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Journal of Pharmaceutical and Biomedical Analysis 37 (2005) 259–264
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Compatibility of nitroglycerin, diazepam and chlorpromazine with a new multilayer material for infusion containers

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Received 15 June 2004; accepted 18 October 2004
Available online 28 November 2004

Abstract

The stability and compatibility of three drugs: nitroglycerin, diazepam and chlorpromazine, with a new multilayer infusion bag were studied. The study was carried out comparatively with PVC bags with which these drugs are incompatible. The drugs were diluted in 5% dextrose or in 0.9% sodium chloride isotonic solutions. Solutions were stored during 8 or 48 h with or without any protection against light. Remaining concentrations of drug were determined by high-performance liquid chromatography (HPLC) during the storage. The admixtures were also monitored for precipitation, color change and pH. Whatever the isotonic solution used, the loss of drugs is in discredit of the use of PVC bags for their storage. So, these three drugs would not be stored in PVC bags. In multilayer bags, no loss of drugs and no color change were detected throughout the storage period. pH values were stable during the same storage period. These three drugs were compatible with multilayer bags in all tested conditions for 8 or 48 h. The leaching of the plasticizer di-(2-ethylhexyl) phthalate (DEHP), that is incorporated into PVC to make the bags soft and pliable was not detected in the three drug solutions during storage period. Our study confirms that these three drugs are incompatible with PVC bags, on the contrary the new materiel tested was proved to be interesting for drug storage.

Keywords: Compatibility; Nitroglycerin; Diazepam; Chlorpromazine; Multilayer bags; PVC bags

1. Introduction

Polyvinyl chloride (PVC) materials for infusion bags are commonly used for the administration of infusion drug admixtures because they offer several advantages over conventionnal glass containers, such as easier storage and shipping because of their resistance of breakage. However, there are still some drawbacks to resort to them because possible drug-package interactions can occur. Two major problems are often discussed in the literature. The first one is that some compounds of plastic as plasticizers can be leached into solutions. Several studies have shown the leaching of di-(2-ethylhexyl) phthalate (DEHP) from PVC bags [1,2]. DEHP is the predominant plasticizer used to make the bags soft and pliable. This plasticizer is known to be responsible for change in structure and function of liver in animals, reduction body weight and liver weight in adult male rats [3,4]. In rats, DEHP is both a male and female reproductive toxicant. Data from few studies in rodents reported that phthalates effects on reproductive cells are influenced by the stage of development at exposure [5,6]. Non-PVC bags such as multilayer containers do not contain plasticizers and are recommended by manufacturers for admixture of total nutrient solution, containing lipophilic constituents, used for delivering total parenteral nutrition. The other main problem is the possible adsorption of drugs on the inner plastic surface of container [7,8] leading to the loss of drugs and a decrease of the injection concentrations. Therapeutic consequences can be observed because the

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doi:10.1016/j.jpba.2004.10.020

patient does not receive the dose, which has been prescribed him and the precise dose itself is unknown.

Furthermore, stability of the drug and the possible leaching of plasticizer can sometimes be related to the choice of the solution used for dilution [9,10] or to the volume of bag [11]. So, for every plastic material and each drug, it is necessary to carry out some tests of compatibility and stability. Indeed, the nature of the plastic material is the most important factor, since it determines the nature and the amount of drug binding. It is recognized that PVC causes the largest and the most numerous interactions with drugs, whereas polyethylene or polypropylene materials are considered more compatible. So, multilayer plastic materials would provide useful solutions: maintaining physical properties, compatibility with contents, protection against exterior agents [12].

