Drug Development and Industrial Pharmacy, 33:35–44, 2007

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040600815228

informa
healthcare

The Effect of Rubber Closures on the Haze State of Ceftriaxone Sodium for Injection

Xia Zhao, Shao-Hong Jin and Chang-Qin Hu
National Institute for Control of Pharmaceutical and Biological Products, Beijing 100050, China

ABSTRACT The migration of volatile components into the headspace of glass vials from rubber closures is a potential source of haze formation in reconstituted solutions of powders for parenteral administration. In this paper, a headspace method was used to extract volatile substances from different types of rubber closures used in ceftriaxone sodium for injection whose clarity were poor. The extracts obtained were analyzed by gas chromatography (GC)-mass spectrometry (MS). An antioxidant in rubber closures, butylated hydroxytoluene (BHT), was found to affect the haze state of ceftriaxone sodium for injection.

KEYWORDS Rubber closures, GC-MS, Ceftriaxone sodium, BHT, Headspace method, Compatibility

INTRODUCTION

Parenterals that are unstable in solution are usually formulated as powders that are reconstituted just prior to use. Such powdered or freeze-dried drug can usually be stored in glass vials, which use rubber closures to seal the drugs. Rubber closures are comprised of many compounds including different additives in variable quantities. The closures are in contact with the pharmaceutical compounds either directly or via the headspace. After being stored, the powdered or freeze-dried drug is reconstituted with water or other aqueous vehicles prior to injection. Reconstituted solutions sometimes show haze formation, and probably one of the causes is that volatiles released from rubber closures are adsorbed by the pharmaceutical compounds (Jaehnke et al., 1990). The volatiles are mostly nonpolar or weak polar compounds that can cause the reconstituted solutions to show haze formation. Indeed, the contamination of drug solutions with compounds originating from rubber closures has already been observed, and many evaporated or leached materials are active chemicals that can be toxic, pyrogenic, or can even affect the stability of the active ingredient or interfere with the assay (Lachman et al., 1963; Royce & Sykes, 1957; Wiener, 1955; Wing, 1956; Berry, 1953; Zhang, 1996; Chrzanowski, 1976). Drug manufacturers are expected to investigate the potential of compounds to leach into the drug products and determine the effect on the quality and/or safety of their products.

Address correspondence to Chang-Qin Hu, National Institute for Control of Pharmaceutical and Biological Products, Beijing100050, China; Fax: +86-10-65115148; E-mail: hucq@nicpbp.org.cn

In fact the phenomenon of haze formation in injections has been investigated previously (Pikal & Lang, 1978; Portnoff et al., 1983; Preston et al., 1986; Leebron et al. & Jennings, 1981; Maldener et al., 1986; Buddenbaum & Sykes, 1985). In order to prevent the effect of volatiles released from rubber closures on the clarity of reconstituted solutions, drug manufacturers use a compatibility experiment to select rubber closures. In China Pharmacopoeia, clarity is also used to examine the compatibility between the drug and the drug packaging.

Numerous types of rubber closures with varying compositions are available for drug packaging. The complex formulations consist of elastomers and additives. The additives are introduced to prevent degradation during both processing and use and to optimize specific product properties. Common additives are vulcanizing (or crosslinking) agents, plasticizers, antioxidants, antiozonants, accelerators, and retardants. They belong to many compound classes and represent a wide range of molar mass, volatility, and polarity. Moreover, many additives are labile and contain impurities. They are introduced into the rubber in complex mixtures and at quite low concentrations (<1–5%). Traces of residual unreacted solvents of monomers and oligomers become encapsulated in the polymeric matrix. Finally, potential contaminants originating from the environment may also be present in rubber closures (Delaunay-Bertoncini et al., 2004). This explains why the identification of the compounds in the rubber is complicated and researching which chemicals are responsible for the hazy state of solutions after storage is difficult, and until now, the conclusion about this problem has not been confirmed.

Ceftriaxone sodium for injection is one of the third generation cephalosporins and is widely used in China. Reconstituted solutions often show haze formation after storage, especially when the samples have contacted the rubber closures and were stored at higher temperatures. The clarity of these solutions also becomes worse with time. Such solutions do not meet the requirement for clarity of reconstituted solutions in Chinese Pharmacopoeia. But no literature mentions the reason for the haze formation in ceftriaxone sodium for injection. To be able to adequately determine which volatile compounds might migrate into the formulated drug, we report here on the contribution of butyl rubber closures to the haze state of ceftriaxone sodium for injection.

MATERIALS AND METHODS

Materials

Ceftriaxone sodium raw material (Lot No.03130507) was a gift from Ruiyang Pharmaceuticals Co., Ltd. (Shandong, China). Rubber closures and ceftriaxone sodium for injection were derived from a commercial source. Detailed information about the rubber closures (20 mm diameter) is listed in Table 1 and the surface area of the rubber closures used in this experiment is almost the same. The detailed information about ceftriaxone sodium for injection obtained from different pharmaceutical companies and used in these experiments will not be disclosed in this report. Butylated hydroxytoluene (BHT) was obtained from Sigma Company. Ultrapure water prepared by reverse osmosis and filtered through a 0.45 μm membrane filter was used in all experiments.

