International Journal of Pharmaceutics, 77 (1991) 47–55

ADONIS 037851739100366

IJP 02549

Content/container interactions: The phenomenon of haze formation on reconstitution of solids for parenteral use *

Richard W.O. Jähnke **, Jörg Kreuter and Gerhard Ross

Institute of Pharmaceutical Technology, J.W. Goethe University, Frankfurt am Main (Germany)

(Received 18 April 1991)
(Modified version received 23 May 1991)
(Accepted 25 May 1991)

Key words: Packaging material; Elastomeric closure; Butyl rubber; Migration; Volatile; Injection; Solids for reconstitution; Clarity of solution; Haze formation

Summary

The migration of non-polar volatiles into the headspace of rubber-capped vials is a potential source of haze formation in solutions of reconstituted solids for parenteral use. This investigation shows that high product surface areas are a driving force for the adsorption of volatiles released from rubber stoppers. It was found that products with high surface areas show high levels of turbidity after their reconstitution and those with small areas show low levels of turbidity. Additionally, feasible steps are suggested to prevent haze formation in solutions of reconstituted solids for parenteral administration.

Introduction

Drugs which are intended to be administered via the parenteral route and are unstable in water must be formulated as solids for reconstitution, examples of such drugs are β-lactam, aminoglycoside and glycopeptide antibiotics or antineoplastic drugs, polypeptide hormones and enzymes.

Such drugs can be presented in vials or in two-compartment cartridges with powder in one side and diluent in the other. For these containers, rubber closures are used as primary packaging material because of their unique properties such as elasticity for piercing and self-sealing (Stafford, 1981). The elasticity is still maintained under freeze-drying conditions. In addition, vial seals made from butyl or halogenated butyl rubber show low moisture vapour and gas transmission rates (Wang and Chien, 1984). Low transmission rates protect the vial contents against external hazards such as moisture and oxygen and the resealability maintains the sterility of the product after piercing.

During storage, rubber closures are often in intimate contact with the vial contents and are unfortunately a potential source of product contamination. Examples are shedding of particles

* Dedicated to Professor E. Mutschler, Institute of Pharmacology, J.W. Goethe University, Frankfurt, on the occasion of his 60th birthday.

** *Correspondence (present address):* R.W.O. Jähnke, SmithKline Beecham Pharmaceuticals, Headquarters of Research & Development, Department of Pharmaceutical Science, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ, U.K.

(Lee et al., 1981; Jensen, 1985; Borchert et al., 1986), leaching of metal ions (Motola and Clawans, 1972; Milano et al., 1982; Ellin et al., 1985) and migration of benzothiazoles (Peterson et al., 1981; Reepmeyer and Juhl, 1983; Airaudo et al., 1984; Meek and Pettit, 1985; Wells et al., 1986), antioxidants and oligomers (Maldener, 1986; Pattinson and Wilkins, 1989; Jähnke et al., 1990a) or silicone oil, sulfur and paraffin wax (Pikal and Lang, 1978; Portnoff et al., 1983).

After storage, the powdered or freeze-dried product is reconstituted with water or other aqueous vehicles prior to injection. Reconstituted solutions frequently show haze formation. Haze formation may arise from precipitation in oversaturated solutions, polymerization of decomposed drug or incompatibility between product components such as formation of insoluble aluminum phosphate or calcium citrate. Previous research suggests that non-polar volatiles released from rubber closures are the common source of haze in solutions of reconstituted powders and lyophilisates (Pikal and Lang, 1978).

Non-polar volatiles detected in the headspace of butyl and halogenated butyl rubber closures comprise saturated hydrocarbons, unchlorinated or chlorinated olefins, alkylbenzenes and low molecular weight polydimethylsiloxanes (Gramiccioni et al., 1989; Jähnke et al., 1990a). The main components found in the complex mixture of volatile hydrocarbons are C_{13}-oligomers (Maldener, 1986) which have been identified as 1-isopropenyl-2,2,4,4,-tetramethylcyclohexane and 1-(1-chloromethylethenyl)-2,2,4,4,-tetramethylcyclohexane in butyl and chlorobutyl rubber, respectively (Jähnke et al., 1990b).

