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Biomaterials 20 (1999) 655–661

Biomaterials

Effects of PVC bags sterilization process on the 5-fluorouracil stability

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Received 16 February 1998; accepted 12 October 1998

Abstract

The stability and compatibility of 5-fluorouracil (5-FU) in undiluted or diluted admixtures stored in β-radiation sterilized portable poly(vinyl chloride) (PVC) infusion bags were investigated. Admixtures containing 5-FU 50 mg ml^{-1} not diluted or 25 mg ml^{-1} diluted in 0.9% sodium chloride injection were placed in 100 or 250 ml empty PVC reservoirs sterilized initially by β-irradiation. They were protected from light and placed at 37°C. Two ml quantities were withdrawn immediately after preparation and after storage for 1, 2, 3, 4, 5, 6, 7 and 14 days. For each condition, samples from each admixture were tested for drug concentration by stability-indicating high-performance liquid chromatography. The admixtures were also monitored for precipitation, color change and pH. Evaporative water loss from the containers was also measured. 5-FU was compatible with PVC containers in all tested conditions for 14 days. No loss of drug and no color change were detected throughout the storage period. pH values were stable and neither precipitation nor loss of water through the reservoirs was observed when drug 50 or 25 mg ml^{-1} (diluted using 0.9% sodium chloride) was stored in 100 ml capacity polyvinyl PVC bags. However, when stored in 250 ml capacity PVC bags, the 5-FU solution showed precipitation after 13 and 14 days of storage, but no drug loss was detected due to a substantial loss of water. The precipitation of the drug was due to the decrease of pH induced by the dehydrochlorination of PVC during β-irradiation leading to the formation of hydrochloric acid in solution. Differences observed between 100 and 250 ml capacity bags can be explained by the greater area of PVC present in 250 ml reservoirs, and consequently more HCl formed. Finally, more plasticizer, di-(2-ethylhexyl) phthalate (DEHP), was then detected in drug solutions stored in 250 ml PVC bags. So, we recommend the use of 100 ml bags to store 5-FU at longer storage times and higher temperatures.

Keywords: 5-FU; Stability; PVC bag; pH; HPLC; Sterilization process

1. Introduction

Although 5-fluorouracil (5-FU) is one of the oldest anticancer drugs, it remains the standard therapy of advanced colorectal cancer and is also one of the major drugs in the treatment of head and neck cancer and breast cancer [1, 2]. Used for several years, prolonged infusions of 5-FU have demonstrated their efficacy to treat cancer patients with a high clinical response-rate and low adverse effects [3, 4]. Particularly, it has been shown in patients with metastatic colorectal cancer, there is a therapeutic benefit of using continuous rather than bolus 5-FU [5–7]. For continuous venous infusion, the drug is diluted in parenteral injection solution (5% dextrose or 0.9% sodium chloride) or used undiluted. The containers used are often made of glass or plastic such as bottles, cassettes, syringes or bags. Polyvinyl chloride (PVC) bags containing injection solution 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 [8], and the leaching of potentially harmful substances into the solution [9, 10], particularly a plasticizer, di-(2-ethylhexyl) phthalate (DEHP), that is incorporated into PVC to make the bags soft and pliable.

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0142-9612/99/$ – see front matter
PII: S0142-9612(98)00221-X

Recently, a new formulation of 5-FU is available in vials containing 50 mg ml^{-1} of the drug with sodium hydroxide (NaOH), whereas the old formulation contained a Tris buffer. Several studies are reported in the literature about stability and compatibility of 5-FU with PVC materials and showed a satisfactory stability of the new formulation of 5-FU [11–13]. However, studies [14, 15] showed the possible precipitation of 5-FU when injection solutions are stored at undesirable conditions of temperature. Other factors can influence the stability of 5-FU such as concentration, light, pH and polymer (latex) [16, 17], but no information concerning the sterilization process of PVC materials. The major sterilization process of PVC containers is by steam autoclaving above 120°C for 15 min. However, this process can not be used for empty PVC bags, because the internal sides of the container can adhere between themselves during the sterilization process due to the high temperature. The sterilization by gas, especially by ethylene oxide, then can be used. However, with this type of process, the residual ethylene oxide, limited at 2 ppm, into the polymer can induce toxic reactions. In the 1960s, the third generation of sterilization appeared: the ionizing radiations. However, such type of sterilization can induce organoleptic damage of the packed product and some physico-chemical modifications of the plastic material, such as degradation of their additives [18]. However, these transformations depend on the type of polymer and on the irradiation dose.