The aim of this study was to evaluate the compatibility between a new multilayer materials for infusion containers (named M312) and three drugs: nitroglycerin, diazepam and chlorpromazine. These drugs have been chosen according to their known uncompatibility with PVC bags. For instance, the loss of potency of nitroglycerin after 24 h was almost 30% [8]. Remaining concentrations of diazepam after 24-h storage was only 60% of initial concentration [8]. It was also proved that chlorpromazine was able to interact with PVC container [13]. For these reasons, bags made of multilayer materials have been manufactured for some years [12]. Among them, M312 is a film made of five layers which might be assumed to combine a minor degree of sorption and a vapour barrier-effect as the inner layer in direct contact with the solution is made of a co-polymer of polyethylene and polypropylene, and a oxygen barrier-effect which does not permit the oxygen to enter and to oxidize the drugs because the nature of other layers in the middle and the outside of the film.

This paper presents the compatibility results obtained for three drugs administered in infusion solution from PVC and multilayer containers.

2. Materials and methods

2.1. Chemicals and drugs

HPLC-grade methanol was obtained from JT Baker (Devender, Holland). The water used was de-ionized and purified by Milli-Q Academic water purification (Millipore, Saint Quentin en Yvelines, France). Analytical grade ammonium acetate was purchased from Prolabo (Paris, France). Nitroglycerin, chlorpromazine, diazepam, as specimen, and clonazepam, used as internal standard, were obtained from Sigma (Saint-Quentin Fallavier, France).

The drugs studied were the commercial products suitable for clinical use. Nitroglycerin applied to the treatment of angor and cardiac failure, chlorpromazine hydrochloride, a phenothiazine antipsychotic drug and diazepam, a benzodiazepine anxiolytic drug were provided in injection forms. Nitroglycerin was the current clinical formulation Lenitral® intravenous injection. It was generously donated by Besins-Iscovesco Laboratories (Paris, France) in ampuls of 3 or 15 mg diluted in, respectively, 2 or 10 ml of injectable solvent. Chlorpromazine hydrochloride was used as Largactil® intravenous injection. It was provided from Specia Rhone-Poulenc-Rorer Laboratories (Paris, France) in ampuls of 25 mg diluted in 5 ml of injectable solvent. Diazepam was used as injections of Valium® and provided from Roche Laboratories (Neuilly sur seine, France) in ampuls of 10 mg diluted in 2 ml of injectable solvent.

2.2. Materials and chromatographic conditions

During the experiments, the remaining concentrations of drugs in injection solutions were determined by high-performance liquid chromatography (HPLC). Chromatographic analysis was performed using a HP 1090 M HPLC system (Hewlett-Packard, Orsay, France) equipped with a variable volume injector, an automatic sampling system and a Hewlett-Packard Model 79994A linear photodiode array UV detector operating at suitable wavelengths. The output from the detector was connected to a Hewlett-Packard 9000 model 300 integrator to control data acquisition and integration. Retention times and peaks areas were determined by a computer connected to a Hewlett Packard Thinkjet terminal printer. Drugs analyses were performed on a 5 μm Hypersil BDS C_{18} column (150 mm × 4.6 mm) (Life Sciences International, Epargny, France), operating at room temperature.

- Nitroglycerin separation was based on an isocratic method using a mobile phase consisting of methanol and water (50/50, v/v). After degassing with helium stream for 15 min, the mobile phase was pumped through the column at a flow rate of 1.5 ml min^{-1}. Samples (20 μl) were injected into the analytical column and the chromatographic separation was achieved with final detection at 215 nm.
- Diazepam analyses were carried out at 254 nm with a mobile phase consisting of mixture methanol–water (65/35, v/v) pumped at a flow rate of 1.7 ml min^{-1} and degassing with helium stream. The volume of injection was 20 μl.
- For chlorpromazine, analyses were carried out at 254 nm with a mobile phase consisting of the mixture methanol–acetate buffer pH 4 (65/35, v/v) pumped at a flow rate of 0.8 ml min^{-1}. For all drug analysed, clonazepam was used as the internal standard.

The leaching of DEHP was also investigated using previous conditions described by Faouzi et al. [1].

A pH meter was used to measure the pH of injection solutions during storage in PVC or multilayer containers at 20 °C. It was a model HI 8520 N microprocessor equipped with a Micro pH electrode HI 1083 (Hanna Instruments, Lingolstein, France).