In this study, non-polar volatiles released from butyl rubber were used to investigate and quantify the interaction between volatiles and drug substance.

Materials and Methods

Butyl rubber

Uncured butyl rubber was used as a source of non-polar volatiles since its migration pattern concerning volatiles has been well characterized (Jähnke et al., 1990a) and its quantity within the butyl rubber formulations is superior to all other ingredients (Stafford, 1981). Volatiles from uncured butyl rubber form a baseline with which the other modified butyl rubber formulas could be compared. Samples of uncured butyl rubber were cut into cubes (6 mm) prior to use. Each test run was prepared with 10 g of material so treated. The butyl rubber was supplied by the moulder Pharma-Gummi Wimmer West GmbH, Eschweiler, Germany.

Drug substances

The following drug substances were used in powder form: the sodium salt of mezlocillin monohydrate (Baypen®), the disodium salt of cefodizim, the sodium salt of apalcillin (Lumota®) and the monohydrate of pirenzepine hydrochloride (Gastrozepin®). Freeze-dried formulations were used from apalcillin and pirenzepine. All powders and lyophilisates contained no excipients. Lactose monohydrate was employed as a dummy drug. Several types of lactose powder with different particle size distributions were obtained from Meggle Co., Wasserburg, Germany (EPD-10, -20, -30, -80 and Microtose®, see Table 3).

Test assembly and sample preparation

A purge and cold trap apparatus was used for sample preparation as shown in Fig. 1. The volatile components were desorbed from butyl rubber in a double surface tube under elevated conditions at 80 °C over 18 h. Comparison of chromatograms showed the same pattern of volatiles to that observed at 40 °C, although the overall levels were higher at 80 °C. The desorption compartment was purged with nitrogen at a flow rate of 5 ml/min.

The nitrogen, loaded with volatiles, was driven through a reaction tube containing either solid active agents or lactose. The fill weight of each test specimen was 575 ± 21 mg ($\pm$SD) and the reaction tube was tapped several times to achieve a fairly dense packing of the tested material. The drug substances were kept at room temperature to emulate normal storage conditions and to avoid any kind of decomposition induced by heat.

The residual volatiles which passed the reaction tube were trapped in a cold trap via a capillary inlet tube fitted with a gas distribution filter. The trap contained 4 ml of carbon disulfide especially purified for the analysis of hydrocarbons. The assembled trap was immersed in Dewar flasks which were continuously supplied with cooled propan-2-ol to maintain a temperature of −15 °C.

At the end of the experiment, the pre-column of the cold trap (part 5 in Fig. 1) was rinsed with carbon disulfide to extract all sparingly volatile components. This rinsing solution was then combined with the carbon disulfide of the cold trap (part 6 in Fig. 1) to make up for losses caused by evaporation.

The trapped mixture of volatiles was separated and quantified using capillary gas chromatography coupled with a flame ionization detector. Blank runs without drug were performed to determine the composition and overall level of volatiles released from butyl rubber (global migration). The difference between blank and test run exhibited the actual amount of volatiles adsorbed to the drug's surface.

Detection and quantification of volatiles

The volatiles entrapped in carbon disulfide were traced using a Hewlett Packard 5890 gas chromatograph fitted with an SE 54-CB-1 capillary column (25 m × 0.32 mm i.d.), and a flame ionization detector. The detailed operation con-

