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Gas-phase transfer of polymer cross-linking agents and by-products to solid oral pharmaceuticals

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Abstract

In the pharmaceutical industry, solid oral compressed tablets (OCT) are frequently transported in bulk containers prior to packaging. While in this state, the product is generally protected from interaction with liquid and solid contaminants by physical barriers (e.g., polyethylene bags, drums, etc.). Vapor phase contamination, although generally less frequently observed, is possible. A specific example of the detection and identification of volatile by-products (acetophenone and 2-phenyl-2-propanol) of a common polymer cross-linking agent (dicumyl peroxide) is presented. The product tablets were compressed, placed into double polyethylene bags, and subsequently placed into a polyethylene drum for shipment overseas. To cushion the product during transit, a cross-linked polyethylene foam disk (designed to fit into the bottom of the drum) was placed below the bag of tablets. Initially, these contaminants were detected by HPLC with UV detection at the receiving laboratory, and assumed to be degradates of the active components of the product. Further analysis showed that neither the collected UV absorbance data nor the observed levels of the contaminants were consistent with known degradates of the product. Liquid extraction followed by GC–MS analysis of the product as well as the cross-linked foam disk exhibited measurable quantities of the contaminants in question. Vapor phase transfer of these cross-linking agent by-products, originating in the cross-linked foam pads, was determined to be the root cause for the presence of these compounds in the product.

Keywords: Cross-linking agent; Polymer; Impurity; Gas-phase transfer; Dicumyl peroxide

1. Introduction

The use of polymeric materials for the containment and protection from environmental factors has been commonplace for more than 40 years in the pharmaceutical, cosmetic and food industry. Such materials have many desirable attributes over other materials (i.e., glass, paper, metal). Much effort has been put into understanding the potential interactions of such materials when placed in direct contact with such consumer products [1–3]. Primary packaging components such as bottles, blisters, pouches, and sachets are generally assessed for product protection and interaction prior to any usage (especially for ophthalmic or parenteral products) [4]. Additionally, labeling and adhesives are generally screened for any potentially harmful substances prior to being put into common use [5]. Unfortunately polymeric materials have frequently been shown to allow foreign substances to diffuse into the product [6]. Such contaminants can either originate in the polymeric material itself or from adjacent unrelated materials, and can be to the potential detriment to the patient/consumer [7]. Although to a lesser extent, adhesives and labeling components have also been found to be related to product contamination for both liquid and solid products [8].

The vast majority of processing of pharmaceuticals prior to final packaging is performed with stainless steel instruments, and has, in general, not been related to significant product contamination. Isolated metallic contamination, however, has been noted and can be detected visually or by a metals screening chemical analysis [9]. Such contamination may be due to leaching of metals from processing components or from remaining metallic catalysts used in the synthesis process. Additionally, such contamination can lead to rather infrequent visible contamination which can be assessed with microscopy.

Bulk shipment of pharmaceutical products is commonplace in both large and small firms. Large firms may ship product made at one site to be packaged at another. Small firms may purchase product in bulk to be packaged in specialty packaging.

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In each case, tablets, capsules, and liquids may be shipped in large drums. Because the product spends a fairly short amount of time in this bulk container (<2 weeks), rigorous analysis of these packaging components is not always conducted. In most cases the product is analyzed after being held in such containers for prescribed periods of time to determine if degradation of the active ingredient or changes in other physical parameters (i.e., hardness, dissolution profile) have occurred due to the storage in a particular vessel.

In this work, we report the discovery, identification and source determination of two packaging related contaminants which were found to exist in oral compressed tablets. The contaminants were detected in the tablets immediately after bulk shipment, but were not seen in any analysis prior to this shipment. The contaminants were found to have migrated in the gas phase into the tablets from a secondary packaging component foam. These contaminants had originated as by-products of a cross-linking reaction in the foam. (In a similar study an impurity in a solid dosage form was found to be the condensation product of famotidine with formaldehyde liberated from the packaging material (foil pouches) upon thermal degradation in the course of stressed degradation studies [10].)

2. Experimental

2.1. Reagents

All experiments were conducted using reagent grade or better. Purified water was obtained from a Millipore Elix 10 system at a minimum of 18.2 MΩ. Sodium phosphate monobasic (ACS reagent grade) and methylene chloride (Optima grade) were obtained from Fisher (Allentown, PA). 85% *o*-phosphoric acid (HPLC grade) was obtained from Aldrich (St. Louis, MO). Acetophenone and 2-phenyl-2-propanol were also obtained from Fisher.