2.3. Preparation of admixtures in multilayer and PVC bags

PVC infusion bags (Macoflex) containing dextrose 5% injection or sodium chloride 0.9% injection were kindly provided by Macopharma Laboratories (Tourcoing, France). Multilayer bags were manufactured by Macopharma Laboratories using a new multilayer film, named M312 made of five layers, which is from the inner to the outer side of the bags, made of polyethylene, polypropylene and polyester. This multilayer material might be assumed to combine a minor degree of drug sorption as its inner layer is made of a polyethylene, and an oxygen barrier-effect and vapour barrier-effect because of the nature of some of the layers.

A number of drug ampuls, chosen to obtain concentrations of the same magnitude as therapeutics, was added to 5% dextrose or 0.9% sodium chloride isotonic injections, contained in PVC bags and in multilayer bags.

- For nitroglycerin, one ampul (3 mg) was added to 50 ml of 5% dextrose or 0.9% sodium chloride isotonic solutions. The solutions were stored at room temperature (20–25 °C) during 48 h without any protection against light.
- For chlorpromazine, 25 mg were added to 100 ml of 5% dextrose or 0.9% sodium chloride isotonic solutions. These admixtures had to be stored in the dark because the aqueous solutions of phenothiazine-like compounds are very quickly oxidized in the daylight. So, the solutions were stored in the dark during 8 h because of the photosensitivity of the molecule.
- For diazepam, 20 mg were added to 500 ml of 5% dextrose or 0.9% sodium chloride isotonic solutions. The solutions were stored at room temperature (20–25 °C) during 48 h without any protection against light.

Optimally, drug compatibility and stability trials should include both visual and chemical tests. The bags containing the drug solutions were agitated by bending, flexing, massaging and shaking for about 1 min after preparation to simulate the agitation that a bag may undergo during preparation, transportation and administration.

At specified time intervals, the bags were agitated and samples were directly taken from both PVC and multilayer bags up to the end of the storage period and placed in clear glass test tubes and were visually inspected for color and clarity by following European Pharmacopeia protocols V.6.1. (1983) and V.6.2. (1980). At the same time, the pH values of solutions were measured immediately. Then, samples were kept frozen in polypropylene tubes at −20 °C until analysis. The remaining concentrations of drug and DEHP contents were then determined by suitable methods mentioned above.

3. Results and discussion

3.1. Chromatography

Drug concentrations were determined by using a stability-indicating HPLC assay. All assays were performed isocratically at ambient temperature. The compounds were resolved with a satisfactory baseline separation under developed conditions. No, degradation product interfered or was eluted with the same retention time of the parent drug peak.

- Nitroglycerin calibration curve was constructed at a concentration range of 10–30 μg/ml. A good linear response was found with a correlation coefficient better than 0.999. Within-run precision of the method was evaluated by replicate analysis ($n = 5$) of different concentrations (10, 15, 20 and 30 μg/ml), it was less than 2.83%.
- For diazepam, calibration curve was constructed at a concentration range of 2.5–15 μg/ml and the correlation coefficient was better than 0.999. The precision was validated by establishing the relative standard deviation (R.S.D. < 2.61%) with four concentrations (2.5, 5, 10 and 15 μg/ml).
- In the same way, a good linear response was found for chlorpromazine assays. Correlation coefficient was 0.999 for calibration curve (1.25–10 μg/ml) and precision was established by determination of R.S.D. ($n = 5$), with four concentrations (1.25, 2.5, 5, 10 μg/ml), which was less than 2.81%.

Since DEHP is a persistent environmental polluant, rigorous precautions were taken to avoid contamination during both sample handling and sample analysis. All the samples were prepared and diluted in glass or polypropylene tubes washed previously with a methanol/acetonitrile mixture, and rinsed with hexane.

The intra-assay and inter-assay coefficients of variation (RDS values) were lower than 0.75 and 4.36%, respectively. A good linear response was found with a correlation coefficient better than 0.999.