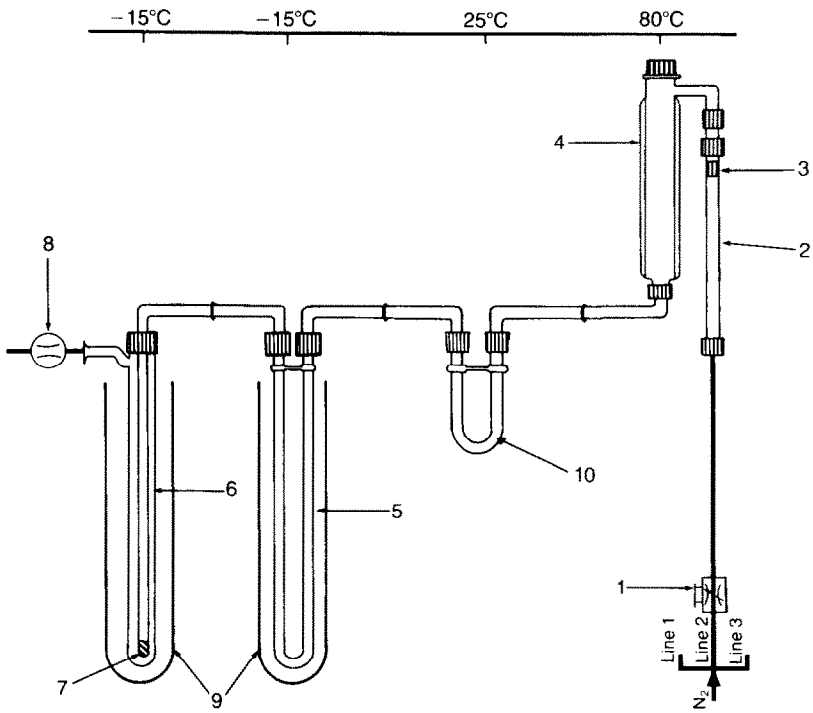

Fig. 1. Thermal desorption of volatiles released from butyl rubber. (1) Combined membrane- and needle-valve (HP Flow Module 19246A) for nitrogen flow timing; (2) column (200 mm, 9 mm i.d.) packed with microsieve (0.3 μm) for the purification of nitrogen; (3) sintered glass filter (pore size 16–40 μm) serving as dust filter; (4) double surface tube (175 mm, 24 mm i.d.) serving as desorption compartment. The upper inlet port was used to fill in the butyl rubber. This inlet port was closed with a melamine screwcap (Schott GL32). A PTFE washer protected the content of the tube from contact with the screwcap; (5) U-tube (610 mm, 9 mm i.d.) for pre-cooling of the nitrogen and freezing up of residual moisture; (6) cold trap (300 mm, 9 mm i.d.) with a long inlet tube (290 mm, 2 mm i.d.); (7) sintered glass filter (pore size 160–250 μm) serving as gas distribution filter; (8) flow control unit; (9) Dewar flasks; (10) reaction tube filled with drug substance. Spherical and screwthread joints were used to couple the purge and cold trap system made from DURAN® glass.

ditions are as follows: injection temperature, 250°C; injection volume, 2.3 μl; injection split, 1:25; septum purge, 1 ml/min; temperature program: onset 100°C, increased by 10 °C/min to 250 °C; detection temperature, 250 °C; detector sensitivity, 10^0; recorder, HP 3393 dialogue integrator; chart speed, 0.4 cm/min.

The run time of the chromatograms was 15 min. All peaks with retention times above 4.5 min were integrated using the standard method supplied by the integrator's software. Butylhydroxyanisole at a concentration of 0.05 μg/ml (50 ppm) was added to the sample solution as an external standard. Thus, the amounts of volatiles traced in the cold trap were expressed in equivalent weights of butylhydroxyanisole. The difference between the level of volatiles in the global migration study and the retrievable levels after contact with the drug substance were used to calculate the actual amount of volatiles adsorbed to the drug's surface (Table 2).