The purpose of our work is to study the stability of the new formulation of 5-FU in empty PVC bags sterilized by β-radiation and stored at 37°C to simulate the clinical use of 5-FU in continuous venous infusion using an electronically controlled portable infusion pump and PVC containers placed at the human body temperature. The use of empty bags for drug infusion over a long period of time is interesting to avoid handling and contamination risks, and allows to gain time during the reconstitution of cytostatics in a centralized unit.

A stability-indicating high-performance liquid chromatography (HPLC) was developed to measure 5-FU concentrations in the PVC bags containing diluted or undiluted drug. The leaching of DEHP and the pH of the solution were also investigated.

2. Materials and methods

2.1. Chemicals

The drug substance was the commercial product suitable for clinical use. 5-FU used was the current clinical formulation Fluorouracile® intravenous injection and was generously donated by Produits Roche (Neuilly sur Seine, France) in vials of 250 mg diluted in 5 ml of injectable preparation water containing sodium hydroxide (pH 9.4).

DEHP and di-*n*-nonyl phthalate (DNNP) used as internal standards were obtained from Aldrich Chemical Company (Saint-Quentin-Fallavier, France).

Acetonitrile and methanol were HPLC grade and obtained from Alchym (Marchiennes, France). Carbon tetrachloride used for extraction of DEHP was analytical grade and purchased from Prolabo (Paris, France). The water used for the mobile phase and dilutions was deionized and purified by distillation, and obtained from Macopharma Laboratories (Tourcoing, France). Sodium chloride 0.9% was supplied by Macopharma Laboratories.

2.2. Materials

Chromatographic analysis was performed using a HP 1090M HPLC system (Hewlett Packard, Orsay, France) equipped with a variable volume injector, an automatic sampling system and a Hewlett Packard 79994 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 Thinjet terminal printer.

The pH meter, used to measure the pH of injection solutions during storage in PVC bags at 37°C, was a model HI 8520 N microprocessor equipped with a Micro pH electrode HI 1083 (Hanna Instruments, Lingolstein, France). PVC infusion bags (Macoflex®) were kindly provided by Macopharma Laboratories (Tourcoing, France). Containers were emptied and sterilized by β-irradiation using an electron accelerator and in line with the French Pharmacopeia specification (Caric, Orsay, France). The β-irradiation is used with an energy of 9.8 MeV and for which the total penetration is of 2.5 g cm$^{3-1}$ and the effective penetration is 2 g cm$^{3-1}$. The maximal medium intensity of the electronic beam is 20 kW. Consequently, one run corresponds to a dose of 25 kGy.

2.3. Chromatographic conditions

5-FU analyses were performed on a 5 μm C_{18} Hypersil ODS column (150 × 4.6 mm i.d.) (Life Sciences International, Epargny, France), operating at room temperature. Drug separation was based on an isocratic method using a mobile phase consisting of water and methanol (98/2: v/v). After degassing with helium stream for 15 min, the mobile phase was pumped through the column at a flow rate of 1 ml min^{-1}. Samples (20 μl) were injected into an analytical column and the chromatographic separation was achieved with final detection at 270 nm.

DEHP analyses were performed using previous conditions described by Faouzi et al. [9]. The analytical

column was a 5 μm C_{18} Hypersil ODS column, the mobile phase consisted of acetonitrile and water (90/10, v/v) and UV detector operated at 222 nm. DNNP was used as internal standard.

2.4. Calibration curves and stability-indicating capacity

5-FU calibration curve was constructed at a concentration range of 1.25–10 μg ml^{-1}. A standard stock aqueous solution of 5-FU (1 mg ml^{-1}) was prepared in polypropylene tubes. The standards were immediately aliquoted (1 ml) and stored at −20°C. After defreezing an aliquot, suitable dilutions were made with water to prepare standard solutions of desired concentrations. The calibration curve was fitted by a linear regression analysis of 5-FU peak area versus 5-FU concentration. Samples were diluted to obtain a drug concentration into the range of the calibration curve with the mobile phase before injection into the column. The 5-FU peak area was calculated and the amount of drug determined by reference to the calibration curve.

