these volatile compounds are more readily available to release in the headspace

Step 4- As the concentration of VOCs in headspace increases, it leads to enhanced sensitivity for the VOCs [9]

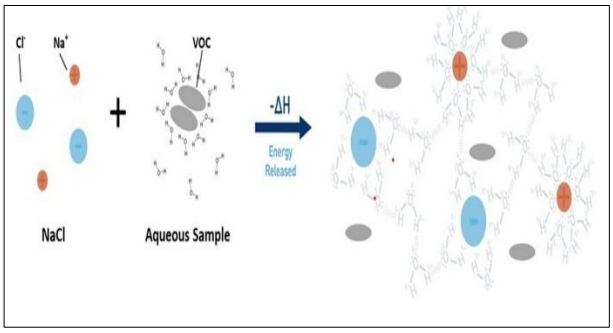

Fig 2: Salt Mechanism in Aqueous Solution

Solvent Depletion Approach

Solvent + Depletion ⟶ Reduction in the quantity of solvent

Solvent depletion is achieved by hydrate forming inorganic salts in low-volume aqueous samples. Hydrated inorganic salts are the reagents that interact with water molecules and change their crystalline structure. Examples of hydrate-forming salts include sodium sulphate decahydrate (Na2SO4 · 10H2O), Magnesium sulphate heptahydrate (MgSO4 · 7H2O), and Sodium carbonate decahydrate (Na2CO3 · 10H2O), among others.

Magnesium sulphate Anhydrous is a slightly acidic drying agent. It is a fast-drying agent, in part because it comes as a fine powder with a large surface area.[10]

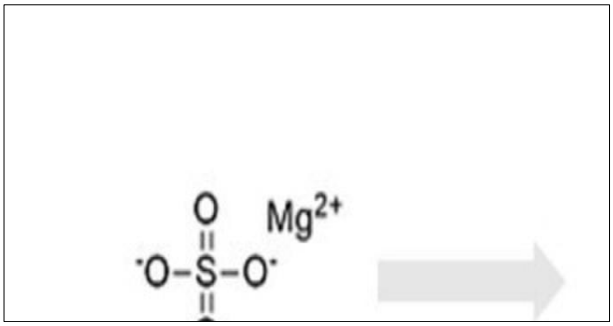

Fig 3: Magnesium sulfate forming Magnesium sulfate heptahydrate in the presence of water

Sodium sulphate Anhydrous has a very high capacity and is mainly used for very wet solutions. it also absorbs other polar compounds like alcohols, etc. Additionally, it is slower compared to magnesium sulphate, etc [11].

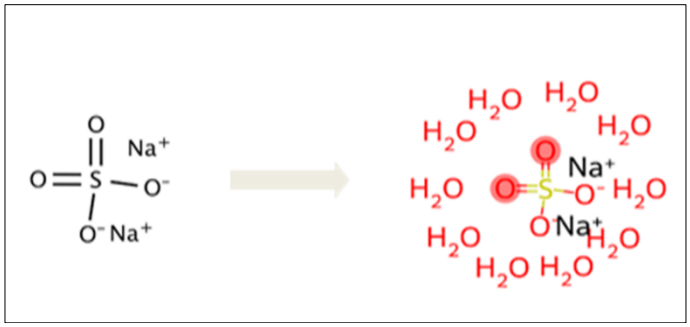

Fig 4: Sodium sulfate forms sodium sulfate decahydrate in the presence of water

In chemistry, a hydrate is a hydrated ionic compound that absorbs water molecules from its environment and incorporates them into its structure, thereby reducing the aqueous component in the sample solution (Figure 5).

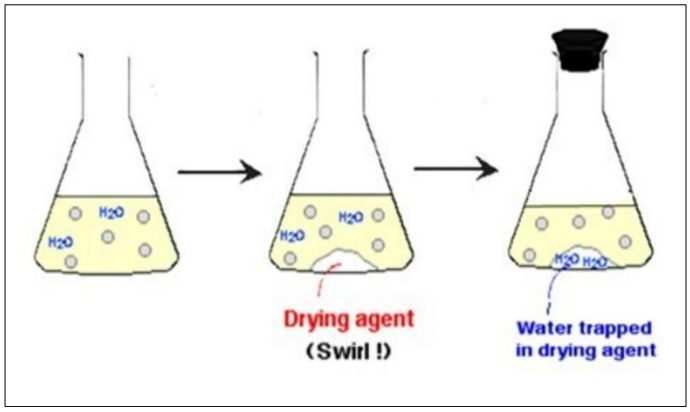

Fig 5: Hydrate formations by inorganic salt in aqueous sample

Gas chromatography uses this phenomenon in the analysis of volatile organic compounds.