Detection and quantification of haze

The turbidity of the aqueous drug solution was measured using the LTP Turbidity Photometer made by Dr. Bruno Lange Co., Düsseldorf, Germany. Light, passing through the drug solution, was deflected by 90 °. The deflected stray light was detected via a photocell. The calibration of the nephelometer took place using a formazin standard solution as described in the German industrial standards DIN 38404 C2. The detected level of haze was expressed in nephelometric turbidity units (NTU). The linearity of the system was valid up to 100 NTU. The drug solutions were placed in a sample cell with a path length of 10 mm. The sample solutions were prepared by dissolving 575 ± 21 mg (±SD) of drug in 5.0 ml of Water for Injection. The final drug concentration was 11.5% w/v. The intensity of haze was determined immediately after the sample preparation. The figures obtained were evaluated using opalescent reference solutions established in the European Pharmacopoeia II for a limitation test on clarity of parenteral solutions (Tables 1–3).

Determination of the specific surface area

The specific surface areas of lactose, powdered, and lyophilized drugs were determined via the B.E.T. equation isotherms using the Surface Area Analyzer 2100 D from Micromeritics Instrument Corp. Nitrogen and krypton were used as adsorbates. Nitrogen was applied when the anticipated surface area of the sample was higher than 5 m^2/g and krypton if the surface area was lower than that value. The physical dimensions of single gas molecules were taken from McClellan and Harnsberger (1967). The actual dimension used for a single nitrogen molecule was 16.2×10^{-20} m^2 and for a single krypton molecule 21.0×10^{-20} m^2.

Prior to the actual measurements, the solids were dried, weighed and freed of adsorbed gas and vapours picked up from the atmosphere by

TABLE 1

Clarity of solution assessed via aqueous hydrazone reference suspensions of the European Pharmacopoeia II, nephelometry and visible appearance

Opalescent reference solutions according to Ph. Eur. II [a]	Nephelometric turbidity units (NTU) (±SD)	Appearance
Water for injection	0.8 ± 0.2	clear such as purified water
Class I	4.1 ± 0.1	still clear
Class II	7.6 ± 0.2	very slightly hazy
Class III	21.7 ± 0.6	slightly hazy
Class IV	34.3 ± 0.6	hazy
Above class IV	≥ 35.0	very hazy

[a] According to the pharmacopoeial requirements, it is not tolerated that parenteral solutions are more hazy than reference solution I. The USP XXII states that constituted solutions shall not be significantly less clear than purified water. The Japanese authorities accept only parenteral solutions which are as clear as Water for Injection.

pulling a vacuum at room temperature. This sample preparation took 24 h for the drug and 16 h for the lactose material. The matrix of freeze-dried pirenzepine and apalcillin was carefully cut into small pieces in order to introduce a sample into the appropriate sample container of the Surface Area Analyzer 2100 D.

Ten testing points were used to plot the adsorption isotherms for each drug and type of lactose. The volume of a monomolecular layer of adsorbed gas molecules was readily calculated from the slope and intercept of the straight adsorption isotherms (Brunauer et al., 1938). Isotherms with a correlation coefficient of less than 0.9995 were rejected. The quoted values for the specific surface areas (Tables 2 and 3) are the mean of three measurements, unless otherwise stated.

Results and Discussion

Interactions between non-polar volatiles from butyl rubber and the drug substance were visualized via gas chromatograms which show the patterns and levels of volatiles before and after contact with the solids for reconstitution (Fig. 2). Cefodizim, apalcillin and mezlocillin powder were used in this experiment.

Reference chromatogram D in Fig. 2 describes the composition and overall levels of volatiles in the headspace of butyl rubber before contact with the pharmaceutical compounds. The volatiles are isobutylene-isoprene oligomers which are random site products of the butyl rubber synthesis (peaks 1–4 and 6). Butylhydroxytoluene, a common antioxidant in synthetic rubber, is represented by peak 5.

The migration rate of volatiles was 625 ng per 10 g butyl rubber after 18 h of exposure to 80 °C. This migration rate matches the contamination rate observed by Gramiccioni et al. (1989). In the latter study, rubber closures immersed in water released up to 310 ng hydrocarbons per cm^2 after 12 h of storage at 80 °C. The hydrocarbons were identified as hexane isomers, xylene and toluene.