The accuracy and precision of the assay were validated by establishing the intra-assay and the inter-assay variations evaluated by relative standard deviations (RSD). At four different levels (1.25, 2.50, 5.00, 10.00 μg ml^{-1}), five sets of samples were prepared on the same day to establish the intra-assay variation. The assay was repeated weekly for five weeks to establish the inter-assay variation. The HPLC method was validated as stability-indicating by accelerating the decomposition of 5-FU. The stability-indicating assay for 5-FU was established by boiling and by adding concentrated hydrochloric acid for the acidic conditions, 1 N sodium hydroxide solution for the alkaline conditions and 1% hydrogen peroxide to samples of 5-FU. In addition, the purity and homogeneity of 5-FU peak in samples was confirmed by quantitating the drug at three wavelengths (230, 250 and 280 nm) using the corresponding calibration curves.

At the same time, standard stock solutions of DEHP and DNNP, used as internal standard, were prepared daily in acetonitrile at 1 mg ml^{-1}. 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 test-tubes washed beforehand with methanol:acetonitrile mixture and analyzed in duplicate. From the standard stock solutions of DEHP and DNNP, working solutions in the concentration range of 1.25–20 μg ml^{-1} were prepared by suitable dilutions with acetonitrile. DNNP concentration was 10 μg ml^{-1}. Samples (1 ml) containing DEHP and DNNP known concentrations were treated with 1 ml carbon tetrachloride. The solution was mixed for 15 s and shaken for 15 min at room temperature, followed by centrifugation for 10 min at 2600 rpm. The organic phase was transferred into a clean glass tube and evaporated to dryness at 50°C under a gentle nitrogen stream. The residue was reconstituted in 100 μl of acetonitrile and 20 μl were injected onto HPLC column. Calibration curves were constructed from a linear plot of peak-area ratio (DEHP/DNNP) versus concentration.

2.5. Preparation of admixtures in PVC bags

The target concentrations of 5-FU tested in our study were selected on the basis of either standardized concentrations of solutions recommended by the manufacturer or usual doses administered to cancer patients. Since the doses of 5-FU investigated are usually titrated to achieve a clinical effect, an infinite number of possible concentration combinations could have been tested. All admixtures were prepared under aseptic conditions in vertical laminar-air-flow biological safety cabinets.

Three series of four radiotreated PVC bags were subjected to analysis. Bags were stored at 37°C to simulate the temperature of a continuous venous infusion using an ambulatory portable pump connected to the bag via administration sets and placed underneath the patient's clothing.

Bags were prepared as described below:

- First series: four bags of a 100 ml capacity were filled with 60 ml of a 5-FU not diluted solution at 50 mg ml^{-1}. So, 12 vials of 5-FU (250 mg/5 ml) were introduced in each container using a transfer device, giving a final solution at 3000 mg/60 ml. Bags were stored in a dark place for 14 days at 37°C away from light.
- Second series: four bags of a 100 ml capacity were filled with 100 ml of a 5-FU diluted solution with 0.9% sodium chloride at 25 mg ml^{-1}. So, 10 vials of 5-FU (250 mg/5 ml) corresponding to 2500 mg in 50 ml, were introduced in each container using a transfer device and diluted with 50 ml of 0.9% sodium chloride, giving a final solution at 2500 mg/100 ml. Bags were stored in a dark place for 14 days at 37°C away from light.
- Third series: four bags of a 250 ml capacity were filled with 60 ml of a 5-FU not diluted solution at 50 mg ml^{-1}. So, 12 vials of 5-FU (250 mg/5 ml) were introduced in each container using a transfer device, giving a final solution at 3000 mg/60 ml. Bags were stored in a dark place for 14 days at 37°C away from light.

Optimally, drug compatibility and stability trials should include both visual and chemical tests. The bags containing the drug solution were agitated by bending, flexing, massaging and shaking for about one minute after preparation to simulate the agitation that a bag may undergo during preparation, transportation and administration, then stored at 37°C in an incubator. Two milliliters were removed from each bag at time zero and every day during storage duration (0, 1, 2, 3, 4, 5, 6, 7 and 14 days). After agitation at each time point, the samples were

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 and during the course of the experiment using a properly standardized pH meter. Then, samples were kept frozen in polypropylene tubes at −20°C until analysis by HPLC for 5-FU and DEHP concentrations.