TABLE 1 **Details of Rubber closures**

Sample Code	Basic Polymer	Quality Code
MIIR-1	Butyl rubber (coating with inert film A)	/
MIIR-1	Butyl rubber (coating with inert film B)	/
BIIR	Bromobutyl rubber	58
IIR-1	Butyl rubber	305027
IIR-1	Butyl rubber	0312054 (Silicone Class I)
IIR-3	Butyl rubber	0311062 (Silicone Class IV)
IIR-4	Butyl rubber	20031004
CIIR-1	Chlorobutyl rubber	310052057
CIIR-2	Chlorobutyl rubber	0309081–09

Calibration of the Hach 2100AN Nephelometer

The Hach 2100AN nephelometer used in this experiment, a light scatter turbidiment obtained from Hach Company in the United States, was calibrated by using the turbidity standard solutions according to the calibration procedure supplied from the Hach Company. The calibration results indicated that the linearity and the precision of the Hach 2100AN nephelpmeter met the requirements for the study.

Approach to Determine the Interaction Between Ceftriaxone Sodium and Rubber Closures

Influence of Rubber Closures on Turbidity

To show the influence of rubber closures on the clarity of reconstituted solutions of ceftriaxone sodium for injection, we used an exaggerated condition to mix powders of ceftriaxone sodium for injection with rubber closures.

An integrated rubber closure (comprised of MIIR-1, MIIR-2, BIIR, IIR-1, IIR-2, IIR-3, IIR-4, CIIR-1, and CIIR-2), mixed with about one gram of ceftriaxone sodium raw material was placed in a weighing bottle and sealed with a septum. It was then placed in a thermostat and kept at 60°C for fifteen days. A weighing bottle was also placed in the same thermostat for the same time in which there was only about one gram of ceftriaxone sodium raw material without a rubber closure as a blank sample. The contact area of the powdered drug and butyl rubber closures directly affected the clarity of the sample solutions, thus the drug powder was completely covered with the rubber closures to ensure the same area of the drug powder contacted with different rubber closures.

When the time elapsed, all the weighing bottles were removed from the thermostat. After the samples cooled to ambient temperature, an accurately weighed quantity of the drug was dissolved in water to produce a solution of 100 mg per mL and was used as a test solution. The turbidity (NTU, Nephelomefric Turbidity Unit) of the solutions was measured using a Hach 2100AN nephelometer.

Influence of Different Heating Modes on the Turbidity

As a rule, it is thought that the clarity of the reconstituted solutions would be worse after the drug powders adsorbed the volatiles released from rubber closures. The experiment to compare the clarity of ceftriaxone sodium for injection before and after heating for some time was used to prove the hypothesis.

One lot of ceftriaxone sodium for injection (Lot No. 000124) whose clarity (about 3.77 NTU) did not meet the requirement for the clarity of reconstituted solutions in Chinese Pharmacopoeia was used. After being subjected to different disposal conditions (one sample was placed undestroyed in its package, one sample was placed in a open clean dry weighing bottle without packaging, and one sample without packaging was placed in a clean dry weighing bottle sealed with a septum) the samples were placed in a thermostat and kept at 60°C for forty-eight hours. When the time elapsed, the clarity of the samples was measured separately as in “Influence of Rubber Closures on Turbidity.”

Analysis of the Extracts by GC-MS

In order to determine which compounds migrated into the pharmaceutical compounds, rubber closure samples and ceftriaxone sodium samples mixed with different rubber closures were analyzed separately by GC-MS. The purpose was to identify the compounds present in rubber closures samples and ceftriaxone sodium samples together, which were the potential compounds that migrate into pharmaceutical compounds and probably affected the clarity of the reconstituted solutions.

Preparation of Samples of Rubber Closures

An integrated rubber closure was placed in a 20 mL headspace vial with a septum, was sealed with a protective aluminum cap and was used as a test sample. An empty 20 mL headspace vial with a septum was sealed with a protective aluminum cap and was used as a blank sample.

Preparation of Ceftriaxone Sodium Samples

Approximately 200 mg of ceftriaxone sodium for injection (Lot No. 000124) was weighed and treated as for **"Influence of Rubber Closures on Turbidity."** The powder was placed in a 20 mL headspace vial with a septum, which was sealed with a protective aluminum cap and used as a test sample.

Approximately 200 mg of ceftriaxone sodium raw material was weighed (Lot No. 03130507), was placed unheated in a 20 mL headspace vial with a septum, which was sealed with a protective aluminum cap and used as a blank sample.

