Thermal desorption (TD) system as a quick screening tool for drug product packaging components

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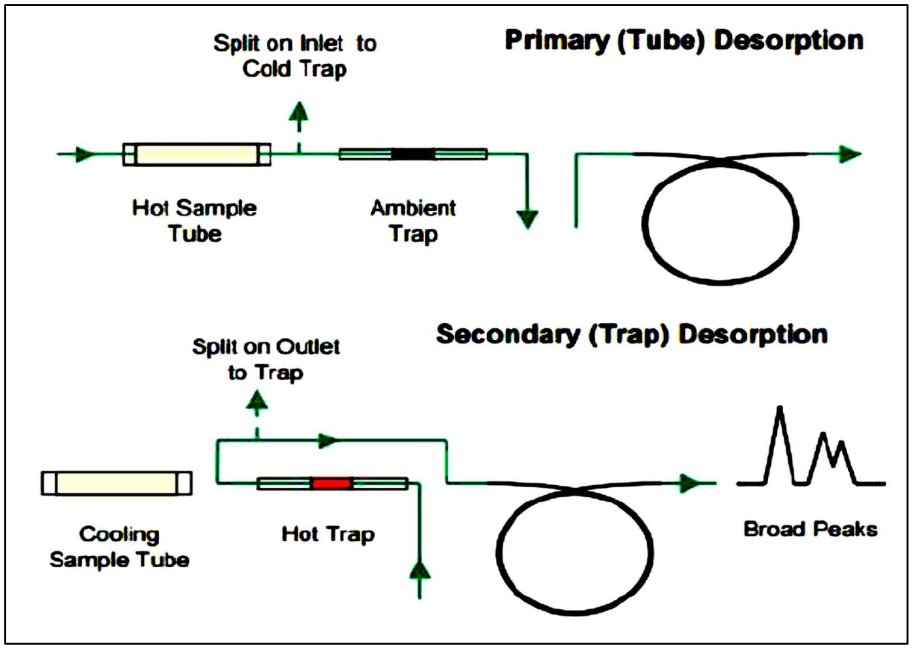
Introduction of thermal desorption system (TDS):

Thermal desorption (TD) is the technique in which materials are heated to release adsorbed compounds as volatiles. During analysis of many sample matrices, because of the nature of samples i.e. solid, viscous or incompatibility with columns, direct sample injection into a gas chromatograph is not feasible. Hence, some kind of sample work-up or extraction is required before analysis. Analysis by thermal desorption requires introduction of small amount of sample into the sample tube directly without any work-up and use of inert carrier gas to pass through the volatile sample constituents into a cooled trap. The trap is then rapidly heated to desorb the concentrated volatile compounds into a gas chromatographic column for separation and subsequent detection and identification by mass spectrometry. Thermal desorption – gas chromatography – mass spectrometry (TD-GC-MS) technique is fully automated and hence provides consistent and reliable screening of difficult samples such as foods, drinks, soil samples or cosmetics.

In the first pre-concentration cycle of thermal desorption, materials of interest are heated to suitable temperature and volatiles/semi-volatile compounds are collected in a cold trap which is maintained at lower temperatures. Pre-concentration of samples enhances the response of the low-concentration compounds which otherwise would not be possible to detect with any regular method of analysis.



Apart from direct introduction of samples into the sampling tube, thermal desorption system can be used in analysis of Volatile organic compounds (VOCs) in air samples, automobile-VOCs. In this type of testing, air samples (e.g. environmental or automobiles etc.) are collected and are passed through sampling tube containing sorbent Tenax [Poly (2,6-diphenylphenylene oxide) resin]. Tenax is well known for the use in trapping of volatiles and semi-volatiles from air samples. After collection in sampling tube, second step is same as for the direct sample analysis.

Advantages of Thermal desorption:

- **Sensitivity** – Two-stage desorption technique with sorbent tube enriches concentration of volatiles and hence enhancing the detection limits of analytical technique (GC-MS).

- **Ease in analysis** – Because of concentration step followed by rapid heating of trap, samples are introduced in-to the GC with less gas volume, resulting in sharp peaks. It yields good response and hence improves quality of the analysis.