3. Results and discussion

3.1. Chromatography

5-FU concentrations were determined by using a stability-indicating HPLC assay. All assays were performed isocratically at ambient temperature. 5-FU was resolved with a satisfactory baseline separation under developed conditions. The retention time for 5-FU was 3.10 min. During stability-indicating assay and specificity assay, 5-FU was chemically unstable in alkaline conditions and a reduction in the peak for intact drug was observed. The percentage of that reduction was approximately 40% after 2 h of storage. On the other hand, in acidic conditions, 5-FU solution precipitated immediately. However, no decomposed product, particularly fluoroacetaldehyde and fluoromalonaldehydic acid formed with time in the basic medium, was detected with HPLC conditions and interfered with the intact 5-FU peak. The homogeneity of the 5-FU peak was confirmed by quantitating the drug at the three wavelengths (230, 250 and 280 nm) using the respective calibration curves. The monitoring at 270 nm yielded the best relative standard deviation and was thus selected for further studies. The resulting chromatograms were compared with chromatograms of intact 5-FU solution and sodium chloride 0.9%. No degradation product interfered or was eluted with the same retention time of parent 5-FU peak.

The precision of the 5-FU assay was determined by using five series of five measurements at four theoretical concentrations. The intra-assay and inter-assay coefficients of variation expressed as percent relative standard deviation (RSD values) were lower than 0.96 and 1.16%, respectively, indicating good reproducibility for 5-FU. The four-points calibration curve of 5-FU at 1.25–10 $\mu g\,ml^{-1}$ was constructed with absorbance at 270 nm and showed good linearity, as can be seen from the regression equation $y = 35.9x - 0.03$, $r = 0.9999$, where x and y are the concentration of the compounds ($\mu g\,ml^{-1}$) and the peak area, respectively, and r is the correlation coefficient. After statistical analysis, no significant differences were observed between equation parameters and retention times (Student's t-test, $P > 0.05$).

For the assay of DEHP, the intra-assay and inter-assay coefficients of variation (RSD values) were lower than 0.75 and 4.36%, respectively. The calibration curve covered the range of 1.25–20 $\mu g\,ml^{-1}$ with a correlation coefficient better than 0.999. The retention times for DEHP and DNNP were 10.10 and 12.55 min, respectively.

3.2. Stability of 5-FU in PVC bags

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 5-FU 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. Drug instability and incompatibility with PVC were defined as a $>10\%$ decrease from the initial drug concentration.

As detailed in Table 1 (5-FU mean concentrations and standard deviations on four assays), 5-FU at 50 $mg\,ml^{-1}$ not diluted solution (first series) and 5-FU at 25 $mg\,ml^{-1}$ diluted solution with 0.9% sodium chloride injection (second series) stored at 37°C, with protection from light, in 100 ml capacity PVC bags was stable throughout the 14 days survey. All concentrations remained above 90% of the initial value, and most were near 100%. There was no substantial difference between 5-FU concentrations at time zero and at any subsequent time point. The concentrations of 5-FU present in solution after various periods of storage showed that there was effectively no loss ($>10\%$) of drug. This demonstrates that the drug was not adsorbed by the plastic infusion bags sterilized by β-radiation and stored at 37°C. No additional peak corresponding to degradation products was observed on chromatograms. These findings are consistent with those of Barberi-Heyob et al. [16].

After storage for 14 days at 37°C, an evaporative water loss from the containers may be observed leading to an increase of drug concentration in the containers. This however, remains less than 10% of the initial concentration. The percentage of evaporative water loss was estimated between 5 and 8% of initial volume.

No 5-FU precipitation or crystallization and no solution color change was observed in any 5-FU solutions stored in bags of the first and second series. The pH of the admixtures was initially determined to be between 9.30 and 9.35 in any of the containers at this temperature. After 14 days of storage, the pH range was 9.20–9.30, and therefore do not differ significantly from the initial pH.