2.2. Instrumental analysis

Liquid chromatography was carried out using a Waters (Billerica, MA) Alliance instrument, in conjunction with Millenium software. The HPLC column was supplied by Varian/Metachem (Palo Alto, CA) as 150 mm × 4.6 mm packed with Phenomenex Luna phenylhexyl 3 μm particles. The initial mobile phase conditions were acetonitrile-sodium phosphate buffer (pH 4.0, 25 mM) (20:80). The mobile phase was altered in a linear fashion from 0 to 27 min until the ratio of sodium phosphate buffer–acetonitrile was (35:65). Immediately after this point, the mobile phase was reverted back to the original conditions and remained under those conditions until the end of the chromatographic run (37 min).

Gas chromatography–mass spectrometry (GC–MS) was conducted using a Finnigan (Thermo Electron Corp.) GCQ (Waltham, MA). The column used was a Restek (State College, PA) RTX-5, 30 m, 0.25 mm ID, 0.5 mm film thickness. Upon injection, the column oven was held at 40 °C for 3 min, thereafter the temperature was ramped linearly (20 °C/min) until reaching a final temperature of 300 °C. The oven was held at this temperature for an additional 14 min at which point the chromatographic run was ended (total runtime = 30 min).

3. Results and discussion

3.1. Demonstration of unknown peaks in HPLC analysis

The product in question contains two active pharmaceutical ingredients (API A and API B). API A is known to be partic-

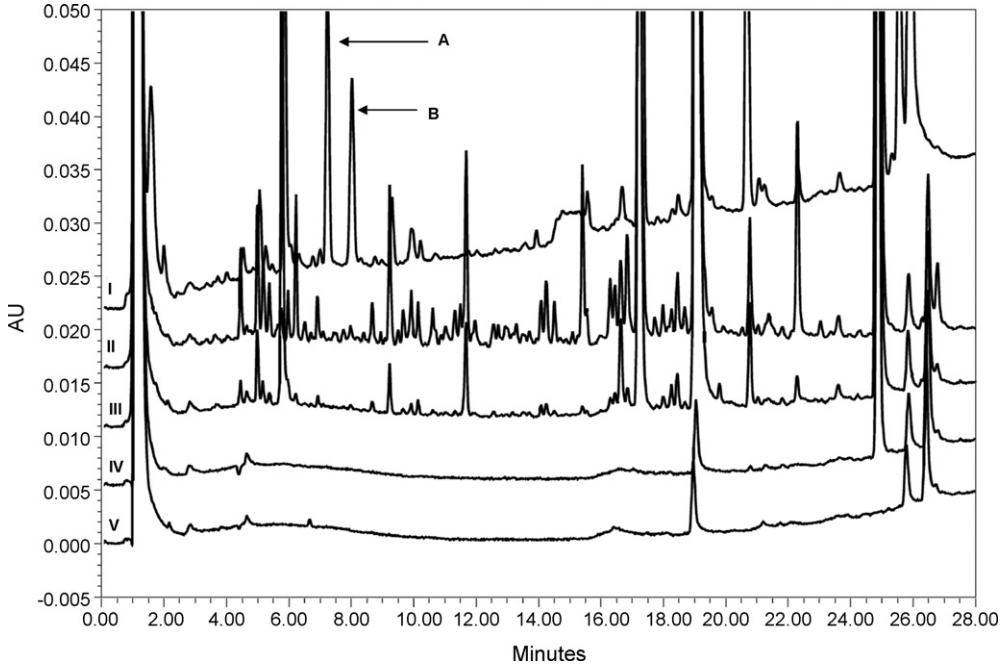


Fig. 1. HPLC separation with UV absorbance detection at 205 nm for (I) contaminated sample, (II) stressed sample, (III) typical sample, (IV) quantitative standard, (V) blank. Peaks at 7.2 (A) and 8.0 (B) min are unknown product contaminants.

ularly susceptible to oxidative degradation. Indeed, not only is the compound labile to oxidation, but degrades into a rather large number of similar compounds, each at fairly low concentration. For this reason, not only were two separate HPLC methods developed and validated to assay each API, but a third HPLC method was developed and validated to track formation of such oxidative degradates. This method (see experimental) was designed to separate and detect over 30 different oxidative degradates of varying polarities. Additionally, to effectively detect such oxidative degradates, the wavelength of detection for this method was set at 205 nm. This combination of vast change in mobile phase polarity during the chromatographic separation, relatively high peak capacity (by use of 3 μm particles in the separating column), and low detection wavelength puts this method in a unique position of being especially sensitive to interference from sample and/or product contamination.