- **Analysis time and efforts:** Sample preparation is minimal. It reduces the analytical errors at the same time saves time and effort. This in turn makes it much easier to automate.

- **Selective analytical tool** – Optimising the sample tube sorbents and TD protocols allows only the compounds of interest to be introduced to the GC, eliminating chances of introduction of incompatible sample components into the column.

- **Sample compatibility** – TD can be hyphenated with a variety of GC sampling procedures, making it possible to sample from a wide range of sample types, whether gas, liquid or solid.

Applications of thermal desorption:

Most of the thermal desorption system related applications were related to occupational health monitoring in initial times. In recent times, it has extended to cover a wider range.

- Environmental monitoring
- Workplace monitoring
- Residual volatiles or actives emitted from materials
- Breath analysis
- Aroma profiling of food, drink
- Automobile and component volatiles
- Fragrances profiling in cosmetics and homecare products

Introduction of extractables and leachables:

Extractables and leachables studies are related to the evaluation of packaging material and drug product interaction. These interactions may lead to migration of compounds from packaging materials into the drug products. The term “leachables” is used for the compounds, which may leach from a packaging components into the packaged product under regular storage conditions. These consist of compounds leached as well as compounds formed in reaction between the packaging material and the product. The term “extractables” is used for compounds found in packaging materials and which can be extracted from the material under extreme conditions, for example using solvent extraction.

Thermal desorption is one of the most effective tool in packaging material characterisation for potential extractables and leachables. Solvent dilution or extraction is not necessary for this testing, hence polymer samples can be analysed by just introducing few mg of samples into the sample tubes. Thermal desorption provides most neutral and precise picture of the extractables profile irrespective polarity of compounds which is not the case if samples are dissolved or extracted in any of the solvents. For extractables analysis, this is a major advantage over solvent extraction, in which analyte extraction rates depend more on the polarity of the solvent than on their mobility. Most of the extractables are determined by gas chromatographic techniques. By this kind of determination, emission potential of the material is characterized.

In multiple component systems like ophthalmic or metered dose inhalers (MDI), identification of source of leachables is very critical. TD-GC-MS data after testing of each component prior to performing

extraction study can be used to understand the source of leachable. This information can be used in device development and minimising leachables level.

Although, extractables and leachables is defined as interaction between the solvents/drug products and packaging components (which are in direct contact with drug product), one needs to consider other components like blister packs, printed labels or other secondary packaging materials. Some compounds like Benzophenone, Isopropyl thioxanthone (ITX) are observed as potential leachable migrating from secondary packaging through polymer materials like LDPE bottles into the products.

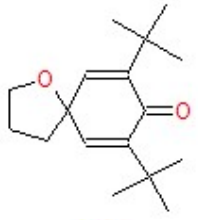
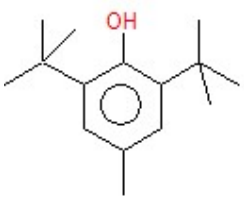
Thermal desorption for extractables screening in ophthalmic drug products:

Generally ophthalmic drug products consist of bottle, nozzle and caps with printed label affixed on bottles. Polymer materials used for bottle, nozzle and cap are generally low density polyethylene (LDPE), High density polyethylene (HDPE) and Polypropylene (PP). Labels consist of printed face paper, adhesive, release coating and backing.

List of potential extractables is unlimited but few groups are very common to be observed in LDPE, HDPE and PP. Generally, phthalate compounds (characterised by m/z 149), antioxidants like Irganox 1010 (Irganox 1010 does not elute out properly in GC-MS but it's degradation product is characterised by m/z 205, butylated hydroxy toluene (BHT) and related compounds (characterised by m/z 205)) are observed in packaging polymer materials. Similarly, potential leachables like Benzophenone is observed in printed labels.

