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Sorption of unoprostone isopropyl to packaging materials

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Abstract

This study investigated the stability of an ophthalmic solution formulation of unoprostone isopropyl (UI), a prostaglandin like compound, in two types of packaging materials, polypropylene (PP) and low-density polyethylene (LDPE). We determined the concentration of UI and its degradation products as a function of time and found that the rate of disappearance of drug was faster for the formulation stored in LDPE bottles than that stored in PP bottles. Further studies indicated that the inferior stability observed with the LDPE packaging was primarily due to the sorption of UI to the packaging material and to a lesser degree, chemical degradation. The sorption was temperature dependent, lowering the temperature reduced the sorption, thus improving the shelf-life of the product.

Keywords: Sorption; Polypropylene; LDPE; Stability; Unoprostone isopropyl

1. Introduction

Unoprostone isopropyl (UI) is a docosanoid, a structural analog of an inactive biosynthetic cyclic derivative of arachidonic acid. It has been found to reduce intraocular pressure by facilitation of aqueous humor drainage. UI 0.15% eye drops is marketed as Rescula® for ophthalmic use for the treatment of elevated intraocular pressure in patients with primary open angle glaucoma or ocular hypertension (Sponsel et al., 2002).

Prostaglandins in general have low water solubility and are unstable. They are subject to both oxidation and hydrolytic degradation (Younger and Szabo, 1986; Stehle and Oesterling, 1977). Efforts to stabilize prostaglandins have mostly focused on formulation strategies (Yamamoto et al., 1992; Oh et al., 1994), for example, by inclusion complexation with methylated-β-cyclodextrins (Hirayama et al., 1984). Weiner et al. (2001) reported that stability of prostaglandin aqueous compositions could be improved by storage in polypropylene (PP) rather than low-density polyethylene (LDPE) containers. However, the mechanism by which PP offers better stability was not reported. As part of formulation development for Rescula®, it was desired to understand the mechanism behind this improved stability, and therefore, packaging compatibility studies, originally reported in the Weiner patent, were expanded upon to include quantification of the active and degradation products in a solution formulation of UI and quantification of the amounts of UI and degradation products sorbed by the LDPE and PP primary packaging components.

2. Materials and methods

2.1. Materials

The unoprostone isopropyl was manufactured by Ueno Fine Chemical (Sanda, Japan). Polypropylene and low-density polyethylene bottles, tips and caps were obtained from Wheaton Science Products and sterilized by ethylene oxide before use. All excipients met USP and EP standards. All chemical reagents were of HPLC grade.

2.2. Drug formulation

UI was formulated as an aqueous solution containing the drug (0.15%) and Tween 80 as a solubilizing agent. The ophthalmic solution also contains 0.015% benzalkonium chloride as a preservative, mannitol as a tonicity agent, EDTA as an antioxidant and stabilizer. NaOH or HCL is used to adjust pH during manufacture to be between 5.0 and 6.5 to minimize drug degradation. The formulation was filter sterilized and aseptically filled

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into 7.5 ml bottles. The bottle and the corresponding tip were either made of polypropylene, Rexene copolymer (hereafter PP bottles) or of low-density polyethylene copolymer (hereafter LDPE bottles). The outer cap for both types of bottles was 15 mm turquoise PP closure. The fill volume was 5.5 ml.

2.3. Stability study

The packaged UI formulation was placed in temperature controlled stability chambers at 5 °C, 25 °C/40% RH, 30 °C/40% RH and 40 °C/15% RH. Samples were withdrawn at predetermined intervals (0, 3, 6, 9, 12, 18, 24, 30, and 42 months) and assayed for potency, degradation products, pH, and weight loss. Five replicates were done for each time point.

2.4. Sorption of UI to packaging materials

Samples of packaged UI product were placed in stability chambers at 5 °C, 25 °C/40% RH and 30 °C/40% RH, respectively, for up to 12 months. UI and drug related impurities were extracted (described below) from the packaging materials and assayed.