Once in contact with the pharmaceutical compound, the sparingly volatile components such as

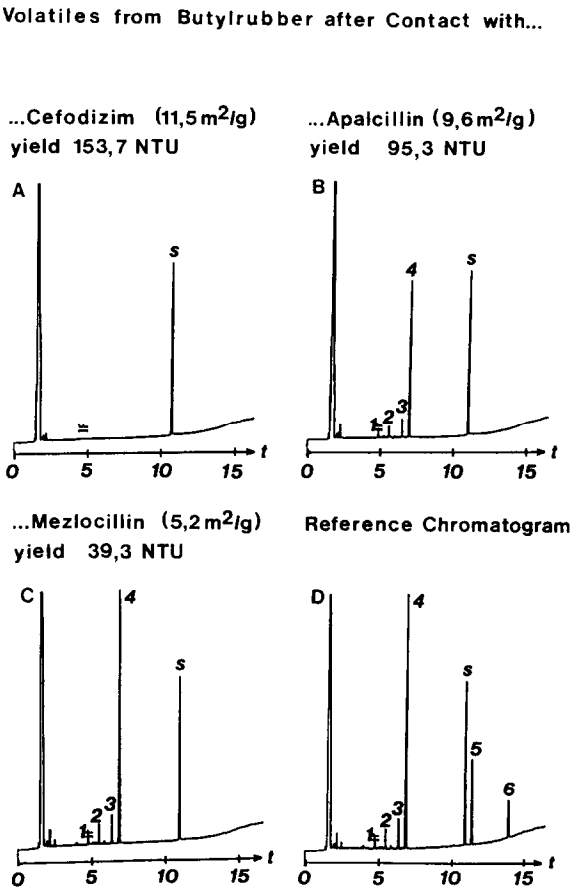

Fig. 2. Gas chromatograms from volatiles before (D) and after contact with powdered cefodizim (A), apalcillin (B) and mezlocillin sodium (C). The chromatograms show volatiles released from butyl rubber as follows: (1–3) unidentified oligomers; (4) diisobutene-isoprene oligomer: 1-iso-propenyl-2,2,4,4-tetramethylcyclohexane; (5) butylhydroxytoluene; (6) C_{18}-oligomer; (s) butylhydroxyanisole as external standard. t = min.

butylhydroxytoluene (peak 5) disappear immediately, followed gradually by more readily volatile components such as the C_{13}-oligomer (peak 4). The gradual disappearance of volatiles increased with increasing surface areas of the drug substances. In due course, the turbidity detected in the corresponding drug solutions also increased.

For example, cefodizim powder shows a very high specific surface area of 11.5 m^2/g. Hence, all volatiles were adsorbed. Not even trace amounts of volatiles were found in the cold trap

as shown in chromatogram A of Fig. 2. As a consequence, solutions of cefodizim powder appeared very hazy (153.7 NTU).

The above-mentioned chromatograms were evaluated quantitatively in Table 2. This evaluation included the freeze-dried products of sodium apalcillin and pirenzepine hydrochloride. The surface areas of the solids were associated with the levels of adsorbed volatiles and with the propensity of haze formation after their reconstitution in Water for Injection.

The correlation between the magnitude of the solid's surface and the uptake of volatiles supports the hypothesis of physical adsorption of volatiles onto the drug's surface. The more volatiles that are picked up by the solid drug, the higher is the level of haze formation in the reconstituted solutions. Based on this fact, the turbidity measured in the aqueous solution of the drug indirectly represents the amount of volatiles previously adsorbed by the drug in the dry state. The turbidity is caused by insoluble volatiles which form a hazy emulsion.

A chemical reaction between the drug and the volatiles is less likely. A prerequisite for a chemical reaction would have been the selective disappearance of a reactive volatile in the gas chromatograms of Fig. 2. However, such a selective disappearance has not been observed.