Potential extractables from primary packaging components like bottle, nozzle and cap can be estimated by extracting with suitable solvent systems. Extractions are generally carried out by incubating container closure systems (CCS) for 2-3 days. But when it comes to secondary packaging materials like printed label or cartons (which are not in direct contact with drug products), migration of potential leachables from secondary packaging through primary packaging barrier into the drug product is long term process. Hence, direct extraction of secondary packaging materials is not practical solution to find out the leachables profile. Direct TDS-GC-MS screening of secondary packaging materials is the most suitable tool to get the potential leachables list. Further this compound list can be straight away monitored in stability samples of the drug products.

Table 1: Structures of general potential leachables observed in TDS-GC-MS

Application	Name of the compound	Structure
Antioxidant and related degradation products	7,9-Di-tertbutyl-1-oxaspiro [4,5] deca-6,9-dien-8-one	
Antioxidant and related degradation products	Butylated hydroxy toluene	

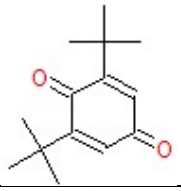
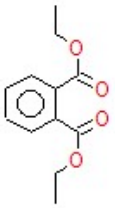
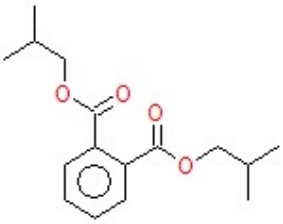
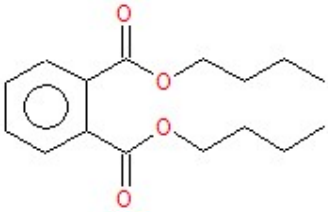
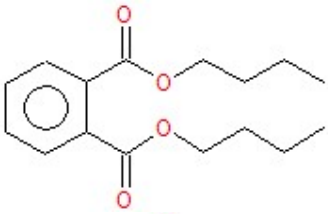
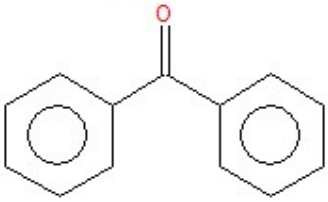
Application	Name of the compound	Structure
Antioxidant and related degradation products	2,6-Di-tert-butylbenzoquinone	
Plasticizer	Diethyl phthalate	
Plasticizer	Diisooctyl phthalate	
Plasticizer	Di-n-butyl phthalate	
Plasticizer	Diethylhexyl phthalate	
UV-curing	Benzophenone	

Figure-1: TD-GC-MS chromatogram of LDPE bottle/nozzle; a. Total ion chromatogram (TIC), b. Selective ion monitoring (SIM) mode chromatogram with m/z 149, SIM mode chromatogram with m/z 205

