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Short communication

Stability problems of polyether ether ketone and ethylene-tetrafluoroethylene copolymer tubing in simulated moving bed operation

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Abstract

Polymeric capillaries made from polyether ether ketone (PEEK) or ethylene-tetrafluoroethylene copolymer (Tefzel) are considered as highly inert and chemically resistant materials used as standard equipment in HPLC and simulated moving bed (SMB) applications. During several racemate separations using a SMB unit equipped with these tubes a formation of micro-holes was observed. All separations had in common that a high content of an alkane was used in the mobile phase. The patterns of damage and possible reasons causing the leakages of the capillaries are discussed. Polymeric tubing had to be replaced by stainless steel capillaries for the enantiomer separations in order to ensure safety of workers, GMP status of products and control leakages.

Keywords: Simulated moving bed chromatography; SMB; PEEK; Tefzel and stainless steel capillaries

1. Introduction

Multi column chromatography (MCC) processes, such as simulated moving bed (SMB) [1,2] or Varicol [3], are today established procedures for the purification of intermediates or active pharmaceutical ingredients (APIs). MCC units consist of a series of chromatographic columns, which are connected to multiposition valves with capillaries in a closed loop. Opening and closing of the valves allows to circulate the mobile phase and to introduce the eluent and feed streams and to withdraw the so-called extract and raffinate streams through pumps with defined flow rates. Laboratory-scale units (i.e. column diameter up to 5 cm) are equipped for convenience by the supplier with flexible capillaries made of polyether ether ketone (PEEK) or ethylene-tetrafluoroethylene (Tefzel copolymer, ETFE, PTEFE) (cf. Fig. 1).

The polyaryl ether ketone PEEK is obtained via a nucleophilic displacement of activated aromatic halides in polar solvents by alkali metal phenolates or Friedel-Crafts processes [4]. PEEK polymer is an exceptionally strong thermoplastic that retains its mechanical properties even at very high temperatures. The semi-crystalline material is tough and abrasion resistant with high impact strength and excellent flexural and tensile properties. The material also resists attack by a wide range of organic and inorganic chemicals and solvents.

The fluorinated thermoplastic Tefzel, poly(ethylene-*alt*-tetrafluoroethylene), is a alternating copolymer of tetrafluoroethylene and ethylene [5]. In addition to its chemical resistance Tefzel has excellent mechanical strength, stiffness and abrasion resistance.

Both polymers show a high resistance to a multitude of solvents and buffers used in chromatography. Capillaries made of these materials with an O.D. of 1/8 in. allow high linear flow rates and are able to withstand pressures up to 210 bar (PEEK) and 70 bar (Tefzel) for several weeks or even months. Polymer capillaries have several benefits in comparison to stainless steel tubing (cf. Table 1) and can be obtained by all major laboratory ware suppliers. A significant body of information regarding the

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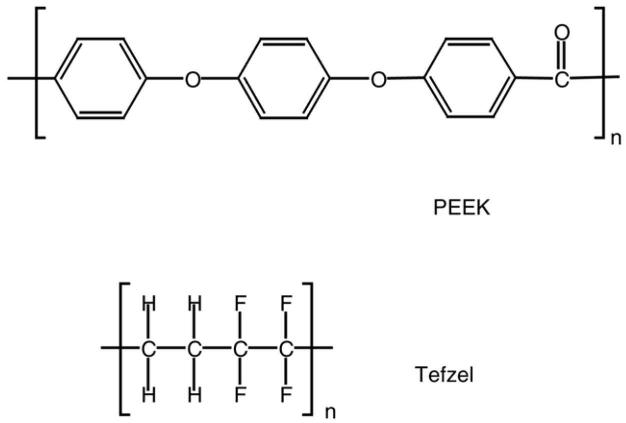

Fig. 1. Chemical structure of PEEK and Tefzel polymers.

compatibility of these two polymers to solvents, gases, chemicals, monomers and solutions can be found in material data sheets or on web-pages of the suppliers [6]. Due to their proven inertness and high stability both polymers comply with the US Food and Drug Administration (FDA) regulations part 177 of Title 21 CFR (PEEK: regulation 177.2415; Tefzel: regulation 177.1550).

Tefzel and PEEK capillaries have been used successfully in our laboratories on SMB and preparative HPLC systems for more than 20 000 h using a broad range of solvents, ranging from lower alcohols, ethers, ketones, acetonitrile to various mixtures of alkanes and lower alcohols as well as basic and acidic modifiers.

These two polymers have become a popular replacement for stainless steel tubing and offer some advantages (flexibility, easy to cut, excellent mechanical stability and chemical compatibility). Tetrahydrofuran, dimethyl sulfoxide, methylene chloride and concentrated nitric and sulfuric acid should not be used with PEEK tubing [6].