Concerning the third series (Table 1), no change above 10% of the initial 5-FU concentration was detected at any time interval throughout the 14 days period for 250 ml capacity PVC bags. These results support the findings of Martel et al. [12]. However, we also observed

Table 1
5-FU concentrations (mean ± standard deviation) into solutions stored at 37°C over 14 days in PVC bags initially sterilized using β-irradiation ($n = 4$)

Time (days)	First series (3000 mg/60 ml)	Second series (2500 mg/100 ml)	Third series (3000 mg/60 ml)
T0	3000 ± 0	2500 ± 0	3000 ± 0
T1	2996 ± 4	2466 ± 3	2911 ± 4
T2	2959 ± 7	2462 ± 11	3053 ± 12
T3	3005 ± 12	2447 ± 8	3025 ± 12
T4	2978 ± 5	2506 ± 10	3022 ± 10
T5	3010 ± 16	2510 ± 2	3059 ± 17
T6	3064 ± 14	2478 ± 13	2909 ± 7
T7	2938 ± 6	2506 ± 6	2898 ± 9
T8	2990 ± 8	2508 ± 10	3114 ± 6
T9	3008 ± 12	2487 ± 4	2917 ± 7
T10	3067 ± 5	2546 ± 16	2976 ± 10
T11	3055 ± 11	2482 ± 11	3015 ± 4
T14	3085 ± 9	2598 ± 7	3108 ± 13

an increase of 5-FU concentrations remaining less than 10% due to the evaporative water loss. On the other hand, we observed a precipitate after 13 days of storage in two bags. In the other two bags of the series, the precipitation of 5-FU was observed later, after 25 days for the third bag and 35 days for the fourth bag. Firstly, needle-shaped crystals appeared and after 16 days of storage, progressively cluster-shaped crystals were visually found in solutions. So, the precipitation of 5-FU occurred over 14 days in only two out of the four 250 ml capacity bags tested. The pH of solutions in those two bags which showed precipitation of 5-FU was determined and was 9.00 and 9.05, respectively after 14 days of storage at 37°C, when the pH of solutions in the other two bags of the same batch which did not show precipitation of 5-FU was 9.10 and 9.15, respectively after 14 days of storage at 37°C. These data do not corroborate those of Martel et al. [12], since they observed no precipitation or crystallization of 5-FU solutions. This discordance could be explained by the difference of the sterilization process used to treat the PVC containers. Indeed, the widely used technique to protect the plastic raw materials against contamination by microorganisms is steam autoclaving. However, this process is unsuitable to sterilize the empty PVC bags. On the other hand, this sterilization process causes no or little change to the polymer properties or the degradation of additives. Another technique can be used, the sterilization by gas, especially ethylene oxide.

In our study, the plastic containers have been sterilized using β-radiation, the third generation of sterilization process. However, the consequences of this process are not negligible. Indeed, such a mode of sterilization can induce organoleptic damage of the packed product and some physical or chemical modifications of the plastic material, such as color change and degradation of their additives. So, after β-radiation, PVC containers initially clear become yellow-orange colored. This discoloration can be explained by a physical reaction between the ionizing radiations and the polymer. The structural modifications observed consist of the formation of free-radical induced by β-radiation leading to the scission of the carbon–chlorine bond of polymer (Fig. 1). The liberated chloride free-radical reacts with a methylene hydrogen of PVC chain leading to the formation of carbon–carbon double bonds. The polyenes formed during these reactions lead to the discoloration of polymer due to their absorption in UV-visible spectra. Finally, during reaction, HCl (hydrochloric acid) is produced and leached from the polymer. HCl formed is leached into the 5-FU solution leading to the decrease of pH. pH values of solutions were determined after 14 days of storage. During storage of PVC containers, when pH of the solution is less than 9.10, a precipitate of 5-FU can be observed in solution. To confirm these observations, 5-FU solutions ($50\ mg\,ml^{-1}$ and $25\ mg\,ml^{-1}$) were prepared in polypropylene tubes and adjusted to pH 9.10 with HCl solution. Tubes were stored in the same conditions of PVC bags (light protection, temperature, duration). After 13 and 14 days of storage, a precipitate was visually observed in the tubes. So, the precipitation of 5-FU in β-radiotreated infusion PVC bags could be due to the decrease of pH solution. These findings are consistent with those of Stiles et al. [15]. In conclusion, 5-FU precipitation was not observed in first and second series, because the hydrochloric acid formation after β-radiation and its leaching into solutions were dependent on the area of PVC, and consequently on the capacity of bags. So, the 100 ml capacity bags have a 168 cm^2 PVC area, whereas the 250 ml capacity PVC bags have a 252 cm^2 PVC area. Consequently, the amount of hydrochloric acid leached is more important when 5-FU solutions are stored in 250 ml PVC bags. The precipitation of 5-FU solution was pH-dependent when drug was stored in β-radiotreated bags. However, this phenomenon is so time-dependent and varies significantly for some bag or other. The dehydrochlorination and consequent production of HCl, but also the evaporative water loss were not similar in all radiotreated bags. These differences are more important according to the PVC area and consequently with the 250 ml capacity bags. The 5-FU precipitation is not immediate and systematic, due certainly to the kinetics of reactions (HCl formation, particularly). This can be explained by the sterilization process of our bags, which depends not only on the real dose received by all bags but also on other parameters leading to changes of the polymer properties caused by β-irradiation [18]. Yagoubi et al. [18] showed that the structural modifications of a plastic material after radiotreatment (loss of mass, reticulation and scission, modification of crystallinity, degradation of additives, presence of oligomers) were heterogeneous degradation