The hypothesis of the physical adsorption of volatiles is additionally supported by the experiment with lactose (Table 3). Different lactose products with different particle size distributions were exposed to volatiles. Again, a correlation between the surface area of the lactose products and the intensity of haze formation in the corresponding aqueous lactose solutions is observed. Neither the chemical structure of lactose nor those of the volatiles favours a chemical reaction, particularly at room temperature.

The most unexpected observation was the low propensity of freeze-dried pirenzepine hydrochlo-

TABLE 2

Relation between surface area, level of adsorbed volatiles and haze formation in constituted solutions of solids for parenteral use

Solids for reconstitution	Specific surface area (B.E.T.) (m^2/g) ($\pm$SD)	Amount of volatiles adsorbed to the solid in the dry state [b] (ng) ($\pm$SD)	Intensity of haze in solutions of reconstituted solid [c] (11.5% w/v) (NTU) [d] ($\pm$SD)	Charge of active agent in solution
Pirenzepine lyophilisate	0.66 $\pm$ 0.01	98 $\pm$ 38	33 $\pm$ 8	+
Pirenzepine powder	1.06 $\pm$ 0.03 [a]	103 $\pm$ 41	42 $\pm$ 3	+
Apalcillin lyophilisate	0.17 $\pm$ 0.01	traces	16 $\pm$ 1	–
Mezlocillin powder	5.15 $\pm$ 0.51	160 $\pm$ 30	39 $\pm$ 4	–
Apalcillin powder	9.62 $\pm$ 0.37 [a]	379 $\pm$ 25	95 $\pm$ 8	–
Cefodizim powder	11.53 $\pm$ 1.58 [a]	625 $\pm$ 0 [e]	154 $\pm$ 3	–

[a] $n = 2$ whereas $SD = (X_{mean} - X) \cdot \sqrt{2}$, in all other cases $n = 3$.

[b] 575 $\pm$ 21 mg of solid were used in each test.

[c] Solids which were not exposed to volatiles showed levels of turbidity in a range from 2 to 5 NTU.

[d] Nephelometric turbidity units.

[e] The uptake of volatiles was limited by the overall release of volatiles from butyl rubber. This level represents the maximal release after 18 h.

ride and sodium apalcillin to form hazy aqueous solutions after reconstitution (Table 2). This low propensity of haze formation is consistent with the low surface areas observed for the lyophilisates. In contrast, the corresponding powdered formulations show higher surface areas and accordingly a higher tendency of haze formation.

The same observation was made with tobramycin sulfate (Pikal and Lang, 1978). Hazy solutions of tobramycin sulfate (10% w/v) were induced by vacuum equilibration of the solid drug with butyl closures. Clear aqueous solutions were obtained from freeze-dried amorphous tobramycin sulfate with low surface area (approx. 1 m^2/g) and very hazy solutions from precipitated amorphous tobramycin sulfate with high surface area (approx. 40 m^2/g). Hence, lyophilization can assist in avoiding haze formation by reducing the available surface area of the drug.

Further attempts to impede haze formation, ranging from the use of solubilizers to rare closure materials such as bromobutyl or teflon-lined

TABLE 4

Methods to impede haze formation in constituted solutions of solids for parenteral use

Methods used	Solids for reconstitution	Reference
Freeze-drying	Cefamandole Cephalotin Tobramycin	Pikal and Lang (1978)
	Apalcillin Pirenzepine	This work
Increase of crystal size	Lactose	This work
Solubilizer:		
Polysorbate 80	Cefazolin	Buddenbaum and Robison (1985)
Pluronic F 68	Cefazolin	
Emulphor EL 719	Cefazolin	
Kollidon 25	Cefodizim	Jähnke (1988)
Bromobutyl closures	Mezlocillin	Maldener (1986)
Teflon-lined closures	Cefoxitin	Portnoff et al. (1983)

TABLE 3

The surface area of diverse lactose products associated with haze formation after reconstitution in water for injection; [a] *lactose was exposed to volatiles from butyl rubber prior to reconstitution* [b]