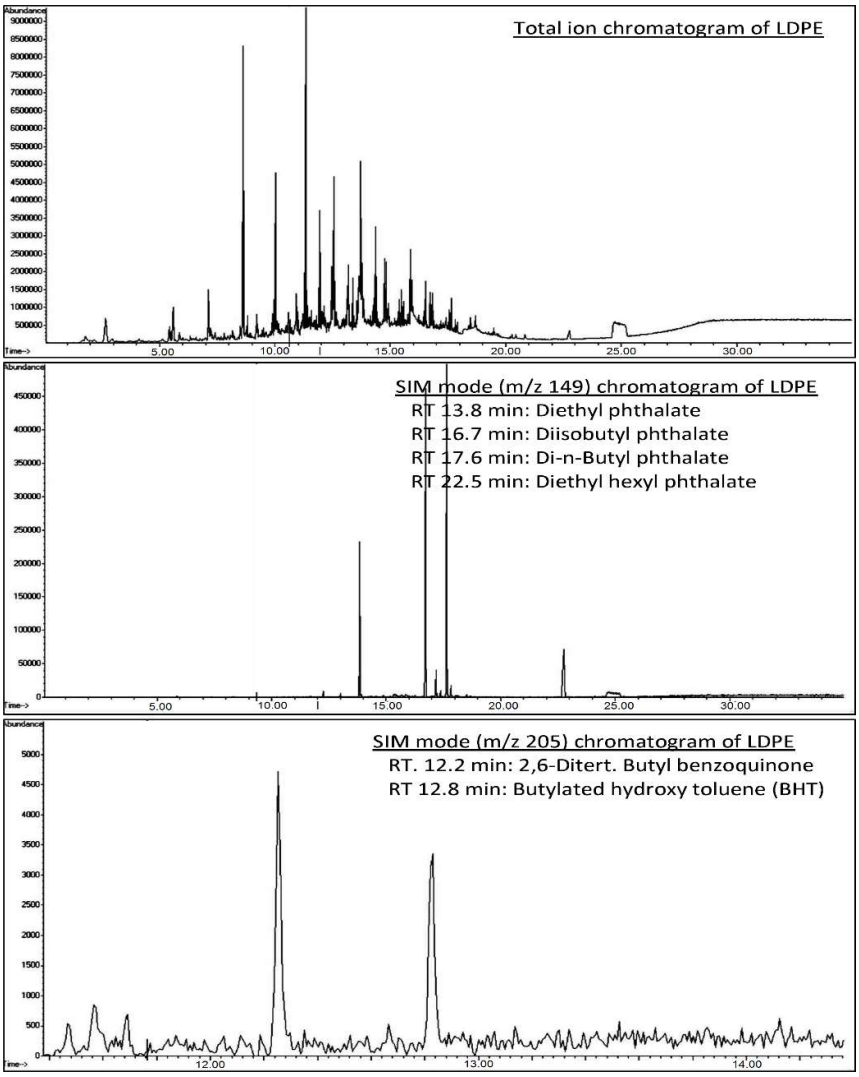

Total ion chromatogram of LDPE
SIM mode (m/z 149) chromatogram of LDPE
RT 13.8 min: Diethyl phthalate
RT 16.7 min: Diisobutyl phthalate
RT 17.6 min: Di-n-Butyl phthalate
RT 22.5 min: Diethyl hexyl phthalate
SIM mode (m/z 205) chromatogram of LDPE
RT. 12.2 min: 2,6-Ditert. Butyl benzoquinone
RT 12.8 min: Butylated hydroxy toluene (BHT)

Figure-2: TD-GC-MS chromatogram of HDPE bottle/nozzle; a. Total ion chromatogram (TIC), b. Selective ion monitoring (SIM) mode chromatogram with m/z 149, SIM mode chromatogram with m/z 205