2.5. Extraction of UI from packaging materials

The solution was completely emptied from each bottle. The bottle and tip were thoroughly rinsed with deionized water- and air-dried. Caps were not examined because they did not come into direct contact with the product. The bottle was cut into very small pieces (~2 mm × 2 mm) and the tip was quartered. The pieces of materials from the entire bottle and tip were placed in a tared glass vial. Five milliliters of HPLC mobile phase (5.4% (v/v), 2-propanol in half water-saturated *n*-hexane; see below) was added to the vial and the vial was capped. The capped vial was weighed to obtain the initial weight. The vial was then placed in a 55 °C oven. After incubation for 24 h, the vials were cooled to room temperature, vortexed for 20 s and sonicated for 3 h. After sonication, the weight of the vial was weighed again and additional mobile phase was added to its initial weight to compensate for the solvent evaporation during incubation. After thorough mixing, a portion of the supernatant was assayed for UI and its related degradation products by the HPLC methods. The samples were done in triplicate.

2.6. HPLC assay

Two separate HPLC assays were established: one was optimized for assay of the parent drug, UI, and the other, for degradation products. Both methods were fully validated for their intended applications.

2.6.1. UI assay

The HPLC system comprised of a Waters 600E pump, 717 autosampler, 486 UV–vis detector and a Chiralpak AD 4.6 mm × 250 mm, 10 μm column (Chiral Technologies). The detector was set at 204 nm. The mobile phase was 100% denatured ethanol, filtered and sparged with He. The flow rate was 0.43 ml/min. The concentration of UI was calculated from the response values of the standard and the sample.

2.6.2. Degradation products assay

A Hewlett Packard HPLC system (HP-1000) with a variable wavelength UV detector and a YMC Pack-Sil column (5 μm, 6 mm × 150 mm, YMC Inc., Morris Plains, NJ) were used. UV detector was set at 210 nm. The HPLC mobile phase was composed of 5.4% (v/v) 2-propanol in half water-saturated *n*-hexane. Half water-saturated *n*-hexane was prepared by mixing equal volumes of water-saturated *n*-hexane and *n*-hexane. The flow rate was 1.5 ml/min. Prior to injection on the silica column, stability samples were passed through a diatomaceous earth extraction column, Extrelut 3 (EM Science, Gibbstown, NJ) to remove water, dried over vacuum and reconstituted with the mobile phase. For sorption samples, the supernatant was injected directly. This normal phase HPLC method adequately resolves the degradation products as shown in Fig. 1. It should be noted that Fig. 1 shows the forced degradation profile of UI. In most stability studies, we observed only the major degradation products (#3, #5 and #7). The level of each degradation product was expressed as area% corrected for response factor (RF) by the following formula,

$$\text{Area}\,(\%) = \frac{A_i - A_p}{A_{\text{all}}} \times \text{RF}_i \times 100$$

where A_{all} is the sum of all peaks in the sample after placebo peak area has been subtracted. RF_i is the RF value corresponding to peak *i*.

3. Results and discussion

3.1. Stability of UI formulation in PP and LDPE bottles

UI is a clear, colorless, viscous liquid that is very soluble in acetonitrile, ethanol, ethyl acetate, isopropanol, dioxane, ether, octanol, and hexane. It is practically insoluble in water. Thus, UI has a very high octanol/water partition coefficient. Like most prostaglandins, UI is unstable. The degradation pathways for UI include oxidation and hydrolysis.

Preformulation studies showed that UI is most stable at pH 4.5–6.5, the basis for formulating the UI ophthalmic solution at pH 5.0–6.5. Within the pH range of 4.5–6.5, hydrolysis is not typically observed and oxidation is the primary degradation pathway (Fig. 2). The major degradation products are [F–H_2O], [G–H_2O] and [F–H_2O reduced] as shown in Fig. 1 (peaks #3, #5, and #7, respectively).

The most important factor, which affects the stability of the UI formulation, is atmospheric oxygen. Packaging the formulation in glass bottles could improve the stability of the product. However, the glass container is inconvenient and prone to breakage. A plastic container such as a PP bottle or a LDPE bottle is more desirable.

We investigated the stability of UI in PP and LDPE by monitoring the concentrations of UI and its degradation products as a function of time. Figs. 3 and 4 show the change in concentrations of UI and degradation products, respectively, as a function

