

Development of a Database for full Identification of Extractables related to components of CCS for OINDP's by means of High Resolution GC-ToF analysis.

INTRODUCTION

The importance of Extractable / Leachable (E/L) testing for Container Closure Systems (CCS) in the Pharmaceutical Industry has grown considerably in the last few years, driven by an increase in global regulatory requirements (1-7) as well as by well-documented incidents where impurities in the contained drug product – introduced by the Container Closure System via leaching – were found to be harmful to the patients (8). An initial step in the E/L evaluation process is to perform Extractable Studies on the Containers / Closures to learn as much as possible about the extractables profile of the materials used in the manufacture of pharmaceutical containers. The outcome of such a first pass Controlled Extraction Study does not always allow a full identification of all compounds in the extractables profile of a material. In order to guarantee this full identification, further efforts need to be made in second pass extractables testing. These additional efforts typically rely on high level analytical testing, such as NMR, GC-NMR, GC-FTIR, GC-ToF-MS and LC-ToF-MS. It is evident that, if the level of identification in first pass experiments could be increased substantially (*e.g. by the development of an "Identification Database"*), the efforts for further identifications in second pass experiments could be reduced significantly. In 2010 (9) Nelson Labs Europe developed an Extractables Database specifically designed to identify Extractables and Leachables at a low level in complex matrices. In addition, Nelson Labs Europe has started up a research program to further substantiate the Screener Database and identify additional unknown extractable compounds. The main objective of this programme is to evaluate whether GC-ToF-MS is a suitable analytical technique to assist in the structure elucidation of 'unknown' volatile and semi-volatile compounds, observed in first pass extractable studies, performed on the materials, used in the manufacture of the different components of inhalation devices.

METHODS

The development of the Extractables Screener Database was described in earlier work (9). The list of selected compounds included into the Database was mainly based upon the identification results of Controlled Extraction Studies, carried out by Nelson Labs Europe over the last 10 years. This database was built from exposure to different types of polymeric materials and rubbers, sterilization modes, and process treatments. The identification results of polymeric/rubber extractables, found in over 2000 projects, were bundled and prioritized, based upon importance and frequency of occurrence. In addition, compounds referred to in literature

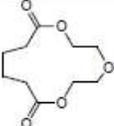
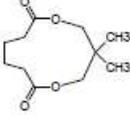
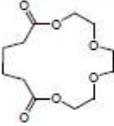
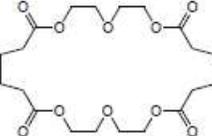
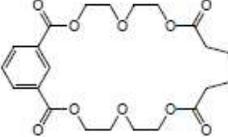
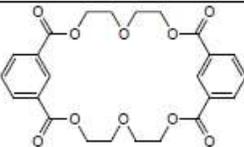
or compounds presented in case studies at E/L-conferences were also included. Finally, regulatory guidelines also contributed to the list of selected compounds.

In order to further develop the existing Screener Database, Nelson Labs Europe has started up a Research Project to identify unknown compounds, often detected in Controlled Extraction Studies of materials used in the manufacture of inhalation devices. Three materials were identified as a major source of “unknown compounds” in Controlled Extraction Studies on inhalation devices: polyacetal (used in the manufacture of a component of a valve for pMDI’s), multilayer foils, (blister for DPI’s), and rubbers (gaskets for MDI’s). The first step in the approach was to analyze the extracts of these materials, investigated at Nelson Labs Europe using Accurate Mass GC-ToF-MS. The GC-ToF-MS instrument, selected for this research is a Jeol AccuTOF JMS-T100GC mass spectrometer, combined with an Agilent 7890A Gas Chromatograph. Using Chemical Ionization (CI) GC-ToF-MS, more information was obtained about the elemental composition of the molecule. Combining these results with the data, acquired via Electron Impact (EI) GC-ToF-MS measurements of the fragments, lead to more information about substructures or functional groups within the molecule.

RESULTS

The accurate mass GC-ToF-MS measurements lead to the identification of a number of compounds, often encountered as an extractable from multilayered aluminum foils, used in the construct of inhalation devices or a leachable in OINPD’s. The structural formulas, identified via the above described method, are presented in table 1.

Table 1: Chemical structures of compounds identified through HR GC-ToF analysis in aqueous extracts of multilayered aluminum foils used as primary or secondary packaging material for OINDPs.

Chemical name; synonyms [CAS No.]	formula	mol. wt.	Structure
1,4,7-Trioxacyclotridecane-8,13-dione			
[6607-34-7]	C ₁₀ H ₁₆ O ₅	216.23	
Bislacton	C ₁₁ H ₁₈ O ₄	214.26	
[-]	C ₁₁ H ₁₈ O ₄	214.26	
26) Adipic acid triglycol bislactone			
-	C ₁₂ H ₂₀ O ₆	260.28	
Cyclic polyester Di-(Adipic acid di-glycol bis-lactone)			
-	C ₂₀ H ₃₂ O ₁₀	432.46	
Cyclic polyester Heterodimer of Adipic acid di-glycol bis-lactone and Isophthalic acid di-glycol bis-lactone			
-	C ₂₂ H ₂₈ O ₁₀	452.45	
Cyclic polyester Di-(Isophthalic acid di-glycol bis-lactone)			
-	C ₂₄ H ₂₄ O ₁₀	472.44	

CONCLUSIONS

Accurate mass measurements on volatile and semi-volatile compounds, using GC-ToF-MS as an analytical technique, have proven to be a very powerful tool to assist in the structural elucidation of unknown compounds. Although the project is still ongoing, structural formulas of extractable compounds could be postulated. However, the identification of these compounds will need to be confirmed via chemical synthesis of the postulated structures. The synthesized compounds will allow developing quantitative methods to monitor these compounds in leachable studies. The identification of unknown compounds from Polyacetal components and rubber gaskets is still ongoing.

REFERENCES

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