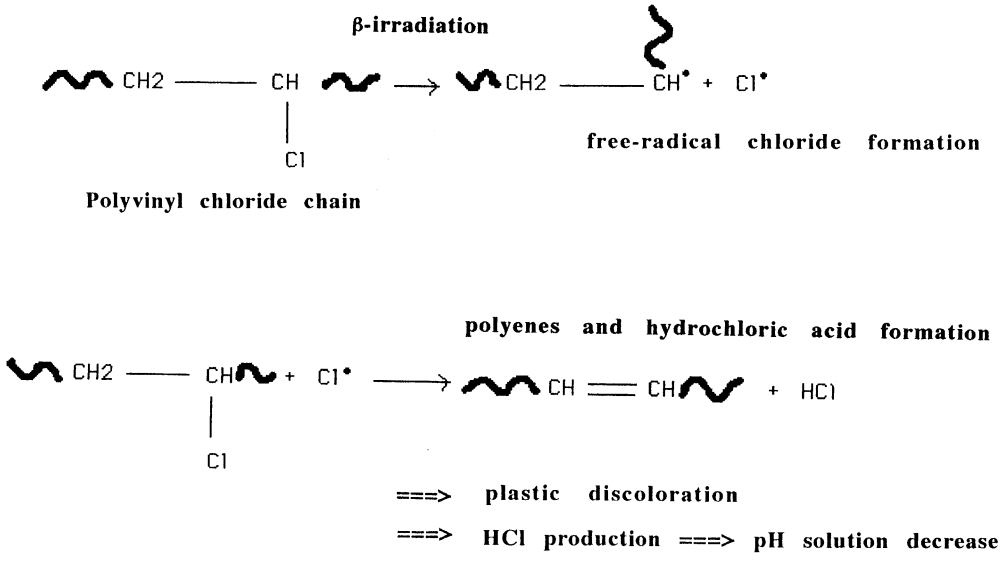

Fig. 1. Reaction and mechanism of chlorhydric acid production by polyvinyl chloride after β-irradiation.