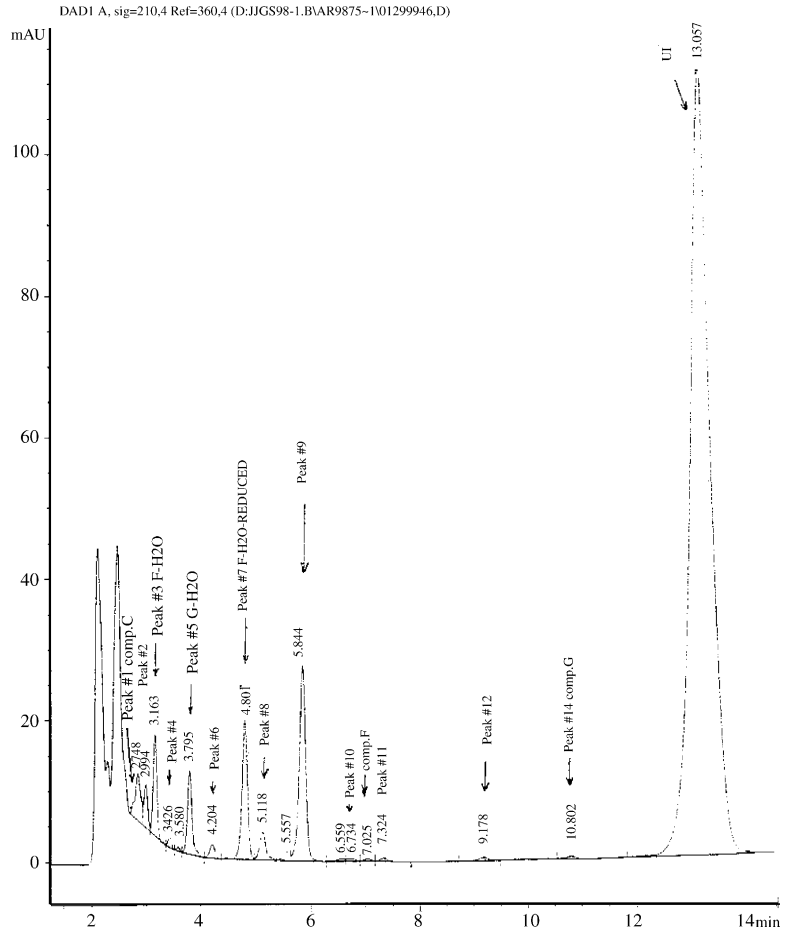

Fig. 1. Chromatogram of degradation products of UI and unrelated impurities. Peaks #3, #5 and #7 are major degradation products seen in the stability studies.

of time for the product stored at 5, 25 and 30 °C. The data show that the rate of disappearance of UI was faster for the product stored in LDPE than that stored in PP bottles at three temperatures studied, consistent with the patent publication (Weiner et al., 2001). The trend of appearance of the degradation products, however, is less clear. At early time points, the concentration and time profiles for the degradation products were similar for the PP and LDPE at all three temperatures. Only at the last time point and at higher temperatures (25 and 30 °C), did the concentration and time profiles diverge with the LDPE samples showing

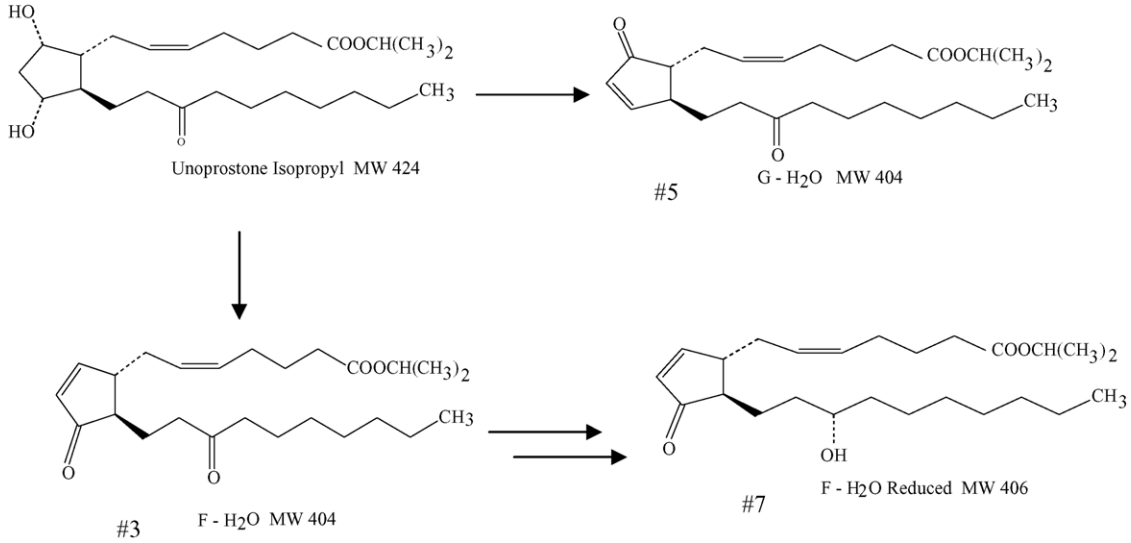

Fig. 2. Major degradation pathway of unoprostone isopropyl.

