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Note

Effect of storage on the stability of DL-PLA microspheres containing methadone

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Abstract

This work presents the changes in the characteristics of DL-PLA microspheres of different polymer molecular weights and *dl*-methadone contents, prepared by the solvent evaporation method, after a 3-year storage at room temperature (20 ± 2°C) under desiccated conditions. Size, shape and loading did not change, while degradation index (DI) increased during storage independently of the methadone content. The most stable polymers were those of weight average molecular weight 63000 and 33000. The mechanism involved in the polymer degradation depending on the polymer molecular weight. The methadone release was evaluated through dissolution efficiency (DE). The DE variation with time was kept in the $\pm 20\%$ range.

Keywords: Methadone; DL-PLA; Microspheres; Stability; Degradation index; Dissolution efficiency

Formulation stability is one of the most important pharmaceutical aspects and, despite the fact that biodegradable polymers are widely studied as drug delivery systems, little is known about the stability of biodegradable polymer formulations in solid state. Changes in the T_g of progesterone microspheres (Benoit et al., 1986), microsphere aggregation or fusion (Jalil and Nixon, 1990) depending on the polymer molecular weight, and polymer crystallization and hydrolysis (Aso et al., 1993), have been reported to occur during storage at determined temperatures or humid conditions, drug release pattern being affected at the end.

On the other hand, nothing has been reported on the effect of basic substances in biodegradable polymer formulations during storage; however, some authors have mentioned the ability of these

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substances to hydrolyse lactic acid polymers in aqueous media (Maulding et al., 1986; Cha and Pitt, 1988, 1989; Delgado et al., 1996a,b).

This work is intended to study the changes in the characteristics of DL-PLA microspheres of different molecular weights containing different amounts of a basic drug, *dl*-methadone, after a 3-year storage at room temperature (20 ± 2°C) under desiccated conditions. Polymer degradation and methadone release were evaluated in order to investigate whether, at the end of this time, the formulations were equivalent in vitro.

Thirteen PLA–*dl*-methadone formulations were prepared by the solvent evaporation method according to a second-order composite rotational experimental design; the drug load and DL-PLA weight average molecular weight (M_w) were the two variables under study (Delgado et al., 1996a). Freeze-dried microsphere formulations were stored for 3 years in plastic tubes at room temperature (20 ± 2°C) in the dark, in a glass vessel containing silica gel as protection from atmospheric humidity.

Under storage conditions, microsphere size, shape and methadone loading (ranging from 18 to 47%) were unchanged throughout the 3 years.

To carry out the degradation study of DL-PLA microspheres during storage, a sample of each formulation was analyzed by GPC at 0, 1 and 3 years. To quantify polymer degradation, the degradation index (DI) was used (Glynn et al., 1976).

From the first year, changes in the polymers were found, the molecular weight decreased and, therefore, the DI increased. From a pharmaceutical point of view it can be concluded that the formulations are not stable, even when the increase of DI for the lowest molecular weights (60000 and 33000) was negligible.

As shown in Fig. 1, the evolution of weight distribution of molecular weight (Delgado et al., 1996b) with time of degradation assay, showed different breakage mechanisms for high- and low-molecular weight chains. Fig. 1a shows the weight distribution for lot A (M_w 60000 and 38.3% methadone content), it can be seen that, after 1 and 3 years of storage, some small molecules were formed but the effect on the bulk molecular weight was minimal. On the contrary, lot H (34.7% methadone content) elaborated with the highest molecular weight polymer (M_w 100000) presented a different scission pattern (Fig. 1b). From the first year small molecules were formed and the distribution curve became slightly wider; after 3 years the curve was much wider and moved toward lower molecular weights. It seems that the low-molecular weight polymer degradation is due to the loss of small molecules from the chain ends, or is due to the high breakage probability of short chains, but the molecular weight remains practically unaltered. In the high molecular weight degradation process, two mechanisms must be implicated, one the formation of small molecules as above and, simultaneously, the scis-