Analytical Conditions

A Thermo Finnigan Trace GC-MS system and a Thermo Finnigan Polaris Q GC-MSD were used for the GC and MS. The following GC conditions were used. A capillary column (DB-1MS, 30 m × 0.25 mm × 0.25 μm, coated with 100% dimethylpolysiloxane, J&W (USA) was used with helium as the carrier gas at a flow rate of 1.0 $\text{mL}\cdot\text{min}^{-1}$. The injection temperature was 200°C. The ion-source temperature was 200°C. The capillary column temperature was programmed as follows, 50°C initially for 5 min; then linearly increased to 200°C at a rate of $5^{\circ}\text{C}\cdot\text{min}^{-1}$. The headspace oven temperature was 121°C and the sample incubation time was 30 min. The sample injection volume was 1 mL at splitless mode. The MS analyses were preformed under electron ionization (EI) conditions, and the electron energy was set at 70 ev. All MS data were taken in positive ion mode. The all scan mode was full scan and the mass range was from 50 to 650.The work station for the GC-MS is the Xcalibur.

Extract Identification

Peaks characterized by GC-MS were compared with commercially available reference substances of BHT for identification. The reference solutions contained 100 ppm reference standard. The solvent was N, N-dimethylformamide.

Validated Influence of BHT on Turbidity

In order to confirm the influence of BHT on turbidity, simulated experiments of adsorption of BHT by ceftriaxone sodium was carried out, and the BHT contents in the actual samples of ceftriaxone sodium for injection were determined.

Simulated Experiment of the Adsorption of BHT by Ceftriaxone Sodium

To improve the adsorption between ceftriaxone sodium for injection and BHT, an exaggerated condition was used to place together powders of ceftriaxone sodium for injection and BHT. Both ceftriaxone sodium raw material and BHT reference substances were placed in different weighing bottles without caps and in an airtight container. The airtight container was then placed in a thermostat kept at 60°C for fifteen days. When the time elapsed, the turbidity of the drug samples was measured as in **"Influence of Rubber Closures on Turbidity."**

Determination of BHT Content in Ceftriaxone Sodium Solutions by Using GC-flame-ionization Detector (FID)

The contents of BHT in the ceftriaxone sodium for injection from eight batches without any disposal were determined by GC- flame-ionization detector (FID). The batches were obtained from eight different pharmaceutical companies. Among the eight batches the clarity of five batches did not meet the requirement of clarity of solution in Chinese Pharmacopoeia but the other three batches were good.

Preparation of Samples

A weighed quantity of approximately 200 mg of ceftriaxone sodium for injection was placed in a 20 mL headspace vial with a septum, which was sealed with a protective aluminum cap and used as a test sample.

Analytical Conditions

An Agilent GC6890 Series, equipped with an HP7694 automated headspace sampler and a FID, was used for gas chromatography. The following GC conditions were used. A capillary column (SPB-1, 30m × 0.32mm × 0.25um, coated with 100% dimethylpolysiloxane) was used with nitrogen gas as a carrier gas at a flow rate of 2.0 $\text{mL}\cdot\text{min}^{-1}$. The injection temperature was 200°C. The detection temperature was 250°C. The oven temperature was 150°C. The headspace oven temperature was 150°C and the sample incubation time was 45 min. The sample injection time was 2 min at splitless mode. The BHT in the samples was measured.

RESULTS AND DISCUSSION

Influence of Rubber Closures on Turbidity

The turbidity of the reconstituted solutions increased to different extents compared with the sample mixed with the rubber closures coated with film. The turbidity of ceftriaxone sodium for injection mixed with bromobutyl rubber was 1.90 NTU (RSD 1.09%, $n = 3$); but the turbidity of the solutions with butyl rubber closures and chlorobutyl rubber closures was greater than 10.0 NTU. At the same time, the turbidity of the sample solutions not mixed with rubber closures did not show any obvious variation (0.49 NTU, RSD 1.45%, $n = 3$). The results show that the compatibility between ceftriaxone sodium and rubber closures is correlated with the clarity of the reconstituted solutions.

Possible Interaction Between Rubber Closures and Ceftriaxone Sodium

Influence of Different Heating Modes on Turbidity

It is very difficult to study the components released from the rubber closures because the quantities are trace. As a rule, the components of the rubber closures that are released and come into contact with the drug are more volatile. In order to identify the compounds that contaminate the pharmaceutical compounds, rubber closure samples and ceftriaxone sodium samples mixed with different rubber closures were analyzed separately by using GC-MS.

Measurements were made of the turbidity of the reconstituted sample solutions produced by ceftriaxone sodium for injection whose clarity did not meet the requirement of Chinese Pharmacopoeia before and after disposal by different heating modes and the results are listed in Table 2. The turbidity of sample B was better than sample A, sample C, and the unheated sample. The turbidity of sample B also met the requirement of the pharmacopoeia, and thus was not thicker than the No.1 turbidity standard solution (State Pharmacopoeia Commission of P. R. China, 2005). The results proved that the main interaction between the drug and the rubber closures was adsorption. Thus when the sample was heated for some time, the volatile substances that had been released from the rubber closures and adsorbed by the drug evaporated and the clarity of the sample solutions improved.