3.2. Stability of nitroglycerin

The analysis of each sample was performed by HPLC after a suitable dilution in the mobile phase in order to fit the calibration curve. At time zero, the initial concentration of nitroglycerin was designated as 100% and all subsequent measured concentrations were expressed as percentages of the initial concentration. Stability was defined as a concentration representing 90–105% of the initial one, in accordance with the Health Registration of France, the French Regulatory Agency for drug and drug-related products. So, drug instability and incompatibility with material in contact were defined as $a > 10\%$ decrease from the initial drug concentration.

Fig. 1 shows the behaviour of nitroglycerin in both PVC and multilayer bags.

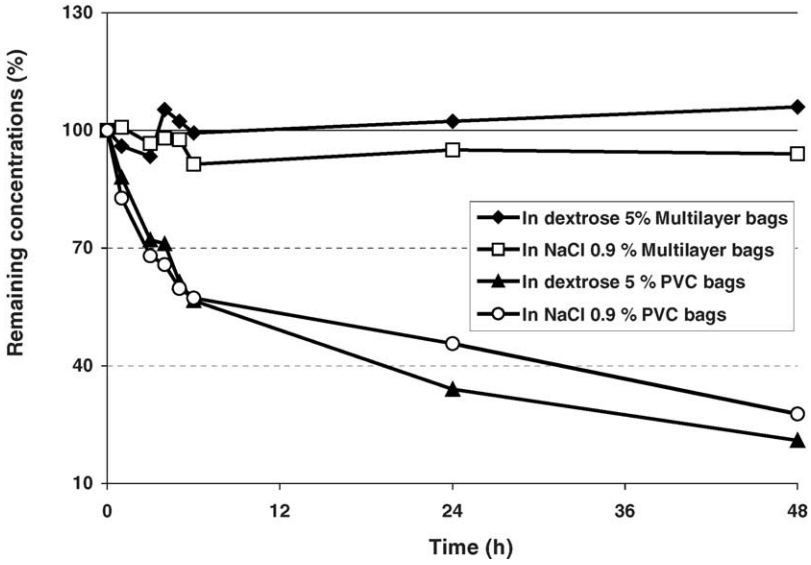

Fig. 1. Remaining concentrations of nitroglycerin after storage in multilayer or PVC bags.

- In PVC bags, after 4 h, loss of nitroglycerin averaged 30%. During a 48-h period, remaining concentration were 20% of the initial concentration in dextrose solution and 30 % in sodium chloride solution.

These findings indicated that, nitroglycerin was adsorbed by the plastic infusion bags that it comes in contact with during storage. Because this adsorption process is very fast with nitroglycerin, it is difficult to measure the exact initial concentration. Consequence, the phenomenon could affect the response elicited in patient-treated with an i.v. nitroglycerin formulation. The results also confirmed that the loss is not due to degradation, since the assay method used is precise and specific and can detect degradation compounds. The rate of loss from sodium chloride injection appears to be slower than with dextrose injection. This indicates that adsorption is affected by the solution used to deliver nitroglycerin.

- In multilayer bags, no loss was highlighted whatever the infusion solution. All concentrations remained above 90% of the initial value, and most were near 100%. There was no substantial difference between nitroglycerin concentrations at time zero and at any subsequent time point. Nitroglycerin concentrations after various periods of storage showed no loss (>10%) of the drug. In contrast with PVC bags, the drug was not adsorbed by the plastic infusion bags. In conclusion, nitroglycerin remains stable for up to 48 h in multilayer bags whatever the infusion solution used.

3.3. Stability of chlorpromazine

As shown Fig. 2, chlorpromazine slightly interacted with PVC bags and not with multilayer bags. After 8-h storage, about 30% of the drug were lost. Long-term stability tests confirmed these results [14]. No difference was noticed between both sodium chloride or dextrose solutions. As previously discussed, the present study is reported so as to alert clinicians of this phenomenon and to promote efforts to utilize non-PVC bags and the shortest possible infusion sets. Therefore, chlorpromazine dilutions may be prepared in multilayer containers as an alternative to PVC bags and stored in the dark.