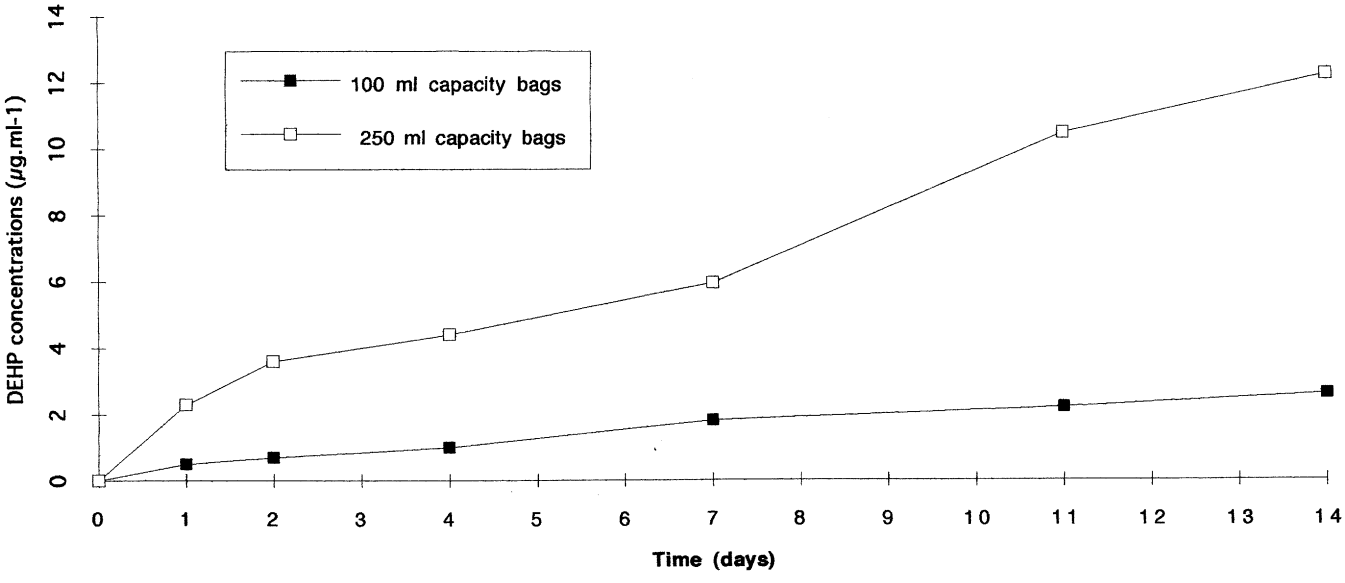

Fig. 2. Leaching of DEHP into 5-FU solutions stored in 100 or 250 ml capacity PVC bags at 37°C over 14 days.

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

On the other hand, the release of DEHP from polymer into 5-FU solution was measured in the three series of bags. The plasticizer is not chemically bound to the polymer and may thus, under certain conditions, leach out from the plastic matrix. Figure 2 shows the results obtained after HPLC analysis. In all solutions stored at 37°C, DEHP was detected by HPLC analysis. The leaching of DEHP increases with the time and the temperature of storage.

The amount of DEHP leached into 5-FU solutions increased progressivly during storage. So, after 14 days at 37°C, the concentration of DEHP was 12.21 $\mu g\,ml^{-1}$ in 5-FU solution stored in 250 ml PVC bags, when it was 2.6 $\mu g\,ml^{-1}$ in those stored in 100 ml PVC bags. This phenomenon has been previously described in studies on other drugs [9, 10]. In the third series, the leaching of DEHP was more important, certainly due to the greater area of PVC for a 250 ml capacity bag. Indeed, the DEHP content of medical grade plasticized PVC depends on the application of the plastic, but, in general, it is between 20% and 40% of the weight, with 30% as a reasonable average. DEHP, like fibrates, belongs to the class of agents described as nongenotoxic and peroxisome proliferator [19]. These chemicals can induce in

animals, after prolonged exposure, changes in hepatocellular structures and liver functions, and the development of hepatic carcinoma. Because of regular and prolonged exposure, patients with end-stage renal failure requiring maintenance haemodialysis are particularly at risk for cumulative retention of DEHP because of its highly lipophilic chemical structure. They are therefore at risk for toxic consequences. So, Gibson et al. [20] estimated that the DEHP amount delivered during a single dialysis session ranged from 100 to 150 mg, when Nässberger et al. [21] estimated the DEHP leaching between 0.8 and 4.2 $\mu g\,ml^{-1}$.

On the other hand, to estimate the effect of DEHP on 5-FU solubility, 5-FU solutions (50 $mg\,ml^{-1}$) were prepared in polypropylene tubes with 12.50 $\mu g\,ml^{-1}$ of DEHP. The tubes were stored for 14 days at 37°C. No precipitation was observed in solutions, showing that the DEHP is not responsible for the 5-FU precipitation.

In conclusion, to minimize patient exposure to DEHP, it is recommended that the 5-FU solution be prepared and stored in 100 ml capacity infusion PVC bags. Finally, in these conditions, when the 5-FU solution is infused to a patient for 14 days using a portable infusion system, the potential risk of drug precipitation is also decreased.

4. Conclusion

Continuous intravenous infusion of some anticancer drugs may have advantages over conventionnal intravenous bolus injection. So, the myelosuppression of 5-FU may be reduced by continuous infusion. Advances in computer technology have made it possible to develop infusion devices that can deliver programmed quantities of a drug over an extended period. Various types of plastic are used in the drug reservoirs. So, PVC bags are widely used with portable infusion-pump devices, but drugs stored in these reservoirs must be stable and compatible. In our study, we demonstrated that the sterilization process of containers influences the stability of 5-FU, particularly decreasing the pH of the drug solution.

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