Lactose products	Particle size distribution	Specific surface area (B.E.T.) (m^2/g) (±SD)	Intensity of haze in aqueous lactose solutions (11.5% w/v) [c] (NTU) (±SD)
EP-D-10	100% < 800 μm 12–35% < 400 μm 7% < 200 μm	0.08 ± 0.00 [c]	13.3 ± 0.9
EP-D-20	100% < 600 μm 10–35% < 200 μm 5% < 100 μm	0.12 [d]	18.5 ± 3.5
EP-D-30	100% < 250 μm 25–50% < 100 μm	0.17 ± 0.03 [c]	22.0 ± 2.2
EP-D-80	100% < 250 μm 95% < 100 μm 80–90% < 63 μm 45–75% < 32 μm	0.63 [d]	45.0 ± 11.3
Microtose®	100% < 63 μm 95% < 32 μm	1.32 ± 0.03 [c]	65.7 ± 5.3

[a] Water for injection: 0.8 ± 0.2 NTU, $n = 15$.

[b] Intensity of haze in aqueous solutions of untreated lactose: 3.5 ± 1.2 NTU, $n = 10$.

[c] $n = 2$, $SD = (X_{mean} - X) \cdot \sqrt{2}$.

[d] $n = 1$.

[e] $n = 3$.

rubber stoppers, are collated in Table 4. In respect of haze inducement, closures made by bromobutyl rubber show superiority over closures made by butyl or chlorobutyl rubber (Maldener, 1986). The good performance of bromobutyl closures is concordant with their poor release of volatile hydrocarbons (Jähnke et al., 1990a).

Another attempt to reduce the migration of volatiles and thus product contamination is often the exposure of rubber stoppers to heat or vacuum within sophisticated washing cycles. Such attempts remain unreliable as long as the level of volatiles in the rubber closures is unknown (Vom Bruck et al., 1979) or differs between different types of closures (Gramiccioni et al., 1989). To validate the washing cycles, an accurate and precise analytical method needs to be developed for the quantification of volatiles in the rubber matrix. This is a project for future investigations.

Conclusions

This investigation shows that non-polar volatiles released from vial closures are adsorbed onto the product surface of dry powders for parenteral use. After dissolution of the product in water, the volatiles remain insoluble and form an emulsion which appears as haze. The level of turbidity depends on the amount of volatiles found in such solutions. The amount of volatiles in the reconstituted solutions again depends on the amount of volatiles previously attracted by the product in the dry state. Thus, the magnitude of the product's surface area controls indirectly the level of turbidity in solutions of the reconstituted product. In addition to high temperature and low pressure, high product surface area appears to be one of the major driving forces to equilibrate high and low concentrations of volatiles between rubber seals and vial contents, respectively.

Acknowledgements

The authors express their sincere vote of thanks to Dr F. Sitzius, Hoechst AG, for the specific surface area measurements. This work was financially supported by a grant from Hoechst AG, Frankfurt/M. (Germany), and Pharma-Gummi Wimmer West GmbH, Eschweiler (Germany). The authors wish to thank these companies for their support.

References

Airaudo, C.B., Assaf, A., Gayte-Sorbier, A., Salmona, G. and Vincent, E.J., Interactions entre les seringues non reutilisable et les medicaments. *Anal. Chim. Acta*, 166 (1984) 221–231.

Borchert, S.J., Abe, A., Aldrich, D.S., Fox, L.E., Freeman, J.E. and White, R.D., Particulate matter in parenteral products: a review. *J. Parenter. Sci. Technol.*, 40 (1986) 212–241.

Brunauer, S., Emmett, P.H. and Teller, E., Adsorption of gases in multimolecular layers. *J. Am. Chem. Soc.*, 60 (1938) 309–319.

Buddenbaum, H.C. and Robison, R.L., Pharmaceutical composition for storage in plastic containers and process therefore. *US Patent* 4,533,542, Aug. 1985.

Ellin, R.I., Kaminskis, A., Zvirblis, P., Sultan, W.E. and Shutz, M.B., Leaching of zinc compound from rubber stoppers into the contents of automatic atropine injectors. *J. Pharm. Sci.*, 74 (1985) 788–790.