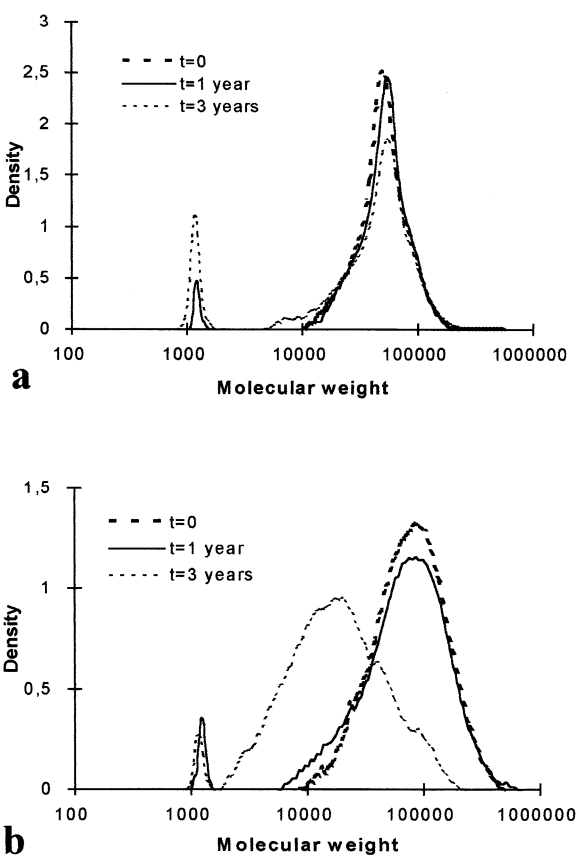

Fig. 1. Distribution function in weight of molecular weight evolution during the 3-year stability assay: (a) formulation A (M_w 60000 and 38.3% methadone content); and (b) formulation H (M_w 100000 and 34.7% methadone content).

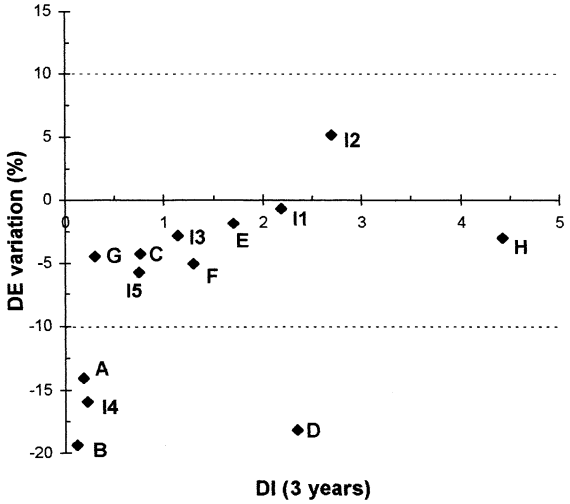

Fig. 2. Percentage of DE variation versus DI, after a 3-year storage, for the 13 formulations involved in the stability assay.

sion of large chains at random positions. This second mechanism gets stronger with time. On the other hand, as was expected in solid state, the methadone content did not affect the rate or extent of degradation.

Dissolution efficiency, DE (Khan, 1975), was used to quantify the effect of storage on in vitro methadone release. DE was calculated from the quotient of the area under the release curve up to 7 days and the area of the rectangle described by 100% released at the same time. The release assays were carried out as described previously (Delgado et al., 1996a).

As can be observed in Fig. 2, DE is reduced after 3 years, but no correlation was found with DI. DE reduction was within the range of $\pm 20\%$ limit. This variation could be acceptable for considering equivalent formulations. The decision could be justified, because at least 10% of the reduction in the methadone release is due to a decrease in the burst effect (amount of methadone released in the first 24 h); and, due to the pharmacokinetic characteristics of this drug, large $t_{1/2}$, the burst effect is not relevant from a therapeutic point of view.

Despite the fact that freeze-drying minimizes microsphere degradation, the variable degradation observed for similar M_w and methadone content values could probably be due to the residual amount of water after freeze-drying. The residual water could allow polymer autocatalysis and, simultaneously, dissolve a very small amount of methadone base producing a slightly basic catalysis.

Acknowledgements

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