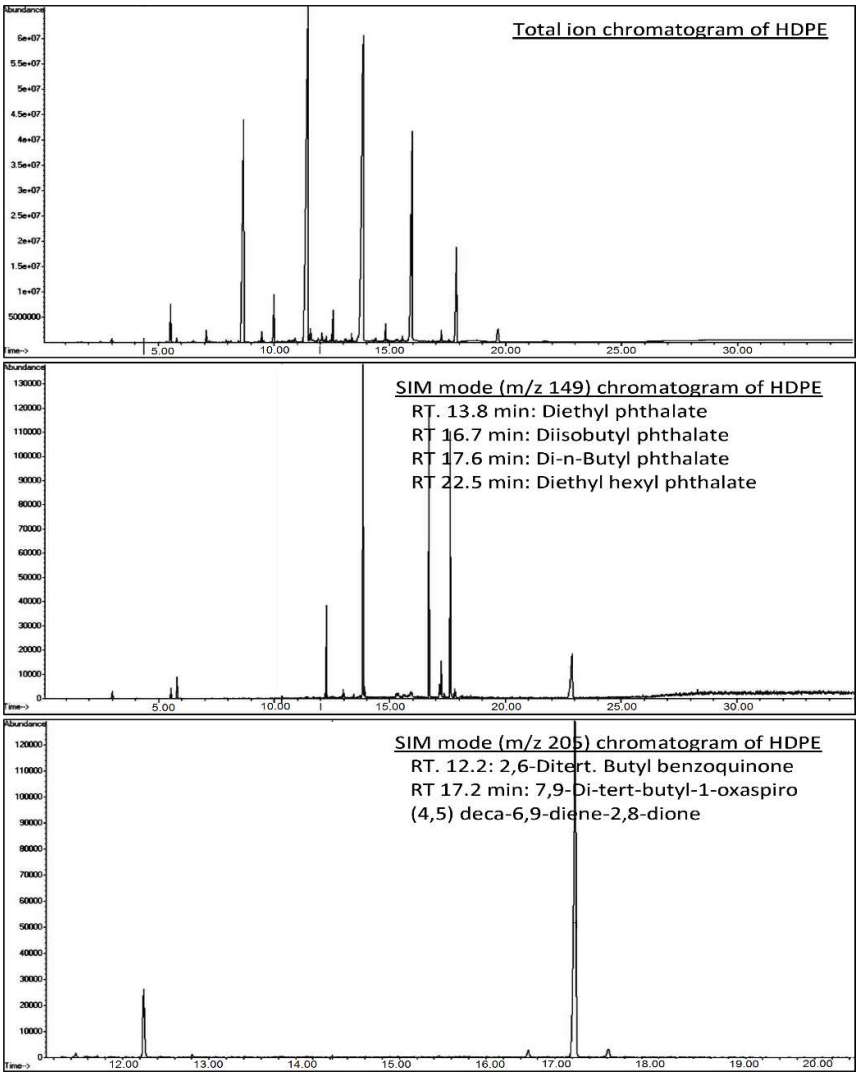
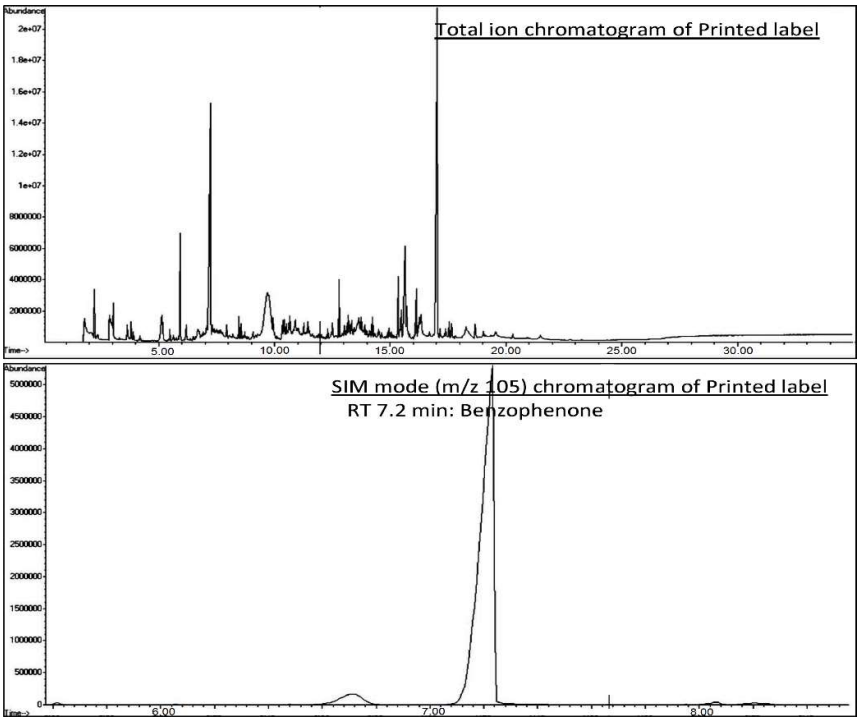


Figure-3: TD-GC-MS chromatogram of printed label; a. Total ion chromatogram (TIC), b. Selective ion monitoring (SIM) mode chromatogram with m/z 105



Conclusion/recommendation:

Thermal desorption is the important tool for understanding extractables profile in packaging components and is recommended in the guidelines by product quality research institute (PQRI) and USP. Selection of the solvent systems can be based on the data obtained from thermal desorption system with GC-MS analysis. Drug product composition, recommended storage period and storage conditions are also the equally important points.

Thermal desorption can be used successfully for evaluating polymer materials from different sources. Also, TD-GC-MS can be used as an alternative for extraction study of secondary packaging materials. This kind of screening can ease the material selection and hence the supplier selection process.

References:

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