Product initially packaged in Europe was shipped to the U.S. Upon receipt, the product was tested for quality attributes (assay (API A and B), dissolution, preservative assay, and oxidative degradate assay). During the analysis of data collected for determination of oxidative degradates, two chromatographic peaks of unknown origin were observed (Fig. 1). However, neither the relative retention time nor the ultra-violet absorbance spectra of the observed peaks showed any similarity to known impurities or degradates of either API or any of the product excipients. For this reason, degradates or impurities related to the APIs in this product were ruled out as potential sources for these unknown peaks. The investigation to identify the source of these peaks was then focused on packaging materials and any potential compounds related to packaging materials which may have been transferred to the product during processing.

3.2. Identification of the product contaminants

Initial assessment of the product via the oxidative degradate method, did show two peaks of unknown origin in the product. Although the retention time for these peaks placed them within the range previously observed for such oxidative degradates of API A, the associated UV absorbance spectrum for each did not appear similar to typical API A oxidative degradates. Indeed, the observed UV spectrum with its strong absorption maximum at 244 nm for the peak at 8.0 min retention time was thought to be associated with a small molecule containing a benzene ring conjugated with a carbonyl group. Working on this lead, the investigation team began reviewing UV absorbance spectra for known polymer cross-linking agents [11]. Published spectra collected for acetophenone showed a remarkable resemblance to the UV absorbance spectra collected for the peak at 8.0 min. Another small benzene derivative's UV absorbance spectra was observed to show similarity to the peak at 7.2 min. Authentic samples of each compound were then procured. Low concentration (10 ppm) solutions of each compound were then separated using the same HPLC method as had been used to initially assess the product. Based on the collected data, the retention time (data not shown) and UV absorbance spectrum (Figs. 2 and 3) for each of these compounds was observed to be exceedingly similar to that seen for the unknown peaks in the product sample chromatogram.

Like many oral pharmaceutical dosage forms, this final saleable product is packaged in high density polyethylene bottles with 1 g desiccant canisters included. Analysis of extracts of desiccant canisters contained in contaminated product bottles, were also found to contain large quantities of the same contami-