An experiment was performed using a 10 mL headspace vial. Methanol was used as a volatile reference standard and was spiked in the purified water to prepare the aqueous solution with a concentration of 0.1 µg/mL. 2 mL of this solution was transferred to each vial. Magnesium sulphate was employed as a hydrate-forming salt, and sodium chloride was used as a control salt to compare its response with that of the hydrate-forming salt. Methanol was used as a volatile reference standard Table 1. Similar experiment was performed with Sodium sulfate anhydrous salt Table-2

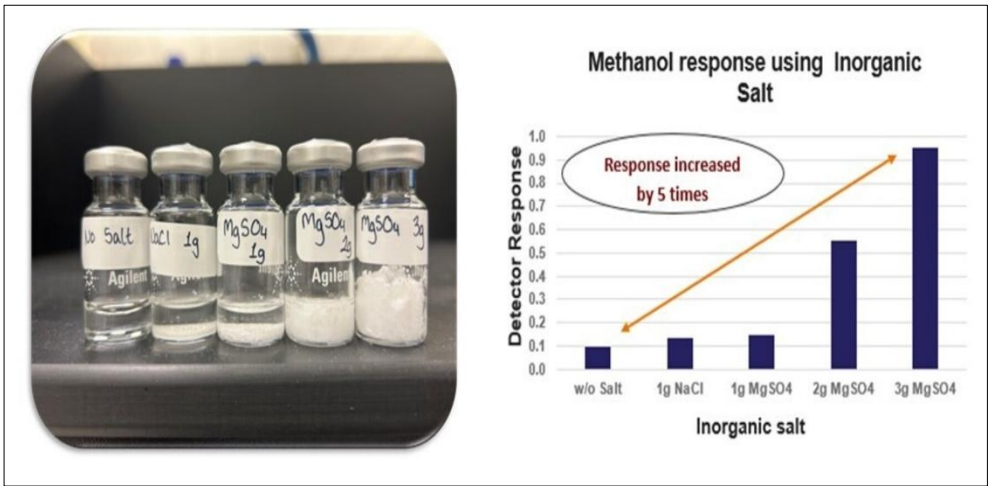

Fig 6: Magnesium salt forming the hydrates in the presence of water

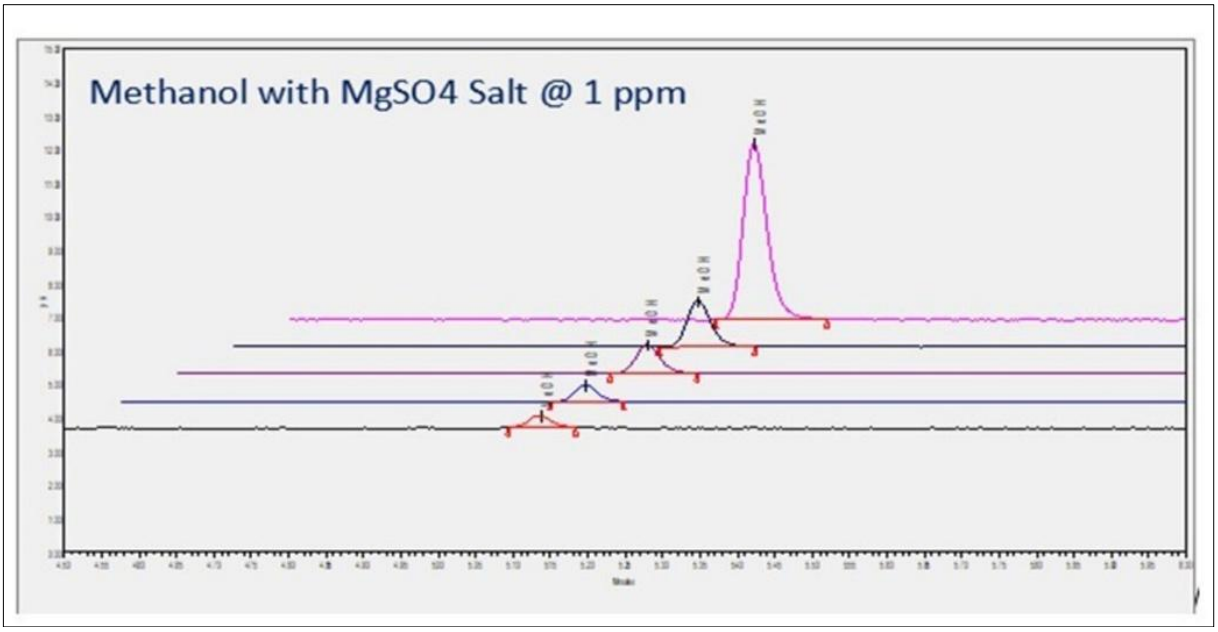

Fig 7: Chromatograms for the methanol peak (1 ppm) response with various salt concentrations