In pharmaceutical environments Tefzel capillaries are preferred over PEEK tubing due to the higher inertness and the possibility to employ chlorinated solvents. The transparent fluoro polymer allows observing the fluid flow and to monitor colored compounds and to track air bubbles visually, which makes its use very attractive, especially as it simplifies troubleshooting of chromatographic systems.

All columns intended for use in SMB units are tested before installation with attached capillaries in preparative HPLC units in order to ensure uniform packing characteristics, such as plate count, reproducible retention times and to test tightness of the columns and fittings.

Table 1
Properties of capillaries for chromatographic purposes

Properties	Polymers	Stainless steel
Flexibility	+	(+)
Resistance to organic solvents	+	+
Cl^- buffers	+	–
Cutting and handling	+	–
No metal ions leaching	+	–
High pressure resistance	+	+

2. Experimental

2.1. Equipment and chemicals

The laboratory-scale SMB system was a Licosep 10-50 (NovaSep, Pompey, France). The chiral stationary phases (CSPs) used for the separations were obtained from Chiral Technologies Europe, Illkirch, France as 20 μm bulk materials and were packed into eight 4.8 cm I.D. stainless steel columns (Merck, Darmstadt, Germany). All equipment used at CarboGen has recently been described in this journal [7]. All chemicals for purification were synthesized in the laboratories and plants of Pharmacia (Skokie, IL and St. Louis, MO, both USA) or CarboGen (Aarau, Switzerland). The solvents were reagent grade or better and obtained from a variety of sources. PEEK capillaries (1/8 in. O.D.) were obtained from Supelco, Buchs, Switzerland; Tefzel tubing (1/8 in. O.D.) from YMC Europe through Stagroma, Reinach, Switzerland.

3. Results

In a joint project Pharmacia and CarboGen were synthesizing and separating a series of racemic compounds. The racemic compounds had been resolved chromatographically on CSPs using solvent mixtures of an alkane, a lower alcohol, and an acidic modifier, where the heptane content is greater than 90% and the acidic modifier is trifluoroacetic acid (TFA) or acetic acid. Five different racemates were separated via batch HPLC on a 200 g scale. Great care had to be taken in order to avoid racemisation of the separated enantiomers, which is catalyzed by daylight within minutes. All flexible tubing used on the batch HPLC system was made from stainless steel.

For the enantiomer separation of larger amounts the SMB technology was preferred over batch chromatography, since for the former typically the productivities (i.e. kg racemate separated per 24 h/kg CSP) are higher and the solvent consumption is lower [8]. A Licosep Lab system (Novasep, Pompey, France) was equipped with eight Merck NW-50 columns connected to the unit via Tefzel capillaries. The transparent tubing was covered with a black insulation preventing light entry and thus avoiding racemisation of separated enantiomers.

To our surprise several of the capillaries were punctured (cf. Fig. 2) after about 8 h use without any mechanical influence or pressure increase in the system. The punctures led to a loss of solvent and product and rendered the internal flow rates in the SMB unit uncontrollable. The product solution was sprayed as a fine mist in the cabinet containing the eight columns; the dry powder had to be removed by intensive cleaning. This quite unexpected failure of capillaries regarded as chemically inert and almost “indestructible” necessitated a detailed investigation.

A typical pattern of damage is represented in Fig. 2. A black channel structure is forced into the Tefzel polymer, which led us to assume that a static discharge could have taken place. However, the eluent mixture (*n*-heptane/EtOH/acidic acid, 95:5:0.1, v:v:v) is not likely to create high static charges, even at the

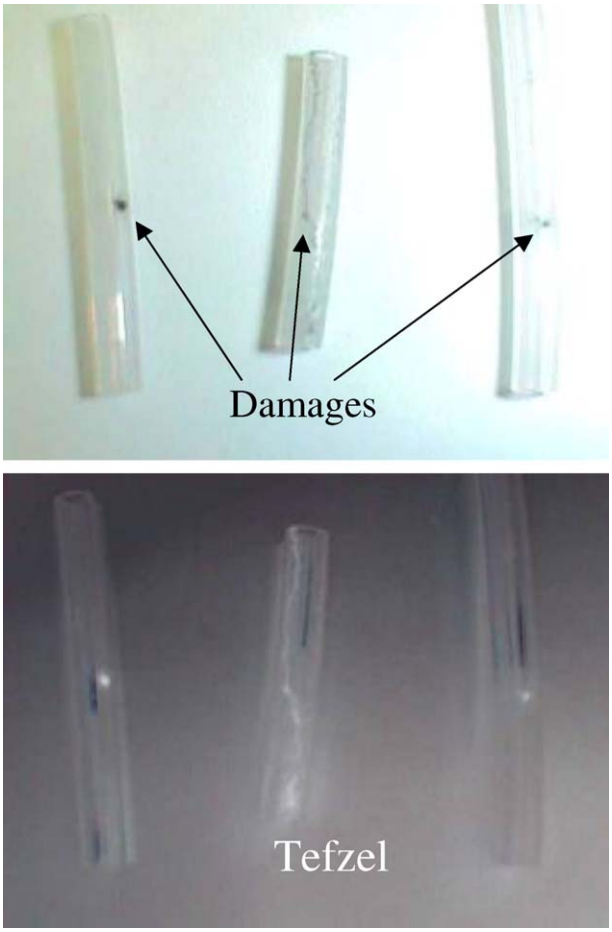

Fig. 2. Three pieces of damaged Tefzel capillaries, top: real colors, bottom: colors inverted.

maximum flow rate of 450 ml/min, which is equivalent to a linear velocity of approximately 4 m/s in an 1/8 in. O.D. capillary.