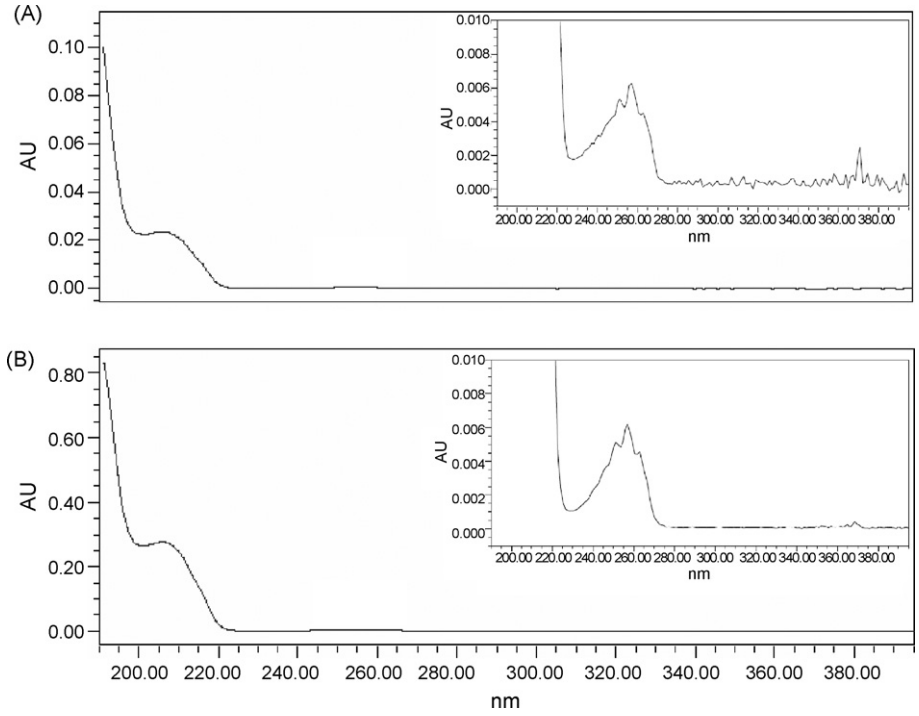


Fig. 2. (Top, A) UV absorbance spectrum for product contaminant (Fig. 1, peak at 7.2 min); (Bottom, B) UV absorbance spectrum for 10 ppm 2-phenyl-2-propanol.

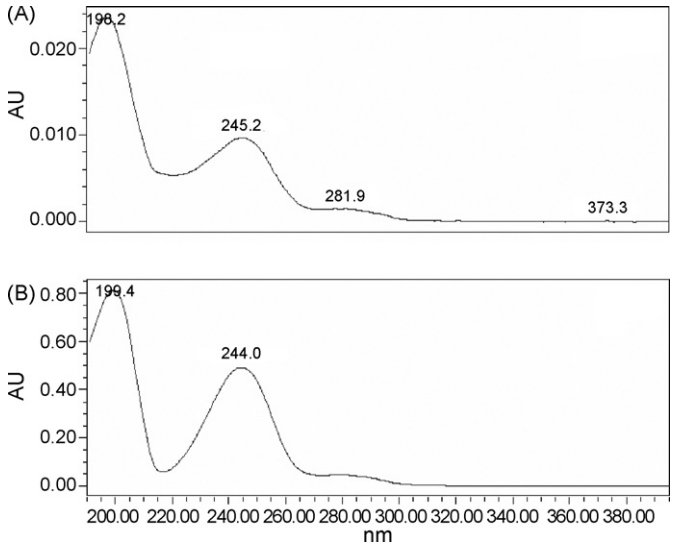


Fig. 3. (Top, A) UV absorbance spectrum for product contaminant (Fig. 1, peak at 8.0 min); (Bottom, B) UV absorbance spectrum for 10 ppm solution of acetophenone.

nants. Analysis by gas chromatography led to the chromatogram shown in Fig. 4. The fragmentation pattern and retention time for each peak is consistent with data collected for authentic samples of each proposed contaminant (acetophenone and 2-phenyl-2-propanol). Acetophenone spectra (proposed contaminant and standard) exhibited a parent ion peak (120), as well as a prominent methyl ketone fragment ion (43). 2-phenyl-2-propanol spectra exhibited prominent peaks consistent with a loss of a methanol ion (M − 31 = 105), as well as a phenyl ion (77).

3.3. Determination of the source of the product contaminants

Subsequent to final production steps, compressed tablets are placed into double polyethylene bags and contained in 26 liter polyethylene drums, as shown in Fig. 7. Because it seemed apparent that a packaging component may be at the root of this contamination issue, extractions were performed on all of the polymer packaging components. Unfortunately, most yielded no evidence of extractable compounds with similar chromatographic retention or UV spectral response to those observed in both the product tablets and desiccant canister (taken from the product bottle).

In an effort to reduce moisture uptake by the product during transit, several large (∼10 g) pouches of silica gel desiccant had been added in with the loose tablets (inside the double polyethylene bags). Although new unused silica gel desiccant pouches were not found to show any evidence of the compounds in question, when the specific pouches used in the transit of the product in question were extracted, large amounts of the two species (>100 ppm) were observed (data not shown). Because, the new desiccant pouches had not shown the compounds in question, it was thought that the desiccant pouches were not the source of the foreign substances, but rather an absorbing sink for a gas-phase contaminant present inside the shipping container. That is, a gas-phase contaminant had infiltrated (or was present in) the polyethylene drum and the silica gel desiccant had preferentially absorbed these compounds.