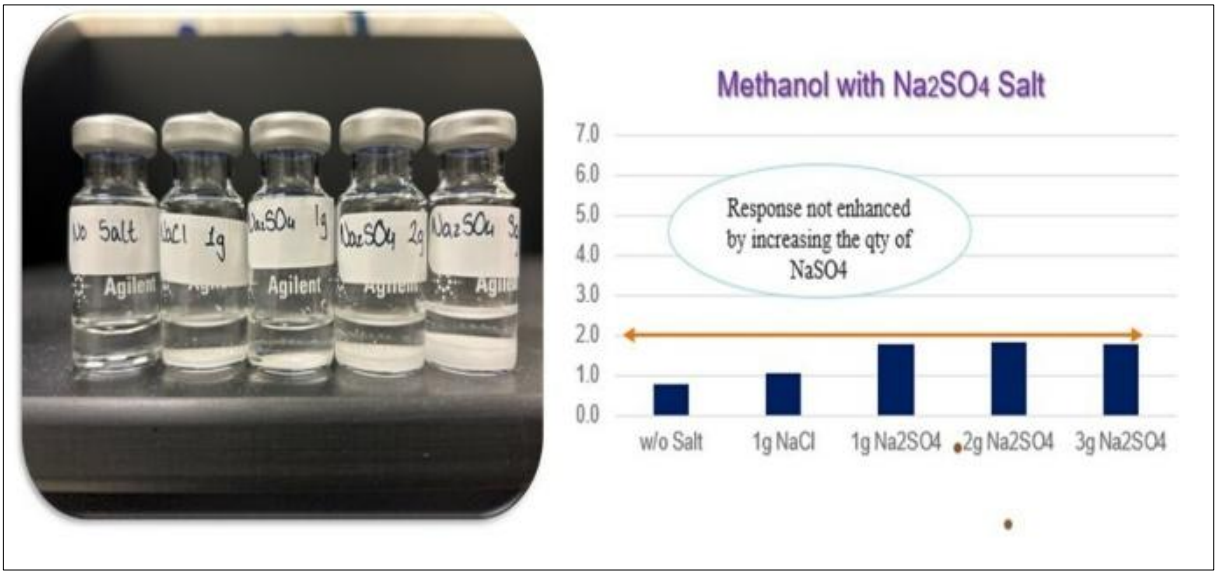

Fig 8: Magnesium salt forming the hydrates in the presence of water

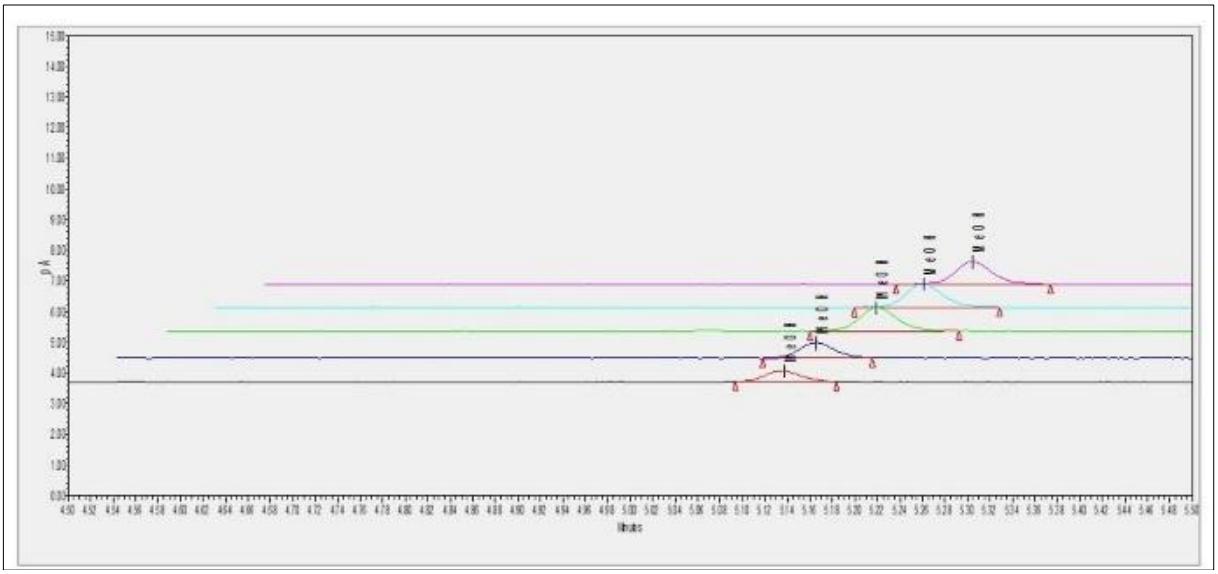

Fig 9: Chromatograms for the methanol peak (1 ppm) response with sodium sulfate salt concentrations