Gramiccioni, L., Milana, M.R., Maggio, A., Feliciani, R. and Gesumundo, C., An experimental study of residual chemicals in elastomeric stoppers for injectables: a MS/GC survey and a headspace/GC purity test. *Chromatographia*, 28 (1989) 545–550.

Jähnke, R.W.O., Doctoral Thesis, University of Frankfurt am Main (Germany), 1988, p. 213 (Ger.).

Jähnke, R.W.O., Kreuter, J. and Ross, G., Interactions of rubber closures with powders for parenteral administration. *J. Parenter. Sci. Technol.*, 44 (1990a) 282–288.

Jähnke, R.W.O., Linde, H., Mosandl, A. and Kreuter, J., Contamination of injectable powders by volatile hydrocarbons from rubber stoppers. *Acta Pharm. Technol.*, 36 (1990b) 139–148. (Ger.).

Jensen, T.H., Interactions between rubber closures and medical preparations. *Arch. Pharm. Chem., Sci. Ed.*, 13 (1985) 1–32.

Lee, M.G., Fenton-May, V., Brown, C.M. and Tarr, M.J., DIN bottles and rubber closures for intravenous fluids. *Pharm. J.*, 226 (1981) 670–672.

Maldener, G., 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 Pharm. Technol. (Mainz) held in Aachen, June 1986 (Ger.).

McClellan, A.L. and Harnsberger, H.F., Cross-sectional areas of molecules adsorbed on solid surfaces. *J. Colloid Interface Sci.*, 23 (1967) 577–599.

Meek, J.H. and Pettit, B.R., Avoidable accumulation of potentially toxic levels of benzothiazoles in babies receiving intravenous therapy. *Lancet*, ii (1985) 1090–1092.

Milano, E.A., Waraszkiewicz, S.M. and Dirubio, R., Extraction of soluble aluminum from chlorobutyl rubber closures. *J. Parenter. Sci. Technol.*, 36 (1982) 116–120.

Motola, S. and Clawans, C., Identification and surface removal of incompatible group II metal ions from butyl stoppers. *Bull. Parenter. Drug Assoc.*, 26 (1972) 163–171.

Pattinson, S.J. and Wilkins, J.P.G., Investigation by gas chromatography - mass spectrometry of potential contamination incurred by the use of crimp-cap vial closures. *Analyst*, 114 (1989) 429–434.

Peterson, M.C., Vine, J., Ashley, J.J. and Nation, R.L., Leaching of 2-(2-Hydroxyethylmercapto)benzothiazole into contents of disposable syringes. *J. Pharm. Sci.*, 70 (1981) 1139–1143.

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

Portnoff, J.B., Henley, M.W. and Restaino, F.A., The development of sodium cefoxitin as a dosage form. *J. Parenter. Sci. Technol.*, 37 (1983) 180–185.

Reepmeyer, J.C. and Juhl, Y.H., Contamination of injectable solutions with 2-mercaptobenzothiazole leached from rubber closures. *J. Pharm. Sci.*, 72 (1983) 1302–1305.

Stafford, P., Rubber and its pharmaceutical applications. *Manuf. Chem. Aerosol News*, 52 (1981) 25–27.

Vom Bruck, C.G., Rudolph, F.B., Figge, K and Eckert, W.R., Application of the diffusion theory to migration of plastic components into packed goods: Survey of recent migration studies. *Food Cosm. Toxicol.*, 17 (1979) 153–157.

Wang, Y.J. and Chien, Y.W., Sterile pharmaceutical packaging: compatibility and stability. *Parenter. Drug Assoc., Tech. Rep.* 5, Philadelphia, 1984, p. 123.

Wells, C.E., Juenge, E.C. and Wolnik, K., Contaminants leached from rubber stoppers into a water soluble Vit E intravenous injectable product. *J. Pharm. Sci.*, 75 (1986) 724–725.