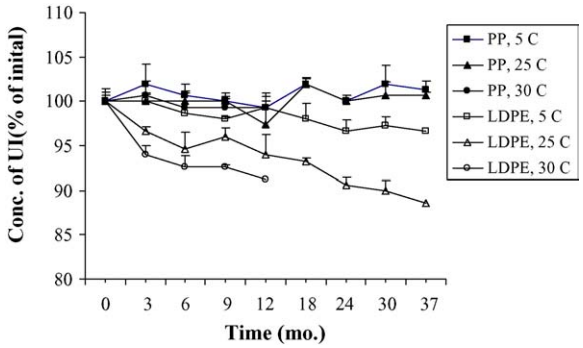

Fig. 3. Effect of packaging material on potency of UI at 5 °C, 25 °C/40% RH and 30 °C/40% RH. Error bars represent five replicates.

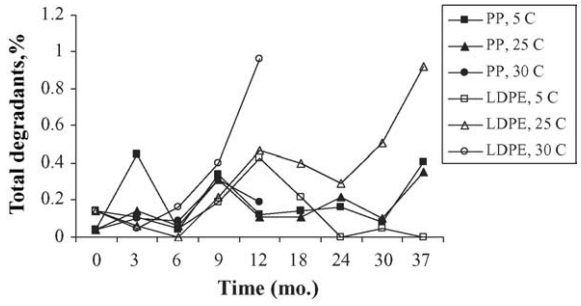

Fig. 4. Comparison of degradation profile of UI in PP and LDPE bottles at 5 °C, 25 °C/40% RH and 30 °C/40% RH.

a greater degradation. To further investigate the apparent disagreement between the potency and degradation profiles of UI, we did the accelerated stability study at 40 °C. Table 1 shows the concentration of UI, total degradation products and weight loss of the UI product in PP and LDPE bottles when stored at 40 °C/15% RH. Mass balance, calculated by the following formula is shown:

$$\text{MB}\,(\%) = \frac{P_t + I_t}{P_i + I_i}(100 - W_t)$$

where MB is mass balance at time t, P_i and P_t are concentrations of UI at initial time and time t, respectively, expressed as percentage of initial concentration. I_i and I_t are area% of total degradation products. W_t is the percentage weight loss at time t.

Similar to the stability profiles shown in Fig. 3, UI potency loss was greater in LDPE than in PP bottles at 40 °C. The total degradation products were slightly higher in LDPE than in PP bottles. Because it is known that the oxygen permeability of LDPE is about four times greater than that of PP (Wheaton Science Products technical publication) and that oxidation is the major degradation pathway for the UI formulation, the increased degradation of UI in LDPE could be attributed to the higher oxygen permeability of LDPE. However, at all temperatures studied, the loss of drug in LDPE bottles cannot be accounted for by degradation alone. There was a significant loss in mass balance for the LDPE samples as compared to the PP samples even after weight loss was taken into consideration (Table 1).

Weight loss occurs by evaporation of water through the container. Thus a weight loss of say, 4%, should result in an increase in potency by 4%. However, in these samples, no increase in potency was observed, and degradation products could not account for the lack of mass balance. Thus, new experiments were initiated to allow for the analysis of drug and its degradation products, which potentially had migrated into the product container due to sorption.

3.2. Sorption of UI to packaging components

To further investigate the cause of potency loss and lack of mass balance of the formulation in the LDPE bottle, we studied potential sorption of UI to packaging materials. We extracted UI and its degradation products from the packaging containers after 9 and 12 months of storage at 30 °C/40% RH and analyzed the concentrations. The data are shown in Fig. 5. Interestingly, it was found that the amount of UI associated with the packaging material increased with increase in storage time and much more drug was retained in the LDPE. UI degradation products also were found in the packaging materials but to a much lesser degree. Additionally, the sorption of UI and its degradation products to packaging materials was temperature dependent as shown in Table 2 where the amount of UI and its degradation products extracted from the PP and LDEP bottles at 5, 25 and 30 °C at 12 months was reported.