GC-MS Determination of the Volatile Substances Absorbed by the Drug from Rubber Closures

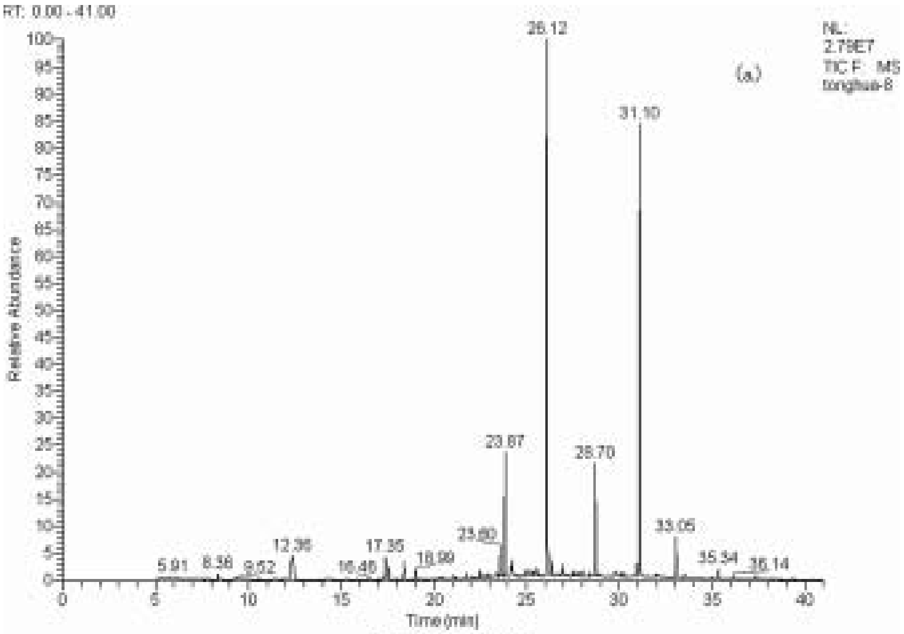
GC-MS chromatograms were done to identify the volatile substances from the rubber closures that were absorbed by the drugs disposed by using different heating modes and the results are shown in Fig. 1. The initial temperature of the capillary column in the experiment was 50°C, thus the residual solvents in the drug samples would effuse out of the capillary column within the first 5 min.

The substances whose retention times exceeded 5 min should be the volatile substances from the rubber closures or from the GC-MS system. It can be seen that according to the improvement in the clarity of the sample solution (Table 2), the intensity of the peak area obtained from the drug was reduced. The solution clarity of the sample heated in the open weighing bottle was the best, and the unheated sample was the worst. The experimental results also show that the interaction between the components from the rubber closures and the drug is probably due to adsorption.

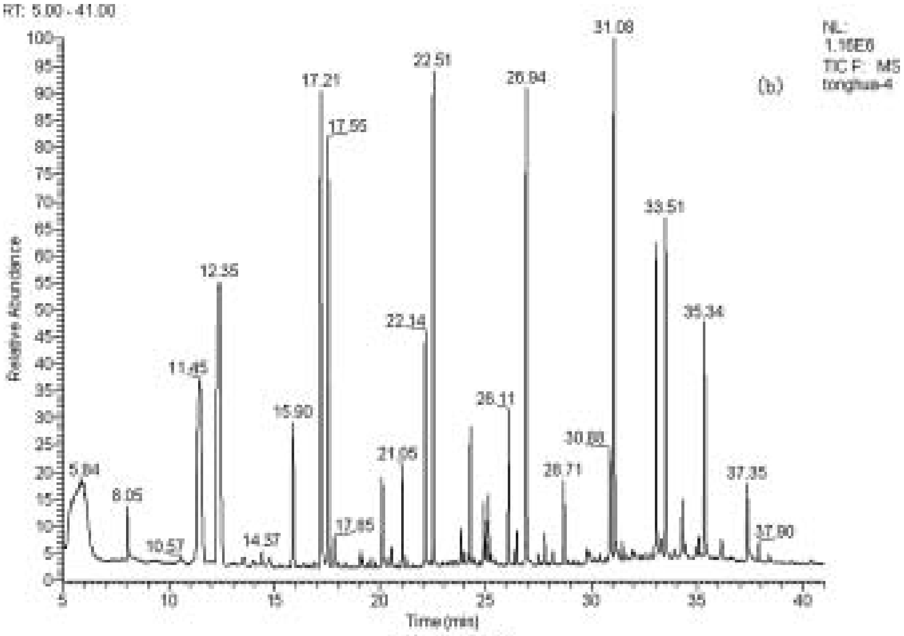
TABLE 2 Results of the Ratio* of the Area of the Main Peaks in the Chromatograms and the Turbidity of Reconstituted Solutions