To reduce tablet attrition (due to excessive vibration) during transit, a disc-shaped pad was used to cushion the large mass of unpackaged bagged tablets during transit. These pads were made from expanded cross-linked polyethylene foam. The cross-linking of this polymer is thought to proceed as described in Scheme 1. Note that two prominent by-products of this reaction are acetophenone (formed via a β-scission reaction) [12] and 2-phenyl-2-propanol (formed by hydrogen atom abstraction from the polymer matrix). A hypothesis was immediately put forward that the product contaminants had originated in this cross-linked polyethylene expanded foam and had migrated (in the gas phase) to the product tablets. To test this hypothesis, a sample of the foam was obtained and subjected to an extraction similar to that performed on all other packaging components. Indeed, when subjected to the same HPLC separation used to analyze the product, a number of peaks were observed, specifically, two peaks with similar retention times (see Fig. 5) and spectral response (data not shown). To be certain that these compounds did exist in the foam, the extract was also subjected gas chromatographic separation with mass spectral detection (see Fig. 6). Indeed, not only did the foam extract contain measurable quantities of the two compounds of interest (acetophenone and 2-phenyl-2-propanol) but several other intermediates and by-products of the reaction in Scheme 1 were also observed,

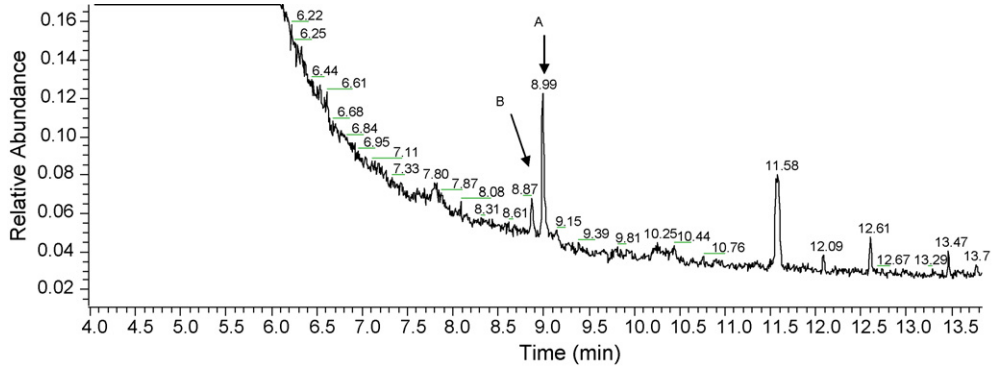
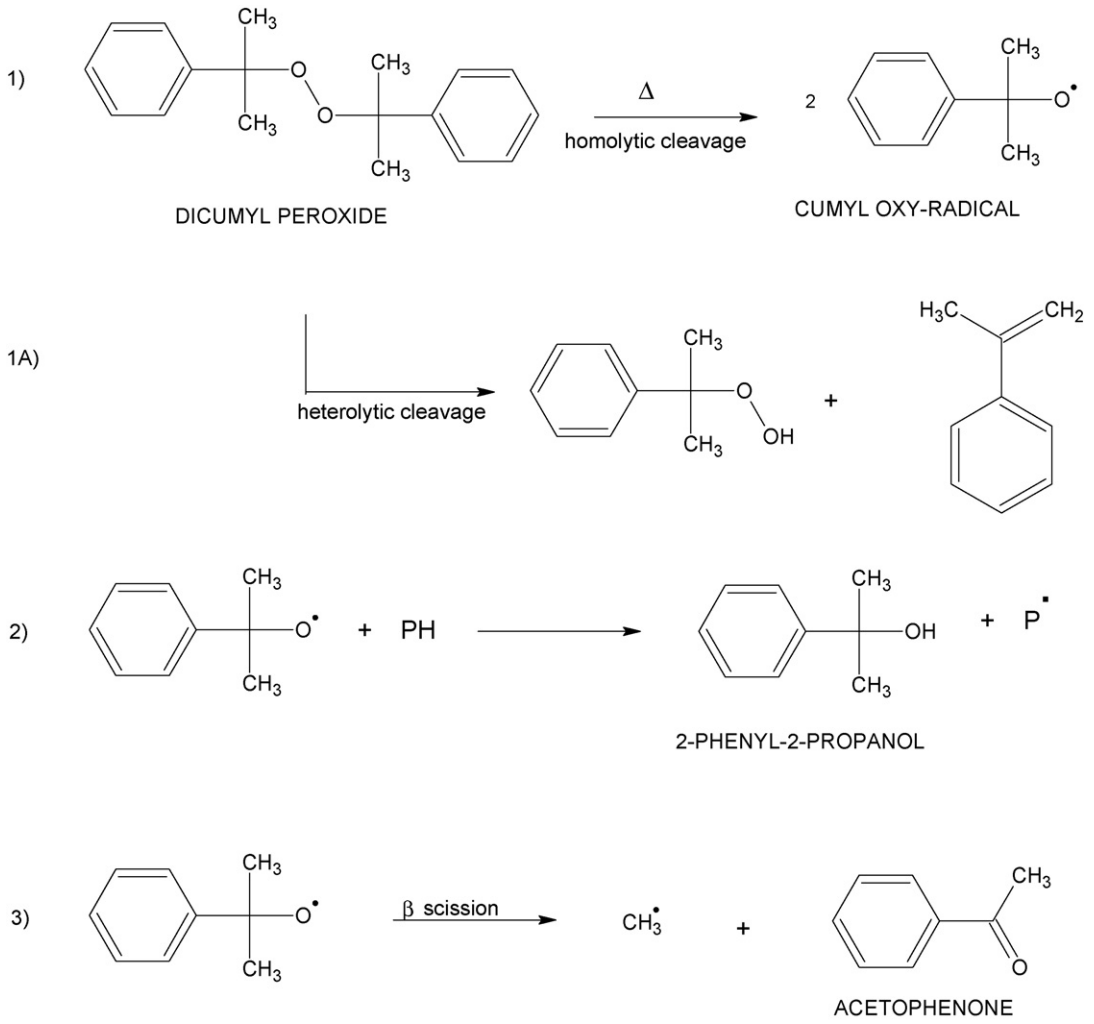