3.4. Stability of diazepam

The loss of diazepam after 24-h period reached 50% of the initial concentration in PVC bags whereas no interaction was noticed in multilayer bags. So, extremely rapid loss of diazepam occurred in PVC containers. The loss was so rapid that accurate time-zero determinations were not possible. Losses of 50% or more occurred in both dextrose 5% injection and in sodium chloride 0.9% injection. In multilayer bags, diazepam remained stable for at least 48 h (Fig. 3).

The leachability of DEHP into intravenous solutions was not highlighted with the various studied drugs. Moreover, no drugs precipitation or crystallization and no solution color change were observed in any solutions stored in PVC or multilayer bags. In the same way, no modification of pH was observed with the various solutions neither with the PVC bags nor with the multilayer ones.

The new materiel tested (multilayer bags) was proved to be interesting for drug package. Multilayer bags were manufactured using a new multilayer film, named M312, which provides superior performance for packaging pharmaceutical solutions. Several polymers, each contributing a specific property, are coextruded into a multiply film. The result is an exceptionally clear benefit: exceptional product protection with optimum leach resistance, no presence of plasticizers, adhesives or chlorine and ultra-low particulate levels. M312 is a highly inert material exhibiting extremely low extractables with a wide variety of solutions. Moreover, this material

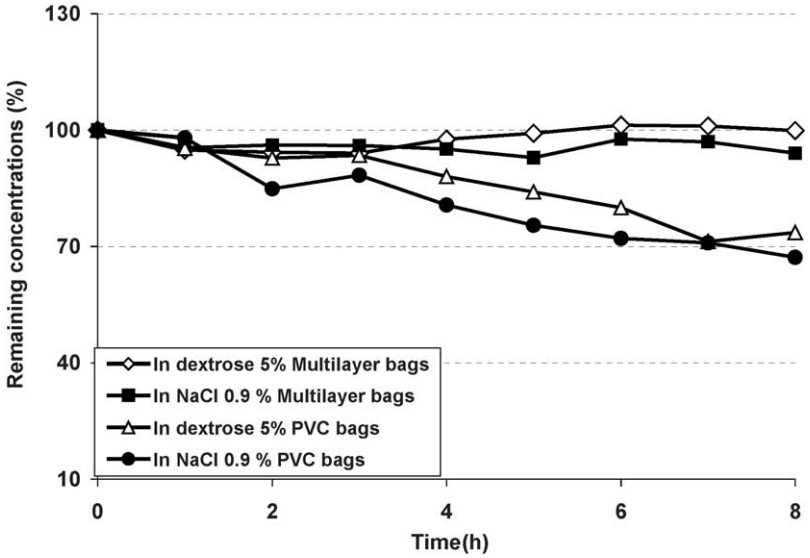

Fig. 2. Remaining concentrations of chlorpromazine after storage in multilayer or PVC bags.

minimises oxygen transfer, improves long-term stability and can facilitate 48 h or more therapy for stable patients. Other types of multilayer films for their anti-adhesive property are used not to manufactured bags, but to manufactured a material making it possible to reduce the bacterial adherence of surface of implants [15].

PVC bags containing injection solutions offer several advantages over conventional glass containers, such as easier storage and shipping because of their resistance to breakage. However, several problems are reported with their use such as the loss of substantial amounts of drug from the solution by adsorption or absorption onto the plastic bags, and the leaching of potentially harmful substances into the solution, particularly a plasticizer, DEHP [1,7,8,11,16]. This plasticizer is known to be responsible for change in structure and function of liver in animals, reduction body weight and liver weight in adult male rats [3,4]. In rats, DEHP is both a male and female reproductive toxicant. Data from few studies in rodents reported that phthalates effects on reproductive cells are influenced by the stage of development at exposure [5,6]. So, patients on regular exposure of this plasticizer are therefore at risk for toxic consequences.