	Ration of the area of the main peaks					
	23.87min	26.12min	28.7min	31.1min	33.05min	Turbidity (NTU)
Ultra-pure water	/	/	/	/	/	0.41
No. 1 turbidity standard solution	/	/	/	/	/	0.93
Sample A*	18.97%	17.27%	37.03%	46.24%	50.26%	1.44
Sample B*	1.31%	1.13%	2.92%	4.24%	30.42%	0.62
Sample C*	41.34%	83.31%	71.71%	92.37%	73.74%	1.51
Unheated sample	100.00%	100.00%	100.00%	100.00%	100.00%	3.37

*Ratio is the peak area of sample A or sample B or sample C compared with the unheated sample.
Sample A, the sample was placed undestroyed in its packaging.
Sample B, the sample was placed without packaging in a clean dry weighing bottle without a cap.
Sample C, the sample was placed without packaging in a clean dry weighing bottle with a cap.



(a) unheated sample



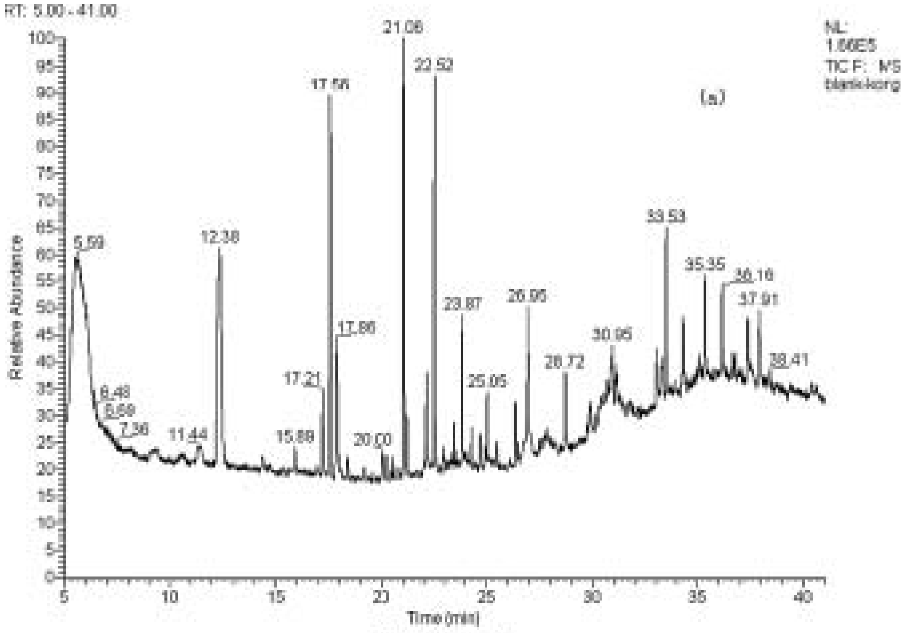
(b) sample B

FIGURE 1 Full Scan Total Ion Current Chromatograms of Samples Disposed of by Different Heating Modes (a) Unheated Sample (b) Sample B.

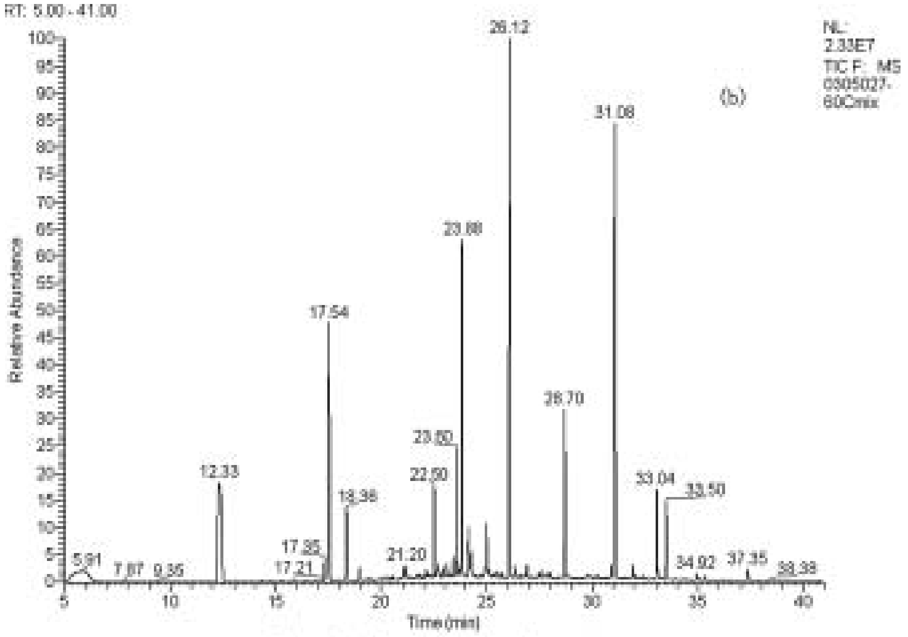
Analysis of the Volatile Components from the Rubber Closures Which Affect the Turbidity