Fig. 4. Gas chromatographic separation showing mass spectral total ion current (TIC) data for desiccant canister contained in product bottle immediately adjacent to product tablets. Peaks labeled as A and B are identified (by mass spectral response) as 2-phenyl-2-propanol and acetophenone, respectively.



Scheme 1. Proposed formation mechanism for product contaminants from di-cumyl peroxide. Contaminant products are formed as by-products of the polyethylene polymer cross-linking process. (PH represents a polymer element and associated hydrogen atom available for abstraction.)

as well as some other unknown compounds (presumably also related to the cross-linking reaction).

While it is difficult to unequivocally prove the exact path of this observed contamination in this product, it is clear that this expanded cross-linked polyethylene foam is certainly a potential source of the two contaminants observed in this product. Based on the data and observations presented here, the conclusion drawn holds that the foam placed in this particular drum contained perhaps a higher than normal amount of the two specific by-products of the cross-linking process (trapped within the foam matrix). Certainly, this is the only logical explanation as to why a similar problem had never been observed in past shipments.

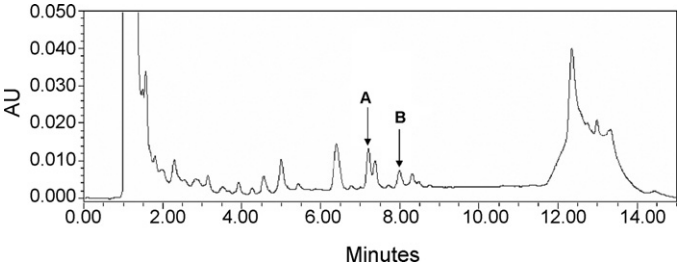


Fig. 5. HPLC separation of compounds extracted from the cross-linked polyethylene foam, UV detection at 205 nm. Peaks A and B identified as 2-phenyl-2-propanol and acetophenone, respectively.

As each foam disc ages these semi-volatile components slowly diffuse out of the foam matrix and their relative concentration within the matrix declines. In this case, a proposal has been put forward which holds that the foam discs in these drums were perhaps newer than typically used discs and when placed into the shipping drum, had a higher concentration of the cross-linking by-products. In the confined space of the shipping container, the semi-volatile compounds began to diffuse out of the foam matrix and into the airspace within the drum. An equilibrium was then achieved between the other solid items within the drum and the surrounding airspace. Silica gel, due to its designed affinity for small molecules, uptook much of these compounds. As observed herein, a measurable portion of these compounds was absorbed by the compressed tablets in the drum. For this hypothesis to be valid, significant amounts of these compounds would need to either diffuse through the double