It can be seen from Table 2 that the higher the temperature, the more the sorption. The sorption of UI to LDPE is much greater than that to PP, however, the sorption of UI degradation products to LDPE is not significantly different from the sorption to PP. This could be explained by the low chemical potential due to the low concentrations of degradation products in the formulation.

Table 1
Stability of UI formulation in PP and LDPE bottles stored at 40 °C/15% RH

Time (months)	PP				LDPE			
	Potency (%)[a]	Total degradants (%)	Weight loss (%)	Mass balance (%)	Potency (%)	Total degradants (%)	Weight loss (%)	Mass balance (%)
0	100.0	LOQ[b]	0	100	100.0	LOQ	0	100
1	100.7	0.05	0.90 ± 0.01	99.84	92.7	0.05	0.73 ± 0.20	92.07
2	100.0	0.70	1.69 ± 0.03	99.0	90.7	0.14	1.57 ± 0.41	89.41
3	100.7	0.20	2.47 ± 0.04	98.41	88.0	0.46	2.15 ± 0.49	86.56
6	100.7	0.16	4.82 ± 0.08	96.0	86.0	0.71	4.35 ± 0.72	82.94

[a] Percent of initial concentration.
[b] Limit of quantification.

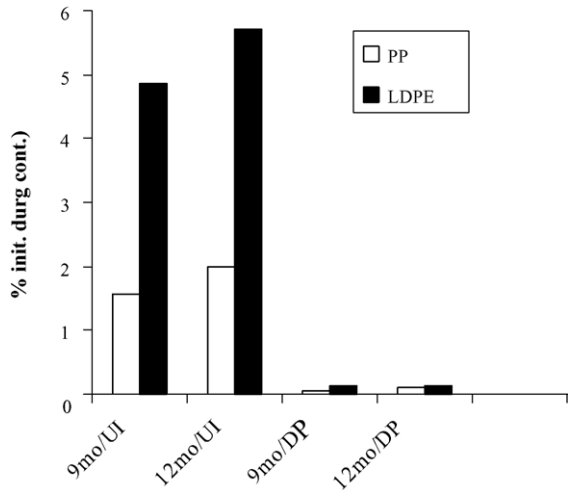

Fig. 5. Amount of UI and its degradation products (DP) associated with the packaging material at 30 °C/40% RH.

Table 2
Amount of UI and degradation products sorbed by PP and LDPE bottles at 12 months (expressed as percentage of initial drug concentration)

	5 °C		25 °C/40% RH		30 °C/40% RH	
	UI	Degradants	UI	Degradants	UI	Degradants
PP	LOQ[a]	LOQ	1.12	0.10	1.98	0.11
LDPE	3.11	0.08	4.76	0.12	5.70	0.15

[a] Limit of qualification.

Table 3
Mass balance (%) at 12 months, taking into account the amounts of drug and degradation products sorbed into the primary packaging components (PP or LDPE)

	5 °C	25 °C/40% RH	30 °C/40% RH
PP	99.48	97.01	99.02
LDPE	102.95[a]	97.68	96.40

[a] Weight loss data is not available for 5 °C but typically it is negligible.

Furthermore, after correcting for the total amount of drug and its degradation products sorbed and the weight loss at 12 months, the mass balance, shown in Table 3, became more comparable between PP and LDPE. These results suggest that UI may be sorbed to the plastic containers.

The sorption of drugs to plastics, particularly to plastic infusion devices, has been well documented. The uptake of drugs by plastics is most appropriately described by the diffusion model (Roberts et al., 1991). It is generally recognized that lipophilic compounds and unionized compounds tend to be sorbed to hydrophobic plastics to a greater extent (Jenke, 1993; Roberts, 1996). The hydrophobicity of UI may render the drug more susceptible to sorption to the plastic container. However, it is not clear why UI is sorbed more to LDPE than to PP given that both LDPE and PP are semi-crystalline polymers and have similar physicochemical properties. It is postulated that LDPE and PP may possess different properties of sorption activity and that the amount of adsorption sites may vary between the two polymers. This is the thermodynamic basis for polymer resistance to substance. Because LDPE has a higher gas permeability than PP, LDPE may have a higher sorption activity as shown for UI.

4. Conclusion

These studies showed that the stability of UI solution is influenced by the packaging materials, PP and LDPE. The inferior stability observed with the LDPE packaging is primarily due to the sorption of UI into the packaging material and to a lesser degree, chemical degradation. The sorption is temperature dependent, lowering the temperature reduces the sorption, thus improving the shelf-life of the product.

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