Identification of BHT

Comparing the GC-MS chromatograms of the volatile components from the rubber closures (Fig. 2), it was found that a substance whose retention time was about 26.10 min was present in all the samples but not present in the blank sample, and its intensity was very high in comparison with other substances. Thus the substance was thought to be one of the components affecting the clarity of ceftriaxone sodium for injection. The structure of the substance was identified by referring to the NIST chromatography library in the Xcalibur workstation, and its identity was confirmed by its identical ESI



(a) blank sample



(b) sample mixed with rubber closure A

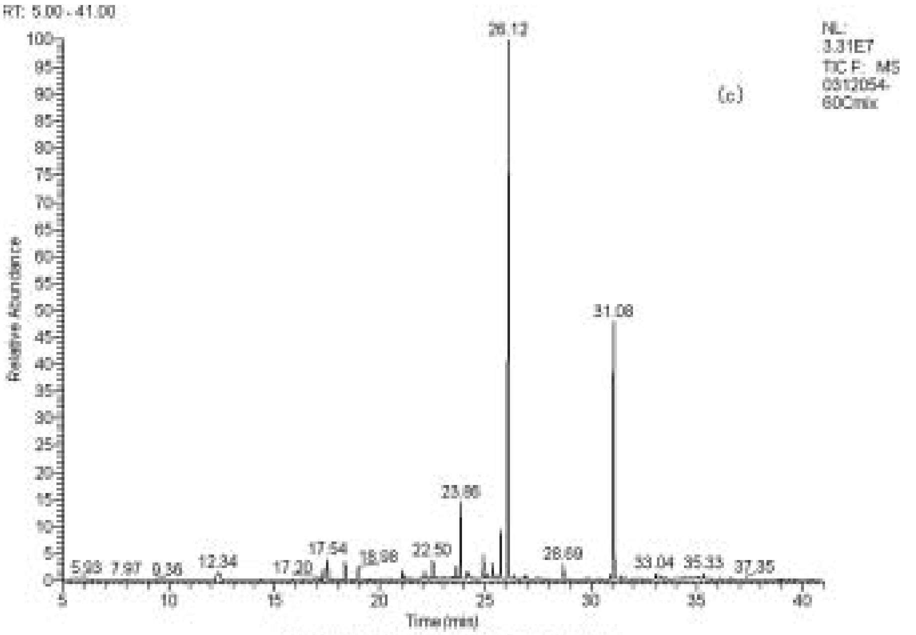
FIGURE 2 **Full Scan Ion Chromatograms of Samples Mixed with Different Rubber Closures (a) Blank sample (b) Sample Mixed with Rubber Closure A (c) Sample Mixed with Rubber Closure B (d) Sample Mixed with Rubber Closure C.**

mass spectrum and GC retention time compared with that of the standard substance. The name of the substance is BHT, 2, 6-di-tert-butyl-4-methylphenol.

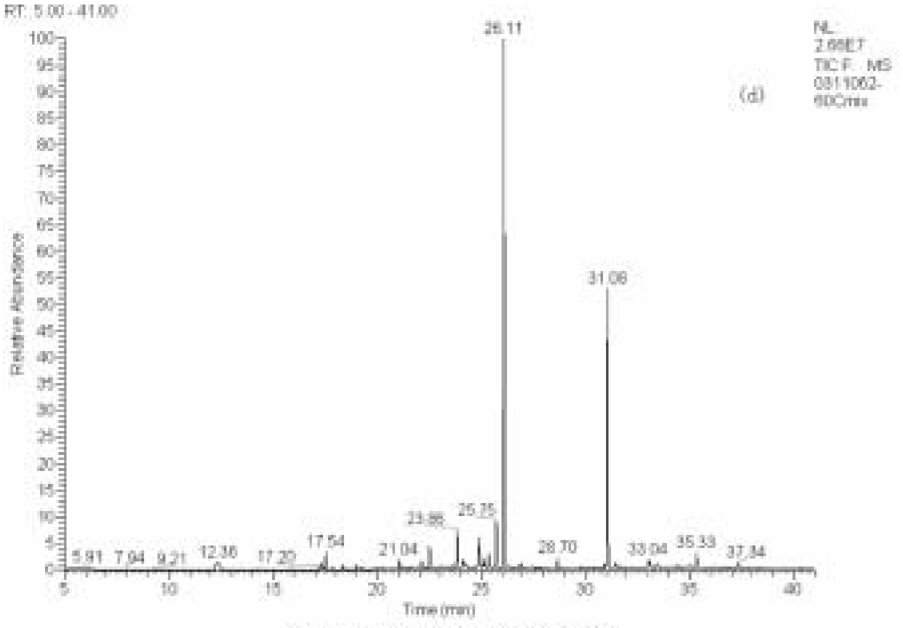
BHT is an antioxidant often used in the rubber and plastic industry. Some scholars (Kehrer, 1989; Powell et al., 1986) found that BHT is harmful to lung and liver and it can increase the risk of developing a tumor, though the results so far are inconclusive, and the amounts of the compound used in the study were much greater than the amounts typically found in the drug solutions.