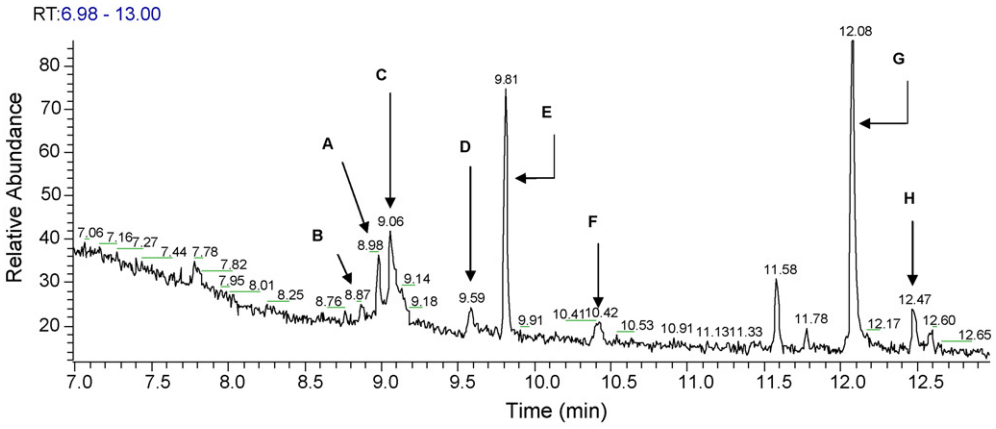


Fig. 6. Total ion current chromatogram of the polyethylene foam (used to cushion the tablets during transit) extracted into diluent, then into methylene chloride. The observed peaks were identified by their resultant mass spectrum in comparison to a spectral library. (A) 2-Phenyl-2-propanol, (B) acetophenone, (C) cumene hydroperoxide, (D) unknown, (E) α-tetralone (1,2,3,4-tetrahydro-1-naphthalenone), (F) unknown, (G) α-methylstyrene, (H) unknown.

polyethylene bags or progress through a route around the bags into the interior space wherein the tablets resided. There is certainly reason to believe that each route is plausible. The bags, like many in this situation, were merely twist-tied to achieve closure. Indeed, the reason for the closure was only to contain the tablets in the bag, and certainly not to preclude vapor phase contamination.

Diffusion of such small organic molecules through low density polyethylene has been studied [13]. The low density polyethylene films (0.08 mm thickness) used in the shipment of the tablets is of a thickness such that at room temperature, the energy required to diffuse through the polymer is modest. Further, because the shipping time for the drum was several days, an amount of the two compounds was able to diffuse through to the product. Indeed, the high concentration of these compounds observed in the silica gel (in close proximity to the product) confirms this.

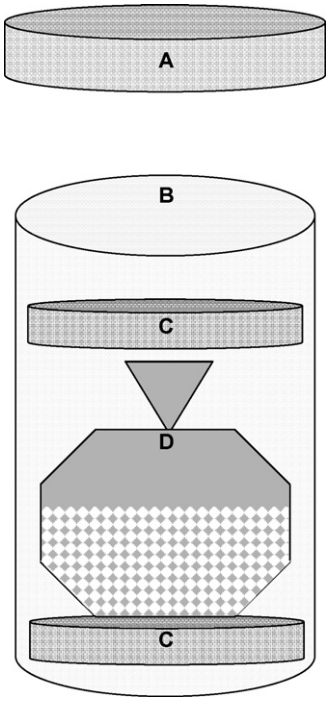


Fig. 7. Schematic for product container (bulk shipping container). (A) Polyethylene screw-top lid, (B) 26 liter polyethylene drum, (C) cross-linked polyethylene disc-shaped padding, and (D) loose oral compressed tablets held in double polyethylene bags.

4. Conclusion

Two unknown peaks which had presented themselves in the routine HPLC analysis of an oral compressed tablet were identified as acetophenone and 2-phenyl-2-propanol using gas chromatography and mass spectrometry. The contaminating species were determined to be originating in an expanded cross-linked polyethylene foam used to cushion bulk tablets during shipment. These contaminants apparently migrated in the gas phase through the double layer polyethylene bagging material and eventually absorbed to the tablets contained therein. As a result of this issue, a corrective action was implemented in that, such foam cushions have been removed from use in this capacity and replaced by non-cross-linked polyethylene foam.

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