The container-content (PVC-drug) interactions with loss of drugs were not limited to the three studied drugs. Interactions of the same type exist with other drugs. Fentanyl citrate was rapidly lost when admixed with fluorouracil in PVC containers, losing about 25% in the first 15 min and about 50% in the first hour [17]. Clomipramine hydrochloride and

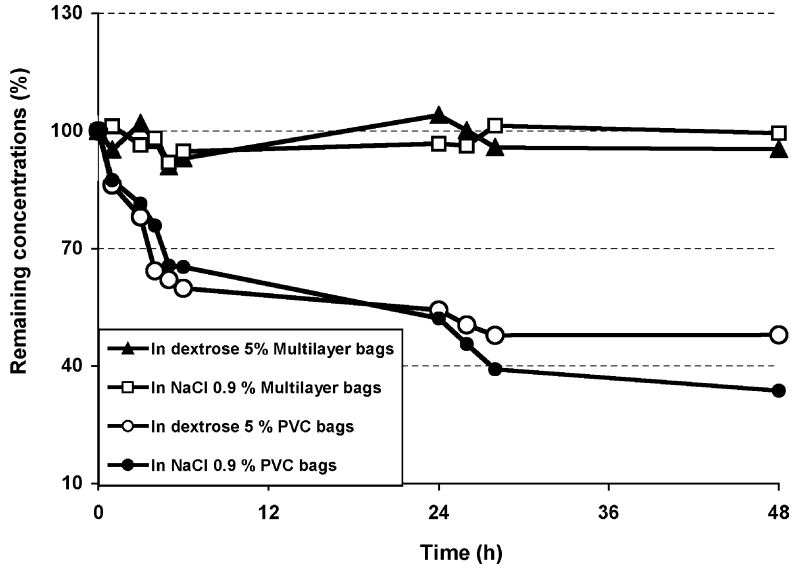

Fig. 3. Remaining concentrations of diazepam after storage in multilayer or PVC bags.

clorazepate dipotassium salt slightly interact with PVC bags [13]. In certain cases, one can note that there is not loss of drugs, but a strong leaching of the plasticizer DEHP occurred. Thus, strong amounts of DEHP were extracted from PVC i.v. infusion bags of taxol, teniposide, 5-FU, quinine and cyclosporine [1,11,16,18,19]. The magnitude of leaching of the plasticizer appeared to be directely dependent on the area of PVC, the duration of storage and the concentrations of Cremophor. Sometimes, one can note a physical drugs incompatibility with the PVC bags such as pH change, color change or the formation of precipitates [11,16]. All these interactions with PVC involving the loss of drugs or the leaching of the plasticizer DEHP were not observed with the multilayer bags. So, the multilayer bags represent a better alternative in the preparation and the storage of the medicamentous formulations incompatible with PVC bags.

So, that is why, specific content/container studies are necessary to prove the drug compatibility with plastic packagings.

4. Conclusion

This study confirms that these three drugs are incompatible with PVC container; in contrast, the new materiel tested was proved to be interesting for drug package. Moreover, it clearly indicates that diazepam and nitroglycerin undergo marked adsorption on the PVC bags surface. No significant difference was observed between the infusion solutions used as vehicles of the drugs. So, nitroglycerin (3 mg/50 ml) and diazepam (20 mg/500 ml) in dextrose 5% or sodium chloride 0.9% solutions could be stored 48 h at room temperature, without precaution with light in this multilayer bag. Chlorpromazine (25 mg/100 ml) in dextrose or sodium chloride solution is stable for 8 h in the dark in the multilayer bags.

This study highlights the interest of multilayer infusion bags. Further studies should be conducted with additional drugs in order to explore the behaviour of these new materials extensively.

Acknowledgements

The technical assistance of F. Khalfi and X. Meersseman is acknowledged.

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