Simulation Experiment

When ceftriaxone sodium raw material and BHT were placed in different weighing bottles without caps and in the same airtight container in a thermostat kept at 60°C for fifteen days, the turbidity of sample solutions produced



(c) sample mixed with rubber closure B



(d) sample mixed with rubber closure C.

FIGURE 2 Continued.

by ceftriaxone sodium raw material became much higher than before. BHT was detected in the drug samples by GC-MS, which showed that the interaction between ceftriaxone sodium and BHT was due to adsorption.

GC-FID Determination of the Adsorption of BHT by the Ceftriaxone Sodium Solution

Because the contents of BHT in ceftriaxone sodium for injection were trace and the mode of headspace was gas-solid equilibrium, it was very difficult to prepare the reference samples using BHT reference substance. So in the experiment, the reference substance of BHT was only used for orientation and was not used for quantitative analysis of BHT in ceftriaxone sodium for injection. The contents of BHT in ceftriaxone sodium for injection were determined by using peak area of unit mass (A/W). The result is listed in Table 3, and the typical GC-FID chromatogram is shown in Fig. 3.

TABLE 3 Determination of BHT in Ceftriaxone Sodium for Injection

Sample name	Peak area of BHT/mass (A/W)	Turbidity (NTU, 100 mg·mL^{-1})
NO.1sample	126.2	1.80
NO.2sample	100.99	7.79
NO.3sample	63.45	3.50
NO.4sample	5.28	0.38
NO.5sample	23.84	2.46
NO.6sample	5.65	0.72
NO.7sample	6.00	0.84
NO.8sample	44.51	2.02

The results indicate that ceftriaxone sodium for injection in which the content of BHT was high had the worst clarity. But the content level of BHT in the samples could not completely account for the poor clarity of the reconstituted solutions, suggesting that there were other factors that affected the clarity of the reconstituted solutions and the haze state of reconstituted solutions resulted from multiple factors. The phenomenon of haze formation in injections has been investigated previously. Pikal et al. (Pikal & Lang, 1978) thus demonstrated the relationship between the haze in reconstituted freeze-dried products and the concentrations of sulfur and paraffin wax released from vial closures during freeze-drying. They concluded that the observed haze was directly proportional to the amounts of sulfur and paraffin found in the reconstituted solution. Portnoff et al. (Portnoff et al., 1983) identified paraffin, silicone (high molecular weight), and zinc in hazy solutions of cefoxitin sodium. However, closures which were essentially wax-free, silicone-free, and low in zinc were also found to contribute to haze formation. Preston et al. (Preston et al., 1986) detected trace amounts of silicone oil in vials after lyophilization and associated this finding with haze formation. Leebron et al. (Leebron et al. & Jennings, 1981) examined the outgassing properties of elastic closures under vacuum. The closures released hydrocarbons whose molecular weights did not exceed 72Da. Maldener (Maldener et al., 1986) found some unidentified oligomers in the headspace of vials sealed with butyl and chlorobutyl closures. He linked the migration of oligomers with haze formation in solutions of reconstituted meclozillin sodium. Buddenbaum et al. (Buddenbaum & Sykes, 1985) reported that the storage of sterile cefazolin sodium powder in flexible plastic pouches with an inner layer of medium density polyethylene resulted in the formation of a turbid solution after reconstitution. They suggested that additives, including monomers and oligomers, migrated from the plastic pouch and were adsorbed onto the pharmaceutical compound. This phenomenon may be responsible for the hazy state of solutions obtained after the reconstitution of sterile cefazolin sodium.

Through the above experiments we demonstrated that the antioxidant BHT does cause turbidity of the ceftriaxone sodium solution. In conclusion, it appears that BHT is the contaminant causing the haze state in ceftriaxone sodium for injection.

CONCLUSIONS

Ceftriaxone sodium for injection can adsorb BHT, an antioxidant used in the rubber and plastic industry, from rubber closures during storage and this can affect the clarity of the ceftriaxone sodium solution.