This salt can be used in excess amounts in low-volume aqueous samples to absorb water and form a hydrate, resulting in a reduction in the total aqueous volume of the sample. See figure 6-7**.** This approach demonstrated a slight increase in the response in the sample containing 1g of salt (Sodium chloride and Magnesium sulphate anhydrous) compared to the sample with no added salt. This response was further enhanced to 5 times when the salt quantity was increased to 3g. On the other hand, when the amount of sodium sulfate was increased (1g to 3g), no significant increase in the response was observed Fig: 8-10. These results demonstrated that increasing the salt amount caused more hydrate to be formed, thus releasing polar to mid-polar volatile organic compounds to the headspace. This process increases the concentration of VOCs in the headspace, which is further extracted by the injection loop and transferred to the detector for determination.

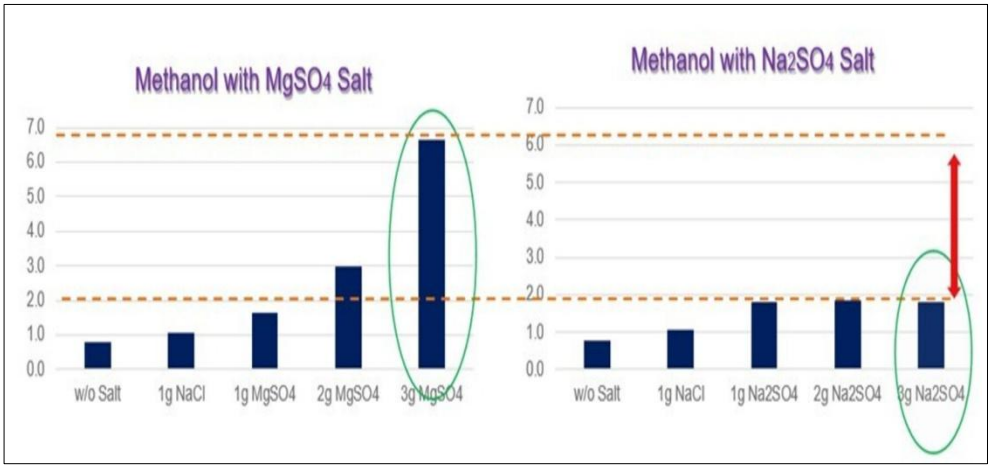

Fig 10: Graph comparing the methanol peak (1 ppm) response with Magnesium Sulfate salt and sodium sulfate salt

Table 1: Headspace sample vials preparation using magnesium salt amounts

Head Space Vial Size	Sample Volume	Addition of Inorganic Salt	Role
10 mL	2 mL Aqueous Sample	No salt added	Blank
10 mL	2 mL Aqueous Sample	1g Sodium Chloride	Control
10 mL	2 mL Aqueous Sample	1g Mg Sulphate Anhydrous	Sample-1
10 mL	2 mL Aqueous Sample	2g Mg Sulphate Anhydrous	Sample-2
10 mL	2 mL Aqueous Sample	3g Mg Sulphate Anhydrous	Sample-3

Table 2: Headspace sample vials preparation using sodium sulfate salt amounts

Head Space Vial Size	Sample Volume	Addition of Inorganic Salt	Role
10 mL	2 mL Aqueous Sample	No salt added	Blank
10 mL	2 mL Aqueous Sample	1g Sodium Chloride	Control
10 mL	2 mL Aqueous Sample	1g Sodium Sulphate Anhydrous	Sample-1
10 mL	2 mL Aqueous Sample	2g Sodium Sulphate Anhydrous	Sample-2
10 mL	2 mL Aqueous Sample	3g Sodium Sulphate Anhydrous	Sample-3

Conclusion

This review article discussed the challenges associated with detecting VOCs in aqueous samples, especially for polar to mid-polar VOCs. Changing the phase ratio and partition coefficient can sometimes enhance sensitivity to a lesser extent. Implementing the solvent depletion approach by using hydrate-forming inorganic salts, such as anhydrous MgSO4 and anhydrous Na2SO4, in low-volume aqueous samples is an effective method. It could be a game-changer, especially for large-volume parenteral formulations and aqueous biological samples. Large volume parenterals are mostly aqueous and often have very low levels of AET due to their maximum daily dose. This approach will help achieve low-level AET significantly and will minimize the probability of missing low-response VOCs during the extractable and leachable study.

Acknowledgments

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