All eight columns were unpacked, cleaned, fitted with PEEK capillaries, repacked, tested and re-installed into the SMB unit. Again no problems with tightness or sparking were observed during a run with pure solvents, but overnight, running the system with feed solution, the capillaries were punctured and a loss of solvent through punctures was observed (cf. Fig. 3). We had to discover that also using PEEK tubing was not possible for the enantiomer separation of the racemates.

For a better view on the site of damage (cf. Fig. 3) in the non-transparent PEEK the surroundings of the micro-holes were embedded into a cyano-acrylate resin. Microtome cuts and light microscopic enlargements gave patterns of damage as shown in Fig. 4.

A crack perforates the capillary and leads to percolation. The capillary in Fig. 4 is slightly deformed by the force of the microtome cuts. A comparative experiment with a new PEEK capillary and one used overnight for the separation did not show any significant difference in the stress-elongation curves (modulus of extension 3.55–3.95 kN/mm^2; tensile strength between 64 and 78 N/mm^2). Therefore, we concluded that the damage is locally restricted and does not affect the entire length of the tubing.

Fig. 3. Puncture of PEEK capillary, crystallization of compound on surface.

4. Discussion

In the cases observed in our laboratory a cleaning of surfaces was possible and no person present in the laboratory did come into skin or eye contact with the sprayed substance. No source of ignition was present in the area where the heptane solution was involuntarily distributed.

It has to be stressed that incidents as those described above cannot be tolerated in view of environmental, safety and health regulations. Also the requirements of good manufacturing practice (GMP) compel a clean and safe production environment.

Similar experiences were made by Chiral Technologies Europe (CTE), where an eluent composed of *n*-heptane/isopropanol (90:10, v:v) was used. Also at CTE punctures of the PEEK capillaries were observed [9], which led to leaks and sprays of mists containing pharmaceutical intermediates. This observation in a different laboratory seems to confirm that the tubing type of the SMB unit has to be modified

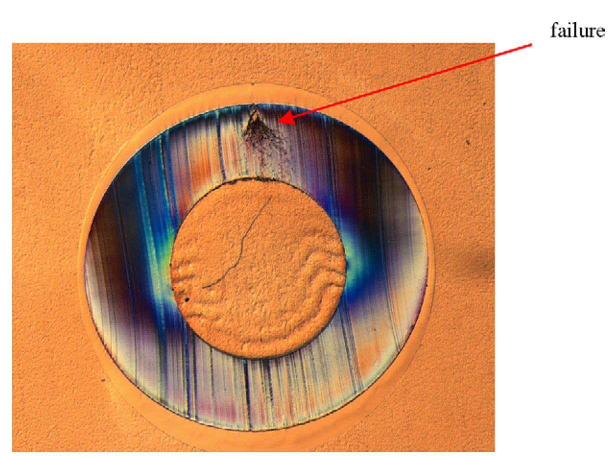

Fig. 4. Microscopic inspection of cut through capillary failure.

for eluents containing high alkane contents, which are used frequently in normal-phase chromatography for enantiomer separations.

We have no reason to believe that a chemical interaction of the racemates to be separated with the highly inert polymers PEEK and Tefzel has taken place, especially as the racemate separated at Chiral Technologies Europe belongs to a different compound class. The only common factors for all operations leading to destruction of polymeric capillaries are the use of a solvent mixture containing a high amount of an alkane, high linear flow rates and the possibility to induce electrical charges between the grounded stainless steel columns and the frame of the SMB unit and the electrically insulating polymeric capillaries. We therefore tentatively assume that electric sparking has caused the micro-holes in the capillaries. This assumption seems to be supported by the fact that after all flexible capillaries on the SMB system were replaced by fixed stainless steel tubing no further damages of tubes, also after extended use of more than three months, could be detected.

5. Conclusions

Two different types of polymeric capillaries were destroyed during chromatographic runs on a SMB unit. Thus we rule out that we are observing an artifact. When eluents with a high alkane content are used micro holes can be formed which prohibit using capillaries produced from either Tefzel or PEEK for chromatographic separations in the SMB mode. The authors recommend using stainless steel tubing for alkane/alcohol eluent mixtures in which the polar modifier is below 10% in volume.

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