When selecting rubber closures for pharmaceutical compounds, compatibility experiments should be

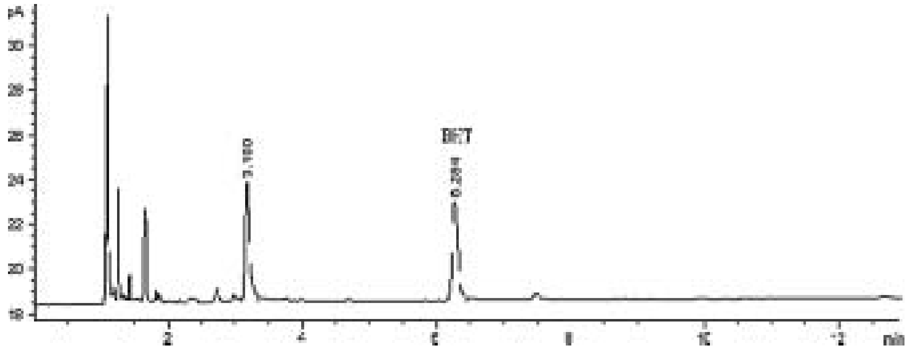


FIGURE 3 GC-FID Chromatogram of Ceftriaxone Sodium for Injection.

done. According to the results of the experiments done in this paper, there should be as little BHT as possible in the rubber closures selected for storing ceftriaxone sodium, because BHT can affect the clarity of ceftriaxone sodium. Of course, there are also other influencing factors, for example the sulfur in the rubber closures, which should be studied extensively in the future.

REFERENCES

Berry, H. (1953). Pharmaceutical aspects of glass and rubber. *J Pharm Pharmacol, 5*(12), 1008–1017.

Buddenbaum, H. C., & Robison, R. L. (1985). Pharmaceutical composition for storage in plastic containers. *United States Patent, 4*, 533–534.

Chrzanowski, F., Niebergall, P. J., Mayock, R., Taubin, J., & Sugita, E. (1976). Interference by butyl rubber stoppers in GLC analysis for theophylline. *J. Pharm. Sci*., *65*(5), 735–736.

Delaunay-Bertoncini, N., vander Wielen, F. W., & de Voogt, P., Erlandsson, B., & Schoenmakers P. J. (2004). Analysis of low-molar-mass materials in commercial rubber samples by Soxhlet and headspace extractions followed by GC-MS analysis. *J Pharm and Biomed Analysis, 35*(5), 1059–1073.

Jaehnke, R. W., Kreuter, J., & Ross, G. (1990). Interaction of rubber closures with powders for parenteral administration. *Journal of Parenteral Science and Technology, 44*(5), 282–288.

Kehrer, J. P. (1989). Blenmycin and cyclophosphamide toxicity in mice with damaged lung tissue. *Toxicology, 57*(1), 69–82.

Lachman, L., Urbanyi, T., & Weinstein S. (1963). Stability of antibacterial preservatives in parenteral solutions. IV. Contribution of rubber closure composition on preservative loss. *J Pharm Sci*., 52, 244–249.

Leebron, K. S., & Jennings, T. A. (1981). Determination of the vacuum outgassing properties of elastic closures by mass spectrometry. *J Parenter Sci Technol.*, 35(3), 100–105.

Maldener, G. (1986). Rubber closures: A simple and fast test methodology for the determination of product compatibility. Paper presented at a Continuing Education Course of the Int. Assoc. for Pharamceutical Technology (D-Mainz, Task Group Packaging), June (Germany).

Pikal, M. J., & J. E. (1978). Rubber closures as a source of haze in freeze-dried parenterals: Test methodology for closure evaluation. *J Parenter Drug Assoc., 32*(4), 162–173.

Portnoff, J. B., Henley, M. W., & Restaino, F. A. (1983). The development of sodium cefoxitin as a dosage form. *J Parenter Sci Technol., 37(5)*, 180–186.

Powell, C. J., Connelly, J. C., Jones, S. M., Grassop, P., & Bridges, J. W. (1986). Hepatic responses to the administration of high doses of BHT to the rat: their relevance to hepatocarcinogenicity. *Food Chem Toxicol., 24*(10–11), 1131–1143.

Preston, W. A. (1986). A device for coring tendency determination in rubber closures. *J Parenter Sci Technol., 40*(5), 207–211.

Royce, A., & Sykes, G. (1957). Losses of bacteriostats from injections in rubber-closed containers. *J Pharm Pharmacol., 9*(12), 814–822.

State Pharmacopoeia Commission of P. R. China. (2005). In: Pharmacopoeia of the People's Republic of China, Chemical Industry Press, Beijing.

Wiener, S. (1955). The interference of rubber with the bacteriostatic action of thiomersalate. *J Pharm Pharmacol, 7*(2), 118–125.

Wing, W. T. (1956). An examination of rubber used as a closure for containers of injectable solutions. III. The effect of the chemical composition of the rubber mix on phenol and chlorocresol absorption. *J Pharm Pharmacol., 8*(10), 738–744.

Zhang, X. K., Dutky, R. C., & Fales, H. M. (1996). Rubber stoppers as sources of contaminants in electrospray analysis of peptides and proteins. *Anal Chem., 68*(18), 3288–3289.